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

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

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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 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

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See accompanying commentary, p. 2349.
used criteria proposed by the WHO Expert Committee on Diabetes Mellitus
invited for blood collection after an
Assessments of blood glucose and type 2 diabetes.

To explore whether the associations between fetal exposure to severe
famine and hyperglycemia were affected by an improved nutritional environ-
ment 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.

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 nonex-
posed 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
2-h plasma glucose ≥7.8 mmol/l, including impaired fasting glucose, impaired
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
earlier (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 CNNHS, 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 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.

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 examine whether the associations between fetal exposure to severe
famine and hyperglycemia were affected by an improved nutritional environ-
ment 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 ≥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 associa-
tion analyses, or by excluding participants with a family history of diabetes.

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 expo-
sure 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
concentration was measured using the glucose oxidase 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
≤FPG >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.
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 1
Basic characteristics of study population according to Chinese famine exposure

<table>
<thead>
<tr>
<th></th>
<th>Childhood-exposed cohorts</th>
<th>Fetal-exposed cohort</th>
<th>Nonexposed cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late childhood</td>
<td>Mid childhood</td>
<td>Early childhood</td>
</tr>
<tr>
<td>Severely affected area</td>
<td>896</td>
<td>888</td>
<td>940</td>
</tr>
<tr>
<td>Less severely affected area</td>
<td>777</td>
<td>700</td>
<td>714</td>
</tr>
<tr>
<td>Birth date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(From October 1, year)</td>
<td>1952</td>
<td>1954</td>
<td>1956</td>
</tr>
<tr>
<td>(To September 30, year)</td>
<td>1954</td>
<td>1956</td>
<td>1958</td>
</tr>
<tr>
<td>Age in 2002 (years)</td>
<td>48–49</td>
<td>46–47</td>
<td>44–45</td>
</tr>
<tr>
<td>Women (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54.9</td>
<td>54.2</td>
<td>54.0</td>
</tr>
<tr>
<td>Height (cm)**</td>
<td>159.3 (0.2)†</td>
<td>159.4 (0.4)†</td>
<td>159.4 (0.2)†</td>
</tr>
<tr>
<td>Weight (kg)**</td>
<td>59.4 (0.4)</td>
<td>58.9 (0.5)</td>
<td>59.0 (0.05)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))**</td>
<td>23.3 (0.1) †</td>
<td>23.1 (0.2)</td>
<td>23.2 (0.2)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)**</td>
<td>4.99 (0.05)†</td>
<td>4.88 (0.04)†</td>
<td>4.87 (0.04)†</td>
</tr>
<tr>
<td>Hyperglycemia (%)*</td>
<td>5.89†</td>
<td>3.40</td>
<td>3.93</td>
</tr>
<tr>
<td>Type 2 diabetes (%)*</td>
<td>3.89†</td>
<td>1.69</td>
<td>2.78</td>
</tr>
</tbody>
</table>

*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, \( P < 0.05 \).

### 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

<table>
<thead>
<tr>
<th></th>
<th>Childhood-exposed cohorts*</th>
<th>Fetal-exposed cohort</th>
<th>Nonexposed cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE, mmol/l)</td>
<td>4.95 (0.07)</td>
<td>4.84 (0.04)</td>
<td>4.87 (0.05)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.008</td>
<td>0.059</td>
<td>0.037</td>
</tr>
<tr>
<td>Less severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE, mmol/l)</td>
<td>5.09 (0.09)</td>
<td>4.97 (0.08)</td>
<td>4.88 (0.04)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.011</td>
<td>0.113</td>
<td>0.321</td>
</tr>
<tr>
<td>( P ) for interaction between area and cohort</td>
<td>0.898</td>
<td>0.793</td>
<td>0.271</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>5.19</td>
<td>2.68</td>
<td>3.76</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.38 (1.11–5.11)</td>
<td>1.21 (0.57–2.55)</td>
<td>1.77 (0.82–3.83)</td>
</tr>
<tr>
<td>Less severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>7.17</td>
<td>5.22</td>
<td>4.34</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.27 (1.02–5.06)</td>
<td>1.94 (0.89–4.72)</td>
<td>1.16 (0.56–2.40)</td>
</tr>
<tr>
<td>( P ) for interaction between area and cohort</td>
<td>0.542</td>
<td>0.766</td>
<td>0.341</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>3.51</td>
<td>1.19</td>
<td>2.90</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>3.51 (0.91–6.87)</td>
<td>0.75 (0.26–2.12)</td>
<td>2.07 (0.82–5.24)</td>
</tr>
<tr>
<td>Less severe famine area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>4.60</td>
<td>2.99</td>
<td>2.48</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.34 (0.72–7.62)</td>
<td>1.86 (0.53–6.45)</td>
<td>1.02 (0.35–2.93)</td>
</tr>
<tr>
<td>( P ) for interaction between area and cohort</td>
<td>0.606</td>
<td>0.424</td>
<td>0.243</td>
</tr>
</tbody>
</table>

*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.
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 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 2A3 shows that overweight subjects in the fetal-exposed cohort had the highest prevalence of hyperglycemia (13.9%). However, the risks of

![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).](diabetesjournals.org)
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 (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 economic 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 \(-\) 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.
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 observed 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, nutritional 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-
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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.

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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 supervised the study.

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