

ARIC Manuscript Proposal #2465

PC Reviewed: 11/11/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Operationalizing frailty in the ARIC cohort

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

2. Writing Group:

Writing group members: Anna Kucharska-Newton, Priya Palta, Sheila Burgard, Michael Griswold, Jennifer Lund, Benjamin Capistrant, Karen Bandeen-Roche (awaiting comments), Beverly Gwen Windham.

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

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3. Timeline: Analyses outlined in this proposal are timely with respect to multiple ARIC projects; therefore analytical work will begin immediately following approval. We plan to

submit an abstract based on this proposal to the AHA Quality of Care and Cardiovascular Outcomes Research Conference QCOR (abstracts due Feb 4, 2015).

4. Rationale:

Frailty is a geriatric syndrome characterized as decreased reserve and resistance to stressors which causes an individual to become more vulnerable to adverse health outcomes. The most widely accepted definition of frailty was first operationalized using data from the Cardiovascular Health Study (CHS).¹ The co-occurrence of multi-system, age-associated declines is the impetus for defining frailty as a syndrome that includes unintentional weight loss, weakness, exhaustion, decreased physical activity and slowness.¹ According to analyses performed as part of CHS, a person is identified as frail if s/he exhibits three or more of five characteristics.¹ The CHS-defined frailty phenotype has been used to describe frailty in several cohorts of community-dwelling older adults.²⁻⁵ Comparing the frequency distributions of frailty states between the CHS and the Women's Health and Aging Studies (WHAS I and II), formal tests for internal construct validity showed similar distributions of frail (11.6 vs. 11.3, respectively) and pre-frail (55.2 vs. 43.8, respectively) between the two studies.² Comparable distributions were also observed in the MOBILIZE Boston Study.⁴ A systematic review of cross-sectional data from community-based cohorts suggests that approximately 10.7% of adults 65 years or older are considered frail, with an additional 41.6% described as pre-frail.²

In the absence of a gold standard, validation of the frailty phenotype through replication in cohort studies is necessary to examine the utility of this metric to accurately estimate the prevalence of frailty and to estimate its ability to predict future adverse health outcomes. In several studies based on cohorts of community-dwelling older adults, frailty has been found to be associated with a number of adverse outcomes, including, falls,^{6,7} disability,⁵ hospitalizations,⁵ cognitive impairment,⁸⁻¹⁰ and mortality.^{5,11}

Using the CHS-defined frailty phenotype, we will utilize extant Visit 5 data to estimate the prevalence of frail, pre-frail and robust frailty states within the ARIC Study cohort. To estimate the criterion validity of the frailty phenotype defined in ARIC, we will examine the associations between frailty and related adverse outcomes (e.g. falls, physical health, mental health, and all-cause mortality).

5. Main Hypothesis/Study Questions:

Specific Aims of this study are to use data obtained during the ARIC Visit 5 examination to:

1. Examine frequency of the occurrence of the five individual components that define the frailty phenotype:
 - a. Compare the prevalence estimates of frailty (frail, pre-frail, and robust) in ARIC to that available from other comparable cohorts of community-dwelling older adults (e.g. CHS, WHAS, WHI).
2. Examine internal consistency of the individual components of frailty within the final frailty construct.
3. Examine validity of the frailty construct with respect to prevalent comorbid disease status, physical and mental health status, and self-rated health (SRH) (concurrent frailty construct validity) as well as change in physical and mental health status, physical ability, the risk of falls, and mortality (predictive frailty criterion validity).

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 population: Analyses will be conducted using information obtained during ARIC Visit 5. Excluded from analyses will be study participants with missing information on all 5 component characteristics defining frailty.

Definition of frailty: The ARIC Study Coordinating Center in collaboration with members of the ARIC Physical Function working group has created a frailty variable based on the a widely accepted frailty construct, developed initially by Fried et al on the basis of data collected in the

Characteristics of frailty	Definition
Unintentional weight loss	10 percent of unintentional weight lost from V4 to V5 or BMI<18.5 at Visit 5
Low energy expenditure	Gender-specific 10 th 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 will be defined as the 20 th percentile of the distribution.
Low level of physical energy (Exhaustion)	Responded “some of the time” or “most of the time” to the following CESD questions: CES3 (<i>I felt everything I did was an effort</i>) or CES11 (<i>I could not get “going”</i>)
Low grip strength	Gender- and BMI- specific grip strength in the lowest 20% percentile of distributions

Cardiovascular Health Study.¹ Component elements of the frailty construct were ascertained at ARIC Visit 5, with the exception of weight loss which was calculated from visit 4 data (Table 1). The composite frailty variable was categorized into the following three categories: no frailty, if none of the listed component phenotypes were present; pre-frailty, if one or two of the component phenotypes were present; and robust, if three or more of the component phenotypes were present. In a sensitivity analysis and to assure consistency with existing frailty definitions, we will convert information on energy

expenditure that is currently provided as the sports activity index, to metabolic equivalents (METs) and then to kcal per week. We will define low energy expenditure as the 20th percentile of the resulting distribution. An alternate frailty construct will be created to incorporate this modified definition of energy expenditure.

Estimates of the prevalence of frailty and pre-frailty will be obtained overall and according to gender, race, and age groups (with age at Visit 5 categorized as <80 and ≥ 80 years). We hypothesize that estimates of the prevalence of frailty will be comparable between the two proposed frailty definitions.

Internal consistency: We will use the following definition of Cronbach’s alpha coefficient to examine the internal consistency of the frailty construct:

$$\alpha = N \times c / (v + (N - 1) \times c)$$

Where N is the number of frailty component characteristics (N=5), c is the average inter-item covariance, and v is the average item variance. We will examine the correlation of the individual

frailty component phenotype characteristics with the final frailty construct and will assume Cronbach's alpha >0.7 as indicative of high internal validity of the construct.

Outcomes:

Cross-sectional associations (concurrent frailty construct validity): We will examine the association of individual components of the frailty phenotype and the composite frailty and pre-frailty constructs with the Visit 5 prevalence of low and fair self-rated health, with physical and mental health status based on responses to the SF-12 questionnaire, and with Visit 5 prevalence of multiple chronic disease conditions. The latter will be defined as the presence of at least two chronic disease conditions, including heart failure, coronary heart disease, stroke, peripheral artery disease, arthritis, cancer, diabetes, and hypertension. We will use extant ARIC Visit 5 definitions of prevalent disease status to ascertain disease prevalence.

Longitudinal associations (predictive frailty criterion validity): Using Cox proportional hazard models, we will examine the association of individual components of the frailty phenotype and the composite frailty and pre-frailty constructs with the following outcomes:

- Change in physical and mental health status. The SF-12 questionnaire was administered to study participants at the time of Visit 5 and during the GNC semi-annual follow-up interview (administration period 01/2014-03/2015). In addition to examining the outlined above cross-sectional association of frailty with cohort participants' physical and mental health status, we will take advantage of the availability of repeat SF-12 measures to examine the association of frailty with change in these composite quality of life measures. The composite physical and mental health SF-12 scores exist as ARIC study derived variables.
- Risk of falls. Questions concerning falls were administered to the study participants during the GNB semi-annual follow-up interview, which was conducted from 01/2013 through 03/2014. At that time participants were asked if in the previous 6 months they had experienced a fall and if so how many falls did they have. We will examine the association of frailty with the incidence of falls.
- Physical ability: The ability of study participants to perform activities of daily living (ADL) and instrumental activities of daily living was ascertained through the physical ability questionnaire which was administered at the time of the GEN and the GNB semi-annual follow-up interviews (administration periods: 01/2012-03/2013 and 01/2013-03/2014, respectively). We will examine the association of frailty with physical ability at both time periods and as a change in physical ability occurring during the intervening year.
- Mortality: Information concerning deaths occurring among ARIC cohort participants is obtained from the Annual Follow-up interviews, death certificate data and the National Death Index. Although currently final mortality data are available only through 2012, we expect that mortality information based on the AFU and death certificate data will be available in time to perform an exploratory analysis of the association of frailty with the risk of death within one year of the Visit 5 examination.

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 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 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.csc.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)?

ARIC mp#13030 Godino J. et al. "Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study". Dr. Liz Selvin, the senior author on this proposal has been consulted and Dr. Karen Bandeen-Roche has been invited to participate in this proposal.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes 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)* 2013.10)

*ancillary studies are listed by number at <http://www.csc.unc.edu/atic/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.csc.unc.edu/atic/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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