1.a. **Full Title**: Comparison of cardiac and clinical characteristics between frailty and heart failure in the elderly: The ARIC Study

**b. Abbreviated Title (Length 26 characters):**
Frailty and heart failure in ARIC

2. **Writing Group:**

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]

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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. 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. Subjects with one or two of these characteristics are considered to be pre-frail and are at a higher risk to develop frailty. Frail older adults are a group at increased risk of adverse outcomes, including hospitalization, disability, and mortality.

Heart failure (HF) disproportionately affects the elderly, in whom the majority of HF cases occur in the setting of preserved left ventricular ejection fraction (HFpEF). Previous studies have suggested a close relationship between frailty and HF. Elderly patients with HF have a high prevalence of frailty, while frail individuals frequently demonstrate abnormalities in cardiac structure and function and have an increased risk for developing HF. HF and frailty show many similar phenotypic characteristics. In the elderly, both HF and frailty are more likely to occur in women with advanced age, who are obese, hypertensive and diabetic. Frailty and HF are also associated with higher prevalence of impairments in multiple other organ systems, including alterations in vascular, pulmonary, hematologic and kidney systems. Additionally, several components of the frailty syndrome may be part of the clinical constellation of HF, especially in the setting of low output, such as low strength, low energy, exhaustion, slowed motor performance and unintentional weight loss. A potential explanation for the similarities between frailty and HF may relate to systemic inflammation, which has been reported to play a role in the pathogenesis of frailty and HF, particularly with preserved ejection fraction. Together, these observations suggest that frailty and HF may share similar pathophysiological pathways and also raise the hypothesis that frailty might be part of the phenotypic spectrum of HF syndrome in the elderly.

Detailed phenotyping of cohort participants in ARIC Visit 5 offers the unique opportunity to provide novel insight into the similarities and discrepancies between frailty and HF syndromes.

5. **Main Hypothesis/Study Questions:**

We hypothesize that elderly frail subjects without established diagnosis of HF share similar cardiac and clinical features when compared to elderly subjects with established diagnosis of HF. We also hypothesize that frail individuals without heart failure will demonstrate a similar prognosis with respect to all-cause mortality compared to elderly persons with established HF and a higher incidence of heart failure hospitalization when compared with non-frail and pre-frail subjects with no HF diagnosis.

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).

6.1. Study design:
This will be a cross-sectional and longitudinal analysis based on data collected at ARIC Visit 5.

6.2. Inclusion/exclusion criteria:
Participants with missing data on frailty, heart failure or other covariates at visit 5 used in the analysis will be excluded.

6.3. Key variables of interest:

Exposures variables:

Participants will be categorized into 4 groups based on data obtained at Visit 5:
   a. Non-frail without heart failure
   b. Pre-frail without heart failure
   c. Frail without heart failure
   d. Heart failure (prevalent at visit 5)

Definitions of exposure variables:

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. 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>
<thead>
<tr>
<th>Characteristics of frailty</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Unintentional weight loss</td>
<td>10% of unintentional weight loss from Visit 4 to Visit 5 or BMI&lt;18.5kg/m² at Visit 5</td>
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<tr>
<td>Low energy expenditure</td>
<td>Gender-specific 20th percentile rank of the Baecke leisure sports activity index</td>
</tr>
<tr>
<td>Low walking speed</td>
<td>Gender- and height-adjusted time in seconds used to walk 4 meters. Slowest speed was defined using the cutoff values established from CHS.</td>
</tr>
<tr>
<td>Low level of physical energy</td>
<td>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”)</td>
</tr>
</tbody>
</table>

Table 1. Operationalization of the frailty construct in ARIC cohort
Low grip strength  Gender- and BMI-specific grip strength. Lowest grip strength was defined using the cutoff values established from CHS.

**Definition of HF:** Prevalent HF at ARIC Visit 5 will be defined as (1) an adjudicated HF hospitalization since 2005 (2) hospitalization with a HF ICD code prior to 2005, and (3) among those without a prior hospitalization, self-report of HF or treatment for HF with at least one of the following: (a) subsequent confirmation of self-report by treating physician or the participant, or (b) an NT-proBNP at Visit 4 or 5 of at least 125 pg/ml\(^{15, 16}\).

**Predictor variables:**

**Cross-sectional analysis:**

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) Clinical covariates (visit 5): age, gender, race/ethnicity, field center, systolic blood pressure, diastolic blood pressure, heart rate, smoking status, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, prior stroke or TIA, hemoglobin, estimated glomerular filtration rate, C-reactive protein, NT-proBNP, high-sensitivity troponin-T, spirometric variables (FEV1 and FVC), carotid-femoral pulse wave velocity, ankle-brachial index, measures of body fat/body fat distribution (BMI, fat mass, lean mass and % of fat mass), leg edema and dyspnea scale (Based on Respiratory Questionnaire items 5-10).

**Longitudinal analysis:**

a) Incident HF hospitalization and all-cause mortality after Visit 5.

**6.4. Data analysis:**

Basic descriptive statistics will be performed in the population stratified by frailty and heart failure status: frailty, pre-frailty, non-frailty and heart failure. 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. We will explore whether these associations differ based on HF phenotype (preserved versus reduced LVEF based on LVEF from Visit 5 echocardiogram). Sensitivity analysis will be performed restricting the above comparison by gender and race/ethnicity. To further quantify the impact of possible bias due to selective attrition before visit 5 due to non-attendance among living cohort participants, we will calculate inverse probability weights to estimate the likelihood of visit 5 participation among cohort participants known to be alive at Visit 5. Both univariate and multivariable analysis will be performed as described above. Cox-regression analysis will be performed to evaluate the association between the studied groups and incident HF after Visit 5 among those without HF diagnosis.

6.5. **Anticipated methodologic limitations:**

A major limitation will be relatively short time of follow-up for incident HF after Visit 5, which will limit the statistical power of this analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
____ 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?  
____ 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  
____ 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.cscce.unc.edu/ARIC/search.php](http://www.cscce.unc.edu/ARIC/search.php)

____ 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)?


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


