ARIC Manuscript Proposal # 3378

PC Reviewed: 4/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Life's Simple 7 and Risk of Recurrent Cardiovascular Disease and All-Cause Mortality after Stroke: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **LS7 and Recurrent CVD after stroke**

2. Writing Group:

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

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3. Timeline: Analysis to begin as soon as the proposal is approved with submission to ARIC review in <6 months.

4. Rationale:

Cardiovascular disease (CVD) including stroke is a leading cause of morbidity and mortality in the United States with direct and indirect costs over $350 billion annually.[1] The Data from the Global Burden of Disease Study suggests that approximately 90% of CVD can be prevented through optimization of modifiable risk factors such as high blood pressure, obesity, hyperglycemia, hyperlipidemia and 74% of strokes are attributable to health behaviors such as smoking, sedentary lifestyle and unhealthy diet.[2] Modifying health behaviors can avert the occurrence and recurrence of CVD. However, there is ample data which suggest that most adults in the United States eat poorly and have sedentary lifestyles.[3,4]

The American Heart Association developed the "Life's Simple 7(LS7)" metric which includes seven modifiable components, including 3 health factors (glucose, cholesterol, and blood pressure) and 4 health behaviors (body mass index, physical activity, diet, and cigarette smoking), with each 7 indices categorized into ideal, intermediate, and poor levels. Only 2% of adults in the U.S. meets all 7 cardiovascular health metrics.[5,6] Prior studies of adults who are free from cardiovascular disease suggests that having ideal levels of the LS7 metric is associated with lower cardiovascular and all-cause mortality.[7,8]

In a recent Atherosclerosis Risk in Communities (ARIC) study, we demonstrated that LS7 at middle age was inversely associated with adverse outcomes after myocardial infarction (MI) independently of access to care and MI severity. However, it is unknown whether a similar pattern holds for stroke. This line of investigation is important because stroke is the leading cause of long-term disability. The pathophysiology of stroke is not identical to MI. There are also distinct differences in pathophysiology, prognosis, and treatment across stroke subtypes, so examining the association between the LS7 metric and recurrent CVD events for individual stroke subtypes may contribute to more effective secondary prevention of CVD.

Since the impact of ideal levels of the LS7 metric on the recurrence of CVD outcomes and all-cause mortality after incident stroke is unknown, we seek to characterize the associations of the LS7 metric at middle-age with the risk of CVD and all-cause mortality after an incident stroke hospitalization. The ARIC study is ideal for answering this research question because it consists of an established community-based cohort with carefully adjudicated cardiovascular endpoints, active surveillance for vital status and hospitalizations, and long follow-up of over 25 years.

5. Main Hypothesis/Study Questions:

We propose to characterize the prevalence of "ideal cardiovascular health" at middle-age among stroke survivors with incident stroke through December 31, 2016 in the ARIC study and the impact of meeting midlife LS7 metrics on recurrent CVD and all-cause mortality after incident stroke.

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).

Design: We will conduct a prospective cohort analysis to assess the association between LS7 at Visit 1 and CVD and all-cause mortality after incident stroke. We will first examine the association between LS7 score at middle age (Visit 1) and incident stroke. After the occurrence of the first stroke event, we propose to examine the association between midlife LS7 scores and the recurrence of CVD. We hypothesize that LS7 at midlife is associated not only with the incidence of stroke but also with the recurrence of CVD and mortality after stroke. Furthermore, we will examine the individual LS7 components at Visit 1 to examine which of them are more strongly associated with incident stroke and post-stroke recurrent CVD. Since time-varying data are available for some of the LS7 score components, we will study associations between updated data on specific components and the recurrence of CVD.

Inclusion criteria:
All black and white participants who were free of stroke at Visit 1 will be included in the analysis. We will capture incident stroke occurring between Visit 1 and December 31, 2016, in order to allow for follow up of at least one year after incident stroke. Those who have an incident stroke will be followed to evaluate the recurrence of any cardiovascular event and all-cause mortality.

Exclusion criteria:
Participants with missing data on LS7 metrics at Visit 1 or covariates will be excluded. Individuals who are neither white nor black and black participants from the Minnesota or Washington field center will also be excluded.

Exposure
The AHA definitions for ideal, intermediate, and poor health will be used for blood pressure (BP), cholesterol, body mass index (BMI), and physical activity, fasting plasma glucose (FPG), smoking, and diet score (**Table 1**). These definitions have been used in other ARIC investigations.[9,10] By assigning 2 points for ideal, 1 point for intermediate, and 0 points for poor health, we will create a sum of the scores from each metric with a range of 0 to 14. Data on the various components of LS7 are available at different ARIC visits and follow-up calls. Time-varying data are available on BP, total cholesterol, fasting blood glucose, BMI, and smoking status, therefore, as an additional analysis, we propose to assess associations between time-varying components of the LS7 and recurrent CVD.

Table 1: American Heart Association Life's Simple 7 criteria

Metric	**Level of Cardiovascular Health**		
	Poor	**Intermediate**	**Ideal**
Health Factors			
Blood pressure	Treated BP ≥140/90 mm Hg, and BP ≥140/90 mm Hg	SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg or treated to <120/80 mm Hg	SBP<120 and DBP< 80 mm Hg, without BP-lowering meds

Total cholesterol	≥ 240 mg/dL	200 to 239 mg/dL or treated to <200 mg/dL	<200 mg/dL, without lipid-lowering medication
Fasting blood glucose	≥126 mg/dl	100-125 mg/dl or treated to goal	<100 mg/dl (untreated)
Health Behaviors			
Smoking	Current Smoker	Former smoker and quit ≤12 months	Never smoker or former and quit >12 months
Body Weight	BMI ≥ 30kg/m^2	25 to 29.9 kg/m^2	< 25 kg/m^2
Physical Activity (Modified Baecke questionnaire)	None	1-149 min/wk moderate or 1-74 min/wk vigorous intensity or 1-149 min/2k combination	≥150 min/wk moderate or ≥75 min/wk vigorous intensity or ≥150 min/wk combination
Diet *(modified 66-item Harvard food frequency questionnaire)	0-1 components	2-3 components	4-5 components
* Fruits and vegetables ≥4.5 cups/day (approximated as ≥4.5 servings/day); Fish ≥3.5 oz servings/wk servings/wk (approximated ≥2 3- to 5-oz servings/wk); Whole grain ≥3 1 oz serving or 1.1 g/10g carbohydrates servings/day (approximated as ≥3 servings/day); Sodium ≤1500 mg/day; Sugar-Sweetened beverages <450 kcal or 36 oz/wk (approximated as ≤4 glasses/wk) BMI-Body Mass Index; SBP-Systolic Blood Pressure; DBP-Diastolic Blood Pressure;			

Covariates

We will consider the following covariates in our analyses: age, gender, race-center, education, income, atrial fibrillation, antiplatelet and anticoagulant therapy. We will update the covariates across examinations and in instances where this is not possible, we will use the data from the most immediate examination.

Outcomes

Our primary outcomes are 1) incident stroke after Visit 1 and through December 31, 2016, and 2) recurrent CVD (incident fatal or non-fatal coronary heart disease [myocardial infarction, fatal coronary disease, or revascularization], stroke, and heart failure) and all-cause mortality after incident stroke through December 31, 2017. We define coronary heart disease, and stroke as adjudicated events in ARIC and heart failure is based on discharge diagnosis. All-cause mortality is determined as identification of death by telephone contact with participant proxy, obituaries, hospital records, death certificates, or vital statistics from the National Death Index.

In ARIC, strokes are classified into definite or probable hospitalized ischemic (cardioembolic, thrombotic or lacunar) or hemorrhagic stroke using neuroimaging studies and autopsy. A computer algorithm initially classifies strokes into 1 of 4 main types: subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), thrombotic brain infarction, or embolic brain infarction using criteria from the National Survey of Stroke criteria. [11] A case of stroke is eligible if the medical record revealed a diagnostic CT or MRI scan with cerebrovascular findings or if a patient was admitted to the neurological intensive care unit. This classification is reviewed by physicians at the adjudication of stroke events. A case is included if there is concordance of computer and reviewer classification or if adjudicated by physician reviewers. [12]

Statistical Analysis

We will examine the distributions of each covariate using descriptive statistics (means, SDs, medians for continuous variables and proportions for categorical variables). We will summarize baseline (Visit 1) characteristics across categories of LS7 summary scores of 0 to 3, 4 to 6, 7 to 9, and ≥10.[10] We will use Cox proportional hazards regression models to estimate hazard ratios and their 95% confidence intervals for the association between LS7 (summary score as well as individual factors) with the risk of incident stroke, adjusting for covariates. Among those who had an incident stroke during follow-up, we will evaluate the association of LS7 score (summary score as well as individual factors) and cardiovascular outcomes after stroke using the Kaplan-Meier method as well as Cox proportional hazards regression models accounting for covariates. We will also explore potential interaction by age, sex, and race-center. We will also assess the association between LS7 metrics and recurrent CVD events by stroke subtypes if the number of cases permits.

Potential challenges and Limitations

- We may not have enough power to perform a separate analysis for hemorrhagic stroke and the various subtypes of ischemic stroke.
- ARIC does not include data on all the components of the LS7 metric after Visit 1 to allow the examination of the potential effects of LS7 trajectories on the study outcomes.

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 ICTDER 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

8.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/mantrack/maintain/search/dtSearch.html

__**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)?

MP#2845 Life's Simple 7 at middle-age and the prognosis after myocardial infarction
The goal of this proposal was to quantify the associations of Life's Simple 7 evaluated at middle-age with the risk of adverse outcomes after MI occurrence later in the life course.

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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