

Exposure to the Chinese Famine in Early Life and the Risk of Hyperglycemia and Type 2 Diabetes in Adulthood

Yanping Li,^{1,2} Yuna He,^{1,3} Lu Qi,^{2,4} Vincent W. Jaddoe,^{2,5} Edith J.M. Feskens,³ Xiaoguang Yang,¹ Guansheng Ma,¹ and Frank B. Hu^{2,4}

OBJECTIVE—Early developmental adaptations in response to undernutrition may play an essential role in susceptibility to type 2 diabetes, particularly for those experiencing a “mismatched rich nutritional environment” in later life. We examined the associations of exposure to the Chinese famine (1959–1961) during fetal life and childhood with the risk of hyperglycemia and type 2 diabetes in adulthood.

RESEARCH DESIGN AND METHODS—We used the data for 7,874 rural adults born between 1954 and 1964 in selected communities from the cross-sectional 2002 China National Nutrition and Health Survey. Hyperglycemia was defined as fasting plasma glucose ≥ 6.1 mmol/l and/or 2-h plasma glucose ≥ 7.8 mmol/l and/or a previous clinical diagnosis of type 2 diabetes.

RESULTS—Prevalences of hyperglycemia among adults in nonexposed, fetal exposed, early-childhood, mid-childhood, and late-childhood exposed cohorts were 2.4%, 5.7%, 3.9%, 3.4%, and 5.9%, respectively. In severely affected famine areas, fetal-exposed subjects had an increased risk of hyperglycemia compared with nonexposed subjects (odds ratio = 3.92; 95% CI: 1.64–9.39; $P = 0.002$); this difference was not observed in less severely affected famine areas (odds ratio = 0.57; 95% CI: 0.25–1.31; $P = 0.185$). The odds ratios were significantly different between groups from the severe and less severe famine areas (P for interaction = 0.001). In severely affected famine areas, fetal-exposed subjects who followed an affluent/Western dietary pattern (odds ratios = 7.63; 95% CI: 2.41–24.1; $P = 0.0005$) or who had a higher economic status in later life experienced a substantially elevated risk of hyperglycemia (odds ratios = 6.20; 95% CI: 2.08–18.5; $P = 0.001$).

CONCLUSIONS—Fetal exposure to the severe Chinese famine increases the risk of hyperglycemia in adulthood. This association appears to be exacerbated by a nutritionally rich environment in later life. *Diabetes* 59:2400–2406, 2010

From the ¹National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing, China; the ²Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the ³Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands; the ⁴Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the ⁵Departments of Epidemiology and Pediatrics, Erasmus MC, Rotterdam, the Netherlands.

Corresponding authors: Yanping Li, liyanping72@yahoo.com; or Guansheng Ma, mags@chinacdc.net.cn; or Frank B. Hu, nhbfh@channing.harvard.edu. Received 19 March 2010 and accepted 24 June 2010. Published ahead of print at <http://diabetes.diabetesjournals.org> on 9 July 2010. DOI: 10.2337/db10-0385.

Y.L. and Y.H. contributed equally to this study.

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

See accompanying commentary, p. 2349.

The developmental origins hypothesis postulates that adaptations in response to fetal undernutrition lead to metabolic and structural changes, which are beneficial for early survival, but may increase the risk of common diseases such as type 2 diabetes in adulthood (1,2). The risks of adverse long-term consequences are further increased in a nutritionally rich environment in later life (1,2). Indirect support for this hypothesis comes from studies showing consistent associations of low birth weight with increased risks of type 2 diabetes (2,3). Because of ethical and practical reasons, direct evidence connecting fetal malnutrition and later diabetes risk in humans is sparse. Famine periods provide unique opportunities to investigate these relationships. Ravelli et al. (4) and de Rooij et al. (5) showed that adults who had been exposed to the Dutch famine during World War II had higher insulin resistance measures than those who had not been exposed. However, this association was not observed in another famine cohort study, the Leningrad Siege Study (6). These inconsistent results may be caused by differences in postnatal environmental life exposures. Although the Dutch population rapidly developed into a wealthy and rich population after the famine, the Leningrad cohort remained relatively poor.

The Chinese famine lasted from the late 1950s to the early 1960s and caused millions of excess deaths (7). It was more devastating in rural areas. The most severe period with the highest mortality rate was between 1959 and 1961 (8). Fetal exposure to the Chinese famine has been associated with risks of overweight and schizophrenia in adult life (7,9–12). However, no study has examined the Chinese famine effects in early life on the risk of abnormalities in glucose metabolism and diabetes.

We used data from the 2002 China National Nutrition and Health Survey (CNNHS) to examine the associations between famine exposure in fetal life and childhood with risks of hyperglycemia and type 2 diabetes in adulthood, and to examine whether a nutritionally rich environment in later life modifies these associations.

RESEARCH DESIGN AND METHODS

The 2002 CNNHS is a nationally representative cross-sectional study on nutrition and chronic diseases. A stratified, multistage probability cluster sampling design was used in this survey (13). Based on socioeconomic characteristics, the country was divided into six regions. As shown in Fig. 1, in the first stage of sampling, 22 counties were randomly selected from each of the 6 regions in China. In the second stage, three townships were randomly selected from each of the selected counties. From each of the townships, 2 residential villages were randomly selected; and 90 households were then randomly sampled from each village for physical examination. One-third of the households were selected to participate in the dietary survey and blood draw. For the present study, we used residents who were living in rural areas and were born between October 1, 1952, and September 30, 1964, as our

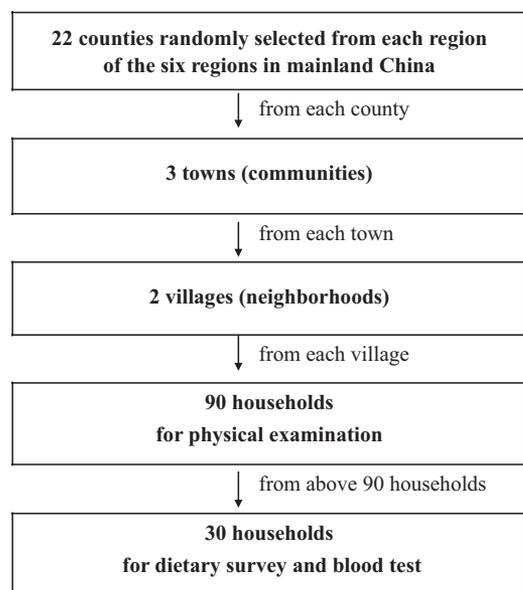


FIG. 1. Flow chart on the sampling method in each region* of the 2002 China National Nutrition and Health Survey. *The mainland of China is classified into 6 regions defined by the Chinese Bureau of Statistics according to their socioeconomic development. They are metropolis, general city, type I rural site, type II rural site, type III rural site, and type IV rural site.

analytic population. To minimize misclassification of the exposure periods, subjects who were born between October 1, 1958, and September 30, 1959, and between October 1, 1961, and September 30, 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. Our total sample size was 7,874 people.

Famine cohorts and areas. Subjects were categorized into five exposure cohorts: nonexposed cohort, fetal-exposed cohort, early childhood-exposed cohort, mid childhood-exposed cohort, and late childhood-exposed cohort. All cohorts were defined according to the subjects' birth dates. Subjects who were born between October 1, 1962, and September 30, 1964, were classified as the nonexposed cohort; and subjects who were born between October 1, 1959, and September 30, 1961, were classified as fetal-exposed cohort. Subjects who were born between October 1, 1952, and September 30, 1958, were grouped by every 2 years and were classified into one of the three childhood-exposed cohorts. Mean ages for subjects in nonexposed cohort, fetal-exposed cohort, early childhood-exposed cohort, mid childhood-exposed cohort, and late childhood-exposed cohort were 39, 42, 45, 47, and 49 years, respectively.

The Chinese famine affected the entire mainland of China, but the severity varied across regions due to different weather conditions, population density, and local policies regarding food shortage (7). As previously described, we used the excess death rate of each province to determine the severity of the famine (7). The excess death rate was calculated as the percentage change in mortality rate from the mean level in 1956–1958 to the highest value during the period 1959–1961 (7). An excess death rate of 50% was used as the threshold: regions that had an equal or higher rate than this cutoff were categorized as severely affected famine areas, and otherwise as less severely affected famine areas. We split all five cohorts into severely affected famine areas and less severely affected famine areas. This enabled us to test the hypothesis that the famine effect is stronger in the severely affected famine areas than that in the less severely affected famine areas and to consider both birth cohort effects and regional differences.

Assessments of blood glucose and type 2 diabetes. All subjects were invited for blood collection after an ~10 to 14 h overnight fast. The plasma was separated by centrifugation at 3,200 rpm for 10–15 min within 1 h of collection, and kept at room temperature without sunshine. Fasting plasma glucose (FPG) concentration was measured using the glucose oxidize enzymatic method within 3 h of plasma preparation. Every tenth sample was measured twice (the correlation coefficient of duplicate measurements was 0.98). All individuals had fasting glucose levels measured. A 75-g oral glucose tolerance test was performed in subjects whose FPG was ≥ 5.5 mmol/l. We used criteria proposed by the WHO Expert Committee on Diabetes Mellitus (14). Type 2 diabetes was defined as FPG ≥ 7 mmol/l and/or 2-h plasma glucose ≥ 11.1 mmol/l. Hyperglycemia was defined as FPG ≥ 6.1 mmol/l and/or

2-h plasma glucose ≥ 7.8 mmol/l, including impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes. In addition, subjects who had been previously diagnosed with type 2 diabetes were added as cases of hyperglycemia and type 2 diabetes.

Stratification factors. Dietary patterns, economic status, and BMI measured in 2002 were used as measures of the nutritional environment in adulthood and to examine the “mismatch” between fetal nutrition and adult nutrition.

The method for assessing dietary patterns has been described in detail elsewhere (15). Briefly, four dietary patterns were derived through cluster analysis, which were labeled as “green water,” “yellow earth,” “new affluence,” and “Western adopter.” “Green water” and “yellow earth” patterns represent the traditional Chinese diets in the South and the North, respectively, whereas the other two represent Westernized dietary patterns. In this study, we combined the clusters of “green water” and “yellow earth” as the traditional dietary pattern, and we combined the clusters of “new affluence” and “Western adopter” as the affluent/Western pattern.

Current economic status was assessed by the mean annual income in the year prior to the 2002 CNHNS, which was treated as a dichotomous variable. The mean level of the current sample (2,000 Chinese yuan per person per year) was used as a cutoff point for economic status.

BMI was calculated by measured height and fasting body weight. We used the criteria recommended for Chinese adults and classified subjects as overweight if BMI ≥ 24 kg/m², or otherwise normal (16).

The protocol of the 2002 CNHNS 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.

Statistical analyses. We performed survey analyses with SAS 9.2 for Windows (SAS Institute, Cary, NC) to estimate statistics for this complex, multistage-designed survey sample. Survey weights were derived from the 2000 China National Population Census and associated administrative data. The population of 2000 China National Population Census was also used for sex standardization.

Mean FPG differences between the exposed cohorts and the nonexposed cohort were tested by generalized least squares estimation (17). Risks of hyperglycemia and type 2 diabetes among fetal and childhood-exposed subjects, compared with nonexposed subject, were examined with the method of maximum likelihood by using the survey logistic regression model. Interaction between famine exposure cohort (fetal- or childhood-exposed vs. nonexposed) and area (severely affected and less severely affected) was tested by adding a multiplicative factor in the survey logistic regression model. Analyses were adjusted for sex, family history of diabetes, 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 hyperglycemia were affected by an improved nutritional environment in later life, we subsequently stratified the analyses by dietary patterns, economic status and BMI in adulthood. Prevalence of hyperglycemia was plotted according to cohort and classification of the stratification factors. The odds ratio of hyperglycemia in the fetal-exposed cohort compared with the nonexposed cohort was calculated within each category of the stratified factor.

To distinguish severely and less severely affected famine areas more appropriately, we performed sensitivity analysis by using a more stringent cutoff point, i.e., we used an excess death rate $\geq 100\%$ to define the severity of famine. In addition, we performed analyses by using the cohort born during October 1, 1962, to September 30, 1968, as a nonexposed cohort for association analyses, or by excluding participants with a family history of diabetes.

RESULTS

Basic characteristics of the study population are shown in Table 1. In our main study population ($n = 7,874$), 1,005 (12.8%) subjects had been exposed to the Chinese famine during fetal life, and 4,915 (62.4%) subjects had been exposed during childhood. As compared with the nonexposed individuals, fetal-exposed subjects were 0.9 cm shorter as adults, and childhood-exposed subjects were 1.5 cm shorter (Table 1). The prevalence of hyperglycemia among adults in the nonexposed, fetal-exposed, early childhood-, mid childhood-, and late childhood-exposed birth cohorts was 2.4%, 5.7%, 3.9%, 3.4%, and 5.9%, respectively.

In severely affected famine areas, FPG concentration was significantly higher in the fetal-exposed cohort than in the nonexposed cohort with a mean difference of 0.20

TABLE 1
Basic characteristics of study population according to Chinese famine exposure

	Childhood-exposed cohorts			Fetal-exposed cohort	Nonexposed cohort
	Late childhood	Mid childhood	Early childhood		
<i>N</i>	1,673	1,588	1,654	1,005	1,954
Severely affected area	896	888	940	503	1,132
Less severely affected area	777	700	714	502	822
Birth date					
(From October 1, year)	1952	1954	1956	1959	1962
(To September 30, year)	1954	1956	1958	1961	1964
Age in 2002 (years)	48–49	46–47	44–45	41–42	38–39
Women (%)	54.0	54.2	54.0	53.2	55.5
Height (cm)*	159.3 (0.2)†	159.4 (0.4)†	159.4 (0.2)†	160.0 (0.4)†	160.9 (0.2)
Weight (kg)**	59.4 (0.4)	58.9 (0.5)	59.0 (0.05)	59.6 (0.5)	59.2 (0.3)
BMI (kg/m ²)**	23.3 (0.1) †	23.1 (0.2)	23.2 (0.2)	23.2 (0.2)	22.9 (0.1)
Fasting plasma glucose (mmol/l)**	4.99 (0.05)†	4.88 (0.04)†	4.87 (0.04)†	4.88 (0.05)†	4.77 (0.03)
Hyperglycemia (%)*	5.89†	3.40	3.93	5.65†	2.43
Type 2 diabetes (%)*	3.89†	1.69	2.78	1.70	1.57

*Sex standard. **Data are adjusted means (SE). Adjusted factors included sex, educational level, family history of diabetes (only for glucose), current smoking, alcohol use, and physical activity level. Height was adjusted only for sex. †Compared with the nonexposed cohort, †*P* < 0.05.

mmol/l (95% CI: 0.06–0.35, *P* = 0.007). No significant difference was observed in the less severely affected famine areas (*P* for interaction = 0.001, Table 2). Compared with nonexposed subjects, FPG was higher in the late childhood-exposed cohort in both the severely affected famine areas and less severely affected famine areas. Differences were not significant for the early and

mid childhood-exposed cohorts. A significant interaction between the exposed cohort and areas was found only for the fetal-exposed cohort (Table 2).

Subjects exposed to famine during fetal life in severely affected famine areas had a higher prevalence of hyperglycemia than the nonexposed cohort. This difference was not significant in the less severely affected famine areas.

TABLE 2
Concentrations of fasting plasma glucose and prevalence rates of hyperglycemia and type 2 diabetes by birth cohort and severity of the Chinese famine area

	Childhood-exposed cohorts*			Fetal-exposed cohort	Nonexposed cohort
	Late childhood	Mid childhood	Early childhood		
Fasting plasma glucose					
Severely affected famine area					
Mean (SE, mmol/l)	4.95 (0.07)	4.84 (0.04)	4.87 (0.05)	4.95 (0.07)	4.75 (0.03)
<i>P</i>	0.008	0.059	0.037	0.007	Ref.
Less severely affected famine area					
Mean (SE, mmol/l)	5.09 (0.09)	4.97 (0.08)	4.88 (0.04)	4.73 (0.04)	4.81 (0.05)
<i>P</i>	0.011	0.113	0.321	0.234	Ref.
<i>P</i> for interaction between area and cohort	0.898	0.793	0.271	<0.0001	
Hyperglycemia					
Severely affected famine area					
Prevalence (%)	5.19	2.68	3.76	7.29	2.02
Odds ratio (95% CI)	2.38 (1.11–5.11)	1.21 (0.57–2.55)	1.77 (0.82–3.83)	3.92 (1.64–9.39)	Ref.
Less severely affected famine area					
Prevalence (%)	7.17	5.22	4.34	2.14	3.46
Odds ratio (95% CI)	2.27 (1.02–5.06)	1.94 (0.80–4.72)	1.16 (0.56–2.40)	0.57 (0.25–1.31)	Ref.
<i>P</i> for interaction between area and cohort	0.542	0.766	0.341	0.001	
Type 2 diabetes					
Severely affected famine area					
Prevalence (%)	3.51	1.19	2.90	2.01	1.37
Odds ratio (95% CI)	2.51 (0.91–6.87)	0.75 (0.26–2.12)	2.07 (0.82–5.24)	1.43 (0.53–3.87)	Ref.
Less severely affected famine area					
Prevalence (%)	4.60	2.99	2.48	1.08	2.08
Odds ratio (95% CI)	2.34 (0.72–7.62)	1.86 (0.53–6.45)	1.02 (0.35–2.93)	0.41 (0.12–1.35)	Ref.
<i>P</i> for interaction between area and cohort	0.606	0.424	0.243	0.102	

*Data are adjusted means (SE) for fasting plasma glucose, sex standard prevalence, and odds ratio for hyperglycemia and diabetes. All odds ratios use a nonexposed cohort as the reference cohort. Adjusted factors included sex, education level, family history of diabetes, and current smoking, alcohol use, and physical activity level.

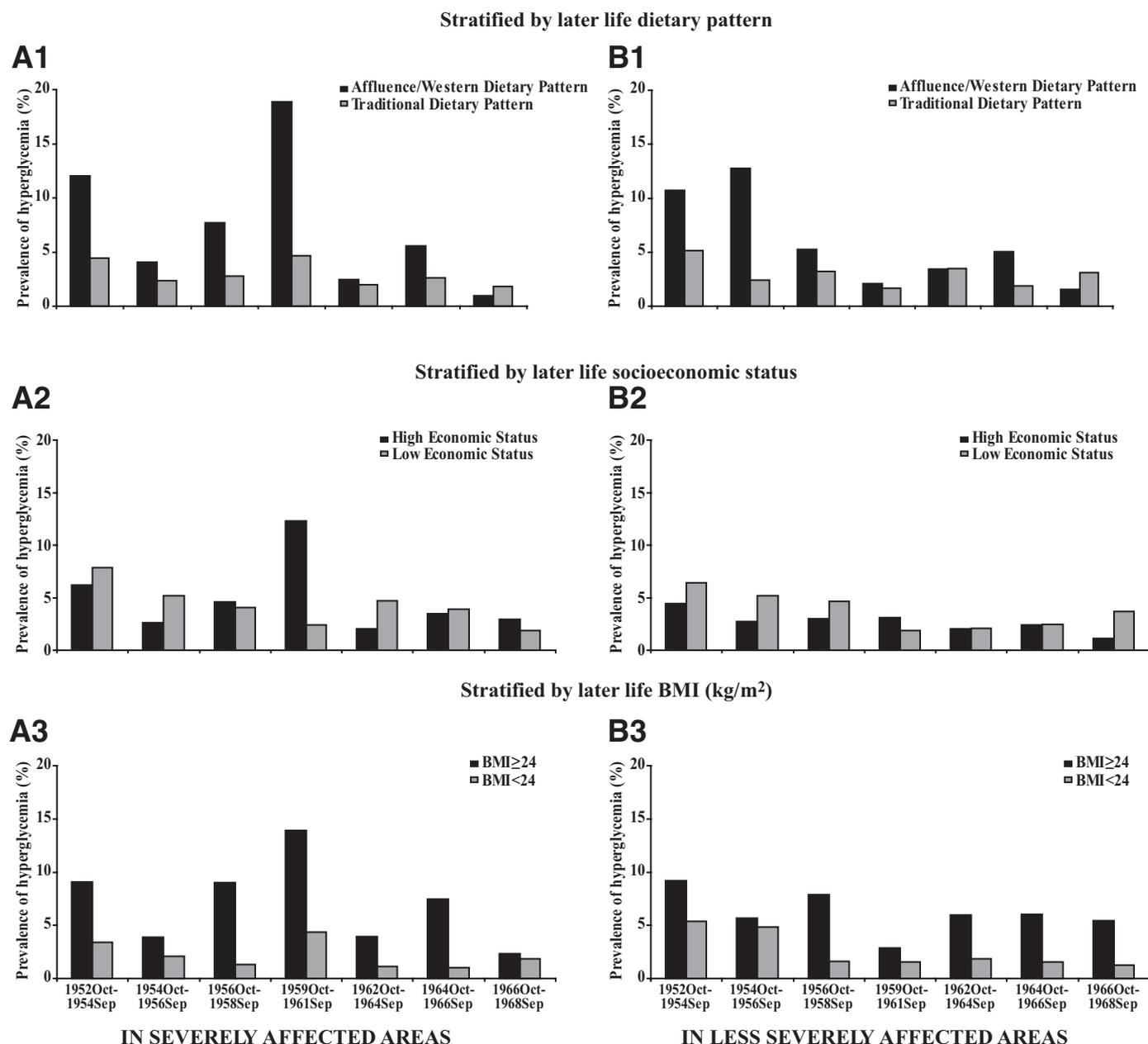


FIG. 2. Prevalence of hyperglycemia among birth cohorts according to early life famine exposure and later life dietary patterns (A1 and B1), socioeconomic status (A2 and B2), and BMI (A3 and B3) in severely (column A) and less severely affected famine areas (column B).

The odds ratios were significantly different between the severe and less severe famine areas (Table 2), suggesting a stronger famine effect in the severely affected famine areas. Compared with the nonexposed cohort, subjects in the late childhood-exposed cohort had a higher risk of hyperglycemia in both severely and less severely affected famine areas, but the odds ratios were not significantly different between the severe and less severe famine areas (Table 2).

A significantly higher prevalence of type 2 diabetes was observed among subjects exposed in late childhood as compared with the nonexposed cohort (Table 1). However, Table 2 shows that after stratification of this group by severity of famine exposure, no significant difference of type 2 diabetes risk was observed anymore between different famine cohorts.

Stratified analyses by dietary pattern, economic status,

and BMI for severely affected famine areas are shown in Fig. 2. Figure 2A1 shows that the prevalence of hyperglycemia was highest (18.9%) in subjects in the fetal-exposed cohort and who consumed an affluent/Western diet. As compared with the relatively nonexposed cohort, the odds ratio of hyperglycemia in the fetal-exposed cohort was 7.63 (95% CI: 2.41–24.1, $P = 0.0005$) for those who had an affluent/Western dietary pattern, and 2.34 (95% CI: 0.82–6.70, $P = 0.112$) for those with a traditional dietary pattern.

Figure 2A2 shows that as compared with nonexposed subjects, the odds ratio of hyperglycemia in the fetal-exposed cohort was 6.20 (95% CI: 2.08–18.5, $P = 0.001$) in subjects with a higher adult economic status, and 1.68 (95% CI: 0.50–5.71, $P = 0.404$) in subjects with a lower adult economic status. Figure 2A3 shows that overweight subjects in the fetal-exposed cohort had the highest prevalence of hyperglycemia (13.9%). However, the risks of

TABLE 3
Prevalence rate of hyperglycemia by birth cohorts and severity of famine areas: sensitivity analyses

	Childhood-exposed cohorts			Fetal-exposed cohort	Nonexposed cohort
	Late childhood	Mid childhood	Early childhood		
Defining severity of famine by excess death rate $\geq 100\%$					
Severely affected famine area					
Prevalence (%)	3.92	2.56	2.60	8.11	1.39
Odds ratio (95% CI)	2.15 (0.90–5.14)	1.56 (0.62–3.88)	1.80 (0.66–4.92)	6.28 (2.16–18.3)	
Less severely affected famine area					
Prevalence (%)	7.92	4.42	5.32	3.39	3.74
Odds ratio (95% CI)	2.54 (1.24–5.20)	1.33 (0.62–2.88)	1.40 (0.68–2.88)	0.89 (0.42–1.90)	
<i>P</i> for interaction between area and cohort	0.492	0.373	0.362	0.003	
Classifying adults born during October 1, 1962, to September 30, 1968, as nonexposed cohort					
Severely affected famine area					
Prevalence (%)	5.19	2.68	3.76	7.29	3.11
Odds ratio (95%CI)	2.18 (1.21–3.93)	1.10 (0.59–2.03)	1.51 (0.79–2.87)	3.38 (1.55–7.36)	
Less severely affected famine area					
Prevalence (%)	7.17	5.22	4.34	2.14	2.33
Odds ratio (95% CI)	2.47 (1.34–4.53)	1.83 (0.86–3.91)	1.30 (0.74–2.30)	0.61 (0.30–1.26)	
<i>P</i> for interaction between area and cohort	0.966	0.395	0.693	0.001	
Excluding people with family history of diabetes					
Severely affected famine area					
Prevalence (%)	5.06	2.64	3.51	7.08	1.98
Odds ratio (95% CI)	2.40 (1.10–5.22)	1.23 (0.57–2.63)	1.73 (0.78–3.86)	4.00 (1.64–9.73)	
Less severely affected famine area					
Prevalence (%)	6.03	5.02	3.93	2.16	3.10
Odds ratio (95% CI)	2.41 (1.00–5.81)	1.83 (0.71–4.70)	1.30 (0.61–2.77)	0.67 (0.29–1.563)	
<i>P</i> for interaction between area and cohort	0.505	0.826	0.488	0.003	

All odds ratios used the nonexposed cohort as the reference cohort. Adjusted factors include sex, educational level, family history of diabetes, and current smoking, alcohol use, and physical activity level in 2002.

hyperglycemia were largely comparable in these two groups; the odds ratio of hyperglycemia in the fetal-exposed cohort was 3.71 (95% CI: 1.13–12.2, $P = 0.031$) in overweight subjects and 4.37 (95% CI: 1.15–16.5, $P = 0.030$) in normal weight subjects, respectively, compared with the nonexposed cohort. Similar analyses were performed in subjects exposed to less severely affected famine areas during fetal life and childhood (Fig. 2, right column, graphs B1, B2, and B3), but did not show consistent associations.

When we defined the severely affected famine areas as those with an excess death rate $\geq 100\%$, the prevalence of hyperglycemia among the fetal-exposed cohort in severely affected famine areas increased to 8.1%, but this did not change the associations between fetal exposure to famine and risk of hyperglycemia in adulthood. In addition, neither using subjects who were born between October 1, 1962, and September 30, 1968, as a nonexposed cohort nor excluding subjects with a family history of diabetes materially changed the associations (Table 3).

DISCUSSION

In this study of a large sample of Chinese adults, we found a significant association between severe famine exposure during the fetal period and an increased risk of hyperglycemia in adulthood. This association was stronger in subjects with a Western dietary pattern or higher eco-

nomics status in adulthood. No consistent association was observed between famine exposure during childhood and hyperglycemia.

Several mechanisms might explain the associations between fetal famine exposure and risk of diabetes in later life. Exposure to extreme starvation in rats led to poor development of pancreatic β -cell mass and function and insulin resistance, which might persist in later life (18). A poor intrauterine environment may also reduce skeletal muscle development (19), which may subsequently lead to insulin resistance in peripheral tissues (20). It has also been suggested that stress suffering from fetal famine exposure could change the setpoint of the hypothalamic-pituitary-adrenal (HPA) axis, which could result in long-term changes in secretion of neuroendocrine mediators of the stress response, and predispose to cardiovascular and metabolic disease in later life (21,22).

To our knowledge, thus far three studies have assessed the associations of exposure to famine with measures of glucose intolerance. These studies were performed in the Netherlands (the Dutch Famine Study) (4,5), Russia (the Leningrad Siege Study) (6), and China (our Chinese Famine Study). The Dutch Famine Study reported higher 2-h glucose and insulin levels among subjects who were exposed to famine during fetal life (4,5), but this association was not observed in the Leningrad Siege Study

(6). The inconsistent results might be due to differences in postnatal environmental life exposures. Although the Dutch population rapidly developed into a wealthy and rich population after the famine, the Leningrad people remained relatively poor. In our study, we observed that fetal exposure to the severe Chinese famine increases the risk of hyperglycemia in adulthood, which was exacerbated by an unhealthy adult diet and higher economic status. Our results support the hypothesis that exposure to a nutritionally rich environment modifies the association between fetal famine exposure and disease in later life (1,20,23).

The association between fetal famine exposure and hyperglycemia was stronger in participants with an affluent/Western dietary pattern. These subjects were, to a large extent, less poor and more highly educated (15), and they have benefited most from dramatically enhanced economic opportunities and have broken away from traditional Chinese food patterns (15). Their diet is characterized by a high intake of meat, eggs, dairy, sugary beverages, edible oils, and a low vegetable use (15). Apparently, this nutrition “rich” environment did not match the fetal starvation environment that people of fetal exposed cohort experienced, which in turn increased the risk of hyperglycemia in later life (1,20,23).

Our study used annual mean income as the cutoff to categorize economic status (2,000 Chinese yuan/person/year). Subjects in the lower economic group might consume mostly traditional plant foods with little meat. Therefore, the discrepancy between the nutritional environment in adulthood and fetal undernutrition conditions may be less evident for those with a higher economic status. In other words, there was probably greater “mismatch” between in utero and adulthood environments in the higher economic group, which triggered an increased prevalence of hyperglycemia in the fetal-exposed cohort.

Overweight may also represent a nutritional “rich” environment. Overweight subjects in the fetal-exposed cohort had the highest prevalence of hyperglycemia. Similar results were described in the Dutch Famine Study (4), showing that 2-h glucose concentrations were especially high among people exposed to the famine during fetal life and who became obese in later life. However, the relative risk of hyperglycemia in overweight subjects was not different from that in normal weight subjects. This may be partly due to the increased prevalence of hyperglycemia in the nonexposed cohort in overweight subset. These results therefore indicate that both improving fetal nutritional environmental and controlling BMI in later life are important for prevention of a disturbed glucose metabolism.

Childhood nutritional status, particularly during infancy, is another key factor in influencing the propensity to develop disease in adulthood (23). Animal studies have shown that postnatal caloric restriction might hamper β -cell development (24) and might disturb glucose metabolism in later life in rats (25). Our study found significantly increased FPG in the early childhood-exposed cohort in the severely affected famine areas, but no significant differences in FPG in the less severely affected famine areas. We also observed a higher risk of hyperglycemia among subjects exposed in late childhood in both severely and less severely affected famine areas. These results suggest that famine exposure during childhood may increase the risk of hyperglycemia in later life. However, we cannot exclude a potential cohort effect, such as aging

(26). Similar risks of hyperglycemia among subjects exposed during childhood in both famine-exposed areas and nonfamine-exposed areas suggest rather a cohort (older age) effect than a famine effect. However, since almost all rural regions in China were affected by the famine during 1959–1961, no valid nonfamine-exposed cohort comprising subjects born in the same time period was available. Thus, the association between childhood exposure to famine and risk of hyperglycemia needs to be studied in more detail.

Some limitations should be noticed. First, we assumed that the residents we investigated at the time of the survey were born in the same province and in a similar rural area. This may not be the case for all of our subjects. However, severe restrictions on migration and relocation in China made our sample quite stable. Migration with permanent resident permission still needed to be approved by authorities on a case-by-case basis in China. According to the 2000 China National Population Census, 2.68% of the rural population lived in provinces other than the provinces of their birthplaces (27). Our study sample was based on the residence registration system; only subjects with permanent resident permission in local areas were involved in our study. Therefore, we do not expect that intraprovince migration leading to measurement error in the coding of birth place is a major concern in our results (12). Second, subjects in our fetal-exposed cohort may have actually experienced severe famine during both the fetal period and the infancy period because the famine lasted approximately 3 years. It was therefore difficult to distinguish whether the fetal period or the infancy period was more important. However, the early childhood cohort also included subjects exposed to famine in infancy, which did not have a substantial influence on the risk of hyperglycemia. Thus, our results indicate that the fetal period should be considered as the primary critical period. Third, our subjects who experienced severe famine in the fetal period were in their early 40s in 2002, and the cases of type 2 diabetes were few. The small numbers may partly explain why we did not observe significant associations with the risk of type 2 diabetes. We used the excess death rate as an indirect measure of famine exposure. With this method, we could not distinguish death due to famine from death due to unfavorable weather conditions or infections. We also did not have reliable information about individual food availability during the famine period. Therefore, from our data, we cannot conclude that the higher risk of hyperglycemia among subjects exposed to famine is exclusively due to malnutrition in early life. However, nutrition deficiency was highly prevalent during the Chinese famine. China's grain output declined by 15% in 1959 and in the following 2 years, and its food supply plunged further to 70% of its 1958 level (8). As almost all foods were delivered through communal kitchens at that time, no social groups were spared from the effects of the famine (9). In addition, we did not have data on birth size and childhood growth. However, since the famine effect on glucose intolerance did not depend on birth size in the Dutch Famine Study (4), we do not consider the lack of information about individual birth outcomes as a major limitation.

In conclusion, we found that exposure to severe famine in fetal life increased the risk of hyperglycemia in adulthood. The “mismatched nutrition postnatal environment” represented by a Western dietary pattern and improved economic status further increased susceptibility to hyper-

glycemia in those who experienced fetal exposure to famine. Together with previous studies, our study emphasizes that early life environment is critical for the risk of hyperglycemia in adult life.

ACKNOWLEDGMENTS

The 2002 CNNHS was supported by the Ministry of Health and the Ministry of Science and Technology in China (2001-DEA30035, 2003-DIA6N008), UNICEF, WHO, Unilever China, and Danone Nutrition Institute China. V.W.J. also acknowledges personal funding from the Netherlands Organization for Health Research (ZonMw 90700303). Y.L. was also a Takemi fellow in the Department of Global Health and Population at the Harvard School of Public Health. No other potential conflicts of interest relevant to this article were reported.

Y.L. had full access to all of the data in the study, analyzed the data, contributed to the discussion, interpretation of the data, and the manuscript writing, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y.H. had full access to all of the data in the study, analyzed the data, contributed to the discussion, interpretation of the data, and the manuscript writing. G.M. and X.Y. were the principal investigators of the 2002 CNNHS, contributed to the discussion, interpretation of the data, and the manuscript writing. V.W.J. and L.Q. contributed to the analysis framework, interpretation of the data, the discussion, and the writing of the manuscript. E.J.M.F. contributed to the discussion and interpretation of the data. F.B.H. contributed to the discussion, interpretation of the data, and manuscript writing, and conceptualized and supervised the study.

The authors thank all team members and participants from the 31 provinces in the 2002 CNNHS.

REFERENCES

- Gluckman PD, Hanson MA, Bateson P, Beedle AS, Law CM, Bhutta ZA, Anokhin KV, Bougnères P, Chandak GR, Dasgupta P, Smith GD, Ellison PT, Forrester TE, Gilbert SF, Jablonka E, Kaplan H, Prentice AM, Simpson SJ, Uauy R, West-Eberhard MJ. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *Lancet* 2009;373:1654–1657
- Hales CN, Barker DJP. The thrifty phenotype hypothesis. *Br Med Bull* 2001;60:5–20
- Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsén T, Grill V, Gudnason V, Hulman S, Hyppönen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;300:2886–2897
- Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998;351:173–177
- de Rooij SR, Painter RC, Roseboom TJ, Phillips DI, Osmond C, Barker DJ, Tanck MW, Michels RP, Bossuyt PM, Bleker OP. Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. *Diabetologia* 2006;49:637–643
- Stanner SA, Bulmer K, Andrès C, Lantseva OE, Borodina V, Poteen VV, Yudkin JS. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad Siege Study, a cross sectional study. *BMJ* 1997;315:1342–1348
- Luo Z, Mu R, Zhang X. Famine and overweight in China. *Rev Agricultural Econ* 2006;28:296–304
- Yang DT. China's agricultural crisis and famine of 1959–1961: a survey and comparison of Soviet famines. *Comparative Economic Studies* 2008;50:1–29
- St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P, He L. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. *JAMA* 2005;294:557–562
- Yang Z, Zhao W, Zhang X, Mu R, Zhai Y, Kong L, Chen C. Impact of famine during pregnancy and infancy on health in adulthood. *Obes Rev* 2008;9(Suppl. 1):S95–99
- Wang Y, Wang X, Kong Y, Zhang JH, Zeng Q. The great famine leads to shorter and overweight females in Chongqing Chinese population after 50 years. *Obesity* 2010;18:588–592
- Chen Y, Zhou LA. The long-term health and economic consequences of the 1959–1961 famine in China. *J Health Econ* 2007;26:659–681
- Wang L. Report of China Nationwide Nutrition and Health Survey 2002 (1): Summary Report. Beijing, China, People's Medical Publishing House, 2000
- Puavilai G, Chanprasertyotin S, Sriprapadaeng A. Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO Consultation criteria, and 1985 WHO criteria. *Diabetes Res Clin Pract* 1999;44:21–26
- He Y, Ma G, Zhai F, Li Y, Hu Y, Feskens EJ, Yang X. Dietary patterns and glucose tolerance abnormalities in Chinese adults. *Diabetes Care* 2009;32:1972–1976
- Cooperative Meta-analysis Group of China Obesity Task Force. Predictive value of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. *Zhong Hua Liu Xing Bing Xue Za Zhi* 2002; 23:5–10. (in Chinese)
- Spritzer K, Hays RD, Liu H. Adjusting for clustering (non-independence among observations) using SAS. 2008. From the University of California Los Angeles website. Available from http://gim.med.ucla.edu/FacultyPages/Hays/UTILS/svyreg_032808.doc. Accessed 30 Jan 2010
- Fowden AL, Hill DJ. Intra-uterine programming of the endocrine pancreas. *Br Med Bull* 2001;60:123–142
- Yajnik CS, Fall CHD, Coyaji KJ, Hirve SS, Rao S, Barker DJ, Joglekar C, Kellingray S. Neonatal anthropometry: the thin-fat Indian baby: the Pune Maternal Nutrition Study. *Int J Obes Relat Metab Disord* 2003;27:173–180
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359:61–73
- Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 2001;13:113–128
- Clark PM. Programming of the hypothalamo-pituitary-adrenal axis and the fetal origins of adult disease hypothesis. *Eur J Pediatr* 1998;157(Suppl. 1):S7–10
- Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004;305:1733–1736
- Garofano A, Czernichow P, Bréant B. Beta-cell mass and proliferation following late fetal and early postnatal malnutrition in the rat. *Diabetologia* 1998;41:1114–1120
- Garofano A, Czernichow P, Bréant B. Effect of ageing on beta-cell mass and function in rats malnourished during the perinatal period. *Diabetologia* 1999;42:711–718
- Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090–1101
- State Statistical Bureau. *Quanguo Gesheng Zizhiqu Zhixishi Lishi Tongji Ziliao Huibian, 1949–1989 (A Compilation of Historical Statistical Data of Provinces, Autonomous Regions, and Municipalities)*. Beijing China Statistical Press, 1990