Original research

Multiple, objectively measured sleep dimensions including hypoxic burden and chronic kidney disease: findings from the Multi-Ethnic Study of Atherosclerosis

Chandra L Jackson,[1,2] Chizoba Umesi,[1,3] Symielle A Gaston,[1] Ali Azarbarzin,[4,5] Joseph Lunyera ,[6] John A McGrath,[7] W Braxton Jackson II,[7] Clarissa J Diamantidis,[3,6] Ebony Boulware,[3,6] Pamela L Lutsey ,[8] Susan Redline[4,5,9]

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For numbered affiliations see end of article.

Correspondence to
Dr Chandra L Jackson, Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA; Chandra.Jackson@nih.gov

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ABSTRACT

Background Poor sleep may contribute to chronic kidney disease (CKD) through several pathways, including hypoxia-induced systemic and intraglomerular pressure, inflammation, oxidative stress and endothelial dysfunction. However, few studies have investigated the association between multiple objectively measured sleep dimensions and CKD.

Methods We investigated the cross-sectional association between sleep dimensions and CKD among 1895 Multi-Ethnic Study of Atherosclerosis Sleep Ancillary Study participants who completed in-home polysomnography, wrist actigraphy and a sleep questionnaire. Using Poisson regression models with robust variance, we estimated separate prevalence ratios (PR) and 95% CIs for moderate-to-severe CKD (glomerular filtration rate <60 mL/min/1.73 m^2 or albuminuria >30 mg/g) among participants according to multiple sleep dimensions, including very short (≤5 hours) sleep, Apnoea–Hypopnoea Index and sleep apnoea-specific hypoxic burden (SASHB) (total area under the respiratory event-related desaturation curve divided by total sleep duration, %min/hour)). Regression models were adjusted for sociodemographic characteristics, health behaviours and clinical characteristics.

Results Of the 1895 participants, mean age was 68.2±9.1 years, 54% were women, 37% were white, 28% black, 24% Hispanic/Latino and 11% Asian. Several sleep metrics were associated with higher adjusted PR of moderate-to-severe CKD: very short versus recommended sleep duration (PR=1.40, 95% CI 1.06 to 1.83); SASHB (Box-Cox transformed SASHB: PR=1.06, 95% CI 1.02 to 1.12); and for participants in the highest quintile of SASHB plus sleep apnoea: PR=1.28, 95% CI 1.01 to 1.63.

Conclusions Sleep apnoea associated hypoxia and very short sleep, likely representing independent biological mechanisms, were associated with a higher moderate-to-severe CKD prevalence, which highlights the potential role for novel interventions.

Key messages

What is the key question?

► If any, what dimensions of sleep are associated with moderate-to-severe chronic kidney disease (CKD) in a multiethnic cohort of study participants in the USA?

What is the bottom line?

► Sleep apnoea-associated hypoxia and very short sleep, likely representing independent biological mechanisms, were associated with a higher moderate-to-severe CKD prevalence.

Why read on?

► Although poor sleep may contribute to CKD, a common condition affecting approximately 15% of adults in the USA, through several pathways (including hypoxia-induced systemic and intraglomerular pressure, inflammation, oxidative stress and endothelial dysfunction), few studies have investigated the association between multiple objectively measured sleep dimensions and CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a common condition, affecting approximately 15% of adults in the USA and is associated with high morbidity and mortality.[1] Insufficient sleep and sleep disturbances may be understudied contributors to the development and progression of CKD by contributing to its established risk factors like dyslipidaemia, hypertension and type 2 diabetes.[2] A meta-analysis and systematic review of 18 mostly cross-sectional studies among mainly Asian and European participants found a 77% increased odds of decreased kidney function and a dose-response relationship with increasing obstructive sleep apnoea (OSA) severity, defined largely by the Apnoea-Hypopnoea Index (AHI).[3] In addition to inflammation, oxidative stress and systemic endothelial dysfunction, intermittent hypoxia—a hallmark of OSA—may promote a rise in sympathetic tone and activation of the renin–angiotensin system causing systemic and intraglomerular pressure to rise.[4–6] OSA, which affects approximately 24% of US adults, has been reported to be prevalent among individuals with CKD (especially those with end-stage renal disease),[7 8] and individuals with OSA have been

shown to have a higher likelihood of reduced kidney function and increased prevalence of CKD.[9]

Other sleep disturbances have been less consistently associated with CKD.[2] For instance, a meta-analysis of nine observational studies found a positive but non-significant association between short sleep duration and both proteinuria and CKD.[10] An additional study concluded that wrist actigraphy-assessed short sleep duration and poor subjective sleep quality were associated with decreased kidney function over 10 but not 5 years.[11] Studies of other indices of disturbed sleep related to efficiency, fragmentation and insomnia are sparse. Distinct abnormal sleep dimensions may have both independent and shared biological pathways that lead to kidney dysfunction. For instance, short sleep duration has been shown to lead to sympathetic nervous system stimulation, less dipping of blood pressure during sleep and an imbalance of (as well as suboptimal responsiveness to) metabolic hormones.[2] Sleep fragmentation and low sleep efficiency are associated with an increase in time spent in lighter, less restorative stages of sleep and decreased time in slow wave sleep.[12] This may lead to decreased vagal tone and a reduction in nocturnal dipping of blood pressure, which is important in regulation of autonomic nervous system activity.[13 14]

While relatively few studies have investigated the relationship between sleep (especially across multiple dimensions) and CKD, very few include racial/ethnic minorities in the USA, despite these groups being generally more likely to experience both suboptimal sleep[15] and kidney dysfunction.[16] Furthermore, most studies were limited in their use of only one sleep dimension (eg, duration or OSA), and use of self-reported sleep data, which has measurement error.[17 18] To address these important gaps in the literature, we investigated the association between multiple polysomnography (PSG) and actigraphy-measured indices of sleep disturbances (eg, efficiency, fragmentation, insomnia symptoms, AHI and a novel, more sensitive measure of sleep apnoea-specific hypoxic burden (SASHB)) with moderate-to-severe CKD in a racially ethnically diverse US population. We hypothesised that sleep insufficiency and sleep disturbances are associated with a higher prevalence of CKD and the associations are strongest for sleep-associated hypoxia.

METHODS

Multi-Ethnic Study of Atherosclerosis

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA),[19] which started in 2000 to investigate the prevalence, incidence and progression of subclinical cardiovascular disease (CVD) in an ethnically diverse (39% white, 28% Black/African-American, 22% Hispanic/Latino and 12% Asian (predominately of Chinese descent; therefore, referred to as Chinese hereafter) sample of 6800 men and women ages 54–84 years. Of the 4077 participants approached to join the MESA Exam 5 Sleep Ancillary Study (conducted in conjunction but at approximately a median of 1 year after the cross-sectional MESA Exam 5 core exam (2010–2013)), 147 (3.6%) were ineligible (due to a history of positive airway pressure, oral appliance use or oxygen use) and 141 participants lived too far away to participate. Of the remaining 3789 participants, 2261 participated in the sleep examination. Our final analytic sample included 1895 participants with complete measurements on in-home PSG, a sleep questionnaire (including data on sleep apnoea and insomnia), estimated glomerular filtration rate (eGFR) and albuminuria. Participants also had 7-day wrist actigraphy (we analysed N=1862 with at least four valid days of wrist actigraphy).

Exposure ascertainment: poor sleep characteristics

In-home PSG

PSG was employed in participants' home using a 15-channel type 2 monitor (Somte System; Compumedics, Abbotsville, Australia) with trained staff members completing signal calibrations and checking impedance. The recording included electroencephalography (EEG), bilateral electrooculograms, bipolar ECG, a chin electromyography, thoracic and abdominal respiratory inductance plethysmography, finger pulse oximetry, airflow measured by thermocouple and nasal pressure cannula, and bilateral limb movements. Data were scored at a centralised reading centre at Brigham and Women's Hospital by trained technicians using standardised guidelines.[20] Quantitative assessments of overnight hypoxemia levels, apnoeas as well as hypopnoeas, and sleep stage distributions were made. Sleep stages and EEG (cortical) arousals were scored according to published guidelines that were adapted from the Sleep Heart Health Study.[21–23]

Apnoeas were scored when the thermocouple signal flattened or nearly flattened for >10 s. Hypopnoeas were scored when the amplitude of the abdominal and thoracic inductance signals or the nasal pressure flow signal decreased by ≥30% for ≥10 s. Events were classified as either 'central' or 'obstructive' according to the presence or absence of respiratory effort. Specialised software linked apnoeas and hypopnoeas with data from the oxygen saturation and EEG signals, which allowed each event to be characterised according to the degree of associated desaturation and presence or absence of arousal. *AHI*. Sleep apnoea was measured using the AHI ≥3% (ie, the number of all apnoeas and hypopnoeas with ≥3% oxygen desaturations per hour of sleep); moderate or more severe OSA was defined as an AHI ≥15 events per hour (referred to as OSA hereafter). OSA was further categorised into none (0 to <5/hour), mild (≥5 to <15/hour), moderate (15 to 30/hour) or severe (>30/hour).

Sleep apnoea-specific hypoxic burden

SASHB was defined as the total area under the respiratory event-related desaturation curve for individual apnoeas and hypopnoeas.[24] This includes the frequency, duration and depth of the respiratory-event contribution to arterial hypoxaemia. SASHB quantifies the severity of sleep apnoea by measuring the area under the oxygen saturation curve associated with each individual respiratory (airflow) obstruction (individual apnoeas and hypopnoeas). These individual desaturation areas are summed and divided by total sleep time. SASHB values are expressed as minutes of per cent desaturation per hour (%min)/hour. For example, a hypoxic burden of 20 (%min)/hour is equal to 20 min of 1% desaturation per hour or 5 min of 4% desaturation per hour. We normalised the highly skewed SASHB values using Stata's zero-skewness Box-Cox transformation function 'bcskew0,' and a transformation formula of $(HB^{L} - 1)/L$, where L=0.1866394. Similar to the original study,[24] we created 5 quantiles of SASHB, with the lowest quantile serving as the reference group.

Wrist actigraphy

Eligible participants agreed to wear Actiwatch Spectrum actigraphs (Philips Respironics, Murrysville, Pennsylvania, USA) on the non-dominant wrist for seven consecutive days. A minimum of four valid days were required, and the mean was 6.98 days. Data were scored at a central Sleep Reading Centre at Brigham and Women's Hospital in 30 s epochs as sleep or wake using Actiware-Sleep V.5.59 software.[25] The main sleep interval was manually identified based on a self-actuated event marker, sleep diary and light sensors. (Daytime naps were not analysed). The following variables were calculated:

Table 1 Sociodemographic, health behaviour and clinical characteristics among MESA sleep ancillary study participants, N=1895

	Total N=1895	White n=696 (37%)	Black n=531 (28%)	Hispanic/Latino n=453 (24%)	Chinese n=215 (11%)	P value (for race/ethnicity differences)
Age, mean years±SD	68.2 (9.1)	68.4 (9.1)	68.3 (8.9)	68.2 (9.4)	67.6 (9.0)	
Mean age categories						0.780
54–64 years	778 (41.1)	282 (40.5)	214 (40.3)	187 (41.3)	95 (44.2)	
≥65 years	1117 (58.9)	414 (59.5)	317 (59.7)	266 (58.7)	120 (55.8)	
Sex/gender (female)	1018 (53.7)	372 (53.5)	294 (55.4)	239 (52.8)	113 (52.6)	0.829
Marital status						<0.001
Married/living with partner	1137 (61.3)	451 (65.5)	257 (49.9)	253 (57.5)*	176 (83.4)	
Widowed/divorced/separated	584 (31.5)	180 (26.1)	211 (41.0)	163 (37.1)*	30 (14.2)	
Never married	134 (7.2)	58 (8.4)	47 (9.1)	24 (5.5)*	5 (2.4)	
Educational attainment						<0.001
<High school	274 (14.5)	23 (3.3)	37 (7.0)	178 (39.3)*	36 (16.7)	
High school/GED	305 (16.1)	99 (14.3)	84 (15.9)	95 (21.0)*	27 (12.6)	
Some college or technical degree	563 (29.8)	170 (24.5)	216 (40.8)	128 (28.3)*	49 (22.8)	
≥College	749 (39.6)	402 (57.9)	192 (36.3)	52 (11.5)*	103 (47.9)	
Total annual gross household income						<0.001
<US$25 000	481 (26.1)	80 (11.8)	116 (22.7)	198 (44.9)	87 (41.0)	
US$25 000–US$34 999	222 (12.1)	68 (10.0)	80 (15.6)	52 (11.8)	22 (10.4)	
US$35 000–US$74 999	614 (33.3)	241 (35.6)	183 (35.7)	145 (32.9)	45 (21.2)	
≥US$75 000	526 (28.5)	289 (42.6)	133 (26.0)	46 (10.4)	58 (27.4)	
Employment (yes)	455 (24.1)	192 (27.6)	142 (27.1)	84 (18.6)	37 (17.3)	<0.001
Work schedule						0.057
Day/afternoon shift	635 (33.6)	240 (34.6)	170 (32.1)*	139 (30.9)	86 (40.0)	
Night shift/irregular shift	200 (10.6)	86 (12.4)	55 (10.4)*	39 (8.7)	20 (9.3)	
Not working	1054 (55.8)	368 (53.0)	305 (57.6)*	272 (60.4)	109 (50.7)	
Smoking status						<0.001
Never	1021 (54.6)	331 (47.9)	245 (47.0)	266 (59.5)	179 (84.4)	
Former	728 (38.9)	323 (46.7)	215 (41.3)	162 (36.2)	28 (13.2)	
Current	122 (6.5)	37 (5.4)	61 (11.7)	19 (4.3)	5 (2.4)	
Current alcohol use						<0.001
Yes	831 (44.1)	431 (62.0)	224 (42.7)	142 (31.5)	34 (15.9)	
Moderate/vigorous physical activity†						<0.001
Low	563 (29.9)	173 (24,9)*	142 (27.1)*	178 (39.6)	70 (32.7)	
Medium	618 (32.8)	261 (37.6)*	169 (32.3)*	104 (23.1)	84 (39.3)	
High	702 (37.3)	261 (37.6)*	213 (40.7)*	168 (37.3)	60 (28.0)	
Blood pressure categories (systolic/diastolic)‡						<0.001
Optimal (<120 and < 80)	930 (49.1)*	381 (54.7)*	206 (38.8)	228 (50.3)*	115 (53.5)	
Normal (<130 and <85) or high-normal (130–139) or (85–89)	618 (32.6)*	207 (29.7)*	211 (39.7)	137 (30.2)*	63 (29.3)	
Stage 1 (140–159) or (90–99)	255 (13.5)*	84 (12.1)*	77 (14.5)	69 (15.2)*	25 (11.6)	
Stage 2 (160–179) or (100–109)	70 (3.7)*	19 (2.7)*	28 (5.3)	14 (3.1)*	9 (4.2)	
Stage 3 (≥180 or ≥110)	22 (1.2)*	5 (0.7)*	9 (1.7)	5 (1.1)*	3 (1.4)	
Diabetes§						<0.001
Normal: fasting plasma glucose (fpg) <100 mg/dL	1144 (60.4)	485 (69.7)	312 (58.8)	228 (50.3)*	119 (55.4)	
Impaired fasting glucose: fpg=100–125 mg/dL	381 (20.1)	131 (18.8)	77 (14.5)	108 (23.8)*	65 (30.2)	
Treated or untreated diabetes: fpg ≥126 mg/dlL	370 (19.5)	80 (11.5)	142 (26.7)	117 (25.8)*	31 (14.4)	
Cholesterol (mg/dL)						0.941
Desirable (<200 mg/dL)	1278 (67.5)	475 (68.4)*	355 (66.9)*	306 (67.6)*	142 (66.1)	
Borderline high (200–239 mg/dL)	478 (25.2)	166 (23.9)*	139 (26.2)*	114 (25.2)*	59 (27.4)	

Continued

Table 1 Continued

	Total N=1895	White n=696 (37%)	Black n=531 (28%)	Hispanic/Latino n=453 (24%)	Chinese n=215 (11%)	P value (for race/ethnicity differences)
High (>240 mg/dL)	138 (7.3)	54 (7.8)*	37 (7.0)*	33 (7.3)*	14 (6.5)	
Medication use						
Total no of medications, mean±SD	4.6 (3.6)	5.1 (3.9)	4.9 (3.7)	4.1 (3.4)	3.2 (2.8)	0.001
Diuretics (yes)	361 (19.1)	131 (18.8)	156 (29.4)	60 (13.3)	14 (6.5)	<0.001
Lipid-lowering drugs (yes)	709 (37.4)	286 (41.1)	184 (34.7)	178 (39.3)	61 (28.4)	0.003
Anti-HTN (yes)	1007 (53.1)	330 (47.4)	352 (66.3)	234 (51.7)	91 (42.3)	<0.001
Cholesterol-lowering medications—visit 1 (yes)	296 (15.6)	127 (18.3)	77 (14.5)	66 (14.6)	26 (12.1)	0.087
Sleep medications—past 4 weeks (yes)	258 (13.6)	124 (17.8)	53 (10.0)	69 (15.3)	12 (5.6)	<0.001
Body mass index (kg/m^2), mean±SD	28.8 (5.6)	28.0 (5.2)	30.4 (5.6)	30.1 (5.5)	24.2 (3.4)	<0.001
Underweight (<18.5 kg/m^2)	12 (0.6)	4 (0.6)	2 (0.4)	0 (0.0)	6 (2.8)	
Normal (18.5 to <25.0 kg/m^2)	494 (26.1)	213 (30.7)	85 (16.0)	68 (15.0)	128 (59.5)	
Overweight (25.0–29.9 kg/m^2)	716 (37.8)	272 (39.1)	185 (34.8)	189 (41.7)	70 (32.6)	
Obese (≥30 kg/m^2)	672 (35.5)	206 (29.6)	259 (48.8)	196 (43.3)	11 (5.1)	
N (%) with moderate-to-severe CKD (GFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/g of creatinine)	380 (20.1)	132 (19.0)	117 (22.0)	89 (19.7)	42 (19.5)	0.594
N (%) with self-reported CKD	23 (1.2)	5 (0.7)	12 (2.3)	3 (0.7)	3 (1.4)	0.057

Data shown as mean±SD or n (%).
*Rounded percentages do not add to 100.
†Based on Physical Activity Guidelines for Americans by the US Department of Health and Human Services.
‡JNC VI Hypertension criteria (1979).
§2003 ADA fasting criteria for diabetes.
ADA, American Diabetes Association; CKD, chronic kidney disease; GED, general education development; GFR, glomerular filtration rate; HTN, hypertension; MESA, Multi-Ethnic Study of Atherosclerosis.

Average sleep duration

Average sleep duration was calculated as the average sleep duration across each main (typically nighttime) sleep interval over the 7-day monitoring period. Participants were categorised into very short (≤5 hours), short (<7 hours), recommended (≥7 to ≤9 hours) and long (>9 hours) sleep duration.[26]

Average sleep maintenance efficiency

Average sleep maintenance efficiency was defined as the average proportion of time spent asleep between sleep onset and final awakening. Low sleep efficiency was categorised as <85% vs ≥85%.

Average sleep fragmentation

Average sleep fragmentation was calculated as the sum of per cent mobile epochs and per cent immobile bouts <1 min duration to the number of immobile bouts for the given interval. This is also known as the index of restlessness or movement and fragmentation index. Participants were categorised into ≤15% or >15%.

Self-report

Insomnia symptoms

Insomnia symptoms were assessed with the Women's Health Initiative Insomnia Rating Scale (WHIR).[27] WHIR questions were scored on a 5-point scale (from 0 to 4), then added to develop a summary score, which could range from 0 to 20. A score ≥9 was considered clinically significant insomnia and categorised as yes versus no.

Daytime sleepiness

In a sleep questionnaire from Exam visit 4, participants reported feeling overly sleepy during the day: never, rarely, sometimes, often or almost always, which we dichotomised as often or almost always versus never, rarely or sometimes.

Sleep dimension combinations

Since certain combinations of sleep measures may represent particularly important characteristics that impact health outcomes, we also a priori combined certain sleep features, including short sleep plus insomnia symptoms, short sleep plus low sleep maintenance efficiency, OSA plus sleep fragmentation, and OSA plus highest quintile of SASHB. 'Suboptimal' sleep was defined as ≥1 of the following sleep dimensions: short or long sleep duration, low sleep maintenance efficiency or insomnia symptoms.

Covariates

Sociodemographic characteristics

Participants self-identified race/ethnicity as non-Hispanic white, non-Hispanic black/African-American, Hispanic/Latino and Chinese participants. Other sociodemographic characteristics included age groups (54–64 and 65+ years), males or females, marital status (married, widowed/divorced/separated or never married), educational attainment (≤high school, some college or technical degree, or ≥college), total annual gross household income (<US$25 000, US$25 000–US$34 999, US$35 000–US$74 999 or ≥US$75 000), current employment (yes or no), and work shift schedule ('day/afternoon shift,' 'night shift/irregular shift,' or 'do not work').

Health behaviour characteristics

Answers to questionnaires were used to categorise smoking status into 'never', 'former' and 'current' smokers. Alcohol consumption was based on self-reported current use. Questionnaire-assessed physical activity categories included 'adequate' or

Table 2 Sleep characteristics among MESA sleep ancillary study participants, N=1895

	Total N=1895*	White n=696 (37%)	Black n=531 (28%)	Hispanic/Latinx n=453 (24%)	Chinese n=215 (11%)	P value (for race/ethnicity differences)
Sleep characteristics						
Actigraphy-assessed sleep characteristics						
Average sleep duration†						<0.001
<7 hours (short)	1175 (63.1)	362 (52.9)	403 (76.7)‡	276 (62.2)	134 (64.1)	
7–9 hours (recommended)	659 (35.4)	311 (45.5)	120 (23.0)‡	156 (35.1)	72 (34.5)	
>9 hours (long)	28 (1.5)	11 (1.6)	2 (0.4)‡	12 (2.7)	3 (1.4)	
Very short sleep (≤5 hours)	239 (12.8)	54 (7.9)	104 (19.8)	48 (10.8)	33 (15.8)	<0.001
Average sleep maintenance efficiency§						0.043
<85% (low)	103 (5.5)	25 (3.7)‡	38 (7.2)	26 (5.9)	14 (6.7)	
≥85% (recommended)	1759 (94.5)	659 (96.4)‡	487 (92.8)	418 (94.1)	195 (93.3)	
Average fragmentation index¶						<0.001
>15% (high)	1419 (76.2)	481 (70.3)	441 (84.0)	346 (77.9)	151 (72.3)‡	
≤15% (recommended)	443 (23.8)	203 (29.7)	84 (16.0)	98 (22.1)	58 (27.8)‡	
Insomnia symptoms (yes)**	681 (35.9)	245 (35.2)	204 (38.4)	173 (38.2)	59 (27.4)	0.025
Polysomnography-assessed obstructive sleep apnoea (OSA)/ resp. sleep disturbance (3% desaturations)††						0.110
None (0 to <5/hour)	395 (20.8)‡	152 (21.8)‡	118 (22.2)	78 (17.2)	47 (21.9)‡	
Minimal (5 to <15/hour)	603 (31.8)‡	239 (34.3)‡	168 (31.6)	130 (28.7)	66 (30.7)‡	
Mild/moderate (15 to 30/hour)	476 (25.1)‡	167 (24.0)‡	131 (24.7)	129 (28.5)	49 (22.8)‡	
Severe (>30/hour)	421 (22.2)‡	138 (19.8)‡	114 (21.5)	116 (25.6)	53 (24.7)‡	
Sleep apnoea-specific hypoxic burden (SASHB)‡‡ mean±SD, % min/hour	56.5 (65.1)	52.2 (50.5)	53.6 (77.8)	65.2 (70.0)	59.8 (60.2)	
SASHB: means/SDs by quintile, % min/hour						
Quintile 1: 0.02–16.24	8.8 (4.4)	9.0 (4.1)	8.5 (4.9)	9.4 (4.0)	8.3 (4.4)	
Quintile 2: 16.25–29.29	22.5 (3.7)	22.7 (3.6)	22.4 (3.7)	22.1 (3.8)	22.1 (3.8)	
Quintile 3: 29.30–47.74	37.8 (5.6)	37.7 (5.4)	37.4 (5.9)	38.1 (5.2)	38.6 (6.0)	
Quintile 4: 47.75–84.395	64.1 (10.9)	62.2 (10.2)	64.2 (11.0)	65.9 (11.3)	66.5 (11.4)	
Quintile 5: 84.3951–1099.61	149.8 (92.1)	136.2 (60.4)	166.4 (135.2)	156.6 (87.4)	139.8 (67.5)	
Box-Cox normalised SASHB: mean±SD	5.3 (2.1)	5.3 (1.9)	5.0 (2.3)	5.6 (2.1)	5.4 (2.2)	0.111
Sleep apnoea plus highest quintile of SASHB						0.003
≥15 episodes/hour and high SASHB	370 (19.6)	122 (17.5)	88 (16.7)	108 (23.9)	52 (24.2)	
≥15 episodes/hour or high SASHB	534 (28.2)	186 (26.7)	158 (29.9)	139 (30.8)	51 (23.7)	
No apnoea and not high SASHB	987 (52.2)	388 (55.8)	282 (53.4)	205 (45.4)	112 (52.1)	
Short sleep plus insomnia symptoms						<0.001
<7 hours and insomnia symptoms	428 (23.2)	122 (18.0)	160 (30.5)	108 (24.8)	38 (18.5)	
<7 hours or insomnia symptoms	987 (53.6)	357 (52.7)	283 (54.0)	231 (53.1)	116 (56.3)	
7–9 hours, no insomnia symptoms	427 (23.2)	198 (29.3)	81 (15.5)	96 (22.1)	52 (25.2)	
Short sleep plus low maintenance efficiency						<0.001
<7 hours and low maintenance efficiency	90 (4.9)	20 (3.0)‡	36 (6.9)‡	22 (5.1)	12 (5.8)	
<7 hours or low maintenance efficiency	1098 (59.9)	347 (51.6)‡	369 (70.6)‡	258 (59.7)	124 (60.2)	
7–9 hours and efficient maintenance	646 (35.2)	306 (45.5)‡	118 (22.6)‡	152 (35.2)	70 (34.0)	
Sleep apnoea plus fragmentation						<0.001
≥15 episodes/hour and >15% frag	724 (38.9)‡	237 (34.7)‡	213 (40.6)	191 (43.0)	83 (39.7)	
≥15 episodes/hour or >15% frag.	854 (45.9)‡	307 (44.9)‡	258 (49.1)	205 (46.2)	84 (40.2)	
No apnoea and ≤15% frag.	284 (15.3)‡	140 (20.5)‡	54 (10.3)	48 (10.8)	42 (20.1)	
'Suboptimal' sleep§§	1624 (87.2)	569 (83.2)	470 (89.5)	404 (91.0)	181 (86.6)	0.001
Feeling overly sleepy during the day¶¶						<0.001

Continued

Table 2 Continued

	Total N=1895*	White n=696 (37%)	Black n=531 (28%)	Hispanic/Latinx n=453 (24%)	Chinese n=215 (11%)	P value (for race/ethnicity differences)
Never	430 (23.0)‡	92 (13.3)	91 (17.4)‡	158 (35.4)	89 (42.2)‡	
Rarely	562 (30.1)‡	226 (32.7)	181 (34.7)‡	102 (22.9)	53 (25.1)‡	
Sometimes	557 (29.8)‡	245 (35.5)	160 (30.7)‡	108 (24.2)	44 (20.9)‡	
Often	232 (12.4)‡	101 (14.6)	62 (11.9)‡	48 (10.8)	21 (10.0)‡	
Almost always	89 (4.8)‡	27 (3.9)	28 (5.4)‡	30 (6.7)	4 (1.9)‡	

*N with actigraphy data=1862: 684 white, 525 black, 444 Hispanic/Latinx and 209 Chinese.
†The average time spent asleep during main sleep periods (sum of all time asleep across recording divided by the total main sleep periods).
‡Rounded percentages do not add to 100.
§The average sleep maintenance efficiency in main sleeps (percentage of time spent asleep between falling asleep (sleep onset) and waking up (sleep offset)).
¶The sum of per cent mobile epochs and per cent immobile bouts less than 1 min duration to the number of immobile bouts for the given interval. Also known as the index of restlessness or movement and fragmentation index.
**Insomnia symptoms were based on self-reported questionnaire using a Women's Health Initiative Insomnia Rating Scale score of ≥9 (range: 0–20).
††OSA/resp. sleep disturbance was measured using the Apnoea-Hypopnoea Index (AHI) ≥3% (ie, the number of all apnoeas and hypopnoeas with ≥3% oxygen desaturations per hour of sleep); OSA was defined as an AHI≥15 events per hour.
‡‡Hypoxic burden calculated as the area under the oxygen saturation curve associated with each individual respiratory (airflow) disruption (individual apnoeas and hypopnoeas). These individual burden measures are summed and divided by total sleep time.
§§'Suboptimal' sleep is coded positive if any of the following exists: short sleep (<7 hours), long sleep (>9 hours), low sleep maintenance efficiency (<85%), and insomnia symptoms.
¶¶Exam 4.
frag, fragmentation; MESA, Multi-Ethnic Study of Atherosclerosis.

'inadequate' based on Physical Activity Guidelines for Americans as defined by the US Department of Health and Human Services.[28]

Clinical characteristics

Measured body mass index (BMI) was categorised as 'Underweight' (<18.5 kg/m^2), 'Normal' (18.5–25 kg/m^2), 'Overweight' (25–29.9 kg/m^2) and 'Obese' (≥30 kg/m^2). Hypertension was identified based on self-reported hypertension treatment with one of six common antihypertensive medications classes (ie, thiazide diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin-2 receptor blockers and other (beta-blockers or peripheral vasodilators), a systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg. Measured blood pressure was also categorised as 'optimal' (<120 SBP and < 80 DBP), 'normal' (<130 SBP and <85 DBP) or 'high normal' (130–139 SBP or 85–89 DBP), stage 1 (140–159 SBP or 90–99 DBP), stage 2 (160–179 SBP or 100–109 DBP) or stage 3 (≥180 SBP or ≥110 DBP). Diabetes status was categorised as 'normal' (fasting plasma glucose (fpg) <100 mg/dL), 'impaired fasting glucose' (fpg 100–125 mg/dL) and 'diabetes' (treated or untreated) (fpg >125 mg/dL) and then dichotomised into normal (fpg <100 mg/dL) vs not (fpg ≥100 mg/dL) for analyses. Diabetes status was ascertained based on self-reported physician diagnosis, use of insulin and/or oral hypoglycaemic agent or fasting glucose at the MESA examination. Total cholesterol level was categorised as 'desirable' (<200 mg/dL), 'borderline high' (200–239 mg/dL) and 'high' (≥240 mg/dL). Participants' medication use was assessed for total number, diuretics, lipid-lowering drugs, antihypertensive drugs, cholesterol-lowering drugs and sleep medications.

Outcome ascertainment: moderate-to-severe CKD

Moderate-to-severe CKD

CKD was assessed using participants' collected samples of urine and fasting venipuncture during MESA Exam 5. Moderate-to-severe CKD was defined as an eGFR <60 mL/min/1.73 m^2 or albuminuria >30 mg/g. The Modification of Diet and Renal Disease GFR prediction equation was used to estimate GFR (estimated GFR (eGFR)) and categorise CKD.[29] This formula, eGFR (mL/min/1.73 m^2)=186 (S.Cr in μmol/l×0.011312)$^{-1.154}$×(age)$^{-0.203}$ × (0.742 if female)×(1.212 if African/American Black), estimates GFR using serum creatinine and adjusts for age, black race and sex/gender.

Statistical analysis

Means and SD or percentages were used to summarise study participant characteristics; χ^2 and regression analyses were applied to assess differences in demographic, clinical and sleep characteristics by race/ethnicity among participants, and also to compare sleep study participants with other exam 5 participants who were not included in the sleep study. We used Poisson regression with robust variance to estimate the adjusted prevalence ratios (PRs) and 95% CIs for moderate-to-severe CKD, separately among participants with vs without poor sleep dimensions. The sample size was too small (1.5%) to investigate long sleep duration separately, but it was incorporated into the previously described 'suboptimal' sleep measure. Additionally, we ran regression models with the normally distributed transformation of SASHB and with dichotomised daytime sleepiness. The following a priori dichotomised sleep combinations were also analysed: short sleep plus insomnia symptoms, short sleep plus low sleep maintenance efficiency, sleep apnoea plus fragmentation and sleep apnoea plus highest quintile of SASHB. In the main analyses, we adjusted for age, sex/gender, race/ethnicity, educational attainment, smoking status and current alcohol use.

In sensitivity analyses shown in online supplemental tables, we investigated sleep measures and CKD (defined as eGFR <90 mL/min/1.73 m^2 or albuminuria >30 mg/g)—and not moderate-to-severe CKD—in the overall sample and by race/ethnicity, using Poisson regression as above, and testing for interactions between the sleep measures and race/ethnicity. Potential confounders were adjusted for in three separate models with the first model including demographics and health behaviours, race/ethnicity, educational attainment, smoking, current alcohol use and night or irregular shift work; the second model adding BMI (a

potential mediator); and the third model adding blood pressure and diabetes (potential mediators). We also separately investigated sleep–CKD associations by age categories, sex/gender and BMI in fully adjusted models across the overall sample and each racial/ethnic group for CKD—instead of moderate-to-severe CKD—due to its smaller sample size/caseload.

All analyses were conducted using Stata SE V.15, and a two-sided p value of 0.05 was used to determine statistical significance.

RESULTS

Study population characteristics

Table 1 shows sociodemographic, health behaviour, and clinical characteristics among the 1895 eligible MESA Sleep Ancillary Study (Exam 5) participants. Mean age ±SD was 68.2±9.1 years and 54% were women. Racial/ethnic composition was 37% White, 28% Black, 24% Hispanic/Latino, and 11% Chinese. Eligible study participants overall were generally slightly younger, more physically active and employed, and were less likely to have mild-to-moderate-to-severe CKD than the other Exam five participants (online supplemental table 1).

Disturbed sleep indices were prevalent in the overall study population and generally highest among black participants (table 2). For instance, black participants had the highest prevalence of short sleep duration (<7 hours), very short sleep duration (≤5 hours), average sleep maintenance efficiency <85%, average sleep fragmentation index >15% and presence of insomnia symptoms. Hispanic/Latino participants had the highest prevalence of AHI-determined OSA, and the highest mean SASHB (65% min/hour), followed by Chinese (60% min/hour), black (54% min/hour) and white (52% min/hour) participants.

There were 380 (20%) cases of moderate-to-severe CKD, and black participants had a higher prevalence of moderate-to-severe CKD (22%) than whites (19%), Hispanics/Latinos (20%) and Asians (20%) (online supplemental table 2).

Associations between sleep insufficiency as well as sleep disturbances and moderate-to-severe CKD

Table 3 shows the adjusted prevalence of moderate-to-severe CKD according to the presence or absence of insufficient or disturbed sleep. In the overall sample, participants reporting very short sleep had a 40% higher prevalence of moderate-to-severe CKD (PR=1.40, 95% CI 1.04 to 1.83). There was no association between insomnia symptoms and moderate-to-severe CKD overall. Participants with OSA showed a suggestive 20% higher prevalence (PR=1.20, 95% CI 1.00 to 1.44) for moderate-to-severe CKD. For participants in the highest vs lowest SASHB quantile, we observed a 36% significantly higher moderate-to-severe CKD prevalence (PR=1.36, 95% CI 1.00 to 1.86); likewise, the prevalence was significantly higher with higher normalised (continuous) SASHB (PR=1.06, 95% CI 1.02 to 1.12). Participants in the highest quintile of SASHB plus OSA had a 28% (PR=1.28, 95% CI 1.01 to 1.63) increased moderate-to-severe CKD prevalence.

Sensitivity analyses

As shown in online supplemental table 2 and although these results need to be interpreted with caution due to relatively small sample sizes and multiple comparisons, very short sleep was associated with a 72% higher prevalence (PR=1.72, 95% CI 0.97 to 3.04) of moderate-to-severe CKD among Hispanic/Latino participants, which was comparable among black participants while the also non-statistically significant associations were of similar magnitude among white and Chinese participants. Also, the dose-response pattern of SASHB and moderate-to-severe CKD that was observed in the overall sample was also observed by race/ethnicity. Additional sensitivity analyses regarding age groups, sex/gender and BMI are reported in online supplemental tables 3–5. For instance, low sleep maintenance efficiency among Hispanics/Latinos aged ≥65 years old and Hispanic/Latino men was associated with a lower CKD prevalence in fully adjusted models, which was also observed for all participants aged ≥65 years. However, low sleep maintenance efficiency was associated with higher risk of CKD in Chinese females, Chinese subjects aged 54–64 and obese white participants. Black women in highest versus lowest quantile of SASHB also had a higher CKD prevalence. Chinese participants ≥65 years old who reported excessive daytime sleepiness (often or almost always) had a higher prevalence of CKD.

DISCUSSION

Among racially/ethnically diverse participants of the MESA with multiple objectively measured dimensions of sleep disturbances, we found that both increased SASHB and very short sleep duration were associated with moderate-to-severe CKD. Notably, we observed a dose–response relationship between quintiles of SASHB and the prevalence of both CKD and moderate-to-severe CKD for the overall sample. This analysis suggests that two distinct sleep disturbances—sleep apnoea-associated hypoxic burden and very short sleep are associated with increased prevalence of moderate-to-severe CKD. Moreover, short sleep duration was nearly twice as prevalent among the black or African American compared with white participants, suggesting that short sleep duration may be a modifiable target for kidney disease prevention and for decreasing health disparities.

These findings were consistent with the literature suggesting that several poor sleep health dimensions are associated with CKD. For instance, prior data support an association between OSA and kidney dysfunction,[30] including two meta-analyses among populations with and without diabetes as well as in participants with mild OSA.[3 31] Direct and indirect biological mechanisms linking OSA to CKD have been proposed.[2 32] For example, OSA is characterised by intermittent hypoxia, and reoxygenation with formation of reactive oxygen species may promote inflammation and endothelial dysfunction.[33] OSA-induced activation of the sympathetic nervous system and attenuation of nocturnal dipping of systemic blood pressure could, at least indirectly, lead to development and exacerbation of known CKD risk factors such as hypertension, type 2 diabetes and obesity.[34]

We observed a higher prevalence of moderate-to-severe CKD for OSA defined by AHI; however, associations were stronger and more consistent when we considered SASHB. SASHB is a novel measure that expands beyond AHI-defined OSA to capture frequency, duration and depth of respiratory events or hypoxaemia.[24] In the event whereby AHI measurement of sleep apnoea poorly predicts CVD in older adults, Azarbarzin *et al*[24] found SASHB predicts CVD-related mortality.[24 35 36] Given that OSA exerts much of its deleterious effects on the kidney through hypoxaemia, it is possible that measurements to quantify SASHB may be able to better characterise the effects of OSA compared with frequency measures of respiratory events such as the AHI. Furthermore, Ahmed *et al*[37] found accelerated loss of kidney function among participants with nocturnal hypoxia (ie, oxygen saturation below 90% for ≥12% of nocturnal monitoring time) over a mean period of 2.1 years. This risk remained threefold higher even after adjusting for participants with OSA

Table 3 Prevalence ratios (and 95% CIs) of moderate-to-severe chronic kidney disease (CKD)* for participants with poor sleep characteristics compared with their counterparts with non-poor sleep characteristics, MESA sleep ancillary study (N=1895)

	Moderate-to-severe CKD		
	n=380 (20%)††		
	N with exposure	N events among exposed	Prevalence ratio (95% CI)
Short (<7 hours) versus recommended sleep (actigraphy measured)‡	1175	231	0.99 (0.81 to 1.20)
Very short (≤5 hours) versus recommended sleep (actigraphy-measured)	239	678	**1.40 (1.06 to 1.83)**
Low Sleep Maintenance Efficiency (<85%)§	103	22	0.89 (0.58 to 1.35)
Sleep fragmentation (>15%)¶	1419	292	1.05 (0.84 to 1.32)
Insomnia**	681	137	1.02 (0.85 to 1.23)
Obstructive sleep apnoea (OSA)††	897	206	1.20 (1.00 to 1.44)
Sleep apnoea-specific hypoxic burden: % min/hour‡‡ (quintile 1 (0.02–16.24] is reference)	378	59	–
Quintile 2 (16.25–29.29)	378	65	0.99 (0.72 to 1.36)
Quintile 3 (29.30–47.74)	377	79	1.20 (0.88 to 1.63)
Quintile 4 (47.75–84.395)	378	84	1.24 (0.92 to 1.69)
Quintile 5 (84.3951–1099.61)	377	92	**1.36 (1.00 to 1.86)**
Box-Cox normalised SASHB	–	–	**1.06 (1.02 to 1.12)**
Sleep apnoea plus highest quintile SASHB	370	89	**1.28 (1.01 to 1.63)**
Short sleep plus insomnia§§	428	85	0.98 (0.75 to 1.28)
Short sleep plus poor sleep maintenance efficiency¶¶	90	22	1.01 (0.65 to 1.56)
Sleep apnoea and fragmentation***	724	169	1.26 (0.92 to 1.72)
'Suboptimal' sleep†††	1624	329	1.14 (0.85 to 1.53)
Daytime sleepiness (Exam 4): often/almost always versus never/rarely/sometimes	321	63	1.06 (0.83 to 1.36)

Bold value estimates denote statistical significance.
*Moderate-to-severe CKD is defined as GFR <60 mL/ min/1.73 m^2 or albuminuria ≥30 mg/g of creatinine.
†N with moderate-to-severe CKD and actigraphy data=370 (19.9% of 1862).
‡Average time spent asleep during main sleep periods (sum of all time asleep across recording divided by the total main sleep periods).
§Average sleep maintenance efficiency in main sleeps (percentage of time spent asleep between falling asleep (sleep onset) and waking up (sleep offset)).
¶Sum of per cent mobile epochs and per cent immobile bouts less than 1 min duration to the number of immobile bouts for the given interval. Also known as the index of restlessness or movement and fragmentation index.
**Insomnia based on self-reported questionnaire using a Women's Health Initiative Insomnia Rating (WHIR) Scale score of ≥9 (range: 0–20).
††OSA/resp. sleep disturbance was measured using the Apnoea-Hypopnoea Index (AHI) ≥3% (ie, the number of all apnoeas and hypopnoeas with ≥3% oxygen desaturations per hour of sleep); OSA was defined as an AHI ≥15 events per hour.
‡‡Hypoxic burden calculated as the area under the oxygen saturation curve associated with each individual respiratory (airflow) disruption (individual apnoeas and hypopnoeas). These individual burden measures are summed and divided by total sleep time.
§§Short sleep <7 hours and insomnia symptoms based on WHIR of ≥9 (range: 0–20).
¶¶Short sleep <7 hours and sleep efficiency <85%.
***AHI ≥15 and fragmentation <15%.
†††'Suboptimal' sleep is coded positive if any of the following exists: short sleep (<7 hours), long sleep (>9 hours), low sleep maintenance efficiency (<85%) and insomnia symptoms.
GFR, glomerular filtration rate; MESA, Multi-Ethnic Study of Atherosclerosis.

determined by AHI,[37] supporting the importance of relative depth of hypoxic burden in characterising its burden.

Available data are mixed regarding the relationship between other measures of sleep disturbances and CKD. For example, a meta-analysis of nine observational studies concluded that self-reported short sleep duration was not associated with CKD.[10] Petrov *et al*[11] concluded that wrist actigraphy-determined short sleep duration was associated with decreased kidney function over 10 but not 5 years. Our observed associations between short sleep duration and moderate-to-severe CKD are consistent with more recent findings by Ricardo *et al*[38] in a prospective study among a diverse US population with CKD, which reported a significant association between actigraphy-assessed short sleep duration (<6.5 hours) and an accelerated decline in kidney function. Furthermore, in an 11-year prospective study, McMullan *et al*[39] found a higher likelihood of experiencing rapid decline (≥30%) in eGFR among nurses aged 30–55 years who reported habitual short sleep (≤5 and <7 hours) compared with participants reporting 7–8 hours per night. Plausible biological mechanisms include the deregulatory effects of short sleep duration on circadian rhythm, hormonal regulation (ie, leptin, ghrelin, insulin) and sympathetic activation (ie, renal–angiotensin system) with subsequent development of known CKD risk factors such as obesity, hypertension and type 2 diabetes.[2 40 41] Epidemiological studies have shown short sleep duration to be significantly associated with obesity,[42] hypertension[43] and type 2 diabetes.[44] Reverse causality is also possible. For example, renal dysfunction may result in nocturia, which may disturb sleep among individuals who are at risk for CKD. Agarwal and Light[45] found that patients with CKD had greatly disturbed sleep, and those on haemodialysis had more severe disturbed sleep than those not on dialysis. A separate cross-sectional study among young and middle-aged adults found that long sleep was associated with CKD and glomerular hyperfiltration[46] while another nationally

representative cross-sectional study found that short and long sleep duration was associated with higher odds of reporting CKD.[47]

Our study found no significant association between low sleep maintenance efficiency and CKD in the overall population. Other studies with a diverse US population have used the Pittsburgh Sleep Quality Index to capture sleep quality and found no significant association[38 48] or significant associations with impaired kidney function in 10 but not 5 years, again.[11] Low sleep maintenance efficiency was associated with CKD in some strata and protective in others, but these findings need to be interpreted with caution due to low numbers of participants in various strata. For example, there were 26 Hispanic/Latino and 15 Chinese participants with low sleep maintenance efficiency. In contrast, prior studies have found a significant association between actigraphy-assessed sleep fragmentation and decreased kidney function among adults with CKD and young-to-middle-aged black and white adults without CKD, respectively.[11 38] Evidence of an association between insomnia and renal function is sparse. However, a prospective study on a large sample of US veterans showed that chronic insomnia was associated with higher risk of incident CKD and progressive loss of kidney function.[49] Differences in sample size, sociodemographic characteristics and study design/methodology may have also contributed to variation in results.

Limitations of this study include its cross-sectional design, which precludes causal inference. As in all observational studies, there is the potential for residual confounding. We had only one measure of CKD. Within sex/gender and race/ethnicity stratum, we had a relatively small sample size. Future studies should use prospective designs, larger sample sizes, a broader age range, and employ kidney function equations that replace the correction factor for race with a formula based on serum creatinine, age, and sex normalized to 1.73 m^2 body surface area for all participants. Furthermore, we tested multiple associations and did not adjust for multiple comparisons to identify associations that offer more exhaustive opportunities for future research. Additional research is needed to confirm our findings. Despite these limitations, this study has important strengths. For instance, we used objective sleep measures (including a novel, more sensitive measure of SASHB) using both PSG and actigraphy. We also had access to multiple sleep dimensions beyond sleep duration. Furthermore, our sample was racially/ethnically diverse.

In summary, we found that sleep dimensions related to hypoxia (ie, AHI and particularly SASHB) and very short sleep were associated with moderate-to-severe CKD. This study contributes to identification of modifiable CKD risk factors, which enhance our understanding of CKD aetiology and may lead to novel approaches for preventing, delaying or treating/managing renal disease. SASHB can be readily measured by two sensors—an airflow channel and oximeter, thus suggesting its clinical utility as a means for identifying individuals at high risk for adverse health outcomes, such as moderate-to-severe CKD. Furthermore, obesity can contribute to apnoea/hypoxic burden and is a driver of health sequelae including CKD, which underscores the importance of reducing its burden. Ultimately, more research is warranted in hopes of identifying novel approaches to address this debilitating and costly burden on health.

Author affiliations
[1]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
[2]Intramural Program, National Institute on Minority Health and Health Disparities, Bethesda, Maryland, USA
[3]Duke University School of Medicine, Durham, North Carolina, USA
[4]Division of Sleep Medicine, Harvard Medical School, Boston, Massachusetts, USA
[5]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Massachusetts, USA
[6]Division of General Internal Medicine, Duke University School of Medicine, Durham, North Carolina, USA
[7]Social & Scientific Systems Inc, Durham, North Carolina, USA
[8]School of Public Health, Division of Epidemiology and Community Health, University of Minnesota Twin Cities, Minneapolis, Minnesota, USA
[9]Department of Medicine, Division of Pulmonary Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Twitter Joseph Lunyera @JosephLunyera

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ORCID iDs
Joseph Lunyera http://orcid.org/0000-0002-9350-320X
Pamela L Lutsey http://orcid.org/0000-0002-1572-1340

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