Malnutrition in early life and neurodevelopmental disabilities in adulthood: Evidence from the Chinese 1959-61 famine

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ABSTRACT

We use the Chinese 1959-61 Chinese famine as a natural experiment to test the hypothesis that environmental insults during gestation and the early postnatal period may increase the risk of neurodevelopmental disabilities in adulthood. The data was from the 2006 China Second National Survey on Disability (CSNSD). Results from our difference-in-difference model show that compared with the 1963-1964 birth cohort, who were conceived after the famine, the cohort born during the famine (between 1959-1961) had a 1.66 (CI: 1.39-1.97; $p<0.001$) higher odds of having an intellectual disability and a 1.48 (CI: 1.20-1.82; $p<0.001$) higher odds of having a speech disability. No relationships were observed between famine exposure and vision or hearing disability. Our findings suggest that severe and prolonged nutritional deprivation in the critical early period of life (conception to year two) may adversely impact neurologic development. These findings may have significant implications for pregnant women and infants undergoing poverty and chronic malnutrition in both developed and developing countries.

INTRODUCTION

Existing evidence suggests that the first thousand days of life (from conception to age two) is the most critical stage of human brain development(Andersen 2003; Schore 2003). The volume of the human brain increases more during the first year of life than during any other period of life(Giles 1993; Schore 2003), and most brain functions such as vision, hearing, speech, and the expression of higher cognitive function are largely developed by age two(Grantham-McGregor et al. 2007; Thompson and Nelson 2001). Disruptions in the normal course of development during this critical phase may have profound long-term consequences and may lead to neurodevelopmental disability (Andersen 2003; Grantham-McGregor et al. 2007; Thompson and Nelson 2001). Neurodevelopmental disabilities in adults are an important global public health issue and an estimated 5-30 per thousand people in the world are afflicted with this condition(Maulik et al. 2011; Wen 1997; Westerinen et al. 2007). In the United States, an estimated 2.5 million people, approximately 1% of the total population, suffer from intellectual disability, among whom only 31% are employed(Blanck 1998; Disability 2004). The lifetime *per capita* costs of significant intellectual disability are estimated to exceed more than $1 million in the US(Prevention 2004).

The biological basis of neurodevelopmental disability is poorly understood(Ramakers 2000). Genetic abnormalities and prenatal exposure to alcohol or drugs are known to be associated with neurodevelopmental defects in adulthood(Harris 2005; Heikura et al. 2008; Morgane et al. 1993). Increasing scientific evidence indicates that malnutrition experienced during the critical period of brain development from conception to two years of age also has lifelong consequences that are not reversed by adequate nutrition later in life(de Groot et al. 2011; Galler and Barrett 2001; Hoorweg 1976; Stein et al. 1972).

In the absence of randomized trials on undernutrition due to ethnical concerns, famines provide a quasi-experimental setting for examining the potential long-term impact of malnutrition(Lumey et al. 2007; Susser 1977). The most extensively-studied famine is the Dutch Hunger Winter, which occurred at the end of World War II from 1944-1945 and was caused by an embargo on food transports imposed by the German occupying forces(de Rooij et al. 2010; Lumey et al. 2007). Research to date suggests that exposure to the Dutch famine during gestation has been associated with an increased risk of schizophrenia(Susser et al. 1996), schizoid personality disorder(Hoek et al. 1996), and white matter hyperintensities(Pol et al. 2000). However, evidence regarding famine exposure and cognitive function is conflicting. One study found no association between prenatal famine exposure and intelligence quotient (IQ) (assessed by Raven Progressive Matrices scores) among 19-year-old men(Stein et al. 1972). Another study found no effects of prenatal famine exposure on general intelligence, memory function, or perceptual motor learning, but found an association between famine exposure during the early stage of gestation and a selective attention task for men and women aged 56-59 years(de Rooij et al. 2010). A third study found no overall association between prenatal famine exposure and cognitive performance among 59-year-old women, but investigators could not exclude an association specific to early pregnancy exposure during weeks 1-10(de Groot et al. 2011).

The Dutch famine had a well-defined but brief duration (~5 months) and, while severe, it afflicted an otherwise well-nourished population that may have been somewhat buffered from the effects of malnourishment (Huang et al. 2010b). In contrast, the Chinese famine of 1959-1961 occurred in a setting of chronic nutritional deficiencies, had a longer duration and caused widespread severe undernutrition, which resulted in an estimated 30 million fatalities(Ashton et al. 1984; Huang et al. 2010b; Smil 1999). The famine was caused by a combination of harsh

forced policy and institutional changes, in particular the Great Leap Forward campaign, which prioritized industrialization at the expense of agricultural development. In addition, adverse weather conditions including floods and droughts may have exacerbated the famine(Ashton et al. 1984; Chen and Zhou 2007; Dikötter 2010; Huang et al. 2010a; Huang et al. 2010b; Smil 1999). Many studies have been published examining the association between exposure to the Chinese famine and long-term health outcomes(Huang et al. 2010a; Huang et al. 2012; Huang et al. 2010b; Luo, Mu and Zhang 2006; Mu and Zhang 2011; Song, Wang and Hu 2009; St Clair et al. 2005; Yang et al. 2008; Yi et al. 2010).

We examined the relationship between famine exposure during gestation and/or the postnatal period and risk of a spectrum of neurodevelopmental disorders including intellectual, speech, vision, and hearing disabilities in adulthood among 538,454 Chinese participants in a national survey on clinically-significant disabilities. We hypothesized that famine exposure would be associated with a higher risk of neurodevelopmental disorders measures among Chinese born during the famine years (1959-1961) who were exposed to famine during both during gestation and in infancy when compared with cohorts born after the famine.

METHODS

Classification and Evaluation of Neurologic and Physical Disabilities

We used data from the 2006 China Second National Survey on Disability (CSNSD), which is archived at the China Research Center for Disability and Development at Peking University in Beijing. The CSNSD contains current, detailed, and nationally representative data on neurologic and physical disabilities. Using a stratified, multi-phase, and cluster probability sampling design, the CSNSD covers all provinces, autonomous regions, and directly-controlled municipalities in mainland China. More than 2.5 million Chinese from 31 provinces and 734

cities/counties were interviewed(Chen, Cui and Zhang 2007; Liu et al. 2009a; Liu et al. 2009b). Results of a post-survey quality check showed omission rates of 1.31 per thousand in the resident population and 1.12 per thousand in the disabled population(China 2006). Based upon the conceptual framework of the International Classification of Functioning, Disability and Health(Organization 2001), the CSNSD defines a disabled person as having at least one abnormality in anatomical structure or the loss of a certain organ or function (either psychological or physiological) or the loss of (totally or in part) the ability to perform an activity normally(Stein et al. 2007). Diagnoses of disability with the CSNSD were performance-based instead of self-reported, which is common in other studies. During data collection, interviewers screened respondents with questions about the presence of disabilities and those identified as potentially disabled were examined by a physician. Trained physicians conducted a variety of tests and examinations to confirm the diagnosis of disability status. Diagnosis of intellectual disability was based on the Wechsler Intelligence Scale for Adults-Chinese Revised short forms and the Adaptive Behavior Assessment System (ABAS II), and was defined as an intelligence quotient <70 and at least two adaptive behavioral disorders present. Other disabilities diagnosed by the physicians included: a) speech: language disorders lasting more than one year b) visual: uncorrectable poor vision or restriction of the visual field in both eyes, and c) hearing: damage to the structure and function of the auditory system and average hearing loss > 40 dB HL in the better ear.

Famine intensity

Using a methodology that was employed in previous studies (Huang et al. 2012; Huang et al. 2010b), we assessed famine severity by the cohort size shrinkage index (CSSI), which relied on the relative size of famine birth cohorts compared to near cohorts in the 1% sample of China's

1990 population census. For each province, we identified the mean cohort size of individuals born during three years before the famine (1956-1958) and three years after the famine (1962-1964), labeled as *N_normal* , as well as the mean cohort size of individuals born during the famine years (1959-1961), labeled as *N_famine*. We then calculated the CSSI as the difference between *N_normal* and *N_famine* divided by *N_normal*; a larger value of the CSSI indicated a more intense or severe famine. As shown in Figure 1, Anhui (CSSI=0.63) and Sichuan (CSSI=0.62) provinces, where famine was the most severe, had the highest CSSI values. The cohort shrinkage was primarily caused by fertility reduction and excess mortality during the famine, which was confirmed by high correlations of the CSSI with the excess mortality rate ($r=0.85$; $p<0.001$) and fertility reduction ($r=0.90$; $p<0.001$)(Huang et al. 2012).

Analysis

We restrict our analysis to four groups: a) those born before the famine in 1956-1958 (the "pre-famine" birth cohort), who were born before the famine and exposed to the famine postnatally, b) those born in 1959–1961 (the "famine" birth cohort), who were born during the famine and exposed to the famine during gestation and postnatally, c) those born in 1962, who were born immediately after the famine but may have been partially exposed to the famine during gestation and d) those born in 1963-1964 (the "post-famine" cohort), who were not exposed to the famine. The famine impact across birth cohorts was also conditional on famine intensity of the region where the individuals were born and raised. Thus, we constructed a difference-in-difference estimator as following to estimate the famine effect on intellectual disability that varied by both birth year and region, similar to the analytical strategy in previous studies(Chen and Zhou 2007; Huang et al. 2012; Huang et al. 2010b).

$$\log(\ E(Y_{irk}\,|\,CSSI_{\ r}, Cohort_{\ k})) = B_0 + \phi_f region_{\ f} + \alpha_k Cohort_{\ k} + \gamma CSSI_{\ r} + \sum_{k=1}^{3} \beta_k (CSSI_{\ r} \times Cohort_{\ k}) + sex$$

where Y_{irk} refers to whether an individual born in province *r* and period *k* (*k*=1 refers to the pre-famine cohorts (1956-1958), *k*=2 refers to the famine cohorts (1959-61), *k*=3 refers to the near-end famine cohort, with the reference group being the post-famine cohort; *i* refers to whether the individual had an intellectual disability or not; α_k is the cohort fixed effect; ϕ_f is the region fixed effect; and $CSSI_r$ is the cohort size shrinkage index in prefecture *r* (an indicator of famine intensity). β_K is the coefficient of the interaction between the CSSI and the cohort group dummy variables (CSSI x COHORT) and is a measure of the double difference representing the impact of famine exposure on intellectual disability. A detailed discussion on estimating "treatment" effect using the interaction term in non-linear difference-in-difference models was presented elsewhere(Athey and Imbens 2006; Puhani and Sonderhof 2010). To estimate the average effect, we multiplied the interaction coefficient by the mean CSSI across all regions. We applied cluster-robust standard errors (confidence intervals) to adjust for clustering. We controlled for the sex of the participants, but not for other covariates such as the socioeconomic status of participants, because such variables may be affected by disability status. Using a similar approach, we estimated the famine effect on speech, vision, and hearing disabilities, and conducted all analyses using Statistical Analysis Software, version 9.0.

RESULTS

Table 1 presents the prevalence of vision, hearing, speech and intellectual disabilities for the sample by birth year. The smaller size for the cohorts born during the Chinese famine (1959-1961) reflects the decline of fertility and excess mortality at that time.

The left panel of Table 2 displays estimates of the average famine impact by birth cohort on intellectual disability. Compared with the post-famine birth cohort (1963-1964) (the reference group), the famine cohort (1959-1961) exhibited an increased risk of intellectual disability (OR=1.66; CI: 1.39-1.97; P<0.001), while the pre-famine cohort (1956-1958) exhibited a decreased risk (OR=0.74; CI: 0.66-0.83; P<0.001) and the 1962 birth cohort showed no effect on intellectual disability. Similarly, famine exposure was associated with speech disability in adulthood (see Table 2, right panel). Compared with the post-famine birth cohort (1963-1964), the famine cohort (1959-1961) had a higher risk of speech disability (OR=1.48; CI: 1.20-1.82; p<0.001); while the pre-famine birth cohort exhibited a marginally significant decreased risk of speech disability (OR=0.89; CI: 0.77-1.02; p<0.096). Famine exposure was not related to vision disability or hearing disability (see Table 3).

As shown in Figure 2, we did a post-hoc secondary analysis of famine exposure on intellectual disability and speech disability by single year of birth rather than combined period of birth, and we extended the study sample to also include the years 1951-1955. When compared to the Chinese conceived after the famine (the 1963-1964 birth cohort), the 1960 birth cohort, who were born at the peak of famine, exhibited the highest risk of intellectual disability (OR=1.97, CI=0.53-2.55, p<0.001) and speech disability (OR=1.82, CI=1.34-2.49, p<0.001), followed by those born in 1961 whose risk of intellectual disability was increased by 63% (OR=1.63, CI=1.23-2.14, p<0.001) and speech disability was increased by 54% (OR=1.54, CI=1.09-2.17, p<0.001).

DISCUSSION

We examined the association between exposure to the Chinese famine of 1959-1961 during gestation and/or the early postnatal period and neurodevelopmental disabilities in

adulthood using data on a nationally representative sample in China. We found significant and strong associations between famine exposure and an increased risk of intellectual and speech disabilities among Chinese born during the famine. These findings were consistent with similar studies on the Dutch Hunger Winter, which found that famine exposure in gestation was associated with an increased risk of neurodevelopment outcomes including lower intelligence quotient (IQ) scores and schizophrenia(Hoek et al. 1996; Susser et al. 1996). Our findings are also consistent with those from previous studies on exposure to the Chinese famine and adult neurological outcomes based on other samples. Specifically, famine exposure was associated with a higher risk of schizophrenia in Wuhu in Anhui province (RR=2.30; CI: 1.99-2.65 for the 1960 birth cohort and RR=1.93; CI: 1.68-2.23 for the 1961 birth cohort)(St Clair et al. 2005) and in the surrounding counties of Liuzhou city in Guangxi province (RR=1.68; CI: 1.48-1.92 for 1960 birth cohort; RR=2.25; CI: 2.00-2.52 for 1961 birth cohort)(Xu et al. 2009), where the famine was the most severe.

A possible mechanism that may explain the association between famine exposure and neurocognitive disorders are deficiencies in macro and micronutrients during gestation and lactation(Monk, Georgieff and Osterholm 2013). Neuroscience research indicates that most brain development including sequential growth, prodigious proliferation, and overproduction of axons and dendrites, as well as synapses formation, occurs during gestation and the first two years of life(Andersen 2003). This critical period of brain development is highly vulnerable to insults, which can result in irreversible neurologic deficits. Nutrients are essential to this cell growth and development and may be particularly important to neurocognitive processes and behavioral adaption in early life(Georgieff and Rao 2001; Monk, Georgieff and Osterholm 2013). Specifically copper, protein B vitamins, folate and iodine are examples of nutrients that have

demonstrated effects on brain development(Georgieff and Rao 2001; Monk, Georgieff and Osterholm 2013). Deficits in maternal nutrients, such as in the case of widespread famine, can constrain cell proliferation during early pregnancy and can impact affect cell differentiation, in complexity and size, possibly altering neuron formation during late pregnancy(Georgieff and Rao 2001; Monk, Georgieff and Osterholm 2013). Furthermore, although the volume of breast milk is generally protected among malnourished women(Allen and Graham 2004), low maternal intake of micronutrients can subsequently reduce the amount of micronutrients that infants receive via breast milk, potentially impacting their development(Allen 2005). A second, less frequently cited mechanism that explains the association between famine exposure and neurocognitive development, is the impact of maternal distress, which may also have neurotoxic effects on the fetus' brain development(Monk, Georgieff and Osterholm 2013). Specifically, under conditions of extreme stress, such as during a famine, developmental pathways may be less strictly regulated, promoting phenotypic diversity(Rosenberg and Hastings 2004; Rutherford 2003; Waddington 1942).

It was noteworthy that individuals born before the famine in regions where famine was severe tend to have lower risk of intellectual disability and speech disability, a similar pattern was also observed in a study on Chinese famine and schizophrenia where the prefamine cohorts showed a lower relative risk of schizophrenia compared with post-famine cohorts(St Clair et al. 2005). In the centrally planned economy of China, the quote of food procurement of a region for a given year was based on its agricultural production of previous years and the productive regions were likely to be over-procured; such a system tended to push the more productive regions into more severe famine than less productive regions(Meng, Qian and Yared 2010). Therefore, those who born before the famine in productive regions may have benefited from a

better nutrition and food supply in fetal and early postnatal life although they may be exposed to a more severe famine later in childhood.

Our study has several limitations. First, we could not draw conclusions regarding the mechanisms underlying the famine exposure and intellectual and speech disability, and we did not have information on diets, maternal body composition and weight gain during pregnancy, macro- and micronutrient deficiencies, toxin exposure, or on distress experienced during the famine. Second, due to uncertainty surrounding the precise duration of the famine, we were unable to assess the effects of the famine by individual months or trimesters, and thus we examined the effect by birth cohorts. A third limitation of this study is that we assumed that the majority of study subjects, who were born in 1951-1964, experienced the famine in the province where they were residing in 2006, the year of the survey. Until the 1990s, there was little internal migration in China because of restrictions imposed by the residence registration system (or *hukou*), which was strictly reinforced in both cities and rural areas by the public security system(Athey and Imbens 2006). Although it is believed that migration was rare among this population, we did not have data to estimate the extent of possible biases that migration might have introduced to our results. It is also important to note that the rates of famine exposure were likely underestimated because of survival selection. It has been well-documented that more robust individuals usually survive periods of extreme stress such as famines and that these survivors represent a group with healthier endowments, however we were unable to adjust for survival selection in this analysis. A final limitation of this study was that, due to the ecologic research design, we were unable to collect information on family medical history. Future research may benefit from a sibling research design, which enables comparison between individuals with comparable familial and genetic backgrounds(Susser, Eide and Begg 2010).

To our knowledge, this was the first study to use data from a national survey to examine the effects of exposure to the Chinese famine of 1959-1961 on intellectual, speech, hearing and vision disabilities. Based on our findings, we can conclude that deprivation of micro- and macronutrients during gestation and/or lactation may markedly elevate the risk of neurodevelopmental disorders that manifest later in life.

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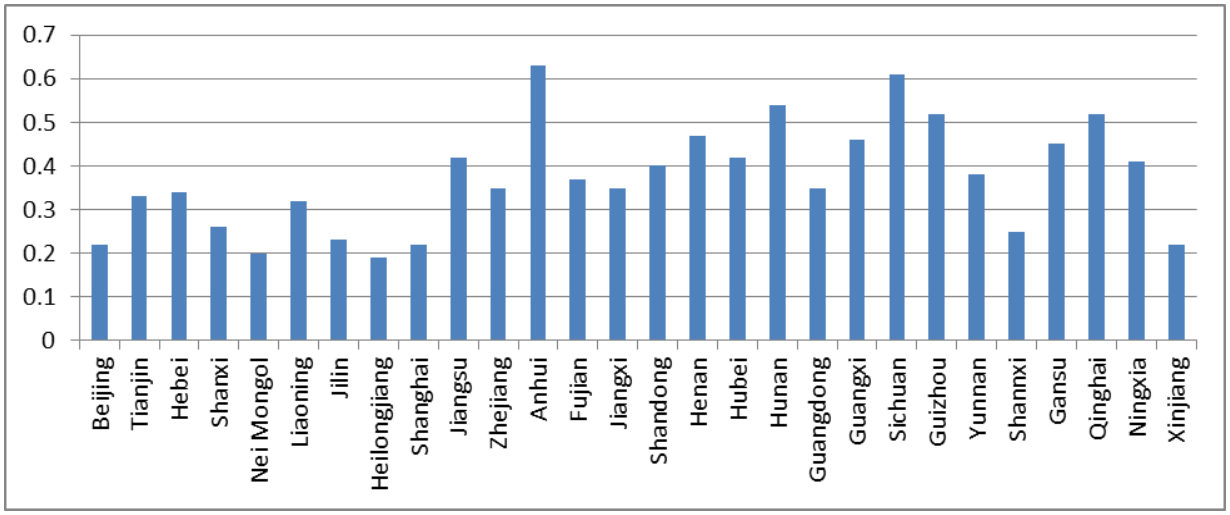
Figure 1. Cohort size shrinkage index (CSSI) by province in China



Source: The 1990 Census of Chinese Population

Table 1. Prevalence of vision, hearing, speech, and intellectual disabilities for the years 1951 through 1964

Birth Year	Cohort size (N)	Prevalence of disabilities (%)			
		Vision	**Hearing**	**Speech**	**Intellectual**
1951	31771	1.19	1.84	0.55	0.63
1952	38748	1.16	1.81	0.67	0.66
1953	38435	0.93	1.53	0.47	0.67
1954	41193	0.87	1.37	0.62	0.70
1955	39631	0.76	1.43	0.55	0.58
1956	38960	0.64	1.28	0.57	0.66
1957	41719	0.70	1.22	0.54	0.65
1958	36704	0.61	1.05	0.48	0.59
1959	27963	0.62	0.86	0.45	0.62
1960	28957	0.57	0.71	0.38	0.59
1961	24381	0.46	0.73	0.39	0.62
1962	46591	0.44	0.68	0.40	0.55
1963	55961	0.43	0.72	0.43	0.56
1964	47440	0.37	0.73	0.43	0.61

Source: The 2006 China Second National Survey on Disability (CSNSD)

Table 2. Famine exposure in gestation and/or early postnatal period and intellectual disability and speech disability in adulthood

Period of birth	Intellectual disability			Speech disability		
	OR	**95% CI**	**P-value**	**OR**	**95%**	**P-value**
Pre-famine cohort (1956-1958)	0.74	(0.66, 0.83)	<0.001	0.89	(0.77, 1.02)	0.096
Famine cohort (1959-1961)	1.66	(1.39, 1.97)	<0.001	1.48	(1.20, 1.82)	<0.001
The 1962 cohort	0.95	(0.77, 1.17)	0.626	1.09	(0.85, 1.39)	0.510

Abbreviations: CI, confidence interval; OR, odds ratio.
*Reference group: 1963-1964 birth cohort

Table 3. Famine exposure in gestation and/or early postnatal period and vision and hearing disabilities in adulthood

Period of birth	Vision disability			Hearing disability		
	OR	**95% CI**	**P-value**	**OR**	**95%**	**P-value**
Pre-famine cohort (1956-1958)	0.96	0.83-1.10	0.526	0.95	0.85-1.05	0.310
Famine cohort (1959-1961)	0.97	0.79-1.19	0.769	1.08	0.91-1.27	0.372
The 1962 cohort	0.96	0.93-0.98	0.01	1.02	0.84-1.25	0.824

Abbreviations: CI, confidence interval; OR, odds ratio.
*Reference group: 1963-1964 birth cohort

Figure 2. Odds ratio of famine exposure on intellectual disability and speech disability by year of birth