

ARIC Manuscript Proposal # 3237

PC Reviewed: 9/11/201
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Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Premorbid physical activity, adverse health events and poor physical function after stroke in the ARIC participants

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

2. Writing Group:

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

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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).

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3. Timeline: Manuscript draft to be completed in 1 year (if abstraction of stroke severity is completed in ~4 months).

4. Rationale:

Extant studies provide evidence of the association of moderate and high levels of physical activity (PA) with reduced risk of total, ischemic, and hemorrhagic strokes¹. Thus, PA is now recommended for primary prevention of stroke^{2,3}. Moderate- to vigorous-intensity aerobic physical activity (40 minutes 3-4 times a week) is recommended for secondary prevention of stroke in patients with a history of ischemic stroke or TIA⁴. Exercise interventions post-stroke have been shown to reduce blood pressure, the strongest modifiable predictor of secondary stroke, and improve other risk factors, such as lipid profile, plasma fasting glucose, and body mass index⁵.

Compared to established contributions of PA to prevention of incident stroke, and post-stroke PA to secondary prevention, it is less clear whether PA prior to stroke is associated with better prognosis after incident stroke. In animal studies, physical activity before ischemia induced neuroprotection⁶, which is associated with better outcome after cerebrovascular events. In humans, a few studies reported that regular pre-stroke PA retrospectively evaluated is linked to less severe stroke^{7,8} and better functional outcome^{8,9}. In contrast, the Physician's Health Study cohort, with over 20 years of follow-up, did not show a significant association between premorbid physical activity and functional outcomes after TIA or stroke¹⁰.

Given conflicting results in a few limited previous studies, we propose to analyze associations between pre-stroke physical activity reported at visit 1 and visit 3 of the Atherosclerosis Risk in Communities (ARIC) study with adverse outcomes (including all-cause mortality and recurrent cardiovascular events) as well as poor physical function after incident stroke.

5. Main Hypothesis/Study Questions:

PA prior to incident cerebrovascular event is associated with risk of all-cause mortality, recurrent cardiovascular events and physical function after incident stroke.

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).

The proposed study follows the design described in MP# 3191 by Yejin Mok and Kunihiro Matsushita.

Study design: Prospective cohort study

We will study the association of PA between 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 stroke, MI and heart failure after stroke. Potential associations between level of PA before stroke and physical function after incident stroke will be assessed as well.

Inclusions:

ARIC participants with definite/probable incident stroke occurring between visit 3 (1993–1995) and December 31, 2015. Stroke is defined as sudden or rapid onset of neurologic symptoms lasting >24 hours or leading to death, in the absence of evidence for a non-stroke cause. In ARIC, strokes are adjudicated as ischemic or hemorrhagic (ICH or SAH) stroke, and ischemic strokes are further classified by pathogenic subtype as thrombotic brain infarction, lacunar infarction, or cardio-embolic stroke, according to criteria adopted from the National Survey of Stroke subtype classification.

Exclusions:

- ARIC participants with stroke prior to visit 3
- Race other than White and Black
- Participants missing data on physical activity and main covariates

Exposures:

Physical activity- defined according to MP# 3191

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 Activities¹¹. 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 guideline²
 - 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 visit 1 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) ¹².

- 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	$5/4 * (\text{Intensity} * \text{Time} * \text{Proportion}) = 0; >0-<4; 4-<8; 8-12; \geq 12$
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: Data on the following covariates collected at ARIC visits, annual or semi-annual follow-up, and from medical records from admission at incident cerebrovascular event admission will be used: age at incident stroke, gender, race, calendar year of incident stroke, time from V3 to incident stroke, hypertension, diabetes, current smoking, atrial fibrillation, kidney dysfunction and peripheral artery disease. Data on severity of stroke are not currently available in ARIC, however, severity by NIHSS will be retrospectively assessed using all available details on the index stroke. Severity will be categorized as NIHSS \leq 5, 6-10, 11-16, >16.

Outcomes:

Composite and individual adverse outcomes of all-cause mortality, cardiovascular mortality, recurrent cerebrovascular event, MI, and heart failure after incident stroke/TIA

Cardiovascular death will be defined as death from coronary heart disease, heart failure, or stroke.

Recurrent cerebrovascular event (stroke overall, by stroke type and ischemic stroke subtype) and MI will be defined as ARIC adjudicated definite or probable events.

Heart failure will be defined as a hospitalization with a heart failure diagnostic code (ICD-9 code 428 or ICD-10 code I50) in any position on the record.

Statistical Analysis:

- Characteristics of participants at both visits and stroke across categories of physical activity at both visits and the summary score of physical activity for 6 years (between visit 1 and visit 3).
- Cumulative incidence of composite and individual adverse outcomes will be estimated across categories of physical activity using the Kaplan-Meier method.
- Cox proportional hazards models will be used to examine the association between PA level and adverse outcomes after incident stroke (overall as well as by stroke type and ischemic stroke subtype), accounting for potential confounders.
- Sensitivity analyses: Separate subgroup analyses will be performed by age group (<55, 55-64, 65-74, 75-84, ≥85), gender, race, hypertension, atrial fibrillation, diabetes and stroke severity category (NIHSS≤5, 6-10, 11-16, >16).

Anticipated limitations:

Given the categorization of PA, power for some of the proposed subgroup analyses may be limited.

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.csc.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 #1677: Association between Physical Activity and Stroke Risk: the ARIC Study

MP #3191: Premorbid physical activity and prognosis after incident myocardial infarction

MP #3220: Changes in Physical Activity and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities Study

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.csc.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.csc.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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