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

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Abstract

The relationship between exposure to famine in early life and the risk of ascending aorta dilatation (AAD) in adulthood is still unclear; therefore, we aimed to examine the association in the Chinese population. We investigated the data of 2598 adults who were born between 1952 and 1964 in Guangdong, China. All enrolled subjects were categorised into five groups: not exposed to famine, exposed during fetal period, and exposed during early, mid or late childhood. AAD was assessed by cardiac ultrasound. Multivariate logistic regression and interaction tests were performed to estimate the OR and CI on the association between famine exposure and AAD. There were 2598 (943 male, mean age 58·3 ± 3·68 years) participants were enrolled, and 270 (10·4 %) subjects with AAD. We found that famine exposure (OR = 2·266, 95 % CI 1·477, 3·477, $P = 0·013$) was associated with elevated AAD after adjusting for multiple confounders. In addition, compared with the non-exposed group, the adjusted OR for famine exposure during fetal period, early, mid or late childhood 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. Subgroup analysis showed that the effect of famine exposure on the association with AAD was more pronounced in female, current smokers, people with BMI ≥ 24 kg/m^2 and hypertensive patients. We observed that exposure to famine during early life was linked to AAD in adulthood.

Key words: **Famine exposure: Early life: Ascending aorta: Ascending aorta dilatation: Adulthood**

Thoracic aortic aneurysms rupture and dissection are often accompanied by high mortality rate despite significant improvements in diagnostic imaging, interventional therapy and surgical techniques[1]. Aortic root diameter increment or ascending aorta dilatation (AAD) was 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]. The incidence of AAD among general population in Europe and America ranged from 3·5 % to 13 %, showing that AAD is not a rare condition[5,6]. The rate of AAD in children with systemic hypertension was approximately 2·8 %[7] and 6 % for children with chronic kidney disease[8]. The prevalence of AAD in middle-aged and aged Chinese population was approximately 10·6 %[9]. Although traditional cardiovascular risk factors, such as hypertension, smoking and obesity are associated with the risk of AAD, the mechanism of AAD aetiology is not fully discovered. Moreover, nutritional status was closely related to peripheral vascular diseases[10,11], such as cervical artery dissection[12]. In addition, exposure to famine in early life was significantly associated with many cardiovascular metabolic diseases, such as diabetes[13], obesity[14], hypertension[15], CHD[16] and dyslipidemia[17]. AAD might also associate with chronic kidney disease and markers of poor nutritional status[8]. However, limited studies have examined the relationship between famine exposure and AAD. In the present study, we explore the relationship between famine exposure during early life and AAD in adulthood and further analyse whether this effect can be modified by traditional cardiovascular risk factors.

Abbreviations: AAD, ascending aorta dilatation; AAO, ascending aorta; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol.

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Subjects and methods

Study subjects

We have analysed the data from the Early Screening and Comprehensive Intervention Program for High Risk Population of CVD in Guangdong province, China. It was a national screening initiative to detect individuals at high risk of CVD in all thirty-one provinces in Mainland China[18]. There were 10 984 participants completed the screening in Guangdong province between 1 January 2017 and 31 December 2018. We included people aged 35 to 75 years and who have completed the evaluation of the diameter of the ascending aorta (AAO) for the analysis. Subjects who did not have AAO inner diameter data or with AAO inner diameter ≥ 45 mm was excluded. Finally, 2598 participants were included for analysis, with the selection process 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 enrolment.

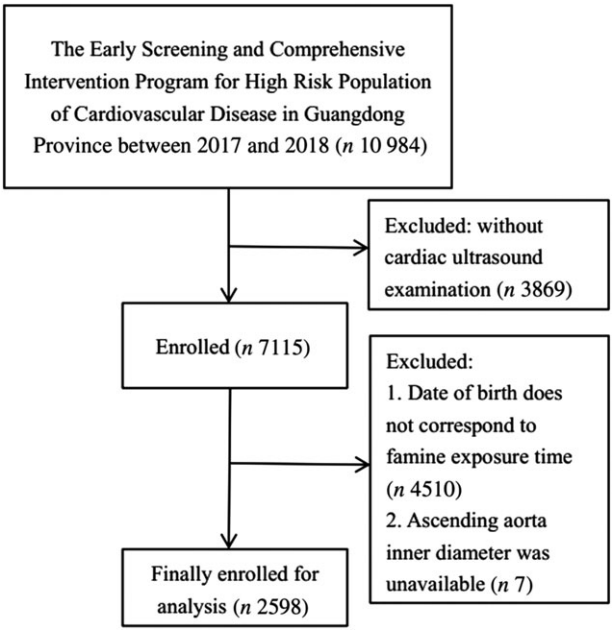

Fig. 1 Research flow chart.

Famine exposure

A famine occurred in China during 1959 and 1961[19]. Since the exact start and end dates of Chinese famine was unclear, participants who were born from 1 October 1958 to 30 September 1959 and from 1 October 1961 to 30 September 1962 were excluded to minimise misclassification. We followed the classification from previous studies to included people who were born between 1 October1952 and 30 September 1964[20,21]. All participants were grouped into five categories: non-exposed group, defined as born from 1 October 1962 to 30 September 1964; exposure in fetal period group, defined as born from 1 October 1959 to 30 September 1961; early-childhood exposure group, defined as born from 1 October 1956 to 30 September 1958; mid-childhood exposure group, defined as born from 1 October 1954 to 30 September 1956 and late-childhood exposure group, defined as born from 1 October 1952 to 30 September 1954.

Ascending aorta assessment

The AAD measurement was performed for all examinations by the same trained physician based on a standardised method. All recordings of cardiac ultrasound examination were collected using Vivid-S6 (GE Medical System) interfaced with a 2·5–3·5-MHz-phased array probe. AAO dimensions were measured using two-dimensional echocardiography, and the detailed measurement method was described previously[22]. In brief, 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 was in accordance with the American Society of Echocardiography guidelines[23]. AAD was defined as an inner diameter of aortic root inner diameter ≥35 mm[24].

Covariates

A face-to-face structured questionnaire was administered to collect socio-demographic (including age, birth data, race, income, education level and marriage) and lifestyle (including smoking, alcohol drinking and diet) data by nurses and physician at baseline. Current alcohol drinking status was dichotomised as whether consumed at least 50 grams alcohol daily in the last 30 d and current smoking habit was dichotomised as whether using at least 100 cigarettes during their lifetime. Dietary intake of fresh vegetables and meat in grams was examined using a semi-quantitative FFQ. History of chronic diseases (such as hypertension and diabetes) were also collected. Laboratory tests included fasting blood glucose, total cholesterol (TC), TAG, LDL-cholesterol and HDL-cholesterol. Body weight, standing height, blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) were measured through standardised processes. BMI was calculated based on the formula: weight (kilograms) divided by height (metres squared). Diabetes was defined as fasting blood glucose ≥ 126 mg/dl, self-reported status or the use of glucose-lowering drugs[25]. Hypertension was defined as SBP/DBP ≥ 140/90 mmHg, self-reported status or the use of antihypertensive drugs[26].

Statistical analysis

All categorical variables were presented as number and percentage, and continuous variables were presented as mean values and standard deviation. Differences in participants' characteristics by famine exposure were compared by one-way ANOVA, Kruskal–Wallis tests or χ^2 tests whenever appropriate. Multivariate logistic regression was used to explore the association between famine exposure and AAD, and crude and adjusted OR and CI were estimated. Age, blood pressure, BMI, heart rate, TC, TAG, LDL-cholesterol, HDL-cholesterol and fasting blood glucose were analysed as continuous variables, while sex, education level, income, smoking status, drinking status, dietary intake status, history of chronic diseases and famine exposure status were analysed as categorical variables. Variables with

$P < 0{\cdot}1$ in univariate logistic regression were included in the multivariate analysis, and traditional cardiovascular risk factors were also included. Adjusted covariates included sex, education and income, smoking status, drinking status, intake of vegetables and meat, hypertension, diabetes, heart rate, SBP, fasting blood glucose, BMI, HDL-cholesterol and LDL-cholesterol. In addition, the collinearity between age and famine exposure status was evaluated by variance inflation factor. Since there has been significant collinearity between age and famine exposure (variance inflation factor > 10), age was not included in the multivariate adjustment model. Subgroup analyses were performed to evaluate whether the relationship between famine exposure and AAD was modified by sex (yes/no), BMI (</≥ 24 kg/m^2), current smoking status (yes/no), hypertension (yes/no) and diabetes (yes/no). The significance on the interaction between famine exposure and the subgroup variables was also evaluated by adding the interaction terms in the regression model. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing), and a two-sided $P < 0{\cdot}05$ was considered as statistically significant.

Results

The characteristics of participants

The characteristics of 2598 participants as classified by AAD were presented in Table 1. Of the all the 2598 subjects, there were 943 (36·3 %) males, and the mean age was 58·3 ± 3·68 years. Compared with non-AAD group, people in the AAD group were older, more prevalent to be current smokers and alcohol drinkers, with hypertension, had higher levels for SBP, DBP, BMI, TC, LDL-cholesterol, and had lower level of HDL-cholesterol. In addition, there was a greater proportion of famine exposure in AAD group compared with those without AAD (86·7 % *v.* 79·0 %, $P = 0{\cdot}003$).

As summarised in Table 2, the prevalence of AAD among participants in non-exposed group, exposure during fetal period, early childhood, mid-childhood and late childhood was 36 (6·8 %), 28 (8·0 %), 57 (11·3 %), 70 (11·2 %) and 79 (13·4 %), respectively. There were significant subgroup differences in marital status, income, current smoking status, meat intake, hypertension history, systolic and DBP, BMI, TC, LDL-cholesterol, heart rate, and AAO inner diameter (all $P < 0{\cdot}05$).

Associations between famine exposure and ascending aorta dilatation

As shown in Table 3, univariate logistic regression analysis demonstrated that age (OR = 1·071, 95 % CI 1·033, 1·112, $P < 0{\cdot}001$), current smoking status (OR = 2·133, 95 % CI 1·612, 2·822, $P < 0{\cdot}001$), hypertension (OR = 1·878, 95 % CI 1·125, 3·134, $P < 0{\cdot}001$), SBP (OR = 1·018, 95 % CI 1·012, 1·023, $P < 0{\cdot}001$), BMI (OR = 1·105, 95 % CI 1·066, 1·146, $P < 0{\cdot}001$) and famine exposure (OR = 1·733, 95 % CI 1·219, 2·533, $P = 0{\cdot}003$) had significant positive associations with AAD, while HDL-cholesterol (OR = 0·528, 95 % CI 0·398, 0·700, $P = 0{\cdot}004$) was inversely related to AAD. Further multivariate logistic regression indicated that famine exposure (OR = 2·266, 95 % CI 1·477, 3·477, $P < 0{\cdot}001$), age (OR = 1·084, 95 % CI 1·04, 1·131, $P < 0{\cdot}001$), current smoking status (OR = 2·139, 95 % CI 1·357, 3·372, $P < 0{\cdot}001$), hypertension (OR = 2·155, 95 % CI 2·284, 4·356, $P < 0{\cdot}001$), SBP (OR = 1·041, 95 % CI 1·025, 1·058, $P < 0{\cdot}001$) and BMI (OR = 1·097, 95 % CI 1·05, 1·145, $P = 0{\cdot}005$) had significant positive associations with AAD, and HDL-cholesterol (OR = 0·896, 95 % CI 0·805, 0·997, $P < 0{\cdot}001$) was inversely related to AAD.

In addition, famine exposure was further subdivided into non-exposed, exposure in fetal period, exposure in early childhood, mid-childhood or late childhood. Table 4 demonstrated the associations between famine exposure in early life and AAD. Using the non-exposed group reference, the crude OR with 95 % CI for increased AAD in fetal, early-, mid- and late-childhood exposure were 1·179 (95 % CI 0·701, 1·967, $P = 0{\cdot}527$), 1·735 (95 % CI 1·127, 2·706, $P = 0{\cdot}013$), 1·713 (95 % CI 1·134, 2·632, $P = 0{\cdot}011$) and 2·100 (95 % CI 1·400, 3·207, $P < 0{\cdot}001$), respectively. Similarly in model 2, the multivariate-adjusted OR with 95 % CI for AAD were 1·374 (95 % CI 0·794, 2·364, $P = 0{\cdot}251$), 1·976 (95 % CI 1·243, 3·181, $P = 0{\cdot}004$), 1·929 (95 % CI 1·237, 3·058, $P = 0{\cdot}004$) and 2·227 (95 % CI 1·433, 3·524, $P < 0{\cdot}001$), respectively.

Subgroup analyses

Subgroup analyses on the relationship between famine exposure and AAD were shown in Fig. 2. We observed that childhood exposure to famine at any stage was associated with AAD in females, people with BMI ≥ 24 kg/m^2, current smokers, hypertensive patients and non-diabetic subjects. However, we also found that famine exposure in fetal period had no relationship with AAD in adulthood. However, no significant interactions were observed from subgroup analyses (all P-interaction > 0·05).

Discussion

In the present study, we found that the exposure to famine in childhood may significantly associate with AAD in adulthood, which has added valuable evidence to the limited body of knowledge. When exposed to famine during early life, subjects in adulthood who were female, BMI ≥ 24 kg/m^2, current smokers and o be with hypertension may have a significant association with AAD. In addition, we also found that age, current smoking status, hypertension, SBP, BMI and HDL-cholesterol were closely related to AAD after adjustment for potential confounders.

AAD often appears asymptomatic but could lead to serious outcomes once rupture occurred. We found that the incidence of AAD was gradually increasing with age, and the prevalence of adults was significantly higher than that of children, which was consistent with the results of some previous studies[5–9]. In addition, our research showed that people with older age, current smoking habit, elevated SBP and elevated BMI were positively related to AAD, while HDL-cholesterol was inversely related to AAD. Our findings were consistent with previous studies[27–30]. In the present study, famine exposure during childhood was found to be closely related to AAD in adulthood after multivariate adjustment. Famine exposure was usually accompanied by malnutrition, such as inadequate intake of protein, vitamins and trace elements. Demir *et al.*[31] found that

Table 1 Baseline characteristics between subjects with and without ascending aorta dilatation group*
(Mean values and standard deviations; numbers and percentages)

	Overall (*n* 2598)				Not AAD group (*n* 2328)				AAD group (*n* 270)				
	n	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD	*P*
Age, years			58·3	3·68			56·0	3·67			59·9	3·37	< 0·001
Sex, *n*,%													< 0·001
Male	943	36·3 %			789	33·9 %			154	57·0 %			
Female	1655	63·7 %			1539	66·1 %			116	43·0 %			
Education level ≥ high school, *n*,%	606	23·3 %			554	23·8 %			52	19·3 %			0·111
Income > 50 000 yuan, *n*,%	1327	51·1 %			1191	51·2 %			136	50·4 %			0·856
Current smoking status, n,%	484	18·6 %			401	17·2 %			83	30·7 %			< 0·001
Vegetable intake ≥ 3 d per week, *n*,%	2285	88·0 %			2041	87·7 %			244	90·4 %			0·386
Meat intake ≥ 3 d per week, *n*,%	1540	59·3 %			1388	59·6 %			152	56·3 %			0·312
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
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/m^2			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
TAG, mmol/l			1·95	1·09			1·95	1·09			1·97	1·12	0·684
LDL-cholesterol, mmol/l			3·37	1·25			3·42	1·25			3·01	1·22	< 0·001
HDL-cholesterol, 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*,%	2072	79·8 %			1838	78·9 %			234	86·7 %			0·003

AAD, ascending aorta dilatation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; FBG, fasting blood glucose; AAO, ascending aorta.
* *P* values are for the comparison of the difference in ascending aorta dilatation conditions.

vitamin D deficiency was an independent factor for aortic dilatation. Moreover, Adam and his team discovered that the concentration of Cu and Zn was significantly associated with the size of the aneurysmal enlargement in the wall of the abdominal aortic aneurysm[32]. Although the interaction might not be significant due to limited sample size, exposure to famine might have a significant relationship with AAD in females, people with BMI ≥ 24 kg/m^2, current smokers and hypertensive patients. However, one common limitation of famine exposure studies is the collinearity issue between age and famine exposure, which is pending to be overcome in future studies.

The full mechanisms of the relationship between famine exposure and AAD remain unclear, but there are several possibilities. First, participants who survived from famine may develop catch-up growth and may lead to over-nutrition, which was independently related to AAD[33]. Second, the Dutch famine study revealed that those exposed to famine in early gestation could increase the responsiveness to oxidative stress[34]. AAD was considered as a disordered response of oxidative stress, and basic research indicated that oxidative stress played an important role in thoracic aortic aneurysms[35]. Third, the exposure to famine during early life was associated with increased risks of obesity in adulthood[36], and obesity was significantly linked with elevated visceral, perivascular and epicardial adipose tissue[37]. A previous study demonstrated that thicker epicardial adipose tissue was correlated with AAD[38]. Fourth, AAD was a chronic inflammatory disorder, and its main feature was the local weakening and dilatation of the aortic wall[1]. Destructive remodelling of the extracellular matrix and endothelial dysfunction played a vital role in AAD[39,40]. Based on animal and human studies, babies with low birth weight and nutrient deficiency were likely to suffer from endothelial dysfunction, less vascular elastin, increased sympathetic tone and liver-derived dyslipidemias[41,42].In addition, under- or over-nutrition both increased sympathetic tone and was commonly associated with hypertension in animal models[43]. The exposure to famine in early life was also related to adulthood hypertension[44], another risk factor for AAD[45]. Despite the possible mechanisms as stated above, further research is required to investigate the physiological linkage between famine exposure and AAD.

Strengths and limitations

The present study has several strengths. First, it was the first study to investigate the relationship between famine exposure in early life and AAD in adulthood among Chinese population. Second, the present study has adjusted for multiple risk factors related to the occurrence of AAD. However, some potential limitations should be noted. First, the present study did not collect birth weight to examine the severity of famine exposure. Second, it was not a prospective study that cannot draw a causal relationship between famine exposure and AAD, as well as the study population does not fully represent Chinese population. Third, self-reported variables, such as dietary factors, disease history and medication history, were not examined in detail and might lead to recall bias. Fourth, some children might die from the famine during early life; therefore, the impact of famine might be underestimated. Fifth, the present study did not collect haematological markers related to nutritional status. Sixth, the high collinearity between age and exposure group could be confounding the

Table 2 Baseline characteristics among different famine exposure groups*,†
(Mean values and standard deviations; numbers and percentages)

	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)				
	n	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD	*n*	%	Mean	SD	*P*
Birth date			/				1962/10/1–1964/9/30				1959/10/1–1961/9/30				1956/10/1–1958/9/30				1954/10/1–1956/9/30				1952/10/1–1954/9/30			
Sex, *n*,%	943	36·3 %			188	35·7 %			111	31·6 %			174	34·5 %			240	38·3 %			230	38·9 %			0·154
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 %			
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 > 50 000 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 d per week, *n*,%	1540	59·3 %			313	59·5 %			211	60·1 %			311	61·7 %			354	56·5 %			351	59·4 %			0·505
Meat intake ≥ 3 d per week, *n*,%	985	37·9 %			170	32·3 %			139	39·6 %			217	43·1 %			225	35·9 %			234	39·6 %			0·005
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
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/m^2			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
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
TAG, 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-cholesterol, 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-cholesterol, 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, beats/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

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; FBG, fasting blood glucose; AAO, ascending aorta; AAD, ascending aorta dilatation.
* Analysed by one-way ANOVA.
† *P* values are for the comparison of the difference in famine exposure conditions.

Table 3 Logistic regression analysis of baseline variables and ascending aorta dilatation (Odd ratios and 95 % confidence intervals)

	Univariate			Multivariate		
Variable	OR	95 % CI	*P*	OR	95 % CI	*P*
Age, years (per SD increased)	1·071	1·033, 1·112	< 0·001	1·084	1·04, 1·131	< 0·001
Education level						
< High school graduated	ref					
≥ High school graduated	0·764	0·556, 1·049	0·196			
Income, yuan						
≤ 50 000	ref					
> 50 000	0·969	0·753, 1·247	0·806			
Current smoking status						
No	Ref			Ref		
Yes	2·133	1·612, 2·822	< 0·001	2·139	1·357, 3·372	< 0·001
Vegetable intake < 3 d per week						
No	ref					
Yes	1·232	0·807, 1·883	0·334			
Meat intake < 3 d per week						
No	ref					
Yes	0·870	0·674, 1·122	0·282			
Hypertension						
No	ref			ref		
Yes	1·878	1·125, 3·134	< 0·001	2·155	2·284, 4·356	< 0·001
Diabetes						
No	ref					
Yes	1·063	0·779, 1·452	0·699			
Systolic blood pressure, mm Hg (per SD increased)	1·018	1·012, 1·023	< 0·001	1·041	1·025, 1·058	< 0·001
BMI, kg/m^2(per SD increased)	1·105	1·066, 1·146	< 0·001	1·097	1·05, 1·145	0·005
Total cholesterol, mmol/l (per SD increased)	1·171	0·707, 1·841	0·182			
TAG, mmol/l (per SD increased)	1·024	0·914, 1·147	0·684			
LDL-cholesterol, mmol/l (per SD increased)	1·166	0·686, 1·856	0·401			
HDL-cholesterol, mmol/l (per SD increased)	0·528	0·398, 0·700	0·004	0·896	0·805, 0·997	< 0·001
Fasting blood glucose, mmol/l (per SD increased)	1·004	0·938, 1·074	0·911			
Heart rate, beats/min (per SD increased)	1·008	0·997, 1·019	0·144			
Famine exposure						
No	ref			ref		
Yes	1·733	1·219, 2·533	0·003	2·266	1·477, 3·477	< 0·001

Table 4 Relationship between famine exposure and ascending aorta dilatation among different groups (Odd ratios and 95 % confidence intervals)

	Model 1†				Model 2‡				Collinearity analysis: age and famine exposure status
Groups	OR	95 % CI	*P*	Adjusted *P**	OR	95 % CI	*P*	Adjusted *P**	VIF
Non-exposed	ref				ref				11·53
Fetal exposed	1·179	0·701,1·967	0·527	0·998	1·374	0·794,2·364	0·251	0·996	13·79
Early-childhood exposed	1·735	1·127,2·706	0·013	0·053	1·976	1·243,3·181	0·004	0·017	16·56
Mid-childhood exposed	1·713	1·134,2·632	0·011	0·047	1·929	1·237,3·058	0·004	0·017	31·65
Late-childhood exposed	2·100	1·400,3·207	< 0·001	0·001	2·227	1·433,3·524	< 0·001	0·001	50·42

VIF, variance inflation factor.
* Bonferroni correction.
† Model 1 with no variable was adjusted.
‡ Model 2 with sex, education, income, smoking status, drinking status, intake of vegetables and meat, hypertension, diabetes, systolic blood pressure, fasting blood glucose, BMI, HDL-cholesterol, LDL-cholesterol and heart rate were adjusted.

effect of famine exposure on AAD. The possibility of residual confounding due to age differences could not be completely excluded.

Conclusions

In conclusion, famine exposure in childhood was closely positively related to AAD in adulthood. These findings are needed to be confirmed by further large-scale prospective studies and have to account for the collinearity issue of age and famine exposure.

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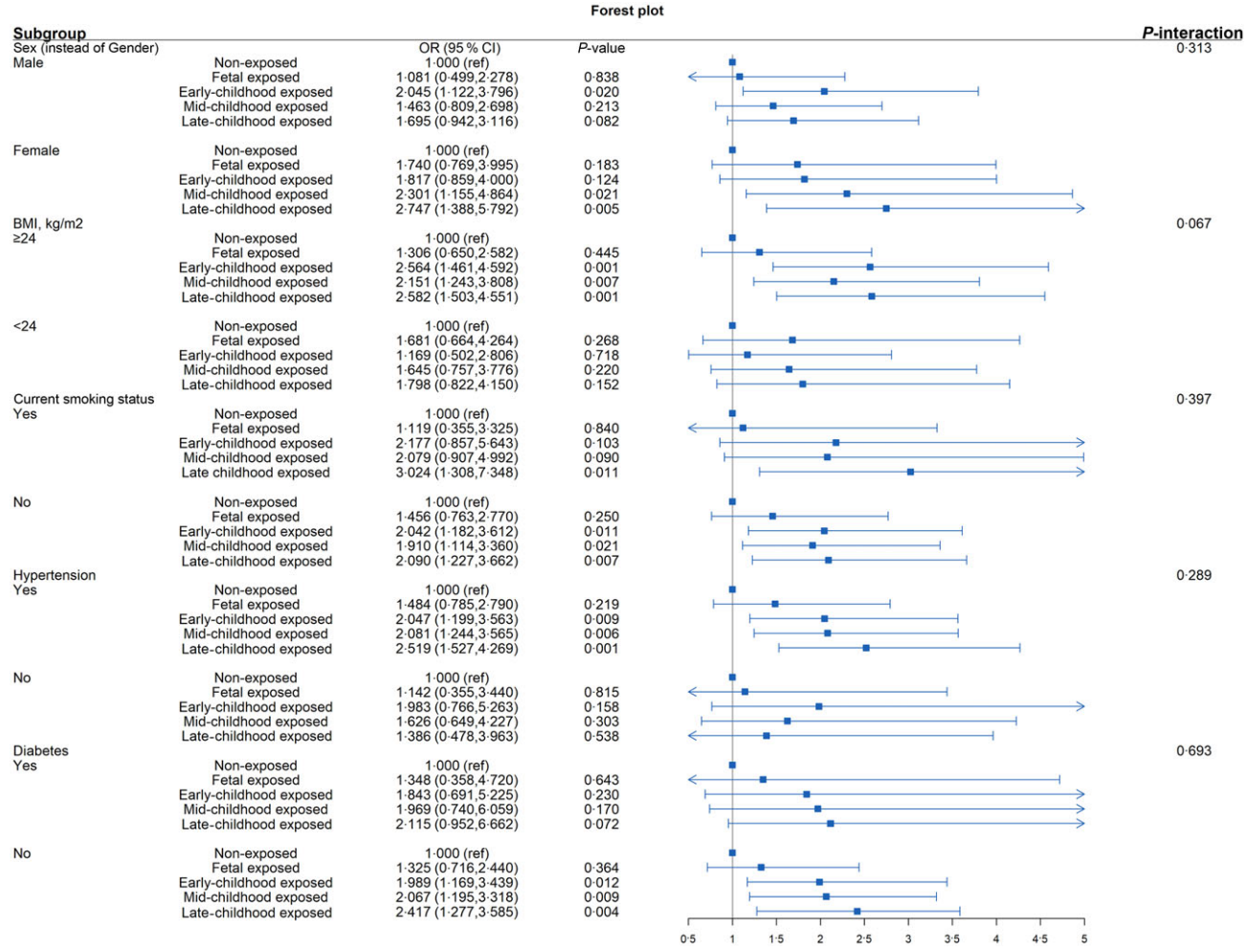

Fig. 2 Subgroup analysis among different famine exposure groups. Data are presented as OR and 95 % CI. *P* values are for the comparison of the difference in subgroup condition.

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