



Original article

Long-term effect of prenatal exposure to malnutrition on risk of schizophrenia in adulthood: Evidence from the Chinese famine of 1959–1961

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ABSTRACT

Background: Schizophrenia is a common major mental disorder and prenatal nutritional deficiency may increase its risk. We aimed to investigate long-term impact of prenatal exposure to malnutrition on risk of schizophrenia in adulthood using the Chinese famine of 1959–1961 as a natural experiment.

Methods: We obtained data from the Second National Sample Survey on Disability implemented in 31 provinces in 2006, and restricted our analysis to 387,093 individuals born from 1956 to 1965. Schizophrenia was ascertained by psychiatrists based on the International Statistical Classification of Diseases, Tenth Revision. Famine severity was defined as cohort size shrinkage index. The famine effect on adult schizophrenia was estimated by difference-in-difference models, established by examining the variations of famine exposure across birth cohorts.

Results: Compared with the reference cohort of 1965, famine cohorts (1959–1962) had significantly higher odds (OR: 1.84; 95% CI: 1.13, 3.00; $P=0.014$) of schizophrenia in the rural population. After adjusting for multiple covariates, this association remained significant (OR: 1.82; 95% CI: 1.11, 2.98; $P=0.018$). We did not observe statistically significant differences in odds of schizophrenia among famine cohorts compared with the reference cohort in the urban population.

Conclusions: Prenatal malnutrition exposure has a detrimental impact on risk of schizophrenia in adulthood in the rural population. Further studies were needed to investigate corresponding mechanisms on this topic.

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1. Introduction

Malnutrition is a long-standing health problem in developing countries and has become a public concern around the world. The target of reducing malnutrition, however, was one of the great missed opportunities in achieving the Millennium Development Goals [1]. For example, research on the 2010 Global Burden of Disease estimates showed that, malnutrition was still ranked the first and the fourth risk factor in Sub-Saharan Africa and South Asia, respectively [2]. In addition, the challenge of malnutrition has triggered global political commitment and economic actions. Despite facing fiscal difficulties, the G8

countries increased by almost 50% investment in the bilateral nutrition programs from 2009 to 2011 [3]. Furthermore, malnutrition has attracted growing attention from the public, as Google Trends showed that the term “malnutrition” had matched “HIV/AIDS” in terms of internet interest until 2013, whereas malnutrition received just one half of interest of HIV/AIDS in 2008 [4]. However, there are few cohort human studies on the effect of in utero malnutrition on adult health outcomes due to apparent ethical considerations.

Famine, as a natural experiment, offers a unique opportunity to investigate the long-term association of prenatal malnutrition and adult health including schizophrenia [5]. Most studies on this issue are based on the Dutch famine of 1944–1945 and the Chinese famine of 1959–1961 [6]. The first study regarding the Dutch famine and risk of schizophrenia found that in the comparison based on birth time controls, those who were prenatally exposed to famine in the first trimester had more than two-fold likelihood of schizophrenia among women [7]. The

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second Dutch study, retrieving hospital register data, suggested a significant association of prenatal exposure to famine with roughly two-fold odds of schizophrenia in both men and women [8]. Subsequent studies on the Dutch famine and schizophrenia observed similar findings [9–11].

The Chinese studies regarding famine exposure and schizophrenia emerged recently and found similar associations with the Dutch studies. Two studies, using hospital records of schizophrenia patients in Wuhu, Anhui province and Liuzhou, Guangxi province, replicated the Dutch studies and both found two-fold increased odds of schizophrenia in adulthood among those who were exposed in utero to the Chinese famine after adjusting for mortality [12,13]. The latter study in Liuzhou also suggested the famine effect on schizophrenia was restricted to the rural population, not in the urban population [13]. Based on data of the 1987 Disability Survey on Disability, another study exploited the estimation approach of simple cohort difference (SCD) and somewhat observed different results, showing that in the urban population, early-life exposure to famine cohorts increased likelihood of schizophrenia than pre-famine and post-famine cohorts, but in the rural population, post-famine cohorts were more likely than famine and pre-famine cohorts to have schizophrenia in adulthood [14].

Previous Chinese studies on prenatal famine and adult schizophrenia have a few limitations. First, two hospital-based investigations were regional because they only based on one psychiatric hospital records separately. Second, the estimation of SCD has methodological deficiencies since it cannot exclude intrinsic cohort differences other than famine; that is, the observed differences across birth cohorts may be a reflection of general cohort effects even without exposure to famine [15,16]. A valid strategy to more robustly capture the famine effect on health outcomes relies on difference-in-difference (DID) models, established by examining the regional variations of famine exposure across birth cohorts [17,18].

In this study, using the Chinese famine of 1959–1961 as a natural experiment, we investigated the potential long-term effect of in utero exposure to malnutrition on schizophrenia in adulthood based on DID methods. An examination on this topic would contribute to the literature in several ways. First, we tested the fetal origins hypothesis [19,20] that the effect of prenatal famine on adult schizophrenia from the national perspective. Second, we exploited DID methods to estimate more precisely long-term effect of famine on schizophrenia.

2. Methods

2.1. Background the Chinese famine

The Chinese famine coincided with a nationwide movement, known as “Great Leap Forward (GLF)”, which started sweeping across China in 1958. The GLF aimed to bring about rapid industrialization and overtake the level of Britain and the United States in a short time [17]. Contrary to the expectation, however, the GLF severely disrupted agricultural production [21]. Consequently, grain output dropped by 15% in 1959, and in the next two years, continued to drop to roughly 70% of the 1958 level [22]. Meanwhile, the central government sharply increased grain procurement from the rural population. The plunge of grain output, excess procurement and severe weather disaster jointly caused a dramatic decline in caloric intake and the famine ensued in all regions of China [23]. From 1959 to 1961, the death rates sharply increased while the fertility rates rapidly decreased at the same time [23]. By 1962, both death and birth rates returned to a normal level [24].

2.2. Study participants

We derived data from the Second National Sample Survey on Disability conducted in 31 provinces in 2006. The aim of the survey was to investigate the prevalence, causes, and severity of disabilities, as well as the living conditions and health service needs of the disabled. Multistage stratified random cluster sampling, with probability proportional to size, was used in 734 counties (districts), 2980 towns (streets) and 5964 communities (villages) from all provinces [25]. The survey sample size was 2,526,145, representing 1.9 per 1000 non-institutionalized inhabitants of China [26].

In the present study, the term “in utero or prenatal exposure” refers to maternal exposure to famine during the roughly 300 days from the peri-conception to delivery [6]. We restricted our analysis to 1956–1965 birth cohorts, mainly because of avoiding other natural disasters before and after the famine, including the extremely cold weather of 1954–1955 and the Chinese Cultural Revolution of 1966–1976 [18].

Adults born in 1959–1962 were exposed to famine in gestation, and thus were defined as famine cohorts. Those born in 1956–1958 and 1963–1965 were not prenatally exposed, and thus were defined as pre-famine and post-famine cohorts, respectively. We selected a subsample of 387,093 adults born in 1956–1965, at the ages of 41–50 years during the survey time. More details of sample selection were presented in Fig. 1.

2.3. Ethics approval

The survey was conducted in 31 provinces by the Leading Group of the National Sample Survey on Disability and the National Bureau of Statistics. The survey was approved by the China State Council (No. 20051104) and implemented within the legal framework governed by the Statistical Law of the People’s Republic of China (1996 Amendment). All respondents provided consent to the Chinese government, which covered their participation in the survey and the clinical assessment process.

2.4. Measures

2.4.1. Ascertainment of schizophrenia

Schizophrenia was ascertained by the combination of self-reports or family members’ reports and on-site medical diagnosis by psychiatrists in the Second National Sample Survey on Disability according to the WHO International Classification of Functioning, Disability, and Health (WHO-ICF) [27].

We recruited interviewers from local primary care institutions and trained them in the methods of survey and screening. Trained interviewers went to the households to screen adults with mental disability using a questionnaire. The questionnaire was developed according to the ‘Guidelines and Principles for the Development of Disability Statistics’ [28], and had been shown very good validity [29]. The detailed screening questions were presented in our previous work [30].

If we found the subjects who have a tendency of mental disability, we would refer them to psychiatrists for final medical diagnosis of mental disability and schizophrenia based on the World Health Organization Disability Assessment Schedule, Version II (WHO DAS II) and the International Statistical Classification of Diseases, Tenth Revision (ICD-10) [31]. The WHO DAS II had been verified for good validation among schizophrenic patients [32]. Psychiatrists with 5 or more years of clinical experience were trained to use ICD-10 criteria for the diagnosis of schizophrenia. The symptom checklist is a semi-structured instrument, which was employed to identify the psychiatric symptoms and syndromes in the F0–F6 categories of the ICD-10. Every category includes a list of symptoms and

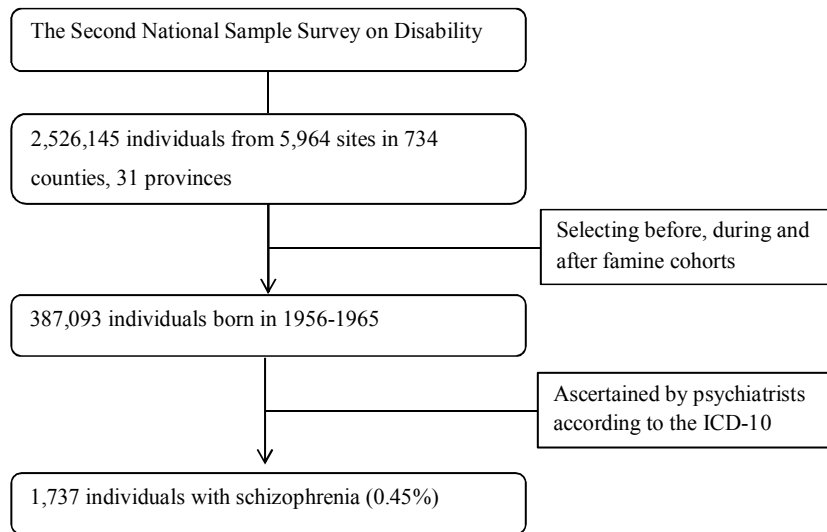


Fig. 1. Flowchart of the study sample.

instructions, which may help psychiatrists considering other possible syndromes. Following the instructions, the psychiatrists filled out the checklist and diagnose schizophrenia and other mental disorders [30]. The ICD-10 diagnostic criteria had been used in the ascertainment of schizophrenia among Chinese people and also presented good validity in China [12].

2.4.2. Famine severity

The Chinese famine not only had long duration and extreme severity, but also had substantial variation in severity across regions [17]. The regional variation in famine severity, combined with differences in schizophrenia across birth cohorts, provides a unique opportunity to identify the famine effect on schizophrenia.

We measured famine severity by comparing the size of the famine cohorts relative to the surrounding non-famine cohorts in the population using the data from China Statistical Yearbook, named as the cohort size shrinkage index (CSSI) [33,34]. The potential assumption of CSSI is that compared with pre- and post-famine cohorts, the smaller size of the famine cohorts due to the plunge of fertility and/or the surge of mortality, the larger the severity of the famine [34]. We calculated the average cohort size of those born during the three years before the famine (1956–1958) and the three years after the famine (1962–1964), namely N_{nonfam} ; we also denoted the mean size of cohorts during the famine (1959–1961), namely N_{fam} . Afterwards, we obtained the CSSI as the difference between N_{nonfam} and N_{fam} divided by N_{nonfam} . The validity and reliability of CSSI has been shown to be reasonably good elsewhere [18,35].

We assessed famine severity at the province level. Per the administrative region division during 1956–1965, Tianjin, Hainan and Chongqing were included in Hebei, Guangdong and Sichuan province, respectively. We dropped Tibet due to lack of population data during the famine period. Thus, we obtained the CSSI values of 27 provinces, ranging from 0.06 to 0.62 with a mean of 0.36, representing that the average cohorts during the famine period were 36% lower than the mean size of the cohorts born in the three years before and after the famine in these provinces. The CSSI values of 27 provinces were listed in Table 1.

2.4.3. Control variables

Control variables in this study included gender (male and female), ethnicity (Han and others), marital status (married and unmarried), education (illiterate, primary school, junior high school, and senior high school and above), and annual family income per capita (in tertiles).

2.5. Analytic approach

The famine effect on adulthood schizophrenia was estimated by DID models, which examined the regional variation of famine exposure across birth cohorts. The idea behind this approach is that we can use birth years to identify whether an individual was prenatally exposed during the famine. We can also rely on the famine severity across regions to identify the variation of famine exposure in the same birth cohorts. The detailed rationale of using this method to identify the famine effect was explained elsewhere [17], and broadly employed in Chinese famine studies

Table 1
The cohort size shrinkage index (CSSI), by province.

Province	N_{nonfam}	N_{fam}	CSSI
Beijing	220625	207940	0.06
Hebei	1406671	914698	0.35
Shanxi	569704	414934	0.27
Nei Mongol	395816	311681	0.21
Liaoning	981357	645586	0.34
Jilin	539490	391973	0.27
Heilongjiang	642545	522049	0.19
Shanghai	274812	269212	0.02
Jiangsu	1436862	828593	0.42
Zhejiang	945345	585217	0.38
Anhui	1228450	472500	0.62
Fujian	569214	361886	0.36
Jiangxi	697476	505286	0.28
Shandong	1916667	1096667	0.43
Henan	1800000	933333	0.48
Hubei	1133400	737603	0.35
Hunan	1349402	678039	0.50
Guangdong	1365486	877825	0.36
Guangxi	721841	360794	0.50
Sichuan	2467172	1247819	0.49
Guizhou	684593	361700	0.47
Yunnan	720890	409346	0.43
Shannxi	642333	478000	0.26
Gansu	461419	208202	0.55
Qinghai	75435	38449	0.49
Ningxia	83840	36647	0.56
Xinjiang	208298	179649	0.14

Tianjin, Hainan and Chongqing were included in Hebei, Guangdong and Sichuan, respectively. We excluded Tibet due to the absence of population data at that time. N_{nonfam} : the mean size of cohorts before (1956–1958) and after the famine (1962–1964); N_{fam} : the mean size of cohorts during the famine (1959–1961). The data of population were derived from the China Statistical Yearbook.

[18,33,36,37]. Logit regression models with DID estimators were fitted as the following:

$$Y_{ijk} = B_0 + \delta CSSI_j + \varphi_k Cohort_k + \sum_{k=1}^3 \beta_k (CSSI_r \times Cohort_k) + VX_{ijk}$$

Where Y_{ijk} is the risk of schizophrenia for individual i , born in province j and year k ($k = 1$ refers to pre-famine cohorts born in 1956–1958, $k = 2$ refers to famine cohorts born in 1959–1962, $k = 3$ refers to post-famine cohorts born in 1963–1964, and the reference group refers to the unexposed 1965 cohort), $CSSI_j$ is the cohort size shrinkage index of province j , φ_k represents the cohort fixed effect, X_{ijk} denotes a vector of control variables, including gender, ethnicity, marital status, residence, education, as well as family income, and V is the scalar that contains corresponding coefficients of covariates. Standard errors are clustered at the province level to deal with potential heteroscedasticity and serial correlation problems [38].

The interaction coefficient between the CSSI and the birth cohort dummy variables, namely β_k , evaluates the effect of prenatal exposure to famine on schizophrenia in DID models. The estimation methods that used the interaction term in non-linear DID models were shown elsewhere [39,40]. To estimate the average effect across provinces, we multiplied the interaction coefficients by 0.36, the mean of CSSI in all provinces.

Due to different famine severity between urban and rural area, following previous studies [21,33,37], we performed statistical analyses in rural and urban subsamples, separately. A p -value of less than 0.05 was considered statistically significant. The software Stata version 12 for Windows (Stata Corp, College Station, TX, USA) was used for the statistical analysis.

3. Results

Table 2 reports the characteristics of participants born during 1956–1965. In the rural sample, among 239,055 adults, 0.45% had schizophrenia, 50.13% were male, 89.34% were Han ethnicity, 94.85% were married, 38.02% had education of junior high school, and 42.98% lived in low-income families. In the urban sample, among 148,038 adults, 0.42% had schizophrenia, 50.37% were male,

Table 2
Characteristics of study participants, by rural and urban residence.

Characteristics	Rural sample (N = 239,055)	Urban sample (N = 148,038)
Schizophrenia (%)	0.47	0.42
Sex (%)		
Male	50.13	50.37
Female	49.87	49.63
Ethnicity (%)		
Han	89.34	93.99
Minority	10.66	6.01
Marital status (%)		
Unmarried	5.15	6.44
Married	94.85	93.56
Education (%)		
Illiterate	14.86	3.10
Primary school	34.45	11.69
Junior high school	38.02	34.62
Senior high school and above	12.07	50.59
Income (%)		
First tertile (lowest)	42.98	13.75
Second tertile	34.23	28.04
Third tertile (highest)	22.79	58.21

93.99% were Han ethnicity, 93.56% were married, 50.59% had education of senior high school and above, and 58.21% lived in high-income families.

Table 3 shows the odds ratios of famine exposure and risk of schizophrenia in the rural population. Famine cohorts (1959–1962) had higher odds (OR: 1.84; 95% CI: 1.13, 3.00; $P = 0.014$) of schizophrenia compared with the reference cohort of 1965. After adjusting for multiple covariates, this association remained significant (OR: 1.82; 95% CI: 1.11, 2.98; $P = 0.018$). We did not find statistically significant associations of pre-famine (1956–1958) and post-famine cohorts (1963–1964) with odds of schizophrenia, compared with the reference cohort of 1965, in the unadjusted and adjusted models, respectively.

Table 4 presents the odds ratios of famine exposure and risk of schizophrenia in the urban population. We did not observe statistically significant differences in odds of schizophrenia among famine cohorts (1959–1962), pre-famine cohorts (1956–1958), and post-famine cohorts (1963–1964), compared with the reference cohort of 1965, in the unadjusted and adjusted models, respectively.

4. Discussion

Fetal origins hypothesis, popularized by David Barker [19,20], conjectures that in utero exposure to malnutrition, combined with the interaction between environmental factors and epigenome, has a profound impact on adult disease [41]. Using the Chinese famine of 1959–1961 as a natural experiment, we investigated whether prenatal exposure to malnutrition would predict risk of adulthood schizophrenia in individuals born from 1956 to 1965, and tested the hypotheses that the famine effects in the rural and urban population. We found a significant association of prenatal exposure to famine with elevated odds of adulthood schizophrenia in the rural population, not in the urban population, after multiple sociodemographic covariates were taken into considerations.

Our findings of increased risk of schizophrenia after famine exposure in utero were similar to those of previous studies in the Dutch and Chinese famines. The two famines are highly exceptional and meet the criteria for studying prenatal exposure and adulthood mental disorders [6]. Earliest Dutch studies suggested approximately two-fold odds of schizophrenia among the famine exposed population compared with the unexposed population [7,8]. Although the difference of two famines in duration and affected population does not allow for direct comparison, the concordant results complement each other and show particularly powerful association of prenatal famine with subsequent schizophrenia from different contexts [6]. In addition, previous studies in two provinces of China replicated the Dutch studies based on the hospital patient records and found the famine cohorts were about twice more likely to have schizophrenia than the unexposed cohorts [12,13]. We further verified the conclusion that prenatal famine exposure was associated with increased odds of schizophrenia in adulthood from a nationally representative, population-based study.

The associations on famine exposure found in this study indicate that prenatal malnutrition has a long-term negative effect on risk of schizophrenia in adulthood. Schizophrenia is increasingly considered as a neurodevelopmental disorder that likely derives from the disruption of brain development caused by the environmental and genetic factors [42]. Malnutrition is associated with elevated risk of schizophrenia through adversely affecting the fetal brain development [12]. This developmental mechanism in the pathogenesis of schizophrenia, initially proposed by Daniel Weinberger [43] and subsequently supported by others [44], states that early-life brain impairment leads to a series of inverse events that occur across childhood and adolescence, such as the reduction of synaptic density, and to change the developmental trajectory

Table 3
Prenatal famine exposure and risk of schizophrenia in adulthood, by famine cohort (Rural sample, N = 239,055).

Group	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Pre-famine cohorts (1956–1958)	1.42 (0.93, 2.18)	0.104	1.37 (0.86, 2.18)	0.192
Famine cohorts (1959–1962)	1.84 (1.13, 3.00)	0.014*	1.82 (1.11, 2.98)	0.018*
Post-famine cohorts (1963–1964)	1.41 (0.90, 2.20)	0.132	1.41 (0.89, 2.24)	0.141
Reference cohort (1965)	1.00		1.00	

OR: odds ratio; CI: confidence interval. Adjusted OR: odds ratio estimated from models controlling for gender, ethnicity, marital status, education, and family income.
* $P < 0.05$.

Table 4
Prenatal famine exposure and risk of schizophrenia in adulthood, by famine cohort (Urban sample, N = 148,038).

Group	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Pre-famine cohorts (1956–1958)	1.35 (0.62, 2.93)	0.449	1.31 (0.60, 2.89)	0.498
Famine cohorts (1959–1962)	1.07 (0.68, 1.68)	0.758	1.10 (0.68, 1.78)	0.695
Post-famine cohorts (1963–1964)	1.18 (0.75, 1.85)	0.471	1.23 (0.79, 1.92)	0.355
Reference cohort (1965)	1.00		1.00	

OR: odds ratio; CI: confidence interval. Adjusted OR: odds ratio estimated from models controlling for gender, ethnicity, marital status, education, and family income.

that ultimately causes the onset of schizophrenia in adulthood [45]. Although nutritional deficiencies were the most possible explanation, other mechanisms, theoretically, remain possible. For example, the psychogenic impact of famine exposure, although indirectly associated with nutritional stress [13], and selective ability to conceive under famine conditions [5], cannot be entirely ruled out.

The long-term association between prenatal famine exposure and risk of adult schizophrenia observed in this study only occurred in the rural population, not in the urban population. Our findings are consistent with prior research in China [13]. One of common explorations is that famine severity was much greater in rural China [37]. As established in this study, compared with pre-famine and post-famine birth cohorts, the reduced number of famine cohorts was much larger in the rural area than that in the urban area. The urban-rural famine disparity is likely due to the passport registration system, namely “Hukou” in China, as well as the grain procurement system from the rural population at that time [46]. The strict registration system of Hukou was launched in 1951, and further reinforced by the end of 1950s. Chinese residents, regulated by the Hukou system, were prohibited from free migration, especially from rural to urban areas [47]. Moreover, despite a huge shrinkage of food production during the famine period, rural families were even forced to turn in larger amount of grain, and consequently, more severe starvation occurred in the rural population. By contrast, urban population had the legal rights to receive certain amount of food from state grain store during the famine, and thus experienced a relatively smaller impact of the famine [13].

This study has several limitations. First, selective mortality caused by famine may have the potential threat to our findings. Those who were more severely affected by the famine were more likely to die during the famine, and the famine survivors with more serious schizophrenia were also more likely to die after the famine. Due to lack of schizophrenia-associated mortality data, we were unable to correct the underlying bias, but like other famine studies, this would likely underestimate rather than overestimate the famine effect. Second, population migration may impact our estimates. We used current living place as birth place at the province level, which may lead to imprecise identification of famine severity across provinces. On the one hand, the Hukou system greatly restricted population migration in China, especially from rural to urban areas [48]. During the famine period, interprovincial migration accounted for less than 1% of the total population [17]. On the other hand, in recent years, starting well

before this survey, there has been massive migration from rural to urban areas, which would probably lead to an underestimate of the association between prenatal famine and schizophrenia. Third, compared with the Dutch famine with high-quality birth and caloric intake statistics across the life course, we acknowledged limitations in the measurement of the Chinese famine severity. Up to now, however, the CSSI used in this study is a reasonable measure to assess the Chinese famine intensity within the scope of available data. Fourth, the breadth of the exposure measure combined a 4-year (1959–1962) measure of CSSI at the provincial level. Thus, it is not possible to make any precise statements about timing of exposure, other than that the respondent's province suffered from more or less severe famine during the period of gestation. From this perspective, the measure of famine exposure is somewhat crude. This is compensated, however, by the use of a method that is now standardized and accepted. Finally, we had no specific data on the reliability of diagnosis following the guidelines of ICD-10 criteria even though we know the psychiatrists' training and diagnostic process of schizophrenia. Despite the limitations, the study design was strongly enhanced by the medical ascertainment of schizophrenia by psychiatrists according to the ICD-10, access to multiple sociodemographic factors, and considering famine intensity across regions from a nationally representative, population-based survey with large sample size.

5. Conclusions

Our study supports the view that prenatal malnutrition exposure has a detrimental impact on risk of schizophrenia in adulthood in the rural population, not in the urban population. Further studies were needed to investigate corresponding mechanisms on this topic. This study implies that Chinese governments need to establish corresponding policies or programs to intervene the rural adults who were prenatally exposed to the Chinese famine.

Conflicts of interest

None declared.

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References

- [1] Horton R, Lo S. Nutrition: a quintessential sustainable development goal. *Lancet* 2013;382:371.
- [2] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2013;380:2224–60.
- [3] USAID. Camp David accountability report: actions, approach and results. Camp David, MD: USAID; 2012.
- [4] Gillespie S, Haddad L, Mannar V, Menon P, Nisbett N, The Maternal and Child Nutrition Study Group. The politics of reducing malnutrition: building commitment and accelerating progress. *Lancet* 2013;382:552–69.
- [5] Lumey LH, Stein AD, Susser E. Prenatal famine and adult health. *Annu Rev Public Health* 2011;32:237–62.
- [6] Susser E, St Clair D. Prenatal famine and adult mental illness: interpreting concordant and discordant results from the Dutch and Chinese Famines. *Soc Sci Med* (1982) 2013;97:325–30.
- [7] Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Arch Gen Psychiatry* 1992;49:983–8.
- [8] Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, et al. Schizophrenia after prenatal famine: further evidence. *Arch Gen Psychiatry* 1996;53:25–31.
- [9] Hoek HW, Susser E, Buck KA, Lumey LH, Lin SP, Gorman JM. Schizoid personality disorder after prenatal exposure to famine. *Am J Psychiatry* 1996;153:1637–9.
- [10] Hoek HW, Brown AS, Susser E. The Dutch famine and schizophrenia spectrum disorders. *Soc Psychiatry Psychiatr Epidemiol* 1998;33:373–9.
- [11] Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, et al. Prenatal exposure to famine and brain morphology in schizophrenia. *Am J Psychiatry* 2000;157:1170–2.
- [12] St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, et al. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. *JAMA* 2005;294:557–62.
- [13] Xu MQ, Sun WS, Liu BX, Feng GY, Yu L, Yang L, et al. Prenatal malnutrition and adult schizophrenia: further evidence from the 1959–1961 Chinese famine. *Schizophr Bull* 2009;35:568–76.
- [14] Song S, Wang W, Hu P. Famine, death, and madness: schizophrenia in early adulthood after prenatal exposure to the Chinese Great Leap Forward Famine. *Soc Sci Med* 1982;2009(68):1315–21.
- [15] Song S. Prenatal malnutrition and subsequent foetal loss risk: evidence from the 1959–1961 Chinese famine. *Demogr Res* 2013;29:707–28.
- [16] Almond D, Edlund L, Li H, Zhang J. Long-term effects of early-life development: evidence from the 1959 to 1961 China famine. The economic consequences of demographic change in East Asia, NBER-EASE, vol. 19. University of Chicago Press; 2010. p. 321–45.
- [17] Chen Y, Zhou LA. The long-term health and economic consequences of the 1959–1961 famine in China. *J Health Econ* 2007;26:659–81.
- [18] Huang C, Phillips MR, Zhang Y, Zhang J, Shi Q, Song Z, et al. Malnutrition in early life and adult mental health: evidence from a natural experiment. *Soc Sci Med* (1982) 2013;97:259–66.
- [19] Barker DJ. The fetal and infant origins of adult disease. *BMJ* 1990;301:1111.
- [20] Barker DJ. The fetal and infant origins of disease. *Eur J Clin Invest* 1995;25:457–63.
- [21] Kim S, Deng Q, Fleisher BM, Li S. The lasting impact of parental early life malnutrition on their offspring: evidence from the China Great Leap Forward Famine. *World Dev* 2014;54:232–42.
- [22] Li W, Yang DT. The great leap forward: anatomy of a central planning disaster. *J Political Econ* 2005;113:840–77.
- [23] Lin JY, Yang DT. Food availability, entitlements and the Chinese famine of 1959–61. *Econ J* 2000;110:136–58.
- [24] Almond D, Edlund L, Li H, Zhang J. Long-term effects of the 1959–1961 China famine: Mainland China and Hong Kong. National Bureau of Economic Research; 2007 NBER working paper series.
- [25] Zheng X, Chen G, Song X, Liu J, Yan L, Du W, et al. Twenty-year trends in the prevalence of disability in China. *Bull World Health Organ* 2011;89:788–97.
- [26] He P, Chen G, Wang Z, Guo C, Zheng X. Children with motor impairment related to cerebral palsy: prevalence, severity and concurrent impairments in China. *J Paediatr Child Health* 2017;53:480–4.
- [27] WHO. International classification of functioning, disability and health: ICF. *Encycl. Public Health* 2001;7:802–22.
- [28] United Nations. Guidelines and principles for the development of disability statistics. 2001 New York.
- [29] Zhang J. Study of disability survey method institute of population research (in Chinese). Beijing: Peking University; 2010.
- [30] Liu T, Song X, Chen G, Buka SL, Zhang L, Pang L, et al. Illiteracy and schizophrenia in China: a population-based survey. *Soc Psychiatry Psychiatr Epidemiol* 2013;48:455–64.
- [31] Liu T, Song X, Chen G, Paradis AD, Zheng X. Prevalence of schizophrenia disability and associated mortality among Chinese men and women. *Psychiatry Res* 2014;220:181–7.
- [32] Ulug B, Ertugrul A, Gögüs A, Kabakcı E. Reliability and validity of the Turkish version of the World Health Organization disability assessment schedule (WHO-DAS-II). *Turk J Psychiatry* 2001;12:121–30.
- [33] Huang C, Guo C, Nichols C, Chen S, Martorell R. Elevated levels of protein in urine in adulthood after exposure to the Chinese famine of 1959–61 during gestation and the early postnatal period. *Int J Epidemiol* 2014;43:1806–14.
- [34] Huang C, Li Z, Wang M, Martorell R. Early life exposure to the 1959–1961 Chinese famine has long-term health consequences. *J Nutr* 2010;140:1874–8.
- [35] Huang C, Li Z, Narayan KV, Williamson D, Martorell R. Bigger babies born to women survivors of the 1959–1961 Chinese famine: a puzzle due to survival selection? *J Dev Orig Health Dis* 2010;1:412–8.
- [36] Meng X, Qian N, Yared P. The institutional causes of China's great famine, 1959–1961. *Rev Econ Stud* 2015;82:1568–611.
- [37] Hu XF, Liu GG, Fan M. Long-term effects of famine on chronic diseases: evidence from China's great leap forward famine. *Health Econ* 2016;26:922–36.
- [38] Bertrand M, Dufo E, Mullainathan S. How much should we trust differences-in-differences estimates. *Q J Econ* 2004;119:249–75.
- [39] Athey S, Imbens GW. Identification and inference in nonlinear difference-in-differences models. *Econometrica* 2006;74:431–97.
- [40] Puhani PA, Sonderhof K. The effects of a sick pay reform on absence and on health-related outcomes. *J Health Econ* 2010;29:285–302.
- [41] Calkins K, Devaskar SU. Fetal origins of adult disease. *Curr Probl Pediatr Adolesc Health Care* 2011;41:158–76.
- [42] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* (London, England) 2016;388:86–97.
- [43] Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987;44:660–9.
- [44] Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* 2002;25:409–32.
- [45] Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol* 2011;93:23–58.
- [46] Kim S, Fleisher B, Sun JY. The long-term health effects of fetal malnutrition: evidence from the 1959–1961 China Great Leap Forward Famine. *Health Econ* 2016;26:1264–77.
- [47] Wang F-L. Organizing through division and exclusion: China's hukou system. Stanford University Press; 2005.
- [48] Gooch E. Estimating the long-term impact of the great Chinese famine (1959–61) on modern China. *World Dev* 2017;89:140–51.