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Exposure to famine during early life and the risk of MAFLD during adulthood: evidence from the China Multi-Ethnic Cohort (CMEC) study

Jianzhong Yin ,[1,2] Nichang Zhang,[1] Yuemei Feng,[2] Qiong Meng,[2] Teng Zhang,[1] Rudan Hong,[2] Xuehui Zhang[2]

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JY, NZ and YF contributed equally.

JY, NZ and YF are joint first authors.

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[1]Baoshan College of Traditional Chinese Medicine, Baoshan, Yunnan, China
[2]Kunming Medical University, Kunming, Yunnan, China

Correspondence to
Professor Jianzhong Yin;
yinjianzhong2005@sina.com

ABSTRACT

Background Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common chronic liver disease, affecting nearly one-third of the global population. The relationship between early-life famine exposure and MAFLD remains unclear in the multiethnic region of less-developed southwest China.

Methods A total of 18 558 participants who came from the baseline survey of the China Multi-Ethnic Cohort Study in Yunnan were included. Participants were divided into four groups according to birth year, including non-exposed (1962–1978 and 1939–1943), fetal exposed (1959–1961), childhood exposed (1949–1958) and adolescence exposed (1943–1949). Logistic regression analysis was used to explore the relationship between famine exposure in early life and the risk of MAFLD in adulthood.

Results Experiencing the shock of early-life exposure to famine would affect adulthood MAFLD. Exposure to famine during fetal life and childhood increased the risk of MAFLD in adulthood, with this association being particularly pronounced in Bai populations. Moreover, famine exposure in males during fetal life raised the risk of MAFLD in adulthood.

Conclusion We suggest that adequate nutrition in early life may be beneficial in preventing MAFLD in adulthood. The prevention of chronic liver disease should adopt a whole-life strategy by extending the prevention window beginning from fetal life.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ This study is the first to analyse the association between early-life exposure to famine and adulthood metabolic dysfunction-associated fatty liver disease (MAFLD) in Han, Bai and Yi populations in the multiethnic region of less-developed southwest China.

WHAT THIS STUDY ADDS

⇒ The results suggested that experiencing early-life exposure to famine would affect adulthood MAFLD. Exposure to famine during fetal life and childhood increased the risk of MAFLD in adulthood, with this association being particularly pronounced in Bai populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The long-term potential effects of early-life exposure to famine on chronic liver disease should be considered while responding to the food and nutrition crisis. The necessity and importance of improving nutritional assistance to populations facing early-life exposure to famine should be fully recognised at present and in the future.

BACKGROUND

In March 2020, the international fatty liver expert panel issued an international expert consensus statement on the new definition of metabolic dysfunction-associated fatty liver disease (MAFLD), and non-alcoholic fatty liver disease (NAFLD) was officially renamed MAFLD.[1] As one of the most common chronic non-communicable diseases with a global prevalence of 30% in the world, MAFLD has become an increasingly severe global public health problem.[2]

The growing burden of MAFLD is mainly driven by excessive calorie consumption and lack of physical exercise. In addition, the Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that malnutrition in early life may also increase one's predisposition to metabolic diseases in later life.[3] According to the DOHaD hypothesis, the occurrence of famines in human history provides us with a quasi-experimental background to test the influence of famine exposure in early life on negative health effects in adulthood, thus providing direct evidence for the hypothesis in humans. The mass famine experienced by China in 1959–1961 is the most devastating famine in modern human history. Compared with the famine in Dutch

and Ukraine, the Great famine in China lasted longer and affected more people, with an estimated excess death toll of 20–30 million.[4] Previous research has shown that early-life exposure to famine may increase the risk of obesity, diabetes, hypertension, metabolic disorders and NAFLD in adulthood,[5] all of which are closely intertwined with MAFLD. Currently, there are few studies on the association between early-life famine exposure and the risk of MAFLD in adulthood. The study by Liu *et al* found that fetal exposure to famine was associated with an increased risk of adulthood MAFLD, and such an association appeared to exist in women only.[6] China, with its 55 different ethnic minority groups, is home to the largest ethnic minority population in the world. Ethnicity not only signifies genetic diversity but also encompasses strong local identities that influence work and daily life. However, there is no research on the correlation between early-life famine exposure and the risk of MAFLD in adulthood in the multiethnic region of less-developed southwest China.

In the context of the global emphasis on the food and nutrition security crisis, this study discussed the association between early-life exposure to famine and the risk of MAFLD in adulthood in the multiethnic region of less-developed southwest China, intending to provide evidence for beginning the chronic liver disease prevention from the fetal stage.

METHODS

Study population

A total of 23 143 participants were recruited in our study. They belonged to the Yunnan region of the China Multi-Ethnic Cohort Study, whose baseline survey was carried out between May 2018 and September 2019. The study design and sampling methods are described in detail elsewhere.[7] We excluded participants who were born before 1939 and after 1978 (n=3713), missing physical examination data (n=703) and reported a history of hepatitis/cirrhosis (n=169). We finally included 18 558 participants in the analysis.

Anthropometric and biochemical measurements

The relevant data about the sociodemographic and lifestyle factors of the participants were collected face to face by questionnaire. Date of birth, sex and ethnicity were obtained from the participants' national identity cards, and age was calculated using the sampling date and birthdate. Weight, height, waist circumference, hip circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standard methods. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres (kg/m^2). Height in light clothing was determined using a standard steel strip stadiometer to the nearest 0.1 cm. Weight without shoes was measured by a digital electronic scale to the nearest 0.1 kg. All participants were investigated for their SBP and DBP to the nearest 2 mm Hg by a trained nurse in a sitting position using an appropriately sized cuff and a standard mercury sphygmomanometer. In addition, after overnight fasting, blood samples for evaluating triglyceride (TG), total serum cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and fasting blood glucose (FBG) were taken from the anterior cubital vein in the morning. Biochemical markers such as TG, TC and fasting blood glucose were tested by Kunming Jinyu Medical Inspection Institute.

Definition of MAFLD

The diagnosis criteria of MAFLD met the Clinical Practice Guidelines for the Diagnosis and Management of MAFLD published by the Asian Pacific Association for the Study of the Liver.[8] MAFLD was defined as liver steatosis detected by ultrasound combined with one of the following three criteria: overweight/obesity (BMI≥23 kg/m^2), the presence of type 2 diabetes or evidence of metabolic dysregulation. In our study, metabolic dysregulation among thin/normal weight individuals with liver steatosis and who did not suffer from type 2 diabetes was determined by the presence of at least two of the following metabolic risk abnormalities:

1. Waist circumference ≥90 cm in men and ≥80 cm in women.
2. Blood pressure ≥130/85 mm Hg or specific drug treatment.
3. TG≥1.70 mmol/L or specific drug treatment.
4. HDL-cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women, or specific drug treatment.
5. Pre-diabetes [FBG levels of 5.6–6.9 mmol/L and/or glycated haemoglobin A1c (HbA1c) levels of 5.7%–6.4%].

Although homoeostasis model assessment-insulin resistance (HOMA-IR) and plasma high-sensitivity C reactive protein (hs-CRP) data are metabolic risk abnormalities, these were not available in our cohort.

Definition of famine exposure

The Chinese Great Famine mainly lasted from 1959 to 1961. Four groups were divided according to participants' age at the time of the famine: fetal life exposure (born 1959–1961), childhood exposure (born 1949–1958), adolescent life exposure (born 1943–1949) and non-exposure (born 1962–1978, 1939–1943) as the control group. To reduce the bias related to age differences between famine exposure subgroups, an 'age-balanced' method was used by combining post-famine and pre-famine births as the control group.[9]

Statistical analysis

SPSS V.26.0 statistical software was used for data processing and analysis. The t-test, one-way analysis of variance and χ^2 test were used to analyse and compare the characteristics of the population. Logistic regression analysis was used to explore the relationship between famine exposure in early life and the risk of MAFLD in adulthood, and further stratified analysis was carried out

Table 1 Characteristics of the participants according to famine exposure in early life

Characteristics	Non-exposed	Fetal exposed	Childhood exposed	Adolescence exposed	P value
No of participants	12341	761	4181	1275	–
Age at baseline, years	49.24±6.37	57.63±0.66	63.55±2.44	71.02±1.71	<0.001
Gender					<0.001
Male	3865 (31.3)	266 (35.0)	1601 (38.3)	458 (35.9)	
Female	8476 (68.7)	495 (65.0)	2580 (61.7)	817 (64.1)	
Ethnic					<0.001
Han ethnicity	5553 (45.0)	393 (51.6)	1869 (44.7)	562 (44.1)	
Bai ethnicity	3452 (28.0)	141 (18.5)	1289 (30.8)	408 (32.0)	
Yi ethnicity	3336 (27.0)	227 (29.8)	1023 (24.5)	305 (23.9)	
Education level					<0.001
Elementary school or below	8512 (69.0)	529 (69.5)	3404 (81.4)	1103 (86.5)	
Middle or high school	3499 (28.4)	228 (30.0)	761 (18.2)	170 (13.3)	
College or above	329 (2.7)	4 (0.5)	16 (0.4)	2 (0.2)	
Annual household income (yuan/year)					<0.001
<20000	5138 (41.7)	361 (47.4)	2299 (55.1)	747 (58.6)	
20000–199999	7034 (57.1)	392 (51.5)	1834 (43.9)	520 (40.8)	
>200000	146 (1.2)	8 (1.1)	43 (1.0)	8 (0.6)	
Place of residence					<0.001
Rural area	11554 (93.7)	725 (95.3)	3861 (92.5)	1131 (88.9)	
Rural town	773 (6.3)	36 (4.7)	314 (7.5)	141 (11.1)	
Smoking status					<0.001
Non-smoker	9589 (77.7)	564 (74.1)	2976 (71.2)	933 (73.2)	
Current smoker	2453 (19.9)	173 (22.7)	999 (23.9)	264 (20.7)	
Previous smoker	299 (2.4)	24 (3.2)	206 (4.9)	78 (6.1)	
Alcohol consumption					<0.001
Never	9157 (74.8)	537 (70.6)	3021 (72.6)	986 (77.6)	
Characteristics	**Non-exposed**	**Fetal exposed**	**Childhood exposed**	**Adolescence exposed**	**P value**
Low/moderate	2363 (19.3)	135 (17.7)	760 (18.3)	189 (14.8)	
High	727 (5.9)	89 (11.7)	378 (9.1)	96 (7.6)	
Tea drinking					<0.001
Never	8085 (65.5)	513 (67.4)	2872 (68.7)	891 (69.9)	
Ever	4256 (34.5)	248 (32.6)	1308 (31.3)	384 (30.1)	
Physical activity, METs-hour/day					<0.001
Low: <20.38	3045 (24.8)	221 (29.1)	1956 (47.1)	916 (72.1)	
Moderate: 20.38–40.36	4335 (35.3)	268 (35.3)	1312 (31.5)	246 (19.4)	
High: >40.36	4893 (39.9)	270 (35.6)	889 (21.4)	108 (8.5)	
Total energy intake, kcal/day	1901.46±627.84	1867.40±645.21	1804.30±618.77	1649.22±557.66	<0.001
High-fat diet					<0.001
Never	6178 (50.4)	407 (53.5)	2310 (55.5)	735 (57.8)	
Ever	6069 (49.6)	354 (46.5)	1849 (44.5)	536 (42.2)	
Insufficient vegetables and fruits intake					<0.001
Never	3758 (30.7)	222 (29.2)	1107 (26.6)	262 (20.6)	
Ever	8489 (69.3)	539 (70.8)	3052 (73.4)	1009 (79.4)	
BMI (kg/m2)	23.26±3.27	23.03±3.42	22.49±3.20	22.17±3.15	<0.001
Waistline (cm)	79.81±9.86	80.16±10.01	79.88±9.89	80.16±10.08	0.53
SBP (mm Hg)	124.26±18.55	131.31±20.35	133.41±20.68	136.24±20.07	<0.001

Continued

Table 1 Continued

Characteristics	Non-exposed	Fetal exposed	Childhood exposed	Adolescence exposed	P value
DBP (mm Hg)	79.79±11.42	82.42±12.29	80.86±11.76	79.10±11.09	<0.001
TC (mmol/L)	5.13±1.01	5.36±1.06	5.44±1.05	5.46±1.08	<0.001
TG (mmol/L)	1.85±1.77	2.05±2.11	1.88±1.67	1.83±1.60	0.015
HDL-C (mmol/L)	1.55±0.42	1.59±0.46	1.62±0.46	1.63±0.45	<0.001
LDL-C (mmol/L)	3.11±0.89	3.23±0.92	3.30±0.92	3.36±0.93	<0.001
FBG (mmol/L)	5.29±1.19	5.51±1.45	5.55±1.45	5.62±1.42	<0.001
HbA1c (%)	5.74±0.76	5.91±0.76	5.98±0.88	6.04±0.92	<0.001

Continuous variables are represented as mean ± SD and categorical variables are represented as n (%).
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin A1c ; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; METs, metabolic equivalents; SBP, systolic blood pressure; TC, total serum cholesterol; TG, triglyceride.

according to gender and ethnicity. The significance criterion for all tests was set at p<0.05.

RESULTS

Of the 18 558 participants, the mean (SD) age was 54.31 years (9.19 years). One-third (33.4%) of them were male (6190 participants), and two-thirds (66.6%) of them were female (12 368 participants). For ethnic groups, 45.1% (8377 participants), 28.5% (5290 participants) and 26.4% (4891 participants) of them were Han, Bai and Yi, respectively (table 1).

The prevalence of MAFLD in the non-exposure (natural population), fetal life exposure, childhood exposure and adolescent life exposure groups were 20.5%, 21.4%,

Table 2 ORs and 95% CIs for MAFLD of famine exposure in early life

	Non-exposed	Fetal exposed	Childhood exposed	Adolescence exposed
Whole cohort*				
Case/total	2532/12 336	163/761	713/4179	188/1275
OR (95% CI)	1.00	1.89 (1.30 to 2.74)†	1.59 (1.13 to 2.23)†	1.35 (0.93 to 1.95)
Male‡				
Case/total	813/3862	58/266	204/1600	52/458
OR (95% CI)	1.00	3.41 (1.81 to 6.44)†	1.56 (0.87 to 2.81)	1.27 (0.67 to 2.41)
Female§				
Case/total	1719/8474	105/495	509/2579	136/817
OR (95% CI)	1.00	1.28 (0.81 to 2.03)	1.51 (0.99 to 2.30)	1.33 (0.85 to 2.10)
Han ethnicity¶				
Case/total	1092/5553	87/393	324/1868	88/562
OR (95% CI)	1.00	1.31 (0.78 to 2.20)	1.17 (0.71 to 1.92)	1.05 (0.61 to 1.80)
Bai ethnicity**				
Case/total	796/3450	30/141	210/1289	54/408
OR (95% CI)	1.00	3.18 (1.50 to 6.75)†	2.29 (1.22 to 4.29)†	1.76 (0.90 to 3.46)
Yi ethnicity††				
Case/total	644/3333	46/227	179/1022	46/305
OR (95% CI)	1.00	1.89 (0.81 to 4.38)	1.58 (0.73 to 3.46)	1.40 (0.61 to 3.21)

*Whole cohort: adjusted for age, gender, ethnicity, place of residence, education attainment, annual household income, smoking, alcohol intake, physical activity, family history of hypertension, family history of diabetes, ALT, AST, AST/ALT, GGT and uric acid.
†p<0.05.
‡Male: the same as whole cohort variables plus tea drinking, without gender.
§Female: without gender, ethnicity,smoking, alcohol intake, the other variables same as whole cohort.
¶Han ethnicity: the same as whole cohort variables plus tea drinking, low fruit and vegetable intake, but without gender and ethnicity
**Bai ethnicity: the same as whole cohort variables plus tea drinking, but without gender, ethnicity, place of residence, smoking, physical activity.
†† Yi ethnicity: the same as variables plus tea drinking, but without gender, ethnicity, alcohol intake and AST. The reason for the different adjustment variables was determined by the results of the univariate analysis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AST/ALT, AST-ALT ratio; GGT, Gamma-Glutamyl Transferase; MAFLD, metabolic dysfunction-associated fatty liver disease .

17.1% and 14.7%, respectively. For the whole cohort, after adjusting confounding factors, exposure to famine during fetal life (OR 1.89, 95% CI 1.30 to 2.74) and childhood (OR 1.59, 95% CI 1.13 to 2.23) was associated with an increased risk of adulthood MAFLD compared with the non-exposure group. In males, famine exposure in fetal life (OR 3.41, 95% CI 1.81 to 6.44) increased the risk of adulthood MAFLD. However, this association was not revealed in females. The Bai ethnic group was more likely to be affected during the fetal (OR 3.18, 95% CI 1.50 to 6.75) and childhood (OR 2.29, 95% CI 1.22 to 4.29) exposure to famine increases the risk of MAFLD in adulthood, though this association was not demonstrated in the Han and Yi groups (table 2).

DISCUSSION

Yunnan Province owns the most abundant ethnic minorities in southwestern China. Its plateau location, less-developed economy and multiethnic population characterise it. Our study is the first to analyse the association between early-life exposure to famine and adulthood MAFLD in Han, Bai and Yi populations in the Yunnan plateau region.

Our results suggested that experiencing the shock of early-life exposure to famine during fetal life and childhood would affect adulthood MAFLD. Previous studies have indicated the association between exposure to famine in early life and the risk of MAFLD.[6] Liu *et al* found that compared with nonexposed participants, fetal-exposed participants showed an increased risk of adulthood MAFLD (OR 1.10, 95% CI 1.00 to 1.21). Unlike our study, they did not find this association in the childhood-exposed group, which may be due to differences in the definition of famine exposure groups in studies and the geographical origin of the survey participants.

According to literature reports, the relationship between early-life famine exposure and MAFLD in adulthood has some biological plausibility. 'Catch-up growth' may be a possible mechanism. A study showed that after exposure to famine in China during the fetal period, there would be 'catch-up growth' after birth, and the risk of glucose and lipid metabolism disorders in the famine-exposed group was significantly higher than that in the non-exposed group.[10] Second, epigenetic modifications (such as DNA methylation) are also a possible influencing mechanism. Many experimental studies have shown that DNA methylation induced by malnutrition in early development can significantly increase the risk of cardiovascular system and metabolic disorders in offspring.[11] In addition, fetal micronutrient deficiencies can lead to impaired organ development and oxidative stress, which can also increase the risk of chronic diseases in adulthood.[12]

We also observed that exposure to famine showed a sex-specific association with the risk of MAFLD in adulthood: famine exposure in males during fetal life raised the risk of MAFLD in adulthood. However, such an association was not revealed in females. This could be due to that males exposed to fetal famine are more likely to have DNA methylation in genes.[13] In addition, we found that exposure to famine during fetal life and childhood increased the risk of MAFLD in adulthood, with this association being particularly pronounced in Bai populations. This disparity may be related to the environmental characteristics, eating habits and lifestyles of different regions.

Currently, the community of nations is concerned about and emphasising the importance of the food crisis. Globally, 828 million people suffered from famine in 2021, with 150 million more added because of the COVID-19 epidemic.[14] The potential long-term effects of early-life exposure to famine on chronic liver disease should be considered while responding to the food and nutrition crisis. The necessity and importance of improving nutritional assistance to populations facing early-life exposure to famine at present and in the future should be fully recognised. Hence, this study is of tremendous significance to public health.

However, several limitations were identified. First, the HOMA-IR and hs-CRP data were not measured or included in the MAFLD definition of our study. Nevertheless, when accumulating the literature, we found some published articles about the MAFLD, that HOMA-IR or hs-CRP was not included in the diagnosis,[15 16] which made our studies comparable. Second, considering the low level of economic and health development in our country during the years of famine, it was difficult to collect more detailed data on fetal exposure to famine in different trimesters. Third, our findings may not be applicable to all groups because all the participants were Chinese from Southwest China. In addition, age as a confounding factor was adjusted using age balance analysis to make the results more reliable, but the grouping based on birthdate remained limited.

Contributors NZ and QM had full take responsibility for the integrity of the data and the accuracy of the data analysis. JY, NZ and YF contributed equally to this work. Concept and design: JY. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: JY, NZ and YF. Statistical analysis: NZ and QM. Administrative, technical or material support: XZ and TZ. Supervision: JY.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol had been approved by the Ethics Committee of Kunming Medical University (KMMU2020MEC078). Participants gave informed consent to participate in the study before taking part.

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ORCID iD
Jianzhong Yin http://orcid.org/0000-0002-1876-387X

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