Published in final edited form as:

Atherosclerosis. 2015 May ; 240(1): 17–20. doi:10.1016/j.atherosclerosis.2015.02.015.

Serum soluble RAGE levels and carotid atherosclerosis: the Northern Manhattan Study (NOMAS)

Barry I Hudson¹, Hannah Gardener², Wen Liu-Mares³, Chuanhui Dong², Ken Cheung⁵, Mitchell SV Elkind^{6,7}, Clinton B Wright^{2,3,4,8}, Ralph L Sacco^{2,3,4}, and Tatjana Rundek^{2,3}

¹Division of Endocrinology, Diabetes & Metabolism, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

²Department of Neurology, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

³Department of Epidemiology and Public Health, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

⁴Evelyn F. McKnight Brain Institute, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

⁵Department of Biostatistics, Mailman Public School of Health, Columbia University, New York, NY., USA

⁶Stroke Division, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY., USA

⁷Department of Epidemiology, Mailman Public School of Health, Columbia University, New York, NY., USA

⁸Neuroscience Program, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA

Abstract

Background—Recent cohort studies suggested that serum levels of soluble Receptor for Advanced Glycation End-products (sRAGE) are associated with the risk of cardiovascular disease. We hypothesized that sRAGE levels are associated with subclinical atherosclerosis in a racially and ethnically diverse population.

Methods and results—828 stroke-free participants from the Northern Manhattan Study (mean age 71.1±8.7yrs; 64% Hispanic, 19% black, and 17% white) underwent high-resolution carotid B-mode ultrasound to measure carotid plaque (present in 62% of subjects) and intima-media thickness (IMT) (mean Total= 0.96±0.10 mm). Serum sRAGE was measured by ELISA and

*To whom correspondence should be addressed: Dr. Barry I. Hudson, University of Miami, 608 Batchelor Building, Miami, FL, 33136, ; Email: bhudson@med.miami.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

associations tested between sRAGE with IMT and plaque presence. Soluble RAGE levels were not associated with plaque presence or IMT after adjusting for sociodemographic, vascular risk factors and medication use. Stratification by race-ethnicity did not reveal any associations with carotid IMT or plaque.

Conclusion—In the present study, sRAGE levels were not associated with carotid atherosclerosis.

Keywords

RAGE (receptor for advanced glycation end products); biological marker; atherosclerosis; Hispanics; IMT; plaque; carotid ultrasound

1. Introduction

Cardiovascular disease (CVD) continue to be the leading causes of death in the Western world, and of increasing burden in developing countries (1). Even with the development of integrative global CVD risk tools such as the Framingham Score and the Northern Manhattan Study Global Vascular Risk Score, a considerable gap in prediction and understanding of CVD exists (2). This has prompted the investigation of novel risk factors, including non-invasive imaging measures of subclinical atherosclerosis and blood biomarkers. Ultrasound imaging markers such as carotid plaque and IMT are well recognized endophenotypes of atherosclerosis associated with increased risk of CVD (3;4). However, gaps still exist in the use and implication of reliable blood biomarkers and their integration with carotid measures as predictors of future CVD events.

Recent attention has focused on the link between serum levels of the soluble Receptor for Advanced Glycation End-products (RAGE) and CVD in clinical studies (5). RAGE is well established in animal models of CVD to be a critical factor in driving atherosclerosis and vascular disease (5–8). Moreover, soluble isoforms of RAGE (sRAGE) formed endogenously can be detected in human serum, and may therefore be a novel biomarker for CVD (5). Soluble RAGE can exist in different isoforms, which include esRAGE (endogenous secreted RAGE) formed through alternative splicing, and an isoform generated by ectodomain shedding of cell-surface RAGE (cleaved or cRAGE) (5). Levels of either the combined serum pool of sRAGE (cRAGE and esRAGE), or just the specific esRAGE isoform, have been associated with CAD (9), carotid artery atherosclerosis (10;11), stroke (12) and chronic heart failure (13). However, the majority of previous studies have focused on small samples, have been amongst homogeneous race-ethnic populations, and been of the frank disease state. Therefore, to evaluate sRAGE as a useful biomarker, large population studies of diverse race-ethnic groups and of pre-clinical disease states are needed. In order to address this, recent studies from our and other groups have demonstrated ethnic differences in sRAGE levels (14)(15) and that sRAGE may be a biomarker for subclinical cerebrovascular disease (14).

In this current study we have investigated the hypothesis that sRAGE levels are associated with subclinical carotid atherosclerosis in a multi-ethnic urban population. These analyses may unravel the role of RAGE and its soluble isoforms in the pathogenesis of CVD.

2. Methods

2.1 Study subjects

NOMAS is a well-defined ethnically diverse community-based study designed to investigate vascular risk factors and risk of incident stroke and cognitive decline. The current analysis includes 828 subjects who had sRAGE levels measured within two years of carotid ultrasound assessment. Detailed methods of the recruitment and characterization of NOMAS subjects has been previously detailed (16;17).

2.2 Subclinical Carotid Atherosclerosis Assessments

High-resolution B-mode carotid ultrasound imaging was performed according to a standardized scanning and reading protocols by a certified sonologist (18). Carotid IMT measurements were performed outside of plaque using the automated edge detection algorithm (M'Ath, IMT, Inc, Paris, France) (19). Total carotid IMT (in mm) was calculated as a composite measure of the 12 sites (mean IMT of the near and the far wall of the maximal common carotid artery, the bifurcation, and the internal carotid artery bilaterally). All these carotid segments were examined for presence of atherosclerotic plaque. Plaque was defined as an area of focal wall thickening >50% greater than surrounding wall thickness (4).

2.3 Laboratory measures

Total serum sRAGE was measured using the Human RAGE Quantikine ELISA (R&D Systems), as previously described (14). This method measures the total sRAGE pool in serum and plasma samples using a monoclonal antibody raised against the whole recombinant extracellular human sRAGE protein (5). The minimal level of detection was 0.05 ng/ml as per manufacturer's instructions and the intra- and interassay coefficients of variation with this ELISA were 6% and 10%, respectively.

2.4 Statistical analysis

Serum sRAGE was examined continuously (unit of measurement=standard deviation). The Student t-test was used to examine the association between sample characteristics and sRAGE after natural log transformation to achieve normality. The outcomes of interest were IMT and plaque presence. For IMT, the relationship with sRAGE was examined using linear regression and for plaque presence using logistic regression. For each of these analyses, two models were constructed. The first model was unadjusted and the second was adjusted for age, sex, race/ethnicity, SBP, DBP, blood sugar, LDL, HDL, BMI, smoking, and the time span from sRAGE measurement to carotid ultrasound. We examined potential interactions between race-ethnicity and sRAGE in relation to the IMT and plaque by including interaction terms in model 2.

3. Results

3.1 Sample Characteristics

The study sample characteristics are presented in Table 1 (N=828). The mean age of the study group at the time of sRAGE measurement was 71.1 (± 8.7) years. The mean sRAGE

was 1044 pg/ml (median=917, range=111–4610, SD=554 pg/ml). Plaque was present in 62% of the participants and the mean and standard deviation (SD) for IMT was 0.96 ± 0.10 mm.

3.2 sRAGE levels are not associated with carotid IMT and plaque

No relationship was seen between sRAGE level (per SD) and IMT ($\beta = 0.002$, $p = 0.62$) or plaque (OR 1.18 (1.02–1.36)) (Table 2). Likewise, after adjustment for demographics and vascular risk factors, no relationship was seen between sRAGE and IMT or plaque.

3.3 sRAGE levels and carotid atherosclerosis by ethnicity

Previous studies, including our own, have demonstrated that sRAGE levels vary across race-ethnic groups (14). Therefore, an analysis by ethnicity was conducted. Unadjusted analyses revealed no associations between sRAGE and either IMT or plaque amongst Hispanic, Blacks or Whites (Table 2). After adjusting for potential confounding factors, no relationships were observed between sRAGE and carotid atherosclerosis in any ethnic group.

3.4 sRAGE levels and cardiovascular drug effects

Finally, we assessed whether common drugs used for treating cardiovascular disease and diabetes affect our data. Studies have shown that commonly used medications including statins, thiazolidinediones and ACE inhibitors increase serum sRAGE levels (20). In those on statins ($N=212$, median sRAGE=989.78) compared to subjects without statin treatment ($N=546$, median sRAGE=877.83), sRAGE levels were significantly elevated ($p=0.03$). In subjects with/without anti-diabetic medications, no difference in median sRAGE levels was seen between groups. We finally performed analysis on the relationship between sRAGE and IMT / plaque, correcting for both statin and anti-diabetic medication use (in addition to other factors corrected for in model 2, Table 2). After adjusting for medication, no relationships were observed between sRAGE and carotid atherosclerosis (IMT, $\beta = 0.00193$, $p=0.57$; plaque presence, OR=1.07, 95% CI=0.90–1.27).

4. Discussion

This is the first study of sRAGE in relation to carotid artery IMT and plaque conducted in a race-ethnically diverse CVD-free cohort, and no associations were observed. Furthermore, no relationship was observed between sRAGE levels and carotid atherosclerosis in any race-ethnic group.

RAGE is a multi-ligand receptor of the immunoglobulin superfamily and has been implicated through its inflammatory role in various cardiovascular disease states. Soluble RAGE may act as a decoy, preventing cellular activation of the RAGE receptor and the resulting RAGE-induced cellular dysfunction/inflammation (5). Although human serum sRAGE (cRAGE and esRAGE) or just the esRAGE isoform, has been associated with CVD (5)(9) (10;11) (12)(13), few studies have focused on the pre-clinical atherosclerosis. Our previous study of sRAGE levels revealed a relationship between sRAGE and silent brain infarcts (14) especially among Hispanics (14). Here, we expand these explorations to the relationships between sRAGE and carotid IMT and plaque. Prior studies have demonstrated

a relationship between total sRAGE or esRAGE and carotid IMT (10;21), but very limited data exists between sRAGE levels and carotid plaque (22). In the current study we did not see any relationship with carotid IMT or plaque presence. This result is unexpected yet interesting as studies from mice clearly show mechanistic links between RAGE and atherosclerotic development and progression (5). Although prior clinical studies have detected similar associations to those seen in mice, most prior studies of IMT were of small samples (<100 subjects), and showed both positive as well as negative correlations between sRAGE and IMT (10;21;23).

These data therefore raise intriguing questions; firstly, sRAGE level may not be associated with subclinical carotid atherosclerosis and may be only a reflector of the overt CVD. Secondly, it is possible that whilst sRAGE may not be associated with carotid IMT or plaque presence per se, an association may exist with plaque morphology, such as plaque calcification. Data from other vascular beds may support this hypothesis as an inverse relationship between sRAGE and coronary artery calcification was seen in the Dallas Heart Study (11). RAGE has been shown to drive vascular cell differentiation to an osteoblast-like state via an inflammatory-mediated mechanism (24;25) and in the vasculature RAGE promotes chondrogenic differentiation and arterial calcification (25), and blocking its ligand interaction leads to lowered plaque calcification and thickness (26). Further, due to the relatively older age of the participants of our study to prior studies of sRAGE and IMT, it is possible different relationships may be seen, especially with advanced plaque phenotypes. However, as IMT should be more pronounced in these subjects, differences in sRAGE levels with IMT should therefore be more apparent if a relationship exists. It is finally possible due to the ethnic differences in sRAGE as seen here, in Hispanics subjects whom make up the majority of our study, a different relationship may exist with sRAGE and IMT compared to other ethnic groups including whites and Asians (10;21;23). This is further highlighted in the recent report by Moriya and colleagues, who reported when sRAGE and esRAGE levels are stratified by “low” and “high” values in a cohort of 284 subjects, low sRAGE and esRAGE levels are associated with higher carotid IMT (20). However, when analysis was performed for carotid plaque calcification, whilst lower total sRAGE levels were associated with higher calcification, esRAGE levels were not.

To address these matters, future studies should focus on the relationship between sRAGE levels and plaque morphology. In the current study we were unable to address these concerns as these plaque measures are ongoing in NOMAS.

This study has several strengths, which include the large population studied, inclusion of a multi-ethnic group living in the same community, and markers of subclinical atherosclerosis systematically measured. Conversely there are various limitations to our study, including a cross-sectional design, which impedes causal inferences. Further, the study cohort was relatively older compared to prior studies of sRAGE and carotid atherosclerosis. In addition, the measurements of sRAGE and ultrasound were performed at one time point, which does not account for changes over time. For future studies, measurement of sRAGE changes over time and changes in carotid plaque and IMT are needed. More importantly, future studies need to address carotid plaque morphology. Finally, we measured the pool of sRAGE isoforms and whilst this approach is necessary to understand any links with atherosclerosis,

future studies should measure the alternatively spliced isoforms separately to ascertain whether changes occur in cleavage or secretion of sRAGE forms. It is possible that differences in the regulation of these distinct biological processes could explain the differences seen in this and prior sRAGE studies.

In conclusion, sRAGE levels were not associated with either carotid IMT or plaque presence in our multi-ethnic population. Future studies are warranted to validate these data and determine whether sRAGE and different sRAGE isoforms are associated with ‘vulnerable’ plaque morphology.

Acknowledgments

This work was supported by the NIH [K24 to T.R. and RO1 013094 to M.E.]; and Evelyn McKnight Brain Institute.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, et al. Heart Disease and Stroke Statistics–2012 Update: A Report From the American Heart Association. *Circulation*. 2012 Jan 3; 125(1):e2–e220. [PubMed: 22179539]
2. van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. *Diabetes Care*. 2009 Nov; 32(11):2094–8. [PubMed: 19875606]
3. Spence JD. Technology Insight: ultrasound measurement of carotid plaque–patient management, genetic research, and therapy evaluation. *Nat Clin Pract Neurol*. 2006 Nov; 2(11):611–9. [PubMed: 17057748]
4. Rundek T, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. *Neurology*. 2008 Apr 1; 70(14):1200–7. [PubMed: 18354078]
5. Kalea AZ, Schmidt AM, Hudson BI. RAGE: a novel biological and genetic marker for vascular disease. *Clin Sci (Lond)*. 2009 Apr; 116(8):621–37. [PubMed: 19275767]
6. Harja E, Bu DX, Hudson BI, Chang JS, Shen X, Hallam K, Kalea AZ, Lu Y, Rosario RH, Oruganti S, et al. Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE^{−/−} mice. *J Clin Invest*. 2008 Jan; 118(1):183–94. [PubMed: 18079965]
7. Koulis C, Kanellakis P, Pickering RJ, Tsorotes D, Murphy AJ, Gray SP, Thomas MC, Jandeleit-Dahm KA, Cooper ME, Allen TJ. Role of bone-marrow- and non-bone-marrow-derived receptor for advanced glycation end-products (RAGE) in a mouse model of diabetes-associated atherosclerosis. *Clin Sci (Lond)*. 2014 Oct; 127(7):485–97. [PubMed: 24724734]
8. Myint KM, Yamamoto Y, Doi T, Kato I, Harashima A, Yonekura H, Watanabe T, Shinohara H, Takeuchi M, Tsuneyama K, et al. RAGE control of diabetic nephropathy in a mouse model: effects of RAGE gene disruption and administration of low-molecular weight heparin. *Diabetes*. 2006 Sep; 55(9):2510–22. [PubMed: 16936199]
9. Falcone C, Emanuele E, D’Angelo A, Buzzi MP, Belvito C, Cuccia M, Geroldi D. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. *Arterioscler Thromb Vasc Biol*. 2005 May; 25(5):1032–7. [PubMed: 15731496]
10. Katakami N, Matsuhisa M, Kaneto H, Matsuoka TA, Sakamoto K, Yasuda T, Umayahara Y, Kosugi K, Yamasaki Y. Serum endogenous secretory RAGE level is an independent risk factor for the progression of carotid atherosclerosis in type 1 diabetes. *Atherosclerosis*. 2009 Sep 2; 204:288–92. [PubMed: 18926539]
11. Lindsey JB, de Lemos JA, Cipollone F, Ayers CR, Rohatgi A, Morrow DA, Khera A, McGuire DK. Association between circulating soluble receptor for advanced glycation end products and atherosclerosis: observations from the Dallas Heart Study. *Diabetes Care*. 2009 Jul; 32(7):1218–20. [PubMed: 19366975]

12. Montaner J, Perea-Gainza M, Delgado P, Ribo M, Chacon P, Rosell A, Quintana M, Palacios ME, Molina CA, varez-Sabin J. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. *Stroke*. 2008 Aug; 39(8):2280–7. [PubMed: 18535284]
13. Raposeiras-Roubin S, Rodino-Janeiro BK, Grigorian-Shamagian L, Moure-Gonzalez M, Seoane-Blanco A, Varela-Roman A, Alvarez E, Gonzalez-Juanatey JR. Soluble receptor of advanced glycation end products levels are related to ischaemic aetiology and extent of coronary disease in chronic heart failure patients, independent of advanced glycation end products levels: New Roles for Soluble RAGE. *Eur J Heart Fail*. 2010 Oct; 12(10):1092–100. [PubMed: 20685687]
14. Hudson BI, Moon YP, Kalea AZ, Khatri M, Marquez C, Schmidt AM, Paik MC, Yoshita M, Sacco RL, DeCarli C, et al. Association of serum soluble receptor for advanced glycation end-products with subclinical cerebrovascular disease: the Northern Manhattan Study (NOMAS). *Atherosclerosis*. 2011 May; 216(1):192–8. [PubMed: 21316677]
15. Hudson BI, Dong C, Gardener H, Elkind M, Wright CB, Goldberg R, Sacco RL, Rundek T. Serum levels of soluble Receptor for Advanced Glycation End-products and metabolic syndrome: the Northern Manhattan Study. *Metabolism*. 2014 In press.
16. Sacco RL, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. *Stroke*. 2001 Aug; 32(8):1725–31. [PubMed: 11486097]
17. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, Sacco RL. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation*. 2005 Mar 15; 111(10):1327–31. [PubMed: 15769776]
18. Rundek T, Elkind MS, Pittman J, Boden-Albala B, Martin S, Humphries SE, Juo SH, Sacco RL. Carotid intima-media thickness is associated with allelic variants of stromelysin-1, interleukin-6, and hepatic lipase genes: the Northern Manhattan Prospective Cohort Study. *Stroke*. 2002 May; 33(5):1420–3. [PubMed: 11988625]
19. Touboul PJ, Labreuche J, Vicaute E, Belliard JP, Cohen S, Kownator S, Pithois-Merli I, Amarenco P. Country-based reference values and impact of cardiovascular risk factors on carotid intima-media thickness in a French population: the 'Paroi Arterielle et Risque Cardio-Vasculaire' (PARC) Study. *Cerebrovasc Dis*. 2009; 27(4):361–7. [PubMed: 19218802]
20. Moriya S, Yamazaki M, Murakami H, Maruyama K, Uchiyama S. Two Soluble Isoforms of Receptors for Advanced Glycation End Products (RAGE) in Carotid Atherosclerosis: The Difference of Soluble and Endogenous Secretory RAGE. *J Stroke Cerebrovasc Dis*. 2014 Oct 1.
21. Katakami N, Matsuhisa M, Kaneto H, Matsuoka TA, Sakamoto K, Yasuda T, Yamasaki Y. Endogenous secretory RAGE but not soluble RAGE is associated with carotid atherosclerosis in type 1 diabetes patients. *Diab Vasc Dis Res*. 2008 Sep; 5(3):190–7. [PubMed: 18777492]
22. Basta G, Castagnini M, Del TS, Epistolato MC, Righini P, Sangiorgi GM, De CR, Tanganelli P. High plasma levels of the soluble receptor for advanced glycation endproducts in patients with symptomatic carotid atherosclerosis. *Eur J Clin Invest*. 2009 Dec; 39(12):1065–72. [PubMed: 19811526]
23. Humpert PM, Djuric Z, Kopf S, Rudofsky G, Morcos M, Nawroth PP, Bierhaus A. Soluble RAGE but not endogenous secretory RAGE is associated with albuminuria in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2007; 6:9. [PubMed: 17343760]
24. Gawdzik J, Mathew L, Kim G, Puri TS, Hofmann Bowman MA. Vascular remodeling and arterial calcification are directly mediated by S100A12 (EN-RAGE) in chronic kidney disease. *Am J Nephrol*. 2011; 33(3):250–9. [PubMed: 21372560]
25. Cecil DL, Terkeltaub RA. Arterial calcification is driven by RAGE in *Enpp1*^{−/−} mice. *J Vasc Res*. 2011; 48(3):227–35. [PubMed: 21099228]
26. Yan L, Bjork P, Butuc R, Gawdzik J, Earley J, Kim G, Hofmann Bowman MA. Beneficial effects of quinoline-3-carboxamide (ABR-215757) on atherosclerotic plaque morphology in S100A12 transgenic ApoE null mice. *Atherosclerosis*. 2013 May; 228(1):69–79. [PubMed: 23497784]

Table 1

Characteristics of the cohort (N=828) and levels of sRAGE

Characteristics	Prevalence n (%)	Median of sRAGE (pg/ml) (Range)	<i>P</i>
Age at sRAGE assessment			
<70 years	436 (52)	895.1 (187.7–3899.4)	0.07
70 years	392 (47)	948.7 (110.9–4610.0)	
Sex			
Men	332 (40)	886.7 (110.9–4585.8)	0.35
Women	496(60)	942.9 (242.5–4610.0)	
Race-ethnicity			
Hispanic	529 (64)	910.2 (110.9–4585.8)	<0.0001
Non-Hispanic black	156 (19)	757.4 (187.7–2448.9)	
Non-Hispanic white	143 (17)	1178.1 (446.3–4610.0)	
Body Mass Index (BMI) (kg/m²)			
<25	204 (25)	1051.0 (190.3–4610.0)	0.002
25–30	351 (42)	925.8 (110.9–2971.5)	
≥30	273 (33)	846.1 (187.7–4585.8)	
Blood sugar (fasting; mg/dl)			
≥126	105 (13)	825.5 (321.2–3793.9)	0.15
<126	717 (87)	928.5 (110.9–4610.0)	
Smoking			
Current	133 (16)	849.0 (242.5–2100.1)	0.10
Past	306 (37)	914.2 (110.9–4585.8)	
Never	389 (47)	948.1 (187.7–4610.0)	
LDL (mg/dl)			
≥100	548 (66)	920.8 (110.9–4610.0)	0.89
<100	280 (34)	911.9 (190.3–4585.8)	
HDL (mg/dl)			
Low (<50 women, <40 men)	293 (35)	902.0 (110.9–3793.9)	0.74
Normal	535 (65)	928.4 (187.7–4610.0)	
SBP (mmHg)			
≥140	357 (43)	878.9 (110.9–4610.0)	0.04

Characteristics	Prevalence n (%)	Median of sRAGE (pg/ml) (Range)	<i>P</i>
<140	471 (57)	952.7 (190.3–3899.4)	
DBP			
>=90	101 (12)	778.0 (110.9–2871.2)	0.0004
<90	727 (88)	946.6 (187.7–4610.0)	
Plaque presence			
Yes	515 (62)	942.9 (110.9–4610.0)	0.20
No	313 (38)	896.1 (187.7–2622.4)	

Abbreviations: sRAGE= soluble Receptor for Advanced Glycation End-products

Table 2

sRAGE levels and carotid ultrasonographic phenotypes: plaque presence and carotid intima-media thickness (IMT)

sRAGE per SD	IMT: beta, p-value	Plaque presence: OR (95 CI)
All subjects (N=828)		
Model 1	0.00171, 0.62	1.18 (1.02–1.36)
Model 2	–0.00164, 0.63	1.10 (0.93–1.29)
Hispanics only (N=529)		
Model 1	–0.00290, 0.51	1.14 (0.95–1.37)
Model 2	–0.00668, 0.11	1.06 (0.86–1.31)
NH-Whites only (N=143)		
Model 1	0.00349, 0.66	1.12 (0.79–1.59)
Model 2	0.00292, 0.73	1.25 (0.82–1.92)
NH – Blacks only (N=156)		
Model 1	0.01383, 0.14	1.19 (0.80–1.78)
Model 2	0.01227, 0.20	1.12 (0.71–1.76)

Model 1: univariate

Model 2: adjusted for age, sex, race/ethnicity, SBP, DBP, blood sugar, LDL, HDL, BMI, smoking, and the time span from SRAGE measurement to carotid ultrasound