ARIC Manuscript Proposal #3736

PC Reviewed: 11/16/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Obstructive Sleep Apnea and Hospitalization with Infection: The ARIC Study

b. Abbreviated Title (Length 26 characters): OSA & Hospitalized infection

2. Writing Group:

Writing group members: Islam Zineldin, Ryan Demmer, Jeffrey Misialek, Kamakshi Lakshminarayan, Junichi Ishigami, Kunihiro Matsushita, Kelsie Full, Logan Cowan, Pamela L. Lutsey

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __IZ___

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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 to being immediately, anticipated draft completion 12/2020

4. Rationale:

Obstructive Sleep Apnea (OSA) is a common and chronic sleep disorder characterized by collapse of the upper airway soft tissue during sleep causing recurrent and intermittent hypoxia with hypercapnia resulting in frequent nocturnal awakening and sleep interruption (1, 2). Sleep interruption occurs because the affected patient alternates between apnea and hyperpnoea as well

as between sleep and arousal resulting in complications of hypoxia and hypercapnia and chronic sleep deprivation (2). Intermittent and chronic hypoxia associated with OSA causes increased oxidative stress, and inflammation (3). Symptoms of OSA include but are not limited to loud snoring, daytime sleepiness, fatigue, nocturnal awakening, and morning headache and morning sore throat (8). According to USPTF, the prevalence of OSA is estimated to be 10% for mild OSA and 3.8% to 6.5% for moderate to severe OSA (3, 4, and 5). OSA is associated with multiple commodities including diabetes (3), hypertension (4, 7), and heart disease like congestive heart failure, cardiac arrhythmia, pulmonary hypertension and coronary artery disease (7, 8). OSA is also associated with stroke and TIA (7, 8, and 9). Studies suggest the pathophysiology of cardiovascular complications in OSA patients include endothelial dysfunction, coagulopathy, impaired sympathetic drive, oxidative stress and inflammatory stress (7, 8). Furthermore, OSA is associated with increase the risk of inflammation and cancer (10).

Sleep and the circadian system play an important role in the immune system regulation (11). Chronic sleep disruption is believed to cause chronic stress and in doing so negatively impacts immune function. It is thought to result in increased susceptibly to infectious agents via alteration of the immune response and persistent low grade systemic inflammation (11, 12, and 13). Most of these studies, however, were cross-sectional or evaluated acute impacts of sleep on inflammatory response. They did not study the long-term implications of OSA on infectious outcomes. Furthermore, pneumonia is the most common infectious cause of hospitalization and death among adults in the United States (21), and recent work showed that patients with OSA who are admitted for pneumonia have higher risk of mechanical ventilation, clinical deterioration and higher resource use but lower risk of inpatient mortality (22). This also suggests that patients with OSA may be more susceptible to severe inflammatory outcomes.

Relatively little is presently known about association of OSA with risk of inflammatory outcomes, such as hospitalization for pneumonia or other infectious conditions. Therefore, we propose to investigate these associations using data from ~2,000 participants of the ARIC cohort who had polysomnography in 1996-1998 and have been followed through 2018 for hospitalizations. The primary outcomes will be risk of incident hospitalized infection (composite) or pneumonia. Secondary outcomes will be other infectious conditions.

5. Main Hypothesis/Study Questions:

Obstructive sleep apnea will be associated with greater risk of incident hospitalized infection (composite), respiratory infection, pneumonia, and other specific hospitalized infections.

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
The study will be a prospective cohort in which we will review data for patients who had polysomnography in 1996-1998 and have been followed through 2018.

Inclusion: Polysomnography data via the ARIC Sleep Heart Health Study (SHHS) which took place shortly after ARIC visit 4.
Exclusion: Central sleep apnea, participants who are not black or white, blacks from the MN and MD centers.

Variables
Exposures: Obstructive sleep apnea (OSA). OSA is defined by AHI as follows:
Normal: Less than 5 events per hour
Mild OSA: 5 – 14 events per hour
Moderate OSA: 15-29 events per hour
Severe OSA: More than 30 events per hour

Outcome: ICD – 9 and ICD – 10 codes will be used to identify hospitalized infection (composite), as well as hospitalized respiratory infection, pneumonia, and other specific infections. We are using the same ICD-9 definitions as in ARIC MS # 2391"Hospitilized infection as a trigger for acute ischemic stroke". We have cross-walked ICD-10 codes to ICD-9 codes to allow for expanded follow up.

Data Analysis: Descriptive statistics (means and proportions) will be provided. Cox proportional hazards regression will be used to evaluate the association between OSA categories and risk of incident pneumonia and hospitalized infection. Person-time will accrue from the date of the SHHS exam until hospitalization with an incident outcome of interest, loss-to-follow-up, death, or administrative censoring.

- The proportional hazards assumption will be tested by evaluating the interaction between OSA categories and the natural log of person- time, and by visual inspection of graphs of the survival function vs survival time stratified by OSA categories.
- Model 1 will adjust for age, sex, race, and center (5-level variable). Model 2 will adjust for education level, physical activity, alcohol use, and smoking. Model 3 will additionally adjust for, and BMI. Model 4 adjusted for COPD, asthma. Model 5 will adjust for kidney function, diabetes and prevalent CVD. Lastly, we will explore whether adjustment for systemic inflammation via CRP attenuates the association.
- Multiplicative interactions by age (median split), sex, and BMI will be tested by including cross-product terms in the models. Stratified results will be reported regardless, given inherent interest

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)?

#1867: Sleep apnea and biomarkers of myocardial stress and inflammation
#3347: Sleep apnea and incidence of CKD
#2871: Cardiac markers and risk of hospitalization with infection
#2894: Infection as a trigger for CVD in the ARIC cohort
#2391: Hospitalized infection as a trigger for acute ischemic stroke in the 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 (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.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.

References

1. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310-318. doi:10.1016/S2213-2600(15)00043-0

2. White DP. Sleep-related breathing disorder: 2—pathophysiology of obstructive sleep apnea. Thorax. 1995;50:797–804. [PMC free article] [PubMed] [Google Scholar]

3. Reutrakul, S., & Mokhlesi, B. (2017). Obstructive Sleep Apnea and Diabetes. *Chest*, *152*(5), 1070-1086

4.Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med. 2000;160(15):2289-2295. doi:10.1001/archinte.160.15.2289

5. Jonas DE, Amick HR, Feltner C, et al. Screening for Obstructive Sleep Apnea in Adults: An Evidence Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Jan. (Evidence Syntheses, No. 146.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK424160/

6.Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230-5.

7. Obstructive sleep apnea and cardiovascular disease, Mehmood Butt, Girish Dwivedi, Omer Khair and Gregory Y.H. Lip. International Journal of Cardiology, 2010-02-18, Volume 139, Issue 1, Pages 7-16. International Journal of Cardiology, 2010-02-18, Volume 139, Issue 1, Pages 7-16, Copyright © 2009 Elsevier Ireland Ltd. Accessed on 08-08-2020

8. Parish, James, Somers, Virend, MD, PhD. Obstructive Sleep Apnea and Cardiovascular Disease. Mayo Clin Proc. 2004;79(8):1036-1046. Cited in: Journals@Ovid Full Text at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftg&NEWS=N&AN=00005625-200408000-00013. Accessed August 08, 2020.

9. Gupta, A., & Shukla, G. (2018). Obstructive sleep apnea and stroke. *Journal of Clinical Sleep Medicine, 14*(10), 1819.

10. Gozal D, Farré R, Nieto FJ. Obstructive sleep apnea and cancer: Epidemiologic links and theoretical biological constructs. *Sleep Med Rev*. 2016;27:43-55. doi:10.1016/j.smrv.2015.05.006

11. Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch*. 2012;463(1):121-137. doi:10.1007/s00424-011-1044-0

12. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation*. 2009;16(5):300-317. doi:10.1159/000216188

13. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev*. 2008;12(3):197-210. doi:10.1016/j.smrv.2007.07.007

14. Bryant PA, Trinder J, Curtis N. Sick and tired: Does sleep have a vital role in the immune system?. *Nat Rev Immunol*. 2004;4(6):457-467. doi:10.1038/nri1369

15. Krista L. Yorita Christensen, Robert C. Holman, Claudia A. Steiner, James J. Sejvar, Barbara J. Stoll, Lawrence B. Schonberger, Infectious Disease Hospitalizations in the United States, *Clinical Infectious Diseases*, Volume 49, Issue 7, 1 October 2009, Pages 1025–1035, https://doi.org/10.1086/605562

16. Lindenauer PK, Stefan MS, Johnson KG, Priya A, Pekow PS, Rothberg MB. Prevalence, treatment, and outcomes associated with OSA among patients hospitalized with pneumonia. *Chest*. 2014;145(5):1032-1038. doi:10.1378/chest.13-1544

17. Curns AT, Steiner CA, Sejvar JJ, Schonberger LB. Hospital charges attributable to a primary diagnosis of infectious diseases in older adults in the United States, 1998 to 2004, J Am Geriatr Soc, 2008, vol. 56 (pg. 969-75)

18.FASTSTATS - pneumonia. Centers for Disease Control and Prevention website. http://www.cdc.gov/nchs/fastats/pneumonia.htm. Accessed August 09, 2020

19. FASTSTATS – Infectious disease . Centers for Disease Control and Prevention website.https://www.cdc.gov/nchs/fastats/infectious-disease.htm. Accessed August 09,2020

20. Lindenauer PK, Lagu T, Shieh MS, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. *JAMA*. 2012;307(13):1405-1413. doi:10.1001/jama.2012.384

21. Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015;373(5):415-427. doi:10.1056/NEJMoa1500245

22. Lindenauer PK, Stefan MS, Johnson KG, Priya A, Pekow PS, Rothberg MB. Prevalence, treatment, and outcomes associated with OSA among patients hospitalized with pneumonia. *Chest*. 2014;145(5):1032-1038. doi:10.1378/chest.13-1544