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ORIGINAL ARTICLE

Association of Chronic Insomnia With Mortality and Adverse Renal Outcomes

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Abstract

Objective: To examine whether chronic insomnia is associated with an increased risk of adverse renal outcomes and all-cause mortality.

Patients and Methods: We examined associations of chronic insomnia (defined as the presence of both *International Classification of Diseases, Ninth Revision* codes 307.42, 307.49, and 780.52 and long-term use of insomnia medications) with adverse renal outcomes (end-stage renal disease, incidence of estimated glomerular filtration rate [eGFR] $\leq$45 mL/min per 1.73 m^2, and eGFR slopes <-3.0 mL/min per 1.73 m^2 per year) and all-cause mortality in a national cohort of 1,639,090 US veterans by using Cox proportional hazards and logistic regression models with multivariable adjustments.

Results: A total of 36,741 patients (2.24%) had chronic insomnia; 32,985 (89.8%) were male and 28,090 (76.5%) were white, with a mean baseline eGFR of 84.1$\pm$16.4 mL/min per 1.73 m^2. Chronic insomnia was associated with a significantly higher risk of eGFR 45 mL/min per 1.73 m^2 or less (multivariable-adjusted hazard ratio [HR], 1.39; 95% CI, 1.34-1.44; $P<.001$), and rapid loss of kidney function (odds ratio, 1.07; 95% CI, 1.03-1.12; $P=.002$), but not end-stage renal disease (HR, 1.25; 95% CI, 0.81-1.93; $P=.32$). Chronic insomnia was not associated with a higher risk of all-cause mortality (HR, 1.00; 95% CI, 0.97-1.03; $P=.99$).

Conclusion: Chronic insomnia is associated with a higher risk of development and progression of chronic kidney disease, but not ESRD. Further studies are needed to establish the underlying mechanisms of action and to determine whether treatment of insomnia could be beneficial to prevent deteriorating kidney function.

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Sleep is a necessary function in our daily life that is essential for biological rejuvenation and organ recovery.[1] Sleep disorders can result in mental or physical dysfunction. Insomnia is one of the most common sleep disorders, affecting as many as one-third of the world's population.[2] *Chronic insomnia* is usually defined as persistent difficulty in initiating sleep, maintaining sleep, or waking up earlier than desired for several months, although the diagnosis of insomnia was revised many times in the *Diagnostic and Statistical Manual of Mental Disorders*[3] and *International Classification of Sleep Disorders* (*ICSD-3*).[4] In addition to its social and psychological effects such as fatigue,[5] deficient performance,[6,7] and decreased memory and attention,[8,9] chronic insomnia causes overactivation of the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system[10,11] and is associated with an increased incidence of cardio- and cerebrovascular diseases[12,13] and metabolic abnormalities.[14,15]

In spite of calls to devote more attention to the adverse effects of sleep disorders,[16,17] to our knowledge no study has examined the effect of chronic insomnia on renal outcomes, such as incidence of chronic kidney disease (CKD) or rate of kidney function deterioration. We hypothesized that chronic insomnia could be associated with adverse renal outcomes. To test this hypothesis, we examined the association of chronic insomnia in a large nationally representative cohort of US veterans with a normal baseline estimated glomerular filtration rate (eGFR).

PATIENTS AND METHODS

Cohort Definition

This study used data from a historical cohort study (Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease [RCAV])

For editorial comment, see page 1540

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examining risk factors and outcomes of incident CKD, which has been previously described.[18,19] Briefly, our parent cohort consisted of patients who received care at any US Department of Veterans Affairs (VA) facility from October 1, 2004, through September 30, 2006, with measurement of at least 1 serum creatinine value, and had an eGFR of greater than 60 mL/min per 1.73 m^2 during this time period. Patients were entered into the RCAV cohort on the date of the first eGFR assessment of greater than 60 mL/min per 1.73 m^2. The algorithm for our present analytical cohort definition is shown in Figure 1. To select only patients with primary chronic insomnia, we used the insomnia research diagnostic criteria suggested by Edinger et al[20] in 2004 and in *ICSD-3*.[4] Chronic insomnia was defined as the presence of *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 307.42, 307.49, and 780.52 and long-term use of insomnia medications (defined as the pharmacy dispensation records of a benzodiazepine, Z-drugs [non-benzodiazepine drug], or ramelteon for at least 3 months and with a medication refill overdue period of <90 days). After we excluded patients with preexisting insomnia and other sleep disorders (sleep apnea, circadian rhythm sleep disorder, hypersomnia, parasomnia,

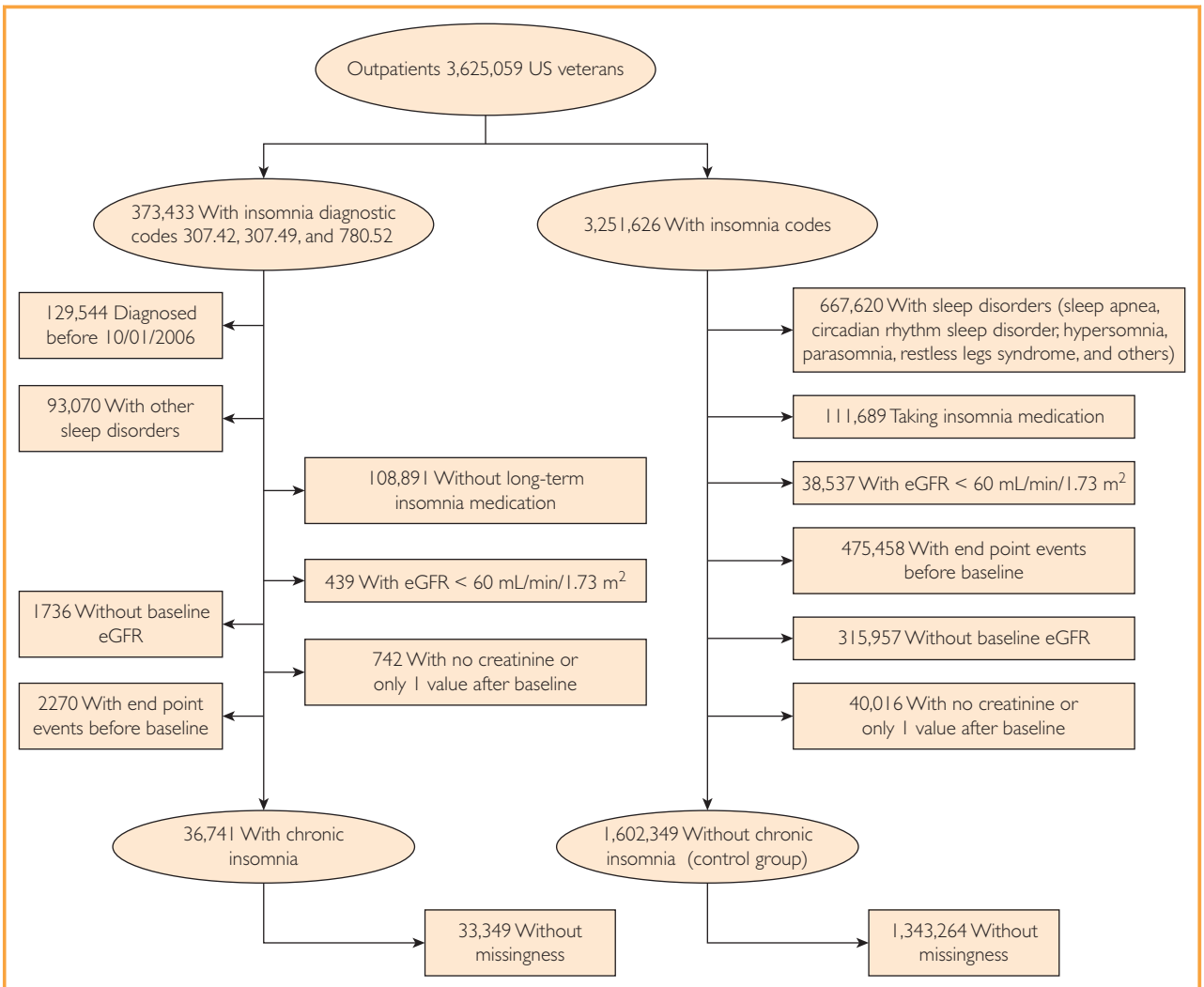

FIGURE 1. Cohort definition: Algorithm used to define the study cohort. eGFR = estimated glomerular filtration rate.

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restless legs syndrome, and other sleep disorders using *ICD-9* codes defined by *ICSD-3*) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org), we identified 36,741 patients with incident chronic insomnia after October 1, 2006. The date of the chronic insomnia diagnosis was defined as the date of cohort entry for this group, and patients who reached a study end point before this date were excluded. The median elapsed time from entry into the parent (RCAV) cohort to the date of diagnosis of insomnia was 3.28 years (interquartile range [IQR], 2.2-4.6 years). Compared with the excluded patients, patients with chronic insomnia had a lower prevalence of most comorbid conditions (data not shown). We identified a comparison group without chronic insomnia (control group) by excluding patients with any kind of sleep disorder or long-term use of insomnia medications. To make the control group more comparable with the chronic insomnia group, their cohort entry date was also delayed (relative to the original entry date in the RCAV cohort) by the median elapsed time mentioned above (3.28 years), and we excluded patients who reached an end point before this date. The baseline characteristics for time-dependent variables (eGFR, body mass index [BMI; calculated as the weight in kilograms divided by the height in meters squared], and blood pressure) were redefined at the new cohort entry date for both groups. After excluding individuals without serum creatinine measurements within 180 days of the cohort entry date and who had only 1 serum creatinine measurement during the entire follow-up period, our final cohort consisted of 1,639,090 patients: 36,741 with chronic insomnia and 1,602,349 in those without chronic insomnia.

Patient Characteristics and Study Outcomes

Information on comorbidities was extracted from the VA Medical SAS Inpatient and Outpatient datasets[21] using *ICD-9* diagnosis and procedure codes and Current Procedural Terminology codes. Patients' demographic characteristics, socioeconomic status (marital status and income), chronic pain, BMI, and blood pressure were obtained from the VA Corporate Data Warehouse. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[22] on the basis of the serum creatinine levels extracted from VA Corporate Data Warehouse LabChem data files.[23] We used the respective means of all eGFR, BMI, and blood pressure recordings within 180 days of the new cohort entry date as baseline values for these variables. For patients without any BMI or blood pressure measured during this time period, we used the last available measurement preceding the baseline date. Information on race was cross-referenced with data obtained from Medicare through the VA Medicare Data Merge Initiative.[24] Data on medication exposure were collected from VA pharmacy dispensing records.[25] Information on all-cause mortality was obtained from the VA Vital Status Files that contain dates of death up to July 26, 2013, from all available sources in the VA system. Information on end-stage renal disease (ESRD) was obtained from the United States Renal Data System up to September 13, 2011. Information on mental health encounters was based on VA mental health clinical service codes and frequency rank (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). Chronic pain scale was defined as a score of greater higher than 5 on the pain scale in at least 3 outpatient encounters.

Statistical Analyses

Descriptive analyses were performed using mean ± SD, median (IQR), and proportion (percentage), as appropriate. Because of the large size of the cohort, all patient characteristics were statistically significantly different ($P<.001$) between patients with and without chronic insomnia, and hence we regarded them as considerable differences only if they were biologically meaningful. Event rates and the corresponding 95% CIs were calculated using the patient-year (PY) approach for mortality, incident eGFR less than 45 mL/min per 1.73 m^2, and ESRD. Cox proportional hazards regression models with adjustment for potential confounders were used for examining the association of chronic insomnia with all-cause mortality, ESRD, and incidence of eGFR 45 mL/min per 1.73 m^2 or less. The association of insomnia with rapid kidney

function decline (defined as eGFR slopes <-3.0 mL/min per 1.73 m^2 per year)[26] was examined using logistic regression models. Patients were followed from the date of cohort entry until death or were censored at the date of the last health care encounter documented in the VA Vital Status Files or on July 26, 2013. For ESRD analyses, follow-up lasted until the first event date, death, last encounter, or September 13, 2011. The eGFR slopes of the insomnia group were estimated using a linear mixed effects model with random intercept and slope based on all available serum creatinine levels after the date of insomnia diagnosis. The slopes of the control group were estimated using all available serum creatinine levels from the date of cohort entry to the end of follow-up.

The effect of potential confounders on outcomes was analyzed by sequential multivariable adjustments including baseline age (model 1), baseline eGFR, sex, race (model 2), BMI, baseline blood pressure (model 3), chronic pain, comorbid conditions (cardiovascular disease, cerebrovascular disease, hypertension, congestive heart failure, malignant neoplasm, liver disease, chronic lung disease, peripheral artery disease, peptic ulcer, human immunodeficiency virus, diabetes, and the Deyo-modified Charlson comorbidity index[27]), mental health encounters, and use of antihypertensive drugs from baseline until the end of follow-up (model 4). A propensity score–matched cohort was created using a 1:1 nearest-neighbor matching without replacement after calculating the propensity scores for the likelihood of presence vs absence of chronic insomnia by using logistic regression models involving all of the above-mentioned variables. Differences between variables were examined by calculating standardized differences, and values less than 0.1 were considered acceptable for matching. We performed subgroup analyses to examine effect modification by prespecified demographic and comorbid characteristics.

Data were mainly missing on race (147,874 patients; 9.0%) and income (111,288 patients; 6.8%); 11.7% (191,138) of patients have 1 missing value, but only 4.4% (71,339) of patients have missing values for more than 1 variable. Eighty-four percent of patients had complete information available for the final multivariable model (model 4). Because of the relatively low proportion of missingness in the main multivariable model, missing data were not imputed. Adjustment for socioeconomic characteristics was performed only in sensitivity analyses because of the relatively higher proportion of missingness for income data. Statistical analyses were performed using Stata/MP version 14 (StataCorp LLC). The study was approved by the institutional review boards of the Memphis VA Medical Center and the Long Beach VA Medical Center.

RESULTS

Overall, 93.4% (1,530,823) of patients were male and 70.0% (1,147,936) were white. The mean baseline age of patients in the chronic insomnia group vs those in the control group was 58.9±13.8 years vs 63.3±13.4 years, and the mean estimated GFR was 84.1±16.4 mL/min per 1.73 m^2 vs 81.0±16.4 mL/min per 1.73 m^2. The baseline characteristics are summarized in the Table. Patients with chronic insomnia were younger, but there were no major differences in comorbidities between the 2 groups, except that more patients with chronic insomnia had chronic pain, received mental health services, and received antihypertensive therapy.

Renal Outcomes

The durations of follow-up for the different renal end points are presented in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org). Overall, 0.07% (1134) of the entire cohort reached ESRD (event rate, 0.24 events per 1000 PY; 95% CI, 0.23-0.25 events per 1000 PY), with 22 events in patients with insomnia (event rate, 0.22 events per 1000 PY; 95% CI, 0.14-0.33 events per 1000 PY) and 1112 events in control patients (event rate, 0.24 events per 1000 PY; 95% CI, 0.23-0.25 events per 1000 PY). Moreover, 7.91% of patients had progression to eGFR 45 mL/min per 1.73 m^2 or less (event rate, 18.77 events per 1000 PY; 95% CI, 18.67-18.88 events per 1000 PY), with 3201 events in patients with chronic insomnia (event rate, 20.57 events per 1000 PY; 95% CI, 19.87-21.30 events per 1000 PY) vs 126,472 events in control patients (event rate, 18.73 events per 1000 PY; 95% CI, 18.63-18.84 events per 1000 PY). Furthermore, 5.62% of the entire cohort displayed rapid kidney function decline, with 2226 events

(6.06%) in patients with chronic insomnia vs 89,916 events (5.61%) in control patients. The median kidney function decline in insomnia patients vs control patients was −0.3 (IQR, −1.1 to 0.6) mL/min per 1.73 m^2 per year vs −0.3 (IQR, −1.1 to 0.4) mL/min per 1.73 m^2 per year. Compared with the control group, the insomnia group had a significantly higher risk of incident eGFR less than or equal to 45 mL/min per 1.73 m^2 and rapid loss of kidney function, but not of incident ESRD. (Figure 2 and Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). The multivariable-adjusted hazard ratio for ESRD, eGFR 45 mL/min per 1.73 m^2 or less, and rapid loss of kidney function was 1.25 (95% CI, 0.81-1.93), 1.39 (95% CI, 1.34-1.44), and 1.07 (95% CI, 1.03-1.12), respectively. These associations remained unchanged after adjustment for socioeconomic status and in subgroup analyses. Similarly, most results were consistent in the examined subgroups, except that young people or people with hypertension had an increased risk of all 3 renal outcomes. In propensity score–matched groups, the associations with 3 renal outcomes have not substantially changed (Supplemental Figures 1, 2, and 3, available online at http://www.mayoclinicproceedings.org).

TABLE. Baseline Characteristics of the Chronic Insomnia Group vs Control Group[a,b,c]

Characteristic	Insomnia group (n = 36,741)	Control group (n = 1,602,349)
Age (y)	58.9±13.8	63.3±13.4
Sex: male	32,985 (89.8)	1,497,838 (93.5)
Race: white	28,090 (76.5)	1,119,846 (69.9)
Baseline eGFR (mL/min per 1.73 m^2)	84.1±16.4	81.0±16.4
SBP (mm Hg)	130±13	131±14
DBP (mm Hg)	77±9.0	76±9.7
BMI (kg/m^2)	28.3±5.0	28.6±5.2
CCI	0 (0-1)	0 (0-1)
CHF	704 (1.9)	35,353 (2.2)
Cardiovascular disease	3088 (8.4)	157,729 (9.8)
Cerebrovascular disease	1537 (4.2)	79,276 (5.0)
Malignant neoplasm	2789 (7.6)	136,817 (8.5)
Liver disease	445 (1.2)	11,838 (0.7)
Lung disease	6002 (16.3)	221,024 (13.8)
Diabetes	6270 (17.1)	348,062 (21.7)
Hypertension	19,064 (51.9)	928,677 (58.0)
Peripheral artery disease	1457 (4.0)	68,848 (4.3)
HIV	320 (0.9)	10,581 (0.7)
Antihypertensive medication	30,703 (83.6)	1,250,459 (78.0)
Chronic pain	16,314 (44.4)	495,385 (30.9)
Mental health encounters	24,511 (66.7)	566,384 (35.4)

[a]BMI = body mass index; CCI = Deyo-modified Charlson comorbidity index; CHF = congestive heart failure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; SBP = systolic blood pressure.
[b]Data are presented as mean ± SD, as median (interquartile range), or as No. (percentage).
[c]The *P* values for between-group differences in each listed variable are <.001.

Mortality

Over a median follow-up period of 4.76 years (IQR, 0.003-6.81 years), 11.19% of cohort died (mortality rate, 25.5 cases per 1000 PY; 95% CI, 25.4-25.6 cases per 1000 PY), with 3730 deaths in the insomnia group (23.2 cases per 1000 PY; 95% CI, 22.5-24.0 cases per 1000 PY) and 179,765 deaths in the control group (25.6 cases per 1000 PY; 95% CI, 25.5-25.7 cases per 1000 PY). Compared with control patients, patients with chronic insomnia did not have a higher risk of all-cause mortality after multivariable adjustments (multivariable-adjusted hazard ratio for all-cause mortality associated with chronic insomnia, 1.00; 95% CI, 0.97-1.03; *P*=.99) (Supplemental Table 3). The results were similar after adjustment for socioeconomic status (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org). The association between chronic insomnia and mortality was consistent in propensity score–matched analyses. In subgroup analyses, several patient characteristics modified the association between chronic insomnia and mortality, with insomnia being associated with lower mortality in older patients and patients with preexisting coronary artery disease and with higher mortality in patients with higher BMI (Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this large cohort of US veterans, we examined the association of chronic insomnia with all-cause mortality, incidence of eGFR 45 mL/min per 1.73 m^2 or less, ESRD, and rapid loss of kidney function. Chronic insomnia was associated with a higher risk of incidence of eGFR 45 mL/min per 1.73 m^2 or less and rapid loss of kidney function, even after accounting for measured confounders. The association of insomnia with

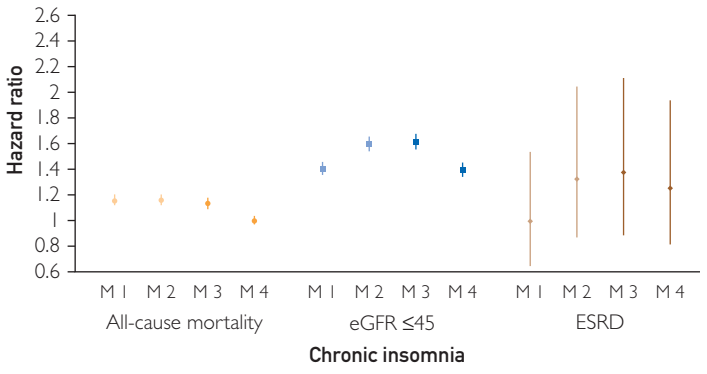

FIGURE 2. Associations between chronic insomnia and adverse outcomes: Multivariable-adjusted hazard ratios for associations between chronic insomnia and all-cause mortality, incidence of eGFR 45 mL/min per 1.73 m^2 or less, and ESRD. Model 1: adjusted for age; model 2: model 1 plus adjustments for sex, race, and the baseline eGFR; model 3: model 2 plus adjustments for systolic blood pressure, diastolic blood pressure, and body mass index; model 4: model 3 plus adjustments for comorbidities (cardiovascular disease, cerebrovascular disease, hypertension, congestive heart failure, malignant neoplasm, liver disease, chronic lung disease, peripheral artery disease, peptic ulcer, human immunodeficiency virus, diabetes, and Deyo-modified Charlson comorbidity index), pain scale, mental disorders, and antihypertensive medication, and all-cause mortality. eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease.

incident ESRD was not statistically significant, but the number of ESRD events were very small.

To our knowledge, only a few previous studies have examined the association of sleep disorders with renal outcomes and none of them studied the effect of strictly defined chronic insomnia on renal end points.[28] Shorter sleep duration was found to be associated with faster renal function decline[16] in the American Nurses' Health Study, but the study was based on self-reported insomnia symptoms. Similarly, a Japanese study found that sleeping for a shorter duration did not increase the risk of CKD overall but it increased the risk significantly in shift workers.[29] Another observational study based on the Taiwan National Health Insurance Database also reported that nonapnea sleep disorders (including most types of sleep disorders, not just chronic insomnia) were associated with a higher risk of CKD[17] and a higher incidence of acute kidney injury.[30] Our study is the first to examine the association between primary chronic insomnia and adverse renal outcomes.

However, the lack of increased risk of mortality reported in our study supports the results from previous studies, which described an association between sleep disorders and a higher risk of cardio- and cerebrovascular events[31] or mortality.[32] A meta-analysis from 15 studies performed in European countries and in the United States reported that difficulty in initiating sleep, maintaining sleep, or having nonrestorative sleep was associated with a higher risk of cardio- and cerebrovascular events.[12] However, the significant association between sleep disorders and mortality or cardio- and cerebrovascular disease incidence was highly correlated with sleep duration.[33] Both shorter and longer sleep durations were associated with a higher risk of clinical events compared with a sleep duration of 7 to 9 hours. The different results for the association between chronic insomnia and all-cause mortality in our cohort may be due to differences in patient populations and differences in available data used to adjust for potential confounding.

The mechanisms of action that could explain the association between chronic insomnia and CKD incidence and progression are complex. Insomnia could have an indirect effect on kidney function by causing or worsening the metabolic syndrome or by worsening hypertension and diabetes. Insomnia symptoms have been associated with worse metabolic abnormalities in several previous studies,[34-36] although some studies indicated that only certain types of insomnias (eg, difficulty in maintaining sleep[37]) had marked effects on the metabolic syndrome whereas other types of insomnia symptoms, such as early morning awakening,[36] displayed no significant association.

In addition, chronic insomnia is highly correlated with chronic stress because stress could be both a cause and a consequence of insomnia. Chronic insomnia results in overactivation of the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system,[10] which is supported by our finding that patients with chronic insomnia had a higher prevalence of mental disorders and chronic pain. The resulting elevated glucocorticoid and epinephrine/norepinephrine levels could cause disorders in glucose metabolism[38] or other endocrine systems,[39] which may result in worsening

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obesity[40] and diabetes[41,42] or cardiovascular tension,[43] which could be manifested as tachycardia or hypertension. Consequently, either diabetes or hypertension could damage the kidney and lead to worsening kidney function.

Our study has limitations that need to be acknowledged. Our cohort was defined using *ICD-9* codes and medication use, and hence we could not determine sleep duration and the type of insomnia. We also could not verify whether patients with chronic insomnia underwent polysomnography to determine which sleep stage was abnormal. We examined male US veterans managed in the VA health care system, and hence our cohort may not be representative of the general population. We adjusted for known confounders, but we cannot rule out the effect of unmeasured confounders. We were unable to account for the presence or severity of proteinuria because of its extensive missingness. We used a stringent definition for chronic insomnia, which resulted in the exclusion of a large number of individuals who did not fit the predefined criteria. Because medication use was part of our criteria, it is possible that the detected associations were a result of the applied medications, and not insomnia per se.[44] To differentiate medication effects from those of insomnia, one would need an assessment of the effectiveness of medication regimens in relieving insomnia, which would require prospective assessments. We did not have information on cause-specific deaths and hence we are unable to confirm whether most deaths were related to cardio- or cerebrovascular events. Consequently, it is possible that the lack of an association between chronic insomnia and all-cause mortality was due to a preponderance of deaths with mechanisms that cannot be attributed to insomnia-related physiological changes.

CONCLUSION

Chronic insomnia is significantly associated with a higher risk of incident eGFR 45 mL/min per 1.73 m^2 or less and rapid loss of kidney function. Randomized controlled trials are warranted to investigate the clinical effects of various interventions used to treat chronic insomnia on these outcomes.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **ESRD** = end-stage renal disease; ***ICD-9*** = *International Classification of Diseases, Ninth Revision*; ***ICSD-3*** = *International Classification of Sleep Disorders-Third Edition*; **IQR** = interquartile range; **PY** = patient-year; **RCAV** = Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease; **VA** = Veterans Affairs

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Potential Competing Interests: Drs Kovesdy and Kalantar-Zadeh are employees of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the authors' and do not represent the official opinion of the Department of Veterans Affairs.

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