

ARIC Manuscript Proposal #2631

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Priority: _____

1.a. Full Title: Physical activity, family history of premature coronary heart disease (CHD), and incident CHD in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): PA, FHx, and CHD

2. Writing Group:

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*(*A note about the multiple Hopkins authors: Erin Michos designed the concept and will guide project as senior author. Roberta Florida, a post-doctoral fellow trainee, wrote the proposal and will take the lead as first author in writing up abstract and manuscript. Di Zhao is the analyst. Eliseo Guallar is Di's mentor and will oversee the statistical analyses. Chiadi Ndumele has experience with using the physical activity data in ARIC and provided critical feedback on proposal. Bill McEvoy has published on impact of family history (including interaction of FH with coronary artery calcium in MESA) and will be working with us on a similar concept in MESA).*

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 an abstract for the AHA Epi meeting (submission deadline is October 2015) with full manuscript by 2016.

4. Rationale:

Family history (FHx) of coronary heart disease (CHD) is a well-established risk factor for incident atherosclerotic cardiovascular disease (ASCVD) [1, 2]. Individuals with a first-degree relative with a history of CHD are at significantly elevated risk of ASCVD events, which include myocardial infarction and stroke, even after accounting for traditional risk factors [1-4]. FHx of premature CHD confers a greater risk than having any FHx of CHD. FHx of premature CHD is typically defined as CHD occurring in a 1st degree relative, in males before the age of 55, and in females before the age of 65.

Family history assessment is a key component of risk assessment as studies have demonstrated clustering of genetic as well as behavioral risk factors [2, 5]. Prior epidemiologic data suggests a small number of families account for many of the premature CV events, therefore these families need to be identified and targeted for aggressive preventive measures (such as promotion of physical activity) [5-7]. Furthermore, it appears that certain interventions may be more effective in those with a positive FHx of CHD. For example, smoking cessation is projected to decrease CHD to a greater extent in men with FHx as compared to those without it [8].

Physical activity (PA) is a key component of preventive strategies to reduce cardiovascular disease and endorsed by all major guidelines and societies [9]. Higher levels of PA are associated with improvement in all forms of cardiovascular disease, including CHD, heart failure, cardiovascular risk factors, and mortality [10-15]. The impact of higher levels of PA among those specifically with a FHx of premature CHD is unknown. Although clustering of behavioral cardiovascular risk factors has been noted in many studies, data has been conflicting regarding levels of PA performed by those without compared to those with a FHx of CHD, with some studies suggesting higher levels of PA in the latter higher risk group [16].

In this analysis of the Atherosclerosis Risk in Communities (ARIC) Study, we will evaluate whether PA modifies the relationship of FHx of premature CHD and incident CHD. We hypothesize that individuals with a FHx of premature CHD with high PA levels will have lower rates of CHD events compared to those with low PA levels. We will determine whether PA confers a greater benefit in CHD reduction among those with a FHx compared to those without a FHx of premature CHD. We will also examine these association among individuals with any FHx of CHD (regardless of premature or not). We will also investigate whether a known FHx of CHD is associated with higher levels of PA at baseline compared to those without a FHx, as public health strategies have emphasized the importance of lifestyle modifications for primary prevention of CHD. In other words, persons with FHx may be more likely to adopt healthy lifestyle due to knowledge of their baseline risk.

5. Main Hypothesis/Study Questions:

a. Aims:

- 1) To evaluate whether higher levels of PA are associated with lower risk of CHD events among individuals with a FHx of premature CHD compared to lower levels of PA.

- 2) To evaluate whether PA is more beneficial in reducing CHD risk among those with a FHx of premature CHD relative to those without a FHx of CHD.
- 3) We will assess whether baseline levels of PA in individuals with a FHx of premature CHD differ from the levels performed by individuals without the same FHx. [If those with a FHx of premature CHD are found to have lower levels of PA, this could be a subgroup that needs increased efforts at targeted intervention to promote activity].
- 4) We will evaluate whether the above associations differ across race, gender and age (\geq or $<$ 60 years) subgroups.
- 5) We will also perform the same analyses using FHx of any CHD (regardless of premature or not).

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).

- b. **Study Design:** We will evaluate the distribution of PA and the prospective association of PA with CHD events among individuals with and without a FHx of premature CHD. We will assess these relationships using PA and FHx data obtained at Visit 1, and incident CHD events occurring after Visit 1.
- c. **Exposures:** The primary exposures will be PA assessed through a modified Baecke questionnaire and FH of premature CHD.
 - 1) **Physical Activity:** 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 tasks (MET) based on the Compendium of Physical Activities. We will then categorize PA 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 calculate overall PA in MET*min/week and categorize PA into quartiles. We will construct restricted cubic spline models to evaluate the continuous association of PA and incident CHD. As little is known about change in lifestyle behavior over time in those with and without a FHx, in a secondary analyses, we will assess the changes in PA from V1 to V3.
 - 2) **Family History of premature CHD:** Interviewer-administered standardized questionnaires were used to determine whether either parent or up to 5 full siblings had a history of heart attack. The age at the first onset of heart attack was also recorded. FHx of premature CHD will be defined as CHD occurring in a 1st degree relative, in males before the age of 55, and in females before the age of 65. In a supplemental analysis, we will also consider any FHx of CHD, regardless of premature or not.
- d. **Outcomes:** The primary outcome will be incident CHD defined as definite or probable myocardial infarction, or definite coronary death occurring after Visit 1 through December 31st 2012, or the most recent follow-up available. As a secondary outcome, we will consider total ASCVD (CHD plus stroke).
- e. **Inclusions/Exclusions:** We will include Visit 1 participants without missing data on FHx of CHD and PA, as well as other covariates of interest. We will exclude the small number of

participants at baseline who were not black or white, as well as the blacks from the MN and MD sites. We will exclude participants with known CHD ascertained at Visit 1.

- f. **Covariates:** Covariates will be from the baseline (visit 1) exam and include: age, sex, race, education, smoking status, alcohol use, BMI, systolic blood pressure, use of anti-hypertensive medications, diabetes, total and HDL-cholesterol, use of lipid lowering medications, and estimated GFR.
- g. **Main analyses:**
- 1) Baseline characteristics of the study population will be described using means, medians, and proportions by FHx of premature CHD (yes/no).
 - 2) We will assess and compare average PA levels and the distribution of the PA categories (poor, intermediate and recommended) among those with and without a FHx of premature CHD.
 - 3) To determine whether the presence of FHx of premature CHD is independently associated with higher PA levels, we will use multivariable-adjusted regression models to evaluate the cross-sectional association of the presence of FHx with each PA measure.
 - 4) To determine whether greater PA compared to lower PA confers reduction in incident CHD risk among those with a FHx of premature CHD, we will use progressively adjusted Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for incident CHD for each PA category.
 - 5) We will assess the association of higher PA, relative to lower PA, with incident CHD risk among individuals with and without a FHx of premature CHD. We will test for an interaction between PA and FHx of premature CHD to assess whether any risk reduction conferred by PA is different among individuals with and without a FHx.
 - 6) Models will be progressively adjusted as follows
 1. Model 1: Age
 2. Model 2: Age + sex, race, education, BMI, smoking status and alcohol intake
 3. Model 3: Model 2 + additional potential mediating variables (of the association between PA and CHD risk) - systolic blood pressure, anti-hypertensive medication use, diabetes, total and HDL-cholesterol, use of lipid lowering medications, and estimated GFR
 - 7) Among individuals with a FHx of premature CHD, Wald tests will be used to formally test for two-way multiplicative interactions of PA with race, sex, age, in relation to incident CHD, by including cross-product terms in the model.
- h. **Secondary analyses:**
- 1) We will evaluate changes in PA levels from Visit 1 to Visit 3 in the overall population and stratified by FH of premature CHD status.
 - 2) As a secondary outcome, we will consider total ASCVD (CHD plus stroke) for main analyses.
- i. **Sensitivity analyses:**
- 1) We will repeat the main analyses using FHx of any CHD, regardless of premature or not.
- j. **Limitations:**
- Physical activity was self-reported not directly measured, and the Baecke questionnaire (although validated) has known limitations. Family history was also self-reported. The strengths of performing this analysis in ARIC are the large number of events, the availability of a large, biracial cohort of men and women to look for demographic differences in the associations of interest.

7. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

8.

k. Will the DNA data be used in this manuscript? ____ Yes __X__ No

l. 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>

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)?

There are several manuscripts about PA and CHD risk, and several manuscripts about FH and CHD risk. But there were no manuscripts proposals evaluating the interaction that PA confers on the association of FH with CHD risk (no overlap).

MS2548: Changes in physical activity and incident heart failure (Florida)

MS2450 Physical activity patterns and predictors of change

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

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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/>

11. 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.

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- [7] Steptoe A, Doherty S, Rink E *et al.* Behavioural counselling in general practice for the promotion of healthy behaviour among adults at increased risk of coronary heart disease: randomised trial. *Bmj* 1999; 319:943-947; discussion 947-948.
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- [10] Arem H, Moore SC, Patel A *et al.* Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015; 175:959-967.
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- [13] Rahman I, Bellavia A, Wolk A. Relationship between physical activity and heart failure risk in women. *Circ Heart Fail* 2014; 7:877-881.
- [14] 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. *J Am Coll Cardiol* 2010; 56:1140-1148.
- [15] Young DR, Reynolds K, Sidell M *et al.* Effects of physical activity and sedentary time on the risk of heart failure. *Circ Heart Fail* 2014; 7:21-27.
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