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ORIGINAL RESEARCH

Correlation of Great Chinese Famine Exposure During Early Life to Prevalence of Kidney Stone in Adulthood

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Background: The Great Chinese Famine, as the famine of 1959–1961 was often known. Famine exposure during early life was proven to be associated with some kidney diseases but has not been studied with kidney stone. We aimed to investigate the relationship between exposure to the Great Chinese Famine in early life and the incidence of kidney stone in adulthood.

Methods: From 1 January 2017 to 31 December 2018, a total of 19,658 eligible adults were recruited in a cross-sectional survey who were born between 1 October 1952 and 30 September 1964 in Guangdong, China. Participants were separated into kidney stone and none-kidney stone groups based on kidney stone status. According to birth data, participants were divided into non-exposed, fetal-exposed, early-, mid-, and late-childhood-exposed groups. Multivariate logistic regression, subgroup analysis and interaction test were used to estimate the odds ratios (ORs) and confidence intervals (CIs) between famine exposure and kidney stone.

Results: In total, 19,658 (12,246 female, mean age 59.31 ± 3.68 years) subjects were enrolled, and 3219 (16.38%) participants with kidney stone. The prevalence of kidney in none-, fetal-, early-, mid-, and late-childhood-exposed groups were 645 (14.9%), 437 (15.9%), 676 (16.3%), 743 (17.0%), and 718 (17.6%), respectively (P<0.001). When compared with the unexposed group, the fully adjusted ORs for kidney stone from fetal-exposed, early-, mid- to late-childhood-exposed groups were 1.37 (95% CI: 1.13, 1.68, P=0.002), 1.98 (95% CI: 1.45, 2.72, P<0.001), 2.94 (95% CI: 1.96, 4.42, P<0.001), and 3.48 (95% CI: 2.11, 5.72, P<0.001), respectively (P for trend<0.001). Subgroup analyses revealed no interactions between the famine effect on kidney stones and body mass index, gender, smoking status, history of diabetes or hypertension (all P for interaction >0.05).

Conclusion: This study found that exposure to the Great Chinese Famine during early life was independently associated with the increased incidence of kidney stone in adulthood.

Keywords: Great Chinese Famine, early life, famine exposure, adulthood, kidney stone

Introduction

Kidney stone disease is one of the oldest diseases known to medicine and a global health care problem, with a high recurrence rate after stone removal.[1] Despite numerous preventive measures were taken, the prevalence of kidney stone disease was increasing worldwide.[2] Importantly, severe kidney stone could lead to serious complications such as hydronephrosis and kidney failure,[3] and it was also one of the important risk factors for chronic kidney disease.[3] Therefore, it was thus crucial to develop effective strategies to prevent the formation of new or recurrent stone. It was now generally accepted that urinary supersaturation and crystallization, Randall's plaques formation, sex hormones dysfunction, the microbiome and the immune response were five entirely different main mechanisms for kidney stone formation.[4] However, the mechanisms of stone formation and development remain largely unclear.

As a common chronic kidney disease, kidney stone is also a disease closely related to the environment and nutrition.[5,6] In recent years, exposure famine in early life was significantly related to the increased risk for chronic kidney diseases that have been confirmed in the Great Chinese Famine,[7,8] the Dutch famine[9] and the Great Ethiopian

Famine.[10] The Great Ethiopian Famine demonstrated that exposure to famine during prenatal stage was significantly related to decreased estimated glomerular filtration rate and higher risk of developing chronic kidney disease in adulthood after adjusting for systolic blood pressure, fasting blood glucose and body mass index (BMI).[10] The Dutch famine found that people exposed to famine in mid gestation had more microalbuminuria in later life.[9] Studies from Chinese population also suggested that prenatal and fetus-stage exposure to famine may have long-term effects on estimated glomerular filtration rate decline after adjusting for numerous potential confounding factors in humans during in later life.[7,8,11] In addition, low birth weight due to poor maternal nutrition was related to low podocyte endowment and glomerulosclerosis, and also was an important risk factor for chronic kidney disease.[12] Taken together, although malnutrition or famine exposure was closely linked with some chronic kidney diseases, the relationship between famine exposure during early life and kidney stone in adults remains unclear until now. Therefore, in the present study, the aim was to explore the relationship between famine exposure to the Great Chinese Famine during early life and kidney stone in adulthood, and to further explore whether this relationship was modified by gender, smoking, hypertension, diabetes and overweight or obesity status.

Methods

Study Population

Data were from the Early Screening and Comprehensive Intervention Program for High-Risk Population of Cardiovascular Disease (CVD) between 1 January 2017 and 31 December 2018 in Guangdong province, China. The Early Screening and Comprehensive Intervention Program for High-Risk Population of CVD was an essential part of China-PEACE (Patient-Centered Evaluative Assessment of Cardiac Events). Million Persons Project was a government-funded public health program and an ongoing prospective population-centered national screening initiative to detect population at high CVD risk in China.[13] Detailed descriptions of the study design and methods were previously reported.[13,14] At baseline, there were total of 96,110 individuals were recruited from the Early Screening and Comprehensive Intervention Program for High-Risk Population of CVD in Guangdong province between 1 January 2017 and 31 December 2018 in Guangdong province. Individuals who wereborn between 1 October 1952 and 30 September 1964 and have received a kidney stone response questionnaire were enrolled. But the start and end of the Great Chinese Famine was not exact, participants who were born from 1 October 1958 to 30 September 1959 and from 1 October 1961 to 30 September 1962 were excluded to minimize misclassification. In addition, when participants answered that it was unknown whether they had kidney stone were also excluded. Finally, a total of 19,658 subjects were enrolled for analysis (Figure 1).

Definition of Famine Exposure and Grouping

It was now generally believed that the great famine in China occurred from 1959 to 1961, namely, 3 years of severe food shortages occurred in China between the spring of 1959 and the fall of 1961, and the "Three-year Natural Disaster" or "Great Chinese Famine" affected 600 million Chinese people, caused 30 million premature deaths, as well as the loss or delay of the birth of 30 million children, the majority of whom died from hunger-related causes.[15] Participants were divided into five groups based on date of birth according to previous studies.[14,16] (1) no exposure group: born from 1 October 1962 to 30 September 1964, n=4319; (2) fetal exposure group: born from 1 October 1959 to 1961/9/30, n=2743; (3) early-childhood exposure group: born from 1 October 1956 to 30 September 1958, n=4149; (4) mid-childhood exposure group: born from 1 October 1954 to 30 September 1956, n=4368; (5) late-childhood exposure group: born from 1 October 1952 to 30 September 1954, n=4079.

Assessment of Kidney Stone

A highly skilled and qualified doctor and nurse used a questionnaire to gather basic data from the participants. The survey's major components were general information, sociodemographic data, a combination of chronic conditions, dietary patterns, and medication use. Information on kidney stone was collected from face-to-face interviews by asking whether you have been diagnosed with kidney stone by a professional physician. The answer results were mainly as
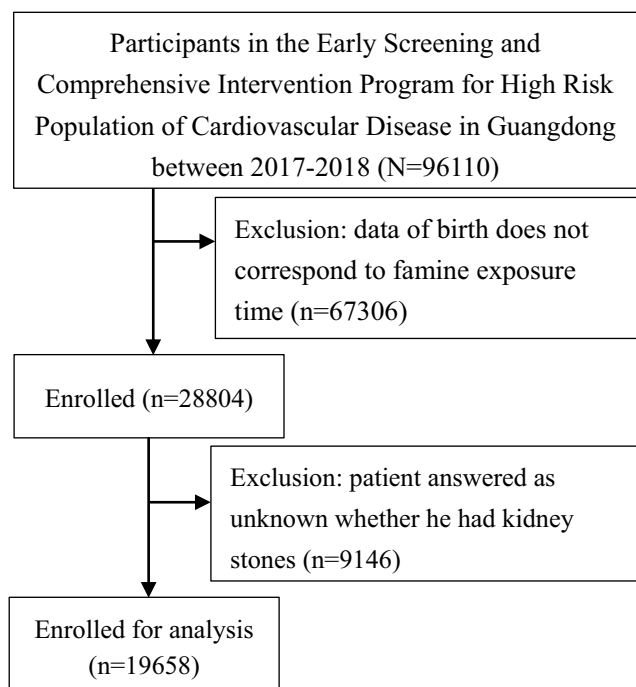
Figure 1 Research flow chart.

follows: "1. Yes; 2. No; 3. Unknown". Furthermore, kidney stone acquisition could be detected from previously self-reported data by imaging examinations such as urine ultrasonography, abdominal X-ray, computed tomography, or magnetic resonance imaging.

Assessment of Covariates

The socio-demographic information, personal diseases history, lifestyle behaviors were collected during face-to-face interviews by trained interviewers according to a standardized structured questionnaire. The socio-demographic information mainly including birth data, gender, education level, income level, marriage status, and residential area. Lifestyle behaviors mainly including smoking and drinking. Personal chronic disease history, primarily hypertension, stroke, coronary heart disease, and diabetes. Current medications include hypoglycemic, antihypertensive, and lipid-lowering agents. The weight and height of participants without shoes and wearing light clothing were then measured by trained technicians. Blood pressure was measured by using an electronic blood pressure monitor (Omron HEM-7430; Omron Corp) on the right upper arm. Fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by fasting blood. BMI was calculated based on weight (kilograms) divided by height (meters squared). BMI$\geq$25kg/m^2 was defined as overweight.[17] Diabetes was defined as fasting blood glucose $\geq$126 mg/dl, self-reported status or taking glucose-lowering drugs.[18] Hypertension was defined as systolic/diastolic blood pressure $\geq$140/90 mmHg, self-reported status or taking antihypertensive drugs.[19]

Statistical Analysis

The continuous and categorial variables were reported as mean ± standard deviation, and a frequency or percentage, respectively. A normality test was first performed on all continuous variable data; comparisons that passed the normality test were analyzed by a Students t-test, and those that did not were analyzed with Mann–Whitney U-test. For comparing the baseline categorical characteristics, the Chi-square test was used for categorical variables. Multiple group comparisons passing normality test were analyzed using analysis of variance (ANOVA) with post hoc tests, whereas nonparametric multiple group comparisons were analyzed using the Kruskal–Wallis test with Dunnett's post hoc testing, when ANOVA assumptions were not met. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) values were

estimated to assess the relationships between famine exposure and kidney stone. Multivariate logistic regression and interaction test was used to estimate the ORs and 95% CI between famine exposure and kidney stone. In model I, none of the covariates were adjusted. In model II, age and gender were adjusted. In model III, BMI, region, education, income, smoking, drinking, BMI, LDL-C, hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs were further adjusted. Subgroups and interaction analysis were performed based on gender (male or female), current smoking (yes or no), BMI (≥ 25.0 kg/m^2 or <25 kg/m^2), combined with diabetes (yes or no) and hypertension (yes or no). 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 (SPSS, Chicago, Illinois, USA).

Results

Characteristics of Participants by Early Life Stage of Exposure to the Great Chinese Famine

As demonstrated in Table 1, there were total of 19,658 individuals (7412 men and 12,246 women) with the average age was 59.31 ± 3.68 years participated in the present study. Among them, 3219 participants were with kidney stone and 16,439 participants were without kidney stone. The baseline parameters of age, gender, BMI, HDL-C, along with hypertension, coronary heart disease, and diabetes, as well as current smoking, drinking, and drug use, were shown to be significantly different between the kidney stone and non-kidney stone groups (all P<0.05). However, no significant changes in blood pressure, total cholesterol, triglyceride, LDL-C, fasting blood glucose, stroke, education, or income levels were found between the two groups (all P>0.05).

In addition, as shown in Table 2, the prevalence of kidney stone in no-exposed, fetal-exposed, early-childhood-exposed, mid-childhood-exposed, and late-childhood-exposed groups were 645 (14.9%), 437 (15.9%), 676 (16.3%), 743 (17.0%), and 718 (17.6%), respectively (P<0.001). Age, gender distribution, systolic blood pressure, BMI, total

Table 1 Baseline Characteristics Between Subjects with and without Kidney Stone Group

Variables	Overall (n=19,658)	No Kidney Stone (n=16,439)	Kidney Stone (n=3219)	P
Age, years	59.31 ± 3.68	59.33 ± 3.68	59.19 ± 3.71	0.041
SBP, mmHg	133.17 ± 18.71	133.20 ± 18.72	133.01 ± 18.64	0.594
DBP, mmHg	79.44 ± 10.92	79.50 ± 10.95	79.16 ± 10.76	0.110
BMI, kg/m^2	24.23 ± 3.32	24.17 ± 3.33	24.50 ± 3.27	<0.001
TC, mmol/L	5.18 ± 1.27	5.18 ± 1.26	5.14 ± 1.29	0.060
TG, mmol/L	1.73 ± 0.98	1.72 ± 0.98	1.74 ± 1.00	0.377
HDL-C, mmol/L	1.52 ± 0.46	1.52 ± 0.46	1.49 ± 0.45	<0.001
LDL-C, mmol/L	2.89 ± 1.03	2.89 ± 1.03	2.87 ± 1.04	0.194
FBG, mmol/L	5.98 ± 1.76	5.97 ± 1.78	6.02 ± 1.66	0.097
Gender – female (%)	12,246 (62.3)	10,461 (63.6)	1785 (55.5)	<0.001
Urban (%)	8866 (45.1)	7502 (45.6)	1364 (42.4)	0.001
Hypertension (%)	8963 (45.6)	7415 (45.1)	1548 (48.1)	0.002
Diabetes (%)	3449 (17.5)	2836 (17.3)	613 (19.0)	0.015
Stroke (%)	130 (0.7)	107 (0.7)	23 (0.7)	0.684
CHD (%)	168 (0.9)	126 (0.8)	42 (1.3)	0.002
Education – high school or above (%)	4359 (22.2)	3628 (22.1)	731 (22.7)	0.425
Income – more than 50k per year (%)	9848 (50.1)	8242 (50.1)	1606 (49.9)	0.799
Current smoking (%)	3607 (18.3)	2905 (17.7)	702 (21.8)	<0.001
Current drinking (%)	1098 (5.6)	894 (5.4)	204 (6.3)	0.042
Lipid-lowering drug (%)	884 (4.5)	657 (4.0)	227 (7.1)	<0.001
Antihypertensive drug (%)	4346 (22.1)	3451 (21.0)	895 (27.8)	<0.001
Hypoglycemic drug (%)	1465 (7.5)	1143 (7.0)	322 (10.0)	<0.001

Notes: Data are presented as mean ± standard deviation or percentage. P values are for the comparison of the difference in kidney stone conditions.
Abbreviations: CHD, coronary heart disease; 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.

Table 2 Baseline Characteristics Among Different Famine Exposure Groups

Variables	No Exposure (n=4319)	Fetal Exposure (n=2743)	Early Childhood (n=4149)	Mid Childhood (n=4368)	Late Childhood (n=4079)	P
Age, years	53.82 ± 0.82	56.81 ± 0.84	59.76 ± 0.81	61.78 ± 0.83	63.70 ± 0.82	<0.001
SBP, mmHg	129.97 ± 18.18	131.62 ± 18.85	133.53 ± 18.62	134.53 ± 18.47	135.75 ± 18.93	<0.001
DBP, mmHg	79.60 ± 11.25	79.20 ± 11.19	79.59 ± 10.88	79.47 ± 10.77	79.27 ± 10.57	0.414
BMI, kg/m^2	24.42 ± 3.37	24.33 ± 3.36	24.25 ± 3.33	24.05 ± 3.26	24.11 ± 3.30	<0.001
TC, mmol/L	5.11 ± 1.24	5.27 ± 1.26	5.20 ± 1.29	5.21 ± 1.28	5.12 ± 1.26	<0.001
TG, mmol/L	1.74 ± 1.00	1.75 ± 1.02	1.73 ± 0.98	1.71 ± 0.96	1.72 ± 0.97	0.365
HDL-C, mmol/L	1.50 ± 0.46	1.53 ± 0.47	1.52 ± 0.46	1.53 ± 0.45	1.51 ± 0.45	0.006
LDL-C, mmol/L	2.85 ± 1.02	2.96 ± 1.03	2.89 ± 1.02	2.93 ± 1.04	2.84 ± 1.03	<0.001
FBG, mmol/L	5.94 ± 1.69	6.01 ± 1.86	5.99 ± 1.77	5.95 ± 1.64	6.01 ± 1.89	0.257
Gender – male (%)	2805 (64.9)	1849 (67.4)	2568 (61.9)	2652 (60.7)	2372 (58.2)	<0.001
Urban (%)	1851 (42.9)	1274 (46.4)	1967 (47.4)	1964 (45.0)	1810 (44.4)	<0.001
Hypertension (%)	1626 (37.6)	1139 (41.5)	1907 (46.0)	2169 (49.7)	2122 (52.0)	<0.001
Diabetes (%)	703 (16.3)	494 (18.0)	760 (18.3)	745 (17.1)	747 (18.3)	0.053
Stroke (%)	21 (0.5)	13 (0.5)	21 (0.5)	43 (1.0)	32 (0.8)	0.012
CHD (%)	26 (0.6)	14 (0.5)	42 (1.0)	42 (1.0)	44 (1.1)	0.023
Education – high school or above (%)	1078 (25.0)	805 (29.3)	977 (23.5)	829 (19.0)	670 (16.4)	<0.001
Income – more than 50k per years (%)	2202 (51.0)	1422 (51.8)	2029 (48.9)	2185 (50.0)	2010 (49.3)	0.086
Current smoking (%)	727 (16.8)	472 (17.2)	758 (18.3)	836 (19.1)	814 (20.0)	0.001
Current drinking (%)	214 (5.0)	135 (4.9)	229 (5.5)	268 (6.1)	252 (6.2)	0.029
Lipid-lowering drug (%)	127 (2.9)	114 (4.2)	191 (4.6)	220 (5.0)	232 (5.7)	<0.001
Antihypertensive drug (%)	702 (16.3)	542 (19.8)	919 (22.1)	1077 (24.7)	1106 (27.1)	<0.001
Hypoglycemic drug (%)	250 (5.8)	216 (7.9)	325 (7.8)	309 (7.1)	365 (8.9)	<0.001
Kidney stone (%)	645 (14.9)	437 (15.9)	676 (16.3)	743 (17.0)	718 (17.6)	<0.001

Notes: Data are presented as mean ±standard deviation or percentage. P values are for the comparison of the difference in famine exposure groups.
Abbreviations: CHD, coronary heart disease; 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.

cholesterol, HDL-C, LDL-C, combined with hypertension, coronary heart disease and stroke, education level, current smoking and drinking, taking lipid-lowering medication, antihypertensive medication, and hypoglycemic medication were all significant subgroup differences (all P<0.05).

Association of Famine Exposure in Early Life Stage with Kidney Stone in Adulthood

As demonstrated in Table 3, the relationship between famine exposure and kidney stone was explored by multivariate logistic regression analysis. In model I, with none of the variables adjusted, the ORs for kidney stone from fetal-exposed, early-childhood-exposed, mid-childhood-exposed to late-childhood-exposed group were 0.92 (95% CI: 0.80, 1.04, P=0.178), 0.89 (95% CI: 0.79, 0.99, P=0.039), 0.97 (95% CI: 0.87, 1.09, P=0.641), and 0.94 (95% CI: 0.84, 1.05, P=0.295) (P for trend was 0.560), respectively, compared to none-exposed group. In model II, age and gender were adjusted, and the ORs for kidney stone from fetal-exposed, early-childhood-exposed, mid-childhood-exposed to late-childhood-exposed group were 1.39 (95% CI: 1.15, 1.68, P=0.001), 1.97 (95% CI: 1.46, 2.65, P<0.001), 2.83 (95% CI: 1.93, 4.15, P<0.001), and 3.50 (95% CI: 2.19, 5.58, P<0.001) (P for trend was <0.001), respectively, compared to none-exposed group. In model III when compared with the unexposed group, the fully adjusted ORs for kidney stone from fetal-exposed, early-childhood exposed, and mid-childhood-exposed groups were 1.37 (95% CI: 1.13, 1.68, P=0.002), 1.98 (95% CI: 1.45, 2.72, P<0.001), 2.94 (95% CI: 1.96, 4.42, P<0.001), and 3.48 (95% CI: 2.11, 5.72, P<0.001), respectively (P for trend <0.001).

Table 3 Multivariate Logistic Regression Analysis the Relationship Between Famine Exposure and Kidney Stone Among Different Groups

Group	Model I	Model II	Model III
	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P
No exposure	Ref	Ref	Ref
Fetal exposure	0.92 (0.80, 1.04) 0.178	1.39 (1.15, 1.68) 0.001	1.37 (1.13, 1.68) 0.002
Early childhood	0.89 (0.79, 0.99) 0.039	1.97 (1.46, 2.65) 0.000	1.98 (1.45, 2.72) 0.000
Mid childhood	0.97 (0.87, 1.09) 0.641	2.83 (1.93, 4.15) 0.000	2.94 (1.96, 4.42) 0.000
Late childhood	0.94 (0.84, 1.05) 0.295	3.50 (2.19, 5.58) 0.000	3.48 (2.11, 5.72) 0.000
P for trend	0.560	<0.001	<0.001

Notes: Data are presented as OR and 95% CI. P values are for the comparison of the difference in famine exposure groups. Model I adjust for none; Model II adjust for age and gender; Model III adjust for age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs.
Abbreviations: OR, odds ratio; CI, confidence interval.

Association of Famine Exposure with Kidney Stone by Subgroup

As shown in Table 4, we observed that childhood exposure to famine at any stage was associated with kidney stone in females, hypertensive patients, subjects without diabetes, none current smoking individuals and people with BMI <25 kg/m^2. In addition,

Table 4 Subgroup Analysis on the Association of Famine Exposure with Kidney Stone

Group	No Exposure	Fetal Exposure	Early Childhood	Mid Childhood	Late Childhood	P for Interaction
		OR (95% CI), P	OR (95% CI), P	OR (95% CI), P	OR (95% CI), P	
Gender						0.94
Male	Ref	1.10 (0.80, 1.50) 0.560	1.40 (0.87, 2.28) 0.169	2.14 (1.14, 4.00) 0.017	2.09 (0.97, 4.49) 0.058	
Female	Ref	1.61 (1.24, 2.09) 0.000	2.58 (1.69, 3.92) 0.000	3.71 (2.16, 6.37) 0.000	5.10 (2.63, 9.91) 0.000	
Hypertension						0.90
No	Ref	1.34 (1.02, 1.74) 0.032	1.77 (1.15, 2.72) 0.009	2.80 (1.61, 4.87) 0.000	3.07 (1.55, 6.06) 0.001	
Yes	Ref	1.44 (1.06, 1.95) 0.020	2.32 (1.45, 3.71) 0.000	3.22 (1.76, 5.89) 0.000	4.14 (1.99, 8.65) 0.000	
Diabetes						0.80
No	Ref	1.34 (1.07, 1.67) 0.010	2.16 (1.53, 3.06) 0.000	3.19 (2.03, 4.99) 0.000	3.69 (2.13, 6.40) 0.000	
Yes	Ref	1.63 (1.01, 2.64) 0.044	1.57 (0.73, 3.36) 0.249	2.45 (0.92, 6.52) 0.074	3.40 (1.02, 11.31) 0.046	
Current smoking						0.72
No	Ref	1.46 (1.17, 1.83) 0.001	2.16 (1.51, 3.08) 0.000	3.12 (1.98, 4.94) 0.000	3.93 (2.24, 6.90) 0.000	
Yes	Ref	1.11 (0.71, 1.74) 0.638	1.50 (0.75, 3.00) 0.253	2.40 (0.97, 5.90) 0.057	2.28 (0.76, 6.80) 0.140	
BMI, kg/m^2						0.66
≥25	Ref	1.36 (1.00, 1.86) 0.053	2.04 (1.24, 3.34) 0.005	3.00 (1.58, 5.69) 0.001	4.02 (1.84, 8.79) 0.000	
<25	Ref	1.39 (1.07, 1.80) 0.013	1.98 (1.31, 2.98) 0.001	2.92 (1.72, 4.97) 0.000	3.19 (1.67, 6.11) 0.000	

Notes: When analyzing a subgroup variable, age, gender, region, education, income, smoking, drinking, body mass index, low-density lipoprotein cholesterol, hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs were adjusted except for the variable itself.

we also found that famine exposure in fetal period was significant relationship with kidney stone in adulthood in females, none current smoking individuals, people with BMI <25 kg/m². Similar results were found when exposed to the fetal period in hypertension and diabetes subgroup, regardless of hypertension and diabetes status. However, no significant interactions were observed from all the subgroup analyses (all P-interaction >0.05).

Discussion

In the present population-based study, we found that individuals who were exposed to the Great Chinese Famine in early life stage had higher kidney stone prevalence in adults. Gender differences existed in the effects of early exposure to famine on the development of kidney stone in adulthood. The independent effects of early exposure to famine on kidney stone in adulthood were not influenced by some traditional chronic disease risk factors including smoking, overweight or obesity, hypertension and diabetes.

Famine exposure was linked to kidney diseases. We discovered a higher likelihood of self-reported kidney stones in adults who had been exposed to the Great Chinese Famine during fetus and infancy. Wang[7] found prenatal exposure to Great Chinese Famine may have long-term effects on declined glomerular filtration rate and the development of chronic kidney diseases in adult humans. The China Health and Retirement Longitudinal Study also indicated famine exposure in fetus might increase the risk of chronic kidney disease in adults.[8] Abate[10] discovered that prenatal exposure to the Great Ethiopian Famine was linked with decreased estimated glomerular filtration rate and higher risk of developing chronic kidney disease among survivors. These findings suggested that early exposure to famine may be crucial for the development of metabolic abnormalities and dysfunction in the kidneys in adults. Reduced glomerular filtration rate and chronic renal disease were risk factors for the development of chronic metabolic abnormalities, and chronic metabolic abnormalities were observed to accelerate the course of frequent stone production and recurrence.[20] They may also suggest that the fetus, infant, and childhood years may be a crucial window of opportunity for the prevention of chronic kidney disease, including kidney stones, in later life.

Subgroup analysis indicated that the relationship between famine exposure during early life and kidney stone in adulthood differed in gender, more pronounced in women. A previous study also found that early life malnutrition had a more significant effect on kidney dysfunction in adult women.[21] The gender difference of early life famine exposure and kidney stone remains unknown. There may be some reasons to explain this phenomenon. On the one hand, there was a phenomenon of "preference of sons to daughters" in some parts of China, which may cause more females to experience more nutritional deficiencies in infancy and early childhood stage. On the other hand, due to the relatively early development of female,[22] lack of nutrition in the early life has a great impact on the development of the neuroendocrine system of female, and the neuroendocrine system also played an important role in the development of kidney structure and function.[23] In a stratified analysis, we also showed that the effect of famine exposure on kidney stone was greater in the non-diabetic population. However, a study from China found that malnutrition during young adulthood significantly increased the risk of renal dysfunction in adult subjects with diabetes.[21] The main reasons for the different results may include differences in study endpoints, study populations and adjustment for covariates. In addition, we also found that the independent relationship between famine exposure and kidney stone did not interact with obesity, smoking status, diabetes and hypertension. These findings suggest that malnutrition in early life may have an important effect on the onset of kidney disease in adults, and prevention of kidney stone should begin in the fetus, infancy and early childhood.

Although the present study demonstrated that famine exposure in fetuses and childhood may significantly increase the risk of kidney stone in adulthood, the mechanisms between them remain unclear. We hypothesized the possible mechanisms or roles as follows: first, the retention of related metabolites in the kidneys caused by renal insufficiency and abnormal metabolism was an important reason for the formation of kidney stone.[4,24,25] Malnutrition may result in incomplete development of renal structure and function, and ultimately affect renal function and renal metabolism.[25,26] Previous researches have shown that body weight was closely related to the total number of glomeruli,[27–29] and nutrition restriction in uterus may lead to low birth weight, resulting in less glomeruli and increased risk of chronic kidney disease in later life.[8,30] Second, the lack of trace elements caused by malnutrition was also an important cause of abnormal kidney development and metabolism.[26] It has been reported that trace elements were closely related to the occurrence of kidney diseases.[31,32] Third, uric acid metabolism was associated with kidney stone,[33] and it has been proven that famine

exposure in early life was an independent risk factor for hyperuricemia in adulthood.[34] Four, food shortages were inevitable during famine, so there may be a lot of food insecurity. A previous study showed that there existed a significant association between food insecurity and kidney stones.[35] In addition, it was now generally accepted that kidney stone was also associated with metabolic abnormalities in the body, such as hyperparathyroidism and hypercortisolism.[36] Both thyroid function and cortisol function were regulated by the brain and nerves, and studies have shown that nutritional deficiencies have a direct and severe impact on brain and nerve development.[37,38] Finally, hypertension, hyperglycemia, insulin resistance and diabetes were all associated with kidney stone formation,[39,40] and studies have found that famine exposure in early life was closely related to the development of diabetes and hypertension in adults.[41,42]

Although we found for the first time in a large population that exposure to the Great Chinese Famine in early life significantly increased the incidence of kidney stone in adulthood, some identified limitations should also be mentioned. First, the causal relationship between famine exposure and kidney stone could not be drawn due to the present study was a cross-sectional survey. Second, kidney stone was mostly self-reported from participants, and recall bias was unavoidable. Third, there were various types of kidney stone, and lacked of information on kidney stone severity, which were not classified in this study. Fourth, incomplete information on famine exposure, the exposure time to famine could not be accurately defined and some population may die due to famine. The current study only analyzed surviving subjects, so it may overestimate or underestimate the effects of famine. Fifth, this study could not distinguish the severity of famine, nor did it measurement for some nutrient elements or dietary habits, and only grouped famine exposure based on the date of birth. In addition, the results of this study may not be extrapolated due to the lack of assessments of renal function and uric acid, although we adjusted for numerous covariates. Finally, this study did not explore the specific mechanism of famine exposure and the occurrence of kidney stone, and more researches were still needed in the future.

Conclusions

In conclusion, early childhood exposure to the Great Chinese Famine was independently related with an increased incidence of kidney stone in adults, indicating that early childhood starvation may play a role in adult renal metabolism and malfunction. This research suggested that the nutritional health of the fetal, infancy, and childhood stages should be prioritized in the prevention of kidney stones. The fundamental processes behind the associations between famine exposure during childhood and an increased risk of kidney stone needed additional investigation.

Data Sharing Statement

The datasets used in this analysis are available from the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of the Guangdong Provincial People's Hospital (No. GDREC2016438H (R2)) and this study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants gave written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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