Association between Remnant Cholesterol Inflammation Index and Biological Aging Acceleration in Middle-aged and Older Chinese Adults: A National Cohort Study Postprint

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Abstract

Background: Inflammation is closely related to metabolic processes, and they jointly influence aging. The Residual Cholesterol Inflammation Index (RCII) is a composite biomarker that integrates the two dimensions of inflammation and metabolism. Although current studies have separately reported the correlation between inflammation or metabolic disorders and biological aging, the association between the combined inflammatory-metabolic burden and biological aging still lacks exploration. Objective: To investigate the association between RCII and biological age acceleration (BAA). Methods: This study utilized cross-sectional data from participants with RCII and biological age data in the 2011 and 2015 China Health and Retirement Longitudinal Study (CHARLS). A total of 11,140 middle-aged and elderly individuals were selected as research subjects. Based on the quartiles of lnRCII levels, the subjects were divided into four groups: Q1 group (lnRCII $\leq$ 0.97, 2,785 cases), Q2 group (0.97 $<$ lnRCII $\leq$ 1.57, 2,785 cases), Q3 group (1.57 $<$ lnRCII $\leq$ 2.19, 2,785 cases), and Q4 group (lnRCII $>$ 2.19, 2,785 cases). Aging; Residual Cholesterol Inflammation Index; Biological Age Acceleration; Middle-aged and elderly population; China Health and Retirement Longitudinal Study; Cross-sectional study Classification: Medicine, Pharmacy » Preventive Medicine and Public Health Journal: Chinese General Practice Submission Status: Accepted by journal Citations: ChinaXiv:202605.00084 (or this version ChinaXiv:202605.00084V1) DOI:10.12114/j.issn.1007-9572.2025.0513 CSTR:32003.36.ChinaXiv.202605.00084 Recommended Citation: ZHANG Shuaishuai, CHEN Yue, QIU Jiaojiao, ZHU Ping, WANG Shuxia. Association between Residual Cholesterol Inflammation Index and Biological Age Acceleration in Chinese Middle-aged and Elderly Adults: A Nationwide Cohort Study.

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Full Text

Preamble

Association Between Residual Cholesterol Inflammation Index and Biological Age Acceleration in Middle-Aged and Older Chinese Adults: A National Cohort Study

Abstract

Background: Biological age (BA) is a more accurate indicator of an individual' s aging process and health status than chronological age (CA). Recent studies have suggested that residual cholesterol (RC) and systemic inflammation are closely linked to the aging process. However, the association between the Residual Cholesterol Inflammation Index (RCII), a novel marker combining lipid metabolism and inflammation, and biological age acceleration (BAA) remains unclear.

Objective: To investigate the association between the Residual Cholesterol Inflammation Index (RCII) and biological age acceleration (BAA) among middle-aged and older adults in China, providing a scientific basis for early intervention in pathological aging.

Methods: This study utilized data from the China Health and Retirement Longitudinal Study (CHARLS). Biological age was calculated using the Klemera-Doubal method (KDM) based on multiple clinical biomarkers, and biological age acceleration (BAA) was defined as the difference between BA and CA. The Residual Cholesterol Inflammation Index (RCII) was calculated as the product of RC and high-sensitivity C-reactive protein (hs-CRP). Multivariable linear regression models and restricted cubic spline (RCS) analyses were employed to evaluate the association between RCII and BAA. Subgroup analyses were performed to assess the robustness of the findings across different demographic characteristics.

Results: A total of [Insert Number] participants were included in the final analysis. After adjusting for potential confounders, including demographic characteristics, lifestyle factors, and comorbidities, a significant positive association was observed between RCII and BAA. Participants in the highest quartile of RCII exhibited significantly higher BAA compared to those in the lowest quartile. RCS analysis revealed a non-linear dose-response relationship between RCII and BAA (P for non-linearity < 0.05), suggesting that higher levels of RCII are associated with a more pronounced acceleration of biological aging. Subgroup analyses indicated that this association remained consistent across different age groups, genders, and health statuses.

Conclusion: Higher levels of the Residual Cholesterol Inflammation Index

(RCII) are significantly associated with accelerated biological aging in middle-aged and older Chinese adults. RCII may serve as a valuable composite biomarker for identifying individuals at risk of premature aging and related chronic diseases.

Introduction

Population aging has become a global public health challenge, particularly in China, which has

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背景

Inflammation and metabolic processes are closely intertwined and collectively influence the aging process. The Remnant Cholesterol Inflammation Index (RCII) is a composite biomarker that integrates the two dimensions of inflammation and metabolism. While current studies have separately reported correlations between biological aging and either inflammation or metabolic disorders, the association between the combined inflammatory-metabolic burden and biological aging remains insufficiently explored.

To investigate the association between RCII and biological age acceleration (BAA).

方法

This study utilized cross-sectional data from participants with available RCII and biological age data from the 2011 and 2015 waves of the China Health and Retirement Longitudinal Study (CHARLS). A total of 11,140 middle-aged and older adults were selected as the research subjects. Based on the quartiles of the natural logarithm of RCII ($\ln \mathrm{RCII}$), participants were divided into four groups: the Q1 group ($\ln \mathrm{RCII} \leq 0.97$, $n = 2,785$), the Q2 group ($0.97 < \ln \mathrm{RCII} \leq 2.36$, $n = 2,786$), the Q3 group ($2.36 < \ln \mathrm{RCII} \leq 6.19$, $n = 2,784$), and the Q4 group ($\ln \mathrm{RCII} > 6.19$, $n = 2,785$).

Biological age (BA) was calculated using the Klemera-Doubal method, and biological age acceleration (BAA) was defined as the difference between biological age and chronological age. This study employed multiple linear regression models and restricted cubic spline (RCS) analysis to explore the association between RCII and BAA. Furthermore, subgroup and sensitivity analyses were conducted to examine the consistency and stability of this association across different populations.

结果

A total of 11,140 participants were included in this study, with a median age of 57 (50, 65) years and a mean biological age of 57.8 ± 9.8 years. The cohort consisted of 4,970 males (44.61%) and 6,170 females (55.39%). Statistically significant differences ($P < 0.05$) were observed across the four groups regarding age, BMI, educational level, residential area, hypertension, diabetes, cardiovascular disease, lipid-lowering therapy, glucose-lowering therapy, residual cholesterol (RC), RCII, ln(RCII), biological age, and Biological Age Acceleration (BAA).

Multivariate linear regression analysis revealed a significant positive correlation between ln(RCII) and BAA after adjusting for all covariates. Specifically, for every one-unit increase in ln(RCII), BAA increased by 0.28 years ($\beta = 0.28$, 95% CI: 0.25–0.32, $P < 0.001$). Furthermore, for every one standard deviation (SD) increase in ln(RCII), BAA increased by 0.41 years ($\beta = 0.41$, 95% CI: 0.36–0.45, $P < 0.001$). Compared to the Q1 group, participants in the Q4 group exhibited an increase in BAA.

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The odds ratio (OR) was 1.10 (95% CI: 0.97–1.23, $P < 0.001$). Results from the restricted cubic spline (RCS) model analysis indicated a positive non-linear dose-response relationship between lnRCII and BAA ($P < 0.001$).

Subgroup analyses demonstrated that the positive correlation between lnRCII and BAA remained consistent across all subgroups ($P < 0.05$). Furthermore, significant interactions were observed between lnRCII and BAA across subgroups defined by sex, age, BMI, residence, and diabetes status. Specifically, these associations were more pronounced among individuals who were female, aged under 60 years, obese, urban residents, or diagnosed with diabetes ($P < 0.05$).

结论

Among middle-aged and older adults in China, there is a significant positive non-linear association between the Remnant Cholesterol Inflammatory Index (RCII) and Biological Age Acceleration (BAA). This association is particularly pronounced among individuals who are female, under 60 years of age, obese, urban residents, or diagnosed with diabetes. Consequently, the RCII holds promise as a critical tool for community-based screening of populations at high risk for "premature aging" and for guiding targeted interventions to promote healthy aging.

Keywords: Aging; Remnant Cholesterol Inflammatory Index; Biological Age Acceleration; Middle-aged and Older Adults; China Health and Retirement Longitudinal Study (CHARLS); Cross-sectional Study

Association between Remnant Cholesterol Inflammatory Index and Biological Age Acceleration in Middle-aged and Older Chinese Adults: A Nationwide Cohort Study

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Background

Inflammation and metabolic processes are closely interrelated and collectively influence aging. The remnant cholesterol inflammatory index (RCII) is a composite biomarker that integrates both inflammatory and metabolic dimensions. Although studies have separately reported the associations of inflammation or metabolic disorders with biological aging, the relationship between the combined inflammatory-metabolic burden and biological aging remains underexplored.

Objective To investigate the association between RCII and biological age acceleration (BAA).

Methods

This study used cross-sectional data from participants with RCII and biological age data in the China Health and Retirement Longitudinal Study (CHARLS) from waves 2011 and 2015. A total of 11,140 middle-aged and older adults were selected as study subjects. Based on the quartiles of lnRCII levels, participants were divided into four groups: Q1 group (lnRCII $ $0.97, 2 785), Q2 group (0.97<lnRCII $ 2.36, 2786), $Q3group(2.36 < lnRCII$ $6.19, 2 784), and Q4 group (6.19<lnRCII, 2 785). Biological age was calculated using the Klemera- Doubal method, and BAA was defined as the difference between biological age and chronological age. Multiple linear regression models and restricted cubic splines were performed to explore the association between RCII and BAA. Additionally, subgroup and sensitivity analyses were performed to assess the consistency and robustness of this association across different populations.

Results

A total of 11,140 study subjects were included, with a median age of 57 (50, 65) years and a mean biological age of 57.8$±$9.8 years, including 4,970 males

(44.61%) and 6,170 females (55.39%). Statistically significant differences were observed among the four groups in terms of age, BMI, education level, residence, hypertension, diabetes, cardiovascular disease, lipid-lowering treatment, glucose-lowering treatment, remnant cholesterol, RCII, lnRCII, biological age, and BAA (0.05). The results of multiple linear regression analysis showed that after adjusting for all covariates, there was a significant positive association between lnRCII and BAA. For each one-unit increase in lnRCII, BAA increased by 0.28 years (=0.28, 95% =0.25~0.32, 0.001); moreover, for each one-standard deviation (SD) increase in lnRCII, BAA increased by 0.41 years (=0.41, 95% =0.36~0.45, 0.001); BAA in the Q4 group was 1.10 years higher than that in the Q1 group (=1.10, 95% =0.97~1.23, 0.001). The restricted cubic spline analysis showed a positive nonlinear dose-response relationship between lnRCII and BAA (nonlinearity <0.001).

Subgroup analysis results showed a positive association between lnRCII and BAA in all subgroups (0.05); there were interactions between lnRCII and BAA in the subgroups of sex, age, BMI, residence, and diabetes, and the associations were more pronounced in females, individuals aged<60 years, obese individuals, urban residents, and those with diabetes (interaction <0.05).

Conclusion

Among middle-aged and older Chinese adults, the Remnant Cholesterol Inflammatory Index (RCII) shows a significant positive nonlinear association with biological age acceleration (BAA). This association is particularly prominent in females, individuals aged under 60 years, obese individuals, urban residents, and those with diabetes. RCII is expected to become a key tool for community-based screening of high-risk populations for "premature aging" and for guiding targeted interventions to promote healthy aging. Aging is characterized by the accumulation of deleterious biological processes throughout the life course, which progressively increases an individual' s susceptibility to mortality [**?**]. Due to the high degree of individual heterogeneity in the aging process, chronological age cannot accurately reflect the true rate of senescence [**?**]. Consequently, Alex Comfort proposed the concept of biological age in 1969. Biological age quantifies the rate of aging by integrating lifestyle, genetic background, and overall health status, thereby providing a more precise measure of an individual' s physiological health than chronological age [**?**]. Furthermore, research has employed biological age acceleration (BAA)—defined as the difference between biological age and chronological age—to assess the extent to which an individual' s biological age deviates from their actual age.

Systemic chronic inflammation (SCI) is a chronic, low-grade, non-infectious state and is considered one of the hallmark features of aging [**?**]. Substantial evidence suggests that SCI is closely associated with various diseases, including hypertension, frailty, and various types of cancer, as well as an increased risk of mortality [**?**].

Remnant cholesterol (RC) refers to the cholesterol content of triglyceride-rich lipoproteins (TRLs) and serves as a reflection of lipid metabolism levels [**?**]. Previous studies have demonstrated that RC is associated with insulin resistance and metabolic disorders [**?**]. Against this background, the Remnant Cholesterol Inflammatory Index (RCII) has emerged as a novel biomarker that integrates the dimensions of both inflammation and metabolism [**?**]. This study aims to explore the association between RCII and biological aging to clarify the dose-response relationship between metabolic-inflammatory burden and senescence. The findings are intended to provide a new theoretical basis and practical guidance for the precision prevention and delay of biological aging.

1.1 资料

The data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS) database, a nationally representative longitudinal survey utilizing a multi-stage stratified sampling method. The baseline survey covered 17,705 individuals across 150 counties and 450 communities (villages) in 28 provinces (autonomous regions and municipalities), reflecting the overall status of the middle-aged and elderly population in China. Demographic and clinical information were collected through standardized questionnaires, with follow-up surveys conducted every 2 to 3 years to monitor health outcomes. The detailed research methodology and data collection procedures of CHARLS have been previously reported. For this study, 11,140 middle-aged and elderly individuals were selected from the 2011 and 2015 CHARLS databases; no additional follow-up was performed.

Key words: Ageing; Remnant cholesterol inflammatory index; Biological age acceleration; Middle-aged and older

Chinese General Practice. Demographic and clinical information was collected through standardized questionnaires. Subsequently, follow-up surveys were conducted every 2–3 years to monitor health outcomes. The detailed research methodology and data collection procedures of CHARLS have been reported in the literature. This study selected 11,140 middle-aged and elderly individuals from the 2011 and 2015 CHARLS databases as research subjects, without conducting additional follow-up.

This study was approved by the Institutional Review Board of Peking University (Approval No.: IRB00001052-11015), and all participants provided written informed consent.

The inclusion criterion was age $\geq$ 45 years. Exclusion criteria were: (1) missing data on gender, educational level, or marital status; (2) lack of data for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, high-sensitivity C-reactive protein (hs-CRP), triglycerides, glycated hemoglobin, blood urea nitrogen, platelet count, or systolic blood pressure.

1.2.1 RCII 的评估

RCII is calculated using the following formula: $RCII = [TC(mg/dL) - HDL\text{-}C(mg/dL) - LDL\text{-}C(mg/dL)] \times hs\text{-}CRP(mg/dL)$.

[**?**]. Due to the skewed distribution of RCII, a natural logarithm transformation (lnRCII) was applied for all statistical analyses. Based on the quartiles of lnRCII levels, the study subjects were divided into four groups: the Q1 group (lnRCII $\leq$ 0.97, n = 2,785), the Q2 group (0.97 $<$ lnRCII $\leq$ 2.36, n = 2,786), the Q3 group (2.36 $<$ lnRCII $\leq$ 6.19, n = 2,784), and the Q4 group (6.19 $<$ lnRCII, n = 2,785).

1.2.2 生物学年龄的评估

The Klemera-Doubal Method (KDM) was employed to assess composite biological age. This method integrates eight specific biomarkers: creatinine, high-sensitivity C-reactive protein (hs-CRP), total cholesterol (TC), triglycerides, glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), platelet count, and systolic blood pressure. The parameters for the KDM biological age (KDM-BA) algorithm were initially trained using data from the China Health and Nutrition Survey (CHNS) cohort and subsequently projected onto the China Health and Retirement Longitudinal Study (CHARLS) dataset [**?**]. This model has been validated within the CHARLS cohort, demonstrating significant potential for predicting all-cause mortality and chronic disease burden. Consequently, it has been widely adopted in numerous studies based on the CHARLS data [**?**].

Furthermore, this study calculated the Biological Age Advance (BAA) by determining the difference between an individual' s biological age and their chronological age. Aging is characterized by a biological age that increases more rapidly than chronological age. This acceleration significantly elevates the burden of chronic diseases in later life, thereby presenting a major challenge to public health.

1.2.3 协变量

Covariates included sociodemographic characteristics (age, sex, marital status, educational level, smoking status, alcohol consumption, and place of residence) and health indicators

indicators (hypertension, diabetes, cancer, cardiovascular disease, and BMI). Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or a self-reported diagnosis of hypertension. Diabetes was defined as fasting blood glucose $\geq$ 7.0 mmol/L, glycated hemoglobin (HbA1c) $\geq$ 6.5%, or a self-reported diagnosis of diabetes.

The presence of cancer and cardiovascular disease, as well as the use of lipid-lowering and glucose-lowering treatments, were determined based on the participants' self-reported information. All of these variables were

1.2.4 模型构建

In this study, multiple linear regression models were constructed to evaluate the association between ln $RCII$ and BAA. Three models were employed: Model 1 was an unadjusted model; Model 2 was adjusted for age and sex; and Model 3 was further adjusted for education level, marital status, place of residence, smoking status, alcohol consumption, hypertension, diabetes, cancer, cardiovascular disease, lipid-lowering therapy, glucose-lowering therapy, and BMI. Additionally, a restricted cubic spline model with four knots was used to evaluate the potential non-linear dose-response relationship between ln $RCII$ and BAA.

Subgroup analyses were conducted to examine the relationship between ln $RCII$ and BAA across different categories of sex (male/female), age (<60 years/$ $60 years), and BMI (underweight/normal/overweight/obese).

The association was further analyzed across subgroups defined by marital status (married/unmarried), place of residence (urban/rural), education level (primary school or below/secondary school/university or above), hypertension (yes/no), diabetes (yes/no), cancer (yes/no), and cardiovascular disease (yes/no). Interaction tests were performed to determine whether the association remained consistent across these various subgroups. These interaction tests were adjusted for covariates including age, sex, education level, marital status, place of residence, smoking status, alcohol consumption, hypertension, diabetes, cancer, cardiovascular disease, lipid-lowering therapy, glucose-lowering therapy, and BMI.

1.2.5 敏感性分析

To enhance the reliability and robustness of the findings, this study conducted a series of sensitivity analyses: (1) E-values for linear regression were calculated to quantify the potential impact of unmeasured confounding on the results; (2) participants receiving glucose-lowering or lipid-lowering treatments were excluded to reduce potential confounding related to pharmacological interventions; (3) participants aged 80 years and older were excluded to address the potential limitations of the Klemera-Doubal method biological age (KDM-BA) in extreme age groups; (4) quantile regression analysis was employed to evaluate the effects of ln $RCII$ across different quantiles of biological age acceleration (BAA) (τ = 0.1 to 0.9); (5) to address significant baseline differences after quartile grouping, participants in groups Q1–Q3 were combined into a "Non-Q4" group and subjected to 1:1 propensity score matching (PSM) with the Q4 group; and (6) statistical outliers, defined as those with an absolute standardized residual value > 3, were excluded.

Data processing was performed using R version 4.4.3. Continuous variables following a normal distribution are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), with intergroup comparisons conducted using one-way analysis of variance (ANOVA). Continuous variables with a non-normal distribution are expressed as median (interquartile range) $[M(Q_1, Q_3)]$, and intergroup comparisons were performed using the Kruskal-Wallis rank-sum test. Categorical data

are presented as frequencies or percentages, with intergroup comparisons analyzed using the χ^2 test.

A P-value < 0.05 was considered statistically significant.

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2 结果

Comparison of Baseline Characteristics Among Study Groups

A total of 11,140 participants were included in this study, with a median age of 57 (50, 65) years and a mean biological age of 57.8 ± 9.8 years. The cohort consisted of 4,970 males (44.61%) and 6,170 females (55.39%).

Statistically significant differences were observed among the four study groups across several variables ($P < 0.05$), including age, body mass index (BMI), educational level, place of residence, and the prevalence of hypertension, diabetes, and cardiovascular disease. Furthermore, significant differences were found regarding lipid-lowering therapy, glucose-lowering therapy, remnant cholesterol (RC), the remnant cholesterol index (RCII), ln(RCII), biological age, and biological age acceleration (BAA).

In contrast, no statistically significant differences were observed among the four groups ($P > 0.05$) in terms of sex, marital status, smoking status, alcohol consumption, or history of cancer.

4 节点限制性立方样条回归分析结果显示，lnRCII

There is a non-linear positive correlation between lnRCII and biological age acceleration (BAA), characterized by an overall S-shaped curve ($P < 0.001$). The inflection points for the effect of lnRCII were identified at -1.26 and 3.27. When lnRCII < -1.26, BAA exhibits a slow and steady upward trend as lnRCII increases. In the range of $-1.26 <$ lnRCII < 3.27, BAA shows a non-linear change, first accelerating and then decelerating as lnRCII rises; the growth rate peaks at lnRCII $= 0.82$ before gradually slowing down. When lnRCII > 3.27, the growth rate of BAA reaches its minimum, returning to a slow and steady upward trend, as shown in [Figure 1: see original paper].

Distribution and Specific Reference Ranges of lnRCII

This study further analyzed the distribution of lnRCII by sex and age groups (45 to <66 years, 66 to <80 years, and $\geq$ 80 years). Reference ranges were calculated based on the 2.5th and 97.5th percentiles, as detailed in .

Subgroup Analysis of the Correlation with lnRCII

Subgroup analysis results demonstrated a positive correlation between lnRCII and BAA across all subgroups ($P < 0.05$). Significant interactions were observed between lnRCII and BAA in subgroups defined by sex, age, BMI, place of residence, and diabetes status. Specifically, the associations were more pronounced among females, individuals aged <60 years, those with obesity, urban residents, and individuals with diabetes ($P < 0.05$). No significant interactions were found in subgroups based on marital status, educational level, hypertension, cancer, or cardiovascular disease ($P > 0.05$), as shown in .

Sensitivity Analysis

Sensitivity analyses further supported the robustness of the findings. (1) The E-value for linear regression was used to quantify the potential impact of unmeasured confounding on the results. For the continuous variable (lnRCII), the point estimate of the E-value was 0.57 for each 1-unit increase in lnRCII, with an E-value of 0.50 at the lower 95% confidence limit. For the quartile comparison (Q4 vs. Q1), the point estimate of the E-value was 2.20, with an E-value of 1.94 at the lower 95% confidence limit. These results suggest that an unmeasured confounder would need to be associated with both lnRCII (or the Q4 group) and BAA with an association strength of at least 0.52 (per 1 unit of lnRCII) or 2.20 (Q4 vs. Q1) to fully explain the observed association. These findings indicate that the results of this study are relatively robust against the influence of unmeasured confounding. (2) After excluding participants receiving glucose-lowering or lipid-lowering treatments, the results remained consistent with the primary analysis (Supplementary). (3) The association remained significant after excluding participants aged $\geq$ 80 years (Supplementary Table 3). (4) Quantile regression analysis was also employed to assess the relationship between BAA and lnRCII.

Note: Panel A represents a smoothed scatter plot, and Panel B represents the restricted cubic spline regression analysis; RCII = Residual Cholesterol Inflammation Index, BAA = Biological Age Acceleration.

The association between lnRCII and BAA

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Abstract

General practice (GP) serves as the cornerstone of the primary healthcare system, playing a vital role in maintaining public health and managing chronic diseases. This paper explores the current state, challenges, and future directions of general practice in China. By analyzing the integration of modern technologies, such as machine learning and deep learning, into clinical workflows, we aim to demonstrate how data-driven approaches can enhance diagnostic accuracy

and patient management. Furthermore, we discuss the importance of standardized training for general practitioners to ensure high-quality care across diverse regions.

Introduction

In recent years, the healthcare landscape in China has undergone significant transformation. The shift from hospital-centric care to a community-based primary care model has placed general practice at the forefront of medical reform. General practitioners are no longer merely "gatekeepers" but are essential providers of continuous, comprehensive, and coordinated care. As the burden of chronic diseases increases due to an aging population, the demand for efficient and effective general practice services has never been higher.

The Role of Advanced Technology in General Practice

The integration of digital health tools has revolutionized the way general practitioners interact with patients and manage health data. Specifically, the application of machine learning algorithms allows for the early detection of risk factors that were previously difficult to identify in a primary care setting.

For instance, predictive models can be used to assess the risk of cardiovascular events by analyzing longitudinal patient data. Consider a simplified model where the risk score R is calculated based on a set of clinical parameters x_i and their corresponding weights w_i:

$$R = \sum_{i=1}^{n} w_i x_i + \epsilon$$

In this context, ϵ represents the error term, and the weights w_i are optimized using large-scale datasets. By utilizing such models, general practitioners can implement personalized intervention strategies, thereby improving patient outcomes.

Challenges in Current Practice

Despite the progress made, several challenges persist in the field of Chinese general practice. One of the primary issues is the uneven distribution of medical resources between urban and rural areas. While top-tier cities benefit from advanced facilities and highly trained staff, rural clinics often face shortages of both equipment and personnel.

As shown in , the ratio of general practitioners per 10,000 inhabitants varies significantly across different provinces. This disparity highlights the need for policy interventions and increased investment in medical education to

a <0.001

57.0 (49.0, 64.0) 58.0 (49.0, 65.0) 57.0 (50.0, 65.0) 58.0 (50.0, 65.0), kg/m

b <0.001

a <0.001

), mg/dL] 10.82 (6.57, 16.24) 19.72 (14.30, 26.68) 25.87 (18.92, 35.14) 37.11 (24.36, 55.67)

a <0.001

RCII [0.51 (0.31, 0.73) 1.54 (1.23, 1.92) 3.67 (2.95, 4.69) 12.72 (8.49, 24.29)

b <0.001

Biological age (56.1 ± 9.5, 57.4 ± 9.7, 58.2 ± 9.7, 59.4 ± 9.9)

b <0.001

a <0.001

-1.85 (-3.31, 0.11), -1.09 (-2.65, 0.60), -0.41 (-2.05, 1.40), and 0.20 (-1.66, 2.23). The residual test statistic was χ^2. Note: RC = residual cholesterol; RCII = residual cholesterol inflammation index; BAA = biological age acceleration.

Multiple linear regression analysis was conducted to examine the correlation between ln $RCII$ and BAA. Using the ln $RCII$ quartile groups (with the Q1 group as the reference), we further evaluated the effects of ln $RCII$ across different quantiles of BAA ($\tau = 0.1$ to 0.9). The results remained largely consistent (see Supplementary Figure 1). Furthermore, the Q1–Q3 groups were merged into a single "Non-Q4" group to be compared against the Q4 group for subsequent analysis.

1 倾向性评分匹配（附

Significant (Supplementary Table 5). (6) After excluding outliers with absolute standardized residuals greater than 3, the results remained largely consistent (Supplementary Table 6). Please scan the QR code on the first page of the article to access the relevant supplementary tables.

3 讨论

In this cross-sectional study of 11,140 middle-aged and elderly Chinese adults, we identified a positive non-linear relationship between lnRCII and biological age acceleration (BAA). This association was particularly pronounced among women, urban residents, patients with diabetes, and individuals with a high BMI. Our findings suggest that by integrating inflammatory and metabolic risk factors, the RCII is closely associated with accelerated aging and can serve as an indicator for assessing biological aging and identifying the risk of age-related diseases.

The RCII is a composite biomarker that integrates the dual dimensions of inflammation and metabolism. Although previous studies have confirmed the predictive value of RCII in cardiovascular and metabolic diseases, this study demonstrates a robust association between RCII and biological aging. Derived from C-reactive protein (CRP) and remnant cholesterol (RC), the RCII provides a comprehensive assessment of the body' s metabolic-inflammatory burden. As a marker of systemic chronic inflammation, CRP levels increase with age. This elevation has been linked to various adverse health outcomes, including a decline in basic activities of daily living, obesity, hypertension, and a reduced probability of successful aging [**?**]. The senescence-associated secretory phenotype (SASP) promotes chronic inflammation and induces senescence in normal cells. Furthermore, chronic inflammation weakens the ability of immune cells to clear senescent cells and inflammatory factors by accelerating immune cell senescence, thereby creating a vicious cycle of "inflamm-aging." The continuous accumulation of this chronic inflammation in key organs such as the bone marrow, liver, and lungs leads to progressive organ damage and ultimately promotes the development of age-related diseases [**?**]. Lipid metabolism disorders are not only associated with age-related diseases but also regulate the process of cellular senescence. Lipid droplet accumulation is observed in senescent cells. A study in mice found that dyslipidemia during aging is primarily characterized by elevated TC, LDL-C, and triglycerides, and decreased HDL-C, and that physical exercise can effectively improve these lipid metabolism abnormalities. Lipid metabolism is closely related to the secretion process of SASP, which in turn exacerbates chronic inflammation to drive aging [**?**]. RC has been reported to have a strong positive correlation with accelerated biological aging. Additionally, the interaction between inflammation and metabolic disorders forms a vicious cycle: inflammation exacerbates insulin resistance and vice versa, synergistically accelerating the physiological decline of multiple organs [**?**]. Consistent with previous research on the effects of aging, our results show a positive correlation between RCII and BAA, suggesting a close link between metabolic-inflammatory burden and the aging process.

The restricted cubic spline (RCS) model results in this study indicate that the positive association with BAA is more pronounced when lnRCII is within the range of approximately -1.26 to 3.27.

Note: Model 1 is unadjusted; Model 2 is adjusted for age and sex; Model 3 is further adjusted for education level, marital status, place of residence, smoking status, alcohol consumption, hypertension, diabetes, cancer, cardiovascular disease, lipid-lowering therapy, glucose-lowering therapy, and BMI based on Model 2.

Gender-age distribution and specific reference cut-off values of lnRCII: Gender-age groups: 45 to <66 years, 0.85 (-1.67, 4.00); 66 to <80 years, 0.82 (-1.90, 3.99); $ $80 years, 1.10 (-1.32, 4.61). 45 to <66 years, 0.81 (-1.81, 3.69); 66 to <80 years, 1.07 (-1.53, 4.21); $ $80 years, 1.09 (-1.54, 4.56).

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Sex: $P < 0.001$

Male: $n = 4,970$ (44.61%), 0.13 (0.07–0.18), $P < 0.001$

Female: $n = 6,170$ (55.39%), 0.45 (0.41–0.48), $P < 0.001$

Age: $P < 0.001$

<60 years: $n = 6,904$ (61.97%), 0.32 (0.28–0.36), $P < 0.001$

$ $60 years: $n = 4,236$ (38.03%), 0.25 (0.19–0.31), $P < 0.001$

BMI <0.001

Normal weight: 5,644 (50.66%), 0.22 (0.18–0.27), $P < 0.001$

Overweight: 3,453 (31.00%), 0.38 (0.32–0.43), $P < 0.001$

Obese: 1,382 (12.41%), 0.39 (0.29–0.49), $P < 0.001$

Primary school and below: 8,552 (76.77%), 0.28 (0.24–0.32), $P < 0.001$

Secondary school: 2,462 (22.1%), 0.30 (0.23–0.37), $P < 0.001$

Married: 9,832 (88.26%), 0.29 (0.26–0.33), $P < 0.001$

Unmarried: 1,308 (11.74%), 0.23 (0.14–0.33), $P < 0.001$

Urban: 2,330 (20.92%), 0.36 (0.28–0.43), $P < 0.001$

Rural: 8,810 (79.08%), 0.27 (0.23–0.30), $P < 0.001$

Yes: 4,435 (39.81%), 0.30 (0.24–0.36), $P < 0.001$

No: 6,705 (60.19%), 0.29 (0.26–0.33), $P < 0.001$

Yes: 1,909 (17.14%), 0.38 (0.29–0.46), $P < 0.001$

No: 9,231 (82.86%), 0.26 (0.23–0.30), $P < 0.001$

No: 11,027 (98.99%), 0.29 (0.25–0.32), $P < 0.001$

Yes: 1,405 (12.61%), 0.32 (0.22–0.42), $P < 0.001$

No: 9,735 (87.39%), 0.28 (0.25–0.31), $P < 0.001$

Note: Subgroup analyses and interaction tests were adjusted for age, sex, educational level, marital status, residence, smoking status, alcohol consumption, hypertension, diabetes, cancer, cardiovascular disease, lipid-lowering therapy, glucose-lowering therapy, and BMI.

This critical interval overlaps extensively with the conventional reference ranges for each subgroup shown in Table 3. This suggests that even when an individual' s ln(RCII) levels are within the conventional reference range, fluctuations in these values may still be associated with an increased risk of accelerated aging. Consequently, in clinical practice, attention should be paid not only to abnormal RCII levels; proactive management of the metabolic-inflammatory burden within the "normal" range may also be of potential significance for healthy aging.

The subgroup analysis results of this study indicate that the association between ln(RCII) and biological age acceleration (BAA) is more pronounced among individuals who are female, aged < 60 years, obese, urban residents, or diabetic ($P < 0.05$). These findings can be interpreted through various biological mechanisms.

For women, estrogen exerts critical protective effects on the cardiovascular, nervous, and skeletal systems through its anti-inflammatory and antioxidant activities; however, the sharp decline in estrogen levels post-menopause is associated with a significant acceleration of vascular and brain aging, leading to an aging rate in women that eventually surpasses that of men [**?**]. For urban residents, the potential mechanism may lie in the higher risk of chronic exposure to fine and ultrafine particulate matter, which has been shown to accelerate the aging process by exacerbating systemic inflammation [**?**]. In patients with diabetes, the condition is characterized by chronic low-grade inflammation and insulin resistance [**?**]; these two states reinforce each other, creating a vicious cycle that collectively drives accelerated aging. Similarly, obesity, as a known factor in accelerated aging, promotes senescence through chronic inflammation and oxidative stress [**?**]. Notably, at the molecular level, each unit increase in BMI is associated with a shortening of telomere length by approximately 4 base pairs.

Several limitations of this study should be acknowledged. (1) Due to the cross-sectional design, this study cannot establish a causal relationship between RCII and biological aging. Future longitudinal or prospective cohort studies are needed to clarify the temporal sequence. (2) Even after adjusting for relevant confounders, the influence of other potential covariates (such as the use of anti-inflammatory drugs or other comorbidities) cannot be entirely excluded, as CHARLS did not collect this detailed information. (3) This study did not assess biological age at the molecular level, relying instead solely on clinical biochemical indicators. (4) The training dataset for the KDM-BA algorithm (CHNS) has an upper age limit of 79 years, whereas this study included some individuals aged 80 and older. Although sensitivity analyses showed that the primary associations remained robust after excluding this population, the performance of the KDM algorithm in the oldest-old may be limited by complex factors such as the non-linearity of physiological changes. Furthermore, the KDM algorithm based on limited biomarkers may not fully represent the complete landscape of individual aging; future validation using multi-omic aging clocks is required. (5) The study population was limited to middle-aged and older adults, which restricts the extrapolation of the results to younger populations. (6) The exclusion of individuals with missing data may affect the generalizability of the results and introduce potential selection bias.

In summary, there is a significant positive non-linear association between RCII and BAA among middle-aged and older adults in China, and this association is particularly prominent in women, individuals aged < 60 years, those with obesity, urban residents, and patients with diabetes. This highlights the potential of RCII as a simple and effective biomarker for assessing the risk of accelerated

aging. Therefore, RCII is expected to become a key tool for community screening of high-risk populations for "premature aging" and for guiding targeted interventions to promote healthy aging.

Author Contributions: Zhang Shuaishuai proposed the primary research objectives, was responsible for the conceptualization and design of the study, and wrote the manuscript; Zhang Shuaishuai and Chen Yue performed data collection, organization, and statistical analysis; Chen Yue and Qiu Jiaojiao refined the drawing and presentation of figures and tables; Zhu Ping performed the revision of the manuscript; Wang Shuxia was responsible for quality control and review of the article and takes overall responsibility for the work.

The authors declare no conflicts of interest.

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Inflammation and Activities of Daily Living Disability Among Chinese Elderly Individuals: The Mediating Role of Handgrip Strength

Abstract

Objective: To investigate the relationship between inflammation and activities of daily living (ADL) disability among the elderly population in China, and to analyze the potential mediating role of handgrip strength in this association.

Methods: This study utilized data from a longitudinal cohort of Chinese elderly individuals. Inflammatory markers, specifically C-reactive protein (CRP), were measured alongside assessments of handgrip strength and ADL status. ADL disability was defined based on standardized scales measuring basic and instrumental activities. Statistical analyses, including mediation modeling, were employed to determine the direct and indirect effects of inflammation on functional disability.

Results: Higher levels of inflammation were significantly associated with an increased risk of ADL disability. Furthermore, reduced handgrip strength was identified as a significant mediator in this relationship. The findings suggest that

chronic low-grade inflammation may contribute to functional decline partly by reducing muscle strength.

Conclusion: Inflammation is a critical risk factor for ADL disability in the Chinese elderly population. Handgrip strength serves as a key mediator, suggesting that interventions aimed at reducing inflammation or maintaining muscle strength may help mitigate the risk of functional disability in older adults.

Introduction

As the global population ages, maintaining functional independence in later life has become a primary public health priority. Activities of daily living (ADL) disability is a significant indicator of functional decline, often leading to a reduced quality of life, increased healthcare costs, and higher mortality rates. In China, the rapid pace of population aging necessitates a deeper understanding of the biological and physiological mechanisms underlying disability.

Chronic low-grade inflammation, often referred to as "inflammaging," is a hallmark of the aging process. Elevated levels of pro-inflammatory markers, such as C-reactive protein (CRP), have been linked to various age-related pathologies, including cardiovascular disease, sarcopenia, and cognitive impairment. Recent evidence suggests that inflammation may also play a direct role in the development of physical disability.

One proposed mechanism for this link is the deleterious effect of inflammation on skeletal muscle. Pro-inflammatory cytokines can promote muscle protein degradation and inhibit muscle synthesis, leading to decreased muscle mass and strength. Handgrip strength, a simple and reliable proxy for overall muscular strength, has been consistently associated with functional status and mortality in older adults. However, the extent to which handgrip strength mediates the relationship between systemic inflammation and ADL disability remains to be fully elucidated in the

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Note: Figure translations are in progress. See original paper for figures.