ARIC Manuscript Proposal # 3830

PC Reviewed: 4/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Midlife Vascular Risk Factors with Late Life Neuropsychiatric Symptoms

b. Abbreviated Title (Length 26 characters): Vascular Risk and NPS

2. Writing Group:

Writing group members: Carla Rodriguez (first author); Gabriela Gomez; David Knopman; Srishti Shrestha; Matthew Peters; Rebecca Gottesman; Keenan Walker (senior author)

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

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3. Timeline:

1-3 months: analysis of data
1-3 months: writing of manuscript

4. Rationale:

Vascular risk factors and cardiovascular disease represent a major public health concern and contribute substantially to morbidity and mortality in middle age and older adulthood. Vascular risk factors additionally contribute to the development of many neurologic conditions, including dementia and late-life cognitive impairment[1,2].

There is an increasing awareness that both cognitive impairment and dementia often co-occur with neuropsychiatric symptoms (NPS), i.e., psychological and behavioral symptoms such as depression, apathy, irritability, anxiety, agitation, aberrant motor behavior, and disinhibition. Recent studies have shown the prevalence of NPS among nursing home residents with dementia to be over 82% with most residents suffering from multiple symptoms[3,4]. This is of increasing concern because NPS are related to increased healthcare expenditure, poor prognosis, and greater caregiver burden[5,6]. Additionally, NPS, when they occur among non-demented individuals, are associated with increased risk for subsequent cognitive decline and dementia onset[2,5,7]. Given the importance of NPS to the wellbeing of older adults with cognitive impairment, it is essential that potentially modifiable risk factors for NPS be identified.

Increasingly, the field is understanding the importance of midlife vascular risk factors as determinants of late-life brain health[8]. Compared to vascular risk factors that occur during later life, midlife vascular risk factors are believed to be especially important because they represent long-term (multi-decade) exposure to vascular comorbidity that precedes the late-life period. Poor vascular health has been associated with neuropsychiatric symptoms previously, especially depression[13]. Studies of late-life depression suggest that vascular disease contributes to mood abnormalities in older adults by promoting cerebral small vessel disease and resulting in damage to fronto-subcortical circuits[14]. However, it remains unclear whether midlife vascular risk factors are associated with late-life depression, other NPSs (e.g., decreased motivation and emotional dysregulation symptoms), or overall NPS severity. There are no studies, to our knowledge, that assess the association between midlife vascular risk factors and late life NPS.

Thus, the aim of this study is to examine the associations between midlife vascular risk factors and late-life NPS presence and severity. Based on previous studies that show race and sex differences in the presentation and severity of NPS,[15,16] this study will also examine whether the associations between midlife vascular risk factors and late life NPS differs across race and sex groups.

5. Main Hypothesis/Study Questions:

1. The presence of midlife vascular risk factors is associated with increased late-life neuropsychiatric symptoms and greater neuropsychiatric symptom severity among participants with and without cognitive impairment.

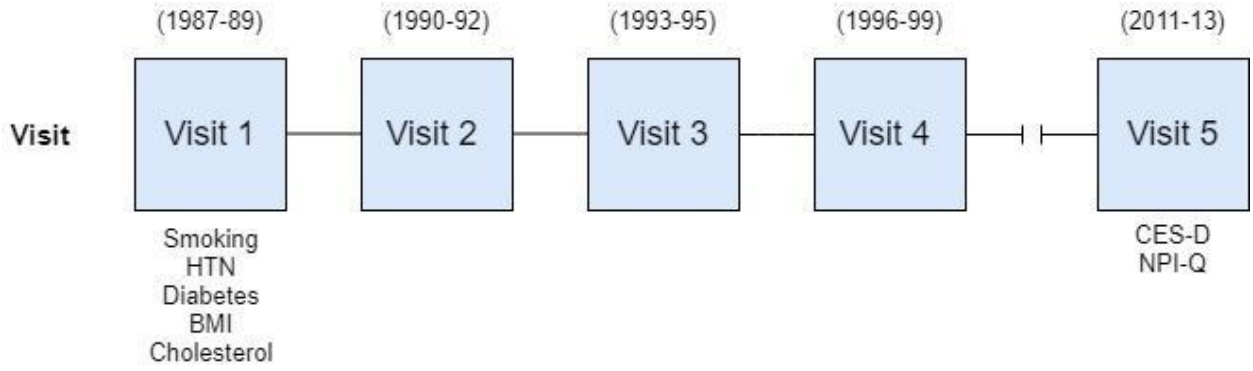
2. Midlife vascular risk factors are most strongly associated with late-life neuropsychiatric symptoms typically associated with frontal lobe dysfunction (i.e., decreased motivation, emotional dysregulation, and disinhibition).

3. The associations between midlife vascular risk factors and late neuropsychiatric symptoms differ across race and sex.

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
Cross-sectional and cross-temporal study design using data from ARIC visits 1 and 5. We will relate vascular risk factors assessed at visit 1 to NPS presence and severity measured at visit 5.

Figure 1. Study design and description of available data



Abbreviations: BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; HTN, hypertension; NPI, Neuropsychiatric Inventory Questionnaire

Participants For the analysis of neuropsychiatric symptoms, we will include White and Black participants with nonmissing data on vascular risk factors at ARIC visit 1 whose informants completed the Neuropsychiatric Inventory Questionnaire (NPI-Q) in Stage 2 at visit 5. For the analysis of late life depression, we will include White and Black participants with nonmissing data on vascular risk factors at ARIC visit 1 who completed the CES-D questionnaire at visit 5. We will exclude participants with missing information on cognitive status (normal vs. mild

cognitive impairment vs. dementia) and participants missing information about essential covariates.

Outcomes

Neuropsychiatric Symptoms. Late-life psychiatric and behavioral changes were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI-Q was obtained via informant report from participants who were selected for Stage II Assessment at Visit 5. The NPI-Q measures the presence and severity of depression, apathy, agitation, delusion, hallucination, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite[17]. Severity of each NPI-Q symptom is rated on a scale of 0 to 3. We will use total NPI-Q symptom severity range (0-36) as the primary outcome measure. NPI-Q symptoms will also be mapped to subdomains consistent with mild behavioral impairment (MBI) subdomains operationalized by the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) research diagnostic criteria[19] (listed below).

- Decreased Motivation (NPI-Q – apathy / indifference)
- Affective Dysregulation (NPI-Q – depression / dysphoria, anxiety, elation/euphoria)
- Impulse Dyscontrol (NPI-Q – agitation/aggression, irritability/lability, aberrant motor behavior)
- Social Inappropriateness (NPI-Q – disinhibition)
- Abnormal Perception/Thought Content (NPI-Q – delusions, hallucination)

Depressive Symptoms. Depressive symptoms were measured using the 11-item version of Center for Epidemiologic Studies Depression Scale (CES-D)[18], which was administered to the full ARIC sample at Visit 5. The CES-D is a measure of depressive symptoms commonly used in epidemiological research. We will evaluate the CES-D as a continuous variable and a dichotomous variable. A cutoff score of 9 will be used as an indicator of probable depression.

Exposure

Participants in the ARIC study had vascular risk factors measured at Visit 1 as per Gottesman et al (2017)[8]. **Smoking** status was self-reported as current, former or never. Individuals will be categorized as current smoker (yes/no). **Body mass index** (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity will be defined as a BMI ≥30. **Diabetes** status was recorded by either a fasting glucose of ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, self-report of physician-diagnosed diabetes, or use of oral diabetes medications or insulin. **Hypertension** was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. **Cholesterol** was measured using enzymatic methods with high cholesterol defined as ≥200mg/dL[8].

Statistical Analysis

H1. For the primary analysis, we will use linear regression to examine the relationship between number of midlife vascular risk factors and total NPIQ symptom severity (range 0-36) and symptom count (1-12). Vascular risk factors will be examined using two methods. The first method will include all five vascular risk factors (listed above) in the model as individual variables. This will allow us to examine the contribution of individual vascular risk factors to

total neuropsychiatric symptom severity. The second method will use a vascular risk factor count. All participants will be coded as having 0, 1-2, or >=3 vascular risk factors. Models will be adjusted for the following covariates: age, sex, race-study center, education, and APOEe4 status. We will examine all models stratified by cognitive status (Cognitively normal, MCI+dementia).

H2. For the secondary analyses of specific neuropsychiatric symptoms subtypes, we will use logistic regression models to relate vascular risk factors (as described in H1) with NPI-Q indicators of clinically significant symptoms (severity rating of 2 or more) in five different neuropsychiatric symptom subdomains (i.e., decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, abnormal perception/thought content). Models would be adjusted for the demographic covariates described in H1. We will examine all models stratified by cognitive status (Cognitively normal, MCI+dementia).

H3. We will repeat analyses described in H1 after stratifying by race and sex. We will formally evaluate race and sex as effect modifiers using multiplicative race*vascular risk factor and sex*vascular risk factor interaction terms.

As part of a secondary analyses, we will use linear and logistic regression to examine the relationship between vascular risk factors and CES-D depressive symptoms. Methods described in H1 and H2 will be used for these analyses.

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

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No

(The 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? __X__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ 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#3574 The association of motoric cognitive risk with neuroimaging and incident dementia: The ARIC Study

MP#2511 Vascular risk factors and brain amyloid deposition: The ARIC-PET Study

MP# 3527 Hearing & Neuropsychiatric Symptoms among Older Adults with Cognitive Impairment

MP# 3104 The association of systemic inflammation with late-life depression symptoms: 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* 2008.06)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2013.10)

*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.

Understood

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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