# ARIC Manuscript Proposal # 3627

**PC Reviewed: 5/12/20**  **Status: _____**  **Priority: 2**
**SC Reviewed: _____**  **Status: _____**  **Priority: ____**

**1.a. Full Title**: Patterns of Leisure-time Physical Activity and Sedentary Behavior with Carotid Artery Atherosclerosis Morphology: the ARIC Carotid-MRI Study

 **b.  Abbreviated Title (Length 26 characters)**: Physical activity, sedentary behavior and carotid atherosclerosis

**2.   Writing Group**:
Writing group members (alphabetical order): Keith Diaz, Kelly Evenson, Aaron Folsom, Kelley Pettee Gabriel, Gerardo Heiss, Aarti Kumar, Thomas H. Mosley (invited), Priya Palta, Ye Qiao, A. Richey Sharrett, Bruce Wasserman, Yiyi Zhang

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AK_ **[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 9-12 months from proposal approval.

**4.   Rationale**:
        Regular physical activity has been associated with cardiovascular benefits through its favorable effect on various risk factors. For example, physical activity can help reduce blood pressure, lower body mass index (BMI), as well as elevate high density lipoprotein (HDL) and to a lesser extent, reduce triglyceride levels.[1] Physical activity may also directly influence vasculature structure and function,[2,3] which can be measured via characteristics such as wall thickness and stenosis.[2,4–6] As higher levels of these carotid characteristics have been linked to a

greater risk for cardiovascular disease and stroke,[7] physical activity may serve as a protective factor of atherosclerotic disease. While ultrasound is considered to be the standard imaging technique for first-line diagnosis of carotid atherosclerosis, MRI allows for a further evaluation of plaque components, including intraplaque hemorrhage, fibrous cap, and lipid rich necrotic core (LRNC).[6] Furthermore, carotid artery wall thickness measured by MRI may be a better predictor of cardiovascular disease, particularly stroke, compared to intima-media thickness measured by ultrasound.[8]

While most studies have shown that higher physical activity is associated with more favorable carotid artery measures, a majority of these studies[2,4,9–11] have been cross-sectional in nature. In addition, some have presented more mixed findings – e.g., only finding a significant association in men.[12] Therefore, we have a unique opportunity in the ARIC Study to examine the role of leisure-time moderate-to-vigorous intensity physical activity (MVPA), its longer term persistence, and changes in leisure-time MVPA over time on carotid artery characteristics.

In contrast, sedentary behavior, particularly TV viewing, has been shown to be a risk factor for greater carotid plaque, larger carotid intima-media thickness, and greater stiffness[5,13–15] as well as other cardiometabolic risk factors (e.g., hypertension, high BMI).[16] However, few studies have explored if leisure-time MVPA interacts with sedentary behavior to mitigate or potentially eliminate the adverse effects of sedentary time.

In this study, we seek to address some key research gaps by using prospective cohort data from the biracial population-based ARIC study. Specifically, while several studies have examined the associations between physical activity and sedentary behavior on carotid artery characteristics independently and at a single timepoint, our study seeks to understand the independent associations of changes in leisure-time MVPA and sedentary behavior (from ARIC Visit 1 in 1987-1989 to Visit 3 in 1993-1995) on carotid wall thickness, stenosis, and plaque characteristics measured by MRI (2004-2006), as well as how leisure-time MVPA and sedentary behavior together may impact the manifestation of these carotid artery characteristics. In addition, we will test for interactions by sex and race, as research has shown that non-Hispanic Blacks[17] as well as women 50 years and older[18] have a higher risk for cardiovascular disease. Therefore, it is important to quantify if these modifiable behaviors (i.e., leisure-time MVPA and sedentary behavior) have differential associations across these subgroups.

## 5. Main Hypothesis/Study Questions:

**Primary Aim 1:** Examine the association of baseline levels (Visit 1: 1987-1989) and changes (Visit 1 to Visit 3: 1993-1995) in leisure-time MVPA in mid-life with carotid atherosclerosis morphology collected in 2004-2006.

*Hypothesis 1.1: High baseline levels of leisure-time MVPA are associated with smaller carotid wall thickness, smaller lipid core volumes (adjusted for wall thickness), and lower levels of stenosis).*

*Hypothesis 1.2: Persistently high leisure-time MVPA compared to persistently low leisure-time MVPA, measured over 6 years, is associated with smaller carotid wall thickness, smaller lipid core volumes (adjusted for wall thickness), and lower levels of stenosis.*

**Primary Aim 2:** Quantify the association of baseline (Visit 1: 1987-1989) and changes (Visit 1 to Visit 3: 1993-1995) in sedentary behavior in mid-life, measured as frequency of TV viewing, with carotid artery atherosclerosis morphology collected in 2004-2006.

*Hypothesis 2.1: Compared to a low frequency of TV viewing ("never" or "seldom") frequent TV viewing ("often" or "very often") is associated with larger carotid wall thickness, larger lipid core volumes (adjusted for wall thickness), and higher levels of stenosis.*

*Hypothesis 2.2: Persistently high frequencies of TV viewing ("often" or "very often") compared to persistently low frequencies of TV viewing ("never" or "seldom"), measured at visits 1 and 3, are associated with larger carotid wall thickness, larger lipid core volumes (adjusted for wall thickness), and higher levels of stenosis.*

**Exploratory Aim:** Determine the joint association of baseline (Visit 1: 1987-1989) leisure-time MVPA and sedentary behavior at mid-life on measures of carotid atherosclerosis (2004-2006).

**Cross-cutting hypotheses**: All primary aims will test for effect modification by race and sex.

**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 leisure-time MVPA and sedentary behavior from visits 1 (1987-1989) and 3 (1993-1995) and their association with carotid artery characteristics from the Carotid MRI Study (2004-2006).

**Inclusion/Exclusion Criteria:** Individuals who participated in the Carotid MRI study will be included. Any participants with missing exposure and outcome data (e.g., missing leisure-time MVPA or TV viewing measurements from visits 1 or 3, incomplete MRI parameters) will be excluded. We anticipate an analytic sample size of ~1769 participants.

**Exposure(s):**

Data on leisure-time MVPA and sedentary behavior were measured using the Baecke Physical Activity questionnaire[19] at ARIC visits 1 (1987-1989) and 3 (1993-1995).

**(1) Baseline Leisure-time MVPA Activity**
Habitual physical activity during leisure and sport were assessed using the Baecke Questionnaire.[19] As completed with prior analyses,[20–24] each activity will be converted into a metabolic equivalent of task (MET) ranging from 1 to 12 based on the Compendium of Physical Activities.[25] MET-minutes per week (MET·min·wk$^{-1}$) will be estimated for each activity by multiplying the MET value, frequency, and duration of the reported activity. Leisure-time MVPA levels will then be categorized according to the American Heart Association (AHA) recommendations[26] as: "ideal" (≥75 min/week of vigorous intensity or ≥150 min/week of any combination of moderate + vigorous intensity exercise), "intermediate" (1–74 min/week of

vigorous intensity or 1–149 min/week of any combination of moderate + vigorous intensity exercise), or "poor" (0 min/week of moderate or vigorous exercise). This categorization for visit 1 will serve as the baseline leisure-time MVPA exposure variable. We will also examine leisure-time MVPA as a continuous variable in MET·min·wk$^{-1}$.

**(2) Persistence and Changes in Leisure-time MVPA**
We will compare leisure-time MVPA level categorizations (i.e., "ideal", "intermediate", or "poor") from visits 1 & 3 and categorize participants according to (1) persistence in leisure-time MVPA ["poor" at both visits, "ideal" at both visits, or "intermediate" at both visits] or (2) changes in leisure-time MVPA [decreased leisure-time MVPA ("ideal" to "intermediate" or "poor"; "intermediate" to "poor"), or increased leisure-time MVPA ("poor" to "intermediate" or "ideal"; "intermediate" to "ideal")]. We will also examine absolute changes in continuous measures of leisure-time MVPA (MET·min·wk$^{-1}$) and an average of continuous measures of leisure-time MVPA across visits 1 and 3.

**(3) Baseline TV Viewing (surrogate measure of leisure-time sedentary behavior)**
Participants were asked about television viewing frequency in a questionnaire, with response options including: "never", "seldom", "sometimes", "often", and "very often". For analysis, we will further classify as low ["never"/ "seldom"], medium ["sometimes"], and high ["often"/ "very often"] as done in prior ARIC studies.[27,28] These levels captured during visit 1 will serve as the baseline TV viewing exposure variable. While TV viewing will be the primary measure of sedentary behavior, we will also consider collected data on occupational sedentary behavior (i.e., frequency of sitting at work) for participants who worked, reported as "never", "seldom", "sometimes", "often", or "always".

> The frequency of reported TV viewing at visit 1 is the following: low (18.5%), medium (46.6%), and high (34.7%) with 2% of the sample having missing data.

**(4) Persistence and Changes in TV Viewing**
We will compare TV viewing levels from visits 1 & 3, and categorize participants as stable high TV viewing ("often"/"very often" during both visits), stable medium TV viewing ("sometimes" during both visits), stable low TV viewing ("never"/ "seldom" during both visits), decreased TV viewing (any decrease from visits 1 to 3), or increased TV viewing (any increase from visits 1 to 3).
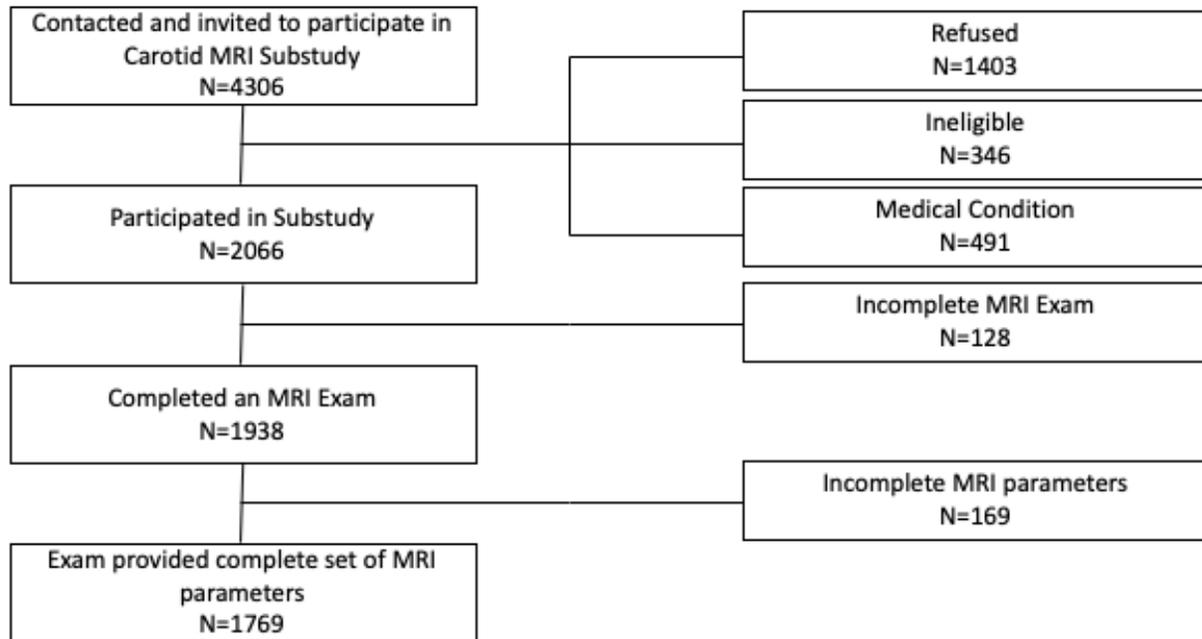
> Preliminary analyses show the following frequency of persistence and changes in TV viewing: stable high (22.1%), stable medium (28.7%), stable low (9.2%), increased TV viewing (23.2%), and decreased TV viewing (16.8%).

**(5) Joint Associations of Leisure-time MVPA and TV Viewing**
In exploratory analyses, we will examine the joint association between leisure-time MVPA and TV viewing on the carotid artery outcomes of interest. We will consider categories of LTPA and TV viewing previously examined in ARIC.[28]

**Outcome(s)**:

The Carotid MRI study was done in a subset of ARIC participants (n=1769) in 2004 - 2006. In order to oversample for plaque, the goal was to recruit approximately 1200 individuals who had a carotid artery wall thickness greater than the 85th percentile based on a prior ultrasound and 800 individuals randomly selected from the remainder of the broader ARIC cohort. Among the 4306 individuals randomly selected to participate using this stratified plan, only 1769 participants completed an MRI with all of the relevant parameters and adequate image quality. See below for a schematic describing the ARIC Carotid MRI sample.

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Contacted and invited to participate in          Refused
Carotid MRI Substudy                             N=1403
N=4306
                                                 Ineligible
                                                 N=346

Participated in Substudy                         Medical Condition
N=2066                                           N=491

                                                 Incomplete MRI Exam
                                                 N=128

Completed an MRI Exam
N=1938

                                                 Incomplete MRI parameters
                                                 N=169

Exam provided complete set of MRI
parameters
N=1769
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Each ARIC field center established a clinic to perform the carotid MRI on a 1.5T MRI using a standardized protocol, and all images were interpreted by seven blinded readers.[29] Various carotid wall and carotid plaque measurements were collected, which will serve as the primary outcomes of interest for our particular study, including but not limited to, wall thickness, percent carotid stenosis, and lipid core volumes (adjusted for wall thickness). These outcome variables are measured on a continuous scale. We will also consider non-continuous measures, including lipid core presence/absence, intraplaque hemorrhage presence/ absence, and stenosis categories.

**Statistical Analysis:**

Our primary analysis will use multivariable linear regression to examine the association between leisure-time MVPA/ sedentary behavior described above with each of the carotid artery outcomes of interest (e.g., wall thickness, percent carotid stenosis, and lipid core volumes (adjusted for wall thickness)) measured continuously. In secondary analyses, we will use multivariable logistic regression to examine the associations between leisure-time MVPA /sedentary behavior described above with binary outcomes of lipid core presence/absence and

intraplaque hemorrhage presence/absence, and use multinomial logistic regression when examining stenosis categories.

As completed in previous studies,[30] analyses will be weighted by the inverse of the sampling fractions in the eight sampling strata (four field centers by the two IMT groups), such that data from individuals in the proportionally underrepresented low IMT group are given less weight than data from individuals in the overrepresented high IMT group.

Primary aims will also test for interactions by race and sex.

Covariates that will be considered include age, sex, smoking, education level, race by ARIC study field center, and dietary intake. We will also consider intermediate vascular risk factors (e.g., hypertension, diabetes, BMI, total cholesterol, medication (i.e., antihypertensives, statins) use) in secondary analyses.

**Methodological Limitations:** Leisure-time MVPA and TV viewing (measure of sedentary behavior) are measured via self-report and may be subject to reporting bias. In particular, the single item TV viewing question used in this study has not been validated, and response choices are non-specific and semi-quantitative, which may result in misclassification. Furthermore, television viewing only captures one form of leisure-time sedentary behavior. In addition, because changes in leisure-time MVPA and TV viewing were assessed over an average of six years, it is possible that there may have been unmeasured changes between visits 1 and 3 and/or between visit 3 and the carotid MRI substudy that may have contributed to carotid artery differences. We are unable to relate changes in leisure-time MVPA and/or TV viewing to changes in core plaque morphology due to the lack of baseline carotid MRI plaque features. With respect to the carotid MRI study, all exams were screened for image quality and protocol adherence, and any "failed" exams were not analyzed. However, reader variability could have contributed to some measurement error, most influenced by the size of the measured structure.[29] Selection biases into the ARIC Carotid MRI Study may impact the results and generalizability of study findings. To understand the extent of bias, we will examine differences (e.g. demographics, clinical and comorbidity factors) between those participants selected for the Carotid MRI substudy compared to the baseline ARIC sample.

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes    __X__ 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 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 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 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/mantrack/maintain/search/dtSearch.html

___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#2372 (Dearborn): Dietary Intake and Carotid MRI Plaque characteristics
MS#459 (Evenson): The relationship between physical activity to incident hypertension: the ARIC Study
MS#2548 (Florido): Changes in Physical Activity and Risk of Incident Heart Failure: the Atherosclerosis Risk in Communities (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 (Carotid MRI)**
    **___ 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 https://sites.cscc.unc.edu/aric/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.**

**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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