ARIC Manuscript Proposal #3776

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

1.a. Full Title: Association of Change in Cardiovascular Risk Factors with Incident Dementia

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

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, David S Knopman, Keenan Walker, 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:

Dementia is a devastating medical condition and extensive efforts to treat this clinical entity have been unsuccessful. This calls for early prevention of cognitive decline decades before full-blown manifestation of dementia. Vascular risk factors are increasingly recognized as important contributors to the development of dementia and thus as targets for future therapies. 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] Recently this metric, also known as "Life's Simple 7", has been put forward as a tool for the promotion of brain health.[2] Several studies have shown that adherence to the Life's Simple 7 and ideal cardiovascular health recommendations in midlife are associated with lower risk of dementia later in life.[3-6] Other studies found that ideal cardiovascular health is also associated with lower risk of dementia in older individuals.[7,8] However, there is no information on whether change in cardiovascular health over time relates to incidence of dementia.

The ARIC Study with multiple cardiovascular health assessments from midlife onwards provides a great setting to study the association of change in cardiovascular health and incident dementia.

5. Main Hypothesis/Study Questions:

Changes in cardiovascular health, within midlife and between midlife and late life, will be associated with risk of dementia. Specifically, improvements in cardiovascular health will be associated with lower dementia risk, whereas reductions in cardiovascular health will be associated with higher dementia risk. We hypothesize that improvement in cardiovascular health within midlife will be more strongly associated with lower risk of dementia compared with improvement in cardiovascular health from midlife to late-life.[9] 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>

We will perform two main analyses:

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 follow-up for incident dementia (from visit 3 onwards).
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 follow-up for incident dementia (from visit 5 onwards). Since diet data is 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 incident dementia.

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 incidence of dementia. 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 incidence of dementia. We will exclude individuals with prevalent dementia and cardiovascular disorders at ARIC visit 1.

Variables

Outcome:

Incidence of dementia (ARIC Level 3 dementia diagnosis) defined according to the standard definition used in the ARIC cohort. This definition includes information from in-person neurocognitive assessments conducted at visits 5 and later, telephone instrument of cognitive status-modified (TICS-m), semi-annual phone six-item screener assessments (with AD8 informant follow-up where appropriate) and ICD-9 hospital discharge diagnostic codes. For change within midlife, we will be including dementia events after visit 3 and for change from midlife to late-life dementia events happened after visit 5.

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	<1 portion per day of each of fresh fruit, raw vegetables, cooked fruit/vegetables and <2

		portions per week of fish	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.

Other variables for sensitivity analysis:
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 incident dementia over the remaining follow-up. 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,[13,14] we are expecting to have constantly low, constantly moderate, constantly high, improved, and declined categories of change in cardiovascular health. Primary analysis will use Cox models with age as the time scale. We will also use change in number of ideal metrics and change in the continuous cardiovascular health score as exposure variables. All models will be adjusted for baseline covariates including sex, race-center, education, income, apolipoprotein E status, and depression. When using continuous scores, we will adjust for cardiovascular health at visit 1 (baseline) to account for participant's baseline cardiovascular health. We will check proportionality and linearity assumptions using visual inspection of the survival curves and by comparing the Akaike information criterion of linear models with models including quadratic and cubic terms, respectively.
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 during follow-up. We will also account for the potential competing risk of CVD or non-dementia death with a competing risks proportional hazards model using the Fine and Gray method. We will repeat the analysis using inverse probability weighting to account for attrition to death and visit non-attendance. Furthermore, we will evaluate each of the Life' Simple 7 components in relation to dementia incident, separately.

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

    MS # # 3051 (lead : Keenan Walker ; ARIC author: Rebecca Gottesman) –The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study

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.

References

1. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121(4):586-613. DOI: 10.1161/CIRCULATIONAHA.109.192703.
2. Gorelick PB, Furie KL, Iadecola C, et al. Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association. Stroke 2017;48(10):e284-e303. DOI: 10.1161/STR.0000000000000148.
3. Gonzalez HM, Tarraf W, Gouskova N, et al. Life's Simple 7's Cardiovascular Health Metrics are Associated with Hispanic/Latino Neurocognitive Function: HCHS/SOL Results. J Alzheimers Dis 2016;53(3):955-65. DOI: 10.3233/JAD-151125.
4. Sabia S, Fayosse A, Dumurgier J, et al. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. BMJ 2019;366:l4414. DOI: 10.1136/bmj.l4414.
5. Gonzalez HM, Tarraf W, Harrison K, et al. Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results. Alzheimers Dement 2018;14(5):579-589. DOI: 10.1016/j.jalz.2017.11.002.
6. Thacker EL, Gillett SR, Wadley VG, et al. The American Heart Association Life's Simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. J Am Heart Assoc 2014;3(3):e000635. DOI: 10.1161/JAHA.113.000635.
7. Samieri C, Perier MC, Gaye B, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. JAMA 2018;320(7):657-664. DOI: 10.1001/jama.2018.11499.
8. Pase MP, Beiser A, Enserro D, et al. Association of Ideal Cardiovascular Health With Vascular Brain Injury and Incident Dementia. Stroke 2016;47(5):1201-6. DOI: 10.1161/STROKEAHA.115.012608.

9. Walker KA, Sharrett AR, Wu A, et al. Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. JAMA 2019;322(6):535-545. DOI: 10.1001/jama.2019.10575.
10. Kivimaki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. Alzheimers Dement 2018;14(5):601-609. DOI: 10.1016/j.jalz.2017.09.016.
11. Abell JG, Kivimaki M, Dugravot A, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. Eur Heart J 2018;39(33):3119-3125. DOI: 10.1093/eurheartj/ehy288.
12. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12(2):207-16. DOI: 10.1016/S1474-4422(12)70291-0.
13. van Sloten TT, Tafflet M, Perier MC, et al. Association of Change in Cardiovascular Risk Factors With Incident Cardiovascular Events. JAMA 2018;320(17):1793-1804. DOI: 10.1001/jama.2018.16975.
14. Liang Y, Ngandu T, Laatikainen T, et al. Cardiovascular health metrics from mid- to late-life and risk of dementia: A population-based cohort study in Finland. PLoS Med 2020;17(12):e1003474. DOI: 10.1371/journal.pmed.1003474.