ARIC Manuscript Proposal # 3364

PC Reviewed: 3/12/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Physical Activity and Incident Heart Failure Among High-Risk Subgroups

b. Abbreviated Title (Length 26 characters):

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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].**

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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:

Heart failure (HF) is highly and increasingly prevalent [1] [2, 3]. Although HF survival has improved over the last decades, long term prognosis remains poor with high rates of hospitalization and 50% mortality in 5 years [3]. Given the high rates of adverse outcomes associated with HF, there is increasing emphasis on refining strategies for HF prevention, especially among "at-risk" individuals. For this purpose, the AHA/ACC guidelines have incorporated a staging system highlighting high-risk populations, classified as Stage A HF. In the most recent version of this document, Stage A HF included individuals with hypertension, atherosclerotic disease, diabetes, obesity or metabolic syndrome.

Current guidelines broadly recommend adherence to a heart healthy lifestyle, including engaging in recommended levels of physical activity as part of strategies to ideally prevent these HF in these high-risk subgroups. Observational studies have consistently shown a dose dependent inverse association between physical activity and incident HF. In a recent systematic review of prospective cohort studies looking into the association of physical activity or fitness levels and incident HF, each unit increase in MET was associated with 21% lower risk of HF [4]. However, complex and distinct mechanisms underlie the HF risk associations for each of these subgroups. Therefore, it is unclear if the same preventive strategies will be uniformly protective across these high-risk groups.

In addition to favorable effects on traditional risk factors, physical activity may improve insulin resistance, inflammation, subclinical myocardial damage and adverse, concentric ventricular remodeling that underlie the associations between HF and cardiometabolic conditions such as obesity, diabetes, and metabolic syndrome [6,7]. On the other hand, coronary heart disease may lead to HF via distinct mechanisms that involve myocyte death and replacement fibrosis that may not be reversible through increased physical activity.

In this analysis of the Atherosclerosis Risk in Communities (ARIC) study, we sought to evaluate the associations of physical activity with incident HF among subgroups considered at high risk for incident HF in the current ACCF/AHA guidelines. We hypothesized that physical activity would be less strongly associated with reduced HF risk among individuals with prevalent self-reported ASCVD than in other high-risk subgroups.

5. Main Hypothesis/Study Questions:

Aims:

1) To evaluate the association of each high-risk subgroup as defined by ACC/AHA guidelines with incident HF

2) To evaluate the association of higher levels of physical activity with incident heart failure among the various high-risk groups

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 of physical activity with incident HF among the various high-risk subgroups.

Exposures: Physical activity level, measured through a modified Baecke physical activity questionnaire at Visit 1 will be evaluated as an exposure (relationship with HF). As has been done for 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 also model physical activity as a continuous variable in METS*min/week and use this continuous variable to generate quartiles of physical activity. We will additionally use physical activity assessed at Visit 3 (6 years after baseline) averaged with activity from Visit 1 and categorize as quintiles of average physical activity.

High-risk subgroups will be defined according to ACC/AHA guidelines as persons with hypertension, obesity, diabetes mellitus, metabolic syndrome, and prevalent ASCVD at baseline (Visit 1). We will conduct additional analyses considering CHD only, rather than ASCVD, as the high-risk group of interest.

Outcomes: The primary outcome of these prospective analyses will be incident HF, defined as hospitalization or death related to HF as identified by ICD codes occurring after baseline (ARIC Visit 1), until 12/31/16 (or the most recent follow-up available).

Exclusions: We will include Visit 1 participants with data on physical activity and on other covariates of interest. We will exclude the small number of participants at baseline who are not black or white. We will exclude participants with known CVD or HF prior to Visit 1.

Covariates: Age, sex, race-center, smoking status, alcohol use, BMI, systolic blood pressure, use of anti-hypertensive medications, diabetes, LDL-, and HDL-cholesterol, and triglycerides.

Main Analyses:

1. We will perform univariate comparisons of baseline characteristics across physical activity categories at Visit 1 (poor, intermediate, recommended).
2. We will use adjusted Cox regression to assess the association of each high-risk subgroup with incident HF after baseline (Visit 1).
3. We will construct Poisson models to estimate the incidence rates of HF (at mean levels of age, sex, race, smoking status and alcohol intake) according to physical activity category, overall and among each high-risk subgroup. We will also calculate p for trend across physical activity categories.
4. Using those with poor activity at Visit 1 as the reference group, we will use Cox regression to assess whether higher categories of physical activity would be associated with higher risk of HF in the overall population and among each high-risk subgroup. We will test for interaction between physical activity and each high-risk subgroup on the outcome of incident HF. We will perform stepwise regression to adjust for the covariates of interest as follows:
    a. Model 1: Adjusted for age
    b. Model 2: Adjusted for Model 1 + sex, race-center, smoking status and alcohol intake at Visit 1
    c. Model 3: Adjusted for Model 2 + systolic blood pressure, anti-hypertension medication use, diabetes, LDL-, and HDL-cholesterol, and triglycerides
5. We will repeat the above analyses in subgroups stratified by demographics (age: > or <= 60 years, race and gender)

Secondary and Sensitivity Analyses:

1. We will repeat the analyses above defining those with CHD (rather than the broader population with ASCVD) at Visit 1 as a high-risk subgroup.
2. We will construct Cox regression models to assess the association between higher categories of physical activity and the risk of incident CHD. Then, modeling incident CHD as a time-varying covariate to account for incident ischemic events preceding the development of HF, we will perform Cox regression analyses assessing the association of physical activity with HF risk with time-varying CHD included in the model. We will also test for an interaction between physical activity and incident CHD on the outcome of HF.
3. In further sensitivity analyses, we will use Visit 3 as a new baseline and evaluate the association of higher quintiles of average physical activity (average of Visits 1 and 3) with incident HF among persons with and without CHD at Visit 3. The definition of prevalent CHD at Visit 3 will include the presence of prevalent CHD at Visit 1 and adjudicated CHD cases (fatal and non-fatal MI, silent MI or coronary revascularization procedure) from Visit 1 through Visit 3.

Limitations:

- There is the likelihood for some residual confounding in our efforts to assess the "independent" association between physical activity and incident HF.
- There is the likelihood for some bias in the self-reporting of physical activity levels.

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___ _____ 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

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