Famine Exposure in Early Life and Risk of Type 2 Diabetes in Adulthood: Findings From Prospective Cohort Studies in China

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Abstract

Background: This study will investigate effect of famine exposure in early life associated with the risk of type 2 diabetes in adulthood during the Chinese Famine.

Methods: A total of 3,418 individuals aged 35-74 years free of diabetes in 2006 and in 2009 study surveys, were prospectively followed up to 2009 and 2012, respectively. Individuals were grouped into non-exposed (1962-1978), fetal-exposed (1959-1961), childhood-exposed (1949-1958) and adolescence/adult-exposed cohorts (1931-1948). Logistic regression model was employed to assess effect of famine exposure on diabetes incidence, adjusting for potential covariates.

Results: During a mean follow up of 3 years, the age-adjusted cumulative incidences of type 2 diabetes were 6.3%, 13.0% 11.0% and 13.8% in non-exposed, fetal, child and adolescence/adult-exposed cohorts, respectively (P=0.026). Compared with non-exposed individuals, relative risks (95% confidence intervals) for diabetes incidence were 2.15(1.29-3.60), 1.53(0.93-2.51), and 1.65(0.75-3.63) in those exposure in fetal, child and adolescence/adult, controlling for covariates. The interactions between famine exposure and obesity, education, family history of diabetes were not observed, except for famine exposure and residential areas. Individuals lived in rural areas increased risk for type 2 diabetes in fetal and child exposure, with an incidence relative risk (95% confidence interval) of 8.79(1.82-42.54) and 2.33(1.17-4.65), respectively.

Conclusions: Our findings indicate that famine exposure in early life is an independent predictor on type 2 diabetes, particularly in women. The identification and intervention on critical time can prevent residents from diabetes in later life.

The clinical trial was registered, more detail linked in https://clinicaltrials.gov/ct2/home, as registration no. NCT01053195.

Background

Diabetes is major cause of mortality and health issue worldwide. Data from recent studies in China showed that prevalence of diabetes increased to 11.6% in 2013 from 2.5% in 1994[1, 2]. Malnutrition in intrauterine and in early life were potential risk factors for metabolic disorders in later life. Meta-analysis indicated famine exposure or low birth weight in fetal increased risk of obesity, diabetes, hypertension and metabolic syndrome in adulthood [3–6].

The Chinese Famine 1959–1961 is a natural disaster, referring to sharp drop on grain production and 30 million excess death. Observational studies across China have indicated that individuals exposed famine was associated with higher prevalence of diabetes than unexposed counterparts [4], while the cause relationship was not well established. In the current study, we recruited two longitudinal studies from the Qingdao Diabetes Prevention Program to investigate the relationship between famine exposure in early life and type 2 diabetes incidence in adulthood in China.

Methods

The survey protocols have been described in our previous reports [7,8]. Briefly, the nondiabetic participants aged 35-74 years from randomly selected community, were invited to assess the relationship between famine effect and diabetes risk over a 3-year-follow-up. After excluding the participants with missing information, a total of 3,418 was included in current data analysis. The Ethics Committee of Qingdao Centers for Disease Prevention and Control approved the studies. Informed consent was obtained from all individuals in the field survey. The clinical trial was registered, more detail linked in https://clinicaltrials.gov/ct2/home, as registration no. NCT01053195.

Definition of type 2 diabetes and famine cohorts

Incident type 2 diabetes were determined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L and/or 2h plasma glucose (2hPG) ≥11.1 mmol/L and/or a self-reported diabetes diagnosed by professional physician during the follow up among participants without diabetes at baseline. According to the birth time during the China Famine exposure, we defined exposed groups as fetal-exposed (born between 01 January 1959 and 31 December 1961), child-exposed (born between 01 January 1949 and 31 December 1958), and adolescent/adult-exposed (born between 01 January 1931 and 31 December 1948), and non-exposed (born between 01 January 1962 and 31 December 1978).

Study parameters

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Family income was categorized into low-income (<3000 Chinese Yuan or 470 US Dollars per month), and high-income level (≥3000 Chinese Yuan or 470 US Dollars per month). Education level was classified to low education and high education divided by 9 school years. Leisure time physical activity was calculated as metabolic equivalent and classified into three categories of sedentary, moderate and vigorous level, respectively.

Statistical analyses

Continuous variables were presented as the mean and standard deviation, and categorical variables as the number (percentage). We used a univariate general linear model adjusted for age to compare differences among the means values of continuous variables, and employed the Chi-square test to conduct categorical data between the four cohorts. Logistic regression analysis was used to estimate the relative risks (RRs) and 95% confidence intervals(CIs) for determining the relationship between famine exposure and type 2 diabetes incidence in later life, adjusting for potential risk factors at baseline. The individual in non-exposed cohort was the reference. Interactions between famine exposure and residential areas, family history of diabetes, education, income, smoking and drinking on type 2 diabetes incidence was tested by using a multiplicative factor in the logistic regression models[9].

Results

The baseline characteristics of individuals separated by famine exposure cohorts were summarized in table 1. As compared with non-exposed cohort, age-adjusted mean values of BMI, waist circumference, total cholesterol, FPG, systolic blood pressure and diastolic blood pressure were significantly greater in three exposed cohorts (P<0.05 for all comparisons). No differences were observed in 2hPG, triglycerides and high density lipoprotein cholesterol.

During 3-year follow up, 343 cases of type 2 diabetes were identified from two longitudinal studies. The age-adjusted cumulative incidence rates were 6.3%, 13.0%, 11.0% and 13.8% in non-exposed, fetal-exposed, child-exposed and adolescence/adult-exposed cohorts, respectively (P=0.026). The resident specific analysis showed that diabetes incidence rate was significantly increased across the famine exposure period in rural, but not in urban areas. The corresponding figures were 4.9%,15.3%,11.6% and 14.6% in rural areas (P=0.001), and 10.4%, 4.9%, 9.2% and 11.9% in urban areas (P=0.530), respectively.

Compared with non-exposed individuals, RRs (95%CI) for type 2 diabetes incidence were 2.15(1.29-3.60), 1.53(0.93-2.51), and 1.65(0.75-3.63) who were exposed to famine in their fetal, child, and adolescence/adult, controlling for covariates in table 2. The RRs(95%CIs) for type 2 diabetes incidence were 3.36(1.88-5.99), 2.06(1.14-3.74) and 2.18(0.84-5.65) among fetal, child and adolescence/adult exposed cohorts in rural areas. The corresponding figures were 0.35(0.08-1.62), 0.69(0.27-1.76) and 0.79(0.18-3.47) in urban areas, respectively. The trends for diabetes risk did not change substantially while waist circumference or waist-to-hip ratio replaced BMI in separated multivariable models. The interactions between famine exposure and obesity, education, family history of diabetes were not observed, except for residential areas. Individuals lived in rural areas increased risk for type 2 diabetes in fetal and childhood exposure, with increased RRs(95%CIs) of 8.79(1.82-42.54) and 2.33(1.17-4.65), respectively.

Age was considered as independent risk factor associated with type 2 diabetes. In order to reduce the effect of age and residential areas, we further discussed the famine exposure in relation to type 2 diabetes in sensitivity analysis. As shown in table 3, fetal exposure was significantly associated with type 2 diabetes incident in adult stratified by birth years of 3-year intervals. The results of multivariable model in women were 2.26(1.03-4.94) in fetal exposed and 1.04(0.37-2.91) in infant exposed cohorts, while famine effect was moderate in men. Mean age of fetal exposed cohort was significantly younger than combined groups including non-exposed, child and adolescent exposed cohorts (47.9 vs.51.2 years, P<0.05). The RR(95%CI) of fetal exposed cohort for type 2 diabetes incidence was 1.74(1.12-2.69) as compared with the combination of child-, adolescent-exposed and non-exposed cohorts. Stratified by residential areas, mean age of fetal exposed cohort was also younger than the counterparts both in urban and rural areas (48.5 vs.51.7 years, P<0.03; 47.7 vs. 51.0 years, P<0.05), whilst the corresponding figures of RRs(95%CIs) were 0.41(0.10-1.75) in urban and 2.34(1.46-3.75) in rural areas.

Discussion

Our findings indicate famine exposure in fetal stage is an independent predictor on type 2 diabetes incidence in later life, especially in women. Individuals lived in rural areas with famine exposure in fetal and childhood will increase the risk of type 2 diabetes.

Based on sensitive analysis, we elucidate that the severity of fetal exposure to famine determined heightened risk for subsequent type 2 diabetes, but no such association observed in adolescent exposure. Several observational studies investigated that prenatal exposure in famine was associated with prevalence of type 2 diabetes, with an increased risk of odd ratios from 1.22 to 2.20[10, 11]. A meta-analysis found that individuals exposed in fetal stage was a 36% higher risk of type 2 diabetes, but not in child exposed, as compared with those unexposed counterparts [4], with the pooled RRs(95%CIs) of 1.36 (1.12–1.65) and 1.40 (0.98–1.99), respectively. Moreover, a recent study including 88,830 participants with a median of 7.3 years follow up showed that, fetal exposure on the Chinese Famine was associated with a 25% increased risk of type 2 diabetes in adult [12]. The Chinese Famine affected almost everyone living in Qingdao, however, it did not include less severely affected regions as controls. Due to the severity differences across the regions during the Chinese Famine, the conclusions required further investigation based on national data.

Our study showed that the association between fetal exposure and diabetes incident was significantly stronger in women, but moderate in men. However, sex specific analysis found that the association during the time of birth were similar in men and women in the Dutch Study and in the Ukraine Study [13, 14]. Several studies also showed that biological difference of sex in hormones, body composition, glucose and fat metabolism, reproduction and some sex-dimorphic mechanisms in the risk development of type 2 diabetes. A recent meta-analysis including 18 cross-sectional or historical studies, indicated significant association between obesity risk and malnutrition exposed in early life and in women, but not in men [15]. The experimental studies also showed that the mechanisms of fetal programming on insulin resistance and insulin secretion contributed to sex differences in glucose tolerance [16, 17]. Inconsistent results were observed in the China health and retirement longitudinal study, suggesting that men were more vulnerable than women to adverse effects of famine exposure in fetal stage [18, 19]. Sex disparity on the association between famine effect and type 2 diabetes requires further investigations.

The underlying mechanism between famine exposure and type 2 diabetes was uncertain. The thrifty phenotype hypothesis indicates famine in early life, including reduced capacity for insulin secretion and insulin resistance, combined with effects of obesity, ageing and physical inactivity in adult, are the most important factors in subsequent type 2 diabetes [20]. For instance, the Dutch Winter Families study has shown that adults exposed to famine in their fetal period were more insulin resistant than those without. Another hypothesis shows that DNA methylation may be a common consequence of prenatal famine exposure and that these changes depend on the gestational timing of the 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 fasting glucose concentrations [22]. It suggested that epigenetic mechanisms play a role in mediating the association between prenatal famine exposure and later-life metabolic health.

The strengths of our study were longitudinal design including two large sizes of the random representative samples from general population. The individuals with known and newly diagnosed diabetes at baseline were excluded to eliminate the bias on the data analysis. All interviews were conducted face-to-face by professional health workers, and the anthropometric measurements were conducted on site. However, we also have some limitations in the current study. Due to extensive urban construction, housing demolition and relocation, some participants were failed to contact and lost to follow up during the recruitment. We compared the baseline anthropometric and laboratory measurements between follow-up and loss-to-follow-up participants. The mean waist circumference, diastolic blood pressure, total cholesterol, triglycerides, FPG and 2hPG were greater in lost-to-follow-up group than follow-up group ($P < 0.05$). But there were not significantly differences on age, BMI and systolic blood pressure across two groups. The Chinese Famine affected almost everyone living in Qingdao at that time period, therefore, the famine exposed age group cannot match to unexposed counterparts. A classification bias may exist referring to the incidence of diabetes increases with age. Therefore, we divided 3-year interval group to reduce age effect on diabetes incidence. The association between famine exposure and incidence risk was robust in a sensitivity analysis. The current findings were not generalized to other regions of China, further nationally representative study requires to investigate the association.

In conclusions, we elucidated the association between famine exposures and type 2 diabetes incidences based on population-based prospective study in Chinese. Fetal, but not adolescent famine exposure increased risk of diabetes process in adult. Appropriate nutrition and health lifestyle in early life may be beneficial to metabolic disorders intervention in later life.

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; DNA: deoxyribonucleic acid; FPG: Fasting Plasma Glucose; 2hPG:2-hour Plasma Glucose; RR: Relative Risk

Declarations

Ethics approval and consent to participate

The observational study was approved by the Ethical Committee of the Qingdao Centers for Disease and Prevention and Control, with ethical committee approvals file no.200509001.Written informed consents were obtained from all participants. The study protocol was conducted according to the principles expressed in the Declaration of Helsinki.

Consent to publish

Our manuscript has not been published previously and that it is not currently being considered by another journal. All co-authors have approved the finalized version to the submission.

Availability of data and material

The ownerships of data belong to the third party. If researchers or institutions want to access to the data, please submit the application to cdcca@qd.shandong.cn.

Competing interests

The authors declare that they have no competing of interests.

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Authors' contributions

R.G, D.Z, Z.P and Q.Q designed the study, F.N, J.Z , L.Z and X.S analyzed the data, and F.N, W.G, YL.Z and H.X wrote the manuscript. All authors approved the final manuscript.

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Tables

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

	Unexposed group	Fetal-exposed group	Childhood-exposed group	Adolescence/adult-exposed group	P value
No.	1407	213	1011	787	
Age (years)	41.2(0.10)	47.9(0.14)	54.1(0.11)	65.3(0.16)	0.000
Men(%)	457(32.5)	57(26.8)	343(33.9)	356(45.2)	0.000
BMI (kg/m^2)	24.5(0.18)	25.1(0.25)	25.8(0.12)	26.4(0.26)	0.000
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)	0.000
FPG (mmol/L)*	5.53(0.03)	5.53(0.05)	5.53(0.02)	5.41(0.05)	0.039
2hPG (mmol/L)†	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	0.000
Education levels (%)					
<= 9 school years	69.9	67.1	81.4	85.1	
> 9 school years	30.1	32.9	18.6	14.9	0.000
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	0.000

Current smoking (%)	19.3	17.4	22.2	26.4	0.000
Current drinking (%)	13.9	13.6	17.2	18.6	0.016

Data are age-adjusted mean (SE) and or as noted. *N=2079, †N=2976.BMI, body mass index; HDL, High-density lipoprotein cholesterol

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

	No. cases/ sample size	Crude	Model1	Model 2
Total				
Non-exposed	76/1331	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)
Men				
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)
Women				
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, 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.

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
Urban areas			
Non-exposed	7.7	1.00(Ref)	1.00(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)
Rural areas			
Non-exposed	4.7	1.00(Ref)	1.00(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.

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

Age groups	N=3,418	Crude	Model 1	Model 2	Model 3
1971-1978	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	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	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	474	Ref.	Ref.	Ref.	Ref.
1959-1961	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	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	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	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	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	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	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 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.