Biogerontology (2025) 26:80
https://doi.org/10.1007/s10522-025-10222-1

RESEARCH ARTICLE

Exploring new markers for biological aging from bioimpedance analysis and cognitive functions in older adults

Dieu Ni Thi Doan · Boncho Ku · Kahye Kim · Kunho Lee · Jaeuk U. Kim

Received: 16 January 2025 / Accepted: 18 March 2025 / Published online: 30 March 2025

Abstract Aging is a complex process that affects human health and lifespan. While chronological age (CA) is a significant risk factor for many diseases, it does not fully capture biological changes that influence health span. This study explores cognitive measures using the Seoul Neuropsychological Screening Battery and body composition profiles as potential biological age (BA) markers in the older population. Multiple linear regression, principal component analysis (PCA), and the Klemera–Doubal (KDM) methods were used to construct sex-specific BA formulas from 296 healthy individuals (160 women, 136 men, mean age: 70.3 years). The BA formulas were applied to a new cohort of 708 diseased people (376 women, 332 men, mean age: 73.5 years) to generate BAs for each sex. Subsequently, we compared the classification power of CA, BAs, and selected variables when differentiating the healthy group from the comorbidity cohort, with sex stratification. As a result, we found that BAs from PCA and KDM were significantly higher than CA in the diseased group but comparable in the healthy group. BAs from PCA and KDM methods yielded higher classification accuracies than CA alone. Notably, frontal executive domain score and body reactance emerged as two promising markers for aging. These findings suggest that body composition measures and cognitive assessments offer a more accurate reflection of biological health than CA alone. A cohort with a wider age range is needed to generalize these findings.

Keywords Bioimpedance analysis · Seoul neuropsychological screening battery · Principal component analysis · Klemera–Doubal method

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10522-025-10222-1.

D. N. T. Doan · B. Ku · K. Kim · J. U. Kim (✉)
Digital Health Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea
e-mail: jaeukkim@kiom.re.kr

B. Ku · J. U. Kim
School of Korean Convergence Medical Science, University of Science and Technology, Daejeon, South Korea

K. Lee
Gwangju Alzheimer's Disease and Related Dementias (GARD) Cohort Research Center, Chosun University, Gwangju, South Korea

K. Lee
Department of Biomedical Science, Chosun University, Gwangju, South Korea

K. Lee
Dementia Research Group, Korea Brain Research Institute, Daegu, South Korea

Introduction

Aging is a complex process that influenced by many factors such as genetics, environmental exposures,

and lifestyle choices, which lead to progressive cellular and molecular changes over time (López-Otín et al. 2013). Chronological age (CA) is the number of years of living since birth that is often used as an indicator of aging, reflecting cumulative exposure to risk factors over time. However, CA alone does not fully capture the intricate changes of biological systems that impact a person's health and life span (Kennedy et al. 2014). As a result, there has been growing interest in the alternative measure of biological age (BA), which may offer a more accurate understanding of an individual's health and aging process (Ho et al. 2023).

BA has been researched for over 50 years, developed to offer a more nuanced estimation of the aging process than CA alone (Baker and Sprott 1988; Jylhävä et al. 2017). A more precise assessment of BA provides a better estimation of the risk of impairments, dysfunctions, morbidities, and mortality since it better reflects the steady decrease of human body structure and function (Levine 2013). Therefore, several models and markers have been used to estimate BA, such as DNA methylation patterns, telomere length, physiological functions, and physical measurements (Jylhävä et al. 2017). Despite these advancements, no single marker has emerged as the gold standard for BA due to the complexity and multifaceted nature of the aging process. Consequently, there remains an ongoing need to discover and validate new and more reliable markers that can add in comprehensive reflection of an individual's BA. Among these, bioimpedance analysis (BIA) and the Seoul Neuropsychological Screening Battery (SNSB) are emerging tools that show promise in reflecting the aging process.

BIA has reported to be a simple but useful tool for evaluating body composition and physiological function that commonly change during aging. By measuring the impedance of body tissues against electric current, BIA non-invasively estimates muscle mass, fat distribution, and hydration status (Kyle et al. 2004a, b). Studies have highlighted crucial roles of body fat and nonfat components in relation with cognition and comorbidities on the aging spectrum (Baumgartner 2000) and BIA-identified muscle loss in association with age-related negative clinical outcomes (Aleixo et al. 2020). Physical profile of body measures has enhanced age prediction accuracy (Bae et al. 2008) and impedance index, such as phase angle, is well correlated with inflammatory factors in old age (Tomeleri et al. 2018).

On the other hand, cognitive abilities that reflected by SNSB domain scores also gradually deteriorate with aging. Using SNSB, several cognitive domains including attention, memory, language, visuospatial, and frontal executive can be evaluated (Ryu and Yang 2023). These cognitive declines are often key markers of accelerated brain aging and are crucial for assessing cognitive health in older adults (Cho et al. 2010).

To construct BAs, there are three common methods including multiple linear regression (MLR), principal component analysis (PCA), and the Klemera–Doubal Method (KDM). In a nutshell, MLR considers BA as the best prediction of CA when linearly combining multiple predictors. This method is straightforward yet falls within the biomarker paradox as it is based on a central distribution approach, often overestimates the age of younger individuals and underestimates the age of older individuals, making it less accurate for those at the extremes of the age spectrum (Dubina et al. 1983). To compensate for this limitation, a correction method was introduced and adopted in biological age research (Dubina et al. 1983). PCA can effectively identifies largest variation of data to simplify complex and redundant dimensions. The 1st component of PCA is thought to capture the most significant variance across aging-related variables and often used to construct BA (Nakamura et al. 1988). More recently, KDM method was introduced based on minimizing the distance between regression lines and biomarker variables in high dimensional spaces and found to be superior in estimating BA (Klemera and Doubal 2006; Wei et al. 2022; Kwon and Belsky 2021).

Previous studies have often suggested modeling BA across a broad age range. However, as older people experience more significant and long-lasting changes in their body composition and cognitive abilities than younger groups, focusing on older populations may provide a better understanding of aging trends in *later life*. Furthermore, identifying significant changes in this age group's physiology and cognition provides more predictive power when estimating the chances of morbidity and death. Considering these variables, the purpose of this study is to examine BA in older persons by utilizing BIA and SNSB measures to offer supplementary understanding of the biological and

neurocognitive facets of aging. These measures are simple yet believed to be powerful tools to reflect age-related changes regarding body composition and cognitive function. With advanced statistical methods, we seek to demonstrate their effectiveness of these markers in reflecting the aging process in the middle-to-old population and identifying illness in diseased individuals. Ultimately, this research aims to provide insight on possible new aging markers for BA and validate them as reliable indicators of BA in older individuals.

Materials and methods

Participants

All participants were recruited from Gwangju community, South Korea, and divided into two cohorts, with ages ranging between 55 and 90 years. The first cohort consisted of 296 healthy individuals who had no record of comorbidities, comprising 160 women and 136 men. Aging markers obtained from this group were used to construct BA formulas for each sex using MLR, PCA, and KDM methods. The second cohort included 708 individuals of 376 women and 332 men. Each person contains at least one of the seventeen diseases listed in the Charlson Comorbidity Index (CCI) (Charlson et al. 1987). As a result, every individual in the second cohort had CCI scores of one or higher. New input values of the same selected aging markers from this second cohort were then applied to the BA formulas to calculate three BA score for each sex. Data was collected from 2019 to 2023. Written informed consent was obtained from each participant in prior of the study. Individuals in both groups must have more than 3 years of education, had no clinical signs of dehydration or excessive hydration, no current acute medical condition that could interfere with body and mental health such as infection or neurological disorders. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital with approval number CNUH-2019-279. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Bioimpedance analysis (BIA)

Anthropometric measurements, including height, weight, and body mass index (BMI), were automatically recorded using the multifrequency bioimpedance analyzer InBody S10 (Korea). This device also provides body composition parameters related to lean mass, fat mass, and intracellular and extracellular water volume based on impedance variables. The InBody S10 measures impedance at different frequencies, from one to a thousand kHz, using a tetrapolar 8-point tactile electrode system to record comprehensive body composition data. In calculating body fat mass and segmental fat-free mass, prior research has shown that this multifrequency BIA methodology compatible with dual energy X-ray absorptiometry method with a good specificity (Kim et al. 2014; Jeon et al. 2020).

In addition to the standard body composition variables, important impedance measures such as reactance and phase angle were derived directly from the same method. Reactance and phase angle are recognized as key indicators of cellular health, strength, and integrity, and they have been strongly correlated with risks of morbidity and mortality in older populations (Garlini et al. 2019; Azevedo et al. 2013). An evaluation of the cellular health of the upper and lower body was made by computing segmental reactance and phase angle, which were calculated as the average values from the left and right arm (reactance-upper, phase angle-upper) and the left and right leg (reactance-lower, phase angle-lower) (Doan et al. 2023). In accordance with the standardized procedures described in the InBody S10 manual, all BIA measurements were performed with individuals in a supine position.

A total of fourteen BIA variables were utilized in this study, including anthropometric measures (height, weight, and BMI), fat-related parameters (percent body fat mass, visceral fat area, and waist circumference), lean-related measures (arm muscle circumference, skeletal muscle mass, and body cell mass), total body water to fat-free mass ratio (TBWFFMR), and two pairs of segmental variables (reactance-upper, reactance-lower), and phase angle (phase angle-upper, phase angle-lower)) measured in both upper and lower extremities. Detailed definitions and computation methods for these variables can be found elsewhere (Doan et al. 2023).

Seoul neuropsychological screening battery (SNSB)

Seoul neuropsychological screening battery is a comprehensive tool designed to assess various cognitive functions across multiple domains, providing valuable insights into age-related cognitive decline and potential neuropsychological disorders. In Korea's population, the SNSB is widely used in clinical and research settings to evaluate cognitive abilities in older individuals at five major cognitive domains: attention, language, visuospatial, memory, and frontal executive function (Ryu and Yang 2023).

The attention domain reflects the ability to concentrate and process information and is known to decrease with age (Yakhno et al. 2007). In addition, the linguistic domain is responsible for both understanding and producing speech, which is essential for communication but is often impaired in the early stages of dementia (Fleming 2014). The visuospatial function domain examines such aspects of an individual as the ability to comprehend visual information, which is commonly associated with activities of daily living such as finding one's way from one place to another (Iachini et al. 2009). The memory domain encompasses short- and long-term memory, where functional impairment of memory is usually acknowledged as one of the signs of cognitive aging at its earliest (Park and Festini 2017). At last, the frontal executive domain evaluates complex skills such as reasoning, organizing, and making judgments and is known to undergo changes either due to normal senescence or to neurodegenerative processes (Buckner 2004). Collectively, these sectors depict cognitive health and associated patterns of decline with aging that is regularly seen among the elderly population.

Variable selection

Beside BIA and SNSB variables, blood pressure measures such as systolic blood pressure and diastolic blood pressure were also utilized as potential indicators of aging. During stepwise selection procedures, only such variables were retained in final analysis which had significant correlation with CA because they represented age-related changes. Moreover, it is common that although these variables assess different domains, such as body morphology, physiological and cognitive aspects, they are often correlated. Therefore, the variance inflation factor with a threshold of four was applied to reduce the effects of multicollinearity which was useful in getting rid of extra variables (see Supplementary Fig. S2). Consequently, systolic blood pressure, six BIA variables and the five SNSB domains were identified as significantly correlated with CA with reasonable intercorrelativity in each sex group. These BIA variables were (1) height, (2) TBWFFMR, (3) reactance-upper, (4) reactance-lower, (5) phase angle-upper, and (6) waist circumference for women and arm circumference for men.

To address the issue of multicollinearity, we opted for a shrinkage technique through penalized linear regression, comprising least absolute shrinkage and selection operator (LASSO), ridge regression, and elastic net (Tibshirani 1996). These methods are effective in minimizing the problem of overfitting by adding penalties to the models' coefficients, thus adjusting weights for the predictors (Tibshirani 1996). Ultimately, while LASSO was selected as the feature selection model, ridge regression and elastic net models were included to ensure sensitivity in the analyses. To improve the strength of the model, a double ten-fold cross-validation was adopted whereby data is done into several training, validation, and test sets to help the model to fit the unseen data efficiently. This procedure is useful for optimizing model predictive accuracy when the variables selected also remain meaningful from a more practical, biological perspective with respect to aging (Berrar 2019).

Finally, eight variables were selected to construct BA formulas for women: systolic blood pressure, reactance-lower, waist circumference, TBWFFMR, and height in body metrics, along with frontal executive, memory, and visuospatial domain scores from SNSB assessments. For men, six variables were included in constructing BA formulas: reactance-lower, phase angle-upper, TBWFFMR, and height in body metrics, as well as frontal executive and memory domain scores from SNSB assessments.

Statistical analysis and machine learning algorithms

To identify potential predictors, we examined the correlation between age and each of the blood pressure-BIA-SNSB variables using Pearson method. Pearson correlation was also utilized to assess the multicollinearity between the selected predictors as well as between predicted CA and true CA. As

abovementioned, variance inflation factor value of four was set to minimize the inter-correlation between the selected variables.

As above mentioned, the variables that passed the above screening steps would be further filtered through penalized linear regression methods such as LASSO, ridge regression, and elastic net that were utilized to address multicollinearity of the BIA variables. Models of linear prediction were built using three distinct subsets of the predictors, namely the blood pressure-BIA variables, the five domains of SNSB, and their merger. To improve bias-variance trade-off in anticipation of deployment on a new unseen test set, a double ten-fold cross-validation approach was applied. In total, 160 healthy female participants were randomly split into 90% training set (n = 144) and 10% test set (n = 16). Similarly, 136 healthy male individuals were randomly split into 90% training set (n = 122) and 10% test set (n = 14). The 90% training set in each sex group was once again stratified into 90% training and 10% validation set. Subsequently, parameters were training on the training set, tuned in the validation set and test on the unseen test set. All predictors were standardized to mean zero and standard deviation (SD) before feeding into the prediction models. Notably, double ten-fold cross validation method was also employed in the logistic regression model that used to classify healthy individuals form diseased people in "Results". The model performance was evaluated using area under the receiver operating characteristic (AUC). Delong's method was employed to compare AUCs between different set of predictors.

The performance of the models was evaluated based on the correlation coefficient between the actual and the predicted ages as well as the intraclass correlation coefficient (ICC). ICC evaluates the reliability or agreement of measurements from different observers or instruments. We used a two-way random-effects model to assess inter-rater agreement. It compares the variability within measurements taken from the same subject to the total variability across all subjects. Higher ICC values indicate stronger consistency and reliability, while lower values show less agreement. Within each combination of learning algorithms and datasets, the optimal model defined by the lowest root mean square error (RMSE) on the unseen test set with the relatively high correlation coefficient and ICC—was selected. All the analyses were done separately for women and men. All statistical analyses and model developments were carried out using R statistical software (version 4.2.3, released 2023-03-15; R Core Team, 2023). BA from KDM method was estimated using the TrueTrait function from the WGCNA R package.

Results

Basic information of participants

Table 1 provides an overview of basic characteristics and the potential aging markers of the healthy and disease group. The healthy cohort consisted of 296 participants, including 160 women and 136 men, all of whom reported no underlying conditions, thus served as the healthy control group for BA construction. Their mean age was about 70 years (68.9 years in women and 71.9 years in men) ranging from 55 to 90 years. Participants had relatively high education levels with the average being about 12–14 years of education.

The disease cohort consisted of 708 individuals of 376 females and 332 males. They had slightly higher mean ages (72.1 years in women and 75.2 years in men) than the healthy cohort. The education level averaged 10.4 years for women and 13.7 years for men. Based on the CCI, participants were divided into four subgroups with CCI scores ranging from one to four and sample sizes of 329, 260, 89, and 30, respectively. The proportions of men and women in these subgroups were comparable however, the disease group was older and had considerably lower education levels than the healthy group.

Compared to the healthy group, the disease group was significantly shorter in height and had higher values in weight, BMI, waist circumference, and TBWFFMR in both sexes. Additionally, the disease group exhibited lower cognitive function scores across five SNSB domains compared to the healthy group.

Given that there are differences in body composition and aging processes between women and men (Bredella 2017; Crimmins et al. 2019), all subsequent analyses will be sex stratified. This helps in comprehending the variability that are sex-specific to BAs and the health outcomes in this population.

Table 1 Comparing age, education levels, and potential aging indicators between the healthy and disease cohorts for women and men

Women	Total (n = 536)	Healthy (n = 160)	Disease (n = 376)	p-value
Age (Years)	71.1 (6.1)	68.9 (5.8)	72.1 (6.0)	**< 0.001**
Education (Years)	10.8 (4.3)	11.9 (4.3)	10.4 (4.3)	**< 0.001**
Systolic blood pressure	127.7 (16.2)	126.1 (16.4)	128.4 (16.1)	0.145
Diastolic blood pressure	72.6 (9.9)	72.4 (9.9)	72.6 (9.9)	0.831
Height	153.9 (5.4)	154.7 (5.4)	153.6 (5.4)	**0.027**
Weight	58.5 (8.0)	57.0 (7.2)	59.1 (8.3)	**0.007**
BMI	24.7 (3.1)	23.8 (2.8)	25.0 (3.1)	**< 0.001**
Waist circumference	81.8 (8.8)	78.9 (8.2)	83.0 (8.8)	**< 0.001**
TBWFFMR	73.8 (0.3)	73.7 (0.2)	73.8 (0.3)	**< 0.001**
SNSB attention	8.9 (2.3)	10.0 (2.3)	8.4 (2.1)	**< 0.001**
SNSB memory	-0.1 (0.7)	0.4 (0.6)	− 0.3 (0.7)	**< 0.001**
SNSB visuospatial	0.3 (0.6)	0.6 (0.4)	0.2 (0.7)	**< 0.001**
SNSB language	0.0 (0.4)	0.2 (0.2)	− 0.1 (0.4)	**< 0.001**
SNSB frontal	− 0.1 (0.7)	0.4 (0.6)	− 0.2 (0.7)	**< 0.001**
Alcohol intake	19 (3.5%)	4 (2.5%)	15 (4.0%)	0.393
Smoking	0 (0%)	0 (0%)	0 (0%)	> 0.999
Men	Total (n = 468)	Healthy (n = 136)	Disease (n = 332)	p-value
Age (Years)	74.2 (6.3)	71.9 (6.3)	75.2 (6.1)	**< 0.001**
Education (Years)	13.9 (4.5)	14.3 (4.7)	13.7 (4.4)	0.145
Systolic blood pressure	125.9 (16.1)	126.7 (15.0)	125.6 (16.6)	0.473
Diastolic blood pressure	70.6 (10.2)	71.4 (9.6)	70.2 (10.4)	0.106
Height	165.7 (5.6)	166.0 (6.0)	165.6 (5.4)	0.397
Weight	67.0 (9.0)	66.0 (9.3)	67.4 (8.9)	0.148
BMI	24.3 (2.7)	23.9 (2.7)	24.5 (2.7)	**0.029**
Waist circumference	86.5 (8.3)	84.1 (8.5)	87.4 (8.0)	**< 0.001**
TBWFFMR	73.9 (0.3)	73.9 (0.2)	74.0 (0.3)	**< 0.001**
SNSB attention	9.3 (2.1)	10.4 (2.1)	8.9 (2.0)	**< 0.001**
SNSB memory	− 0.2 (0.8)	0.4 (0.5)	− 0.5 (0.7)	**< 0.001**
SNSB visuospatial	0.4 (0.5)	0.6 (0.3)	0.3 (0.5)	**< 0.001**
SNSB language	0.1 (0.4)	0.3 (0.2)	0.0 (0.5)	**< 0.001**
SNSB frontal	0.0 (0.7)	0.4 (0.5)	− 0.2 (0.7)	**< 0.001**
Alcohol intake	133 (28%)	49 (36%)	84 (25%)	**0.019**
Smoking	38 (8.1%)	16 (12%)	22 (6.6%)	0.065

The values represent mean (SD) for numerical variables and n (%) for categorical variables. The p-values were obtained from independent two sample t-test for numerical variables and Fisher's exact test or Pearson's Chi-squared test for categorical variables

Bold text indicates a p-value < 0.05

BMI body mass index, *TBWFFMR* total body water to fat free mass ratio

Aging markers selection

The statistical descriptions and correlations coefficients with its 95% confidence interval (95% CI) between CA and blood pressure variables, BIA measures, and SNSB five domain scores are illustrated in Fig. 1 in descending order. Significant correlations were observed between CA and several markers, including the five SNSB cognitive domains, height, TBWFFMR, reactance-upper, reactance-lower, phase angle-upper, as well as systolic blood pressure, waist circumference in women, and arm circumference

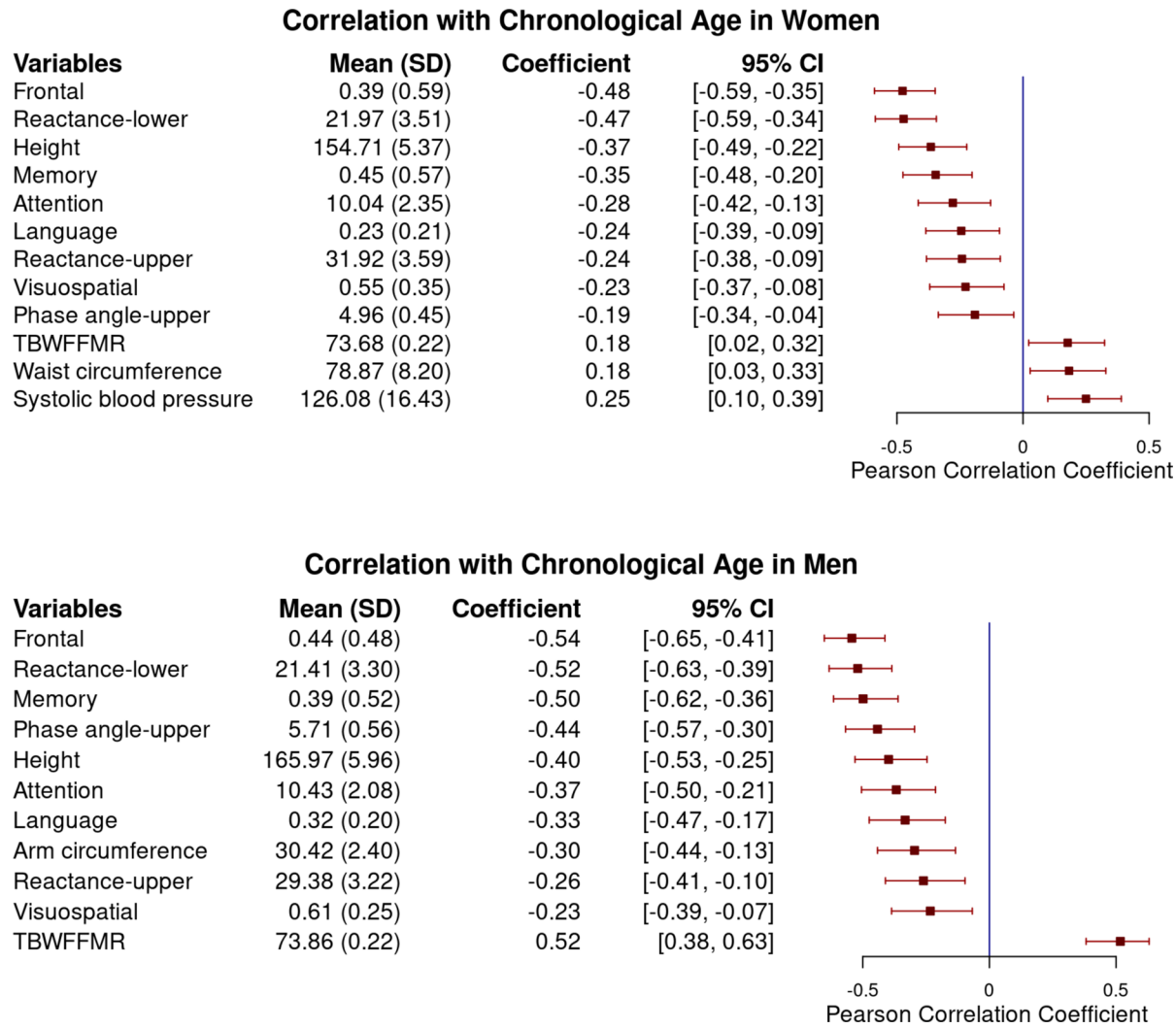


Fig. 1 Forest plots to illustrating the significant correlations between blood pressure, BIA, SNSB variables and chronological age with detailed statistics in women and men. The red box and solid red horizontal line indicate the mean correlation coefficient with the corresponding 95% confidence interval (CI) obtained from Pearson correlation method. SD—Standard deviation

in men. Notably, the frontal executive domain score and reactance-lower exhibited the strongest correlations with CA, with coefficients (95% CI) of -0.48 $(-0.59, -0.35)$ and -0.47 $(-0.59, -0.34)$ in women, and -0.54 $(-0.65, -0.41)$ and -0.52 $(-0.63, -0.39)$ in men, respectively. TBWFFMR also modestly positively correlated with CA in men, with coefficient (95% CI) of 0.52 (0.38, 0.63). The detailed correlations and data distributions of each significant marker with CA for women and men can be found in Supplementary Fig. S1.

Furthermore, the significant markers revealed moderate inter-correlation between several pairs, such as frontal executive and attention scores ($\rho = 0.68$ in women, $\rho = 0.58$ in men) and reactance-lower and TBWFFMR ($\rho = -0.56$ in women, $\rho = -0.59$ in men), as shown in the correlation matrix in Fig. 2. These findings highlight potential concerns regarding multicollinearity when incorporating these variables into linear prediction models.

To minimize the effects of inter-correlation, we applied penalized linear regression models to

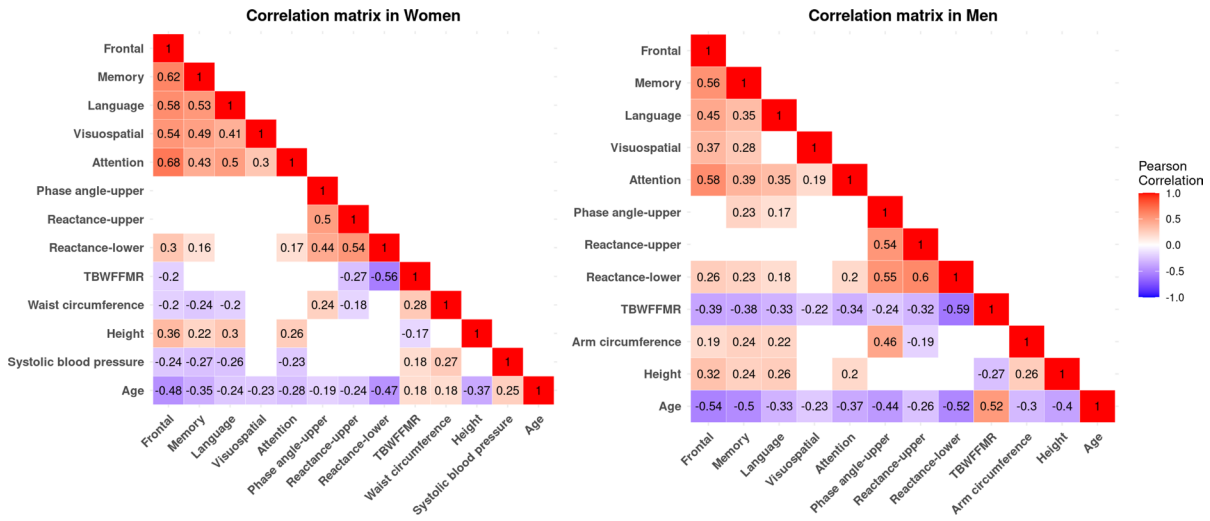


Fig. 2 Correlation matrix illustrating the relationships between the significant markers. Empty cells indicate non-significant correlations among the variables

effectively select aging markers that best reflect CA. Supplementary Table S1 demonstrates the results of predicting CA using various predictor sets through a double ten-fold cross-validation approach. The LASSO model resulted in a strong correlation between predicted CA and true CA, accompanied by a relatively low mean difference and solid ICC. Therefore, the variables identified by the LASSO model were selected as potential markers for constructing BA. Noteworthy, ridge regression and elastic net were presented for sensitivity evaluation.

The selected aging markers from the LASSO model included reactance-lower, frontal executive score, height, memory score, systolic blood pressure, waist circumference, TBWFFMR, and visuospatial score for women, while those for men were frontal executive score, phase angle-upper, reactance-lower, memory, height, and TBWFFMR. These markers were sorted in the descending order based on their importance as displayed in Supplementary Fig. S3. As shown, reactance-lower and frontal executive domain score contributed the most to predicting CA when combined linearly with the other markers.

BAs and CA between healthy group (CN) and disease group (CCI) in women

The eight selected markers obtained in women within the CN group were used to construct BA scores via MLR, PCA, and KDM methods. These BA formulas were then applied to the disease cohort, which was grouped based on CCI scores ranging from one to four. Details of BA formulas can be found in the Supplementary Section. Figure 3 illustrates the relationship between CA and BA across CN and CCI subgroups.

(A) Using MLR method, the correlations between CA and BA were strong, with coefficients (95% CI) of 0.90 (0.86, 0.92) in the CN group and 0.88 (0.86, 0.90) in the CCI groups. Visually, the scatterplot in Fig. 3a shows that the CCI data points were distributed above those of the CN group, indicating that individuals with comorbidities had higher BA than their respective CA. However, the right panel boxplot comparing CA and BA between CN and each CCI subgroups showed no significant differences between BA and CA within any of the groups.

(B) Via the PCA method, the correlations between CA and BA were relatively lower compared to the MLR method, with coefficients (95% CI) of 0.77 (0.69, 0.82) in the CN group and 0.68 (0.62, 0.73) in the CCI group, as shown in Fig. 3b. The same pattern is observed in the scatterplot where it is evident that the BA values of the CCI group are above the CN group. This implies that diseased individuals had higher BA than their

CA counterparts. This was further supported by the right panel boxplot which revealed that BA was significantly higher than CA in all the CCI subgroups; however, no significant difference between BA and CA was noted in the CN group.

(C) Lastly, correlations between BA and CA in the CN and CCI grouping using the KDM method were among the two lowest correlated coefficients of 0.60 (95% CI: 0.49, 0.69) and 0.52 (95% CI: 0.44, 0.59), respectively. Following the trend seen with the other methods, the scatterplot showed that the data points belonging to the CCI group were placed higher up than those from the CN group, indicating that those patients had an increased BA as compared to the healthy CAs. This BA acceleration was further confirmed when comparing BA and CA within the CN and CCI groups which was evident in the right panel of Fig. 3c.

BAs and CA between healthy group (CN) and disease group (CCI) in men

Similarly, the six identified markers from men within the CN group were utilized to generate BA scores through the MLR, PCA, and KDM methods and applied to the comorbidity group. The findings for men closely mirrored those for women, emphasizing the disparity between BA and CA in the CCI group while showing no significant difference in the CN group. Figure 4 illustrates the relationship between CA and BAs across CN and CCI subgroups for men. Notably, the correlations between CA and BAs were stronger in men compared to that in women.

Classifying CCI and CN groups using CA, BA, and the aging markers

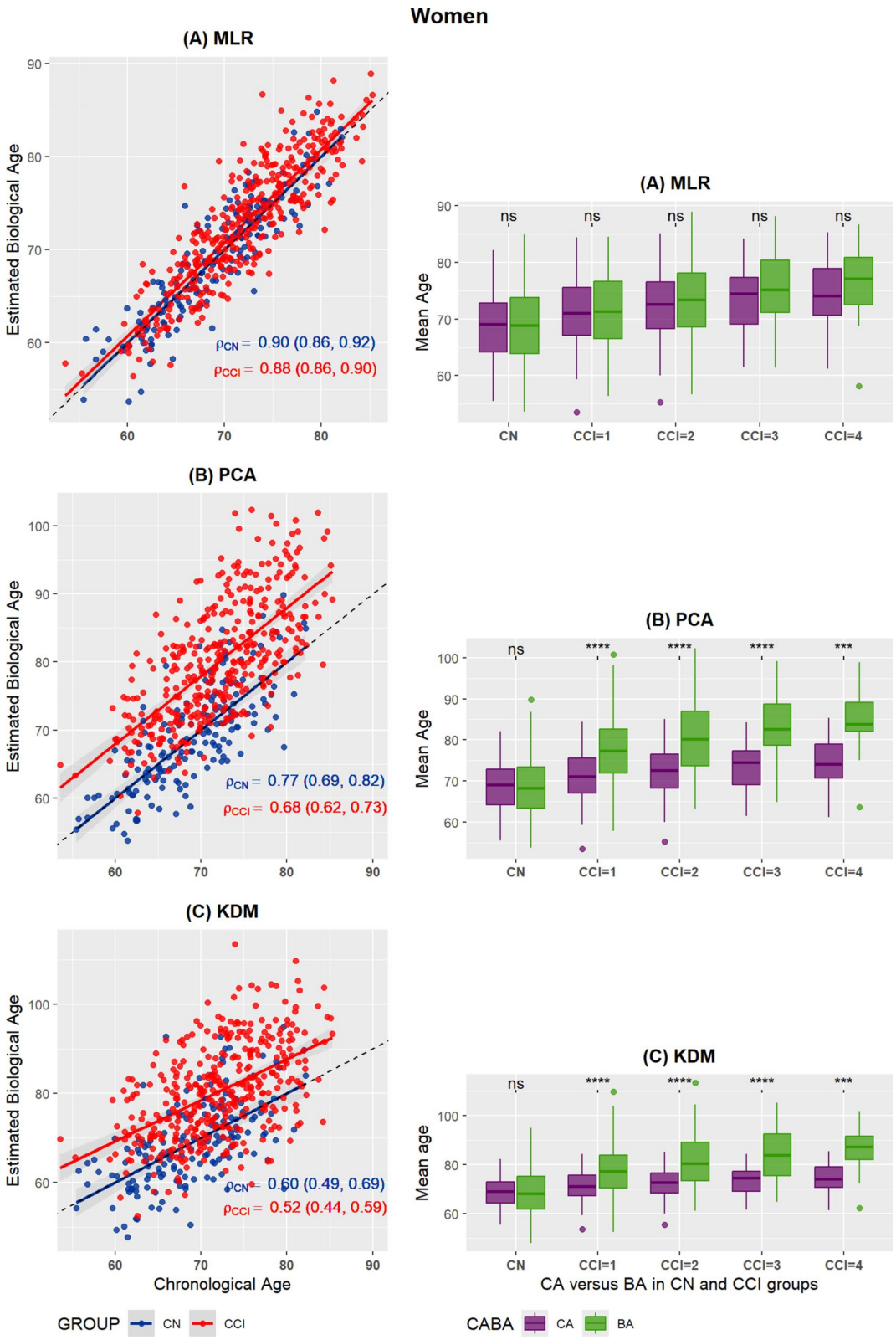
In this section, we compared the predictive power of CA, BA from MLR, BA from PCA, and BA from KDM methods in identifying the presence of comorbidities among all the participants. Additionally, we utilized the selected markers as a set of predictors to classify CCI individuals from CN people.

Figure 5 illustrated the receivers operating characteristics derived from logistic regression model across five different combinations of predictors, namely CA alone, BA from MLR, BA from PCA, BA from KDM, the eight selected markers in women or the six selected markers in men. Our finding revealed that BA models effectively predicted the CCI group better than CA alone. Among the BA models, the BA obtained from the PCA method yielded the highest AUC (95% CI) of 0.843 (0.729, 0.957) in women and the BA obtained from the KDM method produced the highest AUC (95% CI) of 0.853 (0.711, 0.995) in men. Statistically, the AUCs from PCA and KDM methods were significantly greater than that of CA, whereas that from MLR method did not show a significant difference in women. Additionally, the AUCs obtained from the selected aging markers were statistically comparable to the best BA models in both women and men. Lastly, we combined frontal executive domain score and reactance-lower as a simpler set of two potential aging predictors to classify healthy control and comorbidity group. Comparing with the full age markers, the performance of this two-predictors model was poorer in both women and men but not in women but comparable to that obtain from the best BA model.

Discussions

This study investigated the potential of using BIA and SNSB variables as novel aging markers for older individuals. We found that these markers exhibit linear transformations with age, reflecting reductions in body height, body reactance and phase angle, along with an increase in total body water in fat free mass in both women and men. Furthermore, while cognitive functions also declined during the aging process in both gender, waist circumference and systolic blood pressure increased in women and arm circumference decreased in men. Among the numerous variables, a few key markers emerged as particularly significant in capturing biological changes during aging, such as body reactance from the BIA method and scores in the frontal domain of the SNSB.

Numerous studies have highlighted the connection between changes in body composition and the aging process. Aging is commonly linked to a decline in lean mass and an increase in fat mass, resulting in abnormal water distribution and reduced cellular health (Martín et al. 2018). These indicators are sex-specific and critical in detecting changes in body composition, particularly in older adults (Briand


Women
(A) MLR
Estimated Biological Age
ρCN = 0.90 (0.86, 0.92)
ρCCI = 0.88 (0.86, 0.90)
(A) MLR
Mean Age
ns
CN
CCI=1
CCI=2
CCI=3
CCI=4
(B) PCA
Estimated Biological Age
ρCN = 0.77 (0.69, 0.82)
ρCCI = 0.68 (0.62, 0.73)
(B) PCA
Mean Age
ns
****
***
(C) KDM
Estimated Biological Age
ρCN = 0.60 (0.49, 0.69)
ρCCI = 0.52 (0.44, 0.59)
Chronological Age
(C) KDM
Mean age
CA versus BA in CN and CCI groups
GROUP CN CCI
CABA CA BA

◂**Fig. 3** In women. (*Left*) Scatterplot illustrating the distributions of CA and BA derived from the **a** MLR method, **b** PCA method, and (C) KDM method in the normal control (CN) (blue) and group with comorbidities (CCI) (red). ρ is the correlation coefficient. (*Right*) Boxplot comparing the mean CA and respective BAs in the CN and each CCI subgroups. Asterisks indicate statistical significance: ***$p < 0.001$, ****$p < 0.0001$; "ns" denotes not significant

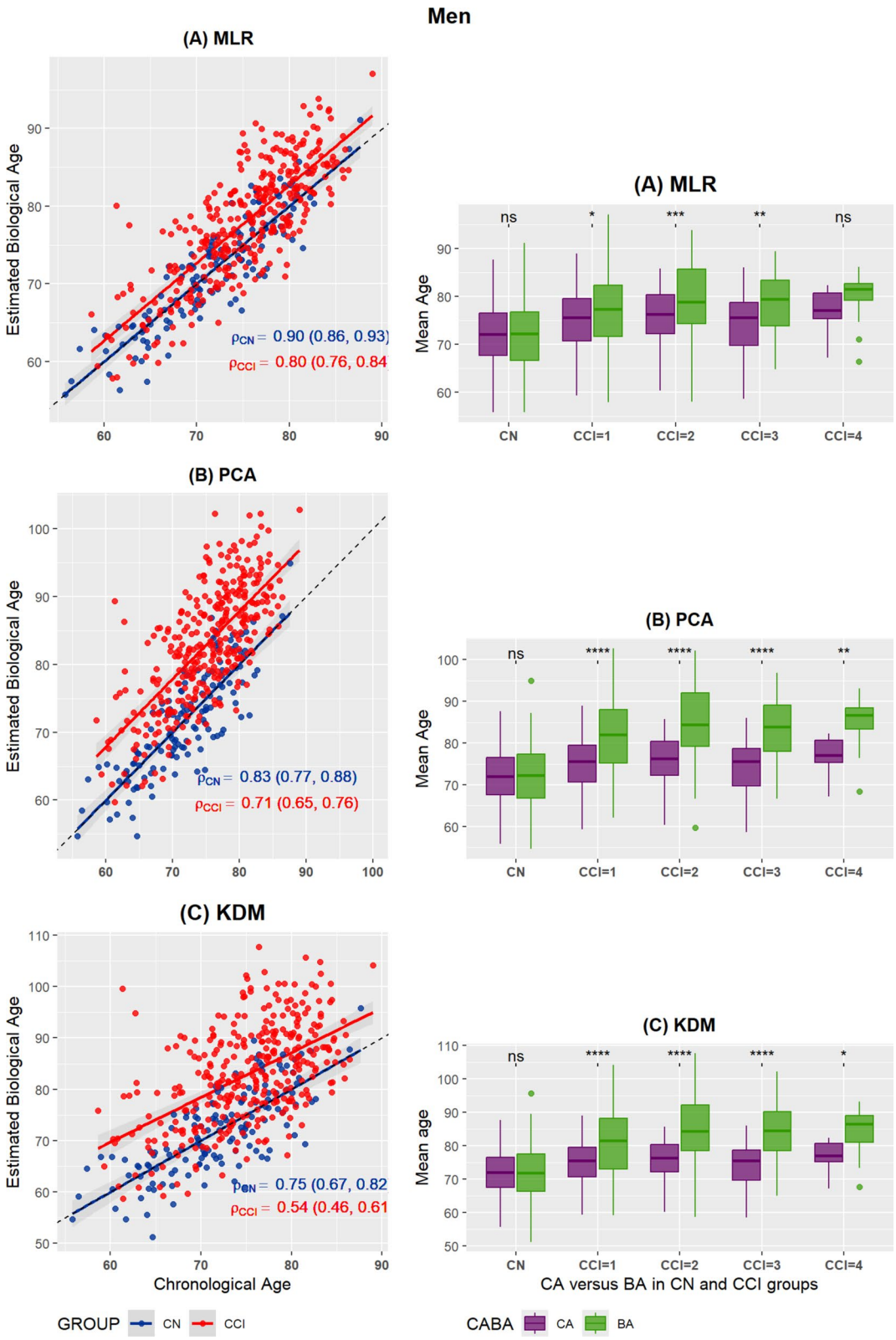
et al. 2024). In confirming these findings, our study demonstrates that age leads to an increase in fat mass indicators, such as waist circumference in females, and a decrease in lean mass indicators, such as arm circumference in males, along with an increase in water content in fat-free mass.

Interestingly, we found that BIA body reactance, a measure of cellular health and membrane integrity (Kyle et al. 2004a, b; Azevedo et al. 2013), to be the potential indicative factor of aging. Cellular health and cell membrane integrity are crucial indicators of age acceleration (López-Otín et al. 2013). As cells age, their membranes become more vulnerable to damage, leading to increased permeability and loss of homeostasis (López-Otín et al. 2023). This allows harmful agents, such as toxins and inflammatory cytokines, to infiltrate cells, accelerating aging and contributing to age-related diseases (Franceschi et al. 2018). Preserving cellular and membrane integrity is essential for preventing premature aging and promoting longevity (DiLoreto and Murphy 2015). López-Otín and Kroemer (2024) emphasized the importance of maintaining barrier integrity to reduce age-related physiological decline (López-Otín and Kroemer 2024). Poorer cell health and reduced muscle mass are often associated with lower reactance value, which can be indicators of sarcopenia and overall frailty which often seen in older people (Yamada et al. 2013). This finding suggests body reactance to be a critical marker of cellular health in assessing biological age in older adults.

On the cognition aspect, it is commonly known that cognitive functions decline during the aging process, influenced by various neurobiological and environmental factors. Research indicates that age-related changes in brain structure significantly correlate with declines in attention, memory, and frontal executive functions (Coffey et al. 2001). Although not all older adults experience cognitive declines, scores across various cognitive domains tend to gradually diminish with age, a pattern consistent with our findings. In this study, among the five cognitive domains assessed by the SNSB, the frontal function emerged as the strongest age-related cognitive marker for both women and men. This domain encompasses executive functions, working memory, and multitasking, which tend to decline with age, even in cognitively healthy individuals (Buckner 2004; Turner and Spreng 2012). Previous research has observed that age-related declines in executive functions is a key feature of brain aging, supporting our finding that frontal domain score, emerged among other cognitive functions, serve as a robust indicator of cognitive aging (Goh et al. 2013).

Following the stepwise selection methods, we selected significant and less inter-correlated variables across various aging models to construct BA formulas and produce BA scores. Our findings show that the scores of BA were better able to distinguish unhealthy individuals with comorbidities from healthy controls. This is in line with the earlier studies which biological markers can offer a more accurate reflection of an individual's health compared to CA because they embody the changes, physiological and pathological that come with age (Levine 2013; Zhong et al. 2020). Among the three models, PCA and KDM approaches produced better prediction outcome than MLR method, consistent with previous studies (Wei et al. 2022, Kwon and Belsky 2021). Interestingly, the BA that derives from PCA worked well for women, whereas KDM worked well for men. These findings highlight the importance of considering sex-specific approaches when assessing biological aging.

Between women and men, the aging markers such as frontal, reactance-lower, and TBWFFFR exhibited relatively stronger correlations with CA in men compared with that in women. This suggests that older men experience more pronounced reductions in frontal function and cellular integrity, along with a greater increase in the water ratio of fat-free mass as they age. Previous studies have highlighted distinct differences between men and women regarding cognitive function and body composition as they age (Bredella 2017; Kheloui et al. 2023). In terms of cognitive function, research has shown that women tend to retain certain cognitive abilities, such as episodic memory tasks and verbal ability, were better performed by women than men, while men may be more advantaged in visuospatial tasks (Kheloui et al. 2023). This may be partly due to hormonal differences, as estrogen has been shown to play a protective


Men
(A) MLR
Estimated Biological Age
ρCN = 0.90 (0.86, 0.93)
ρCCI = 0.80 (0.76, 0.84
(A) MLR
Mean Age
ns
*
***
**
ns
CN
CCI=1
CCI=2
CCI=3
CCI=4
(B) PCA
Estimated Biological Age
ρCN = 0.83 (0.77, 0.88)
ρCCI = 0.71 (0.65, 0.76)
(B) PCA
Mean Age
ns
****
****
****
**
(C) KDM
Estimated Biological Age
ρCN = 0.75 (0.67, 0.82
ρCCI = 0.54 (0.46, 0.61
Chronological Age
(C) KDM
Mean age
ns
****
****
****
*
CA versus BA in CN and CCI groups
GROUP CN CCI
CABA CA BA

◂**Fig. 4** In men. Caption identical to Fig. 3

role in cognitive aging in women, particularly in the frontal regions of the brain (Henderson 1997). Reactance, a marker of cellular integrity and membrane function, which is associated with a greater loss of muscle mass and cellular strength, tends to particularly decrease in the lower extremities (Doan et al. 2023; Yamada et al. 2013). TBWFFMR is also usually found to increase with age in both sexes, reflecting a shift towards higher extracellular water content as lean mass declines (Kyle et al. 2004a, b). In this study, both reactance and TBWFFMR changed more pronouncedly in men than in women. These sex variations might be caused by not only genetic and hormone factors but also life course exposures (Horstman et al. 2012; Hägg and Jylhävä 2021) that may explain the stronger predictive power for distinguishing health status is in men than in women in our study.

Interestingly, our analysis revealed that individuals in the CCI group consistently exhibited higher BAs compared to their CA, suggesting that the early onset of health conditions often reflect accelerated aging. The CCI is a well-established tool used to quantify the cumulative impact of comorbidities, often reflecting an individual's overall health burden (Charlson et al. 1987). This discrepancy suggests that individuals with multiple health issues may experience accelerated aging processes, which could lead to increased morbidity and mortality risks (Chen et al. 2023). Importantly, the ability of BA, particularly when derived from PCA and KDM methods, to predict comorbidities more effectively than CA highlights its relevance in clinical contexts. By identifying individuals at risk earlier, healthcare providers can implement proactive interventions to the specific needs of patients with elevated BA, potentially delaying the onset of further complications (Jylhävä et al. 2017; Levine 2013). This underscores the importance of integrating biological measures into routine assessments to improve health outcomes for aging populations.

The successful identification of significant aging markers, including reactance-lower, frontal executive domain score, and the other brain and body composition metrics, reinforces the notion that a multifaceted approach is necessary to accurately gauge biological aging. Worth mentioning, the sample in this study, with a mean age of 70 years, was used to generate BA scores, providing valuable insights into aging patterns in late adulthood. Although not ideal for representing the full aging spectrum, this age group captures key physiological and cognitive changes typical of older individuals, particularly for conditions like frailty and cognitive decline (López-Otín et al. 2013). Studies suggest that BA assessments are more accurate when the reference population closely matches the demographic, especially in age (Horvath 2013). While this limits generalization to younger cohorts, our approach is suitable for understanding biological aging in older populations. Future research should aim to validate these models across broader age ranges.

In conclusion, this study explores the possible contributions of BIA and SNSB measures as potential aging markers and emphasizes the importance of utilizing BA as a more reliable indicator of health status than CA, particularly in individuals with comorbidities. The integration of advanced statistical methodologies and diverse aging markers paves the way for a better understanding of the aging process and its implications for health and longevity. Future research should aim to refine these models further and explore their applicability in broader clinical contexts.

Despite the promising results, our study has several limitations. The sample size for control group was relatively small and drawn from a specific older community in Gwangju City, South Korea, which may limit the generalizability of our findings. Future studies with larger and more diverse populations are warranted to validate the predictive models across different demographic groups and geographical regions. Additionally, although trying to reduce the redundant variables, there were still significant multicollinearity between predictors. Finally, incorporating additional biomarkers or imaging modalities alongside BIA and SNSB measures could enhance the accuracy and comprehensiveness of age prediction models.

Conclusion

This study underscores the significance of BA as a more accurate reflection of health status than CA, particularly in the older individuals with comorbidities. By utilizing BIA and SNSB measures, we identified critical aging markers, including reactance and

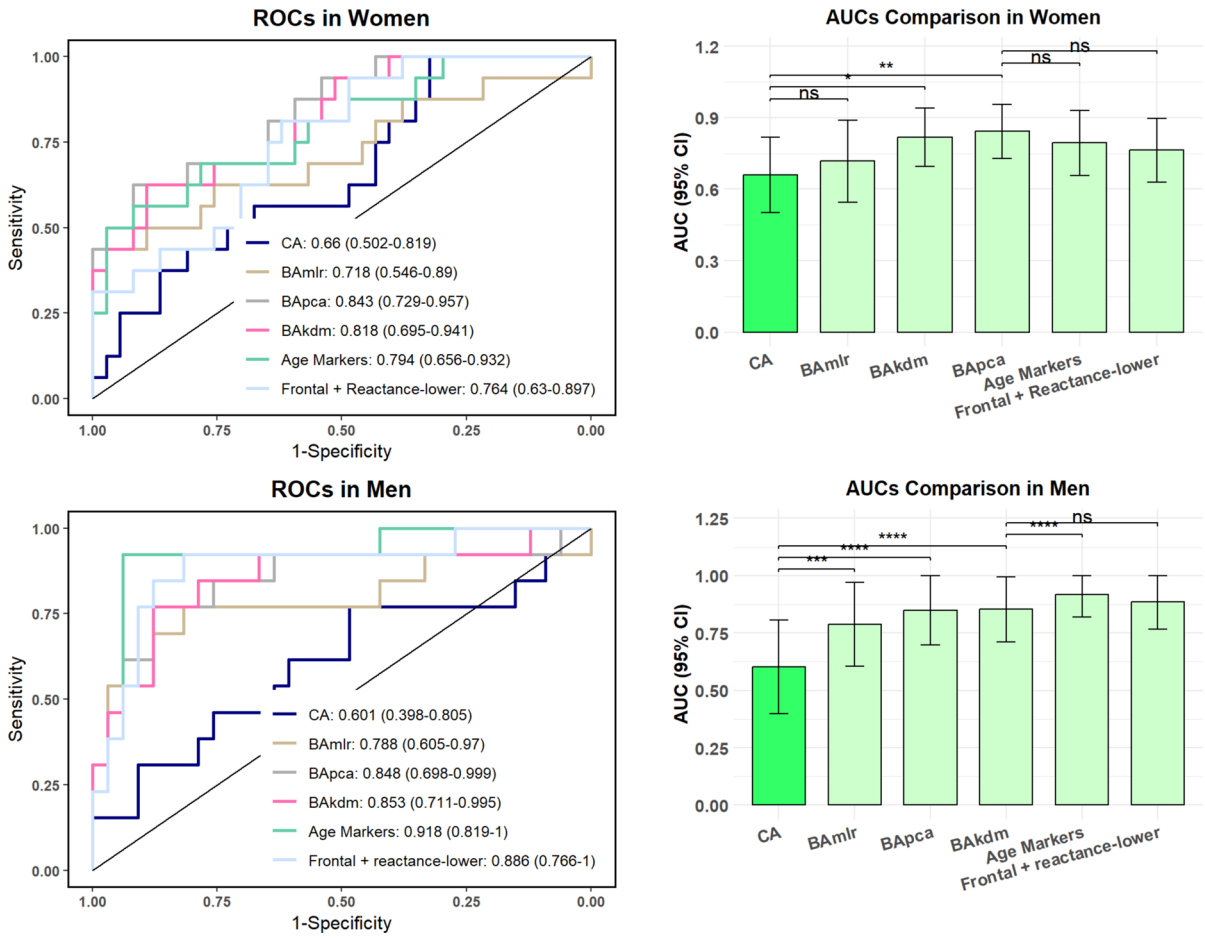


Fig. 5 Receiver operating characteristic curves of the logistic regression model obtained from six sets of predictors, showcasing the comparisons of the area under the curves (AUC) using the DeLong method. Asterisks indicate statistical significance: *p < 0.05, **p < 0.01, *** < 0.001, **** < 0.0001; "ns" denotes not significant

frontal domain scores, that correlate strongly with biological aging processes. Our findings reveal that individuals in the CCI group exhibit higher BA than CA, suggesting that multiple health conditions accelerate the aging process and increase the risk of morbidity and mortality. The superior predictive capabilities of BA derived from PCA and KDM further demonstrate the need for integrating these methods in clinical assessments. Future research should continue to refine and validate these models across diverse populations to enhance their generalizability and applicability in clinical settings.

Acknowledgements We thank all the contributors of this study.

Author's contributions D.D. analyzed the data and wrote the manuscript. B.K. preprocessed the data. K.K. and K.L. handled data collection and curation. J.U.K. designed the study and wrote the manuscript. All authors revised and approved the contents of the manuscript, contributed to the article, and approved the submitted version.

Funding This study was supported by the Korea Institute of Oriental Medicine (KIOM; Grant no.: KSN2313022) funded by the Korean government.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

Aleixo GF, Shachar SS, Nyrop KA, Muss HB, Battaglini CL, Williams GR (2020) Bioelectrical impedance analysis for the assessment of sarcopenia in patients with cancer: a systematic review. Oncologist 25(2):170–182. https://doi.org/10.1634/theoncologist.2019-0600

Azevedo ZMA, Moore DCBC, de Matos FAA, Fonseca VM, Peixoto MVM, Gaspar-Elsas MIC et al (2013) Bioelectrical impedance parameters in critically ill children: importance of reactance and resistance. Clin Nutr 32(5):824–829. https://doi.org/10.1016/j.clnu.2013.01.011

Bae CY, Kang YG, Kim S, Cho C, Kang HC, Yu BY et al (2008) Development of models for predicting biological age (BA) with physical, biochemical, and hormonal parameters. Arch Gerontol Geriatr 47(2):253–265. https://doi.org/10.1016/j.archger.2007.08.009

Baker GT III, Sprott RL (1988) Biomarkers of aging. Exp Gerontol 23(4–5):223–239. https://doi.org/10.1016/0531-5565(88)90025-3

Baumgartner RN (2000) Body composition in healthy aging. Ann N Y Acad Sci 904(1):437–448. https://doi.org/10.1111/j.1749-6632.2000.tb06498.x

Berrar D (2019) Cross-validation. https://doi.org/10.1016/b978-0-323-95502-7.00032-4

Bredella MA (2017) Sex differences in body composition. In: Sex and gender factors affecting metabolic homeostasis, diabetes and obesity, pp 9–27. https://doi.org/10.1007/978-3-319-70178-3_2

Briand M, Raffin J, Gonzalez-Bautista E, Ritz P, Abellan Van Kan G, Pillard F et al (2024) Body composition and aging: cross-sectional results from the INSPIRE study in people 20 to 93 years old. GeroScience, pp 1–13. https://doi.org/10.1007/s11357-024-01245-6

Buckner RL (2004) Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44(1):195–208. https://doi.org/10.1016/j.neuron.2004.09.006

Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chen L, Zhang Y, Yu C, Guo Y, Sun D, Pang Y et al (2023) Modeling biological age using blood biomarkers and physical measurements in Chinese adults. EBioMedicine, 89. https://doi.org/10.1016/j.ebiom.2023.104458

Cho IH, Park KS, Lim CJ (2010) An empirical comparative study on biological age estimation algorithms with an application of Work Ability Index (WAI). Mech Ageing Dev 131(2):69–78. https://doi.org/10.1016/j.mad.2009.12.001

Coffey CE, Ratcliff G, Saxton JA, Bryan RN, Fried LP, Lucke JF (2001) Cognitive correlates of human brain aging: a quantitative magnetic resonance imaging investigation. J Neuropsychiatry Clin Neurosci 13(4):471–485. https://doi.org/10.1176/jnp.13.4.471

Crimmins EM, Shim H, Zhang YS, Kim JK (2019) Differences between men and women in mortality and the health dimensions of the morbidity process. Clin Chem 65(1):135–145. https://doi.org/10.1373/clinchem.2018.288332

DiLoreto R, Murphy CT (2015) The cell biology of aging. Mol Biol Cell 26(25):4524–4531. https://doi.org/10.1091/mbc.E14-06-1084

Doan DNT, Ku BU, Jun MH, Lee KH, Kim GU, Kim JU (2023) Segmental bioimpedance variables in association with mild cognitive impairment due to Alzheimer disease. Alzheimers Dement 19:e064424. https://doi.org/10.1002/alz.064424

Dubina TL, Dyundikova VA, Zhuk EV (1983) Biological age and its estimation. II. Assessment of biological age of albino rats by multiple regression analysis. Exp Gerontol 18(1):5–18. https://doi.org/10.1016/0531-5565(83)90046-3

Fleming VB (2014) Early detection of cognitive-linguistic change associated with mild cognitive impairment. Commun Disord Q 35(3):146–157. https://doi.org/10.1177/1525740113520322

Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A (2018) Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 14(10):576–590. https://doi.org/10.1038/s41574-018-0059-4

Garlini LM, Alves FD, Ceretta LB, Perry IS, Souza GC, Clausell NO (2019) Phase angle and mortality: a systematic review. Eur J Clin Nutr 73(4):495–508. https://doi.org/10.1038/s41430-018-0159-1

Goh JO, Beason-Held LL, An Y, Kraut MA, Resnick SM (2013) Frontal function and executive processing in older adults: process and region specific age-related longitudinal functional changes. Neuroimage 69:43–50. https://doi.org/10.1016/j.neuroimage.2012.12.026

Hägg S, Jylhävä J (2021) Sex differences in biological aging with a focus on human studies. Elife 10:e63425. https://doi.org/10.7554/elife.63425

Henderson VW (1997) Ageing, oestrogen and the brain. Br Menopause Soc J 3(3):15–21. https://doi.org/10.1177/136218079700300306

Ho KM, Morgan DJ, Johnstone M, Edibam C (2023) Biological age is superior to chronological age in predicting hospital mortality of the critically ill. Intern

Emerg Med 18(7):2019–2028. https://doi.org/10.1007/s11739-023-03397-3
Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M (2012) The role of androgens and estrogens on healthy aging and longevity. J Gerontol A Biomed Sci Med Sci 67(11):1140–1152. https://doi.org/10.1093/gerona/gls068
Horvath S (2013) DNA methylation age of human tissues and cell types. Genome Biol 14:1–20. https://doi.org/10.1186/gb-2013-14-10-r115
Iachini T, Iavarone A, Senese VP, Ruotolo F, Ruggiero G (2009) Visuospatial memory in healthy elderly, AD and MCI: a review. Curr Aging Sci 2(1):43–59. https://doi.org/10.2174/1874609810902010043
Jeon KC, Kim SY, Jiang FL, Chung S, Ambegaonkar JP, Park JH, Kim YJ, Kim CH (2020) Prediction Equations of the Multifrequency Standing and Supine Bioimpedance for Appendicular Skeletal Muscle Mass in Korean Older People. Int J Environ Res Public Health 17(16):5847. https://doi.org/10.3390/ijerph17165847
Jylhävä J, Pedersen NL, Hägg S (2017) Biological age predictors. Ebiomedicine 21:29–36. https://doi.org/10.1016/j.ebiom.2017.03.046
Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES et al (2014) Geroscience: linking aging to chronic disease. Cell 159(4):709–713. https://doi.org/10.1016/j.cell.2014.10.039
Kheloui S, Jacmin-Park S, Larocque O, Kerr P, Rossi M, Cartier L, Juster RP (2023) Sex/gender differences in cognitive abilities. Neurosci Biobehav Rev, 105333. https://doi.org/10.1016/j.neubiorev.2023.105333
Kim, J. H., Choi, S. H., Lim, S., Kim, K. W., Lim, J. Y., Cho, N. H., Park, K. S., & Jang, H. C. (2014). Assessment of appendicular skeletal muscle mass by bioimpedance in older community-dwelling Korean adults. Arch Gerontol & Geriatr 58(3):303–307. https://doi.org/10.1016/j.archger.2013.11.002
Klemera P, Doubal S (2006) A new approach to the concept and computation of biological age. Mech Ageing Dev 127(3):240–248. https://doi.org/10.1016/j.mad.2005.10.004
Kwon D, Belsky D (2021) Biological age calculations using data from the National Health and Nutrition Examination Survey (NHANES). J Gerontol 76(5):819–828
Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM et al (2004a) Bioelectrical impedance analysis—part I: review of principles and methods. Clin Nutr 23(5):1226–1243. https://doi.org/10.1016/j.clnu.2004.06.004
Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM et al (2004b) Bioelectrical impedance analysis—part II: utilization in clinical practice. Clin Nutr 23(6):1430–1453. https://doi.org/10.1016/j.clnu.2004.09.012
Levine ME (2013) Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol Series A Biomed Sci Med Sci 68(6):667–674. https://doi.org/10.1093/gerona/gls233
López-Otín C, Kroemer G (2024) The missing hallmark of health: psychosocial adaptation. Cell Stress 8:21–50. https://doi.org/10.15698/cst2024.03.294
López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153(6):1194–1217. https://doi.org/10.1016/j.cell.2013.05.039
López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023) Hallmarks of aging: an expanding universe. Cell 186(2):243–278. https://doi.org/10.1016/j.cell.2022.11.001
Martín MC, de Mateo Silleras B, del Río MR (2018) Body composition in older adults. In: Conn's Handbook of Models for Human Aging. Academic Press, New York, pp. 69–78. https://doi.org/10.1016/b978-0-12-811353-0.00006-3
Nakamura E, Miyao K, Ozeki T (1988) Assessment of biological age by principal component analysis. Mech Ageing Dev 46(1–3):1–18. https://doi.org/10.1016/0047-6374(88)90109-1
Park DC, Festini SB (2017) Theories of memory and aging: a look at the past and a glimpse of the future. J Gerontol B Psychol Sci Soc Sci 72(1):82–90. https://doi.org/10.1093/geronb/gbw066
Ryu HJ, Yang DW (2023) The Seoul neuropsychological screening battery (SNSB) for comprehensive neuropsychological assessment. Dementia Neurocogn Disorders 22(1):1. https://doi.org/10.12779/dnd.2023.22.1.1
Tibshirani R (1996) Regression shrinkage and selection via the lasso. J R Stat Soc Ser B Stat Methodol 58(1):267–288. https://doi.org/10.1111/j.2517-6161.1996.tb02080.x
Tomeleri CM, Cavaglieri CR, de Souza MF, Cavalcante EF, Antunes M, Nabbuco HCG et al (2018) Phase angle is related with inflammatory and oxidative stress biomarkers in older women. Exp Gerontol 102:12–18. https://doi.org/10.1016/j.exger.2017.11.019
Turner GR, Spreng RN (2012) Executive functions and neurocognitive aging: dissociable patterns of brain activity. Neurobiol Aging 33(4):826-e1. https://doi.org/10.1016/j.neurobiolaging.2011.06.005
Wei Y, Li X, Zhou Z (2022) The Klemera-Doubal method and its association with all-cause mortality. Aging Cell, 21
Yakhno NN, Zakharov VV, Lokshina AB (2007) Impairment of memory and attention in the elderly. Neurosci Behav Physiol 37(3):203. https://doi.org/10.1007/s11055-007-0002-y
Yamada M, Nishiguchi S, Fukutani N, Tanigawa T, Yukutake T, Kayama H et al (2013) Prevalence of sarcopenia in community-dwelling Japanese older adults. J Am Med Dir Assoc 14(12):911–915. https://doi.org/10.1016/j.jamda.2013.08.015
Zhong X, Lu Y, Gao Q, Nyunt MSZ, Fulop T, Monterola CP et al (2020) Estimating biological age in the Singapore longitudinal aging study. J Gerontol Series A 75(10):1913–1920. https://doi.org/10.1093/gerona/glz146