ARIC Manuscript Proposal #2671

PC Reviewed: 11/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiovascular characterization of frailty in the elderly: The ARIC study

b. Abbreviated Title (Length 26 characters):
Frailty pathophysiology in ARIC

2. Writing Group:

Writing group members: Wilson Nadruz Junior, Beverly Gwen Windham, Anna Kucharska-Newton, Ken Butler, Priya Palta, Mike Griswold, Dalane Kitzman, Gerardo Heiss, Scott D. Solomon, Hicham Skali, Amil M Shah; **Others welcome**.

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

First author:
Wilson Nadruz Junior
Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street, PBB-1 North
Boston, MA 02115
Phone: 617-971-7867 Fax: 617-582-6027
E-mail: wnadruzjunior@partners.org

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).
Amil M Shah
75 Francis Street
Boston, MA 02115
Phone: 617-525-6733/Fax: 617-582-6027
E-mail: ashah11@partners.org

3. Timeline:
Analysis will begin following proposal approval with anticipated manuscript completion within 6 months.

4. Rationale:

The syndrome of frailty is defined as a state of increased vulnerability to stressors resulting from an accelerated decrease in physiological reserve that accompanies aging.[1, 2, 3] Operational definitions of frailty vary and can include nutritional status, physical activity, mobility, energy, strength, cognition, mood, and social relations and support.[3] The most widely accepted definition of frailty was first operationalized using data from the Cardiovascular Health Study (CHS) and includes the presence of three or more of the following: low strength, low energy, slowed motor performance, low physical activity, or unintentional weight loss.[2] Subjects with one or two of these characteristics are considered to be pre-frail and are at a higher risk to develop frailty. Frailty occurs in approximately 10% of elderly people and increases progressively with age, being reported in approximately 26% of persons >85 years of age.[1, 4] Frail older adults are a group at increased risk of adverse outcomes, including hospitalization, disability, and mortality.[1, 3, 5]

Previous studies have suggested that alterations in cardiovascular function are associated with frailty.[6, 7] However, impairments in multiple other organ systems have also been associated with frailty, including the neurologic, immune, respiratory, renal, hematopoietic, adipose and endocrine systems.[6, 8, 9, 10, 11] Given that multiple comorbidities often co-exist in the elderly, the association of cardiovascular dysfunction with frailty after accounting for coexisting alterations in other physiological systems is not known. Additionally, multiple component measures of cardiac dysfunction, including alterations in left ventricular (LV) systolic and diastolic performance, reductions in right ventricular function, and altered systemic and pulmonary vascular function may contribute to frailty in the elder but their relationship with frailty remain to be established. Furthermore, significant sex-based differences in the prevalence of frailty have been reported in the elderly,[12] although little is known regarding sex-based differences in the underlying physiologic impairments responsible for frailty. Similarly, little data exist regarding race-based differences in the relative contribution of cardiovascular dysfunction to frailty.

Detailed phenotyping of cohort participants in ARIC Visit 5 offers the unique opportunity to provide novel insight into the relative contribution of cardiovascular dysfunction to frailty in the elderly. In addition, this large biracial cohort is uniquely positioned to investigate sex and race/ethnicity-based differences in these relationships.

5. Main Hypothesis/Study Questions:

We hypothesize that impairment in cardiovascular function contributes to frailty in the elderly, and that compared to the elderly without frailty, elderly persons with pre-frailty and frailty will demonstrate worse cardiovascular structure and function. We also hypothesize that the association of impaired cardiovascular function with frailty will persist after accounting for associations with other organ system dysfunction. We expect similar associations will be observed when comparing frail with pre-frail individuals.

Specifically, we aim to:

1. Compare measures of cardiovascular structure and function among participants with frailty, pre-frailty and non-frailty. The following measures will be evaluated (see analysis section below for further details): (1) LV structure and systolic function; (2) LV diastolic function; (3) pulmonary arterial pressure, vascular resistance, and right ventricular function; (4) arterial stiffness and ankle-brachial index (ABI).
2. Investigate whether the relationship between frailty status and cardiovascular features is influenced by sex and race/ethnicity.

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:
This will be a cross-sectional analysis based on data collected at ARIC Visit 5.

Inclusion/exclusion criteria:
Participants with missing data on frailty, echocardiography, vascular stiffness, ankle-brachial index, spirometry, renal function, hemoglobin and anthropometry at Visit 5 will be excluded from the analysis.

Key variables of interest:

1. **Outcome variable:**
   Frailty syndrome: The ARIC Study Coordinating Center in collaboration with members of the ARIC Physical Function working group created a frailty variable based on the construct developed on the basis of data collected in the CHS.[2] Component elements of the frailty construct were ascertained at ARIC Visit 5, with the exception of weight loss which was calculated based on Visit 5 and Visit 4 data (Table 1). The sample will be categorized into 3 groups: non-frailty, if none of the listed component phenotypes were present; pre-frailty, if one or two of the component phenotypes were present; and frailty, if three or more of the component phenotypes were present.

Table 1. Operationalization of the frailty construct in ARIC cohort

Characteristics of frailty	Definition
Unintentional weight loss	10% of unintentional weight loss from Visit 4 to Visit 5 or BMI<18.5kg/m^2 at Visit 5
Low energy expenditure	Gender-specific 10th percentile rank of the Baecke leisure sports activity index
Low walking speed	Gender- and height-adjusted time in seconds used to walk 4 meters. Slowest speed was defined using the cutoff values established from CHS.

Low level of physical energy (Exhaustion)	Responded "some of the time" or "most of the time" to either of the following CESD questions: CES3 (I felt everything I did was an effort) or CES11 (I could not get "going")
Low grip strength	Gender- and BMI-specific grip strength. Lowest grip strength was defined using the cutoff values established from CHS.

2. Predictor variables:

a) Echocardiographic variables (visit 5 echo): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E wave deceleration time, TDI E', and left atrial volume index); (3) LV systolic function (LV ejection fraction, mid-wall fractional shortening, longitudinal strain, circumferential strain); (4) pulmonary hemodynamics (estimated pulmonary artery systolic pressure based on tricuspid regurgitation jet velocity, pulmonary vascular resistance) and right ventricular function (fractional area change, TDI tricuspid annular S').

b) Vascular function variables (visit 5): systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, carotid-femoral pulse wave velocity, and ankle-brachial index.

3. Covariates:

Clinical covariates (visit 5): age, gender, race/ethnicity, field center, heart rate, smoking status, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, heart failure, prior hospitalization for heart failure, hemoglobin, estimated glomerular filtration rate, spirometric variables (FEV1 and FVC), measures of body fat/body fat distribution (BMI, fat mass, lean mass and % of fat mass),

Data analysis:

Basic descriptive statistics will be performed in the population stratified by frailty status: frailty, pre-frailty and non-frailty. Continuous normally distributed data will be presented as mean and standard deviation and continuous non-normally distributed data will be shown as median and interquartile range. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. Continuous data will be compared by Kruskall-Wallis test followed by Wilcoxon rank sum test and 1-way ANOVA followed by Bonferroni test as appropriate. Multivariable adjustment will be performed using linear regression (continuous outcome variables) and logistic regression (categorical outcome variables) as appropriate, adjusting first for age, gender, and race/ethnicity, then additionally by clinical variables that differ significantly between the two groups. Additional sensitivity analysis will be performed restricting the above comparison by gender and race/ethnicity. Both univariate and multivariable analysis will be performed as described above.

To evaluate the independent association of cardiovascular features with frailty, the presence of frailty will be the primary response variable. We will employ multivariable logistic regression analyses adjusting first for age, gender, and race/ethnicity, then additionally by clinical covariates that differ significantly between the frailty and non-frailty groups. The following domains of cardiovascular dysfunction will act as the predictor variables: cardiac dysfunction (LV systolic dysfunction, LV diastolic dysfunction, LV remodeling, pulmonary vascular, right ventricular dysfunction), and systemic arterial dysfunction (elevated arterial stiffness, reduced ankle-brachial index). Predictor variables will be dichotomized for this analysis, creating indicators of absence or presence of dysfunction. Cutpoints for defining abnormal will be based on clinical guideline recommendations or, for echocardiography, will employ sex-specific ARIC reference limits. Multiple measures can characterize a given domain of cardiovascular dysfunction. To identify the optimal measure to represent each cardiovascular domain, for each domain we will employ multivariable logistic regression models with frailty status as the outcome and all candidate measures as predictors and will select the measure with the highest chi-square value. For clinical covariates that have multiple measures, such as spirometric variables (FEV1 or FVC) and measures of body fat/body fat distribution (BMI, fat mass, lean mass or % of fat mass), we will also identify the optimal measure to represent each covariate. Furthermore, we will do the same analyses comparing frail to pre-frail individuals and comparing non-frail to pre-frail individuals.

Anticipated methodologic limitations:

A major limitation for this analysis is its cross-sectional design. Ideally, we would be able to relate cardiovascular measures characterizing frailty with the risk of death or cardiovascular events among persons with frailty. However, this data will not be available for several years and future manuscript proposals will focus on this analysis.

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 ICTDER03 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)?

#2465: Anna Kucharska-Newton, Priya Palta, Sheila Burgard, Michael Griswold, Jennifer Lund, Benjamin Capistrant, Karen Bandeen-Roche, Beverly Gwen Windham. Operationalizing frailty in the ARIC cohort.

#2503: Marina Bessel, Nora Franceschini, Gerardo Heiss, B. Gwen Windham, Thomas H. Mosley, Bruce B. Duncan, Maria Inês Schmidt, Álvaro Vigo, Ellen Demerath, Lisa Wruck. Menopause, cognitive decline and frailty.

#2303: Job G. Godino, Karen Bandeen-Roche, Jennifer A. Schrack, Alden L. Gross, B Gwen Windham, James S. Pankow, Stephen B. Kritchevsky, Lawrence J. Appel, Elizabeth Selvin. Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study.

#2219: Amil M Shah, Brian Claggett, Hicham Skali, Dalane Kitzman, Kunihiro Matsushita, Laura Loehr, Scott D. Solomon. Characterization of Dyspnea in ARIC

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 at http://www.cscc.unc.edu/aric/forms/

12. 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.

References

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10. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J, Fried LP; Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333–41.

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12. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. Age Ageing. 2014;43:222-8.