ARIC Manuscript Proposal #2310

PC Reviewed: 2/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Physical activity and change in cognition and incidence of dementia: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): activity and cognition

2. Writing Group:

Writing group members (alphabetical order): Kelly Evenson (last), Aaron Folsom, Kelly Gabriel, Alden Gross, Gerardo Heiss, Tom Mosley, Priya Palta (first), B. Gwen Windham, others welcome

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

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3. Timeline: Analyses to start upon approval of proposal. Submit for publication within 6 months from proposal approval.

4. Rationale:

Animal studies have shown that increased physical activity improves cognitive functioning.[1] Reductions in amyloid deposition[2] and accumulation of phosphorylated tau[3] are seen in animal models exposed to physical activity. Data in humans also suggest that individuals who engage in aerobic exercise have less cognitive decline[4] and a reduced risk of Alzheimer's disease.[5] Increases in brain vascularization (greater blood flow to the brain) and brain-derived neurotropic factors responsible for neuroplasticity and neuroprotection after aerobic exercise are among the proposed mechanisms that may explain how physical activity is associated with cognitive performance and dementia risk.[6]

One major limitation of previous human observational studies of physical activity and both cognitive decline and incidence of dementia is the lack of repeated measures of physical activity over the lifespan. Considering the variability in activity levels over the adult life span due to changes in work, morbidity, retirement from work, and age-related changes in functional abilities, a one-time measurement of physical activity may not be a reliable or informative measurement of an individual's overall activity exposure. Previous studies have examined the concurrent changes of physical activity with social-cognitive processes, such as, self-efficacy[7] and their association with cognitive functioning. We are aware of only one study that has examined the concurrent association between changes in physical activity and changes in cognition.[8] Results from this study showed a statistically significant direct relationship between baseline physical activity levels and both baseline cognition and rates of change in cognition in Taiwanese older adults who had a relatively stable physical activity level. Significant associations were also observed between changes in physical activity measures and changes in cognition over 11 years in this study. However, only global cognition was assessed, using the Short Portable Mental Status Questionnaire.

Examining this research question in the ARIC cohort will contribute to this limited body of literature by estimating change in multiple domains of cognition (memory, executive function/psychomotor speed and language); quantifying intensity and total volume of physical activity over up to 20 years of follow-up; and providing the opportunity to assess differences by race and sex in this association.

5. Main Hypothesis/Study Questions:

Study Question:

Aim 1: Estimate the association of changes in physical activity (including intensity and total volume) from ARIC exam visits 1 to 5 with change in cognition from visits 2 to 5.

Hypothesis 1.1: Increases in amount of physical activity from midlife to older adulthood are inversely associated with changes in domain-specific cognition.

Hypothesis 1.2: The change in (1) intensity of physical activity and (2) total volume of physical activities from midlife to older adulthood are inversely associated with changes in domain-specific cognition.

Hypothesis 1.3: Increases in amount of physical activity from midlife to older adulthood are inversely associated with the incidence of MCI at visit 5.

Aim 2: Quantify the association of intensity and total volume of physical activity from ARIC exam visits 1 to 5 with incidence of dementia at visit 5.

Hypothesis 2.1: Increases in amount of physical activity from midlife to older adulthood are inversely associated with the incidence of dementia.

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 analysis of physical activity from visits 1 to 5 and their association with change in cognition from visits 2 to 5, incident MCI and incident dementia.

Exclusion: Not Caucasian or African-American

Exposure:

Habitual physical activity during (1) leisure, (2) sport, and (3) work were assessed using the Baecke Questionnaire at ARIC visits 1, 3 and 5. [9]

(1) Leisure Time Physical Activity Index
The following questions from the Baecke questionnaire will be used to assess leisure time activity (Table 1). The calculation of the leisure time index is provided below and ranges from 1 (low) to 5 (high). We will examine the contributions of intensity and total volume of activities, separately and together, over the life span to the putative associations with cognitive decline.

Table 1. Leisure Time Physical Activity Index

Question	V1	V2	V3	V4	V5
Q1. During leisure time do you watch television? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		X
Q2. During leisure time do you walk? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		X
***Q3. During leisure time do you bicycle*?** Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		X
Q4. How many minutes do you walk and/or cycle per day to and from work, school and shopping? Scoring: < 15 min =1; 5-15 min =2; 15-30 min =3; 30-45 min =4; >45 min = 5	X		X		

Calculation of the Baecke <u>Leisure</u> index:
Visits 1 and 3: [(6-Q1) + Q2 + Q3 + Q4]/4
Visit 5: [(6-Q1) + Q2 + Q3]/3

(2) Sport Physical Activity Index of Intensity and Total Volume
Sport physical activity was assessed using the Baecke Questionnaire at ARIC visits 1, 3, and 5 (Table 2). The sport index accounts for intensity of (habitual) physical activity and total volume in physical activity, to allow for the estimation, separately and together, the contributions of intensity and total volume of activities over the life span to the putative associations with cognitive decline.

Table 2. Sport Physical Activity Index in ARIC

Question	V1	V2	V3	V4	V5
Q1. Do you play a sport?* **Scoring: 0 (no)=1; 0.01- <4=2; 4- <8=3; 8- <12=4; ≥ 12=5	X		X		X
Q2. In comparison with others my own age I think my physical activity during leisure time is: Scoring: Much less=1; Less=2; the Same=3; More=4; Much More=5	X		X		X
Q3. During leisure time I sweat? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		X
Q4. During leisure time I play a sport? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		X

*** Calculation of Q1=** [5/4(value for intensity of most frequent sport) * (value for weekly time of most frequent sport) * (value for yearly proportion of most frequent sport)]$_{sport1}$ * [5/4(value for intensity of second sport) * (value for weekly time of second sport) * (value for yearly proportion of second sport)]$_{sport2}$

- Which sport do you play most frequently? *(Intensity)*

0.76 MK/h= low level (e.g. billiards, sailing, bowling, golf)

1.26 MK/h= middle level (e.g. badminton, cycling, dancing, swimming, tennis)

1.76 MK/h= high level (e.g. boxing, basketball, football, rugby, rowing)

- How many hours a week? *(Time)*

<1= 0.5; 1-2=1.5; 2-3=2.5; 3-4=3.5; >4=4.5

- How many months a year? *(Proportion)*

<1=0.04; 1-3=0.17; 4-6=0.42; 7-9=0.67; >9=0.92

****Scoring (1-5) for Q1 based on above calculation**

0 (no) =1; 0.01- <4=2; 4- <8=3; 8- <12=4; ≥ 12=5

Calculation of the Baecke Sport index:
[Q1 + Q2 + Q3 + Q4]/4

Assessment of Total Volume (METs/hr): [frequency * duration *intensity in METs/hr]$_{sport}$

(3) Work Index

Question	V1	V2	V3	V4	V5
Q1. What is your main occupation?	X		X		
Q2. At work I sit? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q3. At work I stand? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q4. At work I walk? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q5. At work I lift heavy loads? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q6. After working I am tired? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q7. At work I sweat? Scoring: Never=1; Seldom=2; Sometimes=3; Often=4; Very Often=5	X		X		
Q8. In comparison with others my own age I think my work is	X		X		

physically: Scoring: Much lighter=1; Lighter=2; As Heavy=3; Heavier=4; Much Heavier=5					

Calculation of the Baecke Work index:
= [Q1 + (6-Q2) + Q3 + Q4 + Q5 + Q6 + Q7 + Q8]/8

Outcome:

(1) 20-year cognitive change

20-year cognitive change will be assessed on three cognitive tests that have data available at Visits 2, 4, and 5: Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale (test of executive function and psychomotor speed), Delayed Word Recall Test (test of memory), and Word Fluency Test (test of language). To facilitate relative comparisons across these domain-specific tests, the raw test scores will be standardized to accommodate the differences in scales. For each neuropsychological test, a race-specific z score will be calculated based on the means and standard deviations at baseline (Visit 2). An estimate of change in cognition will be calculated from first available cognitive measurement to the participant's most recent visit with available cognitive test data.

(2) Incident MCI

(3) Incident Dementia

Covariates: sex, age, educational attainment, cohabitation status, social support, alcohol drinking, smoking, number of chronic diseases, mobility-disability limitations, body mass index

Analysis:

Aim 1: Latent growth curve models will be used to concurrently estimate the association of changes in intensity and total volume of physical activity (from the Baecke Sport Questionnaire) with changes in cognition from visits 1-5 of ARIC. We will also estimate the association of changes in the sport/leisure index (ranging from 1-5) with changes in cognition from visits 1-5. Parallel process latent growth curve models allow us to examine whether within-individual changes in physical activity are associated with within-individual changes in cognitive function. With this modeling approach, we can estimate the following associations:

(1) Baseline PA intercept at visit 1 → Baseline cognitive test intercept at visit 2
(2) Baseline PA intercept at visit 1 → Changes in cognitive tests from visit 2 to visit 5
(3) Changes in PA from visit 1 to visit 5 → Changes in cognitive tests from visit 2 to visit 5

Aim 2: Cox proportional hazard models will be used to estimate the association between baseline sport/leisure index (examined continuously and as quartiles based on previous work in ARIC[10,11]) and incident dementia. Joint latent class and survival mixture models will be used to concurrently estimate the association of changes in (1) sport/leisure index and (2) intensity and total volume of physical activity with incidence of dementia.

For both aims, we will perform sensitivity analyses using inverse probability weighting to account for dropout/missingness.

Methodological limitations: The increases in physical activity may be insufficient to explore incidence of MCI and dementia. Age-related declines in physical activity are inevitable and will be reflected in this particular cohort who is transitioning from midlife to older adulthood from visits 1 to 5.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

MS#1018r (lead: P. Dubbert)- Physical activity and cognitive decline (2004)
MS#1088 (lead: P. Dubbert)- Physical Activity and Cerebral Abnormalities on MRI- published
MS#1374 (lead: Gabriella Tikellis)- Association between Physical Activity and Retinal Microvascular Signs and Age-related Macular Degeneration- published
MS#1677 (lead: Christine Autenreith)- Association between Physical Activity and Stroke Risk: the ARIC Study- published

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

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* 1998.02-Life course SES, social context, and CVD (SESCVD)

___ 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. Agreed

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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