

ARIC Manuscript Proposal #3474 (revised)

PC Reviewed: 12/10/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Associations of accelerometer-derived and reported physical activity with cognition in older adults

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

2. Writing Group:

Writing group members: Priya Palta, Lisa Pompeii, Kelly Evenson, Brady Rippon, B. Gwen Windham, Tom Mosley, Gerardo Heiss, Jennifer Schrack, others welcome

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

First author: Kelley Pettee Gabriel
Address: 1616 Guadalupe St., Suite 6.300
Austin, Texas 78701

Phone: 512-391-2525 Fax: 512-482-6185
E-mail: Kelley.P.Gabriel@uth.tmc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Priya Palta
Address: 622 W. 168th Street; PH9, Room 212
New York, NY 10032
Phone: 212-304-7561 Fax: 212-342-0560
E-mail: pp2464@cumc.columbia.edu

3. Timeline: Analysis to start upon approval of proposal. Plans to submit as a scientific abstract to the Alzheimer's Association International Conference (Abstract Due: 01/27/2020). Submit manuscript for publication within 6 months from when Visit 7 and 8 cognitive function measures are available.

4. Rationale:

Alzheimer's disease (AD), the most common form of dementia, is the sixth leading cause of death (~84,000 deaths in 2010) in the U.S. The burden continues to grow with one in ten people (10%) over the age of 65 years having AD and the prevalence reaching 32% among individuals

aged 85 years and older.¹ The associated financial burden is expected to increase to \$511 billion by 2040; equivalent to every U.S. adult paying approximately \$1,215 to \$1,641 annually to care for those with AD.² Therefore, reducing the substantial burden of cognitive impairment and its sequelae in our aging population is a key public health priority and may be attainable by intervening on modifiable behaviors, including time spent sedentary, and in light-, and moderate to vigorous intensity physical activity.

Collectively, the 2015 *Institute of Medicine (IOM)*³, the 2017 *National Academies of Sciences, Engineering, and Medicine*⁴, and the 2018 *Physical Activity Guidelines Advisory Committee Scientific*⁵ Reports have identified physical activity as a key strategy that could have the greatest non-pharmacologic impact on the projected AD epidemic. Large observational studies have shown that greater levels of physical activity are associated with better cognitive function.^{6,7} However, these studies have been limited by their use of self-reported measures of physical activity that we know to be subject to reporting and recall biases, as well as having considerable variability (e.g. both higher and lower self-reported levels compared to accelerometer measured physical activity).⁸

While studies are still extremely limited, cross-sectional analyses include the Reasons for Geographic and Racial Differences in Stroke (REGARDS), Study of Osteoporotic Fractures (SOF) Studies, and the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).⁹⁻¹¹ In REGARDS⁹, participants in the highest quartile of moderate to vigorous intensity physical activity were less likely to be cognitively impaired compared to those in the lowest quartile. Participants in the highest quartile of moderate to vigorous intensity physical activity were also found to have better performance in the domains of executive function and memory. Time spent sedentary and in light intensity physical activity were not statistically significantly associated with cognitive function in this study sample. In SOF, older adult women without dementia and who were in the highest quartiles of daytime movement, as assessed by accelerometry, were found to have better mean cognitive test scores in the domains of executive function and global cognition.¹⁰ These participants were also less likely to be cognitively impaired. In HCHS/SOL¹¹, higher sedentary time, but not moderate to vigorous intensity physical activity, was related to lower executive functioning scores across all age groups.

In addition, a few small, longitudinal studies have also been conducted.¹²⁻¹⁴ Among 274 community-dwelling Taiwanese adults aged 65 years and older, Ku et al.¹² found that higher amounts of time spent sedentary at baseline had a higher risk of cognitive decline two years later. In this same study sample, Stubbs et al.¹⁴ found that higher accumulated levels of light intensity physical activity, independent from moderate to vigorous intensity physical activity, was related to a reduced rate of cognitive decline over two years. In another small sample of Latinx participants aged 50 years or older residing in Chicago, IL (n=57 with follow-up data), Holloway et al. found that less decline in light intensity physical activity and moderate to vigorous intensity physical activity was related to maintenance of episodic memory and semantic memory 5-years later, respectively. However, given the limited studies still available, and inconsistencies in findings across studies, additional studies are needed to contribute to this growing evidence base.

Further, while prior studies also include report-based physical activity measures, none have directly compared the measures of association and/or interpretation of findings by method of assessment (accelerometer vs. self-reported), or evaluated these relations using a composite estimate using both measurement methods (e.g., latent class analyses). This methodological work is important given the possibility of inconsistent findings by measurement method. Indeed,

several validation studies assessing the convergent validity of self-reported questionnaires compared to accelerometry have found only low to moderate correlation and/or agreement. This may be the result of known reporting and social desirability biases intrinsic to questionnaires and/or the reality that report and device based methods are measuring similar, yet also different constructs.^{15,16} In turn, the decisions that the investigators make related to which results to report can greatly impact the inferences and related recommendations that are communicated to the broader scientific community.

5. Main Hypothesis/Study Questions:

Aim 1. To examine the cross-sectional and prospective relations of accelerometer-determined time spent sedentary and in low and high light- and moderate to vigorous- intensity physical activity with (1) global and domain-specific cognition and (2) prevalence of mild cognitive impairment (MCI)* at Visits 6, 7, and 8.

Hypothesis 1.1: Lower sedentary time and higher time spent in light- or moderate to vigorous intensity physical activity is cross-sectionally and prospectively associated with higher global and domain-specific cognition scores and lower prevalence of MCI.

Hypothesis 1.2: Replacing 30 daily minutes of sedentary time with an equal duration of time spent in low and high light- or moderate to vigorous- intensity physical activity is cross-sectionally and prospectively associated with higher global and domain-specific cognition scores and lower prevalence of MCI.

Aim 2. To examine the cross-sectional and prospective relations of self-reported leisure-time, moderate to vigorous intensity physical activity with (1) global and domain-specific cognition and (2) prevalence of MCI at Visits 6,7, and 8.

Hypothesis 2.1: Higher reported physical activity is cross-sectionally and prospectively associated with higher global and domain-specific cognition scores and lower prevalence of MCI.

Exploratory Aim 1. To compare the relations of moderate to vigorous intensity physical activity with (1) global and domain-specific cognition and (2) prevalence of MCI at Visits 6,7, and 8 using accelerometer versus self-report based measures.

Hypothesis 3.1: The magnitude of the associations will be stronger using accelerometer-determined estimates of moderate to vigorous intensity physical activity, compared to self-reported estimates of moderate to vigorous intensity physical activity.

Exploratory Aim 2. To examine the cross-sectional and prospective relations of latent class groupings (i.e., phenotypes) combining accelerometer and self-reported leisure-time moderate to vigorous intensity physical activity with global and domain-specific cognition at Visits 6, 7, and 8.

Hypothesis 4.1: Three phenotypes will emerge, including 1) high active and low sedentary, 2) moderate activity and moderate sedentary, and 3) insufficient activity and high sedentary.

Hypotheses 4.2: When compared to those classified as “insufficient activity and high sedentary”, those classified in other phenotypes will have higher global and domain-specific cognition scores and a lower prevalence of MCI.

*We are unable to evaluate relations with prevalent dementia given participants with Mini-Mental State Exam (MSSE) score <24 were excluded from accelerometry protocol at Visit 6.

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).

Cross-sectional and prospective design of physical activity (accelerometer and report-based measures) at Visit 6 with cognition and MCI status collected at Visits 6, 7, and 8.

Exclusions: (Aims 1 & Exploratory Aims) Participants who did not attend Visit 6, and did not participate in the 1) Physical Activity and Falls Ancillary Study or had invalid accelerometer wear (<4 days with 10 or more hours of data per day) and missing cognitive factor scores. **(Aim 2)** Participants who did not attend Visit 6, or had missing reported physical activity data or cognitive factor scores.

Exposure(s): (Aims 1 & Exploratory Aim) Accelerometer wear time ($\text{min} \cdot \text{d}^{-1}$), average vector magnitude counts ($\text{VMct} \cdot \text{min} \cdot \text{d}^{-1}$), time spent sedentary ($\text{min} \cdot \text{d}^{-1}$), and in low light ($\text{min} \cdot \text{d}^{-1}$), high light ($\text{min} \cdot \text{d}^{-1}$), and moderate to vigorous intensity physical activity ($\text{min} \cdot \text{d}^{-1}$). **(Aim 2)** Reported moderate to vigorous intensity physical activity ($\text{MET} \cdot \text{min} \cdot \text{wk}^{-1}$ and $\text{min} \cdot \text{wk}^{-1}$) and meeting (or not meeting) 2008/18 Physical Activity Guidelines.

Outcome(s): Cognitive function was assessed with a comprehensive neuropsychological battery administered at Visits 6, 7, and 8. The following domains and cognitive tests were examined: memory (delayed word recall, logical memory, and incidental learning), executive functioning/processing speed (Trail Making Tests, parts A and B; Digit Span Backwards; and Digit Symbol Substitution Test), and language (semantic and phonemic fluency and Boston Naming Test). Factor scores previously derived for general cognitive performance, executive functioning/processing speed, memory, and language will be used, which leverage data from multiple cognitive tests to provide more robust measures of domain-specific function than those provided by individual tests.¹⁷ The interpretation of our factor scores is similar to z scores because they were scaled to have a mean of 0 and a variance of 1.

The following definitions for cognitively normal or mild cognitive impairment were derived by the coordinating center:

Cognitively Normal: all cognitive domain scores are > -1.5 Z scores or the absence of decline in the full ARIC cognitive battery of >0.055 standard deviation units/year.

Mild Cognitive Impairment: performance $\leq$ -1.5 Z scores in at least one domain; a CDR sum of boxes between >0.5 and $\leq$ 3; an FAQ $\leq$ 5; and a decline in the full ARIC cognitive battery >0.055 standard deviation units/per year.

Covariates: Covariates include: 1) race-center, 2) sex, 3) education, and 4) apolipoprotein E ϵ 4 genotype (0 or $\geq$ 1 allele). Other covariates that will be considered include: age (years), cigarette smoking (never vs. ever), body mass index, type 2 diabetes mellitus (fasting glucose $\geq$ 126 mg/dL, non-fasting glucose $\geq$ 200 mg/dL, reported history of type 2 diabetes mellitus from a

physician, or medication use for type 2 diabetes mellitus), hypertension (systolic blood pressure ≥ 140 mm/Hg, diastolic blood pressure ≥ 90 mmHg, or use of blood pressure lowering medication). Visit 1 (baseline) measures will be used for non-time varying measures (e.g., race-center); Visits 6, 7 and 8 will be used for time varying measures (e.g., age).

Statistical Approach:

Aim 1. Three sets of multivariable linear (or logistic for MCI/dementia) regression models will be used to address the hypotheses for Aim 1 (single, partition, and isotemporal substitution models). To optimize interpretation, all accelerometer estimates will be divided by 30, such that a unit increase in that estimate reflects an increase of 30 minutes per day within that given intensity category (sedentary, low and high light intensity, or MVPA). The isotemporal substitution method will be used to estimate the effect of replacing activity from one intensity category (e.g., sedentary) for an equal amount of time in a different intensity category. The models will add total activity time to the partition model and drop, in separate equations, estimates by intensity category. In doing so, the regression coefficient for total activity will represent the activity component omitted from the equation. The remaining regression coefficients for each component will, in turn, represent the effect associated with substituting the omitted activity component with the remaining terms in the model.

Aim 2. Multivariable linear (or logistic for MCI/dementia) regression models will also be used to address the hypotheses for Aim 2.

Methodological Aim 1. Multivariable linear (or logistic) regression models will be used to estimate the relations of moderate to vigorous intensity physical activity (reported and accelerometer-derived) with cognition and MCI/dementia outcomes. Estimates of variability and model fit will be assessed with R² and AIC values, beta coefficients, and an estimate of the root mean square to determine model accuracy.

Methodological Aim 2. Latent class analysis will be used to derive the combined accelerometer and self-report phenotypes. Multivariable linear (or logistic) regression models will be used to estimate the relation of (a) high active and low sedentary or (b) moderate activity and moderate sedentary, compared to insufficient activity and high sedentary, on cognition and MCI/dementia outcomes.

For the above analyses, we will look at 3 sequential models:

- (1) Unadjusted
- (2) Adjusted for sociodemographic factors (i.e. age, sex, education, race-center, ApoE4)
- (3) Adjust for sociodemographic and clinical characteristics (i.e. ever smoking status, body mass index, and prevalent type 2 diabetes mellitus and hypertension)

Attrition: For analyses of cognitive function and MCI/dementia, we will employ methods to address for attrition as recommended by the ARIC-NCS Analysis Workgroup and documented in ARIC Manual 30. Briefly, for the analysis of change in cognitive function, we will consider multiple imputation by chained equations (MICE) to impute missing cognitive data at follow-up visits. Example key variables to incorporate in the imputation model, include, cognitive scores at

prior visits, cognitive screening test scores, indicator variable for death, risk or protective factors of interest, and relevant covariates. As recommended, we will consider a range of 20-40 datasets for the imputation model. Model diagnostics will be performed to confirm good model fit. Inverse probability weights (IPW) will also be considered to account for bias due to attrition in analyses of MCI/dementia. The weights will be calculated as the inverse of the visit-specific probability of being observed such that observations present in the analysis that are similar to those who are missing are up-weighted, implemented similarly to a previous study in ARIC.^{18,19}

Limitations: We acknowledge that the cross-sectional analysis component of this study will be limited by weaknesses associated with this study design. Specific to this project, we will not be able to infer causal relations between physical activity and cognition, and reverse causality is a possibility. Given this, we will only report the findings of the cross-sectional component of this project in an abstract (with limitations noted), and any manuscript based on this work will focus on the prospective component of this project, only. Challenges for the prospective analysis include study participant attrition from Visit 6 to Visits 7 and 8. IPW will be used to account for this, however other methods suggested by the ARIC Physical Activity Working Group and ARIC NCS group will be considered as well, such as multiple imputation by chained equation (MICE). We also acknowledge that accelerometry measures (using an ActiGraph GT9X) are currently being collected at Visit 8. However, with available ActiGraph (wGT3X-BT) measures at Visit 6 in a subsample, we are well poised to evaluate the prospective relations with cognition.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes ☒ 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 ☒ 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

☒ 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)?

#2310 (Palta) Physical activity and change in cognition and incidence of dementia: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

#2961 (Gabriel) A descriptive study of accelerometer-determined physical activity and sedentary behavior in older adults: The ARIC Physical Activity and Falls Study

#3035 (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? ☒ Yes ☐ No

11.b. If yes, is the proposal

- ☒ **A. primarily the result of an ancillary study (list number* 2013.10)**
☐ **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.csc.unc.edu/aric/approved-ancillary-studies>

Data for this proposed analysis will come from the ARIC parent study, the ARIC Physical Activity and Falls Study, and ARIC NCS.

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. Agree.

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.csc.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.

References

1. Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. . *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2019;15(3):321-387.
2. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med*. Apr 4 2013;368(14):1326-1334.

3. Institute of Medicine (U.S.). Committee on the Public Health Dimensions of Cognitive Aging, Blazer DG, Yaffe K, Liverman CT. *Cognitive aging : progress in understanding and opportunities for action*. Washington, D.C.: The National Academies Press; 2015.
4. National Academies of Sciences Engineering and Medicine (U.S.). Committee on Preventing Dementia and Cognitive Impairment, Leshner AI, Landis S, et al. *Preventing cognitive decline and dementia : a way forward*. Washington, DC: The National Academies Press; 2017.
5. U.S. Department of Health and Human Services. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. 2018; https://health.gov/paguidelines/second-edition/report/pdf/PAG_Advisory_Committee_Report.pdf. Accessed March 12, 2018.
6. Carvalho A, Rea IM, Parimon T, Cusack BJ. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clinical interventions in aging*. 2014;9:661-682.
7. McAuley E, Mullen SP, Hillman CH. Physical Activity, Cardiorespiratory Fitness, and Cognition Across the Lifespan In: Hall PA, ed. *Social Neuroscience and Public Health: Foundations for the Science of Chronic Disease Prevention* New York: Springer; 2013.
8. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *The international journal of behavioral nutrition and physical activity*. 2008;5:56.
9. Zhu W, Howard VJ, Wadley VG, et al. Association Between Objectively Measured Physical Activity and Cognitive Function in Older Adults-The Reasons for Geographic and Racial Differences in Stroke Study. *J Am Geriatr Soc*. Dec 2015;63(12):2447-2454.
10. Barnes DE, Blackwell T, Stone KL, et al. Cognition in older women: the importance of daytime movement. *J Am Geriatr Soc*. Sep 2008;56(9):1658-1664.
11. Vasquez E, Strizich G, Isasi CR, et al. Is there a relationship between accelerometer-assessed physical activity and sedentary behavior and cognitive function in US Hispanic/Latino adults? The Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prev Med*. Oct 2017;103:43-48.
12. Ku PW, Liu YT, Lo MK, Chen LJ, Stubbs B. Higher levels of objectively measured sedentary behavior is associated with worse cognitive ability: Two-year follow-up study in community-dwelling older adults. *Experimental gerontology*. Dec 1 2017;99:110-114.
13. Halloway S, Wilbur J, Schoeny ME, Barnes LL. The Relation Between Physical Activity and Cognitive Change in Older Latinos. *Biological research for nursing*. Oct 2017;19(5):538-548.
14. Stubbs B, Chen LJ, Chang CY, Sun WJ, Ku PW. Accelerometer-assessed light physical activity is protective of future cognitive ability: A longitudinal study among community dwelling older adults. *Experimental gerontology*. May 2017;91:104-109.
15. Pettee Gabriel KK, Morrow JR, Jr., Woolsey AL. Framework for physical activity as a complex and multidimensional behavior. *J Phys Act Health*. Jan 2012;9 Suppl 1:S11-18.
16. Troiano RP, Pettee Gabriel KK, Welk GJ, Owen N, Sternfeld B. Reported physical activity and sedentary behavior: why do you ask? *J Phys Act Health*. Jan 2012;9 Suppl 1:S68-75.
17. Gross AL, Power MC, Albert MS, et al. Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiology*. Nov 2015;26(6):878-887.

18. Weuve J, Tchetgen EJT, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology (Cambridge, Mass.)*. 2012;23(1):119.
19. Folsom AR, Shah AM, Lutsey PL, et al. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *The American journal of medicine*. 2015;128(9):970-976. e972.