ARIC Manuscript Proposal # 3347

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

1a. Full Title: Obstructive Sleep Apnea, sleep characteristics, and incidence of chronic kidney disease in the Sleep Heart Health Study (SHHS)

b. Abbreviated Title (Length 26 characters): Obstructive Sleep Apnea and Incident Chronic Kidney Disease

2. Writing Group:
Kelsie M. Full, Pamela L. Lutsey, Chandra Jackson, Kunihiro Matsushita, Casey Rebholz, others welcome

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

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3. Timeline: Data analysis will begin immediately. A manuscript draft will be prepared in less than one year.

4. Rationale:

Chronic kidney disease (CKD) is a prevalent and recognized risk factor for heart failure, coronary heart disease (CHD), and mortality.[1,2] After decades of increasing incidence, the prevalence of CKD (GFR stages 3-4) in the US population has plateaued around 7%.[1] Identifying strategies to continue to curb the incidence of CKD and slow progression of the condition and related morbidity have become public health priorities.[1] Identifying novel lifestyle risk factors for CKD may lead to improved strategies for prevention and better management of disease progression.

Over half of older adults in the US regularly report experiencing poor or disrupted sleep.[3] Commonly reported sleep-related complications, include: difficulty initiating and maintaining sleep, feeling fatigue during the day, waking up very early in the morning and not being able to return to sleep, and changes to sleep architecture.[3–7] Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder, and the proportion of the population diagnosed with the condition is estimated to be 1.7 times higher in the population over 60, as compared to the population younger than 60 years old.[8,9] OSA is a condition characterized by the obstruction of the upper airway during sleep resulting in repetitive arousals and oxygen desaturation. In the ARIC Sleep Heart Health Study (SHHS), 18% of the sample of middle age and older adults (40-99 years) were defined as having severe sleep disordered breathing, or OSA. OSA, other sleep disorders, and poor sleep quality, remain highly underdiagnosed in the older adult population in the US.[5] In previous research, sleep disorders, including OSA and poor sleep quality, have been associated with adverse health effects such as suboptimal physical function, poorer cognition, and incident type II diabetes, and cardiovascular disease.[10–16]

Numerous lines of evidence suggest that OSA and poor sleep quality are associated with the development of CKD. In preliminary cross-sectional analyses, reports suggest a higher prevalence of OSA among individuals with prevalent CKD, as compared to men with normal kidney function.[17,18] Further, OSA has been linked to factors that contribute to the development of CKD including obesity, hypertension, diabetes, and inflammation.[15,19,20] For example, Peppard et al. explored the association between OSA, characterized by sleep disordered breathing (SDB), and incident hypertension over a 4-year period in the Wisconsin Sleep Cohort. Independent of known confounding factors, SDB was a strong predictor of incident hypertension, when compared to individuals with no nightly hypopnea events. The hazard ratio for incident hypertension was 2.89 (95% CI: 1.46 to 5.64) comparing the group with the most severe SDB to those with no SDB, and there was evidence of a dose-response relationship.[19] In the SHHS, which followed 1,453 older adults for up to 13 years, individuals with severe OSA were at greater risk of incident diabetes when compared to individuals who did not experience SDB events (HR: 1.71 (95% CI: 1.08, 2.71)).[15] It is hypothesized that OSA, disrupted sleep, and poor sleep quality, may either stimulate or contribute to CKD development and progression through these pre-existing cardiometabolic conditions.

Few population-based studies have evaluated the prospective relationship between OSA and incident CKD, despite potential biological mechanisms linking the conditions.[18] Using data from the ARIC SHHS we will leverage the polysomnography (PSG) data to examine the association between OSA and incident CKD in a sample of older adults. Additionally, we aim to provide a better understanding of how sleep characteristics, including disrupted sleep and poor sleep quality, may be associated with the development of CKD in the older adult population and whether or not this relationship is independent of related cardiometabolic conditions, i.e. hypertension, diabetes, inflammation, and obesity. With the current population burden of CKD, determining if OSA and poor sleep quality are independently associated with incident CKD may have significant implications for clinical practice and population health.

5. Main Hypothesis/Study Questions:

We hypothesize that a higher severity OSA will be associated with greater risk of CKD in this sample of older adults. We will explore if measures of disrupted sleep and poorer sleep quality (measured by self-reported sleep complaints and PSG-assessed sleep efficiency) are associated with a greater risk of CKD.

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 proposed study will be a longitudinal analysis with follow-up time starting at the time of the SHHS exam (ARIC visit 4) and ending at incident CKD, loss-to-follow-up, death, or end of CKD ascertainment.

Inclusion/Exclusion:

Inclusion: The study will include ARIC participants from suburban Minneapolis, MN and Washington County, MD who participated in the SHSS and underwent an in-home overnight polysomnography (PSG) and completed a sleep questionnaire. The overnight unattended PSG was conducted using a portable monitor (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia).

Exclusion: From the SHHS sample we will exclude participants missing PSG data at ARIC visit 4 and participants with prevalent CKD, defined by an estimated GFR (eGFR) less than 60 mL/min/1.73 m^2 at ARIC visit 1-4 or a previous renal disease hospitalization (including International Classification of Diseases (ICD) 9-codes: for chronic renal disease (codes 581-583 or 585-588), hypertensive renal disease (code 403), hypertensive heart and renal disease (code 404), unspecified disorder of kidney and ureter (code 593.9), DM with renal manifestations (code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (code V42.0, V45.1, or V56), hemodialysis (code 39.95) or peritoneal dialysis (code 54.98), and without acute renal failure (codes 584, 586, 788.9, and 958.5) as the primary or secondary hospitalization code).

Variables of Interest

Exposure: The primary exposures will be OSA, disrupted sleep, and poor sleep quality.

- OSA: OSA severity was defined with a measure of frequency defined by the PSG-measured respiratory event index (REI) and hypoxic burden.[21]

  REI was derived as the sum of all apneas and hypopneas (with at least a 4% decrease in oxygen saturation) per hour of estimated sleep. Central sleep-disordered breathing events were excluded from the REI definition. OSA was defined as an REI ≥15 events per hour. Participants were categorized according to REI:
  - <5.0 events/hour (normal)
  - 5.0–14.9 events/hour (mild)
  - 15.0–29.9 events/hour (moderate)
  - ≥30.0 events/hour (severe)

Hypoxic burden is a measure developed to capture the total amount of respiratory event-related hypoxemia over the sleep period. The hypoxic burden was defined as the total area under the respiratory event-related desaturation curve. In the SHHS, it was derived by estimating the area under the desaturation curve of each individual event and then by adding these individual desaturation areas and dividing the total area by the sleep duration, with the units of hypoxic burden being (%min)/h.

Participants were categorized according to quintiles of hypoxic burden:
- <20th percentile (reference)
- 20th–40th percentile
- 40^{th}-60^{th} percentile
- 60^{th} – 80^{th} percentile
- >80^{th} percentile

- Disrupted Sleep: Defined by the PSG measured arousal index. As in previous analyses of SHHS data[15], arousals were identified as shifts 3 sec in electroencephalogram frequency. The arousal index was defined as the average number of arousals per hour of sleep.
- Sleep Quality:
  - Objective: Defined by PSG measured sleep efficiency (% of in bed time classified as sleep).
  - Self-report: As in a previous analysis of SHHS data[22], from the SHHS questionnaire if a participate responded "often" or "almost always" to any of the following items assessing frequency of complications they would be defined as having self-reported poor sleep (yes/no):
    - "do you have trouble falling asleep?''
    - ''do you wake up during the night and have difficulty getting back to sleep?''
    - ''do you wake up too early in the morning and are unable to get back to sleep?'
    - ''do you take sleeping pills or other medication to help you sleep.''

Outcome: The primary outcome for this analysis will be incident CKD. Participants were followed from visit 4 (1996-1998) to most recent follow-up. Incidence was defined in accordance with previous work completed in the ARIC cohort.[23] CKD incidence was ascertained using ARIC follow-up protocol information based on the following:

- Development of reduced kidney function (estimated glomerular filtration rate [eGFR]: <60 ml/min/1.73 m 2)
- ICD-9/10 code for a hospitalization related to CKD stage 3+ identified through active surveillance of the ARIC cohort
- ICD-9/10 code for a death related to CKD stage 3+ identified through linkage to the National Death Index
- End-stage renal disease identified by linkage to the US Renal Data System (USRDS) registry

Covariates: The covariates included in this analysis were derived from ARIC questionnaire and study visit assessments, including: age, sex, race, study center, educational attainment, smoking status, drinking status, body mass index (BMI), physical activity, diabetes status, systolic and

diastolic blood pressure, glucose, antihypertensive medication use, coronary heart disease, heart failure, sleep medication use (both prescribed and supplemental). Information will come from visit 4 when possible; if data is not available at visit 4 we will carry forward from the most proximal visit with information.

Data analysis

Basic descriptive statistics will be performed and presented including mean ±SD/proportions of the included covariates for the study sample. Descriptive statistics will be presented across categories of OSA severity category (<5, 5-14.9, 15-29.9, ≥30). Between group differences in covariates will be explored using chi-square and one-way ANOVA.

Cox proportional hazards models will be used to assess the associations of OSA and indices of poor sleep quality with risk of incident CKD. Hazard Ratios comparing categories of OSA (REI <5, 5-14.9, 15-29.9, ≥ 30), PSG measured disturbed sleep (quartiles), PSG sleep quality (quartiles), and subjective poor sleep quality (yes/no) will be calculated. The proportional hazards assumption will be evaluated for all independent variables using Schoenfeld residuals.

Model 1: will adjust for socio-demographics (age, sex, race, study center, educational attainment)

Model 2: will include additional adjustment for health behaviors (smoking status, drinking status, physical activity)

Model 3: will further adjust for prevalent CVD and CVD risk factors (obesity, inflammation (CRP), diabetes status, systolic and diastolic blood pressure, glucose, antihypertensive medication use, coronary heart disease, heart failure)

Multiplicative interactions by race, sex, obesity status, type 2 diabetes status, and hypertension status will be assessed by including cross-product terms in the models, and stratified results reported when appropriate.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes __ 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/search.php

__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)?

MS1867: "The association between obstructive sleep apnea, biomarkers of myocardial stress and of inflammation, and cardiovascular outcomes in the Atherosclerosis Risk in Communities study."

MS1297 (SHHS097): "Sleep-disordered breathing and risk of incident cardiovascular disease: The Sleep Heart Health Study"

MS2199: "Sleep Disordered Breathing, Sleep Duration and the Risk of Incident Self-Reported Diabetes: the Atherosclerosis Risk in Communities Study"

MS1653: "The association of glomerular filtration rate and albuminuria with incident hypertension: The Atherosclerosis Risk in Communities (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 at http://www.cscc.unc.edu/aric/forms/

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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