ARIC Manuscript Proposal #3035

PC Reviewed: 8/8/2017_____ **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1a. Full Title: Physical activity in adulthood and subclinical brain MRI markers: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

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

2. Writing Group:
Writing group members (alphabetical order): Kelly Evenson, Aaron Folsom, Kelley Gabriel, Michael Griswold (invited), Gerardo Heiss, Clifford Jack (invited), David Knopman, Thomas H. Mosley, Priya Palta (first), Melinda C. Power, Richey Sharrett, others welcome

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

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3. Timeline: Analyses to start upon approval of proposal. Submit an abstract for AHA- Epi 2018 and submit manuscript within 1 year of proposal approval.

4. Rationale:

Reducing the high burden of cognitive impairment and its sequelae in our aging population is a high priority that may be attainable by intervening on modifiable behaviors such as physical activity. Preliminary work in ARIC on physical activity and change in cognitive function and MCI/dementia risk (MS#2310, unpublished) suggest that compared to participants who were physically inactive in mid-life, moderate or high levels of physical activity were associated with less domain-specific cognitive decline over 14 years of follow-up (Table 1).

Magnetic resonance imaging (MRI) can inform on several subclinical brain markers, including hippocampal volumes, whose changes are associated with cognitive function[1] and progression to MCI and AD.[2-4] Mouse models suggest that physical activity results in increases in hippocampal volumes,[5,6] which is correlated with improved memory and executive function. A few clinical studies have found greater

hippocampal volumes among more physically active older adults,[7,8] but this has not been as widely studied in relation to physical activity at the population level.[7-10]

Reductions in volumes across brain regions are an indicator of neurodegeneration[11,12] and characterizing their association with physical activity may provide insight into the mechanisms that link physical activity with cognitive outcomes. Many of these associations have been evaluated in well-designed acute exercise interventions. Fewer observational studies have examined the effects of physical activity on structural brain changes. Specifically, recent data from the Framingham Offspring Cohort showed that higher scores on a physical activity index were linearly associated with total brain and hippocampal volumes.[13] These findings support those previously observed in the CAIDE cohort.[14] Although consistent, one major limitation of these prior observational studies, is the lack of repeat 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. Furthermore, to inform future interventions, efforts should move beyond examining only total volume of physical activity, to further quantifying possibly independent effects of type, duration, frequency, and intensity of activities on cognitive health outcomes.

Furthermore, few studies have used diffusion tensor imaging (DTI) to estimate the effect of physical activity on the structural integrity of white matter tracts in the brain. DTI measures provide additional information beyond that obtained from a structural MRI, such as white matter hyperintensities (WMH), by indicating potentially early changes that would precede WMH or related cerebral white matter injury.

Examining the association between leisure-time physical activity and structural brain changes in the ARIC cohort will contribute to the existing body of literature by incorporating longitudinal assessments of physical activity, including quantifying the independent effects of duration, frequency, intensity and total volume of physical activity over up to 20 years of follow-up; examining the association between physical activity and white matter microstructural integrity; and further providing the opportunity to assess differences by ApoE4 allele status in this association.

5. Main Hypothesis/Study Questions:

In an effort to provide insight into the mechanisms that link physical activity with cognitive outcomes, we seek to characterize the association of brain MRI markers with physical activity.

Primary Study Question:

1. **Quantify the cross-sectional association of leisure-time physical activity in late-life with subclinical brain MRI markers (i.e. region of interest (ROI) brain volumes; white matter hyperintensity (WMH) burden; white matter (WM) microstructural integrity; cortical and subcortical infarcts) in late-life.**

   Hypothesis 1a: Physical activity in late-life is associated with ROI volumes in late-life.

   Hypothesis 1b: Lower levels of leisure-time physical activity in late-life are associated with brain MRI detected abnormalities (i.e. greater WMH burden, poor WM microstructural integrity, and a higher number of cortical/subcortical infarcts) in late-life.

2. **Estimate the association of baseline leisure-time physical activity and temporal patterns of leisure-time physical activity (change in physical activity and persistence of physical activity) since mid-life with subclinical brain MRI markers (i.e. region of interest (ROI) brain volumes;**

white matter hyperintensity (WMH) burden; white matter (WM) microstructural integrity; cortical and subcortical infarcts) in late-life.

Hypothesis 2a: Mid-life leisure-time physical activity and persistence of leisure-time physical activity levels since mid-life are associated with ROI volumes in late-life.

Hypothesis 2a: Lower levels of leisure-time physical activity at baseline and persistence of low leisure-time physical activity levels since mid-life are associated with brain MRI detected abnormalities (i.e. greater WMH burden, poor WM microstructural integrity, and a higher number of cortical/subcortical infarcts) in late-life.

Secondary Study Question:

3. Perform a mediation analysis to test the hypothesis that subclinical brain MRI measures, specifically hippocampal volumes, mediate the associations of leisure-time physical activity and neurocognitive outcomes (cognitive function and MCI/dementia risk).

Hypothesis 3: Hippocampal volumes will mediate the association between high levels of leisure-time physical activity in mid-life and neurocognitive outcomes in late-life.

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 design of physical activity in mid- and late-life and subclinical brain MRI markers in late-life.

Exclusion: Not Caucasian or African-American, Blacks from Washington County and Minneapolis, no MRI data at visit 5

Exposure: Physical activity assessment—Baecke physical activity questionnaire administered at ARIC visits 1, 3 and 5.

On the Backe questionnaire, participants self-reported the number of hours/week (duration) and number of months/year (frequency) of up to 4 sport activities performed in the past year. Each sport activity was assigned a metabolic equivalent (MET) from the Compendium of Physical Activities (https://sites.google.com/site/compendiumofphysicalactivities/). A multiplicative combination of duration, frequency, and type (assigned a MET value) of all sport activities will be used to quantify the average MET-min/week. Physical activity will then be examined continuously and categorically in the following ways:

- Baseline physical activity in mid- (visit 1 and 3) and late-life (visit 5): tertiles (low, moderate, high) of average MET-min/week in the past year will be estimated at each visit and compared to no physical activity.

- Persistence of physical activity in mid-life (visit 1-3): Persistence of no physical activity and tertiles (low, moderate, or high) of physical activity over 6 years in mid-life and from mid- to late-life over 14 years will be examined in a subsample of ARIC participants.

- Change in physical activity from mid- to late-life: quantify groupings of physical activity identified as (1) stable, (2) increased or (3) decreased over the 20+ years of follow-up.

Outcome: Cerebral characteristics captured from the structural brain MRI (visit 5)

Brain MRIs were obtained from a 3T MRI scan at visit 5/ARIC-NCS (2011-2013).[15] We will examine the associations of physical activity with a variety of subclinical brain MRI markers, including, white matter brain atrophy, hyperintensities, cerebral microbleeds, lacunar infarcts, silent subcortical infarcts, brain volumes, white matter hyperintensity volumes, gray and white matter volumes, and volumes of brain ROIs.

Additional outcomes include those assessed using DTI to estimate white matter microstructural integrity in each ROI and overall.
- Fractional anisotropy (FA): lower values indicating worse white matter microstructural integrity
- Mean diffusivity (MD): higher values indicating worse white matter microstructural integrity

Covariates: Our primary model will adjust for baseline sex, age, educational attainment, race-center, individual-level (i.e. education, household income) and neighborhood-level SES, and smoking. A second model will examine vascular risk factors considered to be intermediary variables between physical activity and neurocognitive outcomes (i.e. diabetes, hypertension, body mass index).

Analysis:

Aim 1: A weighted multivariable linear (for continuous MRI measures, e.g. white matter hyperintensities, volumes) or logistic (for categorical MRI measures, e.g. infarcts and microbleeds) regression model will be used to estimate the cross-sectional association of physical activity (categorized as low, moderate, or high) with subclinical brain MRI markers in late-life.

Aim 2: A weighted multivariable linear (for continuous MRI measures, e.g. white matter hyperintensities, volumes) or logistic (for categorical MRI measures, e.g. infarcts and microbleeds) regression models will be used to estimate the association of baseline physical activity and temporal patterns of physical activity (change in physical activity and persistence of physical activity) since mid-life with subclinical brain MRI markers in late-life.

Aim 3: Preliminary ARIC data (Table 1, unpublished, Palta et al.) has shown an inverse association between physical activity and (1) change in domain-specific cognitive function and (2) risk of MCI and dementia. Therefore, we will perform a subsidiary mediation analysis to examine the extent to which the association between physical activity and cognition/dementia is mediated by cerebral MRI characteristics. Prior to doing a formal mediation analysis, we will first confirm whether both the exposure (physical activity) and the outcome (cognitive function/dementia) are independently associated with the brain MRI measures. A test for mediation will be performed by including the brain MRI measures (i.e. WMH or infarcts) into the final model and assessing whether the estimates are attenuated after its inclusion. If the estimates are attenuated greater than 15%, as recommended in published literature, then it suggests that these brain MRI measures may explain some of the variation in the association between the exposure (physical activity) and the outcome (cognitive function/dementia). An estimate of the mediated effect will be obtained using Sobel's formula. A careful analysis of confounders of the mediators and outcomes will be considered and further causal mediation approaches may be employed to correct for potential measurement bias.

Given prior data suggesting inconsistent differences in the associations of physical activity with neurocognitive outcomes among ApoE4 carriers and non-carriers[16-18], we will examine the associations separately in ApoE4 carriers and non-carriers.

Methodological limitations: The cross-sectional design of Aim 1 (both physical activity and MRI assessed at the visit 5 examination) limits the inferences relating to causality in the observed associations between physical activity and brain MRI measures. However, utilizing the longitudinal physical activity data in ARIC, we can examine the effects of temporal patterns of physical activity in mid-life with later life MRI outcomes. 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#1088 (lead: P. Dubbert)- Physical Activity and Cerebral Abnormalities on MRI- published (data only through visit 4 and Brain MRI substudy)
MS#2310 (lead: P. Palta)- Physical activity and change in cognition and risk of MCI and dementia: the ARIC study

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.

Table 1. Adjusted 14-year change in domain-specific factor scores across tertiles of MET-min/week at Visit 3 (1993-1995), the ARIC Study (n= 11,093)

Visit 3 Tertiles of MET-min/week	Global Cognitive Performance	Memory	Executive Functioning /Processing Speed	Language
	Beta (95% CI)	**Beta (95% CI)**	**Beta (95% CI)**	**Beta (95% CI)**
Exposure Group				
No Physical Activity (PA)	-0.81 (-0.84, -0.78)	-2.07 (-2.12, -2.03)	-0.38 (-0.39, -0.36)	-0.28 (-0.32, -0.25)
Low	-0.78 (-0.81, -0.75)	-1.98 (-2.04, -1.93)	-0.38 (-0.40, -0.36)	-0.23 (-0.27, -0.19)
Moderate	-0.76 (-0.79, -0.72)	-2.00 (-2.05, -1.94)	-0.36 (-0.38, -0.34)	-0.18 (-0.23, -0.15)
High	-0.72 (-0.76, -0.69)	1.91 (-1.96, -1.86)	-0.37 (-0.39, -0.35)	-0.16 (-0.20, -0.12)
Contrast				
Low vs. no PA	0.03 (-0.01, 0.07)	**0.09 (0.03, 0.15)***	-0.001 (-0.02, 0.02)	**0.05 (0.008, 0.10)***
Mod vs. no PA	**0.05 (0.02, 0.09)***	**0.08 (0.02, 0.14)***	0.02 (-0.01, 0.04)	**0.10 (0.05, 0.14)***
High vs. no PA	**0.09 (0.05, 0.12)***	**0.16 (0.10, 0.22)***	0.01 (-0.01, 0.03)	**0.12 (0.07, 0.17)***

* $p<0.05$

Adjusted for V3 age, sex, education, race-center, ApoE4, ever vs. never smoking status, household income, neighborhood SES summary score

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