



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

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