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Original Article

Daytime napping and diabetes-associated kidney disease☆

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ABSTRACT

Background: Diabetes-associated Kidney Disease (DKD) is a common comorbidity in patients with type 2 diabetes. The present study investigates whether daytime sleeping duration in patients, ill with type 2 diabetes, is associated with DKD.

Methods: A total of 733 outpatients of the cross-sectional baseline survey of the DIACORE study were analyzed with respect to their self-reported daytime sleeping duration, assessed by a standardized questionnaire. DKD was defined as eGFR <60 ml/min/1.73 m^2 and/or urinary albumin-to-creatinine-ratio (UACR) > 30 mg/g.

Results: Mean daytime sleeping duration was 17 ± 27 min. With increasing daytime sleeping duration a statistically significant decrease in eGFR ($p = 0.002$) and increase in UACR ($p < 0.001$) were found, respectively. Prevalence of DKD was significantly higher in patients with longer daytime sleeping duration (31% in patients not napping, 40% in patients napping less than 30 min, 47% in patients napping 30–60 min, 56% in patients napping 60 min or more; $p = 0.001$). After accounting for known modulators (Age, sex, BMI, waist-hip-ratio, systolic and diastolic blood pressure, physical activity, diabetes duration, HbA1c, homeostasis model assessment (HOMA-Index), nighttime sleeping duration, apnea-hypopnea-index (AHI), Epworth Sleepiness Scale (ESS)), longer daytime sleeping duration was significantly associated with impaired eGFR [B (95% CI) = −0.05 (-0.09; 0.00), $p = 0.044$] and increased UACR [B (95% CI) = 0.01 (0.01; 0.02), $p < 0.001$], respectively.

Conclusion: Increased daytime sleeping duration is significantly associated with reduced eGFR and higher UACR, independent of known modulators of DKD. The direction of this relationship remains unclear.

1. Introduction

Several studies found a U-shaped relationship between sleeping duration and important health outcomes, including all-cause mortality [1], cardiovascular disease [1,2], chronic kidney disease [3] and diabetes [4]. Most of these studies evaluated nighttime sleeping duration or total daily sleeping duration. While daytime napping is often linked to improvements in performance and memory processes [5], it is also correlated with poor health and underlying illness. Recently, correlations between daytime napping and various health outcomes have been shown. These include all-cause mortality [6], cardiovascular disease [7], metabolic syndrome [8] and diabetes [9–11]. Many studies focused on diabetes, as it is considered one of the world's biggest health problems [12]. The global prevalence of diabetes is estimated to be 10% in adults aged 25 or older [13].

Diabetes mellitus can affect many organ systems [13]. One of the most common and most problematic complications is diabetes-associated kidney disease (DKD) [13], defined as a urinary albumin-to-creatinine ratio (UACR) > 30 mg/g or estimated

☆ Daytime napping duration is independently associated with Diabetes-associated Kidney Disease.

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glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 in patients with diabetes mellitus. Causes for development and progression of DKD are diverse and not yet completely understood [14]. Several important risk factors have been established, including hypertension [15] and poor glycemic control [14]. Both factors are independently associated with habitual daytime napping [10,11,16]. However, there is no study investigating the role of daytime sleeping duration in renal function in a sample of outpatients ill with type 2 diabetes.

It is noteworthy to examine whether or not daytime sleeping duration is associated with DKD due to several reasons: first, the duration of daytime sleep might modify nighttime sleep quantity, which was associated with kidney function in previous studies [17–23]. Second, daytime sleeping is linked to major modulating factors of DKD, as noted above. Third, reasons for the development and progression of DKD are poorly understood, despite its impact as a global health issue [13,14]. Thus, we investigated whether daytime sleeping duration in patients, ill with type 2 diabetes, is associated with DKD, independently from known modulators of DKD.

2. Methods

2.1. Study design

The investigated patients were participants of the DIACORE (DIAbetes COhoRtE) sleep-disordered breathing (SDB) sub-study. DIACORE is designed as a two-center, prospectively planned study of patients ill with type 2 diabetes, of European descent, with a baseline survey conducted during 2010–2014 and recruitment and ascertainment described previously [24]. Briefly, written invitations were mailed to all patients ill with type 2 diabetes, registered with five medical insurance companies in the respective year of the mailing, and to all outpatients ill with type 2 diabetes, of two diabetologists in Regensburg who had visited the offices within the last six months of the mailing. Additional invitations were sent to patients ill with type 2 diabetes, who had received inpatient treatment at the University Hospital Regensburg's Internal Medicine Departments within two years before the mailing. Overall, 4226 patients contacted DIACORE, of which 1226 did not fulfill the in- and exclusion criteria. The status of diabetes was ascertained by assessing diabetes medication or by validating self-report. Patients were subjected to a standardized online questionnaire, blood sampling and physical examination at the two study centers. Among 1036 individuals invited to participate in the DIACORE-SDB sub-study, 770 individuals agreed to participate. 37 patients (5%) were excluded due to missing data on daytime sleeping duration, eGFR or UACR, so that 733 patients were included in the final analysis. A two-year follow-up is currently ongoing [24]; for this investigation, the cross-sectional baseline dataset was used. The protocol, the data protection strategy and the study procedures were approved by the Ethics Committees of participating institutions and are in accordance with the Declaration of Helsinki. Patients participate in DIACORE only after providing informed written consent. The study protocol has been described previously [24,25].

2.2. Study sample

All outpatients with type 2 diabetes, inhabiting the city and county of Regensburg or Speyer were eligible for DIACORE. Further inclusion criteria were the ability to fully understand the study information and to provide written informed consent, age ≥18 years and self-reported Caucasian ethnicity. Exclusion criteria were chronic renal replacement therapy (hemodialysis, peritoneal dialysis or transplantation), history of active malignancy within the last five years, autoimmune-disease potentially affecting kidney function, hemochromatosis, known pancreoprivic or self-reported type 1 diabetes mellitus, acute infection, fever, pregnancy, and chronic viral hepatitis or HIV-infection [24]. For the DIACORE-SDB substudy, patients were included if they consented to perform SDB monitoring and excluded if they currently used positive airway pressure therapy [25]. An overview of the patients excluded is given in Fig. 1.

2.3. Assessment of daytime sleeping duration

Information on sleeping habits was gathered by questionnaire (Supplementary Table 1). Questions included nighttime sleeping and daytime sleeping habits. For comparison, patients were stratified into four groups according to their daytime sleeping duration. In the literature different cut-offs have been established, with no nap, 30 min, 60 min, and 90 min being the most frequent [6–9]. In the present analysis, “group one” consists of all patients not regularly taking an afternoon nap and is used as reference value for the calculation of odds ratios (OR). “Group two” (≤30 min) and “group three” (>30–60 min) contain a similar number of patients and those patients reporting a regular afternoon nap of more than 60 min were defined as “group four.”

2.4. Assessment of sleep-related parameters

Nasal flow and pulse oximetry were measured using the ApneaLink device (ResMed, Australia, Sydney) that has been validated in several studies for monitoring of SDB [26–28]. Trained study personnel instructed the participants about the use of the device in a standardized manner. By comparing ApneaLink to the gold standard polysomnography, studies have reported a sensitivity of 73–94% and a specificity of 85–95% using an apnea-hypopnea-index cut-off value of 15/h [28,29]. Apnea-hypopnea-index, oxygen desaturation index, mean oxygen saturation (SpO2) and minimum SpO2 were documented. The default settings of the monitoring device were used for the definitions of apnea, hypopnea, and desaturation: apnea was defined as ≥80% decrease in airflow for ≥10 s; hypopnea was defined as a decrease in airflow by

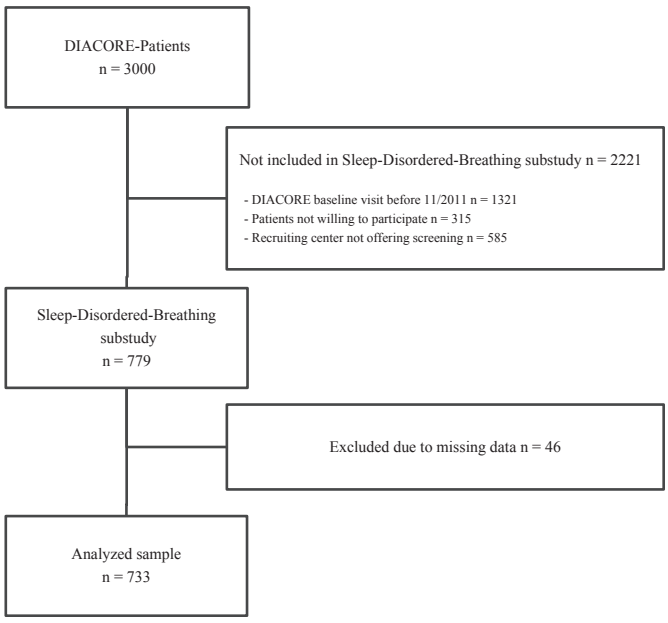

Fig. 1. Flow-chart indicating the recruiting process for the DIACORE Sleep-Disordered-Breathing substudy.

50–80% versus baseline for ≥10 s followed by a ≥4% decrease in oxygen saturation [30].

Additionally, subjective daytime sleepiness was assessed using the self-administered, validated Epworth Sleepiness Scale. Individuals were asked to rate their likelihood of falling asleep in several common situations. Scores range from 0 (least sleepy) to 24 (sleepiest). Excessive daytime sleepiness is defined as a score of 11 or higher [31].

2.5. Assessment of DKD

eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [32]. UACR was determined from a spot midstream urine sample, with dipstick testing on fresh urine to exclude urinary tract infection. DKD was defined as the presence of eGFR <60 ml/min/1.73 m^2 or a UACR >30 mg/g. Microalbuminuria was defined as 30 mg/g < UACR ≤300 mg/g and macro-albuminuria was defined as UACR >300 mg/g.

2.6. Statistical analysis

Descriptive data are presented as a mean ± standard deviation for normally distributed variables, as a median and interquartile range (IQR) for non-normally distributed data and as absolute and relative frequencies for categorical data. Baseline characteristics between the four groups (no daytime sleep, 0–30 mins, 30–60 mins, >60 mins) were compared accordingly by an analysis of variance (ANOVA), the non-parametric Kruskal–Wallis Test or by Pearson's chi-squared tests. Linear regression models were used to determine relationships, independent of known risk factors, with eGFR and UACR, respectively. Only significant covariates with $p < 0.05$, causing an alteration of >10% in the unstandardized regression coefficient (B) for the respective endpoint in bivariable analysis with daytime sleeping duration, were applied as covariates in the multivariable regression model [33]. In a different approach, all significant covariables with $p < 0.05$ in the bivariable analysis with daytime sleeping duration were applied as covariates in the multivariable regression model with no regard to the unstandardized regression coefficient. Outcome variables, as well as potential modulators included in the linear regression models, were either normally distributed or transformed by logarithmic calculus before incorporation in the models (UACR). Furthermore, restricted cubic splines were fitted to unconditional logistic models to examine non-parametrically possible non-linear relationships between nighttime sleeping duration, daytime sleeping duration and the odds ratio for DKD, respectively.

Results for the linear regression models are given as unstandardized regression coefficient (B) and 95% confidence interval (CI). Logistic regression models are presented by odds ratios. P-values < 0.05 were considered to indicate statistical significance. Data were analyzed using the SAS 9.4 (SAS Institute, Inc., NC).

3. Results

Overall, 733 study participants were included in this analysis, of which 450 were men (61%). Mean age was 66 ± 9 years, mean diabetes duration 10 ± 8 years. Participants had an average HbA1c of 6.8 ± 1.1% and were mostly obese with a mean BMI of 31 ± 6 kg/m^2. In patients taking a regular daytime nap the median of the daytime sleeping duration was found to be 45 min with an IQR of 30 min. Clinical characteristics are presented in Table 1. Table 2 displays clinical characteristics according to four categories of daytime sleeping duration: patients that did not regularly take a daytime nap (n = 468; 64%); patients napping less than 30 min per day (n = 126; 17%); patients napping 30–60 min per day (n = 124; 17%) and patients napping more than 60 min per day (n = 26; 4%). Of note, groups vary in sample size, with the smallest group, featuring a daytime sleeping duration of >60 min per day, only containing 26 participants. The four groups showed a statistically significant difference in age ($p < 0.001$). The proportion of men tended to increase with longer daytime sleeping duration ($p = 0.014$). Known modulators of DKD like blood pressure and smoking habits showed no significant difference between the groups (each $p > 0.05$). Daytime sleeping duration tended to increase with patients indicating a higher diabetes duration ($p = 0.008$). Participants with longer sleeping duration were more likely to have a higher waist-hip-ratio ($p = 0.002$) and to suffer from metabolic syndrome ($p = 0.007$) according to NCEP-ATPIII criteria [34]. The difference in HbA1c was statistically significant between groups, but did not show a clinically relevant tendency ($p = 0.002$). Assessment of sleep apnea showed that AHI during monitoring nights tended to increase with longer daytime sleeping duration, but the difference was not statistically significant ($p > 0.05$). Longer daytime sleeping duration was paralleled by longer nighttime sleeping duration ($p = 0.012$) and higher daytime sleepiness (as assessed by ESS) ($p < 0.001$).

Table 1
Clinical characteristics at baseline of 733 participants, 450 men and 283 women.

	Total	Men	Women
N	733	450	283
Age [years]	66 ± 9	66 ± 9	65 ± 9
Systolic blood pressure [mmHg]	138 ± 18	139 ± 18	137 ± 18
Diastolic blood pressure [mmHg]	75 ± 10	77 ± 10	71 ± 9
Duration of Diabetes mellitus type II [years]	10 ± 8	11 ± 8	9 ± 8
Current smokers, n (%)	81 (11%)	52 (11%)	29 (10%)
BMI [kg/m^2]	31 ± 6	31 ± 5	32 ± 6
Waist-Hip-Ratio	0.96 ± 0.08	1.00 ± 0.06	0.90 ± 0.06
HOMA-Index[a,b]	4.6 [IQR 5.6]	4.8 [IQR 5.5]	4.4 [IQR 6.3]
HbA1c [%]	6.8 ± 1.1	6.9 ± 1.2	6.8 ± 1.1
Metabolic Syndrome (NCEP-ATPIII [34]), n (%)	410 (56%)	239 (53%)	171 (60%)
Apnea-hypopnea-index [/hour][a]	10.0 [IQR 13.0]	11.0 [IQR 14.0]	7.0 [IQR 10.0]
Nighttime Sleeping duration (self-estimated) [min]	440 ± 99	443 ± 93	436 ± 107
Epworth Sleepiness Scale	5 ± 3	6 ± 4	5 ± 3
eGFR	78 ± 19	78 ± 19	79 ± 20
UACR[a]	9.9 [IQR 25.5]	11.1 [IQR 33.4]	9.0 [IQR 17.8]

DIACORE study: Sample size n = 733; Data are expressed as mean ± standard deviation.
BMI = body mass index; HOMA = homeostasis model assessment; HbA1c = glycated hemoglobin; NCEP = national cholesterol education program; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine-ratio.
[a] Indicated as median and Interquartile Range.
[b] Sample Size: n = 705.

When examining the relation between nighttime sleeping duration and DKD using a spline regression modeling the OR non-linearly, we found a tendency of a U-shaped relationship (Supplementary Figure 1) that was not statistically significant (modeling a linear relationship, test of association: $p = 0.737$; modeling a non-linear relationship, test of association: $p = 0.695$). When analyzing the prevalence of DKD in dependency of categories of nighttime sleeping duration, there was no statistical difference (Supplementary Figure 2). No association was found between self-reported nighttime sleeping duration and DKD.

Investigating categories of daytime sleeping duration with eGFR (Fig. 2A), we found a statistically significant decrease in eGFR by increased daytime sleeping duration ($p = 0.002$).

To determine whether the association between increasing daytime sleeping duration and decreasing eGFR remained

Table 2
Clinical Characteristics of 733 participants according to groups of daytime sleeping duration.

	No regular nap	≤30 min	>30–60 min	>60 min	p-value (ANOVA)
N	468	126	124	26	
Age [years]	64 ± 9	69 ± 7	67 ± 9	66 ± 9	**p < 0.001**
Sex (men), n (%)[a]	269 (58%)	78 (65%)	82 (68%)	21 (84%)	**p = 0.014**
Systolic blood pressure [mmHg]	138 ± 17	139 ± 21	140 ± 21	140 ± 20	p = 0.520
Diastolic blood pressure [mmHg]	75 ± 10	73 ± 10	75 ± 10	72 ± 9	p = 0.200
Duration of Diabetes mellitus type II [years]	10 ± 8	11 ± 8	11 ± 8	15 ± 12	**p = 0.008**
Smoking, n (%)[a]	56 (12%)	10 (8%)	13 (10%)	2 (8%)	p = 0.649
BMI [kg/m^2]	30.9 ± 5.2	31.0 ± 6.2	31.9 ± 6.1	32.8 ± 5.2	p = 0.166
Waist-Hip-Ratio	0.96 ± 0.08	0.96 ± 0.07	0.97 ± 0.08	1.01 ± 0.07	**p = 0.002**
HOMA-Index[b,c,d]	4.5 [IQR 5.59]	4.2 [IQR 5.2]	5.4 [IQR 7.1]	7.3 [IQR 5.9]	p = 0.051
HbA1c [%]	6.8 ± 1.1	6.8 ± 0.9	7.2 ± 1.4	6.8 ± 1.0	**p = 0.002**
Metabolic Syndrome (NCEP-ATPIII [34]), n (%)[a]	255 (55%)	60 (50%)	76 (63%)	19 (76%)	**p = 0.007**
Apnea-hypopnea-index [/hour][b, d]	9.0 [IQR 13.0]	11.0 [IQR 14.0]	11.0 [IQR 13.3]	14 [IQR 24.5]	p = 0.208
Nighttime sleeping duration (self-estimated) [min]	433 ± 99	451 ± 93	448 ± 100	489 ± 101	**p = 0.012**
Epworth Sleepiness Scale	5 ± 3	6 ± 4	6 ± 3	7 ± 3	**p < 0.001**

DIACORE study: Sample size n = 733; Data are expressed as a mean ± standard deviation, if not indicated otherwise. Groups were compared by ANOVA if not indicated otherwise.
BMI = body mass index; HOMA = homeostasis model assessment; HbA1c = hemoglobin A1c; NCEP = National Cholesterol Education Program; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.
p-values printed in bold were significant (p < 0.05).
[a] Compared by χ^2-Test.
[b] Indicated as median and Interquartile Range [IQR].
[c] Sample Size: n = 705.
[d] Compared by Kruskal-Wallis-Test.

significant when other factors were included, a multivariable linear regression analysis was performed. Age, sex, BMI, waist-hip-ratio, systolic and diastolic blood pressure, physical activity, diabetes duration, HbA1c, and HOMA-Index, as well as self-estimated nighttime sleeping duration, AHI, and ESS, were tested in bivariable linear regression analysis with daytime sleeping duration, respectively. Only statistically significant covariables with p < 0.05 and >10% alteration in the regression coefficient for daytime sleeping duration, namely age, diabetes duration, and ESS, were adopted for the multivariable regression model [33]. Increased daytime sleeping duration remained significantly and independently associated with decreased eGFR [B (95% CI) = −0.05 (-0.09; 0.00); p = 0.044] (Table 3). When additionally including sex into the model, daytime sleeping duration remained significantly associated with decreased eGFR [B (95% CI) = −0.05 (-0.09; −0.00); p = 0.041], as did age [B (95% CI) = −1.08 (-1.22; −0.93); p < 0.001] and diabetes duration [B (95% CI) = −0.21 (-0.36; −0.05); p = 0.010]. In a different approach, all covariates that showed a significant p-Value of p < 0.05 in the bivariate linear regression analysis with daytime sleeping duration, namely age, diabetes duration, ESS, mean systolic and diastolic blood pressure, nighttime sleeping duration, and AHI were adopted for the multivariable linear regression model. In this case, daytime sleeping duration was no longer significantly associated with decreased eGFR [B (95% CI) = −0.05 (- 0.10; 0.00); p = 0.074]. Only age [B (95% CI) = −0.99 (-1.16; −0.82); p < 0.001], diabetes duration [B (95% CI) = −0.19 (- 0.36; - 0.01); p = 0.035], diastolic blood pressure [B (95% CI) = 0.25 (0.09; 0.41); p = 0.003] and the AHI [B (95% CI) = - 0.16 (-0.26; −0.06); p = 0.010] remained significantly associated with decreased eGFR.

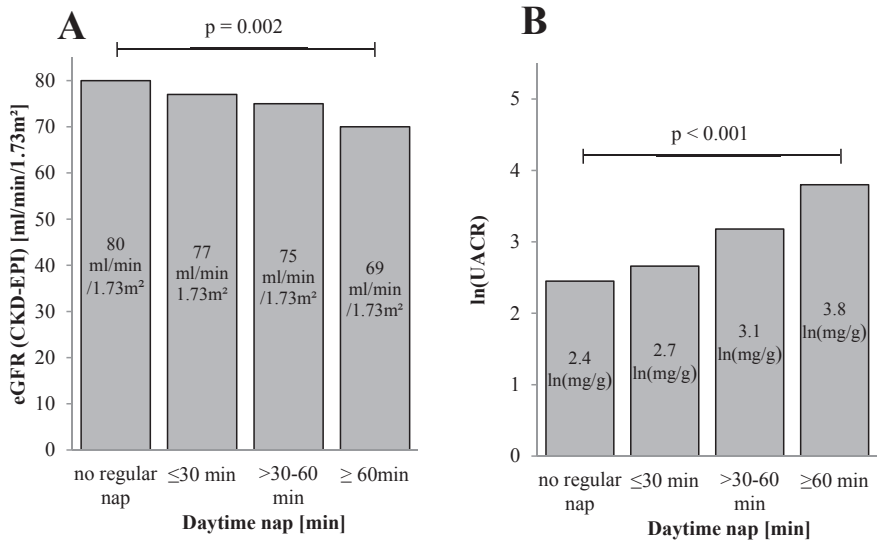

Fig. 2. Bar chart indicating **A** the eGFR according to groups of daytime sleeping duration and **B** the UACR (analyzed on ln-scale) according to groups of daytime sleeping duration. DIACORE study: Sample size n = 733. Data are shown as mean per group. ANOVA p-value is given for overall association. eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

Table 3
Modulators for eGFR and UACR.

Variable	Multivariable Analysis	
	B (95% CI)	p-value
Modulators for eGFR [ml/min/1.73m^2]		
Daytime nap [min]	−0.05 (−0.09; 0.00)	**0.044**
Epworth Sleepiness Scale	0.00 (−0.36; 0.36)	0.993
Age [years]	−1.08 (−1.22.; −0.93)	**<0.001**
diabetes duration [years]	−0.21 (−0.36; −0.05)	**0.010**
Modulators for UACR [ln (mg/g)]		
Daytime sleeping duration [min]	0.01 (0.01; 0.02)	**<0.001**
Apnea-hypopnea-index	0.01 (0.01; 0.02)	**0.004**

DIACORE study: Sample size n = 733; Shown are the results of linear regression models for eGFR and UACR (transformed by logarithmic calculus).
Data show unstandardized regression coefficient (B) by multivariable linear regression analysis, 95% confidence intervals (95% CI) and p-values.
eGFR = estimated glomerular filtration rate; HOMA = homeostasis model assessment; UACR = urinary albumin-to-creatinine ratio.
p-values printed in bold were significant (p < 0.05).

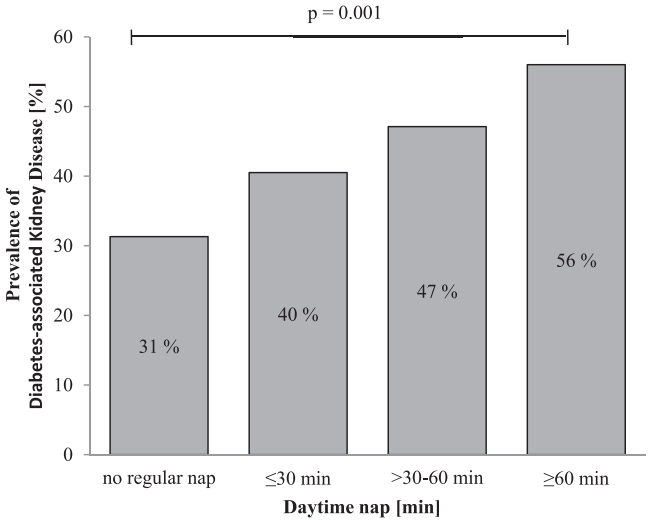

Fig. 3. Bar chart indicating the prevalence of Diabetes-associated Kidney Disease according to groups of daytime sleeping duration. DIACORE study: Sample size n = 733. The p-value for overall association was calculated by chi^2-test.

UACR was significantly increased with longer daytime sleeping duration (p < 0.001, Fig. 2B). When modeling UACR in a linear regression model without additional covariates, we found longer daytime sleeping duration significantly associated with higher UACR [B (95% CI) = 2.34 (1.68; 3.00), p < 0.001]. Including the above-stated factors as covariates, only AHI showed to be a significant modulator of this relationship (alteration of B > 10% and p < 0.05) [33] and was included in the multivariable analysis. Increased daytime sleeping duration remained significantly and independently associated with increased UACR [B (95% CI) = 0.01 (0.01; 0.02), p < 0.001] (Table 3). When additionally including sex into the model, daytime sleeping duration remained significantly associated with higher UACR [B (95% CI) = 0.01 (0.01; 0.02); p < 0.001], as did the AHI [B (95% CI) = 0.01 (0.01; 0.02); p = 0.005]. In a different approach, all covariates that showed a significant p-Value of p < 0.05 in the bivariate linear regression analysis with daytime sleeping duration, namely age, diabetes duration, waist-hip-ratio, mean systolic and diastolic blood pressure, HbA1c and AHI were adopted for the multivariable linear regression model. In this model, daytime sleeping duration remained significantly associated with a higher UACR [B (95% CI) = 0.01 (0.01; 0.01); p < 0.001]. Furthermore, diabetes duration [B (95% CI) = 0.02 (0.01; 0.03); p = 0.008], mean systolic blood pressure [B (95% CI) = 0.02 (0.01; 0.03); p < 0.001] and HbA1c [B (95% CI) = 0.14 (0.04; 0.24); p = 0.006] remained significantly associated with higher UACR.

The prevalence of DKD, defined as eGFR ≤60 ml/min/1.73 m^2 or UACR >30 mg/g, was significantly higher in patients with longer daytime sleeping duration (p = 0.001; Fig. 3). The relation between duration of daytime nap and the OR was proven to be linear by fitting restricted cubic splines to unconditional logistic models (test for non-linear relation: p = 0.646; test for linear relation: p = 0.008; Fig. 4).

Total daily sleeping duration was calculated as the sum of nighttime sleeping duration and daytime napping duration. For the present analysis, patients were stratified into quartiles by reference to their total daily sleeping duration. We found a correlation between longer total daily sleeping duration and a decrease in eGFR that was statistically significant (p < 0.001; Supplementary Figure 3A). We found a moderate increase in UACR correlated with longer total daily sleeping duration. However, this relationship was not statistically significant (p = 0.577; Supplementary Figure 3B).

Applying a multivariable linear regression model following the above-noted method, the relationship between eGFR and total daily sleeping duration was no longer of statistical significance [B (95% CI) = −0.01 (-0.03; 0.00); p = 0.064]. The prevalence of diabetes-associated kidney disease, defined as eGFR ≤60 ml/min/1.73 m^2 or UACR >30 mg/g, is shown in Supplementary Figure 4. eGFR did not differ significantly between quartiles of total daily sleeping duration (each p-Value > 0.050). The overall association assessed by chi^2-test was not statistically significant (p = 0.140).

4. Discussion

This study evaluates the essential parameters of kidney function in relation to sleeping and daytime sleeping habits in a large sample of outpatients ill with type 2 diabetes. Our findings suggest that, while nighttime sleeping duration is not associated with kidney function, longer daytime sleeping duration shows a significant association with impairment of eGFR and UACR. Both relationships were independent of known modulators for eGFR and UACR.

Previous data on the association of daytime sleeping duration on kidney function is limited. Guo et al., investigated the association between self-reported sleeping duration and eGFR in a sample of 5555 hypertensive Chinese patients. In addition, 15% (n = 838) of the study sample additionally suffered from Diabetes mellitus. Contrary to our results no correlation between daytime napping and reduced eGFR was found [18]. However, this discrepancy might be due to important differences in the study populations. In DIACORE we analyzed a European sample of outpatients ill with type 2 diabetes, whereas only a small percentage of the study sample of Guo et al. had diabetes [18]. Patients in DIACORE were older and had a lower eGFR. Guo et al., did not investigate for UACR and DKD [18].

Concerning nighttime sleeping duration, no significant association with DKD was found in the present study. Similar results were described previously by Ohkuma et al., [21] and Yamamoto et al., [23]: neither could find a significant association between eGFR and nighttime sleeping duration in large Japanese study samples. Yet the results are rather incongruent in the literature: several studies also found, that shorter sleeping duration was associated with lower eGFR [18,19,22]. By contrast, Fujibayashi et al., found a lower prevalence of impaired eGFR in short sleepers [17], and Petrov et al., found, that shorter sleeping duration was associated with a modest increase in eGFR [20]. They discussed the increase in eGFR as an expression of elevated sympathetic nervous system activity,

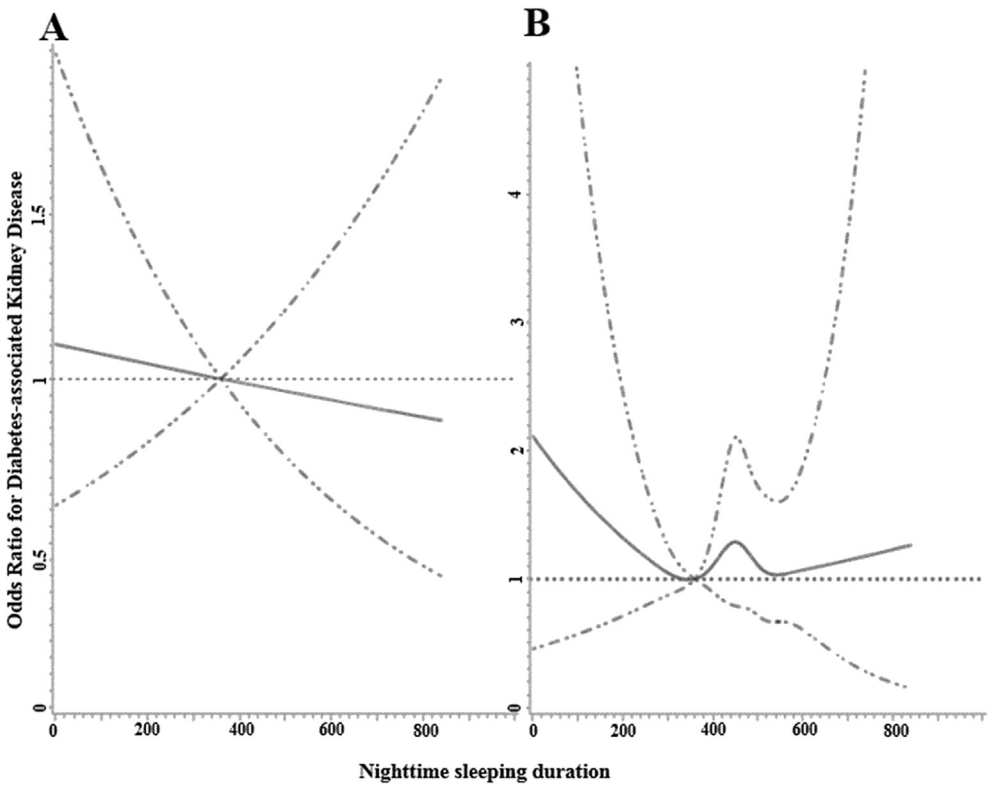

Fig. 4. Relation between daytime sleeping duration and odds ratio for Diabetes-associated Kidney Disease. Modeling a linear relationship, a test of association: p = 0.008 (**A**). Modeling a non-linear relation, test of association: p = 0.646 (**B**). DIACORE study: Sample size n = 733. Restricted cubic splines are fitted to unconditional logistic models to examine non-parametrically the possibly non-linear relationship between daytime sleeping duration and the Odds Ratio for Diabetes-associated Kidney Disease. The reference value for the Odds Ratio = 0 min. Covariables: Epworth Sleepiness Scale, Age [years], Duration of Diabetes Mellitus type II [years]. The dotted lines show the 95% confidence interval.

leading to abnormally high eGFR levels, thus enhancing the risk of glomerular hypertension and renal injury [20].

The correlation between nighttime sleeping duration and UACR has been scarcely investigated. Contrary to our results that showed no significant correlation in a European sample, Ohkuma et al., found a U-shaped association in a sample of Japanese patients ill with type 2 diabetes. Both long and short sleepers had significantly higher UACR levels [21]. Three other studies investigated the relationship between sleeping duration and proteinuria (measured by dip-stick test), without assessing UACR. While Sasaki et al., could not find a correlation [22], the others found a higher prevalence of proteinuria in patients with shorter nighttime sleeping duration [17,23].

Inconsistencies in previous research may be due to relevant differences in study design and samples. Additionally, sleep duration was not defined consistently: some studies assessed nighttime sleeping duration [18,20] while others included daytime napping for the total daily sleeping duration [21]. Several studies did not differentiate nighttime vs daytime sleep durations at all [17,19,22,23]. An overview of the studies cited is given in Table 4.

The direction of the relationship between longer daytime sleeping duration and kidney function remains unclear. Daytime sleeping might be a marker of chronic disease. It has been discussed previously that chronic inflammation, low albumin levels, and depression can promote an increased need for sleep [35,36]. All of these factors are common in kidney disease patients [35,36]. Thus, daytime sleeping duration might become more relevant as a marker for overall health status. On the other hand, there are several pathophysiological mechanisms that might explain how the duration of daytime sleeping can influence kidney function. First, during sleep, the brain and muscles process less glucose, causing serum glucose levels to rise [37]. Second, plasma renin activity and aldosterone levels have been shown to be elevated during nighttime as well as daytime sleep [38,39]. This may lead to higher renal reabsorption of water and sodium-chloride, thus increasing kidney damage in persons with longer sleeping duration. Third, long daytime sleeping, even paralleled by long nighttime sleeping duration, may lead to circadian misalignment. Disrupting the normal sleep-wake-cycle might displace circadian rhythms of various hormones (eg, growth hormone thus influencing glucose tolerance) [40].

The following limitations warrant mention: first, we cannot conclude whether long daytime sleeping promotes DKD or vice versa, or whether there is an association without a causal relationship. Longitudinal data are required to evaluate these questions. Second, daytime sleeping habits were assessed by questionnaire and are therefore self-reported; recall bias might be relevant. Only current sleeping habits have been assessed. Information on the number of years that patients have been taking a daytime nap was not gathered. The potential bias by bed-ridden patients was minimized by excluding patients with chronic illnesses, as stated above. Furthermore, as the inclusion criteria allowed outpatients only, bed-ridden patients likely represent a minority in the study sample. Future studies should assess daytime sleeping duration objectively, for example by using wrist-actigraphy. Moreover, due to the study design, a potential selection bias must be acknowledged, since some patients who are very ill or patients who are unaware of health issues might have participated in the study.

The present study is the first to evaluate the relationship between renal function and daytime sleeping habits in a sample of outpatients ill with type 2 diabetes. One strength of our study is the

Table 4
Studies on the association between nighttime sleeping duration, daytime sleeping duration and kidney function.

Study; Year (Ref.)	Study design	Number of Patients	Sample	Sleep duration	Results -e GFR	Results - Proteinuria
Studies on the association between daytime napping and kidney function						
Franke et al., 2018	**Cross-sectional;** multicenter	n = 733	Patients, ill with type 2 diabetes, Germany	**Daytime sleeping duration** (self-reported)	Longer Daytime sleeping duration is associated with decreased eGFR	Longer Daytime sleeping duration is associated with increased UACR
Guo et al., 2015 [18]	**Cross-sectional;** single center	n = 5555	Hypertensive patients; China	**Daytime napping** (self-reported)	No significant association	n.a.
Ohkuma et al., 2013 [21]	**Cross-sectional;** multicenter	n = 4870	Patients, ill with diabetes regularly attending teaching hospitals; Japan	**TDSD** (self-reported)	No significant association	U-shaped relationship between TDSD and UACR
Studies on the association between nighttime sleeping duration and kidney function						
Franke et al., 2018	**Cross-sectional;** multicenter	n = 733	Patients, ill with type 2 diabetes, Germany	**NSD** (self-reported)	No significant association	No significant association
Guo et al., 2015 [18]	**Cross-sectional**; single center	n = 5555	Hypertensive Patients, China	**NSD** (self-reported)	Shorter NSD is associated with lower eGFR	n.a.
Jaussent et al., 2015 [19]	**Prospective;** Two-center	n = 1105	Community-dwelling elderly; France	**NSD** (objective)	No significant association	n.a.
Sasaki et al., 2014 [22]	**Prospective**; single center	n = 3600	Healthy government employees; Japan	**Not specified** (self-reported)	Short SD as a risk factor for low eGFR	No significant correlation with Proteinuria
Petrov et al., 2014 [20]	**Prospective**; single center	n = 463	Community-based healthy adults; USA	**NSD** (objective)	Shorter NSD is associated with higher eGFR	n.a.
Ohkuma et al., 2013 [21]	**Cross-sectional**; multicenter	n = 4870	Patients, ill with diabetes regularly attending teaching hospitals; Japan	**TDSD** (self-reported)	No significant association	U-shaped relationship between TDSD and higher UACR
Yamamoto et al., 2012 [23]	**Retrospective;** single center	n = 6834	Employees of Osaka University, no impaired kidney function; Japan	**Not specified** (self-reported)	Short SD is associated with lower eGFR	Shorter SD is a predictor for proteinuria
Fujibaya-shi et al., 2012 [17]	**Cross-sectional;** single center	n = 25,493	Employees of NTT company and their families; Japan	**Not specified** (self-reported)	Prevalence of short SD is lower in patients with low eGFR	Prevalence of short SD is higher in patients with Proteinuria

NSD = nighttime sleeping duration; TDSD = total daily sleeping duration; SD = sleeping duration; eGFR = estimated Glomerular filtration rate; UACR = urinary Albumin-to-creatinine-ratio; n.a. = not assessed.

large sample size. Due to our recruitment methods, we were able to analyze a sample with a wide range of diabetes severity. Additionally, detailed phenotyping at baseline allowed us to make various adjustments to investigate possible confounding factors. In summary, we have shown that daytime sleeping habits are significantly associated with kidney function in outpatients ill with type 2 diabetes. Longitudinal data including interventional studies are required to find the direction of this relationship.

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FF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.034.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.10.034.

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