

## 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)

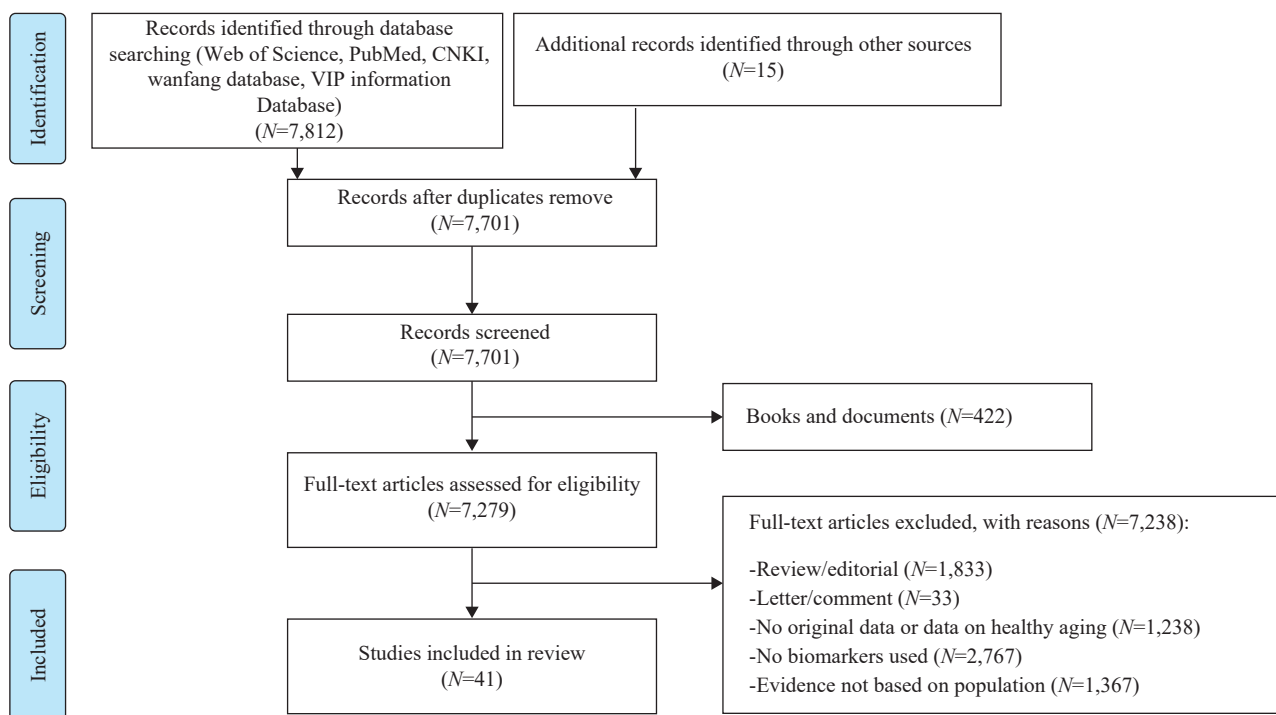


FIGURE 1. Flowchart for study identification, screening, and selection.

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.

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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-1 $\beta$ , TNF- $\alpha$
	Kuzminskaite (10)	2020	2,778 Dutch adult	Cross-sectional study	Linear regression model	Maltreatment	CRP, IL-6, TNF- $\alpha$
	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- $\alpha$ )
	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	Stephoe (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	McCrary (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
	Schrepft (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 104,939	Cross-sectional study	Shapley's value decomposition, hierarchical cluster analysis	SES, Adversity Experiences, Social support	Homeostatic Imbalance
	Cao (40)	2022	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=klemra and doubal method.

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