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Association of short sleep duration and rapid decline in renal function

Ciaran J. McMullan[1,2], **Gary C. Curhan**[1,2], and **John P. Forman**[1,2]

[1]Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

The kidney is influenced by circadian rhythms, and entrained to the sleep-wake cycle allowing anticipation of the metabolic and physiological demands of the kidney throughout a 24-hour cycle. Although sleep disruption has been studied extensively in cardiovascular and metabolic disease, its association with chronic kidney disease has not been shown. We examined this in a prospective cohort study of 4238 participants from the Nurses' Health Study and analyzed the association of self-reported sleep duration with decline in renal function over an 11year period (1989 to 2000). Individuals who reported shorter sleep duration were more likely to experience a rapid decline in estimated glomerular filtration rate (30% or more). Compared with sleeping 7–8 hours per night, the adjusted odds ratios for a rapid decline in renal function were a significant 1.79 (95% CI, 1.06–3.03) for 5 hours or less sleep per night, a significant 1.31 (95% CI, 1.01– 1.71) for 6 hours sleep per night, but an insignificant 0.88 (95% CI, 0.50–1.57) for 9 or more hours sleep per night. Similarly, there was a significant trend in the adjusted annualized decline in estimated glomerular filtration rate of 1.2 ml/min/1.73m^2/year, 0.9 ml/min/1.73m^2/year, 0.8 ml/min/1.73m^2/year, and 0.8ml/min/1.73m^2/year for individuals sleeping 5 hours or less per night, 6 hours per night, 7–8 hours per night, and 9 hours or more per night, respectively. Thus, shorter sleep duration is prospectively and independently associated with faster decline in renal function.

Keywords

Sleep duration; renal function; albuminuria

Correspondence to: Ciaran J. McMullan, M.D.; cmcmullan1@partners.org; 41 Avenue Louis Pasteur, Suite 119, Boston, MA, 02115; 617-264-3070 (T); 617-264-5975 (F).

DISCLOSURE

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INTRODUCTION

Most renal physiologic processes follow a diurnal rhythm, including regulation of the reninangiotensin system, sodium reabsorption, renal blood flow, glomerular filtration, and filtration fraction; similarly, 13% of gene transcription in the kidney is diurnal.(1–6) Coordination of the circadian periodicity of these processes allows the kidney to anticipate changes in metabolic and physiological demands throughout a 24-hour cycle. However, changes to lifestyle and work practices have diminished the amount of nightly sleep many people obtain, thereby altering the times at which workers are required to be awake and desynchronizing basic physiologic rhythms from environmental demands.

There is growing evidence that changes in sleep duration and time of sleep onset may have detrimental effects on renal function. Short sleep duration and shift work are associated with risk factors for chronic kidney disease (CKD), including hypertension, diabetes, and cardiovascular disease.(7–9) As examples, individuals who report sleeping 5 hours or less per night are 20% more likely to develop hypertension,(7) 34% more likely to develop diabetes(8) and 45% more likely to develop cardiovascular disease(9) compared with those sleeping 7 hours per night. A variety of cross-sectional studies have found that patients with kidney disease have shorter average sleep durations overall,(10) and in a single prospective study of 6,834 Japanese adults, those who slept 6 or fewer hours per night were 70% more likely to develop proteinuria than individuals who slept for 7 hours per night.(11) However a prospective association between sleep duration and decline in renal function has not been demonstrated. Thus, we performed a prospective analysis among participants of the Nurse's Health Study (NHS) with self-reported sleep duration ascertained at baseline and renal function measured at two or more time points during an 11 year follow-up.

RESULTS

Participant baseline characteristics

There were 4,238 women in the NHS with serum creatinine measured in 1989 and again in 2000. In 1989, the mean age was 58.0 years (±6.6 years), mean body mass index (BMI) was 25.8 kg/m^2 (±5.1 kg/m^2), and the mean estimated glomerular filtration rate (eGFR) was 88.3 ml/min/1.73m^2 (±25.0 ml/min/1.73m^2). Overall, 9.7% of women were diabetic, 28.7% had a history of hypertension, and 3.8% had a history of cardiovascular disease (Table 1). Median sleep duration was 7 hours (6–8 hours, 25–75th percentile). Individuals who reported sleeping 5 or fewer hours per night had a higher mean BMI and higher prevalences of diabetes, hypertension, and cardiovascular disease at baseline compared with those who reported sleeping 7–8 hours per night. Age, baseline eGFR, snoring patterns, and use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and angiotensin converting enzyme inhibitors (ACE-i) were all similar across categories of sleep duration. The most frequent self-reported sleep duration was 7– 8 hours per night in 2,882 individuals, with 157 individuals reporting 5 or fewer hours per night, 1,007 reporting 6 hours per night, and 192 reporting 9 or more hours per night.

Association of baseline sleep duration with eGFR decline

Rapid decline in renal function was observed in 529 individuals (12%), while the mean annualized decline in eGFR for the cohort was 1.0 ml/min/1.73m^2 (±2.2 ml/min/1.73m^2). The mean eGFR in those with rapid decline was 103.5 ml/min/1.73m^2 at baseline (1989) which decreased to 59.3 ml/min/1.73m^2 at follow-up (2000). Of the 529 subjects who developed rapid decline in renal function, 288 (54%) developed CKD stage 3 or higher.

Compared with participants who reported 7–8 hours of sleep per night, the age adjusted odds ratios (ORs) for experiencing a rapid decline in renal function were 1.91 (95% CI, 1.27–2.88, p = 0.002) among participants who reported 5 or fewer hours of sleep per night and 1.30 (95% CI, 1.05–1.60, p = 0.01) among participants reporting 6 hours per night. After adjustment for age, systolic blood pressure, BMI, eGFR, smoking status (current, previous, never), history of hypertension, history of diabetes, history of hypercholesterolemia, use of acetaminophen at baseline, use of medications which reversibly effect eGFR at baseline and follow-up (ACE-i in 1988, and in 2000, and use of NSAIDs in 1990, and in 2000), the corresponding ORs for experiencing a rapid decline in renal function were 1.79 (95% CI, 1.06–3.03, p = 0.03) for participants who reported 5 or fewer hours of sleep per night and 1.31 (95% CI, 1.01–1.71, p= 0.04) for participants who reported 6 hours of sleep per night (p-value for linear trend across categories of sleep duration 0.005, Table 2). Further adjustment for shift work did not materially alter the results (OR=1.75, 95% CI 1.04–2.96 comparing ≤5 hours with 7–8 hours; p=0.04). For 4063 individuals with normal baseline renal function, the fully adjusted OR of incident CKD at follow-up was 1.95 (95% CI, 1.16 – 3.30, p=0.01) among participants who reported 5 or fewer hours of sleep per night and 1.18 (CI, 0.90 – 1.54, p=0.24) among participants reporting 6 hours of sleep per night compared with those who reported 7–8 hours of sleep per night (p-value = 0.02 for trend of increased CKD risk with shorter sleep duration, Supplementary Table 1).

Individuals in the reference group, 7–8 hours per night, had the slowest rate of decline in renal function, with an annualized eGFR decline of 0.9 ml/min/1.73m^2/year (±1.7 ml/min/1.73m^2/year). This was significantly slower than the rate of decline for those who reported 6 hours per night (annualized eGFR decline of 1.1 ± 3.4 ml/min/1.73m^2/year, p = 0.009). Women who reported sleeping 5 hours or less per night had the most rapid rate of decline in renal function (annualized eGFR decline of 1.3 ± 2ml/min/1.73m^2/year), which was not statistically different from the decline in the reference group (p-value = 0.07). These annualized eGFR decline rates remained virtually unchanged with age and multivariable adjustment, and there was a significant trend toward faster renal function decline with decreased sleep duration (adjusted p-trend = 0.008; Table 3).

Association of baseline sleep duration with albuminuria

A total of 3,489 individuals from the NHS who returned urine samples in 2000 had urine albumin and creatinine measured (urine samples were unavailable in 1989). Albuminuria in 2000 was twice as prevalent among individuals who, in 1986, reported sleeping 5 or fewer hours per night than those who reported 7–8 hours per night (adjusted OR=2.52; 95% CI, 1.42–4.49, pvalue) with a significant trend toward increased prevalence of albuminuria with shorter sleep duration in multivariable models (p-trend=0.002; Supplementary Table 2).

Sensitivity analyses

In a sensitivity analysis, we expanded our analysis to include all women (N=4,268) with serum creatinine measurement available in 1989 and again either in 2000, 2003 or 2007. We included all 17,072 eGFR measures to model eGFR trajectories using linear mixed effects regression employing random intercepts and slopes (Table 4). In age and multivariable adjusted analyses, shorter sleep duration was significantly associated with eGFR decline (adjusted p-value for the group effect of sleep duration = 0.002). In adjusted models, sleeping 6 hours per night was associated with a 30% faster decline in eGFR relative to sleeping 7–8 hours per night ($p < 0.001$).

In other sensitivity analyses we repeated our primary analysis, measuring the association of sleep duration with rapid decline in renal function, with additional adjustment for incident hypertension, incident diabetes and incident cardiovascular disease occurring during the followup period. In these analyses the association of shorter sleep duration with rapid decline in renal function remained significant (p-value for linear trend ≤ 0.007; Supplementary Tables 3–5). Finally, replacing the KDIGO definition of albuminuria with sex-specific definitions did not significantly change the association of shorter sleep duration in 1986 with a greater prevalence of albuminuria in 2000 (p-value for linear trend = 0.02).

DISCUSSION

In this large prospective study of middle aged women with 11 years of follow-up, shorter sleep duration was significantly and independently associated with a more rapid decline in renal function. To our knowledge, this is the first prospective study to find that shorter sleep duration is associated with a more rapid decline in eGFR.

Nearly all human data examining the association of sleep and CKD come from cross-sectional, rather than prospective studies. Patients with advanced CKD have a higher prevalence of several sleep disturbances, including reversal of day-night sleep pattern, increased sleep latency, and fragmented sleep related to sleep apnea or restless leg syndrome.(10) A small study, for example, found that shorter sleep duration (ie, < 5 hours per night measured by actigraphy) was significantly more prevalent among individuals with non-dialysis dependent CKD (31%) and ESRD (53%) as compared with those with normal renal function (11%).(12) Another study that employed polysomnography reported increased sleep fragmentation and decreased REM sleep in patients with ESRD compared with those who had non-dialysis dependent CKD.(13) It is most commonly argued that this relation is mediated by uremic toxins, volume overload, and depression as possible mechanisms, each of which can accompany advanced CKD.(10) In contrast, the potential importance of circadian disruption as a risk factor preceding the development of CKD has received considerably less attention.

Although animal data suggest that circadian disruption may induce kidney damage, prospective human data on the association of sleep factors with incident kidney disease are scarce. In animals, genetic disruption of circadian rhythms produce characteristics of CKD including elevated serum creatinine, glomerular and tubular damage and fibrotic changes in the cortex, all of which are preventable by strictly controlling light-dark periodicity to

restore circadian rhythms.(14) In humans, only two longitudinal analyses of individuals without CKD have studied the association of sleep duration with changes in renal parameters. The first, a study of 6,834 Japanese adults, found that those who slept 6 or fewer hours per night were 1.7 times more likely to develop proteinuria at 4 years than individuals who slept for 7–8 hours per night; changes in eGFR were not reported.(11) Although we lacked information about albuminuria at baseline, the findings of our secondary analysis of albuminuria at 11 years were consistent with this Japanese study. The second, substantially smaller prospective study of 463 adults found that the adjusted risk of a 10-year decline in eGFR of >3% was 0.83 (95% CI 0.64 – 1.08) per additional hour of sleep per night; this potential benefit from additional sleep (or, reciprocally, a determent from less sleep) was not statistically significant, possibly due low statistical power.(15) Consistent with their observations, we found that shorter sleep duration was significantly and independently associated with faster annualized decline in eGFR and a greater risk of having a ≥30% decline in eGFR at 11 years.

The mechanisms underlying a potential association of sleep with incidence of decline in renal function need to be elucidated. Sleep disturbances, such as habitual sleep restriction, may predispose to incident CKD by increasing the risk of developing established CKD risk factors. As an example, individuals who report sleeping 5 or fewer hours per night are 20% more likely to develop hypertension and 57% more likely to develop incident diabetes during a 10 year period than those sleeping 7 hours per night.(7) (8) In short-term studies lasting 3–6 weeks, shortening or lengthening the time slept by healthy individuals increased or decreased insulin resistance and blood pressure, further suggesting that sleep duration is a modifiable determinant of these established CKD risk factors.(16–18) However, in our cohort, adjusting for development of incident hypertension, diabetes, or cardiovascular disease did not materially change effect estimates for the risk of developing rapid renal function decline with shorter sleep duration. This suggests that either short sleep duration is associated with more rapid decline in renal function via a mechanism independent of these established CKD risk factors or, alternatively, these endpoints did not fully capture the metabolic and vascular consequences of short sleep.

Our study has limitations. First sleep duration was self-reported with potential for misclassification. Self-reported or perceived sleep time often differs from objectively measured sleep using polysomnography or wrist actigraphy. In a study of 669 individuals, for example, sleep duration was measured both objectively using wrist actigraphy and subjectively with a sleep questionnaire.(19) In that study, those with objectively short sleep duration subjectively overestimated their sleep duration. Specifically, those with objective sleep measured as 5 hours per night overestimated sleep by 1.3 hours (ie, self-reported 6.3 hours of sleep). In contrast, those with objective sleep measured as 7 hours per night more accurately self-reported their sleep duration (ie, the difference was only 0.3 hours).(19) If this finding is applicable to our study, then the distribution of sleep duration in our population may be narrower than the true distribution, which would have made it more difficult to detect an association rather than find a spurious association. Second, information on sleep duration was collected in 1986, 3 years prior to the initial eGFR measurement. However, there is likely a reasonably good correlation between usual sleep duration separated by three years among healthy middle aged women. As examples, the intra-class

correlation coefficient (ICC) for sleep duration reported on the 1986 and 2000 questionnaires was 0.41, while over the shorter, 6 year period from 2002 to 2008, the ICC was 0.53. Thus, it is likely that the correlation over 3 years in this population would similar or better. Nevertheless, the resulting misclassification of sleep duration would tend to produce an association that actually underestimates, rather than overestimates, the true association. Third, only two measures of eGFR were used in the primary analysis, and therefore if either eGFR measurement was transiently altered due other factors, the calculated eGFR decline from 1989 to 2000 will not accurately reflect the true underlying longitudinal eGFR change during that period. However, this was a relatively healthy population at low-risk for developing acute kidney injury, and we controlled for use of ACEi and NSAIDS, which would be the most likely factors that could reversibly change the eGFR. In addition, our secondary analysis using mixed effects regression to incorporate all available eGFR values was consistent with findings from our primary analysis. Fourth, albuminuria was not measured at baseline since urine was not collected in 1989; therefore, we could not analyze the association of sleep duration with change in urinary albumin secretion, nor could we adjust for albuminuria in the primary analysis. However, our findings that shorter sleep duration was associated with the presence of albuminuria in 2000 is consistent with another large study that reported short sleep duration was a risk factor for incident proteinuria.(11) Fifth, the number of individuals reporting sleep duration of 9 hours or greater was limited and so we were unable to assess if there was a Ushaped association between sleep duration and more rapid decline in renal function (a U-shaped association was found between sleep duration and both diabetes and mortality).(8, 9) Sixth, our study population was limited to women, and most participants were white. Thus, it is unknown whether or not our findings can be applied to men and to other racial groups. Seventh, in this observational study, many of the baseline covariates used in the analyses were self-reported on biennial questionnaires; potential misreporting of this information could produce residual confounding. However, the validity of this questionnaire-based information has been demonstrated. Finally, as with all observational studies, we cannot exclude the possibility that our findings are confounded by factors that we could not ascertain.

In conclusion we have found a robust association between shorter sleep duration and a more rapid decline in renal function that was independent of many established CKD risk factors. Further studies, including those using more accurate measurements of sleep, are required to confirm these findings, and to elucidate potential mechanisms mediating this association, with a view toward potential therapeutic interventions.

METHODS

Study Design and Study Participants

The Nurses' Health Study (NHS)(20) began in 1976 when 121,700 registered nurses aged 30–55 years returned an initial questionnaire. On this and subsequent biennial questionnaires, health status, medications, dietary intake, and lifestyle factors including smoking history, physical activity and sleeping patterns were ascertained. In addition to completing questionnaires, blood samples were provided by sub-populations of these women in 1989 and 2000. First morning urine samples were provided in 2000. Between

1989 and 1990, 32,826 participants provided blood samples that were shipped with a cold pack by overnight mail, where upon they were aliquoted and stored in liquid nitrogen until the time they were assayed. In 2000, 18,720 of these participants submitted a second blood sample and spot urine sample under the same handling conditions. Two additional blood samples were collected in 2003 and 2007 as part of a sub-study of analgesic use and renal function. Serum creatinine was measured in 9,163 participants in 1989, 5,187 participants in 2000, 2,000 participants in 2003 and 1,750 participants in 2007. Of those participants with information on sleep duration from the 1986 questionnaire, 4,238 had serum creatinine measured in 1989 and again in 2000. These individuals made up the population for the primary analysis. In a sensitivity analysis, we included all 4,268 women who had serum creatinine measured in 1989 and at least once during the 2000, 2003 or 2007 blood collections.

All women in this cohort provided implied consent by virtue of voluntarily returning mailed questionnaires and by voluntarily providing blood and urine samples via mailed collection kits. The institutional review board at Brigham and Women's Hospital approved this study.

Sleep duration

Sleep duration was reported on the 1986 biennial questionnaire as the total number per 24 hours that the participant slept. For the purpose of this analysis sleep duration was categorized into 5 or fewer hours, 6 hours, 7–8 hours, and 9 or more hours per 24 hours. Sleep duration was also asked on several other questionnaires. The ICC for sleep duration reported in the 1986 and 2000 questionnaires was 0.41, and was 0.53 between 2002 and 2008, suggesting moderate stability of sleep duration in these nurses during the follow-up period used in the primary analysis.

Renal function

Plasma creatinine was measured using a modified Jaffe reaction (coefficient of variation [CV], 10%). eGFR was estimated from plasma creatinine using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Rapid decline in renal function was defined as a decrease in eGFR ≥30% from 1989 to 2000, and was the primary endpoint.(21) The annualized rate of eGFR decline between 1989 and 2000 was a secondary endpoint, as was development of incident chronic kidney disease defined as eGFR ≤ 60ml/min/ $1.73m^2$(22)

Urinary measurements were performed on spot urine samples obtained from the 2000 collection. Urinary albumin was measured by a solid phase fluorescence immunoassay using the Hitachi 911 analyzer and Roche diagnostic reagents with a lower limit of detection of 0.1 mg/ml (CV, 8.0%). Urinary creatinine was measured using a modified Jaffe reaction (CV, 1.6%). Albuminuria was defined using the KDIGO guidelines as urinary albumin to creatinine ratio (UACR) ≥30mg/g.(23) In a sensitivity analysis albuminuria was defined using a gender specific definition of albuminuria (UACR ≥25mg/g for women, which has been proposed by several groups).(24–26)

Other covariates

Age, self-reported race, and menopausal status, as well as body mass index (BMI, kilograms of body weight divided by the squared height in meters), systolic blood pressure, history of cardiovascular disease (angina, myocardial infarction, coronary artery by-pass or stroke), diabetes, hypertension, hypercholesterolemia, and smoking status (current, past, never) were determined from a questionnaire completed at the time of urine and blood sample submission. Frequency of medication use was also available from questionnaires in 1990 and 2000, and from these we determined the frequency of use off non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, with frequent use categorized as taking these medications more than once per week. Also the use of angiotensin-converting-enzyme inhibitors (ACE-i) was available from the 1988 and 2000 questionnaires.

Statistical Analysis

Distributions of covariates were examined by category of self-reported sleep duration (≤ 5 hours, 6 hours, 7–8 hours, ≥9 hours per 24 hours). The means and frequencies for all covariates were compared with ANOVA or Chi-squared testing between categories of self-reported sleep duration.

The change in eGFR from 1989 to 2000 was calculated for each individual. In the primary analysis, logistic regression was used to examine the association of rapid decline in renal function with category of baseline sleep duration, using the most populous category, 7–8 hours per night, as the reference. Models were adjusted for established risk factors for CKD (age [continuous], systolic blood pressure [continuous], BMI [continuous], history of cardiovascular disease [yes/no], diabetes [yes/no], hypertension [yes/no], hypercholesterolemia [yes/no], smoking status [current/previous/never], and acetaminophen use [≥1 per week, which is associated with renal function decline in this cohort]).(27, 28) In addition, we controlled for factors that could have hemodynamic effects on eGFR (ACE-i use at baseline [yes/no], ACE-I use at follow-up [yes/no], NSAID use at baseline [≥1 per week], and NSAID use at follow-up [≥1 per week]. Hosmer and Lemeshow Goodness-of-Fit test was performed to ensure logistic regression models were appropriate. An additional analysis was performed in which the number of years that a participant worked rotating night shifts was included in the multivariable models. A secondary analysis was performed using multivariable linear regression to examine the association of sleep duration with annualized rate of eGFR decline from1989 to 2000. The association of sleep-duration in 1986 and the presence of albuminuria in 2000 was examined with multivariable logistic regression, adjusting for predictors of CKD. Lastly, among 4063 individuals with normal renal function at baseline, eGFR ≥ 60ml/min/1.73m^2, multivariable logistic regression was used to examine the association of incident CKD with category of baseline sleep duration.

In a sensitivity analysis of repeated measures, the association of baseline sleep duration with decline in eGFR was examined using linear mixed effects analysis; this analysis included all available measurements of serum creatinine from 1989 to 2007 in women with serum creatinine measured on at least two occasions. We assumed random intercepts and slopes to model eGFR over time; the interaction term of sleep category with time was used to assess for an association of sleep duration with annualized eGFR decline. This model was adjusted

for the same covariates included in the primary multivariable model mentioned above. In another sensitivity analysis, we repeated our primary analysis after excluding all 1,214 individuals with baseline hypertension. Lastly we repeated the analysis of the association of sleep-duration and presence of albuminuria with albuminuria measured using a sex specific cut-off (ie, UACR ≥25mg/g).

All analyses were performed with SAS statistical software (Cary, NC). Two-tailed p-values <0.05 were considered statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Comparison of baseline covariates across categories of sleep duration in NHS I with serum Cr measured in 1989 and 2000.

Covariate	All (n=4238)	Category of sleep duration (reported in 1986) ≤ 5 hours (n=157)	6 hours (n=1007)	7–8 hours (n=2882)	≥9 hours (n=192)	P-value[a]
			Mean (SD)			
Age (years)	58.0 (6.6)	57.7 (6.3)	57.6 (6.6)	58.1 (6.5)	58.7 (7.1)	0.08
eGFR[b] (ml/min/1.73m^2)	88.3 (25.0)	89.5 (20.6)	89.9 (37.4)	87.8 (19.5)	86.8 (19.1)	0.11
SBP (mmHg)	127 (14)	130 (15)	128 (14)	127 (13)	129 (14)	0.08
BMI (kg/m^2)	25.8 (5.1)	27.8 (6.3)	26.3 (5.5)	25.5 (4.9)	26.2 (5.7)	<0.001
Activity (METS/week)	16.7 (21.5)	15.0 (19.1)	16.0 (19.0)	17.2 (22.7)	14.8 (16.4)	0.16
			N (%)			
Smoking history						
Current	502 (11.9)	23 (14.7)	130 (12.9)	323 (11.2)	27 (13.5)	0.32
Previous	1744 (41.2)	55 (35.0)	406 (40.4)	1193 (41.5)	90 (46.9)	
Never	1983(46.8)	79 (50.3)	468 (46.5)	1360 (47.2)	76 (39.6)	
Missing	9 (0.2)	0 (0)	3 (0.3)	6 (0.2)	0 (0)	
History of						
Diabetes	410 (9.7)	20 (12.7)	110 (10.9)	252 (8.7)	28 (14.6)	0.009
Hypertension	1214 (28.7)	53 (33.8)	314 (31.2)	781 (27.1)	66 (34.4)	0.01
Cardiovascular disease	164 (3.8)	10 (6.3)	53 (5.2)	91 (3.1)	10 (5.2)	0.005
Hypercholesterolemia	1828 (43.1)	69 (44.0)	454 (45.1)	1218 (42.3)	87 (45.3)	0.41
NSAID[d] use 1990[e]	992 (27.7)	38 (28.2)	258 (30.0)	643 (26.5)	53(32.7)	0.10
NSAID use 2000 [e]	934 (22.0)	29 (18.5)	229 (22.7)	632 (21.9)	44 (22.9)	0.67
Acetamenophen use[e]	672 (18.7)	31 (23.0)	175 20.2)	442 (18.3)	24 (14.9)	0.19
ACE- I[f] use in 1988	108 (2.5)	3 (1.9)	31 (3.1)	70 (2.4)	4 (2.1)	0.63
ACE-I[f] use in 2000	579 (13.7)	17 (10.8)	156 (15.5)	379 (13.2)	27 (14.1)	0.20

[a] P-values are calculated using ANOVA test for continuous variables and Chi-square for categorical variables.

[b] eGFR: estimated glomerular filtration rate calculated using the MDRD equation.

[c] DASH: Dietary approaches to stop hypertension. The DASH diet score is constructed based on how closely a diet resembles a DASH diet; high fruit and vegetable intake and low intake of red and processed meats and sodium(29).

[d] NSAID: Non-steroidal anti-inflammatory drug.

[e] NSAID and Acetaminophen use more than once per week.

[f] ACE-I: Angiotensin converting enzyme inhibitor

Table 2

Odds ratio of eGFR decrease of ≥30% between 1989 and 2000 by category of sleep duration.

Category of sleep duration (reported in 1986)	Number of individuals	Number of events (eGFR decrease ≥30%)	Mean eGFR decline (SD)	Odds Ratio (95% CI)				
				Age adjusted	P-values	Fully Adjusted[a]	P-values	P-trend
≤5 hours	157	31	13.8 (22.6)	1.91 (1.27 – 2.88)	0.002	1.79 (1.06 – 3.03)	0.03	0.005
6 hours	1007	144	12.4 (37.8)	1.30 (1.05 – 1.60)	0.01	1.31 (1.01 – 1.71)	0.04	
7–8 hours	2882	331	9.9 (18.1)	1.00	Reference	1.00	Reference	
≥9 hours	192	23	10.0 (16.2)	1.04 (0.66 – 1.63)	0.88	0.88 (0.50 – 1.57)	0.67	

[a]Adjusted for age, systolic blood pressure, body mass index, baseline eGFR**,** history of diabetes, history of cardiovascular disease, history of hypercholesterolemia, history of hypertension, acetaminophen use, ACE-I use (1988 and 2000), NSAID use (1990 and 2000), and smoking status (current, previous, never).

Table 3

Average annualized change in eGFR from 1989 to 2000 by category of sleep duration.

Category of sleep duration (reported in 1986)	Age adjusted			Fully Adjusted[a]		
	Number of individuals	Annualized eGFR change (SD) (ml/min/ 1.73m^2/year)	P value	Annualized eGFR change (SD) (ml/min/ 1.73m^2/year)	P value	P-trend
≤5 hours	157	− 1.3 (0.2)	0.05	− 1.2 (0.1)	0.01	0.008
6 hours	1007	− 1.1 (0.1)	0.005	− 0.9 (0.1)	0.10	
7–8 hours	2882	− 0.9 (0.1)	Reference	− 0.8 (0.1)	Reference	
≥9 hours	192	− 0.9 (0.2)	0.99	− 0.8 (0.1)	0.81	

[a]Adjusted for Age, systolic blood pressure, body mass index, eGFR, history of diabetes, history of cardiovascular disease, history of hypercholesterolemia, history of hypertension, acetaminophen use, ACE-I use (1988 and 2000), NSAID use (1990 and 2000), and smoking status (current, previous, never).

Table 4

Mixed effects model for average annualized change in eGFR, including all eGFR measurements.

Category of sleep duration (reported in 1986)	Number of Individuals	Age adjusted			Fully Adjusted[a]		
		Annualized eGFR change (ml/min/ 1.73m^2/year)	P-value	P-value for group effect of sleep duration	Annualized eGFR change (ml/min/1.73m^2/ year)	P-value	P-value for group effect of sleep duration
≤5 hours	159	− 1.0	0.27	0.002	− 1.0	0.44	0.004
6 hours	1014	− 1.1	0.0002		− 1.1	0.0004	
7–8 hours	2901	− 0.9	Reference		− 0.9	Reference	
≥ 9 hours	194	− 0.8	0.77		− 0.8	0.55	

[a]Adjusted for Age, systolic blood pressure, body mass index, history of diabetes, history of cardiovascular disease, history of hypercholesterolemia, history of hypertension, acetaminophen use at baseline, ACE-I and NSAID use as time varying covariates and smoking status (current, previous, never).