ARIC Manuscript Proposal # 3220

PC Reviewed: 8/14/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

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

b. Abbreviated Title (Length 26 characters):

Physical Activity Change and Stroke

2. Writing Group:

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

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3. Timeline:

Obtain data set: Summer 2018
Complete statistical analysis: Fall 2018
Complete manuscript: Spring 2019

4. Rationale:

Higher levels of physical activity (PA) and physical fitness are associated with better overall health and lower mortality rates.[1, 2] Those who are physically active are less likely to have coronary heart disease (CHD)[3] and its risk factors including hypertension[4], diabetes[5], and depression.[6] In addition to the beneficial effects on CHD and cardiovascular risk factors, PA is also associated with a lower risk of other cardiovascular events, including ischemic stroke.[7, 8] PA has a graded inverse relationship with incident ischemic stroke with individuals with the highest levels of PA having the lowest ischemic stroke risk.[9]

Despite the cardiovascular benefits of PA, <50% of the US population meets recommended levels of exercise.[10] Given the low levels of PA, national organizations emphasize the cardiovascular benefits of increasing activity in the general population.[11] Meeting the guidelines for PA is one of the American Heart Association's (AHA) 7 components of ideal cardiovascular health for both children and adults.[11]

Previous observational studies have identified an association between physical activity level and stroke risk. Increases in PA over time are associated with lower risks of coronary heart disease (CHD) and total mortality.[12-14] Clinical trials documenting the impact of changes in physical activity on the primary prevention of stroke have not been conducted.[15] If changes in PA over time have a significant association with stroke risk, this finding could have important implications for stroke prevention. Hence, we will use data from the Atherosclerosis Risk in Communities Study to assess the association between changes in PA and incident ischemic stroke risk.

5. Main Hypothesis/Study Questions:
How do changes in physical activity impact future incident ischemic stroke risk.

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 ARIC study is a multi-center population-based prospective cohort study designed to investigate the etiology and natural history of atherosclerosis in middle-aged Americans.[16] At baseline in 1987-1989 (visit 1), 15,792 mostly white and black men and women were selected from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[16] Subsequent exams took place during 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), 2011 to 2013 (visit 5), and 2016-2017 (visit 6).

All participants who attended visit 3 will be included in the analysis (n=11,351). We will exclude those with baseline CHD or ischemic stroke at visit 3 and those with missing physical activity data at visits 1 or 3.

Exposure
Physical activity was assessed at visits 1 and 3 using the Baecke questionnaire. Frequency and duration of leisure time physical activities were converted to METs based on the intensity of activity using the Compendium of Physical Activities.[17] We will use the American Heart Association's definition for recommended (≥75 minutes/week of vigorous intensity or ≥150 minutes/week of any combination of moderate and vigorous intensity exercise), intermediate (1–74 minutes/week of vigorous intensity or 1–149 minutes/week of any combination of moderate and vigorous intensity exercise), or poor (0 minutes/week of moderate or vigorous exercise) to classify physical activity level at both visit 1 and visit 3.[18] We will create cross-categories of physical activity at visit 1 and visit 3 using methodology developed by Florido et al.[19]

Outcome
The primary outcome of interest is ischemic stroke classified as thrombotic or cardioembolic stroke based on discharge codes, signs, symptoms, neuroimaging (computerized tomography/magnetic resonance imaging), and other diagnostic reports.[20] We will look at all ischemic strokes together as well as each ischemic stroke sub-type (lacunar, cardioembolic, nonlacunar thrombotic) separately.[21] All events between visit 3 and end of year 2014 will be included in the analysis.

Analysis
We will performed bivariate comparisons of participant characteristics at visit 3 across the categories of physical activity: poor, intermediate, and recommended. Chi-squared test will be used for categorical variables and ANOVA for continuous variables.

Kaplan–Meier (KM) curves will be used with the log-rank test to assess differences in the stroke-free survival between those who increased their PA category from visits 1 to 3 versus those with stable low activity (stable PA category and below the median average activity across visits 1 and 3) and between those who decreased their PA category from visit 1 to 3 versus those with stable high activity (stable PA category and greater than or equal to the median average activity across visits 1 and 3).

Cox-proportional hazards regression models will be used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for ischemic stroke comparing those who increased their PA category from visits 1 to 3 versus those with stable low activity (stable PA category and below the median average activity across visits 1 and 3) and between those who decreased their PA category from visit 1 to 3 versus those with stable high activity (stable PA category and greater than or equal to the median average activity across visits 1 and 3). Additionally cox models will be used to estimate HRs and 95% CIs for cross-categories of physical activity at visits 1 and 3 using those with poor physical activity at both visits as the referent group. Crude models and those adjusting for potential confounders will be constructed. Adjusted models will include possible confounders such as age, sex, race, smoking status, and alcohol intake measured at baseline (visit 3).

Follow- up time begins at visit 3 and extends to the first outcome, dropping out of the study, death, or else, December 31, 2014.

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/mantrack/maintain/search/dtSearch.html

___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)?

#1677 – Association between Physical Activity and Stroke Risk: the ARIC Study
#2548 – Changes in Physical Activity and the Risk of Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

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2. Berry JD, Willis B, Gupta S, et al. Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men. The Cooper Center Longitudinal Study. *J Am Coll Cardiol* 2011;57:1604-1610.
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16. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687-702.
17. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;43:1575-1581.

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19. Florido R, Kwak L, Lazo M, et al. Six-Year Changes in Physical Activity and the Risk of Incident Heart Failure: ARIC Study. *Circulation* 2018;137:2142-2151.
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