Examining the Complex Relation Between Sleep Problems and Chronic Kidney Disease

by

Monica M Shieu

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2020

Doctoral Committee:

       Professor Hal Morgenstern, Chair
       Research Associate Professor Brenda Gillespie
       Professor Rajiv Saran
       Associate Professor Q. Afifa Shamim-Uzzaman

Monica Shieu

mshie@umich.edu

ORCID iD: 0000-0003-3156-3597

TABLE OF CONTENTS

LIST OF TABLES

Abstract

Sleep-related problems are rapidly growing public-health concerns that often result in adverse short-term consequences (e.g., reduced quality of life) and long-term health effects (e.g., cardiovascular disease). However, the relation between sleep problems and chronic kidney disease (CKD) has been under-investigated. To better understand this relation, we addressed three aims.

The first aim was to examine temporal trends in the prevalence of 5 self-reported sleep problems in U.S. adults and their associations with CKD and all-cause mortality, using data from 5 National Health and Nutrition Examination Surveys (2005-14). The prevalence of trouble sleeping and diagnosed sleep disorder increased over the decade, while nocturia (urinating ≥2 times/night), inadequate sleep (<7 hours/night), and excessive sleep (>9 hours/night) remained stable. All sleep problems, except inadequate sleep, were more common among adults with CKD than without CKD, especially for excessive sleep and nocturia, which were positively associated with all-cause mortality.

Second, we conducted a large retrospective cross-sectional study of obstructive sleep apnea (OSA) in U.S. veterans who sought care in Veteran Administration (VA) facilities in fiscal year (FY) 2018 to better understand the population burden of OSA and its relation with CKD and its risk factors. Using data from 6.2 million veterans for FY2014-18, we estimated OSA point prevalence at the last visit to a VHA facility in FY2018 (index time T) and period prevalence of

OSA (excluding prevalent cases at T) going back to the start of FY2014. Period prevalence for each duration was estimated by taking into account left censoring of veterans followed back for different durations. At time T, OSA point prevalence was 24.9% in veterans with CKD and 15.2% in those without CKD. The overall 60-month period prevalence was 11.6% and was positively associated with CKD, obesity, being male, having hypertension, or diabetes, and inversely associated with age ≥65.

Lastly, we conducted a large retrospective cohort study of U.S. veterans to test the hypothesis that CKD is a mediator in the causal pathway linking race/ethnicity with OSA incidence. Four statistical methods of mediation analysis with different advantages and limitations were used: informal difference method, 4-way decomposition, flexible mediation analysis, and dynamic path analysis. Blacks and Hispanics had higher incidence rates than did non-Hispanic Whites. The percentages of the total race/ethnicity effects mediated by CKD were small and similar using all 4 mediation methods; e.g., using flexible mediation analysis, the percentage of the Black/White effect on OSA incidence mediated by CKD was 5.8%. However, when CKD and its 3 risk factors were treated jointly as mediators in flexible mediation analysis, the percentage mediated increased to 30.3%.

The high prevalence of sleep problems including OSA among persons with CKD, their associations with mortality, and the mediated effect by CKD on racial disparity in OSA incidence suggest their potential importance to clinical practice. Future work could address the feasibility of early identification, objective characterization and management of sleep problems among patients with CKD, and studying the effects of proactive practices including control of mediators (CKD) on disease progression and other outcomes.

CHAPTER 1
Introduction

Sleep-related problems such as getting too little sleep or trouble sleeping are rapidly

growing public-health concerns because they often result in adverse short-term consequences

such as stress responsivity and reduced quality of life as well as long-term health consequences

such as hypertension and cardiovascular disease.[1] Its increasing prevalence may be due to

round-the-clock, night-owl lifestyles, elevated stress, and increasing awareness of the problem,

leading to more reporting, increasing physiological conditions (e.g., obesity and diabetes) and

the increasing use of mediations that may interfere with sleep, and societal factors such as

natural disasters and pandemics.[2] Sleep problems (whether sleeping too much or not enough)

are associated with mortality and mental disorders especially depression.[3] A common but often

unrecognized sleep disorder, sleep apnea, is a public health concern causing repetitive

cessation of breathing while a person is sleeping. Obstructive sleep apnea (OSA), characterized

by transient airway occlusion, is the most common form of sleep-disordered breathing.[4] Fifty

percent of women and 37% of men were reported to have OSA in two recent studies.[5,6] In

contrast, central sleep apnea (CSA) usually involves brain dysfunction rather than significant

upper airway obstruction.[7] Not only does OSA appear to increase the risk of physical and

psychological diseases, but it also impairs the quality of life as well as cognitive function,[8,9]

including vigilance, attention, executive functioning, memory, and motor coordination.[10]

Chronic Kidney Disease (CKD), a common disorder worldwide with the prevalence ranging from 3% to 18% worldwide[11] and nearly 15% in the US adult population,[12] is defined by abnormal kidney function (indicated by an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) or structural damage (indicated by urine albumin-to-creatinine ratio (UACR) > 30 mg/g) persisting for at least three months. About 6% of CKD patients end up with end-stage renal disease (ESRD).[13,14] CKD itself is an important risk factor for all-cause mortality, especially cardiovascular mortality.[12,15,16]

Recent studies have found that OSA is associated with higher risk of cardiovascular disease, especially stroke.[17,18,19] However, unlike the well-established association between OSA and cardiovascular morbidity and mortality, the relation between OSA and CKD is not fully understood. A vicious cycle--positive feedback loop--may exist, in which OSA increases the risk of CKD, which in turn increases the risk or severity of OSA.[20]

Patients with and without CKD could have different etiologies and clinical manifestations of OSA: comparing to people without CKD, OSA patients with advanced CKD tend to be less obese, report less frequent snoring, and more frequently experience apnea during sleep, unrefreshing sleep, and morning headache.[21,22] Therefore, the associations between certain CKD risk factors (older age, male sex, obesity) and the risk of OSA are weak in patients with ESRD in spite of these major determinants of OSA in the general population.[23,24,25]

Veterans are more vulnerable to sleep disturbance because of the high prevalence of possible risk factors including obesity, male sex, hypertension, depression, posttraumatic stress disorder, substance use, and other comorbidities comparing to the general population.[26,27,28,29]

However, there is a dearth of research accurately estimating prevalence of sleep apnea among the veteran population. Different methods were used to estimate prevalence of sleep apnea, so prevalence estimates of sleep apnea might not be comparable.[30,31] Few studies have addressed the importance of sleep apnea prevalence in veterans with CKD versus veterans without CKD, and they involve relatively small sample sizes or selected study populations.[32]

Relative to non-Hispanic Whites (hereafter "Whites"), non-Hispanic Blacks (hereafter "Blacks") have a higher prevalence of CKD, a higher risk of progressing to ESRD, an earlier start of dialysis, and a higher mortality rate after ages 56. The racial inequality in CKD may result from the excess prevalence of important causal risk factors for CKD such as diabetes, hypertension, dietary factors and lifestyle in Blacks. The elevated prevalence of OSA in Blacks relative to Whites is convincing evidence of racial inequalities in the development or course of OSA.[33] Moreover, Hispanics and racial minorities showed higher prevalences of OSA compared to Whites.[34,35] However, research examining CKD as a possible mediator of racial difference in OSA is limited. Previous studies have examined sleep-related variables as mediators of the race effect on cardiometabolic diseases[36] and blood pressure.[37]

This dissertation has three aims related to sleep problems, CKD, and OSA in adults. The first aim, using data from National Health and Nutrition Examination Surveys, is to describe the prevalence and temporal trends in the U.S. of five self-reported sleep problems—trouble sleeping, diagnosed sleep disorder, nocturia, inadequate sleep, excessive sleep—and their associations with CKD prevalence and CKD-specific mortality. The second aim, using data from U.S. Veterans Administration (VA) facilities, is to estimate the point prevalence and period prevalence of OSA among veterans with and without CKD and to evaluate their associations

with several possible risk factors for OSA. The third aim, again using VA data, is to assess

whether and to what extent the excess incidence of OSA in racial/ethnic groups relative to

Whites could be explained by CKD serving as a mediator in the causal pathways linking

racial/ethnic contrasts (e.g., Black vs. White) with OSA incidence.

References

1. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep. 2017;9:151-161.

2. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimäki M. Sleep epidemiology-A rapidly growing field. Int J Epidemiol. 2011;40(6):1431-1437.

3. Trenell MI, Marshall NS, Rogers NL. Sleep and metabolic control: waking to a problem? Clin Exp Pharmacol Physiol. 2007;34(1-2):1-9.

4. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ. 2009;108(5):246-249.

5. Nakayama-Ashida Y, Takegami M, Chin K, et al. Sleep-disordered breathing in the usual lifestyle setting as detected with home monitoring in a population of working men in Japan. Sleep. 2008;31(3):419-425.

6. Franklin KA, Sahlin C, Stenlund H, Lindberg E. Sleep apnoea is a common occurrence in females. Eur Respir J. 2013;41(3):610-615.

7. Dharia SM, Brown LK. Epidemiology of Sleep-Disordered Breathing and Heart Failure: What Drives What. Curr Heart Fail Rep. 2017.

8. Molnar MZ, Novak M, Mucsi I. Sleep disorders and quality of life in renal transplant recipients. Int Urol Nephrol. 2009;41(2):373-382.

9. Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA RS. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001;1;24(1):96.

10. Kylstra WA, Aaronson JA, Hofman WF, Schmand BA. Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: A meta-analysis. Sleep Med Rev. 2013;17(5):341-347.

11. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol. 2016.

12. United States Renal Data System.2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.

13. Patrick Albertus, Hal Morgenstern, Bruce Robinson RS. Risk of ESRD in the United States. Am J Kidney Dis. 2016;68(6):862-872.

14.   Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime Incidence of CKD stages 3-5 in the United States. Am J Kidney Dis. 2013;62(2):245-252.

15.   Dalrymple LS, Katz R, Kestenbaum B, et al. Chronic kidney disease and the risk of end-stage renal disease versus death. J Gen Intern Med. 2011;26(4):379-385.

16.   Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-352.

17.   Yaggi KH, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034-2041.

18.   Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. Am J Respir Crit Care Med. 2010;182(2):269-277.

19.   Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. J Clin Sleep Med. 2014;10(4):355-362.

20.   Mirrakhimov AE. Supine fluid redistribution: Should we consider this as an important risk factor for obstructive sleep apnea? Sleep Breath. 2013;17(2):511-523.

21.   Owen J, Reisin E. Obstructive sleep apnea and hypertension: Is the primary link simply volume overload? Curr Hypertens Rep. 2013;15(3):131-133.

22.   Ozkok A, Kanbay A, Odabas AR, Covic A, Kanbay M. Obstructive sleep apnea syndrome and chronic kidney disease: a new cardiorenal risk factor. Clin Exp Hypertens. 2014;36(4):211-216.

23.   Kimmel PL, Miller G MW. Sleep apnea syndrome in chronic renal disease. Am J Med. 1988;86(3)(308-14).

24.   Beecroft JM, Zaltzman J, Prasad R, Meliton G, Hanly PJ. Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. Access. 2007;(June):3028-3033.

25.   Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. Eur Respir J. 2006;28(1):151-158.

26. Tanofsky-Kraff, M., Sbrocco, T., Theim, K. R., Cohen, L. A., Mackey, E. R., Stice, E., Henderson, J. L., McCreight, S. J., Bryant, E. J., & Stephens MB. Obesity and the US Military Family. Obesity. 2013;21(11):2205-2220.

27. Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. Curr Psychiatry Rep. 2014;16(10):487.

28. Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. Neuropsychopharmacology. 2020;45(1):55-73.

29. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217-1239.

30. Jackson M, Becerra BJ, Marmolejo C, Avina RM, Henley N, Becerra MB. Prevalence and Correlates of Sleep Apnea Among US Male Veterans, 2005-2014. Prev Chronic Dis. 2017;14(5):E47.

31. Alexander M, Ray MA, Hébert JR, et al. The National Veteran Sleep Disorder Study: descriptive epidemiology and secular trends, 2000–2010. Sleep. 2016;39(7):1399-1410.

32. Canales MT, Bozorgmehri S, Ishani A, Weiner ID, Berry R, Beyth R. Prevalence and correlates of sleep apnea among US Veterans with chronic kidney disease. J Sleep Res. 2020:e12981.

33. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep. 1991;14(6):486-495.

34. Dudley KA, Patel SR. Disparities and genetic risk factors in obstructive sleep apnea. Sleep Med. 2016;18:96-102.

35. D. F. Kripke, S. Ancoli-Israel, M. R. Klauber, D. L. Wingard, W. J. Mason and DJ, Mullaney. Prevalence of Sleep-Disordered Breathing in Ages 40–64 Years: A Population-Based Survey. 1997;20(1):65–76.

36. Curtis DS, Fuller-Rowell TE, El-Sheikh M, Carnethon MR, Ryff CD. Habitual sleep as a contributor to racial differences in cardiometabolic risk. Proc Natl Acad Sci. 2017;114(33):201618167.

37. Sherwood A, Routledge FS, Wohlgemuth WK, Hinderliter AlL, Kuhn CM, Blumenthal JA. Blood pressure dipping: ethnicity, sleep quality and sympathetic nervous system activity. AM J Hypertens. 2011;24(9):982-988.

CHAPTER 2

Aim 1: US Trends in Prevalence of Sleep Problems and Associations With Chronic Kidney Disease and Mortality

Abstract

Background: To better understand the relation between sleep problems and chronic kidney disease (CKD), we examined temporal trends in the prevalence of self-reported sleep problems in US adults and their associations with CKD and all-cause mortality.

Methods: Using data from 27,365 adult participants in 5 biannual National Health and Examination Surveys (2005-6 through 2013-14), we studied 5 self-reported sleep problems: trouble sleeping, sleep disorder, nocturia (urinating ≥2 times/night), inadequate sleep (<7 hours/night), and excessive sleep (>9 hours/night); plus a composite index. We conducted 3 types of analysis: temporal trends in the prevalence of each sleep measure by CKD status, using model-based standardization; cross-sectional analysis of associations between 4 CKD measures and each sleep measure, using logistic regression; and survival analysis of the association between each sleep measure and mortality, using Cox regression.

Results: The prevalence of trouble sleeping and sleep disorder increased over the 5 surveys by 3.6% and 2.8%, respectively, while the other sleep problems remained relatively stable. All sleep problems, except inadequate sleep, were more common during the study period among

adults with CKD than without CKD (40.3% vs. 21.4% for nocturia; 5.0% vs 1.9 % for excessive sleep; 30.0% vs. 25.2% for trouble sleeping; and 11.6% vs. 7.9% for sleep disorder). Both eGFR <30 mL/min/1.73m^2 and albuminuria were positively associated with nocturia and excessive sleep. Excessive sleep and nocturia were also associated with higher mortality (adjusted hazard ratio for>9 vs. 7-9 hours/night = 1.7; 95% CI: 1.3, 2.1; and for nocturia=1.2; 95% CI: 1.1, 1.4).

Conclusion: The high prevalence of sleep problems among persons with CKD and their associations with mortality suggest their potential importance to clinical practice. Future work could examine the health effects of identifying and treating sleep problems in CKD patients.

Introduction

Sleep abnormalities are associated with several health conditions including chronic kidney disease (CKD) and end-stage renal disease (ESRD)[1]. The prevalence of sleep problems—including difficulty falling asleep, nightmares, restless legs syndrome, and sleep apnea—has been reported to range from 6% to 49% in older patients in the general population[2] and as high as 80% in patients with ESRD.[1,2] In addition, poor sleep quality has been reported in 40-85% of dialysis patients and up to 85% of patients with CKD.[3,4] Higher prevalences of inadequate sleep, frequent use of sleeping pills, restless legs syndrome, and nocturia were observed in individuals with CKD stages 1-2 than in individuals without CKD (i.e., persons with vs. without an albumin-to-creatinine ratio [ACR] ≥ mg/g among those with an estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2).[5]

The higher burden of sleep problems in patients with kidney disease is important, as they been linked with all-cause mortality.[6] Sleep problems may be an important risk factor for mortality in the ESRD patient population.[7] While the prevalence of sleep disturbances has been shown to be increasing among US adults,[6] temporal trends in sleep problems have been sub-optimally examined in US adults with kidney disease. Moreover, few studies with large national samples have been conducted to document the frequency of sleep problems by CKD status in the United States (US) or to examine their associations with morbidity and mortality.[8]

Our study aims were first to describe the prevalence and temporal trends in the US of five self-reported sleep problems—trouble sleeping, sleep disorder, nocturia, inadequate sleep,

excessive sleep; plus a composite measure—and second, to examine the associations of those sleep problems with CKD prevalence and mortality by CKD status.

Methods
Data source and study design

We utilized data on US adults (aged ≥20 years) with and without CKD from 5 biennial National Health and Nutrition Examination Surveys (NHANES), conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 2005-06 and 2013-14. A series of cross-sectional and longitudinal (trend) analyses were conducted to examine the prevalence of sleep problems and their associations with CKD. NHANES is designed to assess the health and nutritional status of US adults and children.[9] The surveys include demographic, socioeconomic, dietary, and health-related questions from a representative sample of noninstitutionalized US residents, with oversampling of people 60 and older, African Americans, and Hispanics. The analysis was limited to 27,365 NHANES participants during the 10-year study period (2005-14) who were 20 years and older and not on renal replacement therapy at the time of examination. All NHANES participants were required to give written informed consent as part of the NHANES study procedures. This study was deemed "non-regulated" by the Institutional Review Board at the University of Michigan, as NHANES provides publicly available de-identified data as part of the Centers for Disease Control and Prevention's CKD Surveillance System Contract with the University of Michigan.

Study Variables

We examined four self-reported sleep variables: 1) trouble sleeping, obtained from responses to the question, "Have you ever told a doctor or other health professional that you have trouble sleeping?" 2) sleep disorder, obtained from responses to the question, "Have you ever been told by a doctor or other health professional that you have a sleep disorder?" 3) nocturia, obtained from responses to the question, "During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?" and 4) total hours of sleep per night, obtained from responses to the question, "How much sleep do you usually get at night on weekdays or workdays?" Responses to the nocturia question were dichotomized as two or more times per night (nocturia) or less frequently; and responses to the sleep-duration question were categorized according to national and international guidelines[10] as less than 7 hours per night (inadequate sleep), 7 to 9 hours (recommended sleep), and more than 9 hours (excessive sleep). In addition, a composite sleep-problem index was created by first summing indicators of all 5 sleep problems. Because excessive sleep was nearly unrelated to the other sleep problems (and mutually exclusive with inadequate sleep), it was excluded from the index, resulting in a reliable composite measure that is internally consistent (Cronbach's alpha = 0.57).

Demographic information (age, sex, and race/ethnicity) was collected during the interview of each participant. Race/ethnicity was categorized into four groups: Hispanic; non-Hispanic White; non-Hispanic Black/African American; and non-Hispanic other race. Hypertension and diabetes were defined by any of three criteria: self-report of each condition as told by a health professional; self-reported use of condition-specific medications; and laboratory measurements (systolic and diastolic blood pressure, hemoglobin level [A1c], and

blood sugar). Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Serum creatinine

levels were corrected for different laboratory methods used in different years.[11] Urine albumin

was measured by a solid-phase fluorescein immunoassay and urine creatinine by the enzymatic

method.[12] Smoking status was defined as currently smoking on all or some days. Histories of

cancer, cardiovascular disease, and chronic respiratory disease were based on self-reports as

told by a health professional. Prescription medications were recorded by the interviewer from

the bottles provided by the participant, and medications that affect drowsiness and cognition

were extracted from these data and created indicators for sedatives, stimulants, and other

drugs (Table A1).

Because CKD is diagnosed on the basis of both reduced kidney function indicated by low

eGFR and kidney damage indicated by a high urinary ACR or albuminuria, we used four

measures of CKD in our analyses:[13]

1. CKD status (binary; CKD vs. no CKD): eGFR < 60 mL/min/1.73m^2 (using the CKD-EPI

    equation[14]) and/or ACR ≥ 30 mg/g versus eGFR ≥ 60 mL/min/1.73m^2 and ACR < 30

    mg/g (reference group).

2. eGFR category (ordinal): eGFR ≥ 60 mL/min/1.73 m^2 (reference group); 30 ≤ eGFR <

    60 mL/min/1.73^2 ; and eGFR < 30 mL/min/1.73 m^2.

3. ACR category (ordinal): normal to mildly increased (ACR < 30 mg/g; reference

    group); moderately increased (30 mg/g ≤ ACR ≤ 300 mg/g); and severely increased

    (ACR > 300 mg/g).

4. CKD prognosis category defined in KDOQI[13] (ordinal, based on the combination of eGFR category and ACR category): low risk (no CKD; same reference group as in #1), moderate increased risk, high risk, and very high risk (see Table A4 for details).

All-cause mortality data were available for 27,322 (99.8%) of the 27,365 participants. All 5 survey cohorts were followed from their baseline interviews (2005-2014) to the end of 2015. Thus, the follow-up duration of study participants could range from as little as 1 year to as much as 11 years; the median observed follow-up was 77 months. Vital status and date of death were ascertained from the National Death Index (NDI). The primary determination of mortality status for participants was based on matching survey records to the NDI. If a source of mortality other than NDI was available, the participant was considered deceased. The publicly available records from the NDI were linked with NHANES by the National Center for Health Statistics. The linkage of NHANES surveys to the NDI involved identifying eligible participants from the NHANES surveys, creating base submission records plus any alternative records, merging base submission records with NDI data, executing the match process, reviewing match results, selecting matches and determining vital status.[15]

Statistical analysis

Temporal trends in the prevalence of each sleep problem and the mean composite index were estimated across the 5 NHANES surveys, by CKD status (CKD vs. no CKD). The crude and standardized prevalence of the 5 sleep problems were estimated for each two-year survey (2005-06 to 2013-14). Weighted linear regression, as recommended by the Centers for Disease

Control and Prevention,[16] was used to directly standardize for age, sex, and race/ethnicity, using the 2000 US population as the standard[17] and treating survey year as a nominal variable. The ACR was standardized to the covariate distribution of the 2005-06 cohort. To test for a monotonic trend, we treated survey year as an interval variable (coded 1-5).

Cross-sectional associations of each CKD measure (predictor) with each sleep problem (outcome) were examined using data from all 5 NHANES surveys (2005-14). Weighted logistic regression was used to estimate the adjusted prevalence odds ratios (OR) and 95% confidence intervals (CI). In this analysis, amount of sleep each night was treated as a 3-category outcome, using multinomial logistic regression to estimate the effects of each CKD predictor on inadequate and excessive sleep vs. normal sleep. These associations were adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, and use of one or more medications thought to affect sleep problems. To examine age as a possible modifier of the associations between CKD measures and sleep variables, we stratified by age to compare adults who were 65 and older with those who were under 65.

The association between each sleep problem as well as the composite index observed at baseline interviews in all 5 surveys (2005 to 2014) and all-cause mortality through 2015 was estimated in separate models using Cox regression. The hazard ratio (HR and 95% confidence interval [CI]) for the effect of each sleep problem and composite index on time to death was adjusted for survey year, age, sex, race/ethnicity, CKD status, hypertension, diabetes, obesity, current smoking status, cancer, CVD, chronic respiratory disease, the selected medications, and the other sleep problems (excluding the composite index). To assess CKD status as a potential modifier of the effect of each sleep problem on mortality, product terms for each sleep variable

15

and CKD status were added to the models. In addition, separate analyses were conducted for participants with and without CKD.

Multiple imputation was implemented to impute missing values of trouble sleeping (0.05% missing), sleep disorders (0.2% missing), nocturia (29.0% missing), sleep amount (0.2% missing), eGFR (6.5% missing), and ACR (2.5% missing), assuming data were missing at random.[18] First, we imputed values for the missing data 25 times by sampling from the chained equations using PROC MI procedures within SAS software, which included auxiliary variables that may contain information about the missing data, variables and outcomes involved in the planned analysis, and variables accounting for the clusters and strata.[19] From the complete variables and the imputed set, 25 complete datasets were created. Second, we analyzed the 25 complete data sets using SURVEY procedures within SAS. Finally, we combined the 25 parameter estimates and standard errors to calculate pooled estimates and standard errors using PROC MIANALYZE procedures within SAS, which reflect the variability of the imputation process along with the complex sampling design.[20]

Because many participants in our survival analysis were followed for several years (from as early as January 1, 2005 to as late as December 31, 2015), the status of their sleep problems could have changed during follow-up, possibly leading to bias in effect estimation. Unfortunately, we did not have data on changing sleep problems after baseline interviews, so we could not treat each sleep problem as time-dependent. Therefore, we conducted a sensitivity analysis by restricting the follow-up of each survey participant to no more than 1 year. Although changes in sleep problems could still occur over 1 year, the potential for bias

16

would be reduced appreciably, and the number of deaths in 1 year yielded sufficient estimation precision.

All analyses were performed in SAS version 9.4 and account for the survey data structure including sampling weights, primary sampling units, and sample strata.

Results

Table 1 shows summary statistics for selected baseline variables in 27,365 participants. The mean age was 47 years; 48% were male and 68% were non-Hispanic Whites. Compared to participants without CKD, those with CKD were more likely to be older, female, have larger BMIs, have diabetes, hypertension, cancer, CVD, and worsening memory.

Time trends in the age-sex-race-standardized prevalence of each sleep problem and the composite sleep-problem index during the study period are displayed in Figure 1.a-f and Table A2. Overall, there was a steady rise of 3.6% between 2005-06 (24.1%) and 2013-14 (27.7%) in the prevalence of reported trouble sleeping (*P* for trend < 0.001; Figure 1.a) and a sharper rise of 3.1% between 2009-10 (7.1%) and 2013-14 (10.2%) in the prevalence of reported sleep disorders (*P* for trend < 0.001; Figure 1.b). In contrast, there was an overall decrease of 2.9% in the prevalence of inadequate sleep between 2007-08 (38.3%) and 2013-14 (35.4%) (*P* for trend = 0.53; Figure 1.c). The other sleep problems remained fairly stable or varied inconsistently during the study period (Figures 1.d-e). The prevalences of all 5 sleep problems and the composite index were greater for persons with CKD than without CKD during most survey years (Table A2). There was a steady increase of 2.7% between 2005-06 (23.0%) and 2013-14 (25.7%)

in the prevalence of the composite index score >1 (*P* for trend = 0.036; Figure 1.f). There was a downward spike in 2011-12 in the prevalences of trouble sleeping, inadequate sleep, and the composite index among CKD patients, deviating from those overall trends. Since the sleep questions did not change for that one survey among any group, we cannot explain the unusual deviation.

Table 2 shows the cross-sectional associations between each of 4 CKD measures treated as predictors--CKD status, ACR category, eGFR category, and CKD prognostic category (based on both ACR and eGFR; refer to Table A4 for the joint distribution of these two CKD measures)— and each sleep problem treated as the outcome. CKD status was most strongly associated with excessive sleep (OR = 2.2; 1.8-2.5) and nocturia (OR = 1.3; 1.1-1.4); it was inversely associated with trouble sleeping (OR = 0.88; 0.78-0.99) but not associated with inadequate sleep or sleep disorder. ACR category was more strongly and positively associated with each sleep problem than was eGFR category, except for excessive sleep. Compared with eGFR ≥60 mL/min/1.73m^2, the adjusted OR for excessive sleep was 2.4 (1.9, 3.1) for eGFR = 30-59 and 5.8 (3.4, 9.8) for eGFR <30. Compared with ACR <30 mg/g, the adjusted OR for nocturia was 1.2 (1.1, 1.4) for ACR = 30-300 mg/g and 1.6 (1.3, 2.0) for ACR >300 mg/g. Positive monotonic associations were observed between CKD prognosis category and nocturia and between CKD prognosis category and excessive sleep (*P* for trend < 0.001). Nocturia and excessive sleep were positively associated with CKD prevalence (*P* < 0.001) and monotonically associated with the three polytomous measures of CKD (*P* for trend < 0.001). Weighted and standardized prevalences of each of the 5 sleep problems are provided in Table A3 and Table A5 a-e in the supplemental material.

The weighted prevalence of each sleep problem and the index score are shown in Table 3. The overall prevalences, in order from most to least common, were: inadequate sleep (36.5%), trouble sleeping (25.9%), nocturia (24.3%), sleep disorder (8.5%), and excessive sleep (2.4%). For all problems except inadequate sleep, the prevalence was greater in persons with CKD than without CKD. More than 60% of the study population had a sleep-problem index score greater than zero.

Crude and mutually adjusted HRs for the estimated effects of the 5 sleep problems on all-cause mortality, are shown in Table 4. Overall, the sleep problem with the strongest association with mortality was excessive sleep (>9 hours/night), which was reported less frequently (2.4%) than the other sleep problems (Table 3). Compared with recommended sleep (7-9 hours/night), the adjusted HR for excessive sleep was 1.7 (1.3, 2.1) in the total study population. The crude association (HR = 3.6) was reduced appreciably with covariate adjustment; and it was stronger for persons without CKD (P for interaction = 0.08) but did not vary much by age (P for interaction = 0.28; data not shown). A weaker overall association was found for nocturia (adjusted HR = 1.2; 1.1, 1.4) with little difference between age groups; and little or no association overall or by age was observed for trouble sleeping, sleep disorder, and inadequate sleep.

The associations of the sleep-problem index and excessive sleep with mortality, mutually adjusted for each other, are shown in Table 5. A positive monotonic association in the total population was observed for the index score (P for trend = 0.01), and a moderate association was observed for excessive sleep (adjusted HR = 1.7; 1.3, 2.1). While the association

with the index score was a slightly stronger in persons with CKD, the association with excessive

sleep was stronger in persons without CKD.

Results of the sensitivity analysis in which follow-up for mortality was limited to one

year are shown in Table 6. The HR estimates are similar to the estimates in the main analysis

with full follow-up to the end of 2015 (Table 4), but with wider confidence intervals. These

results suggest little bias resulting from unmeasured changes in the prevalence of sleep

problems during follow-up in the main analysis.

Discussion

Our analysis of data from a series of contemporary, nationally representative surveys

over the past decade shows that the prevalence of self-reported sleep problems—trouble

sleeping, sleep disorders, nocturia, inadequate sleep, and excessive sleep—were generally

higher in adults with CKD than those without CKD in the US. We observed monotonic

associations between severity of CKD (based on ACR, eGFR, and CKD prognostic categories) and

sleep problems adjusting for potential confounders. The sleep problems most strongly and

consistently associated with all CKD measures were excessive sleep and, to a lesser extent,

nocturia. All measured sleep problems, except trouble sleeping among CKD patients, were

positively associated with mortality, and we found a dose-response association between the

number of sleep problems and mortality. The sleep problem with the strongest association with

mortality was the one with the lowest prevalence, excessive sleep, which likely reflects the

influence of major chronic health problems. These findings highlight the importance of

remaining alert to the presence of sleep problems among those with CKD both by primary care and by specialist providers.

The prevalence of reported sleep disorders, especially trouble sleeping and sleep disorder, has risen over the past 10 years and almost doubled among persons with CKD. These findings are supported by evidence in the general population of the increasing prevalence of sleep-disordered breathing including obstructive sleep apnea (OSA), purportedly due in part to the obesity epidemic and an aging society.[2,21] Thus, the increasing prevalence of self-reported sleep disorders in this study may not only reflect an artifactual increase in reporting.

The increasing prevalence of self-reported insomnia and excessive daytime sleepiness among the US population from 2002 to 2012 was reported by Ford et al.[22] Moreover, sleep duration has been declining over the years in the US and reached an average of 7.2 hours per night in 2012.[23] According to Knutson et al.,[24] who compiled time-diary data from 8 national studies conducted between 1975 and 2006, the percentage of US adults having less than 6 hours sleep per night ("short sleepers") fluctuated inconsistently from a low of 7.5% in 1992-94 to a high of 11.8% in 1998-99; the prevalence in 2006 was 9.3%. In contrast, we found the prevalence of <6 hours sleep per night in 2005-06 to be 13.4% and relatively stable through 2013-14 (data not shown for <6 hours/night). This inconsistency may be due to the different methods used to measure sleep duration, i.e., time-diaries used by Knutson et al.[24] versus recall-based self-reports used in our study.

We found that the low eGFR category was associated, as expected, with higher prevalences of nocturia and excessive sleep, but not with the other sleep problems; in fact, the

high eGFR category was associated with inadequate sleep, which may, at least in part, potentially reflect longer work hours[23] or other factors (e.g., stress, anxiety or depression). We were not, however, able to assess the influence of employment status or work hours on the associations with eGFR.

Plantinga et al.[5] found a higher prevalence of sleep disorders and inadequate sleep (≤ 6 hours/night) for persons with CKD stages 1 and 2, but not for stages 3 and 4, relative to persons without CKD. We found a similar but very weak association with inadequate sleep (<7 hours/night) but little or no association with sleep disorder (Table 2). Similar to Plantinga et al.,[5] we found that nocturia was strongly associated with CKD, regardless of the method used to characterize CKD. It is possible that people with lower eGFR tend to be more often on multiple medications, be more fatigued, and therefore have longer sleep duration (which may clinically be (mis)interpreted as 'good sleep'). Since GFR has a weaker association with obesity than do the other CKD measures,[25] another possible explanation is that patients with lower eGFR may not be getting the requisite sleep diagnostic work-up as frequently, due either to low index of suspicion by the clinician, or greater attention to kidney-specific complications in the setting of having to deal with multiple clinical domains (e.g., blood pressure control, management of anemia, bone and mineral metabolism and fluid-electrolyte abnormalities, CKD progression, etc.), in the limited time typically available for an average clinical encounter. This could result in the patient not receiving a sleep study, and thus not being aware of the presence of a sleep disorder.

Although only 2.4% of participants reported excessive sleep, that problem was most strongly associated with all four CKD measures (Table 2) and all-cause mortality in the total

sample (Table 4). For the associations between sleep duration and all-cause mortality, a positive monotonic association was found in participants without CKD, indicating that more sleep is associated with mortality; but a U- or J-shaped association was observed among those with CKD, indicating that both inadequate and excessive sleep are associated with mortality (Table 4). A similar U-shaped association has been reported in previous studies.[6,26,27,28] Sleep fragmentation, immune dysfunction, photoperiodic abnormalities, depression, underlying disease process such as sleep apnea, heart disease, or failing health are potential mechanisms linking excessive sleep duration with mortality.[29] The prevalence of sleeping more than 9 hours a night in the US varied a little across studies: 5% reported excessive sleep in 2006 in Patel et al.,[30] 3.6% in 2014 according to Liu et al.,[31] and 2.4% in our study.

Unlike the association between inadequate sleep and mortality, the underlying mechanisms for the association between excessive sleep and mortality are yet to be fully investigated. This association could be confounded by other unmeasured risk factors for mortality such as comorbidities.[32] Comorbidities such as chronic respiratory disease, cancer, and CVD were adjusted for in the study, but they were self-reported; thus, their misclassification may have limited control for confounding. Furthermore, excessive sleep could simply be a marker of poor sleep quality, chronic pain, increased duration of rapid eye movement sleep, or soporific side effects of medications.[33]

Short sleep duration has also been found in several systematic reviews to be associated with a number of adverse health outcomes including mortality.[6,27,28,34,35,36] Possible mechanisms for the health effects of inadequate sleep are endocrinologic, immunologic, and metabolic factors such as increased ghrelin and decreased leptin,[37,38] chronic inflammation, altered

23

cortisol secretion and growth hormone metabolism,[39,40] the development of hypertension from increased sympathetic nervous system activity, and changes in circadian rhythm.[41] In our study, however, we found little positive association between inadequate sleep and CKD or mortality. That apparent discrepancy might be due to our data being derived from self-reports, rather than more objective methods such as actigraphy or polysomnography, which may not strongly correlate with self-reports from surveys.[32]

We found that nocturia was strongly associated with CKD and mortality regardless of the method used to characterize CKD. Nocturia is one of the most common symptoms in patients with CKD,[42] with a prevalence of 40% in our study. A trend of increased mortality with increased number of voiding episodes in the general population was also reported in NHANES lll participants.[43] Krol et al. reported that nocturia was associated with albuminuria,[44] which is consistent with our finding of a dose-response association with ACR (Table 2). Studies have showed that osmotic diuresis rather than water diuresis or urea excretion is the main mechanism of nocturia in CKD.[45] Possible mechanisms of nocturia include an overall increase in urine production (secondary to diminished ability to concentrate urine by a poorly functioning kidney), resulting in continued higher volume of, urine production even at night, a reduced bladder capacity, or any sleep disorder.[46] Aside from urologic conditions, nocturia may also reflect multiple underlying renal or systemic diseases.[47] In addition, it is linked to urinary urgency, prostate cancer, OSA, depression, and the metabolic syndrome.[48,49]

An important limitation of this study concerns the measurement of sleep problems. First, self-reports may be inaccurate, possibly resulting in bias in estimating the prevalence of the sleep problems or their associations with CKD or mortality. Second, detailed information

24

was lacking on reported sleep problems, especially relevant for trouble sleeping and sleep disorder. For trouble sleeping, we did not know the frequency, duration, or timing of reported problems. For sleep disorder, we did not know the type or nature of the disorder that a doctor presumably told the patient he or she had. Third, persons with CKD, especially advanced CKD, are generally more likely than those without CKD to be seeing a physician on a regular basis. Therefore, they may have been more likely to report communicating with their doctors about sleep problems and specific sleep disorders, even if those two problems were not more frequent or severe. Finally, although our composite sleep index was an *ad hoc* measure, there is evidence of its construct validity in Table 5, where it was monotonically associated with mortality, consistent with our hypothesis; and we found the index to have good reliability with Cronbach's alpha of 0.57.

Another limitation is the cross-sectional design for estimating associations between CKD and sleep problems. Thus, we cannot determine whether associations may have been due to the effects of CKD on sleep problems, as hypothesized, or to the possible effects of sleep problems on CKD.[50] Finally, a limitation of this study is residual confounding due to unmeasured risk factors for the outcomes in our analyses (sleep problems or mortality). We adjusted for several demographic and clinical risk factors, but we were not able to adjust for others such as benign prostatic hyperplasia, socioeconomic status, cognitive impairment, and mental-health status. In the analyses of mortality, unmeasured confounders may have exaggerated the positive associations with certain sleep problems, particularly, excessive sleep. The fact that our adjusted associations tended to be noticeably weaker than the corresponding crude associations suggests that it was not possible, with the available data, to fully control for

25

confounding. On the other hand, some covariates we adjusted for may have been mediators in causal pathways linking sleep problems with mortality, which could have resulted in underestimates of the effects of interest.

Several unique aspects, strengths of our study, and advantages over previous NHANES studies of sleep problems in the US, merit attention.[5,28,43] The fact that we analyzed a large, randomly selected, contemporary, representative sample of the US population of persons with and without CKD from several biennial surveys, the use of sampling weights to reflect the complex survey designs, and the use of comparable data collection methods across surveys enhanced our ability to make reliable statistical inferences about the US adult population. We measured 5 sleep problems, a composite sleep-problem index, and 4 complementary measures of CKD;[5,28] we adjusted for several potential confounders; we used a state-of-the-art method, multiple imputation, to handle missing data—all of which helped to enhance causal inference.

In conclusion, the relatively high prevalence of sleep problems among persons with CKD in the US and the associations of those sleep problems with mortality underscore their potential clinical importance of addressing this topic by both primary care providers as well as by specialists. Future work could address the feasibility of early identification, objective characterization and management of sleep problems among patients with CKD and ESRD and studying the effects of those proactive practices on patient health, disease progression and other clinically relevant outcomes.

References

1. Elder SJ, Pisoni RL, Akizawa T, Fissell R, Andreucci V, Fukuhara S, Kurokawa K, Rayner H, Furniss A, Port F, Saran R. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2008;23(3):998-1004.

2. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev. 2017;34:70-81.

3. Guney I, Atalay H, Solak Y, Altintepe L, Toy H, Tonbul HE, Turk S. Predictors of sleep quality in hemodialysis patients. Int J Artif Organs. 2010;33(3):154-160.

4. Turek NF, Ricardo AC, Lash JP. Sleep disturbances as nontraditional risk factors for development and progression of CKD: review of the evidence. Am J Kidney Dis. 2012;60(5):823-833.

5. Plantinga L, Lee K, Inker LA, Saran R, Yee J, Gillespie B, Rolka D, Saydah S, Powe N. Association of sleep-related problems with CKD in the United States, 2005-2008. Am J Kidney Dis. 2011;58(4):554-564.

6. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep. 2010;33(5):585-592.

7. Benz RL, Pressman MR, Hovick ET, Peterson DD. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis. 2000;35(6):1052-1060.

8. Xu J, Young I, Jun H. The effect of sleep apnea on all-cause mortality in nondialyzed chronic kidney disease patients. Sleep Med. 2016;27-28:32-38.

9. Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Examination Survey data, 2005-2014. https://www.cdc.gov/nchs/nhanes/. Accessed April 10, 2017.

10.   National Sleep Foundation Recommends New Sleep Times. https://www.sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times. Accessed May 10, 2018.

11.   Selvin E, Manzi J, Stevens LA, Van Lente F, Lacher DA, Levey AS, Coresh J. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004. Am J Kidney Dis. 2007;50(6):918-926.

12.   Chavers BM, Simonson J MA. A solid-phase fluorescent immunoassay for the measurement of human urinary albumin. Kidney Int. 1984;(25):576-578.

13.   Levey AS, De Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28.

14.   Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

15.   Centers for Disease Control and Prevention, National Center for Health Statistics. Linkage Methods and Analytical Support for NCHS Linked Mortality Data. https://www.cdc.gov/nchs/data-linkage/mortality-methods.htm. Accessed November 10, 2017.

16.   Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Examination Survey data. Age Standardization and Population Counts. https://www.cdc.gov/nchs/tutorials/NHANES/NHANESAnalyses/agestandardization/age_standardization_intro.htm. Accessed November 18, 2017.

17.   Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. Healthy People 2000 Stat Notes. 2001;(20):1-9.

18.   Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, N.J: John Wiley. 2011

19.   Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple Imputation by Chained Equations: What is it and how does it work? Int J Methods Psychiatr Res.2012;20(1):40-49.

20.   Berglund PA. Multiple imputation using the fully conditional specification method: a comparison of SAS, Stata, IVEware, and R. SAS Glob Forum Proceedings, Pap 2081-2015. 2015:1-17.

21.   Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006-1014.

22.   Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among US adults from 2002 to 2012. Sleep Med. 2016;16(3):372-378.

23.   Ford ES, Cunningham TJ, Croft JB. Trends in self-Reported sleep duration among US adults from 1985 to 2012. Sleep. 2012;38(5):829-32.

24.   Knutson KL, Van Cauter E, Rathouz PJ, DeLeire T, Lauderdale DS. Trends in the prevalence of short sleepers in the USA: 1975-2006. Sleep. 2010;33(1):37-45.

25.   Kim YJ, Hwang SD, Oh TJ, Kim KM, Jang HC, Kimm H, Kim HC, Jee SH, Lim S. Association between obesity and chronic kidney disease, defined by both glomerular filtration rate and albuminuria, in Korean adults. Metab Syndr Relat Disord. 2017;15(8):416-422.

26.   Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes : a systematic review, meta-analysis and meta-regression. Sleep Med Rev. 2018;39:25-36.

27.   Gallicchio L, Kalesan B. Sleep duration and mortality: A systematic review and meta-analysis. J Sleep Res. 2009;18(2):148-158.

28.   Ricardo AC, Goh V, Chen J, Cedillo-Couvert E, Kapella M, Prasad B, Parvathaneni S, Knutson K, Lash JP. Association of sleep duration, symptoms, and disorders with mortality in adults with chronic kidney disease. Kidney Int Reports. 2017;2(5):866-873.

29.   Grandner MA, Drummond SPA. Who are the long sleepers? Towards an understanding of the mortality relationship. Sleep Med Rev. 2007;11(5):341-360.

30.	Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep. 2006;29(7):881-889.

31.	Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H CJ. Prevalence of healthy sleep duration among adults — United States, 2014. MMWR Morb Mortal Wkly Rep. 2016; 65(6):137-141.

32.	Hossin MZ. From habitual sleep hours to morbidity and mortality: existing evidence, potential mechanisms, and future agenda. Sleep Heal. 2016; 2(2):146-153.

33.	Pack AI, Dinges DF, Gehrman PR, Staley B, Pack FM, Maislin G. Risk factors for excessive sleepiness in older adults. Ann Neurol. 2006;59(6):893-904.

34.	Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review. Sleep Med. 2017;32:246-256.

35.	Guo X, Zheng L, Wang J, Zhang X, Zhang X, Li J, Sun Y. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. Sleep Med. 2013;14(4):324-332.

36.	Shen X, Wu Y, Zhang D. Nighttime sleep duration, 24-hour sleep duration and risk of all-cause mortality among adults: a meta-analysis of prospective cohort studies. Sci Rep. 2016;6(38):1-8.

37.	Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004;1(3):210-217.

38.	Knutson KL, Spiegel K, Penev P, Van-Cauter E. The Metabolic Consequences of Sleep Deprivation. Sleep Med Rev. 2007;11(3):163-178.

39.	Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: A critical review of measurement and associations. Ann Epidemiol. 2013;23(6):361-370.

40.	Copinschi G. Metabolic and endocrine effects of sleep deprivation. Essent Psychopharmacol. 2005;6(6):341-347.

41.   Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev. 2009;10(SUPPL. 2):37-45.

42.   Wu MY, Wu YL, Hsu YH, Lin YF, Fan YC, Lin YC, Chang SJ. Risks of nocturia in patients with chronic kidney disease - Do the metabolic syndrome and its components matter? J Urol. 2012;188(6):2269-2273.

43.   Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the third National Health and Nutrition Examination Survey. J Urol. 2011;185(2):571-577.

44.   Król E, Rutkowski B, Czarniak P, Kraszewska E, Lizakowski S, Szubert R, Czekalski S, Sułowicz W, Więcek A. Early detection of chronic kidney disease: results of the PolNef study. Am J Nephrol. 2009;29(3):264-273.

45.   Fukuda M, Motokawa M, Miyagi S, Sengo K, Muramatsu W, Kato N, Usami T, Yoshida A, Kimura G. Polynocturia in chronic kidney disease is related to natriuresis rather than to water diuresis. Nephrol Dial Transplant. 2006;21(8):2172-2177.

46.   Cornu J, Abrams P, Chapple CR, Dmochowski RR, Lemack GE, Michel MC, Tubaro A, Madersbacher S. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol. 2012;62(5):877-890.

47.   Dani H, Esdaille A, Weiss JP. Nocturia: aetiology and treatment in adults. Nat Rev Urol. 2016;13(10):573-583.

48.   Tikkinen KAO, Auvinen A, Johnson TM, Weiss JP, Keranen T, Tiitinen A, Polo O, Partinen M, Tammela TLJ. A systematic evaluation of factors associated with nocturia - the population-based FINNO study. Am J Epidemiol. 2009;170(3):361-368.

49.   Zebede S, Lovatsis D, Alarab M, Drutz H. Prevalence of obstructive sleep apnea detected by the Berlin Questionnaire in patients with nocturia attending a urogynecology unit. Int Urogynecol J. 2015;26(6):881-885.

50.   Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, Arah OA, Ma JE, Lu JL, Sim JJ, Streja, E, Kalantar-Zadeh K, Kovesdy CP. Association of incident obstructive sleep apnea with outcomes in a large cohort of US Veterans. Thorax. 2015;70(9):888-895.

Tables and figures

Table 2.1: Summary statistics—weighted proportion (%) or weighted mean (and standard deviation)—of selected baseline variables, by CKD status; total study population, 2005-14

Measure	All (n = 27,365)	No CKD (n = 22,137)	CKD (n = 5,228)
Age (years)	47 (0.27)	45 (0.24)	60 (0.39)
20-34 (%)	28	31	12
35-49 (%)	29	31	17
50-64 (%)	26	26	23
65-74 (%)	10	8	19
>75(%)	7	4	29
Male (%)	48	49	42
Race/ethnicity (%)			
Hispanic	14	14	11
Non-Hispanic White	68	68	70
Non-Hispanic Black	11	11	13
Other non-Hispanic race	7	7	6
Body Mass Index (kg/m^2)	28.8 (0.08)	28.6 (0.09)	29.9 (0.14)
<18.5 Underweight (%)	3	2	2
18.5 to <25 normal weight (%)	29	30	25
25 to <30 overweight (%)	33	34	30
≥30 obese (%)	35	34	43
Diabetes (%)	11	7	28
Hypertension (%)	34	27	71
Smoking (%)	33	33	33
Cancer (%)	10	8	17
Cardiovascular disease (%)	8	6	24
Chronic respiratory disease (%)	18	18	21
Full time job	38	38	37
Worsening confusion or memory loss in the past 12 months[a]	15	12	21

[a]Only among people who were ≥ 60 from 2011-2014

Table 2.2: Estimated cross-sectional association (adjusted[a] odds ratio and 95% CI) between each CKD measure and each binary sleep problem (outcome) in 2005-14 for the total study population

CKD Measure Category	Trouble Sleeping[b]	Sleep Disorder[b]	Nocturia[b]	Inadequate sleep[c]	Excessive sleep[c]
CKD status					
No CKD (ref.)	1	1	1	1	1
CKD	0.88	1.0	1.3	0.98	2.2
	(0.78, 0.99)	(0.87, 1.2)	(1.1, 1.4)	(0.88, 1.1)	(1.8,2.5)
P-value	0.037	0.78	<0.001	0.29	<0.001
ACR category					
ACR<30 (ref.)	1	1	1	1	1
30≤ACR≤300	0.89	1.1	1.2	1.1	1.7
	(0.78, 1.0)	(0.90, 1.3)	(1.1, 1.4)	(0.97, 1.2)	(1.4, 2.2)
ACR>300	1.2	1.3	1.6	1.2	2.7
	(0.92, 1.5)	(0.92, 1.8)	(1.3, 2.0)	(0.97, 1.5)	(1.6, 4.5)
P for trend[d]	0.65	0.11	<0.001	0.16	<0.001
eGFR category					
eGFR≥60 (ref.)	1	1	1	1	1
30≤eGFR<60	0.82	0.89	1.1	0.81	2.4
	(0.68, 0.98)	(0.67, 1.2)	(0.99, 1.3)	(0.67, 0.97)	(1.9, 3.1)
eGFR<30	1.2	1.1	1.6	0.98	5.8
	(0.79, 1.8)	(0.71, 1.8)	(1.0, 2.4)	(0.70, 1.4)	(3.4, 9.8)
P for trend[e]	0.26	0.68	<0.001	0.003	<0.001
CKD prognostic category					
Low (ref.)	1	1	1	1	1
Moderate	0.87	1.0	1.2	0.98	1.7
increased	(0.76, 1.0)	(0.85, 1.2)	(1.1, 1.3)	(0.86, 1.1)	(1.4, 2.2)
High	1.0	1.0	1.3	1.0	3.0
	(0.83, 1.3)	(0.76, 1.4)	(1.1, 1.7)	(0.84, 1.2)	(2.1, 4.4)
Very high	0.86	1.2	1.5	0.92	5.2
	(0.62, 1.2)	(0.80, 1.7)	(1.1, 1.9)	(0.70, 1.2)	(3.5, 7.8)
P for trend[f]	0.19	0.52	<0.001	0.18	<0.001

[a]Adjusted for survey year, age, sex, and race/ethnicity, diabetes, hypertension, obesity, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs).

[b]Using weighted ordinary binary logistic regression.

[c]Using weighted multinomial logistic regression, where inadequate sleep (<7 hours/night) and excessive sleep (>9 hours/night) are compared with recommended sleep (7-9 hours/night).

[d]ACR category were considered as an interval variable (1-3) to test for a monotonic trend.

[e]eGFR categories were considered as an interval variable (1-3) to test for a monotonic trend.

[f]CKD prognostic category were considered as an interval variable (1-4) to test for a monotonic trend.

Table 2.3: Weighted prevalence (%) of each binary sleep problem and category of the sleep-problem index, by CKD status; total study population, 2005-14

Prevalence (%)	All (n=27,322)	No CKD (n=22,100)	CKD (n=5,222)
Trouble sleeping	25.9	25.2	30.0
Sleep disorder	8.5	7.9	11.6
Nocturia	24.3	21.4	40.3
Inadequate sleep	36.5	36.7	35.5
Excessive sleep	2.4	1.9	5.0
Sleep-problem index score[a]			
0	39.0	40.6	30.1
1	36.2	36.2	36.4
2-4	24.8	23.2	33.5

[a]Sleep-problem index was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subject

Table 2.4: Estimated association (crude and adjusted[a] hazard ratios [HR] and 95% CI) between each sleep problem and all-cause mortality, by CKD status; total study population, 2005-14

	All (n=27322)		No CKD (n=22100)		CKD (n=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Trouble sleeping	1.4 (1.2, 1.5)	1.0 (0.88, 1.2)	1.4 (1.1, 1.6)	1.1 (0.89, 1.4)	1.2 (1.0, 1.4)	0.97 (0.81, 1.2)
Sleep disorder	1.6 (1.4, 1.9)	1.2 (0.97, 1.5)	1.6 (1.2, 2.1)	1.1 (0.86, 1.5)	1.2 (0.97, 1.6)	1.2 (0.93, 1.7)
Nocturia	2.9 (2.6, 3.3)	1.2 (1.1, 1.4)	2.5 (2.2, 2.9)	1.3 (1.1, 1.5)	1.8 (1.6, 2.2)	1.2 (0.99, 1.5)
Sleep duration						
Inadequate	1.0 (0.91, 1.1)	1.1 (0.95, 1.2)	0.99 (0.84, 1.2)	0.99 (0.83, 1.2)	1.0 (0.89, 1.2)	1.2 (1.0, 1.4)
Recommended	1	1	1	1	1	1
Excessive	3.6 (3.0, 4.4)	1.7 (1.3, 2.1)	2.7 (1.8, 3.9)	2.3 (1.5, 3.6)	2.6 (2.0, 3.3)	1.5 (1.1, 2.0)

[a]Adjusted for survey year, age, sex, and race/ethnicity, diabetes, hypertension, obesity, smoking, cardiovascular disease, chronic respiratory disease, cancer, other sleep problems, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs). Additional adjustment of CKD status for the analysis for all.

Table 2.5: Estimated associations (crude and adjusted[a] hazard ratios [HR] and 95% CI) of excessive sleep and category of the sleep-problem index score with all-cause mortality, by CKD status; total study population, 2005-14

	All (n=27322)		No CKD (n=22100)		CKD (n=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Excessive sleep vs. Recommended sleep[b]	3.6 (3.0, 4.4)	1.7 (1.3, 2.1)	2.7 (1.8, 3.9)	2.3 (1.5, 3.6)	2.6 (2.0, 3.3)	1.5 (1.1, 2.0)
Sleep-problem index score[c]						
0	1	1	1	1	1	1
1	1.6 (1.4, 1.8)	1.1 (0.98, 1.3)	1.4 (1.1, 1.7)	1.1 (0.85, 1.4)	1.5 (1.2,1.8)	1.2 (1.0, 1.5)
2-4	2.2 (1.9, 2.5)	1.2 (1.1, 1.5)	1.9 (1.5, 2.4)	1.2 (0.95, 1.6)	1.6 (1.3, 2.0)	1.3 (1.0, 1.6)
P for trend[d]	<0.0001	0.01	<0.0001	0.11	<0.0001	0.018

[a]Sleep-problem index was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subject.

[b]Adjusted for survey year, age, sex, and race/ethnicity, diabetes, hypertension, obesity, smoking cardiovascular disease, chronic respiratory disease, cancer, sleep problem index, and medications that affect drowsiness (sedatives, stimulants, and other drugs) . Additional adjustment of CKD status for the analysis for all.

[c]Adjusted for excessive sleep, survey year, age, sex, and race/ethnicity, diabetes, hypertension, obesity, smoking, cardiovascular disease, chronic respiratory disease, and cancer. Additional adjustment of CKD status for the analysis for all.

[d]Sleep problem index was considered as an interval variable (0-4) to test for a monotonic trend.

Table 2.6: Estimated association (crude and adjusted[a] hazard ratios and 95% CI) between each sleep problem and all-cause mortality, overall and by CKD status in 2005-14 for the total study population: Sensitivity analysis of all participants in the study population where follow-up is limited to 1 year.

	All (n=27322)		No CKD (n=22100)		CKD (n=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Trouble sleeping	1.6 (1.1, 2.3)	1.4 (0.89, 2.1)	1.5 (0.89, 2.5)	1.3 (0.76, 2.4)	1.5 (0.97, 2.3)	1.4 (0.77, 2.4)
Sleep disorder	1.9 (1.2, 3.0)	1.3 (0.79, 2.2)	2.2 (1.0, 4.8)	1.7 (0.74, 3.9)	1.2 (0.68, 2.2)	1.1 (0.50, 2.3)
Nocturia	3.2 (2.5, 4.3)	1.3 (0.96, 1.8)	2.7 (1.8, 4.0)	1.4 (0.83, 2.4)	2.1 (1.4, 3.3)	1.3 (0.77, 2.3)
Sleep duration						
Inadequate sleep	1.0 (0.76, 1.5)	0.95 (0.63, 1.4)	0.83 (0.54, 1.3)	0.70 (0.41, 1.2)	1.4 (0.86, 2.1)	1.3 (0.75, 2.3)
Recommended	1	1	1	1	1	1
Excessive sleep	4.7 (3.1, 7.4)	2.1 (1.3, 3.5)	3.1 (1.3, 7.3)	2.5 (1.0, 6.2)	3.6 (2.0, 6.4)	2.2 (1.2, 4.3)

[a]Adjusted for survey year, age, sex, and race/ethnicity, diabetes, hypertension, obesity, smoking, other sleep problems, cardiovascular disease, chronic respiratory disease, cancer, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs). Additional adjustment of CKD status for the analysis for all.

Figure 2.1: Trend in the standardized[a] prevalence (%) of each sleep problem and sleep-problem index[b] (Figs 1.a-g) in 2005-14 for the total study population, by NHANES[c] survey years and CKD

a) Trouble sleeping (%)

b) Sleep disorder (%)

45
40
35
30
25
%
20
15
10
5
0

2005-2006   2007-2008   2009-2010   2011-2012   2013-2014

All   *
CKD   *
No CKD   *

c) Nocturia (%)

45
40
35
30
25
%
20
15
10
5
0

2005-2006   2007-2008   2009-2010   2011-2012

All
CKD
No CKD
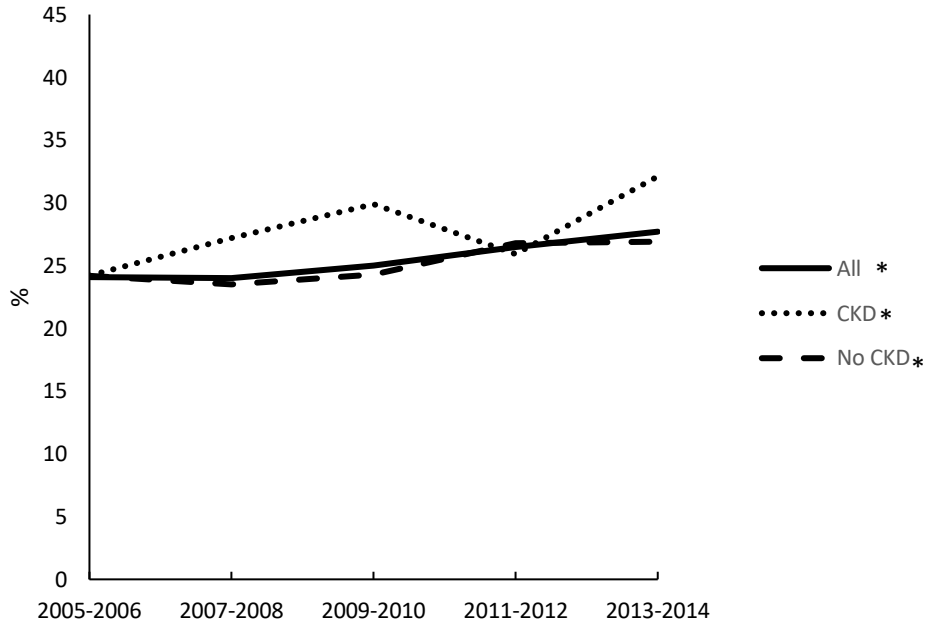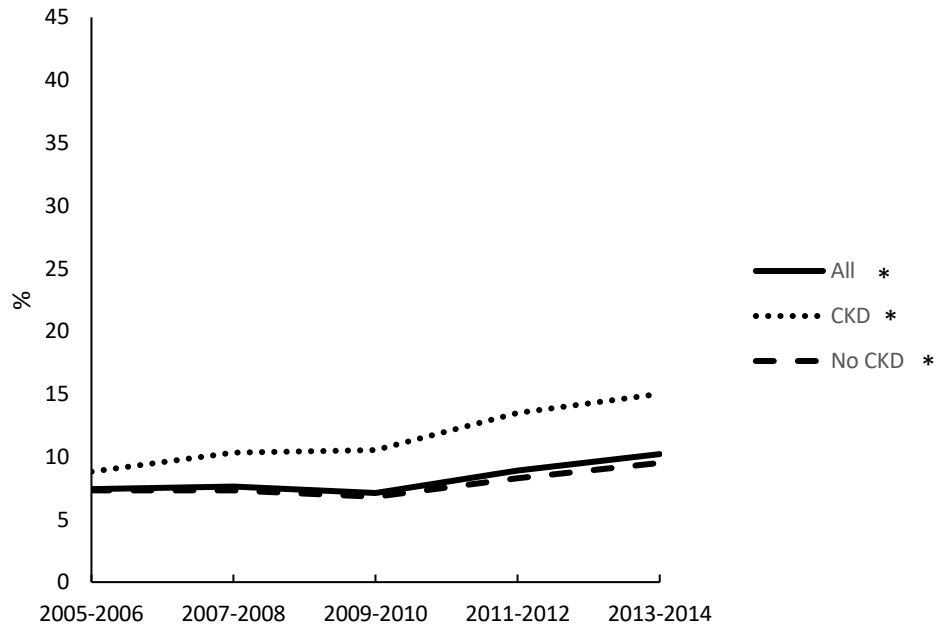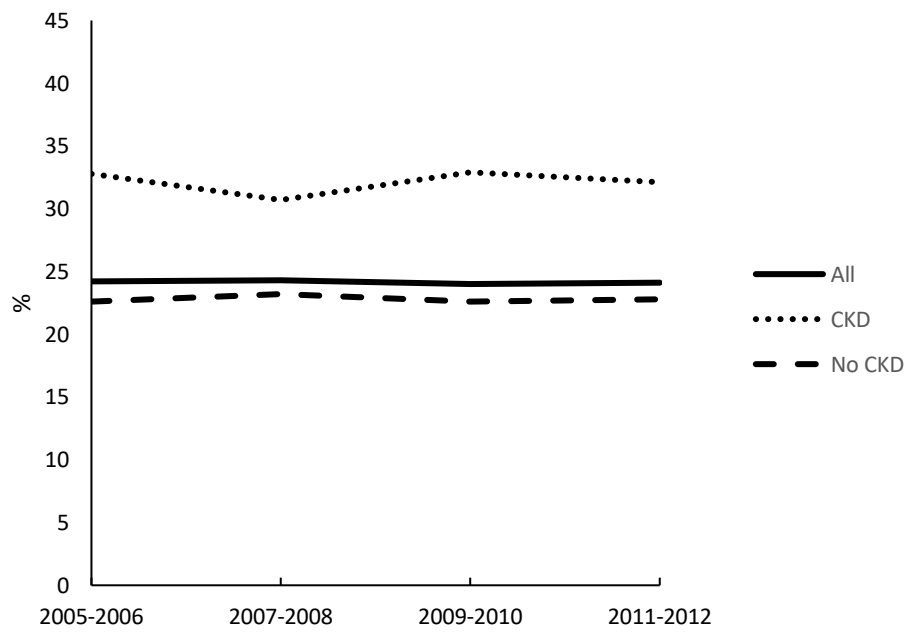
d) Inadequate sleep (% <7 hours/night)
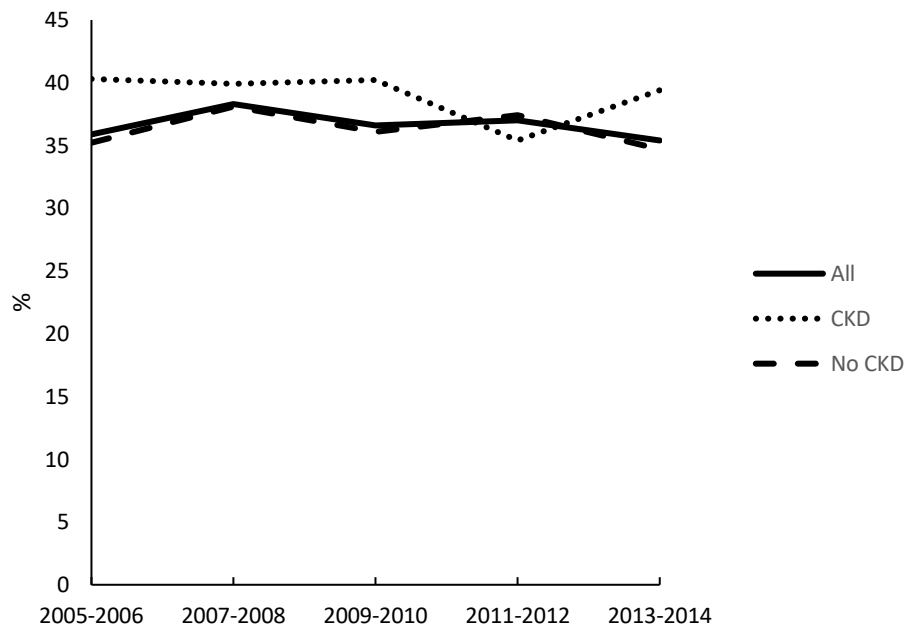
e) Excessive sleep (% >9 hours/night)
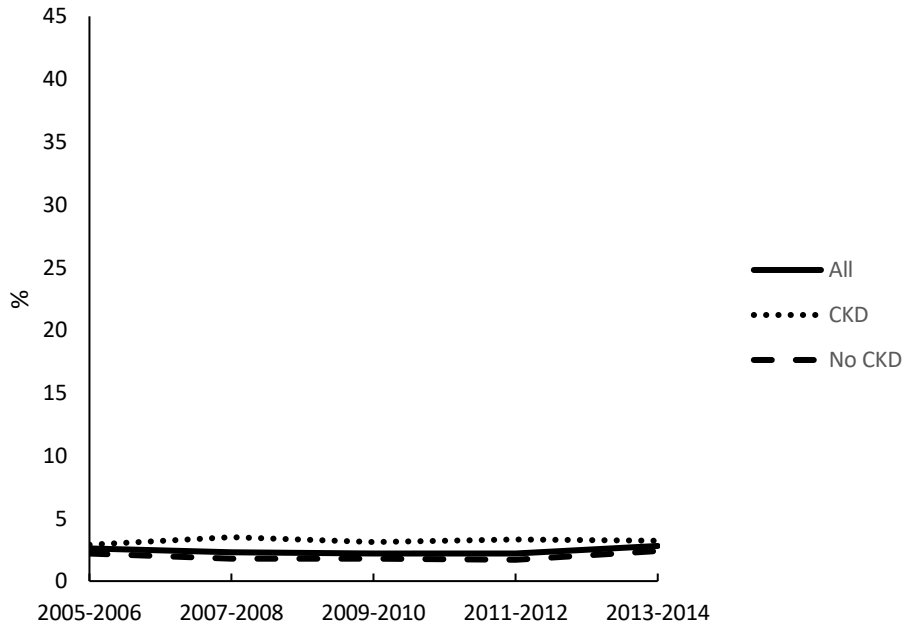
f) Sleep-problem index score>1 (%)
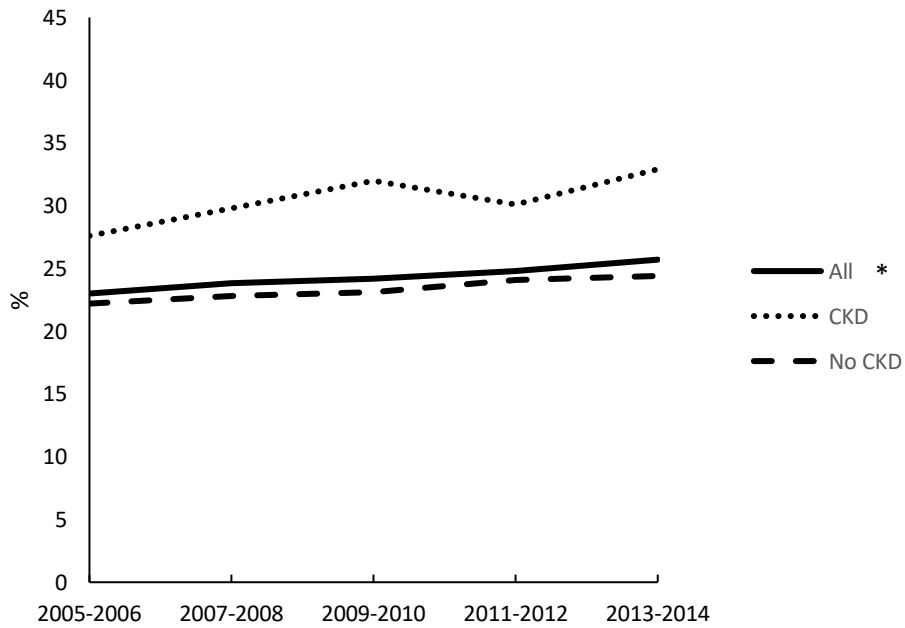
[a]Standardized for age, sex, and race/ethnicity. Using 2000 US Census population as the standard population.

[b]The sleep-problem index ranging from 0 (no problems) to 4, was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subject.

[c]NHANES, National Health and Nutrition Examination Survey.

[d]*P_{trend}<0.05.

Appendix

Table 2.A1: List of medications that affect drowsiness and cognition included in the study

Drug category	Drug name
Sedatives	BETA-ADRENERGIC BLOCKING AGENTS – UNSPECIFIED
	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS – UNSPECIFIED
	MUSCLE RELAXANTS – UNSPECIFIED
	ANTIHISTAMINES – UNSPECIFIED
	ANTIDEPRESSANTS – UNSPECIFIED
	ANTIPSYCHOTICS – UNSPECIFIED
	OPHTHALMIC ANTIHISTAMINES AND DECONGESTANTS – UNSPECIFIED
	ATENOLOL
	CARBAMAZEPINE
	VALPROIC ACID
	METOPROLOL
	PHENYTOIN
	DIPHENHYDRAMINE
	GABAPENTIN
	DIPHENHYDRAMINE; PSEUDOEPHEDRINE
	MELATONIN
	TOPIRAMATE
	CITALOPRAM
	ZALEPLON
	DOXYLAMINE; PYRIDOXINE
	DIPHENHYDRAMINE; PHENYLEPHRINE
	DIPHENHYDRAMINE; HYDROCODONE; PHENYLEPHRIN
	ESZOPICLONE
	RAMELTEON
	DEXTROMETHORPHAN; DIPHENHYDRAMINE; PHENYLEPHRINE
	BROMPHENIRAMINE; DIPHENHYDRAMINE
	BROMPHENIRAMINE; DIPHENHYDRAMINE; PHENYLEPHRINE
	SUVOREXANT
Stimulants	ARMODAFINIL
	FLUOXETINE
	DEXTROAMPHETAMINE
	MODAFINIL
	SERTRALINE
	FLUOXETINE; OLANZAPINE
	METHYLPHENIDATE
	PAROXETINE
	DIURETICS – UNSPECIFIED

	THIAZIDE AND THIAZIDE-LIKE DIURETICS-UNSPECIFIED
Other drugs	FENTANYL
	MORPHINE
	OXYCODONE
	OXYMORPHONE

Table 2.A2: Number of participants, by joint and marginal categories of eGFR and albuminuria; total study population, 2005-14.

Total population

Categories of eGFR (mL/min/1.73 m^2)	Categories of Albuminuria (mg/g)			Total
	<30	30-300	>300	
≥90	14789	1299	247	16335
60-89	7006	964	236	8206
45-59	1014	299	108	1421
30-44	303	197	89	589
15-29	54	49	60	163
<15	4	7	32	43
Total	23170	2815	772	26757

* CKD prognosis cells: white, low risk; light gray, moderate risk; medium gray, high risk; dark gray, very high risk.[13]

Table 2.A3: Standardized[a] prevalence (%) of each sleep problem and sleep-problem index[b], by CKD[c] status; total study population, 2005-14

Year	Trouble sleeping (%)			Sleep disorder (%)		
	All	CKD	No CKD	All	CKD	No CKD
2005-2006	24.1	24.2	24.2	7.4	8.8	7.3
2007-2008	24.0	27.2	23.5	7.6	10.3	7.3
2009-2010	25.0	29.9	24.3	7.1	10.5	6.8
2011-2012	26.5	25.9	26.8	8.9	13.5	8.3
2013-2014	27.7	32.1	26.9	10.2	15.0	9.5
P for trend	<0.001	0.005	0.012	<0.001	0.001	<0.001

Year	Inadequate sleep: <7 hours (%)			Excessive sleep: >9 hours (%)		
	All	CKD	No CKD	All	CKD	No CKD
2005-2006	35.9	40.3	35.2	2.6	2.9	2.2
2007-2008	38.3	39.9	38.1	2.3	3.5	1.8
2009-2010	36.6	40.2	36.1	2.2	3.1	1.8
2011-2012	37.0	35.4	37.4	2.2	3.3	1.7
2013-2014	35.4	39.4	34.7	2.8	3.2	2.4
P for trend	0.53	0.68	0.35	0.79	0.72	0.92

Year	Sleep-problem index score>1 (%)			
	All	CKD	No CKD	
2005-2006	23.0	27.6	22.2	
2007-2008	23.8	29.8	22.8	
2009-2010	24.2	32.0	23.1	
2011-2012	24.8	30.1	24.1	
2013-2014	25.7	32.9	24.4	
P for trend	0.036	0.068	0.056	

Year	Nocturia (%)		
	All	CKD	No CKD
2005-2006	24.2	32.8	22.6
2007-2008	24.3	30.7	23.2
2009-2010	24.0	32.9	22.6
2011-2012	24.1	32.1	22.8
P for trend	0.45	0.65	0.11

[a]Standardized for age and sex. Using 2000 US Census population as the standard population.

[b]Sleep-problem index was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subjects.

[c]CKD, chronic kidney disease; as reduced kidney function (estimated glomerular filtration rate [eGFR] < 60mL/min/1.73m^2, calculated with the CKD-EPI equation[13] and/or the presence of albuminuria (urine albumin-to-creatinine ratio [ACR] ≥30 gm/g, standardized to the 2005-06 cohort.

Table A4

Table 2.A4: Weighted prevalence (% and 95% CI[a]) of each sleep problem, by category of CKD prognosis; total study population, 2005-14

CKD prognosis	Trouble sleeping	Sleep disorder	Nocturia	Inadequate sleep	Excessive sleep
Low risk	25.2	7.9	21.9	36.7	2.0
	(24.2, 26.1)	(7.5, 8.4)	(19.6, 24.2)	(35.5, 37.9)	(1.7, 2.1)
Moderate increased risk	29.1	11.4	36.5	35.9	3.8
	(25.8, 32.4)	(9.3, 13.4)	(31.6, 41.3)	(33.5, 38.2)	(3.0, 4.6)
High risk	35.4	13.0	45.9	35.9	7.1
	(30.2, 40.7)	(9.3, 16.7)	(38.4, 53.5)	(33.1, 38.7)	(5.4, 8.7)
Very high risk	34.7	14.8	56.5	31.3	11.4
	(27.2, 42.3)	(9.9, 19.6)	(47.7, 65.3)	(26.7, 35.9)	(8.5, 14.2)

[a]CI, Confidence interval.

Table 2.A5: Crude prevalence (% and 95% CI) of each sleep problem (a-e), by joint and marginal categories of eGFR and albuminuria; total study population, 2005-14.

a. **Ever told a doctor of having trouble sleeping**

Categories of eGFR (mL/min/1.73 m^2)	Categories of Albuminuria (mg/g)			
	<30	30-300	>300	Total
≥90	23.0 (21.9, 24.1)	27.3 (23.3, 31.3)	36.0 (23.4, 48.7)	23.5 (22.5, 24.6)
60-89	29.1 (27.6, 30.6)	29.0 (24.5, 33.6)	38.5 (28.8, 48.2)	29.4 (26.7, 32.1)
45-59	31.2 (27.5, 35.0)	35.7 (26.4, 45.0)	37.0 (20.1, 54.0)	31.5 (26.9, 36.2)
30-44	35.9 (30.2, 41.7)	28.6 (19.1, 38.0)	28.2 (15.9, 41.4)	32.6 (27.1, 38.1)
15-29	37.6 (22.1, 53.2)	41.0 (22.8, 59.2)	42.2 (25.8, 58.8)	39.9 (29.5, 50.4)
<15	28.1 (0, 72.1)	75.0 (35.4, 100)	40.5 (20.8, 60.3)	49.94 (25.7, 74.1)
Total	25.5 (24.6, 26.5)	28.5 (25.5, 31.5)	32.7 (27.0, 38.3)	25.9 (25.0, 26.8)

b. Even been told by a doctor of having sleep disorder

Categories of eGFR (mL/min/1.73 m^2)	Categories of Albuminuria (mg/g)			Total
	<30	30-300	>300	
≥90	6.9 (6.4, 7.5)	10.4 (7.7, 13.0)	14.1 (5.8, 22.4)	7.3 (6.8, 7.9)
60-89	8.7 (8.7, 10.6)	14.1 (10.9, 17.3)	13.5 (6.1, 20.8)	10.0 (8.4, 11.7)
45-59	10.3 (7.3, 13.3)	13.5 (7.3, 19.6)	15.6 (1.9, 29.2)	11.0 (7.7, 14.3)
30-44	12.2 (7.6, 16.9)	14.5 (5.9, 23.1)	21.4 (7.8, 35.0)	13.4 (9.4, 17.5)
15-29	20.7 (7.6, 33.8)	15.3 (3.7, 26.8)	13.9 (0.44, 27.4)	15.7 (9.5, 21.9)
<15	28.1 (0, 77.1)	0	13.0 (0, 26.5)	12.1 (2.5, 21.5)
Total	8.0 (7.6, 8.5)	11.7 (9.5, 14.0)	13.8 (9.6, 18.0)	8.5 (8.0, 8.9)

c. **Nocturia**

Categories of eGFR (mL/min/1.73 m²)	Categories of Albuminuria (mg/g)			Total
	<30	30-300	>300	
≥90	18.9 (16.6., 21.1)	28.7 (24.4, 33.0)	42.9 (31.8, 53.9)	20.8 (18.0, 22.4)
60-89	25.5 (22.5, 28.4)	43.4 (37.2, 49.5)	47.5 (36.4, 58.7)	27.8 (24.0, 31.6)
45-59	40.7 (35.6, 45.8)	48.1 (39.0, 57.2)	59.6 (43.1, 76.0)	42.7 (37.0, 48.5)
30-44	50.6 (40.8, 60.3)	54.1 (43.9, 64.4)	65.2 (45.0, 85.3)	52.8 (44.1, 61.6)
15-29	50.2 (34.5, 66.0)	64.8 (45.8, 83.8)	66.4 (46.4, 86.3)	61.1 (49.2, 73.0)
<15	55.6 (0, 100)	15.6 (0, 53.4)	77.4 (52.3, 100)	57.3 (30.2, 84.4)
Total	22.5 (20.1, 24.9)	37.4 (32.4, 42.5)	46.0 (37.9, 54.0)	24.3 (21.8, 26.7)

d. Inadequate sleep (<7 hours)

Categories of eGFR (mL/min/1.73 m^2)	Categories of Albuminuria (mg/g)			Total
	<30	30-300	>300	Total
≥90	38.0 (35.5, 39.4)	42.1 (38.9, 45.3)	43.9 (39.2, 48.7)	38.3 (37.0, 39.7)
60-89	34.2 (32.7, 35.7)	36.2 (31.9, 40.5)	39.4 (33.5, 45.3)	34.5 (33.0, 35.9)
45-59	27.9 (24.1, 31.7)	34.3 (27.1, 41.4)	38.0 (27.6, 48.4)	29.6 (26.1, 33.1)
30-44	27.4 (22.8, 32.0)	25.3 (19.4, 31.2)	46.7 (34.5, 58.9)	29.4 (25.7, 33.1)
15-29	23.7 (13.9, 33.6)	29.0 (18.8, 39.0)	36.5 (25.5, 47.4)	30.0 (23.6, 36.4)
<15	33.8 (21.3, 42.3)	59.9 (34.4, 85.3)	48.0 (33.4, 62.7)	49.6 (33.8, 65.4)
Total	36.2 (35.1, 37.3)	38.2 (36.0, 40.3)	41.9 (38.6, 45.2)	36.5 (35.4, 37.5)

e. Excessive sleep (>9 hours)

Categories of eGFR (mL/min/1.73 m²)	Categories of Albuminuria (mg/g)			Total
	<30	30-300	>300	
≥90	2.0 (1.7, 2.2)	2.0 (1.0, 2.9)	3.5 (0.7, 6.3)	2.1 (1.8, 2.3)
60-89	1.7 (1.4, 2.0)	5.0 (3.3, 6.7)	6.4 (0.0, 13.3)	2.2 (1.5, 2.8)
45-59	4.4 (2.8, 5.9)	5.9 (3.1, 8.7)	3.9 (0.0, 8.3)	5.1 (3.6, 6.7)
30-44	8.8 (4.6, 13.0)	11.4 (0.5, 22.1)	1.4 (0.0, 3.4)	9.7 (6.7, 12.6)
15-29	10.8 (1.0, 20.5)	11.3 (0.5, 22.1)	21.0 (8.1, 33.9)	14.1 (7.9, 20.3)
<15	44.4 (0, 100)	0	6.2 (0, 18.8)	8.6 (0, 18.9)
Total	2.1 (1.9, 2.3)	4.3 (3.2, 5.3)	7.2 (4.3, 10.1)	2.5 (2.1, 2.6)

*CKD prognosis cells: white, low risk; light gray, moderate risk; medium gray, high risk; dark gray, very high risk.[13]

CHAPTER 3

Aim 2: Point and Period Prevalence of Obstructive Sleep Apnea (OSA) Among U.S. Veterans With and Without Chronic Kidney Disease (CKD)

Abstract

Background: To better understand the population burden of obstructive sleep apnea (OSA) and its relation with chronic kidney disease (CKD) and its risk factors, we conducted a large retrospective cross-sectional study of OSA in U.S. veterans who sought care in Veteran Administration facilities in fiscal year (FY) 2018.

Methods: Using data from 6.2 million veterans for FY2014-18, we estimated OSA point prevalence (P) at the last visit to a VA facility in FY2018 (index date T) and complementary period prevalence (PP) of OSA before time T as far back as the start of FY2014, stratified by CKD status in FY2018. PP for each duration was estimated using a method that takes into account left censoring of veterans followed back for different durations (analogous to the Kaplan-Meier method for dealing with right censoring in a cohort or randomized study). To examine associations, modified Poisson regression was used to estimate point-prevalence ratios (PR), and Cox regression was used to estimate period-prevalence ratios (PPR). The effects of age, sex, race/ethnicity, diabetes, hypertension, obesity, and CKD were adjusted for potential confounders.

Results: At time T, the P of OSA was 24.9% in veterans with CKD (14.8% of the study population), 15.2% in those without CKD, and 16.6% in the total study population. The 12-and 60-month PPs were 3.5% and 15.0%, respectively, in veterans with CKD, 2.8% and 11.0% in those without CKD, and 2.9% and 11.6% in the total population. Widths of all 95% confidence intervals (CI) were very narrow (<0.2%). The 60-month PP was positively associated with CKD (adjusted 60-month PPR = 1.2; 95% CI: 1.2-1.2), obesity (2.2; 2.2-2.3), being male (1.8; 1.7-2.0), having hypertension (1.3; 1.3-1.3) or diabetes (1.4; 1.3-1.4), and inversely associated with age ≥65 vs. <45 (0.80; 0.80-0.81). The associations of PP with sex were stronger for veterans without CKD than for those with CKD; and there was little association with race/ethnicity, except being less prevalent in other races than in non-Hispanic Whites. Associations of OSA with CKD and all covariates were stronger for P at time T than for 60-month PP.

Conclusion: The population burden of OSA, reflecting both point prevalence at time T and period prevalence before T, is quite high in U.S. veterans, especially among men with CKD. These findings, along with the associations of CKD risk factors with OSA, should be of potential importance to both researchers and providers of primary and specialty care.

Introduction

Obstructive sleep apnea (OSA) is one of the most common sleep disorders,[1] causing repetitive cessation of breathing while a person is sleeping, in both the general U.S. population as well as in the military and veteran populations.[2] The prevalence of OSA in the U.S. population was found to be 9% for women and 24% for men, and the prevalence of the OSA syndrome (combined with daytime hypersomnolence) was 2% for women and 4% for men.[3] OSA has been associated with depression, hypertension, diabetes, cardiovascular disease, and mortality.[4,5,6] A recent meta-analysis of 12 studies showed that the hazard ratio (HR) of all-cause mortality was 1.26 (95% CI: 1.09, 1.43) for persons with OSA compared to those without OSA. The association was stronger for persons with severe OSA (HR = 1.60; 95% CI: 1.30, 1.90).[4]

Chronic Kidney Disease (CKD), a common disorder worldwide with a prevalence of 14.8% in the U.S. population,[7] is currently defined by abnormal kidney function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or kidney damage (albuminuria indicated by albumin-to-creatinine ratio ≥ 30 mg/g) over three months. CKD progression is thought to result in the development of OSA through chemoreflex responsiveness, pharyngeal narrowing, and accumulation of uremic toxins.[8,9] However, unlike the effect of CKD on cardiovascular morbidity and mortality, the hypothesized effect of CKD on OSA risk is not fully understood.

Veterans are more vulnerable to sleep disturbance because of the high prevalence of possible risk factors including obesity, male sex, hypertension, depression, posttraumatic stress disorder, depression, substance use, and other comorbidities comparing to the general population.[10,11,12,13] Of the 21 million veterans in the U.S., about 9 million receive healthcare

each year from the Veterans Health Administration (VHA) system, America's largest integrated health care system.[14,15]

Although the incidence of a disease is more fundamental than prevalence for understanding risk-factor effects on disease (etiology), the burden of a disease in a population—with respect to the need or demand for healthcare and patient needs—is largely a function of prevalence, which can be measured in two ways.[16] The measure most commonly used in epidemiologic research and population surveillance is technically "point prevalence," meaning the proportion of a population that has the disease at one time t, where t may vary among individuals by age, calendar time, or birth year (e.g., persons ages 18-29, who are surveyed between January 1, 2015 and December 31, 2017). The other prevalence measure, "period prevalence," is infrequently used to study disease but often used to study behavioral outcomes such as drug or service use, based on self-reports or records. [17] Although period prevalence can be defined in different ways, here we mean the proportion of persons observed at time t, who had the disease any time during a previous period extending as far back in time to t_0, which may be defined from the person's perspective (age) or the population perspective (calendar time). Thus, the numerator in period prevalence may include persons who became cases during the period, t_0 to t, i.e., incident cases of the disease, and it may include previous cases of the disease who recovered before time t. Despite its infrequent use in contemporary epidemiology, period prevalence can be useful in planning service delivery systems, especially for remittent or episodic conditions such as OSA.

However, there is a dearth of research accurately estimating prevalence of sleep apnea among the veteran population. Different methods were used to estimate prevalence of sleep

apnea so prevalence of sleep apnea might not be comparable.[18,19] Limited studies have addressed the importance of sleep apnea prevalence in veterans with CKD versus veterans without CKD using relatively small sample sizes or selected study populations.[20] Therefore, our study aims were to use data in the U.S. VHA facilities to estimate the point and period prevalence of OSA among non-CKD and CKD population by using a method that takes into account left censoring of veterans followed back for different durations. Finally, we evaluated the associations between selected covariates and prevalence of OSA among non-CKD and CKD populations.

Methods
Source population and study design

This study was deemed "non-regulated" by the Institutional Review Board at the University of Michigan, as VHA system provides de-identified data as part of the Centers for Disease Control and Prevention's CKD Surveillance System Contract with the University of Michigan. The VHA system is the nation's largest integrated health care system, which contains an abundance of health information of veterans followed longitudinally.[21] Veterans Health Information Systems and Technology Architecture (VistA) includes the VA's electronic health records. From VistA, National Data Systems makes the extracts available and turns them into Medical SAS datasets (MedSAS). Inpatient, Outpatient, Lab, and Pharmacy electronic medical records were accessed from MedSAS Dataset and Department of VA Corporate Data Warehouse files using the U.S. Veterans Administration Informatics and Computing Infrastructure (VINCI) system.[22]

The study is a retrospective cross-sectional study of eligible U.S. veterans. Patients were included in the study if they sought care in the VA medical system in FY2018, had information on date of birth, and were at least 18 year-old at index time T, which was defined as the last visit to a VHA facility in FY2018. Theses selected participants at index time T were followed back in time to as early as the start of FY2014 for obtaining outcome information on OSA diagnosis. Period prevalence (PP) for a period of duration Δ (in months)—Δ PP—is defined retrospectively going back in from time T to a previous month as far back as the start of FY2014. The major challenge is dealing with left censoring[40] of study veterans when going back in time, i.e., not all veterans will be available as far back as the start of FY2014; many would not have used VA facilities throughout the 60-month study period. The final study population at time T contained 6.2 million participants.

Study variables

Outcome: OSA

De-identified inpatients and outpatients with OSA diagnoses were extracted from MedSAS databases. Prevalent OSA was based on multiple ICD-9-CM or ICD-10-CM codes related to OSA and CPT code for continuous positive airway pressure (CPAP) treatment (see Table 1 for codes) during the study period (FY2014-FY2018). "New" point-prevalent OSA cases were identified retrospectively, going back in time from index time T. After excluding point-prevalent OSA cases at time T, "new" period-prevalent cases were identified each month, starting one month before T, that were not previously identified in a more recent month (closer

to T). Therefore, the cumulative number of PP OSA cases increases as case detection proceeds back in time (analogous to cumulative incidence in a cohort study).

CKD status

De-identified inpatients and outpatients with CKD diagnoses were extracted from MedSAS databases. CKD prevalence at index time T was based on the presence of at least one of three criteria: having a diagnosis of ICD-9 or ICD-10 CKD (see Table 1 for codes); an eGFR <60 ml/min/1.73 m^2, using the CKD-EPI formula; and the presence of albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g).[23]

Covariates

Data for measuring covariates at index time T were retrieved from MedSAS and CDW databases and included date of birth, date of last VA visit in FY2018, sex, race/ethnicity, height and weight (average of last two values), diabetes status and hypertension status (see codes in Table 1). Race/ethnicity was classified as Hispanic (any race), non-Hispanic white, non-Hispanic black, or other non-Hispanic race (American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, and other). Obesity was defined as a body mass index (BMI) ≥30 kg/m.^{2}

Statistical analysis

Descriptive statistics are reported as percentages for categorical variables and as means and standard deviations (SD) for continuous variables stratified by CKD status. All point- and period-prevalence estimates are expressed as percentages.

Estimating point prevalence and period prevalence of OSA

Point prevalence (P) was defined as the proportion of people with an OSA diagnosis at index time T in the total study population. To handle left censoring in the estimation of period prevalence (PP), we used McFarland's method, which was devised for drug use or service utilization derived from administrative data (more details in the next paragraph and Appendix A).[17] Δ was defined as the period (in months) prior to index time T. McFarland's method was used to estimate the Δ period prevalence (Δ PP) in monthly (and 6-month) intervals going back in time from T−1 (1 month before index time T) to time t among noncases of OSA at time T, to be called the restricted study population. McFarland's method cannot be applied to the inclusion of point-prevalent cases at time T; analogously, the Kaplan-Meier method is not applied to the inclusion of point-prevalent cases in a cohort study of disease incidence.[17] McFarland's method applied to cross-sectional data is thus like doing a survival analysis in reverse, going back in time instead of forward to handle right censoring in a cohort study or randomized trial. McFarland's method was used to estimate the PP at each month from T-1 (1 month before T) to T-60 (the start FY2014). The PP at each month from T-1 to T-60 is shown in Figs 1-3 (which is based on the monthly accumulation of PP cases). Only Tables 3-4 present tabular displays of PP at 6-month intervals.

However, our study differed from the example provided in McFarland's article[17] in two related ways. First, the outcome of McFarland's study was drug use, which would not be measured as point prevalence at index time T whereas our outcome was a chronic condition that was present in many subjects at index time T. The method was created to estimate the PP of drug use during a previous period among survey respondents for whom point prevalence

was not of interest (unlike a chronic condition). Furthermore, while we were interested in estimating associations with PP (i.e., to obtain period prevalence ratios [PPR], McFarland's method was limited to the estimation of PPs for different periods or groups without computing measures of association adjusted for potential confounders. Therefore, the differences described above required that we modify McFarland's method slightly and extend his method to estimate ratio measures of associations.

As a secondary objective, we compared McFarland's method with a simpler approach (naïve method) for estimating PP without taking left censoring into account. With this naïve method, the estimated Δ PP of OSA in the restricted study population is the proportion of all persons who were found to have a diagnosis of OSA between time T−1 and previous time t (i.e., again excluding point-prevalent cases at index time T from the numerator and denominator).

Estimating associations with point- and period-prevalence ratio

Modified Poisson regression[24] was used to estimate point prevalence ratios (PR and 95% CIs) for crude and adjusted associations between individual-level factors and OSA point prevalence at index time T, by CKD status. To estimate crude and adjusted associations of those same factors with period-prevalence, we extended McFarland's method using Cox regression to estimate 60-month period-prevalence ratios (PPR and 95% CI) in the restricted study population. To adjust for potential confounders in both analyses, but not mediators, we used the causal diagram (directed acyclic graph) in Figure 1 to guide the analysis of each exposure including CKD.

Percentage of left censoring

To quantify the effective difference between McFarland's method and the naïve method for estimating OSA PP, we quantified the relative amount of left censoring used in the estimation of the 60-month PP and determined the number and proportion of person-days reduced by left censoring in McFarland's method for estimating the Δ PP of OSA in the restricted study population. This was done by comparing person-days of follow-back using McFarland's method with person-days of follow-back using the naïve method (involving no left censoring). The difference percentage is shown as the percentage of person-days of follow-back lost to left censoring using McFarland's method to estimate the Δ PP of OSA among U.S. veterans, by CKD status and 12-month interval prior to index time T (details are shown in Appendix B).

Sensitivity analyses

Because McFarland[17] did not use his method to model associations with PP, we did a sensitivity analysis to assess the validity of our approach applying Cox regression to estimate crude 60-month PP ratios for each predictor in our main analysis. The model-based PPR for each predictor (e.g., sex) was compared with the corresponding crude 60-month PPR computed manually by taking the ratio of PP, using McFarland's method, for the exposed group versus the unexposed group (e.g., men versus women).

All analyses were performed in SAS version 9.2 and 9.4.

Results

Table 2 shows summary statistics (mean and standard deviation [SD] or percentage) for selected baseline variables, by binary CKD status, in the total study population of 6,220,481

participants (last visit in FY2018). The mean age was 61 years, 88% were male, 62% were non-Hispanic Whites, and 15% were patients with CKD. Compared to participants without CKD, those with CKD were more likely to be older, male, non-Hispanic White, obese, have diabetes and hypertension.

Point prevalence (P) of OSA at index time T of the total study population of 6.2 million veterans was 16.6% (Table 3). It was higher among 5.3 million veterans with CKD (24.9%) than among 0.9 million without CKD (16.6%). As shown in Table 4, the total number of prevalent cases of OSA in the study population was about 1.5 million, of which 1.0 million (67.4%) were point-prevalent cases identified at time T and 0.5 million (32.6%) were additional period-prevalent cases identified in the 5-year period before T (FY2014-18).

Table 5 and Figure 2 present the period prevalence of OSA (Δ-month PP [%] and 95% CI) in 6-month intervals, by CKD status, using McFarland's method among all noncases of OSA observed at time T. The Δ PP of OSA in the total group increased from 0.04% after 6 months to 11.6% after 60 months. The 60-month PP of OSA was higher in veterans with CKD (15.0%; 95% CI: 14.9%, 15.1%) than in those without CKD (11.0%; 95% CI: 11.0%, 11.0%). As shown in Figure 2 (as well as Figures 3-4), there was a sudden increase in the Δ PP every 12 months, which may be explained by increased visits to VA facilities or enhanced documentation of OSA in the medical records at the end of each FY.

Table 6 and Figure 3 show the Δ period prevalence of OSA, by CKD status, using the naive method of PP estimation (ignoring left censoring). The Δ PP of OSA in the total group increased from 0.04% after 6 months to 10.0% after 60 months (Table 6). The overall pattern of

estimated PP, by CKD status, was similar with the naïve method as it was with McFarland's

method (Figure 4), but the naïve estimates were slightly lower. For example, the 60-month PP

of OSA was 1.6% lower in the total group, 0.9% lower in CKD group, and 1.6% lower in the non-

CKD group (Tables 5-6). Although there seemed to be little bias in the naïve method, relative to

McFarland's method, we wanted to quantify the amount of left censoring due to the absence of

visits to VA facilities in the months prior to time T, due either to pre-veteran status or lack of VA

utilization among veterans (see Appendix B). As shown in Table 7, 76.3% of all follow-back time

using McFarland's method was due to left censoring of noncases (analogous to right censoring

in a cohort study), and most of the follow-back more than 2-3 years before index time T was

attributable to left censoring, which makes those estimates of PP much less informative. Yet

the addition of all that follow-back time in the naïve method, which was greater in veterans

with CKD, resulted in little overall bias in the estimation of PP (Figure 4).

Crude and adjusted prevalence ratios (PR and 95% CI) between selected covariates and

OSA point prevalence in the total study population at time T, by CKD status, are shown in Table

8. Each covariate is adjusted for potential confounders, but not mediators, as implied by the

DAG in Figure 1. The point prevalence of OSA at index time T was positively associated with

being male (adjusted PR = 1.8), Black versus White (1.1), Hispanic versus White (1.2), obese

versus non-obese (2.3), having diabetes (1.4), hypertension (1.5), and CKD (1.2), and having an

inverted U-shaped association with age. The positive associations with sex, obesity, diabetes,

and hypertension were stronger in veterans without CKD group than in those with CKD.

Crude and adjusted associations of the same covariates with OSA period prevalence

using McFarland's method are shown in Table 9. The adjusted results are similar to those found

for point prevalence at time T, except the latter associations tend to be a little weaker (PPRs closer to 1), especially for male sex (PPR = 1.4 vs. PR = 1.8). The strongest association observed in both analyses was with obesity; the adjusted PPR in the total restricted study population was 2.1 (95% CI: 2.1, 2.1). The adjusted associations with period prevalence were mostly similar for veterans with and without CKD, except associations for three variables that were stronger in persons without CKD: male sex (adjusted PPR = 1.5 vs. 1.1), other non-Hispanic race versus whites (0.71 vs. 0.84), and age ≥65 versus <45 (0.74 vs. 0.83).

Results of the sensitivity analysis to check the validity of using Cox regression to estimated PPRs for each covariate are shown in Table 10. The crude PPR for each covariate using Cox regression was very similar to the PP ratio manually calculated from separate PPs using McFarland's method. These findings suggest that our use of Cox regression yielded reasonably valid results, at least for crude period-prevalence ratios.

Discussion

Our study was conducted among 6.2 million adult veterans nationwide with extensive claims data from FY2014-2018, which allowed us to estimate the Δ PP of OSA by both McFarland's method and naïve method, stratified by CKD status. In addition, we measured the associations between selected variables and prevalence of OSA. We observed slightly higher Δ PP of OSA estimated by McFarland's method than by the naïve method, which reflects artificial enlargement of denominators in the naive method. The Δ PP of OSA was greater for adults with CKD than for those without CKD. The prevalence of OSA was positively associated with being male, being black, being Hispanic, being obese, having diabetes, having hypertension, and having CKD, but inversely associated with age especially for CKD group. These findings highlight

the importance of paying attention to the potential presence of sleep problems among veterans, both in those with CKD and without CKD both by primary care and by specialist providers.

Our study showed that non-Hispanic Blacks and Hispanics had higher prevalences of OSA comparing to non-Hispanic Whites. On the other hand, other race/ethnicity except for Blacks and Hispanics had lower prevalence of OSA comparing to non-Hispanic Whites. Increased prevalence of OSA in non-Hispanic Black and Hispanic was also reported in Ramos et al,[25] different characteristics of OSA patients, such as more likely to be obese, hypertensive, and diabetic, were shown in Blacks and Hispanics comparing to their White counterparts.[26,27] A review paper showed similar results that OSA prevalence was increased among African Americans, Native Americans, and Hispanics, whereas the prevalence of OSA in Asians and Asian Americans remained similar or lower than in Whites.[28] In contrast, a recent review paper did not see the racial disparity in OSA in 17 articles after adjusting for variables such as obesity, comorbidities and socioeconomic status (SES).[29] These findings indicate that dissimilar OSA prevalence in different racial and ethnicity groups may due to difference in susceptibility of OSA, distribution of risk factors including comorbidities, OSA severity, and sleep apnea phenotypes among different racial and ethnicity groups. Furthermore, these risk factors (e.g., obesity, certain comorbidities, and SES) could be influenced by race/ethnicity, suggesting they are mediators rather than confounders. Of course, distinguishing between confounders and mediators with race effects is not straightforward. We addressed this issue in Aim 3.

Our study consisted of 88% of male participants, who had a higher prevalence of OSA than did females. Male gender has been thought to be a risk factor for OSA.[30] However, the

difference of the OSA prevalence between males and females decreases when women become pregnant or reach menopause.[31] This reduction in OSA prevalence could result from aging, physiological changes including fat mass distribution, sex hormones and upper-airway collapsibility in women.[32] We also observed this decline in the difference of OSA prevalence among males and females who were 65 and older (male: 20.2%; female: 17.1%) vs. who were 45-64 (male: 29.1%; female: 18.4%) (data not show).

The high prevalence of obesity may lead to the increased incidence and prevalence of OSA among veterans, especially among those with CKD. Obesity was the strongest predictor of OSA prevalence in our analyses (PR=2.1 and PPR=2.4). Large cohort studies have shown a monotonic association between elevated BMI and the prevalence of OSA.[33,34,35] In the Wisconsin Sleep Cohort study, a 10% weight gain predicted a 32% increase in the apnea-hypopnea index (AHI), whereas a 10% weight loss predicted a 26% decrease in the AHI.[33] Additionally, in the Cleveland Family Study, an increase of one BMI unit (kg^2/wt = 1) was associated with a 14% increase odds of one unit increase in AHI (numbers of apneas and hypopneas/hour=1). However, the effect of increased BMI declined to 5% for people at age 60 years.[34] In fact, symptoms of OSA have shown to become less severe after the intervention of weight management among OSA patients. Even if obesity only partially accounts for the variance of the AHI,[36] it may be the most effective treatments for male patients with moderate to severe OSA to reduce the severity of the symptoms through diet and exercise for weight loss.[37]

Only a few studies have focused on estimating the prevalence of sleep apnea on veterans defined by ICD codes,[38,19] questionnaires,[39,18,20] or polysomnography.[20] The period

prevalence of OSA in our study ranged from 16.6% to 26.3% from FY2014-2018. Comparing to

4.4% of diagnosed OSA period prevalence from FY2003-2005 reported by Diaz et al.,[38]our

estimates exceed this number. Their study cohort only limited to older veterans (≥65 years) in

the VHA system. Studies reported higher prevalence of OSA in groups with certain underlying

diseases. For example, 69.2% veterans from PTSD outpatient clinic were categorized as high risk

of OSA in participants consisting of more than 70% Hispanic.[39] A sleep apnea point prevalence

of 39% was obtained from another cohort of veterans with moderate to severe CKD.[20] In our

study, we reported a period prevalence of OSA ranged from 24.9% to 36.2% for people with

CKD, which is actually consistent with the previous study since participants in their study had

moderate to severe CKD.[20] These discrepancies in the prevalence of OSA among veterans could

result from different ways for defining and measuring OSA, different types of sleep apnea

included in the study, different study designs, different statistical methods for estimating OSA

prevalence and their associations with possible risk factors, different demographic composition

of the study population, different calendar periods with increasing awareness of sleep problems

and elevated willingness to seek medical attention in recent years

Rassen et al.[40] demonstrated different combinations of observable person-time,

numerator, and denominator of chronic diseases could result in different estimates using both

administrative claims data and electronic health records. Particularly, fixed lookback periods (a

specific retrospective time period to surveil for existing disease) generate more stable

estimates over time; however, they could contribute to lower prevalence and higher incidence

estimates comparing to all-time lookback. These two sources of datasets are often left

truncated and right censored, which makes it harder to decide who is and is not part of a study

population at a given time. Therefore, every study population could have different lengths of enrollment in the VHA system. In our study, we considered the start of the follow-back when a person was last treated in FY2018 in the VHA system; we stopped the follow-back when a veteran was diagnosed with OSA or when those with no OSA diagnosis were last observed back to the start of FY2014. We applied McFarland's method[17] to account for left censoring. As we expected, estimates from McFarland's method[17] were higher since the denominator was smaller considering the left censoring issue. One reason the cross-sectional associations between exposures and OSA are stronger for point prevalence than for period prevalence is due to possible "differential left censoring" in the PP analysis[40]. As we go back in time further to estimation PP, there is more left censoring, which may be more likely to differ between contrasting exposure groups.

We found an inverted U shape of the association between age and the prevalence of OSA. The same results were found in another study using VHA patients from FY2000 and FY 2010; there was not a monotonic association between the sleep apnea prevalence and increased age.[19] The non-monotonic association was also reported in the Sleep Heart Health Study of 5615 community-dwelling participants aged 40 to 98.[41] A peak in the middle of exposure range for the prevalence of an AHI≥15 was shown around age 60 years in the study.[41] In addition, Young et al. suggested that most of the age-related prevalence increase occurs before age 65.[13] Prevalence of a condition is determined by the incidence of the condition and its course among cases (influenced by both the rates of recovery and death). Future research is needed to determine whether the decreased or plateau prevalence of OSA among people more

than 65 could result from decreased incidence, increased mortality or detection bias among this age group.

Higher prevalence of OSA was observed among people with CKD compared to people without CKD in our study. However, patients with CKD could have a different etiology and clinical manifestations of OSA: OSA patients with advanced CKD tend to be less obese, report less frequent snoring, and more frequently experience apnea during sleep, unrefreshing sleep, and morning headache than persons without CKD.[42,43] Therefore, the associations between certain CKD risk factors (older age, male sex, obesity) and the risk of OSA were weak in patients with ESRD in spite of these major determinants of OSA in the general population.[44,45] Ultimately, extra attention of sleep apnea occurrence and treatment should be paid to patients with CKD by both primary care providers and specialists.

Our study had several strengths including our enhanced focus on the burden of OSA in the U.S. veteran population by examining both point and period prevalence of the condition. We had a very large study population comprised of 6.2 million adult veterans with an extensive and frequently updated database including ICD and CPT codes to define OSA and several comorbidities. We also used statistical methods that take into account left censoring of veterans with different durations of follow-back and that adjust for potential confounders when comparing groups.

One limitation of this study is that the identification of OSA diagnoses depends on claims data, which can lead to underdiagnosis or overdiagnosis of OSA and thus possible estimation bias, and it did not include OSA severity or detailed polysomnography findings.

Furthermore, residual confounding cannot be ruled out since we do not have information on certain risk factors for OSA such as smoking, alcohol consumption, socioeconomic status. Because we lacked BMI data on many veterans, we were not able to fully examine associations with obesity or adjust for this potential confounder. Generalization of our findings to all non-veterans, especially women, may be limited. Moreover, our findings suggest that our use of Cox regression yielded reasonably valid results, at least for crude period-prevalence ratios. Although we could not check the validity of estimating adjusted period-prevalence ratios. In addition, the analysis of P and PP involved different mutually exclusive outcomes events. Unfortunately, we were not able to handle both types of events in the same analysis. Finally, we did not investigate OSA incidence in this study, which limits our ability to make causal inferences, but that topic will be addressed in Aim 3.

In conclusion, the population burden of OSA, reflecting both point and period prevalence, is quite high in U.S. veterans, especially men with CKD. These findings, along with the associations of CKD risk factors with OSA, should be of potential importance to both researchers and providers of primary and specialty care. To further interpret and explain these findings, future work could assess trends in both prevalence and incidence of OSA. Future investigations of OSA should focus on identifying risk factors for this condition, assessing interactions of OSA with CKD, and identifying mechanisms that link CKD with OSA. Such efforts will contribute to reducing the burden of OSA and improving the quality of life in veterans and other populations.

References

1. National Center on Sleep Disorders Research. National Institutes of Health Sleep Disorders Research Plan. NIH Publication no. 11-7820. Washington, DC: National Instituetes of Health. November 2011. https://www.nhlbi.nih.gov/files/docs/resources/sleep/201101011NationalSleepDisordersResearchPlanDHHSPublication11-7820.pdf. Accessed March 3, 2020.

2. Young T. Rationale, Design, and Findings from the Wisconsin Sleep Cohort Study: Toward Understanding the Total Societal Burden of Sleep-Disordered Breathing. Sleep Med Clin. 2009;4(1):37-46.

3. 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):1230-1235.

4. Pan L, Xie X, Liu D, Ren D, Guo Y. Obstructive sleep apnoea and risks of all-cause mortality: preliminary evidence from prospective cohort studies. Sleep Breath. 2016;20(1):345-353.

5. Redline S, Kump K, Tishler P V, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med. 1994;149:722-726.

6. Argekar P, Griffin V, Litaker D, Rahman M. Sleep apnea in hemodialysis patients: risk factors and effect on survival. Hemodial Int. 2007;11(4):435-441.

7. United States Renal Data System.2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.

8. Aziz F, Chaudhary K. The triad of sleep apnea, hypertension, and chronic kidney disease: a spectrum of common pathology. Cardiorenal Med. 2017;7(1):74-82.

9. Abuyassin B, Sharma K, Ayas NT, Laher I. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? J Clin Sleep Med. 2015;11(8):915-924.

10. Tanofsky-Kraff, M., Sbrocco, T., Theim, K. R., Cohen, L. A., Mackey, E. R., Stice, E., Henderson, J. L., McCreight, S. J., Bryant, E. J., & Stephens MB. Obesity and the US Military Family. Obesity. 2013;21(11):2205-2220.

11. Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. Curr Psychiatry Rep. 2014;16(10):487.

12. Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. Neuropsychopharmacology. 2020;45(1):55-73.

13. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217-1239.

14. Veterans Health Administration. https://www.va.gov/health/. Accessed March 9, 2020.

15. National Center for Veterans Analysis and Statistics. https://www.va.gov/vetdata/Veteran_Population.asp. Accessed March 9, 2020.

16. Kleinbaum DG, Kupper LL MH. Epidemiologic Research: Principles and Quantitative Methods. New York: John Wiley and Sons; 1982.

17. McFarland BH. Pharmacoepidemiology reports: Comparing period prevalences with application to drug utilization. J Clin Epidemiol. 1996;49(4):473-482.

18. Jackson M, Becerra BJ, Marmolejo C, Avina RM, Henley N, Becerra MB. Prevalence and Correlates of Sleep Apnea Among US Male Veterans, 2005-2014. Prev Chronic Dis. 2017;14(5):E47.

19. Alexander M, Ray MA, Hébert JR, et al. The National Veteran Sleep Disorder Study: descriptive epidemiology and secular trends, 2000–2010. Sleep. 2016;39(7):1399-1410.

20. Canales MT, Bozorgmehri S, Ishani A, Weiner ID, Berry R, Beyth R. Prevalence and correlates of sleep apnea among US Veterans with chronic kidney disease. J Sleep Res. 2020:e12981.

21. Kizer KW, Dudley RA. Extreme makeover: Transformation of the veterans health care system. Annu Rev Public Health. 2009;30:313-339.

22. Overview of VA Data, Information Systems, National Databases & Research Uses. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/3531-notes.pdf. Accessed March 19, 2020.

23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

24. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol. 2004;159(7):702-706.

25.   Ramos AR, Seixas A DS. Obstructive sleep apnea and stroke: links to health disparities. Sleep Heal. 2015;1(4):244-248.

26.   Meetze K, Gillespie MB, Lee FS. Obstructive sleep apnea: A comparison of black and white subjects. Laryngoscope. 2002;112(7):1271-1274.

27.   Redline S, Sotres-Alvarez D, Loredo J, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds: The Hispanic Community Health Study/Study of Latinos. Am J Respir Crit Care Med. 2014;189(3):335-344.

28.   Dudley AK and Patel RS. Disparities and genetic Risk factors in obstructive sleep apnea. Sleep Med. 2016;18:96-102.

29.   Guglielmi O, Lanteri P, Garbarino S. Association between socioeconomic status, belonging to an ethnic minority and obstructive sleep apnea: a systematic review of the literature. Sleep Med. 2019;57:100-106.

30.   Rando J. Obstructive sleep apnea basics. Cleve Clin J Med. 2019;86(9):2-9.

31.   Bonsignore MR, Saaresranta T, Riha RL, Riha R, Bonsignore M. Sex differences in obstructive sleep apnoea. Eur Respir Rev. 2019;28(154):1-11.

32.   Perger E, Mattaliano P, Lombardi C. Menopause and Sleep Apnea. Maturitas. 2019;124:35-38.

33.   Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. J Am Med Assoc. 2000;284(23):3015-3021.

34.   Tishler P V., Larkin EK, Schluchter MD, Redline S. Incidence of Sleep-Disordered Breathing in an Urban Adult Population: The Relative Importance of Risk Factors in the Development of Sleep-Disordered Breathing. J Am Med Assoc. 2003;289(17):2230-2237.

35.   Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: The Sleep Heart Health Study. Arch Intern Med. 2005;165(20):2408-2413.

36.   Joosten SA, Hamilton GS, Naughton MT. Impact of weight loss management in OSA. Chest. 2017;152(1):194-203.

37.   Carneiro-Barrera A, Díaz-Román A, Guillén-Riquelme A, Buela-Casal G. Weight loss and lifestyle interventions for obstructive sleep apnoea in adults: systematic review

and meta-analysis. Obes Rev. 2019;20(5):750-762.

38. Diaz K, Faverio P, Hospenthal A, Restrepo MI, Amuan ME, Pugh MJ V. Obstructive sleep apnea is associated with higher healthcare utilization in elderly patients. Ann Thorac Med. 2014;9(2):92-98.

39. Colvonen PJ, Masino T, Drummond SPA, Myers US, Angkaw AC, Norman SB. Obstructive sleep apnea and posttraumatic stress disorder among OEF/OIF/OND veterans. J Clin Sleep Med. 2015;11(5):513-518.

40. Rassen JA, Bartels DB, Schneeweiss S, Patrick AR, Murk W. Measuring prevalence and incidence of chronic conditions in claims and electronic health record databases. Clin Epidemiol. 2019;11:1-15.

41. Young T, Shahar E, Nieto J, et al. Predictors of sleep-disordered breathing in community-dwelling adults. Arch Intern Med. 2002;162(8):893-900.

42. Owen J, Reisin E. Obstructive sleep apnea and hypertension: Is the primary link simply volume overload? Curr Hypertens Rep. 2013;15(3):131-133.

43. Ozkok A, Kanbay A, Odabas AR, Covic A, Kanbay M. Obstructive sleep apnea syndrome and chronic kidney disease: a new cardiorenal risk factor. Clin Exp Hypertens. 2014;36(4):211-216.

44. Beecroft JM, Zaltzman J, Prasad R, Meliton G, Hanly PJ. Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. Access. 2007;(June):3028-3033.

45. Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. Eur Respir J. 2006;28(1):151-158.

Tables and figures

Table 3.1: List of ICD-9, ICD-10, and CPT codes used to define obstructive sleep apnea, diabetes, hypertension, and CKD

Type of coding	Codes
ICD-9 for obstructive sleep apnea	327.20, 327.22, 327.29, 327.8
ICD-10 for obstructive sleep apnea	G47.30, G47.33, G47.39, G47.8, G47.9, R06.00, R06.09, R06.3, R06.83, R06.89
CPT for obstructive sleep apnea	E0470 and E0601
ICD-9 for diabetes	250, 35673, 36641, 36201, 36202
ICD-10 for diabetes	E08, E09, E10, E11, E13
ICD-9 for hypertension	401, 402, 403, 404, 405
ICD-10 for hypertension	I10, I11, I12, I13, I15
ICD-9 for CKD	016.0; 095.4; 189.0,189.9; 223.0; 236.91; 250.4; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 477.3; 572.4; 581-583; 585- 588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4
ICD-10 for CKD	A18.11, A52.75, B52.0, C64.x, C68.9, D30.0x, D41.0x-D41.2x, D59.3, E08.2x, E09.2x, E10.2x, E10.65, E11.2x, E13.2x, E74.8, I12.xx, I13.0, I13.1x, I13.2, K76.7, M10.3x, M32.14, M32.15, N01.x-N08.x, N13.1, N13.1x-N13.39, N14.x,N15.0, N15.8, N15.9, N16, N17.x, N18.1-N18.5, N18.8, N18.9, N19, N25.xx, N26.1, N26.9, O10.4xx, O12.xx, O26.83x, O90.89, Q61.02, Q61.1xQ61.8, Q26.0-Q26.39, R94.4

Table 3.2: Summary statistics (mean [SD] or %) of the total study population of adult veterans at index time T[a], by CKD status

Measure	Total (n = 6,220,481)	No CKD (n = 5,301,945)	CKD (n = 918,536)
Age (mean [SD] in years)	60.9 (18.6)	59.4 (18.9)	70.8 (12.6)
18-44 (%)	22.2	25.0	3.5
45-64 (%)	28.6	29.4	23.3
≥65 (%)	49.2	45.6	73.2
Male (%)	88.0	86.7	96.2
Race/ethnicity (%)			
Hispanic	5.7	5.6	5.8
Non-Hispanic White	61.6	60.8	66.7
Non-Hispanic Black	14.7	14.1	18.5
Other non-Hispanic race	18.0	19.5	9.0
Obesity[b] (%)	39.7	37.4	55.4
Diabetes (%)	20.0	13.8	60.9
Hypertension (%)	40.2	34.4	78.6

[a]Index time T for each veteran is the last VA visit in FY2018.
[b]BMI ≥ 30.

Table 3.3: Computed point prevalence of OSA at index time T[a] in the study population of adult veterans, by CKD status

Measure	Total (n = 6,220,481)	No CKD (n = 5,301,945)	CKD (n = 918,536)
Numerator	1,033,231	806,454	228,777
Denominator	6,220,481	5,301,945	918,536
Point prevalence	16.6	15.2	24.9

[a]Index time T is the last VA visit in FY2018

Table 3.4: Frequency distribution (number and %) of point-prevalent cases of OSA at time T and period-prevalent cases in 6-month intervals before T in the total study population, going back in time from the index time T in FY2018 to the start of FY2014

Time/Interval	Number (%)
Index time T	1,035,231 (67.4)
Months 1-6	23,306 (1.5)
Months 7-12	202,208 (13.2)
Months 13-18	58,939 (3.8)
Months 19-24	120,025 (7.8)
Months 25-30	35,380 (2.3)
Months 31-36	26,527 (1.7)
Months 37-42	10,451 (0.7)
Months 43-48	16,350 (1.1)
Months 49-54	7,194 (0.5)
Months 55-60	757 (0.05)
Total	1,536,368 (100)

Table 3.5: Δ-month PP (95% CI) (%) of OSA in the study population, by CKD status, using McFarland's method[a], among all persons who did not have an OSA diagnosis at index time T[b]

Δ (months)	Total	CKD	No CKD
6	0.4 (0.4, 0.4)	0.4 (0.4, 0.4)	0.4 (0.4, 0.4)
12	2.9 (2.9, 2.9)	3.5 (3.5, 3.6)	2.8 (2.8, 2.8)
18	6.1 (6.1, 6.2)	8.2 (8.1, 8.2)	5.8 (5.8, 5.8)
24	7.7 (7.7, 7.7)	9.9 (9.8, 10.0)	7.3 (7.3, 7.3)
30	9.9 (9.8, 9.9)	12.9 (12.9, 13.0)	9.3 (9.3, 9.3)
36	10.2 (10.2, 10.3)	13.3 (13.3, 13.3)	9.7 (9.7, 9.7)
42	10.8 (10.8, 10.8)	14.1 (14.0, 14.2)	10.3 (10.2, 10.3)
48	11.1 (11.0, 11.1)	14.4 (14.3, 14.4)	10.5 (10.5, 10.5)
54	11.6 (11.5, 11.6)	15.0 (14.9, 15.1)	11.0 (10.9, 11.0)
60	11.6 (11.6, 11.6)	15.0 (14.9, 15.1)	11.0 (11.0, 11.0)

[a]McFarland's method takes into account left censoring during follow-back in the estimation of Δ PP of OSA.
[b]Index time T is the last VA visit in FY2018

Table 3.6: Δ-month PP (%) of OSA, by CKD status, using the naive method[a], among all persons who did not have any OSA diagnosis at time T[b] in the study population

Δ (months)	Total	CKD	No CKD
6	0.4 (0.4, 0.4)	0.4 (0.4, 0.4)	0.4 (0.4, 0.4)
12	2.7 (2.7, 2.7)	3.4 (3.4, 3.5)	2.6 (2.6, 2.6)
18	5.6 (5.6, 5.7)	7.9 (7.8, 8.0)	5.3 (5.3, 5.3)
24	7.0 (6.9, 7.0)	9.5 (9.4, 9.6)	6.6 (6.5, 6.6)
30	8.8 (8.8, 8.8)	12.3 (12.2, 12.4)	8.2 (8.2, 8.3)
36	9.1 (9.1, 9.1)	12.7 (12.6, 12.7)	8.5 (8.5, 8.6)
42	9.6 (9.5, 9.6)	13.4 (13.3, 13.5)	8.9 (8.9, 9.0)
48	9.7 (9.7, 9.7)	13.6 (14.5, 13.6)	9.1 (9.1, 9.1)
54	10.0 (10.0, 10.0)	14.1 (14.0, 14.2)	9.4 (9.4, 9.4)
60	10.0 (10.0, 10.0)	14.1 (14.0, 14.2)	9.4 (9.4, 9.4)

[a]The naïve method ignores left censoring during follow-back in the estimation of Δ PP.

[b]Index time T is the last VA visit in FY2018

Table 3.7: Percentage of person-days of follow-back lost to left censoring[a] using McFarland's method for estimating the Δ period prevalence (PP) of OSA in the restricted study population, by CKD status and 12-month interval prior to index time T

12-month interval prior to index time T	Total	With CKD	Without CKD
1-12 months	8.2	20.9	8.2
13-24 months	42.2	56.2	41.1
25-36 months	58.8	65.1	58.1
37-48 months	77.1	77.3	77.1
49-60 months	96.1	96.1	95.9
1-60 months	76.3	87.7	74.5

[a]The difference between these two person-month sums reflects the amount of left censoring in McFarland's method. The percentage of left-truncated follow-back was calculated by dividing that difference by the larger person-day sum using the naïve method.

[b]McFarland's method takes into account left censoring during follow-back in the estimation of Δ PP of OSA.

[c]Index time T is the last VA visit in FY2018.

Table 3.8: Estimated associations (crude and adjusted point prevalence ratios [PR] and 95% CI) between selected covariates and OSA point prevalence, by CKD status, using modified Poisson regression, among all persons in the study population at index time T

	Total (n =6,220,481)		No CKD (n = 5,301,945)		CKD (n = 918,536)	
	Crude PR (95% CI)	Adjusted PR (95% CI)	Crude PR (95% CI)	Adjusted PR (95% CI)	Crude PR (95% CI)	Adjusted PR (95% CI)
Age[a]						
18-44 (ref.)	1	1	1	1	1	1
45-64	1.5 (1.5, 1.5)	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1.2 (1.1, 1.2)	1.1 (1.1, 1.2)
≥65	1.0 (1.0, 1.1)	0.95 (0.94, 0.95)	0.93 (0.93, 0.94)	0.84 (0.84, 0.85)	0.82 (0.80, 0.83)	0.79 (0.78, 0.81)
Race[a]						
NH White (ref.)	1	1	1	1	1	1
NH Black	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.1 (1.1, 1.1)	0.98 (0.97, 0.99)
Hispanic	1.2 (1.2, 1.2)	1.2 (1.2, 1.2)	1.3 (1.3, 1.3)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.0 (1.0, 1.0)
Other NH	0.66 (0.65, 0.66)	0.68 (0.68, 0.68)	0.64 (0.64, 0.65)	0.66 (0.66, 0.67)	0.87 (0.86, 0.88)	0.85 (0.84, 0.86)
Male vs. Female[a]	1.7 (1.7, 1.7)	1.8 (1.8, 1.8)	1.7 (1.7, 1.7)	1.8 (1.8, 1.8)	1.1 (1.0, 1.1)	1.2 (1.2, 1.3)
Obesity[b] (BMI ≥30 vs <30)	2.4 (2.4, 2.4)	2.3 (2.3, 2.3)	2.3 (2.3, 2.4)	2.3 (2.3, 2.3)	2.3 (2.3, 2.3)	2.2 (2.2, 2.2)
Diabetes[c] (Yes/No)	1.7 (1.7, 1.7)	1.4 (1.4, 1.4)	1.6 (1.6, 1.6)	1.3 (1.3, 1.3)	1.4 (1.4, 1.4)	1.2 (1.2, 1.2)
Hypertension[d] (Yes/No)	1.8 (1.8, 1.8)	1.5 (1.5, 1.5)	1.7 (1.7, 1.7)	1.4 (1.4, 1.5)	1.4 (1.4, 1.4)	1.3 (1.3, 1.4)
CKD vs. No CKD[e]	1.6 (1.6, 1.7)	1.2 (1.2, 1.2)	---	---	---	---

[a]To estimate the effects of age, sex, and race/ethnicity, adjustment is made for the two other demographic variables.

[b]Obesity (BMI ≥30 vs <30): adjusted for age, sex, and race/ethnicity.

[c]Diabetes: adjusted for age, sex, race/ethnicity, and obesity.

[d]Hypertension: adjusted for age, sex, race/ethnicity, obesity, and diabetes.

[e]CKD: adjusted for age, sex, race/ethnicity, obesity, diabetes, and hypertension.

Table 3.9: Estimated associations (crude and adjusted 60-month period prevalence ratios [PPR] and 95% CI) between selected covariates and OSA period prevalence, by CKD status, using McFarland's method with Cox regression, among all persons in the study population who did not have an OSA diagnosis at index time T[a]

	Total (n =5,007,543)		No CKD (n = 4,319,214)		CKD (n = 688,329)	
	Crude PR (95% CI)	Adjusted PR (95% CI)	Crude PR (95% CI)	Adjusted PR (95% CI)	Crude PR (95% CI)	Adjusted PR (95% CI)
Age[b]						
18-44 (ref.)	1	1	1	1	1	1
45-64	1.2 (1.2, 1.2)	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	1.1 (1.1, 1.1)	1.2 (1.1, 1.2)	1.2 (1.1, 1.2)
≥65	0.86 (0.85, 0.87)	0.80 (0.80, 0.81)	0.79 (0.79, 0.80)	0.74 (0.73, 0.75)	0.84 (0.81, 0.87)	0.83 (0.80, 0.86)
Race[b]						
NH White (ref.)	1	1	1	1	1	1
NH Black	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.1 (1.1, 1.1)	1.0 (0.99, 1.0)
Hispanic	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.2 (1.2, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.1)	0.99 (0.96, 1.0)
Other NH	0.72 (0.71, 0.73)	0.72 (0.72, 0.73)	0.71 (0.70, 0.72)	0.71 (0.70, 0.72)	0.85 (0.83, 0.87)	0.84 (0.82, 0.86)
Male vs. Female[b]	1.3 (1.3, 1.3)	1.4 (1.4, 1.5)	1.3 (1.3, 1.3)	1.5 (1.5, 1.5)	0.92 (0.89, 0.95)	1.1 (1.0, 1.1)
Obesity[c] (BMI ≥30 vs <30)	2.1 (2.1, 2.1)	2.1 (2.1, 2.1)	2.1 (2.1, 2.1)	2.1 (2.1, 2.1)	2.1 (2.0, 2.1)	2.0 (2.0, 2.1)
Diabetes[d] (Yes/No)	1.5 (1.5, 1.5)	1.3 (1.3, 1.3)	1.4 (1.4, 1.4)	1.3 (1.2, 1.3)	1.5 (1.4, 1.5)	1.2 (1.2, 1.3)
Hypertension[e] (Yes/No)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.2 (1.1, 1.2)	1.0 (1.0, 1.1)	1.1 (1.1, 1.1)	1.1 (1.0, 1.1)
CKD vs. No CKD[f]	1.4 (1.4, 1.4)	1.2 (1.2, 1.2)	---	---	---	---

[a]Index time T is the last VA visit in FY2018.
[b]To estimate the effects of age, sex, and race/ethnicity, adjustment is made for the two other demographic variables.

[c]Obesity (BMI ≥30 vs <30): adjusted for age, sex, and race/ethnicity.
[d]Diabetes: adjusted for age, sex, race/ethnicity, and obesity.
[e]Hypertension: adjusted for age, sex, race/ethnicity, obesity, and diabetes.
[f]CKD: adjusted for age, sex, race/ethnicity, obesity, diabetes, and hypertension.

Table 3.10: Validity check of the Cox Regression procedure for estimating adjusted period prevalence ratios (PPR) using McFarland's method[a] with Cox regression, among all persons in the study population who did not have an OSA diagnosis at index time T[b]

Variable	Category	Crude PPR from Cox regression	PP	Ratio calculated by separate PP
Age	18-44	1	11.91	1
	45-64	1.19	13.97	1.17
	≥65	0.86	10.27	0.86
Race	White	1	11.49	1
	Black	1.18	13.47	1.17
	Hispanic	1.17	13.38	1.16
	Other	0.72	8.47	0.74
Sex	Male	1.30	11.86	1.30
	Female	1	9.26	1
Obesity	Yes	1.88	20.60	1.84
	No	1	11.19	1
Diabetes	Yes	1.52	15.44	1.48
	No	1	10.40	1
Hypertension	Yes	1.22	12.71	1.21
	No	1	10.53	1
CKD	Yes	1.40	15.02	1.37
	No	1	10.99	1

[a]McFarland's method takes into account left censoring during follow-back in the estimation of Δ PP of OSA.

[b]Index time T is the last VA visit in FY2018. [c]Period prevalence obtained from McFarland's method for each category separately.

Figure 3.1: Directed acyclic graph illustrating variables included in the study with the outcome (OSA)
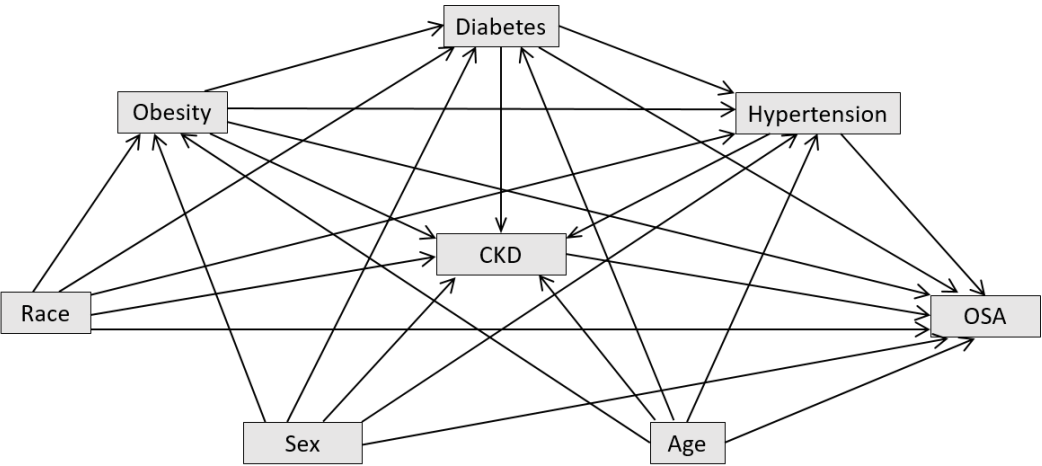
Figure 3.2: Δ period prevalence (PP in %) of OSA, by CKD status at index time T, using McFarland's method[a], among all veterans in the study population who did not have an OSA diagnosis at index time T[b] (Δ = 0)
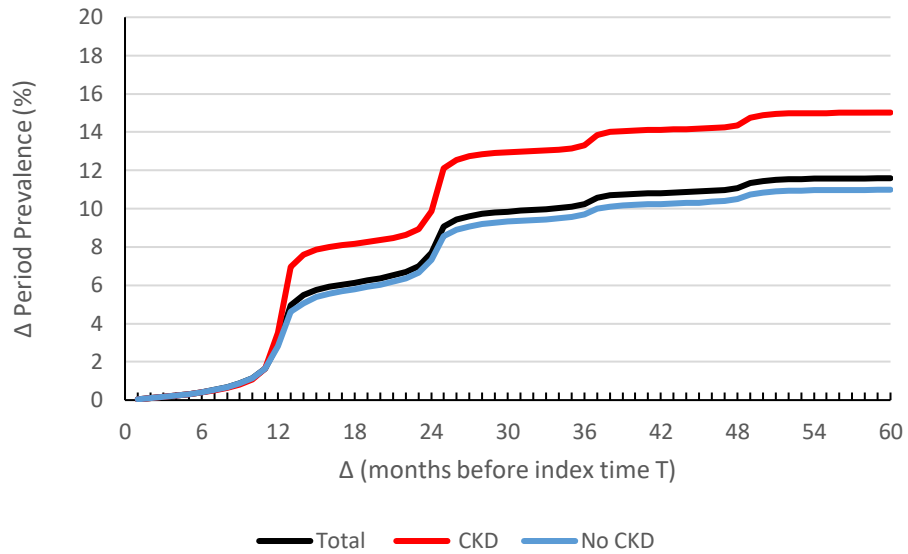
[a]McFarland's method takes into account left censoring during follow-back in the estimation of Δ PP of OSA. [b]Index time T is the last VA visit in FY2018.

Figure 3.3: Δ period prevalence (PP in %) of OSA, by CKD status at index time T, using the naive method[a], among all veterans who did not have an OSA diagnosis at index time T[b] (Δ = 0)
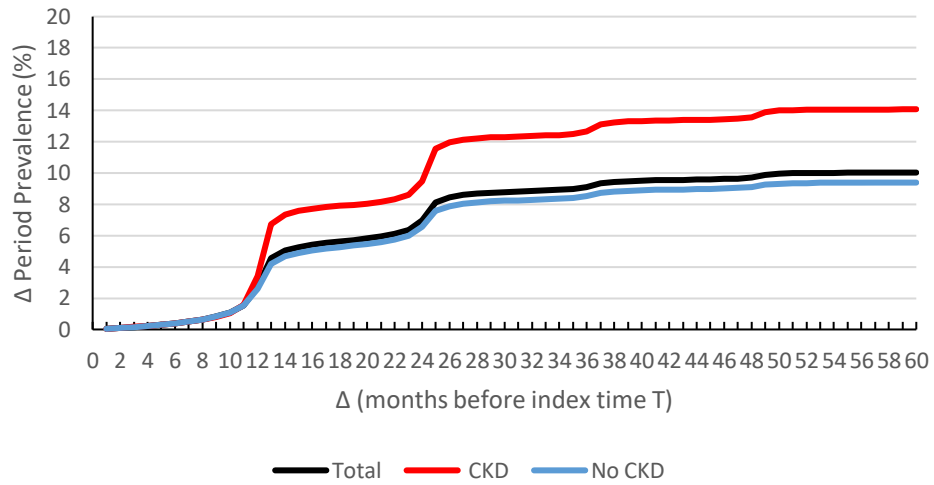
[a]The estimation of Δ PP, using the naïve method, ignores left censoring during follow-back (i.e., it assumes detection of OSA diagnoses during follow-back extends to the start of FY2014). [b]Index time T is the last VA visit in FY2018.

Figure 3.4: Δ period prevalence (PP in %) of OSA, by CKD status at index time T, comparing McFarland's method[a] (red lines) with the naïve method[b] (blue lines), by CKD status (solid vs. dashed lines), among all veterans in the study population who did not have an OSA diagnosis at index time T[c] (Δ = 0)
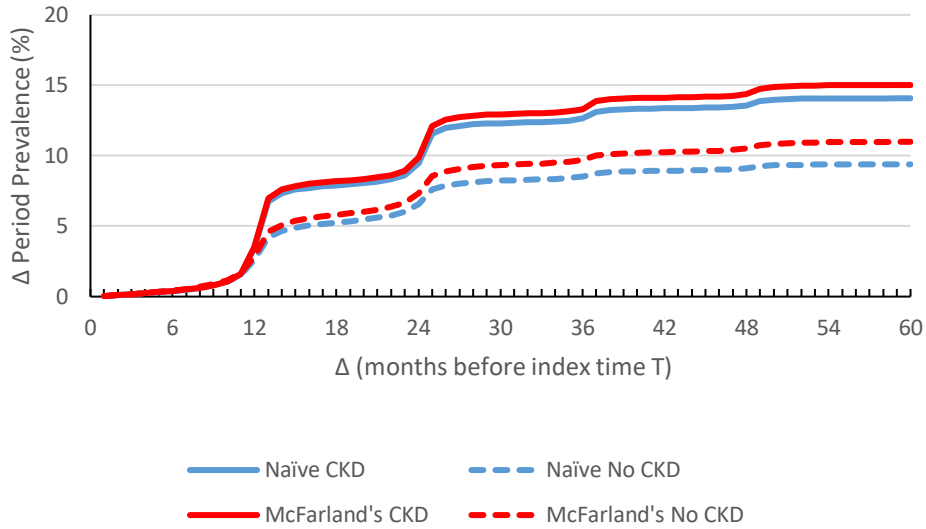
[a]McFarland's method takes into account left censoring during follow-back in the estimation of Δ PP of OSA. [b]The estimation of Δ PP, using the naïve method, ignores left censoring during follow-back (i.e., it assumes detection of OSA diagnoses during follow-back extends to the start of FY2014). [c]Index time T is the last VA visit in FY2018.

Appendix

Table 3A. McFarland's method for estimating period prevalence

We modify McFarland's method slightly and extend his method to estimate ratio measures of associations.

Let

$$R(t) = \sum_{i=1}^{N} U(i,t)[1 - C(i,t)]$$

where U(i,t) is an indicator (coded 1,0) of whether that member of the study population was a

user of VA facilities (not left truncated) at time t; C(i,t) is an indicator (1,0) of whether that VA

user was known to have OSA at time t. Thus, R(t) is the number of VA users who are not known

to have OSA in at time t, i.e., the "risk set," who are eligible to be observed as OSA cases before

time t

Let

$$D(t) = \sum_{i=1}^{N} U(i,t)[C(i,t-1) - C(i,t)]$$

for t > 1. Thus, D(t) is the number of persons in the risk set at time t and are known to have OSA

at time t−1; D(1) is defined as 0.

PP(t) is estimated using the product-limit (Kaplan-Meier) method of "risk" estimation,

$$PP(t) = 1 - \prod_{j=t}^{T} \frac{R(j) - D(j)}{R(j)}$$

The variance of this PP estimate is

$$Var(PP) = (1 - PP)^2 \sum_{j=1}^{T} \frac{D(j)}{R(j)[R(j) - D(j)]}$$

Source: McFarland BH. Comparing period prevalences with application to drug utilization. *J Clin Epidemiol* 1996; 49(4):473-482.

Table 3B. Estimating the proportion of follow-back due to left censoring

In the naïve method, we assume implicitly that all persons in the restricted study population

who were not found to have an OSA diagnosis during the 5-year study period (size N_0) were

followed back from T_i to the start of FY2014 (i.e., $T_i - t_0 \leq 60$ months). All persons who were first

found to have an OSA diagnosis (size N_1) at time t_i during the study period were followed-back

for $(T_i - t_i)$ months. Therefore, the total number of person-months (PM) accrued by the

restricted study population using the naïve method would be:

$$PM_{Naive} = \sum_{i=1}^{N_0}(T_i - t_0) + \sum_{i=1}^{N_1}(T_i - t_i)$$

where the first summation is across all noncases of OSA (i = 1,…,N_0), and the second summation

is across all diagnosed cases of OSA (i = 1,…,N_1).

In McFarland's method, we count person-months of follow-back from T_i to time t_i when the

person is either first found to have an OSA diagnosis or left-truncated as a noncase on or before

reaching t_0. Therefore, the total number of person-months (PM) accrued by the study

population using McFarland's method is:

$$PM_{McFarland} = \sum_{i=1}^{N}(T_i - t_i)$$

where summation is across all persons in the restricted study population (i = 1,…,N).

Thus, the difference between these two person-month sums reflects the amount of censoring in McFarland's method. We can express the proportion of follow-back that is censored (%PM) by dividing that difference by the larger naïve PM, i.e.,

$$\%PM_{Left-truncated} = \frac{PM_{Naive} - PM_{McFarland}}{PM_{Naive}}$$

Source: McFarland BH. Comparing period prevalences with application to drug utilization. *J Clin Epidemiol* 1996; 49(4):473-482.

CHAPTER 4

Aim 3: Explaining Racial Disparity on Obstructive Sleep Apnea Mediated by Chronic Kidney Disease

Abstract

Background: To better understand the effect of race/ethnicity on the incidence of obstructive sleep apnea (OSA), we conducted a large retrospective cohort study of U.S. veterans to test the hypothesis that chronic kidney disease (CKD) is a mediator in the causal pathway linking race/ethnicity with OSA.

Methods: Using data from 3.5 million veterans for FY2016-2018, we estimated direct, indirect, and total effects of race/ethnicity on OSA, and percentages of the total effect mediated by CKD, adjusting for age, sex and other CKD risk factors. Non-Hispanic Blacks, Hispanics, and other non-Hispanic races were compared with non-Hispanic Whites, using 4 methods of mediation analysis: the informal difference method (similar to confounder adjustment, likely to be biased); 4-way decomposition of the race/ethnicity effects (assessing mediation and interaction by CKD); flexible mediation analysis (assessing mediation by CKD and its 3 main risk factors—diabetes, hypertension, and obesity); and dynamic path analysis (accounting for censoring with survival methods).

Results: Compared with Whites, Blacks and Hispanics had moderately higher incidence rates of OSA and other races had lower rates. The percentages of the total race/ethnicity effects mediated by CKD were small and similar using all 4 mediation methods; relative to Whites, it ranged from 5.8% to 7.4% for Blacks, 2.3% to 2.8% for Hispanics, and −0.12% to 0.51% for other races. Most of the total effects (>90%) were due to direct effects. However, when CKD and its 3 risk factors were treated collectively as mediators in flexible mediation analysis, the percentage mediated relative to Whites increased from 5.8% to 30.3% for Blacks, from 2.6% to 2.9% for Hispanics, and from 0.2% to 16.4% for other races. In the 4-way decomposition of the race/ethnicity effects, the percentages of the total effects due to race/ethnic-CKD interactions was small (<3% in all race/ethnicity comparisons).

Conclusion: Most of the racial/ethnic disparity in OSA incidence was not explained by mediation or interaction with CKD, yet a modest percentage of the Black/White disparity was attributable to the combination of CKD and its 3 main risk factors. All 4 mediation methods yielded consistent findings, including the simpler difference method, but such similarities would not necessarily apply to other racial/ethnic disparities in veterans or other populations. As new and refined methods of mediation analysis are developed to handle the many types of data and potential sources of bias encountered in these analyses, they should prove to be valuable in designing effective interventions for clinical practice.

Introduction

Obstructive sleep apnea (OSA), characterized by transient, repetitive partial or complete occlusion of the upper airway, is a growing public-health problem in the United States.[1] Greater prevalence and severity of OSA have been observed in Blacks than in White.[2,3] Wallace et al.[4] focused on race/ethnicity as a modifier of the effect of the adherence of primary treatment (continuous positive airway pressure, CPAP) on functional sleep outcomes, such as difficulty of concentrating because of sleepiness. CPAP adherence was positively associated with social and intimacy functional outcomes among Blacks, while this association was not seen in Whites. Billings et al.[5] showed that sleep duration partially explained the association between race and CPAP adherence in the general population. Sleep disturbances include longer sleep latency (the length of time that it takes to accomplish the transition from full wakefulness to sleep), poor sleep quality, easily awaken and less deep sleep, and more frequent and longer naps resulting in reduced health-related quality of life for Blacks.[6]

In addition to the higher prevalence of OSA compared with Whites, Blacks also have a higher prevalence of CKD, a higher risk of progression to ESRD, an earlier start of dialysis, and a higher mortality rate after age 30.[7] Genetic predisposition (apoliprotein-L1) in Blacks purportedly accounts for 70% of the attributable risk of CKD.[8] In addition, based on the evidence that even after care is standardized, CKD outcomes remain differential for minorities, non-health care system factors may play a crucial role for CKD.[9] Study results have shown that declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia.[10,11] In addition, CKD may lead to OSA through a variety of mechanisms, including alterations in chemoreflex responsiveness, pharyngeal narrowing due to fluid overload, accumulation of

uremic toxins, OSA-related changes in sympathetic tone, neurohumeral output, and tubulointerstitial hypoxia.[12,13] Thus, it is possible that the higher prevalence and incidence of OSA in Blacks can be explained in part by the elevated prevalence of CKD in this group or by the interaction between race and CKD.

This study's goal was to assess whether and to what extent the excess incidence of OSA among race/ethnicity (Hispanics; Blacks; and other NH races) relative to Whites in US veterans could be explained by the occurrence of CKD acting as a mediator of the race "effect." Mediation implies that race affects the risk of CKD, which affects the risk of OSA; i.e., there is an indirect effect of race on OSA, mediated in part by CKD. In addition, there may be a direct effect of race on CKD, which is mediated by other factors. Our hypothesis was that CKD helps to explain race/ethnicity effects, especially Blacks vs Whites, on OSA incidence by mediating the race/ethnicity effects on OSA; i.e., race/ethnicity-->CKD-->OSA . To achieve this objective, we used four types of mediation analysis: the difference method;[14] 4-way decomposition,[15] flexible mediation analysis[16] and dynamic path analysis.[17] The latter three methods have different statistical advantages and limitations for dealing with our data so they complement each other; the first method, which is simpler and has been used informally for many years in epidemiology, is used for comparison.

Methods
Source population and study design

This study was deemed "non-regulated" by the Institutional Review Board at the University of Michigan, as veterans health administration (VHA) system provides de-identified data as part of the Centers for Disease Control and Prevention's CKD Surveillance System

100

Contract with the University of Michigan. The VHA system is the nation's largest integrated

health care system, which contains an abundance of health information of veterans followed

longitudinally.[18] Veterans Health Information Systems and Technology Architecture (VistA)

includes the VA's electronic health records. From VistA, National Data Systems makes the

extracts available and turns them into Medical SAS datasets (MedSAS). Inpatient, Outpatient,

Lab, and Pharmacy electronic medical records were accessed from MedSAS Dataset and

Department of VA Corporate Data Warehouse files using the U.S. Veterans Administration

Informatics and Computing Infrastructure (VINCI) system.[19]

The study is a retrospective cohort study of eligible U.S. veterans. Patients were

included in the study if they sought care in the VA medical system with at least one visit in each

of the three years (FY2014, FY2015, and FY2016), had information on date of birth, and were at

least 18 year-old in FY2016, not having any OSA diagnosis from FY2014-FY2016. Theses selected

participants were followed from the last visit in FY2016 up to the first diagnosis in FY 2017-

FY2018 (incident OSA cases) or to the last visit in FY2017-2018 (noncases). The final study

population contained 3.5 million participants.

Study variables

Outcome: incident OSA

De-identified inpatients and outpatients with OSA diagnoses were extracted from

MedSAS and CDW databases. OSA was based on multiple ICD-9-CM or ICD-10-CM codes related

to OSA and CPT code for continuous positive airway pressure (CPAP) treatment (see Table 1 for

codes). Incident OSA was defined as not having any OSA diagnosis from FY2014-FY2016, but

having a new OSA diagnosis after the last visit in FY2016 to the end of FY2018. Binary incident

OSA status (yes vs. no) was used as the outcome measure in three of the mediation analyses:

the difference method, four-way decomposition, and flexible mediation. Time-to-incident OSA

was used in dynamic path mediation analysis. Participants were followed from the last visit in

FY2016 up (baseline) to the first diagnosis in FY 2017-FY2018 (incident OSA cases) or to the last

visit in FY2017-2018 (noncases). In dynamic path analysis, follow-up time was divided into

follow-up intervals: days 1-250, 251-500, 501-750, and >750.

Binary mediator: prevalent and incident CKD

De-identified inpatients and outpatients with CKD diagnoses were extracted from

MedSAS and CDW databases. CKD status was based on the presence of at least one of three

criteria: having a diagnosis of ICD-9 or ICD-10 CKD (see Table 1 for codes); an eGFR <60

ml/min/1.73 m^2, using the CKD-EPI formula; and the presence of albuminuria (urine albumin-to-

creatinine ratio [UACR] ≥30 mg/g).[20] These three criteria were applied to identify CKD

prevalence at baseline and CKD incidence during follow-up. In dynamic path analysis, the 3

criteria were used to identify CKD incidence during follow-up (prior to becoming an OSA

incident case), i.e., treating CKD as time-dependent.

Covariates: age, sex, hypertension, diabetes, obesity/BMI

Data for measuring covariates at baseline were retrieved from MedSAS and CDW

databases and included date of birth, date of last VA visit in FY2016, sex, height and weight

(average of last two values), diabetes status and hypertension status (see codes in Table 1).

Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. In dynamic path mediation analysis,

BMI was treated as a time-dependent confounder. Covariates believed to be confounders were adjusted for in the models based on the DAG in Figure 1.

<u>Exposure: race/ethnicity</u>

Race and ethnicity were classified together into 4 categories: Whites non-Hispanic (67.3% of the study population) treated as the reference group; Black non-Hispanic (16.1%); Hispanics (any race; 5.5%); and other non-Hispanic races (11.1%, including American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, and other). Hereafter, these groups will be labeled Whites, Blacks, Hispanics, and other races.

Statistical analysis

Descriptive statistics are presented as percentages for categorical variables and as means and standard deviations (SD) for continuous variables. The crude incidence rate of OSA for each race/ethnicity and for the total study population was calculated as the number of new OSA diagnoses, divided by total person-days of follow-up; rates are expressed per 1000/year.

Cox regression was used to estimate hazard ratios (HR and 95% CIs) for crude and adjusted associations between the covariates of interest and OSA incidence rate, by type of model adjustment. In one adjusted model, we only adjusted for age, sex, and race/ethnicity (where needed). To adjust for potential confounders in the analysis, but not mediators, we used the causal diagram (directed acyclic graph) in Figure 1 to guide the analysis of the covariates of interest including CKD in the other adjusted model.

The difference method, 4-way decomposition, flexible mediation analysis, and dynamic path mediation analysis were used in the study because of the need for taking exposure-mediator interaction into account when estimating the direct and indirect effects of the exposure on an outcome (not done in the difference method); the advantage of assessing the amount of that interaction in a mediation analysis (specifically in the 4-way decomposition); the 4th no-confounding assumption, which is particularly relevant in this study because the exposure (race/ethnicity) affects many factors of interest aside from CKD, including risk factors for CKD; the advantage of analyzing multiple mediators to get around that previous issue (with flexible mediation analysis, medflex); and taking censoring into account when outcome events are observed over time (with dynamic path analysis); apparently low estimation precision with dynamic path analysis (wide CIs), presumably due to repeated measures of time-varying mediators and confounders and to use of bootstrapping for obtaining confidence limits. Details of the 4 different mediation analysis methods are provided in the Method section.

Difference method

The "difference method" of mediation analysis is the simple approach used informally by epidemiologists for many years, similar to adjustment for confounders.[14] Two regression models are fit to the data: one includes as predictors the exposure of interest, the hypothesized mediator(s), and potential confounders; the other model is similar but excludes the mediator(s). The estimated exposure effect in the second model is the total effect. The estimated exposure effect in the first model is the direct effect (not mediated by the predictor(s) excluded from the second model). The difference between the estimated exposure effect in those two models is assumed to be the indirect (mediated) effect of the exposure.

Age, sex, diabetes status, hypertension status, and BMI (continuous) were treated as baseline confounders. CKD was treated as fixed baseline mediator. Binary OSA—a new diagnosis any time during follow-up--was treated as the outcome. Two Cox regression models were run for race/ethnicity comparison. One Cox regression adjusted for only age and sex or all baseline confounders (age, sex, diabetes, hypertension, and BMI). The other one adjusted for only age and sex or all baseline confounders in addition to the mediator (CKD). The hazard ratio (HR; 95% CI) of the direct effect is obtained from the regression coefficient for the race/ethnicity predictor in the Cox model with CKD. The HR for the indirect effect is the antilog of the difference between the log HRs for the total effect and the direct effect on the log scale. The total effect (HR; 95% CI) is obtained from the regression coefficient for the race/ethnicity predictor in the Cox model without CKD. The proportion mediated is the log HR for the indirect effect divided by the log HR for the total effect.

A limitation of this approach is that it gives biased results for direct and indirect effects when there is an interaction between the exposure and mediator; that disadvantage does not apply to the other three mediation methods.

Four-way decomposition method

A 4-way decomposition of the exposure effect, as developed by VanderWeele,[21] not only takes exposure-mediator interactions into account, but it decomposes the total effect into 4 components due to: neither mediation nor interaction (controlled direct effect); interaction only ("reference interaction"); both interaction and mediation ("mediated interaction"); and mediation only (pure indirect effect). The sum of the first two components is called the "pure

direct effect," and the sum of the latter two components is called the "total indirect effect." The total indirect effect divided by the total effect—the sum of all 4 components—is the (total) proportion mediated.

The first logistic model was fitted on incident OSA by race variable (race/ethnicity vs White NH), CKD and hypertension, diabetes, BMI, sex, and age. Then the other logistic model was fitted with CKD as the outcome by race variable, hypertension, diabetes, BMI, sex, and age. Covariates adjusted for in the models as potential baseline confounders were age, sex, BMI (continuous), diabetes, hypertension. Binary exposure and binary outcome were used for this analysis. Each race/ethnicity versus Whites was included in a separate model, excluding person in the other two groups. Separate models are required for each exposure comparison because the SAS procedure does not accommodate multiple categories of the exposure. The Causalmed procedure in SAS 9.4 was used to perform this mediation analysis.

One limitation of this approach is violation of no-confounding assumption that is unique to mediation analysis: The exposure should not affect a confounder of the mediator effect on the outcome, which implies that the confounder is also another mediator.[15] This assumption could easily be violated in this study because race/ethnicity affects many conditions including the comorbidities modeled as potential confounders in these analyses. Another limitation is that prediction of the OSA incidence does not take censoring into account.

Flexible mediation analysis

Flexible mediation analysis, developed by Steen and colleagures,[16,22] involves fitting a "natural effect" model to the outcome, conditional on nested counterfactuals, i.e., the

expected value of the outcome, given the exposure and what the mediator would be if everyone's exposure were set to the reference level (Whites in this study). Unobserved counterfactuals are imputed using any appropriate model of the outcome mean; both natural direct and indirect effects are obtained from the coefficients of the model. The flexibility of this approach allows the user to avoid violation of the no-confounding assumption described above by incorporating multiple mediators jointly. Thus, this application of flexible mediation analysis can be used to estimate the natural indirect effect of all measured mediators (provided there are no other unmeasured mediators or confounders).

We applied flexible mediation analysis in three ways: treating CKD as the only mediator; treating CKD and its 3 risk factors (hypertension, diabetes, BMI) jointly as mediators; and treating the 3 risk factors (without CKD) as the mediators. The race/ethnicity effects were adjusted for age, sex, hypertension, diabetes, and BMI when CKD was treated as the only fixed baseline mediator. The race/ethnicity effects were adjusted for age, sex when treating CKD and its 3 risk factors jointly as mediators and treating the 3 risk factors as the mediators. Three indicator predictors (race/ethnicity) and binary outcome (OSA) were used for this analysis. All the race/ethnicity (Blacks, Hispanics, other NH races) versus Whites were included in the same model. The medflex package in R was used to perform this mediation analysis.[22]

First, we fitted a mean model for the outcome by CKD, race/ethnicity, and covariates (age, sex, BMI, hypertension, diabetes) in a logistic regression model. Second, we expanded the data so that the exposure could take on values different from the observed exposure (counterfactual exposure values). Next, we imputed the nested counterfactual outcomes by fitted values based on the imputation model. Finally, after expanding and imputing the data, we

fitted the natural effect model on the imputed data to get the estimates. A logistic model was fitted on incident OSA by race variable (race/ethnicity vs White) and the covariates. Robust stand errors based on sandwich estimator[23] were requested from the model. Adjusted odds ratio (OR; 95% CI) for the natural direct effect (NDE) and natural indirect effect (NIE) were obtained from the models. Total effect was calculated as the product of NDE and NIE. The 95% CI for the TE was not computed because it is computationally complex and not needed for interpretation of the main findings. The percentage mediated on the risk difference scale is NDE(NIE−1)/(NDE×NIE−1), where NDE and NIE are the odds ratios (OR) corresponding to those effects, assuming OSA incidence is a rare outcome event.

A limitation that this approach shared with the previous mediation method is that prediction of OSA incidence does not take censoring into account; the outcome is binary (OSA case/noncase). Another limitation shared with the other methods is that the mediator is a fixed baseline measure; therefore, the magnitude of its associations with the exposure and outcome may depend on mediator changes that occurred years before baseline.

Dynamic path mediation analysis

The mediation method proposed by Vansteelandt et al.[17] is a generalization of dynamic path analysis that involves a time-to-event outcome and treats the mediator and time-varying confounders as time-dependent during follow-up. This approach assumes an additive hazard model for the outcome and a linear regression model for the mediator. The method allows time-dependent confounders to be influenced by the exposure at baseline (time t=0), i.e., avoiding the no-confounding assumption described previously. Pure direct and indirect effects

and the total effect of the exposure are expressed as differences or ratios of counterfactually defined survival probabilities (free of OSA) at time t. The proportion mediated is estimated as the ratio of the pure indirect effect to the total effect, each expressed as a difference in survival probabilities.

CKD was treated as the time-dependent mediator, and BMI was treated as a time-dependent cofounder. Age, sex, diabetes, and hypertension were treated as fixed confounders at baseline. Binary exposure race/ethnicity and time-to-incident OSA (outcome) were used for this analysis. A separate mediation analysis was done for each comparison of a race/ethnicity with Whites, excluding persons from the other two racial/ethnic groups The SAS macros provided by Vansteelandt et al.[17] were used to perform this mediation analysis.

Cox regression models and quasi-binomial regression models (logit link instead of probit link) were used during the procedure to obtain estimated probabilities $S_{0,0}(t)$, $S_{1,0}(t)$, and $S_{1,1}(t)$ for each interval. Total effect was expressed as $S_{1,1}(t)$- $S_{0,0}(t)$ whereas direct effect was expressed as $S_{1,0}(t)$- $S_{0,0}(t)$. Percentage mediated was expressed as (total effect-direct effect)/total effect.

A limitation of this method is low precision for estimating parameters (i.e., wide confidence intervals), which is due to the use of repeated measures of time-varying mediators and confounders (CKD and BMI in this study) and to the use of bootstrapping for obtaining confidence limits; moreover, the SAS macro takes a long time to run and models may not converge.

All analyses were performed in SAS 9.2, SAS 9.4, and R 3.6.1.

Results

Table 2 shows summary statistics (mean and standard deviation [SD] or percentage) for selected measures, by race/ethnicity, in the total study population of 3,529,213 participants (last visit in FY2016). The mean age was 64 years, 91% were male, 67% were White, 16% were Black, 6% were Hispanic, and 11% were other races. Compared to Whites, Blacks were more likely to be younger, female, obese, have diabetes, hypertension, CKD, shorter follow-up time, higher OSA incidence rate. Compared to Whites, Hispanic were more likely to be younger, female, obese, have diabetes, CKD, shorter follow-up time, higher OSA incidence rate. Other races were more likely to be younger, female, less obese, have longer follow-up time, lower OSA incidence rate comparing to Whites.

Table 3 shows crude and adjusted hazard ratios (HR; 95% CI) for the associations between the covariates of interest and OSA incidence rate, by type of model adjustment, in the total study population. Using Cox regression, the hazard ratio (HR; 95% CI) for each covariate was adjusted for race/ethnicity, sex, and age (middle column) in addition to other confounders, but not mediators, as implied by the DAG in Figure 1 (right column). In the fully adjusted model, the HR of OSA for each racial/ethnic group, compared with Whites, was 1.13 (1.12, 1.14) for Blacks, 1.12 (1.11, 1.13) for Hispanics, and 0.82 (0.81, 0.83) for other races. The adjusted HRs for CKD, diabetes, and hypertension (all binary) were about the same (1.21 to 1.26), but the association with OSA was stronger for obesity (adjusted HR = 2.01; 2.00, 2.03).

The informal difference method was used to generate the findings in Table 4, which shows adjusted HR and 95% CI for the direct effect, indirect effect, and total effect of each

race/ethnicity (vs. Whites) on OSA incidence, and the percentage mediated by CKD. Compared with Whites, the OSA incidence rate was higher for Blacks (HR = 1.091; 1.082-1.101) and Hispanics (HR = 1.117; 1.103-1.131), but lower for other races (HR = 0.912; 0.902-0.922). Blacks had the largest % mediated by CKD (6.6%), Hispanics had the second largest % mediated by CKD (2.8%) and other races had the smallest % mediated by CKD (-0.12%). In the model without adjustment of potential mediators (BMI, diabetes, hypertension), all the effects (total, direct, and indirect) increased comparing with the model with adjustment of potential mediators. The percentage mediated relative to Whites increased from 6.6% to 20.1% for Blacks, from 2.8% to 14.3% for Hispanics, and decreased from -0.12% to -1.6% for other races.

The 4-way decomposition method was used to generate results for Table 5. The percentage mediated for pairs of component effects can be summed to reflect the pure direct effect (controlled direct + reference interaction), the total indirect effect (mediated interaction + pure indirect), and total interaction (reference interaction + mediated interaction). Table 5 presents the adjusted odds ratios (OR; 95% CI) for the 4 component effects of each race/ethnicity (vs. Whites) on OSA incidence, due to mediation and/or interaction with CKD, using logistic regression. The OR for the total effect of Blacks versus Whites race was 1.11 (1.10-1.11); the OR for the total effect of Hispanics versus Whites was 1.13 (1.11-1.15); and OR for other races versus Whites was 0.904 (0.894- 0.915).

For Blacks versus Whites, the pure indirect effect accounted for 6.8% (95% CI: 6.0, 7.5) of the total effect; the component due to the mediated interaction was 0.68% (0.64, 0.71); the component due to the reference interaction is 2.2% (2.1, 2.3); and the component due to the controlled direct effect (if CKD were fixed to 0) was 90.4% (89.6, 91.2). Of these four

components, the controlled direct effect was the most substantial. The overall proportion mediated was 7.4%. The overall proportion attributable to interaction was even smaller, 2.9%.

For Hispanics versus Whites, the component due to the pure indirect effect accounted for 2.1% (95% CI: 1.7, 2.4) of the total effect; the component due to the mediated interaction was 0.26% (0.23, 0.30); the component due to the reference interaction is 2.4% (2.2, 2.5); and the component due to the controlled direct effect (if CKD were fixed to 0) was 95.3% (95.9, 95.8). Of these four components, the controlled direct effect was again the most substantial. The overall proportion mediated was 2.3%. The overall proportion attributable to interaction was 2.7%.

For other NH races versus Whites, the component due to the pure indirect effect accounted for 0.57% (95% CI: 0.31, 0.83) of the total effect; the component due to the mediated interaction was -0.05% (-0.08, -0.03); the component due to the reference interaction is 2.4% (2.3, 2.6); and the component due to the controlled direct effect (if CKD were fixed to 0) was 97.1% (96.8, 97.3). Of these four components, the controlled direct effect was the most substantial. The overall proportion mediated was quite small, 0.51%. The overall proportion attributable to interaction was 2.4%. Neither interaction nor mediation components of CKD contributed significantly to the overall effect of race/ethnicity on the risk of incident OSA.

Flexible mediation analysis was used to generate results for Table 6, which shows three sets of analysis: CKD is treated as the only mediator in the top panel; CKD plus its three risk factors (diabetes, hypertension, and BMI) are treated jointly as mediators in the middle panel, and the three risk factors (without CKD) are treated as mediators in the bottom panel. Adjusted

odds ratios (OR; 95% CI) reflect the natural direct effect (NDE), the natural indirect effect (NIE), and the total effect (TE) of each race/ethnicity comparison on OSA incidence; also shown in the table are the percentages mediated. When treating CKD as the only mediator, the ORs of Blacks for the NDE was 1.10 (95% CI: 1.09, 1.11). The OR for the NIE is 1.01 (95% CI: 1.01, 1.01). 5.8 percent of the total effect (OR=1.11) of Blacks vs Whites on incident OSA is mediated by CKD. For Hispanics, the OR for the NDE was 1.13 (1.11-1.14). The OR for the NIE was 1.00 (1.00-1.01). 2.6 percent of the total effect (OR=1.13) of Hispanic vs White on incident OSA was mediated by CKD. For other races, the OR for the NDE was 0.83 (95% CI: 0.82, 0.84). The OR for the NIE is 1.00 (1.00-1.00). Only 0.2% of the total other races vs White effect on OSA incidence was mediated by CKD.

When treating CKD and its three risk factors as mediators (middle panel of Table 6), the NIE for Blacks increased from 1.01 (1.01, 1.01) to 1.04 (1.04, 1.04). This leads to an increase in the percentage mediated from 5.8% to 30.3%. For other NH races, the OR for the NIE decreased from 1.00 (1.00, 1.00) to 0.96 (0.96, 0.96). The percentage mediated increased from 0.2% to 16.4%. Results for Hispanics vs Whites remained similar when treating all 4 comorbidies as mediators.

When treating three risk factors as mediators (lower panel of Table 6), the results remained similar to results from the middle panel. The percentage mediated decreased slightly from 30.3% to 25.3 for Blacks, 2.9% to 1.7% for Hispanics, and 16.4% to 16.1% for other NH races.

Table 7 shows the results from dynamic path mediation analysis. It shows the estimated pure direct effect (PDE), pure indirect effect (PIE), and TE of each race/ethnicity (vs Whites) on OSA incidence, and the percentage mediated by CKD, stratified by follow-up interval during follow-up. For Blacks vs Whites, the percentage mediated decreased over time (from 6.1% for days 250-500, to 4.9% for days 501-750, to 2.6% for days 750+). For Hispanic versus Whites, the percentage mediated decreased from 2.9% for days 250-500, to 2.1% for days 501-750 day, to 0.97% for days 750+). The magnitude of the total effect would have been slightly *greater* in the absence of CKD mediation for other NH races versus Whites; the percentage mediated is very small but negative after day 250.

Discussion

Our analysis of data from 3.5 million veterans for FY2016-2018, using four mediation analysis methods shows that most of the racial/ethnic disparity in OSA incidence was not explained by mediation or interaction with CKD. The percentage of mediated by CKD of the total effect from the largest to the smallest was Black, Hispanic, and other races. Results showed similar mediated effects of CKD across different meditation analysis methods. However, when CKD, hypertension, diabetes and BMI were treated jointly as mediators in flexible mediation analysis, the percentage of mediated for Blacks and other NH races increased appreciably. The percentage mediated by CKD decreased after day 500 using dynamic path mediation analysis.

There are pros and cons of the four mediation methods we applied in our study (Table 8). The difference method is easy to implement since there is no requirement of any package or macro. However, it relies on the assumptions of no interaction between race/ethnicity and CKD

and no measured or unmeasured confounders of the CKD-OSA effect that are influenced by race/ethnicity.

The 4-way decomposition approach is also easy to implement because there is a built-in procedure in the latest SAS 9.4 version. In addition, the total effect of race/ethnicity on OSA can be decomposed into four components. These four components corresponded to the portion of the effect that is due to neither mediation nor interaction, to interaction only, to both mediation and interaction, and to mediation only.[15] However, this SAS procedure cannot be applied to a multi-category exposure such as race/ethnicity. Therefore, we did a separate analysis with each racial/ethnic comparison, excluding all persons from the other two racial/ethnic groups. Furthermore, the estimates can be biased if the data violate the 4th assumption (no measured or unmeasured confounders of the CKD and OSA effect that are influenced by race/ethnicity).

The flexible mediation analysis can be applied to data with multiple mediators. The standard errors of the estimates can be obtained by either bootstrapping or robust standard error based on sandwich estimator. Path-specific indirect effect cannot be estimated with current version of medflex package.

Finally, dynamic path mediation analysis was designed for data with time-to-event outcome, time-varying mediators, and time-varying confounders to capture the full complexity of the mediators. Nevertheless, this approach takes a lot of time and memory to run in SAS, can only be used for data with binary exposure, only generates confidence intervals through

bootstrapping leading to a loss of precision, and might not produce valid results if the model does not converge when the confounders or mediators are binary.

Although similar percentages of mediated by CKD were observed across different mediation methods, it should be noted that valid estimates can only be identified from the data on average for a population under no-confounding assumptions.[21] In particular, the identification of effects relies on four strong assumptions of no unmeasured confounders of: 1) the exposure-mediator effect, 2) the exposure-outcome effect, or 3) the mediator-outcome effect; and 4) no measured or unmeasured confounders of the mediator-outcome effect that are influenced by exposure. In our study, diabetes, hypertension, and BMI could not only be the confounders between CKD and OSA but also be affected by race/ethnicity. Such additional mediation could bias the results. However, flexible mediation analysis and dynamic path mediation analysis are able to deal with measured mediator-outcome confounders influence by the exposure. The flexible mediation analysis,[16] avoid the violation of this assumption by treating all measured mediators jointly as a group. However, a sequential approach enabling effect decomposition of the total indirect effect into multiple path-specific effects embedded in the natural effect model framework is only available in an upcoming version the medflex package.[22] On the other hand, dynamic path analysis does properly control for *measured* mediator-outcome confounders influenced by the exposure if they are treated as time-dependent covariates during follow-up, which was done in this study with BMI.[17] This strategy, however, was not possible with diabetes and hypertension, which could be treated only as fixed baseline covariates. Therefore, time-dependent mediators and confounders are allowed to capture the mediated and direct effect throughout the follow-up.

The association between race/ethnicity and OSA, measured as a ratio, is stronger with prevalence data (see Chapter 3) than with incidence data. The adjusted HR from the model with race/ethnicity as the exposure and prevalent OSA as the outcome for other NH races was 0.72 (0.72, 0.73) for other NH races. In contrast, the adjusted HR from the model with race/ethnicity as the exposure and incident OSA as the outcome for other NH races was 0.82 (0.81, 0.83). Because prevalence is based on both incidence and the course of disease (from recovery and death), relatively high prevalence of a disease in a population could reflect higher incidence and/or prolonged survival without recovery.[24] A systematic review by Saha et al.[25] summarized the sources of racial disparities contributing to differential prevalence in chronic diseases and preventive and ambulatory care in the VHA system. These sources of racial disparity could result from degree of familiarity with and knowledge about medical interventions, less trust and more skepticism in minority veterans, inadequate racially and culturally concordant healthcare environment, lower participation in care in non-white veterans, differential clinicians' diagnostic and therapeutic decision making, limited social support and external resources of illness management and decision making in non-white veterans, fewer available services and lower quality care.[25] Therefore, the stronger ratio-measure association in other NH races vs. White with prevalence data comparing to with incidence data more likely ascribes to different duration of illness (prolonged survival without cure) than lower incidence of OSA in other NH races.

CKD partially mediated the effect of race/ethnicity on incident OSA, especially for Blacks vs. Whites in our study. OSA is an important comorbidity in patients with CKD or end-stage renal disease (ESRD). A few studies have shown the racial disparity in CKD occurrence and

reported the occurrence of OSA in persons with CKD. The prevalence of nocturnal hypoxia was three times higher in patients with eGFR<60 mL/min/1.73 m^2 than in patients with eGFR>60 mL/min/1.73 m^2 (48% vs 16%). In addition, Nicholl et al.[10] demonstrated that the prevalence of sleep apnea increased as eGFR declined (41% for CKD and 27% for eGFR>60 mL/min/1.73 m^2) among patients from outpatient nephrology clinics and hemodialysis units. Sakaguchi et al.[11] found that a 10 ml/min per 1.73 m^2 decrease in eGFR was associated with a 42% increased odds of OSA after adjusted for age, BMI, and diabetes among non-dialysis hospitalized CKD patients. Elias et al.[26] showed that nocturnal rostral fluid shift is associated with the severity of OSA in ESRD patients on conventional hemodialysis. 28% of stages 2-4 non-dialysis CKD patients were at high risk of OSA (2 or more categories where the score is positive) using the Berlin questionnaire to symptoms of sleep apnea. Among those who were at high risk of sleep apnea to the Berlin questionnaire (2 or more categories where the score is positive), the prevalence of OSA was 88%.[27] A study with all male participants aged ≥40 years showed that CKD was associated with OSA (apnea-hypoapnea index [AHI]≥10/hour OR=1.9, 1.1, 4.7; AHI≥30/hour OR=2.6, 1.1, 6.2).[28] The prevalence of OSA was 67% among non-dialysis stage 3b to 4 CKD patients and body adiposity (total and upper) was associated with the presence and severity of OSA.[29] Alterations in chemoreflex responsiveness, pharyngeal narrowing due to fluid overload, and accumulation of uremic toxins might be the mechanisms through which CKD predispose to the occurrence of OSA.[12] However, most studies were limited to small sample size, a single race/ethnicity, and the occurrence of prevalent OSA in which reverse causation may occur between CKD and OSA.

Our study has several advantages. First, this study has a large sample size of 3.5 million veterans and large numbers of persons with incident OSA (n = 417,651) and CKD (100,691 incident cases and 546,556 baseline prevalent cases). Moreover, since there is no single mediation method that can be assured to provide valid and precise results, we used four approaches that have different advantages and limitations to provide some confirmation of our findings. For example, the 4-way decomposition method provided a comprehensive understanding of the mechanistic role of CKD in explaining the total effect of race/ethnicity on OSA, while dynamic path mediation analysis enabled us to account for censoring using survival analysis with the mediator and confounders treated as time-dependent. Additionally, flexible mediation analysis and dynamic path analysis enabled us to deal with the effects of race/ethnicity on mediator-outcome confounders in different ways.

Some limitations of the study should be noted. Misclassification of OSA and CKD may occur because of the usage of claims data and limited information on polysomnography to define OSA. Moreover, residual confounding may be another problem since we did not have information on certain risk factors for CKD or OSA, such as smoking and alcohol consumption. Finally, the study population was comprised of mostly Whites Blacks non-Hispanic males; thus, generalization to females, other racial/ethnic groups, and non-veterans is limited.

In conclusion, the study helped us highlight that most of the racial/ethnic disparity in OSA incidence was not explained by mediation or interaction with CKD. However, a modest percentage of the Black/White disparity was attributable to the combination of CKD and its 3 main risk factors. Therefore, the results can assist us in underlining the potential mediation of CKD and its risk factors in the path between race/ethnicity especially Blacks and OSA.

Interventions to decrease CKD and its risk factors occurrence may combat racial disparity in

OSA. In this way, we gain more insight into possible racial disparities in OSA risk, which might

lead to medical treatments or other interventions for reducing those disparities, e.g., by

treating or preventing CKD, possibly focusing on Blacks. Future work could address the role of

multiple mediators (CKD and other risk factors) in the pathway between race/ethnicity and

incident OSA. As new and refined methods of mediation analysis are developed to handle the

many types of data and potential sources of bias encountered in these analyses, they should

prove to be valuable in designing effective interventions for clinical practice.

References

1. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: A population-based perspective. Expert Rev Respir Med. 2008;2(3):349-364.

2. Durrence HH, Lichstein KL. The sleep of African Americans: A comparative review. Behav Sleep Med. 2006;4(1):29-44.

3. Ruiter ME, DeCoster J, Jacobs L, Lichstein KL. Sleep disorders in African Americans and Caucasian Americans: a meta-analysis. Behav Sleep Med. 2010;8(4):246-259.

4. Wallace DM, Wohlgemuth WK. Does race-ethnicity moderate the relationship between CPAP adherence and functional outcomes of sleep in US veterans with obstructive sleep apnea syndrome? J Clin Sleep Med. 2014;10(10):1083-1091.

5. Billings ME, Rosen CL, Wang R, et al. Is the relationship between race and continuous positive airway pressure adherence mediated by sleep duration? Sleep. 2013;36(2):221-227.

6. Baldwin CM, Ervin A-M, Mays MZ, et al. Sleep disturbances, quality of life, and ethnicity: the Sleep Heart Health Study. J Clin Sleep Med. 2010;6(2):176-183.

7. Norton J. Health Disparities in Chronic Kidney Disease: The Role of Social Factors. Physician Assist Clin. 2016;1(1):187-204.

8. Chen TK, Estrella MM, Parekh RS. The evolving science of apolipoprotein-L1 and kidney disease. Curr Opin Nephrol Hypertens. 2016;25(3):217-225.

9. Norris K, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the United States. J Am Soc Nephrol. 2008;19(7):1261-1270.

10. Nicholl DDM, Ahmed SB, Loewen AHS, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. Chest. 2012;141(6):1422-1430.

11. Sakaguchi Y, Shoji T, Kawabata H, et al. High prevalence of obstructive sleep apnea and its association with renal function among nondialysis chronic kidney disease patients in Japan: A cross-sectional study. Clin J Am Soc Nephrol. 2011;6(5):995-1000.

12. Abuyassin B, Sharma K, Ayas NT, Laher I. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? J Clin Sleep Med. 2015;11(8):915-924.

13. Gildeh N, Drakatos P, Higgins S, Rosenzweig I, Kent BD. Emerging co-morbidities of obstructive sleep apnea: Cognition, kidney disease, and cancer. J Thorac Dis. 2016;8(9):E901-E917.

14. VanderWeele TJ. Mediation analysis: a practitioner's guide. Annu Rev Public Health. 2016;37(1):17-32.

15. VanderWeele TJ. A unificaiton of mediation and interaction: a four-way decomposition. Epidemiology. 2014;25(5):749-761.

16. Steen J, Loeys T, Moerkerke B, Vansteelandt S. Flexible mediation analysis with multiple mediators. Am J Epidemiol. 2017;186(2):184-193.

17. Vansteelandt S, Linder M, Vandenberghe S, Steen J, Madsen J. Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. Stat Med. 2019;38(24):4828-4840.

18. Kizer KW, Dudley RA. Extreme makeover: Transformation of the veterans health care system. Annu Rev Public Health. 2009;30:313-339.

19. Overview of VA Data, Information Systems, National Databases & Research Uses. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/3531-notes.pdf. Accessed March 19, 2020.

20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

21. VanderWeele TJ. A Unification of Mediation and Interaction. Epidemiology. 2014;25(5):749-761.

22.   Steen J, Loeys T, Moerkerke B, Vansteelandt S. Medflex: An R package for flexible mediation analysis using natural effect models. J Stat Softw. 2017;76(1):1-46.

23.   Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986;73(1):13-22.

24.   Center for Disease Control and Prevention, principles of epidemiology in public health practice, third edition, an introduction to applied epidemiology and biostatistics, lesson 3, section 2. https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html. Accessed July 4, 2020.

25.   Saha S, Freeman M, Toure J, Tippens KM, Weeks C, Ibrahim S. Racial and ethnic disparities in the VA health care system: A systematic review. J Gen Intern Med. 2008;23(5):654-671.

26.   Elias RM, Bradley TD, Kasai T, Motwani SS, Chan CT. Rostral overnight fluid shift in end-stage renal disease: Relationship with obstructive sleep apnea. Nephrol Dial Transplant. 2012;27(4):1569-1573.

27.   Shanmugam GV, Abraham G, Mathew M, Ilangovan V, Mohapatra M, Singh T. Obstructive sleep apnea in non-dialysis chronic kidney disease patients. Ren Fail. 2015;37(2):214-218.

28.   Adams RJ, Appleton SL, Vakulin A, et al. Chronic kidney disease and sleep apnea association of kidney disease with obstructive sleep apnea in a population study of men. Sleep. 2017;40(1).

29.   Fernandes JFR, Barreto Silva MI, Loivos CP, et al. Obstructive sleep apnea in non-dialyzed chronic kidney disease patients: Association with body adiposity and sarcopenia. Nutrition. 2019;57:282-289.

Tables and figures

Table 4.1: List of ICD-9, ICD-10, and CPT codes used to define obstructive sleep apnea, diabetes, hypertension, and CKD

Type of coding	Codes
ICD-9 for obstructive sleep apnea	327.20, 327.22, 327.29, 327.8
ICD-10 for obstructive sleep apnea	G47.30, G47.33, G47.39, G47.8, G47.9, R06.00, R06.09, R06.3, R06.83, R06.89
CPT for obstructive sleep apnea	E0470 and E0601
ICD-9 for diabetes	250, 35673, 36641, 36201, 36202
ICD-10 for diabetes	E08, E09, E10, E11, E13
ICD-9 for hypertension	401, 402, 403, 404, 405
ICD-10 for hypertension	I10, I11, I12, I13, I15
ICD-9 for CKD	016.0; 095.4; 189.0,189.9; 223.0; 236.91; 250.4; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 477.3; 572.4; 581-583; 585- 588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4
ICD-10 for CKD	A18.11, A52.75, B52.0, C64.x, C68.9, D30.0x, D41.0x-D41.2x, D59.3, E08.2x, E09.2x, E10.2x, E10.65, E11.2x, E13.2x, E74.8, I12.xx, I13.0, I13.1x, I13.2, K76.7, M10.3x, M32.14, M32.15, N01.x-N08.x, N13.1, N13.1x-N13.39, N14.x,N15.0, N15.8, N15.9, N16, N17.x, N18.1-N18.5, N18.8, N18.9, N19, N25.xx, N26.1, N26.9, O10.4xx, O12.xx, O26.83x, O90.89, Q61.02, Q61.1xQ61.8, Q26.0-Q26.39, R94.4

Table 4.2: Summary statistics (mean [SD] or %) of selected measures in the study population of adult veterans, by race/ethnicity

Measure	Total (n = 3,529,213)	White NH (n = 2,375,347)	Black NH (n =566,572)	Hispanic (n =195,164)	Other NH races[d] (n =392,130)
Age (mean [SD] in years)	64.0 (15.5)	65.6 (15.3)	58.9 (13.6)	58.6 (17.4)	64.2 (16.4)
18-44 (%)	10.2	9.1	10.8	20.7	10.6
45-64 (%)	33.7	28.3	54.8	36.1	34.7
≥65 (%)	56.1	62.6	34.4	43.2	54.7
Male (%)	90.8	93.2	85.3	89.9	85.1
BMI[a] (mean [SD] in years)	29.0 (5.5)	29.0 (5.5)	29.1 (5.9)	29.1 (5.4)	28.7 (5.5)
Obesity[a,b] (%)	37.6	37.4	39.7	38.6	35.1
Diabetes (%)	25.4	24.9	28.5	29.5	22.1
Hypertension (%)	52.1	52.5	57.2	46.2	45.1
CKD[c] (%)	15.5	15.1	18.3	16.4	13.2
Follow-up time (mean days [SD])	636 (218)	637 (217)	634 (220)	630 (222)	640 (214)
OSA incidence rate (per 1000/yr)	68	66	79	81	54

[a]Measured at baseline.

[b]Defined as BMI ≥30 kg/m^2.

[c]Baseline CKD status was based on the presence of at least one of three criteria: having a diagnosis of ICD-9 or ICD-10 CKD (see Table 1 for codes); an eGFR <60 ml/min/1.73 m^2, using the CKD-EPI formula; and the presence of albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g).

[d]Other NH races included American Indian/Alaska Native (0.81%), Asian (0.86%), Native Hawaiian/Pacific Islander (0.77%), and other (8.7%).

Table 4.3: Crude and adjusted hazard ratios (HR; 95% CI) for associations between the covariates of interest and OSA incidence rate, by type of model adjustment: Results of Cox regression in the total study population (n = 3,529,213)

Covariate Group	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Adjusted HR[b] (95% CI)
Race/Ethnicity			
White (ref.)	1	1	1
Black	1.19 (1.18, 1.20)	1.13 (1.12, 1.14)	1.13 (1.12, 1.14)
Hispanic	1.21 (1.20,1.23)	1.12 (1.11, 1.13)	1.12 (1.11, 1.13)
Other race	0.81 (0.81, 0.82)	0.82 (0.81, 0.83)	0.82 (0.81, 0.83)
Obesity (BMI ≥30 vs <30)	2.08 (2.07, 2.10)	2.01 (2.00, 2.03)	2.01 (2.00, 2.03)
Diabetes (Yes/No)	1.34 (1.33, 1.34)	1.46 (1.45, 1.47)	1.26 (1.25, 1.27)
Hypertension (Yes/No)	1.20 (1.20, 1.21)	1.42 (1.41, 1.43)	1.21 (1.21, 1.22)
CKD vs. No CKD	1.35 (1.34, 1.36)	1.47 (1.45, 1.48)	1.23 (1.22, 1.24)

[a] Adjusted for race/ethnicity (where needed), age and sex.

[b] Adjusted for confounders, including race/ethnicity, age and sex, but not mediators (Fig. 1). The effect of diabetes is also adjusted for obesity; the effect of hypertension is also adjusted for obesity and diabetes; and the effect of CKD is also adjusted for obesity, diabetes, and hypertension.

Table 4.4: Adjusted[a] hazard ratios (HR; 95% CI) for the "direct effect," "indirect effect", and total effect of each race/ethnicity (vs. White non-Hispanic [NH]) on OSA incidence, and the percentage mediated by CKD[b]: results of the informal difference method, using Cox regression to model time to first OSA diagnosis

Race/ethnicity vs. White non-Hispanic	HR (95% CI)			% Mediated[f]
	Direct effect[c]	Indirect effect[d]	Total effect[e]	
Model adjusted for age, sex, BMI, diabetes, and hypertension				
Black non-Hispanic	1.084 (1.076, 1.093)	1.006	1.091 (1.082, 1.100)	6.6
Hispanic	1.114 (1.100, 1.128)	1.003	1.117 (1.103, 1.131)	2.8
Other non-Hispanic races	0.911 (0.902, 0.922)	1.000	0.912 (0.902, 0.922)	-0.12
Model adjusted for age and sex only				
Black non-Hispanic	1.101 (1.092, 1.110)	1.025	1.128 (1.119, 1.137)	20.1
Hispanic	1.101 (1.088, 1.115)	1.016	1.119 (1.105, 1.133)	14.3
Other non-Hispanic races	0.822 (0.814, 0.831)	0.997	0.820 (0.811, 0.829)	-1.6

[a] Baseline confounders: age, sex, diabetes status, hypertension status, BMI at baseline.

[b] CKD was treated as fixed at baseline.

[c] The direct effect is obtained from the regression coefficient for the race/ethnicity predictor in the Cox model with CKD.

[d] The HR for the indirect effect is the antilog of the difference between the log HRs for the total effect and the direct effect on the log scale.

[e] The total effect is obtained from the regression coefficient for the race/ethnicity predictor in the Cox model without CKD.

[f] Percentage mediated is the difference in log hazard ratios between the models without and with CKD, divided by the log hazard ratio from the model without CKD. It is also the log HR for the indirect effect divided by the log HR for the total effect.

Table 4.5: Adjusted[a] odds ratios (OR; 95% CI) for the 4 component effects of each race/ethnicity (vs. White non-Hispanic) on OSA incidence, due to mediation and/or interaction with CKD[b]: results of the 4-way decomposition method, using logistic regression

Component effect of race/ethnicity	OR (95%CI)	Percentage of total effect (95% CI)	
Black Non-Hispanic vs White Non-Hispanic			
Controlled direct	1.098 (1.088, 1.11)	90.4 (89.6, 91.2)	92.6[c] (91.8, 93.3)
Reference interaction	1.0024 (1.0021, 1.0027)	2.2 (2.1, 2.3)	
Mediated interaction	1.0007 (1.0006, 1.0008)	0.68 (0.64, 0.71)	7.4[d] (6.7, 8.2)
Pure indirect	1.0073 (1.0069, 1.0077)	6.8 (6.0, 7.5)	
Total	1.11 (1.10, 1.11)	100	---
Hispanic vs White Non-Hispanic			
Controlled direct	1.12 (1.11, 1.14)	95.3 (95.9, 95.8)	97.7[c] (97.3, 98.1)
Reference interaction	1.0030 (1.0027, 1.0035)	2.4 (2.2, 2.5)	
Mediated interaction	1.0003 (1.0003, 1.0004)	0.26 (0.23, 0.30)	2.3[d] (1.9, 2.7)
Pure indirect	1.0027 (1.0023, 1.0031)	2.1 (1.7, 2.4)	
Total	1.13 (1.11, 1.15)	100	---
Other Non-Hispanic races vs White Non-Hispanic			
Controlled direct	0.907 (0.897, 0.918)	97.1 (96.8, 97.3)	99.5[c] (99.3, 99.7)
Reference interaction	0.998 (0.997, 0.998)	2.4 (2.3, 2.6)	
Mediated interaction	1.0001 (1.0000, 1.0001)	-0.05 (-0.08, -0.03)	0.51[d] (0.28, 0.75)
Pure indirect	0.999 (0.999, 0.999)	0.57 (0.31, 0.83)	
Total	0.904 (0.894, 0.915)	100	---

[a] Baseline confounders: age, sex, diabetes status, hypertension status, BMI.

[b] CKD was treated as fixed at baseline.

[c] This % reflects the pure direct effect.

[d] This % reflects the total indirect effect.

Table 4.6: Adjusted[a] odds ratios (OR; 95% CI) for the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) of race/ethnicity on OSA incidence and percentage of the total, by choice of mediator(s): using flexible mediation analysis (with medflex).

Race/ethnicity vs. White non-Hispanic	OR (95% CI)			% Mediated[c]
	NDE	NIE	TE[b]	
CKD as the only Mediator				
Black non-Hispanic	1.10 (1.09, 1.11)	1.01 (1.01, 1.01)	1.11	5.8
Hispanic	1.13 (1.11, 1.14)	1.00 (1.00, 1.01)	1.13	2.6
Other non-Hispanic races	0.83 (0.82, 0.84)	1.00 (1.00, 1.00)	0.83	0.2
CKD and its 3 Risk Factors as Mediators				
Black non-Hispanic	1.10 (1.09, 1.11)	1.04 (1.04, 1.04)	1.14	30.3
Hispanic	1.12 (1.11, 1.14)	1.00 (1.00, 1.01)	1.12	2.9
Other non-Hispanic races	0.83 (0.83, 0.84)	0.96 (0.96, 0.96)	0.80	16.4
3 Risk Factors as Mediators				
Black non-Hispanic	1.11 (1.10, 1.12)	1.03 (1.03, 1.03)	1.14	25.3
Hispanic	1.13 (1.11, 1.14)	1.00 (1.00, 1.01)	1.13	1.7
Other non-Hispanic races	0.83 (0.82, 0.84)	0.96 (0.96, 0.96)	0.80	16.1

[a]All the analyses are adjusted for age and sex; and analyses in the top panel (CKD as the only mediator) are also adjusted for the 3 CKD risk factors.

[b]The 95% CI for the TE was not computed because it is computationally complex and not needed for interpretation of the main findings. Total effect was calculated as the product of NDE and NIE.

[c]The percentage mediated on the risk difference scale is $NDE(NIE-1)/(NDE \times NIE-1)$, where NDE and NIE are the odds ratios (OR) corresponding to those effects, assuming OSA incidence is a rare outcome event.

Table 4.7: Estimated pure direct effect (PDE), pure indirect effect (PIE), and total effect (TE) of each race/ethnicity (vs White non-Hispanic) on OSA incidence, and the percentage mediated by CKD, by race/ethnicity: results of dynamic path mediation analysis[a]

Race/ethnicity vs. White non-Hispanic	PDE[c]	PIE[d]	TE[e]	% Mediated
Black Non-Hispanic	-0.0093352	-0.00073	-0.010061	7.2
Hispanic	-0.012495	-0.00031	-0.0128	2.4
Other non-Hispanic races	0.010501	-0.0001	0.010409	-0.9

[a]CKD (the mediator) and BMI (a confounder) are treated as time-dependent in the analyses; age, sex, diabetes, and hypertension are treated as fixed confounders measured at baseline.

[b]Day 11 to the end of follow-up

[c]PDE is the difference between survival curves $S_{1,0}$ and $S_{0,0}$.

[d]PIE=TE-PDE.

[e]TE is the difference between survival curves $S_{1,1}$ and $S_{0,0}$.

**Table 4.8: Pros and cons of the 4 mediation methods**

Method	Pros	Cons
Difference method[a] (using an informal *ad hoc* procedure)	Easy to implement No requirement of any package or macro	Assume no interaction between race/ethnicity and CKD Assume race/ethnicity does not affect confounders of CKD-OSA Do not deal with data that violate the 4th assumption
4-way decomposition[b] (using the SAS procedure)	Easy to implement with current SAS procedure Decompose the total effect into four parts	Do not deal with data that violate the 4th assumption Cannot be applied for categorical exposure
Flexible mediation analysis[c] (using the medflex R package)	Data with multiple mediators Weight-based approach and imputation-based approach to deal with missing outcome Can obtain standard error by bootstrapping or robust standard error based on sandwich estimator	Can only estimate indirect effect collectively with current version of medflex, that is, no path-specific indirect effect Do not deal with time-to-event outcome
Dynamic path mediation analysis[d] (using a SAS macro)	Data with time-to-event outcome, time-varying mediators, time-varying confounders Capture the full complexity of the mediator	Takes a lot of time and memory in SAS to run Confidence intervals can only be obtained through bootstrapping which takes more than one week to get and is not practical It is still a novel approach, and should be interpreted with caution Can only use binary exposure Need to group the visits Models might not converge if you have binary confounders/mediators

[a]VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016;37(1):17-32.

[b]VanderWeele TJ. A unificaiton of mediation and interaction: a four-way decomposition. Epidemiology. 2014;25(5):749-761.

[c]Steen J, Loeys T, Moerkerke B, Vansteelandt S. Flexible Mediation Analysis with Multiple Mediators. Am J Epidemiol. 2017;186(2):184-193.

Figure 4.1: Directed acyclic graph illustrating variables included in the study with the outcome (OSA)
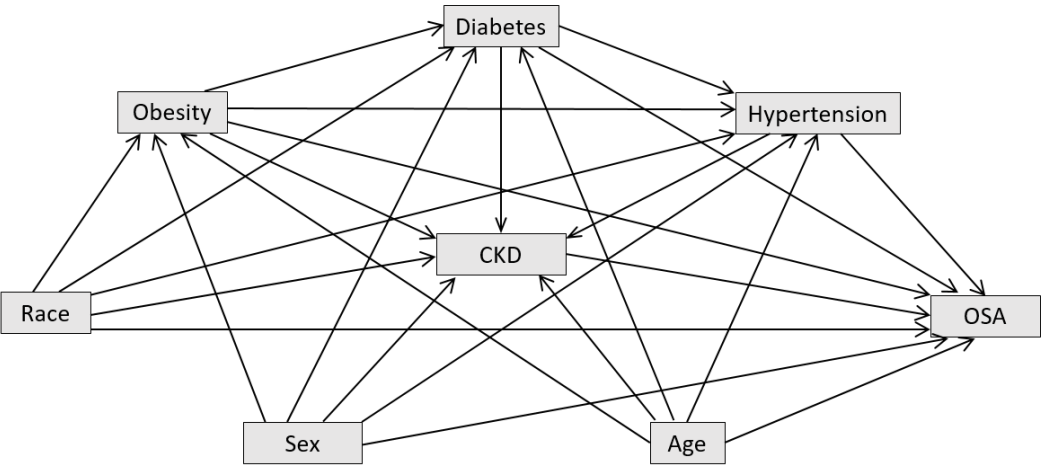
Chapter 5

Conclusion

The purpose of this dissertation was to disentangle the complicated relations between sleep problems, especially obstructive sleep disorder (OSA) and chronic kidney disease (CKD). In chapter 2, the objectives were to estimate the prevalence and temporal trends of five self-reported sleep problems and to examine the associations of those sleep problems with CKD prevalence and mortality by CKD status, using data from National Health and Nutrition Examination Surveys (NHANES). We concluded from the findings that severity of CKD was monotonically associated with sleep problems. Excessive sleep and nocturia were strongly and consistently associated with all CKD measures, and excessive sleep was most strongly associated with all-cause mortality. In chapter 3, we estimated the point and period prevalence of OSA among persons with and without CKD, using a method for period prevalence that takes into account left censoring of veterans followed back for different durations. We also examined the associations between certain covariates and OSA prevalence among non-CKD and CKD populations. We found that the population burden of OSA, reflecting both point prevalence at the index time and period prevalence in the previous 5 years, was quite high in U.S. veterans, especially among men with CKD. Finally, in chapter 4, we evaluated the extent to

which the excess incidence of OSA among minority racial/ethnic groups of veterans, relative to Whites, could be explained by CKD acting as a mediator of the race/ethnicity effects. The results indicate that most of the racial/ethnic disparity in OSA incidence was not explained by mediation or interaction with CKD; however, about 30% of the Black/White disparity in OSA was attributable to the combination of CKD and its 3 main risk factors—diabetes, hypertension, and obesity.

The findings of the dissertation highlight the potential clinical importance of addressing this topic by both primary care providers as well as by specialists. The high prevalence of OSA especially among US male veterans with CKD suggests that extra attention of sleep OSA detection and management should be paid to this population. Controlling the potential mediation of the occurrence of CKD and its risk factors may combat racial disparity in OSA incidence especially for Blacks versus Whites. This could lead to medical treatments or other interventions for reducing those disparities, e.g., by treating or preventing CKD risk factors, especially in Blacks.

In chapter 4, we used four types of mediation analysis: the difference method: 4-way decomposition, flexible mediation analysis and dynamic path analysis. The latter three methods have different statistical advantages and limitations for dealing with our data so they complement each other; the first method, which is simpler and has been used informally for many years in epidemiology, is used for comparison. The percentages of the total race/ethnicity effects mediated by CKD were similar using all 4 mediation methods. Comparing the results from different mediation analysis methods could be a good strategy to examine the mediating role of variables of interest in future studies. However, there is a need for a general analytic

framework of mediation analysis that accommodates all the conditions and constraints we had

to deal with. As new and refined methods of mediation analysis are developed to handle the

many types of data and potential sources of bias encountered in these analyses, they should

prove to be valuable in designing effective interventions for clinical practice.

To better understand the implications of these results, future studies could address the

disease burden of CKD and OSA among both US general population and the US veterans. Future

studies can be done to investigate the clinical outcomes of aggressive treatment of renal

dysfunction such as examining the estimated effect of the change in glomerular filtration rate

and OSA occurrence and prognosis. Further, future research is needed to identify other

potential mediators of reducing the racial disparity of OSA. Potential mediators include risk

factors of CKD and possibly other risk factors of OSA such as social economic status.