ARIC Manuscript Proposal # 3313

PC Reviewed: 12/11/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

b. Abbreviated Title (Length 26 characters): Smoking and Age-Related Hearing Loss in the Atherosclerosis Risk in Communities Study

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

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3. Timeline:
Manuscript will be completed in 12 months.

4. Rationale:
Hearing impairment affects about 538 million Americans and 18 million Americans over the age of 65 [1,2]. This makes up about 40% of all elderly Americans [3]. Although hearing loss affects a large proportion of older individuals, its impact cannot be overlooked. It has been associated with increased rates of dementia, social isolation, and depression [4]. To reduce the detrimental impacts of hearing loss, effective measures directed towards the mechanistic pathways must be developed to prevent hearing loss.

Some theories link smoking to hearing impairment, through the development of free radicals that disrupt metabolic function within the cochlea [5]. Many cross-sectional studies have demonstrated a statistically significant association between current smoking and hearing loss [6-16]. To further strengthen this association, Fransen et al and Dawes et al even identified a dose-dependent response to smoking, quantified by pack-year history [10,14]. Notably three studies by Gates et al, Sousa et al, and Wattamwar et al did not find cross-sectional associations between hearing loss and smoking, but these studies may have been limited by their smaller sample sizes (N=1662, 625 and 433, respectively) [17-19].

Many of these studies are limited by their cross-sectional design. Two longitudinal studies have since been conducted to study the impact of smoking on incident hearing loss. Cruickshanks et al showed increased incidence of hearing loss over a 15 year period among current smokers (HR 1.36, 95% CI 1.05-1.77) but not among former smokers [20]. Similarly Kim et al showed significant differences in hearing thresholds over a 9 year period for the standard four-frequency pure tone averages (PTA) and 8 kHz frequency [21]. However, neither of these studies incorporates racial diversity into their homogenous study groups.

Existing research seems to suggest that there is no increased risk of hearing loss for former smokers, demonstrated by Tan et al, Cruishanks et al 2015, Helzner et al 2005, and Itoh et al [6,15,21,22]. Most studies studying the association between hearing loss and smoking status have grouped former smokers and never smokers into the same category, making it hard to study the difference [7-10,12,14,16-20]. Of note, one study by Helzner et al 2011 grouped former smokers with current smokers, reporting an increased risk of hearing loss related to any history of smoking [11].

Our study builds upon the existing literature that examines the relationship between smoking and hearing loss. It utilizes a large sample size (N=3382) and allows for the inclusion of a more diverse study population. With our study population, we can also look at the impact of mid-life cigarette exposure on hearing impairment measured in late life. With over 25 years of followup between Visits 1-6, we can also study the impact of the smoking cessation and patterns of smoking history on hearing impairment.

5. Main Hypothesis/Study Questions:

Aim 1: To quantify the association between mid-life (Visit 1) or late-life (Visit 6) smoking status and age-related hearing impairment (measured at Visit 6) in older adults.

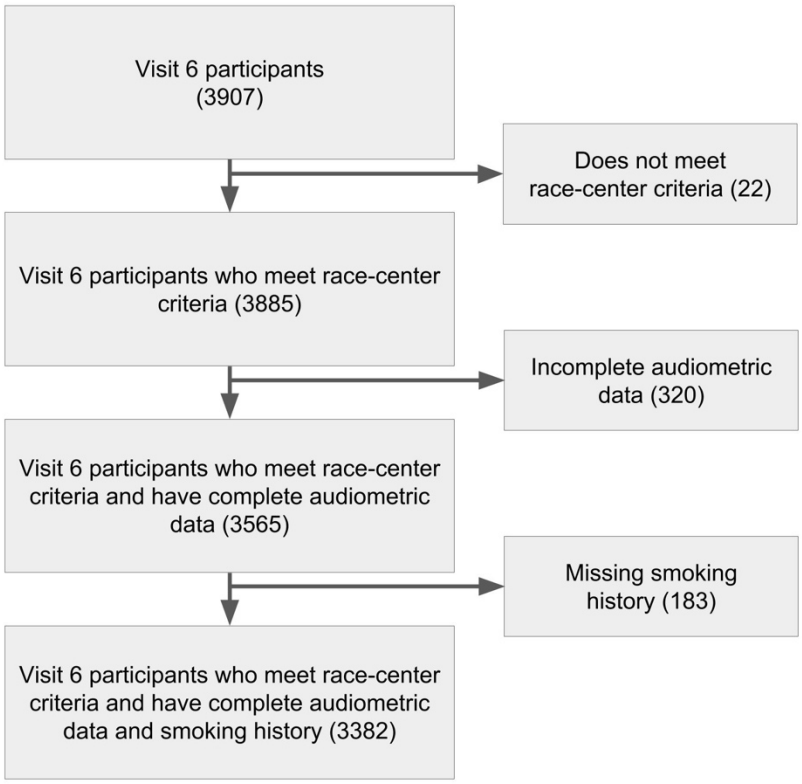
> *We hypothesize that smoking in mid-life (Visit 1) and current smoking in late-life (Visit 6) are associated with increased odds of hearing loss and poorer hearing thresholds in older adults in late life (Visit 6).*

Aim 2: To quantify the association between changes in smoking status from Visit 1 to Visit 4 and hearing impairment measured at Visit 6.

We hypothesize that persistent active smoking from Visit 1 to 4, as opposed to smoking cessation, is associated with poorer hearing thresholds in older adults.

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 Population: Mostly biracial population of 3382 men and women (22% African American) aged 54-74 years at Visit 4, meet race-center criteria, with smoking history recorded at Visits 1, 4, and 6, who underwent audiometry testing at Visit 6, and have at least one instance of smoking history recorded from Visits 1-3.



There are 3097 participants who had smoking histories recorded at Visit 6. Twenty two participants are missing the race-center variable. An additional 320 participants are removed due to having incomplete audiometric testing, which we define as missing any hearing thresholds for 0.5, 1, 2, or 4 kHz. Finally, 183 more participants were excluded since they were missing their smoking history from Visit 1 or 4.

Hearing Loss

Pure tone audiometry was offered to all ARIC participants at Visit 6 (2016-17). A four-frequency (0.5, 1, 2, and 4 kHz) pure tone average (PTA) will be calculated in the better-hearing ear and hearing impairment will be defined using clinically relevant PTA cutpoints as defined by the World Health Organization (WHO): (1) normal hearing: ≤25 decibels hearing loss (dB HL), (2) mild hearing loss: >25 dB HL and ≤40 dB HL, (3) moderate hearing loss: >40 dB HL and

≤60 dB HL, (4) severe or profound hearing loss: >60 dB HL [5]. PTA will also be modeled as a continuous variable (scaled so that one unit change equals a dB HL increase).

In a secondary analysis, hearing thresholds at the higher frequencies (4, 6, and 8 kHz) will be modeled continuously in order to investigate the association between smoking and high frequency hearing impairment. Higher hearing thresholds for a specific frequency correspond to higher volumes needed for participants to hear that frequency, thus corresponding to worse hearing.

Smoking History

At Visits 1-5, the participants were asked to identify themselves as either current, former, or never smokers. However, at Visit 6, participants were not asked to self-identify into one of these three categories; instead they were only asked if they identify as current smokers. With the participants reported smoking history from Visit 5 and their reported smoking status at Visit 6, we will then categorize participants as current, former, or never smokers at Visit 6. Smoking history will be modeled as a categorical variable, with three categories: 1) current smoker, 2) former, and 3) never smoker.

Smoking history not only be categorized but also quantified using pack-years. Pack-years can be calculated over Visits 1-6. At Visit 1, participants were asked to calculate their past pack-year history. At the subsequent visits (Visits 2-4), pack-year history will be increased by the number of cigarettes smoked in a day divided by twenty (to calculate daily cigarette packs smoked in a day) multiplied by time elapsed since the prior visit, as described by ARIC proposal 2262. Between Visits 4 and 6, pack-year history will be calculated as described by ARIC proposal 3170.

For former smokers, pack-years will be calculated as:
$\text{cigarettes/day} \times [(\text{age}_{\text{quit}} - \text{age}_{\text{initiation}}) - \text{years quit in between}] / 20.$

For current smokers, pack-years will be calculated as:
$\text{cigarettes/day} \times [(\text{age}_{\text{Visit 1}} - \text{age}_{\text{initiation}}) - \text{years quit in between}] / 20.$

These equations use data collected at Visits 1-6. Of note, “years quit in between” accounts for the years an individual may have quit before they quit for the last time.

Figure 1: Smoking questionnaire from Visit 1

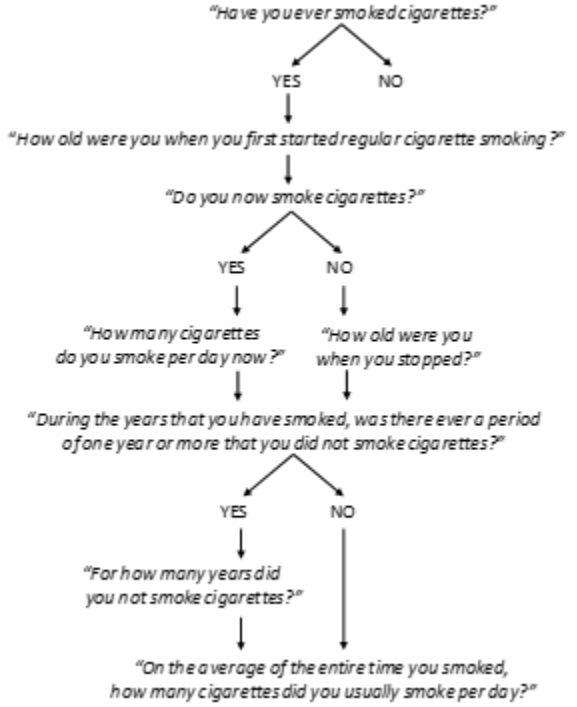
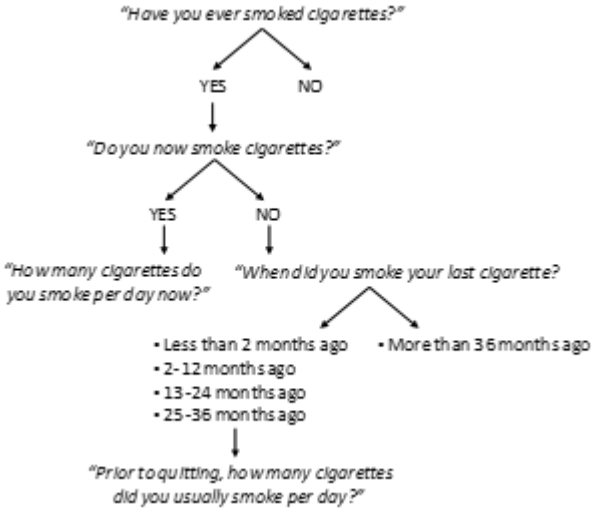


Figure 2: Smoking questionnaire from Visit 2



For Aim 2, we will further categorize participants into one of four possible smoking history trajectories. The first two groups are defined only by their smoking history status at Visit 1: (a) never smoker and (b) former smoker. The next two groups are defined as having been current smokers at Visit 1 but distinguished by their Visit 4 smoking history: (a) former smoker and (b) current smoker. Thus, our four groups are defined (using the naming convention of Visit 1- Visit 4): (a) never smoker-any status, (b) former smoker-any status, (c) current smoker-former smoker, (d) current smoker-current smoker.

Additional independent variables

Demographic information was collected at Visit 1, including age (years), sex, race, and education (highest grade or year of school completed). Education will be categorized according to standardized ARIC algorithms as less than high school, high school or equivalent, or greater than high school.

Body mass index (kg/m2) was calculated at each study visit and will be categorized according to clinical cutpoints: normal weight (<25 kg/m2), overweight (25-30 kg/m2) and obese (>30 kg/m2). Hypertension will be considered present if systolic blood pressure was ≥ 140, diastolic blood pressure was ≥ 90, or the participant self-reported taking medications for lowering blood pressure. Diabetes will be considered present if fasting blood glucose level was ≥ 126 mg/dL, nonfasting level ≥ 200 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes. Medications that may possibly be ototoxic (e.g., ibuprofen) will also be evaluated. Participants were also asked to report their status of drinking alcohol as either current drinker, former drinker, or never drinker at each study visit.

Noise exposure will be considered present if the participant self-reported a history of occupational or leisure loud noise exposure (5+ hours per week) or self-reported ever using firearms. Noise exposure will be modeled as ordinal variable with 0 being assigned to absence of all three types exposures, 1 to presence of any one type of exposure, and 2 to presence of two or more types of exposures.

Statistical analysis

Ordinal logistic regression (hearing impairment categories) and linear regression (PTA) will be used to estimate the association of smoking history reported at Visit 6 and Visit 4 with hearing impairment at Visit 6 (Aim 1). The same models will also be applied for pack-year history cumulative through Visits 4 and 6 as the independent variable (part 2 of Aim 1) and for changes in smoking status from Visit 1 to Visit 4 as the independent variable (Aim 2).

In each of the models, the models will adjust for covariates measured at the latest time period relevant to the smoking status. Thus, for regressions assessing the association between smoking history (through Visit 4) and hearing loss, we will include Visit 4 covariates (e.g. BMI, diabetes, hypertension). For regressions assessing the cross sectional association between smoking history (through Visit 6) and hearing loss, we will include Visit 6 covariates. For the model assessing the relationship between longitudinal history of smoking from Visit 1 through 4, we will include Visit 4 covariates.

Prior studies have shown that hearing thresholds for similar frequencies are more correlated than more dissimilar frequencies. To account for these correlations, we will use linear mixed models to determine the association between hypertension and hearing thresholds at individual frequencies.

Because of the significant amount of time elapsed during Visits 1-6 and the known negative health outcomes for smokers, we are concerned about differential loss of smokers. In fact of the 3457 participants who reported current smoking at Visit 1, only about 16% (675 participants) followed up at Visit 6. This is in contrast to the 26% (1333 participants) of 5072 participants who

reported having formerly smoked at Visit 1, and 30% (1989 participants) of 6572 participants who reported having never smoked at Visit 1. To try to account for the informative attrition due to this selection, we will utilize Inverse Probability of Attrition Weighting (IPAW) to try to account for participants lost to follow-up. Weuve et al describe this technique in a paper that examines the association between smoking and cognitive decline in a longitudinal study [23]. The IPAW technique uses models to determine the probability of attrition due to mortality or other causes. The inverses of these probabilities then serve as weights for participants who are lost to these causes of attrition. In other words, for individuals who self-reported as current smokers at Visit 1 (and participated at Visit 6) will receive a higher weight in the calculation to compensate for their underrepresentation by Visit 6 (as compared to individuals who self-reported as never smokers at Visit 1).

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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

_____ 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)?

ARIC Manuscript Proposal #2262 Deal et al. Cigarette smoking in midlife and subsequent 23-year cognitive decline: The Atherosclerosis Risk in Communities Study

ARIC Manuscript Proposal #224 Power et al. Smoking and progression of white matter hyperintensities: The ARIC-MRI Study

ARIC Manuscript Proposal # 3170 Wu et al. Missing Cognitive Function Imputation Using Multiple Imputation by Chained Equations: ARIC Visit 6 Neural Cognitive Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _x___ No

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.