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ORIGINAL PAPER

Prenatal war exposure and schizophrenia in adulthood: evidence from the Sino-Japanese War of 1937–1945

Ping He[1,2,3] · Yanan Luo[2] · Chao Guo[2,4] · Gong Chen[2] · Xinming Song[2] · Xiaoying Zheng[2,4]

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Abstract

Purpose This study aimed to examine the long-term effect of prenatal exposure to the Sino-Japanese War during 1937–1945 on risk of schizophrenia in adulthood among Chinese wartime survivors.

Methods We obtained data from the Second National Sample Survey on Disability conducted in 31 provinces in 2006. We restricted our analysis to 369,469 adults born between 1931 and 1950. Schizophrenia was ascertained by psychiatrists based on the International Statistical Classification of Diseases 10th Revision. War intensity was assessed by the ratio of war-caused civilian casualties to the pre-war population. The effect of prenatal exposure to war on schizophrenia was estimated by difference-in-difference models, established by examining the variation of war across birth cohorts.

Results In the male population, war cohorts of 1937–1946 had no significant higher odds of schizophrenia compared with the pre-war cohorts of 1931–1936. In the female population, war cohorts were 1.16 (95% CI 1.01, 1.33) times more likely than pre-war cohorts to have schizophrenia. Sensitive analyses show that our estimates of war effect on schizophrenia were robust and valid.

Conclusions Prenatal exposure to the Sino-Japanese War of 1937–1945 had long-run detrimental effect on risk of schizophrenia in the female adults. Further investigations are warranted to extend the enduring wartime impact on other health outcomes in China.

Keywords The Sino-Japanese War · Schizophrenia · Long-term effect · Life course

Introduction

War has a profound and detrimental impact on health and well-being of both combatants and noncombatants [1], and has been identified as a severe public health problem around the world [2]. Over the twentieth century, approximately 191 million people died in battle and a growing number of war-associated deaths emerged in noncombatant civilians [3], showing that two-thirds of deaths were among civilians during the Second World War [4]. In the first decade of the twenty-first century, civilians in nearly one-third of the world's developing countries have suffered from war or violence, and, particularly, early-life and childhood development is more vulnerable to being affected by wartime traumatic events and is hard to be reversed in adulthood [5].

The Sino-Japanese War, lasting for 8 years from 1937 to 1945, occupies a prominent position in the chapter of protracted war in the world military history [6], causing enormous and tragic damage to China in terms of fatalities, injuries and traumas of militants and civilians [7]. Despite debates on the total Chinese casualties during the Japanese invasion, official estimates showed that approximately 20 million combatants and civilians died directly as a result of the war [8]. Up to now, more importantly, over 70 years after the end of the war, the long-term negative impact of the

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✉ Xiaoying Zheng
xzheng@pku.edu.cn

[1] China Center for Health Development Studies, Peking University, Beijing, China

[2] Institute of Population Research, Peking University, No. 5 Yiheyuan Road, Haidian District, Beijing 100871, People's Republic of China

[3] Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

[4] APEC Health Science Academy (HeSAY), Peking University, Beijing, China

war is still lingering not only among wartime survivors, but also among those who did not witness the war [9]. Despite these long-term negative effects, only a few studies have examined the long-term consequences of the Sino-Japanese War on health outcomes in later life.

Regardless of war's apparently immediate damage to humans, previous studies have not fully considered its long-term consequences, especially in the form of psychiatric disorders during the past decades [3]. In addition, there have been a limited number of studies on this topic which have not reached a consensus. On the one hand, two studies found a significant association between prenatal exposure to wartime and later-life risk of schizophrenia in the Germany's invasion of the Netherlands and the Second World War genocide [10, 11]. On the other hand, research on atomic bomb in Nagasaki City of Japan and the Yom Kippur War in Israel failed to identify such a link [12, 13]. The inconsistent findings may be related to sample size, study design and cultural differences.

In this study, using large-scale and nationally representative data from a population-based survey, we attempted to investigate the long-term effect of the Sino-Japanese War of 1937–1945 on the risk of schizophrenia among wartime survivors at ages of 60 years and above. An examination of this issue can fill the gaps in China, and contribute to world literature in a poor nation with eastern context.

Background of the Sino-Japanese War of 1937–1945

The Sino-Japanese War of 1937–1945 began with the Marco Polo Bridge incident of July 7, 1937. Afterward, the conflict escalated, and by 1941, Japan had occupied a majority of lands in northern and coastal China. It ended with the unconditional surrender of Japan on September 2, 1945 to the United Nations allies of the Second World War [6].

The prolonged Sino-Japanese War resulted in unprecedented casualties and property losses in China. The official statistics estimated that the war caused roughly 20 million Chinese soldier and civilian death and 15 million to be wounded from 1937 to 1945 [7]. Also, the war inflicted heavy losses on the Chinese economy; it was estimated that China's property losses by the war were about US$383 billion on the basis of the currency exchange rate of July 1937, approximately 50 times Japan's GDP at that time [14].

Methods

Study population

In addition to wartime data, we obtained data from the Second National Sample Survey on Disability implemented 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 all 31 provinces of Mainland China. The four levels of sampling frame were county (district), town (street), and village (community). The sampling frame was initially based on population, household, disability, registration, and economic data of counties, which was collected by the provincial survey office using the most up-to-date population and address information from the Ministry of Civil Affairs and Public Security. The sample size at each level equaled the proportion of the population in that level to that of the province [15]. A total of 734 counties (districts), 2980 towns (streets), and 5964 communities (villages) were selected for the survey [16]. The sample size was 252,6145, accounting for 1.9 per 1000 inhabitants of China [17].

Fetal origins hypothesis, popularized by David Barker [18, 19], argues that disruptions to the prenatal environment, interactive with the epigenome, have a profound impact on adult disease. Furthermore, the hypothesis underlines prenatal exposure, rather than postnatal conditions, as a health determinant in early life [20]. From this perspective, this study focused on the prenatal war effect on schizophrenia in adulthood, although the cohort of the Sino-Japanese War was in fact exposed from conception until childhood.

We defined prenatal exposure as maternal exposure to wartime during the roughly 300 days from the peri-conception to delivery [21]. Considering great difference in social context between the "Old China" ruled by Kuomintang before 1949 October and the "New China" governed by the Chinese Communist Party after October 1949, we restricted our analysis to 1931–1950 birth cohorts. As a result, we defined adults who were prenatally exposed to the Sino-Japanese War (born in 1937–1946) as war cohorts, and those who were not prenatally exposed as pre-war cohorts (born in 1931–1936) and post-war cohorts (born in 1947–1950). In addition, the three northeastern provinces, including Heilongjiang, Jilin and Liaoning, were occupied by the Japanese much earlier (in 1931) than the rest of China (in 1937), and therefore the influence of the 1937–1945 war on the three provinces probably differed from that of the other areas of China. Hence, we excluded these three regions, yielding a sample of 28 provinces for analysis. In total, we selected a subsample of 369 469 adults born between 1931 and 1950, at ages of 60 to 75 years during the survey time.

Ethical 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.

Measures

Ascertainment of schizophrenia

Individuals with schizophrenia were 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) [22].

First, interviewers, who were recruited from local primary care institutions and trained by the provincial expert teams in the methods of survey and screening, went to the households to screen adults with psychiatric disability using a questionnaire. The questionnaire was developed according to the 'Guidelines and Principles for the Development of Disability Statistics' [23] and had been shown very good validity [24]. The screening questions included whether any of the family members has the following problems: (1) poor memory (forgetful); (2) difficulty in concentration (his/her mind often wanders); (3) difficulty controlling their emotions (moody, too joyful or too joyless); (4) strange language and/or weird behavior that could not be understood or accepted by a normal person; and (5) fasting drinking (for at least five times per week) or hypnotic drug overdose [25]. If any of the screening questions was positively responded, the identified individual was labeled as likely to have psychiatric disability.

Afterward, psychiatrists with five or more years of clinical experience assessed the possible patients with psychiatric disability according to the guidelines of WHO-ICF. World Health Organization Disability Assessment Schedule, Version II (WHO DAS II) was used to evaluate social function limitations. Individuals receiving a score of 52 or above were defined as having psychiatric disability [26]. The WHO DAS II had been verified for good validity [27].

Finally, those who were identified as being psychiatrically disabled were subsequently assigned to diagnosis for schizophrenia by psychiatrists. The International Statistical Classification of Diseases 10th Revision (ICD-10) symptom checklist for mental disorders was administered to diagnose schizophrenia [26]. The ICD-10 diagnostic criteria had been employed in the ascertainment of schizophrenia among Chinese people and presented good validity in China [28].

War intensity

War intensity showed considerable variations across regions, although the Sino-Japanese War influenced most regions in China during 1937–1945. We used civilian casualties, measured by the ratio of civilian casualties to pre-war population at province level in 1936, as a proxy of wartime intensity. Civilian casualties have been verified to be a valid indicator in capturing war damage and particularly powerful in the war-caused psychiatric consequences [7]. The data of civilian casualties were derived from the book "A History of the Investigation of China's Losses during World War II"[29], and the population data prior to the war were obtained from China Statistics Yearbook.

Table S1 shows that the central corridor regions, including Henan, Jiangxi, Hunan, Hubei, Shanxi and Guangxi, were more heavily influenced by the war. By contrast, remote areas, such as Hainan, Qinghai, Tibet, Xinjiang, Gansu, Shaanxi and Sichuan, suffered from less severe casualty. This is likely due to the military strategies of the Japanese army to establish a supply line for its war in the Pacific Ocean, also known as "Operation Ichi-Go" [7]. The large geographical variation in casualties, combined with disparities in the risk of schizophrenia across cohorts, offers a unique opportunity to identify the causal effect of the Sino-Japanese War.

Statistical analyses

We used difference-in-difference (DID) models, established by examining the variations of war exposure across birth cohorts, to estimate the prenatal impact of war on risk of adult schizophrenia. The idea of this approach is that we used birth cohort to identify whether an individual was exposed to war in utero. We also relied on war intensity across provinces to identify the variation of war exposure in the same birth cohorts. This identification strategy has been verified to have good validity and widely used elsewhere [20, 30]. Logit regression models with the DID estimators were fitted as follows:

$$Y_{ijk} = B_0 + \delta \mathrm{CC}_j + \varphi_k \mathrm{cohort}_k + \sum_{k=1}^{3} \beta_k \left(\mathrm{CC}_r \times \mathrm{cohort}_k\right),$$

where Y_{ijk} is a binary outcome variable, referring to risk of schizophrenia for the individual i, born in province j and year k, CC_j is the ratio of war-caused civilian casualties during 1937–1945 to the population of 1936 in province j, and φ_k represents the cohort fixed effect. Standard errors are clustered at the province level to deal with potential heteroscedasticity and serial correlation problems [31].

The coefficient of the interaction between the percentage of civilian casualties and birth cohort dummies, namely β_k, evaluates the impact of prenatal exposure to war on schizophrenia in adulthood in the DID models. The rationale and validity of the interaction term in the non-linear DID models have been presented elsewhere [32] and have also been used in prior research [33]. To estimate the average effect across provinces, we multiplied the interaction coefficient by 1.65, the mean of the percentage of civilian casualties caused by war in all 28 provinces.

In the DID models, control variables need to be exogenous and cannot be affected by the treatment (severity of war exposure, in this case). However, many of the control variables are, in fact, potentially affected by the treatment. For example, any health conditions that affected war survivors in the war cohorts would affect their ability to succeed in the marriage market, their educational outcomes, and their job market outcomes. Studies have argued that these control variables are endogenous [34]. If the control variables are endogenous, then the coefficient estimators are inconsistent. Therefore, we did not include any endogenous control variables in the DID models to obtain consistent estimates of war effect on schizophrenia.

The validity of DID estimation relies on the presence of parallel trends in risk of schizophrenia between the exposed and the control cohorts in regions with varying intensity of war destruction [35]. To test the validity of DID estimation, we applied the same DID strategy using a sample of individuals who were not born when the 1937–1945 Sino-Japanese War began and found if there was evidence of differential trends.

In addition, we performed a falsification test to validate our findings on the prenatal war effect on risk of schizophrenia. One potential complication factor for our estimation is that people who were prenatally exposed to the 1937–1945 Sino-Japanese War also experienced the 1959–1961 Chinese famine during adolescence and early adulthood. To check if the observed effect of prenatal exposure to war on schizophrenia is influenced by such non-war events, we employed the DID estimation on the effect of famine exposure during adolescence and early adulthood on schizophrenia. We used the cohort size shrinkage index (CSSI) [36, 37], measured by comparing the size of the famine cohorts relative to the surrounding non-famine cohorts in the population, as a proxy of famine severity. The details of CSSI and its validity have been shown elsewhere [38, 39].

Considering potential sex difference in the war effect on health outcomes [20], we performed regression analyses with male and female subsamples following previous research [40]. We used an interaction term between years of exposure to the war and war intensity to test whether exposure time to war influenced the risk of schizophrenia among war cohorts. A p value of less than 0.05 was considered statistically significant. The software Stata version 13.0 for Windows (Stata Corp, College Station, TX, USA) was used for statistical analyses.

Results

Table 1 shows the characteristics of participants born during 1931–1950 by birth cohorts. Overall, of the 369 469 individuals, 49.62% were female and 0.45% had schizophrenia. The proportion of females was stable among war cohorts born in 1937–1946, representing about a half of the total population.

Table 2 presents the estimated effect of prenatal exposure to the Sino-Japanese War on schizophrenia with male and female subsamples. In the male group, there was no significant difference in the odds of schizophrenia between war cohorts (born in 1937–1946) and pre-war cohorts (born in 1931–1936). In the female group, war cohorts were 1.16 (95% CI 1.01, 1.33) times more likely than pre-war cohorts to have schizophrenia.

Table 3 presents the validity test of the DID estimation for the impact of war on risk of schizophrenia. The results of war effect rely on the parallel trend assumption: that is, in the absence of the Sino-Japanese War of 1937–1945, the rates of schizophrenia between the exposed and unexposed cohorts would have had no significant differences across provinces with varying war intensity. Using the pre-war cohort as the reference group, the prenatally unaffected cohorts of 1947–1950 did not show significantly higher rates of schizophrenia in both male and female population.

Table 4 illustrates the falsification test of the DID estimation for the effect of prenatal exposure to war on risk of schizophrenia. The estimation of war effect depends on whether it is influenced by other exposure events including the Chinese famine. Using CSSI as a measurement of famine severity and a similar DID strategy, we found that the prenatal war effect on schizophrenia is not influenced by the event of the 1959–1961 Chinese famine. We also observed that the interaction between years of war exposure and war intensity was not statistically significant among male and female war cohorts, indicating that exposure time to war did not affect the risk of schizophrenia (Table S2).

Discussion

War not only has direct immediate effects on fatalities, injuries and property losses, but also has indirect long-term effects on the health and well-being of the succeeding generations [1]. People who were prenatally exposed to the Sino-Japanese War of 1937–1945 were entering or had been in their older adulthood by the survey time. In this study, we investigated the long-term effect of prenatal exposure to the

Table 1 Characteristics of sample, by birth cohorts

Birth cohorts	Year	Sample size, *n*	Female, %	Prevalence of schizophrenia, %
Pre-war cohorts (1931–1936)	1931	10,935	51.74	0.40
	1932	12,137	51.63	0.31
	1933	15,054	50.73	0.28
	1934	13,827	52.14	0.28
	1935	14,929	51.45	0.38
	1936	16,156	49.98	0.48
War cohorts (1937–1946)	1937	15,904	49.36	0.37
	1938	16,937	49.67	0.30
	1939	15,205	49.91	0.32
	1940	17,067	49.05	0.46
	1941	17,838	48.96	0.42
	1942	18,004	49.13	0.51
	1943	17,823	48.99	0.43
	1944	19,758	48.31	0.48
	1945	20,211	49.68	0.45
	1946	22,859	49.49	0.55
Post-war cohorts (1947–1950)	1947	24,224	48.49	0.47
	1948	24,264	49.64	0.57
	1949	28,873	48.41	0.51
	1950	27,464	49.54	0.58
All cohorts	1931–1950	369,469	49.62	0.45

Table 2 Estimated effect of prenatal exposure to the Sino-Japanese War on schizophrenia, based on logit regression with difference-in-difference estimator, by gender

Birth cohorts	Male ($n=132,686$)		Female ($n=131,958$)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
War cohorts (1937–1946)	0.92 (0.78, 1.10)	0.361	1.16 (1.01, 1.33)	0.032*
Pre-war cohorts (1931–1936)	1.00		1.00	

OR odds ratio, *CI* confidence interval

*$P<0.05$

Table 3 The validity test for the DID estimation of prenatal exposure to the Sino-Japanese War on risk of schizophrenia, by gender

Birth cohorts	Male ($n=93,964$)		Female ($n=93,899$)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Post-war cohorts (1947–1950)	0.89 (0.69, 1.15)	0.384	1.09 (0.91, 1.31)	0.351
Pre-war cohorts (1931–1936)	1.00		1.00	

OR odds ratio, *CI* confidence interval

Table 4 Falsification test for the estimated effect of prenatal exposure to the Sino-Japanese War on schizophrenia, by gender

Birth cohorts	Male ($n=123,911$)		Female ($n=123,392$)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
War cohorts (1937–1946)	0.82 (0.55, 1.23)	0.345	1.22 (0.76, 1.95)	0.418
Pre-war cohorts (1931–1936)	1.00		1.00	

OR odds ratio, *CI* confidence interval

Sino-Japanese War on the risk of schizophrenia in adulthood. Such a life-course perspective was of great importance to capture the enduring psychological trauma of the Japanese invasion of China, and to grasp the ways that war affected older adults' well-being, burden of disease, as well as public health systems in post-war developing nations [41]. To our knowledge, this is the first population-based study to examine the long-term war effect on schizophrenia among Chinese adults.

The results showed that, compared with the unexposed cohort, the war-exposed cohorts in utero were at significantly greater risk of schizophrenia. The test of parallel trend assumption of DID estimation suggested our finding of the detrimental effect of war on the risk of schizophrenia was valid. The falsification test indicated that the long-term effect of prenatal exposure to war on schizophrenia found in this study was not influenced by the Chinese famine of 1959–1961. This finding, using the enduring Sino-Japanese War of 1937–1945 as a natural experiment, verified the fetal origins hypothesis, which was first developed by Barker in the 1990s [18]. In addition, due to higher mortality in schizophrenia in all age groups [42], the life expectancy of schizophrenia patients is approximately 20 years lower than that of the general population [43]. The identified cohort was quite old at the time of survey, aged 60–75 years. Given the facts, the war effect on the likelihood of schizophrenia may be influenced by sex difference in survival rate if the mortality rate of women was different from that of men. Furthermore, the overall prevalence of schizophrenia was relatively lower than that in other studies. This is likely due to two reasons. First, the schizophrenics in our data were relatively severe cases who had been affected by psychiatric symptoms for at least 1 year. The mild cases with minimum function limitation have been excluded from the prevalence pool [25]. Second, our study firstly screened for psychiatric disability and only those adults suspected of being disabled could be examined and diagnosed for schizophrenia, which means non-disabled adults with schizophrenia could have been excluded in our survey.

The negative effect of war on schizophrenia in adulthood observed in this study provided new insights into this topic. When comparing our result with previous studies, the first factor that must be considered is the sample representativeness and study design. From this point of view, the most comparable estimates should be population based. For example, one large-scale and population-based study regarding the Holocaust of European Jews found that people who were directly exposed to the genocide in early life were at statistically greater risk (hazard ratio = 1.27) of schizophrenia ascertained by ICD-10 than those in the indirect group [11]. On the other hand, several studies with respect to the 4-day war in the Netherlands, 6-day war in Israel, and the atomic bomb in Nagasaki City of Japan did not draw a conclusion on the early-life effect of war on schizophrenia in later life [10, 12, 13]. As far as we know, there are several reasons that may contribute to different results of war effect. Apart from the study design and sample size, culture and social context may be related to the war effect on schizophrenia. In addition, the prolonged war exposure to stress is as well a possible explanation to the varying war effect on adult disease.

The potential pathways for a link between prenatal war exposure and adult schizophrenia may include violence, infection, malnutrition, as well as destruction of economy and infrastructure [1, 44]. Violence is ubiquitous during war, and an increasing number of civilians, especially women, were affected by war [45]. Studies have found that maternal exposure to physical violence during war was associated with elevated premature birth, perinatal morbidity and congenital malformations [46, 47]. In addition, war may cause the outbreak of infectious diseases, such as cholera, typhoid, acute gastroenteritis, malaria, polio, etc. [1]. Congenital infections have an impact on cognitive impairment, and thus may be connected with future mental health [48]. Furthermore, malnutrition is common in conflicts [1]. Studies repeatedly found that prenatal malnutrition, using the Chinese or Dutch famine as a proxy, is associated with increased schizophrenia in adulthood [28, 49–51]. Finally, the destruction of economy, infrastructure and health systems [3] affects mental health in humans during war [44]. War-induced parental psychiatric stress is negatively correlated with the offspring's mental health as a result of epigenetic changes in the hypothalamic–pituitary–adrenal axis [52].

The current study is subject to a few limitations. First, the retrospective survey in collecting information of war exposure and influence might affect the validity by recall errors, although data of war-caused civilian casualties have been repeatedly verified. Identification of the cohort was by household screening. This method misses out on those people who are in hospitals, nursing homes, hostels and prisons. Therefore, we need to be cautious in interpreting our results. Second, since the Sino-Japanese War of 1937–1945 caused the death of more than 30 million Chinese people, selective mortality was plausible. Given that people with schizophrenia die at a much younger age than the general population, our identified cohort aged 60–75 years may be subject to survival bias. In the absence of schizophrenia-associated mortality data, we were unable to correct the potential bias, but this would likely underestimate rather than overestimate the effect of war because those with serious mental conditions were more likely to die prior to the survey. Third, we identified individuals' regional information based on their current address at province level, and therefore population migration may affect our study. China's strict Hukou (passport) system, which was established in the 1950s, restricted population migration [53], and interprovincial migration

accounted for less than 1% of the total population before the 1960s [54]. Fourth, due to a lack of vital statistics during war, we did not know the exact time of maternal pregnancy, which may influence the risk of schizophrenia [11]. Alternatively, learning from Chinese famine studies [21, 54], we used birth cohorts to identify war exposure from the ecological perspective. Finally, the measure for war intensity was based on province-level civilian casualties. Since sampling went down to the village level, village-level civilian casualties may have been a more accurate exposure. However, due to data restrictions of the 1937–1945 Sino-Japanese War, we failed to give estimates by using more accurate data of war intensity.

Several strengths of this study, to some extent, balance its limitations. First and foremost, our study was a pioneer in examining the long-term impact of the prolonged Japanese invasion of China on the risk of schizophrenia in late adulthood even after the war had ended over seven decades ago. This added new evidence not only to existing studies on wartime influence from the life-course perspective, but also to the cost evaluation on the profound damages of war. In addition, the study design was strongly enhanced by the medical ascertainment of schizophrenia by psychiatrists according to the ICD-10 criteria, and considering the wartime intensity across regions from a nationally representative, population-based survey with large sample size. Furthermore, we found that the effect of prenatal exposure to war on the risk of schizophrenia in late adulthood was sex specific, only occurring in the female population. This extends the previous studies regarding the war effect on schizophrenia.

Conclusion

Our results suggest that prenatal exposure to the Sino-Japanese War of 1937–1945 had a long-run detrimental effect on the risk of schizophrenia in adulthood. Given the biological plausibility of assumed pathways and relatively consistent result with prior research on this issue, further investigations are warranted to extend the enduring wartime impact on other health outcomes in China. Chinese governments need to establish corresponding policies or programs for intervention in older adults who were exposed to the war.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflict of interest.

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