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 JM Feskens[3], Xiaoguang Yang[1], Guansheng Ma[1], Frank B Hu[2,4]

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

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

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Correspondence to:
Yanping Li, PhD
liyanping72@yahoo.com
or
Guansheng Ma, PhD
mags@chinacdc.net.cn
or
Frank B Hu, PhD
nhbfh@channing.harvard.edu

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Objective–Early developmental adaptations in response to undernutrition may play an essential role in the 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 of 7,874 rural adults born between 1954 and 1964 in the selected communities from the cross-sectional 2002 China National Nutrition and Health Survey. Hyperglycemia was defined as fasting plasma glucose ≥6.1mmol/L and/or 2-h plasma glucose ≥7.8 mmol/L and/or clinically diagnosed as type 2 diabetes previously.

Results–Prevalences of hyperglycemia among adults in non-exposed, 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 to non-exposed 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 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 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 severe Chinese famine increases the risk of hyperglycemia in adulthood. This association appears to be exacerbated by a nutritional 'rich' environment in later life.

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 the 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 relations. 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 increased 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 might be due to differences in postnatal environmental life exposures. Whereas 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 the 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 nutritional '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 Figure 1, in the first stage of sampling, 22 counties were randomly selected from each of the six regions in China. In the second stage, three townships were randomly selected from each of the selected counties. From each of the townships, two residential villages were randomly selected; and 90 households were then randomly sampled from each village for physical examination. One-third of households were selected to participate in the dietary survey and blood draw. For the present study, we used residents who were living in rural area and were born between October 1, 1952 and September 30, 1964 as our 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.

Famine cohorts and areas. Subjects were categorized into five exposure cohorts: non-exposed cohort, fetal-exposed cohort, early-childhood exposed cohort, mid-childhood exposed cohort and late-childhood exposed cohort. All cohorts were defined according to subjects' birthday. Subjects who were born between October 1, 1962 and September 30, 1964 were classified as non-exposed 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 two years and were classified into one of the three childhood-exposed cohorts. Mean ages for subjects in non-exposed cohort, fetal-exposed cohort, early-childhood exposed cohort, mid-childhood exposed cohort and late-childhood exposed cohort was 39, 42, 45, 47 and 49 years, respectively.

The Chinese famine affected the whole mainland of China, but the severity varied across regions due to different weather conditions, population density and local policy to food shortage (7). As previously described, we used 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 of 1959-1961 (7). The excess death rate of 50% was used as the threshold: regions had 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 approximately 10 to 14 hours overnight fast. The plasma was separated by centrifugation at 3200 rpm for 10-15 min within 1 h of the collection and kept at room temperature without sunshine. Fasting plasma glucose (FPG) concentration was measured using glucose oxidize enzymatic method within 3 hours of plasma preparation. Every tenth sample was measured twice (correlation coefficient of duplicate measurements was 0.98). All individuals in present study 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 the 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 ≥6.1mmol/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 have been previously diagnosed as type 2 diabetes were added as cases of hyperglycemia and type 2 diabetes.

Stratification factors. Dietary patterns, economic status and body mass index (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 South and North, respectively, while the other two represent westernized dietary patterns. In the present study, we combined the clusters of "green water" and "yellow earth" as the traditional dietary pattern, and 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 past year before 2002CNNHS, which was treated as dichotomous variable. The mean level of current sample (2000 Chinese Yuan per person per year) was used as cut-off point for economic status.

BMI was calculated by measured fasting body weight and height. We used criteria recommended for Chinese adults and classified subjects as overweight if BMI ≥ 24 kg/m^2, or normal otherwise (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 in SAS 9.2 for Windows (SAS Institute Inc, 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 exposed cohorts and the non-exposed cohort were tested by generalized least squares estimation (17). Risks of hyperglycemia and type 2 diabetes among fetal and childhood exposed subjects, compared to non-exposed subjects, were examined with the method of maximum likelihood by using survey logistic regression model. Interaction between famine exposure cohort (fetal or childhood exposed vs. non-exposed) 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 "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. Odds ratio of hyperglycemia in fetal exposed cohort compared to non-exposed 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 cut-off point, i.e. excess death rate ≥100% to define the severity of famine. In addition, we performed analyses by using the cohort born during October 1, 1962-September 30, 1968 as non-exposed cohort for association analyses, or excluding participants with family history of diabetes.

RESULTS

Basic characteristics of the study population are shown in Table 1. In our main study population (n=7874), 1005 (12.8%) subjects had been exposed to the Chinese famine during fetal life and 4915 (62.4%) subjects had been exposed during childhood. As compared to the non-exposed individuals, fetal exposed subjects were 0.9 cm shorter as adults, and childhood exposed subjects were 1.5 cm shorter (Table 1). Prevalence of hyperglycemia among adults in non-exposed, fetal exposed, early-childhood, mid-childhood and late-childhood exposed birth cohort 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 non-exposed cohort with a mean difference of 0.20mmol/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 to non-exposed subjects, FPG was higher in 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 exposed cohort and area was only found for the fetal-exposed cohort (Table 2).

Subjects exposed to famine during fetal life in severely affected famine areas had higher prevalence of hyperglycemia than the non-exposed cohort. This difference was not significant in the less severely affected famine areas. 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 to the non-exposed cohort, subjects in 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 to the non-exposed 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 Figures 2. Figure 2A1 shows that the prevalence of hyperglycemia was the highest (18.9%) in

subjects in the fetal-exposed cohort and who consumed an affluent/western diet. As compared to the relatively non-exposed 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 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 to non-exposed 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*=0.031) in overweight subjects and 4.37 (95% CI 1.15-16.5, *P*=0.030) in normal weight subjects, respectively, as compared to the non-exposed cohort. Similar analyses were performed in subjects exposed to less severely affected famine areas during fetal life and childhood (Figure 2, right column B1, B2 and B3), but did not show consistent associations.

When we defined the severely affected famine areas as those with excess death rate ≥100%, the prevalence of hyperglycemia among 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 non-exposed cohort nor excluding subjects with 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 ß–cell mass and function, and insulin resistance, which might persist to 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 change the set-point 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 the famine with measures of glucose intolerance. These studies were performed in the Netherlands (Dutch Famine Study) (4,5), Russia (Leningrad Siege Study) (6), and China (our Chinese Famine Study). The Dutch Famine Study reported higher 2 hours glucose and insulin levels among subjects who were exposed to the 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. Whereas 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 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 nutritional 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 the dramatically enhanced economic opportunities, and they have broken away from the traditional Chinese food patterns (15). Their diet is characterized by 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 cut-off to categorize the economic status (2000 Chinese Yuan/Person/Year). Subjects in the lower economic group might consume mainly traditional plant-foods with few meats. Therefore, the discrepancy between the nutritional environment in adulthood and fetal undernutrition conditions may be not as evident as that in 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 fetal-exposed cohort had the highest prevalence of hyperglycemia. Similar results have been described in the Dutch famine study (4) showing that the 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 might be partly due to the increased prevalence of hyperglycemia in the non-exposed (reference) cohort in overweight subset. These results therefore indicate that both improving fetal nutritional environmental and controlling BMI in later life are important for the prevention of a disturbed glucose metabolism.

Childhood nutritional status, particularly during infant period, is another key factor in influencing the propensity to develop disease in adulthood (23). Animal studies showed that postnatal caloric restriction might hamper the beta cell development (24) and might disturb glucose metabolism in later life in rats (25). Our study found significantly increased FPG in early-childhood exposed cohort in the severely affected famine areas but not significant 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. Those results suggest that famine exposure during childhood period 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 non-famine exposed areas suggest rather a cohort (older age) effect than famine effect. However, since almost all rural regions in China were affected by the famine during 1959-1961, no real non-famine exposure cohort comprising subjects born in same time period was available. Thus, the association between childhood exposure to famine and risk of hyperglycemia needs to studies in further detail.

Some limitations should be noticed. Firstly, we assumed that the residents we investigated at the time of 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% percent of the rural population lived in provinces other than their birthplaces (27). Our study sample was based on the residence registration system; only the 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 of major concern in our results (12). Secondly, subjects in our fetal-exposed cohort may have actually experienced severe famine during both fetal period and infant period because the famine lasted for around 3 years. It was therefore difficult to distinguish whether fetal period or infant period was more important. However, the early-child cohort also included subjects exposed to famine in the infant period, and it 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. Thirdly, our subjects who experienced severe famine in fetal period were aged in the 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 the death due to unfavorable weather conditions or infections. We also did not have reliable information on 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 food supply plunged further to 70% of the 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 of individual birth outcomes as 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 western dietary pattern and improved economic status further increased the susceptibility to hyperglycemia in those experienced fetal exposure to famine. Together with previous studies, our study highlights that early life environment is critical for the risk of hyperglycemia in adult life.

Author contribution: YL and YH had full access to all of the data in the study. YL takes responsibility for the integrity of the data and the accuracy of the data analysis; GM and XY were the main investigators of 2002CNNHS; Data analyzed by YL and YH; All authors contributed to the discussion and interpretation of the data, and to the writing of the manuscript. The present study was conceptualized and supervised by FH.

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TABLE 1

Basic characteristics of study population according to Chinese famine exposure

	Childhood exposed cohorts			Fetal-exposed	Non-exposed
	Late-child	Mid-child	Early-child	Cohort	Cohort
N	1673	1588	1654	1005	1954
Severe affected area	896	888	940	503	1132
Less severe affected area	777	700	714	502	822
Birth Day (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)
Body mass index (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.

[†] Compared to the non-exposed cohort, [†]$P<0.05$

[**]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 only adjusted for sex.

TABLE 2

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

	Childhood exposed cohorts			Fetal exposed	Non-exposed
	Late-childhood	**Mid-childhood**	**Early-childhood**	**Cohort**	**Cohort**
FASTING PLASMA GLUCOSE (FPG)					
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)
P	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)
P	0.011	0.113	0.321	0.234	Ref.
P for interaction between area and cohort	0.898	0.793	0.271	<.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.
P 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.
P for interaction between area and cohort	0.606	0.424	0.243	0.102	

*Data are adjusted means (SE) for FPG, and sex standard prevalence and odds ratio for hyperglycemia and diabetes. All odds ratios use non-exposed cohort as reference cohort. Adjusted factors included sex, educational level, family history of diabetes, and current smoking, alcohol use and physical activity level

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

	Childhood exposed cohorts			Fetal exposed	Non-exposed
	Late-childhood	Mid-childhood	Early-childhood	Cohort	Cohort
Defining severity of famine by excess death rate ≥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)	
P 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 non-exposed 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)	
P 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)	
P for interaction between area and cohort	0.505	0.826	0.488	0.003	

All odds ratios used non-exposed cohort as reference cohort.
Adjusted factors included sex, educational level, family history of diabetes, current smoking, alcohol use and physical activity level in 2002.

FIGURE LEGENDS

Figure 1. Flow chart on the sampling method in each region* of 2002 China National Nutrition and Health Survey

* Mainland of China is classified into 6 regions defined by 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, type IV rural site.

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

Figure 1

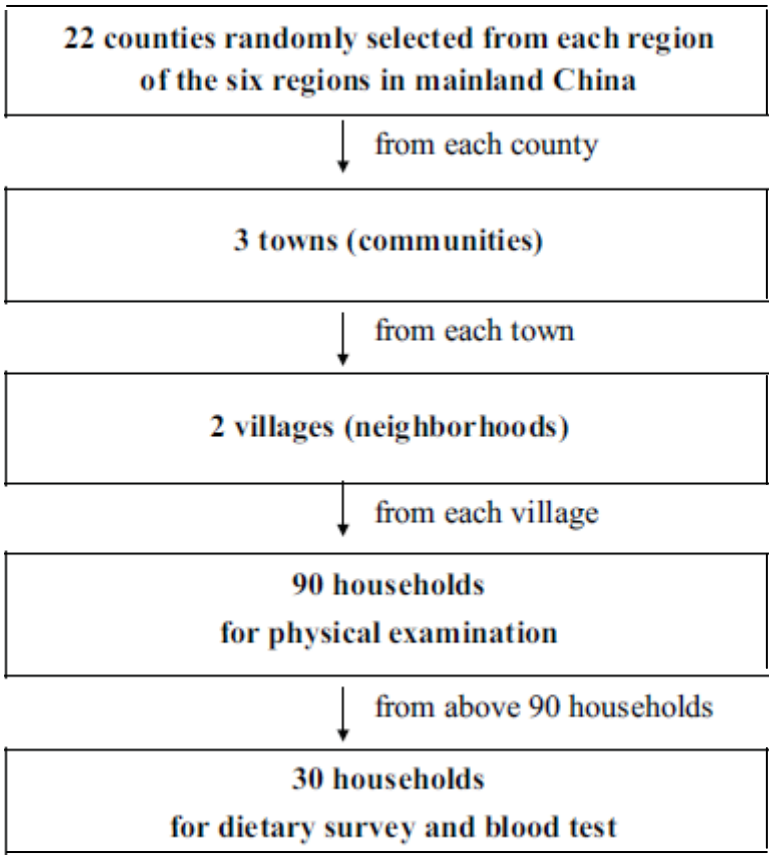
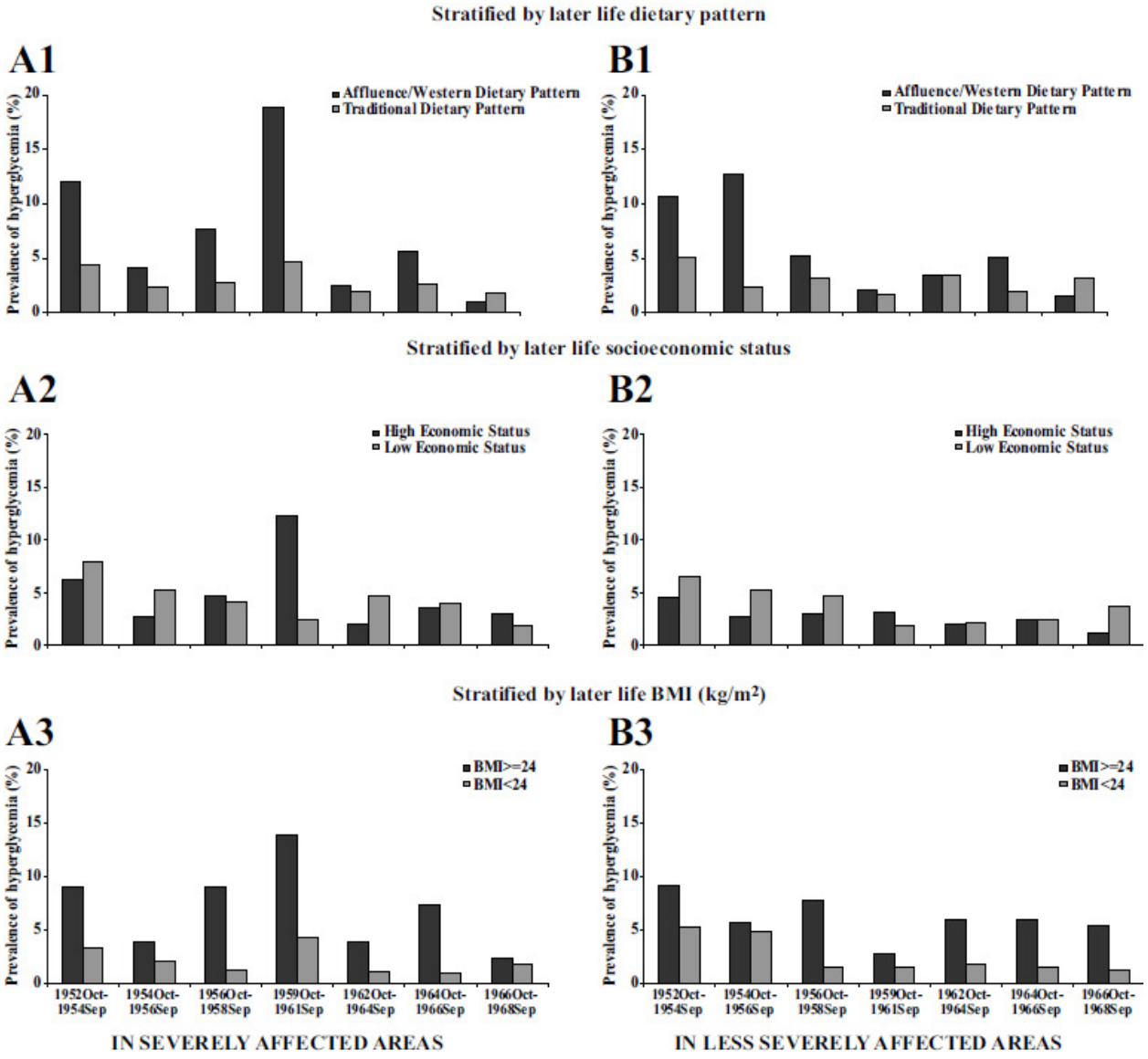


Figure 2


Stratified by later life dietary pattern
A1
B1
Affluence/Western Dietary Pattern
Traditional Dietary Pattern
Prevalence of hyperglycemia (%)
Stratified by later life socioeconomic status
A2
B2
High Economic Status
Low Economic Status
Stratified by later life BMI (kg/m2)
A3
B3
BMI>=24
BMI<24
1952Oct-1954Sep
1954Oct-1956Sep
1956Oct-1958Sep
1959Oct-1961Sep
1962Oct-1964Sep
1964Oct-1966Sep
1966Oct-1968Sep
IN SEVERELY AFFECTED AREAS
IN LESS SEVERELY AFFECTED AREAS