ARIC Manuscript Proposal #2930

PC Reviewed: 02/13/17 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study

b. Abbreviated Title (Length 26 characters):
Midlife inflammation and frailty

2. Writing Group:
Writing group members:
Keenan Walker, Jeremy Walston, Rebecca Gottesman, Anna Kucharska-Newton, Priya Palta, B Gwen Windham, others welcome

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

First author: **Keenan Walker**
Address: Johns Hopkins Hospital, Department of Neurology
Phipps 446
600 North Wolfe St.
Baltimore, MD 21287

Phone: 626-840-6216 Fax: 410-955-0672
E-mail: kwalke26@jhmi.edu

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).

Name: **Beverly Gwen Windham**
Address: Department of Medicine, Division of Geriatrics
2500 N. State St
Jackson, MS 39216

Phone: 601-984-5645 Fax: 601-984-5783
E-mail: gwindham@umc.edu

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

4. Rationale:

As a result of the reduction in early deaths to acute illness, the world's aging population faces new challenges. One consequence of aging is "frailty", which can be defined as a syndrome of reduced physiologic reserve and resistance to stressors resulting from simultaneous declines in multiple biologic systems [1]. Frailty is a risk factor for a number of common geriatric syndromes, such as falls and osteoporotic fractures, and is associated with heightened rates of chronic disease, functional disability, cognitive decline, institutionalization, and mortality [2–6]. The prevalence of frailty ranges from 4% -59% in community samples, with higher rates among older individuals, women, and African Americans [7–9]. Although frailty can be defined in multiple ways, most often used are the Fried et al. (2001) [1] criteria, which operationally define frailty as declines in strength, lean body mass, endurance, walking speed, and reduced physical activity[1,10–12]. Currently the ability to predict the onset of frailty is limited by an incomplete understanding of the underlying biology.

Although associated with increasing age and chronic disease, frailty can occur independent of each of these factors [1,6]. This suggests that biological pathways exist, which promote the development frailty and increase risk for adverse outcomes in the absence of clinically manifested disease. Although the physiological underpinnings of frailty have not yet been identified, previous studies suggest that chronic systemic inflammation may promote disruption to multiple physiologic systems, which in turn contribute to the development of frailty, disability, and ultimately death [13–15]. Supporting this hypothesis, numerous cross-sectional studies have found that frail and pre-frail individuals tend to have higher levels of circulating peripheral inflammatory markers, such as C-reactive protein, white blood cell count (WBC), fibrinogen, Factor VIII, interleukin (IL)-6, and tumor necrosis factor (TNF)-α compared to robustly aging older adults [16–19].

Despite consistent associations between circulating inflammatory markers and frailty, it is still unclear whether chronic inflammation is a cause or consequence of the frailty phenotype. Stronger inferences about a potential causal role of inflammation in the pathogenesis of frailty could be made if chronic systemic inflammation earlier in life was found to predict the onset of frailty later in life. If chronic systemic inflammation does promote frailty, individuals who experience persistent inflammation in the decades leading up to older adulthood (i.e., midlife) will likely be at greatest risk for developing frailty as older adults. Moreover, if systemic inflammation interacts with physiological characteristics that are overrepresented in certain populations, such as low lean body mass in women[1] and cardiovascular disease in African Americans[20], this may account for higher rates of frailty within each of these groups. To date, few studies have examined how baseline markers of systemic inflammation relate to the development of frailty later in life [21–24]. Overall, results have been inconsistent and the follow-up periods have been relatively short, ranging from 3 to 10 years. The goal of the current study is to test the hypothesis that elevated markers of systemic inflammation measured in midlife (age 45-64) independently predict the onset of the frailty phenotype 24 years later in late-life using a large community sample of African American and Caucasian participants. In doing so, we will also examine the hypothesis that sex and race modify this relationship.

5. Main Hypothesis/Study Questions:

1. Higher levels of circulating inflammatory markers in midlife (visit 1 and visit 2) will be associated with increased risk for frailty and pre-frailty in late-life (visit 5). The associations will be stronger among female compared to male participants, and among African American compared to Caucasian participants.

2. The association between higher levels of midlife inflammatory markers and late-life frailty in #1 will exist independent of comorbid chronic disease.

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).

Inclusion/Exclusion Criteria:
Inclusion Criteria:

1) Attended ARIC visit 5
2) Available inflammatory biomarker data collected during ARIC visit 1 or visit 2

Exclusion Criteria:

1) Participants missing information on all 5 component characteristics defining frailty
2) Participants with documented clinical stroke before visit 5, as stroke may affect performance on functional measures of frailty.

Outcome Variables
Definition of frailty: All participants who attended visit 5 NCS have been categorized as *frail*, *pre-frail*, or *robust* based on the frailty phenotype definition operationalized by the Cardiovascular Health Study (CHS)[1] and recently validated in the ARIC study[25]. This definition of frailty is based on 5 components: exhaustion, slowness, low physical activity, and unintended weight loss. Participants are categorized as "frail" if they met 3 or more of the criteria listed below. Participants were categorized as "pre-frail" if they met 1 or 2 of the criteria listed below. Participants meeting none of the frailty criteria will be classified as "robust".

1. *Exhaustion*: Participants who answered "some of the time" or "most of the time" to the following two questions on the Center for Epidemiological Study's-Depression (CES-D) scale [26] (administered at visit 5) were classified as positive exhaustion: "I felt everything I did was an effort" and "I could not get 'going'".
2. *Slowness*: Walking speed was measured at visit 5 as the time needed to walk 4 m at a usual pace. Slow walking speed was defined as a time within the lowest 20th percentile, adjusted for gender and height, as defined in CHS.
3. *Low Physical Activity*: Physical activity was measured at visit 5 using the modified Baecke questionnaire. Low physical activity was defined as reported physical activity in the lowest 20th percentile stratified by gender.
4. *Weakness*: Grip strength in the participant's preferred hand was measured at visit 5 using an adjustable, hydraulic grip strength dynamometer. Weakness was defined as grip strength in the lowest 20th percentile, adjusting for gender and BMI according to

established norms. Grip strength measures were not obtained for participants with bilateral surgery in hands or wrists in the previous 3 months.

5. *Weight Loss*: Weight loss was defined as a 10% weight loss from visit 4 to visit 5 or a body mass index (BMI) at visit 5 less than 18.5kg/m^2.

Exposures

Plasma Inflammatory Markers: Plasma levels of acute-phase reactants and inflammatory biomarkers will be extracted from ARIC visits 1 and visit 2 for each participant. The list of inflammatory markers extracted at each visit is provided in the table below.

Inflammatory Markers Available in Full Cohort		
Visit 1 (1987-1989)	**Visit 2 (1990-1992)**	**Visit 5 (2011-2013)**
WBC	Lp-PLA_2	Frailty Assessment
Fibrinogen	CRP	
Albumin		
vWF		
Factor VIII		

Note: Lp-PLA_2 = Lipoprotein-associated phospholipase A2; vWF = von Willebrand factor

Chronic Medical Conditions: The presence of comorbid medical conditions will be assessed at each visit (visit 1 through visit 5). Specifically, the presence of the following conditions will be determined for our analyses: coronary artery disease, heart failure, atrial fibrillation, hypertension, diabetes, chronic kidney disease (CKD), cancer, and chronic obstructive pulmonary disease (COPD).

Coronary artery disease will be defined as a participant-reported history of myocardial infarction, history of coronary artery bypass graft or angioplasty, or myocardial infarction determined by ECG adjudication.

Heart failure will be defined as the presence of heart failure according to the Gothenburg criteria [27], self-reported heart failure medication use within the past 2 weeks, or evidence of heart failure related hospitalizations.

Atrial fibrillation will be defined based on ECG or using hospital discharge records as described previously [28].

Hypertension will be defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of hypertensive medication.

Cancer diagnosed before visit 1 will be defined based on participant report of previous physician diagnosis. Cancer diagnoses between visit 2 and visit 5 will be ascertained from cancer registries and supplemented by hospital records [29].

Diabetes will be defined as a fasting glucose of ≥ 126 mg/dl or a non-fasting glucose of ≥ 200 mg/dl, current use of diabetes medication or insulin, or participant report of physician-diagnosed diabetes.

CKD will be defined using estimated glomerular filtration rate (GFR). GFR will be estimated using the method recommended by the Modification of Diet in Renal Disease study group [30]:

estimated GFR = 186.3 x (serum creatinine) $^{-1.154}$ x age $^{-0.203}$ x (0.742 if female) x (1.21 if black). Following National Kidney Foundation guidelines, participants will be classified as having CKD if they have an estimated GFR between 15 and 59 ml/min per 1.73 m^2.

COPD will be classified using prebronchodilator spirometry values (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio) in accordance with Global Obstructive Lung Disease (GOLD) criteria [31,32].

- Stage 3 or 4: $FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted
- Stage 2: $FEV_1/FVC < 0.70$ and $FEV_1 \geq 50\%$ predicted
- Stage 1: $FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ predicted

Covariates
Demographic variables, including race, sex, education and center will be extracted from visit 1. Participant age will be extracted at visit 1, visit 2, and visit 5. Additionally, total BMI, total cholesterol, total triglycerides, LDL, smoking status, alcohol use, use of anti-inflammatory drugs, and use of lipid lowering drugs will be extracted from visit 1 and visit 2. Participant-reported physician diagnosis of chronic inflammatory diseases (e.g., gout, lupus, arthritis) will be extracted from visit 4.

Data Analysis
Hypothesis 1: To examine the relationship between midlife inflammatory biomarkers (exposure) and late-life frail and pre-frail status (outcome), we will use logistic regression to estimate odds ratios and 95% confidence intervals. Inflammatory biomarkers will be examined as both continuous and categorical variables. First, to assess for a linear and nonlinear trends, each biomarker will be categorized into quartiles (Q1, lowest; Q2, lower middle; Q3, upper middle; Q4 highest) and entered into the logistic regression equation as a predictor variable. The lowest category will serve as the reference group to which the individual upper categories will be compared. In a separate series of logistic regression equations, each biomarker will be entered as a continuous variable. To assess the effect of overall inflammatory burden, an inflammatory composite score will be created using the five inflammatory biomarkers available at visit 1 (i.e., WBC, fibrinogen, albumin, von Willebrand factor, and Factor VIII). The inflammatory composite score will be created by summing the biomarker levels after each is rescaled to a z-score based on the sample mean and standard deviation. For all analyses, the robust group will be used as the reference. We may also use multinomial logistic regression analyses to determine how independent biomarkers and the inflammatory composite score relate to the total number (0-5) of frailty indicators. The following covariates will be included in the initial multivariable logistic regression model (model 1): age, sex, education, race-center, BMI, total cholesterol, total triglycerides, LDL, smoking status, alcohol use, chronic inflammatory diseases (e.g., gout, lupus), use of anti-inflammatory drugs, and use of lipid lowering drugs. We will use multiplicative interaction terms to evaluate effect modification by sex and race. For each analysis, inflammatory biomarkers and covariates will be derived from the same visit.

Hypotheses 2: To determine whether midlife inflammation is associated with late-life frailty independent of medical comorbidity, we will use three approaches.

1. We will use the methods described for Hypothesis 1 to examine the relationship between midlife inflammation and late-life frailty using a second logistic regression model (model 2) which adjusts for comorbid disease in addition to those covariates included in model 1.

The following covariates will be added to model 2: coronary heart disease, heart failure, atrial fibrillation, hypertension, diabetes, CKD, cancer, and COPD.

2. We will use the methods described for Hypothesis 1 to examine the relationship between midlife inflammation and late-life frailty after excluding all participants diagnosed with one or more medical comorbidities (i.e., coronary heart disease, heart failure, atrial fibrillation, hypertension, diabetes, CKD, cancer, and COPD) at the time of midlife inflammatory biomarker assessment. We will adjust for potentially confounding demographic and physiologic variables (model 1).
3. Using a standard mediation approach [33], we will determine whether the relationship between midlife inflammation and late-life frailty is mediated by incident medical comorbidity developed between the time of inflammatory biomarker assessment and frailty assessment (between visit1/visit 2 and visit 5). First, we will examine the relationship between midlife inflammation and incident medical comorbidity. Second, we will examine the relationship between incident medical comorbidity and late-life frailty. Third, we will examine whether the relationship between midlife inflammation and late-life frailty (Hypothesis 2, Analysis 2) is attenuated in a model that adjusts for incident medical comorbidity occurring after collection of midlife inflammation biomarkers. Structural equation modeling (SEM) will be used to calculate formal mediation estimates [34]. This analysis will be conducted using participants without medical comorbidity at visit 1 or visit 2.

As per PFX working group recommendations, a sensitivity analysis will be conducted that excludes all participants with a diagnosis of cancer before visit 5.

We will conduct the primary analyses using only patients with available data. To examine the effects of attrition on our findings, we will conduct sensitivity analyses as recommended by the ARIC analysis committee to account for missing data using MICE, IPAW, and the Heckman correction as appropriate.

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)?

#2791 Association of Life's simple 7 at mid-life with frailty in older adults

#2503 Menopause aging genes, cognition and frailty: the Atherosclerosis Risk in Communities Study

#2671 Cardiovascular characterization of frailty in the elderly: The ARIC study

#2465 Operationalizing frailty in the ARIC cohort

#2303 Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities 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

___ 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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