ARTÍCULO DE REVISIÓN

Measurement of biological age with biomarkers: A scoping review

Medición de la edad biológica con biomarcadores: una revisión de alcance

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Abstract

Introduction: Studies related to the mechanisms of senescence have allowed the identification and quantification of biomarkers of biological aging. However, the available information is scattered, and there is no uniform definition of the concept. We aimed to overview the current approaches to measuring biological age using biomarkers and summarize the evidence. **Methods**: We use the five-phase methodology developed by Arksey and O'Malley. A comprehensive search was performed in five databases up to March 27, 2023. Original articles that described methods for measuring biological age using ≥2 biomarkers in individuals aged ≥18 years were included, with no restrictions on language or publication date. **Results:** We included 90 articles from 15 countries that were published as early as 1974. Most were observational, utilizing biomarkers ranging from 3 to 900. Eleven methods for calculating composite biological age were described: principal component analysis, Klemera-Doubal, and multiple linear regression analysis being the most used. The outcomes focused on specific risk factors, comorbidities, physical or cognitive functionality, and mortality. The prognostic validity of biological age was assessed by examining its association with mortality risk, highlighting its superior predictive power compared to chronological age or traditional age-related disease biomarkers. **Conclusion:** We conclude that scientific literature exhibits considerable heterogeneity in number and type of biomarkers employed, as well as the methods used to estimate biological age. Currently, there is no universally accepted standard for assessing biological age, and there is lack of research examining its reproducibility and prognostic validity.

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Resumen

Introducción: Los estudios relacionados con los mecanismos del envejecimiento han permitido la identificación y cuantificación de biomarcadores del envejecimiento biológico. Sin embargo, la información disponible está dispersa y no existe una definición uniforme del concepto. Nuestro objetivo fue revisar los enfoques actuales para medir la edad biológica utilizando biomarcadores y resumir la evidencia. **Métodos:** Utilizamos la metodología de cinco fases desarrollada por Arksey y O'Malley. Se realizó una búsqueda exhaustiva en cinco bases de datos hasta el 27 de marzo de 2023. Se incluyeron artículos originales que describían métodos para medir la edad biológica utilizando ≥2 biomarcadores en individuos mayores de ≥18 años, sin restricciones de idioma o fecha de publicación. **Resultados:** Se incluyeron 90 artículos de 15 países, publicándose el primero en 1974. La mayoría fueron observacionales, utilizando desde 3 hasta 900 biomarcadores. Se describieron once métodos para calcular la edad biológica compuesta: el análisis de componentes principales, Klemera-Doubal y el análisis de regresión lineal múltiple, fueron los más utilizados. Los resultados se centraron en factores de riesgo específicos, comorbilidades, funcionalidad física o cognitiva y mortalidad. La validez pronóstica de la edad biológica se evaluó examinando su asociación con el riesgo de mortalidad, destacando su poder predictivo superior en comparación con la edad cronológica o los biomarcadores de enfermedades tradicionales relacionadas con la edad. **Conclusión:** Concluimos que la literatura científica exhibe una considerable heterogeneidad en el número y tipo de biomarcadores empleados, así como en los métodos utilizados para estimar la edad biológica. Actualmente, no existe un estándar universalmente aceptado para evaluar la edad biológica, y falta investigación que examine su reproducibilidad y validez pronóstica.

Palabras clave: Edad biológica; Enfermedades crónicas; Longevidad; Biomarcadores; Revisión sistemática, envejecimiento.

Introduction

Aging is a multidimensional phenomenon, and chronological age is just one of its relevant dimensions **(1)**. Conventional measures of aging tend to overlook other important aspects, such as health and physiological function **(2)**. With the improvement of health services, medical advancements, and technological progress, the population pyramid is being inverted, with adults over 65 years of age now comprising 10% of the global population **(3)**. This shift can be attributed to increased life expectancy, which has consequently resulted in a higher prevalence of frailty, disability, and chronic noncommunicable diseases associated with age-related physiological decline **(4)**. Consequently, there has been a growing need for research focused on understanding and quantifying the ageing process **(5)**.

Studies exploring the mechanisms of ageing have identified and measured early markers of biological decay, offering valuable insights for the development of preventive and therapeutic strategies **(6)**. These markers encompass various indicators of advancing age, including: i) external physical manifestations of aging **(7)**; ii) morphological and physiological modifications of different organs **(8)**; iii) neuropsychological changes **(9)**; iv) phys-

ical work capacity **(10)**; and v) biochemical and clinical markers **(11)**. It is worth noting that there are additional measurements, such as frailty indices, deficit accumulation scores, multimorbidity scores, multifactorial risk indices, and prognostic indices, which are beyond the scope of this work **(11)**. These biomarkers serve as composite measures of the senescence process, which often occurs asynchronously with chronological age.

In the scientific literature, different methods of quantifying biological age have been described. These methods range from composite estimates that include multiple biomarkers pointing at measurable and quantifiable biological parameters, serving as indices for assessing health and physiology **(12)**. However, the information on this topic is dispersed throughout the literature **(13)**, lacking a unified definition of biological age **(14)** and a consensus on the optimal biomarkers to be included **(15)**. Moreover, methodologies for assessing biological age have evolved over time **(16)**, yet there is a surprising lack of validation studies supporting their use **(17)**. Therefore, the objective of this scoping review is to provide a comprehensive characterization of the measurement of biological age using multiple biomarkers in the general population, including the methods employed, the selection of biomarkers, the types of research designs utilized, and the validation of the estimates. By identifying gaps in the existing literature, this review also offers suggestions for future research priorities in this field.

"There is no universally accepted standard for assessing biological age, and there is a lack of research examining its reproducibility and prognostic validity"

Methods

Study design

This scoping review was conducted following the five-phase methodology developed by Arksey and O'Malley **(18)**. Unlike a systematic review, a scoping review is employed to explore relatively new or emerging concepts, aiming to identify the breadth of evidence, key concepts, and core factors related to the topic, while also highlighting knowledge gaps and suggesting future research directions **(19)**. The findings of this study are presented in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines, specifically the extension for scoping reviews (PRISMA-ScR), which includes a checklist and explanation **(20)**. It should be noted that this systematic review did not have a pre-registered protocol.

Eligibility criteria

The research question for this study was formulated using the Population, Intervention, Comparison, and Outcome (PICO) framework, aiming to identify composite biomarker predictors of biological age in the general population. Thus, the research question of this study was: "What is the existing knowledge on the measurement of biological age using multiple biomarkers in the general population?" This scoping review included observational studies, clinical trials, systematic reviews, and meta-analyses involving individuals aged 18 years and older, without restrictions on previous medical history or associated conditions. However, studies specifically focused on a particular medical condition were excluded.

Information sources

A systematic three-step search strategy was implemented to identify relevant literature published up to March 27, 2023. Firstly, the PubMed database was searched using key terms and MeSH terms such as "biological age," "biological aging," "measure," and "biomarker." Secondly, five databases including PubMed, CINAHL, Embase, SCOPUS, and Cochrane Central were searched

for relevant published articles. There were no restrictions on publication date or language. The search terms used in this step included "biological age," "biological aging," "measure," "quantification," "evaluation," "assessment," "estimation," and "biomarker."

Search

For each database, specific search parameters were applied, including keywords and specifiers for time, language, and types of study. The search strategies used for each database are as follows:

PubMed: ((biological age[Title/Abstract] OR biological aging[Title/Abstract]) AND ((measure[Title/Abstract] OR quantification[Title/Abstract] OR evaluation[Title/Abstract] OR assessment[Title/Abstract]) OR (biomarker[Title/Abstract]))).

CINAHL: ((AB(biological age OR biological aging)) AND (AB((measure OR quantification OR evaluation OR assessment OR estimation) OR (biomarker)))).

Embase: ('biological age':ab,ti OR 'biological aging':ab,ti) AND (measure:ab,ti OR quantification:ab,ti OR evaluation:ab,ti OR assessment:ab,ti OR estimation:ab,ti OR biomarker:ab,ti) AND ([systematic review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [controlled clinical trial]/lim) AND [1900-2021]/py.

SCOPUS: ((TITLE(biological AND age) OR TITLE (biological AND aging)) AND ((TITLE-ABS (measure) OR TITLE-ABS (quantification) OR TITLE-ABS (evaluation) OR TITLE-ABS (assessment) OR TITLE-ABS (estimation) OR (TITLE-ABS (biomarker))))) AND (LIMIT-TO (DOCTYPE, "ar")).

Cochrane Library: ((biological age): ti OR (biological aging): ti) AND (((measure): ti, ab, kw OR (quantification): ti, ab, kw OR (evaluation): ti, ab, kw OR (assessment): ti, ab, kw) OR (estimation): ti, ab, kw) OR (biomarker): ti, ab, kw).

Furthermore, additional articles were identified by manually searching the reference lists of the included studies. Please refer to **Figure 1** for more details.

Selection of sources of evidence

Studies meeting the following criteria were included in the review: i) described the measurement of biological age using more than two clinical or paraclinical variables; ii) involved subjects older than 18 years, with or without previous medical history; iii) classified as observational studies, clinical trials, systematic reviews, or meta-analyses. Studies were excluded if they: i) described measurements not related to biological age or described a single marker; ii) did not refer to the direct assessment of biological age; iii) referred only to organ measurements instead of general measurements; and iv) were specifically related to the prognosis of a single condition.

Data recording process

To record the data, electronic databases from the Google system were accessed and the search results were reviewed. One researcher (DAEF) filled out the data extraction forms based on the predefined inclusion criteria. The extracted information was then reviewed by a second researcher (AMPC) to identify any inconsistencies. Any discrepancies or disagreements were resolved through discussion and consensus between the two researchers.

Extracted and evaluation of sources of evidence

The following information was collected from each of the included articles: i) article title; ii) Digital Object Identifier (DOI); iii) year of publication; iv) name of the main author; v) language of publication; vi) country and affiliation of the main author; vii) type of methodological design viii); description of data collection; ix) stated main objective; x) mathematical or standardized method used to estimate biological age; xi) number of patients included; xii) general characteristics of the

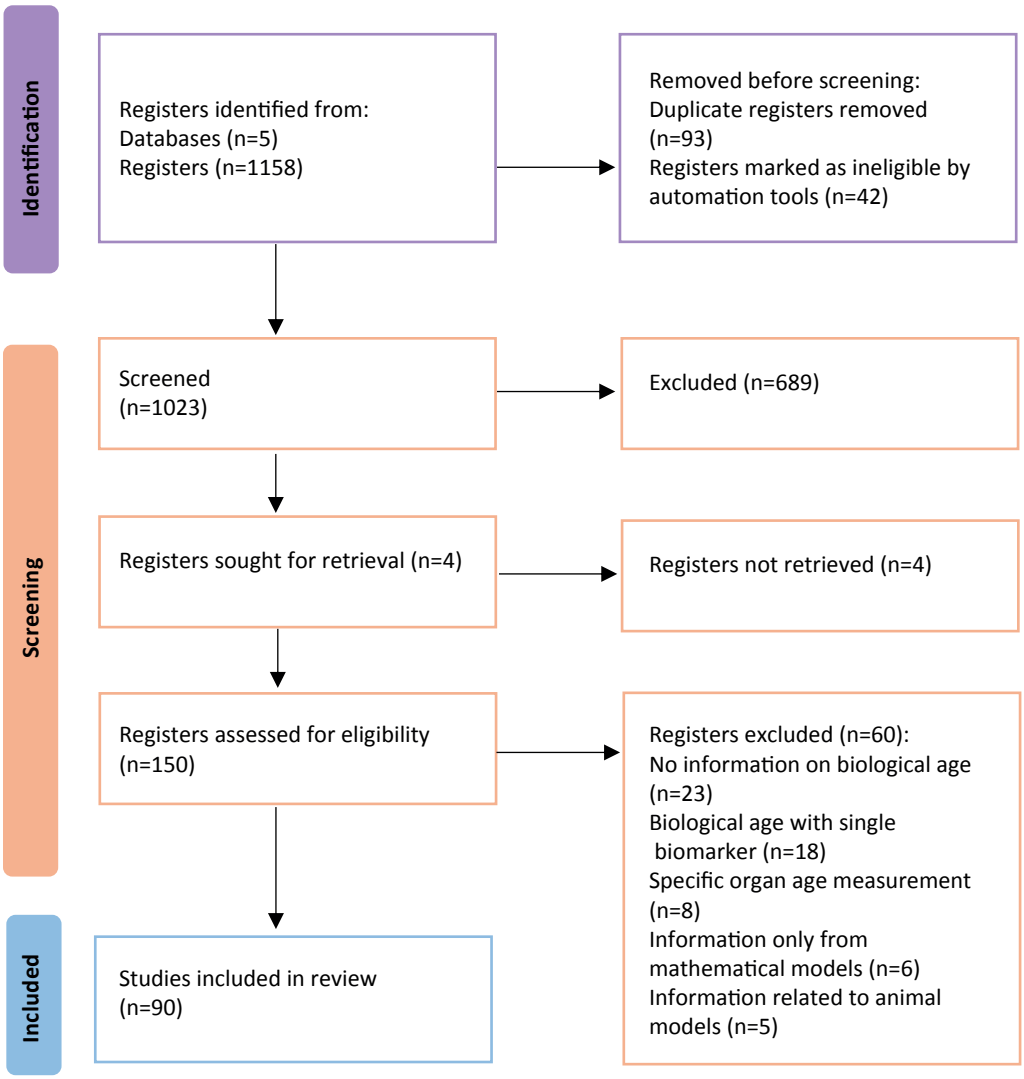


Figure 1. A PRISMA flow chart of study selection process in the scoping review.

population; xiii) average age of participants; xiv) percentage of women included; xv) average biological age; xvi) for clinical trials, the type of intervention performed and its respective comparison; xvii) validity criteria of the estimation method; xviii) evaluation of reproducibility xix); number and type of biomarkers used to estimate composite biological age; xx) expected outcome; xxi) main findings reported; and xxii) relevant comments raised by the researcher.

Summary of results

The studies were categorized based on the search engine and year of publication to extract the relevant information. They were further grouped according to the type of study design and the mathematical or standardized method employed to estimate biological age. Information from each article was then extracted and recorded in the designated database, following the predefined characteristics.

Results

A total of 15 nationalities were represented in the articles found, spanning from 1974 to the present. The first article originated from Finland (n=1; 1%) **(21)**, while others were from Germany (n=4; 5%) **(22–25)**, Australia (n=1; 1%) **(26)**, Canada (n=3; 3%) **(27–29)**, China (n=13; 15%) **(30–42)**, Korea (n=10; 11%) **(43–52)**, United States (n=24; 26%) **(53–75)**, England (n=3; 3%) **(76–78)**, Japan (n=8; 9%) **(79–86)**, Poland (n=1; 1%) **(87)**, Czech Republic (n=2; 2%) **(88,89)**, Russia (n=11; 12%) **(88,90–99)**, Singapore (n=2; 2%) **(100,101)** Switzerland (n=1; 1%) **(102)**, Ukraine (n=1, 1%) **(103)**, Italy (n=3; 3%) **(104–106)**, Taiwan (n=1; 1%) **(107)**, Denmark (n=1; 1%) **(108)**, Israel (n=1; 1%) **(109)**, and Mexico (n=1; 1%) **(110)**.

Authors with multiple publications included Nakamura, E. (n=6) **(59–62,64,65),** Belsky, D.W. (n=4) **(41,44,45,57)**, Jee, H. (n=3) **(26,29,31)**, Zhang, W.G. (n=3) **(13–15)**, Pyrkov, T.V. (n=2) **(73,74)**, Bae, C. (n=3) **(23,27,32)**, Liu, Z. (n=2) **(17,50)**, and Graf, G.H. (n=2) **(52,55)** Most articles were published in English (n=84; 93%) **(21,25–59,61–83, 85–89, 93, 94, 96, 98–101, 103–115),** while a few were in Russian (n=5; 6%) **(90–92, 95, 97)**, German (n=1; 1%) **(116)**, and Japanese (n=1; 1%) **(84)**. In terms of study type, one nonrandomized clinical trial was found (n=1; 1%) **(102)**, along with 12 prospective cohort observational studies (n=12; 13%) **(29, 37, 38, 55, 70, 73, 75, 76, 78, 89, 103, 107)**, 45 observational retrospective cohort studies (n=46; 50%) **(25, 27, 28, 31, 36, 40–45, 49, 51–54, 56–59, 61–69, 71, 72, 74, 77, 80–82, 93, 94, 100, 101, 106, 109–112)**, and 33 cross-sectional observational studies (n=33; 37%) **(21, 26, 32–35, 39, 46–48, 50, 79, 83–88, 90–92, 95–99, 104, 105, 108, 113–116)**. The most frequently used methods to calculate biological age were principal component analysis (PCA) (n=25; 28%) **(26, 28, 34, 35, 39, 44–52, 56, 79–82, 85, 86, 93, 94, 101, 108, 113)**, the Klemera-Doubal method (KDM) (117) (n=32; 36%) **(25, 36, 37, 39, 42, 46, 48, 49, 54–57, 59, 61, 62, 64, 65, 67–69, 72–75, 77, 78, 88, 89, 100, 101, 109, 118)**, multiple linear regression analysis (MLRA) (n=22; 25%) **(21, 23, 24, 30–32, 39, 46–49, 51, 76, 83, 84, 87, 94, 101, 103, 104, 111, 115)**, the Levine method **(119)** (n=6, 7%) **(53,66–69,77)**, the formula of Voitenko, V. **(120)** (n=4; 4%) **(90,92,97,99)**, the BioAge scale **(121)** (n=4; 4%) **(29,92,98,107)**, the formula of Belozerova, L. **(122)** (n=2; 2%) **(90,96)**, functional biological age (fBioAge) **(123)** (n=1; 1%) **(63)**, Hochschild method **(115)** (n=1; 1%) **(48)**, Podkolzin, A. **(124)** (n=1; 1%) **(95)**, machine learning (n=2; 2%) **(36,40)**, deep neural network (n=2; 2%) **(105,106)**, and novel methods (n=13; 15%) with specific recommendations without specifying the mathematical procedure performed **(31, 33, 38, 43, 51, 58, 66, 75, 87, 94, 101–103, 110, 112)**.

The highest number of biomarkers applied in an article was 900, including genomic, proteomic, and metabolomic measures **(56)**, while the lowest number was 3, encompassing strength, memory, and vibrotactile sensitivity **(103)**. On average, 28 features were included, with a median of 9 and a mode of 9 biomarkers.

The developed methods incorporated a wide range of biomarkers based on the expected outcome, and most studies demonstrated significant variation in aging estimates. The variables included in these methods encompassed various individual characteristics, such as the presence of gray hair, baldness, and cutaneous elasticity **(76)**, personal history of smoking or chronic noncommunicable diseases **(94,100)**, anthropometric measures such as weight, height, and body mass index **(21,33,38,42,52,87,90,96,101,109,110,113)**, vital signs like blood pressure and heart rate, hematological, metabolic, renal, inflammatory, and infectious parameters **(23, 25, 27–29, 32, 34–36, 39, 41, 43, 45–47, 49–51, 53–55, 57–59, 61, 62, 64–67, 69, 72–75, 77–85, 88, 90–92, 96, 98, 100, 101, 105–107, 120)**, molecular tests such as telomere length and methylation **(33, 71)**, neuromuscular capacity including grip strength, gait speed, and monopodal balance **(23, 26, 28, 37, 48, 51, 78,**

86, 100, 101, 103, 104, 112, 118), musculoskeletal characteristics like muscle mass and bone mineral density, lung capacity assessed through forced expiratory volume, forced vital capacity, and maximum oxygen consumption **(26, 38, 39, 42, 46, 47, 49–51, 57–59, 61–63, 65, 73, 74, 78, 80–82, 88, 89, 101, 108, 115, 118)**, cardiovascular and arterial characteristics such as pulse pressure, intima media thickness, and ankle-brachial index **(27, 32–35, 43, 92)**, basic neuropsychological tests including minimental, verbal memory, and semantic fluency **(23, 48, 100, 101, 103, 115, 118)**, basic neurological sensitivity assessed with visual and auditory acuity (**26, 28, 83, 85, 98, 112, 114)**, and self-reports such as perceived health and perception of vision or hearing **(54, 63, 90, 98)**. These variables collectively contributed to estimating biological age in different studies.

The studies included a considerable number of participants, with an average of 173,467 patients. The minimum number of participants in a study was 15 **(104)**, while the maximum number reached 6,518,532 **(43)**. On average, the percentage of women included in the studies was 45%. The participants consisted of healthy adults, volunteers, or frequent visitors to community health centers where the research was conducted. The reported mean age varied across studies, with an average reported mean age of 48 years. The minimum age reported was 18 **(34, 55, 68, 92–94, 113)**, while the maximum age reached up to the tenth decade of life **(67)**. Participants were often described as healthy adult volunteers or individuals from retrospective and prospective cohorts of longitudinal studies.

The research objectives of the included studies were diverse but primarily focused on examining the association between biological age and measured biomarkers **(30, 32, 47, 54, 60, 78, 82, 88, 90),** risk factors **(40, 43, 51, 81, 100, 101, 107),** comorbidities **(44, 52, 53, 56, 57, 86, 93, 118),** physical functionality **(43, 54, 61, 65, 72, 79, 87)**, and mortality **(25, 31, 36–38, 41, 42, 44, 45, 53, 54, 67, 70–72, 74, 76, 93, 94, 109, 110)**.

In most articles, biological age was not specified as an absolute value or compared with chronological age. Instead, it was analyzed in relation to different outcomes based on the authors' preferences, although the reasons for their choices were not explicitly stated.

Prognostic validity was assessed in 21 studies that considered mortality as an outcome. These studies found that a higher biological age was associated with an increased risk of mortality, particularly for all-cause mortality **(25, 31, 36–38, 41, 42, 44, 45, 53, 54, 67, 70–72, 74, 76, 93, 94, 109, 110)**. This association remained significant even after adjusting for sex and chronological age **(31)**. The use of biological age showed a stronger association with mortality compared to chronological age or traditional biomarkers of age-related diseases **(25, 31, 36–38, 41, 42, 44, 45, 53, 54, 67, 70–72, 74, 76, 93, 94, 109, 110)**.

Regarding internal validity, only one study out of the 89 included articles specifically analyzed it **(57)**. This study compared a biological age algorithm using nine versus ten biomarkers and found similar results for risk ratios and model performance **(57)**. Reproducibility analysis was not reported in any of the studies.

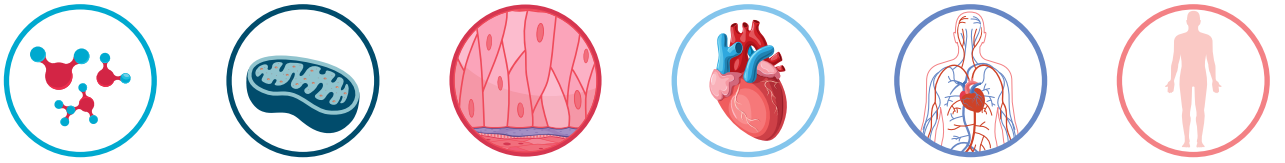
Some specific findings from the included studies were as follows: biological age was found to increase with tobacco or alcohol consumption habits **(43,107)**. It also increased with sedentary lifestyle or low fruit intake **(100)**, while greater physical activity **(79)** or participation in wellness programs were associated with decreased biological age **(56)**. Biological age was related to impaired cognitive ability **(53)**, fragility **(101)**, all-cause morbidity **(25, 37, 38, 52, 74)**, dental health **(111)**, and the incidence of chronic diseases such as metabolic syndrome, cerebrovascular accidents, cancer, or diabetes mellitus **(25, 37, 38, 44, 52, 74)**. It was also associated with disability **(36)**, emergency room visits, hospitalization **(118)**, and survival **(45)**. Higher biological age was linked to lower self-reports of health status and older physical appearances **(58)**. Metabolites such as amino acids,

fatty acids, acylcarnitine, sphingolipids, and nucleotides were frequently associated with the rate of biological aging **(55)**. Furthermore, 481 genes were identified to be significantly associated with biological age **(59)**. Measures of biological age were found to predict physical, cognitive, and mortality outcomes, although the performance of different methods varied depending on the specific study **(54, 101)**. Among the interventions described, double filtration plasmapheresis was found to reduce biomarkers of aging **(30)**.

It is important to note that these findings are based on the available literature and should be interpreted in the context of each study's design and methodology.

Discussion

In this scoping review, the focus was on the measurement of biological age using composite biomarkers. A total of 90 relevant original articles were identified, and various methods were employed for estimating biological age, with PCA being the most frequently applied method, followed by KDM and MLRA. The median number of biomarkers to estimate biological age was 9. These biomarkers encompassed a wide range of variables, including personal traits, anthropometric measurements, laboratory tests, neuromuscular, musculoskeletal, neuropsychological, pulmonary, cardiovascular characteristics, as well as tissue, cell, or molecular features (**Figure 2**).



Molecule	Cell	Tissue	Organ	System	Whole organism characteristics
Telomere length	Proinflammatory cytokines	Lipid peroxidation	Verbal memory	WBC	Gait speed
DNA methylation	TNF-α	Apolipoprotein B	Executive function	IFN-γ	Gray hair
Full-length RNAs	IL-8	Advanced glycation end-products	Inflammatory markers	Lipid Metabolism	Baldness
β-galactosidase activity	mtDNAcn	α-2-macroglobulin	NT-proBNP	Growth Hormone/IGF-1	Cutaneous elasticity
Cell-free DNA	Gut Microbiome	Inflammatory activity	Increased intestinal permeability	Glucose metabolism (i.e., $HbA1_c$)	Habits (i.e., smoking)
		Adiponectin	Bone mineral density	Forced expiratory volume	Monopodal stance
		CD4/CD8 ratio	Cystatin-c	Blood pressure/pulse pressure	Body mass index
		hs-CRP	Pulse wave velocity	VO_2maximum	Grip strength
			Auditory acuity		

Figure 2. Range of biomarker employed in composite measures of biological age. Features are grouped in six categories and the list is non exhaustive but illustrative, indicating areas of biological functioning where these biomarkers are indicative of physiological reserve or evidence damage to cellular functions. TNF-α: Tumor Necrosis Factor-α; IL-8: Interleukin 8; mtDNAcn: mitochondrial DNA copy number; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal (NT)-pro hormone BNP; WBC: White blood cells; IFN-γ: Interferon gamma; VO2maximum: maximum oxygen consumption.

The concept of biological age has gained recognition in aging research as a means to capture the heterogeneous and progressive decline in biological functions associated with chronological age **(125)**. It is understood that individuals age at different rates, and biological age has been proposed as a crucial factor in explaining the variations in longevity among people **(14)**. The findings of this scoping review highlight the importance of assessing biological age as part of the analysis of population longevity to predict adverse health outcomes **(16)**. It has been observed that a higher biological age, compared to chronological age or traditional biomarkers of age-related diseases, is associated with an increased risk of mortality **(25, 31, 36–38, 41, 42, 44, 45, 53, 54, 67, 70–72, 74, 76, 93, 94, 109, 110)**. Moreover, a faster rate of biological aging is linked to a worse health prognosis, characterized by greater morbidity and mortality (**31, 44, 45, 53, 54, 67, 76, 93, 94)**.

These findings underscore the significance of considering biological age in understanding the aging process and its implications for health. By incorporating composite biomarkers and employing various predictive methods, researchers can gain insights into individual differences in aging and identify individuals at higher risk for adverse health outcomes **(16)**.

In the management of chronic noncommunicable diseases, the use of biological age can help identify individuals who require greater healthcare interventions or who have a fragile health condition **(15)**. This point is well supported by evidence, as observed in the results of the scoping review (**Table 1**). However, there are still important questions that need to be addressed regarding the assessment of biological age, including the number of biomarkers needed and the best method for its estimation. In our review, we found that the number of biomarkers considered varied widely, ranging from 3 to 900 in different studies **(56,103)**.

These findings highlight three central questions in this field: i) What is the optimal number of biomarkers required to reliably identify a higher biological age? ii) Which composite biomarkers provide greater accuracy and precision in estimating biological age? iii) Which method yields greater validity in assessing biological age?

Among the studies included in our review, commonly employed biomarkers encompassed hematological, inflammatory, renal, metabolic, pulmonary, and cardiovascular assessments. The number of biomarkers considered varied depending on the method used and the desired outcomes. It appears that different measurements of biological age capture heterogeneous aspects of the aging process, contributing to the heterogeneity of results. Therefore, the performance of a specific calculation method cannot be automatically extrapolated to another method that employs a different set of biomarkers or outcomes.

Blood-related biomarkers frequently exhibit changes with chronological age (**23, 27, 28, 32, 34, 35, 43, 45–47, 49–51, 53–55, 57–59, 61, 62, 64–67, 69, 77, 79–85, 88, 90–92, 96, 98, 100, 101, 120)**. However, it is important to note that these variations are often non-linear over time **(126)**. Consequently, in the studies evaluated, it becomes challenging to separate the biochemical changes associated with age from the results obtained through cross-sectional methods used for estimating biological age.

In summary, while biological age shows promise in identifying individuals with greater healthcare needs and fragility, there is a need for further research to determine the optimal number of biomarkers, identify the most accurate composite biomarkers, and establish the most valid method for assessing biological age. This will contribute to the refinement and standardization of biological age estimation, ultimately enhancing its utility in the management of chronic noncommunicable diseases.

	Author	Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
1	Heikkinen, E.	(21)	1974	Finland	C	MLRA	460	25 to 57 years	0%	6: neurological sensitivity, neuropsychological tests, lung capacity.	Biological age measurement.
2	Nakamura, E.	(84)	1982	Japan	C	MLRA	390	30 to 76 years	0%	9: blood labs, cardiovascular characteristics, neurological sensitivity, lung capacity, vital signs.	Biological age measurement.
3	Takeda, H.	(83)	1982	Japan	C	MLRA	200	20 to 69 years	0%	6: neurological sensitivity, lung capacity, vital signs, blood labs.	Relevance of biological age measurement in health screening.
4	Dubina, T.L.	(103)	1984	Ukraine	PC	Multiple regression equation that is a statistical relationship between age and the three parameters measured in the population under study.	250	60 to 100 years	38.0%	3: neuromuscular capacity, neuropsychological tests, neurological sensitivity.	Relation of biological age measurement and MLRA.
5	Nakamura, E.	(85)	1988	Japan	C	PCA	462	50.8 ± 12.1 years	0%	11: blood labs, neurological sensitivity, vital signs, lung capacity.	Biological age measurement.
6	Hochschild, R.	(60)	1989	United States	C	MLRA	2462	Men: 45.9 years Women: 44.7 years	60.0%	12: neurological sensitivity, neuropsychological tests, lung capacity.	Relationship of biological, chronological age and biomarkers.
7	Nakamura, E.	(79)	1990	Japan	C	PCA	65	42.1 ± 8.1 years	100%	9: lung capacity, vital signs, blood labs, cardiovascular characteristics.	Compare biological age and physical fitness.
8	Lee, M.S.	(86)	1996	Japan	C	PCA	322	49.5 ± 14.3 years	0%	1 method, 4 biomarkers: lung capacity, neuromuscular capacity, musculoskeletal characteristics; 2 method, 3 biomarkers: neuromuscular capacity.	Compare both methods and ischemic heart disease, hypertension, obesity or diabetes.
9	Anstey, K.J.	(26)	1999	Australia	C	PCA	180	70.6 ± 7.1 years	100%	5: neurological sensitivity, neuromuscular capacity, lung capacity.	Relation with cognitive performance.
10	Martin, H.	(24)	2002	Germany	C	MLRA	404	Specified by decade and gender	50.0%	13: blood labs	Biological age measurement.
11	Nakamura, E.	(82)	2003	Japan	RC	PCA	86	51.2 years	0%	9: lung capacity, vital signs, blood labs.	Relation of Biological age and biomarkers.
12	MacDonal, S.W.S.	(28)	2004	Canada	RC	PCA	125	67 to 80 years: 75.9 ± 2.9 years; 81 to 95 years: 84.3 ± 3.5 years	62.0%	6: neurological sensitivity, neuromuscular capacity, lung capacity, anthropometric measures, vital signs.	Cognitive changes at 12 years.

Table 1. Description of the studies included in the scoping review.

C: Cross-sectional; RC: Retrospective cohort; PC: Prospective cohort; CCT: Controlled clinical trial; MLRA: Multiple linear regression analysis; PCA: Principal component analysis; KDM: Klemera-Doubal method; LM: Levine method; SEM: Structural equation model.

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Author		Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
13	Goggins, W.B.	(31)	2005	China	RC	Inverse regression of the square root of age on the square root of the mean frailty and sex to calculate a biological age corresponding to a particular sex and a frailty index value.	2032	79.7 years	51.0%	62 clinical history markers: physical, psychological, and socioeconomic.	Relation of biological age and mortality.
14	Nakamura, E.	(81)	2007	Japan	RC	PCA	86	54.1 ± 12.1 years	0%	5: lung capacity, vital signs, blood labs.	Factors related to biological age.
15	Mrázová, R.	(88)	2007	Czech Republic	C	KDM	55	33 to 54 years	0%	6: anthropometric measures, vital signs, lung capacity, neurological sensitivity.	Biomarker differences between healthy and paraplegic men.
16	Bulpitt, C.J.	(76)	2009	England	PC	MLRA	397	47.9 ± 5.8 years	0%	1 equation, 7 biomarkers: individual characteristics, vital signs, blood labs. 2 equation, 8 biomarkers: individual characteristics, vital signs, blood labs.	Mortality.
17	Nakamura, E.	(80)	2009	Japan	RC	PCA	179	Men: 54.1 ± 12.1 years Women: 55.3 ± 11.7 years	52.0%	5: lung capacity, vital signs, blood labs.	Gender differences in biological age.
18	Bae, C-Y.	(47)	2009	South Korea	C	MLRA	3575	58.0 ± 8.1 years	64.0%	15 biomarkers: musculoskeletal characteristics, anthropometric measures, vital signs, lung capacity; blood labs. Women: additional blood labs. Men: additional blood labs.	Examine the linear relationship between age and some biomarkers.
19	Freude, G.	(23)	2009	Germany	C	MLRA	371	45.6 ± 8.1 years	61.0%	23 not specified: vital signs, neuromuscular capacity, neurological sensitivity, neuropsychological tests.	Compare types of work and relationship with biological age.
20	Park, J.	(50)	2009	South Korea	C	PCA	1588	50.0 ± 9.6 years	0%	11: lung capacity, musculoskeletal characteristics, anthropometric measures, vital signs, blood labs.	To examine if some pathological conditions such as diabetes affect the biological age developed.
21	Cho, I.H.	(48)	2010	South Korea	C	5 methods: (i) MLRA, (ii) PCA and somewhat unique methods developed by (iii) Hochschild, (iv) KDM, and (v) a variant of the KDM.	200	30 to 70 years	0%	11: neurological sensitivity, lung capacity, neuromuscular capacity, neuropsychological tests.	Compare biological age methods.
22	Bai, X.	(32)	2011	China	C	Linear regression: The biological age score was taken as the dependent variable and the chronological age as the independent variable.	2876	30 to 98 years	53.0%	7: cardiovascular characteristics, blood labs.	Relationship between biological age and differences in some biomarkers of aging.
23	Jee. H.	(51)	2012	South Korea	RC	PCA, MLRA, adjustment methods.	4345	Men: 53.3 ± 8.5 years Women: 52.4 ± 8.8 years	28.0%	8 according to sex: neuromuscular capacity, lung capacity, neuromuscular capacity, musculoskeletal characteristics, lung capacity, anthropometric measures, vital signs.	Biological age and difference with chronological age, with clinical risk factors.
24	Bashkirev, A.S.	(96)	2013	Russia	C	L.M. Belozerova formula	300	Study group: 43.3 ± 0.9 years. Control group: 42.8 ± 0.9 years	0%	5: neuromuscular capacity, vital signs.	Relationship between biological age and risk groups with signs of premature and/or accelerated aging.
25	Zhang, W.G.	(35)	2013	China	C	PCA	505	35 to 91 years	Not specified	8: neuropsychological tests, cardiovascular characteristics, lung capacity, blood labs.	Biological age measurement.
26	Fadeeva, N.I.	(90)	2014	Russia	C	Determination of biological age according to V.P. Voitenko and L..M. Belozerova.	Not specified	44.5 ± 0.17 years	52.0%	Belozerova: 5: anthropometric measures, lung capacity, neuromuscular capacity. Voitenko: 8: vital signs, lung capacity, neuromuscular capacity, neuropsychological tests, self-reports.	Correlation with metabolic disorders with the enzymatic provision of metabolic processes and other parameters in relation to biological age determination methods.

Author		Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
27	Negasheva, M.	(98)	2014	Russia	C	BioAge Software, National Gerontological Center, Moscow, Russia, http://www.ngcrussia.org/	119	Women from 60 to 74 years. Women from 90 to 104 years	100%	At least 8: vital signs, lung capacity, neurological sensitivity, musculoskeletal characteristics, self-reports, neuropsychological tests.	Somatic features, components of body mass and functional characteristics.
28	Zhang, W.G.	(33)	2014	China	C	Own method by factor analysis	139	60.3 ± 14.3 years	51.0%	7: molecular labs, cardiovascular characteristics, neuropsychological tests, blood labs.	Biological age measurement.
29	Belsky, D.W.	(61)	2015	United States	RC	KDM	954	38 years	48.0%	10: blood labs, lung capacity, vital signs.	Relations between the rate of aging, physical and cognitive capacity, and self-perception.
30	Gołąb, S.	(87)	2015	Poland	C	Regression equations for somatic variables and age, and for total body water and age.	1400	Men: 20 to 70 years	0%	5: anthropometric measures, musculoskeletal characteristics.	Relation with physical activity and capacity.
31	Schaefer, J.D.	(62)	2016	United States	RC	KDM	1037	38.0 ± 3.0 years	48.0%	10: blood labs, lung capacity, vital signs.	Relation of biological age and intelligence.
32	Mikhaylova, N.A.	(91)	2016	Russia	C	Method of the Institute of Gerontology of the Academy of Medical Sciences of the USSR (Kiev, 1984).	85	42.7 ± 1.2 years	0%	4: vital signs, neuromuscular capacity, lung capacity, self-reports.	Difference between chronological and Biological Aging.
33	Belsky, D.W.	(64)	2017	United States	RC	KDM	220	38.0 ± 7.0 years	70.0%	10: blood labs, vital signs.	Aging-related changes in organ system function.
34	Yoo, j.	(45)	2017	South Korea	RC	PCA	469754	43.5 years	43.0%	15: anthropometric measures, vital signs, lung capacity, blood labs, musculoskeletal characteristics.	Mortality.
35	Finkel, D.	(63)	2017	United States	RC	Functional biological age (fBioAge)	740	Not specified	59.0%	5: neuromuscular capacity, neuromuscular capacity, lung capacity, self-reports.	Possible gender differences and genetic and environmental influences on change with age.
36	Jee, H.	(46)	2017	South Korea	C	MLRA, PCA and KDM statistical methods were applied to obtain three different sets of biological age prediction models.	3642	30 to 80 years	100%	8: vital signs, anthropometric measures, lung capacity, blood labs.	Biological age as a function of chronological age.
37	Negasheva, M.	(113)	2017	Russia	C	PCA	481	Moscow: 72.8 ± 1,97 years; Tiraspol: 75.2 ± 1.0 years; Barnaul: 75.4 ± 0.7 years	47.0%	7: anthropometric measures, musculoskeletal characteristics.	Correlation with chronological age.
38	Zhang, W.G.	(34)	2017	China	C	PCA	1373	Men: 57.1 years. Women: 55.1 years	58.0%	5: cardiovascular characteristics, neuropsychological tests, blood labs.	Difference between biological and chronological age.
39	Li, X.	(102)	2018	China	CCT	Own regression equations derived from MLRA	915	Men: 50.9 ± 10.6 years Women: 51.2 ± 11.8 years	36.0%	7: blood labs	Change of biomarkers in aging.
40	Belsky, D.W.	(65)	2018	United States	RC	KDM	964	38 .0 ± 3.0 years	48.0%	10: blood labs, lung capacity, vital signs.	Worsening of physical functioning, impairment, cognitive impairment, and subjective perceptions of impaired health.
41	Lin, H.	(59)	2018	United States	RC	KDM	2163	67.0 ± 9.0 years	55.0%	6: vital signs, lung capacity, blood labs.	Relation between chronological age and gene expression in whole blood measured using the Affymetrix Human Exon 1.0st Array.
42	Kang, Y.G.	(44)	2018	South Korea	RC	PCA	484724	50.7 ± 14.1 years	46.0%	Men 7 biomarkers: anthropometric measures, vital signs, blood labs. Women 10 biomarkers: anthropometric measures, vital signs, blood labs.	Mortality and morbidity.

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Author		Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
43	Pyrkov, T.V.	(94)	2018	Russia	RC	PCA, a multivariate linear regression and a state-of-the-art deep convolutional neural network.	7454	35.0 ± 23.0 years	51.0%	7: individual characteristics, personal history, neuromuscular capacity.	Mortality.
44	Pyrkov, T.V.	(93)	2018	Russia	RC	PCA	11839	35.0 ± 23.0 years	51.0%	Not specified	Mortality and chronic diseases.
45	Mikhaylova, S.V.	(92)	2018	Russia	C	Voitenko method and Bio-Age scale	602	20 .0 ± 2.0 years	58.0%	9: blood labs, vital signs, musculoskeletal characteristics, cardiovascular characteristics.	Difference between biological and chronological age.
46	Liu, Z.	(70)	2018	United States	PC	Phenotypic Age	11432	45.5 years	50.8%	9: Blood labs	All-cause mortality and cause-specific mortality
47	Levine, M.E.	(71)	2018	United States	RC	DNAm PhenoAge	456	21-100 years	51.0%	513: blood labs, epigenetic information, DNA methylation levels	All-cause mortality, cancers, healthspan, physical functioning, and Alzheimer's disease
48	Johnson, L.C.	(55)	2019	United States	PC	KDM	604	59.0 ± 1.0 years	42.0%	13: anthropometric measures, musculoskeletal characteristics, vital signs, blood labs, cardiovascular characteristics, lung capacity.	Plasma metabolomic signatures associated with biological age, including some that could predict whether individuals would age at a faster or slower rate.
49	Earls, J.C.	(56)	2019	United States	RC	KDM with transformation of PCA	3558	47.6 ± 12.2 years	58.0%	900: Genomic, proteomic and metabolomic.	Rate of aging, inflammation, bioaccumulation of toxins, chronic diseases.
50	Hastings, W.J.	(69)	2019	United States	RC	KDM, LM	6731	49.6 ± 17.7 years	48.0%	KDM: 12: blood labs, vital signs. LM: 9: blood labs.	Relation with functional capacities, healthy life, low educational level, deficit of material and social resources and mental health problems.
51	Jee, H.	(49)	2019	South Korea	RC	MLRA, PCA, KDM	940	49.9 ± 10.8 years	0%	6: lung capacity, vital signs, blood labs, anthropometric measures.	Compare the mobility dimension of the Euro Quality of Life-5 for the viability test of each biological age model.
52	Elliott, M.L.	(58)	2019	United States	RC	Own: Aging rate: The change over time in each biomarker was modeled with mixed-effects growth models, and these rates of change were combined into a single years-scaled index of physiological change occurring per chronological year.	869	45.1 ± 0.7 years	48.0%	19: anthropometric measures, vital signs, blood labs, lung capacity, individual characteristics.	Relationship between biological aging and cognitive decline.
53	Meisel, P.	(111)	2019	Germany	RC	MLRA to construct biological age, separated for both sexes.	2049	Men: 46.2 ± 13.4 years Women: 44.7 ± 13.2 years	52.0%	Not specified	Predict tooth loss in the follow-up cohort compared to the chronological age of each participant.
54	Sternäng, O.	(112)	2019	Switzerland	RC	Own: Variables were transformed into z-scores	400	68.6 ± 5.4 years	52.0%	4: neuromuscular capacity, lung capacity, neurological sensitivity.	Relations with cognitive skills (episodic recall and recognition, verbal fluency, semantic knowledge, and processing speed).
55	Waziry, R.	(57)	2019	United States	RC	KDM	1699	70.0 (65.0–76.0) years	57.0%	9: blood labs, vital signs, lung capacity.	Association with death and the appearance of age-related diseases.
56	Bush, M.P.	(95)	2019	Russia	C	A.A. Podkolzin method	110	30.2 (29.7–30.7) years	0%	Not specified	State of the cardiovascular and respiratory systems and static balance.
57	Pierleoni, P.	(104)	2019	Italy	C	MLRA	15	61 to 81 years	46.0%	5: anthropometric measures, neuromuscular capacity	Determine biological age

	Author	Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
58	Beam, C.R.	(66)	2020	United States	RC	Own with LM recommendations	40	51.1 ± 5.6 years	62.0%	7: blood labs, vital signs.	Association between cognitive functioning and biological age.
59	Belsky, D.W.	(77)	2020	England	RC	KDM, LM	954	45.0 years	48.0%	8: blood labs, vital signs.	Association between the rate of aging and a predictor of DNA methylation.
60	Crimmins, E.M.	(53)	2020	United States	RC	LM	4287	68.0 ± 8.3 years	55.0%	Biological age (extended) 10 biomarkers: blood labs, vital signs, lung capacity.	Multimorbidity, loss of physical functioning, cognitive dysfunction, and mortality.
61	Gaydosh, L.	(54)	2020	United States	RC	KDM	951	67.4 ± 8.9 years	Not specified	11: blood labs, vital signs.	Analysis of physical and cognitive function and mortality, comparing measures of biological aging with a norm-based biomarker index within our analysis sample and with participants' ratings of their own health.
62	Tze Pin, N.G.	(100)	2020	Singapore	RC	KDM	2844	55 to 94; 67.0 ± 7.9 years	62.0%	Men, 8 biomarkers: blood labs, vital signs, lung capacity, neuromuscular capacity, neuropsychological tests. Women: 10 biomarkers: musculoskeletal characteristics, blood labs, vital signs, lung capacity, neuromuscular capacity, neuropsychological tests.	Relation with education, housing status, loss of a spouse, living alone, lifestyle and health activity, smoking, alcohol consumption, nutritional risks, consumption of milk, soy, fruits, vegetables, coffee and tea, sleep parameters and satisfaction with life.
63	Parker, D.C.	(67)	2020	United States	RC	KDM, LM	1374	78.0 ± 5.4 years	65.0%	12: blood labs, vital signs.	Associations of biological aging measures with participant-reported activities of daily living, instrumental activities of daily living dependencies, and mortality.
64	Shirazi, T.N.	(68)	2020	United States	RC	KDM, LM	4418	Premenopausal: 20 to 61; 34.9 years Postmenopausal: 41 to 84; 63.5 years	100%	9: blood labs.	Biological age associated with parity.
65	Zhong, X.	(101)	2020	Singapore	RC	PCA, MLRA and the KDM, and explored the use of machine learning methods for the prediction of mortality and frailty.	2844	Men from 55 to 94 years, 67.9 years. Women from 55 to 93 years, 66.8 years.	62.0%	17: blood labs, vital signs, anthropometric measures, lung capacity, musculoskeletal characteristics, neuropsychological tests.	Associations with risk factors and health outcomes.
66	Bae, C-Y.	(43)	2021	South Korea	RC	Self-described and biological age of metabolic syndrome.	6518532	Men: 48.8 ± 14.12 years Women: 52.0 ± 14.3 years	52.0%	5: anthropometric measures, cardiovascular characteristics, blood labs.	Identify the relationship between age and lifestyle factors, such as smoking, drinking, and physical activity.
67	Verschoo, C.P.	(27)	2021	Canada	RC	KDM in 6 different panels (panels: optimized, complete, blood, physical, performance and cognitive).	30097	63.0 ± 10.3 years	50.0%	40: blood labs, vital signs, lung capacity, musculoskeletal characteristics, neuromuscular capacity, neuropsychological tests.	Frailty, multimorbidity, chronic disease domains, disability, emergency room visits, and hospitalization.
68	Berezina, T.N.	(97)	2021	Russia	C	V.P. Voitenko method	987	35 to 70 years	58.0%	Not specified: lung capacity, cardiovascular characteristics, musculoskeletal characteristics, self-reports.	Relation between personality traits and biological age.
69	Cao, X.	(36)	2021	China	RC	Machine learning (Gradient Boosting Regressor, Random Forest, CatBoost Regressor, and Support Vector Machine), KDM.	9771	59.1 ± 9.2 years	53.5%	16: blood labs, cardiovascular characteristics.	Association with disability in basic activities and instrumental activities of daily living, morbidity, and mortality.
70	Graf, G.H.	(72)	2021	United States	RC	KDM, PhenoAge, and homeostatic dysregulation	9005	69 ± 9 years	49.0%	8: blood labs.	Functional impairment, activities of daily living, chronic conditions, self-rated health, and mortality.

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Author		Ref.	Year	Nationality	Type of study	Biological age estimation method	Number of subjects	Age	Women	Biomarkers	Outcomes
71	Lin, W.Y.	(107)	2021	Taiwan	PC	BioAge	94443	Men: 48.9 ± 11.1 years Women: 50.5 ± 11.2 years	62.0%	6: blood labs.	Body mass index, smoking status, alcohol status, and single nucleotide polymorphisms.
72	Chan, M.S.	(78)	2021	England	PC	KDM	141254	56.0 years	53.0%	72: blood labs, vital signs, lung capacity, cardiovascular characteristics, musculoskeletal characteristics.	Overall biomarker, mortality, and age-related hospital admissions.
73	Liu, Z.	(37)	2020	China	PC	KDM, physiological dysregulation	17423	1: 49.9 ± 14.1 years and 2: 59.3 ± 9.4 years	53.4%	12: blood labs, vital signs, musculoskeletal characteristics.	Morbidity, mortality, and health behaviors.
74	Zinatullina, A.M.	(99)	2021	Russia	C	V.P. Voitenko	347	56-69 years	61.0%	Not specified..	Difference between working and non-working people.
75	Farina, M.P.	(73)	2022	United States	PC	KDM	4134	68.1 ± 98.3 years	55.3 %	22: demographics, blood labs, vital signs, cardiovascular and lung capacity.	Lifetime socioeconomic conditions contributed to racial/ethnic differences in biological aging.
76	Wang, S.	(38)	2022	China	PC	Multidimensional aging measure (MDAge) - random forest algorithm.	308951	41.9 ± 14.0 years	52.8%	14: anthropometric measures, blood labs, lung capacity.	Morbidity and mortality.
77	Husted, K.L.S.	(108)	2022	Denmark	C	PCA	31	18-54 years	52.0%	9: anthropometric measures, vital signs, blood labs, lung capacity.	Calculate biological age.
76	Jáni, M.	(89)	2022	Czech Republic	PC	KDM	262	28–30 years	48.0%	9: vital signs, blood labs, lung capacity.	Body mass index and body fat.
77	Li, Z.	(39)	2023	China	C	KDM, MLRA, PCA	1207	21-91 years	51.0%	9: blood labs, vital signs, cardiovascular and lung capacity.	Compare biological ages.
78	Shapiro, I.	(109)	2022	Israel	RC	KDM	1473	32.0 ± 1.1 years	50.3%	13: anthropometric measures, blood labs, vital signs.	Parental all-cause and cause-specific mortality.
79	Dmitrieva, N.I.	(74)	2022	United States	RC	KDM	15752	45-66 years	53.0%	15: vital signs, blood labs, lung capacity.	Chronic diseases, and premature mortality.
80	Fermín-Martínez, C.A.	(110)	2022	Mexico	RC	AnthropoAge	6284	45.0 (31.0-64.0) years	50.6%	3-5: anthropometric measures.	Cause-specific mortality and comorbidities.
81	Yang, Q.	(40)	2022	China	RC	Machine learning	77144	45–90 years	Not specified	17: anthropometric measures, vital signs, blood labs, anthropometric measures.	Models, healthy risk indicators and disease.
82	Drewelies, J.	(25)	2022	Germany	RC	KDM	1517	68.66 ± 3.62 years	51.0%	12: blood labs.	Morbidity and mortality.
83	Verschoor, C.P.	(29)	2022	Canada	PC	BioAge	292	76 .0 ± 7.11 years	65.0%	10: blood labs.	Antibody responses.
84	Wei, K.	(41)	2022	China	RC	KDM	130918	20-80 years	52.0%	5: blood labs.	All-cause mortality.
85	Bae, C-Y.	(52)	2022	South Korea	RC	PCA	6971810	47.0 ± 13.9 years	49.0%	17: anthropometric measures, vital signs, blood labs, anthropometric measures.	Incidence of age-related diseases.
86	Graf, G.H.	(75)	2022	United States	PC	KDM	607	41 .0 ± 4.0 years	55.0%	9: blood labs.	Differences of maltreatment effect.
87	Esposito, S.	(105)	2022	Italy	C	Deep Neural Network	4510	55.6 ± 11.6 years	52.0%	36: bood labs.	Relationship of four a priori–defined dietary patterns.
88	Beltrán-Sánchez, H.	(130)	2022	United States	RC	SEM (outcome-free and outcome-dependent), MLRA, PCA, KDM	9197	49.7 ± 13.6 years	50.5%	9: vital signs, blood labs, lung capacity.	Biological age measurement.
89	Gialluisi, A.	(106)	2022	Italy	RC	Deep neural network	23858	55.9 ± 11.9 years	51.7%	40: blood labs.	Mortality and hospitalization risk for all and specific causes.
90	Chen, L.	(42)	2023	China	RC	KDM	12377	57.0 ± 10.5 years	50.2%	25: anthropometric measures, vital signs, blood labs, anthropometric measures, lung capacity.	Long-term risk of all-cause mortality.

Recently, Jazwinski and Kim, emphasized the need to incorporate additional elements to improve the interpretation of the model used **(127)**. For instance, including functional measurements that reflect the physiological state at any age could help identify physiological alterations marking the transition from a healthy to a vulnerable condition **(128)**. In longitudinal studies, tracking hematological, renal, inflammatory, metabolic, pulmonary, and cardiovascular biomarkers over time could be beneficial **(77)**. However, reference values or thresholds to determine these transitions have not been proposed yet. The models used to estimate biological age, especially those recently adopted in the aging phenotype to measure the pace of aging, could be considered a good starting point **(16)**. These models incorporate different biomarkers with biological plausibility and evaluate the occurrence of adverse outcomes over time, which could help define health trajectories, the rate of functional decline, and the transition from a healthy to a vulnerable state.

Mathematical modeling for the estimation of biological age with biomarkers was proposed 50 years ago **(21)**. According to our findings, the most frequently applied methods are PCA, KDM, and MLRA. It is important to highlight that the statistical method used can influence the validity and reproducibility of the estimation of biological age, as each method has its advantages and disadvantages (**Table 2**) **(129)**. For example, while PCA and MLRA select biomarkers based on their relationship with chronological age, which may produce distortions in the case of extreme values, KDM includes chronological age as an independent variable, overcoming the limitations of the former **(117)**. Nevertheless, in all those methods biological age is modeled as a linear function of chronological age and multiple biomarkers which constrain the functional form of its relation. Structural equation model-based estimators recently proposed transcends the limitations of those methods and allow modeling the biological age as a latent variable expressed in multiple biomarkers and relax assumptions about functional relationship without restrictions on parameters (**Table 2**) **(130)**. New prospective longitudinal studies are needed to compare current methodologies and determine which produces a satisfactory estimate with potential clinical utility.

Limitations

This review was not previously registered. However, we rigorously followed the methodological design proposed a priori, in accordance with the PRISMA guidelines.

Our search was limited to five databases accessible to the authors. Nonetheless, by cross-referencing the cited literature, we evaluated most publications in the field, except for three inaccessible articles.

In scoping reviews, critical evaluation of research is not a generalized recommendation. However, conducting a critical evaluation could contribute to determining the methodological quality of ongoing research in the field.

Perspectives

Given the heterogeneity and variability of biological age determinants, relying on a single biomarker may not adequately account for its underlying complexity, as observed in our scoping review. Therefore, a panel of carefully selected biomarkers may accelerate progress towards a more reliable determination of biological age. There is a growing trend favoring a group of biomarkers that reflect different interconnected health processes or serve as biological indicators predicting functional capacity at a specific time point, surpassing the effectiveness of chronological age. We have identified that composite measures of biological age need to encompass different aspects of the aging process, ranging from developmental programs and DNA replication to tissue and organ function and whole-body physiological capacity. Therefore, as a by-product of the current scoping review and recent analysis of comparative measurement of biological age using various methods **(131,132)**, we propose that future studies should analyze biological age

Method	Concept	Advantage	Disadvantage
Multiple linear regression analysis	To predict biological age based on the linear coincidence of several biomarkers of aging associated with a given value of chronological age with a multiple linear regression.	· Preliminary method used. · Easy to run.	· Cannot avoid the paradox of chronological age. · Deforms the biological age at the edge of regression and ignores the discontinuity in the aging rate. · Presence of multicollinearity.
Principal component analysis	It is a statistical method that is based on the observation of a series of biomarkers, generally correlated with each other, reducing them to a set of small factors called principal components, not correlated with each other.	· Biomarkers are not correlated. · Avoids the influence of regression edge. · Resolves the multicollinearity.	· Cannot avoid the paradox of chronological age.
Klemera-Doubal method	This is a computational analysis that tries to limit the distance between the values of the biological markers and the regression line determined by the regression functions in the space of all the biomarkers.	· Better correlation for morbidity and mortality. · More precise than other methods. · Solve the paradox of chronological age.	· Complex to run.
Structural equation model	Structural equation model-based estimators allow modeling the biological age as a latent variable expressed in multiple biomarkers.	· Relax assumptions about functional relationship without restrictions on parameters. · Improve empirical performance and admit interpretations multiple as indicators of latent physiological deterioration. · The estimator of biological age must be anchored on the modeling of an outcome of physiological aging (morbidity and mortality).	· Method still under development · Prospective longitudinal studies are lacking

Table 2. Comparison of different methods to estimate biological age

as a composite phenotype (**Table 3**). To achieve this, quantitative measurement must encompass key elements, such as defining the composite measure and developing a statistical model that combines the selected biomarkers and physiological measures to estimate biological age. This model can be based on machine learning algorithms or other novel mathematical approaches, such as structural equation model-based estimators **(130)**. These new methods, when applied to biological age estimation, improve empirical performance, and allow for multiple interpretations, serving as indicators of latent physiological deterioration. Additionally, the estimator of biological age should be anchored in the modeling of outcomes of physiological aging, such as morbidity and mortality **(130)**.

Finally, the analysis should include exploring the associations between biological age and relevant outcomes, such as disease risk, mortality, and functional decline. With these provisions, the validity of composite biomarkers for determining biological age will enhance their utility as a clinical tool.

Component	Description
Phenotype definition	Biological age is a measure of an individual's physiological state relative to their chronological age.
Composite measure	A specified composite measure derived from multiple biomarkers and physiological indicators that capture various aspects of aging.
Statistical model	Techniques like machine learning and structural equation model employed to analyze and extract patterns from the data, enabling a more accurate estimation of biological age based on the combined information from various biomarkers, physiological measures, and outcomes.
Associations and predictive power	The associations between biological age and relevant outcomes, such as disease risk, mortality, and functional decline, can be examined by comparing them to other traditional risk factors.
Interventions	By examining how interventions affect biological age over time, researchers can gain a deeper understanding of the mechanisms underlying the aging process and identify effective strategies to promote healthy aging and potentially extend lifespan.
Longitudinal studies (preferred)	Longitudinal studies as an effective approach to track changes in biological age over extended periods, allowing researchers to observe how biological age evolves and understand the factors that influence age trajectories.

Table 3. A proposed approach to studying biological age as a complex phenotype through six key components.
A combined measure involves taking into account various components that collectively contribute to the quantification of the biological aging process. By breaking it down into distinct components, researchers can focus on specific biomarkers, advanced statistical methods, and physiological systems that are more relevant to biological aging. This approach allows for a more precise and nuanced evaluation of an individual's aging status, potentially leading to more accurate estimates of biological age and a better understanding of the underlying factors contributing to age-related biological decline.

Conclusion

In recent years, the study of biological age has been a highly active research area due to the increasing longevity of populations worldwide. However, there is significant variability in the number and types of biomarkers used, as well as the methods employed to estimate biological age. Currently, there is no universally accepted gold standard for assessing biological age. Additionally, there is a need for studies to evaluate the reproducibility and prognostic validity of current measurement approaches. Based on our scoping review, we have identified key aspects that should be considered when proposing new research related to the study of biological age as a useful indicator of healthy longevity.

Conflicts of interest

The authors declare no conflicts of interest with the work.

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