# ARIC Manuscript Proposal Form

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Publication Committee Review Date: **03/11/25**
ARIC Manuscript Proposal Number: **# 4625**

**1.a. Full Title**: Accelerometer-measured daily physical activity patterns and dementia in the ARIC neurocognitive Study

**b. Abbreviated Title (Length 26 characters)**: Accelerometry and dementia

**2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:**
Writing group members: Keran W. Chamberlin; Lacey Etzkorn; Anis Davoudi; Ryan J. Dougherty; Priya Palta; Amal A. Wanigatunga; Adam P. Spira; Lin Yee Chen; Jennifer A. Schrack

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


**First author [please provide a middle initial; EX: Adam L Williams]:**

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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**3. Timeline**: Analyses will be conducted immediately, and the manuscript draft is expected to be completed within 6 months

**4. Rationale**:

Dementia affects about 1 in 10 older adults in the US[1]. Physical activity (PA), mostly self-reported, has been consistently associated with lower risk of dementia regardless of baseline age or follow-up duration[2]. However, its relationship with dementia is likely bidirectional. On one hand, PA may protect against dementia[3], as it can increase brain blood flow and strengthen brain plasticity and resilience[4,5]. On the other hand, the underlying neuropathology of dementia may affect the ability to engage in daily PA. These pathologies often develop decades before apparent dementia symptoms[6] and compromise brain integrity[7], interfering with one's daily routine and affecting PA quantities and patterns. For example, older adults at risk of developing dementia may have a lower PA with higher day-to-day variation, since depressed mood, a prodromal symptom of dementia, may diminish their desire to move, and early memory disturbances may interrupt their daily regular activity. As such, certain patterns of PA may be suggestive of dementia risk.

Self-reported PA has been most frequently used to examine the PA-dementia relationship[2]. While it serves as an informative proxy of PA, especially for volitional exercise[8], self-reported PA in older adults is coarse and may be imprecise, especially given that the majority of PA in older adults is likely to be light intensity. More importantly, self-reported PA may be subject to significant differential measurement error, as impaired cognitive function may affect one's reporting ability. In contrast, accelerometer-based PA measures present an objective and comprehensive view of an individual's free-living daily activity. The abundant sensor data not only provides precise measurements of PA intensity and duration but also offers a unique opportunity to identify novel early indicators of dementia through PA patterns, for example, day-to-day PA variability, PA fragmentation, and length and timing of active and sedentary bouts[9–11]. Given that these characteristics are often interrelated, it is also of interest to determine which specific PA features are most strongly associated with future dementia.

Several longitudinal studies have examined accelerometer-based PA in relation to dementia risk in older adults[12–18]. However, their study populations were relatively homogeneous, consisting primarily of White[12–14,16–18] or female individuals[15]. In addition, while recent studies have begun examining certain PA patterns in relation to dementia risk[17,18], most of the previous studies have focused solely on overall PA intensity and duration[12–16] and showed mixed results regarding sedentary behavior[15,16]. By leveraging extensive data from the ARIC Neurocognitive Study, we propose to further investigate the relationships between different aspects of device-measured daily PA and risk of dementia in older adults. This study will improve our understanding of the PA-dementia relationship and potentially provide insights for future intervention studies.

**5. Main Hypothesis/Study Aims**:

1) To evaluate the associations of PA quantity and patterns with incident dementia in older adults.

Hypothesis: Lower average PA level, longer sedentary activity and shorter moderate-to-vigorous PA (MVPA) will be associated with a higher risk of dementia. Using a 0-to-0 24-hour time scheme, those with a higher risk of dementia will have their first non-sedentary activity epoch either earlier or later in the day, compared to those with lower dementia risk. More fragmented PA will be associated with a higher risk of dementia. Further, higher inter-daily variability in daily PA intensity, timing of the first non-sedentary epoch, activity duration, and daily PA fragmentation will be associated with a higher risk of dementia.
2) To examine whether detailed information on sedentary activity bouts provides additional insights into incident dementia in older adults beyond total sedentary duration.
Hypothesis: The duration of each sedentary bout and the longest sedentary bout at different time of-day intervals will be associated with the risk of dementia in older adults, independent of total sedentary duration.
3) To investigate whether detailed information on MVPA bouts provides additional insights into incident dementia in older adults beyond total MVPA duration.
Hypothesis: The duration and intensity of each MVPA bout will be associated with the risk of dementia in older adults, independent of total MVPA duration.
4) To investigate which PA features are most strongly predictive of incident dementia in older adults.
Hypothesis: This aim is primarily data-driven, but we hypothesize that the timing of daily activity, duration of sedentary and activity bouts, PA fragmentation, and inter-daily variability will improve the prediction of future dementia beyond average PA intensity.

**6. Design and analysis - please address the following aspects:**

a) **inclusion/exclusion**

Inclusive criteria: Participants who were free of dementia at Visit 6 and wore the Zio XT Patch for at least three full valid days.

Exclusive criteria: Participants who self-reported as Asian or American Indian or Pacific Islander, or Black participants from Washington County or Minneapolis suburbs due to small numbers, and those with Parkinson's disease.

b) **study design**

Longitudinal

c) **outcome and other variables of interest with specific reference to the time of their collection**

Outcome:

Incident dementia (diagnosed at level 3) before the end of 2022. Briefly, incident dementia were identified and adjudicated from in-person neuropsychological evaluation, or identified from telephone cognitive assessment, informant rating, or hospitalization[19].

Exposures of interest:

Accelerometer data was collected using the chest-worn Zio XT Patch tri-axial accelerometer at Visit 6[20].

1) Average PA level was measured as the minute-level daily average mean amplitude deviation (MAD).

2) Sedentary status is defined as MAD < 9.041 milli-g, intermediate PA as 9.041-58.083 milli-g, and MVPA as ≥ 58.083 milli-g[21]. Using these cut-offs, we will calculate the

corresponding timing, duration, and frequency of sedentary bouts and activity bouts at different intensities.

We will also calculate the durations of sedentary bouts, as well as the timing and duration of the longest sedentary bouts during six time-of-day intervals, including 12:00 am to 3:59 am, 4:00 am to 7:59 am, 8:00 am to 11:59 am, 12:00 pm to 3:59 pm, 4:00 pm to 7:59 pm, and 8:00 pm to 11:59 pm. Additionally, we will assess the intensity and duration of MVPA bouts.

3) The timing of the first daily sedentary epoch is defined as the first active epoch lasting at least 5 consecutive minutes, starting from midnight.

4) We will use the root square of successive differences (RMSSD) across all days to define inter-daily PA variability. A lower RMSSD indicates a higher regularity of daily PA.

5) Activity fragmentation will be quantified by using the between-states transition probability[22]. Specifically, we will consider active-to-sedentary and sedentary-to-active transition probability.

Covariates:

We will consider age in years, sex, race-center, education level, APOE4 carrier, body mass index, smoking status, drinking status, prevalent hypertension, diabetes, major cardiovascular diseases (including coronary heart disease, stroke, and heart failure), chronic lung disease, depressive symptoms, and physical functioning as covariates. Covariates were mostly measured at Visit 6 except that age, sex, race, and education was self-reported at Visit 1.

**d) summary of data analysis**

Primary analyses:

In Aim 1-3, we will use the cause-specific hazard model to examine different aspects of PA patterns in relation to incident dementia among at-risk older adults.

In Aim 4, given that death is the dominant competing risk in this population, we will use the Fine-Gray sub-distribution hazard model to predict the risk of dementia and identify which PA features have the strongest predictive ability for dementia.

Covariates will be added to the model in a sequential manner. Model 1 will adjust for age, sex, race-center, and education level. Model 2 will further adjust for APOE4 carrier, body mass index, smoking status, drinking status, prevalent hypertension, diabetes, chronic lung disease, and major cardiovascular diseases. Model 3 will additionally adjust for depressive symptoms, and physical functioning.

Subgroup analyses:

(Aim 1) We will conduct subgroup analyses by age groups, sex, and race.

Sensitivity analyses:

1) As the number of accelerometer-recorded days may affect the inter-daily variability, we will restrict the analysis to participants with at least 13 days with 1440 wear-minutes.

2) Given that RMSSD is subject to consecutive daily variability, we will also consider using the coefficient of variation to evaluate the associations of interest.

3) As participants may have different day-time periods, we will also calculate the between-states transition probability during the 10 consecutive hours of the day with maximum-intensity PA to examine the result robustness.

**e) Any anticipated methodologic limitations or challenges if present**

1) We do not have sleep information in this study, which may make it difficult to distinguish between sleep and sedentary status.
2) We will also consider to use the additive functional Cox Model[23] to evaluate the 24-hour smoothed PA intensity in relation to incident dementia. However, as the PA intensity during night/sleep is primarily around very low MAD, such data sparsity may lead to spurious extrapolation in the additive functional Cox model, affecting statistical inference.

**f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.**

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ No**

**b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ Yes ☐ No**
(The file ICTDER is distributed to ARIC PIs annually, 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: APOE ☐ No**

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No**

**9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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 2310 | Leisure-time physical activity sustained since midlife and preservation of cognitive function: The Atherosclerosis Risk in Communities Study. Alzheimers Dement. | Palta, P |
| MS 4472 | Accelerometer-Measured Activity and All-Cause Mortality Risk in ARIC | Etzkorn, LH |
| MS 4442 | Overall and domain-specific cognitive trajectories and objective physical activity in the ARIC Neurocognitive Study | Gao, S |
| MS 4420 | Association between circadian rest/activity rhythms and incident dementia in older adults: the Atherosclerosis Risk in Communities Study Impairment | Wang, W |
| MS 4336 | Associations of Accelerometry-Derived Sleep, Sedentary Behavior, and Physical Activity with Cognitive Outcomes: A Compositional Data Analysis Approach | Rabinowitz, JA |
| MS 4340 | Physical activity using heart rate and accelerometry and near-term all-cause dementia | Wanigatunga, AA |
| MS 4134 | Definition and Validation of Activity Cut Points for the Zio XT Patch Accelerometer | Etzkorn, LH |
| MS 3474 | Associations of accelerometer-derived and reported physical activity with cognition in older adults | Gabriel, KP |
| MS 3464 | Validation of Zio XT Patch accelerometer for objective assessment of physical activity in community-dwelling individuals | Urbanek, JK |
| MS 3390 | Interaction between Heart Rate Variability and Physical Activity in Relation to Cognitive Function and Dementia: the ARIC Neurocognitive Study | Marino, F |

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)?** ☒ **Yes** ☐ **No → Skip to question 12**

**11.b. If yes to 11.a., is the proposal**

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

**11.c. If yes to 11.a., list number*2021.01 __**

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies Approved Ancillary Studies]

**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.**

Acknowledged

**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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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