ARIC Manuscript Proposal # 3191

PC Reviewed: 06/12/2018   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Premorbid physical activity and prognosis after incident myocardial infarction

  b. Abbreviated Title (Length 26 characters): Physical activity and prognosis after MI

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

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3.   Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4.   Rationale:
Physical activity has been inversely associated with mortality and incidence of cardiovascular disease (CVD) in the general population [1-3]. Accordingly, clinical practice guidelines recommend ≥150 min of moderate or ≥60 to 75 min of vigorous exercise each week for the prevention of incident CVD [4-6].
    Clinical guidelines recommend regular physical activity among patients with CVD as well for secondary prevention [7, 8]. However, it is controversial whether physical activity prior to myocardial infarction (MI) ("premorbid" physical activity) will impact prognosis after MI. For

example, Gerber et al., reported no significant relationship between physical activity in the year preceding the index MI and subsequent prognosis [9]. Also, we recently demonstrated that physical activity as a component of the American Heart Association's Life Simple 7 at middle age is not significantly associated with adverse outcomes after MI in later life [10]. However, in our previous study, by the definition of Life Simple 7, we only explored three-group categories of physical activity (ideal, intermediate, and poor) at a single time point.

Therefore, to more comprehensively evaluate potential contributions of premorbid physical activity to prognosis after MI, we will examine the association of physical activity at visit 1 and visit 3 of the Atherosclerosis Risk in Communities (ARIC) study with adverse outcomes after incident MI in later life.

5. Main Hypothesis/Study Questions:
We hypothesize that physical activity prior to incident MI is associated with subsequent prognosis after incident MI.

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: Prospective cohort study
We will quantify the association of average physical activity assessed at visit 1 and visit 3 (approximately a 6-year interval) with risk of composite and individual adverse outcomes of all-cause mortality, cardiovascular mortality, recurrent MI, heart failure and stroke after incident MI. As detailed below, we will use covariates evaluated prior to or at MI occurrence using data from clinic visits, annual (or semi-annual) follow-up data, and medical records from incident MI admission. For each covariate in each participant, a data point closest to MI occurrence or within 12 months prior to MI occurrence will be used for the analysis.

Inclusions:
- We will capture all ARIC participants who developed MI after visit 3 through December 31, 2015. MI will be defined as definite or probable fatal or non-fatal MI cases adjudicated by the ARIC physician panel.

Exclusions:
- Individuals with CVD diagnosis (coronary heart disease, heart failure or stroke) prior to visit 3
- Race other than White and Black
- Participants missing data on physical activity and covariates of interest

Exposures: Physical activity
Physical activity (leisure time, sport, and work activities) in ARIC was assessed via a modified interviewer-administered Baecke Questionnaire. We will consider current American Heart Association (AHA) physical activity guidelines and total volume of activity. Participants itemized leisure time exercise activities and answered questions regarding the frequency of participation in each, hours per week and months per year performing each activity. Each activity is converted into a metabolic equivalent of task (MET) based on its intensity, as per the

Compendium of Physical Activities [11]. No exercise or light intensity will be defined as those involving a workload of <3 METs, moderate intensity as those involving a workload of 3-6 METs, and vigorous intensity as those involving a workload of >6 METs.

- American Heart Association (AHA) ideal physical activity guideline [12]
    a. Physical activity levels will be categorized by current AHA recommendation at visit 1 and visit 3.
        - Ideal: ≥75 min/week of vigorous intensity or >150 min/week of moderate, or ≥150 min/week of any combination of moderate + vigorous intensity exercise
        - Intermediate: 1-74 min/week of vigorous intensity or 1-149 min/week of moderate, or 1-149 min/week of any combination of moderate + vigorous intensity exercise
        - Poor: 0 min/week of moderate or vigorous exercise
    b. The score of AHA physical activity guideline for 6 years (between visit 1 and visit 3)
        - In order to comprehensively characterize physical activity over six years between visits 1 and 3, we will create a summary score by providing 2 points for ideal, 1 points for intermediate, and 0 points for poor at both visit1 and visit 3, separately, and then sum the scores across the two visits. The summary score will range from 0 to a maximum of 4 points, with a higher score indicating higher levels of physical activity over the six years between visits 1 and 3 (e.g., 4 points indicates meeting 'ideal' levels of physical activity at both visits 1 and 3).

- Total volume of activity (a continuous variable of MET*min/week; a multiplicative combination of intensity, duration, and frequency of physical activity) was derived at visit 1 and visit 3
    a. We will create distribution-based tertiles of total volume of physical activity intensity (MET*min/week) at visit 1 and visit 3.
    b. The score of total volume of physical activity for 6 years (between visit 1 and visit 3)
        - In order to examine the persistence of physical activity, the score of total intensity of activity will be calculated by providing 2 points for the third tertile, 1 points for the second tertile, and 0 points for the first tertile at both visit 1 and visit 3. The summary score will range from 0 to a maximum of 4 points, with a higher score indicating higher total volume of physical activity over the six years between visits 1 and 3 (e.g., 4 points indicates being in the highest tertile at both visits 1 and 3).
    c. We will also create distribution-based tertiles of total volume of physical activity of moderate and vigorous intensity. As described above, a total score of activity of moderate and vigorous intensity will be calculated separately, ranging from 0 to a maximum of 4 points.

In addition to AHA physical activity guidelines and total volume of activity described above, we will also consider sport, leisure and work activities. Scores from the sport, leisure and work index of Baecke questionnaire were previously derived from 1 (low) to 5 (high) [13].

- Sport index (sport and exercise-related leisure index)
  a. Sport index was expressed as the average of the four items with one through five-point score. The four items included participants itemized sport activities and questions regarding the frequency of participation in each, hours per week and months per year performing each activity (**Table 1**). These items were scored from one to five. Sport index was expressed as the average of the eight items one to five-point score.

Table 1. Four items comprising of sport index

	Question	(Score: 0=1, >0-<4=2, 4-<8=3, 8-<12=4, ≥12=5; Much lighter=1, Lighter=2, As heavy=3, Heavier=4, Much heavier=5; Never=1, Seldom=2, Sometimes=3, Often=4, Very often/Always=5).
Q1	Do you exercise or play sports? **Intensity:** Which sport or exercise do you do most frequently? low intensity=0.76 MJ/h; Moderate intensity=1.26MJ/h; High intensity=1.76 MJ/h **Time:** How many hours a week? <1=0.5; 1-2=1.5; 2-3=2.5; 3-4=3.5; >4=4.5 **Proportion:** How many months a year? <1=0.04; 1-3=0.17; 4-6=0.42; 7-9=0.67; >9=0.92	5/4 * (Intensity * Time * Proportion)= 0; >0-<4; 4-<8; 8-<12; ≥12
Q2	In comparison with others of your own age do you think your work is physically?	Much lighter; Lighter; As heavy; Heavier; Much heavier
Q3	During leisure time Do you sweat?	Never; Seldom; Sometimes; Often; Very often
Q4	During leisure time do you play a sport?	Never; Seldom; Sometimes; Often; Very often

  b. We will create quartile of sport index at visit 1 and visit 3
  c. The score of sport index for 6 years (between visit 1 and visit 3)
     – In order to comprehensively characterize sport index over six years between visits 1 and 3, we will create a summary score by providing 3 points for fourth quartile, 2 points for third quartile, 1 points for second quartile, and 0 points for first quartile at both visit1 and visit 3 and sum a score at each visit. Thus, this summary score for 6 years will range from 0 to a maximum of 6 points, with a higher score indicating more active status over six years between visits 1 and 3.

- Leisure index (non-sport and exercise leisure index)
  a. Leisure index was assessed as the average score for the four questions summarized in **Table 2** below. These items were scored from one to five. Leisure index was expressed as the average of the four items one to five-point score.

Table 2. Four items comprising of leisure activity score

	Question	(Score: Never=1, Seldom=2, Sometimes=3, Often=4, Very often=5; <5=1, 5 to <15=2, 15 to <30=3, 30 to <45=4, ≥45=5). The score for Q1 (watching television) is reverse.

Q1	During leisure time do you watch television?	Never; Seldom; Sometimes; Often; Very often
Q2	During leisure time do you walk?	Never; Seldom; Sometimes; Often; Very often
Q3	During leisure time do you bicycle?	Never; Seldom; Sometimes; Often; Very often
Q4	How many minutes do you walk and /or bicycle per day to and from work or shopping?	<5; 5 to <15; 15 to <30; 30 to <45; ≥45

b. We will create quartile of leisure index at visit 1 and visit 3
c. The score of leisure index for 6 years (between visit 1 and visit 3)
   – In order to comprehensively characterize leisure index over six years between visit 1 and visit 3, we will create a summary score by providing 3 points for fourth quartile, 2 points for third quartile, 1 points for second quartile, and 0 points for first quartile at both visit 1 and visit 3 and sum a score at each visit. Thus, this summary score for 6 years will range from 0 to a maximum of 6 points, with a higher score indicating more active status over six years between visit 1 and visit 3.

- Work index
  a. Work index was assessed as the average score for the eight questions summarized in **Table 3** below. These items are scored from one to five. Work index was expressed as the average of the eight items one to five-point score.

Table 3. Eight items comprising of work activity score

	Question	(Score: Never=1, Seldom=2, Sometimes=3, Often=4, Very often/Always=5; Much lighter=1, Lighter=2, As heavy=3, Heavier=4, Much heavier=5). The score for Q2 (sitting at work) is reverse.
Q1	What is your main occupation?	
Q2	At work do you sit?	Never; Seldom; Sometimes; Often; Always
Q3	At work do you stand?	Never; Seldom; Sometimes; Often; Always
Q4	At work do you walk?	Never; Seldom; Sometimes; Often; Always
Q5	At work do you lift heavy loads?	Never; Seldom; Sometimes; Often; Very often
Q6	After working are you physically tired?	Never; Seldom; Sometimes; Often; Very often
Q7	At work I sweat?	Never; Seldom; Sometimes; Often; Very often
Q8	In comparison with others of your own age do you think your work is physically?	Much lighter; Lighter; As heavy; Heavier; Much heavier

b. We will create quartile of work index at visit 1 and visit 3
c. The score of work index for 6 years (between visit 1 and visit 3)
   – In order to comprehensively characterize work index over six years between visits 1 and 3, we will create a summary score by providing 3 points for fourth quartile, 2 points for third quartile, 1 points for second quartile, and 0 points for first quartile at both visit1 and visit 3 and sum a score at each visit. Thus, this summary score for 6 years will range from 0 to a maximum of 6 points, with a higher score indicating more active status over six years between visits 1 and 3.

Covariates:

We will consider the nine predictors included in the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P) for recent MI patients [14]. Nine predictors in TRS2°P includes the following factors at incident MI: age at MI, current smoking, kidney dysfunction, and a history of heart failure, hypertension, diabetes, stroke, coronary artery bypass graft, and peripheral artery disease. As mentioned above, we will use data from clinic visits, annual (or semi-annual) follow-up data, and medical records from incident MI admission. Nine predictors in TRS2°P will be defined as below (**Table 3**).

Table 3. Definition of nine predictors in TRS2°P

Predictors	Definition
Age	Age at the time of index MI
Current smoking	Within 1 year prior to incident MI.
Kidney dysfunction	Estimated glomerular filtration rate <60 ml/min/1.73m^2 within 1 year prior to incident MI or chronic kidney disease-related ICD-9 codes
Heart failure	ICD-9 discharge code
Hypertension	Blood pressure ≥140/90 mmHg, self-reported doctor diagnosed hypertension, or medication
Diabetes	Fasting glucose ≥126mg/dL, non-fasting glucose ≥200 mg/dL, self-reported doctor diagnosed diabetes, or medication
Stroke	Definite or probable stroke cases adjudicated by ARIC physician panel
Coronary artery bypass graft	ICD-9 procedure code
Peripheral artery disease	ICD-9 discharge or procedure code

In addition to the TRS2°P predictors, gender, race, body mass index, and self-rated health prior to MI will be treated as covariates and calendar year of incident MI also will be treated as a covariate since management of MI could change over time. We will determine MI severity, using a modified score of the Predicting Risk of Death in Cardiac Disease Tool (PREDICT) that uses several clinical variables (cardiogenic shock; history of MI, stroke, or angina; age; severity of electrocardiographic changes; congestive heart failure; and Charlson Comorbidity index) based on MI hospitalization data.

Outcomes:

- Primary: composite and individual adverse outcomes of all-cause mortality, cardiovascular mortality, recurrent MI, heart failure, and stroke after incident MI
    - Cardiovascular death will be defined as death from coronary heart disease, heart failure, or stroke.
    - Recurrent MI and stroke will be defined as definite or probable cases adjudicated by ARIC physician panel.
    - Heart failure will be defined as a hospitalization having in any position an ICD-9 code 428 or ICD-10 code I50 for heart failure diagnosis.
- Secondary: all-cause hospitalization after incident MI

Statistical Analysis:

1. We will summarize characteristics at both visits and MI occurrence across categories of physical activity at both visits and the summary score of physical activity for 6 years (between visit 1 and visit 3)
2. Cumulative incidence of composite and individual adverse outcomes will be estimated across categories of physical activity using the Kaplan-Meier method.
3. We will quantify the association of physical activity (as detailed above) with adverse outcomes after incident MI using Cox proportional hazards models accounting for potential confounders.
4. We will conduct a few sensitivity analyses.
    a. We will repeat analysis in several subgroups by demographic (age, gender and race) and cardiovascular risk factors (body mass index [$\geq$30 vs. <30 kg/m^2], hypertension, and diabetes).
    b. Since those with lower levels of physical activity were likely to develop MI earlier than those with higher levels, leading to longer follow-up after MI to capture adverse outcomes, we will restrict follow-up time after incident MI to 1, 3, or 5 years.
    c. We will additionally adjust for MI severity (represented by the PREDICT score).
    d. Since those with a long interval between the physical activity at visit 3 and incident MI may have changed their activity or may have a different association than those with a short interval, we will restrict to all MI cases within certain period like 5 years from visit 3.
    e. We will also consider sport and leisure index assessed at the ARIC Carotid MRI study to confirm stability of physical activity measures and their associations.

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 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 _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__ 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)?
MP #2548: Changes in Physical Activity and the Risk of Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study
MP #2845: Life's Simple 7 at middle-age and the prognosis after myocardial infarction

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* _2002.02 and_ 2011.07_____)**
  ___ **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/

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.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x_ No.

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