ARIC Manuscript Proposal #3646

PC Reviewed: 6/9/20 **Status: _____** **Priority: 2**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1.a. Full Title: The Association Between Midlife Leisure-Time Physical Activity and Hearing Impairment in Late-life in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): physical activity-hearing

2. Writing Group:

Writing group members:
Pablo Martinez-Amezcua (first author)
Emmanuel Garcia-Morales
Priya Palta (senior author)
Nicholas S. Reed
Kevin Sullivan
Matthew Waggenspack
James S. Pankow
Kelley Pettee Gabriel
A.Richey Sharrett
Josef Coresh
Jennifer A. Schrack
Frank R. Lin
Jennifer A. Deal (second senior author)

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

First author: Pablo Martinez-Amezcua
Address: Center on Aging and Health
2024 E Monument Street
Baltimore, MD, 21205
Phone: 443-707-6497
E-mail: pablov489@jhu.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: Jennifer A. Deal, PhD
Address: 2024 E Monument Street
Baltimore, MD, 21205

Phone: 410-955-1909
E-mail: jdeal1@jhu.edu

3. Timeline: Analyses and manuscript to be completed within 1 year

4. Rationale:

Nationally representative surveys estimate that two-thirds of adults over 65 years have hearing loss(1), which is associated with negative health outcomes including cognitive impairment(2), dementia(3), social isolation(4), and hospitalizations(5).

Known risk factors for age-related hearing loss include genetic predisposition, increasing age, white race, male sex, and noise exposure. Identifying modifiable risk factors for age-related hearing loss could help preserve communication and quality of life in older adults, and potentially, prevent or delay the age of onset of other downstream adverse outcomes associated with hearing loss.

Cardiovascular risk factors have also been identified as potential risk factors for hearing loss. One of the underlying hypothesis is that hearing loss results from reduced blood flow in the inner ear(6,7). The compromised blood flow might affect mostly the stria vascularis—rich in vasculature, with a high metabolic rate, and responsible for maintaining the endolymphatic potential — leading to its atrophy and decreased endolymphatic potential, which manifests as increased hearing thresholds (worse hearing)(8). Another potential explanation for this association is hair cell damage from oxidative stress, also resulting from a lower vascular supply(9).

Lower levels of physical activity are associated with obesity, and in particular with increased fat mass; type 2 diabetes; dyslipidemia; and hypertension; all of which have been associated with hearing loss, potentially through the mechanism described above(10–12) Through these pathways, an association between lower levels of physical activity and hearing loss is hypothesized.

In 2013, a publication from the Nurses' Health Study found that higher midlife physical activity was associated with better hearing in later life(6). However, the assessment of hearing loss in that study was subjective, which is more prone to misclassification than pure-tone audiometry(13). Similarly, in 2019, a publication from the Jackson Heart Study, found an association between physical activity and hearing(14). This study used pure-tone audiometry to measure hearing. Still it was a cross-sectional examination and the results were inconsistent (intermediate levels of physical activity [compared to poor] were protective, but ideal levels were not).

Epidemiological studies have investigated the association of cardiovascular risk factors, other than physical activity, with age-related hearing loss. An association between retinal signs of microvascular disease and hearing loss was found in the ARIC-NCS study(15). Additionally, using ARIC data, two manuscripts have found an association between midlife hypertension and late-life hearing loss(16), and low speech-in-noise hearing capacity (MP #3254, in preparation). The second manuscript analyzed a much greater sample size and did not find an association between hypertension and peripheral hearing loss measured by pure-tone audiometry. Potentially, these findings are explained by vascular damage caused by hypertension affecting the brain in greater degree than the inner ear. If that is the case for other cardiovascular factors too, we would expect to see similar findings with regards to physical activity.

In response to the limitations of previous studies, we aim to investigate the association between midlife physical activity measured in ARIC visits 1 (1987-1989) and 3 (1993-1995) and hearing measured in visit 6 (2016-2017). We will have a measurement of physical activity (exposure) preceding hearing loss (outcome) by 15-20 years, and our measures of hearing will be by pure-tone audiometry and a speech in noise test, a measure of central hearing, allowing for better understanding of the association. Additionally, we will also use physical activity measures from visit 5 to identify mid-to-late-life trajectories and investigate the association between these trajectories and hearing loss in late-life.

Our proposed project will help to clarify the association between midlife physical activity and age-related hearing loss. Our work will also address some limitations from the previous literature in this field, specifically by having an objective assessment of hearing and up to 20 years of follow-up.

5. Main Hypothesis/Study Questions:

1. Investigate the association between midlife physical activity (at visits 1 and 3 [1987-1995]) and hearing impairment (peripheral and central) measured at visit 6 (2016-2017).
   - *We hypothesize that lower midlife physical activity is associated with poorer peripheral and central hearing later in life.*

2. Investigate the association between physical activity trajectories from mid-to-late-life (visits 1,3,5 [1987-2013]) and peripheral hearing impairment measured at visit 6.
   - *We hypothesize that greater decline in physical activity and sustained lower levels of physical activity are associated with poorer peripheral and central hearing*

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:
Cross-temporal study of the association between midlife physical activity (measured at visits 1 and 3) and hearing measured 15-20 later (visit 6)

Study Population:
Our study sample originates from the full cohort of 15,792 participants and incorporates data from Visit 1 through Visit 6. Audiometry was offered to all participants who attended Visit 6 (2016-2017), with complete audiometry available for 3628 (91% of the 4003 participants who attended Visit 6).

<u>Exposure:</u>

Leisure time, moderate to vigorous intensity physical activity (LTPA) was measured at ARIC visits 1 (1987-1989), 3 (1993-1995), 5 (2011-2013), using a standardized interviewer-administered questionnaire that utilizes a past-year recall time frame(17). Participants were asked to report up to 4 leisure-time activities or sports that s/he did. Physical activity intensity was estimated by assigning each reported activity type a metabolic equivalent of task (MET) value ranging from 1 to 12 METs based on the 2011 Compendium of Physical Activities(18). Then, for each reported activity type, participants reported the number of hours within a week and the number of weeks over a month that they performed each activity. Activity specific estimates (both MET/min/week and min/week) were obtained by multiplying the reported intensity, duration and frequency. Estimates of LPTA (both MET/min/week and min/week) were obtained by summing activity-specific estimates. For these analyses, the summary estimate in MET/min/week will be used.

Midlife physical activity (Aim 1)

Midlife physical activity will be defined as the average (MET/min/week and min/week) from visits 1 and 3. Late-life physical activity will be defined as LTPA at visit 5.

Midlife and late-life LTPA (minutes/week) will also be dichotomized (meets vs does not meet guidelines) based on the physical activity guidelines for Americans developed by the Department of Health and Human Services. The guidelines establish that adults should perform 150+ min/week of moderate, or 75+ of vigorous physical activity(19). We will first calculate the average of visits 1 and 3 for the continuous variables of LTPA and then dichotomized based on the guidelines.

In addition, to investigate the possible dose-response association, we will be categorized LTPA further into 4 groups (no=0 min/week, low=1-149 min/week, medium=150-299 min/week, high=300+ minutes/week) using the guidelines as reference.

We will use the midlife LTPA (continuous and categorical) at visit 1as the exposure in our primary analyses.

Mid-to-late-life physical activity trajectories (Aim 2)

For the continuous variables of LTPA, we will calculate the change in LTPA, from mid-to-late-life, in min/week and MET/min/week by subtracting the value at late-life (v5) from the value at midlife (average of v1 and v3).

For the dichotomized LTPA variable, we will identify 4 trajectories (sustained high, sustained low, increase, decrease) based on meeting guidelines (high) or not (low) at each period. Participants who met guidelines in both periods will be considered sustained high; participants who did not meet guidelines in both periods will be considered sustained low; participants who met guidelines in midlife but did not in late-life will be considered as decreasing; and those who did not meet in midlife but met in late-life will be considered increasing. When we compare these groups, we will consider the sustained high group as the reference.

Alternatively, for secondary analyses, physical activity trajectories will be also identified using latent class analyses. Using this method, previous work in ARIC identified 4 trajectories (sustained high, sustained low, increase, and decrease)(20).

Outcome:

At ARIC visit 6, among participants who completed on-site follow-up visits, pure tone audiometry was completed in a sound-proof booth using the Interacoustics AD629 audiometer (Interacoustics A/S, Assens, Denmark). For participants with a home visit, a portable audiometer was used after testing that ambient noise levels were low enough to ensure valid testing. Air conduction audiometry was completed at standard octaves at 500, 1000, 2000, 4000, 6000, and 8000 Hz. For analysis, we will calculate a four-frequency pure-tone average (PTA) in each ear (the hearing sensitivity or threshold is measured at each one of the four sound ("speech") frequencies [500,1000,2000,4000 Hz]), and use the PTA (continuous variable) for the worse hearing ear as outcome for our main analysis. Additionally, hearing impairment will be categorized using WHO standards: Normal hearing, PTA≤25; mild loss, PTA 26-40 dB; moderate/greater loss, PTA >40 dB in the worse hearing ear(21).

Speech-in-noise performance is a comprehensive measure that reflects all aspects of the auditory system from peripheral encoding sound in the cochlea to central decoding and processing the signal in the auditory cortex. In ARIC, speech-in-noise performance was assessed using the Quick Speech-in-Noise Test (QuickSIN). Participants are asked to repeat sentences presented to them in the presence of multitalker background noise that is similar to the sound of various conversations in a crowded restaurant. Each list consists of six syntactically correct sentences that offer few contextual cues for the listener. Sentences are presented at 70 dB which is similar to conversation level. With each sentence, the volume of the background noise increases until it is equal to the presented sentence on the sixth sentence (i.e., signal to noise ratio of 0dB). Each sentence is scored in a scale from 0-5 based on the correct identification of 5 target words. The final score is the sum of the scores for each one of the six sentences and ranges from 0-30 (higher scores are better)(22)

Additional Independent Variables:

Basic demographic information, body mass index (BMI), and smoking; type 2 diabetes; and hypertension status, were collected at Visit 1. Demographic data included birthdate for calculating age at study visit, sex, education, and race-study site. BMI will be calculated as weight in kilograms divided by height in meters squared. Cigarette smoking status was self-reported as never, former, or current. Diabetes will be defined by fasting glycemia ≥126 mg/dL, non-fasting glycemia ≥200 mg/dL, self-reported diagnosis by physician, or use of medication for diabetes). Hypertension will be considered when diastolic blood pressure was ≥ 90 mm Hg; or systolic blood pressure was ≥140 mm Hg, or self-reported diagnosis by physician; or antihypertensive medication use.

Noise exposure was collected at visit 6 and will be dichotomized based on the presence of self-report of ever being exposed to: firearm use (target shooting, hunting, military, job, or other), a job with very loud sounds or noise for more than 10 hours per week, or very loud noise or music more than 10 hours per week outside of a job.

Statistical Analysis:

1. **Investigate the association between midlife physical activity (v1-v3) and late-life hearing capacity:**

We will investigate differences in summary measures of demographic and clinical characteristics across the different levels of LTPA using chi-square and analysis of variance (ANOVA) tests as appropriate.

Linear regression will be used to estimate the association between midlife LTPA and hearing thresholds (peripheral and central) 15-20 later in life. In these models, we will estimate the mean differences in hearing thresholds by a one-unit difference in LTPA. Using our categorical definition of physical activity, we will also estimate the difference in hearing thresholds between participants who met and did not meet guidelines.

Ordinal logistic regression models will be used to assess the association between midlife LTPA and hearing loss categories15-20 later in life. Similarly, we will use our continuous and categorical definitions of midlife LTPA in separate models. Models will be adjusted for age, sex, race-center, education, smoking, hypertension and BMI

We will also use linear mixed models with a random intercept to estimate the association between midlife LTPA and hearing threshold at each frequency in the whole range of frequencies tested with the pure-tone audiometry (0.5-8 kHZ). These models account for the correlation of thresholds coming from the same individual, and, including an interaction term between LTPA and hearing frequencies, the model allows to assess if there are differences in the associations across hearing frequencies.

Additionally, we will also use an alternative definition the outcome (pure-tone audiometry) as the PTA in the better hearing ear to assess the robustness of our results, and we will stratify by the presence of noise exposure, which is associated with hearing loss and cardiovascular health (1,23), and might modify the association between midlife LTPA and hearing (among those exposed to noise the association between of LTPA and hearing loss might be attenuated). Selection bias due to differential attrition might be a limitation of our analyses. In sensitivity analyses, we will calculate inverse-probability weights of attrition, and perform weighted analyses to address this limitation.

2. **Investigate the association between trajectories of physical activity (mid-to-late life) and hearing in late-life:**

We will investigate the association between physical activity trajectories from mid-to-late-life (continuous and categorical) and PTA in the worse hearing ear in later life (visit 6) using linear regression models adjusted for the same set of covariates described above.

The models where we use the continuous trajectory of LTPA (change from visits 1&3 to visit 5) will estimate the mean PTA at visit 6 per 1-unit change in min/week and MET/min/week. The models where we use the categorical trajectory of LTPA (sustained low, increase, decrease, compared to sustained high) will estimate the difference in mean PTA across trajectories.

In addition, we will use ordinal logistic regression to investigate the association between physical activity trajectories and hearing loss categories in later life.

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 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 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.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)?

MP#3356 Ideal cardiovascular health and age-related hearing loss in the Atherosclerosis Risk in Communities Study

MP#2418 Hearing Impairment and Physical Function in the Atherosclerosis Risk in Communities (ARIC) Hearing Pilot Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _________)

___ 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.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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