ARIC Manuscript Proposal # 3104

PC Reviewed: 1/9/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: The association of systemic inflammation with late-life depression symptoms: The ARIC Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Natalia Sonsin-Diaz (first and corresponding author); Rebecca Gottesman; Elizabeth Fracica; Jeremy Walston; Thomas Mosley; David Knopman; Keenan Walker (last author)

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

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3. Timeline: 6-9 months; manuscript submission summer 2017.

4. Rationale:

Depression and other neuropsychiatric symptoms are highly prevalent among older adults[1] and produce a great deal of distress for both affected individuals and caregivers[2]. It has become increasingly apparent that depressive symptoms that emerge during late-life differ in several ways from depressive symptoms that begin earlier in life. For example, late-life depression (LLD), the most common neuropsychiatric symptom among older adults[3], differs from early onset depression in terms of associated comorbidity, co-occurrence with cerebrovascular disease, and genetic determinants[4]. Three distinct hypotheses regarding the etiology of LLD have gained support: (1) the degenerative hypothesis suggests that LLD precedes or occurs concurrently with cognitive decline in the context of neurodegenerative disease[5,6]; (2) the vascular hypothesis states that brain structural and functional alterations caused by lacunar strokes, white matter hyperintensities, and other forms of small vessel disease may promote LLD[7–11]; and (3) the inflammatory hypothesis suggests that aging leads to increased peripheral and central nervous system immune responses, which result in the manifestation of mood and neurovegetative symptoms of depression[5,12–14].

In support of the inflammatory hypothesis, previous work has demonstrated that late-life depressive[15–18] and other neuropsychiatric symptoms[19–21] are strongly associated with higher levels of circulating inflammatory markers, including CRP, IL-1alpha, IL-1beta, IL-6 and IL-8. In support of the relationship between inflammation and depression, pharmacological studies have demonstrated that antidepressants decrease the production of pro-inflammatory cytokines[22,23]. A number of studies which aimed to understand the mechanism by which inflammation may promote neuropsychiatric symptoms in older adults have found that elevated inflammation causes over-stimulation of the noradrenergic and HPA system, which can, in turn, promote depressive symptomology, apathy, and anxiety[24,25]. Another proposed mechanism involves the catabolism of neurotransmitters, such as 5-HT, or their precursors (i.e., tryptophan and kynurenine), which could contribute to the onset or worsening of neuropsychiatric symptoms[24,26].

Although a link between systemic inflammation and neuropsychiatric symptoms has been established, it remains unclear whether systemic inflammation has a causal role in promoting psychiatric and behavioral changes, or if systemic inflammation occurs as a result of such changes. Because much of the evidence supporting the inflammation hypothesis comes from cross-sectional studies, it is difficult to draw conclusions about directionality and causality. To date, only a handful of prospective studies have been published that come closer to addressing this question of directionality[27]. Some, but not all, of these studies suggest that higher levels of circulating inflammatory markers in older adults relate to greater depressive symptoms 1-6 years later[28–32]. There is a clear need to better understand the temporal relationship between systemic inflammation and LLD, as it is possible that exposure to systemic inflammation in the decades leading up to older adulthood may increase risk for LLD. Relatedly, it is necessary to understand whether systemic inflammation influences late-life depressive symptoms by promoting small vessel disease (which has a well-documented association with late-life depression)[7–11] and whether the inflammation-depression association occurs exclusively among individuals experiencing late-life cognitive decline.

The primary goal of the current study is to provide additional insights into the temporal relationship between systemic inflammation and late-life depressive symptoms using the Atherosclerosis Risk in Communities Study (ARIC), a large community-based prospective cohort study. Specifically, we will examine the association of high-sensitivity C-reactive protein

(CRP) (measured at multiple time points spanning from middle to late-life) and other midlife inflammatory markers with depressive symptoms measured during late life. CRP is a non-specific indicator of systemic inflammation that has been previously associated with depressive symptomology[32–36]. We will further test the inflammatory hypothesis by assessing the modifying effect of late-life cognitive decline (neurodegenerative hypothesis)[5] and by examining whether the association between systemic inflammation and late-life depressive symptoms is mediated by cerebral small vessel disease (vascular hypothesis)[7–11]. Given evidence for a stronger relationship between systemic inflammation and late-life depression among women[36], we will additionally explore whether sex differences exist.

5. Main Hypothesis/Study Questions:

1. Higher levels of inflammatory markers during midlife and persistently elevated high-sensitivity C-reactive protein from midlife through late-life will be associated with elevated late-life depressive symptoms on the Center for Epidemiologic Studies Depression (CES-D) and higher rates of neuropsychiatric symptoms on the Neuropsychiatric Inventory (NPI).

2. The association between midlife systemic inflammation and late-life depressive symptoms will be partially mediated by white matter structural abnormalities and cerebral small vessel disease (*vascular depression hypothesis*).

3. Associations between systemic inflammation and late-life depressive symptoms will be stronger among participants who have experienced interim cognitive decline compared to those who have not (*the degenerative hypothesis*).

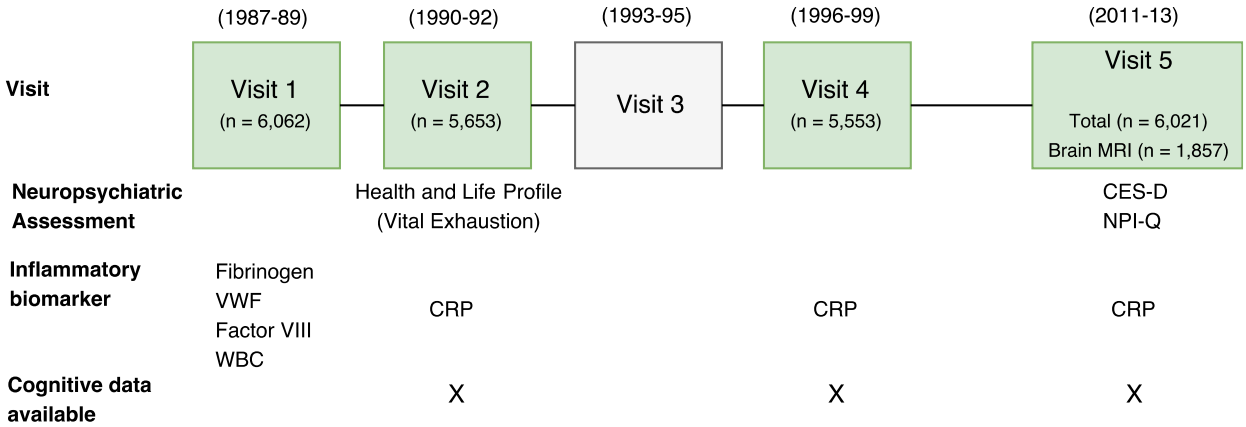
4. Associations between midlife systemic inflammation and late-life depressive and other neuropsychiatric symptoms will be stronger among female, compared to male, participants.

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

ARIC is a prospective, observational, population-based study. Exposure information (circulating inflammatory markers) is available at Visits 1, 2, 4, and 5. Participants completed cognitive testing at Visits 2, 4, and 5. Depression was assessed at Visit 2 using the Vital Exhaustion Questionnaire and at Visit 5 using the Center for Epidemiologic Studies Depression (CES-D) scale.

Figure 1. Study design and description of available data



Note. CRP = C-reactive protein; CES-D = Center for Epidemiologic Studies Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire; VWF = von Willebrand Factor; WBC = white blood cell count

N.B. Only data for participants with available Visit 5 depression ratings are shown.

Participants

Inclusion criteria: White and African American participants with one or more available inflammatory biomarker and non-missing covariates will be included in this analysis. Analyses which examine the 21-year pattern of CRP will only include participants with CRP levels available for Visits 2, 4, and 5.

Exclusion criteria: To reduce the likelihood of reverse causation, we will exclude participants with elevated depressive symptoms at Visit 2 (the highest 14th percentile for women and the highest 14th percentile for men on a depressive symptom rating scale [the Vital Exhaustion Questionnaire – also identified as Part B of the Health and Life Profile]). Percentile cutoffs are based on the sex-specific prevalence of midlife depression [37]. Because the phenomenology of depressive symptoms in non-demented participants may differ from that of demented participants, we will also exclude participants with incident dementia before Visit 5 in our primary analysis of depressive symptoms. Analyses examining neuropsychiatric symptoms using the NPI will not exclude participants with incident dementia.

Exposures

Blood Inflammatory Markers: The primary exposure will be CRP levels, which have been previously measured at Visits 2, 4, and 5 for all ARIC participants (see Figure 1). CRP levels for each visit will be modeled as a continuous parameter. We will also conduct an exploratory analysis using a *Visit 1 inflammation composite score* created using inflammatory biomarkers available at Visit 1 (i.e., WBC, fibrinogen, albumin, von Willebrand factor, factor VIII), as used in prior ARIC manuscripts. The inflammatory composite score will be created by summing the biomarker levels after each is rescaled to a z-scores based on the sample mean.

Longitudinal characterization of CRP levels

To examine the association of the longitudinal pattern of CRP levels with late-life depressive symptoms, each participant will be categorized as having "low" or "high" CRP levels at each visit using a cut-off of 3 mg/L. A CRP level above 3 mg/L is suggestive of ongoing low-grade systemic inflammation[38–40]. Using this "low" versus "high" CRP dichotomization, participants will be categorized into one of six categories based on their patterns of CRP over three Visits (Figure 2).

- *Stable low*: low CRP levels at all three visits
- *Early ascending*: low CRP at Visit 2, and high CRP at Visits 4 and 5
- *Late ascending:* low CRP at Visits 2 and 4, and high CRP at Visit 5
- *Early descending:* high CRP at Visit 2, and low CRP at Visits 4 and 5
- *Late descending:* high CRP at Visits 2 and 4, and low CRP at Visit 5
- S*table high:* high CRP at Visits 2, 4, and 5.

The *stable low* group will be used as the referent group and will be compared to other groups using methods described above.

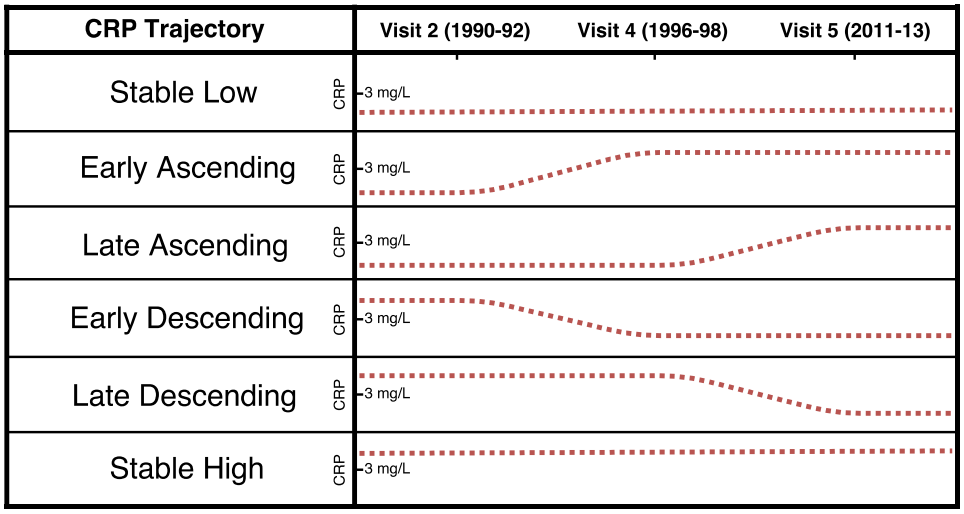


Figure 2. An illustration of the six longitudinal patterns of C-reactive protein using data from Visits 2, 4, and 5.

Primary Outcome

Depressive Symptoms. Depressive symptoms will be measured using the 11-item version of Center for Epidemiologic Studies Depression Scale (CES-D)[41], 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[42]. 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.

Secondary Outcome

Neuropsychiatric Symptoms. Late-life personality and behavioral change 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[43].

Other Variables

Covariates. Demographic variables, including race, sex, age, education, *APOE* ε4 status, and center will be extracted. Additionally, laboratory and physiologic data, including systolic and diastolic blood pressures, total/high density lipoprotein cholesterol, statins, and body mass index (BMI, kg/m^2) will be extracted from study Visits 1, 2, 4, and 5. Cardiovascular risk factors and disease information (i.e., diabetes, hypertension, coronary heart disease, cigarette smoking and alcohol use), and medication use will also be extracted from Visits 1, 2, 4, and 5. Information about chronic inflammatory disease diagnoses (i.e., lupus, gout, and arthritis) will be extracted from Visit 4.

MRI Variables. Markers of small vessel disease will be extracted for the subset of participants who received an MRI scan at Visit 5. MRI markers of interest include white matter hyperintensity (WMH) volume, lacunar infarcts (> 3mm and < 15mm), cerebral microbleeds, and a small vessel disease composite score which includes WMH, lacunar infarcts, and cerebral microbleeds, as described previously[44].

Cognitive Variables. We will identify participants who have experienced cognitive decline using the ARIC cognitive battery administered at Visits 2, 4, and 5 as part the serial cognitive assessment. Per ARIC-NCS Analysis Manual recommendations, cognitive decline will be defined as evidence of decline below the 10^{th} percentile on one test or below the 20^{th} percentile on two tests in the serial ARIC cognitive battery administered at Visits 2, 4, and 5. Cognitive status at Visit 5 (MCI/dementia) will also be extracted, as will incident dementia (defined by levels 1, 2, or 3) during cohort follow-up.

Data Analysis

To examine the association of Visit 2, 4, and 5 CRP levels and mid to late-life CRP trajectory with continuous and dichotomous Visit 5 CES-D rating, we will use multivariable linear and logistic regression (**H1**). Continuous CES-D ratings will be log-transformed to correct for skewness. To examine whether associations between CRP and late-life depressive symptoms are independent of white matter dysfunction and cerebral small vessel disease, we will repeat analyses after adjusting regression models for WMH volume, lacunar infarct frequency, and cerebral microbleed frequency to consider mediation by these small vessel markers (analyses will first be repeated without these MRI markers, but among those individuals in whom MRI data is available, to allow comparison of estimates before and after including small vessel disease markers). Analyses will be repeated using the small vessel disease composite score rather than independent measures of small vessel disease (**H2**).

Covariates & Interactions

Model 1 will include covariates to adjust for potentially confounding demographic factors: age, sex, race-center (Washington county white; Minneapolis white; Forsyth County white; Forsyth County African American; Jackson African American), education (less than high school; high school/GED/vocational school; or any college), and *APOE* ε4 status (0, 1, or 2 ε4 alleles). *Model 2* will additionally adjust for cardiovascular risk factors and disease variables: BMI, total

cholesterol, HDL, hypertension, diabetes, coronary heart disease, chronic inflammatory conditions (i.e., arthritis, gout, and lupus), anti-inflammatory medication use, cigarette and alcohol use status (current/former/never). Multiplicative interaction terms and stratification will be used to evaluate effect modification by cognitive decline (decline/no decline; **H3**) and sex (**H4**). We will also conduct a sensitivity analysis to examine the moderating effect of statin use.

Sensitivity Analysis
Inverse probability of attrition weighting (IPAW) will be used to assess the potential effects of differential attrition due to dropout.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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? __X__ 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/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)?
MP 2678 - Association of Depression with Neuroimaging Markers of Brain Vascular Disease. Fracica et al.

#MP2211 - Midlife psychosocial factors and cognitive decline. Kats et al.

MP 2866 - The association of midlife and late-life inflammatory biomarkers with cerebral small vessel disease and white matter integrity in the elderly: The ARIC Study. Walker et al.

MP2930 - Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study. Walker et al.

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

___ A. primarily the result of an ancillary study (list number* _____)

_X__ 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 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.
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.
Understood

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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