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Participant-Reported Health Status Predicts Cardiovascular and All-Cause Mortality Independent of Established and Nontraditional Biomarkers: Evidence From a Representative US Sample

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Background—Participant-reported health status is a key indicator of cardiovascular health, but its predictive value relative to traditional and nontraditional risk factors is unknown. We evaluated whether participant-reported health status, as indexed by self-rated health, predicted cardiovascular disease, and all-cause mortality risk excess of 10-year atherosclerotic cardiovascular disease (ASCVD) risk scores and 5 nontraditional risk biomarkers.

Methods and Results—Analyses used prospective observational data from the 1999–2002 National Health and Nutrition Examination Surveys among those aged 40 to 79 years (N=4677). Vital status was ascertained through 2011, during which there were 850 deaths, 206 from cardiovascular disease (CVD). We regressed CVD and all-cause mortality on standardized values of self-rated health in survival models, adjusting for age, sex, education, existing chronic disease, race/ethnicity, ASCVD risk, and standardized biomarkers (fibrinogen, C-reactive protein [CRP], triglycerides, albumin, and uric acid). In sociodemographically adjusted models, a 1-SD decrease in self-rated health was associated with increased risk of CVD mortality (hazard ratio [HR], 1.92; 95% CI, 1.51–2.45; $P<0.001$), and this hazard remained strong after adjusting for ASCVD risk and nontraditional biomarkers (HR, 1.79; 95% CI, 1.42–2.26; $P<0.001$). Self-rated health also predicted all-cause mortality even after adjustment for ASCVD risk and nontraditional biomarkers (HR, 1.50; 95% CI, 1.35–1.66; $P<0.001$).

Conclusions—Self-rated health provides prognostic information beyond that captured by traditional ASCVD risk assessments and by nontraditional CVD biomarkers. Consideration of self-rated health in combination with traditional risk factors may facilitate risk assessment and clinical care. (*J Am Heart Assoc*. 2016;5:e003741 doi: 10.1161/JAHA.116.003741)

Key Words: biological markers • cardiovascular disease risk factors • epidemiology • health policy and outcomes research • mortality • patient reported outcomes • quality of life

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States.[1] As a complement to traditional CVD risk factors, such as smoking status, hypertension, diabetes mellitus, and cholesterol, current national guidelines recommend assessment of participant-reported health status.[2] Participant or self-reported health status is considered a key indicator of cardiovascular health,[2] predicting morbidity,[3,4] and mortality,[5,6] above and beyond traditional and nontraditional risk factors.[7–9] In addition to predicting mortality risk among healthly individuals, self-reported health status remains a robust predictor of cardiovascular mortality within diseased populations.[10] In 2014, CVD risk formulations were updated to more optimally model the impact of multiple risk factors, now known as the 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculation. Importantly, this model's risk prediction is not duplicated by, or achievable through, consideration of traditional risk factors individually.[11] No studies to date have evaluated the prognostic value of self-reported health status relative to current CVD risk formulations.[11] Comparisons of self-reported health status with nontraditional risk factors are also sparse. Hence, the prognostic value of self-reported health over optimized consideration of traditional and nontraditional risk factors together is unknown.

Our objective was to evaluate the prognostic value of participant-reported health status, as indexed by self-rated health, for risk of incident cardiovascular and all-cause mortality after controlling for 10-year ASCVD risk. We also examined this association after further adjustment for 5

nontraditional CVD risk factors (fibrinogen, C-reactive protein [CRP], triglycerides, albumin, and uric acid).[12] We evaluated these associations in a probability sample of US residents aged 40 to 79 years (N=4677) followed for 9 to 12 years.

Methods

Data Source

We analyzed data from the combined 1999–2002 National Health and Nutrition Examination Surveys (NHANES), a representative sample of US residents aged 1 month to 85 years and older.[13,14] Participants were interviewed in their homes and a subset completed a physical examination in a mobile examination center. Among all participants in the 1999–2002 survey years, 83% of those screened participated in the interview and 93% of interviewed participants were examined.[15] Examined participants are weighted to represent the civilian noninstitutionalized US population.[15] Current CVD risk assessment formulae are relevant to adults aged 40 to 79 years of age, so we restricted our analyses to this age range (N=5701). Participants missing data on ASCVD risk variables, self-rated health, education (coded less than high school, high school diploma, some college, or college graduate or higher) and the other biomarkers reduced the

analytic sample to 4677 (82% of those aged 40–79 who were examined; Figure 1). All participants provided informed consent, and the study was approved by the National Center for Health Statistics (NCHS) Ethical Review Board.

Vital Status

Vital status on all participants in this analysis was ascertained through December 31, 2011 using the National Death Index.[16] Specific causes of death were classified using the 10th revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death and these categories were collapsed into the 10 leading causes of death in the public use file. Cardiovascular deaths included combined deaths from diseases of heart (I00–I09, I11, I13, I20–I51) and cerebrovascular diseases (I60–I69).

Risk Factors

Traditional CVD risk factors

Blood pressure was measured up to 4 times by trained personnel using a mercury sphygmomanometer. Blood pressure was defined by the average of values excluding the first reading unless there was only 1 measurement, in which case
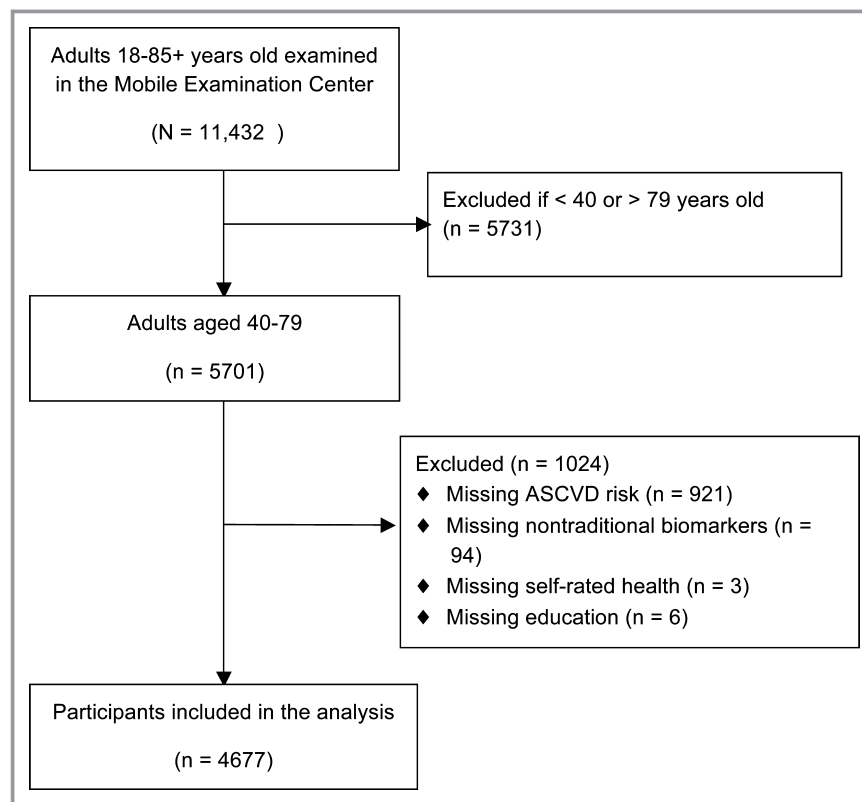
Figure 1. Participant selection flow diagram, 1999–2001 National Health and Nutrition Examination Surveys. ASCVD indicates atherosclerotic cardiovascular disease.

the single reading was used as the average. Diabetes mellitus was defined by glucose ≥126 mg/dL or taking insulin.[17] Current smoking status was determined by affirmative answers to both "have you ever smoked at least 100 cigarettes in your life?" and "do you currently smoke?" Total cholesterol and high-density lipoprotein (HDL) were assessed at the Johns Hopkins University Lipoprotein Analytical Laboratory (Baltimore, MD) using standard reference methods.[18,19]

ASCVD risk calculation

Ten-year risk for an ASCVD event was derived for each participant following described methods[11,20] and specifically used sex- and race-specific regression coefficients for age, treated or untreated systolic blood pressure, total and low-density lipoprotein (LDL) cholesterol, current smoking (yes/ no), and history of diabetes mellitus (yes/no) to calculate ASCVD risk. Our purpose in calculating ASCVD risk scores was to optimally partition health risk among our participants rather than to make treatment decisions. Therefore, we included ASCVD risk calculations risk for the few participants with systolic blood pressure higher than 200 mm Hg (N=27) and with LDL ≥190 mg/dL (N=94); these values are precluded from online risk calculators. Similarly, we calculated ASCVD risk for those reporting a past diagnosis of stroke, heart attack, or other coronary heart disease.

Nontraditional risk biomarkers

NHANES includes a number of laboratory assays. We selected CRP, fibrinogen, urinary albumin, triglycerides, and uric acid because they represent 5 of the most studied nontraditional CVD risk factors.[12] Quantitative CRP (sensitive to 0.2 mg/dL) was assessed with latex enhanced nephlometry using a Behring Nephelometer. Fibrinogen concentration was assayed using a STA-Compact (Diagnostica Stago, Inc., Parsippany, NJ).[21,22] Albumin, triglycerides, and uric acid concentrations were determined with a Hitachi Model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN).[23,24] NHANES laboratory staff complete comprehensive laboratory procedure training and formal retraining is conducted annually. Examination protocol fidelity and quality assurance is monitored regularly during unscheduled evaluations by NCHS staff and contractors.[23]

Diagnosed Chronic Diseases

Participants were asked whether a doctor or other health professional ever told them they had had a heart attack, a stroke, coronary heart disease, congestive heart failure, or cancer. Diabetes mellitus history is captured in the ASCVD risk calculation.

Participant Reported Outcome

Self-rated health was assessed by the question, "Would you say your health in general is excellent, very good, good, fair or poor?" This global rating reflects subjective and objective perceptions of mental and physical disease burden[25] and is shaped by individual and social characteristics.[26,27] We chose this item because of its importance in population health surveillance[28] (http://www.cdc.gov/hrqol/overview.htm) and because it complements other assessments, such as the medical history and laboratory tests.[2] This single-item assessment has comparable predictive validity for mortality irrespective of wording and when compared to more-complex multi-item assessments.[6,29] We did not evaluate change in health status over the last year or subjective health questions that were not assessed across both survey cycles.

Statistical Analysis

Self-rated health (in 5 categories) and biomarkers were standardized within the analytical sample to provide comparable unit scaling for comparison.[30] CRP was log transformed before standardizing. Thus, unless otherwise noted, all reported hazard ratios reflect a 1-SD change in the predictor. We used Cox regression to estimate the association between self-rated health and the 2 mortality outcomes. Participants who died from non-CVD causes (N=644) were excluded from CVD mortality analyses. We used participants' attained age as the time scale to correctly specify age-dependent mortality risk[31] and also stratified on 5-year birth cohorts to adjust for study entry age.[32] Models including education and sex as covariates failed to meet proportional hazards assumptions. Therefore, education and sex were modeled as stratification variables, an approach that permits adjustment for these characteristics without explicitly modeling their hazard functions.[33,34] We further examined model specification by evaluating squared predicted scores generated from fully adjusted hazard models. These squared terms were not statistically significant, providing additional evidence of adequately specified regression models.[35]

To evaluate the prognostic value of self-rated health, we entered self-rated health in survival models that cumulatively adjusted for (1) race/ethnicity and diagnosed chronic diseases (summed and categorized into 0, 1, 2, or more), (2) ASCVD risk, and (3) the 5 nontraditional CVD biomarkers. We also report parallel analyses for each of the 5 biomarkers (entering self-rated health in the third model) to compare the prognostic strength of each to self-rated health. Finally, we report sensitivity analyses for self-rated health restricting the sample to participants free of baseline CVD as well as comparisons of categorical self-rated health.

We used StataMP software (version 13.1; Stata Corp LP, College Station, TX) for all estimates and incorporated

NHANES clustering, stratification, and 4-year exam weights.[15] The analytical sample was identified with the *subpop* option to preserve the integrity of the complex survey design. CIs that did not include 1.0 were considered statistically significant.

Results

Participant characteristics by vital status are presented in Table 1. During follow-up, there were 850 deaths (18.2%), including 206 (5.1%) from CVD.

Table 1. Baseline Characteristics of 1999–2002 NHANES Participants

Characteristic	Total	Alive	Deceased
Participants, n	4677	3827	850
Age y, mean (SE)	55.0 (0.24)	53.5 (0.22)	64.3 (0.46)
Female sex, % (N)	52 (2321)	53 (1982)	45 (339)
Race/ethnicity, % (N)			
Mexican American	5 (1122)	5 (933)	4 (189)
Other Hispanic	6 (215)	6 (183)	6 (32)
White (non-Hispanic)	77 (2347)	77 (1920)	77 (427)
Black (non-Hispanic)	9 (871)	9 (683)	11 (188)
Other race	4 (122)	4 (108)	2 (14)
Education level, % (N)			
<9th grade	8 (885)	6 (643)	15 (242)
9th–11th grade, no diploma	14 (827)	13 (638)	23 (189)
High school diploma	25 (1010)	25 (838)	25 (172)
Some college	27 (1070)	28 (909)	25 (161)
College graduate or higher	26 (885)	29 (799)	12 (86)
Diagnosed chronic diseases, % (N)			
Myocardial infarction	5.0 (270)	3.7 (152)	12.6 (118)
Other coronary heart disease	5.1 (260)	3.7 (152)	13.3 (108)
Congestive heart failure	3.0 (168)	1.8 (78)	10.0 (90)
Stroke	2.9 (174)	1.9 (92)	8.8 (82)
Cancer	7.3 (358)	5.8 (229)	16.3 (129)
Self-rated health, % (N)			
Poor	4 (275)	3 (157)	12 (118)
Fair	15 (988)	13 (733)	27 (255)
Good	30 (1493)	29 (1217)	35 (276)
Very good	30 (1160)	32 (1023)	19 (137)
Excellent	20 (761)	22 (697)	8 (64)
Mean (SD) self-rated health	3.24 (1.13)	3.36 (1.11)	2.73 (1.12)
ASCVD risk, % (95% CI)*	8.9 (8.5–9.4)	7.5 (7.1–7.9)	17.8 (17.0–18.7)
Fibrinogen, mg/dL (95% CI)	364 (358–370)	359 (352–365)	396 (388–405)
CRP mg/dL (95% CI)	0.45 (0.42–0.49)	0.42 (0.39–0.46)	0.63 (0.55–0.71)
Triglycerides, mg/dL (95% CI)	160 (151–168)	155 (146–164)	187 (157–218)
Albumin, μg/mL (95% CI)	42.0 (31.8–52.2)	27.6 (17.6–37.7)	129.1 (90.1–168.1)
Uric acid, mg/dL (95% CI)	5.43 (5.37–5.50)	5.37 (5.29–5.44)	5.84 (5.72–5.97)

All values except for mean self-rated health are weighted to represent the civilian noninstitutionalized population ages 40 to 79 years. Some percentages may not sum to 100 because of rounding. ASCVD indicates atherosclerotic cardiovascular disease; CRP, C-reactive protein; NHANES, National Health and Nutrition Examination Survey.
*Ten-year risk based upon national guidelines.[11]

CVD Mortality

In a stratified model with race/ethnicity and chronic disease covariates, self-rated health was inversely associated with CVD mortality (Table 2, CVD mortality, model 1). This association persisted after further adjusting for ASCVD risk (Table 2, CVD mortality, model 2) and the 5 nontraditional biomarkers (hazard ratio [HR], 1.79; 95% CI, 1.42–2.26; Figure 2).[36] This fully adjusted association was observed when analyzing women (HR, 2.31; 95% CI, 1.71–3.11) and men (HR, 1.62; 95% CI, 1.18–2.23) separately. We repeated the fully adjusted regressions for participants who did not report a previous diagnosis of stroke, heart attack, congestive heart failure, or other coronary heart disease. The inverse association between self-rated health and CVD mortality risk persisted among participants free of baseline CVD (HR, 1.67; 95% CI, 1.27–2.18; N=3627; 124 CVD deaths). Using self-rated health categories referenced to those reporting very good or excellent heath, CVD mortality for the full sample was progressively higher for those reporting good (HR, 2.09; 95% CI, 1.15–3.81), fair (HR, 2.72; 95% CI, 1.51–4.90), and poor health (HR, 6.46; 95% CI, 3.09–13.53).

All-Cause Mortality

Self-rated health showed a similar inverse association with deaths from all causes. In the stratified model adjusted for race/ethnicity and chronic disease, self-rated health was inversely associated with mortality (HR, 1.58; 95% CI, 1.43–1.75; N=4677; 850 deaths) and this association persisted after adjustment for ASCVD risk (Table 2, All-cause mortality, model 2) and when further adjusting for the 5 nontraditional biomarkers (HR, 1.50; 95% CI, 1.35–1.66; Figure 2). This fully adjusted association was observed when analyzing women (HR, 1.59; 95% CI, 1.36–1.87) and men (HR, 1.45; 95% CI, 1.26–1.66) separately.

This inverse association with all-cause mortality risk was also observed when restricting participants to those free of baseline CVD (HR, 1.56; 95% CI, 1.37–1.77; N=4119; 616 events). Using self-rated health categories, all-cause mortality risk increased in a dose-response manner for those reporting good (HR, 1.51; 95% CI, 1.15–1.98), fair (HR, 2.34; 95% CI, 1.86–2.94), and poor (HR, 3.16; 95% CI, 2.19–4.55) health relative to those with very good/excellent health. Biomarkers and ASCVD risk were strongly stratified by self-rated health categories (Table 3). Higher self-rated health was consistently associated with lower ASCVD risk and more-favorable nontraditional biomarker concentrations.

Discussion

We evaluated whether self-rated health was associated with CVD and all-cause mortality in a probability sample of US adults aged 40 to 79 years of age. Poor self-rated health was
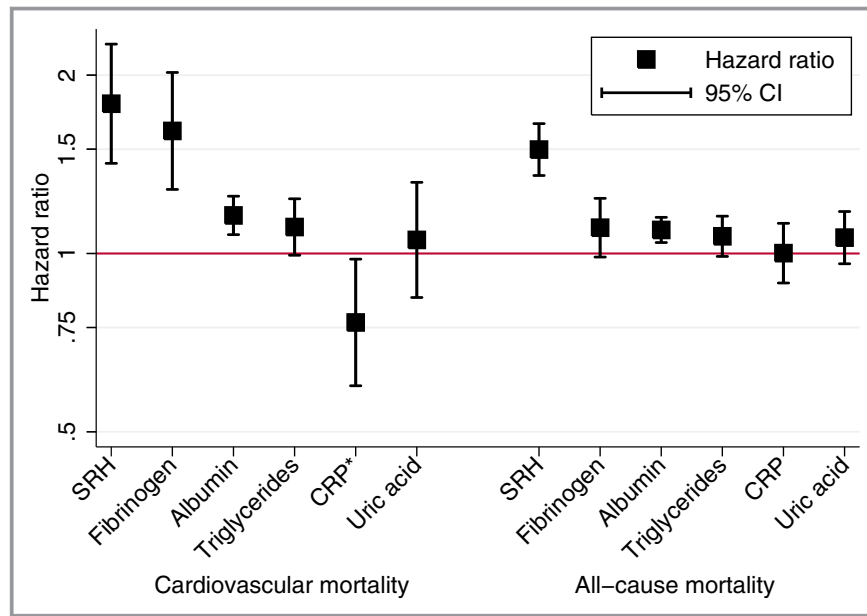
Table 2. CVD and All-Cause Mortality Hazard Ratios (95% CI) for Self-Rated Health and Nontraditional Biomarkers

Variable*	Model 1			Model 2		
	HR	95% CI	P Value	HR	95% CI	P Value
CVD mortality (N=4033)						
Self-rated health	1.92	1.51 to 2.45	<0.001	1.84	1.45 to 2.35	<0.001
Log CRP	1.22	0.97 to 1.52	0.086	1.17	0.92 to 1.50	0.189
Urinary albumin	1.22	1.12 to 1.32	<0.001	1.20	1.11 to 1.30	<0.001
Triglycerides	1.16	1.06 to 1.27	0.002	1.10	1.00 to 1.21	0.056
Uric acid	1.10	0.84 to 1.44	0.475	1.08	0.84 to 1.39	0.522
Fibrinogen	1.52	1.26 to 1.82	<0.001	1.48	1.22 to 1.81	<0.001
All-cause mortality (N=4677)						
Self-rated health	1.58	1.43 to 1.75	<0.001	1.54	1.38 to 1.71	<0.001
Log CRP	1.19	1.09 to 1.30	<0.001	1.15	1.06 to 1.26	0.003
Urinary albumin	1.13	1.07 to 1.19	<0.001	1.11	1.05 to 1.17	0.001
Triglycerides	1.13	1.06 to 1.21	0.001	1.08	1.02 to 1.15	0.017
Uric acid	1.11	1.00 to 1.22	0.045	1.10	1.00 to 1.22	0.049
Fibrinogen	1.19	1.08 to 1.30	0.001	1.16	1.06 to 1.28	0.003

Both models stratify on 5-year age cohort, sex, and education. Model 1 includes race/ethnicity and chronic disease as covariates; model 2 also includes 10-year atherosclerotic cardiovascular disease risk. Each hazard ratio reflects a 1-SD change in the predictor. CRP indicates C-reactive protein; CVD, cardiovascular disease.
*Standardized mean=0, standard deviation=1.0.

Figure 2. Hazard ratios for cardiovascular and all-cause mortality by self-rated health and nontraditional biomarkers, National Health and Nutrition Examination Surveys 1999–2002. Models are simultaneously adjusted for all predictors as well as age, race/ethnicity, diagnosed chronic disease (heart disease, stroke, and cancer), and 10-year atherosclerotic cardiovascular disease risk. All predictors are standardized to unit variance. *The CRP coefficient for cardiovascular disease (CVD) mortality reverses because fibrinogen is included in this model. CRP and fibrinogen are correlated 0.55 and correlated predictors in simultaneous regression models can cause a reversal of one of the regression coefficients.[36] CRP is positively associated with CVD mortality risk when excluding fibrinogen from the model (Table 2). CRP indicates C-reactive protein; SRH, self-rated health.

associated with a 79% greater risk of CVD mortality and a 50% greater risk of all-cause mortality after statistically controlling for ASCVD risk[11] and 5 nontraditional biomarkers.[12] Self-rated health had the strongest association with mortality relative to the nontraditional biomarkers and, in absolute terms, was large in magnitude. Thus, self-rated health meets

several requirements for a prognostic variable—it is statistically associated with mortality, is independent of other established predictors,[37,38] and the magnitude of association is large enough to discount residual confounding.[12]

This study is the first to show that self-rated health predicts CVD mortality risk beyond that captured in current

Table 3. Nontraditional Biomarkers and ASCVD Risk (95% CI) by Category of Self-Rated Health, NHANES 1999–2002

Variable*	Self-Rated Health (n)										P Value
	Poor (275)		Fair (988)		Good (1493)		Very Good (1160)		Excellent (761)		
Fibrinogen	417	399 to 434	381	373 to 390	371	364 to 378	356	349 to 362	342	331 to 353	<0.001
CRP	0.92	0.68 to 1.16	0.60	0.55 to 0.66	0.49	0.45 to 0.53	0.39	0.35 to 0.43	0.30	0.25 to 0.34	<0.001
Triglycerides	187	164 to 211	178	165 to 192	173	156 to 189	148	135 to 160	138	123 to 152	<0.001
Urinary albumin	206	49 to 363	76	47 to 105	41	22 to 60	21	13 to 29	16	11 to 22	<0.001
Uric acid	5.9	5.6 to 6.3	5.5	5.3 to 5.7	5.6	5.5 to 5.6	5.4	5.3 to 5.5	5.2	5.1 to 5.3	<0.001
ASCVD risk, %	14	13 to 16	11	10 to 12	10	9 to 11	8	7 to 8	6	6 to 7	<0.001

All estimates incorporate the complex survey design. *P* values were obtained by regressing each variable on self-rated health. ASCVD indicates atherosclerotic cardiovascular disease; CRP, C-reactive protein; NHANES, National Health and Nutrition Examination Survey.
*Values are mg/dL except for urinary albumin (µg/mL) and ASCVD risk.

CVD risk formulations. We also show that this predictive capability is independent of, and generally larger than, a set of popular nontraditional CVD biomarkers. With the exception of fibrinogen for CVD mortality, mortality hazards for a 1-SD change in self-rated health were consistently of larger magnitude than all other biomarkers for both mortality outcomes. Our risk estimates for nontraditional biomarkers are consistent with previous studies[12,39]; however, the utility of nontraditional biomarkers for improved risk prediction[40] remains controversial.[39,41]

Unlike laboratory data, self-rated health does not reflect a biological pathway to mortality risk. Instead, we view self-rated health as an integrated or synthesized summary of conditions that are on the path.[27] That is, the layperson's perspective on their health draws upon a knowledge base that overlaps with, but extends beyond, biomedical assessments.[42] Our study provides further support for this view because both 10-year ASCVD risk and poorer biomarker status robustly worsen in parallel with poorer self-rated health. However, adjusting for biomarkers did little to weaken the association between self-rated health and mortality. This pattern has been observed elsewhere[7,9] and challenges the notion that self-rated health judgments are necessarily informed by—and entirely accounted for by—objective clinical and physiological states.[27]

No assessment battery perfectly reflects health status and therein lies the advantage of self-rated health—it empirically captures a wide range of health-relevant domains beyond any biomarker panel yet available.[7,9,43] In addition to single baseline assessments, trajectories of self-rated health predict recurrent events within clinical samples, such as myocardial infarction patients.[10] The validity of self-rated health is further supported by the independence of self-rated health from extraneous influences, such as transient moods.[44] Beyond its utility as a global indicator of health risk and health status, self-rated health is intrinsically valuable as a gold-standard indicator of health-related quality of life.[2,26] Self-rated health may also improve mortality risk classification vis-à-vis ASCVD risk scores, but evaluating this potential requires a much larger number of CVD events than observed here.

Strengths of this study include objective assessment of a number of traditional and nontraditional biomarkers in a large, diverse representative sample followed for over a decade. We adopted recommendations to concurrently evaluate multiple risk factors using standardized scaling for biomarkers.[12] This head-to-head approach provides a less-biased determination of which risk factors are most important[12] and shows that self-rated health is among the most potent indicators of survival over 9 to 12 years. This taxonomy of the most potent health indicators can help clinicians identify patients that may benefit from more-aggressive risk factor management or other clinical interventions. Another possible application is to include self-rated health in the primary care examination. Poor health evaluations could be used to initiate further discussion of why patients expressing low self-rated health hold that opinion (ie, family history, other health problems, functional limitations, etc). Such discussions may unveil information unknown to the provider and could lead to altered risk factor interventions. Currently, guidelines for integration of self-rated health and other patient-reported outcomes into clinical decision making are poorly developed and represent an important area for future research.[45]

This study has several limitations. We lacked data on nonfatal CVD outcomes, and we did not examine complementary participant-reported health domains, such as symptom burden, functional status, health behaviors, and other diagnostic labels (eg, arthritis). These theoretically important[46] assessments are associated with self-rated health[47–52] and may provide a more-complete picture of CVD burden.[2] We included ASCVD risk as a covariate in models beyond the context in which they were developed (ie, extending to persons with existing CVD at baseline and considering nonatherosclerotic causes of death). Nonetheless, survival models with ASCVD risk scores are more likely to accurately reflect risk and are more parsimonious relative to traditional risk factors modeled individually.

In summary, self-rated health had the strongest associations with CVD mortality risk beyond that captured in current CVD risk formulations and after accounting for traditional and nontraditional CVD risk factors. In addition to the predictive power of self-rated health for CVD mortality, asking patients about their general health status is exceedingly simple, inexpensive, and safe to measure. These advantages reinforce the value of self-rated health as a key metric of cardiovascular health[2] and align with broader national trends to emphasize patient-centered approaches to the measurement of health and the delivery of health care.

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Steven D. Barger, Matthew R. Cribbet and Matthew F. Muldoon

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