

**ARIC Manuscript Proposal #3737**

**PC Reviewed: 11/16/20**  
**SC Reviewed: \_\_\_\_\_**

**Status: \_\_\_\_\_**  
**Status: \_\_\_\_\_**

**Priority:   2**  
**Priority: \_\_\_\_\_**

**1.a. Full Title:**

Sleep characteristics and hearing loss: The Atherosclerosis Risk in Communities Study (ARIC)

**b. Abbreviated Title (Length 26 characters):**

Sleep and hearing in ARIC

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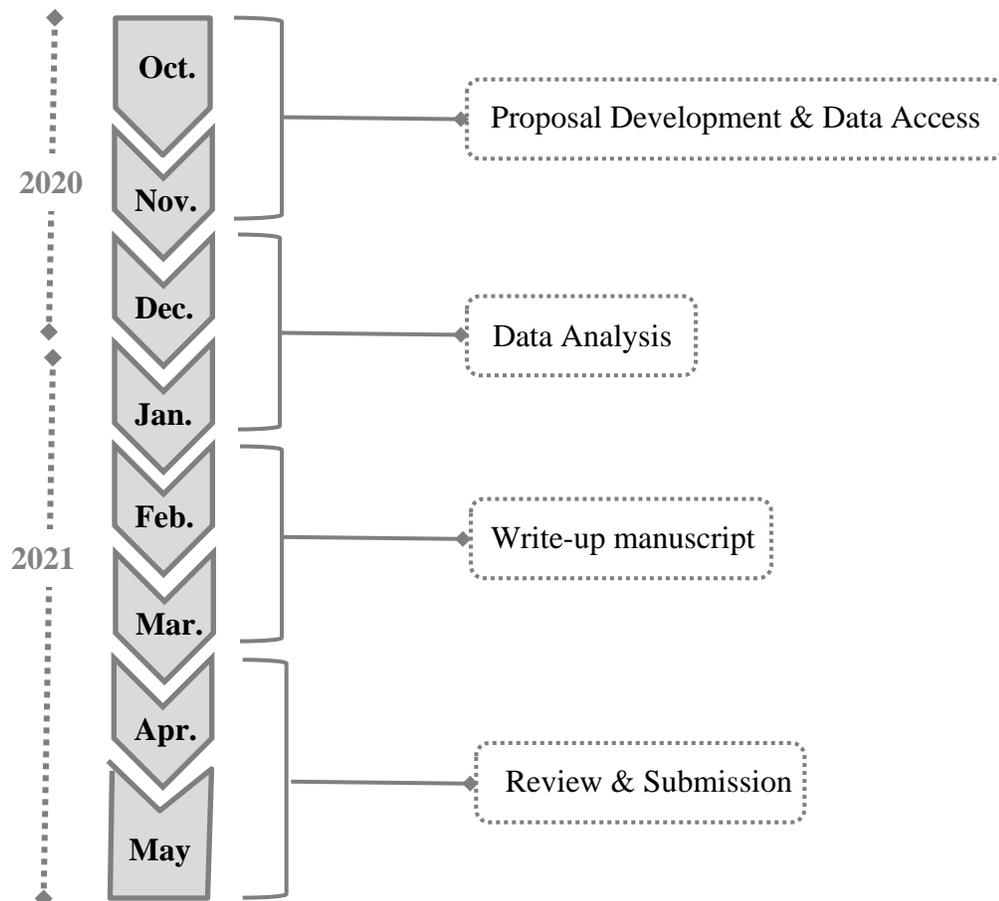
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### 3. Timeline:



### 4. Rationale:

Hearing loss is prevalent among older adults, with around two thirds of older adults aged 70 years and over presenting with a clinically significant hearing loss.<sup>1</sup> Hearing loss has been linked with adverse outcomes including cognitive decline and dementia,<sup>2,3</sup> poor physical functioning,<sup>4</sup> social isolation<sup>5</sup> and mortality.<sup>6</sup>

Sleep disturbances are potential novel risk factors for hearing loss. They are common among older adults, with approximately half of older adults complaining of sleep disturbances.<sup>7</sup> Sleep disturbances can be a novel target given their modifiable nature and are also associated with various adverse outcomes including cognitive decline and dementia,<sup>8</sup> poorer physical function,<sup>9</sup> cardiovascular factors<sup>10</sup> and mortality.<sup>11</sup>

The mechanism of the association between sleep and hearing is yet to be elucidated. With regard to peripheral hearing, it's hypothesized that the cochlea, as the most metabolically active organ in the body, might be impaired by sleep disturbances through disturbed energy metabolism and disrupted cochlear blood flow.<sup>12,13</sup> For central auditory processing, sleep disturbances can impact brain neurophysiology and lead to changes in cortical and subcortical structures.<sup>14</sup> In addition, sleep disturbances might exacerbate cardiovascular risk<sup>10</sup> and then impair hearing through circulatory alterations, increased oxidative stress, etc.<sup>12,15</sup>

Prior evidence regarding the association between sleep and hearing is limited, especially when it comes to longitudinal analyses and incorporation of objective assessment of sleep. Two prior population-based studies have quantified this association, though both of them are cross-sectional in nature. One study reported higher risk of hearing loss among those who sleep for 7, 8 and  $\geq 9$  hours at 4 kHz and those who sleep for  $\geq 9$  hours at 1 kHz when compared to those who sleep for  $\leq 5$  hours among the general population aged 20-79.<sup>16</sup> Another study found an association between sleep apnea and both high-frequency and low-frequency hearing loss among Hispanic/Latinos aged 18-74.<sup>17</sup> Other case control studies with small clinical samples generally focus on obstructive sleep apnea (OSA) and have reported lower speech discrimination rates,<sup>18</sup> cochlear function impairment<sup>19</sup> and damage of the auditory pathway in the brainstem among OSA patients.<sup>20</sup>

Our proposed study will add to the currently limited body of literature by evaluating the prospective relationship between objectively measured sleep characteristics and hearing. Our findings might contribute to a better understanding of risk factors of hearing loss and clarify the underlying mechanisms. Given the high prevalence of sleep disturbances, even a small contribution of sleep disturbances to hearing loss may make a meaningful impact at population level.

## **5. Main Hypothesis/Study Questions:**

### **Study Question**

This study aims at investigating the association of poorer sleep quality and quantity at Visit 4 (1996-1998) with poorer hearing (peripheral hearing and speech-in-noise performance) measured around 20 years later at Visit 6 (2016–2017) in The Atherosclerosis Risk in Communities Study (ARIC). We will explore numerous sleep characteristics (sleep architecture, respiratory parameters and self-reported sleep habits), however, given our hypotheses about how sleep may potentially cause hearing loss, our primary exposures will be sleep time and obstructive sleep apnea.

### **Main Hypothesis**

We hypothesize that participants with sleep disturbances are more likely to have worse peripheral hearing (higher PTA) and worse speech-in-noise performance (lower QuickSIN score).

## **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**

Around the time of the fourth examination of the ARIC cohort (1996-1998), a total of 1920 ARIC participants aged 54–73 years from the suburban Minneapolis, MN, and Washington County, MD underwent sleep measurements as part of the Sleep Heart Health Study (SHHS).<sup>21</sup> An audiometric hearing assessment was conducted in ARIC Visit 6 (2016–2017). Of the 1920 ARIC participants with sleep measurements, 808 (42.1%) participants aged 72-94 years attended Visit 6. A detailed description of the study population is presented in Figure 1.

### **Sleep Measurements**

Overnight unattended polysomnography (PSG) was conducted using a portable monitor (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).<sup>22</sup> A list of sleep measurements is included below with sleep time and apnea-hypopnea index (AHI) as our primary exposures.

| <b>Polysomnography</b>   |  |
|--|--|
| <b>Sleep architecture</b>                                      |  |
| Total sleep time*  | Total sleep time in hours  |
| Stage N1 sleep time  | Total time scored as stage 1 rounded to nearest minute   |
| Stage N2 sleep time  | Total time scored as stage 2 rounded to nearest minute   |
| Stage N3/N4 sleep time   | Total time scored as stage 3/4 rounded to nearest minute   |
| Rapid eye movement (REM) sleep time                            | Time in REM sleep in minutes   |
| Sleep efficiency   | The ratio of total sleep time to total time in bed, expressed as a percentage (%)  |
| Sleep latency  | Time from lights out time to beginning of sleep, rounded to nearest minute   |
| Wake After Sleep Onset (WASO)                                  | Total amount of time spent awake after going to sleep in minutes   |
| <b>Respiratory parameters</b>                                  |  |
| Apnea-hypopnea index (AHI)*                                    | The average number of obstructive apneas regardless of the oxygen desaturation level and plus hypopneas with at least a 4% (3% will also be considered) decrease in oxygen saturation per hour of sleep. AHI will be categorized to demonstrate the severity of obstructive sleep apnea (OSA): Normal (AHI: <5.0 events/hr); Mild (AHI: 5.0–14.9 events/hr); Moderate (AHI: 15–29.9 events/hr); Severe (AHI: ≥30.0 events/hr). |
| Percent of sleep time with less than 90% oxygen saturation (%) | Ratio of the number of minutes with oxygen saturation under 90% to the total sleep time. We will also dichotomize the variable into <10% and ≥ 10%.  |
| Percent of sleep time in Apnea (%)                             | Ratio of the number of minutes in apnea to the total sleep time.   |
| Percent of sleep time in Hypopnea (%)                          | Ratio of the number of minutes in hypopnea to the total sleep time.  |
| <b>Self-reported sleep habits</b>                              |  |
| Frequency of trouble falling asleep                            | 1: Never; 2: Rarely (once/month or less); 3: Sometimes (2-4 times/month); 4: Often (5-15 times/month); 5: Almost Always (16-30 times/month)  |
| Frequency of waking up too early and unable to resume sleep    | 1: Never; 2: Rarely (once/month or less); 3: Sometimes (2-4 times/month); 4: Often (5-15   |

|                                |  |
|--------------------------------|--|
|                                | times/month); 5: Almost Always (16-30 times/month)   |
| Frequency of feeling unrested  | 1: Never; 2: Rarely (once/month or less); 3: Sometimes (2-4 times/month); 4: Often (5-15 times/month); 5: Almost Always (16-30 times/month)  |
| Epworth Sleepiness Scale score | A subjective measure of a participant's sleepiness, with the score ranging from 0-24. The total score can be categorized as: unlikely to be abnormally sleepy (0-7); average amount of daytime sleepiness (8-9); May be excessively sleepy depending on the situation (10-15); Excessively sleepy (16-24). We will also consider dichotomizing the score into normal ( $\leq 10$ ) and excessive sleepiness ( $>10$ ). |

\*Primary exposures for inference

## **Audiometric Assessment**

### Peripheral hearing

Hearing thresholds were assessed at Visit 6 using pure tone air conduction audiometry in a sound-treated booth.<sup>23</sup> A speech-frequency pure tone average (PTA) was calculated by averaging hearing thresholds at 0.5, 1, 2, and 4 kHz; low-frequency PTA was calculated by averaging hearing thresholds at 0.5, 1 and 2 kHz; high-frequency PTA was calculated by averaging hearing thresholds at 4, 6 and 8 kHz. Higher values indicate worse hearing. PTAs in better ear will be used in primary analyses while PTAs in worse ear will be used in secondary analyses.

### Central auditory processing

Speech-in-noise performance was quantified by the Quick Speech-in-noise (QuickSIN) test.<sup>24</sup> Following a practice session to account for learning effects, participants completed two trials where they were presented with six sentences (different for each trial), in the presence of multi-talker babble such as might be experienced in a noisy restaurant, under successively more difficult listening conditions. The sentences were presented binaurally with a fixed presentation level for speech (70 dB HL), and with 5 dB incremental increases in noise level for each sentence, ranging from +25 dB speech-to-noise ratio (SNR) for the first sentence to no difference in volume between speech and noise for the final sentence (0 dB SNR). After each sentence, participants were instructed to repeat the sentence and to guess if unsure. Scoring for each sentence is on a scale of 0-5 based on correct identification of five target words. For the analysis, scores for the two trials will be averaged to give the mean number of words correctly identified, with a possible range from 0 to 30 (higher scores are better).

## **Other Covariates**

- Demographic variables: age, sex, education, study site;
- Lifestyle variables: smoking, drinking, body mass index (BMI), noise exposure;
- Cardiovascular diseases variables: hypertension, diabetes, coronary heart disease, stroke.

## **Statistical Analysis**

Multivariable-adjusted linear regression will be used with speech-frequency PTA, low-frequency PTA, high-frequency PTA or QuickSIN score as the outcome. Separate models will be run with each of the primary sleep measurements, including sleep time and AHI. Other measurements of sleep will also be explored. Models will be adjusted with demographic, lifestyle and cardiovascular variables. For models with QuickSIN score as the outcome, PTA will also be adjusted since central processing depends on peripheral hearing. To address the concern of a potential selection bias over around 20 years of follow-up, we will compare characteristics of participants with polysomnography who did not complete follow-up and will use inverse probability weighting (IPW) in our models to account for attrition due to either death or failure to attend the follow-up audiometric assessment. Weights for each individual will be the inverse of the product of the estimated probabilities of (1) being alive at the time of the follow-up audiometric assessment and (2) attending the follow-up audiometric assessment conditional on being alive at the time of follow-up audiometric assessment.<sup>25,26</sup> Stabilized weights will be used and winsorization of extreme weights will be considered.<sup>26</sup>

### **Limitations**

In the proposed study, the outcome of interest (hearing loss) was measured after around 20 years when sleep measurements were completed. Though this provides us with a unique opportunity to examine the prospective relationship between sleep characteristics and hearing loss, this large gap in time also poses methodologic challenges, with over 50% of participants lost to follow-up. IPW will be used to address the limitation. Also, despite the long prospective follow-up time, because audiometric assessment was introduced in ARIC at Visit 6, we are not able to determine who had prevalent hearing loss at baseline (Visit 4). Last, since the SHHS only recruited participants from two study sites of the ARIC cohort, a limitation of the study is that it will be conducted in exclusively white participants.

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript?** \_\_\_\_\_ 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 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 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.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)?**

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  No (Sleep Heart Health Study)**

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

- A. primarily the result of an ancillary study (list number\* 1995.12)**  
 **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.csc.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.**

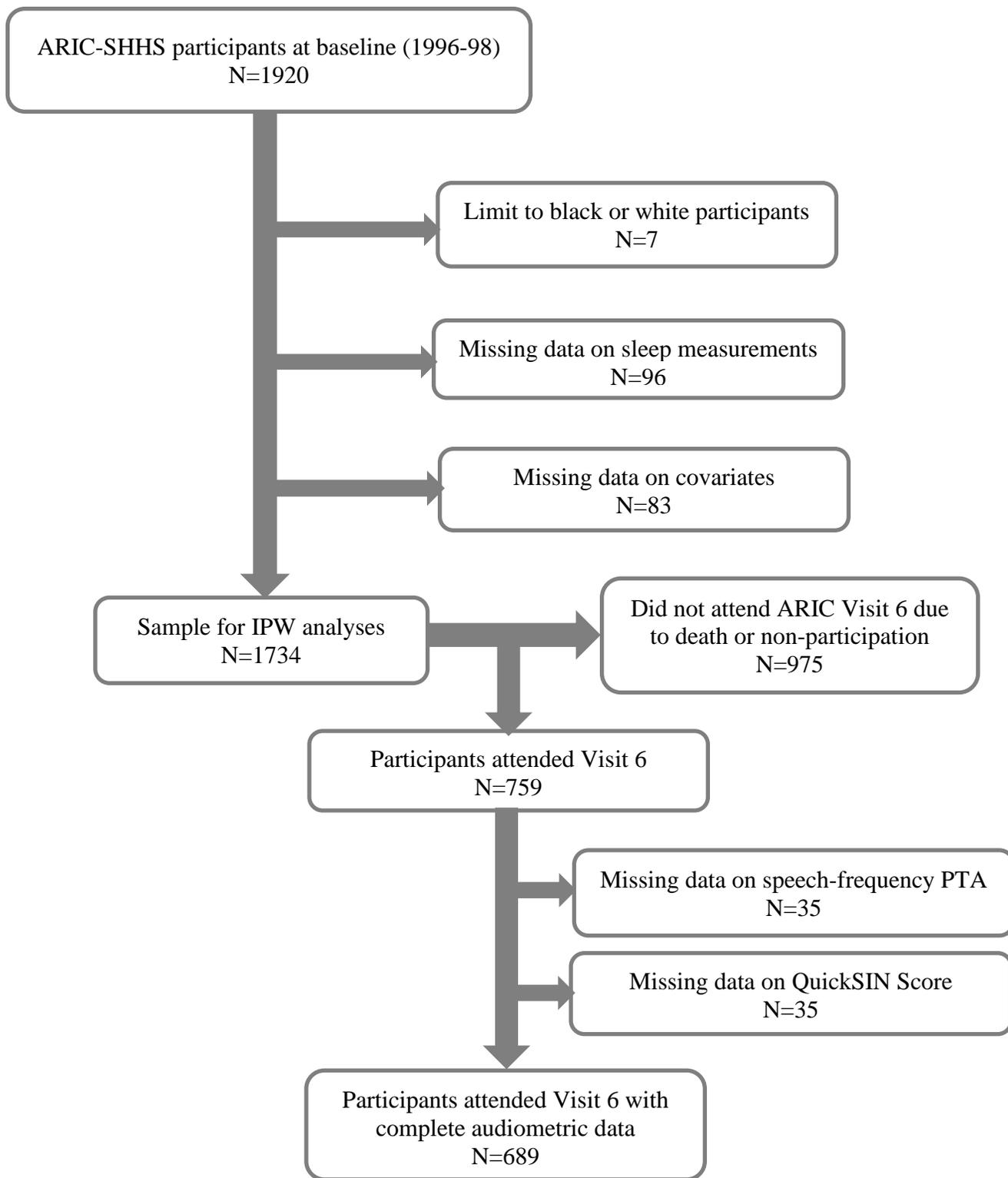
**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

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**Figure 1. Study population of the proposed study**