

ARIC Manuscript Proposal #3851

PC Reviewed: 6/8/21

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title:

Association of Obstructive Sleep Apnea with Late Onset Epilepsy among ARIC participants

b. Abbreviated Title (Length 26 characters): Assoc. OSA and LOE in ARIC

2. Writing Group:

Writing group members:

Christopher M. Carosella – first author

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Others welcome

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

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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 (this must be an ARIC investigator).

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3. Timeline:

Data analysis and manuscript preparation will take place over one year (2021-2022).

4. Rationale:

Late-onset epilepsy (LOE; i.e., starting at age 65 or older¹) affects a large and growing number of persons worldwide. The yearly incidence of first seizure is higher in the elderly than at any other time of life² at 175 per 100,000 people after age 80³. In comparison, the incidence of epilepsy is low in earlier adulthood (20 per 100,000 from ages 20-60), and moderately high in infants under 1 year of age (100 per 100,000). In older adults without a prior history of seizures, the yearly incidence of epilepsy is 1.85% in those 80-84 and 3.25% in those who live to 90-94³. The risk factors for development of LOE are not fully understood. Emerging evidence (mostly cross-sectional) has demonstrated an association between epilepsy and obstructive sleep apnea (OSA)⁴. The risk of adult onset OSA tends to increase with age⁵. Furthermore, OSA intersects with other known LOE risk factors such as hypertension, diabetes, stroke, and neurodegenerative diseases. Therefore OSA may be an important potential risk factor for the development of LOE, and could be a promising target for intervention.

OSA is the most common subtype of sleep disordered breathing and common in elderly patients⁵. The consequences of OSA can be severe and include hypertension, stroke, and arrhythmias. Risk factors for OSA include obesity, enlarged neck circumference, and airway dysmorphism or abnormalities. Studies have demonstrated a relationship with epilepsy severity and likelihood of concomitant OSA diagnosis, with drug resistant epilepsy patients (DRE) experiencing the highest burden of OSA⁴. Patients with epilepsy are at higher risk to develop OSA as compared to the general population⁶. Patients with epilepsy and concomitant OSA demonstrate worsened seizure control than their peers without OSA, and treatment of OSA has demonstrated improvement in seizure control among patients with both conditions⁷. Understanding the relationship between OSA and LOE may yield improvements of diagnosis and treatment in both conditions.

References:

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3. Hesdorffer DC, Logroscino G, Benn EKT, Katri N, Cascino GD, Hauser WA. Estimating risk for developing epilepsy: A population-based study in Rochester, Minnesota. *Neurology*. 2011;76(January):23-27.
4. Sarkis RA, Willment KC, Pennell PB, Marshall G. Late-onset unexplained epilepsy: What are we missing? *Epilepsy Behav*. August 2019:106478. doi:10.1016/j.yebeh.2019.106478
5. Shochat T, Pillar G. Sleep apnoea in the older adult: Pathophysiology, epidemiology, consequences and management. *Drugs and Aging*. 2003;20(8):551-560. doi:10.2165/00002512-200320080-00001
6. Liu F, Wang X. Diagnosis and treatment of epilepsy and sleep apnea comorbidity. *Expert Rev Neurother*. 2017;17(5):475-485. doi:10.1080/14737175.2017.1262259
7. Vendrame M, Auerbach S, Loddenkemper T, Kothare S, Montouris G. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. *Epilepsia*. 2011;52(11):e168-e171. doi:10.1111/j.1528-1167.2011.03214.x

5. Main Hypotheses/Study Questions:

H1: We hypothesize that ARIC participants with self-reported of obstructive sleep apnea (OSA) at Visit 5 (2011-2013) will demonstrate a higher rate of late-onset epilepsy (LOE) following Visit 5 than will participants without a diagnosis of OSA, independent of other risk factors.

H2: We hypothesize that ARIC participants (who also participated in the Sleep Heart Health Study) with a history of more severe OSA (as demonstrated by a higher apnea-hypopnea index) will demonstrate a higher rate of incident LOE than will participants with mild or no OSA, independent of other risk factors.

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).

H1:

This will be an analysis of the association between OSA self-reported at Visit 5, and late-onset epilepsy (LOE) ascertained from CMS claims.

The *dependent variable*, LOE, will be defined as two or more seizure-related claims from CMS data, with the first seizure-related claim occurring after at least 2 years of seizure-code-free CMS coverage (to identify incident cases).

The *independent variable* of interest, OSA, will be obtained from self-reported sleep apnea at Visit 5 (variable rse23).

Covariates will include baseline (Visit 1) sex, race, field center, level of education, and apolipoprotein E4 genotype, and Visit 5 age. Other covariates will be obtained from the visit closest to age 67 (the age at which participants become eligible for the definition of LOE using Medicare claims) and will include hypertension and smoking and alcohol use history. We will use time-varying covariates to adjust for diabetes and BMI from visits 1-5. We will also adjust for stroke (as reported at Visit 1 and as identified and adjudicated in ARIC) and dementia (using the Level 3 dementia ascertainment at Visit 5), and the Apolipoprotein E4 genotype which was obtained at Visit 1

Data Analysis:

We will use logistic regression with LOE as the outcome and sleep apnea as the exposure of interest, adjusting for covariates as above.

Inclusion criteria: Since the definition of LOE relies on Centers for Medicare Services fee-for-service (CMS FFS) claims codes, Black (NC and MS) and White (MD, MN, and NC) participants with at least 2 years of continuous CMS FFS coverage will be included, to allow the 2-year seizure-code-free period prior to first seizure code for incident LOE.

Exclusion criteria: Since the definition of LOE relies on CMS FFS claims codes, participants without 2 years of continuous CMS FFS coverage or with noncontiguous coverage periods will be excluded. We will also exclude those who did not give consent for DNA to be used.

Sensitivity analysis: We will examine the relationship between self-reported OSA and subsequent LOE, excluding participants whose first seizure code was prior to Visit 5.

H2:

In 1996-1998, 1667 ARIC participants had home polysomnography as part of the Sleep Heart Health Study. This will be a *survival analysis* using Cox proportional hazards modelling with age 67 as the origin, prior severity of sleep apnea from the Sleep Heart Health Study as the exposure of interest, and subsequent development of LOE using the first seizure-related code as the failure time. We will censor participants at date of death.

Exposure: Sleep apnea will be categorized using the apnea-hypopnea index derived from home polysomnography, classified as: <5.0 (normal), 5.0-14.9 (mild), 15.0-29.9 (moderate), and \geq 30.0 events/hour (severe).

In secondary analyses, we will also examine the exposures of hypoxemia, sleep fragmentation, and sleep duration as exposures.

We will adjust for demographics and medical comorbidities as above in H1.

Inclusion criteria: Only those participants who were included in the Sleep Heart Health study will be included for H2. Since the definition of LOE relies on Centers for Medicare Services fee-for-service (CMS FFS) claims codes, participants with at least 2 years of continuous CMS FFS coverage will be included.

Exclusion criteria: Since the definition of LOE relies on CMS FFS claims codes, participants without 2 years of continuous CMS FFS coverage or with noncontiguous coverage periods will be excluded. We will also exclude those who did not give consent for DNA to be used.

One challenge and limitation may be limited numbers of ARIC participants who both participated in the Sleep Heart Health study and developed LOE; therefore we also include H1 which will include data from all ARIC participants who attended Visit 5.

An additional limitation is that only ARIC participants from Minneapolis and Washington County were included in Sleep Heart Health, so that no information on races other than white will be available.

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? ___x___ 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)?

#3181 – Cognitive Trajectories and Cognition in Late-Onset Epilepsy (Johnson)

#2947 – Late-onset seizures and cardiovascular risk factors (Johnson)

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* 1995.12)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

This proposal requests data from the Sleep Heart Health study.

*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.

The authors agree.

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 shows you which journals automatically upload articles to PubMed central.