ARIC Manuscript Proposal # 3096

PC Reviewed: 1/9/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Systemic inflammation, cognitive decline and dementia

b. Abbreviated Title (Length 26 characters): Inflammation and cognition

2. Writing Group:

Writing group members: Keenan Walker (first and corresponding author); Rebecca Gottesman; Aozhou Wu; Alden Gross; David Knopman; Elizabeth Selvin; Thomas Mosley; Beverly Gwen Windham (last author); Others welcome

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

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3. Timeline: 3-9 months; manuscript submission in spring 2018.

4. Rationale:

In light of the growing body of literature linking aberrant immune functioning with dementia[1], understanding association between systemic inflammation, cognitive decline, and dementia risk has become a priority in recent years. While a number of studies have demonstrated a link between elevated levels of peripheral inflammatory markers, accelerated cognitive decline[2,3], and incident dementia[4,5], others have found no such relationship[6]. Inconsistent findings may be a result of several factors, including age differences, relatively short follow-up periods, small sample sizes, and the single time-point assessment of inflammatory biomarkers. The majority of studies linking systemic inflammation to cognitive impairment and dementia risk have been cross-sectional, and have therefore been limited in their ability to clarify the temporal relationship between systemic inflammation, cognitive decline, and dementia.

Cardiovascular risk factors occurring during midlife have been associated with adverse neurocognitive outcomes among older adults[7–9], suggesting that middle adulthood may be an etiologically relevant exposure period. While one previous study has demonstrated a relationship between midlife systemic inflammation and late-life dementia risk[4], the association of inflammation with time to dementia onset remains unknown. Relatedly, it is unclear whether midlife systemic inflammation is associated with accelerated cognitive decline over this mid- to late-life period, and whether the trajectory or chronicity of what is likely an evolving inflammatory process influences such neurocognitive outcomes.

In the proposed study, we will assess the association of midlife systemic inflammation with dementia incidence and cognitive decline over the span of 21 years from mid- to late-life in a large, bi-racial community-based sample within the Atherosclerosis Risk in Communities (ARIC) Study. We will also examine the 21-year pattern of C-reactive protein (CRP) to determine whether having persistent systemic inflammation from mid- to late-life confers greater risk for cognitive decline and dementia. Given previous findings which suggests that race[10], sex[11], and *APOE* ε4 status[12] may affect the association between systemic inflammation and the presence of structural brain abnormalities, we will examine the modifying effects of each of these demographic variables in the present study.

5. Main Hypothesis/Study Questions:

H1. A higher level of inflammatory markers measured during midlife (Visits 1 and 2) will be associated with a faster rate of global and test-specific cognitive decline.

H2. Participants with chronically elevated systemic inflammation from mid- to late-life, as defined by CRP > 3mg/L at Visits 2, 4, and 5, will have a faster rate of global and test-specific cognitive decline.

H3. A higher level of inflammatory mediators measured during midlife will be associated with increased dementia incidence and greater MCI risk.

H4. Participants with chronically elevated systemic inflammation from mid- to late-life, as defined by CRP > 3mg/L at Visits 2, 4, and 5, will have increased dementia incidence and greater MCI risk.

H5. Associations of systemic inflammation with cognitive decline, dementia incidence, and MCI risk will be stronger among white participants, male participants, and participants who possess one or more *APOE* ε4 allele.

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. Participants completed cognitive testing at Visits 2, 4, and 5, as shown below. Exposure information (circulating inflammatory markers) is available at Visits 1, 2, 4, and 5.

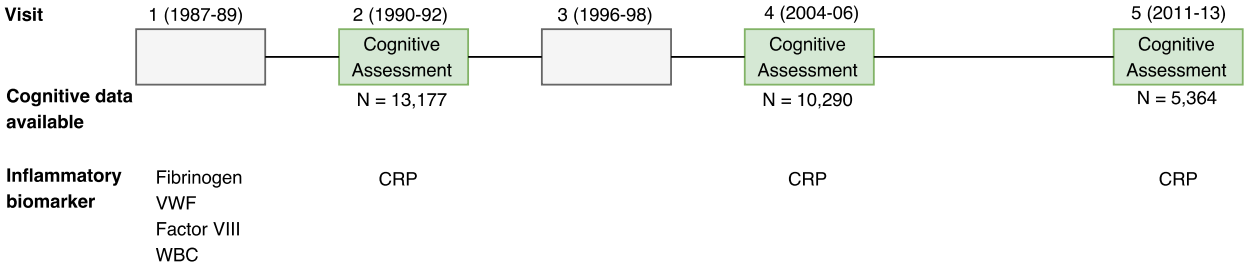

Figure 1. Study design and longitudinal cognitive assessment
Note. CRP = C-reactive protein; VWF = von Willebrand factor; WBC = white blood cell

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 longitudinal pattern of CRP will only include participants with CRP levels available for Visits 2, 4, and 5. Only participants with two or more cognitive assessments will be included in the analyses of cognitive decline.

Exclusion criteria: We will exclude participants with missing baseline cognitive data (Visit 2), clinical stroke prior to Visit 2, and those who scored below the 5th percentile on any cognitive test at Visit 2. The latter two criteria will reduce the impact of prevalent CNS disease on midlife inflammatory biomarker levels (i.e., reverse causality) and limit potential floor effect.

Exposures

Blood Inflammatory Markers: As illustrated in Figure 1, we will use fibrinogen, von Willebrand factor, white blood cell count, and Factor VIII levels previously measured at Visit 1, and CRP levels, previously measured at Visits 2, 4, and 5 for all ARIC participants (see Figure 1). Inflammatory markers measured at Visit 1 will be standardized (z-score) and averaged to derive a Visit 1 inflammation composite.

Longitudinal characterization of CRP levels (H2 & H4)

To examine the association of the longitudinal pattern of CRP levels with cognitive decline, dementia incidence, and MCI risk (**H2** & **H4**), 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[10–12]. 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.

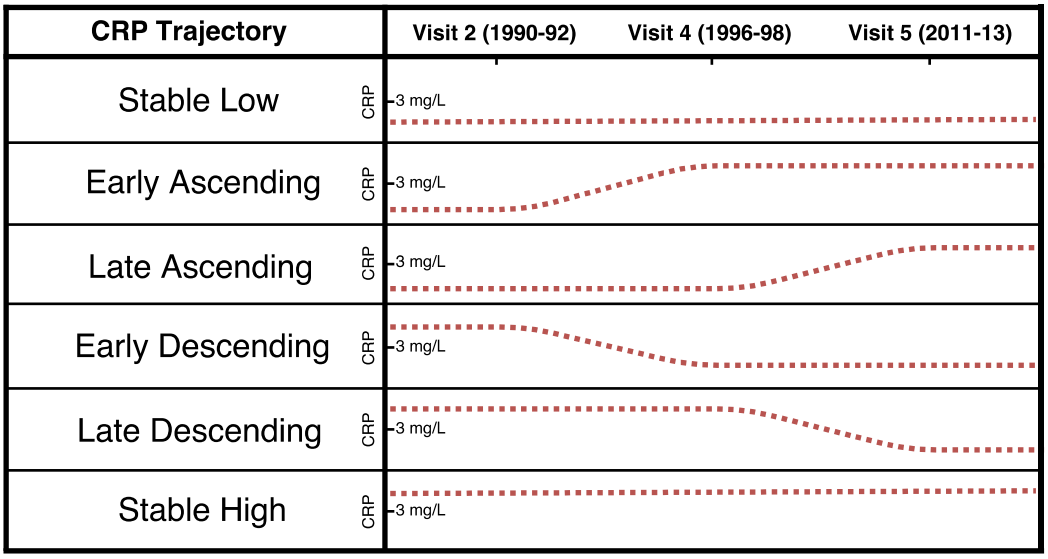

Figure 2. An illustration of the six longitudinal patterns of C-reactive protein using data from Visits 2, 4, and 5.

Primary Outcomes

Cognitive Decline

Cognitive Decline. 21-year pattern of global and test-specific cognitive function was measured in the entire cohort at three time points using three standardized neuropsychological measures: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), and the Word Fluency Test (WFT). We may also include cognitive data from Visits 3 and the Brain/Carotid MRI Visit (2004-06), which is available in a subset of the study population.

The DWRT is a measure of verbal memory for which participants are asked to learn 10 common nouns by reading each noun and using it in a sentence. After a 5-minute distractor-filled delay period, participants are asked to recall each of the 10 nouns. The DWRT is scored from 0 to 10 based on the number of correctly recalled words.

The DSST is a measure of processing speed and executive function. Participants are provided with a key that uniquely associates a number with a nonsense symbol. Participants are asked to

translate a series of numbers based on their corresponding symbol. The total score is calculated based on the total number of correctly completed symbols in 90 seconds.

The WFT is a measure of verbal fluency. Participants are asked to list as many words as possible that begin with the letter "F", "A" and "S" (excluding proper nouns) within three 1-minute word-naming trials. The total score is based on the total number of words generated.

All tests will be standardized to z-scores in order to facilitate the creation of a composite score and the comparisons across tests. For each cognitive assessment, a Global cognitive score will be created for each participant based on the mean of the three standardized z-scores.

Incident Dementia

Dementia incidence was ascertained using three methods, as has been outlined in detail previously[13].

- *Level 1* was based on adjudication from a complete evaluation at the ARIC-NCS visit based on criteria put forth by the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups[14] and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[15]. Adjudication was based on longitudinal cognitive evaluations from Visits 2, 4, and 5, a complete neuropsychological battery at Visit 5, and an informant interview. Using this information, a computer algorithm was used to generate a dementia classification, which was then confirmed by experts. Dementia was classified as ≥2 cognitive domains worse than -1.5 Z, a CDR sum of boxes >3 or an FAQ >5, and cognitive decline below the 10th percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery administered at Visits 2, 4, and 5. Participants with low MMSE scores (<19 for African Americans, <21 for whites) were also classified as having dementia.
- *Level 2* included participants who met level 1 dementia criteria, as well as participants who did not attend Visit 5, but were classified as having dementia based on a telephone interview (modified TICS) for cognitive status (≤23), or for those who were alive at the beginning of ARIC-NCS, an informant telephone interview (≥3 CDR sum of boxes and FAQ >5) on a subset of participants identified previously as having a likelihood of dementia.
- *Level 3* included participants who met levels 1 and 2 dementia criteria, as well as participants diagnosed with dementia according to routinely collected ICD-9 hospital discharge diagnosis codes or diagnostic codes from death certificates[16] for all ARIC participants before the date of last participant contact until September 1, 2013.

Mild Cognitive Impairment Risk

MCI was defined at Visit 5 as at least one domain score worse than -1.5 Z, a CDR sum of boxes between >0.5 and ≤3 or an FAQ ≤5, and a decline on the serial ARIC cognitive battery below the 10th percentile on one test or below the 20th percentile on two tests[13].

Secondary Outcomes

Dementia Etiology

We may also examine whether the relationship between systemic inflammation and incident dementia varies by suspected etiological diagnosis. Using NIA-AA criteria[13], participants were

classified as having Alzheimer's disease- dementia (AD) if they demonstrated a gradual pattern of cognitive change that included memory impairment without features of other diagnoses (described below) sufficient to cause cognitive impairment[12]. Participants were diagnosed as having *Cerebrovascular disease (CVD)-related dementia* using an algorithm derived from the National Institute of Neurological Disorders and Stroke-Associated Internationale pour la Recherche et l'Enseignement en Neurosciences criteria[16], which is outlined in detail elsewhere[12]. The etiologic diagnosis of *Lewy body disease-related dementia* was given if participants met at least two of the following four criteria: (1) a diagnosis of Parkinson's disease, (2) a history of fluctuation in alertness or cognition, (3) informant report of dream reenactment, or (4) hallucinations[17].

NCS Comprehensive Cognitive Battery

We may also examine the relationship between midlife inflammatory markers and late-life domain-specific cognitive functioning in areas of memory, language, processing speed and executive function[19]. These associations will be examined in the total sample, and among non-demented participants. The composition of each cognitive domain composite score is described.

Memory Composite

Delayed Word Recall Test (DWRT)
Logical Memory I & II
Incidental Learning

Language Composite

Word Fluency Test (WFT)
Animal Naming
Boston Naming Test

Processing Speed/Executive Function Composite

Digit Symbol Substitution Test (DSST)
Digit Span Backwards
Trail Making Test-A
Trail Making Test-B

Additionally, we will consider using a latent variable approach for the assessment of cognitive domains (memory, processing speed/executive function, language). Detailed methods for the construction of these latent variables have been described previously[20].

Other Variables

Demographic variables, including race, sex, age, *APOE* genotype (0, 1, or 2 ε4 alleles), and center will be extracted. Additionally, laboratory and physiologic data, including systolic and diastolic blood pressures, total/high density lipoprotein cholesterol, triglycerides, and 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, heart failure, cigarette smoking and alcohol use), previous cancer diagnoses, 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.

Data Analysis

Cognitive Change Analysis (H1 & H2)

As per ARIC-NCS Analysis Manual recommendations, generalizing estimating equations with an unstructured correlation matrix and robust variance will be used to estimate the difference in population-averaged trajectories of cognitive change over time by midlife inflammatory biomarker level (based on quartiles; **H1**) and mid- to late-life CRP trajectory (**H2**). An interaction term between inflammatory biomarker exposure and time will be included in the models to examine whether rates of cognitive change over time differ in accordance with inflammatory biomarker level and CRP trajectory. Time on study with a two-piece linear spline with a knot at Year 6 will be used as the time variable. This will permit the examination of differential rate of cognitive change before and after Year 6 (Visit 4). The decision to place a spline at Year 6 was made a priori because there is a large gap between study Visits 4 and 5, resulting in sparse outcome data over this period of time. Diagnostic plots and fit statistics, such as the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC), will be used to assess model fit.

Dementia Incidence & MCI Risk (H3 & H4)

Time to dementia onset was used as the primary outcome for this set of analyses. The date of the comprehensive neurocognitive assessment (2011-2013) will be used to define dementia onset for participants classified using Level 1 criteria. In the event these participants had a previous dementia hospitalization, this date will be used. For Level 2 and Level 3 dementia cases, the earliest date of dementia classification based on the TICSm interview, informant interview, hospitalization discharge or death certificate code will be used to define dementia onset. Participants without dementia diagnosis on any level will be censored at the date of their latest assessment up to September 1, 2013. Cox proportional hazard models will be used to examine the association of midlife inflammatory biomarker levels (based on quartiles; **H3**) and mid- to late-life CRP trajectory (**H4**) with dementia incidence. Binary logistic regression will be used to examine the association of midlife inflammatory biomarker levels (**H3**) and mid- to late-life CRP trajectory (**H4**) with MCI risk.

Covariates & Interactions

Model 1 will include covariates to adjust for potentially confounding demographic factors: linear and a quadratic term for baseline age, sex, race-center (Maryland white; Minnesota white; North Carolina white; North Carolina African American; Mississippi African American), education (less than high school; high school/GED/vocational school; or any college), *APOE* ε4 status (0, 1, or 2 ε4 alleles), anti-inflammatory medication use, and for cardiovascular risk factors and disease variables (i.e., BMI, total cholesterol, HDL, hypertension, diabetes, coronary heart disease, heart failure, cancer, cigarette and alcohol use status. To examine the effect of potential mediators (disease that may lie in the causal pathway between inflammation and cognitive decline), we will additionally adjust for incident cardiovascular disease occurring between Visit 2 and Visit 5 in *Model 2*. As part of the cognitive change analysis, time-interaction terms for demographic characteristics and medical comorbidity which contribute to the slope of cognitive change will be included. Values for time-varying covariates will be derived from the visit concurrent with inflammatory biomarker assessment, when available. Multiplicative interaction

terms (**H5**) will be used to evaluate effect modification by race (white/African American), sex (male/female), and *APOE* ε4 allele status (0/≥1).

Sensitivity Analysis
Inverse probability of attrition weighting (IPAW) and/or multiple imputation by chained equations (MICE) will be used to assess the potential effects of differential attrition due to death or dropout. Additionally, to determine whether these associations occur independent of stroke, which may mediate a relationship between systemic inflammation, cognitive decline, and dementia, we will repeat analyses censoring participants with incident clinical stroke between Visits 2 and 5.

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? __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 file ICTDER03 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/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# 2175, Gottesman et al. Midlife blood pressure and 20-year cognitive change: The ARIC Neurocognitive Study
MP# 2698, Wu et al. Hemostatic Factors and Long-term Cognitive Change
MP# 2944, Wu et al. Effect of Aspirin Use on Cognitive Decline, Dementia and Brain Morphologic Change
MP# 2215, Gross et al. Development of longitudinal measures of general and domain-specific latent factors for cognitive performance
MP# 1771, Knopman et al. Cognitive, vascular risk factor and APOE genotype predictors of hippocampal volume

MP# 3011, Walker et al. Systemic inflammation and brain amyloid deposition: The ARIC-PET Study
MP# 2865, Walker et al. Inflammatory biomarkers at midlife and late-life and brain atrophy in older adults: 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)* _____ _____ _____)

*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.

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.

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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