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Prenatal Malnutrition and Adult Schizophrenia: Further Evidence From the 1959-1961 Chinese Famine

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***Objective*: Evidence from the 1944–1995 Dutch Hunger Winter and the 1959–1961 Chinese famines suggests that those conceived or in early gestation during famines, have a 2-fold increased risk of developing schizophrenia in adult life. We tested the hypothesis in a second Chinese population and also determined whether risk differed between urban and rural areas. *Method*: The risk of schizophrenia was examined in Liuzhou prefecture of Guangxi autonomous region. Rates were compared among those conceived before, during, and after the famine years. Based on the decline in birth rates, we predicted that those born in 1960 and 1961 would have been exposed to the famine during conception or early gestation. All psychiatric case records in Liuzhou psychiatric hospital for the years 1971 through 2001 were examined and clinical/sociodemographic data extracted by psychiatrists blind to exposure status. Data on births and deaths in the famine years were also available, and cumulative mortality was estimated from later demographic surveys. Evidence of famine was verified, and results were adjusted for mortality. Relative risks (RRs) for schizophrenia were calculated for the region as a whole and for urban and rural areas separately. *Results*: Mortality-adjusted RR for schizophrenia was 1.5 (1960) and 2.05 (1961), respectively. However, the effect was exclusively from the rural areas RR = 1.68 (1960) and RR = 2.25 (1961). *Conclusions:* We observe a 2-fold increased risk of schizophrenia among those conceived or in early gestation at the height of famine with risk related to severity of famine conditions.**

Key words: prenatal/famine/china/schizophrenia

Introduction

Schizophrenia is a complex psychiatric disorder with both environmental and genetic factors contributing to overall risk.[1] Schizophrenia is increasingly viewed as a neurodevelopmental disorder with environmental influences during early brain development able to affect risk of schizophrenia. Prenatal nutritional deficiency may be such an environmental exposure. The main evidence comes from studies of the 1944–1945 Dutch Hunger Winter and the *1959–1961 Chinese famine.[2–5] In the former, there was a sharp and time-limited decline in food intake. It lasted from shortly after the Nazi blockade of occupied western Holland in 1944 until liberation in May 1945. There was a 2-fold increase in risk of schizophrenia among children conceived and in early gestation at the height of the famine. The overall RR was 2.0. For men the RR was 1.9, and for women RR was 2.2. However, the study size was modest. The 1959–1961 Chinese famine affected all provinces in China.[6–8] It followed a period of immense social and economic upheaval often called the Great Leap Forward. There was collectivization of agriculture, adoption of flawed agricultural practices of the Russian geneticist Lysenko, and reduction of cultivated land. The findings from Anhui province, on a sample size many times larger than the Dutch series, showed for the most exposed cohorts an effect size similar to the Dutch. Based on the Dutch findings, we predicted that as the birth rate dropped, the relative risk (RR) of schizophrenia would increase. The mortality-adjusted RR of schizophrenia for the 2 key years in which the birth rate declined was 2.30 for 1960 and RR = 1.93 for 1961.[5]

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*The Chinese famine is traditionally referred to as the 1959–1961 famine, and this article follows the convention. However, the timing of the famine and its intensity varied from province to province. 1959 and 1960 were the key famine years, and in half of the provinces the worst of the famine was over by early 1961. Sichuan province was a notable exception with famine conditions persisting throughout 1961.

The Chinese findings are highly statistically significant, but in contrast to the Dutch study there are no data on month of birth for cases or controls nor is detailed information available on dietary intake from month to month. They nevertheless are consistent with and point to early gestation being the period of critical exposure[5]. Our main concern was difficulty in assessing their reliability. Not only was the effect size of 2 modest but the Chinese famine took place in a developing country nearly 50 years ago. Infant mortality rates during the famine years, especially in Anhui province, where the study was conducted, were high and could only be estimated indirectly from incomplete later census data. Undetected confounders may also have been present in the official statistics for births and deaths during the famine years. In view of these potential sources of statistical artifact, we therefore felt it essential to try replicating the Chinese findings by conducting a second study. In contrast to the Dutch study, there were no records of daily nutritional intake. However, on almost all indices famine conditions were more severe in the countryside than in city areas with average daily caloric intake below 1500 kilocalories.[6,7] We therefore decided to see if risk was related to the severity of famine conditions by comparing RR rates in the exposed cohorts in rural and city areas separately.

Methods

Selection of Second Chinese Location

Our aims were try to replicate the Chinese famine findings in a second population drawn from a separate part of China where famine conditions, although severe, were not on the same catastrophic scale. A number of criteria required to be satisfied in our selection of a second Chinese location. These included a large psychiatric hospital acting as sole source of referral for a well-defined surrounding geographical region, evidence of famine conditions in this region, good psychiatric case records extending over a period of 1971–2001, willingness to participate in the study, and access to local annual birth records as well as data from subsequent censuses. Liuzhou city and surrounding counties in Guangxi autonomous region (AR) were able to satisfy these criteria. The famine was less severe in Guangxi AR than in Anhui province but nevertheless considerable by any standards other than that of the Great Leap Forward famine itself (estimates of abnormal deaths for Guangxi AR for 1959–1961 famine cluster range from 500 000 to 900 000.[8–10] Judging by the reductions in birth rates, conditions were similar to the Dutch Hunger Winter at its height. Liuzhou, located on the banks of the Liu River, is some 1700 km south west of Anhui province. It is the second largest city in Guangxi (total population 45 million) and the main industrial center. The climate is milder, and the diet is based on rice rather than noodles. Ethnic minority groups form a high proportion of the rural population in the area of study. Zhuang, a Tai people, is the biggest minority group, but there are also Miao, Yao and Yi peoples. The great majority of the minority peoples live in the countryside.

The Longquanshan psychiatric hospital sited in Liuzhou is one of the biggest in China and provides inpatient and outpatient psychiatric care to the people of Liuzhou city and 18 surrounding counties. These latter were overwhelmingly rural and agricultural at the time of the famine. We surveyed all inpatient and outpatient referrals from 1971 to 2001. All psychiatric case records were examined by psychiatrically trained medical practitioners, blind to the nature of the exposure. Clinical and socioeconomic details were systematically extracted from the case notes, along with the most recent Chinese Classification of Mental Disorders (CCMD) diagnosis made by the responsible psychiatrists. The 3rd Edition (CCMD-3) closely follows the World Health Organization *International Classification of Diseases* (*ICD*), *Tenth Edition* in its criteria for schizophrenia.[11] Prior versions of CCMD have also demonstrated high concordance with *ICD* criteria for diagnosing schizophrenia, eg, CCMD-2 and *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, over 98% agreement, $k = 0.98$.[12] We interrogated the case notes employing the same 50-item checklist used in the Anhui study. For each case, this included patient sociodemographics, clinical diagnosis, psychiatric symptoms, and presence or absence of family history of major mental illness. The information was then coded by designating each case with an identification number and entered into a computer database. For the purpose of the present study, we selected all cases with a CCMD diagnosis of schizophrenia. (*International Classification of Diseases, Eighth Edition*, and *International Classification of Diseases, Tenth Edition*, code 295, corresponding to *International Classification of Diseases, Tenth Edition*, codes F20, F21, F23.1–F23.2, F25) between 1971 and 2001.[13] Examination of checklists for verification of schizophrenia diagnoses is described in Supplement Part one.

Birth and Death Rates for Liuzhou and Surrounding Counties

We used the same official source of population data as used in the Anhui study.[14] These gave number of

Table 1. Number of Births, Birth Rates, and Death Rates for Years 1956 Through 1965 in Liuzhou City and 18 Surrounding Counties of Liuzhou Prefecture

	No. of Births			Birth Rate %[a]			Death Rate %[b]		
Year	Urban Area	Rural Area	Whole Area	Urban Area	Rural Area	Whole Area	Urban Area	Rural Area	Whole Area
1956	9409	91 860	101 269	38.24	31.44	30.83	7.26	13.62	13.11
1957	8838	105 787	114 625	43.29	33.47	34.06	7.2	12.77	12.43
1958	9208	104 087	113 295	35.79	32.38	32.61	7.39	11.99	11.67
1959	9106	85 742	94 848	29.66	26.54	26.79	12.83	24.22	23.31
1960	10 617	56 467	67 084	31.01	17.65	18.94	10.34	37.88	35.22
1961	7484	52 011	59 495	22.15	16.65	17.19	11.67	19.61	18.83
1962	12 562	130 371	142 933	39.48	41.11	40.96	7.94	10.08	9.88
1963	13 787	160 380	174 167	43.86	48.71	48.29	6.71	12.77	11.84
1964	10 578	138 117	148 695	33.03	40.44	39.8	6.43	10.42	10.08
1965	9017	162 805	171 822	27.01	46.05	44.41	5.25	9.58	9.2

[a]Birth rate indicated the natality or per 1000 people per year.
[b]Death rate indicated the total number of deaths per 1000 people per year.

births and deaths for each of the calendar years under investigation for Liuzhou city and each of the surrounding 18 counties.

Statistical analyses were essentially identical to those in Anhui study. Exposed birth years 1960 and 1961were compared with 6 years 1956 through 1958 and 1963 through 1965. Those born in 1960 and 1961 were considered exposed birth cohorts under the assumption they were exposed at conception or during early gestation to famine conditions.

The risk of schizophrenia for each year of birth was measured by the cumulative incidence of outpatient consultations and inpatient admissions from the years 1971 to 2001. Individuals were only counted once. More than 97% of cases examined were born in Guangxi and, from the recorded addresses, lived in the Liuzhou area at the time of first referral. The cumulative risk for the birth cohorts was calculated by dividing the number of persons with schizophrenia born in each year by the total number of recorded births for each year. This gave an unadjusted cumulative risk. Because detailed mortality data were not available for all the years spanned by the study, statistics using survival methods could not be performed. To adjust for differential mortality, we adopted the same approach as the Anhui study and calculated the number of individuals in each birth cohort surviving childhood.[3] The procedure is described in the previous article.[3] We allocated those born in the six years 1956 through 1958 and 1963 through 1965 as unexposed birth cohorts because individuals were conceived or in utero well outside the famine period. Those born in 1960 and 1961 were considered exposed birth cohorts under the assumption they were exposed at conception or during early gestation to famine conditions. RR was obtained by comparing exposed vs unexposed birth cohorts. Mortality-adjusted risks were then calculated using estimates of cumulative mortality rates derived from the 1982 and the 1988 population surveys.[25–27.] In an attempt to explore possible mechanisms underlying any observed change in cumulative risk and relative risk during the famine years, we performed stratified analyses to calculate the schizophrenia risks and RRs according to area (Liuzhou city vs surrounding counties). Exploratory analyses were also performed stratifying by ethnicity. All the above statistical analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, IL), and a 2-tailed probability P value less than .05 was considered statistically significant.

The study was reviewed and approved by the ethics committee of the National Genome Center, Shanghai.

Results

Evidence of Famine From Birth Rates and Mortality Rates

Table 1 provides the birth and death rate for Liuzhou and its 18 surrounding districts that were served by Longquanshan psychiatric hospital, Liuzhou, for the years before, during, and after the famine. Fertility or birth rate decline, which is an accurate indicator of starvation in the periconceptional period or during early gestation, showed a modest (13%) drop in 1959, followed by 38% and 45% drops in 1960 and 1961, respectively. A rebound increase in fertility occurred in 1962 after the famine was over. The death rate doubled in 1959, tripled in 1960, but was only 50% above its prefamine level by 1961. This clearly indicates that severe famine started in 1959, peaked in 1960, and fell off rapidly in 1961.This is consistent with the historical records which report that severe famine conditions started to appear in Guangxi AR in the

summer of 1959 and were relieved in early 1961. Birth rates decreased by around 50% for the years 1960 and 1961 in the rural areas. In Liuzhou city, the birth rate decrease was substantially less and occurred predominantly in 1961. Mortality was also considerably higher in the countryside than in the city. By 1962, fertility was above prefamine levels in town and countryside. These data provide conclusive evidence of famine in Liuzhou area most severe in the years 1959 and 1960.

Increased Risk of Schizophrenia

The decline in birth rates during the famine years was accompanied by at most a modest decline in the absolute number of cases of schizophrenia in 1960 and no decline in 1961 (see table 2). Both sexes were equally affected, and there was no difference in age of first treatment of schizophrenia among those born before, during, or after the famine years. The proportion of cases with a first-degree relative with major mental illness (familial cases) showed no clear cut pattern. Table 3 shows the numbers of cases of schizophrenia born in each of the years from 1956 through 1965 and gives the risk of schizophrenia as a percentage of the number of births. The cumulative risk of schizophrenia during the years 1960 and 1961 increased compared with the rates in the reference years, both before and after.

Table 3 also compares the famine exposed birth cohorts of 1960 and 1961 with 6 years (1956–1958 and 1963–1965) well outside the famine epoch to produce RRs. These years selected for comparison were identical to the years used in Anhui study. Mortality-adjusted relative risks were RR = 1.50 (95% confidence interval [CI] = 1.35–1.68) (1960) and RR = 2.05 (95% CI = 1.86–2.27) (1961).

Increased Risk Worse in Countryside

Table 4 shows the rates of schizophrenia 1956 through 1965 separately for the surrounding counties and Liuzhou city. The absolute rate of schizophrenia was higher in Liuzhou city than in the surrounding countryside in all the years observed. For interpretation of these findings, see "Discussion." The RR in the countryside was RR = 1.68 (95% CI = 1.48–1.92) (1960) and RR = 2.25 (95% CI = 2.00–2.52) (1961). But in Liuzhou city, there was no increased RR of schizophrenia in the years 1960 and 1961 compared with the unexposed nonfamine reference years. Indeed, the RR for 1960 was apparently reduced.

Is the Countryside Risk Similar for Han Chinese and Ethnic Minorities?

We do not have separate birth rates for Han Chinese and minority Chinese so only exploratory analyses could be performed. We used the total birth rates of each year (from 1956 to 1965) and made the assumption that the ratio of Han vs minority births would remain essentially unchanged from year to year. We divided the number of Han Chinese cases and the number of minority Chinese cases who were born in each year by total number of births and then compared rates in exposed birth cohorts 1960 and 1961 with rates in the reference years separately for Han Chinese and minority Chinese. Increased RR was present in both Han Chinese and ethnic minorities, with RR in Han Chinese slightly higher than in the ethnic minorities. Han Chinese: RR = 1.88 (95% CI = 1.54–2.29) (1960) and RR = 2.36 (95% CI = 1.97–2.86) (1961) and Ethnic minorities RR = 1.55 (95% CI = 1.30–1.84) (1960) and RR = 2.17 (95% CI = 1.87–2.51) (1961). Chi square and P values are 25.05 and 5.578×10^{-7} and 107.56 and 3.354×10^{-25} for 1960 and 1961, respectively, for ethnic minorities.

It should be noted however that these are crude estimates because separate birth rates for Han Chinese and ethnic minorities were unavailable.

We saw no age of first treatment effects, and there was no change in proportion cases reporting a positive family history in those born in the years 1960 and 1961.

Discussion

Epidemiological investigations of the effect of prenatal famine on human populations are rare. It is highly unusual to have reliable clinical and demographic information. Although the 1959–1961 Chinese famine took place in a developing country undergoing a major political and economic upheaval, the information currently available is unexpectedly good. Longquanshan psychiatric hospital is one of the largest psychiatric hospitals in China and is the single referral hospital for Liuzhou city and 18 surrounding counties. A smaller number of cases are also referred from other parts of Guangxi AR, but during 1971–2001, virtually all patients from Liuzhou and surrounding counties, if referred, were referred to Longquanshan hospital. We included in our sample only patients born in Guangxi and resident in Liuzhou and the surrounding 18 counties at the time of first treatment. The sample size was roughly double our previous study in Anhui. We were able to stratify into urban and rural. The psychiatric case records were excellent with more or less complete data on age of onset, ethnicity, and gender.

It is important also to consider the limitations of the data. Almost all records had data on presence or absence of family history. However, this was not systematically recorded, with details of family structure and size; it was little more than presence or absence of schizophrenia or other psychosis in a first-degree relative. Comprehensive records of births and deaths in the Liuzhou prefecture for the years before, during, and after the famine were also available for analysis. The birth rates for the present study were derived from the same official source of population statistics, compiled by Department of Police as in the Anhui study. In this respect, the 2 studies are

Table 2. Clinical and Demographic Characteristics of Schizophrenia Cases Born Before, During, and After the Famine Years

		No Treated		Age of onset				Ethnicity (Nationality)		Area		Family History	
Year	No. of cases	Outpatient	Inpatient	No of Early Onset (%)	No of Late Onset (>25)	Average Age of Onset(SD)	Male (%)	Han Chinese	Minority	City	Country-side	With Family History (%)	Without Family History
1956	450	234	216	194 (43.11)	256	27.48 (8.02)	222 (49)	256	194	133	317	62 (14)	388
1957	457	247	210	221 (48.36)	236	27.26 (7.94)	243 (53)	229	228	141	316	52 (11)	405
1958	385	188	197	196 (50.91)	189	25.85 (7.71)	216 (56)	227	158	114	271	29 (8)	356
1959	386	183	203	210 (54.40)	176	25.59 (7.44)	201 (52)	218	168	129	257	52 (13)	334
1960	355	157	198	181 (50.99)	174	26.10 (7.04)	189 (53)	198	157	102	253	35 (10)	320
1961	451	182	269	243 (53.88)	208	26.09 (7.18)	238 (53)	232	219	120	331	53 (12)	398
1962	559	225	334	298 (53.31)	261	25.91 (6.72)	299 (53)	271	288	156	403	76 (14)	483
1963	654	270	384	388 (59.33)	266	24.76 (6.58)	350 (54)	342	312	197	457	100 (15)	554
1964	634	261	373	396 (62.46)	238	24.24 (6.19)	347 (55)	288	346	160	474	78 (12)	556
1965	643	260	383	421 (65.47)	222	23.51 (5.89)	341 (53)	307	336	152	491	100 (16)	543
Total	4974	2207	2767	2748 (55.25)	2226	25.50 (7.09)	2646 (53)	2568	2406	1404	3570	637 (13)	4337
1956–1958 and 1963–1965	3223	1460	1763	1816 (56.35)	1407	25.27	1719 (53)	1649	1574	897	2326	421 (13)	2802

Table 3. Estimated Mortality, Adjusted Risk, and Adjusted Relative Risk for Schizophrenia for Years 1956 Through 1965 in Liuzhou City and Surrounding Counties

Year	No of cases	No of Births	Unadjusted Risk %	Estimated Mortality %	Adjusted Risk %	Adjusted RR (95% CI)[a]	χ^2	*P* Value
1956	450	101 269	0.44	8	0.48			
1957	457	114 625	0.40	11	0.45			
1958	385	113 295	0.34	14	0.40			
1959	386	94 848	0.41	14	0.47	1.10 (0.99–1.23)	3.28	0.070
1960	355	67 084	0.53	18	0.65	1.50 (1.35–1.68)	53.61	2.446×10^{-13}
1961	451	59 495	0.76	14	0.88	2.05 (1.86–2.27)	212.10	4.783×10^{-48}
1962	559	142 933	0.39	9	0.43	1.00 (0.92–1.10)	0.001	.976
1963	654	174 167	0.38	7	0.40			
1964	634	148 695	0.43	7	0.46			
1965	643	171 822	0.37	8	0.41			
1956–1958 and 1963–1965	3223	823 873	0.39	8.9	0.43	1.00		

[a]The reference group was the years of 1956–1958 and 1963–1965. RR= relative risk, CI = confidence interval.

directly comparable. We think that these records are the most accurate available as a source of information on births and deaths for the years of interest. They are internally consistent, eg, patterns of changes in births and deaths were similar when examined at level of prefecture, region, and province: they were also compatible with population age structure for Liuzhou prefecture as documented in the 1982 and 1988 census.[15,16] These latter data are not directly comparable; however, because the census figures are for fiscal (June 30−June 30) years,

Table 4. Stratified Estimated Mortality, Adjusted Risk, and Adjusted Relative Risk for Schizophrenia for Years 1956 Through 1965, According to Area

Year	No of cases	No of Births	Unadjusted Risk %	Estimated Mortality %	Adjusted Risk %	Adjusted RR (95% CI)[a]	χ^2	*P* Value
18 Counties Surrounding Liuzhou City								
1956	317	91 860	0.35	9	0.38			
1957	316	105 787	0.3	12	0.34			
1958	271	104 087	0.26	15	0.31			
1959	257	85 742	0.3	16	0.36	1.06 (0.93–1.20)	0.73	.393
1960	253	56 467	0.45	21	0.57	1.68 (1.48–1.92)	62.66	2.460×10^{-15}
1961	331	52 011	0.64	16	0.76	2.25 (2.00–2.52)	198.85	3.724×10^{-45}
1962	403	130 371	0.31	10	0.34	1.02 (0.92–1.13)	0.11	.738
1963	457	160 380	0.29	8	0.31			
1964	474	138 117	0.34	8	0.37			
1965	491	162 805	0.3	8	0.33			
1956–1958 and 1963–1965	2326	763 036	0.31	9.6	0.34	1		
Liuzhou city								
1956	133	9409	1.41	5	1.49			
1957	141	8838	1.6	6	1.7			
1958	114	9208	1.24	8	1.35			
1959	129	9106	1.42	8	1.54	0.99 (0.82–1.19)	0.01	.929
1960	102	10 617	0.96	11	1.08	0.70 (0.57–0.85)	12.1	.001
1961	120	7484	1.6	8	1.74	1.12 (0.93–1.36)	1.39	.239
1962	156	12 562	1.24	5	1.31	0.84 (0.71–1.00)	3.9	.048
1963	197	13 787	1.43	4	1.49			
1964	160	10 578	1.51	4	1.58			
1965	152	9017	1.69	4	1.76			
1956–1958 and 1963–1965	897	60 837	1.47	5	1.55	1		

[a]The reference group was the years of 1956–1958 and 1963–1965.

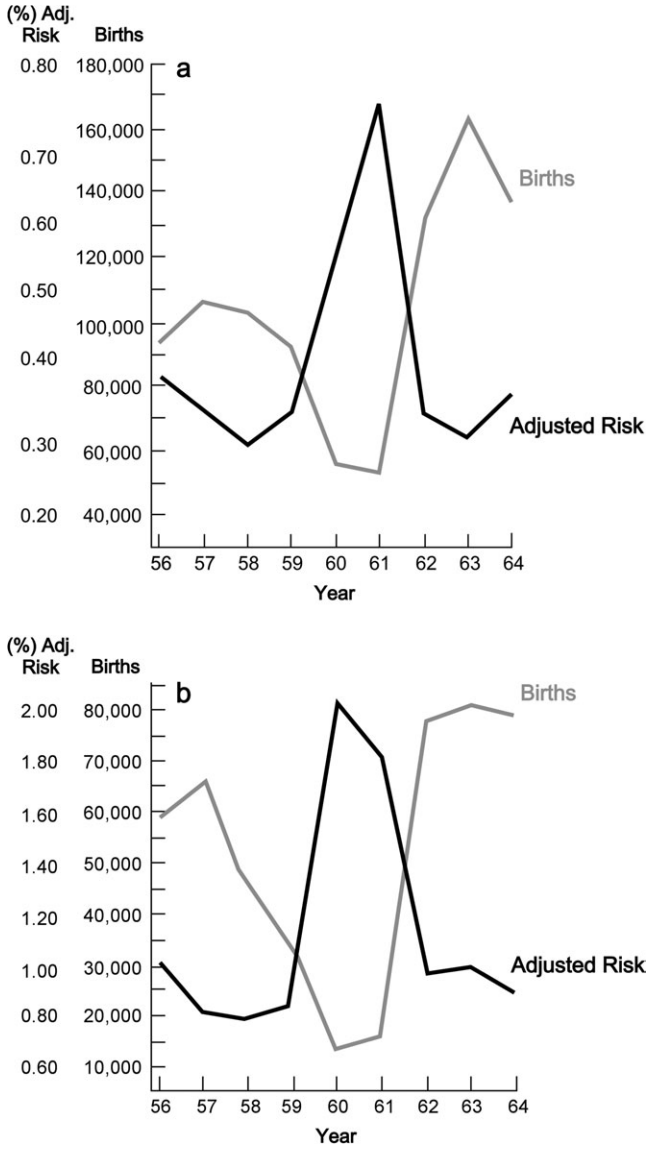

Fig. 1. a. Adjusted Risk of Schizophrenia Vs Birth Rate for Years 1956–1964 in Rural Liuzhou Prefecture. b. Adjusted risk of schizophrenia vs birth rates for 1956–1964. Wuhu Prefecture, Anhui.

whereas calendar years were used for the statistics of births and deaths. The figures are generally reliable but are not free of occasional errors. Absolute numbers for Liuzhou city were small and more vulnerable to the effects of inward and outward migration. Nonetheless, for consistency, the figures for all births used in the Anhui and Guangxi studies come from the same statistical sources.

Table 3 shows that the decline in births was paralleled by an increased risk of schizophrenia in adults born during this period. The RRs were 1.50 (95% CI = 1.35–1.68) (1960) and RR = 2.05 (95% CI = 1.87–2.27) (1961). Increased RRs are highly statistically significant for both 1960 and 1961 when analysed separately and would be even more so if analysis was performed on the 2 years combined (data not shown). Both years witnessed around a 50% decrease in the birth rate compared with prefamine years. Decline in fertility/births is an accurate proxy indicator of starvation and is an excellent method for timing the exposures. Although birth rates can be affected by events at any point until term, the further a pregnancy advances the less likely this is to abort. For this reason, dramatic declines in populations are normally associated with starvation around conception or during early gestation. These data fully concord with and extend the conclusions drawn from our previous Dutch and Chinese studies. See figures 1a and 1b for comparison of the 2 Chinese studies. The peak RRs of around 2 are remarkably similar across the 3 studies in spite of differences in diet, ethnicity, and severity of the famines. Our data suggest that individuals most at risk of schizophrenia were those who were conceived or in early gestation in the second half of 1959 and through 1960, namely the time when the famine was at its height. Because they are born 6–9 months later, if our predictions are correct, we should observe elevated relative rates in the years 1960 and 1961. This is precisely what we observe. Although we cannot rule out an effect in late gestation, this seems unlikely. In this latter case, because the severe famine was evident by summer 1959 and ended early 1961, one might expect to observe increased risk beginning in 1959, peaking in 1960 and showing only a modest increase in 1961.This is not the pattern observed in either of the Chinese studies. The authors appreciate however that these analyses are based on data grouped by year rather than by monthly birth cohorts as in the Dutch study, and this is a limitation of the data. It is also true given the length of the famine that individuals born in 1960 could have been exposed both prenatally and postnatally to the effects of famine.

Table 4 shows that in the Liuzhou prefecture the increased risk of schizophrenia comes almost exclusively from the countryside. Indeed, the city population shows no increased RR at all for any of the famine years. This lack of increased risk is consistent with the much less pronounced drop in birth rates observed in Liuzhou city (and even absence of drop in 1960) and the very modest increase in death rate compared with the countryside. The apparent drop in risk for the year 1960 in the city is probably a statistical artifact due to the anomalous lack of drop in birth rate. A similar pattern of no increase in risk has now also been observed in Wuhu city in Anhui (Yongyong Shi personal communication). The disparity in the extent of famine between the city and countryside may partly be explained by poor transport and communications in rural Guangxi at the time of the famine, but another factor was the division of China's people introduced in the early 1950s into separate urban and rural populations. Urban or rural status was determined at birth and movement between countryside and city was restricted and controlled by an internal passport system. The state undertook to provide those living in the cities

with food from state grain stores. They had legal rights to a certain amount of food. For those in the countryside, entitlements were poorly defined that essentially meant they were allowed to retain residual grain after they had delivered government-imposed quotas. These latter arrangements are classic circumstances, according to Amartya Sen, in which famine can arise.[6,15] The gulf between city and countryside was commented on at the time. Many city dwellers in China were barely aware that people were dying from famine in the countryside. Food availability and the proportion of the population with defined entitlements in the affected provinces were the 2 main determinants of mortality rates during the famine years.[6]

The absolute rates of schizophrenia for all years were substantially higher in Liuzhou city than in the surrounding counties. This may be partially accounted for by the well-documented increased rates of schizophrenia associated with urbanization that is observed in both developed and developing countries.[16] A second contributor may be the reduced level of provision and access to psychiatric services in contemporary rural as compared with urban China.[17] On the other hand, there is nothing to suggest that rural referral patterns would differ between those born before, during, or after the famine years. This cannot account for the elevated relative rates of schizophrenia among those conceived during the exposed years.

Similar limitations on interpreting the findings from Guangxi apply as in the Anhui study. The figures for population at risk ignore the effects of emigration or death after 1988. However, the population in the region of Guangxi has, until recently, been static, and, in any case, there is no reason to expect more than a very modest bias for effects of emigration among those born before, during, or after the famine years. There are no reliable data on coincident factors, such as epidemics occurring in the Liuzhou region during the famine years. Ingestion of food substitutes such as bark from trees was common, and some may have been toxic. However, all these factors are unlikely to account for the fact that 3 separate studies have now demonstrated the same phenomenon, with different food substitutes in all 3.

Only a minority of schizophrenia cases were admitted to hospital for initial assessment. However, the clinical notes were well-documented, and reliability of diagnosis was good as our validation study described above demonstrates. We observed no difference in sex, age of onset, or proportion of cases with a first-degree relative with major mental illness (familial) between those conceived in the exposed vs nonexposed years. These findings are similar to the Anhui study.

The data on familiality are subject to the same limitations as the previous study of lack of specificity of diagnosis and no systematic data on family size. None the less the apparent lack of reduction in familiality in the exposed cohorts in both the Anhui and Guangxi studies suggests that a simple explanation that famine acts as an independent cause of schizophrenia, regardless of genetic liability to schizophrenia is less likely. If it was independent, half of the cases of schizophrenia among individuals born during the famine would be representative of the general population in terms of liability. This would result in a reduction in rate of positive family history among the exposed birth cohorts. This was not observed. However, in view of the limitations of the data, any conclusions must be provisional.

It could be also be argued that in view of the differing severity of famine conditions reported in the 3 studies one might expect that the RRs of schizophrenia would show a wider range of outcomes than we observe with perhaps the severer the famine the higher the RR. This is not the case. A possible explanation is that there is a threshold and ceiling effect; a drop to 2000 calories per day is required for the effect to occur. Any more severe starvation and there is failure of menstruation/ conception/gestation and/or live term births.

The mechanisms by which prenatal nutritional stress could produce increased risk of schizophrenia have been discussed in detail elsewhere.[5,18,19] Although prenatal nutritional deficiency is the most likely explanation, preconceptual effects on sperm cannot be ruled out. Psychogenic effects of experiencing famine, only indirectly related to nutritional stress, are also possible. Alternatively it is possible that those with schizophrenia risk alleles have an advantage in times of famine so that more individuals at risk conceive, implant, come to term, and survive postnatally. Nutritional deficiency, especially of micronutrients involved in the folate pathway, may either directly affect growth of the developing fetal brain or indirectly affect it by interfering with DNA stability and/or epigenetic regulation of genes critical for brain development.[20,21] The folate pathway has a key role in DNA synthesis, methylation, and repair. Nutritional stress can also alter molecular regulatory mechanisms and release previously accumulated but unexpressed variation.[22,23] Both heat shock proteins 70 and 90 are elevated in vertebrates in response to starvation during early development.[24] Prenatal nutritional stress could therefore shift the threshold for phenotypic expressivity of a trait such as schizophrenia. These potential psychological, physiologic, and molecular responses to prenatal nutritional stress are of course not mutually exclusive. All 3 studies have associated strengths and weaknesses; the Chinese studies are particularly vulnerable to the reliability of statistics collected half a century ago in a large, poor country in a time of chaos. However, the clinical epidemiological findings from all 3 famine studies show a remarkable consistency that makes a compelling case that our observations are in essence correct.

What remain unknown are the mechanisms. Famines are rare even in developing countries. However, micronutrient deficiencies are common. Large strides have been made in

reducing fetal iodine deficiency–related disorders and neural tube defects by iodine and folate supplementation. It is possible that a similar strategy could also impact on rates of schizophrenia.

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