sRAGE and Risk of Diabetes, Cardiovascular Disease, and Death

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Advanced glycation end products (AGEs) and their receptors are strongly implicated in the development of diabetes complications. When stimulated by AGEs, the receptors for AGEs (RAGEs) induce inflammation and are thought to fuel disease progression. Soluble circulating RAGE (sRAGE) may counteract the detrimental effects of RAGE. We measured sRAGE in stored plasma from a random sample of 1,201 participants in the Atherosclerosis Risk in Communities (ARIC) Study who were aged 47–68 years, had normal kidney function, and had no history of cardiovascular disease. In cross-sectional analyses, black race, male sex, higher BMI, and higher C-reactive protein were independently associated with low sRAGE. The racial difference was striking, with blacks approximately three times more likely to have low sRAGE compared with whites even after adjustment. During ~18 years of follow-up, there were 192 incident coronary heart disease events, 53 ischemic strokes, 213 deaths, and 253 cases of diabetes (among the 1,057 persons without diabetes at baseline). In multivariable Cox models comparing risk in the first quartile with that in the fourth quartile of baseline sRAGE, low levels of sRAGE were significantly associated with risk of diabetes (hazard ratio 1.64 [95% CI 1.10–2.44]), coronary heart disease (1.82 [1.17–2.84]), and mortality (1.72 [1.11–2.64]) but not ischemic stroke (0.78 [0.34–1.79]). In conclusion, we found that low levels of sRAGE were a marker of future chronic disease risk and mortality in the community and may represent an inflammatory state. Racial differences in sRAGE deserve further examination.
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Advanced glycation end products (AGEs) are strongly implicated in the development of diabetic vascular disease (1–3) and are of particular interest as novel biomarkers because they are a postulated etiologic link between hyperglycemia and diabetes complications (3–8). It is also thought that AGEs contribute to the development of vascular disease in nondiabetic people through their pro-oxidant activities (4,5). AGEs bind a variety of receptors, and circulating levels of AGE receptors are thought to be influenced by a number of endogenous (e.g., glucose, inflammation) and exogenous (e.g., smoking, diet) factors. The most widely studied AGE receptor is receptor for AGEs (RAGE), which is expressed in the vasculature, retina, kidney, and inflammatory cells. RAGE is considered a multiligand receptor of the immunoglobulin superfamily, binding, in addition to AGEs, S100/calgranulins, high-mobility group box-1, amyloid-β peptide, and other molecules (9). The COOH terminus of the protein is located on the extracellular surface. The NH_2-terminus of RAGE is essential in activating proinflammatory nuclear factor (NF)-κB–mediated signaling. When stimulated by AGEs, RAGE induces inflammation, contributes to tissue injury, and fuels the progression of chronic disease through NF-kB–mediated signaling (10–13). The soluble receptor for AGEs (sRAGE) is the isoform of RAGE found in serum and is primarily formed by proteolytic cleavage of RAGE and secondarily by endogenously secreted RAGE (esRAGE). esRAGE can be measured independently, comprises roughly one-quarter of total serum RAGE (14,15), and is highly correlated with total sRAGE levels (14,16). sRAGE has been described as a "sponge" for AGEs and may have protective functions, as it lacks the NH_2-terminus and cannot activate NF-κB signaling. Levels are primarily dependent on cell-surface RAGE levels (17).

Recent studies have demonstrated inverse associations of serum sRAGE with clinical outcomes in persons with diabetes or kidney disease (18–21) and inverse cross-sectional associations with measures of coronary heart disease or atherosclerosis in more general populations (15,22–24). However, few prospective studies have been conducted in diverse, community-based populations using robust ELISA methods for measurement of sRAGE. The objective of this study was to characterize the association of sRAGE with risk of diabetes, coronary heart disease, stroke, and all-cause mortality in a community-based population.

RESEARCH DESIGN AND METHODS

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort of 15,792 middle-aged adults from four U.S. communities. The first examination of participants (visit 1) took place during 1987–1989, with three follow-up visits taking place: each approximately every 3 years. A fifth examination is currently ongoing (2011–2013). The study population for the current study is comprised of a subsample of participants who attended visit 2 during 1990–1992. A random sample of 1,289 participants with normal kidney function (estimated glomerular filtration rate >60 mL/min/1.73 m^2) was selected from the 14,348 participants who attended visit 2. The final sample sizes used in the current study were 1,201 after excluding those who were missing sRAGE or covariates of interest and those with a history of cardiovascular disease and 1,057 after further excluding persons with diabetes defined by a fasting glucose ≥126 mg/dL, a nonfasting glucose ≥200 mg/dL, an HbA_{1c} value ≥6.5%, a self-reported physician diagnosis of diabetes, or diabetes medication use at visit 2.

Measurement of sRAGE. sRAGE was measured in 2010 by ELISA (R&D Systems, Minneapolis, MN) from plasma samples that had been in storage since collection from 1990 to 1992. The intra- and interassay coefficients of variation for the assay were 2.8 and 9.6%, respectively. sRAGE has been shown to be highly stable when measured from stored samples and robust to multiple freeze-thaw cycles (25).

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TABLE 1
Baseline characteristics of the study population by quartiles of sRAGE (N = 1,201)

	sRAGE (pg/mL)				
	Q1 (119.4–711.6)	Q2 (711.6–966.3)	Q3 (965.6–1,263.4)	Q4 (1,263.4–4,650.4)	Total
Male	48.7	44.0	43.7	30.9	41.8
Age (years), mean	56.6	56.6	56.7	56.4	56.6
Black	46.0	22.0	12.3	6.6	21.7
Diabetes*	19.3	13.3	11.7	5.7	12.5
BMI (kg/m^2), mean	30.3	28.0	27.5	25.8	27.9
C-reactive protein (mg/L), mean	5.2	3.3	3.3	2.7	3.6
Total cholesterol ≥200 mg/dL	57.0	63.7	54.7	49.5	56.2
Low HDL cholesterol†	38.7	41.0	40.7	36.2	39.1
Hypertension‡	45.0	30.3	29.3	24.6	32.3
Current smoker	15.0	21.3	20.7	16.3	18.3

Data are percent unless otherwise indicated. Q, quartile. *Nonfasting glucose ≥200 mg/dL, fasting glucose ≥126 mg/dL, self-reported diagnosis, medication use, or HbA_{1c} ≥6.5%. †Low HDL cholesterol was defined as <40 mg/dL in males and <50 mg/dL in females. ‡Diastolic blood pressure ≥90 mmHg, systolic blood pressure ≥140 mmHg, or blood pressure–lowering medication use.

Other variables of interest. Plasma lipid levels (26,27), BMI (28), and blood pressure (29) were measured according to published methods. C-reactive protein was measured in 2008 from stored plasma samples using an immunoturbidimetric assay on the Siemens (Dade Behring, Deerfield, IL) BNII analyzer (Dade Behring). Hypertension was defined as average systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 Hg, or blood pressure–lowering medication use in the past 2 weeks. Participants reported their age, race, and smoking status.

Surveillance for incident diabetes. During each ARIC visit, information was obtained on self-reported diabetes, glucose-lowering medication use, and serum glucose. After visit 4, diabetes cases were identified exclusively on the basis of information on self-reported diagnosis or diabetes medication use obtained during the annual telephone calls to all participants. We combined these two sources of information to define incident diabetes according to a standard time-to-diabetes definition based on the visit-based information (30,31) and self-reported information on diagnosed diabetes or glucose-lowering medication use obtained during a median of 12 years of annual telephone calls after visit 4 (32).

Surveillance for incident coronary heart disease, stroke, and all-cause mortality. The ascertainment of deaths and classification of cardiovascular events have previously been described (33,34). Briefly, potential cardiovascular hospitalizations were reported annually by participants and also identified through community-wide hospital surveillance. Trained personnel abstracted hospital records related to possible cardiovascular events (34). Silent myocardial infarctions, as detected by means of electrocardiography during the visits, were identified and recorded. We defined newly diagnosed coronary heart disease as a definite or probable myocardial infarction, a death from coronary heart disease, a cardiac procedure, or electrocardiographic evidence of a silent myocardial infarction. We also examined definite or probable ischemic stroke. Adjudicated follow-up data for cardiovascular events were available up to 1 January 2010.

Statistical analysis. Baseline characteristics of the study population were calculated overall and by quartiles of baseline sRAGE levels. We evaluated crude cross-sectional associations between sRAGE and the continuous variables using Spearman correlations and compared mean sRAGE levels across categorical variables using t tests. We constructed kernel density plots to visually compare sRAGE distributions by race group, diabetes, and hypertension status. We used multivariable logistic regression models to evaluate the cross-sectional associations of participant characteristics with low sRAGE (lowest quartile) at baseline. We also conducted supplemental cross-sectional analyses using Poisson regression, since the odds ratio (OR) from the logistic regression model is a nonconservative estimate of the prevalence ratio in this setting; the prevalence of the outcome is 25% by definition (quartile 1 of sRAGE). For prospective analyses, adjusted hazard ratios (HRs) and corresponding 95% CIs for each outcome were estimated using Cox proportional hazards models. Baseline sRAGE was modeled continuously using linear and restricted cubic spline (35) models (centered at the 50th percentile of sRAGE) and in quartiles, with quartile 4 as the reference group. Model 1 was adjusted for age, sex, and race. Model 2 was adjusted for Framingham Risk Score (which includes age, sex, current smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, and diabetes status [except for models of diabetes]) plus C-reactive protein (milligrams per liter), BMI (weight in kilograms divided by the square of height in meters), and race. Models of incident diabetes excluded persons with a history of diabetes at baseline (N = 144). We conducted sensitivity analyses with additional adjustment for family history of diabetes, estimated glomerular filtration rate, and fasting glucose and analyses of risk of cardiovascular outcomes and death after excluding persons with diabetes (diagnosed or undiagnosed) at baseline.

RESULTS

Cross-sectional associations with low sRAGE. Compared with the higher quartiles, the lowest quartile of sRAGE had a higher proportion of men, black participants, and participants with diabetes or hypertension (Table 1).

TABLE 2
Unadjusted and adjusted* ORs for the lowest quartile of sRAGE

	Unadjusted OR (95% CI)	Adjusted OR*
Age per 10 years	1.03 (0.82–1.29)	1.08 (0.83–1.41)
Male (vs. female)	1.45 (1.12–1.89)†	1.97 (1.42–2.73)†
Black (vs. white)	5.39 (4.01–7.25)†	5.42 (3.88–7.59)†
Cigarette smoking		
Current smoker (vs. never)	0.93 (0.63–1.38)	0.95 (0.60–1.49)
Former smoker (vs. never)	1.59 (1.19–2.12)†	1.77 (1.26–2.48)†
Total cholesterol ≥200 mg/dL (vs. <200 mg/dL)	1.04 (0.80–1.36)	1.13 (0.84–1.53)
Low HDL cholesterol‡	0.97 (0.75–1.27)	0.83 (0.61–1.13)
Hypertension§	2.10 (1.60–2.74)†	1.15 (0.84–1.58)
BMI (kg/m^2)		
25–30 (vs. <25)	1.89 (1.31–2.72)†	1.40 (0.94–2.09)
≥30 (vs. <25)	4.35 (3.03–6.25)†	2.59 (1.67–4.01)†
C-reactive protein (mg/L)		
1–3 (vs. <1)	1.90 (1.30–2.78)†	1.67 (1.10–2.54)†
≥3 (vs. <1)	3.30 (2.31–4.76)†	2.66 (1.73–4.10)†
Diabetes‖	2.11 (1.47–3.02)†	0.98 (0.64–1.50)

*Adjusted for all variables listed. †P value <0.05. ‡Low HDL cholesterol was defined as <40 mg/dL in males and <50 mg/dL in females. §Diastolic blood pressure ≥90 mmHg, systolic blood pressure ≥140 mmHg, or blood pressure–lowering medication use. ‖Nonfasting glucose ≥200 mg/dL, fasting glucose ≥126 mg/dL, self-reported diagnosis, medication use, or HbA_{1c} ≥6.5%.

TABLE 3
HRs for incident diabetes, coronary heart disease, ischemic stroke, and mortality by sRAGE quartile at baseline

	Events (*n*)	HR Model 1†	HR Model 2‡
Incident diabetes (*N* = 1,057)			
Q4 (1,263.4–4,650.4)	45	1.00 (ref.)	1.00 (ref.)
Q3 (965.6–1,263.4)	64	1.56 (1.06–2.29)*	1.36 (0.92–2.00)
Q2 (711.6–966.3)	66	1.72 (1.17–2.53)*	1.45 (0.99–2.14)
Q1 (119.4–711.6)	78	2.28 (1.54–3.37)*	1.64 (1.10–2.44)*
P value for trend		<0.001*	0.015*
Coronary heart disease (*N* = 1,201)			
Q4 (1,263.4–4,650.4)	37	1.00 (ref.)	1.00 (ref.)
Q3 (965.6–1,263.4)	44	1.10 (0.71–1.70)	1.10 (0.71–1.71)
Q2 (711.6–966.3)	49	1.26 (0.81–1.93)	1.22 (0.79–1.89)
Q1 (119.4–711.6)	62	1.68 (1.09–2.58)*	1.82 (1.17–2.84)*
P value for trend		0.018*	0.01*
Ischemic stroke (*N* = 1,201)			
Q4 (1,263.4–4,650.4)	12	1.00 (ref.)	1.00 (ref.)
Q3 (965.6–1,263.4)	12	0.89 (0.40–2.00)	0.81 (0.36–1.83)
Q2 (711.6–966.3)	13	0.86 (0.38–1.92)	0.64 (0.28–1.47)
Q1 (119.4–711.6)	16	0.89 (0.39–2.03)	0.78 (0.34–1.79)
P value for trend		0.766	0.463
All-cause mortality (*N* = 1,201)			
Q4 (1,263.4–4,650.4)	37	1.00 (ref.)	1.00 (ref.)
Q3 (965.6–1,263.4)	43	1.06 (0.68–1.65)	1.03 (0.66–1.61)
Q2 (711.6–966.3)	55	1.30 (0.85–2.00)	1.14 (0.74–1.76)
Q1 (119.4–711.6)	78	1.89 (1.25–2.87)*	1.72 (1.11–2.64)*
P value for trend		0.002*	0.015*

Q, quartile. *P value <0.05. †Model 1: adjusted for age, race, and sex. ‡Model 2: adjusted for Framingham Risk Score (which includes age [years], sex, current smoking, systolic blood pressure [mmHg], total cholesterol [mg/dL], HDL cholesterol [mg/dL], and diabetes status) plus C-reactive protein (mg/L), BMI (kg/m^2), and race group.

Mean levels of C-reactive protein and BMI also were highest in the lowest quartile of sRAGE. The distribution of sRAGE in blacks was substantially shifted toward lower levels compared with whites; mean (SD) sRAGE in blacks was 756 (413) pg/mL compared with 1,122 (469) pg/mL in whites ($P < 0.0001$) (Supplementary Fig. 1*D*). There also was a significant difference in mean sRAGE comparing persons with and without diabetes (905 vs. 1,052 pg/mL, $P = 0.0114$) (Supplementary Fig. 1*C*). The strongest crude (Spearman) correlations between baseline sRAGE and the continuous variables examined were for BMI ($r = -0.32$), C-reactive protein ($r = -0.25$), HbA_{1c} ($r = -0.22$), fasting glucose ($r = -0.22$), and systolic blood pressure ($r = -0.18$) (Supplementary Table 1). All other correlations were low to moderate ($|r| < 0.12$). After simultaneous adjustment for each of the risk factors in a multivariable logistic regression model, male sex, black race, former smoking, obesity (BMI $\geq$30 kg/m^2), and C-reactive protein remained significantly associated with low sRAGE (Table 2). In this model, diabetes was no longer significantly associated with low sRAGE after adjustment for the other variables. Race remained highly associated with sRAGE. The prevalence of low sRAGE among blacks was almost three times the prevalence in whites, even after adjustment (Supplementary Table 2).

Prospective associations of sRAGE with outcomes. The median follow-up time was ~18 years. In the study population of 1,057 persons without diabetes or cardiovascular disease at baseline, there were 253 cases of incident diabetes. In the study population of 1,201 persons without cardiovascular disease at baseline, there were 192 cases of incident coronary heart disease, 53 cases of ischemic stroke, and 213 total deaths. Low baseline levels of sRAGE were associated with risk of diabetes, coronary heart disease, and all-cause mortality (Table 3 and Fig. 1). Adjustment for traditional risk factors attenuated but did not eliminate these associations. Compared with persons in the highest quartile of sRAGE, persons in the lowest quartile had a significant and independent increased risk of diabetes (HR 1.64 [95% CI 1.10–2.44]), coronary heart disease (1.82 [1.17–2.84]), or all-cause mortality (1.72 [1.11–2.64]). There was no significant association of baseline sRAGE and incident ischemic stroke before or after adjustment. The shape of the association of sRAGE with incident diabetes was roughly linear (Fig. 1), with lower sRAGE levels associated with higher risk across the range of the exposure. For coronary heart disease, the slope appeared steeper for sRAGE levels below the median (965.6 pg/mL) (P value = 0.016 for slope from the piecewise linear model for coronary heart disease before the median). The P value for the slope from the piece-wise linear model for mortality was <0.001 before the first knot (711.1 pg/mL). The results for coronary heart disease, stroke, and all-cause mortality were not appreciably altered after exclusion of persons with diagnosed or undiagnosed diabetes at baseline (Supplementary Table 3). Results were also similar after additional adjustment for family history of diabetes, kidney function, and fasting glucose. Censoring of incident cases of diabetes that occurred during follow-up but prior to the onset of coronary heart disease also did not change the associations observed with incident coronary heart disease (data not shown).

Because we observed substantial racial differences in baseline levels of sRAGE, we conducted race-specific sensitivity analyses. In analyses stratified by race (Supplementary Tables 4 and 5), our results remained significant in whites but the trends for the associations of quartiles

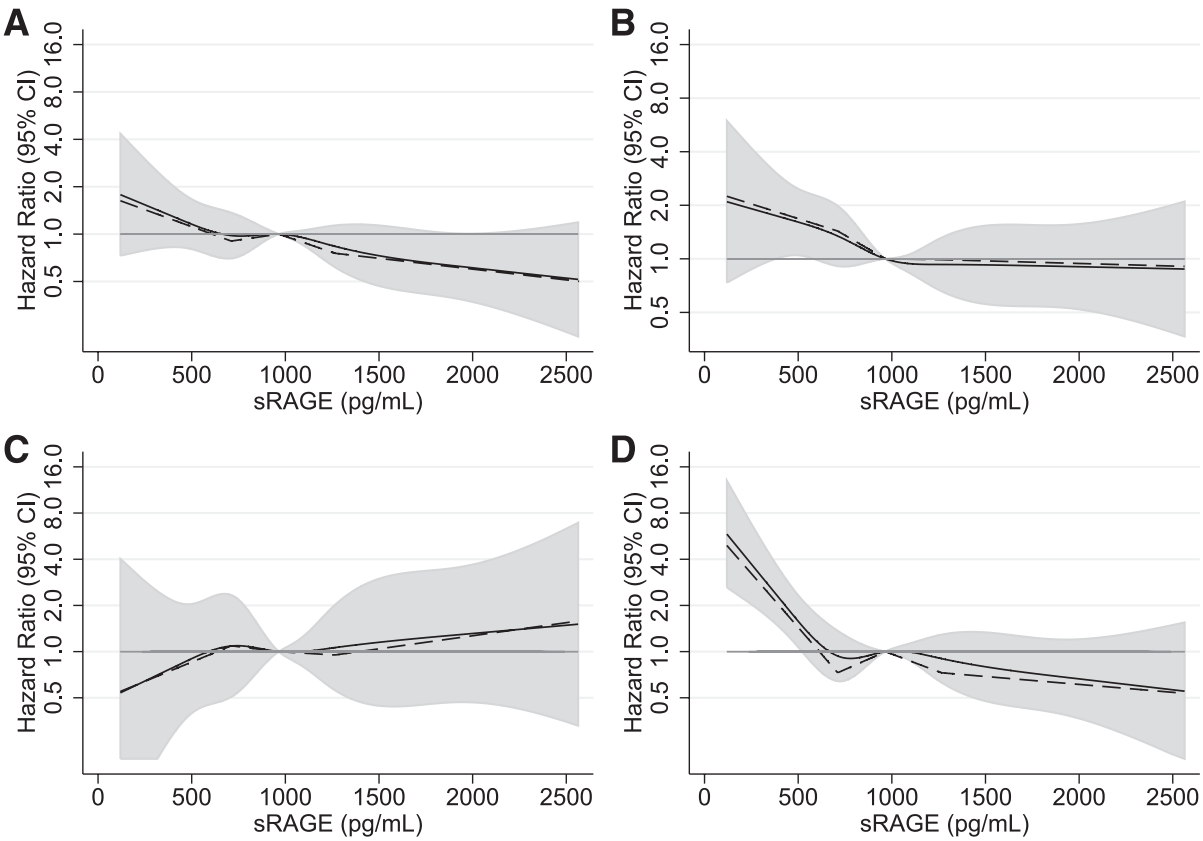

FIG. 1. Adjusted HRs (95% CI) for baseline sRAGE and incident diabetes (*A*), coronary heart disease (*B*), ischemic stroke (*C*), and all-cause mortality (*D*). Adjusted HRs are from Cox proportional hazards models with adjustment for Framingham Risk Score (which includes age [years], sex, current smoking, systolic blood pressure [mmHg], total cholesterol [mg/dL], HDL cholesterol [mg/dL], and diabetes status) plus C-reactive protein (mg/L), BMI (kg/m^2), and race group. Baseline sRAGE was modeled using restricted cubic splines (solid lines) with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles and piece-wise linear splines (dashed lines) with knots at the quartiles of sRAGE (711.1, 965.6, 1,263.8 pg/mL). Both models are centered at the 50th percentile (sRAGE 965.6 pg/mL). The shaded areas are the CIs for the restricted cubic spline models. The graphs are truncated at the 99th percentile of sRAGE.

of sRAGE with incident diabetes, stroke, and all-cause mortality in blacks were not significant, likely owing to the small number of black participants in this study (N = 261). The association of sRAGE with incident coronary heart disease in blacks was actually opposite the direction (Supplementary Table 4) of the association in whites but not in a graded fashion (i.e., no significant trend); however, there were only 36 total coronary heart disease events among blacks in our study population, suggesting that these results are highly unreliable.

DISCUSSION

During a median of 18 years of follow-up, we found that low levels of sRAGE at baseline were independently associated with risk of diabetes, coronary heart disease, and all-cause mortality, but not stroke, in this community-based population. We also found that blacks were substantially more likely to have low levels of sRAGE levels at baseline compared with whites and that this racial difference was not explained by demographic, metabolic, or inflammatory factors. Even after adjustment, blacks were approximately three times as likely to have low sRAGE ($<$711.6 pg/mL) compared with whites. The magnitude of this race difference is striking and deserves further examination. Male sex, BMI, and C-reactive protein were also independently associated with low sRAGE at baseline. After adjustment, sRAGE levels did not differ by diabetes status at baseline, suggesting that sRAGE may not be as specific to diabetes as previously thought. The robust associations of sRAGE with risk of coronary heart disease and mortality, in addition to incident diabetes, suggest that sRAGE may be a generalized marker of ill health.

The glycation and chemical modification of long-lived proteins through a series of slow reactions (Schiff, Amadori, and Maillard reactions) to form AGEs and their cross-linking of extracellular matrix materials such as collagen are thought to result in vascular stiffness (36,37) and vascular complications of diabetes (2,38–41). There is evidence from laboratory studies, particularly in animal models, that circulating RAGE (sRAGE) counteracts the detrimental effects of cellular RAGE by binding serum AGEs (42,43). Perhaps mechanisms that promote cleavage and shedding of full-length RAGE to create sRAGE may be beneficial to health. ADAM10 and other metalloproteinases cleave RAGE resulting in sRAGE shedding (44). Our results provide further evidence that low levels of sRAGE may be a marker of long-term chronic disease risk.

Few studies have characterized AGEs in serum and investigated their associations with long-term health outcomes in a general population. Previous studies have documented inverse correlations between sRAGE with C-reactive protein (45–47) and low levels of sRAGE among persons with coronary heart disease (22,47,48). Our finding of substantially lower sRAGE levels in blacks compared with whites suggests that racial differences in sRAGE

are an important area for further investigation. Previous studies also have reported significantly lower levels of sRAGE in blacks compared with whites (14,22,49). Nonetheless, owing to small numbers of events in the subgroup of black participants in our study, we were unable to rigorously evaluate potential effect modification by race on the association of sRAGE with long-term outcomes.

Important limitations of this study include the reliance on a single measurement of sRAGE at baseline, which will vary within individuals over time. Indeed, there is evidence that aerobic exercise (50) and use of certain medications (51,52) may acutely affect circulating sRAGE levels. Because of sample size limitations and correspondingly low power in subgroups, we were unable to rigorously examine the associations of sRAGE in subpopulations or evaluate possible effect modification. Indeed, our power was particularly limited for analyses of incident ischemic stroke (N = 53 cases overall) and for race-stratified analyses (N = 261 black participants at baseline). Owing to the observational nature of this investigation, the possibility of residual confounding cannot be eliminated. Nonetheless, this report is one of the first to investigate sRAGE in a racially diverse, community-based cohort with long-term follow-up for clinical outcomes. Major additional strengths include the rigorous measurement of cardiovascular disease risk factors and the use of comprehensive surveillance and adjudication of cardiovascular events.

In summary, our study demonstrated significant, independent associations between low sRAGE and future risk of diabetes, coronary heart disease, and all-cause mortality but not ischemic stroke in the general population. Our observation of substantially lower levels of sRAGE in blacks compared with whites suggests underlying racial variation in sRAGE production. In cross-sectional analyses, we found that male sex, higher BMI, and higher C-reactive protein were independently associated with low sRAGE. Taken as a whole, our results suggest that low levels of sRAGE are a marker of future chronic disease risk and mortality in the general population and may represent an inflammatory state.

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E.S. wrote the manuscript and analyzed data. M.K.H. reviewed and edited the manuscript and contributed to the discussion. A.M.R. analyzed the data and reviewed and edited the manuscript. R.C.H. and C.M.B. were responsible for laboratory measurements and reviewed and edited the manuscript. J.C. helped design the study, contributed to discussion, and reviewed and edited the manuscript. B.C.A. designed the study, contributed to discussion, and reviewed and edited the manuscript. E.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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