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David St Clair; Mingqing Xu; Peng Wang; et al.

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Rates of Adult Schizophrenia Following Prenatal Exposure to the Chinese Famine of 1959-1961

David St Clair, MD, PhD

Mingqing Xu, PhD

Peng Wang, MD

Yaqin Yu, MD

Yourong Fang, MD

Feng Zhang, MD

Xiaoying Zheng, MD

Niufan Gu, MD

Guoyin Feng, MD

Pak Sham, MD, PhD

Lin He, PhD

SCHIZOPHRENIA IS A COMMON form of severe mental illness characterized by thought disorder, hallucinations, and delusions, as well as deterioration of social functioning and social withdrawal¹ It is universally distributed worldwide with a lifetime risk of approximately 1%. Schizophrenia is almost certainly a multifactorial disorder with genetic and environmental elements contributing to overall risk. Monozygotic twin concordance rates for schizophrenia approach 50%, and these data together with family studies indicate a heritability of about 85%.²

Schizophrenia is increasingly viewed as a neurodevelopmental disorder with environmental influences during early brain development modifying risk of schizophrenia.^{3,4} These influences, none of which are yet firmly established, may

For editorial comment see p 621.

Context Schizophrenia is a common major mental disorder. Intrauterine nutritional deficiency may increase the risk of schizophrenia. The main evidence comes from studies of the 1944-1945 Dutch Hunger Winter when a sharp and time-limited decline in food intake occurred. The most exposed cohort conceived during the famine showed a 2-fold increased risk of schizophrenia.

Objective To determine whether those who endured a massive 1959-1961 famine in China experienced similar results.

Design, Setting, and Participants The risk of schizophrenia was examined in the Wuhu region of Anhui, one of the most affected provinces. Rates were compared among those born before, during, and after the famine years. Wuhu and its surrounding 6 counties are served by a single psychiatric hospital. All psychiatric case records for the years 1971 through 2001 were examined, and clinical and sociodemographic information on patients with schizophrenia was extracted by researchers who were blinded to the nature of exposure. Data on number of births and deaths in the famine years were available, and cumulative mortality was estimated from later demographic surveys.

Main Outcome Measures Evidence of famine was verified, and unadjusted and mortality-adjusted relative risks of schizophrenia were calculated.

Results The birth rates (per 1000) in Anhui decreased approximately 80% during the famine years from 28.28 in 1958 and 20.97 in 1959 to 8.61 in 1960 and 11.06 in 1961. Among births that occurred during the famine years, the adjusted risk of developing schizophrenia in later life increased significantly, from 0.84% in 1959 to 2.15% in 1960 and 1.81% in 1961. The mortality-adjusted relative risk was 2.30 (95% confidence interval, 1.99-2.65) for those born in 1960 and 1.93 (95% confidence interval, 1.68-2.23) for those born in 1961.

Conclusion Our findings replicate the Dutch data for a separate racial group and show that prenatal exposure to famine increases risk of schizophrenia in later life.

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Author Affiliations: Bio-X Center, Shanghai Jiao Tong University, Shanghai (Drs St Clair and Xu), Institute for Nutritional Sciences, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences (Drs Xu and He), Fourth People's Hospital, Wuhu, Anhui (Drs Wang and Yu), Second People's Hospital, Huang Shan, Anhui (Dr Fang), Institute of Population Research, Peking University (Dr Zheng), Shanghai Institute of Mental Health, Shanghai (Drs Gu and Feng), Department of Psychiatry, University of Hong Kong, Hong Kong (Dr Sham), and NHGG, Shanghai Jiao Tong University, Shanghai (Dr He),

People's Republic of China; Department of Mental Health, University of Aberdeen, Scotland (Drs St Clair and Zhang); and Division of Psychological Medicine, Institute of Psychiatry, London, England (Dr Sham).

Corresponding Author: Lin He, PhD, Institute for Nutritional Sciences, Shanghai Institute of Biological Sciences, 294 Taiyuan Rd, Shanghai 200031, China (helin@nhgg.org) or David St Clair, MD, PhD, Department of Mental Health, University of Aberdeen, Foresterhill, Aberdeen, Scotland (d.stclair@abdn.ac.uk).

Table 1. Total Population and Birth, Death, and Growth Rate Per 1000 Individuals Living in Wuhu and Its 6 Surrounding Counties Before, During, and After the Famine Years

Year	Population	Birth Rate	Death Rate	Growth Rate
1956	1 610 304	37.43	13.88	23.55
1957	1 699 779	41.21	10.27	30.94
1958	1 767 835	28.28	17.77	10.51
1959	1 691 266	20.97	32.13	-11.16
1960	1 501 444	8.61	92.61	-84.00
1961	1 454 320	11.06	15.63	-4.57
1962	1 536 282	50.4	10.95	39.45
1963	1 588 127	52.28	10.98	41.30
1964	1 606 008	49.11	9.42	39.69
1965	1 674 303	50.93	8.41	42.52

include prenatal influenza exposure,⁵⁻⁷ obstetric complications,⁸⁻¹⁰ season of birth,¹¹ prenatal maternal psychological stress, and maternal and fetal nutritional deficiency.¹²⁻¹⁵ Nutritional deficiency may increase risk of schizophrenia by adversely affecting the developing fetal brain independent of genetic liability to schizophrenia. Alternatively, as with folic acid deficiency and neural tube defects, risk may be greatest in those genetically predisposed.¹⁶ The main evidence that prenatal nutritional deficiency may increase risk of schizophrenia and antisocial personality disorder comes from studies of the 1944-1945 Dutch Hunger Winter when there was a sharp and time-limited decline in food intake.¹⁷⁻²⁰ 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 during the famine and born to severely malnourished mothers. However, the number of cases in the most exposed cohort conceived during the critical period was small (20-25 cases) and the findings were only modestly statistically significant. For those conceived at the height of the famine and who had experienced serious nutritional deprivation during the first or second trimester, the overall relative risk was 2.0 (95% confidence interval, 1.2-3.4; $P < .01$). For men the relative risk was 1.9 (95% confidence interval, 1.0-3.7; $P < .05$) and for women it was 2.2 (95% confidence interval 1.0-4.7;

$P < .04$).^{17,18} Many famines have occurred worldwide since 1945, but because conditions were disorganized or the populations remote, they have seldom lent themselves to detailed epidemiological investigations.

The 1959-1961 Chinese famine was one of the 20th century's great horrors. All provinces in China were affected^{21,22} due to the bad weather. It followed on the heels 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. Anhui province was one of the most severely affected. By spring festival of 1959, Anhui was starving and people began to die in large numbers. The famine was relieved in Anhui in the first months of 1961.²² In other parts of China, it continued throughout the year. We set out to test the hypothesis that prenatal exposure to famine would increase the rate of schizophrenia in adult life. Because 40 years had elapsed since the famine, individuals born during the famine would have passed through 80% to 90% of the lifetime risk of developing schizophrenia.

METHODS

Collection of Data

We selected the Wuhu region of Anhui province, which has an overall population of 62 million. The region includes the city of Wuhu, which has a population of about 500 000 and is the

second largest city of Anhui. Wuhu is situated at the junction of the Xinyi and Yangtze rivers and is bounded by 6 counties. Wuhu is the main commodity distribution and food processing center for the region. The region currently has a population of approximately 3 million. At the time of the famine the population was about half that size (TABLE 1). The overwhelming majority of residents were peasant farmers and agricultural workers who had recently been collectivized. Agriculture remains the main industry in the Wuhu region. Until the last decade, there was little inward or outward migration.

The Fourth People's Hospital is the only psychiatric hospital in the region and serves Wuhu and its surrounding 6 counties. Details of all psychiatric referrals from 1971 are available at this hospital. We surveyed all inpatient and outpatient referrals to the Fourth People's Hospital of Wuhu from 1971 to 2001.

Clinical and socioeconomic details were systematically recorded in the case notes and a World Health Organization *International Classification of Diseases (ICD-10)* diagnosis was entered.²³ We designed a 50-item checklist. 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 made anonymous by designating each case with an identification number and entered into a computer database.

We selected all cases with an ICD diagnosis of schizophrenia (ICD-8 and ICD-9 code 295, corresponding to ICD-10 codes F20, F21, F23.1-F23.2, F25) between 1971 and 2001. One of us (D.St.C.) assessed the reliability of the ICD diagnosis of schizophrenia with the symptom checklist on 100 randomly selected cases. In more than 95% of cases, sufficient details and symptoms recorded in the checklist verified an ICD diagnosis of schizophrenia. In the remaining cases, some data were lacking. No attempt was made to

classify cases retrospectively using the narrower *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria.²⁴

Clinical presentation between cases managed as outpatients or inpatients was similar. Age of onset of illness was estimated from age of first contact with the psychiatric services. All recordings of diagnoses and symptom checklists from the case notes were also made by researchers blinded to our research aims of investigating famine exposure as a risk factor for schizophrenia.

Records were available for the number of births and deaths recorded for the years 1956 through 1965 for Wuhu and its surrounding counties²⁵ (TABLE 2). We also had access to data on the age structure of the population of Anhui province as a whole at the time of the 1982 census.²⁶ A second set of data on age structure was also available from a family planning survey, which sampled the population of Anhui in 1988.²⁷ These provided a breakdown of the numbers of those who were alive in 1982 and 1988 and who were born before, during, or after the famine years. Using these 2 independent surveys, we were able to estimate cumulative mortality among those born immedi-

ately before, during, or after the famine years. This in turn allowed us to calculate mortality-adjusted risk of schizophrenia.

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

Measures of Effect

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 and, from the recorded addresses, lived in the Wuhu area during the years 1955 through 1965.

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. Mortality-adjusted risks were also calculated by subtracting estimates of cumulative death for each of the birth cohorts (TABLE 3). Relative risk was obtained by comparing exposed vs un-

Table 2. Clinicodemographic Information About Schizophrenia Cases Born Before, During, and After the Famine Years

Birth Year	No. of Schizophrenia Cases	No. (%) of Men	Treatment, No. (%)		Age of Onset, Mean (SD), y		No. (%) of Familial Cases*
			Outpatient	Inpatient	Men	Women	
1956	483	264 (55)	230 (48)	253 (52)	27.8 (7.9)	27.9 (8.4)	77 (16)
1957	455	248 (55)	233 (51)	222 (49)	27.1 (7.2)	28.3 (8.9)	82 (18)
1958	307	182 (59)	138 (45)	169 (55)	27.3 (7.5)	27.5 (7.4)	61 (20)
1959	197	106 (54)	88 (45)	109 (55)	24.9 (6.9)	28.1 (8.3)	32 (16)
1960	192	98 (51)	88 (46)	104 (54)	26.9 (7.3)	26.8 (6.8)	36 (19)
1961	191	101 (53)	87 (46)	104 (54)	26.1 (7.3)	28.4 (7.1)	31 (16)
1962	536	273 (51)	267 (50)	269 (50)	24.8 (6.5)	27.5 (6.9)	96 (18)
1963	779	388 (50)	387 (50)	392 (50)	24.6 (6.3)	25.8 (6.7)	132 (17)
1964	762	418 (55)	380 (50)	382 (50)	24.2 (6.2)	25.4 (6.5)	152 (20)
1965	695	377 (54)	312 (45)	383 (55)	24.1 (6.1)	24.8 (6.1)	132 (19)

*The variation in family history of mental illness over the 10 birth cohorts was nonsignificant ($\chi^2_3 = 7.04$, $P = .63$).

Table 3. Risk for Schizophrenia for Years 1956 Through 1965 in Wuhu and Surrounding Counties*

Year	Cases	No. of Births	Unadjusted Risk, %	Mortality Estimate, %†	Adjusted Risk, %	Adjusted RR (95% CI)‡	χ^2	P Value
1956	483	59 088	0.82	20	1.02			
1957	455	68 210	0.67	20	0.83			
1958	307	49 037	0.63	20	0.78			
1959	197	36 261	0.54	35	0.84	0.89 (0.78-1.03)	2.34	.13
1960	192	13 748	1.40	35	2.15	2.30 (1.99-2.65)	128.8	<.001
1961	191	16 339	1.18	35	1.81	1.93 (1.68-2.23)	80.68	<.001
1962	536	75 365	0.71	20	0.89	0.95 (0.87-1.04)	1.16	.28
1963	779	81 674	0.95	5	1.00			
1964	762	78 437	0.97	5	1.02			
1965	695	83 536	0.83	5	0.88			
1956-1958 and 1963-1965			0.83		0.93			

Abbreviations: CI, confidence interval; RR, relative risk.

*Because detailed mortality data were not available for all the years spanned by the study, statistics using survival analysis methods could not be performed. To adjust for differential mortality, we calculated the number of individuals in each birth cohort surviving childhood. These estimates were derived from the 1982 and 1988 population surveys for the whole of Anhui province.^{26,27} Minimal inward or outward migration took place until very recently. Both surveys gave breakdowns of the age distribution of the population for the respective survey years. Data were given in 4-year age groupings. Data were not available for individual years or for individual counties. The 4-year time frames differed between the 2 sets of data, so when calculating mortality for each birth cohort, we made estimates that were compatible with both sets of data. Since the figures in both surveys were similar, we are confident that the estimates of mortality are broadly correct. They are conservative estimates because overall mortality during the famine was higher in the Wuhu region than in Anhui as a whole.

†Cumulative mortality by 1988.

‡Relative to 6 years 1956-1958 plus 1963-1965.

exposed birth cohorts. We allocated the 6 years 1956 through 1958 and 1963 through 1965 as unexposed years because they were well outside the famine period. In an attempt to explore possible mechanisms underlying any observed change in relative risk during the famine years, we examined all cases with schizophrenia born before, during, and after the famine years for presence or absence of a family history of major mental illness. We hypothesized that familial incidence could point to the extent to which genetic mechanisms were operating in any observed effect. All statistical analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, Ill), and $P < .05$ was considered statistically significant.

RESULTS

Evidence of Famine From Birth Rates and Mortality Rates

Table 1 provides the birth and death rate for Wuhu and its 6 surrounding districts that are served by the Fourth People's Hospital of Wuhu for the years before, during, and after the famine. Birth rates decreased by approximately 80% for the years 1960 and 1961; mortality started rising in 1959 and peaked in 1960. The overall mortality rate in Anhui was 12%. For Wuhu and its surrounding 6 counties, the overall mortality was 15%. The figures provide conclusive evidence of famine in Anhui in the years 1959 through 1961.

Increased Risk of Schizophrenia

The decline in birth rates during the famine years was accompanied by a decline in the absolute number of cases of schizophrenia born during the famine years (Table 2). However, as a proportion of total births in each year, the cumulative risk of schizophrenia during the years 1960 and 1961 increased compared with the rates before or after. 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. Increased risk was similar in hospitalized and

nonhospitalized cases. Both sexes were equally affected, and there was no difference in age of onset of schizophrenia among those born before, during, or after the famine years.

Mortality-adjusted risks were then calculated using estimates of cumulative mortality rates derived from the 1982 and the 1988 population surveys. Both surveys indicated cumulative mortality rates of 35% to 40% among children conceived or born during the famine years and rates of 20% to 30% among children born in the years immediately preceding the famine. For those born in 1963 and after, the cumulative mortality rates decreased to 5% to 10%. Table 3 compares the famine and aftermath of the famine years 1959 through 1962 with 6 years (1956-1958 and 1963-1965) well outside the famine epoch to produce relative risks. Mortality-adjusted relative risks were 2.3 (95% confidence interval, 1.99-2.65) for those born in 1960 and 1.93 (95% confidence interval, 1.68-2.23) for those born in 1961.

Proportion of Familial Cases

The increased rate of schizophrenia among those born during the famine years was not accompanied by any change in the proportion of familial cases (Table 2). The proportion of probands with schizophrenia recorded as having a relative with major mental illness remained the same whether born before, during, or after the famine years. The average rate for the years 1960 and 1961 was 17% compared with 18% for the average before and after the famine years. The variation in family history rate over the 10 birth cohorts was nonsignificant ($\chi^2 = 7.04$, $P = .63$).

COMMENT

Epidemiological investigations of the effect of famine on human populations are rare because it is highly unusual to have reliable clinical and demographic information. The 1959-1961 Chinese famine provides the best such opportunity since the Dutch Hunger Winter. The sample sizes are larger and the death rates higher in the Chinese

famine. Given that the famine took place in a much less developed country undergoing a major political and economic upheaval, the information available is unexpectedly good. The years 1960 and 1961 witnessed a dramatic decrease in birth rates and an increase in mortality. The period of fertility decline, which is an accurate indicator of preconceptional starvation, is consistent with the historical records, which report that famine conditions started to appear in Anhui province after the spring of 1959. The evidence that prenatal exposure to famine during the same period increases the risk of schizophrenia in adult life is also convincing. The 2-fold increased relative risk that we observed in the prenatally exposed vs the nonexposed cohorts is strikingly similar to the Dutch figures (relative risk, 1.9 for men; 2.2 for women).¹⁸ Comparisons by individual months were not possible, and this is the biggest weakness of the current study compared with the Dutch data. However, one can infer similar conclusions.

By early 1961, the worst aspects of the famine were relieved,²² but the relative risk for the year as a whole is still around three quarters of the 1960 figure. This would be expected if the increased risk of schizophrenia only started dropping among those conceived in the first 3 months of 1961. Alternatively, if exposure during the later stages of pregnancy was a key event, one would expect a lower overall figure since those conceived in the later months of 1960 would also not be at increased risk. Similarly, if postnatal exposure was an important risk factor, one would certainly expect children born in 1959 and by definition exposed postnatally to the famine to be at increased risk of schizophrenia. This is not observed. The most economical interpretation of our findings is that exposure through early gestation is the critical period for increased risk of schizophrenia. This is fully consistent with the Dutch data.

Using the adjusted figures, the risk of schizophrenia in the nonfamine years

is around 0.93%, which is consistent with international surveys and surveys of the rate of schizophrenia in the total Chinese population.²⁸⁻³⁰ The figures for population at risk ignore the effects of emigration or death after 1988. However, the population in the region of Anhui 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. Only those born in Wuhu and the 6 counties were included. Ascertainment of cases was as comprehensive as possible. Almost all cases of schizophrenia in the region were referred to the Fourth People's Hospital of Wuhu. Most cases were assessed and treated with medication, usually for a month in the first instance, as out-patients. Only a minority were admitted for initial assessment. Reliability of diagnosis was good with well-documented clinical notes. Nutritional restriction during the famine years encompassed all strata of society. Most food was delivered through communal kitchens, and no social groups were spared the effects of the famine. Fat, carbohydrates, and protein were all severely deficient. However, we do not have reliable data on coincident factors, such as epidemics occurring in the Wuhu region during the famine years. Similarly, ingestion of food substitutes such as bark from trees was universal, and some may have been toxic. However, the widespread use of the green algae *Chlorella*, often grown at home in vats of urine, generated vital supplies of essential amino acids.³¹ *Chlorella* was probably not toxic and almost certainly saved many lives.

The unadjusted rates of schizophrenia show a lower risk among those born before the famine compared with those born in the years immediately after the famine. This apparent anomaly is explained by the attrition rates through death during the famine. When the rate of schizophrenia is adjusted for cumulative mortality, it is similar among those born before and after the famine years. This is reassuring because the mortal-

ity rates that we use are indirect estimates. They are conservative because mortality during the famine in Anhui province as a whole was less than what it was in Wuhu and its surrounding 6 counties. The population data used are derived from official Chinese government publications. They are internally consistent, and there is no reason to doubt their general accuracy. Recording of birth rates is also likely to be accurate. Without a record of the birth, the family would not receive extra allocations of food from communal sources. Age of onset of schizophrenia was estimated from age when first seen at psychiatric hospital and is therefore approximate. There is a trend toward apparently later age of onset in those born in the earlier years of the study. This may be due to later referral to a psychiatric hospital in the earlier years. However, we observed no significant difference in the apparent age of onset in the exposed vs the nonexposed cohorts. Similarly the proportion of so-called familial to nonfamilial cases remained unchanged among those born during the famine period. Interpretation of this observation is also complex. Data on family size are missing and relatives with major mental illness other than schizophrenia were also included.

Our finding that prenatal exposure to the famine increases risk of schizophrenia is consistent with the concept of "canalization" originally described by Waddington.³² Developmental pathways are normally tightly regulated, but under conditions of extreme stress the buffering mechanisms that operate under stable conditions can be compromised, leading to increased phenotypic diversity.³²⁻³⁴ Famine may represent such a condition of extreme stress. Susceptibility alleles for schizophrenia may also be enhanced in some way in times of famine, so that women with at risk alleles are more susceptible to conception, implantation, and term completion and their infants more likely to survive than women whose alleles are not at risk. Exposure to endemic famines has been the fate of the majority of humankind for most of history. A

modest selection advantage during periods of famine for carriers of alleles that predispose to schizophrenia offers a possible explanation for why, in spite of reduced fertility and survival among cases, schizophrenia has been observed in all societies and racial groups studied.

Our study strongly supports the view that prenatal exposure to famine increases the risk of schizophrenia in later life. Using a much larger sample size with clear evidence of exposure, our findings are internally consistent and almost exactly replicate the Dutch findings. Since the 2 populations are ethnically and culturally distinct, the processes involved may apply in all populations undergoing famine.

Author Contributions: Drs St Clair, Sham, and He had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs St Clair and Xu contributed equally to this work.

Study concept and design: St Clair, He.

Acquisition of data: Xu, Wang, Yu, Fang, Zhang, Zheng, Gu, Feng.

Analysis and interpretation of data: St Clair, Xu, Zhang, Gu, Sham.

Drafting of the manuscript: St Clair, Zhang.

Critical revision of the manuscript for important intellectual content: Xu, Wang, Yu, Fang, Zheng, Gu, Feng, Sham, He.

Statistical analysis: Xu, Zhang, Sham.

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Study supervision: St Clair, Gu, He.

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