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Physical Activity and Self-reported Symptoms of Insomnia, Restless Legs Syndrome and Depression: the Comprehensive Dialysis Study

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Abstract

Background—Symptoms of sleep and mood disturbances are common among patients on dialysis and are associated with significant decrements in survival and health-related quality of life. We used data from the Comprehensive Dialysis Study (CDS) to examine the association of self-reported physical activity with self-reported symptoms of insomnia, restless legs syndrome (RLS) and depression in patients new to dialysis.

Methods—The CDS collected data on physical activity, functional status, and health-related quality of life from 1678 patients on either peritoneal (n=169) or hemodialysis (n=1509). The Human Activity Profile was used to measure self-reported physical activity. Symptoms were elicited in the following manner: insomnia using three questions designed to capture difficulty in initiating or maintaining sleep, RLS using three questions based on the National Institutes of Health workshop, and depression using the 2-item Patient Health Questionnaire.

Results—We obtained data on symptoms of insomnia and depression for 1636, and on symptoms of RLS for 1622 (>98%) patients. Of these, 863 (53%) reported one of three insomnia symptoms as occurring at a persistent frequency. Symptoms of RLS and depression occurred in 477 (29%) and 451 (28%) of patients, respectively. The Adjusted Activity Score of the Human Activity Profile was inversely correlated with all three conditions in models adjusting for demographics, comorbid conditions, and laboratory variables.

Conclusion—Sleep and mood disturbances were commonly reported in our large, diverse cohort of patients new to dialysis. Patients who reported lower levels of physical activity were more likely to report symptoms of insomnia, RLS and depression.

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Keywords

dialysis; cohort study; physical activity; insomnia; restless leg syndrome; depression

Introduction

Sleep and mood disturbances comprise a significant proportion of symptoms experienced by patients on dialysis[1]. Compared with age-matched controls, patients on dialysis are more likely to report symptoms of insomnia and demonstrate shorter and less efficient sleep on polysomnography[2–4]. The prevalence of restless leg syndrome (RLS) in patients on dialysis is 3-to 4-fold higher than that seen in the general population; RLS is also associated with mortality and withdrawal from dialysis[5]. Numerous studies have highlighted the prevalence of depression in end-stage renal disease (ESRD) and the association between depression and mortality[6–8]. Patients suffering from such symptoms also report sizeable decrements in health-related quality of life[1].

In the general population, low levels of physical activity have been linked to sleep disturbance[9–10] and depression, especially among the elderly[11]. As a corollary, boosting physical activity can be an effective non-pharmacologic intervention for these conditions. Moderate intensity exercise ameliorated insomnia and RLS symptoms in small randomized controlled trials[12–14]. Exercise has proved effective as a treatment for depression[15]; in one trial, patients with depressive symptoms enrolled in a moderate exercise program had a higher rate of symptom remission as well as a lower rate of relapse than patients treated with sertraline[16].

No prior study has examined associations of physical activity with these distressing and often overlooked conditions in patients new to dialysis. We used data from the Comprehensive Dialysis Study (CDS) to describe the prevalence, severity and correlates of self-reported sleep and mood disturbances with a particular focus on physical activity. We hypothesized that self-reported physical activity would be inversely correlated with symptoms of insomnia, RLS and depression.

Methods

Study Design and Participants

Adult patients who started maintenance dialysis within randomly selected centers throughout the United States were enrolled in the CDS between September 2005 and June 2007. The sampling frame of dialysis units was based on the April 7, 2005 version of the Dialysis Facility Compare database, which was merged with the 2003 Center for Medicare & Medicaid Services (CMS) ESRD Facility Survey containing information about the number of annual incident patients in each unit. The size measure allowed for probability proportional to estimated size (ppes) sampling. The following types of facilities were eliminated from the sampling frame: Veterans Affairs, children only, outside the 50 states and District of Columbia, and transplant only.

The final sampling frame contained 4,410 facilities and was sorted by ESRD Network, then by adjacent states within Network, and finally within state in a serpentine manner by size, using SAS PROC SURVEYSELECT. A sample of 335 dialysis units was selected using equal probability systematic random sampling. The facility sample matched the facility population closely on size, dialysis chain affiliation, Network, and whether peritoneal dialysis was offered.

Patients received information about the study at their dialysis facility or through the mail. Those willing to participate completed and returned a signed consent form or provided verbal consent by telephone. The study was approved by institutional review boards at the location of the United States Renal Data System (USRDS) Coordinating Center (University of Minnesota), the USRDS Rehabilitation/Quality of Life Special Studies Center (Emory University), and the USRDS Nutrition Special Studies Center (University of California San Francisco).

Self-reported physical activity

Study participants were asked about physical activity as part of a structured interview administered by professional interviewers using a Computer-Assisted Telephone Interviewing system. Physical activity was assessed using the 94-item Human Activity Profile (HAP), which includes assessment of activities across a broad range of energy requirements. The Human Activity Profile was reproduced for use in the CDS with permission of the author, David Daughton. Patients were asked to indicate whether they were still doing, have stopped doing or have never done activities such as cooking meals (ranked 21), carrying a heavy load of groceries (ranked 58) and running two miles (ranked 90). The Maximum Activity Score (MAS) is the most demanding activity that the respondent still performs. The Adjusted Activity Score (AAS) is determined by subtracting from the MAS the total number of less demanding activities the respondent has stopped doing. The AAS is interpreted as a measure of usual physical activity[17]. We previously validated the HAP in ESRD[17a].

Covariates

To complement data from the Patient Questionnaire, we obtained data from the Medical Evidence Form (CMS form 2728), including height, weight, primary cause of kidney disease and selected laboratory values (serum hemoglobin, creatinine and albumin) noted within 45 days before the initiation of dialysis. We considered the following comorbid conditions: diabetes mellitus, heart failure, and atherosclerotic vascular disease, the latter defined as one or more of the following diagnoses: atherosclerotic heart disease, peripheral arterial disease, amputation or stroke.

Self-reported symptoms of insomnia, RLS and depression

We assessed insomnia with three questions designed to capture difficulty in initiating or maintaining sleep. The patient reported whether he or she had trouble with: (1) falling asleep, (2) waking up during the night, and (3) waking up too early and not being able to fall asleep again. The patient also indicated the frequency with which these symptoms occurred as “all or most of the time,” “some of the time,” “a little of the time,” or “none of the time.” Similar questions have been used in large epidemiology studies to describe symptoms of insomnia[18–19], including in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) study[20].

For symptoms of RLS, questions were based on the clinical criteria established by the RLS diagnosis and epidemiology workshop at National Institutes of Health[21]. Patients reported whether they had an urge to move their limbs accompanied by “creepy or crawly” sensations, and whether the sensations were relieved by movement and worse in the evening or night.

We used the Patient Health Questionnaire-2 (PHQ-2) to evaluate for the symptoms of depression. A score of 3 or above on this 2-item questionnaire—which asks about feelings of depression and anhedonia over a 2-week period—yields a positive predictive value of

75% for the presence of any depressive disorder[22]. The PHQ has been validated in the general population[23] as well as in patients on dialysis[24].

Statistical analysis

Continuous data are presented using means (± standard deviation) and compared using Student's t-test. Categorical data are presented as proportions and compared using the Chi square test. We used logistic regression to determine associations among participant characteristics and symptoms of insomnia, depression and RLS. Self-reported physical activity, assessed using the AAS, was the primary exposure of interest. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) from model parameter coefficients and standard errors, respectively. For the three symptoms of insomnia, we calculated the odds of experiencing each of the three symptoms “all of the time.” In addition we used a composite variable for insomnia for which we modeled the odds of experiencing at least one of the three symptoms “all or most of the time.” For RLS symptoms, we modeled the odds of the patient answering “yes” to all three questions (i.e., the presence of symptoms, worsening at night or with rest and relief with activity). For symptoms of depression, we modeled the odds of a PHQ-2 score of 3 or above.

We examined the crude association between AAS score and each of the three conditions (insomnia, RLS and depression). We then fit models adjusting for demographics (age, sex and race), body size, education, smoking, comorbid conditions, dialysis modality and laboratory variables (*vide supra*). Given the known association between depression and insomnia, we fit one additional model with insomnia as the dependent variable in which we adjusted further for symptoms of depression using the PHQ score. We conducted all analyses using SAS v9.2 and v9.3 (SAS Institute Inc, Cary, NC, USA). We considered 2-tailed p-values <0.05 statistically significant.

Results

Symptoms of Insomnia, RLS and Depression

Of the 1678 CDS participants, 1643 responded to the patient questionnaire. The average length of time that CDS participants had been on dialysis at their baseline interview was about 4 months (median = 122 days; mean = 129 days). We obtained information on symptoms of insomnia, RLS and depression in 1636, 1622 and 1636, respectively (> 98%). Table 1 shows the characteristics of our cohort (n=1639 with data for at least one set of symptoms) according to median AAS scores. Older, female participants were more likely to report AAS scores below the median of the cohort. A larger percentage of participants reporting lower AAS scores used hemodialysis as modality of treatment, experienced comorbid conditions, and had lower serum creatinine and albumin concentrations.

Close to half of the patients reported symptoms of insomnia as occurring at least with moderate frequency (Figure 1). Eight hundred and thirteen (50%) patients reported trouble falling asleep, 962 (59%) reported trouble with waking up during the night, and 798 (49%) reported trouble waking up too early in the morning some or all or most of the time. Eight hundred and sixty three patients (53%) reported at least one of these symptoms as occurring all or most of the time.

Four hundred and seventy-seven (29%) patients reported symptoms of RLS. A PHQ-2 score consistent with depression was reported by 451 (28%) patients. Patients who reported symptoms of any of the three complaints (insomnia, RLS, depression) often also reported symptoms of another of these complaints (Figure 2). For example, 16% of participants reporting insomnia reported concurrent RLS and depression symptoms as well; 31% of participants reporting depression reported insomnia and RLS symptoms.

Self-reported Physical Activity and Symptoms of Insomnia, RLS and depression

Symptoms of insomnia were inversely correlated with the AAS score (Pearson r=−0.17 for trouble with falling asleep, r=−0.14 for trouble with waking up during the night and r=−0.21 for trouble with waking up too early in the morning, all with p<0.001). Patients who reported symptoms of insomnia occurring “all or most of the time” had lower AAS scores when compared with patients with symptoms occurring “some of the time” who in turn had lower AAS scores than patients with symptoms occurring “little or none of the time” (Figure 3a, p<0.001). Similar to patients with insomnia, patients with RLS and depression had lower AAS scores compared with patients who were not experiencing these symptoms (Figure 3b).

AAS scores were inversely correlated with all three symptoms of insomnia as well as symptoms of RLS and depression. In fully adjusted models, every 10 points higher on the AAS were associated with 24%, 16% and 24% lower odds of experiencing trouble falling asleep, waking up during the night and waking too early in the morning, respectively. For the composite insomnia variable, every 10 points higher on the AAS were associated with 20% lower odds of experiencing at least one of the three symptoms “all of the time.” Parallel analyses showed 17% and 37% lower odds of experiencing symptoms of RLS and depression, respectively.

Table 2 shows the results for fully adjusted models for symptoms of insomnia, RLS and depression. In an analysis which further adjusted for the presence of depression, the association between symptoms of insomnia and AAS did not change.

Discussion

In a large, diverse sample of patients new to dialysis, we found that over half reported symptoms of insomnia as occurring at a moderate frequency; over one-quarter reported symptoms of RLS and depression. There was significant overlap among patient reports of the three conditions. All three conditions were inversely correlated with self-reported physical activity, though the associations were relatively weak on unadjusted analyses. On adjusted analyses, for each ten-point higher AAS—which would reflect, for example, a usual activity level difference between walking 2 blocks on level ground and walking 6 blocks on level ground—there was a 17 to 37% decrease in odds of experiencing symptoms of insomnia, RLS and depression.

The burden of insomnia, RLS and depression reported in our cohort of patients new to both hemo- and peritoneal dialysis confirms and extends findings from prior studies. In a well-conducted single-center study, Weisbord *et al.* surveyed 162 patients on hemodialysis. Forty-three percent of the patients reported symptoms of insomnia, 29% reported RLS and 26% reported depression[1]. In the largest prior study to examine RLS in ESRD, Chen *et al.* examined sleep disturbances in 706 prevalent Taiwanese patients on hemodialysis, reporting that the prevalence of nighttime sleep complaints exceeded 60% with RLS present in about 20%[25]. Both of these studies included prevalent patients, in contrast to our study in which only patients new to dialysis were included. Others showed that symptoms of RLS were associated not only with sleep disturbance[5], but also with shortened dialysis sessions[5, 26] impaired quality of life [26–27] and a 2- to 3-fold increase in the risk of death[5, 26–27].

Symptoms of depression are among the most common psychological symptoms reported by patients on dialysis[28]. Although a variety of instruments have been used to examine its prevalence, in the Dialysis Outcomes and Practice Patterns, nearly 20% of roughly 5000 patients surveyed reported feeling either downhearted or “down in the dumps”[6]. These symptoms were associated with a 20% increase in the relative risk of hospitalization and 35–40% increase in the relative risk of death. This link between symptoms of depression and/or

positive screens on various instruments for depression and increased mortality has been corroborated[29–30].

Despite the burden of mood and sleep disturbances and the associations among these symptoms, mortality and health-related quality of life, physicians tend not to detect their presence or recognize their severity[31]. Population-based studies suggest that fewer than one-third of patients on dialysis with severe depressive symptoms or a physician diagnosis of depression are prescribed antidepressants[7, 32]. Similarly, pharmacologic treatment for symptoms of insomnia was limited to one quarter of patients experiencing the symptoms in a small study [33].

Given our cross-sectional analyses, we cannot ascertain the directionality of the relationship between physical activity, and symptoms of insomnia, RLS and depression. However prospective data support physical activity as a potentially effective therapeutic strategy for mood and sleep disturbances in the general population. In a survey of adults in Arizona (U.S.), walking more than 6 blocks per day at a brisk pace was associated with 50% lower odds of difficulty in sleep initiation[34]. In one study, 48 patients were randomly assigned to a moderate intensity endurance program for 16 weeks or to health education classes; exercise reduced sleep onset latency and increased sleep duration by 42 minutes[13]. An extended year-long exercise program in another trial led to improved sleep architecture as well as reduced night-time awakenings[12]. In a trial of patients with RLS, aerobic and resistance training exercise training three times per week improved symptoms by 39% on a severity scale[14]. Interventions involving exercise have led to sizable (as high as 50%) decreases in depressive symptoms (as measured by Beck Depression Inventory) in at least two small trials[15].

Putative explanations for the improvement in symptoms due to exercise include improved thermoregulation, vasodilation and modifications in the release of monoamine neurotransmitters. Sleep state initiation has been linked to a relative drop in body temperature at the end of the day. As exercise leads to a rise in body temperature followed by a regulatory activation of heat loss, it is hypothesized that this downregulation of body temperature may trigger sleep[9]. The vasodilatory effects of exercise may augment blood supply to the lower extremities and thereby relieve symptoms of RLS[35]. In patients with depression, the release of monoamines (dopamine, serotonin and noradrenalin) that accompanies physical activity may boost mood and attention[36].

Our study has several strengths, including a relatively large sample size, near complete data collection, and diversity by age, sex, race, geography, comorbid conditions and dialysis modality. The study also has several important limitations. First, while the HAP has been validated in ESRD, it describes *self-reported*, rather than *measured* physical activity. Similarly, symptoms of insomnia, RLS and depression were not confirmed by polysomnography or direct examination by physicians, sleep specialists or psychiatrists. Since interviews were conducted by telephone, participants may have been reluctant to disclose selective symptoms, particularly depression. Indeed, we may have underestimated the prevalence of all three of these conditions. Because the CDS did not collect data on medication use, we cannot determine what proportion of our cohort sought treatment for their symptoms. Moreover, insomnia, RLS and depression may worsen over time, as patients on dialysis experience additional complications and accrue new comorbid conditions.

In summary, in a relatively large sample of patients new to dialysis, we describe an exceptionally high prevalence of symptoms of insomnia, RLS and depression. Levels of self-reported physical activity were inversely correlated with each of these conditions. It would be advisable to screen patients new to dialysis for these conditions; assessment of

symptoms of insomnia, RLS and depression should be performed before and after any intervention aimed to enhance physical activity.

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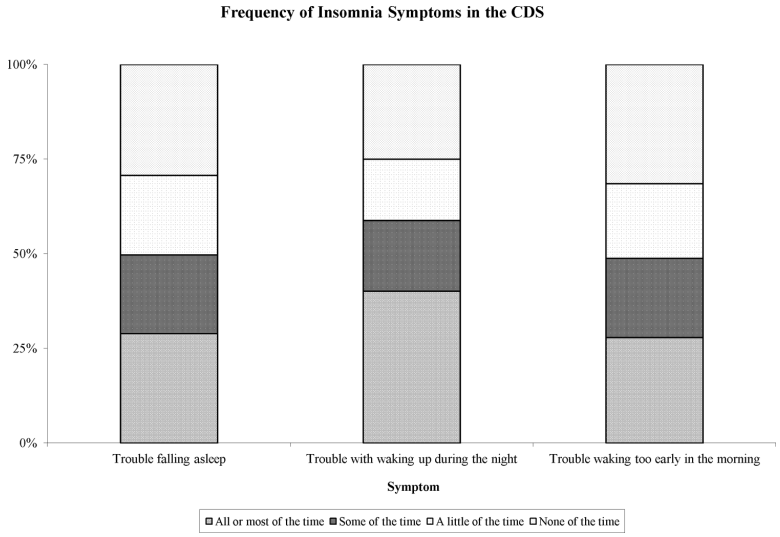

Figure 1. Frequency of Insomnia symptoms in the CDS

Data were available for 1636 (>99%) of the participants. Abbreviations: CDS-Comprehensive Dialysis Study.

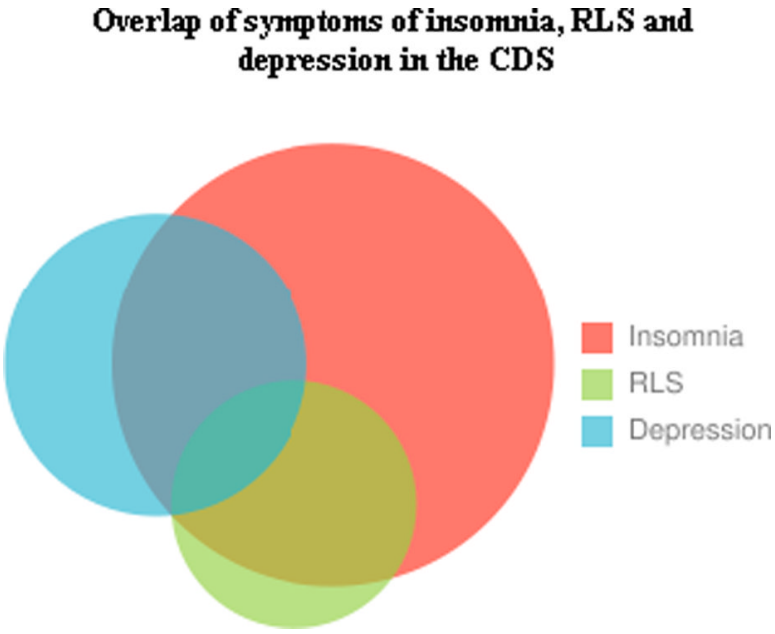

Figure 2. Overlap of symptoms of insomnia, RLS and depression in the CDS

Insomnia (defined here as at least one of the insomnia symptoms reported as occurring "all or most of the time") was most common in the analytic cohort. Nine percent of the cohort reported all three symptoms. Participants reporting insomnia reported RLS, depression, or both symptoms concurrently 19%, 22% and 16% of the time, respectively. Abbreviations: CDS-Comprehensive Dialysis Study, RLS-Restless legs syndrome.

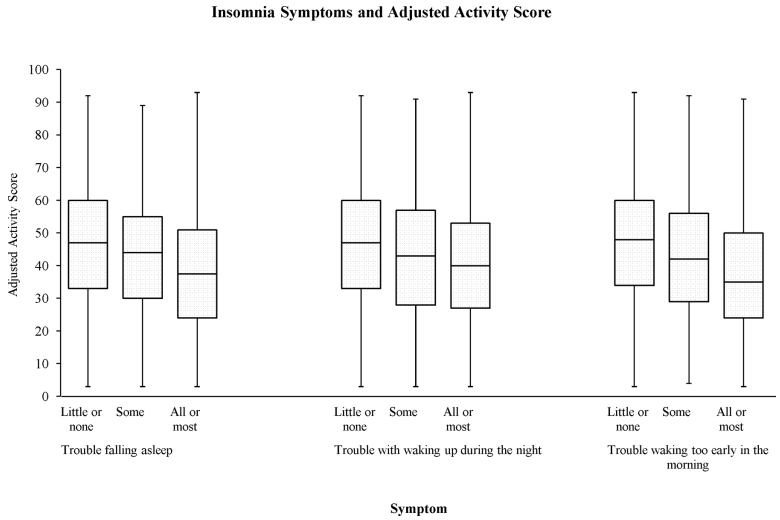

Figure 3a. The associations among symptoms of insomnia and Adjusted Activity Score from the Human Activity Profile

Median Adjusted Activity Scores are lowest for participants who reported insomnia symptoms to be occurring all or more the time.

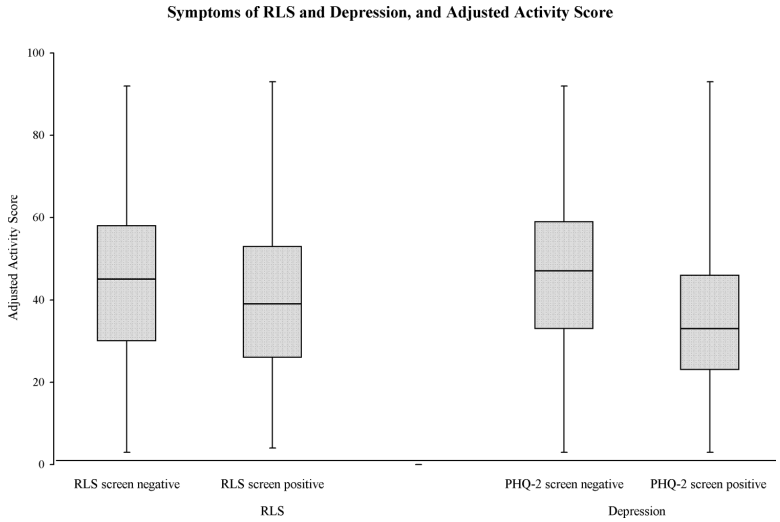

Figure 3b. The association between RLS and Adjusted Activity Score, and depression and Adjusted Activity Score

Median Adjusted Activity Scores are lower for participants who reported RLS or depression, compared with participants who did not report these symptoms. Abbreviations: RLS-Restless legs syndrome. PHQ-2: Patient Health Questionnaire-2.

Table 1
Patient Characteristics stratified by Adjusted Activity Score

Characteristics of participants in the Comprehensive Dialysis Study according to Adjusted Activity Score. The analytic cohort consists of 1639 participants with data available for symptoms of insomnia, RLS or depression. Data are expressed as mean ± standard deviation, or as N (% of analytic cohort) where appropriate. Median AAS score was 43.

Characteristic	AAS below median (N=788)	AAS at or above median (N=851)	p value
Age (years)	62.5 ± 13.3	58.6 ± 14.7	<0.0001
Female	448 (56.9%)	290 (34.1%)	<0.0001
Race, non white	245 (31.1%)	266 (31.3%)	0.94
College education or more	299 (37.9%)	425 (49.9%)	<0.0001
Body mass index (kg/m^2)	31.0 ± 8.7	28.7 ± 7.2	<0.0001
Current smoker	113 (14.3%)	136 (16.0%)	0.36
Peritoneal dialysis	56 (7.1%)	113 (13.3%)	<0.0001
Hemodialysis access via catheter†	446 (61.4%)	369 (50.5%)	<0.0001
Diabetes mellitus	535 (67.9%)	413 (48.5%)	<0.0001
Atherosclerotic vascular disease	317 (40.2%)	245 (28.8%)	<0.0001
Congestive Heart Failure	291 (36.9%)	213 (25.0%)	<0.0001
Hemoglobin (g/dL)‡	10.1 ± 1.8	10.1 ± 1.8	0.74
Creatinine (mg/dL)‡	6.2 ± 3.0	7.5 ± 3.8	<0.0001
Albumin (g/dL)‡	3.0 ± 0.7	3.3 ± 0.7	<0.0001

Abbreviations: AAS-Adjusted activity score.

†Proportions presented in this row are for patients on hemodialysis only.

‡Laboratory values were taken from the Centers for Medicare and Medicaid Services Medical Evidence Report (form 2728).

Table 2

Multivariable associations among self-reported symptoms of sleep and mood disturbance, and patient characteristics including self-reported physical activity

The ratios reflect odds of the symptom being reported, with an odds ratio greater than one indicating increased odds of the symptom being reported. Significant covariates for each symptom are presented in bold.

Covariates	Insomnia†	RLS	Depression
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Age (per 10 years)	**0.77 (0.70–0.85)**	**0.75 (0.68–0.84)**	**0.76 (0.68–0.85)**
Sex, Female	0.89 (0.69–1.16)	1.09 (0.82–1.45)	**0.66 (0.49–0.90)**
Race, nonwhite	0.85 (0.65–1.11)	0.84 (0.62–1.12)	1.02 (0.75–1.39)
BMI, obese‡	0.79 (0.62–1.02)	1.01 (0.77–1.34)	0.76 (0.56–1.02)
Current smoking	**1.45 (1.03–2.05)**	1.26 (0.88–1.80)	**1.62 (1.12–2.35)**
College education or more	1.13 (0.88–1.44)	0.77 (0.59–1.01)	**0.73 (0.55–0.98)**
Modality, peritoneal dialysis	0.81 (0.53–1.23)	**1.62 (1.04–2.50)**	0.75 (0.44–1.26)
Diabetes Mellitus	0.98 (0.75–1.28)	0.96 (0.71–1.28)	0.97 (0.71–1.32)
Atherosclerotic Vascular Disease	**0.69 (0.53–0.91)**	0.94 (0.69–1.27)	0.75 (0.54–1.03)
Congestive Heart Failure	**1.38 (1.04–1.82)**	1.07 (0.78–1.45)	1.08 (0.78–1.50)
Albumin (g/dL)	1.14 (0.96–1.37)	1.16 (0.96–1.42)	1.06 (0.86–1.30)
Hemoglobin (g/dL)	0.99 (0.92–1.07)	0.99 (0.91–1.07)	**1.13 (1.04–1.23)**
Creatinine (mg/dL)	0.97 (0.93–1.00)	0.97 (0.93–1.02)	0.98 (0.93–1.02)
Adjusted Activity Score (per 10 points)	**0.80 (0.74–0.86)**	**0.83 (0.77–0.90)**	**0.63 (0.57–0.69)**

Abbreviations: RLS-restless legs syndrome, BMI-body mass index.

†Insomnia is defined as the occurrence of at least one of three insomnia symptoms “all of the time.”

‡BMI, obese indicates a BMI ≥30 kg/m^2.