ARIC Manuscript Proposal #3777

PC Reviewed: 2/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Change in Cardiovascular Risk Factors with Brain MRI Structural Abnormalities

b. Abbreviated Title (Length 26 characters): CVD risk factors & brain MRI

2. Writing Group:
Writing group members: Sanaz Sedaghat, Pamela Lutsey, Thomas van Sloten, Yuekai Ji, Jean-Philippe Empana, Timothy Hughes, Thomas H Mosley, Rebecca F Gottesman, Cliff R Jack Jr, other interested investigators are welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. Sanaz Sedaghat

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
Data analysis to begin immediately after proposal approval and data access
Draft completion spring/Summer 2021
Send to coauthors summer 2021
Submission fall 2021

4. Rationale:

Vascular risk factors are increasingly recognized as important contributors to cerebrovascular injury, cognitive impairment, and development of dementia. The American Heart Association (AHA) developed a simple 7-item tool consisting of 4 behavioral metrics (nonsmoking, and ideal levels of body weight, physical activity, and diet) and 3 biological metrics (ideal levels of untreated blood pressure, fasting blood glucose, and total cholesterol) for promoting ideal cardiovascular health.[1] Achieving ideal cardiovascular health based on this metric, also known as "Life's Simple 7", is suggested to not only reduce heart disease and stroke, but also improve brain health.[2] Epidemiologic research has shown that meeting ideal status for a greater number of Life's Simple 7 components is associated with better cognitive function and lower risk of developing dementia.[3,4] Structural brain abnormalities, including white matter hyperintensities, silent brain infarcts, and brain atrophy, are common in the population and important risk factors for cognitive decline and dementia.[5] A few studies have shown that adherence to the Life's Simple 7 and ideal cardiovascular health recommendations are associated with less structural brain abnormalities.[6-9] However, there is no information on whether change in cardiovascular health within midlife and from midlife to late-life relates to structural brain abnormalities evident on brain MRI in late-life.

The ARIC Study with multiple cardiovascular health assessments from midlife onwards and late-life brain MRI provides a great setting to study the association of change in cardiovascular health and structural brain abnormalities.

5. Main Hypothesis/Study Questions:

Changes in cardiovascular health, within midlife and between midlife and late life, will be associated with brain MRI abnormalities. Specifically, improvements in cardiovascular health will be associated with fewer brain MRI abnormalities in late life, whereas reductions in cardiovascular health will be associated with more brain MRI abnormalities in late life.
We hypothesize that the association of change in cardiovascular health within midlife with structural brain abnormalities will be stronger that the association of change in cardiovascular health from midlife to late-life with structural brain abnormalities. The reasons include death and attrition and reverse causation (risk factors in late-life may not adequately reflect a person's past history of cardiovascular health).[10-12]

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).

<u>Study design</u>

1- Change in cardiovascular health within midlife: Prospective cohort study, with examinations of cardiovascular health from ARIC visit 1 (1987-1989) and visit 3 (1993-1995) and brain MRI performed at visit 5.
2- Change in cardiovascular health from midlife to late-life: Prospective cohort study, with examinations of cardiovascular health from ARIC visit 1 (1987-1989) and visit 5 (2011-2013) and MRI performed at visit 5. Since diet data are not available at visit 5, we will use 6 metrics to define cardiovascular health change from midlife to late-life.

Using the 7 metrics of the American Heart Association (nonsmoking; and ideal levels of body mass index, physical activity, diet, blood pressure, fasting blood glucose, and total cholesterol), cardiovascular health will be calculated assigning 0 score for poor metrics, 1 score for intermediate metrics, and 2 scores for ideal metrics. We will categorize cardiovascular health status as low (0 to 5 scores), moderate (6 to 9 scores), or high (10 to 14 scores). When only the 6 metrics are available, cardiovascular health will be categorized as low (0 to 4 scores), moderate (5 to 7 scores), or high (8 to 12 scores), respectively. Change in cardiovascular health in midlife and from midlife to late-life will be related to structural abnormalities on brain MRI as measured at the ARIC Neurocognitive Study visit 5. We will assess the association of change in cardiovascular health with white and gray matter volumes, white matter hyperintensities, lobar and subcortical microbleeds, cortical infarcts, and lacunar infarcts and cerebral small vessel disease burden composite score (which has been described previously)[13,14] on brain MRI performed at visit 5.[15]

Inclusion/Exclusion

Included will be all ARIC Study participants with complete information on Life's Simple 7 metrics at ARIC visits 1 and 3 and brain MRI data at visits 5. We will exclude individuals with prevalent dementia and cardiovascular disorders at ARIC visit 1. For change in cardiovascular health from midlife to late-life, we will include participants with information on behavioral and biological metrics of Life's Simple 7 at ARIC visits 1 and 5 and brain MRI data at visits 5. We will exclude individuals with prevalent dementia and cardiovascular disorders at ARIC visit 1.

Variables

Outcomes:

White and gray matter volume, white matter hyperintensities, lobar and subcortical microbleeds, cortical infarcts, and lacunar infarcts on brain MRI performed at visit 5.

To examine the overall burden of cerebral small vessel disease, we will also consider using a composite score, which has been described previously.[13,14] The score will reflect the cumulative presence of elevated white matter hyperintensity, cerebral microbleeds, and lacunar infarcts.

Exposure:

Life's Simple 7 including smoking, body mass index, physical activity, diet, systolic and diastolic blood pressure, fasting blood glucose, and total cholesterol (Table).

Table. Definition of cardiovascular health metrics according to the American Heart Association

Metric	**Recommended ideal level**	**Intermediate level**	**Poor level**
Smoking	Never or quit ≥12 months	Quit <12 months	Current smokers
Body mass index	<25 kg/m^2	25-29.9 kg/m^2	≥30 kg/m^2
Physical activity	≥75 min/week of vigorous activity, ≥150 min/week of moderate activity or a combination of the two	1–74 min/week vigorous activity, 1–149 min/week moderate activity or a combination of the two	None

Healthy diet *	≥1 portion per day of each of fresh fruit, raw vegetables, cooked fruit/vegetables and ≥2 portions per week of fish	≥1 portion per day of each of fresh fruit, raw vegetables, cooked fruit/vegetables or ≥2 portions per week of fish	<1 portion per day of each of fresh fruit, raw vegetables, cooked fruit/vegetables and <2 portions per week of fish
Blood pressure	< 120/80 mmHg, untreated	< 120/80 mmHg on medications or 120-139/80-89 mmHg	≥ 140/90 mmHg
Fasting plasma glucose	< 100 mg/dL, untreated	100 -126 mg/dL or < 100 mg/dL treated	≥ 126 mg/dL
Total cholesterol	< 200 mg/dL, untreated	200 -240 mg/dL or < 200 mg/dL treated	≥ 240 mmol/L

* Diet assessed with the 66-item Harvard food frequency questionnaire. Persons with extreme energy intake of <600 or >4,200 kcal/day for men or <500 or >3,600 kcal/day for women (approximate lower and upper 1 per-centiles) were excluded. The following 5 components were used to designate an ideal diet: fruits and vegetables: ≥4.5 cups per day; fish: ≥ two 3.5-oz servings per week; fiber-rich whole grains: ≥three 1-oz-equivalent servings per day; sodium: <1500 per day; sugar sweetened beverages: ≤450 kcal (36 oz) per week

Covariates:
Age, sex, race/ethnicity, educational attainment (less than high school, high school or vocational, college), income, depression, apolipoprotein E status, history of cardiovascular disorders, total intracranial volume.

Other variables for sensitivity analysis:
Dementia incidence, fatal and non-fatal cardiovascular disorders, mortality.

Data analysis

The AHA criteria will be used to define 7 metrics of cardiovascular health at ARIC visits 1 and 3. For ARIC visit 5, we will use 6 metrics of cardiovascular health (excluding diet). We will evaluate the association between change in cardiovascular health categories (high, moderate and low) between visit 1 and 3, and visit 1 and 5 in relation to abnormalities in brain MRI. We will define change in cardiovascular health categories, by studying possible combinations and including categories in the analysis that are sufficiently large. Based on previous literature,[16,17] we are expecting to have constantly low, constantly moderate, constantly high, improved, and declined categories of change in cardiovascular health. We will also use change in number of ideal metrics and change in the continuous cardiovascular health score as exposure variables. We will use linear regression models (when using white matter hyperintensity and white matter and gray matter volumes as outcome), logistic regression models (when using microbleeds and infarcts as outcome) and ordered logistic regression (when using cerebral small vessel disease composite score as outcome). All models will be adjusted for baseline covariates including sex, race-center, education, apolipoprotein E status, and depression. White matter hyperintensity volume will be log-transformed to adjust for skewness and models will be additionally adjusted for total intracranial volume.

Models will be stratified by race, sex and APOE status (1 or 2 ε4 alleles versus no ε4 alleles), with test for interaction on a multiplicative scale.

Sensitivity analysis

In sensitivity analyses, we will repeat the analysis after excluding all individuals with incident stroke and dementia during follow-up. We will repeat the analysis using inverse probability weighting to account for attrition to death, visit non-attendance and selection and inclusion into brain MRI study. Furthermore, we will repeat the analysis adjusting for cardiovascular health at visit 1 (baseline) to account for participant's baseline cardiovascular health.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? No

8.a. Will the DNA data be used in this manuscript? 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 Yes

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)?**

    MS # 1898 (lead: Hector M. González, Wassim Tarraf; ARIC author: Thomas H. Mosley) – Life's Simple 7's of neurocognitive health

    MS # 3677 (lead: Adrienne Tin, ARIC author: Thomas H. Mosley) – An Evaluation of Life's Simple 7 Score in Midlife in Offsetting the Genetic Risk of Dementia

    MS # 3581 (lead: Mark Lee; ARIC author: Pamela Lutsey) – The Moderating Influence of Education and Lifestyle on Genetic Risk for Dementia

    MS # 3508 (lead: Keke Schuler; ARIC author: Melinda C. Power) – Mediation of the Association Between Midlife Blood Pressure and Late-life Dementia and Cognitive Decline

    MS # 2351 (lead: Melinda Power; ARIC author: Rebecca Gottesman) – Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI

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* 1999.01; 2008.06)

___ 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 https://sites.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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