The relationship between famine exposure in early life and ascending aorta dilatation in adulthood

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Research

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Abstract

Background

The relationship between malnutrition and ascending aorta dilatation (AAD) is still unclear. Therefore, the aim of this study was to examine the association of exposure to the Chinese famine during early life with AAD in adulthood.

Methods

We investigated data of 2598 adults born between 1952 and 1964 from Guangdong, China. All enrolled subjects were divided into five groups: no exposed, fetal exposed, early, mid and late childhood exposed. AAD was assessed by cardiac ultrasound. Multivariate logistic regression and interaction tests were used to estimate the odds ratio (OR) and confidence interval (CI) between famine exposure and AAD.

Results

There were 2598 (943 male, mean age 59.1 ± 3.65 years) participants were enrolled, among them consist of 270 (10.4%) subjects with AAD. Compared with no exposed group, the adjusted ORs for AAD widening from fetal-exposed, early, mid to late childhood exposed were 1.374 (95% CI: 0.794, 2.364, P = 0.251), 1.976 (95% CI: 1.243, 3.181, P = 0.004), 1.929 (95% CI: 1.237, 3.058, P = 0.004) and 2.227 (95% CI: 1.433, 3.524, P < 0.001), respectively. Stratified analysis showed that the effect of famine exposure on AAD was more pronounced in female, smokers, BMI ≥ 24 kg/m² and hypertensive patients.

Conclusions

We observed that exposure to famine during early life was an independent risk factor for AAD in adulthood; this effect was not modified by gender, BMI, smoking, hypertension and diabetes.

Yu-qing HUANG and Lin LIU are equally to this paper.

Introduction

Thoracic aortic aneurysms rupture and dissection are one of the most devastating cardiovascular diseases (CVD) of the aorta vascular diseases, and these diseases are often accompanied by high mortality despite significant improvements in diagnostic imaging, interventional therapy and surgical techniques[1]. It has been showed that aortic root diameter increased or ascending aorta dilatation (AAD) was one of the main risk factor for thoracic aortic dissection and rupture[2]. The measurement of aortic diameters could play a vital role in the clinical evaluation and management of aorta related diseases[3, 4]. At present, the mechanism of AAD is still unclear. Previous studies have shown that nutritional status was closely related to peripheral vascular diseases[5, 6], such as cervical artery dissection [7]. In addition, in recent years, more and more studies have showed that exposure to famine in early life was significantly associated with cardiovascular metabolic diseases, such as diabetes[8], obesity[9],...
hypertension[10], coronary heart disease[11] and dyslipidemia[12]. However, currently, there were very limited studies on famine exposure and AAD. Therefore, the aim of the present study was to explore the relationship between famine exposure during early life and AAD in adulthood, and further analyze whether this effect can be modified by other cardiovascular risk factors including gender, hypertension, diabetes, smoking and overweight/obesity.

Subjects And Methods

Study subjects

The data used in the current study were obtained from the samples from the Early Screening and Comprehensive Intervention Program for High Risk Population of CVD in Guangdong province, China. The Early Screening and Comprehensive Intervention Program for High Risk Population of CVD was a population-centred national screening initiative to detect populations at high risk of CVD in all 31 provinces in mainland China[13]. There were total of 10984 participants completed the screening in Guangdong province between 1 January 2017 and 31 December 2018. Among them aged 35 to 75 years and who completed the evaluation of the diameter of the ascending aorta (AAO) were included. Subjects who was missing AAO inner diameter data, and AAO inner diameter $\geq$ 45 mm was excluded. Finally, a total of 2598 subjects were enrolled for analysis. The research flow chart was shown in Fig. 1. The protocol of the present study has been approved by the Ethics Committee at the Institute of Guangdong Provincial People's Hospital (No.GDREC2016438H (R2)). Informed written consent was obtained from all participants before enrolled in this study.

Famine Exposure

It was generally accepted that the Chinese famine happened from 1959 to 1961[14]. In addition, considering the beginning and ending dates of Chinese famine was unclear, participant who was born from 1958/10/1 to 1959/9/30, and from 1961/10/1 to 1962/9/30 were excluded to minimize misclassification. In this study, according to previous studies[15, 16], subjects who were born between 1952/10/1 and 1964/9/30 were enrolled, and all participants were grouped into five famine exposure groups based on the birth data: no exposed group, defined as born from 1962/10/1 to 1964/9/30; fetal exposed group, defined as born from 1959/10/1 to 1961/9/30; early-childhood exposed group, defined as born from 1956/10/1 to 1958/9/30; mid-childhood exposed group, defined as born from 1954/10/1 to 1956/9/30 and late childhood exposed group, defined as born from 1952/10/1 to 1954/9/30.

Ascending Aorta Assessment

All recordings of cardiac ultrasound examination were by using Vivid-S6 (GE Medical System, Milwaukee, Wisconsin, USA) interfaced with a 2.5–3.5 MHz phased-array probe. AAO dimensions were measured using two-dimensional echocardiography, the detailed measurement method was described
previously[17]. In briefly, aortic root diameter was measured at the sinus level and sinotubular junction, and the AAO inner diameter was measured from a parasternal long axis view, as the maximal distance between the two leading edges in accordance with the American Society of Echocardiography guidelines[18]. AAD was defined as an inner diameter of aortic root inner diameter ≥ 35 mm[19].

Covariates

A face-to-face structured questionnaire was performed to collect socio-demographic (including age, birth data, race, income, education level, census and marriage) and lifestyle (including smoking, drinking, physical activity and diet) data by well-trained study workers at baseline. Chronic diseases (such as hypertension and diabetes) and drugs currently in using (such as glucose lowering, antihypertensive and lipid-lowering drugs) were also collected. At baseline, laboratory tests mainly include fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Body weight, standing height, blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) were measured through standard processes. Body mass index (BMI) was calculated based on the formula: weight (kilograms) divided by height (meters squared). Diabetes was defined as FBG ≥ 126 mg/dl or self-report or taking glucose lowering drugs[20]. Hypertension was defined as SBP/DBP ≥ 140/90 mmHg or self-report or taking antihypertensive drugs[21].

Statistical analysis

All categorical variables were presented as number or percentage, and continuous variables as mean ± standard deviation. Differences in basic characteristics across famine exposure and AAD were compared by one-way analysis of variance (ANOVA), Kruskal-Wallis tests or Chi-Squared tests, where appropriate. Multivariate logistic regression was used to explore the correlation between famine exposure and AAD, and crude and adjusted odds ratio (OR) and confidence interval (CI) were calculated. Adjusted covariates included gender, education and marital status, income, smoking status, drinking status, intake of vegetables and meat, physical activity, hypertension, diabetes, heart rate, systolic and diastolic blood pressure, fasting blood glucose, BMI, TG, TC, HDL-C, LDL-C, taking hypoglycemic, antihypertensive and lipid-lowering drugs. Stratified analyses were performed to evaluate whether the relationships between famine exposure and AAD would be modified by potential confounders, including gender, BMI, smoking, hypertension and diabetes. Interaction tests were estimated by including the multiplicative stratified variables in the multivariate models. A 2-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).

Results

The characteristics of participants
Basic characteristics of the 2598 participants by whether the AAD was presented in Table 1. Of the all the 2598 subjects, there were 943 (36.3%) male population, and the mean age was 59.1 ± 3.65 years. Compared to no AAD group, those in the AAD group were older, more likely to be smokers and drinkers, to be with hypertension, have higher SBP, DBP, BMI, TC, LDL-C and lower HDL-C. In addition, there was a greater proportion of exposed famine in AAD group compared with those without AAD (86.7% vs. 76.1%, P = 0.003).
Table 1
Baseline characteristics between subjects with and without ascending aorta dilatation group

|                                | Overall (n = 2598) | Not AAD group (n = 2328) | AAD group (n = 270) | P-value |
|--------------------------------|--------------------|--------------------------|---------------------|---------|
| Age, years                     | 59.1 ± 3.65        | 59.0 ± 3.67              | 59.9 ± 3.37         | < 0.001 |
| Gender, n,%                    |                    |                          |                     |         |
| Male                           | 943 (36.3%)        | 789 (33.9%)              | 154 (57.0%)         | < 0.001 |
| Female                         | 1655 (63.7%)       | 1539 (66.1%)             | 116 (43.0%)         |         |
| Married, n,%                   | 2393 (92.1%)       | 2146 (92.2%)             | 247 (91.5%)         | 0.775   |
| Education level ≥ high school, n,% | 606 (23.3%) | 554 (23.8%)              | 52 (19.3%)          | 0.111   |
| Income > 50000 yuan, n,%       | 1327 (51.1%)       | 1191 (51.2%)             | 136 (50.4%)         | 0.856   |
| Smoking, n,%                   | 484 (18.6%)        | 401 (17.2%)              | 83 (30.7%)          | < 0.001 |
| Vegetable intake ≥ 3 days per week, n,% | 2285 (88.0%) | 2041 (87.7%)             | 244 (90.4%)         | 0.386   |
| Meat intake ≥ 3 days per week, n,% | 1540 (59.3%) | 1388 (59.6%)             | 152 (56.3%)         | 0.312   |
| Physical activity ≥ 3 days per week, n,% | 985 (37.9%) | 881 (37.8%)              | 104 (38.5%)         | 0.947   |
| Alcohol drinking, n,%          | 131 (5.0%)         | 106 (4.6%)               | 25 (9.3%)           | 0.001   |
| Hypertension, n,%              | 1606 (61.8%)       | 1384 (59.5%)             | 222 (82.2%)         | < 0.001 |
| Diabetes, n,%                  | 515 (19.8%)        | 459 (19.7%)              | 56 (20.7%)          | 0.760   |
| Hypoglycemic drugs, n,%        | 217 (8.4%)         | 193 (8.3%)               | 24 (8.9%)           | 0.825   |
| Antihypertensive drugs, n,%    | 800 (30.8%)        | 671 (28.8%)              | 129 (47.8%)         | < 0.001 |

Data are presented as mean ± standard deviation or percentage.

AAO: ascending aorta; AAD: ascending aorta dilatation; 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.
|                           | Overall (n = 2598) | Not AAD group (n = 2328) | AAD group (n = 270) | P-value |
|---------------------------|--------------------|--------------------------|---------------------|---------|
| Lipid lowering drug, n,%  | 168 (6.5%)         | 147 (6.3%)               | 21 (7.8%)           | 0.426   |
| SBP, mm Hg                | 143 ± 23.1         | 142 ± 23.0               | 152 ± 22.3          | < 0.001 |
| DBP, mm Hg                | 83.1 ± 12.4        | 82.4 ± 12.2              | 89.0 ± 12.3         | < 0.001 |
| BMI, kg/m²                | 24.8 ± 3.34        | 24.7 ± 3.32              | 25.9 ± 3.37         | < 0.001 |
| TC, mmol/L                | 5.81 ± 1.52        | 5.87 ± 1.51              | 5.30 ± 1.45         | < 0.001 |
| TG, mmol/L                | 1.95 ± 1.09        | 1.95 ± 1.09              | 1.97 ± 1.12         | 0.684   |
| LDL-C, mmol/L             | 3.37 ± 1.25        | 3.42 ± 1.25              | 3.01 ± 1.22         | < 0.001 |
| HDL-C, mmol/L             | 1.64 ± 0.468       | 1.65 ± 0.473             | 1.52 ± 0.410        | < 0.001 |
| FBG, mmol/L               | 6.13 ± 1.85        | 6.13 ± 1.86              | 6.14 ± 1.78         | 0.911   |
| Heart rate,beats/min      | 79.7 ± 11.6        | 79.6 ± 11.6              | 80.7 ± 11.1         | 0.144   |
| AAO inner diameter, mm    | 31.3 ± 3.37        | 30.5 ± 2.65              | 37.6 ± 1.70         | < 0.001 |
| Famine exposure, n,%      | 0.003              |                          |                     |         |
| Non-exposed               | 526 (20.2%)        | 490 (21.0%)              | 36 (13.3%)          |         |
| Fetal exposed             | 351 (13.5%)        | 323 (13.9%)              | 28 (10.4%)          |         |
| Early-childhood exposed   | 504 (19.4%)        | 447 (19.2%)              | 57 (21.1%)          |         |
| Mid-childhood exposed     | 626 (24.1%)        | 556 (23.9%)              | 70 (25.9%)          |         |
| Late-childhood exposed    | 591 (22.7%)        | 512 (22.0%)              | 79 (29.3%)          |         |

Data are presented as mean ± standard deviation or percentage.

AAO: ascending aorta; AAD: ascending aorta dilatation; 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.

As summarized in Table 2, the prevalence of AAD among participants in unexposed, fetal-exposed, early-childhood, mid-childhood and late childhood exposed groups was 36 (6.8%), 28 (8.0%), 57 (11.3%), 70 (11.2%) and 79 (13.4%), respectively. There were significant differences in married status, income status, smoking status, meat intake, hypertension history, systolic and diastolic blood pressure, BMI, TC, LDL-C,
heart rate, AAO inner diameter, taking antihypertensive and lipid lowering drugs among unexposed, fetal-exposed, early-childhood, mid-childhood and late childhood exposed groups (all $P < 0.05$).
Table 2
Baseline characteristics among different famine exposure groups

|                         | Overall (n = 2598) | Non-exposed (n = 526) | Fetal exposed (n = 351) | Early-childhood exposed (n = 504) | Mid-childhood exposed (n = 626) | Late childhood exposed (n = 591) | P-value |
|-------------------------|--------------------|-----------------------|-------------------------|----------------------------------|-------------------------------|-------------------------------|---------|
| Birth date              | /                  | 1962/10/-1-1964/9/3   | 1959/10/-1-1961/9/3     | 1956/10/-1-1958/9/3              | 1954/10/-1-1956/9/3           | 1952/10/-1-1954/9/3           |         |
| Age, years              |                    |                       |                         | 0.138                            |                               |                               |         |
| Gender, n,%             | 943 (36.3%)        | 188 (35.7%)           | 111 (31.6%)             | 174 (34.5%)                      | 240 (38.3%)                   | 230 (38.9%)                   |         |
| Male                    | 1655 (63.7%)       | 338 (64.3%)           | 240 (68.4%)             | 330 (65.5%)                      | 386 (61.7%)                   | 361 (61.1%)                   |         |
| Female                  | 2393 (92.1%)       | 497 (94.5%)           | 322 (91.7%)             | 467 (92.7%)                      | 568 (90.7%)                   | 539 (91.2%)                   | 0.154   |
| Married, n,%            | 606 (23.3%)        | 128 (24.3%)           | 108 (30.8%)             | 140 (27.8%)                      | 118 (18.8%)                   | 112 (19.0%)                   | <0.001  |
| Education level ≥ High school, n,% | 1327 (51.1%) | 274 (52.1%) | 185 (52.7%) | 258 (51.2%) | 334 (53.4%) | 276 (46.7%) | 0.169   |
| Income > 50000 yuan, n,% | 484 (18.6%)   | 104 (19.8%)         | 58 (16.5%)              | 81 (16.1%)                       | 138 (22.0%)                   | 103 (17.4%)                   | 0.060   |
| Smoking, n,%            | 2285 (88.0%)       | 450 (85.6%)           | 296 (84.3%)             | 450 (89.3%)                      | 559 (89.3%)                   | 530 (89.7%)                   | 0.027   |
| Vegetable intake ≥ 3 days per week, n,% | 1540 (59.3%) | 313 (59.5%)  | 211 (60.1%) | 311 (61.7%) | 354 (56.5%) | 351 (59.4%) | 0.505   |

Data are presented as mean ± standard deviation or percentage.

Analyzed by one-way analysis of variance.

AAO: ascending aorta; AAD: ascending aorta dilatation; 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.
|                                      | Overall (n = 2598) | Non-exposed (n = 526) | Fetal exposed (n = 351) | Early-childhood exposed (n = 504) | Mid-childhood exposed (n = 626) | Late childhood exposed (n = 591) | P-value |
|--------------------------------------|--------------------|-----------------------|-------------------------|----------------------------------|---------------------------------|---------------------------------|---------|
| Meat intake ≥ 3 days per week, n,%   | 985 (37.9%)        | 170 (32.3%)           | 139 (39.6%)             | 217 (43.1%)                      | 225 (35.9%)                     | 234 (39.6%)                     | 0.005   |
| Physical activity ≥ 3 days per week, n,% | 131 (5.0%)        | 27 (5.1%)             | 18 (5.1%)               | 27 (5.4%)                        | 29 (4.6%)                       | 30 (5.1%)                       | 0.987   |
| Hypertension, n,%                   | 1606 (61.8%)       | 286 (54.4%)           | 196 (55.8%)             | 318 (63.1%)                      | 395 (63.1%)                     | 411 (69.5%)                     | < 0.001 |
| Diabetes, n,%                       | 515 (19.8%)        | 105 (20.0%)           | 66 (18.8%)              | 110 (21.8%)                      | 109 (17.4%)                     | 125 (21.2%)                     | 0.335   |
| Hypoglycemic drugs, n,%             | 217 (8.4%)         | 33 (6.3%)             | 30 (8.5%)               | 43 (8.5%)                        | 48 (7.7%)                       | 63 (10.7%)                      | 0.111   |
| Antihypertensive drugs, n,%         | 800 (30.8%)        | 111 (21.1%)           | 90 (25.6%)              | 167 (33.1%)                      | 206 (32.9%)                     | 226 (38.2%)                     | < 0.001 |
| Lipid lowering drug, n,%            | 168 (6.5%)         | 17 (3.2%)             | 25 (7.1%)               | 28 (5.6%)                        | 46 (7.3%)                       | 52 (8.8%)                       | 0.002   |
| SBP, mm Hg                           | 143 ± 23.1         | 140 ± 23.8            | 140 ± 22.4              | 144 ± 22.4                       | 144 ± 22.2                      | 147 ± 23.9                      | < 0.001 |
| DBP, mm Hg                           | 83.1 ± 12.4        | 84.2 ± 13.1           | 83.1 ± 12.8             | 83.0 ± 12.4                      | 82.2 ± 11.8                     | 83.0 ± 12.2                     | 0.037   |
| BMI, kg/m²                           | 24.8 ± 3.34        | 25.2 ± 3.37           | 25.0 ± 3.33             | 24.7 ± 3.48                      | 24.5 ± 3.25                     | 24.9 ± 3.27                     | 0.011   |

Data are presented as mean ± standard deviation or percentage.

Analyzed by one-way analysis of variance.

AAO: ascending aorta; AAD: ascending aorta dilatation; 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.
|               | Overall (n = 2598) | Non-exposed (n = 526) | Fetal exposed (n = 351) | Early-childhood exposed (n = 504) | Mid-childhood exposed (n = 626) | Late childhood exposed (n = 591) | P-value  |
|---------------|---------------------|-----------------------|-------------------------|----------------------------------|--------------------------------|--------------------------------|---------|
| TC, mmol/L    | 5.81 ± 1.52         | 5.93 ± 1.46           | 5.93 ± 1.57             | 5.79 ± 1.51                      | 5.79 ± 1.51                    | 5.69 ± 1.54                    | 0.003   |
| TG, mmol/L    | 1.95 ± 1.09         | 2.01 ± 1.13           | 1.92 ± 1.15             | 1.92 ± 1.05                      | 1.88 ± 1.04                    | 2.01 ± 1.11                    | 0.707   |
| LDL-C, mmol/L | 3.37 ± 1.25         | 3.50 ± 1.29           | 3.48 ± 1.23             | 3.31 ± 1.21                      | 3.39 ± 1.23                    | 3.24 ± 1.27                    | 0.001   |
| HDL-C, mmol/L | 1.64 ± 0.468        | 1.62 ± 0.470          | 1.68 ± 0.483            | 1.66 ± 0.477                     | 1.64 ± 0.457                   | 1.61 ± 0.461                   | 0.465   |
| FBG, mmol/L   | 6.13 ± 1.85         | 6.10 ± 1.96           | 6.05 ± 1.65             | 6.15 ± 1.83                      | 6.02 ± 1.53                    | 6.32 ± 2.18                    | 0.112   |
| Heart rate, beat s/min | 79.7 ± 11.6 | 80.3 ± 11.1 | 80.3 ± 11.0 | 79.3 ± 11.7 | 80.0 ± 12.3 | 78.7 ± 11.4 | 0.040   |
| AAO inner diameter, mm | 31.3 ± 3.37 | 30.8 ± 3.30 | 30.7 ± 3.17 | 31.3 ± 3.45 | 31.4 ± 3.39 | 31.8 ± 3.34 | < 0.001 |
| AAD, n, %     | 270 (10.4%)         | 36 (6.8%)             | 28 (8.0%)               | 57 (11.3%)                       | 70 (11.2%)                     | 79 (13.4%)                     | 0.003   |

Data are presented as mean ± standard deviation or percentage.

Analyzed by one-way analysis of variance.

AAO: ascending aorta; AAD: ascending aorta dilatation; 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.

**Associations Between Famine Exposure And Ascending Aorta Dilatation**

Table 3 demonstrated the associations between famine exposure in early life and AAD, as the non-exposed group reference, the crude ORs with 95% CI for widening of AAD in fetal, early, mid and late childhood exposed were 1.179 (95% CI: 0.701,1.967, P = 0.527), 1.735 (95% CI: 1.127,2.706, P = 0.013), 1.713 (95% CI: 1.134,2.632, P = 0.011) and 2.100 (95% CI: 1.400,3.207, P < 0.001), respectively. In model 2, after potential cofounders were adjusted, the multivariate adjusted ORs with 95% CI for AAD in fetal, early,
mid and late childhood exposed were 1.374 (95% CI: 0.794,2.364, P = 0.251), 1.976 (95% CI: 1.243,3.181, P = 0.004), 1.929 (95% CI: 1.237,3.058, P = 0.004) and 2.227 (95% CI: 1.433,3.524, P < 0.001), respectively.

| Groups          | OR(95%CI)   | P-value | OR(95%CI)   | P-value |
|-----------------|-------------|---------|-------------|---------|
| Non- exposed    | ref         |         | ref         |         |
| Fetal exposed   | 1.179(0.701,1.967) | 0.527   | 1.374(0.794,2.364) | 0.251   |
| Early-childhood exposed | 1.735(1.127,2.706) | 0.013   | 1.976(1.243,3.181) | 0.004   |
| Mid-childhood exposed | 1.713(1.134,2.632) | 0.011   | 1.929(1.237,3.058) | 0.004   |
| Late-childhood exposed | 2.100(1.400,3.207) | < 0.001 | 2.227(1.433,3.524) | < 0.001 |

Data are presented as OR and 95%CI.

OR odds ratio, CI confidence interval.

Model 1 with no variable was adjusted.

Model 2 with gender, education and marital status, income, smoking status, drinking status, intake of vegetables and meat, physical activity, hypertension, diabetes, systolic and diastolic blood pressure, fasting blood glucose, BMI, TG, TC, HDL-C, LDL-C, heart rate, taking hypoglycemic, antihypertensive and lipid-lowering drugs were adjusted.

**Stratified Analyses**

Stratified analyses of famine exposure and AAD by selected factors were shown in Tables 4. We observed that childhood exposure to famine at any stage, it appears that there was a stronger risk of AAD in female, BMI ≥ 24 kg/m², smokers, hypertensive patients and non-diabetes subjects. However, we also found that famine exposure in fetal period has no obvious relationship with AAD in adulthood. In addition, no statistically significant multiplicative effect modifications were found among the strata factors including gender, BMI, smoking, hypertension and diabetes (all P-interaction > 0.05).
Table 4
Subgroup analysis among different famine exposure groups

| Subgroup                  | Non-exposed | Fetal exposed | Early-childhood exposed | Mid-childhood exposed | Late childhood exposed | P-interaction |
|---------------------------|-------------|---------------|-------------------------|-----------------------|------------------------|---------------|
| Cases/total               |             | OR(95%CI)     | OR(95%CI)               | OR(95%CI)             | OR(95%CI)             |               |
| Gender                    |             |               |                         |                       |                        | 0.313         |
| Male                      | 154/943     | 1.00(ref)     | 1.081(0.499, 2.278)     | 2.045(1.122, 3.796)   | 1.463(0.809, 2.698)    | 1.695(0.942, 3.116) |
| Female                    | 116/165     | 1.00(ref)     | 1.740(0.669, 3.995)     | 1.817(0.594, 4.000)   | 2.301(1.155, 4.864)    | 2.747(1.188, 5.792) |
| BMI, kg/m²                |             |               |                         |                       |                        | 0.067         |
| ≥ 24                      | 183/1490    | 1.00(ref)     | 1.306(0.502, 2.582)     | 2.564(1.461, 4.592)   | 2.151(1.143, 3.808)    | 2.582(1.034, 5.511) |
| < 24                      | 86/1095     | 1.00(ref)     | 1.681(0.664, 4.264)     | 1.169(0.502, 2.806)   | 1.645(0.757, 3.776)    | 1.798(0.822, 4.150) |
| Smoking                   |             |               |                         |                       |                        | 0.397         |
| Yes                       | 83/484      | 1.00(ref)     | 1.119(0.555, 2.325)     | 2.177(0.575, 5.643)   | 2.079(0.704, 5.992)    | 3.024(1.087, 7.348) |
| No                        | 187/2114    | 1.00(ref)     | 1.456(0.632, 2.770)     | 2.042(1.182, 3.612)   | 1.910(1.143, 3.360)    | 2.090(1.273, 3.662) |
| Hypertension              |             |               |                         |                       |                        | 0.289         |
| Yes                       | 222/1606    | 1.00(ref)     | 1.484(0.852, 2.790)     | 2.047(1.199, 3.563)   | 2.081(1.244, 3.565)    | 2.519(1.274, 2.629) |
| No                        | 48/992      | 1.00(ref)     | 1.142(0.553, 2.440)     | 1.983(0.665, 5.263)   | 1.626(0.494, 4.227)    | 1.386(0.783, 3.963) |
| Diabetes                  |             |               |                         |                       |                        | 0.693         |
| Yes                       | 56/515      | 1.00(ref)     | 1.348(0.584, 2.720)     | 1.843(0.915, 3.225)   | 1.969(0.406, 4.059)    | 2.115(0.526, 6.662) |
| No                        | 214/2079    | 1.00(ref)     | 1.325(0.762, 2.440)     | 1.989(1.069, 3.439)   | 2.067(1.195, 3.318)    | 2.417(1.277, 3.585) |

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.
**Discussion**

To explore the risk factors associated with AAD has important clinical significance. This study was the first time to found that exposure to famine in childhood may significantly increase the risk of AAD in adulthood, and this effect will not be modified by other cardiovascular risk factors, such as smoking, hypertension and diabetes.

AAD often appears asymptomatic, but once ruptured it often lead to serious outcomes. In this study, famine exposure during childhood was found to be an independent risk factor for AAD in adulthood after some potential confounding factors were adjusted. Famine exposure was usually accompanied by a lack of nutrient intake, such as protein, vitamins, and trace elements. Demir, et al[22] found that vitamin D deficiency was an independent factor for aortic dilatation. Adam and his team discovered the concentration of Copper and Zinc was significant associated with the size of the aneurysmal enlargement in the wall of the abdominal aortic aneurysm[23]. In addition, although there was no research has specifically evaluated the relationship between Chinese early life famine exposure and AAD in adulthood, we further found that there was a stronger risk of AAD in female, BMI $\geq 24$ kg/m$^2$, smokers, hypertensive patients, and this effect has not been adjusted by the above traditional risk factors for AAD. This suggested that prevention of AAD should pay attention to nutrition status run through the entire life process from early life, and different population may need different nutritional support.

The mechanisms of the relationship between famine exposure and AAD remain unclear, but there have been several possibilities. First of all, subjects who survived from famine may develop compensatory nutrition or nutritional catch-up growth, which may lead to over-nutrition, and further lead to overweight or obesity. It has been found that obesity was independently related to AAD[24]. Second, the Dutch famine study revealed that those exposed to famine in early gestation could increase stress responsiveness[25]. AAD was considered as a disorder of oxidative stress, and basic research indicated that oxidative stress played an important role in thoracic aortic aneurysms[26]. Third, exposure to famine during early life was associated with increased risks of obesity in adulthood[27], and obesity was significantly linked with increased visceral, perivascular, and epicardial adipose tissue[28]. A previous study demonstrated that increased epicardial adipose tissue thickness was correlated with AAD[29]. Fourth, AAD was a chronic inflammatory disorder disease; its main feature was the local weakening and dilatation of the aortic wall[1]. Destructive remodeling of the extracellular matrix and endothelial dysfunction played a vital in AAD[30, 31]. Based on animal and human studies, low birth-weight babies and nutrient deficiency were likely to have endothelial dysfunction, less vascular elastin, increased sympathetic tone and liver-derived dyslipidemias[32, 33]. In addition, increased sympathetic tone was commonly associated with hypertension in animal models of both under nutritional and over nutritional states[34]. It was now generally accepted that exposure to famine in early life was closely related to adult hypertension[35], and that hypertension was an independent risk factor for AAD[36]. The mechanism of AAD is unclear. Therefore, further research is required to investigate the correlation between famine exposure and AAD.
The present study has several strengths. First, to our best knowledge, it was the first study to investigate the relationship between famine exposure in early life and AAD in adulthood among Chinese population. Second, this study adjusted as many as possible risk factors related to the occurrence of AAD. However, some potential limitations should also be noted. First, this study did not collect birth weight and the severity of famine. These confounding factors have a certain impact on the results of the study. Second, it was a cross-sectional study, and the study population cannot represent the entire Chinese population. Third, some baseline variables, such as disease history and medication history come from self-reporting, so there may be a recall bias. Fourth, since children with poor health when exposed to famine during early life may have partially died, and the present study was to analyze the population that was still alive, so the impact of famine may be underestimated. In addition, the specific start and end time of famine in China was not clear, so the grouping according to the date of birth may be different from the actual famine exposure. Finally, although the study group based on birth data, and the birth data was related to age, the possibility of residual confounding due to age differences could not be completely excluded.

**Conclusions**

In conclusion, the key findings of the current study revealed that famine exposure in childhood was closely related to AAD in adulthood, but exposure in the fetal period has nothing to do with it. Famine exposure in childhood was an independent risk factor for AAD in adult. When exposed to famine during early life, subjects who were female, BMI $\geq 24$ kg/m$^2$, smokers, and to be with hypertension, may have a higher risk of AAD. The effect of exposure to famine on AAD will not be adjusted by other risk factors, including BMI, gender, smoking, hypertension and diabetes. These findings are needed to be confirmed by further large-scale prospective studies.

**Abbreviations**

AAO: ascending aorta; AAD: ascending aorta dilatation; 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; 95% CI: 95% confidence interval; OR: odds ratio;

**Declarations**

**Conflict of interest**

The authors declare that they have no conflicts of interest.

**Availability of data and materials**
The datasets generated and/or analyzed during the current study are not publicly available due to privacy protection of the participants but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The survey protocol was approved by the Institutional Review Board of the Guangdong Provincial People's Hospital (No.GDREC2016438H (R2)). All participants gave written informed consent.

**Consent for publication**

All authors read and approved the final manuscript.

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**Authors’ contributions**

LJ and FYQ conceived the study; LL and HYQ wrote the manuscript; LL and HYQ performed the statistical analyses; LK, LJ and FYQ contributed to the critical review of the manuscript; CCL, YYL and HJY participated in the acquisition of the data; FYQ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; and all authors read and approved the final manuscript.

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Figures
The Early Screening and Comprehensive Intervention Program for High Risk Population of Cardiovascular Disease in Guangdong Province between 2017-2018 (n=10984)

Excluded: without cardiac ultrasound examination (n=3869)

Enrolled (n=7115)

Excluded:
1. Date of birth does not correspond to famine exposure time (n=4510)
2. Ascending aorta inner diameter was unavailable (n=7)

Finally enrolled for analysis (n=2598)

Figure 1
Research flow chart