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Exposure to the Chinese Famine in Childhood Increases Type 2 Diabetes Risk in Adults[1–3]

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Abstract

Background: Evidence shows that exposure to poor conditions in early life is associated with an increased risk of chronic diseases in adults.

Objective: We investigated whether exposure to the Chinese famine (1959–1961) in the fetal stage or in childhood (0–9 y) was associated with type 2 diabetes (T2D) and hyperglycemia in adulthood.

Methods: We included 7801 subjects aged 56.4 ± 3.3 y from the Dongfeng-Tongji cohort. Subjects were classified into late-, middle-, and early-childhood–exposed, fetal-exposed, and unexposed groups. Excess mortality rate was used to evaluate the severity of famine. Logistic regression models were used to analyze the famine-dysglycemia associations. Generalized linear models were used to assess the famine effects on dysglycemia risk during the 5-y follow-up period among 3100 subjects.

Results: In descriptive analyses, the risk of T2D was significantly greater in the middle-childhood–exposed group (OR: 1.44; 95% CI: 1.10, 1.87; $P = 0.007$), and the risk of hyperglycemia was higher in the middle- and late-childhood–exposed groups than in the unexposed group (OR: 1.54; 95% CI: 1.26, 1.88 and OR: 1.51; 95% CI: 1.23, 1.85, respectively). In sex-specific analyses, women exposed in middle childhood (OR: 1.55; 95% CI: 1.16, 2.06) and late childhood (OR: 1.40; 95% CI: 1.05, 1.87) had a higher risk of T2D than unexposed women. This association was not found in men. Similar associations were found for hyperglycemia risk. Moreover, subjects who experienced severe famine in childhood had a 38% higher T2D risk (95% CI: 1.05, 1.81) than those exposed to less severe famine. In retrospective cohort analyses, participants who experienced famine in middle childhood had a higher hyperglycemia risk relative to the unexposed group (RR: 2.06; 95% CI: 1.08, 3.90).

Conclusion: Exposure to the Chinese famine in childhood was related to an increased risk of adulthood T2D and hyperglycemia, particularly in women. *J Nutr* 2016;146:2289–95.

Keywords: type 2 diabetes, fetal, childhood, famine, China

Introduction

In recent decades, the prevalence of type 2 diabetes (T2D)[8] in China has risen from <1.0% to 11.6% (1), and 109.6 million adults were affected by T2D in 2015 (2). The developmental origins of health and disease hypothesis proposes that exposure to poor conditions in early life and subsequent mismatched environments may increase the risk of chronic diseases, including diabetes in adulthood (3–5). Such a hypothesis may at least partly explain the rise of diabetes in China.

Several famine studies have shown that famine exposure in early life was related to dysglycemia in later life. The Dutch Famine Birth Cohort Study reported that prenatal exposure to famine decreased glucose tolerance in adults (6). A retrospective cohort study in women also indicated that self-reported famine exposure in childhood was associated with increased T2D risk (7).

The Chinese famine lasted ~3 y (1959–1961), and almost all people living in the Chinese mainland were affected (8). A previous Chinese famine study reported that fetal exposure to severe famine increased the risk of hyperglycemia in adults (9). However, this study did not observe a substantial association between famine exposure and T2D risk. How the Chinese famine affected T2D risk and to what extent it affected the epidemiology of T2D remains to be further investigated. In this study, we investigated the relation between Chinese famine exposure in early life and subsequent T2D risk in adults from the Dongfeng-Tongji (DFTJ) cohort.

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Methods

Study population. Participants were selected from the DFTJ cohort (**Supplemental Figure 1**). This cohort is an ongoing dynamic prospective cohort that includes 27,009 retirees from the Dongfeng Motor Corporation (DMC) with a mean age of 63.6 y at study inception in 2008 (10). More retirees were recruited into the cohort during the first follow-up conducted from April to October 2013. A total of 38,295 retirees were included in the first follow-up. Participants without fasting glucose measurements (n = 387) or a specific birthdate (n = 1936) were excluded. Participants born during the Chinese famine were selected (n = 9358) (9). Because the beginning and end of the Chinese famine is not exact, participants born between 1 October 1958 and 30 September 1959 (n = 703) and 1 October 1961 and 30 September 1962 (n = 854) were excluded to minimize misclassification. Overall, 7801 individuals (1313 men and 6488 women) aged 56.4 ± 3.3 y and with a BMI (in kg/m^2) of 24.0 ± 3.3 were eligible for the descriptive analyses in 2013. Of these subjects, 3279 had baseline information in 2008, and 3100 free of T2D were included in the retrospective cohort analyses. This study was approved by the Medical Ethics Committee of the School of Public Health, Tongji Medical College, and Dongfeng General Hospital, DMC. All participants provided written informed consent.

Exposure to famine and famine severity. We did not collect information about individual famine exposure in this study. We used birthdate and birthplace instead to classify famine exposure. In China, the mobility of the population was tightly controlled by the government during the 1950s and early 1980s. In most cases, only when individuals were employed or admitted to universities would they migrate to other places (11). Low population mobility made it possible to estimate the famine exposure by participants' birthdates and birthplaces. Consistent with a previous Chinese famine study (9), we divided the participants into 5 groups. Those born between 1 October 1962 and 30 September 1964 were classified as the unexposed group; those born between 1 October 1959 and 30 September 1961 were classified as the fetal-exposed group; and those born between 1 October 1952 and 30 September 1958 (before the famine) were classified into late-, middle-, and early- childhood–exposed groups by every 2 y.

All provinces in the Chinese mainland were affected by the famine; however, famine severity was regionally different. According to the mortality rates reported in previous studies (9, 12), an excess mortality rate of 50% was set as a threshold value to distinguish the participants born in a severely or less-severely affected area.

Assessments of T2D and hyperglycemia. All participants had a physical examination after an overnight fast of ≥10 h. Plasma glucose concentrations were measured with an Aeroset automatic analyzer (Abbott Laboratories) with the use of the glucose oxidase method. Whole-blood samples obtained from participants were immediately assayed for glycated hemoglobin concentrations with the D-10 System (Bio-Rad Laboratories) with the use of HPLC. WHO criteria (13) were used to diagnose T2D. Diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L, self-reported physician-diagnosed diabetes, or the use of antidiabetic medications. Hyperglycemia was defined as FPG ≥6.1 mmol/L and <7.0 mmol/L or diabetes. We also used American Diabetes Association criteria (14) to define diabetes and hyperglycemia (diabetes: FPG ≥7.0 mmol/L or glycated hemoglobin ≥6.5%; hyperglycemia: FPG ≥5.6 mmol/L and <7.0 mmol/L, glycated hemoglobin ≥5.7% and ≤6.4%, or diabetes).

Assessment of covariates. In the DFTJ cohort baseline (2008) and the first follow-up period (2013), we used similar semistructured questionnaires to collect demographic information, family and personal disease histories, and lifestyle factors, including cigarette smoking, drinking, physical activity, and diet. Physical activity in the past year was collected by investigators. Metabolic equivalent (MET) hours per week was used to assess physical activity levels. METs were calculated by MET coefficient of activity × duration (hours per time) × frequency (times per week) (15) and then converted to 5 grades according to quintile. BMI was also calculated, and participants were categorized as overweight (BMI ≥24) or otherwise normal. Men and women with a waist circumference >85 and >80 cm, respectively, were defined as central obesity (16).

Statistical analysis. In descriptive analyses, continuous variables were expressed as means ± SDs for normally distributed variables or medians ± IQRs for skewed parameters. Discrete variables were expressed as percentage values. The differences of height, weight, BMI, waist circumference, FPG, glycated hemoglobin, hyperglycemia rate, and T2D rate between the exposed groups and unexposed group were tested by generalized linear models and expressed by adjusted least-square means ± SEs for continuous variables or adjusted rates for discrete variables. The least-square means were compared by least significant difference. We used logistic regression models to estimate ORs and 95% CIs. Analyses were adjusted for sex, smoking status, drinking status, MET (0–4 grades), family history of diabetes, BMI, and famine severity. Analyses were further stratified according to sex, BMI, and famine severity. The interaction between famine and other covariates was tested by adding a multiplicative factor in logistic regression models. We also used logistic regression models to compare famine-dysglycemia associations between severely and less severely famine-exposed groups. Sex, age, BMI, smoking status, drinking status, MET, and family history of diabetes were adjusted in the fully adjusted model. In retrospective cohort analyses, to assess the famine effects on the incidence of T2D from 2008 to 2013, we calculated RRs and 95% CIs of dysglycemia by generalized linear models and adjusted for covariates. The statistical analyses were performed with the use of SPSS version 13.0 (IBM). $P < 0.05$ was considered statistically significant.

Results

General characteristics of participants in descriptive analyses. **Table 1** shows basic characteristics of participants in descriptive analyses. In total, 1313 men and 6488 women were included. Among these participants, 1266 (16.2%) were exposed to the Chinese famine during the fetal stage, and 5597 (71.7%) were exposed during childhood. The overall prevalence of diabetes was 14.5% (1128 cases). There were fewer men in the fetal-exposed and unexposed groups.

The famine-exposed groups had a lower educational status and higher proportions of current smoking and drinking than the unexposed group. Participants in the famine-exposed groups were shorter than those in the unexposed group. Waist circumference, concentrations of glycated hemoglobin, and the prevalence of hyperglycemia was higher in the childhood-exposed groups. FPG concentrations were higher in both fetal- and childhood-exposed groups than the unexposed group. The prevalence rates of diabetes in the late- and middle-childhood–exposed groups were higher than the unexposed group.

The association between famine exposure and dysglycemia. **Table 2** shows the relations between famine exposure and subsequent T2D and hyperglycemia risk. Participants in the childhood-exposed groups had a higher risk of T2D in the crude

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[3] Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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[8] Abbreviations used: DFTJ, Dongfeng-Tongji; DMC, Dongfeng Motor Corporation; FPG, fasting plasma glucose; MET, metabolic equivalent; T2D, type 2 diabetes.

TABLE 1 General characteristics of participants of the Dongfeng-Tongji cohort in 2013 according to famine exposure in early life (n = 7801)[1]

Characteristics	Famine exposure group				
	Late childhood	Middle childhood	Early childhood	Fetal	Unexposed
n	1953	1712	1932	1266	938
Birthdate	1952–1954	1954–1956	1956–1958	1959–1961	1962–1964
Age, y	60.2 ± 0.6	58.1 ± 0.6	56.1 ± 0.6	53.1 ± 0.6	50.0 ± 0.6
Women, %	72.9	79.4	84.5	95.3	92.4
Smoking status, %					
Never	81.2	85.0	86.9	95.2	93.0
Former	5.3	3.2	2.6	0.6	1.0
Current	13.5	11.7	10.5	4.3	6.1
Drinking status, %					
Never	72.8	76.9	78.5	80.2	78.5
Former	3.6	3.1	2.1	1.4	1.8
Current	23.6	20.0	19.5	18.4	19.7
MET, h/wk	24 (31)	21 (33)	21 (32)	23 (32)	21 (33)
Family history of diabetes, %	13.0	15.4	18.9	16.9	17.4
Height, cm	158.4 ± 0.1*	159.1 ± 0.1*	159.2 ± 0.1*	159.2 ± 0.2*	160.4 ± 0.2
Weight, kg	60.9 ± 0.2	60.8 ± 0.2	61.0 ± 0.2	60.9 ± 0.3	61.2 ± 0.3
BMI, kg/m^2	24.1 ± 0.1*	24.0 ± 0.1	24.1 ± 0.1	24.0 ± 0.1	23.8 ± 0.1
Waist circumference, cm	81.9 ± 0.2*	81.7 ± 0.2*	81.6 ± 0.2*	80.5 ± 0.3	80.3 ± 0.3
Fasting plasma glucose, mmol/L	5.48 ± 0.02*	5.48 ± 0.02*	5.40 ± 0.02*	5.44 ± 0.02*	5.31 ± 0.02
Glycated hemoglobin,[2] %	5.49 ± 0.02*	5.46 ± 0.02*	5.41 ± 0.02*	5.34 ± 0.02	5.30 ± 0.03
Hyperglycemia, %	32.6*	31.4*	27.3*	26.0	23.6
Type 2 diabetes, %	15.4*	16.5*	14.3	12.0	12.3
Born in severely affected area,[3] %	89.3	89.6	85.7	84.8	—

[1] Data are presented as follows: age, means ± SDs; MET, medians (IQRs); height, least-square means ± SEs adjusted for sex; weight, BMI, and waist circumference, least-square means ± SEs adjusted for sex, smoking status, alcohol use, and MET; fasting plasma glucose and glycated hemoglobin, least-square means ± SEs adjusted for sex, smoking status, drinking status, MET, family history of diabetes, BMI, and exclusion of participants with type 2 diabetes; hyperglycemia and type 2 diabetes, percentages adjusted for sex. *Compared with the unexposed group, $P < 0.05$ (the least significant difference was used to adjust for multiple comparisons). MET, metabolic equivalent.
[2] Data are missing for 1212 participants.
[3] Data are missing for 40 participants.

model than the unexposed group. In the fully adjusted model, famine exposure was related to a 44% increased risk of T2D among the middle-childhood–exposed participants (P = 0.007), whereas participants exposed to famine in late and middle childhood had a higher risk of hyperglycemia than those in the unexposed group. Based on American Diabetes Association criteria, the association of famine exposure with dysglycemia risk was even stronger. The risk of T2D in late- and middle-childhood–exposed participants increased 33% and 54%, respectively, compared with the unexposed group. All participants in the famine-exposed groups had an increased risk of hyperglycemia (Table 2).

Stratified analysis by sex, BMI, and severity of famine. We further stratified analyses by sex, BMI, and severity of famine (**Figure 1**). The famine-dysglycemia associations were more evident in women and those born in regions severely affected by famine. However, only famine-sex interactions were found on T2D (P-interaction = 0.008) and hyperglycemia risk (P-interaction = 0.013). The T2D risk increased 40%, 55%, and 28% in late-, middle-, and early-childhood–exposed groups, respectively, compared with the unexposed women. No significant associations between famine and T2D risk were found in men. A similar famine-sex interaction was found on hyperglycemia risk (Figure 1, **Supplemental Table 1**).

Association between severity of famine and dysglycemia risk. To control for the potential confounding of aging on the associations of famine exposure with dysglycemia risk, we classified the participants into a group severely affected by famine and a group less severely affected by famine. We additionally controlled for age in the final logistic model. In this analysis, we combined late-, middle-, and early-childhood groups into 1 childhood-exposed group. Individuals exposed to severe famine had a 38% higher diabetes risk (OR: 1.38; 95% CI: 1.05, 1.81) than those exposed to less severe famine (**Supplemental Table 2**). The famine-dysglycemia association was not observed in the fetal-exposed group.

Association between famine exposure and dysglycemia risk in the retrospective cohort analysis. We also collected information from participants without T2D (n = 3100) or hyperglycemia (n = 2717) at baseline and conducted a retrospective cohort analysis. At the end of the 5-y follow-up, 229 (7.4%) incident T2D cases and 464 (17.1%) incident hyperglycemia cases were recorded (**Table 3**). The risk of T2D was not significantly different among the 5 groups; however, participants who experienced famine in middle childhood had a 2.06-fold higher risk of hyperglycemia than those in the unexposed group.

Discussion

We found in this study that subjects who experienced famine in childhood, especially middle childhood, had increased T2D

TABLE 2 Associations of famine exposure with dysglycemia risk in the Dongfeng-Tongji cohort in 2013[1]

	Famine exposure group				
	Late childhood	Middle childhood	Early childhood	Fetal	Unexposed[2]
WHO criteria,[3] *n*	1953	1712	1932	1266	938
Type 2 diabetes					
Cases, *n*	311	285	276	145	111
Model					
Crude	1.41 (1.12, 1.78)	1.49 (1.18, 1.88)	1.24 (0.98, 1.57)	0.96 (0.74, 1.25)	
Model 1[4]	1.31 (1.04, 1.66)	1.42 (1.12, 1.80)	1.21 (0.95, 1.53)	0.97 (0.75, 1.27)	
Model 2[5]	1.26 (1.00, 1.60)	1.38 (1.09, 1.76)	1.17 (0.92, 1.49)	0.94 (0.72, 1.23)	
Model 3[6]	1.26 (0.97, 1.64)	1.44 (1.10, 1.87)	1.18 (0.91, 1.53)	1.03 (0.77, 1.38)	
Hyperglycemia					
Cases, *n*	649	541	526	321	217
Model					
Crude	1.65 (1.38, 1.98)	1.54 (1.28, 1.84)	1.24 (1.04, 1.49)	1.13 (0.93, 1.38)	
Model 1[4]	1.57 (1.31, 1.89)	1.49 (1.24, 1.78)	1.22 (1.02, 1.46)	1.14 (0.93, 1.39)	
Model 2[5]	1.52 (1.27, 1.83)	1.46 (1.21, 1.76)	1.19 (0.99, 1.43)	1.11 (0.90, 1.35)	
Model 3[6]	1.54 (1.26, 1.88)	1.51 (1.23, 1.85)	1.21 (0.99, 1.48)	1.19 (0.96, 1.47)	
ADA criteria,[7] *n*	1623	1419	1647	1085	815
Type 2 diabetes					
Cases, *n*	288	261	252	137	104
Model					
Crude	1.48 (1.16, 1.88)	1.54 (1.21, 1.97)	1.24 (0.97, 1.58)	0.99 (0.75, 1.30)	
Model 1[4]	1.38 (1.08, 1.76)	1.47 (1.15, 1.88)	1.20 (0.94, 1.53)	1.00 (0.76, 1.31)	
Model 2[5]	1.33 (1.04, 1.70)	1.43 (1.11, 1.83)	1.17 (0.91, 1.50)	0.97 (0.73, 1.28)	
Model 3[6]	1.33 (1.01, 1.75)	1.54 (1.17, 2.03)	1.19 (0.90, 1.56)	1.03 (0.76, 1.39)	
Hyperglycemia					
Cases, *n*	1064	892	971	629	417
Model					
Crude	1.82 (1.53, 2.16)	1.62 (1.36, 1.92)	1.37 (1.16, 1.62)	1.32 (1.10, 1.58)	
Model 1[4]	1.80 (1.51, 2.14)	1.60 (1.35, 1.91)	1.03 (0.76, 1.39)	1.32 (1.10, 1.58)	
Model 2[5]	1.75 (1.47, 2.09)	1.59 (1.33, 1.89)	1.36 (1.14, 1.61)	1.31 (1.09, 1.58)	
Model 3[6]	1.95 (1.61, 2.36)	1.86 (1.53, 2.25)	1.45 (1.21, 1.75)	1.46 (1.20, 1.79)	

[1] Values are ORs (95% CIs) unless otherwise indicated. ADA, American Diabetes Association.
[2] Reference value for all models is 1.00.
[3] Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L, self-reported physician-diagnosed diabetes, or the use of antidiabetic medications. Hyperglycemia was defined as diabetes or impaired fasting glucose (fasting plasma glucose ≥6.1 mmol/L and <7.0 mmol/L) (13).
[4] Adjusted for sex.
[5] Additionally adjusted for BMI (in kg/m^2) and famine severity.
[6] Additionally adjusted for drinking status, smoking status, metabolic equivalent, and family history of diabetes.
[7] Diabetes was defined on the basis of WHO criteria plus glycated hemoglobin ≥6.5%. Hyperglycemia was defined as diabetes or fasting plasma glucose ≥5.6mmol/L and <7.0mmol/L or glycated hemoglobin ≥5.7% and ≤6.4% (14).

and hyperglycemia risk in adulthood. In addition, there was an interaction between famine exposure and sex on dysglycemia risk. Women who were exposed to famine in childhood were more likely to develop diabetes and hyperglycemia in adulthood than men.

Ravelli et al. (6) reported that subjects who were exposed to the Dutch famine during late gestation had higher 2-h glucose and insulin concentrations at the age of 50 y. Li et al. (9) further confirmed this finding based on data from the Chinese National Nutrition and Health Survey. Similarly, Lumey et al. (17) found that prenatal exposure to the Ukraine famine increased the risk of T2D in a large sample. In addition, van Abeelen et al. (7) observed that T2D risk in adulthood was associated with famine exposure during postnatal development (0–9 y). Wang et al. (18) recently reported that famine exposure in the fetal and childhood periods increased diabetes risk in the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors study. Our analyses showed that exposure to famine in childhood increased dysglycemia risk, but this association was not observed among those exposed to famine during the fetal period. The small sample size of the fetal-exposed group might have decreased the statistical power and caused the inconsistent findings.

We notably found that famine-dysglycemia association might be sex-specific. Previous studies reported that relations of famine with overweight, metabolic syndrome, and height were also sex-specific (19, 20). A recent study indicated that birth weight was more strongly associated with T2D risk in women than in men (21). We found that exposure to famine in childhood was associated with a higher risk of dysglycemia in women but not in men. The relatively small sample size of men in the fetal-exposed and unexposed groups might have limited our ability to detect the famine-dysglycemia association in men; however, similar findings were also found in a representative Chinese population (18). The sex difference could be partly explained by mortality selection and hypotheses regarding son preference. During the severe famine period, the mortality of men was greater than for women, and the surviving men might have been healthier than those who prematurely died (22, 23); in addition, in Chinese traditional culture, parents prefer to protect boys in tough

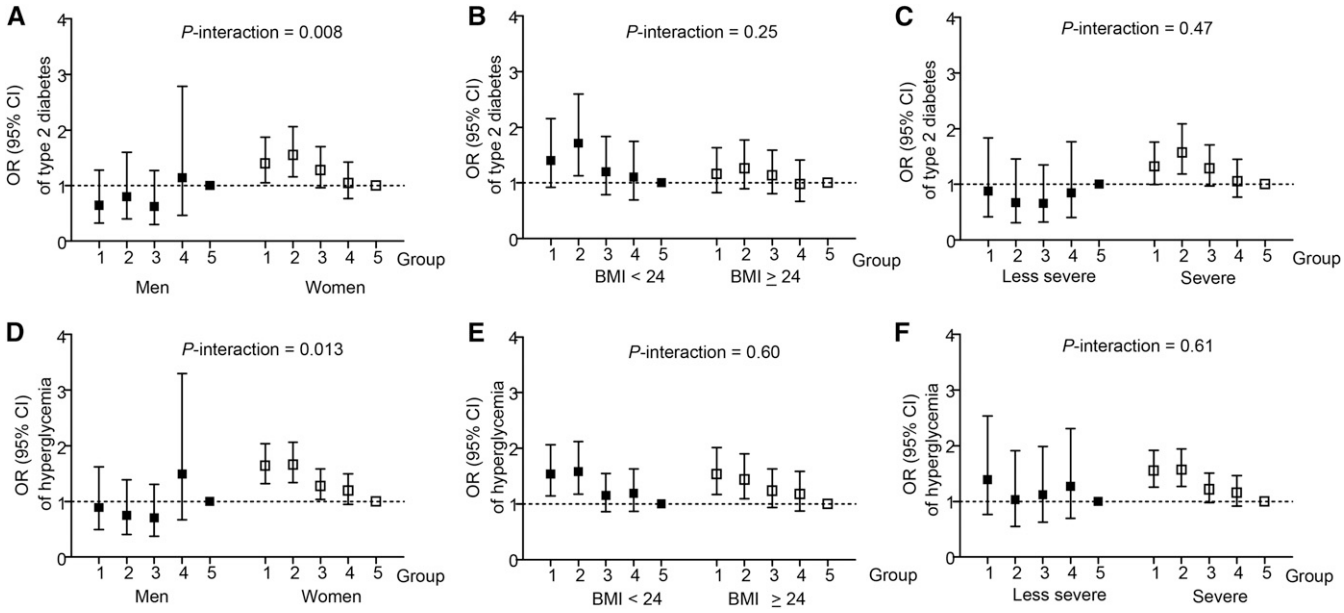

FIGURE 1 Associations between the Chinese famine exposure and risk of type 2 diabetes (A–C) and hyperglycemia (D–F) stratified by sex (A, D), BMI (in kg/m^2) (B, E), and famine severity (C, F) among participants of the Dongfeng-Tongji cohort in 2013. Results are presented as adjusted ORs with 95% CIs after adjusting for sex, BMI, famine severity, smoking status, drinking status, metabolic equivalent, and family history of diabetes except for the stratifying factors. 1, late-childhood–exposed group; 2, middle-childhood–exposed group; 3, early-childhood–exposed group; 4, fetal-exposed group; 5, unexposed group.

conditions, and girls might receive less food and care, which might lead to worse health outcomes for women later in life (24). Future studies that evaluate the underlying mechanisms are needed to validate our findings.

We did not find an interaction between BMI and famine exposure on dysglycemia risk. Rapid postnatal weight gain may play a key role in the developmental origins of the health and disease hypothesis (25). Eriksson et al. (26) found that low birth weight, thinness in infancy, and rapid body mass gain in childhood (2–11 y) collectively increased the risk of dysglycemia in adulthood. Moreover, a recent study (27) showed that early-adulthood BMI influenced T2D prevalence after midlife independent of current BMI. In our study, the information on BMI from early life was missing, whereas current BMI might have changed after the onset of diabetes.

Few studies, to our knowledge, have longitudinally followed the effects of famine on dysglycemia risk. A Dutch famine study indicated that the famine effect was not pronounced with aging (28). In our retrospective cohort analyses, we observed a significant association between famine exposure and risk of hyperglycemia.

TABLE 3 Associations of famine exposure with dysglycemia risk in the retrospective cohort analysis (n = 3100)[1]

	Famine exposure group				
	Late childhood	Middle childhood	Early childhood	Fetal	Unexposed[2]
Type 2 diabetes, *n*	1018	869	901	188	124
Cases	77	67	69	10	6
Model					
Crude	1.56 (0.70, 3.51)	1.59 (0.71, 3.60)	1.58 (0.70, 3.57)	1.10 (0.41, 2.95)	
Model 1[3]	1.63 (0.72, 3.67)	1.68 (0.74, 3.83)	1.68 (0.74, 3.82)	1.13 (0.42, 3.04)	
Model 2[4]	1.41 (0.63, 3.18)	1.49 (0.66, 3.38)	1.56 (0.69, 3.53)	1.06 (0.40, 2.83)	
Model 3[5]	1.47 (0.66, 3.31)	1.49 (0.66, 3.38)	1.50 (0.66, 3.40)	1.07 (0.40, 2.85)	
Hyperglycemia, *n*	872	764	805	168	108
Cases	153	149	124	29	9
Model					
Crude	2.11 (1.11, 4.00)	2.34 (1.23, 4.45)	1.85 (0.97, 3.53)	2.07 (1.02, 4.20)	
Model 1[3]	2.05 (1.08, 3.89)	2.24 (1.18, 4.27)	1.76 (0.92, 3.37)	2.02 (0.99, 4.09)	
Model 2[4]	1.83 (0.97, 3.47)	2.07 (1.09, 3.93)	1.65 (0.86, 3.14)	1.92 (0.95, 3.88)	
Model 3[5]	1.83 (0.96, 3.47)	2.06 (1.08, 3.90)	1.59 (0.83, 3.04)	1.91 (0.95, 3.86)	

[1] Values are RRs (95% CIs) unless otherwise indicated.
[2] Reference value for all models is 1.00.
[3] Adjusted for sex.
[4] Additionally adjusted for BMI (in kg/m^2) and famine severity.
[5] Additionally adjusted for drinking status, smoking status, metabolic equivalent, and family history of diabetes.

Although famine exposure was also related to higher T2D risk in adults, the associations did not reach statistical significance. This finding might have resulted from the relatively small sample size (n = 3100) and short follow-up period (<5 y). Moreover, the Chinese famine occurred from 1959 to 1961, and we only investigated the effects of famine over a short period of time (2008–2013). The individuals affected by dysglycemia before 2008 were excluded from the retrospective cohort, which might have attenuated the association. Based on findings from other Chinese famine studies (9, 18) and ours from 2002 to 2013, we speculated that famine exposure in early life had long-term effects on adult T2D risk. Whether or how aging may modify the effects of famine needs to be further investigated.

Several potential mechanisms might be involved in the association of famine exposure in early life and dysglycemia risk in later life. Systematic reviews have suggested that low birth weight was related to the risk of diabetes (29, 30). Small babies might have small abdominal viscera and low muscle mass, but they preserve body fat during their intrauterine development. Such body composition might persist postnatally and predispose the small babies to insulin resistance (31). Animal experiments have shown that pre- and postnatal undernourishment affect islet development, cause structural and functional changes of the pancreas, and disrupt the hypothalamus (32–34). In addition, a recent genomic-scale analysis showed that DNA methylation signals linked to prenatal malnutrition were associated with an adverse metabolic phenotype in later life (35).

Some limitations to our study should be mentioned. First, the participants were registered retired employees of the DMC. According to the *China Statistical Yearbook*, the mean wage of state-owned units was above the national average (36). Subjects in this economic group might not represent the general population. Second, we did not collect accurate personal famine exposure information and anthropometric measurements from birth to adulthood. Therefore, the data provided evidence of association rather than a causal relation. Third, despite results that showed that the middle-childhood–exposed group had a higher risk of T2D, we could not conclude that middle childhood was the most critical and sensitive period. Because the Chinese famine lasted ~3 y, some subjects in the fetal-exposed group also experienced the famine in infancy, and some subjects in the early-childhood group also experienced the famine in infancy. Such misclassification might have also attenuated the relation between fetal famine exposure and T2D risk. Fourth, the cases of diabetes in this study might include some type 1 diabetes. However, because the subjects included were retired workers aged >50 y, the proportion of type 1 diabetes included might be very limited. Finally, aging is a known risk factor for the development of diabetes (37). Because the famine affected all provinces in the Chinese mainland, it is difficult to define a concurrent nonfamine-exposed group. We alternatively classified the participants into severely and less severely affected groups and adjusted for age in the final analysis model, which partially minimized this limitation. More detailed and large-scale investigations are needed.

In summary, we found that famine exposure in early life, especially childhood, was related to a higher risk of T2D and hyperglycemia in adulthood. This relation might be sex-specific. Famine has a long-term impact on the T2D epidemic in China. Further studies with large samples in different populations are needed to validate our results and elucidate the underlying mechanisms.

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JW, HY, FBH, TW, and MH conceived and designed the study; JW, Y Li, XH, BL, HH, and FW analyzed the data and wrote the first draft of the paper; XL and KY collected and analyzed the data; and JY, PY, XM, SW, YW, Y Liang, XZ, HG, and TW supervised the field activities and designed the analytic strategy. All authors read and approved the final manuscript.

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