Exposure to the Chinese Famine in Early Life and the Risk of Metabolic Syndrome in Adulthood

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OBJECTIVE—To examine whether exposure to the Chinese famine during fetal life and early childhood is associated with the risks of metabolic syndrome and whether this association is modified by later life environment.

RESEARCH DESIGN AND METHODS—We used data of 7,874 adults born between 1954 and 1964 from the 2002 China National Nutrition and Health Survey. Famine exposure groups were defined as nonexposed; fetal exposed; and early childhood, midchildhood, or late childhood exposed. Excess death rate was used to determine the severity of the famine. The ATP III criteria were used for the definition of metabolic syndrome (three or more of the following variables: elevated fasting triglyceride levels, lower HDL cholesterol levels, elevated fasting glucose levels, higher waist circumference, high blood pressure).

RESULTS—In severely affected famine areas, adults who were exposed to the famine during fetal life had a higher risk of metabolic syndrome, as compared with nonexposed subjects (odds ratio 3.13 [95% CI 1.24–7.89, $P = 0.016$]). Similar associations were observed among adults who were exposed to the famine during early childhood, but not for adults exposed to the famine during mid- or late childhood. Participants who were born in severely affected famine areas and had Western dietary habits in adulthood or were overweight in adulthood had a particularly high risk of metabolic syndrome in later life.

CONCLUSIONS—Exposure to the Chinese famine during fetal life or infancy is associated with an increased risk of metabolic syndrome in adulthood. These associations are stronger among subjects with a Western dietary pattern or who were overweight in adulthood.

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F amine studies may give direct evidence for the hypotheses that early malnutrition plays a role in the origins of hypertension (1–3), insulin resistance (4,5), central obesity (6), and dyslipidemia (7), which are all components of the metabolic syndrome. Fetal famine exposure has been shown to be associated with the risk of hypertension in later life in subjects exposed to the Dutch Hunger Winter (1944–1945) (1), Leningrad Siege (1941–1944) (2), and Chinese famine (1959–1961) (3). Prenatal exposure to both the Dutch Hunger Winter and Chinese famine was also associated with impaired glucose tolerance among adults (4,5,8). Maternal famine exposure during gestation was also associated with higher BMI and waist circumference in Dutch (6) and Chinese women (9,10) and a more atherogenic lipid profile among Dutch adults (7).

The only famine study that examined the associations of fetal famine exposure with metabolic syndrome was conducted in the Dutch Famine Cohort and did not observe significant associations (11). This might be because of the limited period of the Dutch Hunger Winter, which did not last for the whole gestation period, whereas the different metabolic syndrome components have different underlying origins and critical periods (11).

The risks of adverse long-term consequences of famine exposure during early life may be further increased in a nutritionally rich environment in later life (12,13). The associations between low birth weight and later risk of hypertension seem to be stronger among subjects who become overweight in later life (13,14). Our previous study indicated that the association of fetal famine exposure with the risk of hyperglycemia appeared to be exacerbated by Western dietary pattern and improved economic status (8). No previous study had examined the joint association of early life famine exposure and later life nutritional rich environments with the risk of metabolic syndrome during adulthood.

The purpose of present study was to examine whether exposure to Chinese famine during fetal life and childhood was associated with the risk of metabolic syndrome and whether this association was modified by later life nutritional environment.

RESEARCH DESIGN AND METHODS

Study design and participants
We used data from the 2002 China National Nutrition and Health Survey (CNNHS), which is a nationally representative cross-sectional study on nutrition and chronic diseases. As has been described in detail previously (8), a stratified, multistage probability cluster sampling design was used in this survey. The final sample size for the analyses was 7,874.

Famine cohorts and areas

Subjects were categorized into five exposure cohorts according to the subject's birthday and corresponding exposure period (8). To minimize misclassification of the famine exposure periods, subjects who were born between 1 October 1958 and 30 September 1959 or between 1 October 1961 and 30 September 1962 were excluded since the exact dates of the start and the end of the Chinese famine were not available and not the same across regions. Adults who were born between 1 October 1962 and 30 September 1964 were classified as nonexposed cohort. Subjects who were born between 1 October 1959 and 30 September 1961 were classified as fetal-exposed cohort whose mother was exposed to famine during the whole gestation period. Subjects who were born between 1 October 1952 and 30 September 1958 were grouped by every 2 years and were classified into one of the three childhood-exposed cohorts.

As previously described, excess death rate of each province was used to determine the severity of the famine (8,9). The excess death rate was calculated as the percent change in mortality rate from the mean level in 1956–1958 to the highest value during the period of 1959–1961. The excess death rate of 100% was used as the threshold: regions that had equal or higher rate than this cutoff were categorized as severely affected famine areas, and otherwise as less severely affected famine areas. Accordingly, all five birth cohorts were divided into severely affected and less severely affected famine areas.

The protocol of the 2002 CNNHS was approved by the Ethical Committee of the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. Signed consent forms were obtained from all participants.

Study parameters

Fasting plasma glucose (FPG) concentration was measured using glucose oxidize enzymatic method within 3 h of plasma preparation (8). Plasma triglyceride and HDL cholesterol were measured enzymatically with a Hitachi 7060, 7180 autoanalyzer (Hitachi, Tokyo, Japan). Subjects' seated blood pressures were measured on the right arm after 5 min of rest to the nearest 2 mmHg according to 1999 World Health Organization/International Society of Hypertension guidelines on hypertension (15). The waist circumference was

measured to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest at the end of exhalation.

Definition of metabolic syndrome

The ATP III criteria (16) were used for the definition of metabolic syndrome, as three or more of the following variables and cutoff points; *1*) fasting triglyceride: ≥1.69 mmol/L (150 mg/dL); *2*) HDL cholesterol: men <1.04 mmol/L (40 mg/dL), women <1.29 mmol/L (50 mg/dL); *3*) fasting glucose: ≥5.5 mmol/L (100 mg/dL) (17); *4*) waist circumference: men >102 cm, women >88 cm; *5*) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.

Adult nutritional risk factors

Dietary patterns and BMI measured in 2002 were used as measures of the nutritional environment in adulthood. A validated semiquantitative food frequency questionnaire (FFQ) was used to assess diet in the previous year before the study. The method for assessing dietary patterns has been described in detail elsewhere (18). Briefly, two major dietary patterns, the traditional dietary pattern and Western dietary pattern (8), were derived through cluster analysis of food consumption data

collected by the FFQ. We classified subjects as overweight if BMI ≥24 kg/m^2, or normal otherwise, using criteria recommended for Chinese adults.

Statistical analysis

Risks of metabolic syndrome among fetal- and childhood famine-exposed subjects, compared with nonexposed subjects, were examined with the method of maximum likelihood by using a survey logistic regression model. Interactions between famine exposure cohort (fetal or childhood exposed vs. nonexposed) and area (severely affected vs. less severely affected) were tested by adding a multiplicative factor in the survey logistic regression model. Analyses were adjusted for sex, economic status, family history of diabetes and hypertension, educational level, current smoking, alcohol use, and physical activity level, all assessed in 2002. To explore whether the associations between fetal exposure to severe famine and metabolic syndrome were modified by improved nutritional environment in later life, we subsequently stratified the analyses by dietary patterns and BMI in adulthood. We conducted two sensitivity analyses: one applying lower cutoff points of waist circumference (men ≥90 cm and women ≥80 cm) (19) to the definition of the

Table 1—*Prevalence and ORs of metabolic syndrome among different birth cohorts stratified by severity of Chinese famine area* *†*

			Cohort		
	Nonexposed	Fetal exposed	Early childhood exposed	Midchildhood exposed	Late childhood exposed
Severely affected famine area					
N	834	334	641	630	613
Prevalence (%)	3.1	7.8	7.1	5.7	6.4
OR	1.0 (ref)	3.13	2.85	2.07	2.21
95% CI		1.24–7.89	1.19–6.83	0.77–5.53	0.91–5.40
P		0.016	0.019	0.15	0.08
Less severely affected famine area					
N	1,120	671	1,013	958	1,060
Prevalence (%)	9.4	7.4	9.7	10.1	11.6
OR	1.0 (ref)	0.80	0.91	0.97	1.29
95% CI		0.46–1.41	0.55–1.51	0.57–1.64	0.76–2.19
P		0.44	0.72	0.91	0.34
P for interaction between area and cohort		0.016	0.026	0.19	0.17

*Metabolic syndrome was defined using criteria of ATP III as at least three of the following: *1*) fasting triglycerides ≥1.69 mmol/L (150 mg/dL), 2) HDL <1.04 mmol/L (40 mg/dL) for men and <1.29 mmol/L (50 mg/dL) for women, 3) waist circumference >102 cm for men and >88 cm for women, 4) fasting glucose ≥5.5 mmol/L (100 mg/dL), and 5) blood pressure ≥130/≥85 mmHg. †Prevalence of metabolic syndrome was sex standardized. All ORs use nonexposed cohort as reference cohort (ref). ORs were adjusted for sex, family income, family history of diabetes and hypertension, educational level, current smoking, alcohol use, physical activity level, and BMI.

metabolic syndrome based on the Asian criterion for abdominal obesity and the other excluding abdominal obesity from the definition of the metabolic syndrome (three or four of: elevated fasting triglyceride levels, lower HDL cholesterol levels, elevated fasting glucose levels, and high blood pressure).

RESULTS—The prevalences of metabolic syndrome among adults in non-, fetal-, and early childhood–, midchildhood-, and late childhood–exposed cohorts were 5.7, 7.7, 8.4, 7.6, and 8.9%, respectively, in 2002.

Table 1 shows that in severely affected famine areas, adults who were exposed to the famine during fetal life had a higher risk of metabolic syndrome, as compared with nonexposed subjects (odds ratio

[OR] 3.13 [95% CI 1.24–7.89, P = 0.016]). No difference was observed in less severely affected famine areas (P for interaction between famine cohort and area = 0.016). Similar associations were observed among adults who were exposed to the famine during early childhood. As compared with the nonexposed subjects, the risks of metabolic syndrome among adults who were exposed to the famine during their early childhood were 2.85 (95% CI 1.19–6.83, P = 0.019) and 0.91 (95% CI 0.55–1.51, P = 0.72) in severely and less severely affected areas, respectively, with a significant interaction between famine cohort and area (P for interaction = 0.026) (Table 1).

Results for the analyses stratified by adult dietary patterns and BMI for the associations of early famine exposure with

metabolic syndrome are shown in Fig. 1. The fetal famine-exposed cohort with a Western diet in later life had a particularly high prevalence of the metabolic syndrome (34.6%), whereas the prevalence among the fetal famine-exposed cohort with a traditional diet in later life was only 4.2% (Fig. 1A1). No significant difference of metabolic syndrome was found in less severely affected area (Fig. 1B1). Similarly, higher prevalences of metabolic syndrome were observed among overweight adults who were exposed to the Chinese famine during their fetal life (22.6%) and early childhood (22.5%) as compared with nonexposed subjects (10.2%) (Fig. 1A2). Among adults with normal weight, the prevalences of metabolic syndrome were low among adults who were exposed to famine during early
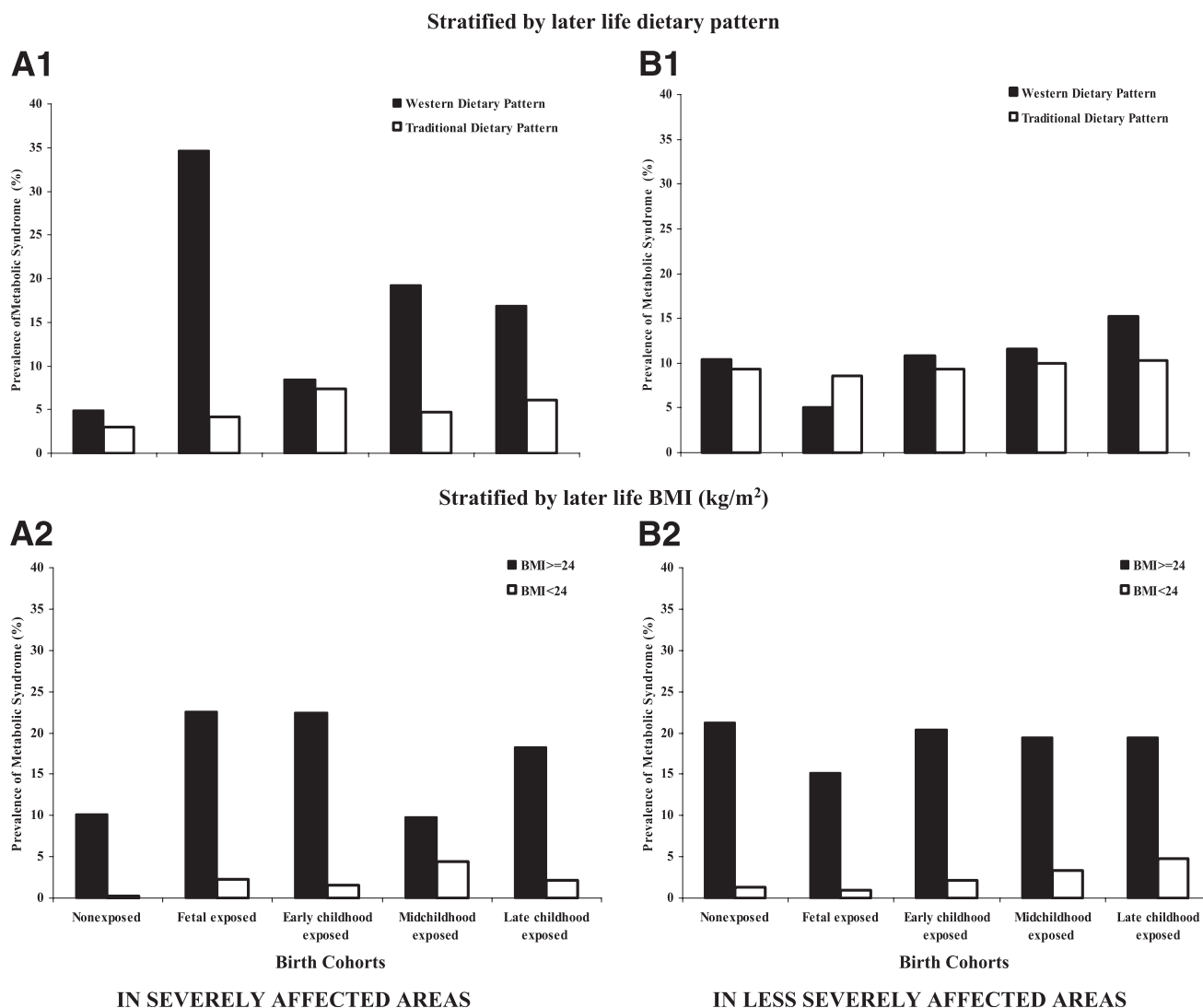
Stratified by later life dietary pattern

Stratified by later life BMI (kg/m²)

IN SEVERELY AFFECTED AREAS   IN LESS SEVERELY AFFECTED AREAS

Figure 1—*Prevalence of metabolic syndrome among birth cohorts according to early life famine exposure and later life dietary patterns (1) and BMI (2) in severely (A) and less severely (B) affected famine areas.*

childhood (1.6%) and fetal period (2.3%) or were not exposed to famine (0.2%) (Fig. 1*A2*). Overweight adults had significantly higher risk of metabolic syndrome regardless of the severity and age period of the famine exposure (Fig. 1*B2*). In sensitivity analysis, applying lower cut points for waist circumference (men ≥90 cm and women ≥80 cm) to the definition of the metabolic syndrome (Supplementary Fig. 1) or excluding abdominal obesity from the definition of the metabolic syndrome (Supplementary Fig. 2) did not materially change the main effect estimates.

CONCLUSIONS—We found that exposure to Chinese famine during fetal life and early childhood was associated with a higher risk of metabolic syndrome in later life. These associations were stronger in subjects who had a Western dietary pattern and subjects who were overweight in adulthood.

Barker et al. (12) and Gluckman and Hanson (13,20) suggested that environmental factors during fetal life and infancy play a role in the origin of the metabolic syndrome and its components. A mismatch between fetal and postnatal environments might exacerbate this effect. To support this hypothesis, the Dutch famine study found that prenatal exposure to famine was associated with higher BMI, higher waist circumference, lower glucose tolerance, higher risk of coronary heart disease, more atherogenic lipid profile, and increased levels of plasma fibrinogen in later life (21). Men who had experienced the siege of Leningrad (1941–1944) during early life had increased mortality from ischemic heart disease and stroke in their adulthood (22). Early life exposure to Chinese famine (1959–1961) was also associated with the increased risk of overweight (9,10), hyperglycemia (8), and hypertension (3) in adult life. The current study provides further evidence that both fetal and infant exposure to severe famine increased the clustering of the metabolic risk factors that predispose a person to type 2 diabetes and cardiovascular disease.

The association between fetal exposure to famine and higher risk of metabolic syndrome was exacerbated by a nutritionally rich environment in later life represented by Western dietary pattern and overweight. This dietary pattern was characterized by high intake of meat, eggs, dairy, sugary beverages, and edible oils and a low intake of vegetables (18).

Our results provide evidence to support the hypothesis that the mismatch between the early life starve environment and later life rich environment magnified the risk of metabolic diseases in later life.

A potential limitation of this study is resident migration across different regions in China, which might lead to misclassification of famine exposure. However, the mobility of the population in rural China is relatively low because relocation of permanent residents needed to be approved by authorities. According to the 2000 China National Population Census, only 2.68% of the rural population lived in provinces other than their birthplaces (23). Therefore, we do not expect that intraprovince migration led to serious misclassification in famine exposure. Another limitation of our study is the lack of birth weight data, which precludes us from examining the interactions between birth weight and adult overweight or dietary patterns on risk of metabolic syndrome.

Despite these limitations, the current study provided a unique opportunity to test the hypothesis of the joint association between early life famine exposure and later life environment with the risk of metabolic syndrome in adulthood. When compared with other famine studies, the Chinese famine lasted much longer and affected more people.

In conclusion, we found that exposure to severe famine in fetal life and infant period was associated with higher risk of metabolic syndrome in adulthood. A nutritionally rich environment, represented by a Western dietary pattern and overweight, further strengthened the association. Our study indicates that both the early life environment and later life overnutrition are critical for the cardiometabolic health in adult life.

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