Supplementary appendix

Early-life famine exposure and subsequent risk of chronic diseases in later adulthood: A population-based retrospective cohort study

Supplementary appendix

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eMethods 1 Study design and participants

The CHARLS's baseline survey includes one person per household aged 45 years of age or older and their spouse, totaling 17,708 individuals, living in 10,257 households in 450 villages / urban communities (1). A stratified (by per capita GDP of urban districts and rural counties) multi-stage (county / district-village / communityhousehold) probability proportional to size (PPS) random sampling strategy was adopted.

At the first stage, all county-level units were sorted (stratified) by region, within the region by urban district or rural county, and by GDP per capita (Tibet was the only province not included). The region was a categorical variable based on the NBS division of provinces. After this sorting (stratification), 150 counties or urban districts were chosen with probability proportional to population size (2). For each county-level unit, 3 Primary Sampling Units (PSU) (villages and urban neighborhoods) are randomly chosen with probability proportional to population (3). Hence CHARLS is nationally representative and representative of both rural and urban areas within China. Counties and districts in 28 provinces are included in the CHARLS sample.

In light of the outdated household listings at the village/community level due to population migration, CHARLS designed a mapping/listing software (Charls-GIS) that makes use of Google-earth map images to list all dwelling units in all residential buildings to create sampling frames

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eMethods 2 Excess death rate and area categories

The Excess Death Rate refers to the difference between the normal death rate and the death rate during the famine period. This difference reflects the additional mortality burden caused by the famine. The Normal Death Rate is typically defined as the average death rate in the years leading up to the famine, serving as a baseline for comparison. The Death Rate During Famine refers to the mortality rate during the famine years.

For data preparation, death rate data is obtained from the "China Statistical Yearbook" for the years before and during the famine. Specifically, the period of includes the three years before the famine (1956-1958) and the three years during the famine (1959-1961). These data points are essential for calculating the normal and famine-related death rates, which are central to the subsequent analysis.

To calculate the Excess Death Rate, first, the Normal Death Rate is determined by computing the average death rate from 1956 to 1958. Then, the Death Rate During Famine is calculated as the average death rate for the years 1959 to 1961. The Excess Death Rate is then derived using the formula:

Excess Death Rate = (Death Rate During Famine−Normal Death Rate) / Normal Death Rate×100%

Lastly, a threshold of 50% is used to classify the severity of the famine’s impact across different regions. Provinces with an excess death rate below 50% are classified as mildly affected by famine, while those with an excess death rate above 50% are classified as severely affected.

eMethods 3 MET values and physical activity intensity categories

According to the CHARLS questionnaire, the duration of daily physical activity types is divided into 5 categories (0 min, 10~29 min, 30~119 min, 120~239 min, ⩾ 240 min), and the median is used to calculate the exercise time for high, moderate, and low-intensity physical activities. The weekly duration of physical activity = number of days performing each type of physical activity × duration of each type per day (1).

The amount of high-intensity physical activity is calculated using the Metabolic Equivalent (MET). MET is a measure of the intensity of physical activity. According to the International Physical Activity Questionnaire (IPAQ) assessment criteria, walking has a MET value of 3.3, moderate-intensity activity has a MET value of 4.0, and high-intensity activity has a MET value of 8.0 (2).

The score of physical activity is calculated by the formula: 8.0 × total duration of high-intensity activity per week + 4.0 × total duration of moderate-intensity activity per week + 3.3 × total duration of walking per week [15]. The weekly level of physical activity is categorized into low-intensity physical activity (< 600 METs/week), moderate-intensity physical activity (600~3,000 METs/week), and high-intensity physical activity (> 3,000 METs/week) (3).

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eTable 1 Harmonized definitions for key covariates in the study

Variables	Values
Education	
Primary school or lower	No formal education (illiterate)/Did not finish primary schoo/Sishu/home school/Elementary school/
Junior high school	Middle school
Senior high school	High school/Vocational school
University and above	Two-/Three-Year College/Associate degree/Four-Year College/Bachelor's degree/Maste's degree/Doctoral degree/Ph.D.
Marital	
Married or partnered	Married and living together with
Single	Widowed/Single/Divorced/Separated
Cigarette smoking	
No	Never
Yes	Previous, and current
Alcohol drinking	
No	Never
Yes	⩽1 time/month
	>1 time/month
Famine severity	
Less severely	The excess death rate is less than 50%.
Severely	The excess death rate is greater than 50%.

eTable 2 Questionnaire items and prevalence of chronic diseases in CHARLS

Types of Chronic Diseases	Questionnaire Items（codes：DA007）	Prevalence (%)
Hypertension	Have you been diagnosed with Hypertension by a doctor?	10.7
Dyslipidemia	Have you been diagnosed with Dyslipidemia (elevation of low density lipoprotein, triglycerides (TGs),and total cholesterol, or a low high density lipoprotein level) by a doctor?	10.0
Diabetes	Have you been diagnosed with Diabetes or high blood sugar by a doctor?	5.8
Cancer	Have you been diagnosed with Cancer or malignant tumor (excluding minor skin cancers) by a doctor?	1.1
Chronic lung disease	Have you been diagnosed with Chronic lung diseases, such as chronic bronchitis , emphysema (excluding tumors, or cancer) by a doctor?	4.7
Liver disease	Have you been diagnosed with Liver disease (except fatty liver, tumors, and cancer) by a doctor?	3.3
Heart disease	Have you been diagnosed with Heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems by a doctor?	5.9
Stroke	Have you been diagnosed with Stroke by a doctor?	4.0
Kidney disease	Have you been diagnosed with Kidney disease (except for tumor or cancer) by a doctor?	3.0
Digestive disease	Have you been diagnosed with Stomach or other digestive diseases (except for tumor or cancer) by a doctor?	6.6
Psychiatric disease	Have you been diagnosed with Emotional, nervous, or psychiatric problems by a doctor?	1.1
Memory-related disease	Have you been diagnosed with Emotional, nervous, or psychiatric problems by a doctor?	1.2
Arthritis	Have you been diagnosed with Arthritis or rheumatism by a doctor?	7.4
Asthma	Have you been diagnosed with Asthma by a doctor?	1.7

eTable 3 Association between famine and subsequent chronic diseases in adulthood: additionally adjusted for social activity

	Model 1 : Crude model OR (95% CI)			Model 2 : Adjusted model OR (95% CI)		
	Group 0	Group 1	Group 2	Group 0	Group 1	Group 2
Hypertension	Ref	1.08(0.83-1.42)	**1.29(1.02-1.64)**	Ref	1.08(0.76-1.53)	1.17(0.85-1.61)
Dyslipidemia	Ref	0.86(0.65-1.13)	1.03(0.81-1.30)	Ref	0.87(0.62-1.24)	1.12(0.83-1.52)
Diabetes	Ref	1.00(0.70-1.44)	**1.43(1.06-1.94)**	Ref	1.46(0.94-2.28)	**1.88(1.28-2.77)**
Cancer	Ref	**2.18(1.06-4.49)**	1.46(0.71-3.04)	Ref	2.18(0.91-5.24)	1.57(0.66-3.76)
Chronic lung disease	Ref	1.03(0.70-1.52)	1.14(0.81-1.60)	Ref	1.27(0.78-2.04)	0.91(0.57-1.67)
Liver disease	Ref	0.75(0.48-1.19)	0.70(0.46-1.06)	Ref	0.78(0.45-1.36)	0.81(0.49-1.33)
Heart disease	Ref	0.97(0.68-1.38)	1.21(0.89-1.63)	Ref	0.97(0.62-1.51)	1.29(0.88-1.89)
Stroke	Ref	1.43(0.93-2.19)	**1.80(1.24-2.62)**	Ref	1.64(0.92-2.92)	**1.97(1.17-3.29)**
Kidney disease	Ref	**1.79(1.15-2.79)**	1.20(0.77-1.89)	Ref	**1.87(1.05-3.34)**	1.22(0.67-2.21)
Digestive disease	Ref	1.15(0.84-1.59)	1.11(0.83-1.49)	Ref	1.32(0.89-1.95)	1.28(0.89-1.86)
Psychiatric disease	Ref	0.94(0.42-2.11)	1.21(0.62-2.39)	Ref	0.74(0.30-1.85)	1.09(0.52-2.27)
Memory-related disease	Ref	**2.87(1.38-5.99)**	2.06(0.99-4.28)	Ref	2.38(0.96-5.88)	1.94(0.80-4.70)
Arthritis	Ref	1.14(0.85-1.53)	0.87(0.65-1.15)	Ref	1.28(0.89-1.84)	0.88(0.61-1.27)
Asthma	Ref	1.19(0.65-2.20)	1.11(0.63-1.96)	Ref	1.67(0.76-3.68)	1.04(0.47-2.32)

Note: Group0, Unexposed; Group1, Infant-exposed; Group2, Toddler-exposed; OR, odds ratio; 95% CI, 95% confidence intervals; Ref, reference. Model 1: crude model. Model 2 was adjusted for Gender, Residence, Education, Marital status, Severity, PA, Smoking status, and Drinking habits, Social activity. The bold values indicate statistically significant.

eTable 4 Association between famine and subsequent chronic diseases in adulthood: adjusted for per capita income

	Model 1 : Crude model OR (95% CI)			Model 2 : Adjusted model OR (95% CI)		
	Group 0	Group 1	Group 2	Group 0	Group 1	Group 2
Hypertension	Ref	1.09(0.83-1.46)	1.34(1.03-1.72)	Ref	1.21(0.76-1.92)	1.40(0.92-2.12)
Dyslipidemia	Ref	0.84(0.61-1.15)	1.05(0.80-1.36)	Ref	1.07(0.67-1.69)	1.36(0.91-2.04)
Diabetes	Ref	1.00(0.66-1.51)	**1.55(1.11-2.17)**	Ref	1.28(0.71-2.29)	1.52(0.92-2.53)
Cancer	Ref	**1.99(0.94-4.19)**	1.37(0.65-2.89)	Ref	2.03(0.69-5.95)	1.14(0.37-3.50)
Chronic lung disease	Ref	1.18(0.79-1.75)	1.12(0.78-1.60)	Ref	1.55(0.83-2.89)	0.85(0.44-1.64)
Liver disease	Ref	0.82(0.51-1.34)	0.76(0.49-1.18)	Ref	0.77(0.37-1.59)	0.91(0.49-1.70)
Heart disease	Ref	1.06(0.73-1.54)	1.18(0.85-1.64)	Ref	0.87(0.49-1.57)	1.27(0.78-2.07)
Stroke	Ref	1.31(0.80-2.14)	**1.85(1.22-2.79)**	Ref	1.63(0.71-3.73)	**2.49(1.22-5.09)**
Kidney disease	Ref	**1.79(1.10-2.89)**	1.27(0.79-2.03)	Ref	1.65(0.48-5.66)	1.48(0.46-4.79)
Digestive disease	Ref	1.18(0.82-1.69)	1.21(0.88-1.67)	Ref	1.28(0.76-2.17)	1.38(0.85-2.44)
Psychiatric disease	Ref	1.27(0.55-2.94)	1.08(0.49-2.38)	Ref	0.21(0.03-1.67)	1.74(0.71-4.26)
Memory-related disease	Ref	**3.74(1.58-8.87)**	**3.12(1.35-7.20)**	Ref	2.01(0.39-10.41)	**4.58(1.21-17.42)**
Arthritis	Ref	1.08(0.78-1.49)	0.92(0.68-1.25)	Ref	1.28(0.80-2.06)	0.94(0.59-1.51)
Asthma	Ref	1.35(0.66-2.75)	1.30(0.68-2.49)	Ref	2.53(0.65-9.87)	2.19(0.60-7.97)

Note: Group0, Unexposed; Group1, Infant-exposed; Group2, Toddler-exposed; OR, odds ratio; 95% CI, 95% confidence intervals; Ref, reference. Model 1: crude model. Model 2 was adjusted for Gender, Residence, Education, Marital status, Severity, PA, Smoking status, and Drinking habits, per capita income. The bold values indicate statistically significant.

eTable 5 Association between famine and multimorbidity in the overall study

	Multimorbidity OR (95% CI)		
	Unexposed	Infant-exposed	Toddler-exposed
Model 1	Ref	1.07(0.85-1.34)	**1.30(1.07-1.59)**
Model 2	Ref	1.11(0.88-1.40)	**1.31(1.07-1.61)**
Model 3	Ref	1.31(0.99-1.73)	**1.39(1.08-1.80)**

Note: OR, odds ratio; 95% CI, 95% confidence intervals; Ref, reference. OR represents the probability ra tio of developing multimorbidity chronic diseases for individuals who were exposed to famine, compared with those who were not exposed to famine, at 95% CIs. Model 1: crude model. Model 2: adjusted for Gender,Residence, Education,Marital status,Severity Model 3: further adjusted for PA,Smoking status, Drink ing habits based on Model 2 The bold values indicate statistically significant.

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eTable 6 Comparison of prevalence of chronic diseases between less severely and severely famine

	Less severely OR (95% CI)			Severely OR (95% CI)		
	Group 0	Group 1	Group 2	Group 0	Group 1	Group 2
Hypertension	Ref	1.02(0.64-1.61)	1.13(0.74-1.73)	Ref	1.20(0.71-2.05)	1.22(0.76-1.96)
Dyslipidemia	Ref	0.86(0.54-1.37)	1.27(0.85-1.92)	Ref	0.90(0.53-1.53)	0.99(0.63-1.58)
Diabetes	Ref	1.14(0.59-2.21)	**2.05(1.19-3.52)**	Ref	1.72(0.93-3.17)	1.67(0.96-2.91)
Cancer	Ref	1.54(0.37-6.73)	0.90(0.19-4.18)	Ref	2.82(0.90-8.79)	2.12(0.72-6.28)
Chronic lung disease	Ref	1.17(0.63-2.16)	0.91(0.50-1.67)	Ref	1.55(0.71-3.37)	0.90(0.41-1.96)
Liver disease	Ref	0.66(0.31-1.39)	0.60(0.30-1.22)	Ref	0.94(0.41-2.14)	1.10(0.54-2.24)
Heart disease	Ref	1.13(0.63-2.05)	1.38(0.80-2.37)	Ref	0.87(0.44-1.71)	1.20(0.70-2.08)
Stroke	Ref	1.71(0.75-3.89)	**2.69(0.28-1.56)**	Ref	1.65(0.73-3.74)	1.38(0.63-3.03)
Kidney disease	Ref	2.23(1.01-4.94)	1.85(0.84-4.06)	Ref	1.57(0.66-3.76)	0.68(0.25-1.83)
Digestive disease	Ref	1.42(0.86-2.34)	1.27(0.78-2.07)	Ref	1.16(0.61-2.21)	1.37(0.78-2.39)
Psychiatric disease	Ref	1.30(0.39-4.37)	2.16(0.77-6.04)	Ref	3.78(0.08-1.82)	4.09(0.11-1.53)
Memory-related disease	Ref	1.80(0.56-5.79)	1.58(0.51-4.84)	Ref	3.71(0.86-15.90)	2.77(0.65-11.86)
Arthritis	Ref	1.44(0.90-2.30)	0.68(0.40-1.16)	Ref	1.03(0.58-1.83)	1.12(0.67-1.86)
Asthma	Ref	1.34(0.46-3.94)	1.49(0.56-3.95)	Ref	1.95(0.60-6.36)	0.41(0.08-2.06)

Note: Group0, Unexposed; Group1, Infant-exposed; Group2, Toddler-exposed; OR, odds ratio; 95% CI, 95% confidence intervals; Ref, reference.

Model was adjusted for Gender, Residence, Education, Marital status, PA, Smoking status, and Drinking habits..

The bold values indicate statistically significant.

eTable 7 Comparison of prevalence of chronic diseases between male and female

	Male OR (95% CI)			Female OR (95% CI)		
	Group 0	Group 1	Group 2	Group 0	Group 1	Group 2
Hypertension	Ref	1.80(0.89-3.66)	**1.90(1.05-3.45)**	Ref	0.94(0.63-1.41)	1.00(0.68-1.45)
Dyslipidemia	Ref	0.72(0.30-1.75)	1.93(0.99-3.74)	Ref	0.90(0.61-1.13)	1.01(0.71-1.43)
Diabetes	Ref	0.95(0.38-2.34)	**2.20(1.09-4.45)**	Ref	1.46(0.88-2.41)	**1.69(1.08-2.66)**
Cancer	Ref	5.82(0.46-73.34)	1.43(0.08-24.10)	Ref	1.79(0.69-4.61)	1.55(0.62-3.89)
Chronic lung disease	Ref	1.57(0.58-4.26)	1.28(0.53-3.13)	Ref	1.19(0.69-2.05)	0.78(0.44-1.37)
Liver disease	Ref	0.65(0.13-3.37)	1.56(0.54-4.52)	Ref	0.78(0.43-1.40)	0.67(0.37-1.19)
Heart disease	Ref	0.76(0.23-2.50)	1.25(0.51-3.01)	Ref	1.04(0.65-1.68)	1.31(0.86-2.01)
Stroke	Ref	**3.38(1.05-10.92)**	1.48(0.45-4.90)	Ref	1.35(0.69-2.67)	**2.12(1.19-3.77)**
Kidney disease	Ref	2.08(0.65-6.72)	0.92(0.27-3.06)	Ref	1.86(0.95-3.64)	1.29(0.65-2.58)
Digestive disease	Ref	1.78(0.77-4.14)	1.20(0.53-2.68)	Ref	1.20(0.77-1.88)	1.31(0.87-1.98)
Psychiatric disease	Ref	0.94(0.42-2.11)	1.21(0.62-2.39)	Ref	0.75(0.32-2.00)	0.98(0.45,2.14)
Memory-related disease	Ref	1.67(7.86-360.0)	6.01(0.38-94.70)	Ref	2.05(0.77-5.43)	1.74(0.67-4.50)
Arthritis	Ref	1.15(0.50-2.66)	0.62(0.27-1.43)	Ref	1.31(0.88-1.97)	0.98(0.65-1.48)
Asthma	Ref	1.19(0.10-14.20)	2.01(0.33-14.76)	Ref	1.66(0.72-3.83)	0.82(0.33-2.03)

Note: Group0, Unexposed; Group1, Infant-exposed; Group2, Toddler-exposed; OR, odds ratio; 95% CI, 95% confidence intervals; Ref, reference.

Model was adjusted for Residence, Education, Marital status, Severity, PA, Smoking_status, and Drinking_habits..

The bold values indicate statistically significant.

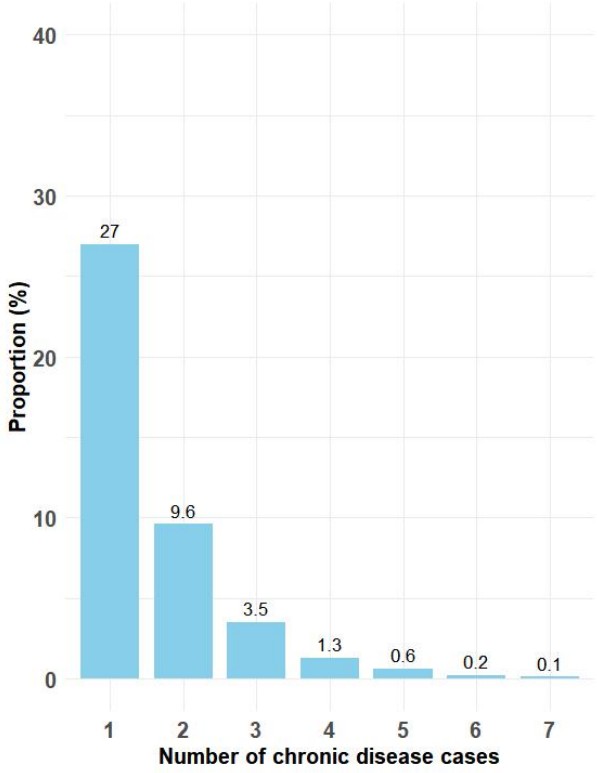
eTable 8 Comparison of prevalence of chronic diseases between rural and urban

	Rural OR (95% CI)			Urban OR (95% CI)		
	Group 0	Group 1	Group 2	Group 0	Group 1	Group 2
Hypertension	Ref	1.23(0.82-1.85)	1.25(0.86-1.82)	Ref	0.85(0.43-1.69)	1.01(0.55-1.82)
Dyslipidemia	Ref	0.96(0.63-1.46)	1.18(0.82-1.72)	Ref	0.65(0.34-1.25)	1.02(0.59-1.77)
Diabetes	Ref	**2.05(1.21-3.46)**	**2.38(1.49-3.80)**	Ref	0.57(0.22-1.46)	1.02(0.49-2.09)
Cancer	Ref	1.89(0.69-5.19)	1.06(0.36-3.11)	Ref	3.00(0.46-19.30)	4.07(0.76-21.77)
Chronic lung disease	Ref	1.65(0.96-2.86)	1.01(0.57-1.78)	Ref	0.46(0.15-1.43)	0.71(0.28-1.79)
Liver disease	Ref	0.94(0.48-1.87)	1.00(0.54-1.83)	Ref	0.61(0.23-1.60)	0.50(0.20-1.27)
Heart disease	Ref	0.81(0.45-1.46)	1.37(0.85-2.19)	Ref	1.28(0.64-2.56)	1.19(0.62-2.31)
Stroke	Ref	1.61(0.80-3.24)	1.43(0.74-2.76)	Ref	1.68(0.61-4.64)	**2.97(1.23-7.17)**
Kidney disease	Ref	1.70(0.79-3.66)	1.21(0.56-2.59)	Ref	2.59(1.04-6.47)	**1.27(0.47-3.38)**
Digestive disease	Ref	1.48(0.93-2.36)	1.51(0.98-1.49)	Ref	0.96(0.45-2.03)	0.81(0.38-1.73)
Psychiatric disease	Ref	1.14(0.36-3.58)	1.16(0.41-3.24)	Ref	0.42(0.09-2.07)	1.17(0.40,3.44)
Memory-related disease	Ref	2.43(0.91-6.49)	1.78(0.67-4.75)	Ref	2.90(0.25-33.35)	3.28(0.33-32.64)
Arthritis	Ref	1.19(0.78-1.81)	0.73(0.47-1.13)	Ref	1.58(0.77-3.26)	1.51(0.775-3.00)
Asthma	Ref	1.92(0.80-4.63)	0.87(0.87-2.29)	Ref	1.09(0.17-7.23)	1.52(0.31-7.45)

Note: Group0, Unexposed; Group1, Infant-exposed; Model was adjusted for Gender, Education, Marital status, Severity, PA, Social activity, Smoking status, and Drinking habits..

The bold values indicate statistically significant.

eFigure 1 The quantity and prevalence of chronic disease types



eEthics approval

Ethical approval for all the CHARLS waves was granted from the Institutional Review Board at Peking University. The IRB approval number for the main household survey, including anthropometrics, is IRB00001052-11015; the IRB approval number for biomarker collection, was IRB00001052-11014.

During the fieldwork, each respondent who agreed to participate in the survey was asked to sign two copies of the informed consent, and one copy was kept in the CHARLS office, which was also scanned and saved in PDF format. Four separate consents were obtained: one for the main fieldwork, one for the non-blood biomarkers and one for the taking of the blood samples, and another for storage of blood for future analyses.

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