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ORIGINAL ARTICLE

Sleep duration and cognitive function among older adults with chronic kidney disease: results from the National Health and Nutrition Examination Survey (2011–2014)

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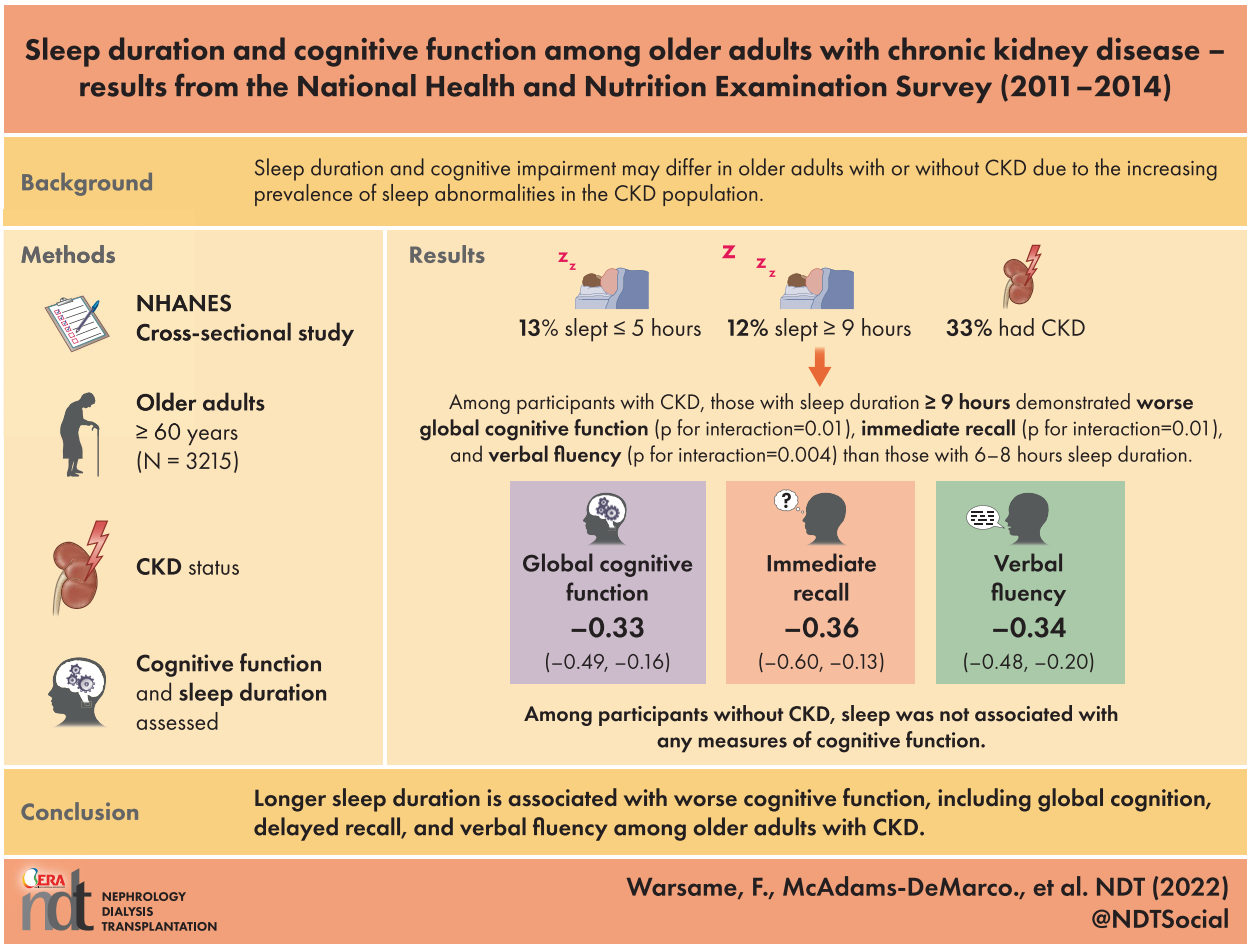
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Sleep duration is an extensively studied component of sleep quality and has been found to have a U-shaped association with cognitive decline. Given that shorter and longer sleep durations are associated with cognitive dysfunction, we sought to explore whether this association differs among persons with CKD.

What this study adds?

- Long sleep duration is more common among persons with CKD. There were no significant associations between cognitive function and sleep duration among those without CKD. Among participants with CKD, those with long sleep duration demonstrated worse global cognitive function, immediate recall and verbal fluency compared with those with shorter sleep duration.

What impact this may have on practice or policy?

- Sleep duration may be a salient factor in the relationship between kidney function and cognitive decline. Primary care physicians and nephrologists should consider counseling patients with CKD about excessive sleep and further studies should identify any underlying sleep disturbances in this patient population that may mediate cognitive decline.

ABSTRACT

Background. Short and long sleep durations are associated with cognitive dysfunction. Given the increased prevalence of sleep abnormalities in the chronic kidney disease (CKD) population, we tested whether the association between sleep duration and cognitive function differed between older adults with and without CKD.

Methods. This was a study of 3215 older adults (age ≥60 years) enrolled in the National Health and Nutrition Examination Survey (2011–14) evaluating sleep duration, cognitive function (immediate recall, delayed recall, verbal fluency, executive function and processing speed and global cognition) and kidney function. We quantified the association between sleep duration and cognitive function using linear regression and tested whether the associations differed among those with CKD and without using a Wald test for interaction.

Results. Among 3215 participants, 13.3% reported 2–5 hours of sleep/day, 75.2% reported 6–8 hours, and 11.5% reported ≥9 hours. Persons with CKD were more likely to sleep ≥9 hours [odds ratio 1.73 (95% confidence interval 1.22–2.46)]. Among participants with CKD, those with a sleep duration ≥9 hours demonstrated worse global cognitive function (P for interaction = .01), immediate recall (P for interaction = .01) and verbal fluency (P for interaction = .004) than those with a sleep duration of 6–8 h; no differences were observed for participants with CKD who slept 2–5 hours. Among participants without CKD, sleep was not associated with any measures of cognitive function.

Conclusions. Longer sleep duration is associated with worse cognitive function only among persons with CKD, and global cognition, delayed recall and verbal fluency are particularly affected. Studies should identify interventions to improve sleep patterns and quality in this population.

Keywords: cognitive function, cognitive impairment, chronic kidney disease, sleep duration

INTRODUCTION

Individuals with chronic kidney disease (CKD) have a higher risk of developing cognitive impairment compared with the general population and cognitive impairment increases in severity as kidney function declines [1–4]. Lower kidney function is associated with worse cognitive functioning across multiple cognitive domains, including global cognition, verbal memory, visual-spatial organization, attention, naming and executive function [4–6]. Cognitive dysfunction across these domains is significant because of its impact on health behaviors and downstream effects on morbidity and mortality [7]. For instance, impaired executive function and verbal memory are associated with medication regimen and dialysis nonadherence [8,9]. Among patients with CKD, cognitive dysfunction is associated with a lower chance of transplant listing and increased waitlist mortality [10]. Potential mechanisms underlying the pathophysiological relationship between brain and kidney function include vascular injury, neuronal injury from uremic toxins, glymphatic dysfunction and endothelial dysfunction [2,11]. Mitigating the risk factors of cognitive dysfunction in CKD is important to potentially curtail cognitive decline and limit downstream effects.

Sleep-related problems, including abnormal sleep duration and poor sleep quality, are prevalent among people with CKD [12]. Appropriate durations of sleep promote memory consolidation, procedural memory, executive function and attention [13]. Among older adults in the general population, sleep duration has been identified as a modifiable risk factor for dementia and the literature suggests a U-shaped associated between cognition and sleep [14–16]. Both extremes of sleep duration have been linked to a greater likelihood of developing dementia in later life [17]. Further, longitudinal studies conducted over decades suggest inadequate sleep may precede changes in cognitive function [16]. It is unclear whether the relationship between sleep duration and cognitive impairment

differs among individuals with CKD, however, the association is likely stronger in this population given more rapid cognitive declines and illness-related sleep abnormalities.

Given the association between sleep duration and cognitive impairment among older adults, we sought to test whether the relationship between sleep duration and cognitive function differed among older adults with and without CKD. We utilized the National Health and Nutrition Examination Survey (NHANES, 2011–14) to examine whether the relationship between sleep and cognitive function differs among older adults with and without CKD.

MATERIALS AND METHODS

Study design

The NHANES is a cross-sectional survey of noninstitutionalized US residents conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC) [18]. The NHANES sampling model is not random, but instead uses a multistage probability sampling design in order to select participants representative of the US population. The participant selection process also oversamples certain subgroups to increase reliability estimates for these groups. We used sampling weights for all analyses to account for the differential probabilities of study selection as recommended by the NHANES. Data collection for the NHANES includes a brief household screening interview, an in-depth household interview and a medical examination conducted in a mobile examination center. The NHANES survey and consent form were approved by the NCHS Research Ethics Review Board.

Among NHANES participants from the 2011–12 and 2013–14 cycles, 3215 participants were adults ≥60 years of age with measured serum creatine and at least one assessment of cognitive function. Participants' health information was ascertained via direct measurement or self-report, including hypertension [systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥80 mmHg, or current use of antihypertensive medication], diabetes (fasting blood glucose level ≥126 mg/dl, non-fasting blood glucose level ≥200 mg/dl, reported history of diabetes and/or current use of medications for diabetes or high blood sugar), anemia (hemoglobin <12 g/dl in males and <11 g/dl in females or reported taking treatment for anemia in the past 3 months), body mass index (kg/m^2), clinically significant depressive symptoms [Patient Health Questionnaire (PHQ-9) ≥10] and physical activity (collected using the Global Physical Activity Questionnaire and converted to MET-min/week) [19]. Participants with ≥600 MET-min/week were categorized as 'physically active' based on the US physical activity guidelines [20]. Histories of coronary heart disease (CHD), myocardial infarction (MI), stroke and smoking (smoked at least 100 cigarettes over a lifetime) were also self-reported.

Additionally, NHANES participants were asked if they took prescription medications in the previous 30 days. Medication names were identified by inspecting medication containers or by self-report and then matched to a standard generic drug name. A therapeutic classification was assigned to each drug and each ingredient of the drug. Participants were classified as taking sleep or cognitive function–affecting medications if they had taken one or more types of medication with the following therapeutic classification: central nervous system (CNS) agents (anxiolytics, sedatives and hypnotics; analgesics; anticonvulsants; CNS stimulants); psychotherapeutic agents (psychotherapeutic combinations; antidepressants; antipsychotics; antimanic agents) and respiratory agents (antihistamines).

CKD and sleep duration

Serum creatinine (mg/dl) and albuminuria [albumin:creatinine ratio (ACR), mg/g] were measured during each study cycle. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR) [21]. We categorized CKD as no CKD (eGFR ≥60 ml/min/1.73 m^2 and ACR <30 mg/g) and CKD (eGFR <60 ml/min/1.73 m^2 and/or ACR ≥30 mg/g) [22]. Participants on dialysis were excluded from the study, as the sample was insufficient. Sleep duration was assessed with the question 'How much sleep do you get (hours)?' and participants' responses were the number of hours ranging from 2–11 or ≥12, refuse to answer or don't know. Normal sleep duration was defined as 6–8 hours, short sleep duration as <6 hours, and long sleep duration as ≥9 hours, based on common cutoffs in previous studies investigating sleep duration in the CKD population [23, 24]. Additionally, the NHANES further assessed participants' sleep using the questions, 'Have you ever told a doctor or other health professional that you have trouble sleeping?' and 'Have you ever been told by a doctor or other health professional that have a sleep disorder' (yes/no).

Cognitive function

In the 2011–12 and 2013–14 NHANES cycles, a series of cognitive function assessments were administered, including word learning modules from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery [25], the Animal Fluency (AF) Test and the Digit Symbol Substitution test (DSST). All participants who were ≥60 years of age were eligible for cognitive testing and assessments were presented to participants in the language of their choosing.

The CERAD neuropsychological battery is used to detect cognitive decline in older adults at risk for Alzheimer's disease [26]. The CERAD word learning modules assess both immediate (CERAD-WL) and delayed memory (CERAD-DL) of novel verbal information. Participants are presented with 10 unrelated words and are then asked to recall the words during three consecutive learning trials [27]. The number of words correctly identified across three trials comprises the immediate recall score (CERAD-WL). Delayed recall (CERAD-DL) is tested after participants complete both the AF and DSST assessments and the score is the number of words recalled out of 10. Diminished recall is an early sign of dementia, and the

word learning tests have been found to efficiently distinguish older adults with dementia from those with normal cognition [25, 28, 29].

In the AF test, participants are asked to name as many animals as they can in 1 minute, with a point given per named animal. Naming animals from memory allows for participants to identify common animals across cultural backgrounds. This task relies on verbal fluency and having adequate semantic memory storage as well as the executive functioning to explore memory stores in a time-efficient manner [30]. The AF test is also able to sensitively discriminate patients with normal cognition from those with cognitive impairment and dementia [31].

In the DSST, participants are given a key with a series of nine numbers and corresponding symbols. Participants are then instructed to match numbers with their corresponding symbol in a 2-minute time span. The DSST score is the count of correctly matched numbers and symbols. This test assesses a range of executive functions, including attention, scanning and processing speed, and has been validated to sensitively capture cognitive dysfunction [32]. In each of the above four tests, participants were given 1 point for each correct response, with higher scores reflecting better cognitive performance [27, 33]. A composite measure of global cognition function was assessed based on the four objective tests. Each domain score was standardized to a mean of 0 and standard deviation (SD) of 1 and then averaged into a global cognitive function score, as described previously [34].

Descriptive statistics

The characteristics of the study sample were summarized by the proportion of the overall sample for categorical variables, by means and SDs for normally distributed continuous variables or by medians and interquartile ranges (IQRs) for nonnormally distributed continuous variables. The data were summarized and presented in groups of participants with reported sleep durations of 2–5 hours, 6–8 hours or ≥9 hours (Table 1). The NHANES sample weights were accounted for in the analysis to calculate nationally representative estimates that are appropriately adjusted for survey nonresponse [35].

CKD, sleep duration and cognitive function

Using a linear regression model, differences in cognitive function by sleep duration were estimated using Cohen's *d*. Cohen's *d*, or the standardized mean difference, measures the difference between two means, even when the dependent variables are measured using different scales [36]. A Cohen's *d* of 1 indicates that two groups differ by 1 SD; a *d* of 0.2, 0.5 or 0.8 suggests small, medium or large effect sizes, respectively [37]. To test whether the association between cognitive function and sleep duration differed by CKD status, we tested this interaction using a Wald test. Models were adjusted for potential confounders of sleep duration and cognitive impairment (age, sex, race, education, hypertension, diabetes, CHD, MI, stroke, anemia, physical activity, depressive symptoms and smoking). The above were covariates that satisfied criteria for potential confounding: (1) associated with the outcome (cognitive function), (2) unequally distributed between exposure (sleep duration) groups (Table 1) and (3) must not be an effect of the exposure. We calculated variance inflation factors (VIFs) and did not find multicollinearity.

Table 1: Characteristics of participants ≥60 years of age with and without CKD from the NHANES (2011–2014; *N* = 3215).

Characteristics	Values	Sleep (hours)		
		2–5	6–8	≥9
Overall, *n*	3215	427	2418	370
Non-CKD[a], *n*	2052	258	1606	178
CKD, *n*	1163	169	802	192
Age (years)				
60–69	53.6	58.9	55.1	40.0
70–79	29.5	24.2	29.5	33.7
≥80	16.9	16.9	15.4	26.3
Race				
Mexican American	3.8	5.2	3.6	3.5
Other Hispanic	3.7	6.7	3.5	2.8
Non-Hispanic White	78.4	60.3	79.9	83.0
Non-Hispanic Black	8.4	18.7	7.5	6.6
Non-Hispanic Asian	4.0	6.0	3.9	2.6
Other	1.7	3.1	1.6	1.6
Female	54.2	57.3	53.8	54.8
Education ≥12 years	81.5	74.1	82.7	79.8
CKD	33.0	37.9	30.1	48.4
Hypertension	75.4	79.9	74.4	78.5
Diabetes	23.1	30.4	21.8	26.5
CHD	9.9	7.3	10.0	11.5
MI	8.8	8.1	8.8	9.7
Stroke	7.6	11.8	6.8	9.8
Anemia	7.0	10.6	5.8	11.9
Physically active	49.4	43.9	52.3	34.5
Depressive symptoms	7.6	21.4	5.9	7.7
Prescription medication use	35.8	40.2	33.8	45.3
Ever smoker	50.1	53.0	50.1	48.3
BMI (kg/m^2), median (IQR)	27.9 (7.3)	30.4 (9.3)	27.7 (7.1)	28.0 (7.4)

Values are presented as proportions (%) unless stated otherwise, accounting for NHANES sampling weights. eGFR was calculated using serum creatinine and the CKD-EPI equation. CKD was defined as an eGFR <60 ml/min/1.73 m^2 or ACR ≥30 mg/g. Depressive symptoms were defined as a PHQ-9 score >9. Physical activity was collected using the Global Physical Activity Questionnaire and converted to MET-min/week. Physically active was defined as ≥600 MET-min/week. Prescription medication use was defined as taking prescription medicine that potentially affected sleep or cognitive function in the past 30 days.

[a]Indicates preweighted sample sizes of participants with and without CKD.

BMI, body mass index.

Sensitivity analysis

A sensitivity analysis was conducted to test whether the associations between CKD, sleep duration and cognitive function were robust to the exclusion of participants with depressive symptoms. The presence of depressive symptoms could introduce uncertainty in the true effect sizes given the association with CKD, sleep duration and cognitive function [38, 39]. Participants reported depressive symptoms on the PHQ-9 (a score ≥10 was indicative of clinically significant depressive symptoms), which has been validated against Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for clinical depression in the dialysis and primary care settings [40, 41].

Table 2: Association between sleep duration, CKD and global and domain-specific cognitive function among participants ≥60 years of age from the NHANES (2011–2014; $N = 3215$)

Sleep (hours)	Overall, mean (95% CI)	No CKD, mean (95% CI)	CKD, mean (95% CI)	*P* for interaction
Global function				
2–5	−0.02 (−0.11–0.07)	0.01 (−0.10–0.12)	−0.07 (−0.21–0.08)	0.38
6–8	0 (ref)	0 (ref)	0 (ref)	
≥9	−0.20 (−0.31 to −0.08)	−0.07 (−0.21–0.06)	−0.33 (−0.49 to −0.16)	0.01
Immediate recall (CERAD-WL)				
2–5	−0.06 (−0.17–0.04)	−0.03 (−0.15–0.09)	−0.13 (−0.31–0.05)	0.35
6–8	0 (ref)	0 (ref)	0 (ref)	
≥9	−0.16 (−0.31 to −0.02)	0.01 (−0.15–0.17)	−0.36 (−0.60 to −0.13)	0.01
Delayed recall (CERAD-DL)				
2–5	−0.00 (−0.13–0.13)	0.08 (−0.07–0.23)	−0.15 (−0.37–0.07)	0.09
6–8	0 (ref)	0 (ref)	0 (ref)	
≥9+	−0.28 (−0.46 to −0.11)	−0.19 (−0.41–0.03)	−0.41 (−0.64 to −0.17)	0.13
Verbal fluency (AF)				
2–5	−0.02 (−0.15–0.11)	−0.09 (−0.24–0.07)	0.08 (−0.15–0.30)	0.23
6–8	0 (ref)	0 (ref)	0 (ref)	
≥9	−0.13 (−0.29–0.02)	0.06 (−0.17–0.29)	−0.34 (−0.48 to −0.20)	0.004
Executive function (DSST)				
2–5	−0.02 (−0.13–0.10)	−0.01 (−0.17–0.14)	−0.01 (−0.23–0.21)	0.99
6–8	0 (ref)	0 (ref)	0 (ref)	
≥9	−0.14 (−0.25 to −0.03)	−0.09 (−0.22–0.04)	−0.18 (−0.35 to −0.01)	0.35

Cognitive test scores were standardized to a mean of 0 and SD of 1. Global cognitive function was defined as an average score of all four objective cognitive tests. Models were adjusted for age, sex, race, education, hypertension, diabetes, CHD, MI, stroke, anemia, physical activity, depressive symptoms and smoking. NHANES sampling weights were accounted for in linear regression analyses to obtain nationally representative estimates. eGFR was calculated using serum creatinine and the CKD-EPI equation. CKD was defined as an eGFR <60 ml/min/1.73 m^2 or ACR ≥30 mg/g.

We also assessed whether inferences remained robust after accounting for the use of prescription medications that can influence sleep or cognitive function.

Statistical analysis

For all analyses, *P*-values <.05 were used as the cutoff for statistical significance. All analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA).

RESULTS

Participant characteristics

In this weighted sample of 3215 participants, 53.6% were 60–69 years old, 29.5% were 70–79 years and 16.9% were >80 years (Table 1). A total of 78.4% of participants identified as White, 8.4% as Black, 3.7% as Hispanic and 4.0% as Asian. Additionally, 54.2% of participants were female and 81.5% attained greater than a high school education. Using the CKD-EPI equation, 33% of participants were identified as having CKD. Medical comorbidities in the sample included hypertension (75.4%), diabetes (23.1%), coronary heart disease (9.9%), myocardial infarction (8.8%), stroke (7.6%) and anemia (7.0%). A total of 7.6% of participants screened positively for clinically significant depressive symptoms and 50.1% reported ever smoking (at least 100 cigarettes over their lifetime). Among the participants, 13.3% reported sleeping for 2–5 hours, 75.2% for 6–8 hours and 11.5% for ≥9 hours (Table 1).

Sleep duration and cognitive function

After adjustment, participants with a sleep duration of ≥9 hours had significantly worse global cognitive function than those with a sleep duration of 6–8 hours {Cohen's $d = -0.20$ [95% confidence interval (CI) −0.31 to −0.08]}. Overall, a sleep duration of ≥9 hours was also associated with worse performance on three of four domain-specific tests, including delayed recall [Cohen's $d = -0.28$ (95% CI −0.46 to −0.11)], immediate recall [Cohen's $d = -0.16$ (95% CI −0.31 to −0.02)] and executive function and processing [Cohen's $d = -0.14$ (95% CI −0.25 to −0.03)] compared with participants who slept 6–8 hours (Table 2). Additionally, those with a sleep duration of 2–5 hours had higher odds of reporting sleep problems compared with those with a sleep duration of 6–8 hours ($P < .05$). Participants with a sleep duration of ≥9 hours were as likely as those sleeping 6–8 hours to report trouble sleeping ($P > .05$).

Sleep duration, CKD and cognitive function

Nonoptimal sleep durations were more common in participants with CKD (Fig. 1). Participants with CKD were significantly more likely to sleep longer [≥9 hours/day; OR 1.73 (95% CI 1.22–2.46)] compared with those without CKD. The association between sleep duration and cognition differed between those with and without CKD. Among participants without CKD, there was no association found between sleep duration and the measured markers of cognitive function (Table 2). However, among participants with CKD, sleep duration of ≥9 hours was associated with worse global cognitive function [Cohen's $d = -0.33$ (95% CI −0.49 to −0.16), *P* for interaction = .01], immediate recall [Cohen's $d = -0.36$ (95% CI −0.60 to −0.13), *P* for interaction = .01)] and verbal fluency [Cohen's $d = -0.34$ (95% CI −0.48 to −0.20), *P* for interaction = .004] compared with those with sleep durations of 6–8 hours.

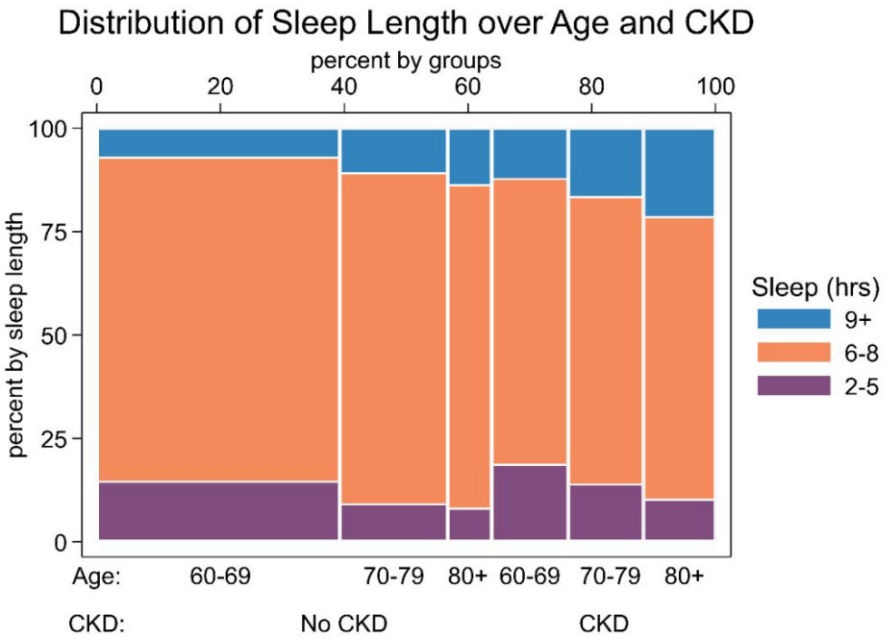


Figure 1: Distribution of sleep length of participants ≥60 years of age with and without CKD from the NHANES (2011–2014; $N = 3215$). Spline plot displaying stacked frequencies of sleep duration (2–5, 6–8 and >9 hours). Participants with and without CKD were categorized into three age groups: 60–69, 70–79 and >80 years. Sleep duration was assessed by self-report on the NHANES household interview. No CKD was defined as eGFR >60 ml/min/1.73 m^2 or ACR <30 mg/g and CKD was defined as eGFR <60 ml/min/1.73 m^2 or ACR ≥30 mg/g.

Among those with CKD, sleep duration ≥9 hours was associated with worse delayed recall [Cohen's $d = -0.41$ (95% CI −0.64 to −0.17)] and executive functioning and processing [Cohen's $d = -0.18$ (95% CI −0.35 to −0.01)] among those with CKD; however, these domains did not significantly differ from participants without CKD (P for interaction = .13 and .35, respectively). There were no significant differences in cognitive test scores in all participants sleeping <6 hours compared with 6–8 hours, regardless of CKD status.

Sensitivity analysis

The results above were robust to exclusion of participants with clinically significant depressive symptoms (Supplementary Table 1). After exclusion of participants with depressive symptoms, sleep duration ≥9 hours remained associated with worse performance on global cognitive function [Cohen's $d = -0.30$ (95% CI −0.50 to −0.10)] and three of four domain-specific tests among those with CKD. The association between sleep duration ≥9 hours and immediate recall (P for interaction = .03) and verbal fluency (P for interaction = .02) differed between those with and without CKD. Similar to previous analyses, there were no significant differences in cognitive performance on global or domain-specific tests between those with a sleep duration <6 hours versus 6–8 hours.

After accounting for neurotropic and psychotropic medications that have the potential to impact sleep or cognitive function, we found results remained similar after adjustment for prescription medication use (Supplementary Table 2). Among participants with CKD, sleep duration ≥9 hours was associated with worse performance in global cognitive function [Cohen's $d = -0.32$ (95% CI −0.48 to −0.16)] and in four domain-specific tests. The association between sleep duration ≥9 hours and global cognitive function (P for interaction = .008), immediate recall (P for interaction = .008) and verbal fluency (P for interaction = .003) differed between those with and without CKD.

DISCUSSION

We characterized the association between sleep duration and cognitive function among people with and without CKD. Using a nationally representative survey of 3215 NHANES participants, CKD was present in 33% and was independently associated with 1.7 times higher odds of sleep duration ≥9 hours. Overall, long sleep duration was associated with delayed recall [Cohen's $d = -0.28$ (95% CI −0.46 to −0.11)] and executive functioning and processing [Cohen's $d = -0.14$ (95% CI −0.25 to −0.03)]; these associations did not differ by CKD. Among participants with CKD, there was an association between sleep duration ≥9 hours and immediate recall (P for interaction = .01), verbal fluency (P for interaction = .004) and global cognitive performance (P for interaction = .01). When participants who reported clinically significant depressive symptoms were excluded in a sensitivity analysis, the effect sizes remained consistent. Additionally, results were robust in a sensitivity analysis accounting for medications impacting sleep.

Our finding of 1.7 times higher odds of long sleep duration among CKD participants is in line with findings in other cross-sectional studies. Using the National Health Interview Survey, participants reporting a sleep duration ≥8 hours had nearly 2-fold higher odds of reporting a CKD diagnosis

compared with those with an average sleep duration [42]. This finding was also comparable to a cohort study that found long sleep duration was associated with 2.31-fold higher odds of renal insufficiency compared with those with an average sleep duration [43]. Additionally, a previous national study reported a higher prevalence of short sleep duration among participants with CKD stage 1 or 2; however, those with CKD stage 3 or 4 were more likely to sleep >7 hours. This is in line with findings in our study that focused on a population with CKD stage 3 and 4 (eGFR <60 ml/min/1.73 m^2) [12]. Sleep disorders are likely highly prevalent in CKD due to the physiological multifaceted and bidirectional relationship between sleep and CKD [44]. Altered sleep may affect the dampening of sympathetic activity overnight, resulting in a nocturnal nadir of systolic and diastolic blood pressure [45]. Elevated nocturnal BP has been associated with a higher risk of developing microalbuminuria, which may explain the association between sleep and CKD progression [46].

Our study extended prior findings by focusing on the potential role of sleep duration in cognitive impairment among older adults with and without CKD. Nonoptimal sleep duration has been extensively linked with cognitive impairment in community-dwelling older adults [17, 47, 48]. An NHANES of older adults found long sleep durations were an independent risk factor for worse performance on immediate recall, delayed recall, verbal fluency and executive function [49]. In CKD and ESRD populations, lower eGFR was associated with worse performance on global cognitive function, recall and executive function domains, leading to subsequent dementia [5, 50–53]. Our study suggests that older adults with CKD and long sleep durations may be more vulnerable to cognitive decline. Interestingly, participants with CKD and short sleep durations did not demonstrate significantly worse cognitive function across these domains compared with non-CKD participants. Potential explanations include that in patients with CKD, buildup of uremic toxins is correlated with somnolence and daytime sleepiness and has been shown to cause uremic neurotoxicity in experimental models [11]. In the general population, long sleep duration rather than short sleep duration is linked to higher inflammatory markers [54]. Additionally, long (versus short) sleep duration may be an indicator of sleep disordered breathing, leading to chronic hypoxic episodes that may have worse neurocognitive effects [55].

In this novel nationally representative study, the interaction between long sleep duration and CKD was most notable in specific cognitive domains, namely immediate recall, verbal fluency and global cognition. Previously, recall on the CERAD and other similar 10-word learning trials were found to be a sensitive measure for mild cognitive impairment and early Alzheimer's disease [56, 57]. Additionally, verbal fluency is useful for detection of mild cognitive impairment and vascular cognitive impairment without dementia [58]. While our study did not find a significant interaction on the executive function domain, verbal fluency tasks also require some executive control functions, such as tracking of working memory and inhibition of responses [59]. Verbal memory and executive functioning appear to have a significant degree of overlap and it is suggested that executive function impacts both the storage and retrieval of information [60]. Several mechanisms may explain these findings and the impact of sleep duration and CKD on these cognitive domains. A meta-analysis synthesizing 44 studies showed CKD patients with eGFR ≤60 ml/min/1.73 m^2 appear to experience cognitive changes in the domains of orientation, attention, memory, executive function and global cognition [6]. Long sleep duration may reflect worse renal function as a result of buildup of uremic toxins, nocturnal hypoxia secondary to obstructive sleep apnea and fatigue in this patient population [61, 62]. Additionally, abnormal sleep duration may independently mediate cognitive declines due to sleep fragmentation, higher sympathetic tone and increased inflammatory cytokines [44, 63, 64].

This study has several important strengths, including capturing a national sample of older adults with objective measures of cognitive and renal function. Given that depression may be an important confounder in an association between sleep duration and CKD, we conducted a sensitivity analysis excluding participants with clinically significant depressive symptoms and findings remained robust. We also leveraged data on medication use and demonstrated that findings remained robust after accounting for the use of sleep aids and other medications that can impact sleep.

The main limitation was the cross-sectional nature of the study, which limits insight into the directionality or causality in the association between sleep duration, CKD and cognitive function. Additionally, prospective studies may be able to better assess for bidirectional associations between sleep and cognitive function. While sleep duration was a self-reported measure, it is possible that the use of large categories (short, normal, long sleep durations) decreased the impact of self-report bias. Further studies using objective assessments of sleep quality, home-based actigraphy or laboratory-based sleep studies could be a future research direction. While the presence of obstructive sleep apnea was not ascertained in the NHANES 2011–14, it may be an important mechanism in the association between long sleep duration and cognitive performance [65, 66].

Additionally, the Cohen's *d* effect sizes suggested small to moderate effects. One potential explanation is that sleep duration does not capture the full scope of sleep disturbances among patients with CKD. Sleep problems in this population also include sleep apnea, fragmented sleep, daytime somnolence and poor sleep quality [67, 68]. Sleep disordered breathing as measured by actigraphy is associated with cognitive dysfunction in CKD [55]. Future studies could investigate the combined impact of sleep duration, quality and sleep-related disorders on cognitive function.

In conclusion, our findings support a relationship between sleep duration and cognitive function among older persons with CKD. Older adults with CKD and long sleep durations demonstrated worse performance in the domains of memory and verbal fluency compared with those without CKD. Providers may need to screen patients with CKD for long sleep duration, particularly as these patients are less likely to inform a provider they have trouble sleeping. Patients who endorse long sleep duration may need to be counseled regarding the

potential impact on cognitive function. Cognitive screening initiatives and sleep hygiene training in patients with CKD may mitigate cognitive decline in later life among this highly vulnerable population.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

F.W. participated in the concept design, interpretation of data, drafting, critical revision and approval of the article. N.M.C. and M.A.M.-D participated in the concept design, analysis and interpretation of data, drafting, critical revision and approval of the article. J.H. participated in analysis and interpretation of data, drafting, critical revision and approval of the article. A.M., D.C.C. and G.B. participated in critical revision and approval of the article. D.L.S. participated in concept design, critical revision and approval of the article.

DATA AVAILABILITY STATEMENT

The data underlying this article are available from the NHANES.

CONFLICT OF INTEREST STATEMENT

None declared.

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