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Research Article

Beyond Chronological Age: A Multidimensional Approach to Survival Prediction in Older Adults

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Abstract

Background: There is a growing interest in generating precise predictions of survival to improve the assessment of health and life-improving interventions. We aimed to (a) test if observable characteristics may provide a survival prediction independent of chronological age; (b) identify the most relevant predictors of survival; and (c) build a metric of multidimensional age.

Methods: Data from 3 095 individuals aged ≥60 from the Swedish National Study on Aging and Care in Kungsholmen. Eighty-three variables covering 5 domains (diseases, risk factors, sociodemographics, functional status, and blood tests) were tested in penalized Cox regressions to predict 18-year mortality.

Results: The best prediction of mortality at different follow-ups (area under the receiver operating characteristic curves [AUROCs] 0.878–0.909) was obtained when 15 variables from all 5 domains were tested simultaneously in a penalized Cox regression. Significant prediction improvements were observed when chronological age was included as a covariate for 15- but not for 5- and 10-year survival. When comparing individual domains, we find that a combination of functional characteristics (ie, gait speed, cognition) gave the most accurate prediction, with estimates similar to chronological age for 5- (AUROC 0.836) and 10-year (AUROC 0.830) survival. Finally, we built a multidimensional measure of age by regressing the predicted mortality risk on chronological age, which displayed a stronger correlation with time to death (R = –0.760) than chronological age (R = –0.660) and predicted mortality better than widely used geriatric indices.

Conclusions: Combining easily accessible characteristics can help in building highly accurate survival models and multidimensional age metrics with potentially broad geriatric and biomedical applications.

Keywords: Biological age, Chronological age, Multidimensional assessment, Personalized medicine, Survival

One of the most important understandings of the last years is that no single parameter can capture the complexity of aging and fully reflect how biologically old we have become (1,2). At the same time, the need has grown for clinicians, public health policymakers, and researchers to be able to predict individuals' risk of developing negative health outcomes. Even though chronological age can provide useful indications, better predictions are needed (3). Early identification of people with an unexpectedly high or low relative health status could help, for example, to adjust their lifestyle and implement prevention strategies to delay severe disease and disability onset. Additionally, optimal measures of biological age and health could help to determine the medical benefits of various treatments and interventions. To this end, several biological clocks and frailty measures have been proposed (4,5)

First-generation biological clocks are based on the linear prediction of chronological age, using, among others, DNA methylation status, telomere length, metabolomics, or their combination (6–8). Such tools can predict chronological age with exceptional precision across different populations and in different tissues. However, their performance in predicting geriatric phenotypes as well as survival has not always been optimal (9). On the one hand, this may be caused by such clocks being based on the biological variance of drivers (eg, genetic, or epigenetic) that reside far upstream from the outcomes that are being predicted, namely disease and death (10). On the other hand, being developed by predicting chronological age, these metrics could fail to fully capture the biological heterogeneity within people of the same chronological age (11). To overcome these limitations, a new generation of aging metrics have been developed based on individuals' phenotype or health traits (eg, diseases, functional status, serum biomarkers, etc.) and aiming to predict time to death instead of chronological age (9,12). Along these lines, several measures of frailty have been suggested, as a means to assess the accumulation of clinical and functional deficits, which reflect the downstream result of the interaction between genetics and environment (13).

In humans, chronological age is a strong predictor of disease development, functional decline, and remaining life expectancy (14). However, the accumulation of biological deficits that we experience between conception and death does not happen linearly across time. An interindividual mismatch in the association between chronological age, disease, and survival exists and becomes greater during the seventh and eighth decade of life (15). Such complexity and heterogeneity of the aging process make chronological age an imperfect proxy of our actual biological age. Still, due to its high predictive performance, chronological age remains largely employed in the new generation of age clocks (16), and the extent of its contribution to these clocks is not always reported among the studies' findings. Thus, the development of a measure that predicts survival better than chronological age alone, and that can do so even without using information on chronological age, remains an attractive goal. Finally, it is well-known that peoples' living conditions influence aging and health (17–19), but only a few of the abovementioned measures include such variables, for example, socioeconomic characteristics. The interest in health and survival prediction tools is growing fast, but there is still a basic lack of knowledge on the ability of variables from various domains to make precise survival predictions. Therefore, in this study we aimed (a) to determine the ability of observable characteristics from various health domains to predict short- and long-term mortality along with and beyond chronological age, (b) to quantify the relative contributions of these variables to mortality predictions and identify a minimum set of significant predictors, and (c) to derive—as proof of concept—a multidimensional metric of age that reflects both chronological age but also health status, and thereby provides superior predictions of mortality.

Materials and Methods

Study Population

Data were derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), including participants aged 60 years and older and living at home or in institutions. A random sample (n = 5 111) from 11 age cohorts born between 1982 and 1939 were invited to participate in the study. A total of 4 590 individuals were eligible and 73.3% (n = 3 363) attended the baseline examination conducted between March 2001 and June 2004. Follow-up assessments are performed every 6 years for individuals younger than 72 years and every 3 years for those 78 years or older. Over the 18 years of follow-up, participation rates have varied between 87.0% and 88.0%. In the current study, we included 3 095 participants after excluding 268 people with more than 50% of missing data. Excluded people were more likely to be older (84.5 vs 73.9 years, p value < .001), women (78.0% vs 63.7%, p value < .001), and with low education (35.1% vs 16.4%, p value < .001). The Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm, Sweden, approved baseline and follow-up protocols of the SNAC-K study. All participants or a proxy (in the case of cognitively impaired persons) provided written informed consent.

Data Collection

During baseline and follow-up visits, SNAC-K participants undergo comprehensive assessments including face-to-face interviews, clinical examinations, and laboratory tests by trained staff following standard procedures. The predictors considered in the present study were divided in 5 domains.

The *sociodemographic characteristics* domain includes 6 variables obtained through face-to-face interviews by trained nurses. (i) Educational level was measured as total years of formal schooling and categorized as primary (<8 years) and secondary or above (≥8 years). (ii) Marital status was categorized as partnered (including married or equivalent, in case of civil union, and living together) and single (including widowed, unmarried, and divorced). (iii) Living arrangement was divided into living in the community and living in an institution. (iv) Gender. (v) Social connections were estimated considering the following data: marital status, living arrangement, parenthood, and friendships. We also asked about the number of living children, and the frequency of direct or remote contacts with relatives, neighbors, and friends. The social connections index was calculated as the average of the abovementioned normalized variables. (vi) Social support was assessed based on the following items: reported satisfaction with aforementioned contacts, perceived material and psychological support, and sense of affinity with relatives and residence area. The social support index was calculated as the average of the abovementioned normalized variables (20).

The *risk factors* domain includes 7 characteristics. (i) Smoking history was assessed by asking participants whether they had ever smoked, how long they have smoked, and the number of cigarettes smoked per day. We categorized the participants as never or former smokers and current smokers. (ii) Alcohol consumption was categorized based on the quantity and frequency of alcohol intake: never/occasional (never or a standard drink per month) or light/moderate (less than 4 standard drinks a week for men; less than 2 standard drinks a week for women), and heavy (more than 5 standard drinks a week for men; more than 3 standard drinks a week for women). A standard drink was defined as 45 cl of medium–strong beer, 33 cl of strong beer, a glass of red or white wine, a small glass of fortified wine, or 4 cl of liquor. (iii) Body mass index was obtained by dividing the weight by their squared height. (iv and v) Systolic and diastolic blood pressure. Arterial blood pressure was measured twice at a 5-minute interval in a sitting position on the left arm with a sphygmomanometer, and the mean of the 2 readings was considered. (vi) Sleep disorder. (vii) Dyslipidemia.

The *functional status* domain includes 5 characteristics. Physical performance was assessed by walking speed and grip strength test. (i) Walking speed was measured by asking the participants to walk 6

or 2.4 m at their usual speed. (ii) Grip strength was assessed through a validated dynamometer (Grippit). (iii) Disability was defined by the number of limitations in activities of daily living (ADL)—bathing, dressing, toileting, transferring, and eating—and (iv) instrumental activities of daily living (I-ADL)—grocery shopping, managing money, using the telephone, and using public transportation. (v) Global cognitive function was measured with the Mini-Mental State Examination (MMSE).

The *chronic diseases* domain includes 51 chronic conditions. Physicians collected information on diagnoses of chronic diseases via physical examination, medical history, consulting medical charts, lab tests, and from the Swedish National Patient Registry system. All diagnoses were coded in accordance with the International Classification of Disease, 10th revision (21). The following diseases were considered: allergy, autoimmune diseases, cataract and lens diseases, chronic infectious diseases, chronic ulcer of the skin, ear nose and throat diseases, glaucoma, inflammatory bowel diseases, neurotic stress somatoform disorders, other musculoskeletal and joint diseases, other eye diseases, other neurological diseases, Parkinson and Parkinsonism, prostate diseases, thyroid diseases, dementia, bradycardias and conduction diseases, anemia, visual impairment, deafness and hearing loss, chronic kidney disease, chronic obstructive pulmonary disease, epilepsy, heart failure, ischemic heart disease, osteoarthritis degenerative joint diseases, other cardiovascular diseases, other genitourinary diseases, other psychiatric and behavioral diseases, peripheral neuropathy, schizophrenia and delusional disorders, venous and lymphatic diseases, depression and mood diseases, cardiac valve diseases, asthma, hematologic diseases, colitis and related diseases, chronic pancreatic and biliary diseases, dorsopathies, upper digestive diseases, inflammatory arthropathies, migraine and facial pain syndromes, osteoporosis, other digestive diseases, other metabolic diseases, other respiratory diseases, peripheral vascular diseases, solid neoplasms, cerebrovascular diseases, atrial fibrillation, diabetes.

The *blood tests* domain includes 14 routine parameters. Venous blood samples were taken at baseline (fasting was not compulsory) and analyses were performed following standard procedures within 2 hours from sampling at Karolinska Hospital in Stockholm. The following analytes were considered: hemoglobin, creatinine, total cholesterol, leucocytes, calcium, glycated hemoglobin, vitamin B12, thryroid-stimulating hormone [Thyroid Stimulating Hormone (TSH)], alkaline phosphatase, thyroxine, albumin, folic acid, C-reactive protein (CRP), gamma glutamyl transferase (GT).

Survival status

Information about the vital status of the participants was derived from the National Death Registry provided by Statistics Sweden from SNAC-K baseline until December 31, 2016, and assessed directly by SNAC-K nurses, by means of regular telephone contacts with participants and their relatives, until January 2019.

Statistical Analyses

Data analysis

All analysis were carried out in R version 4.1.2 (2021-11-01), using the magrittr package (22) and packages loaded by the tidyverse library (23). Pearson correlation was calculated with the base R function "cor."

Data imputation

Only a small fraction of data was missing (0.7%). Variables with missing values (Supplementary Table 1) were imputed using the multivariate imputation by chained equations method, via the R package mice (24,25) with the predictive mean matching method (26), generating 5 imputed data sets. All the predictors and responses were used in the multiple imputation model. All data analyses were performed using the imputed data. Results from the complete case (n = 2 237) analyses are reported in all Supplementary Tables and Supplementary Figures. For all analyses performed on the imputed data sets, degrees of freedom (DOF) and pooled standard errors were estimated using Rubin's rule (27). For the complete case, the DOF was the number of observations minus the number of fitted variables. These DOF and standard errors were then used to derive the 95% confidence interval [Confidence Interval (CI)] based on the t-distribution.

Building and evaluating survival models for each domain

Cox proportional hazards models with ridge penalization were fitted, using the glmnet (28) and the caret (29) packages, in order to predict survival from different domains of variables. Multicollinearity is an issue with large numbers of variables. Ridge regularization alleviates this issue by biasing coefficients toward zero. Six domains were evaluated: sociodemographic (6 variables), diseases (51 variables), risk factors (7 variables), functional status (5 variables), blood tests (14 variables), and all domains (83 variables). Each domain was modeled with and without including chronological age as a covariate. A 10-fold cross-validation, with 5 repeats, was employed to select the optimal lambda parameter—which is the strength of the regularization—and to estimate model performance. In each testing fold, the corresponding model's ability to predict survival was assessed by computing the area under the receiver operating characteristic curve (AUROC) at 5, 10, and 15 years of follow-up, using a fast *auroc* function (30). The mean of the AUROC values at 5, 10, and 15 years was then computed. Standard errors were estimated as the standard deviations of AUROC values divided by the square root of the number of folds (i.e., 10). To find more parsimonious models with similar prediction performance, the same cross-validation procedure was repeated for each domain by building models using only significant variables (see next section).

Estimation of coefficient significance

In each domain, the optimal lambda value (highest mean AUROC across all folds) was used to build models with all observations. Standardized coefficients (31) were extracted to assess variable importance in each model. Coefficient variability was determined by bootstrapping: 1 000 bootstrap samples were generated for each data set, and L1-penalized Cox regression models were fitted, using the optimal lambda value. Standard errors were estimated as the standard deviation of bootstrapped coefficients. Finally, a 2-step test procedure was used to determine the 95% CIs corrected for multiple testing as described by Jung et al. (32). In the first step, a 2-sided t test was performed to determine significant coefficients after Benjamini–Hochberg (33) false discovery rate adjustment. In the second step, an adjusted significance level α^* was used to estimate the t-statistics from which was derived the margin of the CI. The adjusted significance level was computed as $\alpha^* = k \cdot \alpha / m$, with k being the number of significant coefficients and m the number of estimated coefficients.

Estimation of multidimensional age

Multidimensional age was derived from the models containing all domain variables (one for each imputed data set) built by including age and only significant variables (15 variables in total). Relative risks from each final Cox model were averaged across imputed data sets and

log2-transformed. Multidimensional age was estimated via weighted regression of log2-transformed relative risk on chronological age. Chronological age was split into 7 bins of similar size and each bin was given a similar weight overall. This weighting strategy was used because data are unbalanced with more individuals in the younger age bins. The cutting points used for binning were: 59, 63, 68.8, 74.6, 80.4, 86.2, 92, and 103. The R package cocor (34) was used to determine the significance of the difference between 2 correlation coefficients.

Computing Area Under the Curve (AUC) for single variables

For multidimensional age and other variables of interest, AUROCs were computed using the roc function from the pROC package (35). Standard errors were estimated using the method from DeLong et al. (36), as implemented in the var function of the pROC package. The following geriatric indices were chosen for this analysis: Health Assessment Tool (37), gait speed, disease count, handgrip strength, drug count, basic activities of daily living, and I-ADL.

Results

The mean age of the study sample was 73.9 ± 10.8 years, and 63.7% were females. During the 18 years of follow-up (median follow-up time 14 years), 1 729 (55.9%) participants died. Those who died, compared to survivors, were older, more likely to be single, to have lost their partner due to divorce or death, or to live in nursing homes, and they took more medications, had more diseases, and showed lower physical and cognitive performance (Table 1; Supplementary Tables 1, 2 and 3).

Mortality Prediction Based on Observable Characteristics and Chronological Age

We built several models to predict 5-, 10-, or 15-year mortality, by including the individual health domains, as well as the 83 candidate predictors at once, and testing the additive value of chronological age to the prediction. We found that models based solely on chronological age had a strong ability to predict survival (AUROC at 5 years: 0.822, at 10 years: 0.839, at 15 years: 0.871; Figure 1; Supplementary Table 4). They significantly outperformed all other domain-specific models at 15-year follow-up. While age had a significantly better ability to predict long-term than short-term survival, risk factors were significantly better at predicting short-term than long-term survival (AUROC at 5 years: 0.711, at 10 years: 0.680, at 15 years: 0.665). We observed that the functional status domain yielded the best predictions of survival despite being the domain

Table 1. Baseline Sample Characteristics by 18-Year Survival Status

Characteristics	Alive *N* = 1 366 (44.1)	Dead *N* = 1 729 (55.9)	Total *N* = 3 095
Chronological age (mean; *SD*)	66.1 ± 6.5	80 ± 9.5	73.9 ± 10.8
Female sex (count; %)	864 (63.3)	1 109 (64.1)	1 973 (63.7)
Living in institution (count; %)	2 (0.2)	65 (3.8)	67 (2.2)
MMSE score (mean; *SD*)	29.2 ± 1.3	27.2 ± 4.03	28.1 ± 3.3
Without partner (count; %)	529 (38.7)	1 114 (64.4)	1 643 (53.1)
BMI kg/m^2 (mean; *SD*)	26.2 ± 3.9	24.9 ± 4.12	25.5 ± 4.1
≥1 impaired B-ADL (count; %)	9 (0.659)	170 (9.83)	179 (5.8)
≥1 impaired I-ADL (count; %)	22 (1.61)	491 (28.4)	513 (16.6)
Hand grip strength, kg (mean; *SD*)	28.5 ± 11.9	20.6 ± 10.4	24.1 ± 11.7
Gait speed, m/s (mean; *SD*)	1.30 ± 0.30	0.78 ± 0.44	0.99 ± 0.50
Number of drugs (mean; *SD*)	2.8 ± 2.7	4.8 ± 3.5	3.89 ± 3.36
Number of diseases (mean; *SD*)	2.8 ± 1.8	4.9 ± 2.5	4.0 ± 2.5

Notes: ADL = activities of daily living; BMI = body mass index; MMSE = Mini-Mental State Examination; *N* = count of individuals; *SD* = standard deviation.

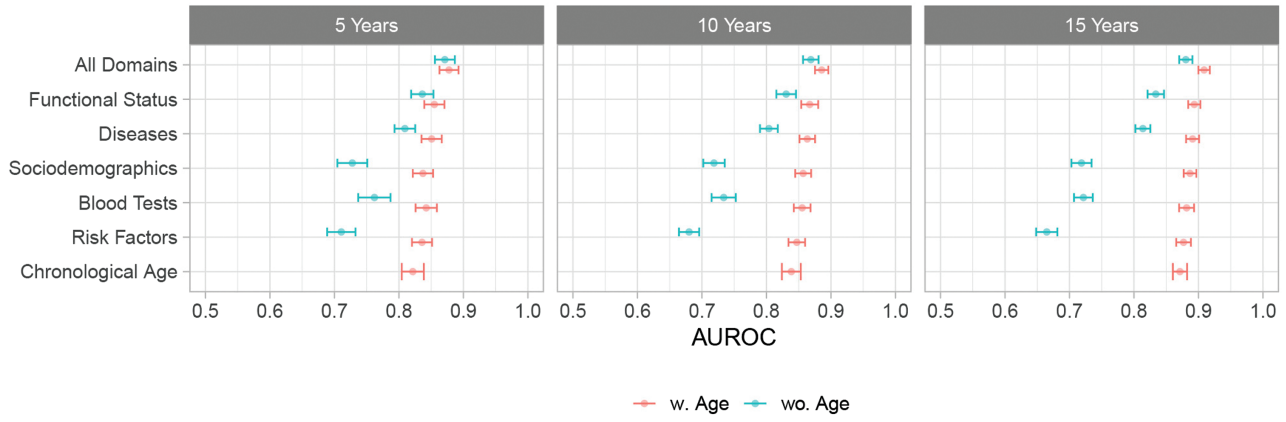

Figure 1. Accuracy (AUROC) of different health domains in predicting mortality. A 10-fold cross-validation strategy was used to estimate through penalized Cox regressions the predictive abilities of models built from various domains, after adjusting and not adjusting by chronological age. Domains were sorted by their mean AUROC with age across the 3 follow-up time points. Bars indicate 95% confidence intervals of the estimations. Analyses were carried after imputing missing data. AUROC = area under the receiver operating characteristic curve.

containing the least number of variables. Finally, we found that combining the full set of 83 observable variables with chronological age strongly improved the predictive performances of the models (AUROC at 5 years: 0.878, at 10 years: 0.886, at 15 years: 0.909; Figure 1; Supplementary Table 4). Removing chronological age as a covariate significantly worsened the discriminative ability of the models for the 15-year follow-up but not for the 5- and 10-year follow-ups. Similar trends were observed for the complete case analyses (Supplementary Figure 1; Supplementary Table 4).

Variables Importance Within and Across Domains for Survival Prediction

To investigate which and how many variables were necessary to reach the maximal predictive ability within each domain, we repeated the cross-validation by including only the significant variables, as estimated from a bootstrapping approach (see Materials and Methods section). Almost identical performances were obtained for all domains indicating that more parsimonious models could be built while maintaining high predictivity (Supplementary Figure 2; Supplementary Table 5). Further, this analysis revealed that adding age as a covariate was reducing the number of significant features from all domains, with the exception of the functional domain (Figure 2A; Supplementary Table 6). However, this reduction was large only for the disease domain (29 and 12 features kept, respectively, without or with age). Finally, when all variables were tested, those significantly predicting mortality went down to only 15 or 21 when chronological age was added or not as a covariate, respectively.

Figure 2B shows the standardized coefficients and 95% CIs of the 15 variables that were significantly associated with survival in the full model (Figure 2B; Supplementary Table 7). All health domains were represented among the significant variables. Chronological age was by far the most predictive individual characteristic. After age, being a smoker and having atrial fibrillation were the highest positively associated variables. Gait speed and female sex were the second and third most predictive variables, with twice greater coefficients than any other negatively associated variables.

We observed consistent results with a model covering multidomain observable characteristics but not chronological age (Figure 2C). However, in this case, more variables contributed significantly to mortality prediction, including some diseases (chronic kidney disease, deafness), systolic blood pressure, and living without a partner (all showing positive coefficients), and hand grip strength (with a negative coefficient). Similar results were observed for the

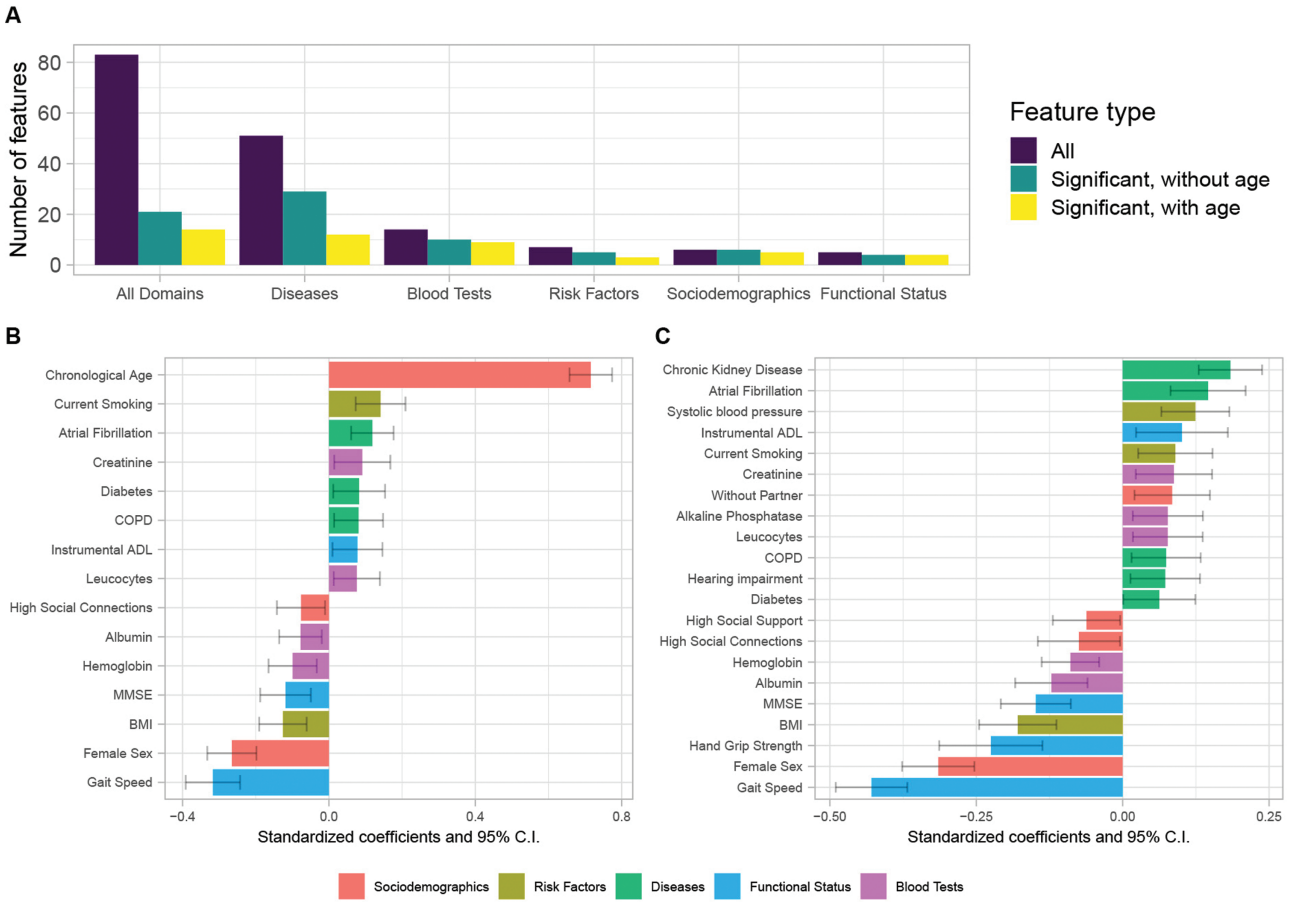

Figure 2. Significant predictors of mortality in different health domains Coefficients were derived by penalized Cox regression models with mortality as the outcome. (A) Number of total or significant features by domain when adjusting or not by chronological age. (B, C) Coefficients of the multidimensional model including (B) or not including (C) chronological age among the potential predictors. Positive coefficients indicate a positive association with mortality risk. Negative coefficients indicate a negative association with mortality risk. Bars indicate 95% confidence intervals of the estimations. Analyses were carried out after imputing missing data. ADL = activities of daily living; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MMSE = Mini-Mental State Examination.

complete case analyses (Supplementary Figure 3; Supplementary Table 6).

Deriving a Multidimensional Metric of Age

We used the 15-variable multidomain model that includes chronological age, to derive a multidimensional metric of age expressed in years, with the purpose of predicting survival more reliably than by using chronological age alone (Figure 3B). Our multidimensional metric of age showed a significantly ($p < .001$) higher negative Pearson's correlation coefficient with time to death (–0.760; Figure 3C) than chronological age (–0.660; Figure 3A). According to this measure, participants with the same chances of dying over the follow-up will display similar multidimensional age. For example, 2 individuals with 36 years of difference in chronological age had similar multidimensional age (Figure 3B) and time to live after their study entry (Figure 3C). Ultimately, we used Cox regression analysis to obtain relative risks for determining the strength of the association of our metric with mortality. For every year increase in multidimensional age, an 17.4% (95% CI: 16.7%–18.2%) increase in mortality rate was observed, while chronological age showed a 12.3% (95% CI: 11.7%–12.9%) increase in mortality rate per calendar year.

Comparison Between Multidimensional Age and Established Geriatric Indices

As the last step, we compared the performance of our measure of multidimensional age with chronological age and widely used geriatric indices and health scales (Figure 4; Supplementary Table 8). Our measure of multidimensional age showed significantly higher AUROCs (0.879 at 5 years; 0.887 at 10 years; and 0.910 at 15 years) for predicting survival than any of the other measures. Besides our multidimensional age measure, the disease count showed good predictivity of survival (AUROC range: 0.729–0.755). Hand grip strength, drug count, and I-ADL showed only fair performances (AUROC range: 0.642–0.704), while Personal Activities of Daily Living (P-ADL) showed poor performance (AUROC range: 0.548–0.591). Interestingly, unlike chronological age, we observed that I-ADL provided significantly better predictions for short-term than for long-term survival (AUROC at 5 years: 0.704, at 15 years: 0.642). Similar patterns were observed in the complete case analyses (Supplementary Figure 4; Supplementary Table 8).

Discussion

In this study, we found that the simultaneous utilization of observable measures from several health domains like functional status, diseases, blood tests, sociodemographics, and risk factors allows for highly performant survival predictions, in a manner that is independent of chronological age, particularly for up to ~10 years shorter-term survival predictions.

Previous work has already shown that observable phenotypic characteristics are easily accessible in clinical and research settings—and their combinations can improve the appraisal of health status in old age (14). Measures of biological age have been built regressing biological, functional, and clinical characteristics on chronological age—and more recently time to death—with the goal of selecting a core set of variables with sufficient capacity to predict health status and survival (38). For example, Levine et al. proposed a measure of phenotypic age, using chronological age and 9 blood tests commonly available in clinical practice including parameters of renal, liver, glucose, and immune function and metabolism (12). In a validation study of this metric, the authors showed that their measure was associated with all-cause and cause-specific mortality (16). In the present study, we did not select our predictors based on their independent correlation with chronological age (39,40), nor did we select them using predefined rules based on the scientific literature or clinical knowledge. We rather implemented a data-driven methodology aiming at better modeling mortality in older adults. Interestingly, we found that the inclusion of chronological age in our model decreased the predictivity of some observable characteristics (ie, chronic kidney disease, systolic blood pressure, being unpartnered, alkaline phosphatase, albumin, and hand grip strength) suggesting that chronological age harbors the prognostic information brought in by such features, while several other observable characteristics offered prognostic information that was independent of chronological age.

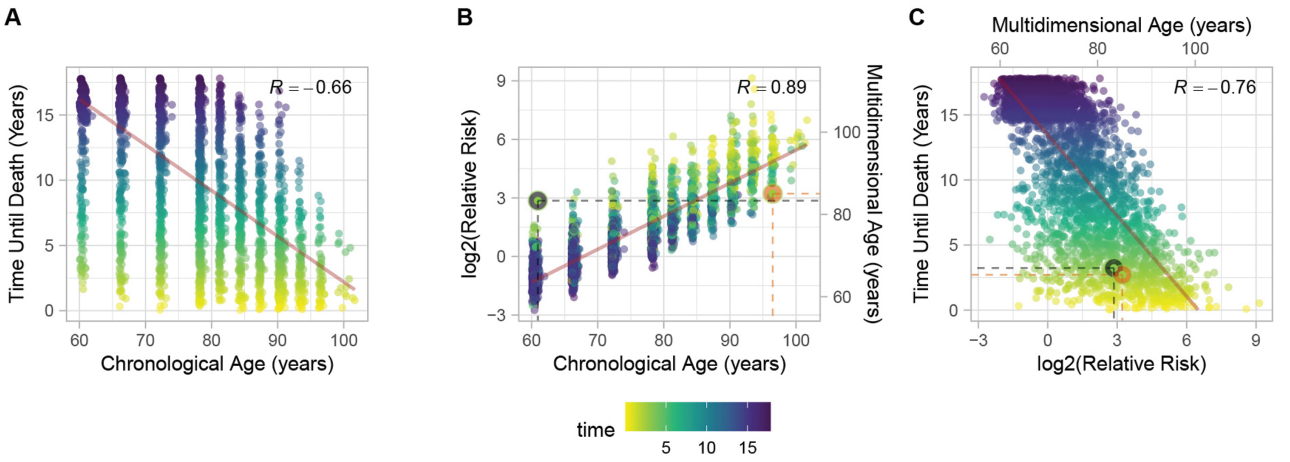

Figure 3. Multidimensional age prediction and its correlation with time to death. Relative risks from the multidomain models were averaged across imputed data sets, and then log2-transformed. Multidimensional age was obtained by regressing averaged risks on chronological age, using weights by age groups (see Materials and Methods section). For each panel, the red line shows the weighted regression (by age groups) of x on y, and *R* shows the Pearson correlation coefficients between the 2 variables. Highlighted points show 2 individuals with 36 years of age difference but with similar relative risk (B), multidimensional age (B, C), and time until death (C). Analyses were carried out after imputing missing data.

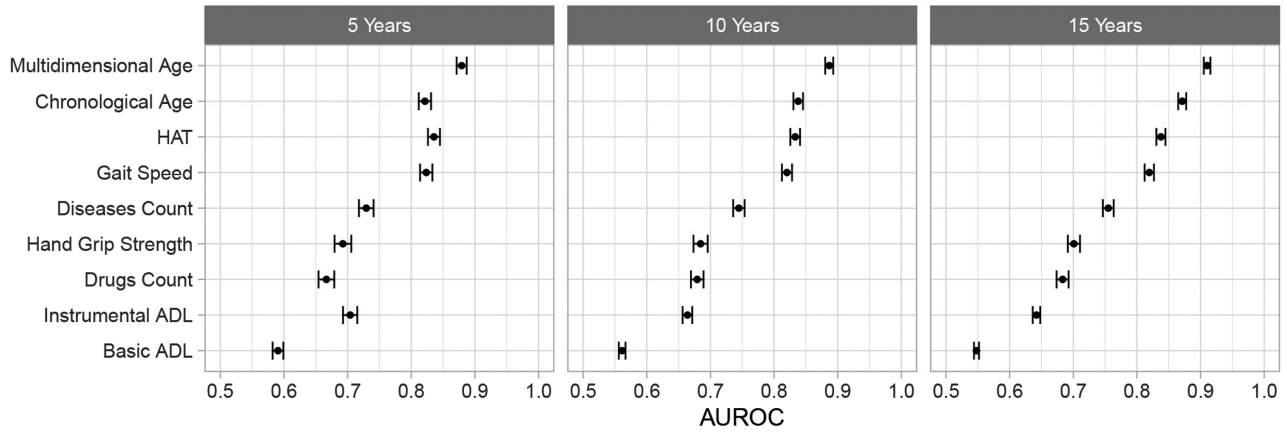

Figure 4. Comparison of the predictive accuracy for mortality of multidimensional age, chronological age, and other clinical and functional geriatric indices. The predictive accuracy was compared by mean of AUROC values. Bars indicate 95% confidence intervals of the estimations. Analyses were carried out after imputing missing data. ADL = activities of daily living; AUROC = area under the receiver operating characteristic curve; HAT = Health Assessment Tool.

Our findings point to the importance of maintaining a holistic approach to measuring health and making prognoses in old age. At the same time, we could also demonstrate the greater relative importance of specific measures over others within the same health domain. Beyond sociodemographic characteristics, the variables found to be significantly associated with mortality in our multidomain model include established risk factors such as systolic blood pressure and smoking but not dyslipidemia, chronic diseases such as atrial fibrillation and diabetes but not ischemic heart disease, blood markers such as creatinine and hemoglobin but not CRP, and physical and cognitive function measures such as gait speed and MMSE. Such observation is in consonance with a study by Goldman et al. that showed that serum creatinine and homocysteine, as well as CRP, were predictive of mortality more than traditional cardiovascular risk factors (41). A very similar selection of variables was reported in a previous study which included, among other predictors of biological age, hand grip strength, knee extension, hemoglobin, estimated glomerular filtration rate, MMSE, and blood pressure (40). A key difference between both studies is that Zhong et al. built models predicting chronological age, while our models predict survival, which should be closer to the phenotypes that the concept of biological age aims to describe. Indeed, a model perfectly predicting chronological age would have limited value because age is usually already known from the beginning.

Another key aspect of our study that has rarely been explored before is the inclusion of several variables that describe contextual characteristics of the individual, on top of those more linked to the biology. Due to these inclusions, our measure of multidimensional age cannot strictly be considered a measure of biological age. Still, we believe that the same predictive goals foreseen for measures of biological age can be achieved by measures based on a multidimensional array of predictors, perhaps even in a more efficient way. This is in line with the emerging importance of studying the contribution of extrinsic factors to biological aging in humans (10). In our study, individuals' social connections and civil status were identified as meaningful predictors of mortality. Although they cannot be considered proper biomarkers of aging, these features may be extrinsic compensatory mechanisms that help to counteract the numerous biological and phenotypic impairments that accumulate throughout life and/or proxies of higher-level functioning roles such as social interactions, which require the integrity of several organs and systems. Our observation of a significant role of socioenvironmental characteristics such as civil status and leisure activities in the prediction of death is coherent with results from previous studies (42). Of particular note is a study by Liu et al., in which behavioral and socioenvironmental circumstances during the entire life course explained ~30% of the interindividual differences in phenotypic age (19). Our group previously demonstrated the involvement of such characteristics in the development of several age-related conditions (17,18,43,44). Moreover, our study confirms the strong prognostic role of physical function (45). The functional status domain, encompassing several measures of physical performance and dependency, was the only single domain that showed comparable predictive performance to chronological age. These results were however limited to the prediction of short-term mortality. Dynamic changes in health and functioning in old age may be responsible for the reduced predictive power of physical function measures during longer follow-ups.

To the best of our knowledge, this is the first study that integrates multidimensional health-related observable features including contextual characteristics into an age metric that predicts survival. While it includes chronological age, it also works well regardless of it, demonstrating that the added value of chronological age in survival prediction when using variables across different health domains is lost. Other strengths of our work are the long follow-up and the wide age range of our study population, as well as the availability of a vast number of observable and measurable characteristics collected through comprehensive evaluations or official registries. The quality and depth of our data set allows for an unbiased comparison of the prognosis strength of these variables, which has rarely been addressed before (41). Besides its strengths, some limitations of our study should also be mentioned. First, we lack an external validation of our measure of multidimensional age, which restricts its applicability to different contexts and data sets. However, our intention was not to propose a new age clock to the scientific community, but rather to explore how multiple health domains and their interplay with chronological age can be employed to build such a measure. Second, although we tested many variables across different health domains, some could have been assessed more comprehensively (eg, sociodemographics, lab tests). Nevertheless, all domains contributed with at least 2 variables to our best model and thus made significant contributions to our mortality predictions.

In conclusion, a multidimensional age metric based on a comprehensive assortment of observable individual and contextual characteristics can predict mortality independently of chronological age and outperforms the mortality predictions by well-established geriatric indices. Our work provides important insights into the health domains and individual characteristics that can be used to predict human mortality in late life. We expect that the relevance of these different domains will be further investigated in the future to achieve an optimal prediction of biological age. Such measures will be of great value in both clinical and research applications.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

J.S., A.C.-L., L.F., C.G.R., and D.L.V. conceived the study. J.S. and D.R. conducted the data analyses and predictions. A.Z. provided advice on data analyses and interpretation of the results. J.S., D.R., C.G.R., and D.L.V. interpreted the results and wrote the manuscript. All the coauthors approved the final version of the manuscript.

Data Availability

The source data underlying all the figures and tables (including supplementary ones) are represented by the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) project, a population-based study on aging and dementia (http://www.snac-k.se/). Access to these original data is available to the research community upon approval by the SNAC-K data management and maintenance committee. Applications for accessing these data can be submitted to Maria Wahlberg (Maria.Wahlberg@ki.se) at the Aging Research Center, Karolinska Institutet.

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