ARIC Manuscript Proposal Form

ARIC Publication Admin Use Only

Publication Committee Review Date: **07/09/24**
ARIC Manuscript Proposal Number: **# 4489**

1.a. Full Title: Association of General and Exertional Fatigue in Stage B Pre-heart Failure with Risk of Clinical Heart Failure

b. Abbreviated Title (Length 26 characters): Fatigue in Pre-heart failure

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members:

Noelle Pavlovic, PhD, RN
Martha Abshire Saylor, PhD, RN
Cheryl R. Himmelfarb, PhD, RN
Yvonne Commodore-Mensah, PhD, RN
Christopher S. Lee, PhD, RN
Sabra C. Lewesy, MD MPH
Amil Shah, MD, PhD
Kunihiro Matsushita, MD, PhD
Chiadi E. Ndumele, MD, PhD

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

First author [please provide a middle initial; EX: Adam L Williams]:

Noelle **V.** **Pavlovic**
First name Middle initial Last name

Address: 615 N Wolfe St, Baltimore, MD 21205
Postdoctoral Fellow
Johns Hopkins Bloomberg School of Public Health

Phone: 7032299288
E-mail: npavlov3@jhu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

Name: Chiadi E. Ndumele, MD, PhD
Address: 600 N. Wolfe St, Carnegie 568
Associate Professor of Medicine
Division of Cardiology
Johns Hopkins University School of Medicine
Phone: 410-502-2319
E-mail: cndumel2@jhmi.edu

3. Timeline: Analyses will be completed by December 2024 and manuscript will be submitted for publication by August 2025.

4. Rationale:

Heart failure (HF) manifests on a continuum, with stages A-D reflecting progression from pre-clinical (stages A and B) to clinical HF (stages C and D).[1] While there is strong research and clinical attention on the treatment and associated outcomes of clinical HF (Stages C and D), there is growing emphasis on individuals with changes in cardiac structure/function who have not yet developed clinical HF, defined as pre-HF (stage B HF). Approximately 24-36% of the United States population has stage B HF.[1,2] This group is at highest risk for developing clinical HF; there is therefore need to further characterize this group to indentify individuals most at risk of disease progression and to inform novel preventative strategies.

In those with clinical HF, fatigue symptoms are common and distressing.[3,4] These fatigue symptoms present as two types, general and exertional fatigue, that are distinct [5,6] but often co-occur.[7,8] General fatigue in multiple chronic conditions, including HF, has been described as a full-body, multidimensional, persistent lack of energy that is not related to exertional activity and not usually relieved by rest.[5] Exertional fatigue is fatiguability that is related to an exertional activity, is often linked with dyspnea in HF, and is relieved by rest.[9] In clinical HF, general and exertional fatigue, particularly when co-occurring, are associated with poorer quality of life, and higher rates of HF hospitalization and mortality.[4] Although general and exertional fatigue are common symptoms in clinical HF, little is known about their prevalence and distribution in stage B HF.

Additionally, there is evidence to suggest that individuals with stage B HF, despite not having a clinical diagnosis of HF, experience quality of life-limiting functional impairment such as reduced physical function and exercise capactity.[10] However, the distribution and clinical implications of general and exertional fatigue symptoms in stage B HF overall are unknown.

Because general and exertional fatigue symptoms are associated with patient-reported and clinical outcomes in clinical HF, it is possible that early manifestations of these symptoms in

stage B HF serve as signals of disease progression and may provide prognostic information regarding risk for clinical HF. Therefore, to enhance our understanding of general and exertional fatigue in persons with stage B HF, we will conduct a cross-sectional and longitudinal analysis to determine the distribution of general and exertional fatigue categories in persons with stage B HF and to quantify the association of fatigue categories with quality of life and the development of clinical HF.

5. Main Hypothesis/Study Aims:

In those with stage B HF:

1. Determine the distribution of general and exertional fatigue categories.
2. Quantify the association of fatigue category with quality of life (cross-sectionally), and incident HF (longitudinally).

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion
b) study design
c) outcome and other variables of interest with specific reference to the time of their collection
d) summary of data analysis
e) Any anticipated methodologic limitations or challenges if present

Study design: This study will be a cross-sectional and longitudinal analysis of visit 5 participants classified as having stage B heart failure.

Inclusion/exclusion:

We will include participants at visit 5 who:

1. are classified as having stage B HF (see below),
2. who have complete data for scoring of fatigue scales (PROMIS fatigue and MRC Breathlessness Scales),
3. who self-identify as Black or White race,
4. and have complete data on key covariates.

Definition of Stage B HF:

- The definition for stage B HF that will be used in this analysis is based on the 2021 universal definition and classification of heart failure and the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[1,11]
- **No documentation of clinical HF as defined by the derived variable "prevhf52":** Exclude if:
    - Any adjudicated HF event on or prior to Visit 5 exam date.
    - Any first position ICD code of 428.X before 2005.
    - Any physician report of HF is "yes" on or prior to Visit 5 exam date.
    - Only using data collected AFTER the most current physician report of "No" to HF, or using all data if no physician report has ever been completed:

- A non-1st position ICD code of 428.x before 2005.
- An initial instance of self-reported HF or self-reported HF medications AND at least one subsequent self-report of HF or self-report of HF meds on or before Visit 5 exam date, but after the first self-report date.
- An initial instance of self-reported HF OR self-reported HF meds reported on or before Visit 5 exam date AND elevated NT-proBNP >125 from Visit 4 or Visit 5.

- **AND evidence of 1 of the following:**
  - **Structural heart disease**
    - Reduced left ventricular or right ventricular systolic function (left ventricular ejection fraction <50%; global longitudinal strain <16%).
    - Ventricular hypertrophy (left ventricular wall thickness ≥ 12 mm; left ventricular mass index > 116 g/m2 for males and > 95 g/m2 for females; left atrial volume index ≥ 29 ml/m2).
    - Wall motion abnormality (staff report).
    - Moderate or greater valvular heart disease (aortic stenosis, aortic regurgitation or insufficiency, mitral stenosis, mitral regurgitation).
  - **Evidence for increased filling pressures**
    - Average E/e` ≥ 15 by noninvasive imagining study (e.g., doppler echo).
  - **Risk factors and elevated BNP/Troponin in the absence of competing diagnoses resulting in such biomarker elevations** (ie. acute coronary syndrome, chronic kidney disease, pulmonary embolis, or myopericarditis).
    - Increased level of NT-proBNP ≥ 125 pg/mL.
    - Persistently elevated cardiac troponin ≥ 22 for males and ≥ 14 for females.

Exposure: The exposure will be fatigue category, as determined through general and exertional fatigue scale score and cross categorization.

General fatigue:
We used the Patient-Reported outcomes Measurement Information System (PROMIS)[12] fatigue scale items measured in ARIC at the first semi-annual follow-up call post visit 5 (2012-2014) to operationalize general fatigue. The PROMIS fatigue item bank is psychometrically validated in diverse populations to measure general fatigue.[13,14] The ARIC study collected data on 5 items from the PROMIS fatigue item bank asking: In the past 7 days 1) how often did you feel tired? 2) how often did you experience extreme exhaustion? 3) how often did you run out of energy? 4) how often were you too tired to think clearly? and 5) how often were you too tired to take a bath or shower? The de-identified responses to these items in our sample will be uploaded to the HealthMeasures automated scoring tool developed by the PROMIS development team. With 5 items, each with 5 response selections (never, rarely, sometimes, often, always), the summative score would range from 0-25 with higher score indicating higher fatigue. These scores are then standardized to a standard general population mean of 50 with a standard deviation of 10 units as recommended by HealthMeasures for comparability and interpretation. [15,16]

Exertional Fatigue

We used the modified Medical Research Council (MRC) breathlessness scale measured at visit 5 (2011-2013) to operationalize exertional fatigue in this analysis. This scale is validated for the measurement of dyspnea on exertion. [17,18,19] Patient reported dyspnea on exertion is the closest construct to exertional fatigue that is measured in ARIC. Subjective perception of exertion and dyspnea (eg. Borg perceived exertion scales) are closely interrelated and used together in cardiopulmonary exercise testing to evaluate perceived exertion level and to identify fatigue limitations with exertion.[20,21] Therefore, in this analysis, we have used exertional dyspnea as a reflection of exertional fatigue. The Modified MRC Breathlessness scale includes 5 items asking 1) are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? 2) do you have to walk slower than people of your age on the level because of breathlessness? 3) do you ever have to stop for breath with walking at your own pace on the level? 4) Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level? 5) are you too breathless to leave the house or breathless on dressing or undressing? Participant responses to each of these items are dichotomous (yes/no). Score on the MRC breathlessness scale ranges from 0-4 with increasing score indicating increasing breathlessness (fatigue) with exertion.

We will examine general and exertional fatigue scale score categories individually based on the following thresholds previously identified in the literature . [15,22 23]

- General Fatigue (PROMIS Fatigue Scale) Score Cutoffs:
    - No general fatigue (score < 42.5)
    - Mild general fatigue (score ≥ 42.5 and < 52.5)
    - Moderate general fatigue (score ≥ 52.5 and < 62.5)
    - Severe general fatigue (score ≥ 62.5)
- Exertional Fatigue (MRC Breathlessness Scale Score Cutoffs:
    - No exertional fatigue (score = 0)
    - Mild exertional fatigue (score = 1)
    - Moderate exertional fatigue (score = 2 or 3)
    - Severe exertional fatigue (score = 4)

To examine the co-occurrence of general and exertional fatigue, we will also generate general and exertional fatigue cross-categories, using the thresholds for moderate to severe fatigue described above (see thresholds above and table below). Interpretive guides (T-score maps) and T-score cutoffs have been previously identified for the PROMIS fatigue (general fatigue) scale.[15,22] None to mild general fatigue is defined as a T-score <52.5, moderate to severe general fatigue ≥52.5. Score cutoffs for exertional fatigue using the MRC Breathlessness Scale have been identified previously. [23] A score of 0-1 indicates none to mild exertional fatigue, and 2 or above indicates moderate to severe exertional fatigue.

		General Fatigue (PROMIS Fatigue Scale)	
		None/Mild (score <52.5)	**Moderate/Severe** (score ≥ 52.5)
Exertional Fatigue (MRC Breathlessness Scale)	**None/mild** (score <2)	Low/No Fatigue	High General Fatigue
	Moderate/Severe (score ≥ 2)	High Exertional Fatigue	High General & High Exertional Fatigue

Outcomes:

- **Cross-sectional analysis:**
  - Primary outcome: Quality of life. Quality of life will be measured using the SF-12 scale which has a score range of 0-100, with higher score indicating better quality of life, and has been validated to measure health-related quality of life in several different populations.[24–26] The SF-12 scale can be divided into two summary component scales: physical quality of life and mental quality of life. We will determine the association of general and exertional fatigue with both summary component scales separately.
- **Longitudinal analyses:**
  - Primary outcome: incident heart failure collected through 2020 (or the most recent follow-up available). [27,28]

Covariates: age, race, education level, sex, smoking status, drinking status, BMI, hypertension medications, systolic blood pressure, diabetes, coronary heart disease, atrial fibrillation, depressive symptoms, estimated glomerular filtration rate (determined using serum creatinine and cystatin C), triglycerides, and total cholesterol.

Summary of Data Analysis:

- We will describe sociodemographic and clinical characteristics. For continuous variables, data will be described using means and standard deviations or medians and IQR depending upon data distributions. Categorical or dichotomous variables will be described with percentages and frequency counts. Data will be evaluated for data distributions, skewedness, and missing data. To compare characteristics across fatigue score categories, as well as cross-categories, we will use univariate chi-square test for frequency/percentages, and ANOVA for continuous variables. Alpha will be set at 0.05 and all inference tests will be two-sided.
- **Cross-sectional analyses:**
  - We will perform multivariable linear regression to determine the cross-sectional relationship of individual general and exertional fatigue scale categories (see score cutoffs described above) with physical and mental quality of life score, adjusting for covariates (see adjustment models below).
  - We will also perform multivariable linear regression to determine the cross-sectional relationship of general and exertional fatigue cross-categories (see cross-categorization method above) with physical and mental quality of life score, adjusting for covariates (see adjustment models below).

- **Prospective analyses:**
    - We will describe incidence rates of HF overall and across fatigue categories.
    - Association of general fatigue scale score categories and exertional fatigue scale score categories (each assessed individually) with risk of incident HF:
        - Cox proportional hazards regression, adjusting for covariates (see adjustment models below).
    - Association of general and exertional fatigue cross-categories with risk of incident HF:
        - Cox proportional hazards regression adjusting for covariates (see adjustement models below).
- **Adjustment models:**
    - Model 1: age, race, education level, sex, smoking status, drinking status
    - Model 2: Model 1 + BMI, anti-hypertensive medications, systolic blood pressure, diabetes, coronary heart disease, atrial fibrillation, depressive symptoms, estimated glomerular filtration rate (determined using serum creatinine and cystatin C), triglycerides, and total cholesterol.
        - For associations of general and exertional fatigue with mental quality of life, we will peform regression analyses with and without adjustment for depressive symptoms.

- **Sensitivity Analyses:**
    - Stratifying analyses on sex, race, and physical activity level.
    - We will conduct analyses again removing individuals who had an incident HF ≤ 1 year, and ≤ 3 years, after visit 5, to rule out the possibility of early undiagnosed HF explaining any observed associations.
    - We will conduct analyses using a more liberal exclusion criteria for prevalent heart failure (derived variable “prevdefposshf1”) which would exclude more individuals due to a possible diagnosis of prevalent HF at V5. This definition includes the following criteria:
        - Prior hospitalization (01/01/2005 onward but before V5 visit) classified as Definite (A), Probable (B), or Chronic (C) HF.
        - Physician Heart Failure Survey with HF onset date prior to V5 (from those with self-reported HF) in which the physician answers YES to "has this patient ever had HF or CM?".
        - Hospitalization with an ICD code 428.x in first position (before 01/01/2005).
        - Hospitalization with an ICD code 428.x in any position other than the first position (any time before 01/01/2005).
        - Self-report of HF at AFU prior to V5 or at visits 3-4, not refuted by the physicians health survey (temporal association will need to be considered).
        - Self-report of treatment for HF from any study visit or AFU prior to V5.
- **Secondary Analyses**:
    - We will perform an exploratory secondary analysis using CMS data linked to ARIC to additionally exclude individuals with outpatient diagnoses of clinical HF from this analysis.

- We will compare the distribution of general and exertional fatigue scores individually, as well as of fatigue cross-categories, between individuals in stage B and stage A HF (HF risk factors without subclinical HF).
- We will assess whether general and exertional fatigue correlate with specific echocardiographic measures in those with stage B HF.

f) Will the author need Limited data to complete the proposed manuscript? ☒ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☐ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

There is the possibility that we would be including individuals classified as stage B HF in ARIC who actually have clinical HF but were diagnosed in the outpatient setting, which is not captured in the ARIC de-identified dataset. Therefore, we will need access to CMS data to confirm whether participants had an outpatient clinical HF diagnosis to more accurately classify participants as having stage B HF.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?

Manuscript proposal #1276: Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study

Manuscript proposal #4032: Association of circulating biomarkers with fatigue, depressive symptoms, and physical function in persons with AF in the ARIC study

Manuscript proposal #3854: Fatigue in Heart Failure: Predictors and Outcomes

Manuscript proposal #537: The relationship of excess fatigue to incident myocardial infarction

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ Yes ☒ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☐ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* __

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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.

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References:

1. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. 2021;27(4):387-413. doi:10.1016/j.cardfail.2021.01.022
2. Bozkurt B, Ahmad T, Alexander KM, et al. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. *California Journal of Cardiac Failure*. 2023;19(10):1412-1451. doi:10.1016/j.cardfail.2023.07.006
3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics - 2023 Update: A Report from the American Heart Association. *Circulation*. 2023;147(8):E93-E621. doi:10.1161/CIR.0000000000001123
4. Pavlovic N V, Gilotra NA, Lee CS, et al. Fatigue in Persons with Heart Failure: A Systematic Literature Review and Meta-Synthesis Using the Biopsychosocial Model of Health. *J Card Fail*. 2022;28(2):283-315. doi:10.1016/j.cardfail.2021.07.005
5. Tiesinga LJ, Dassen TWN, Halfens RJG. DUFS and DEFS: development, reliability and validity of the Dutch Fatigue Scale and the Dutch Exertion Fatigue Scale. *Int J Nurs Stud*. 1998;35:115-123. doi:https://doi.org/10.1016/S0020-7489(98)00005-4
6. Smith ORF, Michielsen HJ, Pelle AJ, Schiffer AA, Winter JB, Denollet J. Symptoms of fatigue in chronic heart failure patients: Clinical and psychological predictors. *Eur J Heart Fail*. 2007;9(9):922-927. doi:10.1016/j.ejheart.2007.05.016
7. Lee KS, Song EK, Lennie TA, et al. Symptom clusters in men and women with heart failure and their impact on cardiac event-free survival. *Journal of Cardiovascular Nursing*. 2010;25(4):263-272. doi:10.1097/JCN.0b013e3181cfbb88
8. Pavlovic N, Ndumele CE, Abshire Saylor M, et al. Identification of fatigue subtypes and their correlates in prevalent heart failure: A secondary analysis of the Atherosclerosis Risk in Communities Study. *Circ Cardiovasc Qual Outcomes*. 2024;In press. doi:https://doi.org/10.1161/CIRCOUTCOMES.123.010115
9. Kitzman DW, Groban L. Exercise Intolerance. *Cardiol Clin*. 2011;29(3):461-477. doi:10.1016/j.ccl.2011.06.002
10. Sacre JW, Wong C, Chan YK, Carrington MJ, Stewart S, Kingwell BA. Left Ventricular Dysfunction and Exercise Capacity Trajectory: Implications for Subclinical Heart Failure Staging Criteria. *JACC Cardiovasc Imaging*. 2019;12(5):798-806. doi:10.1016/J.JCMG.2017.10.023
11. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421. doi:10.1016/J.JACC.2021.12.012
12. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap Cooperative Group During its First Two Years. *Med Care*. 2007;45(5):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55
13. Cella D, Lai JS, Jensen SE, et al. Clinical Validity of the PROMIS Fatigue item Bank across Diverse Clinical Samples. *J Clin Epidemiol*. 2017;73:128-134. doi:10.1016/j.jclinepi.2015.08.037
14. Cella D, Riley W, Stone A, et al. Initial adult health item banks and first wave testing of the Patient–Reported Outcomes Measurement Information System (PROMIS) network: 2005–2008. *J Clin Epidemiol*. 2010;63(11):1179-1194. doi:10.1016/j.jclinepi.2010.04.011
15. Rothrock NE, Amtmann D, Cook KF. Development and validation of an interpretive guide for PROMIS scores. *J Patient Rep Outcomes*. 2020;4(16):1-7. doi:10.1186/s41687-020-0181-7
16. HealthMeasures. PROMIS Scoring Manuals. Published September 8, 2023. Accessed December 4, 2023. https://www.healthmeasures.net/index.php?option=com_content&view=article&id=180&Itemid=994
17. Sandberg J, Johnson MJ, Currow DC, Ekström M. Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness. *J Pain Symptom Manage*. 2018;56(3):430-435.e2. doi:10.1016/j.jpainsymman.2018.05.002
18. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93(3):580-586. doi:10.1378/chest.93.3.580

19. Cazzola M, Hanania NA, Macnee W, Rüdell K, Hackford C, Tamimi N. A review of the most common patient-reported outcomes in COPD – revisiting current knowledge and estimating future challenges. *International Journal of COPD*. 2015;10:725-738. doi:10.2147/COPD.S77368
20. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104(14):1694-1740. doi:10.1161/HC3901.095960
21. Del Buono MG, Arena R, Borlaug BA, et al. Exercise intolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 2019;73(17):2209-2225. doi:https://doi.org/10.1016/j.jacc.2019.01.072
22. Bingham Iii CO, Butanis AL, Orbai AM, et al. Patients and clinicians define symptom levels and meaningful change for PROMIS pain interference and fatigue in RA using bookmarking. *Rheumatology*. 2021;60:4306-4314. doi:10.1093/rheumatology/keab014
23. Ramalho SHR, Santos M, Claggett B, et al. Association of Undifferentiated Dyspnea in Late Life With Cardiovascular and Noncardiovascular Dysfunction: A Cross-sectional Analysis From the ARIC Study. *JAMA Netw Open*. 2019;2(6):e195321. doi:10.1001/jamanetworkopen.2019.5321
24. Gandek B, Sinclair SJ, Kosinski M, Ware JE. Psychometric evaluation of the SF-36® health survey in medicare managed care. *Health Care Financ Rev*. 2004;25(4):5-25.
25. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. *J Clin Epidemiol*. 1998;51(11):1171-1178. doi:10.1016/S0895-4356(98)00109-7
26. Clement ND, Weir D, Holland J, Gerrand C, Deehan DJ. Meaningful changes in the Short Form 12 physical and mental summary scores after total knee arthroplasty. *Knee*. 2019;26:861-868. doi:10.1016/j.knee.2019.04.018
27. Rosamond WD, Chang PP, Baggett C, et al. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study a comparison of diagnostic criteria. *Circ Heart Fail*. 2012;5(2):152-159. doi:10.1161/CIRCHEARTFAILURE.111.963199
28. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: Design and Objectives. *Am J Epidemiol*. 1989;129(4):687-702. doi:https://doi.org/10.1093/oxfordjournals.aje.a115184

To view publications materials, click "Log in" at the top right of the ARIC website. Click "Forgot Password" if you are experiencing issues with logging in.