**ARIC Manuscript Proposal #4032 (Revised)**

**PC Reviewed: 6/14/22** **Status: _____** **Priority: 2**
**SC Reviewed:_____** **Status:_____** **Priority: ____**

**1. a. Full Title**:

Association of circulating biomarkers with fatigue, depressive symptoms, and physical function in persons with AF in the ARIC study

**b. Abbreviated Title (Length 26 characters)**: Fatigue in AF

**2. Writing Group**:

Writing group members:

- Kathryn Wood, PhD, RN
- Aniqa Alam, MPH
- Lin Yee Chen, MD, MS
- Elsayed Soliman, MD, MSc
- Arshed Quyyumi, MD
- Alvaro Alonso, MD, PhD

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

**First author**:


- **Kathryn A. Wood**, PhD, RN, FAHA, FAAN
  Nell Hodgson Woodruff School of Nursing
  Emory University
  1520 Clifton Rd NE
  Atlanta, GA 30322-4207
  Phone: (404) 727-4076 | Fax: (404) 727-4645
  Email: kathryn.wood@emory.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).


- Alvaro Alonso, MD, PhD
  Department of Epidemiology
  Rollins School of Public Health, Emory University
  1518 Clifton Road NE
  Atlanta, GA 30322
  Phone (404) 727-8714
  Email: alvaro.alonso@emory.edu


**3. Timeline**:

Within one year of manuscript approval.

## 4. Rationale:

Atrial fibrillation (AF) is a common, costly cardiac arrhythmia, associated with stroke, heart failure [HF], dementia, and death.[1-6] Moreover, 9% of people ≥ 65 have AF, forecasting an epidemic as the population ages.[7-9] Common symptoms are palpitations, fatigue, dyspnea, exercise intolerance, anxiety, and depression.[10-15]

AF ablation, cauterization of areas in the left atrium, is currently the most effective therapy to decrease AF episodes and improve symptoms in paroxysmal or persistent AF.[1,4] In 46-64% of AF ablation cases, AF recurrences and worsened symptoms, related to procedural induced endocardial inflammation, occur during the first 3-6 months post-procedure, often requiring additional AF ablation procedures.[1,4] Dynamic symptom challenges can occur during the first 3-6 months after AF ablation.[1,4,15] In prior work, we demonstrated that recovery after AF ablation is a slow process, leaving some patients struggling with debilitating fatigue for 3-6 months after the ablation procedure, highlighting the need for tailored interventions to improve early outcomes for those patients most at risk.[15,16] We found that all patients in our sample (N=20) reported fatigue as a much larger symptom challenge during the 6-months post-AF ablation than was previously recognized.[15,16] Many reported this fatigue post-AF ablation as more severe and prolonged than the fatigue they experienced during AF episodes before the ablation procedure. Patients are discharged post AF ablation with instructions to rest for 1-2 days and then resume normal activities. However, 40% of subjects reported difficulty returning to even part-time work or activities within 3 weeks due to fatigue.[15,16] Fatigue was reported by 75% of subjects (n=15) at 1-month post-AF ablation as incapacitating, and continued at 3-months in 50% of subjects, delaying return to work or physical activity. This differs greatly from ablation outcomes for other types of arrhythmias, where patients return to full time work in 1-3 days.[17,18] In order to identify those at highest risk of AF-fatigue and develop effective fatigue reducing interventions, it is critical to understand the biological mechanisms of AF-fatigue.

Fatigue, defined as an awareness of a decreased capacity for physical or mental activity,[19] is a common and distressing symptom in adults with many types of chronic conditions (cancer, HIV, HF) and growing evidence suggests there are multiple biological mechanisms involved.[20-29] Because many of these chronic conditions are not curable, symptom management has become an increasingly important focus of research. There has been compelling evidence of an inflammatory mechanism underlying the symptom of fatigue in chronic conditions such as cancer,[26,27,29-36] HIV,[21,25,37,38] and diabetes.[39,40] A cascade of complex downstream responses occur when cytokines are released as a protective and reparative response,[41] and then enter the brain, changing brain function leading to neuroinflammation, and causing fatigue.[42-44] Pro-inflammatory cytokines (IL-1ß, tumor necrosis factor [TNF]-α) and C-reactive protein (CRP) have been implicated in fatigue, depression and mood disorders in a variety of conditions.[26,45] Fatigue is an important early predictor of relapse or poor treatment outcomes in other chronic conditions,[21,25,29,33] and this may also be true for AF-fatigue.

Xiao and colleagues found that independent predictors of fatigue in cancer patients included depressive symptoms and increased inflammatory biomarkers.[34] Depression has been linked to inflammation in cancer, demonstrating that those depressed patients who had the highest CRP levels at baseline were the patients who showed significant improvement from antibody treatment used in autoimmune diseases.[46] These biomarkers, once identified, served as important target endpoints in intervention studies to build the science in this area, demonstrating the effect of pharmaceutical and non-pharmaceutical interventions to reduce depression.[29,47,48]

Although conditions such as cancer, HIV, and AF greatly differ from one another, the symptom of fatigue may share biological mechanisms of onset and exacerbation across conditions as these mechanisms can influence each other and activate other systems.[49] Other correlates of fatigue linked to increased inflammation in cancer and HIV have included increased depressive symptoms and decreased physical activity.[27,50]

Though our understanding of fatigue-related mechanisms in chronic conditions such as cancer, HIV and HF is growing, associated factors of AF-fatigue have not been previously explored. Markers of cardiac injury, such as high sensitive troponin (hs-TnT) and N-terminal fragment B-type natriuretic peptide (NT-proBNP), and oxidative stress [cystine and glutathione ratios] are linked to increased AF occurrence, higher risk of stroke and death post-AF ablation,[51-59] but, as with hsCRP, have never been tested or linked to any AF patient symptom. Association of AF-fatigue and specific immune/cardiac injury biomarkers could establish more effective treatment targets to examine in future studies testing AF-fatigue interventions. AF ablation is designed as a palliative treatment to decrease AF patient symptoms. Even more critical to understanding symptom mechanisms is the need for exploration of why individual symptom differences occur, allowing risk stratification of who may benefit most from certain interventions or treatments. Addressing these gaps in our knowledge in the future will lead to more effective means of personalizing AF patient care through prediction of individuals' response to treatment.

Our goal in the current study is to identify biomarkers associated with fatigue and selected correlates (depressive symptoms and physical function) in participants with AF in the Atherosclerosis Risk in Communities (ARIC) database to guide proposal development for future prospective study of mechanisms of AF-fatigue. Understanding associated factors of AF-fatigue is a critical first step to future studies that can lead to identification of those at highest risk of AF-fatigue.

## 5. Main Hypothesis/Study Questions:

To examine the association of biomarkers of inflammation and cardiac injury (hsCRP, NT-proBNP, hs-Troponin), with fatigue, and other known correlates of fatigue, such as depressive symptoms and physical function, in the ARIC cohort of participants with AF.

## 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

We will use the ARIC database for this secondary analysis. The ARIC study is a multiracial community based prospective, cohort study from 4 communities in the United States (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD). At baseline (Visit 1, 1987-1989), there were 15,792 men and women, aged 45-64 years of age. The ARIC study included additional in-person examinations, the last one in 2019-2020 (visit 8). Additionally, participants undergo annual follow-up calls (semi-annual starting in 2012). For the current cross-sectional analysis, we will use data from Visit 5 and the GNB semi-Annual Follow-up interview (shortly after Visit 5) because that survey includes the PROMIS 5-item Fatigue scale (items C14 - C18).

Study population: inclusion/exclusion criteria

Inclusion criteria include all patients with a diagnosis of AF at Visit 5 (N=597) who also completed the GNB semi-annual follow-up interview form with PROMIS 5-item Fatigue scale. Exclusion criteria include those subjects missing responses: on the GNB semi-annual follow-up interview PROMIS 5-item Fatigue scale; at Visit 5 on the Center for Epidemiological Studies Depression (CESD) survey, and the Short Physical Performance Battery (SPPB) test; missing biomarker results at Visit 5 for hsTnT, NT-proBNP, hsCRP; missing variable responses from Visit 5 for Body Mass Index (BMI), smoking history, and history of hypertension, diabetes, HF, myocardial infarction (MI), and stroke or use of anticoagulants; and missing variable responses at Visit 1 for level of education. Final study sample will be N=446.

Main predictor: cardiovascular-risk biomarkers (hsTnT, NT-proBNP, hsCRP) assessed in blood samples collected at visit 5.

Endpoints:
Our primary outcome variable from the ARIC database will be the 5-item PROMIS Fatigue scale score for items C14-C18 at the GNB semi-annual follow-up visit. PROMIS Fatigue scale questions include "How often did you feel tired?" (C14); How often did you experience extreme exhaustion?" (C15); "How often did you run out of energy?" (C16); "How often were you too tired to think clearly?" (C17); and "How often were you too tired to take a bath or shower?" (C18). The Likert-type response options for each item range from "Never" (0) to "Always" (4), with higher scores indicating higher levels of fatigue. PROMIS Fatigue scale item scores will be summed and transposed to T-scores ranging from 0-100. T-scores over 50 are considered higher fatigue than normal. Other dependent variables assessed at Visit 5 include: CESD scores and SPPB scores. Covariate/confounder variables to be assessed include age, sex, race/center, education, BMI, smoking, hypertension, diabetes, HF, MI, stroke, and anticoagulants. All covariate/confounder variables assessed will be obtained from Visit 5 data, except education that will be assessed at Visit 1.

Statistical analysis
Measures of central tendency (means, SD, frequencies) will be used to describe sample demographics and clinical variables by subject levels of the inflammatory biomarkers and Fatigue scale items (*always*, *often*, *sometimes*, *rarely*, *never*). Fatigue scale response option categories will be collapsed to total 3 categories: *always* and *often*, *sometimes* and *rarely*, and *never*. Separate multiple linear regression will be used to estimate the association between circulating biomarkers and the outcome variables (Fatigue scale scores, CESD scores, SPPB scores). In Model 1, we will adjust for age, sex, race/center, education. In Model 2, we will include Model 1 covariates and BMI, smoking, hypertension, diabetes, HF, MI, stroke, and anticoagulants.

Limitations
Our analysis is restricted to participants who survived to visit 5 and were healthy enough to participate in the visit in person. This may result in lack of generalizability and potential selection bias if factors associated with the exposure and the outcome also affect participation. This issue will be addressed by adjusting for available potential predictors of participation and by a careful interpretation of our findings. An additional limitation includes the limited information on clinical aspects related to the diagnosis of AF and the lack of longitudinal information on fatigue symptoms.

**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.)

**8a. Will the DNA data be used in this manuscript?_____Yes X____No**

**8b. 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"?_____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)?**
No other relevant manuscripts

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?_____Yes X____No**

**11.b. If yes, is the proposal**
**___ A. primarily the result of an ancillary study (list number*_____)**
**___ 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.**

We understand and agree with this statement.

**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.

We understand and agree with this statement.

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