Original Article

Association of insomnia and short sleep duration, alone or with comorbid obstructive sleep apnea, and the risk of chronic kidney disease

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Abstract

Study Objectives: Obstructive sleep apnea (OSA), sleep fragmentation, and short sleep duration (SD) have been associated with chronic kidney disease (CKD). However, these potential mechanisms for CKD have not been compared in the same cohort. This study investigated the independent and combined impact of OSA and insomnia with short sleep duration on the risk of CKD progression in a sleep clinic population.

Methods: In a cross-sectional study design, adults with suspected OSA completed an overnight sleep study and a questionnaire that included the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI). They also provided blood and urine samples for measurement of the glomerular filtration rate and urine albumin:creatinine ratio, from which the risk of CKD progression was determined.

Results: Participants ($n = 732$, 41% female, 55 ± 13 years) were categorized into four groups: no/mild OSA without insomnia (NM-OSA, $n = 203$), insomnia with SD without OSA (Insomnia-SD, $n = 104$), moderate-to-severe OSA without insomnia (MS-OSA, $n = 242$), and comorbid insomnia and OSA with SD (COMISA-SD, $n = 183$). After stratification, 12.8% of NM-OSA, 15.4% of Insomnia-SD, 28.9% of MS-OSA, and 31.7% of the COMISA-SD participants had an increased risk of CKD progression. Compared to NM-OSA, the odds ratio (OR) for an increased risk of CKD progression was not increased in Insomnia-SD (OR 0.95, confidence interval [CI]: 0.45–1.99) and was increased to the same degree in MS-OSA (OR 2.79, CI: 1.60–4.85) and COMISA-SD (OR 3.04, CI: 1.69–5.47). However, the ORs were similar between the MS-OSA and COMISA-SD groups across all statistical models ($p \geq .883$).

Conclusions: In a sleep clinic population, insomnia with short sleep duration does not increase the risk of CKD progression; nor does it further increase the risk of CKD progression associated with moderate-to-severe OSA.

Statement of Significance

Chronic kidney disease (CKD) is a common global health concern that is associated with increased cardiovascular morbidity and mortality. Obstructive sleep apnea (OSA), sleep fragmentation, and short sleep duration have individually been associated with CKD progression, but their relative contributions and interaction have not been assessed in the same cohort. Using conventional measurements of kidney function, we estimated the risk of CKD in a sleep clinic cohort of 732 patients and found that insomnia with short sleep duration did not increase the risk of CKD progression; nor does it further increase the risk of CKD progression associated with moderate-to-severe OSA. These findings suggest that OSA is the predominant sleep risk factor for CKD.

Introduction

Chronic kidney disease (CKD) is a common global health burden [1]. It is found in more than 10% of the adult population and is a major risk factor for cardiovascular disease [2–4]. Progression of CKD to end-stage kidney disease (ESKD), requiring renal function replacement with chronic dialysis or kidney transplantation, has significant implications for individual patients and healthcare systems [5–7]. The predominant causes of CKD are hypertension, diabetes, and glomerular disease [8]. However, CKD may progress despite optimal treatment of these underlying conditions [9] which highlights the need to consider additional factors such as comorbid medical conditions that may contribute to this. One potential candidate is obstructive sleep apnea (OSA) which is very common in the general population [10] and even more prevalent in patients with CKD [11]. Studies have shown that OSA is independently associated with an increased prevalence [12, 13] and incidence of CKD [14] and, more recently, we reported that OSA is an independent risk factor for CKD progression [15].

One mechanism through which OSA contributes to the pathogenesis of CKD is exposure to intermittent hypoxemia during sleep. Experimental animal models have shown that hypoxemia can cause renal tissue hypoxia [16], activation of the renal sympathetic nervous system and changes in renal hemodynamics [17], all of which can cause kidney injury. Furthermore, tubulointerstitial injury due to renal tissue hypoxia is considered to be the best predictor of progression to ESKD [18]. Human studies have also found associations between nocturnal hypoxemia due to OSA and physiologic changes in the kidney, including glomerular hypertension and activation of the renin–angiotensin system [19, 20]. Consequently, it is not surprising that large human cohort studies have shown an association between nocturnal hypoxemia and CKD [15, 21].

In addition to OSA and intermittent hypoxemia, nonrespiratory sleep characteristics have also been associated with adverse renal outcomes. Studies in patients with CKD have reported positive associations between short sleep duration and sleep fragmentation and CKD progression [22], short sleep duration and accelerated decline in the estimated glomerular filtration rate (eGFR) [23], short duration and poor sleep quality and progression to ESKD [24], and short sleep duration with an increased risk of death [25]. The combination of insomnia and short sleep duration has been identified as a unique phenotype [26] that is associated with an increased risk of cardiovascular disease [27]; the proposed underlying mechanisms include dysregulation of the hypothalamic–pituitary–adrenal axis [28] and glucose metabolism [29], and alterations in cardiovascular autonomic control [30]. These mechanisms, in addition to renal sympathetic nervous system activation [31], would also be deleterious to the kidney.

Although it is possible that both OSA and nonrespiratory mechanisms, such as insomnia and short sleep duration, modulate the relationship between sleep and kidney function, there have been no head-to-head comparisons of their contributions within the same cohort. We addressed this in the current study by determining if insomnia with short sleep duration (Insomnia-SD) increases the risk of CKD progression and if the association between OSA and the risk of CKD progression reported in our recent study [15] was further increased by comorbid insomnia with short sleep duration (COMISA-SD).

Methods

The study was performed on the cohort of patients we have previously investigated for the association between OSA and the risk of CKD progression [15] who met our criteria for categorization into four distinct clinical phenotypes as outlined below.

Individuals ≥18 years of age referred to five Canadian academic sleep centers for suspected OSA were recruited between July 2016 and September 2021 and enrolled in the Canadian Sleep and Circadian Network's (CSCN) adult OSA observational cohort database. The study was performed according the *Declaration of Helsinki* and approved by the Conjoint Health Research Ethics Board of the University of Calgary (REB16-0211), the Biomedical Research Ethics Board of the University of Saskatchewan (BIO-REB16-106), the University of British Columbia Clinical Research Ethics Board (H16-00422), the McGill University Health Centre (MEO-10-2019-4718), and the Institut Universataire de Cardiologie et de Pneumologie de Quebec at Université Laval (MP-10-2018-2938). All participants were informed of study requirements prior to providing written informed consent.

Study protocol

OSA was diagnosed by unattended home sleep apnea testing (HSAT) at the University of Calgary (UC) and Université Laval, and by in-laboratory polysomnography (PSG) at the University of Saskatchewan (US), University of British Columbia (UBC), and McGill University. Following enrollment in the CSCN adult OSA observational cohort all participants completed a comprehensive sleep and medical history questionnaire and provided a venous blood sample and midstream urine sample prior to any treatment for OSA. Participants were excluded from the current study if they did not answer all questions related to medical history of renal function included in the sleep questionnaire, did not provide both a venous blood sample and urine sample, were on dialysis or had a prior kidney transplant.

Home sleep apnea testing HSAT was performed using monitors validated against PSG [15]. These included the Remmers Sleep Recorder (Sagatech, Calgary, AB, Canada), ApneaLink Air (Resmed, San Diego, CA), Apnea Risk Evaluation System (ARES, SleepMed, Kennesaw, GA), Embletta MPR Sleep System (Natus, Middleton, WI), and the Alice PDx (Philips Healthcare, Markham, ON, Canada). HSAT monitors record arterial oxyhemoglobin saturation using pulse oximetry (SpO_2), respiratory airflow via nasal cannula connected to a pressure transducer, snoring via a microphone and sleep position (supine/not supine) from an accelerometer. For all HSAT monitors, the SpO_2 signal is analyzed using proprietary scoring algorithms and the oxygen desaturation index (ODI) was calculated as the number of times SpO_2 decreased by ≥4% divided by the total time of oximetry recording. Mean SpO_2 and the duration when SpO_2 was <90% (T90) were also indexed to the total oximetry recording time. All HSATs were reviewed and interpreted by a sleep physician.

Polysomnography PSG was performed according to American Academy of Sleep Medicine (AASM) guidelines [32]. Recordings included electroencephalography (channels: C3, C4, M1, M2, O1, O2), bilateral electro-oculograms, submental electromyograms (EMG) surface electrodes, bilateral tibialis anterior EMG, airflow using nasal pressure and oral thermistor, chest and abdominal

respiratory efforts via inductance plethysmography and finger SpO_2. All channels were continuously recorded at AASM recommended frequencies [32] or higher and saved electronically (Sandman, Tyco Healthcare, Kanata, ON, Canada; Sleepware G3, Philips Healthcare, Amsterdam, Netherlands; or Polysmith, Nihon Kohden, Irvine, CA) for subsequent manual scoring by experienced registered polysomnographic technologists according to AASM criteria [32].

Sleep questionnaire

The sleep questionnaire included questions regarding demographics (age, height, weight, and sex), lifestyle (cigarette smoking, caffeine, and alcohol consumption), medical history, comorbidities, medications, sleep schedule, sleep-related symptoms (e.g. snoring and witnessed apneas), and coexisting sleep disorders of insomnia and restless legs syndrome (RLS). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) [33] and daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [34].

Presence and severity of insomnia symptoms were determined using the Insomnia Severity Index (ISI) [35]. The ISI consists of five questions related to the severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep patterns, the degree to which sleep problems interfere with daily functioning, the noticeability of sleep problems to others and the degree of worry or distress a patient has about their sleep problems. The total score ranges from 0 to 28 with a score of 0–7 indicating no clinical insomnia; 8–14 indicating subthreshold insomnia; 15–21 indicating moderate insomnia; and 22–28 indicating severe insomnia. As the ISI total score encompasses symptoms common to both insomnia and OSA, a subscore (range: 0–12) was also calculated using the first three questions on the ISI to assess symptoms unique to insomnia; higher subscores were indicative of greater problems falling asleep, maintaining sleep, early awakenings, and returning to sleep [36, 37]. Additional questionnaire details, including the criteria for diagnosis and severity of RLS, are provided in Supplementary Material.

Measurement of eGFR and urine albumin:creatinine ratio

Venous blood samples were collected by trained phlebotomists into serum separator tubes and analyzed by local laboratories for serum creatinine, which was used to estimate glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [38] as recommended by international guidelines [39].

Midstream urine samples were collected into sterile containers and analyzed by local laboratories for albumin and creatinine levels. Urine albumin values were indexed to urine creatinine values to calculate the urine albumin:creatinine ratio (ACR). For urine albumin below detectable limits a value 0.01 mg/L lower than the detectable limit was used [40]. The lower limits of detection were 3 (UC and US), 5 (UBC and Laval), and 7 mg/L (McGill). For albumin values above the detectable limit a value 0.01 mg/L higher than the detectable limit was used.

Technical details employed by local laboratories to quantify serum creatinine, urine creatinine, and albumin are provided in Supplementary Material.

Data analyses

Each participant was categorized as having low, moderate, high, and very high risk of CKD progression based upon the intersection of their eGFR and ACR values in a heat map as outlined in the Kidney Disease: Improving Global Outcome guidelines [39]. Participants with an eGFR ≥60 mL/min/1.73 m² and an ACR <3 mg/mmol were categorized as low risk, while participants with an eGFR <60 mL/min/1.73 m², an ACR ≥3 mg/mmol, or both, were categorized as being at moderate-to-very high risk of CKD progression.

To harmonize HSAT and PSG measurements of OSA severity and nocturnal hypoxemia, ODI (based upon ≥4% desaturations), mean SpO_2, and T90 from PSG studies were indexed to the total recording time (time between "lights off" and "lights on"), which is the denominator used in HSAT. Based upon the ODI, participants were categorized as having no/mild OSA (0 ≤ ODI < 15), moderate OSA (15 ≤ ODI ≤ 30), and severe OSA (ODI > 30).

A PSQI >5 indicated poor sleep quality [33], and short sleep duration was defined as a self-report of ≤6 h of sleep/night in response to question 4 on the PSQI ("How many hours of actual sleep do you get at night?") [41]. An ESS >10 indicated excessive daytime sleepiness [34].

For our main analyses, participants with an ODI <15, an ISI total score <15, an ISI subscore <5, and a self-reported sleep duration >6 h/night were categorized as having no/mild OSA with no insomnia (NM-OSA); participants with an ODI <15, an ISI total score ≥15, an ISI subscore ≥5, and a self-reported sleep duration ≤6 h/night were categorized as having insomnia with short sleep duration (Insomnia-SD); participants with an ODI ≥15, ISI total score <15, an ISI subscore <5, and a self-reported sleep duration >6 h/night were categorized as having moderate-to-severe OSA with no insomnia (MS-OSA); and participants with an ODI ≥15, ISI total score ≥15, an ISI subscore ≥5, and a self-reported sleep duration ≤6 h/night were categorized as having COMISA-SD. We also modified our diagnostic criteria to address the fact that (1) short sleep duration does not accompany all cases of insomnia and COMISA and (2) the diagnostic criteria for COMISA are not standardized and do not always include the ISI subgroup score. Specifically, we stratified participants by removing the sleep duration criteria (alternative criteria #1), and additionally, the ISI subscore criteria (alternative criteria #2). All three sets of diagnostic criteria are summarized in Supplementary Table S1.

Self-reported medications were categorized according to their drug classification [42]. We specifically identified participants using nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs), since chronic use of these medications is associated with CKD progression [43, 44].

Statistical analyses

Participant characteristics and renal measures were compared across groups using one-way analyses of variance for continuous, normally distributed variables and Kruskal–Wallis H tests for continuous, nonnormally distributed variables. Post hoc group comparisons were adjusted using a Tukey–Kramer correction or the Dwass, Steel, Critchlow–Fligner analyses, respectively. Categorical variables and the proportion of participants at moderate-to-very high risk of kidney disease progression were compared using Fisher's exact test with post hoc group comparisons incorporating a Bonferroni correction.

Next, binary logistic regression analyses were used to estimate the odds ratios (ORs) for the Insomnia-SD, MS-OSA, and COMISA-SD groups to have moderate-to-very high risk of kidney disease progression compared to the NM-OSA group, which acted as the reference. ORs were first estimated adjusting for age, sex, and body mass index (BMI) (model 1); model 2 added adjustments for comorbidities; and model 3 added adjustment for use of NSAID and PPI medications. For OR analyses, missing data were handled using multiple imputation similar to our previous publication [15]. Briefly, assuming data were missing at random, 50 imputed datasets were created on which ORs were calculated independently and results pooled across all 50 analyses. Analyses were repeated on complete case analyses and on imputed data for our two alternative diagnostic criteria, as sensitivity analyses.

As in our prior study investigating the risk of CKD in OSA [15], primary analyses were performed using all participants. Secondary analyses excluded participants at moderate-to-very high risk of CKD progression with a history of reduced kidney function and/or proteinuria. Tertiary analyses additionally excluded participants with a history of common CKD risk factors (diabetes, hypertension, NSAID, or PPI use).

Analyses were performed with Statistical Analysis Software (v9.4, Cary, NC) and an alpha ≤0.05 was considered significant.

Data availability

Anonymized data will be made available to other qualified researchers on reasonable request to the corresponding author.

Results

Participant flow is shown in Figure 1. Briefly, 2100 participants were enrolled in the CSCN's adult OSA database between July 2016 and September 2021, of which 732 participants were included in our primary analyses, 690 in our secondary analyses, and 272 in our tertiary analyses. Complete case analyses were performed on 714, 672, and 263 participants, respectively.

Table 1 outlines characteristics across the four participant groups. Participants were predominantly white males with BMI increasing from the NM-OSA group to the COMISA-SD group. By study design, ODI was higher and nocturnal hypoxemia more severe in the MS-OSA and COMISA-SD groups compared to the NM-OSA and Insomnia-SD groups but were not different between the NM-OSA and Insomnia-SD groups and between the MS-OSA and COMISA-SD groups. Participants with Insomnia-SD reported greater daytime sleepiness and worse sleep quality than the NM-OSA and MS-OSA groups, who were not different in regard to these sleep indices. All sleep characteristics were more severe in the COMISA-SD group than NM-OSA and MS-OSA groups. Although the prevalence of RLS was higher in those with insomnia, the mean severity score and the proportion of patients with a severity score >5 (defined as RLS symptoms >2–3 times/week) were not different between the groups. The prevalence of hypertension, high cholesterol, and diabetes was similar between the MS-OSA and COMISA-SD groups and tended to be higher than the NM-OSA and Insomnia-SD groups. Insomnia-SD and COMISA-SD participants reported the highest prevalence of NSAID and PPI. Supplementary Table S2 shows the patient characteristics for the entire cohort.

Renal measures and risk of CKD progression

Measures of renal function are shown in Table 2. Serum creatinine was higher and eGFR tended to be lower in participants with MS-OSA and COMISA-SD compared to those with NM-OSA and Insomnia-SD. Although urine albumin was higher in the MS-OSA and COMISA-SD groups than the NM-OSA group, ACR was not different between the four groups. Following categorization of patients into low, moderate, high, and very high risk of CKD progression, based upon the intersection of their eGFR and ACR values, the prevalence of moderate-to-very high risk of CKD progression increased from 12.8% in the NM-OSA group, to 15.4% in the Insomnia-SD group, to 28.9% in the MS-OSA and 31.7% in the COMISA-SD groups (Figure 2). However, the prevalence was similar between the NM-OSA and Insomnia-SD groups, and between the MS-OSA and COMISA-SD groups (*p* = 1.0 for both comparisons). Similar results were observed after removing 42 participants at moderate-to-very high risk of CKD progression with a history of reduced kidney function and/or proteinuria (Figure 3).

When analyses were performed on imputed datasets, the greater prevalence of increased risk of CKD progression in the MS-OSA and COMISA-SD groups translated into ORs of 3.0 and 3.53 for being at moderate-to-very high risk of CKD progression compared to the NM-OSA group after adjusting for age, sex, and BMI (Table 3; primary analyses—model 1). Moreover, participants with MS-OSA and COMISA-SD remained with ORs of 2.79 and 3.04, respectively, after adding adjustments for comorbidities (primary analyses—model 2), and 2.79 and 3.04, respectively, after further adjustments for use of NSAID and PPI medications (primary analyses—models 3) compared to the NM-OSA group. Of note, the ORs for the Insomnia-SD group were not different to the reference group (*p* ≥ .956) and were also similar between the MS-OSA and COMISA-SD groups across all models (*p* ≥ .883). After removing participants at moderate-to-very high risk of CKD progression with a history of reduced kidney function and/or proteinuria, results were comparable with the MS-OSA and COMISA-SD groups maintaining ORs of 2.69 and 2.89, respectively, for being at moderate-to-very high risk of CKD progression in the fully adjusted model (secondary analyses—model 3). Similar to our primary analyses, the ORs between the MS-OSA and COMISA-SD groups were not different (*p* ≥ .991). In our tertiary analyses, the ORs were not significant for any of the three groups compared to the reference group. Results were equivalent in complete case analyses (Supplementary Table S3) and when analyses were repeated on larger cohorts based upon the alternative, less restrictive diagnostic criteria for insomnia and COMISA (*n* = 1043 and 1292, respectively; Supplementary Table S4).

In follow-up analyses, we investigated the interaction between OSA and insomnia on the risk of CDK progression by repeating our primary, secondary, and tertiary binary logistic regression analyses after dichotomizing participants based upon the presence of OSA (NM-OSA and MS-OSA) and the presence of insomnia with short sleep duration (no Insomnia-SD and Insomnia-SD). For analyses on both imputed and complete data, the interaction between OSA and insomnia-SD was not significant in all models (Supplementary Table S5).

Discussion

Although both OSA and nonrespiratory sleep characteristics have been implicated as potential mechanisms associated with
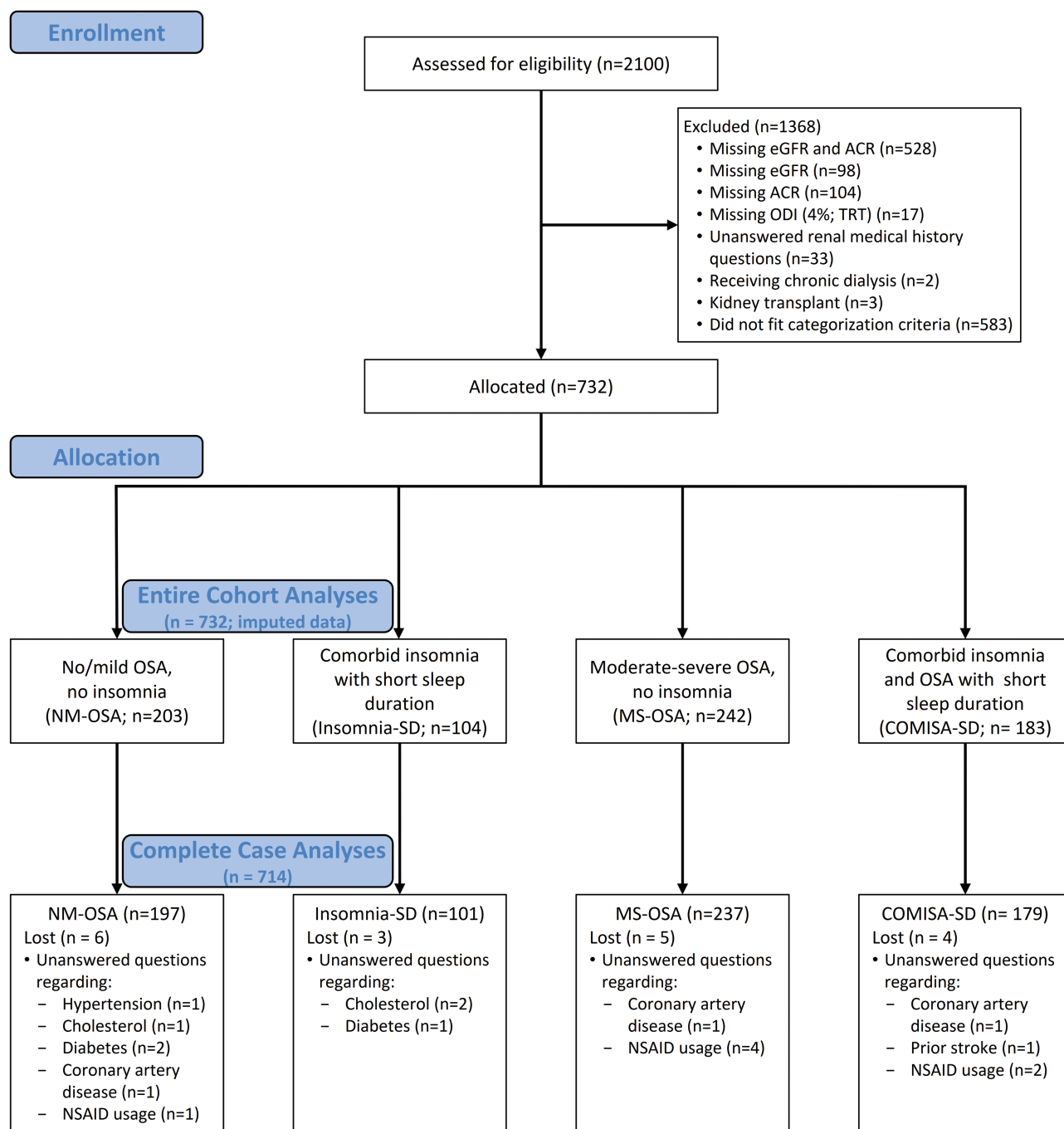
Figure 1. Flow of participants in our primary analyses.

the development of CKD, they have not been compared in the same cohort. The high prevalence of OSA and poor sleep in our cohort provided the opportunity to compare the contribution of these mechanisms to the risk of CKD progression. In our primary analysis, we found that OSA, reflected by an index of intermittent hypoxemia (ODI), was associated with an increased risk of CKD progression, as we previously reported in a larger number of patients from the same cohort [15] and comorbid insomnia with short sleep duration did not increase this risk further.

Our inclusion and exclusion criteria were designed to create four groups of patients with distinct clinical phenotypes that enabled us to compare exposure to respiratory and nonrespiratory

sleep characteristics. Our reference group (NM-OSA) had no or minimal OSA without features of insomnia or a history of short sleep duration. Furthermore, the level of nocturnal hypoxemia was similar to that of a control group without OSA that we have reported previously, which was not associated with changes in renal hemodynamics [19]. The Insomnia-SD group had poor sleep and short sleep duration of similar severity to that of the COMISA-SD group but without OSA or nocturnal hypoxemia. The group with moderate-to-severe OSA (MS-OSA) had significant nocturnal hypoxemia, which we have previously shown to cause adverse physiologic changes in the kidney [20], but did not have features of either insomnia or short sleep duration.

Table 1. Participant characteristics across groups[♭]

	NM-OSA	Insomnia-SD	MS-OSA	COMISA-SD	p
N	203	104	242	183	
Female, n (%)	88 (43.3)	65 (62.5)*	70 (28.9)*,†	78 (42.6)†,‡	<.001
Age (years)	54.6 ± 13.9	53.2 ± 13.1	55.9 ± 12.8	53.5 ± 11.2	.170
BMI (kg/m²)	29.5 ± 6.5	30.9 ± 6.7	35.1 ± 7.6*,†	38.0 ± 8.4*,†,‡	<.001
White, n (%)	178 (87.7)	84 (80.8)	200 (82.6)	154 (84.2)	.345
OSA severity					
ODI (4%, events/h; TRT)	5.7 ± 4.7	5.9 ± 4.6	38.1 ± 21.5*,†	42.0 ± 24.8*,†	<.001
Mean SpO₂ (%; TRT)	93.0 ± 2.8	92.5 ± 3.4	88.6 ± 4.4*,†	88.0 ± 4.4*,†	<.001
T90 (% TRT)	14.3 ± 25.7	13.4 ± 24.8	46.6 ± 34.9*,†	53.1 ± 33.9*,†	<.001
Daytime sleepiness and sleep quality					
ESS score	8.0 ± 4.6 (n = 197)	10.7 ± 5.6*	8.4 ± 4.7†	11.5 ± 5.4*,‡	<.001
ESS >10, n (%)	67 (34.0)	60 (57.7)*	96 (39.8)†	111 (61.0)*,‡	<.001
PSQI global score	5.3 ± 2.5 (n = 189)	13.3 ± 3.2* (n = 98)	5.5 ± 2.3† (n = 235)	13.4 ± 3.1*,‡ (n = 179)	<.001
PSQI >5, n (%)	109 (57.7)	98 (100.0)*	147 (62.6)†	179 (100.0)* ,‡	<.001
Sleep duration (h)	7.5 ± 0.8	5.0 ± 1.0*	7.7 ± 1.1†	4.9 ± 1.1*,‡	<.001
ISI total score	7.6 ± 3.6	19.0 ± 3.0*	7.9 ± 3.5†	19.7 ± 3.4*,‡	<.001
ISI subscore	2.0 ± 1.4	7.2 ± 1.7*	1.8 ± 1.4†	7.4 ± 1.8*,‡	<.001
RLS, n (%)	35 (17.4)	37 (36.3)*	44 (18.3)†	50 (27.5)	<.001
RLS severity	4.4 ± 1.4	4.9 ± 2.0	4.3 ± 1.7	5.2 ± 1.5	.057
RLS severity >5, n (%)	16 (45.7)	22 (59.5)	19 (43.2)	33 (66.0)	.097
Comorbidities					
Kidney disease, n (%)	10 (4.9)	9 (8.7)	18 (7.4)	15 (8.2)	.492
Proteinuria, n (%)	7 (3.4)	9 (8.7)	15 (6.2)	18 (9.8)	.060
Smoking					
Never smoker, n (%)	107 (52.7)	57 (54.8)	105 (43.6)	78 (42.6)	.063
Past smoker, n (%)	81 (39.9)	35 (33.7)	109 (45.2)	77 (42.1)	
Current smoker, n (%)	15 (7.4)	12 (11.5)	27 (11.2)	28 (15.3)	
Hypertension, n %	70 (34.7)	39 (37.5)	131 (54.1)*,†	100 (54.6)*,†	<.001
High cholesterol, n (%)	64 (31.8)	34 (33.3)	118 (48.8)*,†	85 (46.4)*	<.001
Diabetes, n (%)	17 (8.5)	14 (13.6)	52 (21.5)*	42 (23.0)*	<.001
Coronary artery disease, n (%)	14 (7.0)	6 (5.8)	30 (12.4)	16 (8.8)	.140
Heart failure, n (%)	10 (5.0)	3 (2.9)	14 (5.8)	4 (2.2)	.268
Atrial fibrillation, n (%)	23 (11.4)	9 (8.7)	15 (6.2)	9 (4.9)	.086
Past stroke, n (%)	9 (4.5)	2 (1.9)	12 (5.0)	4 (2.2)	.363
COPD, n (%)	10 (5.0)	6 (5.8)	18 (7.4)	6 (3.3)	.314
Asthma, n (%)	34 (16.9)	19 (18.3)	47 (19.5)	42 (23.0)	.511
Medications					
NSAIDs, n (%)	8 (4.0)	15 (14.4)*	15 (6.3)	21 (11.6)*	.003
PPIs, n (%)	32 (15.9)	28 (26.9)	44 (18.5)	60 (33.1)*,‡	<.001

Number (%), categorical variables (p value = χ²); mean ± SD, continuous variables (p value = ANOVA). COMISA-SD, comorbid insomnia and OSA with short sleep duration; COPD, chronic obstructive pulmonary disease; Mean SpO₂, mean arterial oxyhemoglobin saturation; ODI, oxygen desaturation index based upon 4% desaturations; RLS severity >5, symptom occur >2–3 times/week; T90, percentage of total recording time (TRT) with SpO₂ <90%. Bold typeface highlights the P values that are significant between the groups.

[♭]Sample sizes indicated for variables missing ≥5 participants.

*p < .05 versus NM-OSA (no/mild OSA, no insomnia).

†p < .05 versus Insomnia-SD (insomnia with short sleep duration).

‡p < .05 versus MS-OSA (moderate–severe OSA, no insomnia).

Table 2. Measures of kidney function across groups

	NM-OSA	Insomnia-SD	MS-OSA	COMISA-SD	p
N	203	104	242	183	
Serum creatinine (µmol/L)	76 (66.0, 88.0)	77.0 (63.0, 86.0)	83.5*,† (72.0, 95.0)	83*,† (70.0, 93.5)	<.001
eGFR (mL/min/1.73 m²)	91 (78, 98)	89 (77, 98)	84* (70, 97)	85 (72, 96)	.016
Urine albumin (mg/L)#	7.7 (5.0, 12.8)	9.0 (6.0, 15.1)	9.5* (5.0, 22.8)	10.0* (5.0, 34.5)	.010
Urine creatinine (mmol/L)	11.0 (6.4, 15.6)	11.8 (7.0, 16.9)	11.8 (7.1, 16.5)	11.0 (7.5, 16.2)	.844
ACR (mg/mmol)	0.8 (0.5, 1.6)	0.9 (0.5, 1.5)	1.1 (0.5, 2.2)	1.0 (0.5, 2.9)	.072

Median (interquartile range); p value = Kruskal–Wallis H. COMISA-SD, comorbid insomnia and OSA with short sleep duration; MS-OSA, moderate-to-severe OSA, no insomnia. Bold typeface highlights the P values that are significant between the groups.

#Urine albumin was below detectable limits in 96 participants.

*p < .05 versus NM-OSA (no/mild OSA, no insomnia).

†p < .05 versus Insomnia-SD (insomnia with short sleep duration).

Figure 2. Risk of CKD progression for participants with no/mild OSA and no insomnia (A: NM-OSA, *n* = 203), insomnia with short sleep duration (B: Insomnia-SD, *n* = 104), moderate-to-severe OSA and no insomnia (C: MS-OSA, *n* = 242), and COMISA with short sleep duration (D: COMISA-SD, *n* = 183). Colored boxes indicate the number (% of group) with low (green), moderate (yellow), high (orange), and very high (red) risk of CKD progression. Blue line surrounds the 12.8% of NM-OSA, 15.4% of Insomnia-SD, 28.9% of MS-OSA, and 31.7% of COMISA-SD who are at moderate-to-very high risk of kidney disease progression.

Risk of CKD progression: **Low risk** **Moderate risk** **High risk** **Very high risk**

Increased risk of CKD progression

A: NM-OSA

GFR Categories (ml/min/1.73m²)		Albumin:Creatinine Ratio		
		A1: Normal-to-Mild increase <3 mg/mmol	**A2: Moderate increase** 3-30 mg/mmol	**A3: Severe increase** >30 mg/mmol
G1: Normal to High	≥90	93 (46.7)	12 (6.0)	-
G2: Mild decrease	60-89	84 (42.2)	4 (2.0)	1 (0.5)
G3a: Mild-to-Moderate decrease	45-59	2 (1.0)	3 (1.5)	-
G3b: Moderate-to-Severe decrease	30-44	-	-	-
G4: Severe decrease	15-29	-	-	-
G5: Kidney Failure	<15	-	-	-

→ 11.1%

B: Insomnia-SD

GFR Categories (ml/min/1.73m²)		Albumin:Creatinine Ratio		
		A1: Normal-to-Mild increase <3 mg/mmol	**A2: Moderate increase** 3-30 mg/mmol	**A3: Severe increase** >30 mg/mmol
G1: Normal to High	≥90	42 (42.0)	6 (6.0)	-
G2: Mild decrease	60-89	46 (46.0)	2 (2.0)	-
G3a: Mild-to-Moderate decrease	45-59	3 (3.0)	1 (1.0)	-
G3b: Moderate-to-Severe decrease	30-44	-	-	-
G4: Severe decrease	15-29	-	-	-
G5: Kidney Failure	<15	-	-	-

→ 12%

C: MS-OSA

GFR Categories (ml/min/1.73m²)		Albumin:Creatinine Ratio		
		A1: Normal-to-Mild increase <3 mg/mmol	**A2: Moderate increase** 3-30 mg/mmol	**A3: Severe increase** >30 mg/mmol
G1: Normal to High	≥90	83 (36.9)	19 (8.4)	-
G2: Mild decrease	60-89	89 (39.6)	14 (6.2)	1 (0.4)
G3a: Mild-to-Moderate decrease	45-59	12 (5.3)	-	1 (0.4)
G3b: Moderate-to-Severe decrease	30-44	5 (2.2)	1 (0.4)	-
G4: Severe decrease	15-29	-	-	-
G5: Kidney Failure	<15	-	-	-

→ 21.3%

D: COMISA-SD

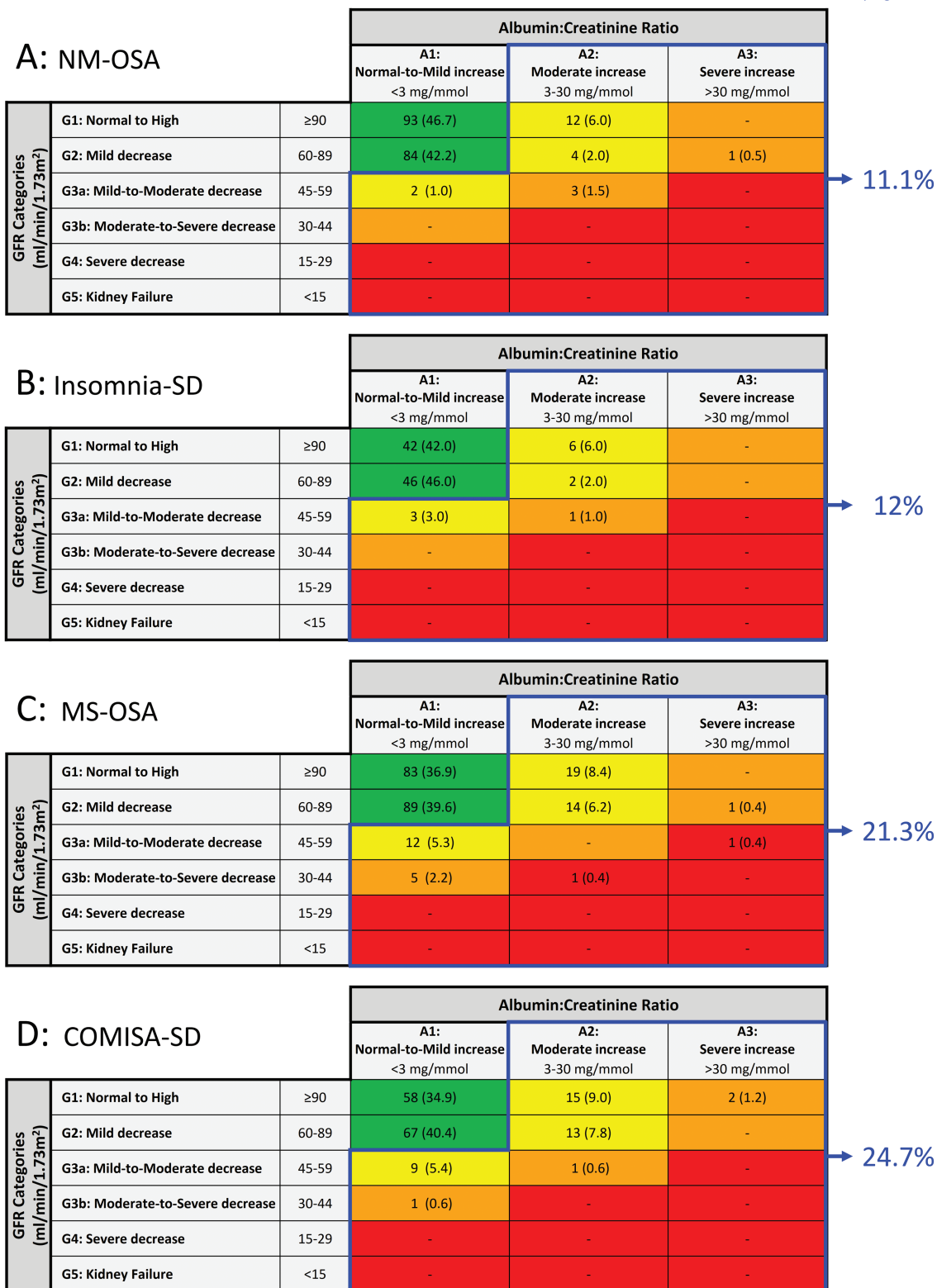| GFR Categories (ml/min/1.73m²)		Albumin:Creatinine Ratio		
		A1: Normal-to-Mild increase <3 mg/mmol	**A2: Moderate increase** 3-30 mg/mmol	**A3: Severe increase** >30 mg/mmol
G1: Normal to High	≥90	58 (34.9)	15 (9.0)	2 (1.2)
G2: Mild decrease	60-89	67 (40.4)	13 (7.8)	-
G3a: Mild-to-Moderate decrease	45-59	9 (5.4)	1 (0.6)	-
G3b: Moderate-to-Severe decrease	30-44	1 (0.6)	-	-
G4: Severe decrease	15-29	-	-	-
G5: Kidney Failure	<15	-	-	-

→ 24.7%

Figure 3. Risk of CKD progression for the participants with no/mild OSA and no insomnia (A: NM-OSA, *n* = 199), insomnia with short sleep duration (B: Insomnia-SD, *n* = 100), moderate-to-severe OSA and no insomnia (C: MS-OSA, *n* = 225), and COMISA with short sleep duration (D: COMISA-SD, *n* = 166) after exclusion of 42 participants at moderate-to-very high risk of CKD progression with a history of reduced kidney function and/or proteinuria. Colored boxes indicate the number (% of group) with low (green), moderate (yellow), high (orange), and very high (red) risk of CKD progression. Blue line surrounds the 11.1% of NM-OSA, 12% of Insomnia-SD, 21.3% of MS-OSA, and 24.7% of COMISA-SD participants who are at moderate-to-very high risk of kidney disease progression.

Table 3. ORs for moderate-to-very high risk of kidney disease in all participants[#]

	Model 1		Model 2		Model 3	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P
Primary analyses: all participants (n = 732)						
NM-OSA	*1.0*		*1.0*		*1.0*	
Insomnia-SD	1.20 (0.60–2.38)	.609	0.95 (0.46–1.97)	.889	0.95 (0.45–1.99)	.892
MS-OSA	3.00 (1.78–5.07)	**<.001**	2.79 (1.60–4.85)	**<.001**	2.79 (1.60–4.85)	**<.001**
COMISA-SD	3.53 (2.04–6.11)	**<.001**	3.04 (1.70–5.45)	**<.001**	3.04 (1.69–5.47)	**<.001**
Secondary analyses: participants without a history of kidney disease and/or proteinuria (n = 690)						
NM-OSA	*1.0*		*1.0*		*1.0*	
Insomnia-SD	1.05 (0.49–2.25)	.905	0.99 (0.46–2.15)	.980	1.00 (0.46–2.20)	.993
MS-OSA	2.90 (1.64–5.14)	**<.001**	2.69 (1.50–4.81)	**<.001**	2.69 (1.50–4.83)	**<.001**
COMISA-SD	3.20 (1.76–5.85)	**<.001**	2.87 (1.54–5.33)	**<.001**	2.89 (1.55–5.40)	**<.001**
Tertiary analyses: participants without CKD risk factors (diabetes, hypertension, NSAID, or PPI use; n = 272)						
NM-OSA	*1.0*		*1.0*			
Insomnia-SD	0.50 (0.12–2.05)	.332	0.50 (0.12–2.05)	.332	—	—
MS-OSA	1.64 (0.60–4.53)	.337	1.64 (0.60–4.53)	.337	—	—
COMISA-SD	2.23 (0.70–7.15)	.176	2.23 (0.70–7.15)	.176	—	—

Model 1: adjusted for age, sex, and BMI >30 kg/m^2. Model 2: model 1 + adjustments for medical history of kidney disease (not in secondary analyses) and proteinuria (not in secondary analyses), smoking, hypertension, high cholesterol, diabetes, coronary artery disease, heart failure, atrial fibrillation, and stroke. Model 3: model 2 + adjustments for use of NSAID and PPI medications (not applied to tertiary analyses). COMISA-SD, comorbid insomnia and OSA and short sleep duration; Insomnia-SD, insomnia with short sleep duration; MS-OSA, moderate–severe OSA, no insomnia; NM-OSA, no/mild OSA, no insomnia. Italic typeface indicates reference group. Bold typeface highlights the P values that are significant between the groups.
[#] Missing data in 15 participants added using multiple imputation.

Finally, the COMISA-SD had OSA and nocturnal hypoxemia of similar severity to the MS-OSA group, but also had features of severe insomnia and short sleep duration. Not surprisingly, the Insomnia-SD and COMISA-SD groups were more symptomatic with poorer sleep quality, reflected by the PSQI, and more severe daytime sleepiness, reflected by the ESS (Table 1). The prevalence of hypertension and diabetes was similar in the MS-OSA and COMISA-SD groups and greater than the reference group. The reason for the higher prevalence of NSAID and PPI medications in the Insomnia-SD and COMISA-SD groups is not clear but may be related to chronic pain and gastroesophageal acid reflux that are common in patients with insomnia [45]; although these medications may cause kidney injury, our statistical analysis controlled for this potential confounding effect.

Although there are currently no standardized diagnostic criteria for COMISA, we used the ISI to define our insomnia groups since this is an established questionnaire that has been widely used for this purpose [35]. We added the criterion of short sleep duration since that has been associated with CKD [22–24]; furthermore, the combination of insomnia with short sleep duration, which has been reported to have an adverse impact on cardiovascular outcomes [27], enabled us to maximize the exposure to sleep disruption and sleep loss. Despite this, we found no association between insomnia with short sleep duration and the risk of CKD progression either in isolation (Insomnia-SD) or with comorbid OSA (COMISA-SD). Of note, results were the same for the larger cohorts included in our two alternative diagnostic criteria for insomnia and COMISA that did not include short sleep duration (alternative criteria #1) and, additionally, the ISI subscore (alternative criteria #2; Supplementary Table S4). Furthermore, we observed no interaction between OSA and Insomnia-SD supporting the results of our original analyses that Insomnia-SD does not increase the risk of CKD progression in patients with moderate-to-severe OSA.

To date, there are no published data linking COMISA to CKD risk. However, sleep fragmentation measured objectively with wrist actigraphy, which is a common feature of chronic insomnia, has been associated with the progression of CKD [22]. In addition, both chronic insomnia [46] and COMISA [47] have been associated with hypertension and diabetes which are major risk factors for the development and progression of CKD [8]. Short sleep duration has also been associated with CKD risk [22–24] and with other comorbidities that are common causes of CKD, such as hypertension [48] and diabetes mellitus [49]. Furthermore, a recent systematic review and meta-analysis reported that the risk of hypertension and diabetes was higher when insomnia was accompanied by short sleep duration compared to normal sleep duration [50]. The mechanisms for these associations are not entirely clear but may include chronobiological alterations of the renin–angiotensin–aldosterone system and sympathetic nervous system activation [51]. A limitation in most of the prior studies reporting an association between nonrespiratory sleep indices and renal outcomes is that they did not control for the impact of coexisting OSA and nocturnal hypoxemia, either because they were not assessed or were not sufficiently severe [22–24].

This study also has limitations. First, our sample size was relatively small for our tertiary analysis which impacted the power of our statistical analysis and may explain the lack of an association between MS-OSA participants and an increased risk of CKD progression which we have reported previously in a larger cohort using a similar tertiary analysis [15]. Although our inclusion/exclusion criteria enabled us to create four distinct clinical phenotypes, some participants were excluded because their ISI values fell between the criteria we used. Secondly, the ISI is primarily used to assess the severity of sleep symptoms and is not a screening instrument for the diagnosis of insomnia per se. Thirdly, our measurement of sleep duration was based on patient self-report which is subjective and open to error [52]. An objective assessment of sleep duration with methodology such as actigraphy would have been preferable. However, many of the studies in the literature on sleep duration have used a similar

subjective measure to ours [23–25]. Fourthly, we did not include an insomnia with "healthy sleep" duration (i.e. >6 h/night) group or a COMISA with healthy sleep duration group in our analyses due to the small number of participants who met these criteria. However, our alternative criteria #1 analyses in which insomnia was defined regardless of sleep duration (Supplementary Table S1) does include these participants within the "Insomnia" and "COMISA" groups, respectively. Inclusion of these "healthy sleepers" did not change the ORs substantially for the Insomnia and COMISA groups (compared to the Insomnia-SD and COMISA-SD groups in our principal analyses), which indicates that sleep duration was not a major contributor to the estimated ORs for these groups. Finally, our assessment of the "risk of CKD progression" was based on a heat map populated by the intersection of eGFR and ACR values from a single time point for individual patients without longitudinal follow-up. This methodology was based on clinical practice guidelines authored by experts in nephrology that are widely used in the management of patients with CKD [39].

In summary, we found that insomnia with short sleep duration, either in isolation or with comorbid OSA, did not increase the risk of CKD in a sleep clinic population. Although the association between OSA and CKD has been established by multiple studies with different methodologies and study design, proof of causality is still lacking. The opportunity to prove causality will be facilitated by targeting the specific mechanisms responsible for this association. The results of this study suggest that the predominant mechanism responsible for patients with OSA to develop or exacerbate CKD is intermittent nocturnal hypoxemia. Consequently, correction of nocturnal hypoxemia is the critical intervention required to confirm a causal relationship between OSA and CKD and, potentially, to reduce the risk of CKD in these patients.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Authors' Contributions

Disclosure Statement

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