

## Original Research



# Famine exposure in early life and type 2 diabetes in adulthood: findings from prospective studies in China

Feng Ning <sup>1,2\*</sup>, Jing Zhao <sup>3\*</sup>, Lei Zhang <sup>4,5</sup>, Weijing Wang <sup>6</sup>, Xiaohui Sun <sup>1,2</sup>, Xin Song <sup>1,2</sup>, Yanlei Zhang <sup>7</sup>, Hualei Xin <sup>1,2</sup>, Weiguo Gao <sup>4,5</sup>, Ruqin Gao <sup>1,2§</sup>, Dongfeng Zhang <sup>6§</sup>, and Zengchang Pang <sup>1,2</sup>

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### §Corresponding Authors:

#### Ruqin Gao

Qingdao Centers for Disease Control and Prevention, Qingdao Institute of Preventive Medicine, Qingdao 266033, China.

Tel. +86-532-85650292

Fax. +86-532-85650292

Email. gaorq2018@163.com

#### Dongfeng Zhang

Department of Epidemiology and Health Statistics, Qingdao University Medical College, Qingdao 266021, China.

Tel. +86-532-82991912

Fax. +86-532-82991912

Email. zhangdf1961@126.com


\*Feng Ning and Jing Zhao contributed equally to this work.

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### ORCID iDs

Feng Ning 

<https://orcid.org/0000-0003-0168-1613>

Jing Zhao 

<https://orcid.org/0000-0001-6736-6136>

<sup>1</sup>Qingdao Centers for Disease Control and Prevention, Qingdao 266033, China

<sup>2</sup>Qingdao Institute of Preventive Medicine, Qingdao 266033, China

<sup>3</sup>School of Public Health, Guangzhou Medical University, Guangzhou 510000, China

<sup>4</sup>Department of Endocrine and Diabetes, Weifang Medical College, Weifang 261000, China

<sup>5</sup>Qingdao Endocrinology and Diabetes Hospital, Qingdao 266033, China

<sup>6</sup>Department of Epidemiology and Health Statistics, Qingdao University Medical College, Qingdao 266021, China

<sup>7</sup>Department of Public Health, University of Helsinki, FI00014, Helsinki, Finland

## ABSTRACT

**BACKGROUND/OBJECTIVES:** This study examined the relationship between famine exposure in early life and the risk of type 2 diabetes in adulthood during the 1959–1961 Chinese Famine.

**SUBJECTS/METHODS:** A total of 3,418 individuals aged 35–74 years free of diabetes from two studies in 2006 and 2009 were followed up prospectively in 2009 and 2012, respectively. Famine exposure was classified as unexposed (individuals born in 1962–1978), fetal exposed (individuals born in 1959–1961), child exposed (individuals born in 1949–1958), and adolescent/adult exposed (born in 1931–1948). A logistic regression model was used to assess the relationship between famine exposure and diabetes after adjustment for potential covariates.

**RESULTS:** During a three-year follow-up, the age-adjusted incidence rates of type 2 diabetes were 5.7%, 14.5%, 12.7%, and 17.8% in unexposed, fetal-exposed, child-exposed, and adolescent/adult-exposed groups, respectively ( $P < 0.01$ ). Relative to the unexposed group, the relative risks (95% confidence interval) for diabetes were 2.15 (1.29–3.60), 1.53 (0.93–2.51), and 1.65 (0.75–3.63) in the fetal-exposed, child-exposed, and adolescent/adult-exposed groups, after controlling for potential covariates. The interactions between famine exposure and obesity, education level, and family history of diabetes were not observed, except for the urbanization type. Individuals living in rural areas with fetal and childhood famine exposure were at a higher risk of type 2 diabetes, with relative risks of 8.79 (1.82–42.54) and 2.33 (1.17–4.65), respectively.

**CONCLUSIONS:** These findings indicate that famine exposure in early life is an independent predictor of type 2 diabetes, particularly in women. Early identification and intervention may help prevent diabetes in later life.

**Trial Registration:** ClinicalTrials.gov Identifier: [NCT01053195](https://clinicaltrials.gov/ct2/show/study/NCT01053195)

**Keywords:** Famine; type 2 diabetes; adult; prospective study

Lei Zhang   
<https://orcid.org/0000-0001-6265-7903>  
 Weijing Wang   
<https://orcid.org/0000-0001-7747-7649>  
 Xiaohui Sun   
<https://orcid.org/0000-0001-9225-9674>  
 Xin Song   
<https://orcid.org/0000-0003-3526-1596>  
 Yanlei Zhang   
<https://orcid.org/0000-0002-1454-0230>  
 Hualei Xin   
<https://orcid.org/0000-0001-8944-3980>  
 Weiguo Gao   
<https://orcid.org/0000-0001-9470-396X>  
 Ruqin Gao   
<https://orcid.org/0000-0002-3845-7829>  
 Dongfeng Zhang   
<https://orcid.org/0000-0001-9308-9371>  
 Zengchang Pang   
<https://orcid.org/0000-0003-4746-0074>

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**Conflict of Interest**

The authors declare no potential conflicts of interests.

**Author Contributions**

Conceptualization: Gao R, Zhang D, Pang Z; Formal analysis: Ning F, Song X, Wang W, Gao W; Funding acquisition: Ning F; Investigation: Ning F, Zhao J, Sun X, Zhang Y, Zhang L, Song X, Gao W; Methodology: Zhang D, Pang Z; Supervision: Gao R, Zhang D; Writing - original draft: Ning F, Zhao J; Writing - review & editing: Wang W, Xin H, Sun X, Zhang Y, Zhang L.

**INTRODUCTION**

Diabetes is a major cause of mortality and a health burden worldwide. The prevalence of diabetes in China increased from 2.5% in 1994 to 12.8% in 2019 [1,2]. Intrauterine and early-life malnutrition are potential risk factors for metabolic disorders in later life. Intrauterine growth restriction caused by malnutrition can lead to severe perinatal and long-term complications, such as the development of insulin resistance. A meta-analysis indicated that famine exposure during the fetal period and low birth weight increased the risk of obesity, diabetes, hypertension, and metabolic syndrome in adulthood [3-6].

The Chinese Famine (1959–1961) was associated with a sharp decrease in grain production and 30 million excess deaths. Observational studies across China have shown that the prevalence of diabetes is higher among individuals exposed to famine than among those not exposed to famine [4]. On the other hand, a causal relationship has not been established. This study analyzed two observational studies from the Qingdao Diabetes Prevention Program to investigate the relationship between famine exposure in early life and type 2 diabetes in adulthood in China.

**SUBJECTS AND METHODS**

The survey protocols are described elsewhere [7,8]. Briefly, nondiabetic participants aged 35 to 74 years from a randomly selected community of two separate studies in 2006 and 2009 were invited to assess the relationship between famine exposure and diabetes risk over a three-year follow-up. The participants of each study did not overlap. After excluding participants with missing measurements, laboratory results, and other covariables, 3,418 participants were included for analysis. The Ethics Committee of Qingdao Centers for Disease Prevention and Control approved the studies (registration no. 20051008). Informed consent was obtained from all participants. The trial was registered at <https://clinicaltrials.gov/ct2/home> (registration no. NCT01053195).

**Definition of type 2 diabetes and famine exposure**

Type 2 diabetes was defined as a fasting plasma glucose (FPG)  $\geq 7.0$  mmol/L, 2-h plasma glucose (2hPG)  $\geq 11.1$  mmol/L, or self-reported diabetes as diagnosed by a professional physician during the follow-up for participants without diabetes at baseline. Famine exposure was determined according to the birth year and divided into four categories: fetal exposed (born between January 1, 1959, and December 31, 1961), child exposed (born between January 1, 1949, and December 31, 1958), adolescent/adult exposed (born between January 1, 1931, and December 31, 1948), and unexposed (born between January 1, 1962, and December 31, 1978).

**Study parameters**

The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The income was classified as low ( $< \text{RMB}3000$  [US\$470] per month) or high ( $\geq \text{RMB}3000$  [US\$470] per month). The education level was classified as low or high according to the years enrolled in school. Physical activity was calculated as the metabolic equivalent and divided into three levels: sedentary, moderate, and vigorous.

### Statistical analyses

Continuous variables were presented as the mean and standard deviation, and categorical variables as a number (percentage). A univariate general linear model adjusted for age was used to compare differences among the mean values of continuous variables and the  $\chi^2$  test to compare categorical data between the four groups. Logistic regression analysis was used to estimate the relative risk (RR) and 95% confidence interval (CI) for determining the relationship between famine exposure and type 2 diabetes after adjusting for age, family history of diabetes, BMI, urbanization type, education level, income, occupation, total cholesterol, physical activity level, and hypertension, tobacco smoking, and alcohol consumption statuses at baseline. The unexposed group was used as a reference. The interaction effects of famine exposure and urbanization type, family history of diabetes, education level, income, and smoking and drinking statuses on type 2 diabetes were tested using a multiplicative factor in the logistic regression model [9]. The additive interactions between famine exposure and urbanization type or other potential factors for type 2 diabetes were estimated using the relative excess risk caused by the interaction obtained using the algorithm proposed by Andersson *et al.* [9]. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The statistical significance was indicated by a two-sided *P*-value of  $< 0.05$ .

## RESULTS

### Participant characteristics

**Table 1** lists the baseline characteristics of individuals in each famine exposure group. Compared to the unexposed group, the age-adjusted mean BMI, waist circumference, total cholesterol, FPG, and systolic and diastolic blood pressure were significantly greater in the three exposed groups ( $P < 0.05$  for all comparisons). The education level, income, and physical activity differed significantly between the exposed groups ( $P < 0.05$  for all comparisons). No differences in mean concentrations of 2hPG, triglycerides, and high-density lipoprotein cholesterol were observed between the groups.

### Comparative analysis of famine exposure and type 2 diabetes by sex

During a three-year follow-up, 336 cases of type 2 diabetes were identified from two longitudinal studies. The age-adjusted incidence rates were 5.7%, 14.5%, 12.7%, and 17.8% in the unexposed, fetal-exposed, child-exposed, and adolescent/adult-exposed groups, respectively ( $P < 0.01$ ). Relative to the nonexposed group, the RRs (95% CI) of type 2 diabetes were 2.15 (1.29–3.60), 1.53 (0.93–2.51), and 1.65 (0.75–3.63) in the fetal-exposed, child-exposed, and adolescent/adult-exposed groups after control for covariates (**Table 2**). Before adjusting for covariates, the relationship between famine exposure and diabetes differed significantly according to sex. After adjustment, however, the relationship between famine exposure and diabetes did not differ according to sex, except for the fetal-exposure group, in which the RR for women was 2.80 (1.50–5.21). This indicates that famine exposure in early life is an independent predictor of type 2 diabetes, particularly in women.

### Comparative analysis of famine exposure and type 2 diabetes by residential areas

According to subgroup analysis, the incidence of diabetes was significantly higher among participants exposed to famine than among those not exposed to famine in rural but not urban areas. The corresponding figures were 4.7%, 15.2%, 11.7%, and 15.0% in rural areas (*P*

**Table 1.** Baseline characteristics of the Qingdao diabetes study population according to famine exposure

Variables	Unexposed group	Fetal-exposed group	Childhood-exposed group	Adolescence/adult-exposed group	P-value
No.	1,407	213	1,011	787	
Age (yrs)	41.2 ± 0.10	47.9 ± 0.14	54.1 ± 0.11	65.3 ± 0.16	< 0.001
Men	457 (32.5)	57 (26.8)	343 (33.9)	356 (45.2)	< 0.001
BMI (kg/m <sup>2</sup> )	24.5 ± 0.18	25.1 ± 0.25	25.8 ± 0.12	26.4 ± 0.26	< 0.001
Waist circumference (cm)	81.9 ± 0.52	83.1 ± 0.71	84.5 ± 0.35	85.9 ± 0.75	0.004
Systolic blood pressure (mmHg)	130.7 ± 1.03	134.0 ± 1.39	134.0 ± 0.69	137.6 ± 1.47	0.019
Diastolic blood pressure (mmHg)	80.0 ± 0.61	83.9 ± 0.82	85.3 ± 0.41	85.9 ± 0.87	< 0.001
FPG (mmol/L) <sup>1)</sup>	5.53 ± 0.03	5.53 ± 0.05	5.53 ± 0.02	5.41 ± 0.05	0.039
2hPG (mmol/L) <sup>2)</sup>	6.53 ± 0.09	6.69 ± 0.12	6.56 ± 0.06	6.57 ± 0.13	0.717
Family history of diabetes (%)	12.1	14.1	12.6	9.0	0.052
Total cholesterol (mmol/L)	5.10 ± 0.05	5.16 ± 0.07	5.34 ± 0.03	5.29 ± 0.07	0.001
HDL-C (mmol/L)	1.66 ± 0.02	1.67 ± 0.03	1.65 ± 0.02	1.58 ± 0.03	0.115
Triglycerides (mmol/L)	1.36 ± 0.05	1.32 ± 0.06	1.32 ± 0.03	1.23 ± 0.07	0.567
Family income (%)					
Low	70.9	76.5	74.1	80.4	
High	29.1	23.5	25.9	19.6	< 0.001
Education levels (%)					
≤ 9 school years	69.9	67.1	81.4	85.1	
> 9 school years	30.1	32.9	18.6	14.9	< 0.001
Physical activity (%)					
Sedentary	43.1	46.9	45.2	55.0	
Moderate	10.1	13.1	15.7	15.0	
Vigorous	46.8	39.9	39.0	30.0	< 0.001
Current smoking (%)	19.3	17.4	22.2	26.4	< 0.001
Current drinking (%)	13.9	13.6	17.2	18.6	0.016

Data are age-adjusted mean ± SE or number (%).

BMI, body mass index; HDL, high-density lipoprotein cholesterol.

<sup>1)</sup>n = 2,079, <sup>2)</sup>n = 2,976.

**Table 2.** Relative risk (95% confidence interval) of type 2 diabetes in relation to different life stages at famine exposure

Variables	No. cases/sample size	Crude	Model 1	Model 2
<b>Total</b>				
Non-exposed	76/1,331	Ref.	Ref.	Ref.
Fetal-exposed	27/186	2.54 (1.60–4.05)	2.21 (1.32–3.68)	2.15 (1.29–3.60)
Childhood-exposed	114/897	2.23 (1.65–3.01)	1.60 (0.98–2.62)	1.53 (0.93–2.51)
Adolescence-exposed	119/668	3.12 (2.31–4.22)	1.74 (0.79–3.83)	1.65 (0.75–3.63)
<b>Men</b>				
Non-exposed	35/422	Ref.	Ref.	Ref.
Fetal-exposed	6/51	1.42 (0.57–3.54)	1.27 (0.48–3.37)	1.29 (0.48–3.47)
Childhood-exposed	48/295	1.96 (1.24–3.11)	1.69 (0.78–3.66)	1.63 (0.74–3.57)
Adolescence-exposed	54/302	2.16 (1.37–3.38)	1.60 (0.46–5.52)	1.47 (0.42–5.20)
<b>Women</b>				
Non-exposed	41/909	Ref.	Ref.	Ref.
Fetal-exposed	21/135	3.45 (1.98–6.01)	2.86 (1.54–5.31)	2.80 (1.50–5.21)
Childhood-exposed	66/602	2.43 (1.62–3.64)	1.46 (0.77–2.81)	1.38 (0.72–2.65)
Adolescence-exposed	65/366	3.94 (2.62–5.93)	1.80 (0.64–5.03)	1.63 (0.58–4.61)

Model 1: adjusted for age, family history of diabetes, body mass index, and residential areas.

Model 2: adjusted for age, family history of diabetes, body mass index, residential areas, educational level, income level, total cholesterol, occupation, hypertension, physical activity, smoking, and drinking status.

= 0.001) and 7.7%, 4.1%, 10.0%, and 15.6% in urban areas ( $P = 0.530$ ), respectively. As shown in **Table 3**, the multivariate-adjusted RRs (95% CI) for type 2 diabetes in the fetal-exposed, child-exposed, and adolescent/adult-exposed groups in rural areas were 3.36 (1.88–5.99), 2.06 (1.14–3.74), and 2.18 (0.84–5.65), respectively. The RRs in the fetal-exposed, child-exposed, and adolescent/adult-exposed groups in urban areas were 0.35 (0.08–1.62), 0.69 (0.27–1.76), and 0.79 (0.18–3.47), respectively. The risk of diabetes was not substantially

**Table 3.** Relative risk (95% confidence interval) of type 2 diabetes in urban and rural areas

Exposure stages	Incidence of type 2 diabetes (%)	Model 1	Model 2
<b>Urban areas</b>			
Non-exposed	7.7	Ref.	Ref.
Fetal-exposed	4.1	0.42 (0.09–1.89)	0.35 (0.08–1.62)
Childhood-exposed	10.0	0.91 (0.37–2.24)	0.69 (0.27–1.76)
Adolescence/adult exposed	15.6	1.07 (0.26–4.46)	0.79 (0.18–3.47)
<b>Rural areas</b>			
Non-exposed	4.7	Ref.	Ref.
Fetal-exposed	15.2	3.80 (2.16–6.70)	3.36 (1.88–5.99)
Childhood-exposed	11.7	2.71 (1.51–4.87)	2.06 (1.14–3.74)
Adolescence/adult exposed	15.0	3.46 (1.36–8.82)	2.18 (0.84–5.65)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, family history of diabetes, residential areas, occupation, body mass index, total cholesterol, hypertension, educational level, income level, leisure time, physical activity, smoking, and drinking status.

different when the waist circumference or waist-to-hip ratio was used instead of the BMI in separate multivariable models. The interactions among famine exposure and obesity, education level, and family history of diabetes were not observed except when adjusting for urbanization type. The risk of type 2 diabetes was higher among participants living in rural areas in the fetal-exposed and child-exposed groups, with increased RRs (95% CIs) of 8.79 (1.82–42.54) and 2.33 (1.17–4.65), respectively.

### Age effect on the association between famine exposure and type 2 diabetes

Age was an independent risk factor for type 2 diabetes. To reduce the effects of age and urbanization type, the association between famine exposure and type 2 diabetes in a sensitivity analysis was further investigated. As shown in **Table 4**, famine exposure in the fetal stage was significantly associated with type 2 diabetes later in life in subgroup analysis in which the participants were divided by age into three-year intervals. The relationship between famine exposure and diabetes in the fetal-exposed group was robust in the age-adjusted multivariate model, with a corresponding RR of 1.82 (1.04–3.18). The sex-adjusted model revealed a RR for women of 2.51 (1.27–4.98) in the fetal-exposed group (**Supplementary Table 1**). The relationship between famine exposure and diabetes was moderate in men based on three-year intervals. Participants in the fetal-exposed group had a significantly younger mean age than did the child-exposed, adolescent/adult-exposed,

**Table 4.** Relative risk (95% confidence interval) of type 2 diabetes in relation to three years intervals at famine exposure (n = 3,418)

Birth years	Exposure stages	No.	Crude	Model 1	Model 2	Model 3
1971–1978	Non-exposed	270	0.66 (0.34–1.26)	0.67 (0.35–1.30)	0.69 (0.31–1.51)	0.67 (0.34–1.30)
1968–1970	Non-exposed	359	0.64 (0.35–1.17)	0.65 (0.35–1.18)	0.65 (0.33–1.28)	0.64 (0.35–1.17)
1965–1967	Non-exposed	304	0.53 (0.27–1.04)	0.53 (0.27–1.04)	0.54 (0.27–1.09)	0.54 (0.27–1.06)
1962–1964	Reference	474	Ref.	Ref.	Ref.	Ref.
1959–1961	Fetal-exposed	213	1.88 (1.10–3.20)	1.79 (1.05–3.07)	1.82 (1.04–3.18)	1.84 (1.07–3.16)
1956–1958	Childhood-exposed	334	1.52 (0.92–2.48)	1.37 (0.83–2.27)	1.34 (0.75–2.39)	1.37 (0.83–2.26)
1953–1955	Childhood-exposed	321	1.48 (0.90–2.45)	1.29 (0.78–2.16)	1.27 (0.65–2.49)	1.32 (0.79–2.20)
1950–1952	Childhood-exposed	267	1.89 (1.14–3.12)	1.70 (1.02–2.82)	1.69 (0.77–3.69)	1.77 (1.06–2.94)
1947–1949	Childhood-exposed	263	2.19 (1.34–3.57)	1.81 (1.10–2.99)	1.74 (0.71–4.27)	1.84 (1.10–3.04)
1944–1946	Adolescence/adult exposed	220	2.20 (1.32–3.68)	1.90 (1.12–3.20)	1.81 (0.64–5.08)	1.94 (1.14–3.28)
1937–1941	Adolescence/adult exposed	393	2.38 (1.53–3.70)	1.88 (1.18–2.99)	1.91 (0.55–6.69)	2.09 (1.31–3.34)

Model 1: adjusted for sex, family history of diabetes, residential areas, educational level, income level, occupation, total cholesterol, hypertension, physical activity, smoking, and drinking status.

Model 2: Model 1 plus age and body mass index.

Model 3: Model 2 without age.

and unexposed groups combined (47.9 vs. 51.2 years,  $P < 0.05$ ). The RR (95% CI) of type 2 diabetes in the fetal-exposed group was 1.74 (1.12–2.69) compared with the child-exposed, adolescent/adult-exposed, and unexposed groups. Stratified by urbanization type, the fetal-exposed group had a younger mean age than the other groups combined in both urban and rural areas (48.5 vs. 51.7 years in urban areas,  $P < 0.05$ ; 47.7 vs. 51.0 years in rural areas,  $P < 0.05$ ), and the corresponding RRs (95% CI) were 0.41 (0.10–1.75) in urban areas and 2.34 (1.46–3.75) in rural areas.

## DISCUSSION

These findings indicate that famine exposure in the fetal stage is an independent predictor of type 2 diabetes in later life, particularly for women. Individuals living in rural areas with famine exposure in early life (fetal stage or childhood) are at an increased risk of type 2 diabetes.

According to a sensitivity analysis, the risk of type 2 diabetes was higher among participants with famine exposure in the fetal stage but not higher among those with famine exposure in the adolescent/adult stage. Several observational studies have shown that prenatal famine exposure is associated with the prevalence of type 2 diabetes. The odds ratios were 1.22 and 2.20 for individuals with prenatal famine exposure and those without famine exposure, respectively [10,11]. A meta-analysis found that individuals with famine exposure in the fetal stage had a 36% higher risk of type 2 diabetes than those without famine exposure [4]. The pooled RRs (95% CIs) were 1.36 (1.12–1.65) and 1.40 (0.98–1.99), respectively. Moreover, a study including 88,830 participants with a median follow-up of 7.3 years showed that exposure to the Chinese Famine in the fetal stage was associated with a 25% increased risk of type 2 diabetes in adulthood [12]. The prevalence of type 2 diabetes was higher in rural than urban areas, as mentioned previously. The relationships between famine exposure and BMI and height were weaker in urban areas than in rural areas. This may explain the region-specific differences in the relationship between famine exposure and type 2 diabetes in the current study.

This study showed that the association between famine exposure and diabetes is significantly stronger in women than men. On the other hand, sex-specific analyses showed that the association between famine exposure and diabetes was similar for men and women [13,14]. Several studies have also confirmed that sex differences in hormones, body composition, glucose and fat metabolism, reproduction, and some sex-dimorphic mechanisms affect the risk of type 2 diabetes. A recent meta-analysis including 18 cross-sectional or historical studies demonstrated a significant association between malnutrition in early life and obesity in women but not in men [15]. Experimental studies have also showed that the mechanisms of fetal programming on insulin resistance and insulin secretion contribute to sex differences in glucose tolerance [16,17]. Inconsistent results were observed in the China health and retirement longitudinal study, suggesting that men are more vulnerable than women to the adverse effects of famine exposure in the fetal stage [18,19]. The sex disparity in the association between famine exposure and type 2 diabetes requires further investigation.

The underlying mechanism by which famine exposure leads to type 2 diabetes is uncertain. The thrifty phenotype hypothesis suggests that famine exposure in early life, including reduced capacity for insulin secretion and insulin resistance, combined with the effects of obesity, aging, and physical inactivity in adulthood, are the primary risk factors for

type 2 diabetes [20]. For example, the Dutch Winter Families study showed that adults exposed to famine in the fetal stage were more insulin resistant than those not exposed to famine. Another hypothesis is that DNA methylation is caused by prenatal famine exposure and that these changes depend on the gestational timing of exposure [21,22]. A genome-wide mediation analysis showed that DNA methylation mediated the association of prenatal famine exposure with adult BMI and triglycerides but not with the fasting glucose concentrations [22]. This suggests that epigenetic mechanisms mediate the association between prenatal famine exposure and metabolic health later in life.

The strengths of this study were the large sizes of the random representative samples from the general population. Individuals with known and newly diagnosed diabetes at the baseline were excluded to eliminate bias. All interviews were conducted face-to-face by professional health workers, and anthropometric measurements were conducted on-site. On the other hand, the present study has several limitations. Follow-up with some participants failed owing to extensive urban construction, housing demolition, and relocation. The baseline anthropometric and laboratory measurements between follow-up and lost-to-follow-up participants were compared. The mean waist circumference, diastolic blood pressure, total cholesterol, triglycerides, FPG, and 2hPG were greater in the lost-to-follow-up group than in the followed-up group ( $P < 0.05$ ). Age, BMI, and systolic blood pressure were comparable between the two groups. The Chinese Famine affected almost everyone living in Qingdao. Therefore, individuals exposed to famine could be matched with anyone not exposed. Age was part of the analysis, but individuals exposed to famine could not be compared with those not exposed to famine of similar age. Classification bias may exist whereby the incidence of type 2 diabetes increases with age. Therefore, participants into groups were divided according to age by three-year intervals to reduce the effects of age on diabetes incidence. The association between famine exposure and diabetes was robust, according to a sensitivity analysis. The current findings may not be generalizable to other regions of China. Further nationally representative studies will be needed to investigate the association.

In conclusion, this study elucidated the association between famine exposure and type 2 diabetes using a population-based prospective study. Fetal but not adolescent famine exposure increased the risk of diabetes later in life. Appropriate nutrition and lifestyle in early life may be beneficial in preventing metabolic disorders later in life.

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## SUPPLEMENTARY MATERIAL

### Supplementary Table 1

Relative risk (95% confidence interval) of type 2 diabetes in relation to three years intervals at famine exposure (n = 3,418)

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