ARIC Manuscript Proposal # 1677r

PC Reviewed: 9/14/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Association between Domains of Physical Activity and Risk of Ischemic Stroke Subtypes: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Physical Activity & Stroke Subtypes

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. CA **[please confirm with your initials electronically or in writing]**

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3. Timeline: Analysis to begin September 2010
First draft December 2010

4. Rationale:

Regular physical activity has many benefits, as it lowers the risk of developing a number of chronic diseases (1,2). The relationship between physical activity and stroke risk has been subject to several studies (3-7). It has been 10 years since a paper focused on physical activity and stroke has been published with ARIC data (3); more ischemic stroke events (from 189 to over 800) can be taken into account for the analyses which will allow for inspection of effect modifiers. Furthermore, most of the previous work on physical activity and stroke has investigated total ischemic stroke risk and has not studied ischemic stroke subtypes.

Currently, there are approximately 188 lacunar, 485 non-lacunar and 186 cardioembolic strokes in ARIC. A recently accepted manuscript by Tetsuya Ohira (8) found that the association between stroke subtypes and carotid artery wall thickness varied by the different types of stroke.

Examining the effect of physical activity on subtypes of ischemic stroke (lacunar, nonlacunar, cardioembolic) may yield important information on possible underlying mechanisms.

5. Main Hypothesis/Study Questions:

The main hypothesis is that regular physical activity will be associated with ischemic stroke events. Specific study questions may be as follows:

1) Are there any differences in the direction/significance of the physical activities' association with ischemic stroke subtypes according to the type of physical activity (e.g., sports vs. leisure vs. work)?
2) Can gender or ethnicity differences be observed with regard to the above-stated hypothesis?
3) Can effect modifications by age, smoking status or occupational status be identified?

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).

<u>Data source:</u>

ARIC visit 1 (1987-1989)

Outcome variables:
The analysis will be focused on ischemic strokes, including sub-analyses of the classification types lacunar (n=188), nonlacunar (n=485), and cardioembolic (n=186) similar to what has been used in previous ARIC manuscripts (8,9).

Exposure variables:
Physical activity (sport, leisure, and work activity) assessed by the validated Baecke Questionnaire at visit 1 will be used. Quartiles according to each physical activity domain as well as total activity will be made.

Covariates:
Model 1: age, race-center, sex
Model 2: age, race-center, sex, education, smoking, systolic blood pressure, hypertension, antihypertensive medication use, fibrinogen, waist to hip ratio, LVH, Lp(a), vWF, WBC, and diabetes

Exclusions:
Subjects with missing data on outcome, exposure or covariates as well as participants with prevalent stroke or CHD at baseline will be excluded from the final dataset.

Statistical analyses:
The proportional hazards assumption will be tested by the inspection of log((-log)event) versus log of event times. Cox proportional hazards models, with days as the timescale, will be applied to compute the hazard ratios and 95% confidence intervals for the ischemic stroke subtypes. Effect modifications will be tested between physical activity and age, as well as selected covariates, on stroke subtypes by additionally entering an interaction term of the respective variables into the Cox model. If event cases are sufficient, further stratification by age groups and ethnicity are also planned. The statistical software package SAS 9.2 (SAS Institute, Inc., Cary, NC) will be used to perform all statistical analyses.

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_ 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)?

Unpublished Work:

ARIC Manuscript Proposal (# 1560). Yatsuya, H. Postural changes in blood pressure and incidence of ischemic stroke subtype in the ARIC study.

Published Work:

ARIC Manuscript Proposal (#332). Evenson KR, Rosamond WD, Cai J, Toole JF, Hutchinson RG, Shahar E, Folsom AR. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study.*Stroke.*1999 Jul;30(7):1333-9.

ARIC Manuscript Proposal (#1090). Tetsuya O, Shahar E, Chambless L, Rosamond W, Mosley T, Folsom A. Risk factors for ischemic stroke subtypes. Stroke 2006;37:2493-2498

ARIC Manuscript Proposal (#1188). Tetsuya O, Shahar E, Iso H, Chambless L, Rosamond W, Richey Sharrett A, Folsom A. Carotid Wall Thickness and Risk of Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2010 [in press].

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

1 . U.S. Department of Health and Human Services. Physical activity and health: A report of the surgeon general. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.

2. Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. Sports Med. 2001;31(2):101-14

3. Evenson KR, Rosamond WD, Cai J, Toole JF, Hutchinson RG, Shahar E, Folsom AR. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study.*Stroke.*1999 Jul;30(7):1333-9.

4. Hu G, Sarti C, Joushilahti P, Silventoinen K, Barengo NC, Tuomilehto, J. Leisure time, occupational, and commuting physical activity and the risk of stroke. *Stroke.* 2005 Sep;36(9):1994-9.

5. Willey JZ, Moon YP, Paik MC, Boden-Albala B, Sacco RL, Elkind MS. Physical activity and risk of ischemic stroke in the Northern Manhattan Study. *Neurology.* 2009 Nov 24;73(21):1774-9.

6. Wendel-Vos GCW, Schuit AJ, Feskens EJM, Boshuizen HC, Verschuren WMM, Saris WHM, Kromhout D. Physical activity and stroke. A meta-analysis of observational data. *International Journal of Epidemiology.* 2004;33:787–798.

7. Sattelmair JR, Kurth T, Buring JE, Lee IM. Physical Activity and Risk of Stroke in Women. *Stroke*. 2010; 41;1243-1250.

8. Tetsuya O, Shahar E, Iso H, Chambless L, Rosamond W, Richey Sharrett A, Folsom A. Carotid Wall Thickness and Risk of Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2010 [in press].

9. Tetsuya O, Shahar E, Chambless L, Rosamond W, Mosley T, Folsom A. Risk factors for ischemic stroke subtypes. *Stroke.* 2006;37:2493-2498.