ARIC Manuscript Proposal # 1905

PC Reviewed: 2/14/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Association of Lifestyle Factors with circulating levels of the Soluble Receptor for Advanced Glycation End Products (sRAGE)

b. Abbreviated Title (Length 26 characters): Lifestyle Factors and sRAGE

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JKB **[please confirm with your initials electronically or in writing]**

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3. Timeline: We aim to complete this manuscript within 1 year of approval.

4. Rationale:

Advanced glycation end products (AGEs) are a group of compounds hypothesized to contribute to vascular complications associated with diabetes [1-3]. Endogenous factors that influence AGE levels include glucose, inflammation, and circulating lipoproteins [4]. The previous literature also suggests that AGE formation and accumulation in the serum and tissues can be influenced by exogenous factors including tobacco, alcohol, certain foods [5], and other lifestyle factors including physical activity and obesity [6, 7].

The receptor for advanced glycation end products (RAGE) (found on endothelial and inflammatory cell surfaces) binds to circulating AGEs in the body, activating a pro-inflammatory protein cascade that contributes to oxidative stress, vascular inflammation, atherosclerosis, and neurological disease [4, 8] The truncated, soluble form of RAGE (sRAGE) is believed to counteract the damaging effects of cellular RAGE, acting as a "sponge" for AGE without propagating deleterious cellular signaling. It is generally present in higher levels in persons with less vascular damage [5, 7, 9].

Previous laboratory studies have established that certain foods — particularly those high in saturated fat and foods typically cooked at high temperatures (especially those that are fried, grilled, roasted, broiled, or seared) — contain elevated levels of AGEs as a result of the Maillard ("browning") reaction (for examples, see Table 1 below) [10, 11]. Thus, several experts have recommended that individuals at increased risk for vascular damage (e.g., individuals with diabetes) should adopt a low-AGE diet [6]. However, there is little evidence linking intake of dietary AGEs (dAGEs) with serum AGE levels and most data come from animal studies or small clinical studies in humans. For example, one study by Koschinsky and colleagues enrolled 38 individuals with diabetes and 5 healthy subjects. Participants were given a single meal of egg whites (56 g of protein) cooked with or without fructose and found a 200-fold increase in AGE immmunoreactivity after consuming the egg whites with fructose [12]. Additionally, Uribarri and colleges performed two investigations of note. The first was a small cross-sectional study of 90 healthy subjects examining the association of self-reported intake of high-AGE content foods with serums AGEs and CRP. A second study took a subgroup of five healthy subjects and exposed them to short-term dietary AGE restriction. The reduction in intake was associated with a mean decrease of 30-40% in serum AGE levels [6].

To our knowledge, there are no large epidemiologic studies in the general population examining the possible association between dietary and other lifestyle factors such as smoking and physical activity, and AGEs in the general population. The purpose of this project is to conduct an evaluation of the association between major lifestyle factors and serum AGE levels in a subgroup of ARIC participants.

Table 1. Examples of ARIC FFQ items with high and low levels of AGEs.

Examples of FFQ items high in AGEs • Butter • Chicken or turkey, with skin • Hamburgers • Hot dogs • Processed meats • Bacon • Fried foods (home-fried food and food fried away from home)
Examples of FFQ items low in AGEs • Skim or low fat milk • Whole milk • Fresh fruits • Rice • Coffee, not decaf • Tea • Low calorie soft drinks • Regular soft drinks

*AGE content values are based on previous lab studies [11].

5. Main Hypothesis/Study Questions:

The primary aim of this study is to evaluate the cross-sectional association of major lifestyle factors with serum sRAGE levels in a subcohort of ARIC participants from Visit 1 and a second subcohort from Visit 2 for whom sRAGE data are available. We hypothesize that the following factors will be associated with lower sRAGE levels: obesity, current smoking, higher alcohol consumption, lower physical activity levels, and lower score on ideal cardiovascular health (defined by current or recent smoking, higher BMI, lower physical activity, poorer dietary behaviors, higher total cholesterol, high blood pressure, and higher fasting serum glucose) [13]. Additionally, we hypothesize that high intake of foods that are known to have higher levels of AGEs (e.g., processed meats and lipid-rich foods) will be inversely associated sRAGE levels; intake of foods known to have low levels of AGEs will be positively association with sRAGE levels.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design and population. The primary analysis will be a cross-sectional analysis of ARIC Visit 2 data. sRAGE was measured on a random subsample (subcohort) of 1289 ARIC participants aged 47-68 years at ARIC Visit 2. Participants were included in Ancillary Study #2006.16. The basis of this study population is the cohort random sample of participants selected for the parent case-cohort study of incident chronic kidney disease. Therefore, all participants had an estimated GFR >60 mL/min/1.73m^2. For those

variables where data were not collected at Visit 2 (e.g., food frequency questionnaire variables), we will use ARIC Visit 1 data.

We will also use a smaller subcohort of 500-600 ARIC participants (ancillary study #1995.09) with sRAGE measured at Visit 1 for a replication study and will consider pooling the data pending that we observe no contraindications to do so. This subcohort represents a random sample of participants after excluding the following individuals: 2018 participants with prevalent diabetes, 95 members of self-reported race/ethnic groups other than black or white, 853 participants not returning to any follow-up visit, 26 members with no valid diabetes determination at follow-up, 6 with restrictions on stored plasma use, 12 with missing baseline anthropometric data, 2514 participants in previous ARIC case-control and case-cohort studies involving cardiovascular disease for whom stored plasma was either previously exhausted or held in reserve, 212 for incomplete fasting (< 8 hours), and 316 with missing information for hypertension (HTN) and inflammation markers. A final sampling frame of 9740 individuals (71% of those in the full cohort without diabetes at baseline) was established after exclusions for this ancillary study.

Inclusion/Exclusion Criteria. Participants missing sRAGE or other variables of interest will be excluded from the analytic sample. We will conduct sensitivity analyses excluding individuals with history of CHD and diabetes since lifestyle changes are often a part of treatment/disease management recommendations.

Outcome. sRAGE measured by ELISA (R&D Systems, CV<3%) from stored plasma samples at ARIC Visit 2.

Risk factors of Interest. We will examine the association between the following factors and sRAGE: physical activity (Baeke physical activity score), measures of adiposity (body mass index and waist-hip ratio), smoking history, alcohol use, C-reactive protein, dietary intake and behaviors (from food frequency questionnaire), lipids, and blood pressure. Additional adjustment variables will include age, sex, clinic site, race/ethnicity, and health history information (e.g., diabetes status).

Potential effect modifiers. We will formally test for effect modification by age, sex, and race/ethnicity.

Statistical Analysis. We will first examine Spearman's correlations of the continuous risk factor variables with sRAGE differences in mean levels across levels of the categorical variables. We will use multivariable regression models (linear and logistic) to examine the independent association of each of the risk factors of interest with sRAGE (modeled continuously) and low levels of sRAGE (i.e, lowest quartile, lowest decile). Finally, we will conduct sensitivity analyses excluding individuals with a history of diabetes and CHD (since lifestyle behavior change is often a part of treatment/disease management recommendations in these populations).

Limitations. Tests for interaction and subgroup analysis will be limited due to small sample sizes. Dietary intake in ARIC has a number of limitations, including a limited number of foods assessed and the fact that diet was not being assessed at the same visit as the sRAGE measurements. Other limitations include the cross-sectional design and no direct measurement of tissue accumulation of AGEs (which is thought to be the most relevant measure for disease etiology but was not feasible for this study).

7.a. Will the data be used for non-CVD analysis in this manuscript?____ Yes X No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC Pis, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes X No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

X Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

1890 Determinants of sRAGE and its Association with Cardiovascular Disease, Diabetes, and Mortality in a Community-based Population

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? X Yes ____ No

11.b. If yes, is the proposal
X A. primarily the result of an ancillary study (list number* 2006.02, 1995.09**)**

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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