Associations between nutritional factors and excessive daytime sleepiness in older patients with chronic kidney disease

Cihan Heybeli[1], Pinar Soysal [2], Mehmet Ası Oktan[3], Lee Smith[4],

Ali Çelik[5], Rumeyza Kazancioglu[6]

[1]Division of Nephrology, Muş State Hospital, Muş, Turkey

[2]Division of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey.

[3]Division of Nephrology, Osmaniye State Hospital, Osmaniye, Turkey

[4]The Cambridge Centre for Sport and Exercise Science, Anglia Ruskin University, Cambridge, UK.

[5]Division of Nephrology, Başkent University, İzmir, Turkey

[6]Division of Nephrology, Bezmialem Vakif University, Faculty of Medicine, Istanbul, Turkey.

Running Title: Excessive daytime sleepiness and CKD

Corresponding author

Cihan Heybeli, MD

heybelic@hotmail.com

Full Postal Adress: Muş State Hospital, Hemodialysis Centre, Muş, TURKEY

Word count of the abstract: 248

Word count of the manuscript: 3481 (excluding references, and tables)

Abstract

Background: Excessive daytime sleepiness (EDS) is prevalent in not only older adults, but also patients with chronic kidney disease (CKD), and is associated with higher risks of morbidity and mortality.

Aims: The aim of the present study is to determine associations between EDS and nutritional status and serum nutrient levels in older patients with CKD.

Methods: This cross-sectional study included years 367 patients (aged ≥65 years) with CKD (eGFR<60ml/min/1.73m^2 and/or >30 mg/day of albuminuria for >3 months). EDS was recorded using the Epworth Sleepiness Scale (a score of ≥11). Malnutrition was diagnosed according to the Minimal Nutritional Assesment (MNA) tool (a score of <17).

Results: The mean age was 81±7 years, and 248 (67%) were female. EDS was seen in 99 (26.9%) patients. Those with EDS had significantly lower MNA scores and more frequent malnutrition than those without EDS (p<0.05). In multivariable analysis adjusted for age, sex, cerebrovascular disease, dementia, drug counts, and number of urinations at night, and the Charlson comorbidity index the relationship between malnutrition and EDS persisted (OR 2.58, 95% CI 1.38 -4.83, p=0.003). There was no significant difference between the presence of EDS and serum levels or deficiencies of vitamin D, vitamin B$_{12}$, and folate (p>0.05).

Conclusions: EDS is associated with malnutrition in older patients with CKD. Therefore, EDS and nutritional status should be evaluated together in clinical practice. However, future studies are needed to determine the direction of the association between malnutrition and EDS and to evaluate if dietary intervention can improve EDS.

Keywords: Chronic kidney disease, excessive daytime sleepiness, nutrition.

Introduction

Sleep disorders are common in patients with chronic kidney disease (CKD) [1], and have been implicated as a possible risk factor for progression to severe CKD [2]. This is in part related to negative effects of poor sleep quality on blood pressure [2, 3], glycemic control [2], obesity [4], and chronobiologic changes in the sympathetic nervous system and renin-angiotensin-aldosterone system [5]. Indeed, ≤5 hour and >8 hour sleep duration have been found to be associated with progression to end-stage kidney disease among patients with CKD [6]. Moreover, one prospective study found that hypoxemia-based measures of sleep apnea were associated with increased mortality risk in patients with severe CKD (stages 4 and 5) [7]. Excessive daytime sleepiness (EDS) which refers to an increased tendency to fall asleep and inability to stay awake during waking episodes is a common sleep symptom [8]. In a study involving over 30,000 adults (mean age 46.6 years) from the United States, the prevalence of EDS in 2012 was reported as 12.7% [9]. Importantly, EDS is frequently observed in older adults, affecting approximately one-third of those aged 80 years or older [10]. Among older adults, EDS is associated with a higher fall risk [11, 12], adiposity [13], metabolic syndrome [14], depressive disorders [15], and a lower hand-grip strength [16]. Moreover, daytime sleepiness has been reported to be associated with cardiovascular and overall mortality among older adults [17].

CKD is most prevalent in older adults, and EDS is common in CKD patients [18]. Factors causing EDS in patients with CKD are not clear. In a preliminary study by Benz et al. [19], correction of anemia with human recombinant erythropoietin improved sleep quality and reduced daytime sleepiness in patients undergoing maintenance hemodialysis [19]. Another study found that missing or shortening dialysis sessions were associated with more severe sleep disturbances among maintenance hemodialysis patients [20]. Studies have also found that sleep

apnea was improved with nocturnal hemodialysis [21, 22]. Taken together these studies demonstrate that loss of kidney function and resulting disorders such as anemia may contribute to an increased risk of EDS among patients with CKD. However, to the best of our knowledge other causes of EDS in patients with CKD are not studied in detail. Several researches have described significant associations between diet, macro-micronutrient intake and sleep disturbances in the general population [23-27]. Malnutrition and micronutrient deficiencies are common in patients with CKD [28], and undoubtedly refer to more unfavourable outcomes [29]. Both EDS and malnutrition are common in CKD, and prior studies showed possible associations between sleep and nutrition in non-CKD populations [30, 31]. CKD represents a unique state for the tremendous increase in the risk of malnutrition. Determination of a possible association between EDS and malnutrition among patients with CKD might be an opportunity for treatment and/or prevention. In this study, we aimed to determine possible associations between nutritional parameters and EDS in this specific patient population.

Methods

Participants

This cross-sectional study included 367 outpatients who were admitted to one geriatric outpatient clinic in Turkey between January 2019 and March 2021. Older patients (≥65 years) with CKD were included. Exclusion criteria were as follows: end-stage kidney disease (glomerular filtration rate of < 15 mL/min/1.73m^2) or kidney replacement therapy, urinary tract infection which may cause proteinuria and erroneously lead to a diagnosis of CKD, severe dementia, active malignancy, fulminant hepatic failure and/or cirrhosis, severe heart failure (class III or IV according to New York Heart Association functional classification), patients who receive nutritional support, patients who receive treatments for daytime sleepiness, patients

with sleep disorders such as sleep apnoea syndrome, or central disorders of hypersomnolance such as narcolepsy, or restless leg syndrome. Those who cannot undergo comprehensive geriatric assessment due to their current clinical condition (e.g., delirium) were also excluded.

Data for age, sex, education, marital and living status, number of medications, comorbid diseases (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, congestive heart failure, dementia) were obtained from electronic medical records. Biochemical measurements were carried out by standard laboratory techniques after venous puncture. CKD was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 and/or albuminuria (>30 mg/day) for more than 3 months. eGFR expressed as mL/min/1.73m^2 was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [32].Thus, patients with normal GFR but albuminuria of over 30 mg/day were also qualified as to have CKD. GFR categories were defined according to consensus guidelines [33].

Comprehensive Geriatric Assessment

The comorbidity burden was assessed using the Charlson Comorbidities Index [34].A geriatrician interviewed the informants of each participant to obtain information on course of participant's cognitive functioning and activities of daily living over the past years, and neurocognitive assessment was carried out on participants who may have cognitive impairment. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5) major cognitive impairment diagnostic criteria [35]. All patients with dementia underwent neuroimaging studies such as cranial magnetic resonance imaging or computed tomography. The question, ''Generally, during the past 30 days, how many times do you usually urinate after you have gone to sleep at night until the time you got up in the morning?'' was used for nocturia [36]. Other tools of the comprehensive geriatric

assessment used in this study were the Geriatric Depression Scale (a score of ≥5 is accepted as depression) [37], and Insomnia Severity Index (a score of >8 was considered as insomnia) [38]. Drug counts were recorded during the outpatient visit.

Definition of Excessive Daytime Sleepiness

EDS was assessed using the Epworth Sleepiness Scale (ESS).[39] It has also been used in previous sleep studies in patients with CKD [40, 18]. The ESS is a 4-point Likert-style questionnaire composed of eight items, in which the subject marks the possibility of napping in routine situations, such as watching television, lying down to rest, and while being a passenger in a vehicle. The scoring for each item varies from 0 (no chance of napping) to 3 (great probability of napping). The total score is based on a scale of 0 to 24. A score of ≥ 11 points indicates EDS. Reliability and validation study of the tool was also carried out in the Turkish language [41]. The informant-completed ESS was administered for patients with dementia [42].

Assessment of Nutritional Status

The Minimal Nutritional Assesement (MNA) is a validated instrument initially developed to assess nutritional status in elderly patients and is mainly indicated for research settings [43, 44]. It is a proven method for the evaluation of nutrition in patients with CKD [45]. The tool contains 18 items and evaluates 4 different aspects: anthropometric assessment (body mass index, weight loss, and arm and calf circumferences); general assessment (lifestyle, medication, mobility and presence of signs of depression or dementia); short dietary assessment (number of meals, food and fluid intake and autonomy of feeding); and subjective assessment (self-perception of health and nutrition). Patients divided in 3 groups using threshold values of <17 for "malnourished", 17-23.5 for "at risk of malnutrition", and ≥24 for "normal nutritional status" with a maximum total score of 30 points [43].

Laboratory findings

Blood samples were collected in the morning following a fasting time of ≥ 8 hours. All samples were studied on the visit day, at the same time with comprehensive geriatric assessment. Folate and vitamin B12 levels were determined in serum with a homogenous chemiluminescent immunoassay using BeckmanCoulter, Woerden, the Netherlands. These biochemical tests were carried out on Diagnostic Modular Systems autoanalyzer (Beckman Coulter DXD 800) [46]. After blood sample collection, the gel tubes were centrifuged within 1 hour and the sera stored at -20^0C for serum vitamin D analysis. 25-(OH)-D was measured using a radioimmunoassay method. Blood lipids including triglycerides (mg/dL), total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/ dL) and high-density lipoprotein cholesterol (HDL-C, mg/dL) were determined using Abbott Architecht c16000 auto-analyser (Abbott Diagnostics, Abbott Park, IL, USA).

Statistics

Quantitative variables were presented as mean with standard derivations. Qualitative variables are shown as proportions. Groups were compared for means using t test if variables were normally distributed, Mann–Whitney U test was used for non normally distributed data. For comparisons between proportions chi-squared tests or Fisher's exact test were used, as appropriate. Logistic regression analysis was used in order to identify independent predictors of EDS. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). In addition to age and sex, variables with a p value of ≤0.05 were included in the multivariate regression model. The Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Of the 367 patients included, the mean age was 81±7 years, and 248 (67%) were female. As comorbidities, 155 (42%) had diabetes mellitus, 277 (75%) had hypertension, and 130 (35%) had dementia. The majority of patients had an eGFR of <60 mL/min/1.73 m^2, while 23 (6.3%) had an eGFR of ≥60 mL/min/1.73 m^2 and the diagnosis of CKD was based on albuminuria. The number of patients in each CKD stage was as follows: 3 patients had stage 1 CKD (eGFR>90 mL/min/1.73 m^2), 20 patients stage 2 (eGFR 60-89 mL/min/1.73 m^2), 299 patients stage 3 (eGFR 30-59 mL/min/1.73 m^2), and 45 patients stage 4 (eGFR 15-29 mL/min/1.73 m^2). Mean eGFR of the cohort was 45±14 mL/min/1.73 m^2 and mean serum creatinine was 1.34±0.46 mg/dL.

EDS was seen in 26.9% (n=99) of the cohort. Among comorbidities, cerebrovascular disease (19.1% vs 10%; p=0.021) and dementia (47.9% vs 30.9%; p=0.003) were more common in the group with EDS. Malnutrition was detected in 37.3% (n=37) of the group with EDS, and 16% (n=43) of the group with no EDS (p<0.001). Frequency of patients with malnutrition, at risk of malnutrition, and with adequate nutrition in the EDS group were 37%, 39%, and 24%, respectively. These rates were 16%, 46%, and 38% in the non-EDS group, respectively (Figure 1, p=0.001). Among biochemical measurements, serum creatinine levels were found to be higher in the EDS group (1.45±0.53 vs 1.29±0.42 mg/dL; p=0.012), but mean eGFR levels were comparable. Serum levels of vitamin D, vitamin B12, folic acid, and lipids (including total cholesterol, triglyceride, HDL-C, and LDL-C) were comparable across EDS and non-EDS groups. There was no significant difference between these groups for the frequency of deficiencies of vitamin D, vitamin B12, and folic acid. Demographic, clinic and patient characteristics of the total cohort, and EDS and non-EDS groups were shown in Table 1.

Male sex, cerebrovascular disease, dementia, higher number of drugs, malnutrition, and higher numbers of nocturia per night were associated with a higher risk of EDS in univariate analysis. The significant association between malnutrition and EDS persisted in the multivariate regression model (OR 2.58, 95% CI 1.38-4.83, p=0.003) after adjustments for age, sex, cerebrovascular disease, dementia, Charlson comorbidity index, drug counts, and numbers of urinations at night. Results of univariate and multivariate regression analysis are given in Table 2.

Discussion

In this cohort of older patients with CKD, the prevalance of EDS was as high as 26.9%. EDS is more common among older adults [10], and in those who have CKD [18]. The considerably high prevalence in our study is likely explained by the combination of an older age and presence of CKD. The prevalance of EDS in our paper was highest among malnourished patients. Malnutrition increased the risk of EDS by 2.58 times, independent of all other variables which were significantly associated with EDS. We did not observe a relationship between EDS and serum concentrations of vitamin D, vitamin B12, folate, and lipids.

In addition to malnutrition, male sex, dementia, and number of nocturia episodes were other independent predictors of EDS in this cohort. Sex differences in EDS may change by age. Among subjects who were ≥60 years of age, EDS was found to be more common in males (16% vs 13.6%) in the study by Hayley and co-workers [11]. Another study by the same group found that the prevalence was higher in females with an age of 20-29 than males with the same age (14.7% vs 5.1%), while EDS was more common in older males than in older females [10]. The overall prevalence was 10.4% for males and 13.6% for females. In a study from the National Health and Nutrition Examination Survey (NHANES) data [47], which included adults with an age of 18 or older, subjects with EDS were more likely to be younger females. Findings from clinical and experimental studies support the role for sex steroids in sleep modulation [48]. This

may be related to hormonal differences. Intake of soy isoflavone which has estrogen-like effects was shown to be associated with a low risk of long sleep duration in both sexes and a low risk of daytime falling asleep in women [49]. Additional mechanisms of sex disparities in sleep disorders are yet to be clarified.

Dementia was one of the independent predictors of EDS in our study. Indeed, sleep parameters and sleep disorders are associated with a higher risk of dementia, but also sleep can be disturbed in dementia [50]. Importantly, sleep disturbances may be a sign of MCI [51], and early dementia [52]. Moreover, sleep disturbances in dementia are associated with more unfavorable outcomes including more severe cognitive decline, neuropsychiatric symptoms, and poorer quality of life [50]. The association between cognitive impairment and sleep duration was reported to be U-shaped, both short and long durations of sleep being associated with cognitive impairments [53]. Effects of different types of cognitive disorders on different sleep patterns may not be the same, and should be studied in more detail.

Studies which evaluate possible associations between drug counts and EDS are lacking. In our study, drug counts was significantly associated with EDS in univariate analysis, while there was a toward significance in the multivariate regression model. In addition to the drug counts, the type of the drug (sedatives, anti-depressants, etc.) possibly affects sleep quality [54]. Nocturia, which is an initial presenting symptom of CKD, is also a well-recognized and common cause of awakenings and is associated with daytime sleepiness [55]. Similar to the general population, higher frequency of urinations per night was an independent predictor of EDS in our CKD cohort, also.

The relationship between EDS and malnutrition is intriguing. This association remained significant in multivariate analysis after adjustment for all other significantly associated variables. Experimental studies have found that restriction of sleep time lead to lower levels of leptin which is a satiety signal, and higher levels of ghrelin, an appetite stimulating hormone

[47]. Restriction of sleep resulted with increased caloric intake without significant change in energy expenditure resulting in weight gain in clinical studies [56-58]. Based on the association of sleep symptoms with weight gain and cardiometabolic diseases, the study by Grandner and colleagues aimed to demonstrate possible relationships between macro- and micronutrients and sleep disorders [47]. Authors could show numerous associations between different nutrients and different sleep symptoms. In another study by the same group [31], significant associations were shown between many nutrient variables and sleep duration. Authors proposed that possible mechanisms between diet and sleep may include appetite dysregulation, short/long sleep and/or physiologic effects on sleep regulation. Moreover, EDS might have impact on nutrition via altered time of intake [30]. Inversely, some foods may alter the availability of tryptophan, and synthesis of serotonin and melatonin, which in turn promote sleep [59]. With this study, we have shown that similar to the general population, significant association appears to exist between some nutritional factors and EDS among older patients with CKD. Given the cross-sectional design, we could not assess if malnutrition causes EDS, or vice versa. Current literature supports that a bidirectional relationship may exist. Longitudunal studies are needed to demonstrate the cause and effect relationship between nutritional state and EDS.

We could not confirm results some of previous papers who reported significant associations between deficiencies of several micronutrients [23, 24]. The NHANES data demonstrated many associations between intake of numerous nutrients with sleep symptoms [47]. In this study, higher dietary potassium was associated with a lower risk of EDS. In another paper by Cao and co-workers, it was shown that dietary magnesium intake may reduce the risk of EDS in women [60]. In a study by McCarty et al., authors found that in patients without vitamin D deficiency (25-OH-vitamin D $\geq$ 20 ng/mL), Epworth sleepiness scale score was inversely correlated with vitamin D concentration. Among the patients who had vitamin D deficiency (25-OH-vitamin D $<$ 20 ng/mL), Epworth sleepiness scale score was directly

correlated with 25-OH vitamin D in black patients, but not in white patients. Moreover, EDS itself may be a modifier for the effects of vitamin D. In a study from United Kingdom it was shown that the relationship between serum vitamin D concentrations and incident type 2 diabetes mellitus was modified by overall sleep patterns [27], and daytime sleepiness was reported to have the strongest interaction with 25-OH-vitamin D[61].

Our study contains a number of limitations. Firstly, our data were collected from clinical records and documentation of any finding depends on clinical need. Secondly, due to the cross-sectional design, a cause and effect relationship between EDS and malnutrition could not be made. Third, only the ESS scale was used for EDS; hence, future studies should consider using objective measures of sleep to diagnose daytime sleepiness, such as actigraphy. Thirdly, possible underestimation of EDS by the Epworth Sleepiness Scale may be another limitation [61], although it is a widely used and reliable method of assessing sleepiness among older subjects. This was demonstrated in a study [62], which found that around 60% of patients and their close relatives were not able to answer at least one question of ESS. Fourthly, EDS is a symptom which especially in older patients frequently occurs due to multifactorial causes including sleep disorders, underlying medical or psychiatric disorder, depression. We did not include patients who were known to have sleep apnoea syndrome, narcolepsy, or restless leg syndrome; however, patients were not specifically evaluated for possible existence of these disorders. Lastly, there are studies showing that EDS may be related with mild cognitive impairment [51], but our patients in our data were divided according to whether they had dementia or not, thus we could not present the rate of mild cognitive impairment. Strengths of our study include performing comprehensive geriatric assessments, some of which include MNA and Epworth sleepiness scale in the same visit with laboratory evaluations. In addition, the diagnosis of CKD was based on both eGFR and albuminuria. A few patients were regarded as to have CKD based on albuminuria, despite an eGFR of >60 mL/min/1.73 m^2. Another

strength of our study is the use of insomnia severity index concurrently with the Epworth sleepiness scale. The insomnia severity index score was quite comparable across groups, which may indicate that a significant contribution of insufficient time sleep at night on EDS is not likely in our sample.

There is a significant relationship between EDS and malnutrition in older patients with CKD. Therefore, daytime sleepiness and nutritional status should be concurrently evaluated during the assessment of those patients. While examining an older CKD patient with EDS, malnutrition should also be questioned, similarly EDS should be checked in a patient with malnutrition in the geriatric nephrology practice. Thus, it would be possible to manage both conditions more effectively. Longitudinal studies and intervention trials are needed to elucidate the complex pathophysiology of relationship between EDS and malnutrition among older adults with CKD.

Declarations

Funding: None

Conflicts of interest/Competing interests: None to declare

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions: Conceptualization, CH, MAO, PS; Data curation, PS; Formal analysis, CH, MAO, AÇ; Investigation, CH, PS, MAO, RK, LS; Methodology, CH, MAO, PS; Project administration, PS, RK; Resources, PS, RK; Software, CH; Supervision, RK, PS, AÇ; Validation, all authors; Visualization, all authors; Roles/Writing, CH - original draft; Writing - review & editing, MAO, PS, LS, AÇ, RK

Ethics approval: The study was approved by the local Ethics Committee.

Consent to participate: All participants provided written informed consent before the study was initiated.

Consent for publication: All participants provided written informed consent for the publication of their data.

References

1. Kurella M, Luan J, Lash JP, Chertow GM. Self-assessed sleep quality in chronic kidney disease. Int Urol Nephrol. 2005;37(1):159-65. doi:10.1007/s11255-004-4654-z.

2. Turek NF, Ricardo AC, Lash JP. Sleep disturbances as nontraditional risk factors for development and progression of CKD: review of the evidence. Am J Kidney Dis. 2012;60(5):823-33. doi:10.1053/j.ajkd.2012.04.027.

3. Zhang J, Wang C, Gong W, Ye Z, Tang Y, Zhao W et al. Poor sleep quality is responsible for the nondipper pattern in hypertensive but not in normotensive chronic kidney disease patients. Nephrology (Carlton). 2017;22(9):690-8. doi:10.1111/nep.12839.

4. Maugeri A, Medina-Inojosa JR, Kunzova S, Agodi A, Barchitta M, Sochor O et al. Sleep Duration and Excessive Daytime Sleepiness Are Associated with Obesity Independent of Diet and Physical Activity. Nutrients. 2018;10(9). doi:10.3390/nu10091219.

5. Li J, Huang Z, Hou J, Sawyer AM, Wu Z, Cai J et al. Sleep and CKD in Chinese Adults: A Cross-Sectional Study. Clin J Am Soc Nephrol. 2017;12(6):885-92. doi:10.2215/CJN.09270816.

6. Yamamoto R, Shinzawa M, Isaka Y, Yamakoshi E, Imai E, Ohashi Y et al. Sleep Quality and Sleep Duration with CKD are Associated with Progression to ESKD. Clin J Am Soc Nephrol. 2018;13(12):1825-32. doi:10.2215/CJN.01340118.

7. Jhamb M, Ran X, Abdalla H, Roumelioti ME, Hou S, Davis H et al. Association of Sleep Apnea with Mortality in Patients with Advanced Kidney Disease. Clin J Am Soc Nephrol. 2020;15(2):182-90. doi:10.2215/CJN.07880719.

8. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-94. doi:10.1378/chest.14-0970.

9. Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among U.S. adults from 2002 to 2012. Sleep Med. 2015;16(3):372-8. doi:10.1016/j.sleep.2014.12.008.

10. Hayley AC, Williams LJ, Kennedy GA, Berk M, Brennan SL, Pasco JA. Prevalence of excessive daytime sleepiness in a sample of the Australian adult population. Sleep Med. 2014;15(3):348-54. doi:10.1016/j.sleep.2013.11.783.

11. Hayley AC, Williams LJ, Kennedy GA, Holloway KL, Berk M, Brennan-Olsen SL et al. Excessive daytime sleepiness and falls among older men and women: cross-sectional examination of a population-based sample. BMC Geriatr. 2015;15:74. doi:10.1186/s12877-015-0068-2.

12. Soysal P, Smith L, Tan SG, Capar E, Veronese N, Yang L. Excessive daytime sleepiness is associated with an increased frequency of falls and sarcopenia. Exp Gerontol. 2021;150:111364. doi:10.1016/j.exger.2021.111364.

13. Hayley AC, Williams LJ, Kennedy GA, Berk M, Brennan SL, Pasco JA. Excessive daytime sleepiness and body composition: a population-based study of adults. PLoS One. 2014;9(11):e112238. doi:10.1371/journal.pone.0112238.

14. Hayley AC, Williams LJ, Kennedy GA, Berk M, Brennan SL, Pasco JA. Excessive daytime sleepiness and metabolic syndrome: a cross-sectional study. Metabolism. 2015;64(2):244-52. doi:10.1016/j.metabol.2014.09.011.

15. Hayley AC, Williams LJ, Berk M, Kennedy GA, Jacka FN, Pasco JA. The relationship between excessive daytime sleepiness and depressive and anxiety disorders in women. Aust N Z J Psychiatry. 2013;47(8):772-8. doi:10.1177/0004867413490036.

16. Cao X, Gu Y, Fu J, Vu TQC, Zhang Q, Liu L et al. Excessive daytime sleepiness with snoring or witnessed apnea is associated with handgrip strength: a population-based study. QJM. 2019;112(11):847-53. doi:10.1093/qjmed/hcz178.

17. Newman AB, Spiekerman CF, Enright P, Lefkowitz D, Manolio T, Reynolds CF et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. J Am Geriatr Soc. 2000;48(2):115-23. doi:10.1111/j.1532-5415.2000.tb03901.x.

18. Roumelioti ME, Buysse DJ, Sanders MH, Strollo P, Newman AB, Unruh ML. Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis. Clin J Am Soc Nephrol. 2011;6(5):986-94. doi:10.2215/CJN.05720710.

19. Benz RL, Pressman MR, Hovick ET, Peterson DD. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (The SLEEPO study). Am J Kidney Dis. 1999;34(6):1089-95. doi:10.1016/S0272-6386(99)70015-6.

20. Agarwal R, Light RP. Sleep and activity in chronic kidney disease: a longitudinal study. Clin J Am Soc Nephrol. 2011;6(6):1258-65. doi:10.2215/CJN.10581110.

21. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344(2):102-7. doi:10.1056/NEJM200101113440204.

22. Lavoie MR, Patel JA, Camacho M. Nocturnal dialysis improves sleep apnea more than daytime dialysis: a meta-analysis of crossover studies. Sleep Med. 2019;64:37-42. doi:10.1016/j.sleep.2019.06.005.

23. Khawaja I, Yingling K, Bukamur H, Abusnina W. Vitamin B12 Deficiency: A Rare Cause of Excessive Daytime Sleepiness. J Clin Sleep Med. 2019;15(9):1365-7. doi:10.5664/jcsm.7936.

24. McCarty DE, Reddy A, Keigley Q, Kim PY, Marino AA. Vitamin D, race, and excessive daytime sleepiness. J Clin Sleep Med. 2012;8(6):693-7. doi:10.5664/jcsm.2266.

25. Melaku YA, Reynolds AC, Gill TK, Appleton S, Adams R. Association between Macronutrient Intake and Excessive Daytime Sleepiness: An Iso-Caloric Substitution Analysis from the North West Adelaide Health Study. Nutrients. 2019;11(10). doi:10.3390/nu11102374.

26. Reid M, Maras JE, Shea S, Wood AC, Castro-Diehl C, Johnson DA et al. Association between diet quality and sleep apnea in the Multi-Ethnic Study of Atherosclerosis. Sleep. 2019;42(1). doi:10.1093/sleep/zsy194.

27. Wang M, Zhou T, Li X, Ma H, Liang Z, Fonseca VA et al. Baseline Vitamin D Status, Sleep Patterns, and the Risk of Incident Type 2 Diabetes in Data From the UK Biobank Study. Diabetes Care. 2020;43(11):2776-84. doi:10.2337/dc20-1109.

28. Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, Bergstrom J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15(7):953-60. doi:10.1093/ndt/15.7.953.

29. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. J Ren Nutr. 2018;28(6):380-92. doi:10.1053/j.jrn.2018.08.006.

30. Dashti HS, Scheer FA, Jacques PF, Lamon-Fava S, Ordovas JM. Short sleep duration and dietary intake: epidemiologic evidence, mechanisms, and health implications. Adv Nutr. 2015;6(6):648-59. doi:10.3945/an.115.008623.

31. Grandner MA, Jackson N, Gerstner JR, Knutson KL. Dietary nutrients associated with short and long sleep duration. Data from a nationally representative sample. Appetite. 2013;64:71-80. doi:10.1016/j.appet.2013.01.004.

32. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12. doi:10.7326/0003-4819-150-9-200905050-00006.

33. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28. doi:10.1038/ki.2010.483.

34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-8.

35. Association AP. 5TH ed. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: 2013.

36. Dutoglu E, Soysal P, Smith L, Arik F, Kalan U, Kazancioglu RT et al. Nocturia and its clinical implications in older women. Arch Gerontol Geriatr. 2019;85:103917. doi:10.1016/j.archger.2019.103917.

37. Durmaz B, Soysal P, Ellidokuz H, Isik AT. Validity and reliability of geriatric depression scale-15 (short form) in Turkish older adults. North Clin Istanb. 2018;5(3):216-20. doi:10.14744/nci.2017.85047.

38. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601-8. doi:10.1093/sleep/34.5.601.

39. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. doi:10.1093/sleep/14.6.540.

40. Plantinga L, Lee K, Inker LA, Saran R, Yee J, Gillespie B et al. Association of sleep-related problems with CKD in the United States, 2005-2008. Am J Kidney Dis. 2011;58(4):554-64. doi:10.1053/j.ajkd.2011.05.024.

41. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008;12(2):161-8. doi:10.1007/s11325-007-0145-7.

42. Kasanuki K, Ferman TJ, Murray ME, Heckman MG, Pedraza O, Hanna Al-Shaikh FS et al. Daytime sleepiness in dementia with Lewy bodies is associated with neuronal depletion of the nucleus basalis of Meynert. Parkinsonism Relat Disord. 2018;50:99-103. doi:10.1016/j.parkreldis.2018.02.003.

43. Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature--What does it tell us? J Nutr Health Aging. 2006;10(6):466-85; discussion 85-7.

44. Kiesswetter E, Pohlhausen S, Uhlig K, Diekmann R, Lesser S, Uter W et al. Prognostic differences of the Mini Nutritional Assessment short form and long form in relation to 1-year functional decline and mortality in community-dwelling older adults receiving home care. J Am Geriatr Soc. 2014;62(3):512-7. doi:10.1111/jgs.12683.

45. Holvoet E, Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, Eloot S. The screening score of Mini Nutritional Assessment (MNA) is a useful routine screening tool for malnutrition risk in patients on maintenance dialysis. PLoS One. 2020;15(3):e0229722. doi:10.1371/journal.pone.0229722.

46. Soysal P, Smith L, Capar E, Kalan U, Arik F, Isik AT. Vitamin B12 and folate deficiencies are not associated with nutritional or weight status in older adults. Exp Gerontol. 2019;116:1-6. doi:10.1016/j.exger.2018.12.007.

47. Grandner MA, Jackson N, Gerstner JR, Knutson KL. Sleep symptoms associated with intake of specific dietary nutrients. J Sleep Res. 2014;23(1):22-34. doi:10.1111/jsr.12084.

48. Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Philos Trans R Soc Lond B Biol Sci. 2016;371(1688):20150110. doi:10.1098/rstb.2015.0110.

49. Cao Y, Taylor AW, Zhen S, Adams R, Appleton S, Shi Z. Soy Isoflavone Intake and Sleep Parameters over 5 Years among Chinese Adults: Longitudinal Analysis from the Jiangsu Nutrition Study. J Acad Nutr Diet. 2017;117(4):536-44 e2. doi:10.1016/j.jand.2016.10.016.

50. Wennberg AMV, Wu MN, Rosenberg PB, Spira AP. Sleep Disturbance, Cognitive Decline, and Dementia: A Review. Semin Neurol. 2017;37(4):395-406. doi:10.1055/s-0037-1604351.

51. Ohayon MM, Vecchierini MF. Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med. 2002;162(2):201-8. doi:10.1001/archinte.162.2.201.

52. Rongve A, Boeve BF, Aarsland D. Frequency and correlates of caregiver-reported sleep disturbances in a sample of persons with early dementia. J Am Geriatr Soc. 2010;58(3):480-6. doi:10.1111/j.1532-5415.2010.02733.x.

53. Lo JC, Groeger JA, Cheng GH, Dijk DJ, Chee MW. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. Sleep Med. 2016;17:87-98. doi:10.1016/j.sleep.2015.08.021.

54. Lande RG, Gragnani C. Relationships between polypharmacy and the sleep cycle among active-duty service members. J Am Osteopath Assoc. 2015;115(6):370-5. doi:10.7556/jaoa.2015.077.

55. Sacomori C, Cardoso FL, Louzada FM, Pereira EF. Excessive daytime sleepiness and nocturia in women. Sleep Med. 2014;15(6):677-80. doi:10.1016/j.sleep.2014.01.017.

56. Calvin AD, Carter RE, Adachi T, Macedo PG, Albuquerque FN, van der Walt C et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. Chest. 2013;144(1):79-86. doi:10.1378/chest.12-2829.

57. Markwald RR, Melanson EL, Smith MR, Higgins J, Perreault L, Eckel RH et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc Natl Acad Sci U S A. 2013;110(14):5695-700. doi:10.1073/pnas.1216951110.

58. St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A et al. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. Am J Clin Nutr. 2011;94(2):410-6. doi:10.3945/ajcn.111.013904.

59. Peuhkuri K, Sihvola N, Korpela R. Diet promotes sleep duration and quality. Nutr Res. 2012;32(5):309-19. doi:10.1016/j.nutres.2012.03.009.

60. Cao Y, Zhen S, Taylor AW, Appleton S, Atlantis E, Shi Z. Magnesium Intake and Sleep Disorder Symptoms: Findings from the Jiangsu Nutrition Study of Chinese Adults at Five-Year Follow-Up. Nutrients. 2018;10(10). doi:10.3390/nu10101354.

61. Sforza E, Pichot V, Martin MS, Barthelemy JC, Roche F. Prevalence and determinants of subjective sleepiness in healthy elderly with unrecognized obstructive sleep apnea. Sleep Med. 2015;16(8):981-6. doi:10.1016/j.sleep.2015.03.010.

62. Onen F, Moreau T, Gooneratne NS, Petit C, Falissard B, Onen SH. Limits of the Epworth Sleepiness Scale in older adults. Sleep Breath. 2013;17(1):343-50. doi:10.1007/s11325-012-0700-8.

Figure Legends

Figure 1. Among patients with excessive daytime sleepiness (EDS, left), the frequency malnutrition, risk of malnutrition, and adequate nutrition was 38%, 40%, and 22%, respectively. In comparison, patients without EDS (non-EDS, right), these rates were 16%, 46%, and 38%, respectively (Figure 1, p=0.001).

Nutrition classes across EDS groups
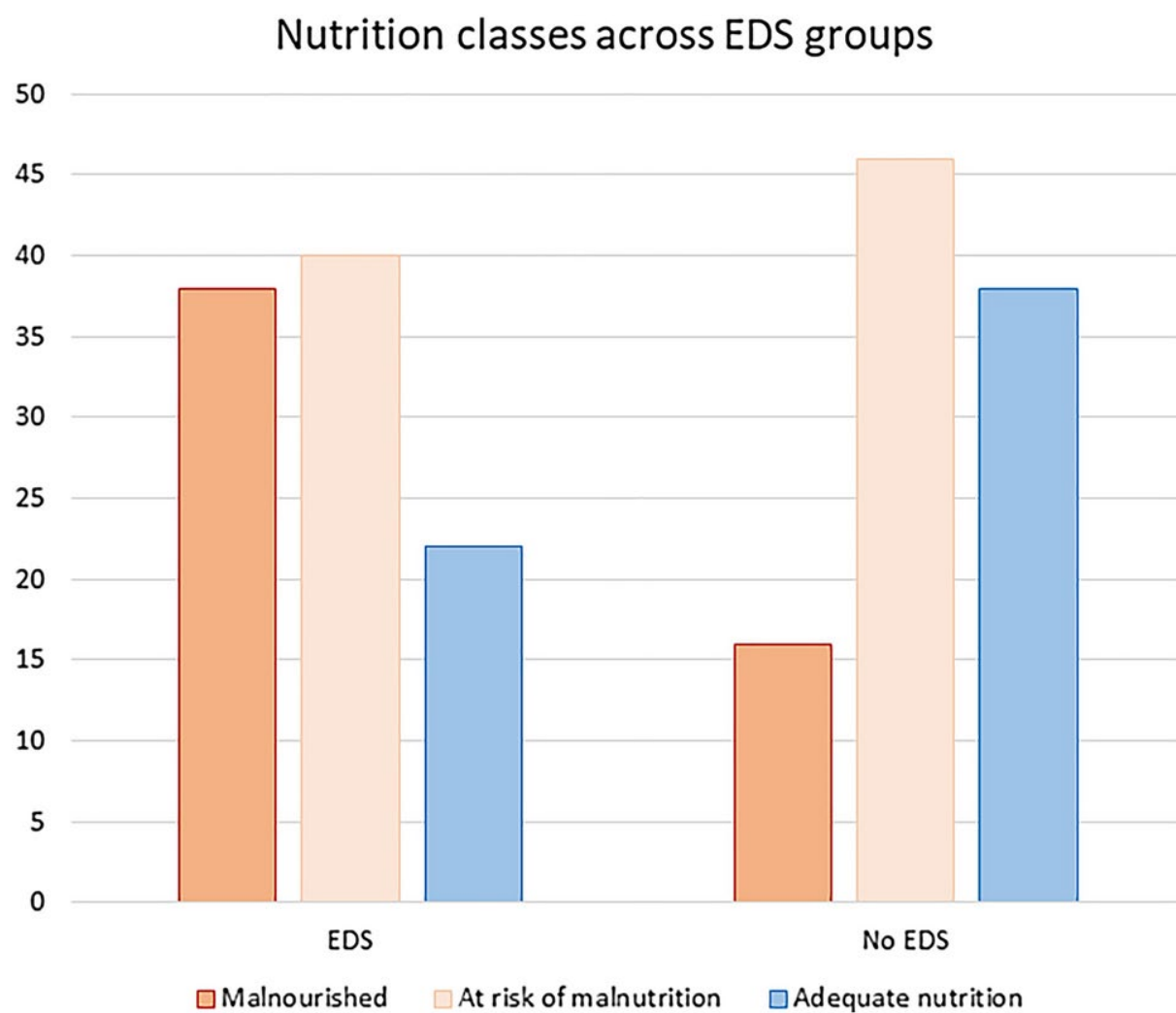
Tables

Table 1. General characteristics of the study sample, and patients with and without excessive daytime sleepiness.

Variable	Total cohort (N=367)	EDS (n=99)	No EDS (n=268)	p-value
Age, years	81±7	82±6	81±7	0.201
Female sex	248 (68%)	50 (51%)	198 (74%)	<0.001
Body-mass index, kg/m^2	29.6±5.7	29.7±5.6	29.1±6.2	0.451
Arm circumference, cm	28.5±3.8	28±4.2	28.6±3.6	0.181
Calf circumference, cm	35.8±4.6	35±4.4	36±4.7	0.179
Number of drugs	6.8±3.4	7.5±3.3	6.5±3.4	0.008
Sedatives and/or anti-depressant drugs	72 of 298 (24%)	21 of 78 (27%)	51 of 220 (23%)	0.507
Epworth Sleepiness scale	7.1±6.5	15.9±4.4	3.8±3.3	<0.001
Insomnia severity index	13.5±9.6	13.6±9.9	13.4±9.6	0.978
MNA score	20.8±5.1	18.8±5.7	22±4.6	<0.001
Malnutrition	80 (22%)	37 (37%)	43 (16%)	<0.001
At risk of malnutrition	160 (44%)	39 (39%)	121 (46%)	
Nocturia	312 (85%)	76 (77%)	236 (88%)	0.622
Number of urinations per night	2.9±2.3	3.3±2.5	2.7±2.2	0.042
Depression	157 of 314 (50%)	40 of 72 (56%)	117 of 242 (48%)	0.283
Charlson comorbidity index	5.2±1.3	5.8±1.4	5.0±1.1	<0.001
Comorbidities				
Diabetes mellitus	155 (42%)	42 (42%)	113 (42%)	0.964
Hypertension	277 (75%)	73 (74%)	204 (76%)	0.638
Cerebrovascular disease	46 (13%)	19 (19%)	27 (10%)	0.021
Heart failure	65 (18%)	18 (18%)	47 (18%)	0.909
Dementia	130 (35%)	47 (47%)	83 (31%)	0.003
Chronic obstructive lung disease	44 (12%)	15 (15%)	29 (10%)	0.262
CKD stage				0.328
Stage 1 (≥90 mL/min/1.73m^2)	3 (1%)	1 (1%)	2 (1%)	
Stage 2 (60-89 mL/min/1.73m^2)	20 (5%)	4 (4%)	16 (6%)	
Stage 3 (30-59 mL/min/1.73m^2)	299 (82%)	77 (78%)	222 (83%)	
Stage 4 (15-29 mL/min/1.73m^2)	45 (12%)	17 (17%)	28 (11%)	
Serum creatinine, mg/dL	1.34±0.46	1.45±0.53	1.29±0.42	0.012
eGFR, mL/min/1.73m^2	45±14	44±15	46±14	0.449
Hemoglobin, g/dL	12.3±5.1	11.8±1.8	12.4±5.9	0.219
Folic acid, ng/mL	7.4±5.6	7.7±4.6	7.4±6	0.414

Vitamin B12, pg/mL	523±440	554±474	516±434	0.861
Vitamin D, ng/mL	25±16	24±17	26±15	0.127
Total cholesterol, mg/dL	205±55	192±41	203±47	0.171
CKD: chronic kidney disease; eGFR:estimated glomerular filtration rate; MNA: mini nutritional risk assessment.				

Table 2. Multivariate model of factors associated with excessive daytime sleepiness.

Variables	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	P
Age	1.02	0.99-1.06	0.230	1.01	0.96-1.04	0.998
Male sex	2.78	1.72-4.48	<0.001	**2.53**	**1.46-4.41**	**0.001**
Cerebrovascular disease	2.10	1.11-3.99	0.023	1.58	0.65-3.84	0.308
Dementia	2.04	1.27-3.28	0.003	**2.78**	**1.46-5.31**	**0.002**
Charlson comorbidity index score (per score)	1.54	1.28-1.85	<0.001	1.12	0.85-1.48	0.430
Drug count (per drug)	1.09	1.02-1.17	0.016	1.08	0.99-1.17	0.083
Malnutrition (MNA of <17)	3.18	1.89-5.38	<0.001	**2.58**	**1.38-4.83**	**0.003**
Number of urinations at night	1.11	1.00-1.23	0.044	**1.15**	**1.03-1.29**	**0.015**