ARIC Manuscript Proposal # 3349

PC Reviewed: 2/12/2019_____	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Physical activity in adulthood and brain amyloid deposition: the ARIC-PET Study

b. Abbreviated Title (Length 26 characters): physical activity and brain amyloid deposition

2. Writing Group:

Writing group members (alphabetical order): Kelly Evenson, Kelley Pettee Gabriel, Rebecca Gottesman (last), Gerardo Heiss, David Knopman (invited), Thomas H. Mosley, Priya Palta (first), A. Richey Sharrett (invited), Keenan Walker, Dean Wong (invited), 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: Submit an abstract for AAIC (February 1st, 2019) 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. Our preliminary work in ARIC on physical activity and change in cognitive function and MCI/dementia risk (MS#2310, published) suggests that compared to participants who were physically inactive in mid-life, moderate or high levels of physical activity were associated with less global and domain-specific cognitive decline and a lower incidence of dementia over 14 years of follow-up.[1] In subsequent analyses (MS#3035, unpublished), we have shown that higher levels of physical activity in mid-life and sustained high levels of physical activity in mid-life are also associated with larger brain volumes in selected regions (frontal cortical, deep gray matter, AD signature region) in older adulthood. The underlying

mechanisms that link physical activity to brain-related outcomes are still unknown and are hypothesized to occur through several pathways, including increased neurogenesis and the reduction of vascular and metabolic risk factors, including blood pressure, blood glucose levels, and systemic inflammation.

Prior studies have hypothesized that physical activity benefits the brain through the release of brain-derived neurotrophic factors, which promote neurogenesis in the brain, particularly in the hippocampal regions associated with memory function. Progression of Alzheimer's disease and related dementias (ADRD) is associated with extracellular deposition of beta amyloid peptides in the brain, which results in the formation of plaques and intracellular neurofibrillary tangles. Some prior evidence suggests that physical activity may attenuate progression of ADRD and/or cognitive impairment through mechanisms that alter beta amyloid deposition, including, increases in brain-derived neurotrophic factors.[2,3]

Animal models have found promising results relating physical activity (i.e. voluntary wheel running) and exercise (i.e. forced wheel running) with lower levels of amyloid deposition in the brain.[3] However, the role of exercise on beta amyloid deposition in the human brain has not been widely studied, and the results to date appear inconsistent. The largest human study thus far to examine the associations between physical activity and PET-quantified brain amyloid deposition, was conducted among elderly French community-dwellings individuals free of dementia. In this cross-sectional analysis of older adults, physical activity was not associated with standardized uptake volume ratio (SUVR), and there was no evidence of differences in volume or level of physical activity between individuals with and without evidence of brain amyloid deposition using Florbetapir (defined as an SUVR>1.10).[4] In a smaller sample of 116 cognitively normal individuals with amyloid PET, lower levels of beta amyloid were observed in the highest tertile of physical activity among ApoE4 allele carriers only.[5] Another study showed that sedentary ApoE4 allele carriers who were cognitively normal (n=201) had the highest levels of brain amyloid deposition.[6] An age-dependent effect was observed in a study of 186 cognitively normal middle-aged participants, showing that those who were physical active exhibited attenuated brain amyloid deposition with age.[7]

Altogether the current literature reflect inconsistencies in the association between physical activity and brain amyloid deposition and highlight the limitations of these studies in part due to the small sample sizes, homogenous samples of cognitively normal participants which does not allow for examination of the associations across cognitive status, and cross-sectional analyses, which are susceptible to reverse causation. One additional limitation 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 major life events including changes in family structure (i.e., caregiving responsibilities) and/or work (i.e., retirement), morbidity, , 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.

Examining the association between leisure-time physical activity and brain amyloid deposition 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 and in the largest human study to date to examine the role of physical activity on PET-quantified brain amyloid deposition. Furthermore, we have the opportunity to assess differences by ApoE4 allele status, across race-ethnic subgroups, and by cognitive status.

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 elevated brain amyloid deposition with physical activity.

Primary Study Questions:

1. **Quantify the cross-sectional association of leisure-time physical activity in late-life (visit 5) with brain amyloid deposition in late-life (visit 5).**

   Hypothesis: Higher levels of physical activity in late-life are associated with lower brain amyloid deposition 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 from visits 1 to 3) since mid-life with brain amyloid deposition in late-life (visit 5).**

   Hypothesis 2: Mid-life leisure-time physical activity and persistence of higher leisure-time physical activity levels since mid-life are associated with lower brain amyloid 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 brain amyloid deposition in late-life.

Exclusion: Not Caucasian or African-American, no MRI and PET data at visit 5, dementia diagnosis, missing ApoE4, missing repeated measures of physical activity.

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

Using the Baecke 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: Brain Amyloid Deposition from PET (visit 5)

Brain MRIs were obtained from a 3T MRI scan at visit 5/ARIC-NCS (2011-2013).[8] Florbetapir PET scans were performed within 1 year of the brain MRI scan with magnetization-prepared rapid gradient echo (MPRAGE) used for coregistration of the PET images. Isotopes were injected 50-70 minutes before a 20-minate uptake scan. Each image was reviewed for incidental findings, image quality, and quantified for standardized uptake value ratios (SUVRs). SUVRs were obtained for each of the 34 total regions of interest (ROIs), but the primary analysis will use the global cortical measure of beta amyloid, calculated as the weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices, lateral temporal, parietal, and occipital lobes, precuneus, and anterior and posterior cingulates.

The primary outcome is an SUVR value dichotomized at the sample median of SUVR >1.2 to indicate elevated brain amyloid deposition. The value of 1.2 was chosen due to the highly skewed distribution of the data and is in line with prior ARIC-PET studies.

Covariates: Our primary model will adjust for baseline sex, age, educational attainment, race-center, individual-level (i.e. education, household income) and neighborhood-level socioeconomic status, 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:

Descriptive: We will first examine descriptive statistics of the data, including box plots for visualization of group comparisons (physical activity levels in those with and without elevated brain amyloid deposition).

Elevated brain amyloid deposition will be analyzed as a dichotomous (SUVR >1.2) outcome in logistic regression models.

Aim 1: A logistic regression model will be used to estimate the cross-sectional association of physical activity (categorized as low, moderate, or high) with elevated brain amyloid deposition.

Aim 2: A multivariable logistic regression model 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 elevated brain amyloid deposition.

Given prior reports of inconsistent differences in the associations of physical activity with neurocognitive outcomes among ApoE4 carriers and non-carriers[9-11], we will examine the associations separately in ApoE4 carriers and non-carriers. We will also evaluate effect modification by race and sex.

Additional sensitivity analyses will evaluate the specific ROIs within the global measure and those locations where amyloid deposition is frequently presented. Additional sensitivity analyses will restrict the analytic sample to those with (1) normal cognition (excluding MCI), (2) no ApoE4 alleles, and (3) other published florbetapir thresholds (1.11, and 1.10).

Methodological limitations: The cross-sectional design of Aim 1 (both physical activity and PET assessed at the visit 5 examination) limits the inferences relating to temporal sequence 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. The SUVR cutoff (>1.2) for elevated amyloid deposition was chosen based on the sample median due to the skewed data and is higher than other published data. Other lower cut points (SUVR>1.1 or

SUVR>1.0) have been suggested in the literature, which we will explore in sensitivity analyses. It is important to note that different studies have also utilized different cut points depending on the isotope used (i.e. cut points for Pittsburgh compound B (PiB) and Florbetapir may differ).

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? __X__ Yes __ __ 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"? _X___ 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?
__X__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 –published
MS#3035 (lead: P. Palta)- Physical activity in adulthood and subclinical brain MRI markers: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

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* ARIC-PET Study)

___ 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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