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Research Article

Association of Biomarker and Physiologic Indices With Mortality in Older Adults: Cardiovascular Health Study

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Abstract

Background: A goal of gerontology is discovering aging phenotypes that reflect biological aging distinct from disease pathogenesis. Biomarkers that strongly and independently associated with mortality and that statistically attenuated chronologic age could be used to define such a phenotype. We determined the association of a Biomarker Index (BI) with mortality and compared it with a validated Physiologic Index (PI) in older adults.

Methods: The indices were constructed in the Cardiovascular Health Study, mean (*SD*) age 74.5 (5.1) years. The BI incorporated circulating levels of new biomarkers, including insulin-like growth factor-1, insulin-like growth factor–binding protein 3, amino-terminal pro-B-type natriuretic peptide, dehydroepiandrosterone sulfate, and interleukin-6, and was built in test (N = 2,197) and validation (N = 1,124) samples. The PI included carotid intima–media thickness, pulmonary capacity, brain white matter grade, cystatin-C, and fasting glucose. Multivariable Cox proportional hazards models predicting death were calculated with 10 years of follow-up.

Results: In separate age-adjusted models, the hazard ratio for mortality per point of the BI was 1.30 (95% confidence interval 1.25, 1.34) and the BI attenuated age by 25%. The hazard ratio for the PI was 1.28 (1.24, 1.33; 29% age attenuation). In the same model, the hazard ratio for the BI was 1.23 (1.18, 1.28) and for the PI was 1.22 (1.17, 1.26), and age was attenuated 42.5%. Associations persisted after further adjustment.

Conclusions: The BI and PI were significantly and independently associated with mortality. Both attenuated the age effect on mortality substantially. The indices may be feasible phenotypes for developing interventions hoping to alter the trajectory of aging.

Keywords: Biomarker, Mortality, Phenotype, Longevity

A central goal of gerontology is to discover aging phenotypes that reflect biological aging distinct from disease pathogenesis. Healthy aging phenotypes could serve as end points for developing interventions that alter the trajectory of aging toward a more desired pattern. Due to wider distribution and possibly incorporating multiple biological processes, composite scores have the potential for improved capability to stratify mortality risk (1).

In 2008, Newman and colleagues published the Physiologic Index of Comorbidity in the Cardiovascular Health Study (CHS) (2). The Physiologic Index combined measurements including carotid intima–media thickness, pulmonary vital capacity, serum cystatin-C, brain white matter grade, and fasting glucose. In the CHS (mean age 74.5 years), only 1.7% of older adults had no evidence of disease on these five tests (2). Their 9-year mortality rate was very low at 7/1,000 person-years (2), frailty was rare (3), and they had longer leukocyte telomere length (4), demonstrating that the tests identify individuals who are exceptional. Furthermore, the Physiologic Index explained 40% of the effect of age on mortality; thus, the Physiologic Index captures aspects of biological aging for which chronologic age is a surrogate.

Although a valuable phenotype, measurement of several key components of the Physiologic Index is resource intensive and costly. An index composed solely of blood-based biomarkers readily measurable in clinical laboratories would have lower expense and greater applicability. We proposed criteria to validate biomarkers of aging in epidemiologic studies (5) that are distinct from definitions of biomarkers of aging derived from laboratory science (6). The criteria include (a) demonstrating biological plausibility that a biomarker describes a basic aging process; (b) demonstrating potential for clinical applicability, using highly reproducible, highly interindividually variable, and low-cost measurements; (c) subsequently assessing associations with important aging outcomes using optimal epidemiologic study designs; and (d) testing these associations in accordance with key statistical considerations. An ideal biomarker of human aging should meet these criteria.

In this study, we developed a Biomarker Index of aging using only blood-based biomarkers demonstrated to have a role in the biology of aging in laboratory and epidemiologic studies. We compared the associations of the Biomarker Index and the Physiologic Index with 10-year mortality, and the ability of each Index to explain the association of age with mortality.

Methods

Study Population

The CHS is an ongoing community-based study of cardiovascular risk in 5,888 men and women over the age of 65 years, from four regions of the United States (7,8). The cohort was enrolled in 1989–1990 and was supplemented with added recruitment of African Americans in 1992–1993. Participants and eligible household members were identified from Medicare eligibility lists. To be eligible, participants should be 65 years and older, should not have cancer under active treatment, should not be wheelchair bound or bed bound in the home, and should not plan to move out of the area within 3 years. We used data from the 1992–1993 examination as baseline to include the supplemental African American cohort and because the brain magnetic resonance imaging scan was conducted at that time. The CHS is approved by the institutional review boards of all participating institutions, and all participants gave informed consent.

Physiologic Index of Comorbidity

The Physiologic Index was calculated as previously described from continuous measures of age-related dysfunction in five major organ systems, each of which predicts mortality and disability across a large continuum of risk (2). Detailed methods are provided in Supplementary Material. The systems included were the vascular (carotid intima–media thickness on ultrasound), neurologic (white matter grade on magnetic resonance imaging), renal (cystatin-C), pulmonary (forced vital capacity), and metabolic (fasting glucose). To construct the Physiologic Index, tertiles were considered for four of the five measures, with the best values classified as 0 and the worst as 2; fasting glucose was scored according to clinical cutoffs. Although the choice of cut points was arbitrary, scores of "0" generally included normal values in healthy young individuals, and values of "2" were in the range of those with chronic disease. Individual scores were summed for a total score ranging from 0 (healthy) to 10 (unhealthy).

Candidate Biomarkers

Candidate biomarkers for inclusion in the Biomarker Index were chosen for their documented association with aging-related processes in laboratory studies and outcomes in epidemiologic studies, though debate remains on their individual role as causative or correlative factors with aging. Candidates included insulin-like growth factor (IGF)-1, IGF-binding protein (IGFBP)-3, adiponectin, interleukin-6 (IL-6), dehydroepiandrosterone sulfate (DHEAS), and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). Fasting blood samples were collected at the 1992–1993 exam using standardized protocols and quality assurance (8,9). IGF-1 and IGFBP-3 were measured after an extraction step using enzyme-linked immunosorbent assays (ELISA; Diagnostics Systems Laboratory, Webster, TX) (10). The analytic coefficient of variation (CV) was 4%–6% for IGF-1 and 3%–5% for IGFBP-3. Adiponectin was measured with an ELISA (R&D Systems, Minneapolis, MN); intra- and interassay CVs were 2.5%–4.7% and 5.8%–6.9%, respectively. IL-6 was measured by ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems); intra- and interassay CV were 2.9%–8.7% and 7.3%–9.0%, respectively. Plasma DHEAS was measured with a competitive immunoassay (Alpco Diagnostics, Windham, NH) with interassay CV of 3.8%–7.2%. NT-proBNP was measured on the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN) with a CV of 2%–5%.

Mortality

Deaths were ascertained through participant surveillance every 6 months from study inception. Confirmation of deaths was conducted through reviews of obituaries, medical records, death certificates, the Center for Medicare Studies health care utilization database, and the National Death Index. Contacts and proxies were also interviewed for participants unavailable for follow-up. Ascertainment of vital status was 100% complete.

Potential Confounders

Age, sex, race, smoking status, alcohol consumption, and diet were determined by self-report (8). The Alternative Healthy Eating Score was used to account for dietary patterns (11). Anthropometrics (weight, height, waist circumference) were measured with standard protocols, and weight and height were used to calculate body mass index in kilogram per square meter. Physical activity was based on the Modified Minnesota Leisure Time Activities questionnaire that assessed frequency and duration of 18 activities in the prior week to calculate kilocalories of energy expended. Prevalent and incident cardiovascular disease (CVD) outcomes were adjudicated by an expert panel using medical records; medication information and prevalent disease status were updated at each examination (12). Incident CVD was defined as a first occurrence of stroke, coronary heart disease,

congestive heart failure, or claudication after the 1992–1993 examination among participants without a history of any component at the time of the exam. Cancer and pneumonia were defined using ICD-9 codes.

Statistical Analysis

CHS participants were included in the development of the Biomarker Index if they had data on all six biomarkers (N = 3,321). We derived the Biomarker Index in a randomly selected test sample of two third of the cohort (N = 2,197) and validated it in the remainder of participants (N = 1,124). In the test sample, the association of each biomarker with mortality was visualized using cubic splines. Because biomarker levels differed by gender and several associations between biomarkers and mortality were not monotonic, cut points to score each biomarker were made using sex-specific quintiles (Tables 1 and 2). Multivariable Cox proportional hazards models including age and all of the biomarkers (as indicator variables for quintiles) were run for men (N = 862) and women (N = 1,335) separately in the test sample. Only biomarkers that were individually associated with mortality at a significance level of less than or equal to .05 were included in the final Biomarker Index. Adiponectin was not associated with mortality for either men or women and IGF-1 and DHEAS were not significantly associated with mortality in men so were not included in the final models. The coefficients from the multivariable biomarker models were used to compute points for each level of each biomarker, selecting the quintile with lowest risk as the reference group. Each beta coefficient was divided by three times the coefficient for age for scaling and rounded to produce a point score. Although 5 years of age has been used in other risk scores, notably the Framingham Risk Score, 3 years of age was selected as a reasonable comparison given the older ages of our cohort. The Biomarker Index was tested in the validation sample and, when found consistent with the results in the test set, the validation and test samples were combined to derive estimates of risk associated with both indices in the full sample.

The associations of the Biomarker and Physiologic Indices with mortality were calculated using Cox proportional hazards models with each index modeled linearly among participants with both indices (N = 2,515). A likelihood ratio test was used to confirm that there was no improvement over the linear model by a model based on indicator variables for categories of the Biomarker Index. The proportional hazard assumption was tested with Schoenfeld residuals, and when violated, baseline hazards were stratified by sex and follow-up was truncated at 10 years to conform to the assumption. Models were built sequentially adjusting for age, sex, race, behaviors (current smoking, diet, any alcohol consumption, and ln(kcal) physical activity), body size (body mass index and waist circumference), prevalent clinical CVD or cancer, and, finally, incident CVD, cancer, or hospitalization for pneumonia during follow-up. All analyses were performed with STATA 14.2 (College Station, TX) or R version 2.13.0 (http://www.r-project.org).

Results

The mean (SD) age of the participants with all biomarkers (N = 3,321) was 74.5 (5.1) years, and 14.1% were black (Table 1). Compared with men, women were less likely to drink alcohol or have a history of coronary heart disease or stroke. Women had higher levels of adiponectin and IGFBP-3; lower levels of DHEAS, IL-6, and IGF-1; and similar NT-proBNP (Table 1). Among the 3,321 participants, there were 2,536 deaths over 19.5 years, and among the 2,525 participants with both indices, there were 1,003 deaths over 10 years.

Cubic spline plots of the associations of the biomarkers with mortality in the test set showed departures from linearity, although data were sparse in the extremes of the distributions, as evidenced by the wide confidence intervals. Scoring of each biomarker is shown in Table 2. When the scores for each biomarker were summed into the total Biomarker Index, there was a clear gradation of mortality across the Biomarker Index score, with lower scores associated with

Table 1. Description of Cardiovascular Health Study Cohort

	Women	Men	All	
Characteristic	N = 2,021	N = 1,300	N = 3,321	p Value
Age, y	74.4 (5.0)	74.7 (5.2)	74.5 (5.1)	.05
Black race	310 (15.3)	158 (12.2)	468 (14.1)	.01
Current smoker	190 (9.4)	117 (9.0)	307 (9.2)	.70
Drinks alcohol	801 (39.6)	711 (54.7)	1,512 (45.5)	<.001
Physical activity, kcals	473 (150–1,110)	907 (907–1,967)	598 (187–1,417)	<.001
BMI, kg/m^2	26.9 (5.2)	26.6 (3.8)	26.8 (4.7)	.07
Waist, cm	95.9 (14.6)	98.9 (10.5)	97.1 (13.2)	<.001
History of CHD[a]	339 (16.8)	359 (27.6)	698 (21.0)	<.001
History of CHF	91 (4.5)	66 (5.1)	157 (4.7)	.45
History of stroke	67 (3.3)	93 (7.2)	160 (4.8)	<.001
Adiponectin, mg/L	14.1 (10.2–19.6)	9.6 (7.0–13.6)	12.2 (8.5–17.5)	<.001
NT-proBNP, pg/mL	143 (76–257)	128 (60–306)	137 (69–268)	.11
DHEAS, µg/mL	0.52 (0.32–0.80)	0.79 (0.48–1.18)	0.61 (0.38–0.94)	<.001
IL-6, pg/mL	2.58 (1.75–3.91)	2.87 (2.02–4.34)	2.70 (1.85–4.08)	<.001
IGF-1, µg/L	89 (70–112.0)	103 (82–126)	94 (74–118)	<.001
IGFBP3, µg/L	3,725 (3,135–4,281)	3,349 (2,836–3,918)	3,565 (3,009–4,162)	<.001

Note: BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; DHEAS = dehydroepiandrosterone sulfate; IGF-1 = Insulin-like growth factor-1; IGFBP3 = IGF-binding protein-3; IL-6 = interleukin-6; NT-proBNP = amino-terminal pro-B-type natriuretic peptide. Entries in table are mean (SD), N (%), or median (interquartile range). p Values comparing men and women are from t test, chi-square test, or Kruskal–Wallis test, corresponding to whether or not the mean, N, or median are reported.

[a]Defined as angina, angioplasty, bypass surgery, or myocardial Infarction.

lower mortality and higher scores associated with higher mortality (Table 3).

The Biomarker Index was similarly distributed in the test and validation samples with a slight right skew (Figure 1, chi-square *p* value = .75). Estimates of the age, sex, and race adjusted hazard ratios (HRs) and 95% confidence intervals of the Biomarker Index with mortality were identical in the test (1.29 [1.24, 1.33]) and validation (1.29 [1.23, 1.35]) subsets, and measures of concordance were similar (Harrell's C-statistic = 0.699 and 0.708 in the test and validation sets, respectively).

Compared with participants with data on both indices, participants with only data for the Biomarker Index were on average of similar age and gender, but were more likely African American, had a larger waist circumference, had lower physical activity, and were more

Table 2. Biomarker Index Scoring

	Women			Men		
Biomarker Quintile	Biomarker Range	β Coefficient	Points[a]	Biomarker Range	β Coefficient	Points[a]
NT-proBNP, pg/mL						
0	≤76	0	0	≤62	0	0
1	78–127	0.2173	1	63–121	0.1673	1
2	128–199	0.2324	1	122–211	0.3381	1
3	200–355	0.5158	2	212–485	0.6764	3
4	>355	0.8539	3	>485	1.141	5
IL-6, pg/mL						
0	≤1.8	0	0	≤2.0	0	0
1	1.9–2.5	0.1333	0	2.1–2.7	0.1577	1
2	2.6–3.3	0.3954	1	2.8–3.6	0.1863	1
3	3.4–4.6	0.4857	2	3.7–5.1	0.4775	2
4	>4.6	0.7344	3	>5.1	0.5773	2
IGF-1, µg/L						
0	≤66	0.1144	0	≤75		0
1	67–80	0.1014	0	76–94		0
2	81–96	0.1284	0	95–111		0
3	97–120	0	0	112–1,332		0
4	>120	0.3517	1	>133		0
IGFBP3, µg/L						
0	≤2,951	0.3066	1	≤2,621	0.2073	1
1	2,952–3,436	0	0	2,622–3,100	0.2306	1
2	3,437–3,881	0.0049	0	3,101–3,495	0.2000	1
3	3,882–4,379	0.1763	1	3,496–4,061	0	0
4	>4,379	0.1287	1	>4,061	0.4038	2
DHEAS, µg/mL						
0	≤0.26	0.2547	1	≤0.41		0
1	0.27–0.42	0.1520	1	0.42–0.61		0
2	0.43–0.61	0	0	0.62–0.87		0
3	0.62–0.90	0.0255	0	0.88–1.24		0
4	>0.90	0.2674	1	>1.24		0

Note: DHEAS = dehydroepiandrosterone sulfate; IGF-1 = Insulin-like growth factor-1; IGFBP3 = IGF-binding protein-3; IL-6 = interleukin-6; NT-proBNP = amino-terminal pro-B-type natriuretic peptide.

[a]Points determined by dividing the β coefficient by three times the β coefficient for age = 0.0912. IL-6 = interleukin-6.

Table 3. Incidence Rates for Mortality by Biomarker Index Score

Biomarker Index	*N*	Person-Years	Number of Deaths	Incidence Rate[a] (95% CI)
0	77	720	15	20.8 (12.6, 34.5)
1	296	2,754	53	19.2 (14.7, 25.2)
2	610	5,574	147	26.4 (22.4, 31.0)
3	718	6,144	260	42.3 (37.5, 47.8)
4	576	4,754	243	51.1 (45.1, 58.0)
5	417	3,222	208	64.6 (56.3, 73.9)
6	287	2,053	178	86.7 (74.9, 100.4)
7	194	1,232	136	110.4 (83.3, 130.6)
8	126	627	106	169.1 (140.8, 204.5)
9	20	87	19	219.3 (139.9, 343.8)

Note: CI = confidence interval. Wide confidence intervals for values of 0 and 9 with few deaths.

[a]Per thousand person-years based on 10 years of follow-up.

likely to have coronary heart disease or congestive heart failure, as well as slightly higher NT-proBNP and IL-6 (Supplementary Table 1). Among the 2,515 participants with data on both indices, combining the test and validation subsets, the mean (*SD*) of the Biomarker Index and Physiologic Index was 3.6 (1.9) and 4.4 (2.1), respectively.

The indices were significantly correlated (Spearman correlation coefficient = 0.35, $p < .0001$). In separate unadjusted Cox models with the baseline hazard stratified by sex, the estimated HRs for the two indices were nearly identical at 1.34 for the Biomarker Index and 1.36 for the Physiologic Index (Table 4) with respective measures of concordance of 0.66 and 0.67. For the unadjusted Biomarker Index (Table 4, Model 1), the C-statistic was 0.656 and area under the curve was 0.685. For the unadjusted Physiologic Index, the C-statistic was 0.669 and area under the curve was 0.714 (test of comparison p value of .02). The HRs were attenuated after adjustment for age and for each other, but remained similar and statistically significant in all adjusted models.

In the model with only age, the HR per year of age was 1.11 (1.10, 1.13; Table 4). Adjusting for the Biomarker Index reduced the HR for age to 1.09 (1.08, 1.10; 20% attenuation in age beta) and adjusting for the Physiologic Index reduced the HR for age to 1.08 (1.07, 1.09; 29% attenuation in age beta). Adjusting for both indices, the HR for age was 1.07 (1.06, 1.08; 39% attenuation in age beta); the HR for the Biomarker Index was 1.21 (1.17, 1.25); and the HR for the Physiologic Index was 1.22 (1.18, 1.26). Associations remained similar with additional adjustment for health behaviors, body size, and clinical CVD, cancer, and pneumonia hospitalization (Figure 2).

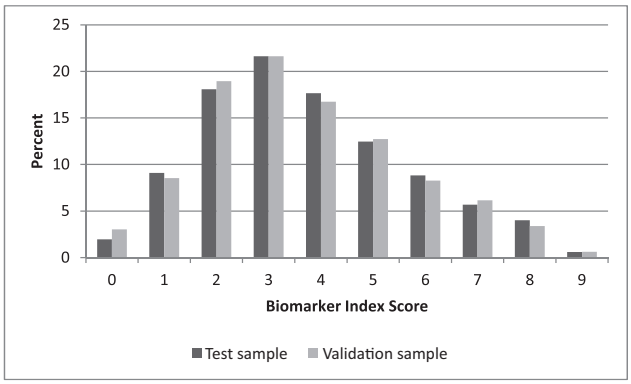

Figure 1. Distribution of Biomarker Index score in test and validation samples of the Cardiovascular Health Study.

Discussion

In this sample of community-dwelling older adults, we show that the relative risk of mortality associated with an index of five new circulating biomarkers is similar to that of an index using physiologic markers that require more resource intensive ascertainment but that both sets of variables remain significant predictors of mortality even in the presence of each other. The Biomarker and Physiologic Indices attenuate age substantially and independently of each other, suggesting that each captures a part of biological aging that is distinct. Previously, we showed that the Physiologic Index and variations thereof are associated with death, disability, age-related chronic disease, frailty and vigor, telomere length, and many health behaviors in the Cardiovascular Health Study and Health, Aging, and Body Composition Study (1,2,4,13). In the Long Life Family Study, a family-based study of exceptional longevity, a variation of the Physiologic Index termed the Healthy Aging Index was also moderately and significantly heritable (14). Supporting prior analyses, the present data suggest that the two indices represent distinct aspects of the aging process. Thus, they may be feasible outcomes for benchmarking interventions being tested to alter the trajectory of aging.

What aspects of aging biology may be reflected by the Biomarker Index? IL-6 is a cytokine produced by immune cells, vascular endothelium, adipose tissue, and muscle. It has proinflammatory and anti-inflammatory effects, rises with age in the absence of disease, and is robustly associated with myriad health outcomes (15,16). NT-proBNP is released primarily by ventricular myocytes in response to elevated filling pressure, acting hormonally on the kidneys to relieve cardiac stress through sodium and water excretion. NT-proBNP elevations occur in a number of cardiovascular aging and disease phenotypes, including coronary artery disease and myocardial infarction, left ventricular hypertrophy, atrial fibrillation, and valvular diseases, reflecting increased myocardial stretch. Higher NT-proBNP levels also occur with decreased renal clearance of NT-proBNP and are seen with advancing age (17,18). Various studies have shown NT-proBNP to be independently associated with mortality (19,20). Thus, NT-proBNP may be a marker of undiagnosed or subclinical cardiovascular damage that occurs with aging and disease, as well as co-existing renal dysfunction.

DHEAS can be thought of as a pool for sex steroid hormones. More than 90% of estrogens in postmenopausal women and 30% of androgens in men are derived from DHEAS (21). DHEAS levels peak at birth and in the third decade of life and fall by 80%–90% by age 80, which partly explains the age-associated decline in estrogen and testosterone (22–24). The cause of this age-associated decline is

Table 4. Hazard Ratios for Death by Age and the Two Indices, With Various Levels of Adjustment

Adjustment Variables	Age (per Year)	Physiologic Index (per 1 Index Point)	Biomarker Index (per 1 Index Point)
Sex	1.11 (1.10, 1.13)	1.36 (1.31, 1.40)	1.34 (1.30, 1.38)
Sex, race, and age[a]	1.08 (1.07, 1.09)	1.28 (1.23, 1.32)	
	1.09 (1.08, 1.10)		1.27 (1.23, 1.32)
+ Both indices	1.07 (1.06, 1.08)	1.22 (1.18, 1.26)	1.21 (1.17, 1.25)
+ Behaviors	1.07 (1.06, 1.09)	1.20 (1.15, 1.24)	1.20 (1.16, 1.24)
+ Body size	1.06 (1.05, 1.08)	1.21 (1.17, 1.26)	1.19 (1.15, 1.23)
+ Prevalent clinical CVD or cancer	1.06 (1.05, 1.08)	1.21 (1.16, 1.25)	1.18 (1.13, 1.22)
+ Incident CVD, cancer, or hospitalization for pneumonia	1.05 (1.03, 1.07)	1.20 (1.15, 1.25)	1.19 (1.14, 1.24)

Note: CVD = cardiovascular disease. The + symbol in the table indicates that each model with the + includes variables included in the prior model.
[a]First line is adjusted for the Physiologic Index and second line for the Biomarker Index.

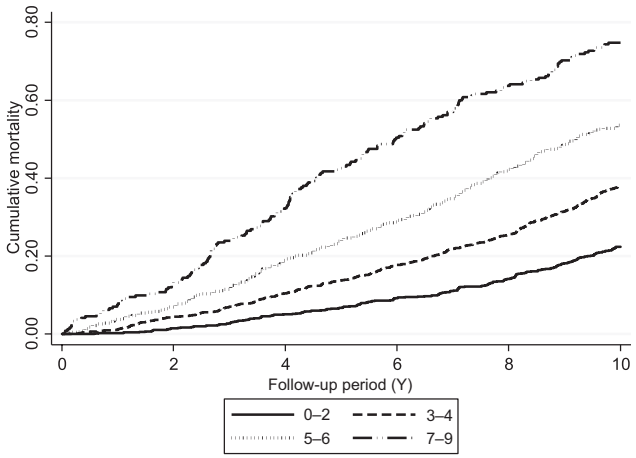

Figure 2. Kaplan–Meier curve of cumulative mortality over the follow-up period by score of Biomarker Index.

unknown, although we reported that in older adults in the CHS All Stars study, CVD, male gender, and black race were associated with greater DHEAS decline over 9 years (25). Epidemiological data on an association between DHEAS and mortality are equivocal (26–29).

The IGF pathway was the first pathway shown to influence aging and life span in animals, conceivably through growth and development and metabolic regulation (30). Studies in model systems are robust and suggest a causal role for IGF-1 and longevity in nonhuman systems, and cross-sectional epidemiologic studies of community-dwelling older adults confirmed that they have lower IGF-1 levels compared with younger persons (31–36). Nonetheless, although the Framingham Heart Study showed that greater baseline IGF-1 was associated with lower mortality (37), no association was initially detected in five other large cohort studies (10,38–41). IGF-1 was not strongly scored in the Biomarker Index, suggesting that at these ages it may be associated with mortality only in the extremes or in the context of other biomarker levels.

We acknowledge several limitations in this analysis. First, the Biomarker Index was specifically scored by weighting its components using regression coefficients from Cox models of death. This methodology was not used to score the Physiologic Index whose components were monotonically associated with mortality and were scored with tertiles summed across the components. Consequently, the Physiologic Index may have been "disadvantaged" compared with the Biomarker Index in predicting death. However, we derived the Biomarker Index scoring in a randomly selected test sample and used it to predict death in a validation sample, where it performed similarly to the test sample, suggesting it was not overcalibrated. Second, the choice of biomarkers to include in the Biomarker Index was made from convenience in that the biomarkers were available in the CHS. However, we had good scientific rationale for including each candidate biomarker in the index. Before inclusion, each biomarker's statistical appropriateness was additionally confirmed (ie, association with mortality independent of age and sex). In the future, high-throughput technology could allow affordable prospective measurement of hundreds or thousands of biomarkers simultaneously, which may increase predictive power and suggest new mechanistic associations. The challenge of incorporating large numbers of biomarkers into clinical practice may eventually be overcome by designing targeted "aging" panels using validated biomarkers, similar to targeted genetic prediction panels already used in clinical oncology. Third, we measured each biomarker only once and levels may have changed throughout time. Previous analyses suggest it is unlikely that participants improved significantly on any component of the Physiologic Index, but there is evidence that biomarkers can have varied trajectories that themselves may predict death better than a single measurement (42,43). Fourth, residual confounding may be present if confounders were not included in our models, such as dietary habits, although adjustment for major health behaviors and clinical disease minimally altered results. Fifth, although some different associations have been detected previously in CHS for some of these biomarkers (eg, association between adiponectin and mortality varying by CVD status (44)), the aim here was to find a biomarker generally predictive of mortality irrespective of disease status. Differences in study population and analytic design may have influenced results compared with prior reports.

In conclusion, an index of five circulating biomarkers can predict death in older community-dwelling adults as accurately as an index of physiologic markers, and both indices substantially and independently attenuate the effect of age on mortality. Although the Biomarker Index needs further validation, these data suggest that Biomarker Index and the Physiologic Index measure important aspects of the underlying aging process, and they may serve as end points for studies seeking to develop interventions to improve aging.

Supplementary Material

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

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Conflict of Interest

None reported.

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