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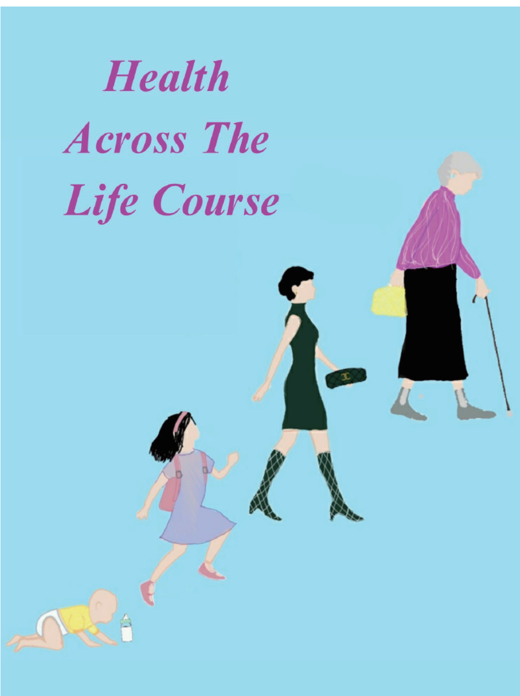

LIFE COURSE HEALTH ISSUE

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Cover Image: credited from Cecelia Chen.
This week's issue was organized by Guest Editor Xi Chen.

Preplanned Studies

A Systematic Analysis of Early Life Exposure to the Chinese Famine (1959–1961) and the Health of Older Adults — China, 2008–2023

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Summary

What is already known about this topic?

There is mounting evidence indicating that the aging process initiates during early life stages, with *in utero* the individual's environment playing a significant role. Consequently, it is crucial to comprehend the enduring effects of early life circumstances on health in old age.

What is added by this report?

In this study, we conducted a meta-analysis to examine the effects of the Chinese Famine (1959–1961) on the health of older adults. We also explored potential mechanisms underlying these effects.

What are the implications for public health practice?

The complex interplay between early life circumstances, multiple health-related sectors, and healthy aging necessitates a comprehensive life-course approach and strategic interventions to enhance public health in an aging society.

The increasing aging population and the prevalence of chronic diseases necessitate a comprehensive life-course approach to address the growing demand for cost-effective prevention, treatment, and long-term care. To achieve healthy aging, it is crucial to understand the factors influencing disease development throughout an individual's life and identify opportunities for effective interventions. This study examines the latest evidence on how early life circumstances impact health in old age, distinguishing between exposures *in utero* and during childhood in various environments. Furthermore, we conduct a meta-analysis utilizing studies on the effects of the Chinese Famine (1959–1961) on the health of older adults, discussing potential mechanisms underlying these associations.

Prenatal conditions have a significant impact on healthy aging, as evidenced by numerous studies (*1*–*2*). The Fetal Origin Hypothesis suggests that disruptions to the prenatal environment, including maternal and fetal health, social and economic shocks, and environmental pollution, can have long-term consequences on developmental health and well-being. These effects become apparent later in life, with an increased susceptibility to diseases persisting into old age.

Childhood represents a critical period during which adverse circumstances can have long-lasting effects on health (*3*). Figure 1 displays the variation in self-rated health among respondents from the China Health and Retirement Longitudinal Study (CHARLS) national sample over three waves, based on retrospective reports of health status before age 16. The data reveals a significant association between good health before age 16 and a higher likelihood of reporting excellent or very good health after the age of 60, with a difference of 5–10 percentage points. Additionally, various other childhood factors, including traumas and adversity, neighborhood safety and cohesion, education, friendship, parent-child relationship, parenting skills, natural environments, exposure to famine, parental health behaviors, disease infections, access to healthcare, parental socioeconomic status, and home and social environments, have also shown associations with health outcomes in later life.

Multiple risk factors *in utero* and early *childhood* have been identified as contributors to various adverse health outcomes, including but not limited to diminished height, disability, premature mortality, depressive symptoms, schizophrenia, cognitive impairment, metabolic syndrome, frailty, reduced lung function, arthritis, anemia, diabetes, coronary heart disease, stroke, and fatty liver disease.

Numerous studies in China have explored the association between early life risk factors and aging, with a particular focus on exposures to the Chinese Famine (1959–1961) (*4*). It is worth noting that a significant proportion of the Chinese population over the age of 60 today was exposed to famine during their

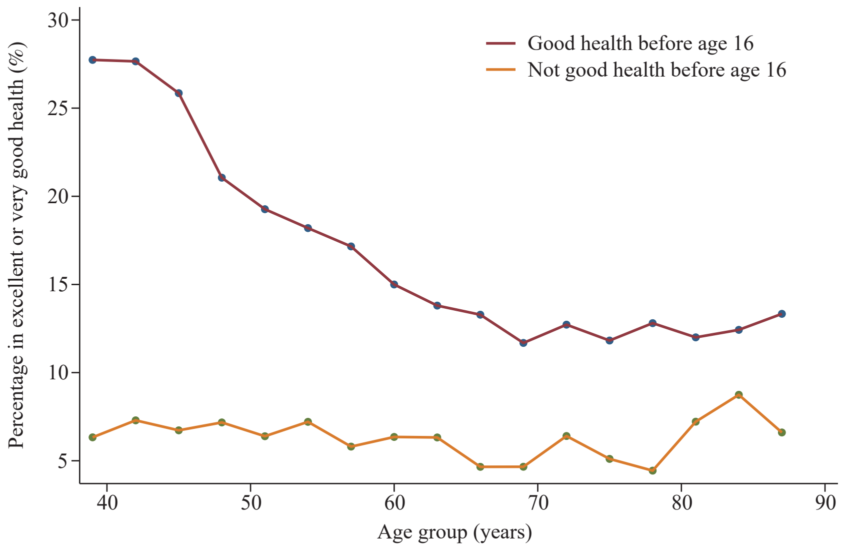


FIGURE 1. Self-rated health among middle-aged and older adults by child health.
Note: In this figure, we included data from the longitudinal survey, ensuring that each respondent is counted only once. If a respondent participated in multiple waves of the survey, we used information from their earliest participation for plotting purposes. The respondents featured in this figure are middle-aged and older adults. Data: CHARLS National Sample (2011, 2013, 2015).
Abbreviation: CHARLS=China Health and Retirement Longitudinal Study.

early years. Both animal and human studies have indicated that the famine may have a substantial long-term impact on the prevalence of chronic diseases. The international literature has extensively documented the link between early-life undernutrition and detrimental health outcomes in later life (*5*).

We conducted a comprehensive search of publications, including journal articles, degree theses, and conference manuscripts, in various databases such as PubMed, Embase, Chinese Wanfang Data, and Chinese National Knowledge Infrastructure (CNKI) databases. The search was conducted until August 31, 2023. The keywords used for the search were [(China OR Chinese) AND (famine OR undernutrition OR starvation OR malnutrition)] OR great leap forward OR great famine. The English language was used for the search in PubMed and Embase, while the Chinese language was used for Wangfang and CNKI. For further details, please refer to the Supplementary Material (available at http://weekly.chinacdc.cn).

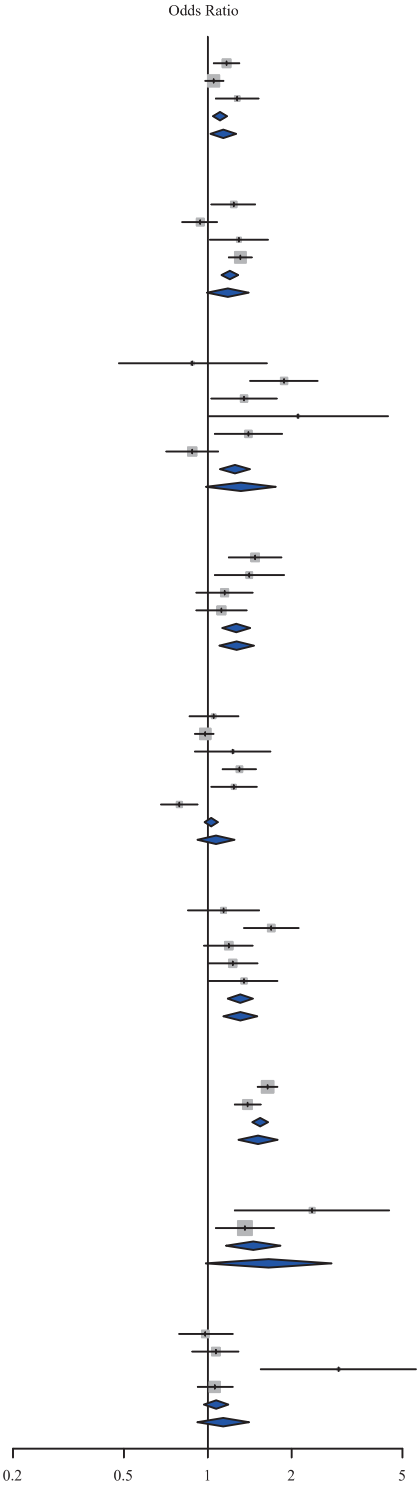
The article selection process involved an independent review of titles and abstracts by two researchers. Data extraction included information on authors, publication details, analytical methods, study size, exposure definitions, control selections, conditions studied, and reported results. Excel spreadsheets were used to collect this data. Additionally, the researchers independently extracted data on the number of disease events and at-risk populations.

The quality of the literature was assessed using the Newcastle-Ottawa scale, which evaluates three main perspectives: study group selection, comparability of study groups, and identification of relevant exposures or outcomes in case-control or cohort studies. Each perspective was assigned a score of "good", "fair", or "poor" based on predefined criteria. Only literature of "good" quality in any perspective was included in the study, with specific criteria of achieving 3 or 4 points in the selection domain, 1 or 2 points in the comparability domain, and 2 or 3 points in the outcome/exposure domain.

The data analysis in this study utilized the "meta" package (version 6.5-0) in R (version 4.2.3; R Core Team, 2023) as the third-party software. Heterogeneity between studies was assessed using the I^2 statistic and analyzed using the χ^2 test. For I^2<50%, a common-effects model (also known as the fixed-effect model) was employed for the meta-analysis. For I^2 values above or equal to 50%, a random-effects model was utilized. Statistical significance was defined as P<0.05.

As shown in Figure 2, data from 30 studies could be used for a meta-analysis of overweight and obesity, diabetes, hyperglycemia, metabolic syndrome, schizophrenia, depression, and arthritis. These studies provided data on famine births and post-famine births. Several reports findings for more than one health condition. The forest plot shows effect estimates for

Study	log*OR*	SE (log*OR*)	Famine births Total	Control Total	*OR*	95% *CI*
Overweight						
1 Yang et al. 2008	0.1556	0.0545	4,363	2,693	1.17	[1.05, 1.30]
2 Wang et al. 2010	0.0488	0.0386	4,056	8,404	1.05	[0.98, 1.14]
3 Chang et al. 2018	0.2437	0.0903	1,092	1,616	1.28	[1.07, 1.52]
Common effect model			9,511	12,713	1.11	[1.04, 1.17]
Random effects model					1.14	[1.02, 1.27]
Heterogeneity: I^2=62%, τ^2=0.0054, P=0.07						
Obesity						
1 Yang et al. 2008	0.2151	0.0925	4,363	2,693	1.24	[1.03, 1.48]
2 Wang et al. 2010	−0.0619	0.0734	4,056	8,404	0.94	[0.81, 1.08]
3 Chang et al. 2018	0.2577	0.1222	1,092	1,616	1.29	[1.02, 1.65]
4 Liu et al. 2019	0.2700	0.0486	4,352	8,163	1.31	[1.19, 1.44]
Common effect model			13,863	20,876	1.20	[1.12, 1.29]
Random effects model					1.18	[0.99, 1.40]
Heterogeneity: I^2=80%, τ^2=0.0236, P<0.01						
Diabetes						
5 Li et al. 2010	−0.1278	0.3119	1,005	1,954	0.88	[0.48, 1.63]
6 Wang et al. 2015	0.6313	0.1422	745	1,808	1.88	[1.42, 2.48]
7 Xu et al. 2016	0.3001	0.1381	664	1,110	1.35	[1.03, 1.77]
8 Wang et al. 2021	0.7467	0.3777	232	256	2.11	[1.01, 4.44]
9 Zhang et al. 2018	0.3365	0.1421	1,442	1,986	1.40	[1.06, 1.85]
10 Sun et al. 2018	−0.1278	0.1094	624	675	0.88	[0.71, 1.09]
Common effect model			4,712	7,789	1.25	[1.11, 1.42]
Random effects model					1.32	[0.99, 1.75]
Heterogeneity: I^2=78%, τ^2=0.0912, P<0.01						
Hyperglycemia						
11 Li et al. 2010	0.3920	0.1112	2,425	5,355	1.48	[1.19, 1.84]
12 Zhang and Luan 2020	0.3436	0.1462	574	1,001	1.41	[1.06, 1.88]
9 Zhang et al. 2018	0.1398	0.1188	1,442	1,986	1.15	[0.91, 1.45]
10 Sun et al. 2018	0.1133	0.1062	624	675	1.12	[0.91, 1.38]
Common effect model			5,065	9,017	1.27	[1.13, 1.42]
Random effects model					1.27	[1.10, 1.47]
Heterogeneity: I^2=33%, τ^2=0.0071, P=0.21						
Hypertension						
13 Li et al. 2011	0.0488	0.1034	1,005	1,954	1.05	[0.86, 1.29]
14 Huang et al. 2010	−0.0202	0.0393	6,914	15,306	0.98	[0.90, 1.05]
15 Chen et al. 2014	0.2070	0.1592	321	623	1.23	[0.90, 1.68]
16 Wang et al. 2012	0.2624	0.0706	2,911	4,872	1.30	[1.13, 1.49]
7 Xu et al. 2016	0.2151	0.0959	793	1,394	1.24	[1.03, 1.50]
17 Zhao et al. 2019	−0.2345	0.0771	880	2,088	0.79	[0.68, 0.92]
Common effect model			12,824	26,237	1.03	[0.97, 1.09]
Random effects model					1.07	[0.92, 1.25]
Heterogeneity: I^2=83%, τ^2=0.0284, P<0.01						
Metabolic Syndrome						
18 Li et al. 2011	0.1310	0.1499	1,005	1,954	1.14	[0.85, 1.53]
19 Wang et al. 2017	0.5247	0.1151	701	1,719	1.69	[1.35, 2.12]
20 Zheng et al. 2012	0.1740	0.1026	1,022	2,674	1.19	[0.97, 1.45]
21 Yao et al. 2022	0.2070	0.1051	1,656	2,787	1.23	[1.00, 1.51]
22 Sun et al. 2022	0.3001	0.1446	2,176	1,954	1.35	[1.01, 1.78]
Common effect model			6,560	11,088	1.31	[1.18, 1.45]
Random effects model					1.31	[1.14, 1.51]
Heterogeneity: I^2=43%, τ^2=0.0110, P=0.13						
Schizophrenia						
23 Xu et al. 2009	0.4947	0.0420	126,579	494,684	1.64	[1.51, 1.78]
24 St Clair et al. 2005	0.3293	0.0549	30,087	243,647	1.39	[1.25, 1.55]
Common effect model			156,666	738,331	1.54	[1.45, 1.65]
Random effects model					1.52	[1.29, 1.78]
Heterogeneity: I^2=83%, τ^2=0.0113, P=0.02						
Depression						
25 Li et al. 2018	0.8629	0.3256	1,569	2,313	2.37	[1.25, 4.48]
26 Liang et al. 2023	0.3075	0.1227	747	1,234	1.36	[1.07, 1.73]
Common effect model			2,316	3,547	1.46	[1.16, 1.82]
Random effects model					1.65	[0.98, 2.78]
Heterogeneity: I^2=61%, τ^2=0.0937, P=0.11						
Arthritis						
27 Wang et al. 2018	−0.0202	0.1129	831	1,530	0.98	[0.79, 1.23]
28 Li and Hong 2022	0.0677	0.0976	847	1,537	1.07	[0.88, 1.29]
29 VanEvery et al. 2021	1.0818	0.3272	6,245	29,396	2.95	[1.55, 5.59]
30 Liu et al. 2021	0.0583	0.0741	22,413	40,038	1.06	[0.92, 1.23]
Common effect model			30,336	72,501	1.07	[0.97, 1.19]
Random effects model					1.14	[0.92, 1.41]
Heterogeneity: I^2=71%, τ^2=0.0301, P=0.02						



Test for subgroup differences (common effect): χ^2_8=105.19, df=8 (P<0.01)
Test for subgroup differences (random effects): χ^2_8=14.72, df=8 (P=0.06)

FIGURE 2. Effect estimates on selected health conditions comparing famine births with controls (post-famine births, meta-analysis).

Note: Summary estimates for the Mantel-Haenszel fixed-effects model and DerSimonian-Laird random-effects model are provided. Each outcome is represented by a box and horizontal lines, indicating the odds ratio (*OR*) and 95% confidence intervals (*CI*s). The size of each box reflects the weight of the report for that particular outcome. Diamonds represent the 95% *CI* for pooled effect estimates, centered on the pooled odds ratio of either the fixed-effects model or the random-effects model for each outcome. The numbering of literature in this Table corresponds to the reference list in the Supplementary Material.

health conditions comparing famine births with post-famine births, which servies as controls.

The meta-analysis findings indicate that there is a significant increase in the odds of overweight [odds ratio (*OR*) 1.14; 95% confidence interval (*CI*): 1.02, 1.27], hyperglycemia (*OR* 1.27; 95% *CI*: 1.13, 1.42), metabolic syndrome (*OR* 1.31; 95% *CI*: 1.18, 1.45), and schizophrenia (*OR* 1.52; 95% *CI*: 1.29, 1.78). However, no significant effects are observed for obesity (*OR* 1.18; 95% *CI*: 0.99, 1.40), diabetes (*OR* 1.32; 95% *CI*: 0.99, 1.75), hypertension (*OR* 1.07; 95% *CI*: 0.92, 1.25), depression (*OR* 1.65; 95% *CI*: 0.98, 2.78), or arthritis (*OR* 1.04; 95% *CI*: 0.86, 1.26). The estimates from both common-effects and random effects models were similar, with the random-effects model having wider 95% *CI*s due to between-study heterogeneity.

DISCUSSION

Evidence shows that infancy is often considered the most crucial period for nutrition-related health outcomes later in life in comparison to the prenatal period or childhood. However, there is some indication that adverse events during the first two trimesters of pregnancy may have an even more significant impact on specific health outcomes. Understanding the reasons for these differential effects of malnutrition during this narrow time window in early life would provide valuable insights.

Gender disparities in the long-term health effects of the Chinese Famine (1959–1961) have been observed. Female survivors tend to experience poorer health outcomes in adulthood and old age compared to their male counterparts (*6*–*7*). This discrepancy may be attributed to the scarring effect, which disproportionately affects women, overpowering the influence of mortality selection. In contrast, mortality selection has a greater impact on male survivors, resulting in relatively less detrimental health consequences (*6*).

The impact of famine on late-life health is more pronounced among vulnerable groups, such as those who are overweight or obese, reside in severely affected areas, or have lower educational attainment (*8*). For example, the famine disproportionately affected rural areas in China due to biased food distribution, resulting in higher excess mortality. As a result, rural survivors show smaller long-term health consequences compared to their urban counterparts, reflecting the combined effects of mortality selection and scarring (*9*). Additionally, rural survivors tend to exhibit null or even positive effects on later-life disease risks, whereas urban survivors are not affected in the same way. This disparity can be attributed, at least in part, to the stronger mortality selection effect observed in rural areas.

Early life exposure to famine, combined with a subsequent nutrient-rich environment later in life, can have negative health consequences in old age, particularly among individuals of high socioeconomic status. In China, two significant historical events, the Chinese Famine (1959–1961) and the subsequent economic reform and opening up since 1978, have played a key role in shaping these health risks. Individuals who experienced undernutrition during the Chinese Famine may have developed a “thrifty genotype” as a survival mechanism, altering their body’s physiological and metabolic function. However, this thrifty genotype can become maladaptive in the context of rapid economic development and increased nutritional abundance in later life, leading to a higher risk of obesity, type 2 diabetes, and coronary heart disease (*10*).

The complex interplay of early life circumstances and various health-related factors impact healthy aging, necessitating a comprehensive life-course approach and strategic measures to enhance public health in an aging society. Effective interventions should be implemented early in life, focusing on women of childbearing age and childhood before disease and disability onset, in order to attenuate the aging process, enhance population health, and improve quality of life in later years.

The implementation of the Healthy China 2030 national initiative since 2016 has highlighted the need for holistic approaches to promoting population health. This includes a shift towards comprehensive life-cycle health management and the adoption of health-in-all policies, as opposed to a narrow focus on disease management. In order to inform policy development and interventions, it is important to consider the substantial scientific evidence linking early life circumstances with health outcomes in elderly populations in China.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIAL

Search Strategy and Research Selection

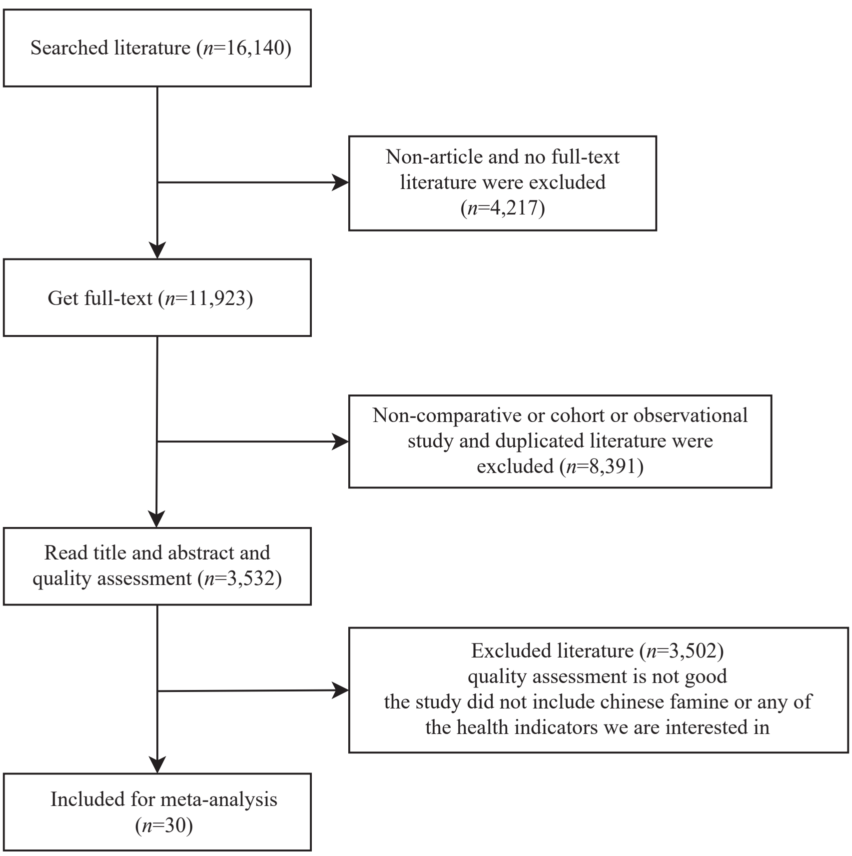
We searched publications including journal articles, degree theses, and conference manuscripts in databases including PubMed, Embase, Chinese Wanfang Data, and Chinese National Knowledge Infrastructure (CNKI) until August 31, 2023. The search terms included [(China OR Chinese) AND (famine OR undernutrition OR starvation OR malnutrition)] OR great leap forward OR great famine. English was used as the search language for PubMed and Embase, while Chinese was used for Wanfang and CNKI.

The inclusion criteria for our study were as follows: 1) Chinese Famine was considered as an exposure or risk factor; 2) the primary outcome of interest was long-term health status or chronic disease; 3) comparable methods were used to assess outcomes for different birth cohorts with and without famine experience; 4) the study population, study design, and analyses were appropriately described; and 5) only literature of "good" quality, as determined by any criteria of the Newcastle-Ottawa scale, was included in our study.

Exclusion criteria: publications on the impact of famine, undernutrition, starvation, malnutrition, or the great leap forward on educational achievements or economic outcomes were not included.

Data Extraction

The titles and abstracts of the articles were independently reviewed by two researchers simultaneously. Data regarding author and publication details, analytical methods, study size, exposure definitions, control selection, studied conditions, covariates, and reported results were extracted. Excel spreadsheets were utilized for data collection, and two researchers independently gathered information on the number of disease events and at-risk populations.



SUPPLEMENTARY FIGURE S1. Flowchart of literature retrieval and screening.

SUPPLEMENTARY TABLE S1. Summary of research features.

Ref No.	Authors	Analytical methods	Study size (famine births/total births)	Conditions studied	Covariate
(*1*)	Yang et al., 2008	Time control	4,363/7,056	Overweight	Yes
(*2*)	Wang et al., 2010	Time control	4,056/12,460	Overweight	Yes
(*3*)	Chang et al., 2018	Time control	1,092/2,708	Overweight	Yes
(*1*)	Yang et al., 2008	Time control	4,363/7,056	Obesity	Yes
(*2*)	Wang et al., 2010	Time control	4,056/12,460	Obesity	Yes
(*3*)	Chang et al., 2023	Time control	1,092/2,708	Obesity	Yes
(*4*)	Liu et al., 2019	Time control	4,352/12,515	Obesity	Yes
(*5*)	Li et al., 2010	Double difference	1005/2959	Diabetes	Yes
(*6*)	Wang et al., 2015	Time control	745/2,553	Diabetes	Yes
(*7*)	Xu et al., 2016	Time control/double difference/instrumental variable	664/1,774	Diabetes	Yes
(*8*)	Wang et al., 2021	Time control	232/488	Diabetes	Yes
(*9*)	Zhang et al., 2018	Time control	1,442/3,428	Diabetes	Yes
(*10*)	Sun et al. 2018	Time control	624/1,299	Diabetes	Yes
(*11*)	Li et al., 2010	Time control	2,425/7,780	Hyperglycemia	Yes
(*12*)	Zhang and Luan, 2020	Time control	574/1,575	Hyperglycemia	Yes
(*9*)	Zhang et al., 2018	Time control	1,442/3,428	Hyperglycemia	Yes
(*10*)	Sun et al. 2018	Time control	624/1,299	Hyperglycemia	Yes
(*13*)	Li et al., 2011	Double difference	1,005/2,959	Hypertension	Yes
(*14*)	Huang et al., 2010	Double difference	6,914/22,220	Hypertension	Yes
(*15*)	Chen et al., 2014	Time control	321/944	Hypertension	Yes
(*16*)	Wang et al., 2012	Time control	2,911/7,783	Hypertension	Yes
(*7*)	Xu et al., 2016	Time control/double difference/instrumental variable	793/2,187	Hypertension	Yes
(*17*)	Zhao et al., 2019	Time control	880/2,968	Hypertension	Yes
(*18*)	Li et al., 2011	Double difference	1,005/2,959	Metabolic Syndrome	Yes
(*19*)	Wang et al., 2017	Time control	701/2,420	Metabolic Syndrome	Yes
(*20*)	Zheng et al., 2012	Time control	1,022/3,696	Metabolic Syndrome	Yes
(*21*)	Yao et al., 2022	Time control	1,656/4,443	Metabolic Syndrome	Yes
(*22*)	Sun et al., 2022	Time control	2176/4,130	Metabolic Syndrome	Yes
(*23*)	Xu et al., 2009	Time control	126,579/621,263	Schizophrenia	Yes
(*24*)	St Clair et al., 2005	Time control	30,087/273,734	Schizophrenia	Yes
(*25*)	Li et al., 2018	Matching/Time control	1,569/3,882	Depression	Yes
(*26*)	Liang et al., 2023	Time control	747/1,981	Depression	Yes
(*27*)	Wang et al., 2018	Time control	831/2,361	Arthritis	Yes
(*28*)	Li and Hong, 2022	Time control	847/2,384	Arthritis	Yes
(*29*)	VanEvery et al., 2021	Time control	6,245/35,641	Arthritis	Yes
(*30*)	Liu et al., 2021	Time control	22,413/62,451	Arthritis	Yes

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Preplanned Studies

The Role of Childhood Circumstances in Healthy Aging Inequalities Among Older Adults — China, 2011–2020

Peng Nie[1,2,#]; Xili Lin[1]; Lanlin Ding[3]

Summary

What is already known about this topic?

Addressing health disparities is a worldwide priority, with a well-established acknowledgment of the influence of childhood circumstances on these discrepancies. In China, particularly among the elderly, health inequalities are a notable concern.

What is added by this report?

The inequality in healthy aging has increased from 2011 to 2020, both in general and concerning childhood factors. Nevertheless, the impact of early-life healthcare access and parental health behaviors on healthy aging gaps has reduced among older adults in better health within the top segment of healthy aging.

What are the implications for public health practice?

Efforts towards reducing regional health disparities and improving healthcare access for children, along with promoting the health and well-being of parents, especially in economically disadvantaged households, are crucial policy considerations.

In response to the global push for health equity following the World Health Organization (WHO) report on the Commission for Social Determinants of Health, reducing health disparities has become a primary goal of public health policies worldwide. In China, inequalities in health, especially among older populations, are widespread (*1*). Healthy aging (HA) is crucial for achieving Sustainable Development Goals (*1*–*2*). However, limited research assesses the inequality of HA, specifically concerning childhood circumstances and its impact on HA inequality, termed inequality of opportunity (IOp) (*3*). Most studies use a mean-based approach to identify sources of IOp in health (*3*). Thus, understanding the role of childhood circumstances in HA inequality across the entire HA distribution in China, especially among individuals with poorer health, is critical but currently unknown. To bridge this gap, we used data from the China Health and Retirement Longitudinal Study (CHARLS) to develop a composite HA index for assessing changes in HA inequality. We explored how childhood circumstances affect IOp in HA across the entire HA distribution. Our findings reveal an increase in both total HA inequality and inequality explained by childhood circumstances from 2011 to 2020. Factors such as household socioeconomic status in childhood and regional/urban-rural status at birth were identified as key drivers of IOp in HA. Notably, the influence of early-life access to healthcare and parental health behaviors decreased as the HA distribution moved towards individuals with better health. These results highlight the significant role of childhood circumstances in HA determination and advocate for policies enhancing childhood nutrition and health, especially within disadvantaged families.

The CHARLS is a nationally representative survey conducted by the National School of Development at Peking University, focused on individuals aged 45 and above. Since its initiation in 2011, the survey has been followed up in 2013, 2015, 2018, and 2020. For this study, data from the 2014 Life History Survey was utilized, concentrating on individuals aged 60 and older. The analysis involved 23,409 participants, with varying numbers from the CHARLS surveys conducted in 2011 (3,317), 2013 (4,038), 2015 (4,919), 2018 (4,781), and 2020 (6,354), respectively. Sample weights were applied to adjust for design effects and survey nonresponses (Supplementary Figure S1, available at https://weekly.chinacdc.cn) (*4*).

The Healthy Ageing Index (HAI) consists of five domains: physical capabilities, cognitive function, physiological health, psychological well-being, and social well-being (*5*). A total of 26 indicators were used, each categorized into quintiles with a code from 0 to 100. The sum of all indicator scores divided by the total number of indicators yielded the HAI score, which ranges from 0 to 100 (Supplementary Table S1, available at https://weekly.chinacdc.cn). A higher HAI score indicates better aging status.

The variables listed in Supplementary Table S2 (available at https://weekly.chinacdc.cn) were categorized into two groups (*6*). The first group comprised demographic variables like age and sex. The second group included six domains: war exposure; childhood household socioeconomic status (SES) encompassing self-reported family financial status, parental educational levels, political status, and housing conditions; geographical location (east, central, west) and urban/rural status at birth; parental health status and behaviors during childhood (e.g., parental bedridden condition, alcohol consumption, smoking); childhood health and nutritional status (e.g., self-reported health compared to peers before age 15, childhood experiences of hunger before age 17); and childhood access to healthcare (e.g., vaccination status and type of initial doctor visit).

We conducted descriptive statistical analyses to compare the circumstances and HAI scores across the years 2011, 2013, 2015, 2018, and 2020 within our sample cohort. Our sample was selected without biases related to observables, and detailed results are available upon request. To measure the IOp in HA, we employed the direct parametric method using ordinary least squares (OLS) regressions, where HAI scores served as the dependent variable and the circumstances as the independent variables. We measured inequality utilizing the mean logarithmic deviation (MLD) index (*7*). The proportion of absolute IOp to overall HA inequality was calculated to determine relative IOp values. We also applied unconditional quantile regression (UQR) to explore disparities in HAI scores due to circumstances at specific points in the HAI score distribution. This involved regressing the re-centered influence function (RIF) of the HAI percentile's ranks against the circumstance variables. To ascertain the relative impact of each contextual element, we used the Shapley value decomposition technique in our regression analyses. All statistical procedures were performed using STATA (version 17.0; StataCorp, College Station, TX, US).

Supplementary Table S3 (available at https://weekly.chinacdc.cn) presents the descriptive statistics of the study sample. The average scores for HAI were similar in 2011 (79.2) and 2013 (79.8), with a significant decrease observed in 2020 (75.9). Throughout this period, the overall inequality in HAI ranged from 0.010 to 0.016, with childhood circumstances accounting for 10.9%–14.8% of this inequality. Furthermore, the total inequality in HAI and the proportion explained by childhood circumstances increased from 2011 to 2020. Among the various childhood circumstances, household socioeconomic status (21.9%–27.6%) and regional and urban/rural status at birth (11.8%–22.1%) were the major contributing factors (Figure 1).

Figure 2 shows a significant IOp across various quantiles, demonstrating a consistent decrease towards the higher end of the HA distribution, irrespective of utilizing the complete dataset or different time points. Furthermore, the impact of parental health status, health-related behaviors, and access to healthcare during childhood on IOp escalates towards the lower end of the HA spectrum, where individuals with the most severe health conditions are predominant (Figure 3).

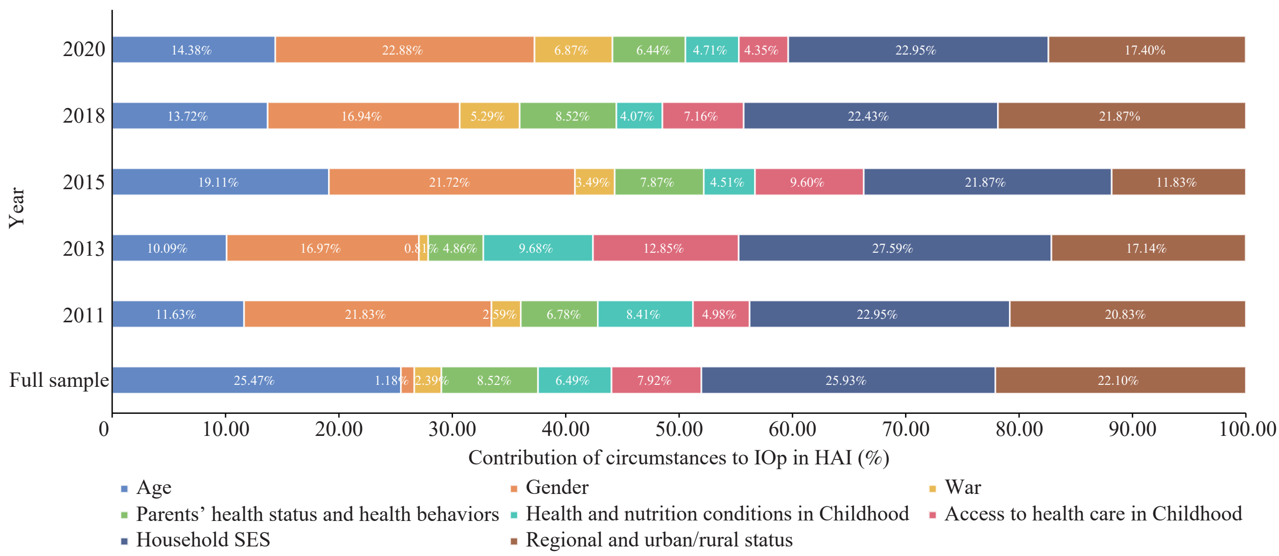

FIGURE 1. Contributions of circumstances to IOp in HAI: Mean-based Shapley decomposition.
Abbreviation: IOp=inequality of opportunity; HAI=healthy aging index; SES=socioeconomic status.

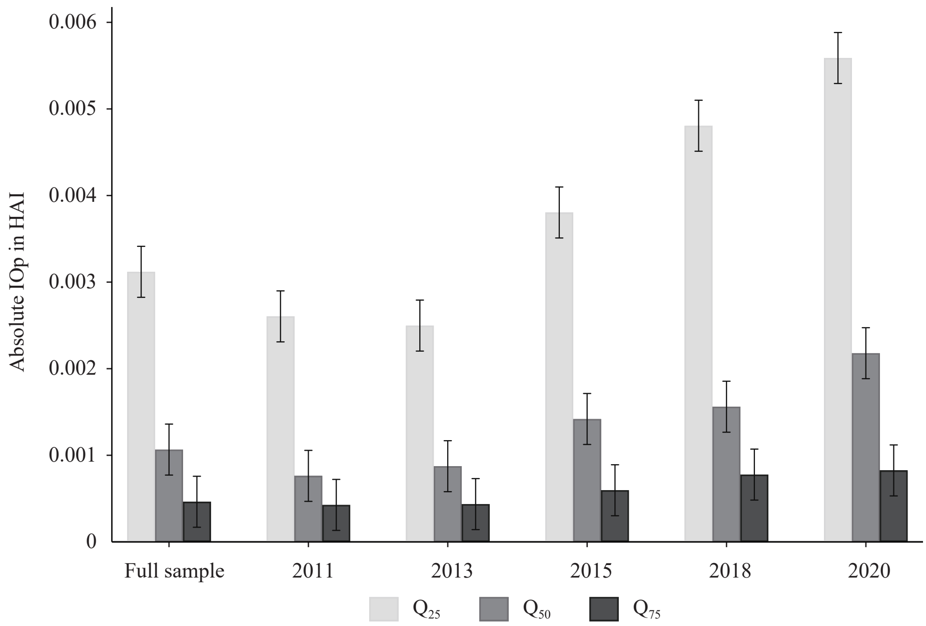

FIGURE 2. IOp in HAI at different quantiles (MLD index).
Abbreviation: IOp=inequality of opportunity; HAI=healthy aging index; MLD=mean logarithmic deviation.

DISCUSSION

The present study has demonstrated a significant and progressive increase in IOp in the HA from 2011 to 2020. Among all variables analyzed, early-life household SES emerges as the most substantial factor contributing to this disparity. This underscores the pivotal influence of household SES in shaping the health status of elderly individuals. A plausible explanation is that a higher level of parental education, typically associated with improved household SES, correlates with increased health literacy and adoption of healthier behaviors among both parents and their offspring, encompassing aspects like dietary habits and medication adherence (*8*). Moreover, enhanced household SES, reflected in superior financial stability, facilitates access to better healthcare services and improved nutrition, thereby limiting children's exposure to detrimental substances and environmental hazards. These elements collectively play a role in promoting better health outcomes in later life (*8*). Hence, enhancing household SES through measures such as elevating parents' educational attainment, improving financial resources within families, and creating healthier living environments during childhood emerges as a viable strategy to mitigate healthcare disparities among the elderly population.

The findings underscore the importance of improving access to healthcare for children and enhancing the health and behaviors of parents in socioeconomically disadvantaged families to reduce health disparities in the Chinese population. Disparities among older adults in China are significantly influenced by geographic location and urban/rural distinctions, possibly due to unequal allocation of healthcare resources, primary healthcare services, and welfare support (*9*). Additionally, our study reveals that health inequality is influenced not only by age and gender but also by differences in childhood experiences.

Moreover, the study revealed that IOp had a greater impact on individuals with poor HA, emphasizing the influence of early-life conditions on disparities, especially in the context of limited household assets. Thus, utilizing distributional decompositions indicated that concentrating solely on mean-based decomposition would neglect crucial aspects associated with early-life conditions, notably when investigating disparities in household assets at the lower spectrum. This aspect is significant as individuals in this bracket are generally perceived as less healthy (*10*).

This study is subject to some limitations. First, data on childhood circumstances relied on retrospective self-reporting, which may lead to recall bias. Second, the mechanisms by which childhood circumstances influence HA are not yet understood.

Our study utilized data from the 2011–2020 CHARLS dataset as our analytical sample. It is crucial in life course research to incorporate thorough

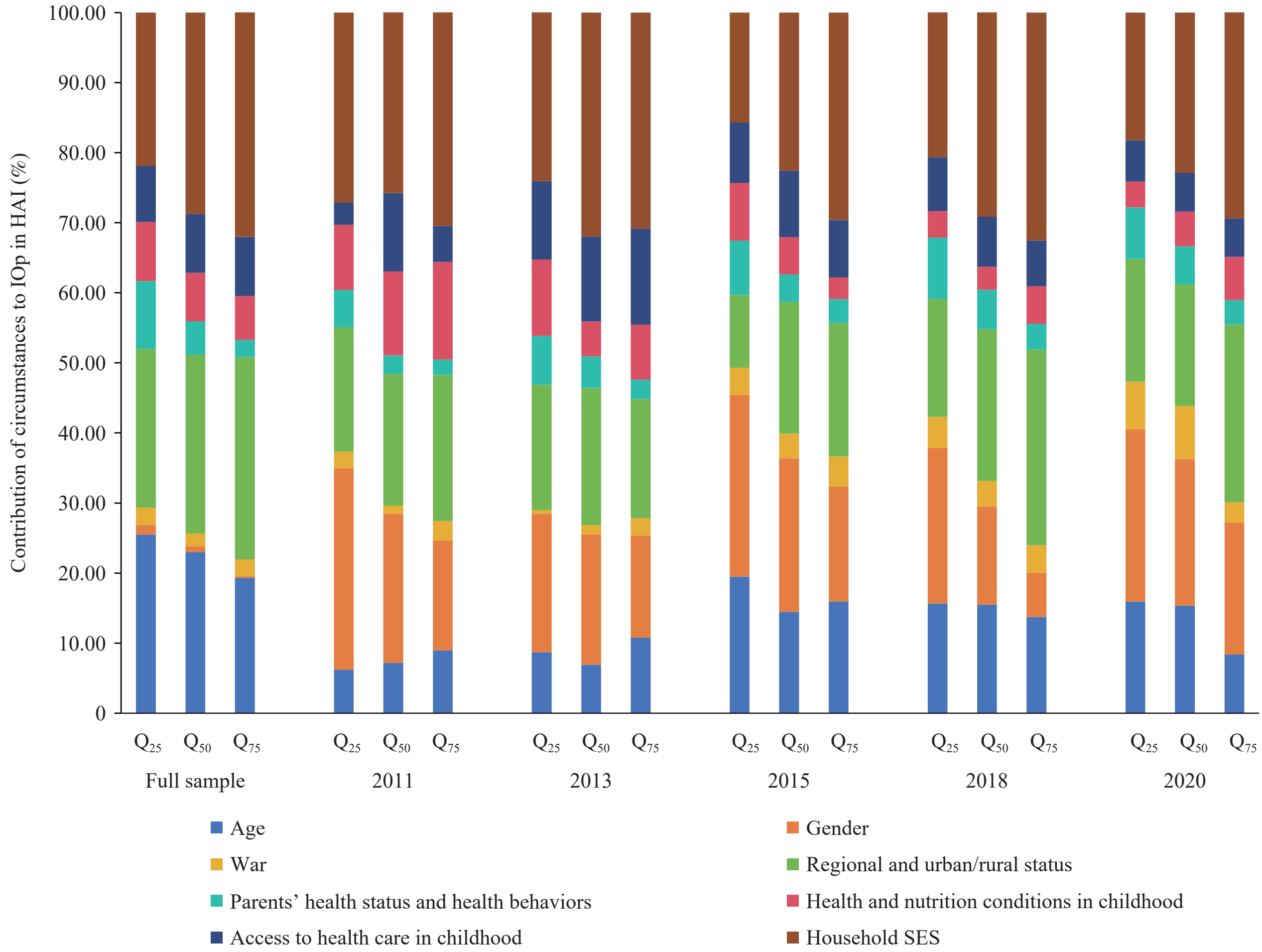

FIGURE 3. Contributions of circumstances to IOp in HAI: RIF-based Shapley decomposition.
Abbreviation: IOp=inequality of opportunity; HAI=healthy aging index; RIF=re-centered influence function; SES=socioeconomic status.

assessments of early-life determinants instead of solely focusing on current adult health status, especially when examining older populations. Therefore, our study contributes significant insights for life course research targeting the reduction of health disparities. Furthermore, our distribution analysis presents valuable findings that can inform the development of targeted public health strategies to tackle health disparities.

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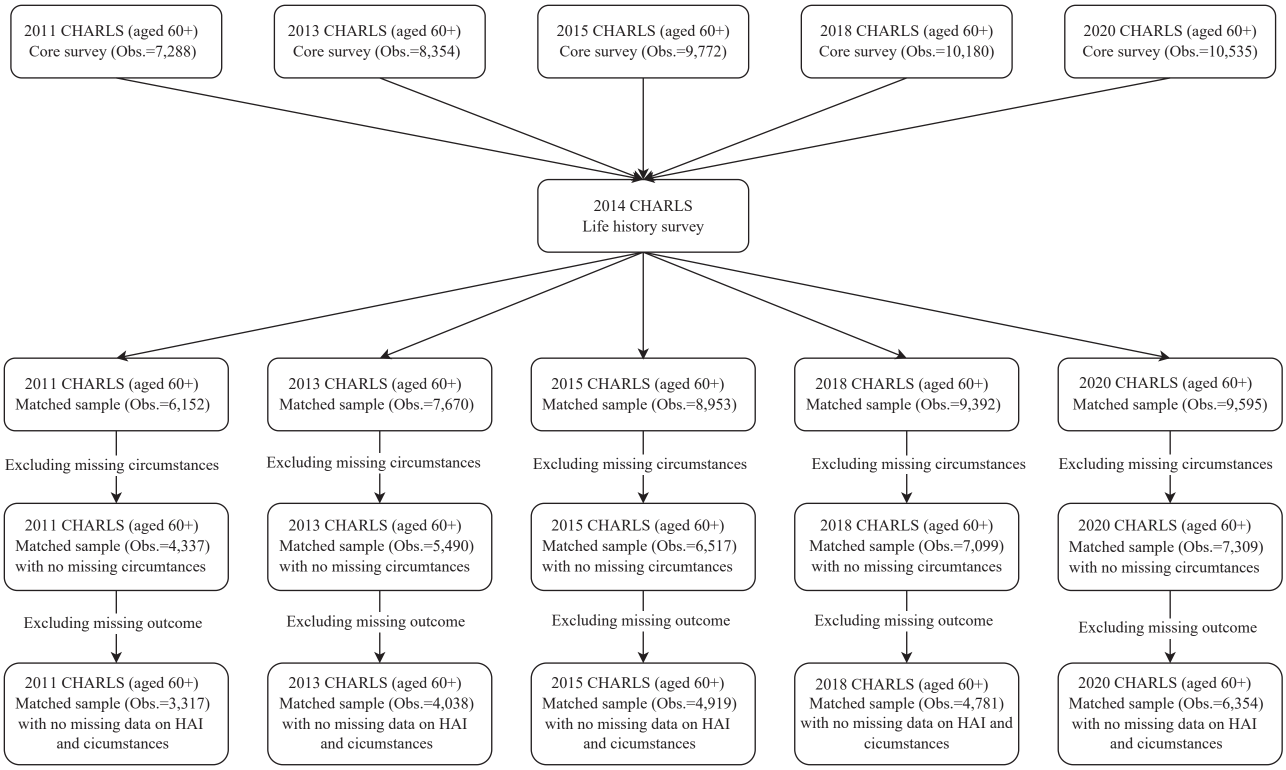
SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. Flow chart of the study sample.
Abbreviation: CHARLS=China Health and Retirement Longitudinal Study; HAI=healthy aging index; Obs.=number of observations.

SUPPLEMENTARY TABLE S1. Indicators of healthy aging index and harmonizing strategies.

Domains	Variables	Categories	Scores
Cognitive functions	Verbal Memory - 10 words immediate recall	0–10	0–2=0 3–4=25 5–6=50 7–8=75 9–10=100
	Verbal Memory - 10 words delayed recall	0–10	0–2=0 3–4=25 5–6=50 7–8=75 9–10=100
	Orientation - date naming- month	0: incorrect 1: correct	0=0 1=100
	Orientation - date naming- day of month	0: incorrect 1: correct	0=0 1=100
	Orientation - date naming- year	0: incorrect 1: correct	0=0 1=100
	Orientation - date naming- day of week	0: incorrect 1: correct	0=0 1=100
Physical capabilities	ADLs: some difficulties in dressing	0: No 1: Yes	0=100 1=0

Continued

Domains	Variables	Categories	Scores
	ADLs: some difficulties in bathing and showering	0: No	0=100
		1: Yes	1=0
	ADLs: some difficulties in eating	0: No	0=100
		1: Yes	1=0
	ADLs: some difficulties in getting in/out bed	0: No	0=100
		1: Yes	1=0
	ADLs: some difficulties in using the toilet	0: No	0=100
		1: Yes	1=0
	IADLs: some difficulties in taking medications	0: No	0=100
		1: Yes	1=0
	IADLs: some difficulties in shopping for groceries	0: No	0=100
		1: Yes	1=0
	IADLs: some difficulties in preparing hot meal	0: No	0=100
		1: Yes	1=0
	IADLs: some difficulties in managing money	0: No	0=100
		1: Yes	1=0
Psychological wellbeing	CES-D score	0–30 (quintiles)	0–6=100
			7–13=75
			14–20=50
			21–26=75
			27–30=0
	Life satisfaction	0: Very satisfied	0=100
		1: Satisfied	1=75
		2: Somewhat satisfied	2=50
		3: Unsatisfied	3=25
		4: Very unsatisfied	4=0
Physiological health	Self-reported high blood pressure	0: No	0=100
		1: Yes	1=0
	Self-reported diabetes	0: No	0=100
		1: Yes	1=0
	Self-reported cancer	0: No	0=100
		1: Yes	1=0
	Self-reported lung disease	0: No	0=100
		1: Yes	1=0
	Self-reported stroke	0: No	0=100
		1: Yes	1=0
	Self-reported heart problem	0: No	0=100
		1: Yes	1=0
	Self-reported psychological problem	0: No	0=100
		1: Yes	1=0
	Self-reported arthritis	0: No	0=100
		1: Yes	1=0
Social wellbeing	Participations in social activities	0: No	0=0
		1: Yes	1=100

Abbreviation: ADLs=activities of daily living; IADLs=instrumental activities of daily living; CES-D=center for epidemiologic studies depression.

SUPPLEMENTARY TABLE S2. Definitions of demographic and circumstance variables.

Domain	Variable Description
Panel A: Demographics	
	Age
	Sex (1: male; 0: female)
Panel B: Childhood circumstances	
War	Born in the Anti-Japanese War era (1937–1945) (1: Yes; 0: No)
	Born in the Civil War era (1946–1949) (1: Yes; 0: No)
Parents’ health status and health behaviors	Parents’ health condition (1: long time in bed; 0: No)
	Father having drinking problem (1: alcoholism; 0: No)
	Mother smoking (1: Yes; 0: No)
	Father smoking (1: Yes; 0: No)
Health and nutrition conditions in Childhood	Self-reported health status before age 15 (1: much healthier; 2: somewhat healthier; 3: about average; 4: some less healthy; 5: much less healthy)
	Ever experienced hunger (1: No; 2: yes after age 5; 3: yes before age 5)
Access to healthcare in childhood	Received vaccination before age 15 (1: Yes; 0: No)
	When ill, first visited doctor (1: general/specialized hospital or township clinics; 2: community health centers/private clinics; 3: others)
Regional and urban/rural status	Rural or urban status at birth (0: rural; 1: urban)
	Regional status at birth (1: East; 2: Center; 3: West)
Household SES	Parents’ political status (1: any party member; 0: No)
	Mother’s literacy (1: literate; 0: illiterate)
	Father’s literacy (1: literate; 0: illiterate)
	Family’s financial status before age 17 (1: a lot worse; 2: somewhat worse; 3: same; 4: somewhat better; 5: a lot better)
	House type at birth (1: concrete; 2 adobe; 3 wood or others)

Note: Source: CHARLS Life History Survey 2014.
Abbreviation: CHARLS=China Health and Retirement Longitudinal Study; SES=socioeconomic status.

SUPPLEMENTARY TABLE S3. Descriptive statistics.

Variables	Full sample		2011		2013		2015		2018		2020	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HAI	77.644	11.397	79.178	10.620	79.763	10.163	77.692	10.994	77.585	11.583	75.860	12.141
Sex (1: male; 0: female)	0.833	0.666	0.537	0.499	0.547	0.498	0.530	0.499	0.543	0.498	1.494	0.500
Age	68.138	6.402	66.996	5.876	67.171	5.855	67.550	6.211	68.304	6.463	69.389	6.742
War												
Born in the Anti-Japanese War era	0.258	0.438	0.400	0.490	0.326	0.469	0.263	0.441	0.204	0.403	0.194	0.396
Born in the Civil War era	0.219	0.414	0.324	0.468	0.277	0.448	0.231	0.422	0.181	0.385	0.160	0.367
Parents' health status and health behaviosr												
Parents' health condition (1: long time in bed; 0: No)	0.173	0.378	0.168	0.374	0.174	0.379	0.178	0.383	0.172	0.377	0.172	0.377
Father having drinking problem (1: alcoholism; 0: No)	0.067	0.251	0.065	0.247	0.068	0.252	0.068	0.252	0.068	0.251	0.068	0.251
Mother smoking	0.113	0.316	0.111	0.314	0.115	0.319	0.110	0.313	0.114	0.318	0.113	0.316
Father smoking	0.497	0.500	0.478	0.500	0.488	0.500	0.489	0.500	0.515	0.500	0.501	0.500
Self-reported health status before age 15												
Much healthier	0.174	0.379	0.171	0.377	0.168	0.374	0.166	0.372	0.176	0.380	0.182	0.386
Somewhat healthier	0.207	0.405	0.210	0.408	0.208	0.406	0.203	0.403	0.210	0.407	0.204	0.403
About average	0.500	0.500	0.507	0.500	0.512	0.500	0.513	0.500	0.490	0.500	0.490	0.500
Somewhat less healthy	0.077	0.267	0.074	0.262	0.069	0.254	0.076	0.264	0.083	0.276	0.080	0.271
Much less healthy	0.042	0.200	0.038	0.191	0.042	0.201	0.042	0.200	0.042	0.201	0.043	0.204
Ever experienced hunger												
Yes after age 5	0.705	0.456	0.718	0.450	0.738	0.440	0.736	0.441	0.694	0.461	0.669	0.470
Yes before age 5	0.047	0.212	0.014	0.116	0.015	0.123	0.032	0.176	0.063	0.243	0.077	0.267
No	0.248	0.432	0.268	0.443	0.247	0.431	0.232	0.422	0.243	0.429	0.253	0.435
Received vaccination before age 15	0.842	0.365	0.810	0.392	0.818	0.386	0.836	0.370	0.867	0.339	0.854	0.354
When ill, first visited doctor at												
General/specialized hospital or township clinics	0.312	0.463	0.311	0.463	0.313	0.464	0.311	0.463	0.324	0.468	0.303	0.460
Community health centers/private clinics	0.290	0.454	0.278	0.448	0.290	0.454	0.283	0.450	0.295	0.456	0.296	0.457
Others	0.398	0.490	0.411	0.492	0.397	0.489	0.406	0.491	0.380	0.486	0.400	0.490
Rural or urban status at birth (1: urban; 0: rural)	0.244	0.429	0.217	0.412	0.225	0.418	0.232	0.422	0.264	0.441	0.259	0.438
Regional status at birth												
East	0.374	0.484	0.378	0.485	0.367	0.482	0.362	0.481	0.375	0.484	0.383	0.486
Center	0.317	0.465	0.307	0.461	0.325	0.468	0.327	0.469	0.318	0.466	0.311	0.463
West	0.309	0.462	0.315	0.465	0.308	0.462	0.311	0.463	0.307	0.461	0.306	0.461
Parents' political status (1: any party member; 0: No)	0.108	0.310	0.074	0.263	0.083	0.276	0.095	0.293	0.126	0.332	0.131	0.337
Mother's education (1: literate; 0: illiterate)	0.087	0.282	0.062	0.241	0.070	0.254	0.076	0.264	0.105	0.307	0.101	0.301
Father's education (1: literate; 0: illiterate)	0.423	0.494	0.393	0.488	0.404	0.491	0.409	0.492	0.454	0.498	0.433	0.496
Family financial status before age 17												
A lot worse	0.220	0.414	0.232	0.422	0.228	0.419	0.221	0.415	0.212	0.409	0.214	0.410
Somewhat worse	0.149	0.357	0.149	0.356	0.146	0.353	0.150	0.358	0.146	0.353	0.153	0.360
Same	0.093	0.290	0.090	0.287	0.090	0.286	0.088	0.283	0.097	0.296	0.095	0.293
Somewhat better	0.526	0.499	0.517	0.500	0.526	0.499	0.530	0.499	0.530	0.499	0.524	0.499
A lot better	0.013	0.112	0.011	0.106	0.010	0.100	0.011	0.102	0.015	0.121	0.014	0.118
House type at birth												
Concrete	0.158	0.365	0.153	0.360	0.150	0.357	0.153	0.360	0.166	0.372	0.162	0.368
Adobe	0.580	0.494	0.582	0.493	0.578	0.494	0.576	0.494	0.575	0.494	0.586	0.493
Wood or others	0.262	0.440	0.265	0.441	0.272	0.445	0.272	0.445	0.259	0.438	0.252	0.434

Note: Sampling weights are applied.

Abbreviation: HAI=healthy ageing index; SD=standard deviation.

Methods and Applications

Applying Machine Learning Approach to Explore Childhood Circumstances and Self-Rated Health in Old Age — China and the US, 2020–2021

Shutong Huo[1]; Derek Feng[2]; Thomas M. Gill[3]; Xi Chen[4,5,#]

ABSTRACT

Introduction: Childhood circumstances impact senior health, prompting the introduction of machine learning methods to assess their individual and collective contributions to senior health.

Methods: Using health and retirement study (HRS) and China Health and Retirement Longitudinal Study (CHARLS), we analyzed 2,434 American and 5,612 Chinese participants aged 60 and above. Conditional inference trees and forests were employed to estimate the influence of childhood circumstances on self-rated health (SRH).

Results: The conventional method estimated higher inequality of opportunity (IOP) values in both China (0.039, accounting for 22.67% of the total Gini coefficient 0.172) and the US (0.067, accounting for 35.08% of the total Gini coefficient 0.191). In contrast, the conditional inference tree yielded lower estimates (China: 0.022, accounting for 12.79% of 0.172; US: 0.044, accounting for 23.04% of 0.191), as did the forest (China: 0.035, accounting for 20.35% of 0.172; US: 0.054, accounting for 28.27% of 0.191). Childhood health, financial status, and regional differences were key determinants of senior health. The conditional inference forest consistently outperformed others in predictive accuracy, as demonstrated by lower out-of-sample mean squared error (MSE).

Discussion: The findings emphasize the need for early-life interventions to promote health equity in aging populations. Machine learning showcases the potential in identifying contributing factors.

INTRODUCTION

The global phenomenon of rapid population aging, coupled with the growing health burden among older adults, highlights the importance of investigating the long-term effects of early life stages on the aging process (*1*). Previous research in the fields of economics and epidemiology has consistently shown that childhood circumstances have a significant impact on later-life health outcomes. This suggests that childhood is a crucial period for implementing interventions aimed at reducing health disparities (*2*). These circumstances encompass a wide range of factors, including parental influences (*3*), family socioeconomic status (SES) (*4*), as well as community and environmental factors such as rural/urban status (*5*) and natural surroundings (*6*).

Both early-life and later-life factors contribute to health outcomes in older age. However, childhood circumstances, particularly those that are beyond an individual's control, are considered to be the most unacceptable and illegitimate sources of health inequality in older age (*7–8*). This type of inequality, attributed to childhood circumstances, is commonly referred to as inequality of opportunity (IOP). The focus on reducing IOP arises from a wide-ranging political and social discussion aimed at creating equal opportunities during the early stages of life and addressing the unfair health inequalities identified by the World Health Organization Commission on Social Determinants of Health (*9*).

Despite the considerable amount of research conducted on the impact of childhood circumstances on health outcomes, there are still methodological challenges that need to be addressed. These challenges include the arbitrary selection of childhood circumstances and potential biases in estimating health inequality among older adults (*10–11*). In our study, we aimed to overcome these challenges by utilizing machine learning techniques to identify the most relevant set of childhood circumstances. By adopting this approach, we allowed the data to inform our understanding of unequal childhood circumstances, thus minimizing the influence of researcher bias on the model specification (*10–12*). Furthermore, we compared our findings to those obtained using the conventional parametric Roemer method in order to highlight the significant improvements our approach offers in measuring inequality throughout an individual's life.

METHODS

Our study utilized data from the health and retirement study (HRS) in the US and the China Health and Retirement Longitudinal Study (CHARLS) in China. We analyzed 2020–2021 wave of HRS and the 2020 wave of CHARLS, both of which matched with life history surveys. The final sample consisted of 2,434 Americans and 5,612 Chinese individuals aged 60 and above. Self-rated health (SRH) was used as the health outcome measure, assessed on a scale from excellent (=1) to poor (=5) in both surveys. The analysis included data on 43 childhood circumstances from HRS and 36 from CHARLS, categorized into seven domains such as birth environment, family SES, and childhood relationships (Supplementary Tables S1 and S2, available at https://weekly.chinacdc.cn/). While there were slight variations, the domains predominantly included the same core measures for both countries. The analysis was conducted using R (version 4.3.1; R Core Team, Vienna, Austria).

Supplementary Material (available at https://weekly.chinacdc.cn/) provides a comprehensive conceptual and analytic framework for this study. Initially, we used the Roemer method with Shapley value decomposition to estimate the individual and collective impact of childhood circumstances on health inequality in later life. This framework serves as a foundation for evaluating policy interventions. By partitioning the population into distinct, non-overlapping groups based on observable circumstances, such as parental education (high *vs.* low) and financial hardship (yes *vs.* no), we can derive a counterfactual distribution of health outcomes. The disparity in health across these groups can be solely attributed to differences in childhood circumstances, which we refer to as the IOP. In our study, we quantified the contribution of childhood circumstances to health inequality using the Gini coefficient (*8*,*11*). We also calculated the IOP by dividing this measure of absolute health inequality by the overall health inequality, representing the proportion of health inequality explained by childhood circumstances. While not establishing causality, this analysis provides valuable insights into the statistical significance of childhood circumstances (*13*).

Conditional inference trees are particularly advantageous for analyzing the impact of childhood circumstances on IOP. They allow for sequential hypothesis tests and provide a visual representation for comparing different childhood circumstances. Each test examines IOP within a specific subset of the population, and the depth of the tree reflects the diversity of childhood circumstances within a society. Additionally, these trees address the issue of arbitrary variable and model selection that often arises in the IOP literature. They consider a comprehensive set of observed variables that qualify as childhood circumstances. In our study, we used these childhood circumstances to divide the population into distinct groups (terminal nodes) in the context of regression trees. We calculated the predicted outcome value for an individual observation as the average outcome of the group to which the individual was assigned, taking into account the number of observations in that group. Furthermore, we used 5-fold cross-validation to optimize the model parameters. We found that our results are consistent regardless of the choice of K.

Conditional inference trees have advantages in providing non-arbitrary population segmentation. However, they have limitations such as using limited data, struggling with highly correlated childhood circumstances, and exhibiting high prediction variance, making them sensitive to sample changes. To address these limitations, random forest is employed to mitigate these issues. Random forest forms a forest of decision trees from bootstrapped samples, utilizing a random selection of predictors at each split to reduce prediction variance, resulting in a more reliable model. In this study, 200 trees were used based on considerations of computational cost-efficiency and prediction accuracy to predict outcomes (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). A 4-step method was applied, involving the random selection of half the observations in each tree, along with random data subsampling and subsets of circumstances, to determine optimal parameters through out-of-bag error minimization. Predictor importance for each childhood circumstance was evaluated using the residual sum of squares (RSS).

To evaluate the potential biases in measuring IOP in healthy individuals that could impact the accuracy of predictions, we divided the dataset into a training set representing 2/3 of the total sample size (N) and a test set representing the remaining 1/3. The training set was used to train our model, while the test set was used to assess the performance of three different methods:

the conventional parametric Roemer method, conditional inference trees, and conditional inference forest.

RESULTS

First, the Gini coefficient indicated that there was a higher level of inequality in self-rated health in the US compared to China. We then used the Gini coefficients to measure the IOP in the counterfactual distribution. Figure 1 illustrates that the conventional parametric Roemer method yielded the highest estimates of IOP, followed by the conditional inference forest method and the conditional inference tree method. Specifically, in China, IOP accounted for 22.67% (0.039 out of 0.172 total Gini coefficient) of the inequality in self-rated health, while in the US it accounted for 35.08% (0.067 out of 0.191 total Gini coefficient). In contrast, the conditional inference tree method accounted for 12.79% in China (0.022 out of 0.172 total Gini coefficient) and 23.04% in the US (0.044 out of 0.191 total Gini coefficient), while the forest method represented 20.35% in China (0.035 out of 0.172 total Gini coefficient) and 28.27% in the US (0.054 out of 0.191 total Gini coefficient).

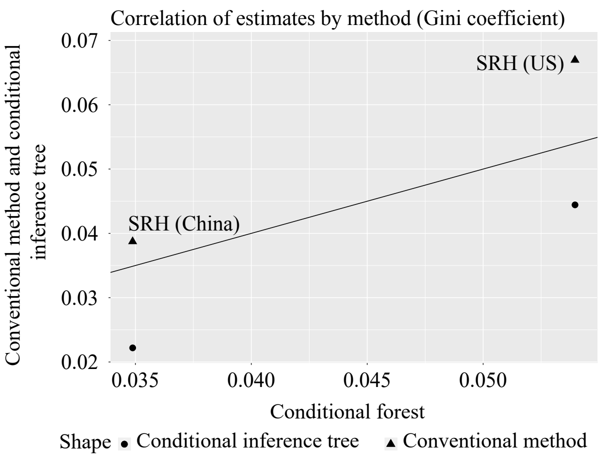


FIGURE 1. Correlation of estimates by method.
Note: The plot shows the estimates using each method (i.e., the conventional parametric Roemer method and the conditional inference trees) against the estimates from conditional inference forest. The x-axis represents the scale of Gini coefficients for the forest method. The Gini coefficients range between 0 and 1. The larger the more unequal. The y-axis represents the scale of Gini coefficients for the Roemer method and tree methods. The black diagonal indicates the 45-degree line, on which all data points should align if the different methods were perfectly congruent. This plot confirms that the conventional parametric Roemer method delivers higher estimates than forest, while tree estimates are lower than those based on forest.
Abbreviation: SRH=self-rated health.

Figure 2A shows the structure of the IOP for self-rated health in China using a tree with five terminal nodes. The tree is formed by factors such as childhood health, birth region, and childhood family financial status. The most advantaged type (terminal node 5) includes people with good childhood health, good family financial status, and born in Eastern China. On the other hand, the group with the worst self-rated health (terminal node 6) typically had poorer child health. In the US, as depicted in Figure 2B, individuals with poor childhood health fell into the disadvantaged circumstance type (terminal nodes 7). In contrast, individuals with certain favorable conditions, such as having more books at home, being healthy in childhood, and being White, generally reported better health in old age (terminal node 6).

Figure 3A reveals that in China, using conditional inference forest, the key factors impacting self-rated health are childhood health and being born in the eastern China, which corroborates findings from the conditional inference trees (Figure 2A). Additionally, parents' health status (staying in bed for a long time) and relationship with parents also have a high impact on self-rated health in older ages. Similarly, Figure 3B demonstrates that in the US, childhood health, number of books at home at age 10, and race/ethnicity are significant factors, which largely align with results obtained through conditional inference trees (Figure 2B).

As previously mentioned, all tested models were designed to minimize the mean squared error (MSE). We derived 95% confidence intervals using 200 bootstrap re-samplings of the test data. The MSE for the random forest model was standardized to a value of 1 to facilitate comparison of prediction performance across models. Therefore, an MSE greater than 1 indicated a poorer out-of-sample fit. In terms of self-rated health, both the conditional inference tree and parametric Roemer methods performed worse than the conditional inference forest, as shown in Figure 4A–B. On average, the conditional inference trees demonstrated lower test error rates compared to the conventional parametric Roemer method.

DISCUSSION

This study utilized two machine learning methods, namely the conditional inference tree and forest, to investigate the effects of various childhood

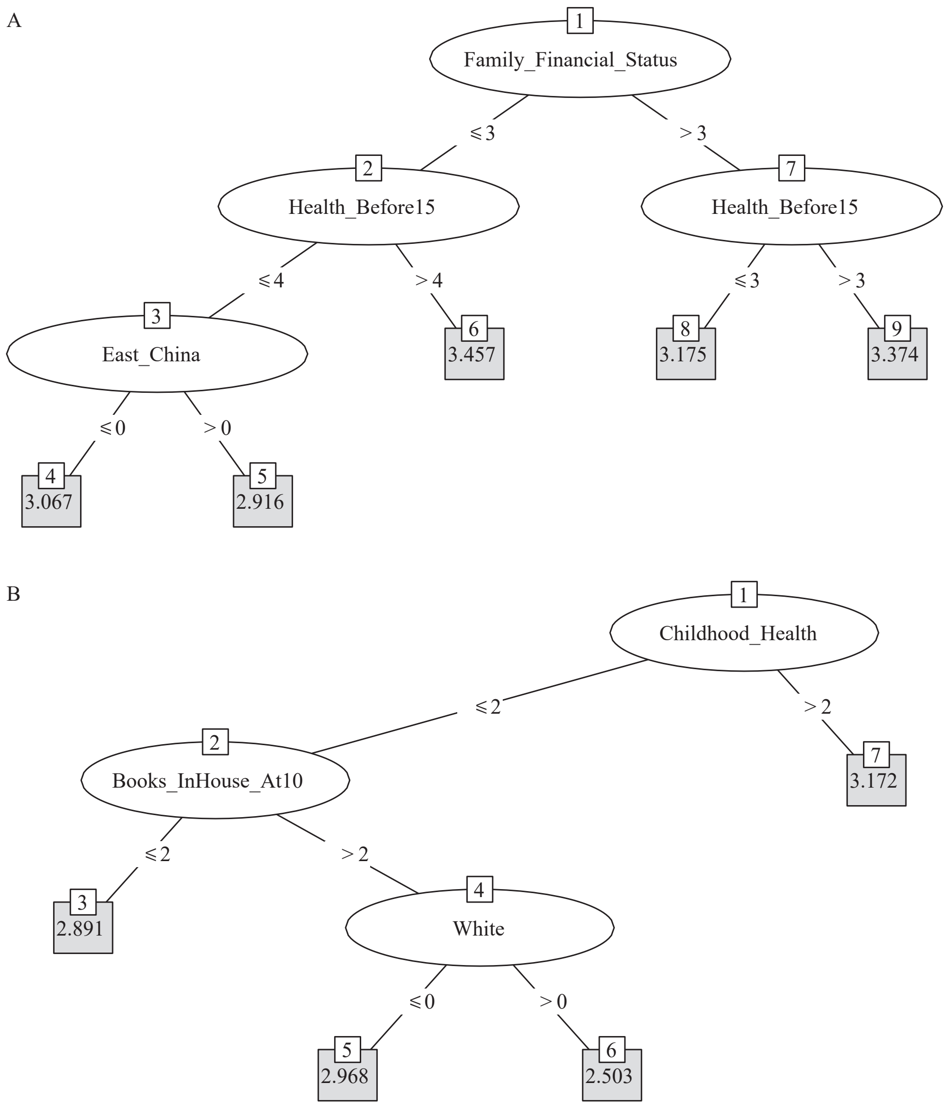


FIGURE 2. Conditional inference tree for self-rated health. (A) China; (B) the US.

circumstances on health disparity among older adults in China and the US. We identified several key predictors of health conditions in older adults, including childhood health, socioeconomic status, number of books at home (in the case of Americans), and birth region (in the case of Chinese). By employing these methods, we aimed to address concerns regarding the arbitrary selection of childhood circumstances and mitigate potential biases in our estimates of the impact of childhood circumstances on health. Our findings emphasize the importance of mitigating health disparities stemming from childhood circumstances, and suggest the need for policy and intervention strategies to promote health equity in both China and the US. Implementing preventive measures during childhood can alleviate the economic burden of diseases, enhance quality of life, and improve longevity, particularly in the absence of effective treatments for chronic diseases like Alzheimer's, hypertension, and diabetes.

The conditional inference forest (CIF) demonstrates superior out-of-sample performance compared to other methods, resulting in the most accurate estimates of childhood circumstances on health inequality in old age. This finding is in line with previous studies in various fields (*14–15*). While conditional inference trees provide a simpler model and a visually accessible representation of childhood circumstances, the CIF leverages information on childhood circumstances more effectively, yielding results consistent with the trees in terms of importance and estimates of influence on health outcomes. These machine learning methods employ explicit algorithms to interpret health outcomes and do not rely on strong assumptions

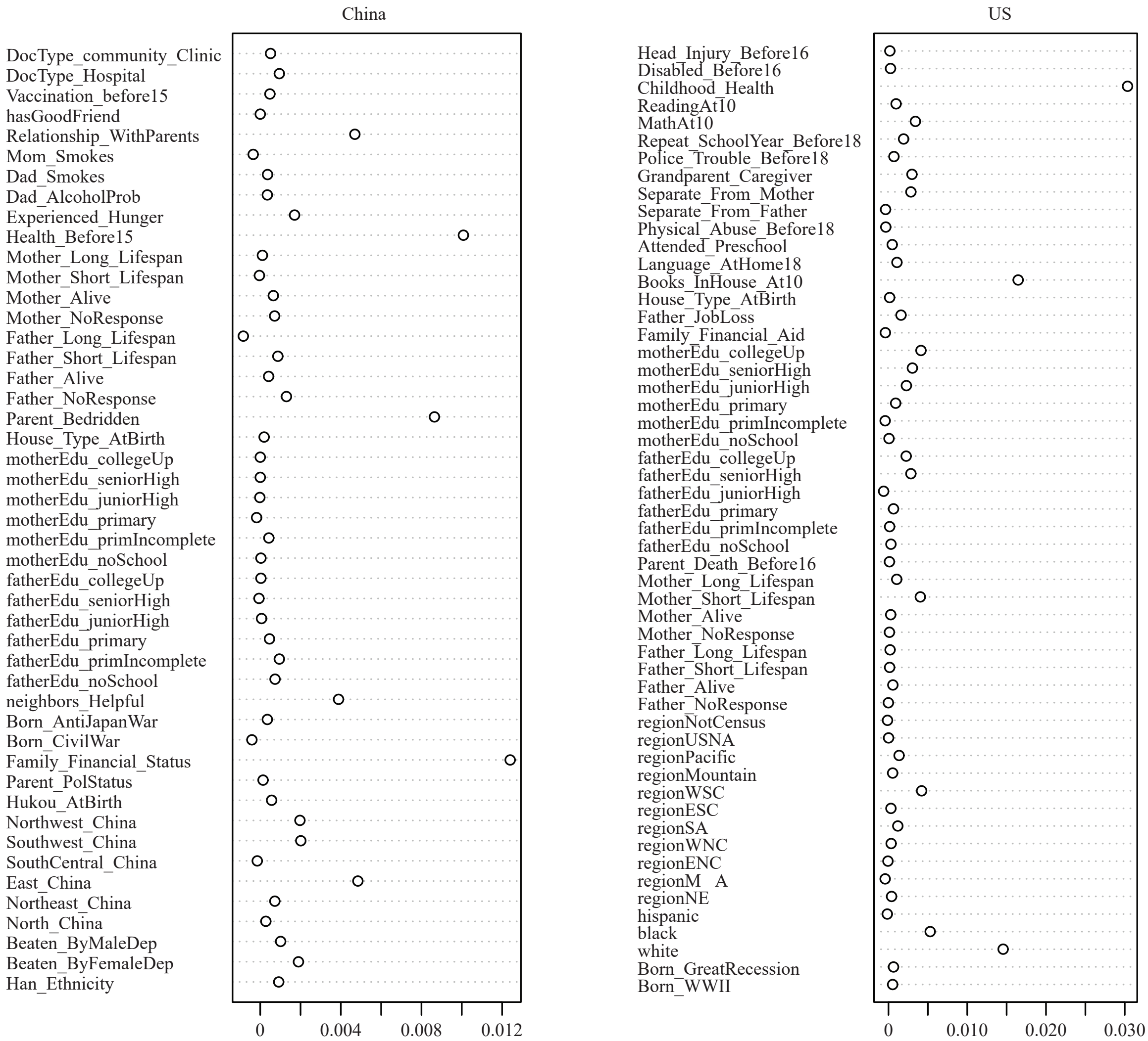


FIGURE 3. Importance of childhood circumstances to self-rated health using conditional inference forest. (A) China; (B) the US.

regarding the significance of specific childhood circumstances. By utilizing statistical techniques such as K-fold cross-validation and bootstrap, our modeling approach becomes more transparent and generalizable.

There are several limitations to this study. First, the life course approach used in this study only focuses on current older adults, which may not accurately reflect the experiences of younger cohorts. Therefore, future research should also consider monitoring younger cohorts. Second, it is important to note that the associations identified in this study should not be interpreted as causal. It is possible that unobservable childhood circumstances may introduce bias to our estimates. Therefore, further research is needed to identify the causal mechanisms at play. Lastly, the data used in this analysis are from the most recently released CHARLS (2020) and HRS (2020–2021) surveys, which overlap with the coronavirus disease 2019 (COVID-19) pandemic. This may introduce bias to self-rated health measures. However, our robustness checks using CHARLS/HRS pre-pandemic waves have yielded consistent results, providing reassurance.

In conclusion, our study utilized a life course approach and machine learning techniques to identify key factors influencing health in older adults. We applied this approach to the two largest economies and aging societies in the world. Our findings underscore the importance of incorporating a life course perspective in public health research and policy development.

Conflicts of interest: No conflicts of interest.

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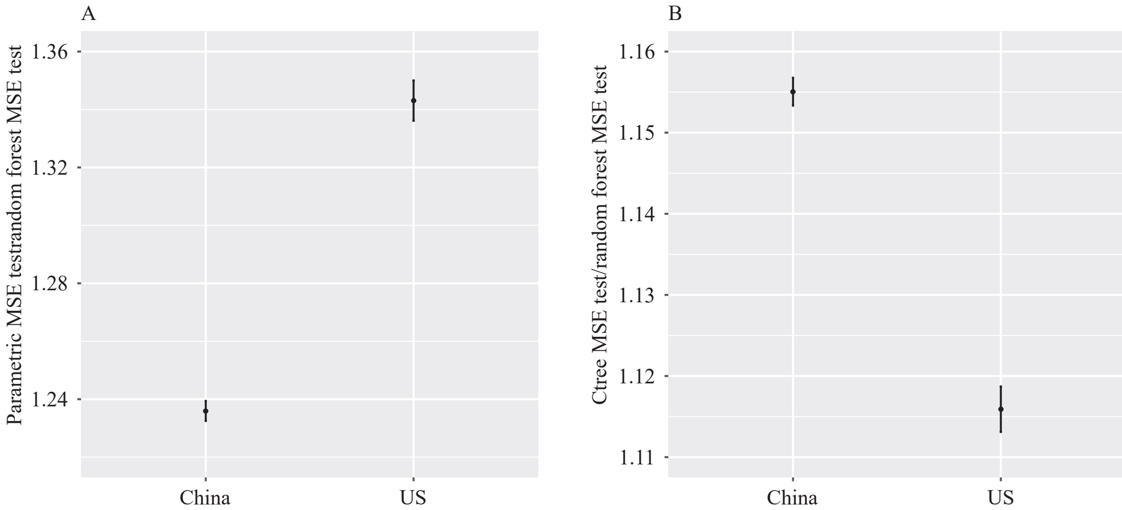

FIGURE 4. Comparison of models' test errors. (A) Parametric method *vs.* random forest; (B) Conditional inference trees *vs.* random forest.

Note: All models aim to minimize the MSE. MSE from Random Forest is used as the reference group. Ratios larger than 1 means the corresponding methods and outcome measures generate larger MSE than using Random Forest. The 95% confidence intervals are derived based on 200 bootstrapped re-samples of the test data.

Abbreviation: MSE=mean squared error.

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SUPPLEMENTARY MATERIAL

CONCEPTUAL AND ANALYTIC FRAMEWORK

Conventional Parametric Roemer Method

The analysis of individual and collective contributions of childhood environments to health inequality in later life can be conducted using the inequality of opportunity (IOP) method. This method allows us to evaluate policy interventions in childhood by identifying the specific impact of different childhood circumstances (Andreoli et al., 2019). To illustrate this, let's consider a simple example with two binary childhood circumstances: parental education (high/low) and financial hardship (no/yes). These circumstances create four distinct groups: (high education, no hardship), (high education, hardship), (low education, no hardship), and (low education, hardship). All individuals are grouped into these four categories. For the sake of simplicity, let's assume that individuals within each group have the same health status in old age. Therefore, any variation in health across the four groups can be attributed solely to differences in childhood circumstances. This variation, as a proportion of the overall health variation among all individuals, defines the IOP. In other words, the IOP represents the proportion of health inequality that can be explained by observable childhood circumstances

In general, existing studies frequently utilize the following linear parametric model.

$$Y_i = \alpha C_i + \varepsilon_i \tag{1}$$

where C is a vector of childhood circumstances beyond the control of the individual, Y is a vector of health outcomes in old age, and i represents individual i. In practice, we do not observe the full set of circumstances C. Instead, we only observe a subset $\check{C} \subseteq C$ from which we further choose a subset $\hat{C} \subseteq \check{C} \subseteq C$. Furthermore, we have to consider limited degrees of freedom and choose P circumstances $C^p \in \hat{C}$. Each circumstance C^p is characterized by a total of X^p possible realizations, where each realization is denoted as x^p. Based on the realization x^p we can partition the population into a set of non-overlapping groups (i.e. types), G = {g_1,…,gm,…,gM}, where each group gm is homogeneous in the expression of each input variable.

We estimated Equation 1 to obtain the counterfactual distribution of Y. The predicted values from Equation 1 were used to construct the counterfactual distribution. IOP was computed using a common inequality measure I(.). Following the approach of Ferreira and Gignoux (2011), we used the Gini coefficient to measure the contribution of childhood circumstances to health inequality, denoted as I(.). To obtain the fraction of variation explained by childhood circumstances, referred to as IOP, we divided this measure of absolute inequality by the same metric applied to the actual outcome.

$$\theta_r = \frac{I(\tilde{Y})}{I(Y)} \tag{2}$$

We utilized the concept of the Shapley value to estimate the relative importance of each childhood circumstance in the decomposition of IOP. This decomposition method allows us to compute the average marginal effect of each circumstance variable on the measure of IOP, regardless of their order. It is worth noting that the order of circumstances for decomposition does not influence the results and that the components of contributions can be summed to obtain the total IOP value. It is important to clarify that while this decomposition provides insight into the relative importance of circumstances, it should not be interpreted as indicating causality (Juarez and Soloaga, 2014; Ferreira and Gignoux, 2013).

SUPPLEMENTARY TABLE S1. Summary statistics of self-rated health in the US and China.

Variable	Country	Obs	Mean	SD	Min	Max	Variable description	CV
Self-rated health	US	2,434	2.835	0.994	1	5	The value of self-rated health in 2020–2021 [Would you say your health is excellent, very good, good, fair, or poor? 1) excellent, 2) very good, 3) good, 4) fair, 5) poor.]	0.351
	China	5,612	3.879	0.772	1	5	The value of self-rated health in 2020 [Would you say your health is excellent, very good, good, fair, or poor? 1) excellent, 2) very good, 3) good, 4) fair, 5) poor.]	0.199

Abbreviation: Obs=number of observations; SD=standard deviation; CV=coefficient of variation.

Conditional Inference Trees

By performing sequential hypothesis tests, tree-based methods can divide the population into distinct groups. Each hypothesis test determines if equal childhood circumstances exist within a specific subset of the population. If the algorithm does not result in any splits, it suggests that the null hypothesis of equal childhood circumstances cannot be rejected. As the tree becomes more extensive, a greater number of groups are required to fully capture the inherent inequalities in the society of interest. Each split indicates that the resulting groups have significantly different childhood circumstances based on an ex-ante interpretation. It should be noted that within each resulting group (terminal node), the null hypothesis of equal childhood circumstances cannot be rejected.

In addition, tree-based methods provide a solution to the issues of arbitrary variable selection and model selection that are common in the IOP literature. Traditional estimation approaches often require researchers to select circumstances C^P, restrict the number of realizations of each circumstance, and determine relevant interactions among these circumstances. However, considering all possible ways to divide the population into groups becomes overwhelming when there is a large set of input variables, particularly when using Reomer's theory. The sheer number of choices often leads to arbitrary model selection. Compared to arbitrarily selecting C^P from all observed childhood circumstances $\breve{C}$ in the conventional regression-based modeling, we retain the full and unrestricted set of observed variables that may qualify as childhood circumstances for trees.

Specifically, we use the circumstances set $\breve{C}$ to partition the population into a set of non-overlapping groups, $G = \{g_1, \ldots, g_{\mathrm{m}}, \ldots, g_M\}$, which are also called terminal nodes in the regression tree context. Then we calculate the predicted value for outcome y of observation I, which is the mean outcome μ m of the group gm to which the individual is assigned. N is the number of observations in m group.

$$\hat{y}_i = \mu_m = \frac{1}{N_m} \sum_{i \in g_m} y_i, \forall i \in g_m, \forall g_m \in G \tag{3}$$

Conditional Inference Forest

Random forest improves over trees via decorrelating the trees, the average of the resulting trees has lower variance of the predicted outcomes and hence is more reliable. We grow a large number of decision trees to form a forest on bootstrapped training samples. Each time a split in a tree is considered when growing these decision trees. A random sample of $\bar{\mathrm{P}}$ predictors is chosen as split candidates from the full set of P predictors, $\breve{C}$. At each split the algorithm uses only one of those $\bar{\mathrm{P}}$ predictors.

This paper creates B number of trees and Count all trees by weight in the prediction of $\hat{y}$. To reduce computational cost, we fix B^* at 200 at which the marginal gain of drawing an additional subsample in terms of out-of-sample prediction accuracy becomes negligible (Supplementary Figure S1). In each tree, we randomly select half of the observations*. Trees are constructed according to the same 4-step procedure outlined in the previous subsection. Each tree is estimated on a random subsample b of the original data. A random subset of circumstances $\bar{\mathrm{P}}$ is used at each splitting point. Then we determine α^* and $\bar{P}^*$ by minimizing the out-of-bag error.

The prediction of y is averaging over the B predictions, which cushions the variance of individual predictions μ_{m}.

$$\hat{y}_i\left(\alpha, \bar{P}, B\right) = \frac{1}{B} \sum_{b=1}^{B} \mu_m^b(\alpha, \bar{P}) \tag{4}$$

Although the collection of bagged trees is much more difficult to interpret than a single tree, we can obtain an overall summary of the importance of each predictor using the residual sum of squares (RSS).

Out-of-Sample Performance Test

To assess potentials of both downward and upward biases of IOP in health that may affect out-of-sample performance, we follow the standard practice to split sample into a training set (2/3*N) and a test set (1/3*N). We fit our model on the training set and compare the performance on the test set for the conventional parametric

* Conventionally, researchers bootstrap to select sample for each tree in random forest. However, it has been shown that the bootstrapping can lead to biased variable selection (Strobl et al., 2007).

Roemer method, conditional inference trees, and conditional inference forest, respectively. Specifically, we follow the same procedure:

1) Run the chosen models on the training data.
2) Store the prediction functions $\hat{f}_{train}(\check{C})$.
3) Predict the outcomes of observations in the test set: $\hat{y}_{i_{test}} = \hat{f}_{train}(\check{C}_{i_{test}})$.
4) Calculate the out-of-sample error: $\mathrm{MSE}^{test} = \frac{1}{N_{test}} \sum_{i_{test}} [y_{i_{test}} - \hat{y}_{i_{test}}]^2$.

SUPPLEMENTARY TABLE S2. Summary statistics of childhood circumstances in the US and China.

Domain	Country	Obs	Mean	SD	Min	Max	Variable description
War or economic crisis	US (2)	2,434	0.077	0.267	0	1	Born in the great recession during 1929–1933 (1: yes; 0: no)
		2,434	0.190	0.392	0	1	Born in the World War II during 1941–1945 (1: yes; 0: no)
	China (2)	5,612	0.295	0.456	0	1	Born in the War of Against Japanese Aggression during 1937–1945 (1: yes; 0: no)
		5,612	0.274	0.446	0	1	Born in the Civil War during 1946–1949 (1: yes; 0: no)
Regional and urban/ rural status	US (11)	2,434	0.051	0.220	0	1	Northeast region: new England division (me, nh, vt, ma, ri, ct) (1: yes; 0: no)
		2,434	0.147	0.354	0	1	Northeast region: middle Atlantic division (ny, nj, pa) (1: yes; 0: no)
		2,434	0.199	0.399	0	1	Midwest region: east north central division (oh, in, il, mi, wi) (1: yes; 0: no)
		2,434	0.115	0.319	0	1	Midwest region: west north central division (mn, ia, mo, nd, sd, ne, ks) (1: yes; 0: no)
		2,434	0.154	0.361	0	1	South region: south Atlantic division (de, md, dc, va, wv, nc, sc, ga, fl) (1: yes; 0: no)
		2,434	0.082	0.274	0	1	South region: east south central division (ky, tn, al, ms) (1: yes; 0: no)
		2,434	0.091	0.287	0	1	South region: west south central division (ar, la, ok, tx) (1: yes; 0: no)
		2,434	0.032	0.175	0	1	West region: mountain division (mt, id, wy, co, nm, az, ut, nv) (1: yes; 0: no)
		2,434	0.063	0.244	0	1	West region: pacific division (wa, or, ca, ak, hi) (1: yes; 0: no)
		2,434	0.008	0.091	0	1	U.S., na state (1: yes; 0: no)
		2,434	0.058	0.234	0	1	Foreign country: not in a census division (includes U.S territories) (1: yes; 0: no)
	China (7)	5,612	0.099	0.299	0	1	Rural or urban status at birth (0: rural; 1: urban)
		5,612	0.106	0.308	0	1	Northern China (1: yes; 0: no)
		5,612	0.074	0.262	0	1	Northeastern China (1: yes; 0: no)
		5,612	0.328	0.469	0	1	Eastern China (1: yes; 0: no)
		5,612	0.241	0.427	0	1	South Central China (1: yes; 0: no)
		5,612	0.181	0.385	0	1	Southwestern China (1: yes; 0: no)
		5,612	0.070	0.255	0	1	Northwestern China (1: yes; 0: no)
Family socioeconomic status	US (10)	2,434	0.020	0.140	0	1	Father: No schooling (1: yes; 0: no)
		2,434	0.776	0.008	0	1	Ethnicity: white (1: yes; 0: no)
		2,434	0.149	0.006	0	1	Ethnicity: black (1: yes; 0: no)
		2,434	0.049	0.004	0	1	Ethnicity: Hispanic (1: yes; 0: no)
		2,434	0.062	0.242	0	1	Father: educated without completing primary school (1: yes; 0: no)
		2,434	0.136	0.342	0	1	Father: Graduated from primary school (1: yes; 0: no)
		2,434	0.300	0.458	0	1	Father: Graduated from junior high school (1: yes; 0: no)
		2,434	0.325	0.468	0	1	Father: Graduated from senior high school (1: yes; 0: no)
		2,434	0.157	0.364	0	1	Father: Graduated from college or above (1: yes; 0: no)
		2,434	0.018	0.134	0	1	Mother: No schooling (1: yes; 0: no)
		2,434	0.035	0.183	0	1	Mother: educated without completing primary school (1: yes; 0: no)

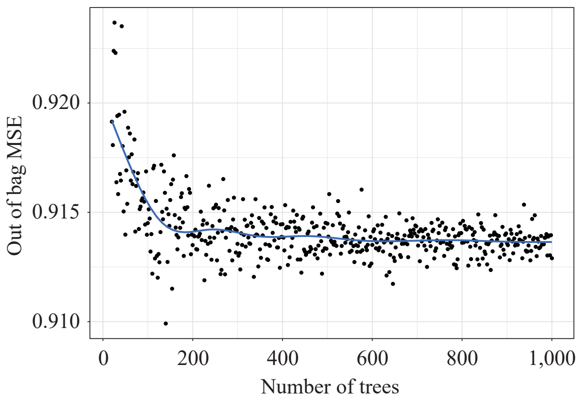
Continued

Domain	Country	Obs	Mean	SD	Min	Max	Variable description
Family socioeconomic status	US (10)	2,434	0.108	0.311	0	1	Mother: Graduated from primary school (1: yes; 0: no)
		2,434	0.271	0.445	0	1	Mother: Graduated from junior high school (1: yes; 0: no)
		2,434	0.430	0.495	0	1	Mother: Graduated from senior high school (1: yes; 0: no)
		2,434	0.138	0.345	0	1	Mother: Graduated from college or above (1: yes; 0: no)
		2,434	0.147	0.355	0	1	Family received financial help (1: yes; 0: no)
		2,434	0.443	0.016	0	3	Father lost job (1: yes, no job for several months or longer; 2: yes, never worked/always disabled; 3: yes, never lived with father/ father was not alive in childhood; 0: no)
		2,434	0.225	0.008	0	1	Before age 16, one or both parents died (1: yes; 0: no)
		2,434	0.875	0.330	0	1	Type of house at birth (1: single-family house; 0 apartment/townhouse/condo or: mobile home)
		2,434	2.153	1.132	1	5	When you were age 10, approximately how many books were in the place you lived? (1: ≤10; 2: 11–27; 3: 27–100; 4: 101–200; 5: >200)
		2,434	0.940	0.238	0	1	Was English the language that you usually spoke at home when you were growing up, before you were age 18?
		2,434	0.131	0.337	0	1	Did you attend any organized pre-school programs (1: yes; 0: no)
	China (5)	8,585	0.075	0.263	0	1	Parents' political status (1: either father or mother is party member; 0: none of them are)
		7,795	0.654	0.476	0	1	Father: No schooling (1: yes; 0: no)
		7,795	0.212	0.409	0	1	Father: educated without completing primary school (1: yes; 0: no)
		7,795	0.082	0.276	0	1	Father: Graduated from primary school (1: yes; 0: no)
		7,795	0.027	0.163	0	1	Father: Graduated from junior high school (1: yes; 0: no)
		7,795	0.015	0.121	0	1	Father: Graduated from senior high school (1: yes; 0: no)
		7,795	0.009	0.095	0	1	Father: Graduated from college or above (1: yes; 0: no)
		8,156	0.945	0.228	0	1	Mother: No schooling (1: yes; 0: no)
		8,156	0.032	0.177	0	1	Mother: educated without completing primary school (1: yes; 0: no)
		8,156	0.015	0.123	0	1	Mother: Graduated from primary school (1: yes; 0: no)
		8,156	0.004	0.062	0	1	Mother: Graduated from junior high school (1: yes; 0: no)
		8,156	0.003	0.053	0	1	Mother: Graduated from senior high school (1: yes; 0: no)
		8,156	0.001	0.022	0	1	Mother: Graduated from college or above (1: yes; 0: no)
		8,484	3.559	0.996	1	5	Family financial status (1: a lot better; 2: somewhat better; 3: same as; 4: somewhat worse; 5: a lot worse)
		8,552	2.168	0.621	1	3	Type of house at birth (1: concrete; 2: adobe; 3: wood or others)
Parents' health status and health behaviors	US (8)	2,434	0.011	0.103	0	1	Non-response (1: yes; 0: no)
		2,434	0.047	0.211	0	1	Alive (1: yes; 0: no)
		2,434	0.422	0.494	0	1	Short life expectancy (1: yes; 0: no) fathers who died younger or same age relative to the median life expectancy in sample
		2,434	0.521	0.500	0	1	High longevity (1: yes; 0: no) fathers who died older than the median life expectancy
		2,434	0.018	0.133	0	1	Non-response (1: yes; 0: no)
		2,434	0.127	0.333	0	1	Alive (1: yes; 0:no)
		2,434	0.355	0.478	0	1	Short longevity (1: yes; 0: no) mothers who died younger or same age relative to the median life expectancy
		2,434	0.500	0.500	0	1	High longevity (1: yes; 0: no) mothers who died older than the median life expectancy
	China (12)	5,612	0.171	0.376	0	1	Parents' health condition (1: anyone spent long time in bed; 0: none)
		5,612	0.062	0.241	0	1	Father having drinking problems (1: alcoholism; 0: none)
		5,612	0.099	0.298	0	1	Mother smoking (1: yes; 0: none)
		5,612	0.444	0.497	0	1	Father smoking (1: yes; 0: none)

Continued

Domain	Country	Obs	Mean	SD	Min	Max	Variable description
Parents' health status and health behaviors	China (12)	5,612	0.203	0.403	0	1	Non-response of father (1: yes; 0: no)
		5,612	0.035	0.184	0	1	Alive father (1: yes; 0: no)
		5,612	0.367	0.482	0	1	Short longevity (1: yes; 0: no) fathers who died younger or same age relative to the median life expectancy
		5,612	0.394	0.489	0	1	High longevity (1: yes; 0: no) fathers who died older than the median life expectancy
		5,612	0.174	0.379	0	1	Non-response of mother (1: yes; 0: no)
		5,612	0.095	0.293	0	1	Alive mother (1: yes; 0: no)
		5,612	0.389	0.488	0	1	Short longevity (1: yes; 0: no) mothers who died younger or same age relative to the median life expectancy
		5,612	0.177	0.382	0	1	High longevity (1: yes; 0: no) mothers who died older than the median life expectancy
Health and nutrition conditions in Childhood	US (5)	2,434	1.685	0.941	1	5	Would you say that your health during that time was (1: excellent, 2: very good, 3: good, 4: fair, 5: poor
		2,434	0.040	0.196	0	1	Before you were 16 years old, were you ever disabled for six months or more because of a health problem? That is, were you unable to do the usual activities of classmates or other children your age?
		2,434	0.104	0.305	0	1	Before you were 16 years old, did you have a blow to the head, a head injury or head trauma that was severe enough to require medical attention, to cause loss of consciousness or memory loss for a period of time?
		2,434	2.583	0.895	1	5	When you were 10 how well did you do in math compared to other children in your class (1: much better, 2: better, 3: about the same, 4: worse, 5: much worse)
		2,434	2.400	0.928	1	5	When you were 10 how well did you do in reading and writing compared to other children in your class? (1: much better, 2: better, 3: about the same, 4: worse, 5: much worse)
	China (5)	5,612	2.684	0.995	1	5	Self-rated health status before age 15 (1: much healthier; 2: somewhat healthier; 3: about average; 4: some less healthy; 5: much less healthy)
		5,612	1.071	0.733	0	2	Have you ever experience hunger (0: no; 1: yes after age 5; 2: yes before age 5)
		5,612	0.787	0.410	0	1	Have you received any vaccinations before 15 years old? (1: yes; 0: no)
		5,612	0.275	0.446	0	1	The type of doctor you visited for the first time was in general hospital specialized hospital or township health clinics? (1: yes; 0: no)
		5,612	0.274	0.446	0	1	The type of doctor you visited for the first time was in community (or village) health centers or private clinics? (1: yes; 0: no)
Relationship with parents	US (5)	2,434	0.064	0.244	0	1	Before you were 18 years old, were you ever physically abused by either of your parents? 0 also for missing data
		2,434	0.131	0.337	0	1	Before age 16 did you ever seperate from your mother for 6 months or longer?
		2,434	0.239	0.427	0	1	Before age 16 did you ever seperate from your father for 6 months or longer?
		2,434	0.072	0.258	0	1	Were your grandparents ever your primary caregiver?
	China (3)	5,612	2.435	1.164	1	5	Relationship with parents (1: excellent; 2: very good; 3: good; 4:fair; 5: poor)
		5,612	0.141	0.348	0	1	Did male dependents ever beat you (1: often or somewhat; 0: rarely or never)
		5,612	0.218	0.413	0	1	Did female dependents ever beat you (1: often or somewhat; 0: rarely or never)
Friendship in childhood	US (2)	2,434	0.141	0.348	0	1	Before you were 18 years old, did you have to do a year of school over again?
		2,434	0.055	0.228	0	1	Before you were 18 years old, were you ever in trouble with the police?
	China (2)	5,612	0.878	0.081	0	1	The average value of neighbors willing to help others at community level, the answers at individual level is 1: very or somewhat, 0: not at all
		5,612	0.438	0.496	0	1	Did you have a good friend (1: yes; 0: no)

Abbreviation: Obs=number of observations; SD=standard deviation.



SUPPLEMENTARY FIGURE S1. Optimal number of trees in conditional random forest.
Note: The x-axis shows the parameter value for B, i.e. the number of trees per forest. The dots show the MSE^{OOB} obtained from estimating a random forest with the given number of trees for the self-rated health in the US. We allow 7 circumstances to be considered at each splitting point. The blue line is a non-parametric fitted line of the MSE^{OOB} estimates and the shaded area is the 95% confidence interval of this line. Evidently, as the tree size approaches 200, on expectation, the MSE^{OOB} stops improving much.
Abbreviation: MSE=mean square error; MSE^{OOB} =out-of-bag mean square error.

Review

Influencing Factors of Healthy Aging Risk Assessed Using Biomarkers: A Life Course Perspective

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ABSTRACT

Assessing individual risks of healthy aging using biomarkers and identifying associated factors have become important areas of research. In this study, we conducted a literature review of relevant publications between 2018 and 2023 in both Chinese and English databases. Previous studies have predominantly used single biomarkers, such as C-reactive protein, or focused on specific life course stages and factors such as socioeconomic status, mental health, educational levels, and unhealthy lifestyles. By summarizing the progress in this field, our study provides valuable insights and future directions for promoting healthy aging from a life course perspective.

INTRODUCTION

Healthy aging refers to the ability to maintain physical and psychological health, as well as social adaptability, as individuals grow older. It involves assessing the extent of health damage caused by irreversible physical changes associated with aging, which can result in reduced functioning and the degeneration of physiological systems at various levels (*1*–*2*). Various assessment methods, such as anthropometric measurements, hematological indicators, molecular/biological markers, and allostatic load, are used to evaluate healthy aging risk in current research. While subjective assessments of healthy aging risk (e.g., self-reported health, cognition) are prone to information bias and can vary across different settings, biomarker-based assessments have gained attention in recent years due to their objectivity and precision. Specific biomarkers can objectively reflect physical changes within the body and predict health outcomes as individuals age. Instead of relying on a single biomarker, using multiple integrated biomarkers, combined with various theories and mathematical/statistical algorithms, provides a more comprehensive approach to assessing healthy aging risks (*3*). Therefore, this approach is recommended for further research, including investigating the factors that influence healthy aging risks.

Various factors (e.g., adversity, lifestyle) at different stages of life could influence the risk of aging. However, there is currently no comprehensive review of the factors that influence healthy aging risks from a life course perspective. Therefore, we summarized the progress in understanding the influencing factors of healthy aging risks assessed through biomarkers from a life course perspective. This study aimed to provide a theoretical foundation for the development of practical and universally applicable strategies to delay the aging process and eventually, prevent chronic diseases.

METHODS

Search Strategy and Selection Criteria

We conducted comprehensive searches in multiple databases, including PubMed, Web of Science, CNKI, Wanfang Database, and VIP Information Database, from January 1, 2018 to March 31, 2023. In addition to database searches, we manually searched for relevant literature and reviewed their references. Our search strategy included various combinations of the following keywords in [Title/Abstract]: childhood, adulthood, adolescence, life course, lifespan, biological age, biomarker, socioeconomic, adversity, inflammation, aging, allostatic load (AL). Both Chinese and English articles were included in our analysis. We utilized NoteExpress as a tool to manage our literature resources.

Eligibility and Exclusion Criteria

To be eligible for inclusion in our review, studies must meet the following criteria. First, the study must evaluate or forecast the risk of healthy aging, either through biomarkers or by other means. Second, the study should investigate the factors that influence biomarker-based risk of healthy aging or explore the association between life course exposure factors and the risk of healthy aging, such as accelerated aging.

Studies were excluded if they did not include original data, only showed a correlation between risk factors and the risk of healthy aging, did not utilize a biomarker-based approach, or involved non-human subjects (e.g., animals).

RESULTS

We first screened the literature by title and abstract according to eligibility and exclusion criteria, then reviewed the full text of potential candidates. A total of 1,833 review/editorial articles, 33 letter/review articles, 1,238 articles without original data or healthy aging data, 2,767 articles without the use of biomarkers, and 1,367 studies without population-based evidence were excluded. Ultimately, 41 articles were included for analysis (Figure 1 and Supplementary Table S1, available at https://weekly.chinacdc.cn/).

Childhood/Adolescence

The factors in childhood and adolescence that influence healthy aging primarily include family socioeconomic status (SES), mental health, and experiences of adversity. These factors highlight the significance of early life exposures and influences.

Two cohort studies conducted in Portuguese and Finnish populations (*4*–*5*) indicated that lower early-life SES is associated with elevated levels of inflammation during the first decade of life. A study in young adults from the United States (*6*) demonstrated that family poverty during adolescence (11–18 years) correlates with increased insulin resistance (IR) in adulthood. Moreover, experiencing emotional symptoms and behavioral problems during childhood and adolescence were associated with biomarkers such as C-reactive protein (CRP) and higher premature death risk (*7*). Mian et al. (*8*) observed that more severe adverse childhood experiences (ACEs) accelerate biological aging, as calculated using Klemera and Doubal's method, and phenotypic age. Similar results were reported by Wang et al. (*9*) and Yang et al. (*10*).

Recent research indicates that childhood stress, trauma, and abuse events are associated with inflammation in adulthood (*11*–*15*). Additionally, childhood abuse experiences are linked to negative outcomes such as adverse cardiometabolic conditions and depression in adulthood (*16*–*17*). There is also a significant association between ACEs and inflammatory biomarkers (*18*). Participants who have experienced childhood victimization and more stressful events have been found to have increased levels of soluble urokinase plasminogen activator receptors (suPAR) (*19*–*20*). A birth cohort study conducted in New Zealand among middle-aged individuals (*21*)

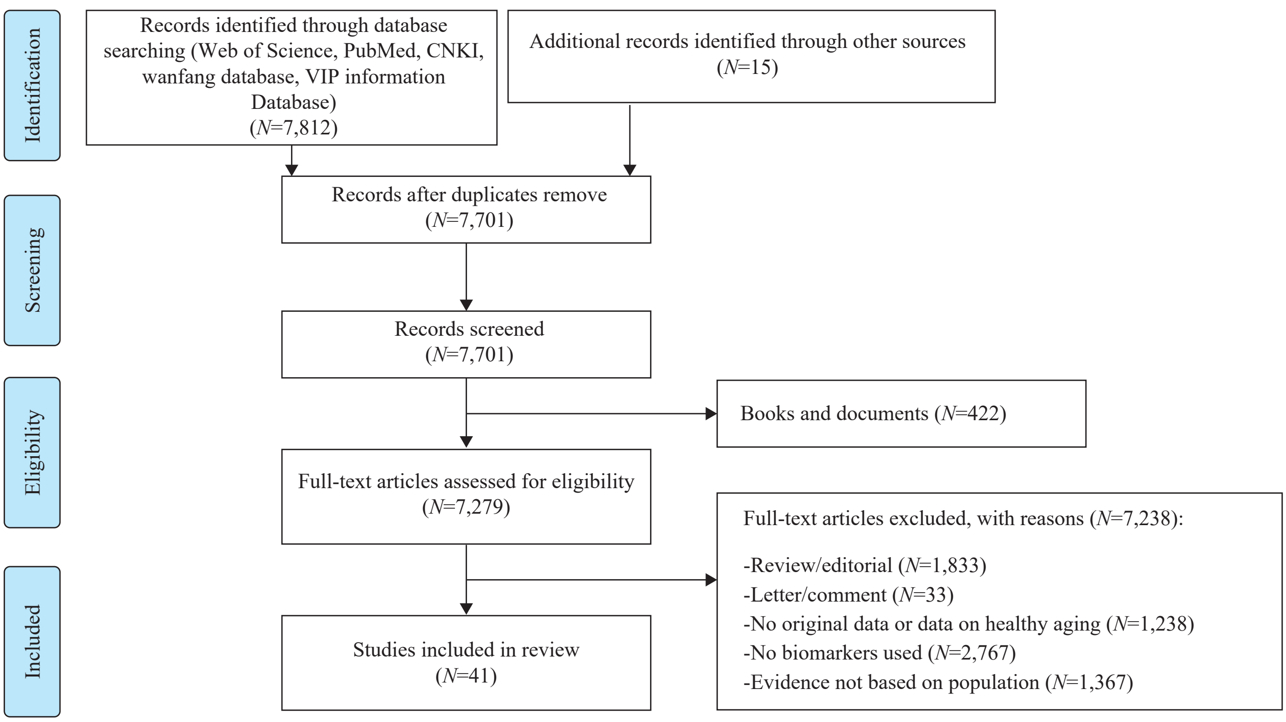

FIGURE 1. Flowchart for study identification, screening, and selection.

revealed that individuals exposed to risk factors for disease and early mortality during childhood, such as poor health, low SES, low intelligence quotient, and low self-control, showed increased serum suPAR levels in adulthood even after controlling for adult health risk factors. Therefore, assessing childhood trauma exposure can provide valuable insights for the development of prevention strategies against aging and related chronic diseases.

Additionally, a cross-sectional study with over 500 Chinese children, revealed that those who experienced separation from their parents in early childhood had elevated levels of AL. AL quantified biological dysregulation across multiple systems that occurs prior to puberty and during early adolescence. This was measured using biomarkers from multiple systems (*22*). Similarly, parental incarceration during childhood was linked to higher AL (*23*). Furthermore, it was observed that children's self-control had an impact on their ability to age healthily. Those with greater self-control during adolescence exhibited slower aging and better adaptation to the aging process (*24*).

Adulthood

In adulthood, key determinants of healthy aging encompass educational level, SES (*25*), and lifestyle choices.

Previous research has shown that higher levels of education can reduce the AL rate by 0.3 units per year, impacting variables like body mass index (BMI) and glycated hemoglobin levels (*26*). In a study by Karimi et al. (*27*), the concept of accelerated aging was expanded using the Synthetic Biological Health Score (BHS), which was based on 16 blood biomarkers. The study found that SES in adulthood was associated with health risks in early adulthood, regardless of disease and lifestyle factors. Chronic workplace stress, including prolonged unemployment and a lack of promotion, was also found to impact healthy aging (*28*). Certain lifestyle factors, such as maintaining a normal BMI, never smoking, moderate alcohol consumption, being physically active, and getting 7–9 hours of sleep per night, have been demonstrated to reduce the risk of unhealthy aging (*29*–*31*).

Life Course Perspective

An increasing body of research indicates that exposure to various factors throughout an individual's life can influence the risks associated with healthy aging.

In a cross-sectional study of 490 middle-aged and older participants from Ireland, lower SES was found to be associated with higher AL (*32*). Additionally, we observed a significant increase in AL over time during adulthood (*33*). Further analysis revealed no significant difference in AL between individuals with upward social mobility and those maintaining a higher SES. However, participants who experienced downward mobility and remained in a lower SES had higher AL. These findings align with previous studies conducted by Graf et al. (*34*) and Schrempft et al. (*35*), suggesting that adverse SES experiences throughout the life course contribute to a greater risk of unhealthy aging. Furthermore, we found a correlation between parental education and the rate of aging, with the father's occupational status significantly influencing this association. Notably, lower educational levels have similarly adverse effects on healthy aging risk in other populations as well (*36*–*37*).

Numerous studies highlight a negative correlation between higher SES and risks associated with healthy aging. However, evidence suggests potential racial disparities. For instance, research indicates that Black Americans exhibit significantly higher levels of inflammatory biomarkers compared to White individuals. Furthermore, even among affluent Black Americans, poorer health aging outcomes are noted compared to wealthy White individuals (*38*–*39*). Moreover, upward social mobility doesn't seem to improve health aging outcomes for Black Americans (*40*). These findings support the conclusion drawn by Ong et al. (*41*), who found a positive correlation between the severity of discrimination experienced throughout the lifespan and the inflammation burden.

In a cross-sectional study of 6,224 middle-aged and elderly Chinese participants, Cao et al. (*42*) found that trauma and adversity during childhood and adulthood are associated with accelerated aging, as determined by phenotypic age and frailty index. A subsequent follow-up study reported a significant increase in cardiovascular disease in individuals with lifelong severe trauma (*43*). Furthermore, middle-aged individuals with a history of antisocial behavior displayed an accelerated rate of biological aging (*44*), as shown in Supplementary Table S1.

DISCUSSION

This study presents the first comprehensive review summarizing factors influencing the risk of healthy aging, as assessed by biomarkers, from a life course perspective. We identify stage-specific factors (childhood, adolescence, and adulthood) contributing to healthy aging risk, including SES, mental health, ACEs, educational levels, and unhealthy lifestyles during adulthood. Importantly, these factors are not limited to their respective life stages but have an impact on healthy aging risk throughout the entire life course. Thus, it is crucial to develop a health management policy for the entire population that adopts a life course perspective to effectively address the challenges of population aging.

SES, mental health, and adversity in childhood are associated with elevated levels of various biomarkers such as inflammation, IR, and CRP (*4–10*). Low SES in childhood can result in inadequate accommodation, reduced quality of life, and insufficient treatment. The interactions between SES, adversity, and mental health have a particularly significant impact during childhood, as children are less resilient physically and mentally compared to adults. Collaborative efforts among families, schools, and society are crucial in childhood to address these factors, such as creating supportive learning and living environments. Educational level, SES, and lifestyle in adulthood significantly affect healthy aging risk (*25–31*). Given that higher educational levels intuitively enhance individuals' work and cognitive abilities, implementing compulsory education could enhance these factors and reduce the overall risk of unhealthy aging.

The factors influencing the risk of healthy aging mentioned earlier are not only relevant to specific stages of the life course, but they persist throughout the entire lifespan and impact the risk of healthy aging as well (*32–44*). Among these, SES, educational level, and adversity are particularly influential, with SES's impact varying across variables like ethnicity. Considering the entire lifespan, not only a specific life stage, is crucial. Implementing personalized interventions tailored to different life stages will result in a more efficient and comprehensive reduction of healthy aging risks across the population.

Our review may assist researchers and healthcare professionals in identifying individuals at higher risk of age-related diseases or conditions, enabling early intervention and the implementation of customized healthcare strategies to promote healthy aging. Future research should delve into the underlying reasons behind the strong associations observed between specific influencing factors and healthy aging risks. It is crucial to collect additional research data on the interactions among these influencing factors at different stages of life, allowing for a more comprehensive evaluation of the underlying mechanisms driving these interactions. Furthermore, prioritizing this research is essential for determining effective biomarker-based methods for assessing healthy aging risks.

CONCLUSION

This study conducted a literature review on biomarker-based indicators of healthy aging and identified factors associated with healthy aging across the life course, including childhood, adulthood, and the entire life span. The findings of this study provide a strong theoretical basis for the development of effective and targeted strategies to reduce the risks of aging-related health issues.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Studies examining the association of factors with healthy aging risks assessed by biomarkers.

Period	1st Author	Year published	Study population	Study design	Statistical analysis methods	Exposure factors	Indicators of healthy aging risk assessment
Childhood/ adolescence	Soares (*1*)	2020	2,510 Portuguese children	Birth cohort study	Linear mixed-effects model	SES	High sensitive CRP
	Carmeli (*2*)	2021	2,329 Finnish adult	Cohort study	Linear regression model	SES	CRP
	Barton (*3*)	2022	342 young Americans (25–29 years)	Cohort study	Linear regression model	SES	IR
	Ploubidis (*4*)	2021	17,415 Middle-aged British	Birth cohort study	Least squares regression model, log-binomial model	Mental health	Fibrinogen, CRP, glycated hemoglobin, HDL cholesterol, LDL cholesterol
	Mian (*5*)	2022	23,354 middle-aged and elderly Canadians	Cross-sectional study	Linear regression model	Adversity experiences	KDM biological age, phenotypic age, homeostatic imbalance
	Wang (*6*)	2022	150 Chinese children	Cross-sectional study	Linear regression model	Adversity experiences	AL
	Yang (*7*)	2022	127,495 middle-aged and elderly British	Cross-sectional study	Linear regression model	Adversity experiences	Phenotypic age
	Rasmussen (*8*)	2020	1,391 young British	Birth cohort study	Least squares regression model	Adversity experiences	CRP, IL-6, suPAR
	Renna (*9*)	2021	157 middle-aged and elderly Americans	Cohort study	Linear mixed-effects model	Maltreatment	IL-6, IL-1β, TNF-α
	Kuzminskaite (*10*)	2020	2,778 Dutch adult	Cross-sectional study	Linear regression model	Maltreatment	CRP, IL-6, TNF-α
	Nguyen (*11*)	2020	304 middle-aged Americans	Cross-sectional study	Linear regression model	Adversity experiences	High sensitive CRP, IL-6
	Wang (*12*)	2019	911 Chinese adolescence	Cross-sectional study	Logistic regression model	Maltreatment	IL-6
	Li (*13*)	2019	9,377 middle-aged British (around 45 years old)	Birth cohort study	Linear regression model, logistic regression model	Maltreatment	Glycated hemoglobin, HDL cholesterol, LDL cholesterol, triglyceride
	O'Shields (*14*)	2022	2,118 middle-aged and elderly Americans	Cross-sectional study	Structural equation model	Maltreatment	Inflammation score（CRP, IL-6, fibrinogen, e-selectin, intracellular adhesion molecule-1, TNF-α）
	John-Henderson (*15*)	2020	90 American adult	Cross-sectional study	Linear regression model	Adversity experiences	
	Trotta (*16*)	2021	1,419 young British	Birth cohort study	Least squares regression model	Adversity experiences	CRP, IL-6, suPAR
	Bourassa (*17*)	2021	828 middle-aged New Zealanders (around 45 years old)	Birth cohort study	Linear regression model	Adversity experiences	CRP, IL-6, suPAR

Continued

Period	1st Author	Year published	Study population	Study design	Statistical analysis methods	Exposure factors	Indicators of healthy aging risk assessment
Childhood/ adolescence	Rasmussen (*18*)	2019	837 middle-aged New Zealanders (around 38 years old)	Birth cohort study	Logistic regression model	Health Status, SES, Adversity Experiences, Self-control Ability, IQ	High sensitive CRP, suPAR
	Sun (*19*)	2020	557 Chinese children (7–12 years)	Cross-sectional study	Linear regression model	Separation from Parents	AL
	Nino (*20*)	2020	13,365 American children (7–12 years)	Cross-sectional study	Negative binomial regression model	Parental Imprisonment	AL
	Richmond-Rakerd (*21*)	2021	938 middle-aged and elderly New Zealanders (around 45 years old)	Birth cohort study	Linear regression model	Self-control Ability	Aging Rate
Adulthood	Steptoe (*22*)	2020	5,018 middle-aged and elderly British	Cross-sectional study	Analysis of variance	SES	Fibrinogen Concentration
	Ding (*23*)	2019	3,935 middle-aged and elderly Americans	Cross-sectional study	Least squares regression model	Educational Level	AL
	Karimi (*24*)	2019	9,088 British adult	Cross-sectional study	Linear regression model	SES	BHS
	Wahrendorf (*25*)	2022	92,715 middle-aged and elderly in France	Cross-sectional study	Mixed-effects negative binomial model	Working Experiences	AL
	Cao (*26*)	2023	5,553 middle-aged and elderly Americans	Cross-sectional study	Linear regression model	Weight Changes	Phenotypic Age, KDM Biological Age
	Rehkopf (*27*)	2019	821 elderly Costa Ricans and 4,110 elderly Americans	Cross-sectional study	Least squares regression model	BMI	Glycated Hemoglobin, HDL Cholesterol, TAG
	Wang (*28*)	2022	14,848 middle-aged and elderly Chinese	Cross-sectional study	Linear regression model	Lifestyle	Biological Age
Whole Life Course	McCrory (*29*)	2019	490 middle-aged and elderly Irish	Cross-sectional study	Linear regression model	SES	AL
	van Deurzen (*30*)	2019	3,824 middle-aged and elderly British	Cohort study	Growth curve model	SES	AL
	Graf (*31*)	2022	9,225 middle-aged and elderly Americans	Cross-sectional study	Linear regression model	SES	KDM Biological Age, Phenotypic Age, Homeostatic Imbalance
	Schrempft (*32*)	2022	5,309 middle-aged and elderly in Switzerland (35–75 years)	Cohort study	Linear regression model	SES	Aging Rate
	Liu (*33*)	2019	2,339 middle-aged and elderly Americans	Cross-sectional study	Shapley's value decomposition, hierarchical cluster analysis	SES, Adversity Experiences, Lifestyle	Phenotypic Age

Continued

Period	1st Author	Year published	Study population	Study design	Statistical analysis methods	Exposure factors	Indicators of healthy aging risk assessment
Whole Life Course	Yang (*34*)	2020	17,713 American adults	Cohort study	Ordered logit model	SES	CRP
	Surachman (*35*)	2020	750 middle-aged and elderly Americans	Cross-sectional study	Potential category analysis model, BCH method	SES	CRP, IL-6, Soluble Intracellular Adhesion Molecule-1
	Lam (*36*)	2021	624 Americans 1,025 Canadians (11–60 years)	Cross-sectional study	Linear regression model	SES	CRP, IL-6
	Thomas Tobin (*37*)	2022	518 middle-aged and elderly Americans	Cross-sectional study	Poisson regression model	SES	AL
	Ong (*38*)	2019	300 middle-aged and elderly Americans (36–85 years)	Cross-sectional study	Linear regression model	Discriminate	Inflammation Burdon Score (CRP, IL-6, Fibrinogen, e-Selectin, Intracellular Adhesion Molecule-1)
	Cao (*39*)	2022	6,224 middle-aged and elderly Chinese	Cross-sectional study	Shapley's value decomposition, hierarchical cluster analysis	SES, Adversity Experiences, Social support	Homeostatic Imbalance
	Cao (*40*)	2022	104,939 middle-aged and elderly British	Cross-sectional study	Linear regression model	Adversity Experiences	Phenotypic Age
	Langevin (*41*)	2022	1,307 middle-aged New Zealanders	Birth cohort study	Linear regression model	Anti-social Behaviour	Aging Rate

Abbreviation: SES=socioeconomic status; AL=allostatic load; CRP=C-reactive protein; IR=increased insulin resistance; HDL=high density lipoprotein; LDL=low density lipoprotein; BHS=biological health score; TAG=triglycerides; KDM=klemera and doubal method.

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