Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 1230–1236

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Exposure to Chinese famine in early life modifies the association between hyperglycaemia and cardiovascular disease

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Received 18 March 2019; received in revised form 12 June 2019; accepted 3 July 2019
Handling Editor: A. Siani
Available online 9 July 2019

KEYWORDS
Cardiovascular disease;
Chinese famine;
Hyperglycaemia;
CHARLS

Abstract *Background and aims:* The Great Leap Forward Famine during 1959–1961 was the world's largest famine, and its adverse long-term effects might be more apparent in the coming decade with ageing of the exposed populations. The aim of this study was to examine whether the Chinese Famine modified the effect of hyperglycaemia on cardiovascular disease (CVD).
Methods and results: We used data of 4337 adults born between 1952 and 1964 collected from the China Health and Retirement Longitudinal Study (CHARLS). Logistic regression was used to estimate the odds ratios (ORs) and confidence intervals (CIs) between hyperglycaemia and CVD. The prevalence of CVD showed significant difference among different famine exposure cohorts ($P = 0.0156$). After multivariable adjustment, the ORs (95% CIs) were as follows: 1.46 (0.94, 2.26) for late childhood, 1.76 (1.06, 2.90) for mid childhood, 1.40 (0.86, 2.27) for early childhood, 2.55 (1.30, 5.02) for the foetal cohort and 1.10 (0.63, 1.95) for the non-exposed cohort. There was a significant interaction between hyperglycaemia and famine exposure for CVD ($P = 0.0374$). In addition, the subgroup analyses showed that the effect of hyperglycaemia on CVD in the foetal exposure cohort was significantly higher than those in any of the other famine-exposed cohorts, especially in those who lived in rural areas (OR: 4.67, 95% CI: 1.70–12.84), those who lived in severe famine areas (OR: 5.01, 95% CI: 1.22–20.66) and those who were men (OR: 3.66, 95% CI: 1.01–13.33).
Conclusion: Exposure to the Chinese Famine, especially during the foetal stage of life, aggravated the association between hyperglycaemia and CVD.
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Introduction

Cardiovascular disease (CVD) is regarded as the leading cause of both mortality and loss of disability-adjusted life years worldwide [1]. It is estimated that CVD accounts for 31% of mortality worldwide, with 80% currently occurring in developing countries [2]. In China, the incidence of CVD is continuously increasing and will remain in an upward trend in the coming decade [3]. In 2015, the mortality rates of CVD were 264.84 per 100,000 people and 298.42 per

Abbreviations: BMI, body mass index; BP, blood pressure; CHARLS, China Health and Retirement Longitudinal Study; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GHB, glycosylated haemoglobin; HDL, high-density lipoprotein; LBW, low birth weight; LDL, low-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

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https://doi.org/10.1016/j.numecd.2019.07.004
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100,000 people in urban and rural areas of China, respectively [4]. In addition, CVD also brings a serious social and economic burden to China. According to statistics, the total cost of direct hospitalisation for acute myocardial infarction and cerebral infarction in 2015 was as high as 15.34 billion China Yuan and 52.426 billion China Yuan, respectively [5]. The prevention and control of CVD has been challenging. Therefore, a better identification of high-risk populations for CVD can lead to appropriate measures for intervention and prevention.

Along with the hypothesis regarding the origin of development, the role of early life experiences such as famine in the risk of future chronic disease has received increasing attention. China has a specific history of the Great Leap Forward Famine (the Great Chinese Famine) during 1959–61, which is the world's largest famine [6,7]. With ageing of the famine-exposed populations, a large number of studies have shown a link between early life exposure to the Chinese famine and an increased risk of cognition deficits [8], diabetes [9], hypertension [10], metabolic syndrome [11], and schizophrenia [12] in adulthood. Furthermore, famine has also been shown to aggravate the influence of traditional risk factors (e.g., hypertension) on CVD in later life [13]. As hyperglycaemia is an important risk factor for CVD [14] and found in high prevalence in China [15], it is of high significance to assess whether the Great Chinese Famine modified the effect of hyperglycaemia on CVD.

Therefore, the purpose of the present study was to address this question by using data from the China Health and Retirement Longitudinal Study (CHARLS). We hypothesised that famine exposure in early life would modify the association between hyperglycaemia and CVD.

Methods

Study population

We used data from the national baseline survey of CHARLS in 2011–2012. CHARLS is a nationally representative longitudinal survey study on adults aged 45 years and above. Details of the study design were described previously [16]. In the current study, we included participants who were born between 1952 and 1964 and collected complete baseline data. To minimise the misclassification of the famine exposure periods, subjects who were born between 1 October 1958 and 30 September 1959 or between 1 October 1961 and 30 September 1962 were excluded, as the exact dates of the start and the end of the Chinese famine are not clear and not the same across regions. The study was approved by the Ethics Review Committee of Peking University and all participants signed informed consent.

Famine cohorts and areas

Date of birth was self-reported by participants, and all Chinese lunar calendar dates of birth were converted to the Western calendar in the present study. Subjects were categorised into five exposure cohorts (Fig. 1) based on previous studies of the Chinese famine [13]. In addition, the areas were categorised as "severely affected by famine" (excess mortality of each province $\geq$100%) or "less severely affected by famine" (excess mortality of each province $<$100%) [17].

Measurement variables

The questionnaire collected information about demographics, health status and functioning, physician-diagnosed chronic diseases and lifestyle and health-related behaviours (e.g. smoking and drinking). Blood pressure levels were recorded three times separately at 45-s intervals by a trained nurse using a HEM-7200 electronic monitor (Omron, Dalian, Japan). Additionally, 8-ml fasting blood samples were collected from every participant in the study, and all blood samples were shipped to Beijing and placed at the Chinese Center for Disease Control and Prevention at a storage environment of -80 °C [16]. The biological determination of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride and fasting blood glucose was performed at the Youanmen Center for Clinical Laboratory of Capital Medical University. During the testing period, quality control samples were used, and all test results were within the target range (two standard deviations of mean quality control concentrations) [18].

Assessment criteria

CVD was defined as a self-reported doctor's diagnosis of stroke or heart problems (including heart attack, coronary heart disease (CHD), angina, congestive heart failure or other heart problems) [19]. Hyperglycaemia was defined as a fasting plasma glucose (FPG) $\geq$6.1 mmol/L and/or 2-h plasma glucose $\geq$7.8 mmol/L or a self-reported doctor's diagnosis of diabetes or high blood sugar [20]. Hypertension was determined by a mean of systolic BP $\geq$ 140 and/or diastolic BP $\geq$ 90 mmHg, or a self-reported history of hypertension [21]. Dyslipidaemia was defined as total cholesterol $\geq$6.22 mmol/L or triglyceride $\geq$2.26 mmol/L or high-density lipoprotein cholesterol $<$1.04 mmol/L or low-density lipoprotein cholesterol $\geq$4.14 mmol/L [22].

Statistical analyses

Continuous and categorical variables were presented as the mean $\pm$ SD (standard deviation) and percentage, respectively. The analysis of variance and χ^2 tests were used to compare differences among groups. Crude and adjusted odds ratio (OR) values were calculated to assess the associations between risk factors and CVD by logistic regression analyses in each famine exposure cohort. The product of hyperglycaemia and the ordinal famine cohort variable (0, 1 and 2 were assigned to the groups of no exposure, childhood exposure and foetal exposure, respectively) was used to test the interaction between hyperglycaemia and exposure to famine in CVD using

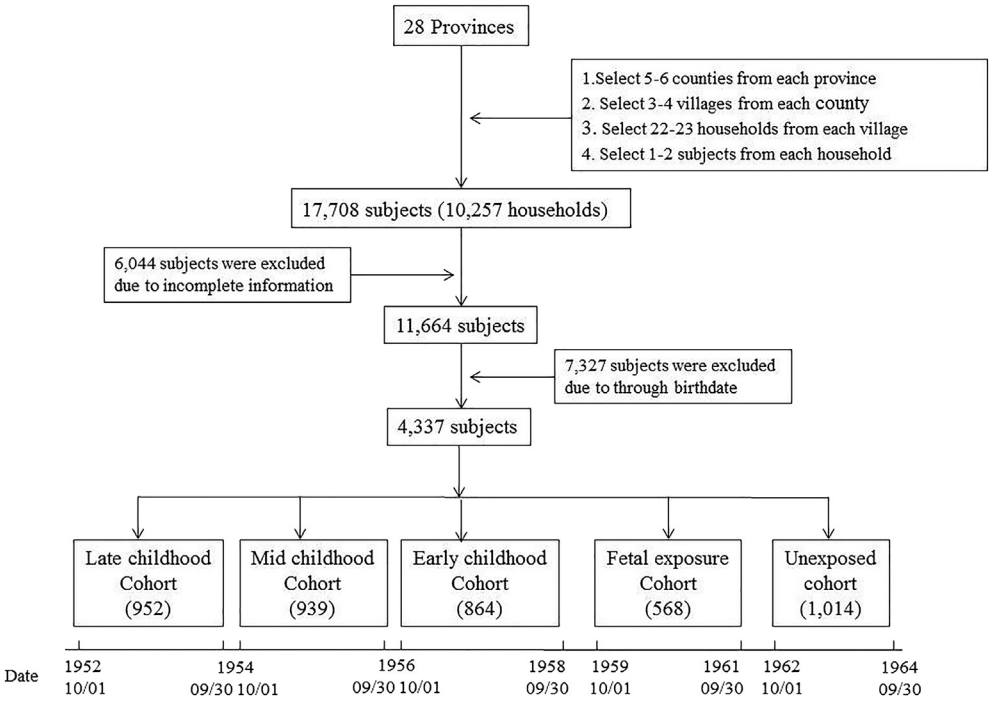

Figure 1 Flowchart showing the step-by-step sample selection of the famine cohort.

logistic regression. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking, alcohol drinking, education, residence, BMI and famine severity. Model 3 was further adjusted for hypertension and dyslipidaemia. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and the significance level was set at 0.05 (two sided).

Results

In the study population, the prevalence of CVD showed significant variation among different famine exposure cohorts ($P = 0.0156$): late childhood exposure (15.24%), mid childhood exposure (12.53%), early childhood exposure (13.55%), foetal exposure (11.86%) and no exposure (10.18%). In addition, the prevalence of hyperglycaemia, hypertension and dyslipidaemia across different famine exposure cohorts showed significant difference ($P < 0.05$) (Table 1).

After adjusting for age and sex, hyperglycaemia was associated with an increased risk of CVD (OR: 1.65; 95% CI: 1.49–1.83) in the entire study population. In different famine exposure cohorts, the ORs (95% CIs) were as follows: 1.56 (1.09–2.25) for late childhood, 1.99 (1.34–2.96) for mid childhood, 1.92 (1.29–2.87) for early childhood, 3.11 (1.84–5.26) for the foetal cohort and 1.42 (0.90–2.23) for the non-exposed cohort. Following further adjustments for smoking, alcohol drinking, education, residence, BMI, famine severity, hypertension and dyslipidaemia, the ORs (95% CIs) were as follows: 1.46 (0.94,2.26) for late childhood, 1.76 (1.06,2.90) for mid childhood, 1.40 (0.86,2.27) for early childhood, 2.55 (1.30,5.02) for the foetal cohort and 1.10 (0.63,1.95) for the nonexposed cohort (Table 2), and the P value of the interaction was 0.0374.

Likewise, the subgroup analyses showed that the OR values of hyperglycaemia in the foetal exposure cohort were almost significantly higher than those in any other famine-exposed cohorts, especially in those who lived in rural areas (OR: 4.67, 95% CI: 1.70–12.84), men (OR: 3.66, 95% CI: 1.01–13.33), those who lived in severe famine areas (OR: 5.01, 95% CI: 1.22–20.66), those who were drinkers (OR: 4.46, 95% CI: 1.42–14.04), those who were overweight (OR: 3.49, 95% CI: 1.43–8.52) and those who had a low education level (OR: 3.36, 95% CI: 1.14–9.88). Furthermore, even hyperglycaemic subjects who did not smoke, lived in a light famine area or who were women had significantly higher CVD risk in the foetal exposure cohort (Fig. 2).

Discussion

Using a national representative dataset, we found that exposure to Chinese famine in early life modified the association between hyperglycaemia and CVD. Notably, foetal exposure had a much stronger effect on this relationship, especially among those who are male, born in severe famine areas, lived in rural areas or had a low education level.

To the best of our knowledge, the possible interaction of famine and hyperglycaemia on CVD risk has not been previously evaluated. Our results were consistent with the results of a previous study in which the Chinese famine

Table 1 Sample characteristics (in 2011) by early life famine exposure ($N = 4337$).

Factor	Late childhood	Mid childhood	Early childhood	Foetal exposure	No exposure	*P* value
N	952	939	864	568	1014	
Birth date						
From 1 October, year	1952	1954	1956	1959	1962	
To 30 September, year	1954	1956	1958	1961	1964	
Age in 2011 (years), mean ± SD	57.48 ± 0.59	55.51 ± 0.57	53.51 ± 0.55	50.57 ± 0.57	47.53 ± 0.58	<0.0001
Men (%)	47.58	46.75	47.45	42.61	42.50	0.0569
Education (%)						
Illiterate	32.67	26.20	25.00	16.02	12.52	<0.0001
Primary	41.81	38.34	35.76	30.28	32.15	
Middle school	17.33	23.00	22.57	28.35	36.69	
High	8.19	12.46	16.67	25.35	18.64	
Urban (%)	38.03	36.85	38.31	41.02	39.84	0.4871
Smoker (%)	40.53	40.88	38.93	34.86	34.95	0.0144
Drinking (%)						0.1398
None drinker	57.89	56.56	59.21	59.68	59.25	
Ex-drinker	7.26	7.47	6.26	4.93	4.45	
Current drinker	34.84	35.97	34.53	35.39	36.30	
BMI (kg/m^2), mean ± SD	23.80 ± 3.99	23.38 ± 3.69	24.08 ± 3.89	24.36 ± 4.55	24.43 ± 3.72	<0.0001
SBP, mean ± SD	131.33 ± 26.76	126.99 ± 22.35	128.76 ± 25.69	126.85 ± 24.95	124.66 ± 18.41	<0.0001
DBP, mean ± SD	77.1 ± 12.39	76.01 ± 12.27	76.89 ± 12.75	76.84 ± 12.80	76.27 ± 12.48	0.4840
TC (mg/dl), mean ± SD	196.73 ± 39.19	195.23 ± 38.32	194.92 ± 39.21	193.33 ± 35.98	187.56 ± 36.56	<0.0001
TG (mg/dl), mean ± SD	138.67 ± 111.74	132.28 ± 93.51	138.05 ± 114.79	150.55 ± 122.14	137.64 ± 112.18	0.3268
FPG (mg/dl), mean ± SD	113.05 ± 42.84	110.48 ± 36.03	108.8 ± 32.89	110.44 ± 39.20	107.11 ± 33.02	0.0010
GHB (%), mean ± SD	5.30 ± 0.81	5.29 ± 0.91	5.24 ± 0.82	5.28 ± 0.87	5.21 ± 0.81	0.0142
CVD (%)	15.24	12.53	13.55	11.86	10.18	0.0156
Hyperglycaemia (%)	34.77	32.37	31.48	31.34	24.85	<0.0001
Hypertension (%)	44.79	38.16	38.79	36.38	33.92	0.0002
Dyslipidaemia (%)	48.15	43.92	45.63	48.47	41.55	0.0202

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; GHB, glycosylated haemoglobin; SD, standard deviation.

modified the association between hypertension and CVD, which had the most significant effect in the foetal exposure famine cohort [13]. In subgroup analyses, individuals who were male or lived in rural areas exhibited a high effect of hyperglycaemia on CVD. It has been reported that oestrogen has a protective effect on cardiovascular risk [23,24], which may explain the higher risk in men than in women in the present study. Differences in the severity of the famine due to the uneven distribution of resources within the region may be a reason for the greater risk for those who lived in rural areas than for those who lived in urban areas. Compared with urban residents, the rural residents usually experience more severe famine because of the grain ration system preferentially supplying urban residents; moreover, rural residents have to reallocate their resources to cities [25]. These findings may be instructive for targeted interventions.

Although mechanisms that underlie the interaction between hyperglycaemia and famine exposure in relation to CVD risk have yet to be elucidated, several possible mechanisms may be proposed. First, experimental animals and epidemiological studies have demonstrated that the foetus would adapt to adverse intrauterine conditions to ensure survival by reducing the ability to produce insulin and by the occurrence of insulin resistance [26]. The immediate consequence for this adaption is low birth weight (LBW), while the long-term consequence is the increased susceptibility of CVD in adult life [27,28]. Second, the thrifty phenotype hypothesis suggests that foetal and early postnatal malnutrition may have selective effects on the

Table 2 OR (95% CI) for the association of cardiovascular disease with hyperglycaemia by early life famine exposure.

Hyperglycaemia	Overall	Famine exposure cohorts				
		Late childhood	Mid childhood	Early childhood	Foetal exposure	No exposure
Unadjusted	1.72 (1.56,1.91)	1.53 (1.07,2.20)	1.97 (1.33,2.91)	1.96 (1.31,2.92)	2.94 (1.75,4.94)	1.36 (0.87,2.12)
Model 1	1.65 (1.49,1.83)	1.56 (1.09,2.25)	1.99 (1.34,2.96)	1.92 (1.29,2.87)	3.11 (1.84,5.26)	1.42 (0.90,2.23)
Model 2	1.48 (1.32,1.67)	1.61 (1.06,2.45)	1.89 (1.18,3.03)	1.74 (1.11,2.72)	2.94 (1.55,5.59)	1.21 (0.70,2.09)
Model 3	1.27 (1.12,1.44)	1.46 (0.94,2.26)	1.76 (1.06,2.90)	1.40 (0.86,2.27)	2.55 (1.30,5.02)	1.10 (0.63,1.95)

OR, odds ratio; CI, confidence interval.
Model 1 adjusted for age and sex.
Model 2 adjusted for age, sex, smoking, alcohol drinking, education, urban/rural area, BMI and famine severity.
Model 3 adjusted for age, sex, smoking, alcohol drinking, education, urban/rural area, BMI, famine severity, hypertension and dyslipidaemia.

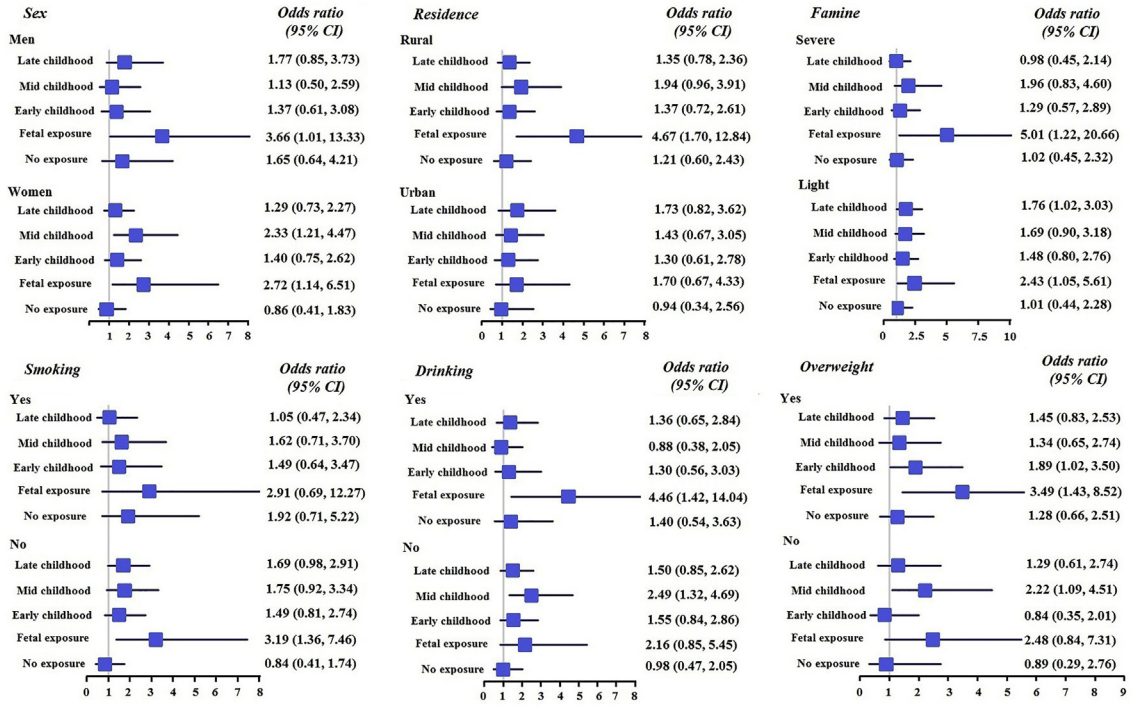

Figure 2 Subgroup analyses of the association between hyperglycaemia and CVD by famine exposure cohorts. Model adjusted for age, sex, smoking, alcohol drinking, education, urban/rural area, BMI, famine severity, hypertension and dyslipidaemia. Stratification variables were not adjusted in corresponding models. CI, confidence interval; CVD, cardiovascular disease.

growth of different organs, protecting the most important organs (e.g., the brain), which can lead to the poor development of other organs (e.g., pancreatic β-cells) [29]. This alteration causes an impaired growth of the pancreatic β-cell as well as the islands of Langerhans and increases the effect of abnormal glucose metabolism on CVD [30]. Additionally, among different famine cohorts, the foetal phase is more vulnerable to malnutrition because the development of the pancreatic β cells proceeds rapidly during that time [30]. Third, prenatal exposure to famine may lead to persistent epigenetic changes in major regulators of DNA methylation [31]. Studies have shown that changes in foetal leptin levels caused by malnutrition may alter the process of appetite and eating behaviour (e.g. increased preference for fatty foods), thereby leading to an increased risk of metabolic diseases, which was confirmed during the Dutch famine [32,33]. Apart from the above mechanisms, diseases associated with adverse foetal growth are associated with oxidative stress, and several lines of experimental evidence suggest that the insulin functional axis may be sensitive targets of oxidative stress programming during the perinatal period [34]. These mechanisms could be interrelated; for instance, reactive oxygen species can modify methylation, leading to changes in gene transcription and expression [35]. Epigenetic mechanisms may also contribute to the development of a thrifty phenotype [36].

The main strength of this study is that it is the first to investigate whether the Chinese famine modified the association between hyperglycaemia and CVD. Moreover, this study used nationally representative samples with a high response rate of 80.5%. Several limitations should be noted. First, CVD in this study is determined by self-reported data. However, self-reported CVD has been shown to be reliable [37]. Second, the migration of residents in different parts of the country may lead to the misclassification of famine exposures. However, the relocation of permanent residents in China requires the approval of the relevant authorities on a level-by-level basis; thus, population mobility is relatively low in China [20]. Third, since the health of the survivors surveyed was better than that of those who died in the famine, the effects of the famine may have been underestimated.

In conclusion, this study provides evidence that Chinese famine modified the effects of hyperglycaemia on CVD, especially in subjects who experienced exposure to famine in the foetal stage of life. The findings indicate that screening hyperglycaemia among Chinese famine survivors and implementing intensive interventions and monitoring measures may benefit the prevention and control of CVD. Additionally, the findings suggest that providing adequate nutrition early in life is critical to preventing chronic diseases in adult life.

Competing interests

The authors have nothing to disclose.

Funding

This work was supported by National Natural Science Foundation of China (project number 81703316), Natural Science Foundation of Jiangsu Province (project number

BK20170350), and A Project Funded by Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Database

The datasets generated and/or analysed during the current study are available in the CHARLS repository (http://charls.pku.edu.cn/en).

Acknowledgements

This analysis uses data or information from the Harmonized CHARLS dataset and Codebook, Version C, as of April 2018 developed by the Gateway to Global Aging Data. The development of the Harmonized CHARLS was funded by the National Institute on Aging (R01 AG030153, RC2 AG036619, and R03 AG043052). For more information, please refer to www.g2aging.org.

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