

ARIC Manuscript Proposal #2548

PC Reviewed: 5/12/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Changes in Physical Activity and the Risk of Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Changes in Activity and HF

2. Writing Group: Roberta Florido; Mariana Lazo; Vijay Nambi; Haitham Ahmed; Gary Gerstenblith; Roger S. Blumenthal; Christie M. Ballantyne; Elizabeth Selvin; Aaron Folsom; Josef Coresh; Chiadi E. Ndumele; others welcome

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

First author: Roberta Florido, MD
Address: Post-Doctoral Fellow, Division of Cardiology
Johns Hopkins University School of Medicine
1800 Orleans Street
Zayed 7215
Baltimore, MD 21287

Phone: 410-955-7376 **Fax:** 410-614-9190
E-mail: rflorid1@jhmi.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).

Name: Chiadi Ndumele, MD, MHS
Address: Assistant Professor of Medicine
Johns Hopkins University
2024 E. Monument Street, Suite 2-600
Baltimore MD 21287

Phone: 410-502-2319 **Fax:** 410-614-8222
E-mail: cndumel2@jhmi.edu

3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. Rationale:

Physical activity is a key component of strategies to reduce cardiovascular risk. In addition to having beneficial effects on several cardiovascular risk factors, physical activity has been associated with a lower risk of cardiovascular events [1, 2], including heart failure (HF) [3-5]. A graded inverse relationship has been observed between physical activity and incident heart failure, with individuals with the highest levels of leisure time physical activity having the lowest risk of heart failure [3, 4]. Importantly, the protective association between physical activity and incident HF persists even after accounting for traditional risk factors, suggesting potential independent effects of exercise on myocardial dysfunction and HF risk.

Given the lower likelihood of HF associated with higher physical activity levels, changes in physical activity over time may also have implications for HF risk. Increases in physical activity over time have previously been associated with lower risks of mortality and CHD [6-8]. However, there are sparse data regarding the relationship between changes in physical activity and incident HF, and even more limited data within demographically diverse populations. If changes in physical activity over time have a significant relationship with the risk of developing HF, this finding could have important clinical implications for HF prevention strategies.

Given the prospective nature of its design, the bi-racial Atherosclerosis Risk in Communities (ARIC) study represents an excellent opportunity for gaining further insight into the association between physical activity changes and heart failure incidence. In this ARIC analysis, we aim to evaluate the relationship between changes in physical activity levels from ARIC Visit 1 to Visit 3 and the subsequent risk of heart failure, and to assess whether this relationship differs across age, race and gender subgroups.

5. Main Hypothesis/Study Questions:

Aims:

- 1) To evaluate the association between changes in physical activity over a 6 year period and incident heart failure
- 2) To determine whether the association of changes in physical activity over 6 years with incident heart failure differs across age, race and gender subgroups.

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 evaluate the prospective association between changes in physical activity from ARIC Visit 1 to Visit 3, and incident heart failure occurring after Visit 3.

We will additionally compare this association across age, race and gender subgroups to assess whether there are demographic differences in this relationship.

Exposures: The primary exposure will be 6-year change in physical activity level. Physical activity levels were measured using a modified Baecke physical activity questionnaire at Visits 1 and 3. As has been done in prior ARIC analyses, we will convert the Baecke sports indices into “minutes per week” of moderate or vigorous exercise. Moderate and vigorous exercise will be defined according to the metabolic equivalent of task (MET) based on the Compendium of Physical Activities. We will then categorize physical activity according to the AHA guidelines as “recommended” (≥ 150 min/wk of moderate intensity or ≥ 75 min/wk of vigorous intensity or ≥ 150 min/wk of moderate + vigorous intensity), “intermediate” (1–149 min/wk of moderate intensity or 1–74 min/wk of vigorous intensity or 1–149 min/wk moderate + vigorous intensity), or “poor” (0 min/wk of moderate or vigorous exercise). We will perform cross tabulations of these physical activity categories at the 2 visits. We will also model physical activity as a continuous variable (MET*min/week) and assess absolute changes in physical activity over time.

Outcomes: The primary outcome will be incident HF, defined as the first hospitalization or death related to HF as identified by ICD codes, occurring after Visit 3 until 1/1/13 (or most recent follow-up available).

Exclusions: We will include Visit 3 participants with data on physical activity from Visits 1 and 3 and available data on other covariates of interest at Visit 3. We will exclude the small number of participants at baseline who are not black or white. We will exclude participants with known CVD prior to Visit 3 (self-reported CVD, adjudicated CHD events, or HF events, at or prior to Visit 3).

Covariates: Age, sex, race, education, smoking status, alcohol use, BMI, systolic blood pressure, use of anti-hypertensive medications, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR (all measured at Visit 3). We will additionally assess the changes in a subset of covariates from Visit 1 to Visit 3, including BMI, systolic blood pressure, fasting glucose and LDL cholesterol.

Main Analyses: We will use Cox regression analyses to examine the association between categories of change or stability in physical activity from Visit 1 to Visit 3 and the risk of HF occurring after Visit 3.

- 1) We will perform univariate comparisons of individuals across physical activity categories at Visit 3 according to AHA guidelines, as described above (poor, intermediate, recommended).
- 2) We will use the physical activity categories to create 9 different groups according to their categories of physical activity at Visit 1 and Visit 3: Poor activity (at V1) to Poor activity (at Visit 3); Poor to Intermediate; Poor to Recommended, Intermediate to Poor, Intermediate to Intermediate, Intermediate to

- Recommended, Recommended to Poor, Recommended to Intermediate and Recommended to Recommended.
- 3) We will evaluate the changes in BMI, systolic blood pressure, blood glucose and LDL cholesterol within each of the 9 groups categorized by physical activity levels at V1 and V3.
 - 4) Using those with poor activity at Visit 1 and Visit 3 as the reference group, we will use Cox regression analyses to estimate the hazard ratios of incident HF and associated 95% confidence intervals associated with each category of physical activity at Visit 1 and Visit 3. We will adjust for covariates (all measured at Visit 3) as follows:
 - a. Model 1: age
 - b. Model 2: age + sex, race, education, smoking status and alcohol intake
 - c. Model 3: Adjusted for all variables in Model 2 + systolic blood pressure, anti-hypertension medication use, diabetes, LDL-, and HDL-cholesterol, triglycerides and estimated GFR.
 - 5) We will evaluate physical activity change from Visit 1 to Visit 3 as a continuous variable (MET*min/week), using 1-SD change in physical activity, quartiles of physical activity change and spline models (with physical activity change modeled continuously) to estimate the continuous association between PA change and incident HF after V3, using Cox regression models. We will perform this analysis in the overall population and in analyses stratified by categories of baseline physical at V1 (poor, intermediate and recommended).
 - 6) We will repeat the above analyses in subgroups stratified by age (> or <= 60 years), race and gender, and we will test for any significant interactions across these demographic subgroups.
 - 7) As an additional approach to evaluating the importance of changes in physical activity over time, we will assess the relationship between physical activity at Visit 1 and incident HF after Visit 3 using regression models that also include physical activity at Visit 3 as a covariate.

Sensitivity Analyses:

- 1) We will assess the relationship between changes in physical activity from V1 to V3 and incident HF after additionally accounting for changes in BMI from V1 to V3 (modeled as both absolute change in BMI and as change in BMI category from V1 to V3).
- 2) We will also control for incident CHD as a time-varying covariate to assess the extent to which ischemic events explain the association of changes in physical activity with incident HF.
- 3) To address reverse causality, we will perform sensitivity analyses excluding HF events occurring in the first year of follow-up.
- 4) We will perform sensitivity analyses excluding individuals with severe pulmonary disease, defined as an FEV1 <30% of predicted, or peripheral arterial disease, defined as an ABI <0.9 or >1.4, as measured at Visit 1.

Limitations:

- There are limitations of the physical activity assessment, with the likelihood of some bias and measurement error in the self-reporting of physical activity levels.
- We may not be able to fully account for other lifestyle changes beyond changes in physical activity that may be related to the risk of incident HF
- Residual confounding
- Lack of adjudication for all heart failure events
- Lack of information on reasons for changes in activity levels

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.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)?

Manuscript #2441: Obesity, Physical Activity and Myocardial Injury: The Atherosclerosis Risk in Communities (ARIC) Study

Manuscript #2029: Obesity, physical activity and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

Manuscript #511 Physical activity and arterial stiffness

Manuscript #321: Physical Activity Patterns and the Risk of Stroke and All-Cause Mortality

Manuscript #1715: Physical activity and incidence of cardiovascular disease in African Americans

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)* _____)

*ancillary studies are listed by number at <http://www.csc.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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- [2] Sattelmair J, Pertman J, Ding EL *et al.* Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; 124:789-795.
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- [4] Young DR, Reynolds K, Sidell M *et al.* Effects of physical activity and sedentary time on the risk of heart failure. *Circulation. Heart failure* 2014; 7:21-27.
- [5] Wang Y, Tuomilehto J, Jousilahti P *et al.* Occupational, commuting, and leisure-time physical activity in relation to heart failure among finnish men and women. *Journal of the American College of Cardiology* 2010; 56:1140-1148.
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- [7] Gregg EW, Cauley JA, Stone K *et al.* Relationship of changes in physical activity and mortality among older women. *JAMA : the journal of the American Medical Association* 2003; 289:2379-2386.
- [8] Lee DC, Sui X, Artero EG *et al.* Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation* 2011; 124:2483-2490.