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 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

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
Type 2 diabetes was defined as FPG ≥11.1 mmol/l. Hyperglycemia was defined as FPG ≥7.0 mmol/l. Fasting 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 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.

Disease Control and Prevention. Signed consent forms were obtained from all participants.

The 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 ≥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 mmol/l.
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>Childhood-exposed cohorts</th>
<th>Fetal-exposed cohort</th>
<th>Nonexposed cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,673</td>
<td>1,005</td>
</tr>
<tr>
<td>Severe affected area</td>
<td>896</td>
<td>503</td>
</tr>
<tr>
<td>Less severely affected</td>
<td>777</td>
<td>502</td>
</tr>
<tr>
<td>Birth date</td>
<td>1952</td>
<td>1959</td>
</tr>
<tr>
<td>Age in 2002 (years)</td>
<td>1954</td>
<td>1961</td>
</tr>
<tr>
<td>Women (%)</td>
<td>54.9</td>
<td>53.2</td>
</tr>
<tr>
<td>Height (cm)**</td>
<td>159.3 (0.2)({}^\dagger)</td>
<td>159.4 (0.2)({}^\dagger)</td>
</tr>
<tr>
<td>Weight (kg)**</td>
<td>59.4 (0.4)</td>
<td>58.9 (0.5)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))**</td>
<td>23.3 (0.1) (\dagger)</td>
<td>23.1 (0.2)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)**</td>
<td>4.99 (0.05)({}^\dagger)</td>
<td>4.88 (0.04)({}^\dagger)</td>
</tr>
<tr>
<td>Hyperglycemia (%)*</td>
<td>5.89({}^\dagger)</td>
<td>3.40</td>
</tr>
<tr>
<td>Type 2 diabetes (%)*</td>
<td>3.89({}^\dagger)</td>
<td>1.69</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. \( \dagger \) 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>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>
</tr>
<tr>
<td>Severe affected area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE, mmol/l)</td>
<td>4.95 (0.07)</td>
<td>4.95 (0.07)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>Less severely affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE, mmol/l)</td>
<td>5.09 (0.09)</td>
<td>4.73 (0.04)</td>
</tr>
<tr>
<td>( P )</td>
<td>0.011</td>
<td>0.234</td>
</tr>
<tr>
<td>( P ) for interaction</td>
<td>0.898</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe affected area</td>
<td>5.19</td>
<td>7.29</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.38,(1.11–5.11)</td>
<td>3.92,(1.64–9.39)</td>
</tr>
<tr>
<td>Less severely affected</td>
<td>2.71</td>
<td>4.34</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.27,(1.02–5.06)</td>
<td>0.57,(0.25–1.31)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe affected area</td>
<td>3.51</td>
<td>2.01</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.51,(0.91–6.87)</td>
<td>1.43,(0.53–3.87)</td>
</tr>
<tr>
<td>Less severely affected</td>
<td>4.60</td>
<td>1.08</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.34,(0.72–7.62)</td>
<td>0.41,(0.12–1.35)</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 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
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, \( P \leq 0.031 \)) in overweight subjects and 4.37 (95% CI: 1.15–16.5, \( P \leq 0.030 \)) 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 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 \( \beta \)-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).

### TABLE 3

<table>
<thead>
<tr>
<th>Childhood-exposed cohorts</th>
<th>Late childhood</th>
<th>Mid childhood</th>
<th>Early childhood</th>
<th>Fetal-exposed cohort</th>
<th>Nonexposed cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defining severity of famine by excess death rate ( \geq 100% )</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe famine area</td>
<td>3.92 (1.21–3.93)</td>
<td>2.68</td>
<td>3.76</td>
<td>7.29 (1.55–7.36)</td>
<td>3.11 (1.23–7.92)</td>
</tr>
<tr>
<td>Less severe famine area</td>
<td>5.19 (1.09–2.03)</td>
<td>1.10 (0.59–2.03)</td>
<td>1.51 (0.79–2.87)</td>
<td>3.38 (1.56–7.37)</td>
<td></td>
</tr>
<tr>
<td>P for interaction between area and cohort</td>
<td>0.492</td>
<td>0.373</td>
<td>0.362</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td><strong>Classifying adults born during October 1, 1962, to September 30, 1968, as nonexposed cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe famine area</td>
<td>5.06 (1.10–5.22)</td>
<td>2.64</td>
<td>3.51</td>
<td>7.08 (1.69–7.33)</td>
<td>1.98 (1.24–3.93)</td>
</tr>
<tr>
<td>Less severe famine area</td>
<td>6.03 (1.09–5.21)</td>
<td>2.34 (1.05–2.63)</td>
<td>1.73 (0.78–3.86)</td>
<td>4.00 (1.64–9.73)</td>
<td></td>
</tr>
<tr>
<td>P for interaction between area and cohort</td>
<td>0.505</td>
<td>0.826</td>
<td>0.488</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

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.
suggest that famine exposure during childhood may in-
and less severely affected famine areas. These results
among subjects exposed in late childhood in both severely
areas. We also observed a higher risk of hyperglycemia
increased FPG in the early childhood–exposed cohort in
rats (25). Our study found significantly
increased 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
environment 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 metab-
olism 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 in-
crease 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 ex-
posed 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 author-
ities 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 perma-
nent 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,
supports in our fetal-exposed cohort may have actually
experienced severe famine during both the fetal period
and the infancy period because the famine lasted approx-
imately 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 in-
cluded subjects exposed to famine in infancy, which did
not have a substantial influence on the risk of hyperglyc-
emia. 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 ex-
clusively due to malnutrition in early life. However, nutri-
tion 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 adult-
hood. 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 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, and the manuscript writing. F.B.H. contributed to the discussion, interpretation of the data, and manuscript writing, and conceptualized and supervised the study.

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