Research Article

Association between Sleep Duration and Incident Chronic Kidney Disease: A Population-Based Cohort Analysis of the NAGALA Study

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Keywords

Chronic renal failure · Epidemiology · Risk factors · Sleep duration

Abstract

Background: The duration of sleep might be a risk factor for chronic kidney disease (CKD). We investigated the relationship between sleep duration and incident CKD. **Methods:** In this retrospective cohort study of 7,752 men and 6,722 women, we divided the subjects into 4 groups according to sleep duration, i.e., those whose reported regular sleep duration was <6 h (the “<6 h group”), those whose sleep duration was >6 but <7 h (the “6 to <7 h group”), those with a sleep duration of 7 to <8 h (the “7 to <8 h group”), and those with ≥8 h sleep (the “≥8 h group”). CKD was defined as the presence of proteinuria and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². The HR of the 4 groups for incident CKD were calculated with a Cox proportional hazards model, with the 7 to <8 h group set as the reference. **Results:** Incident CKD was detected in 1,513 (19.5%) men and 688 (10.2%) women over the median follow-up period of 7.0 (3.3–11.9) years in the men and 6.7 (3.1–10.8) years in the women. There was no association between sleep duration and incident CKD in the women. In the men, the HR of incident CKD was 0.54 (95% CI 0.45–0.64, $p < 0.001$) in the <6 h group, 0.73 (95% CI 0.66–0.82, $p < 0.001$) in the 6 to <7 h group, and 0.93 (95% CI 0.78–1.11, $p = 0.433$) in the ≥8 h group. **Conclusion:** The risk of incident CKD is lowest in those who sleep <6 h. We revealed that the risk of incident CKD is lowest in those who sleep <6 h among apparently healthy men.

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Introduction

Among the several factors that are known to present a risk for the development of end-stage renal disease, chronic kidney disease (CKD) is the most important [1–3]. CKD is also a risk factor for cardiovascular morbidity and mortality [1–3]. The number of individuals with CKD is markedly increasing worldwide, and it has been estimated that 12.5% of the people in Japan have CKD [4]. The changes in the prevalence of CKD are speculated to be a result of the broad prevalence and severity of diabetes and hypertension, which have also become more common due to unhealthy lifestyles. Hypertension, type 2 diabetes, obesity, and cardiovascular disease are important risk factors in the development and progression of CKD [5].

Lifestyle-related factors such as the excessive consumption of salt, calories, and fat and the use of tobacco products (e.g., cigarettes) are established risk factors for the above-mentioned diseases [6, 7]. Lifestyle modifications are thus thought to be required for the prevention of hypertension, type 2 diabetes, obesity, and cardiovascular disease. Similarly, the development of CKD might be prevented, directly and/or indirectly, by lifestyle modifications [8]. Several studies have revealed that an individual's habitual duration of sleep is associated with increased risks of hypertension [9], type 2 diabetes [10, 11], obesity [12], nonalcoholic fatty liver disease [13, 14], and cardiovascular disease [15, 16].

A recent meta-analysis revealed that short sleep duration tended to be associated with the prevalence of CKD [17], although the tendency was not significant. Other than this finding, little is known about the precise association between sleep duration and incident CKD [18]. The optimal duration of sleep that would help prevent CKD and other diseases is not known. A single study (of shift workers) indicated that a short sleep duration poses a risk of incident CKD [19]. We conducted the present analyses to clarify the relationship between individuals' habitual sleep duration at a baseline examination and incident CKD in a large-scale cohort study of a healthy Japanese population.

Materials and Methods

Study Population

The present study is a subanalysis of the NAGALA (NAfId in Gifu Area, Longitudinal Analysis) study, the details of which are described elsewhere [18]. Briefly, the NAGALA study is a historical cohort study of subjects who underwent a medical health checkup at Asahi University Hospital (Gifu, Japan). Many companies in Japan recommend an annual health checkup for their employees. Because many participants employed by several companies were expected to have repeated examinations, we took advantage of the opportunity to conduct a follow-up study. After obtaining informed consent and masking personal identifiable information, the medical data of the subjects were stored in a database. For the present analyses, we extracted the data of the subjects who underwent the medical checkup only once from 1994 to 2013 and whose eGFR was <60 mL/min/1.73 m² at the baseline examination.

The exclusion criteria were as follows: missing data of covariates (including body weight, high-density lipoprotein [HDL] cholesterol, and lifestyle factors); the use of regular medications such as medicine for hypertension, diabetes, dyslipidemia, hyperuricemia, or insomnia (1-time medicine such as painkillers and antibiotics are not included); the presence of CKD at the baseline examination; and no follow-up examinations. The reason we excluded participants with regular medications is that we wanted to determine the relationship between sleep time and development of incident CKD without any influence of the health baseline of each participant. We checked these points at each visit during the study period. The primary endpoint of this study was the development of CKD.

Data Collection

The medical history and lifestyle factors of the subjects were obtained with a self-administered questionnaire [19]. The mean alcohol intake per week was estimated based on the data of the amounts and types of alcoholic beverages consumed per week. We then divided the subjects into the following 4 groups: no or minimal alcohol consumption, <40 g/week; light alcohol consumption, 40–140 g/week; moderate alcohol consumption, 140–280 g/week; and heavy alcohol consumption, >280 g/week [20, 21]. Smoking status was categorized into the following 3 groups: never-, ex-, and current smokers. “Exerciser” was defined as regularly performing any type of sport $\geq 1 \times$ /week [22].

The questionnaire also asked the subjects about their sleep duration, which was defined as the total time in bed per day. The subjects’ BMI was calculated as body weight (kg) divided by height (m) squared. Fasting plasma glucose, creatine, uric acid, triglycerides, and HDL cholesterol were measured using the subjects’ venous blood after an overnight fast. The estimated glomerular filtration rate (eGFR) was determined using the following equation of the Japanese Society of Nephrology: $eGFR = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$ (mL/min/1.73 m²) ($\times 0.739$ for women) [23]. After the subject’s overnight fast, we also gathered urine samples collected from mid-flow. Proteinuria was determined using dipstick testing (positive: 1+ or greater) [24, 25]. CKD was defined as 2 measurements of either proteinuria or an eGFR of <60 mL/min/1.73 m² [25] at least 90 days apart.

Statistical Analyses

Statistical analyses were performed using JMP software (version 13.2; SAS, Cary, NC, USA). $p < 0.05$ was considered statistically significant. We analyzed both the entire series and the men and women separately. Continuous variables were presented as means $\pm$ SD and categorical variables as numbers.

We divided the subjects into the following 4 groups based on sleep duration: those who reported sleeping <6 h (the “<6 h group”), those whose sleep duration was >6 but <7 h (the “6 to <7 h group”); those with a sleep duration of 7 to <8 h (the “7 to <8 h group”); and those with ≥ 8 h sleep (the “ ≥ 8 h group”) [26]. The clinical characteristics of the 4 groups at their baseline examination were compared. The groups’ continuous variables were evaluated by a one-way analysis of variance (ANOVA) and Tukey’s honestly significant difference test, and categorical variables were evaluated using Pearson’s χ^2 test. We also evaluated the difference in sleep duration and change in creatinine (Cr), defined as (Cr of the follow-up examination – Cr of the baseline examination)/Cr of the baseline examination/follow-up duration by scatter plot and linear regression analysis.

Kaplan-Meier analysis was used for a graphical presentation of the time to incident CKD, and a log-rank test was used to assess differences among groups. To correct for family-wise error, we performed a Bonferroni correction and $p < 0.0083$ was considered statistically significant in the log-rank test. Because of the presence of censored cases and the inconsistent follow-up duration, we used the Cox proportional hazards model and calculated the HR of the 4 sleep duration groups. We considered several potential confounders as covariants, i.e., age, sex, alcohol consumption, smoking status, exercise, BMI, creatine, uric acid, triglycerides, and systolic blood pressure.

Results

We found that 19,137 subjects in the NAGALA database satisfied the inclusion criteria of the present study; 4,653 subjects were excluded based on the above described exclusion criteria (Fig. 1). Some of the participants overlapped the exclusion criteria. Our study popu-

Fig. 1. Flow chart of the participants.

lation thus consisted of 14,474 subjects (7,752 men and 6,722 women). The subjects' baseline characteristics are summarized in Table 1.

Over the median (IQR) follow-up period of 7.0 (3.3–11.9) years in the men and 6.7 (3.1–10.8) years in the women, incident CKD was detected in 1,513 (19.5%) men and 688 (10.2%) women. Among the men, the crude number (proportion) of incident CKD cases was 167 (12.5%) in the <6 h group, 588 (17.5%) in the 6 to <7 h group, 608 (25.0%) in the 7 to <8 h group, and 150 (24.2%) in the ≥8 h group. Among the women, the crude number (proportion) of incident CKD cases was 112 (9.4%) in the <6 h group, 316 (10.7%) in the 6 to <7 h group, 201 (9.9%) in the 7 to <8 h group, and 59 (11.2%) in the ≥8 h group.

Although the correlation was weak, the change of Cr was low and the change of eGFR was high in men with a shorter sleep duration ($r = 0.0316$ and $p = 0.006$ for change in Cr [Fig. 2] and $r = -0.0293$ and $p = 0.01$ for change in eGFR [online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000504545]).

Figure 3 shows the Kaplan-Meier curves for the proportion of participants without CKD progression according to sleep duration. A shorter sleep duration was associated with a significantly lower development of CKD in men (<6 h group vs. 6 to <7 h, 7 to <8 h, and ≥8 h group: $p < 0.0083$; 6 to <7 h group vs. 7 to <8 h group: $p < 0.0083$). There was no association between sleep duration and incident CKD in women ($p = 0.894$).

The results of multivariate analysis with the Cox proportional hazards model are shown in Table 2. In the men, compared to the 7 to <8 h group, the HR of incident CKD were 0.54 (95% CI 0.45–0.64, $p < 0.001$) in the <6 h group, 0.73 (95% CI 0.66–0.82, $p < 0.001$) in the 6 to <7 h group, and 0.93 (95% CI 0.78–1.11, $p = 0.433$) in the ≥8 h group after adjusting for potential covariates. There was no association between sleep duration and incident CKD in the women.

Discussion

The results of our analyses demonstrated that the HR of incident CKD were lowest in the men who reported sleeping <6 h. In line with our findings, the meta-analysis cited in the Introduction revealed that a short sleep duration tended to be associated with a low prevalence of

Table 1. Characteristics of the study subjects at the baseline examination

	Overall	<6 h	6 to <7 h	7 to <8 h	≥8 h	p
<i>Men</i>						
Subjects	7,752	1,340	3,361	2,430	621	–
Age, years	42.1±8.4	40.6±7.8	41.6±8.0*	43.0±8.7*,†	43.8±9.4*,†	<0.001
BMI	23.0±3.0	23.5±3.2	23.1±3.0*	22.8±3.0*,†	22.7±3.0*,†	<0.001
SBP, mm Hg	119.4±14.3	119.3±14.0	119.4±14.1	119.3±14.5	120.1±14.6	0.640
DBP, mm Hg	75.0±9.9	74.5±10.0	75.0±9.9	75.1±10.0	76.0±9.9	0.026
Fasting plasma glucose, mmol/L	5.4±0.8	5.5±0.8	5.4±0.8	5.4±0.8	5.4±0.7	0.094
Triglycerides, mmol/L	1.2±0.9	1.1±0.8	1.2±1.0	1.2±0.8*	1.3±0.9*,†	0.001
HDL cholesterol, mmol/L	1.3±0.4	1.3±0.3	1.3±0.4	1.3±0.4	1.3±0.3	0.062
Uric acid, μmol/L	333.1±66.7	334.6±65.8	332.5±65.7	333.5±67.4	331.2±70.5	0.685
Creatinine, μmol/L	80.2±9.2	79.4±9.3	80.2±9.2*	80.8±9.2*	80.4±9.4	0.001
eGFR, mL/min/1.73 m ²	75.4±10.9	77.1±10.9	75.6±10.6*	74.4±10.7*,†	74.6±12.2*	<0.001
Ratio of ex-/current smokers	2,067/3,202	341/531	903/1,300	643/1,080	180/291	<0.001
Exercise habit	1,297	181	579	426	111	0.007
Light/moderate/heavy alcohol consumption	1,308/1,130/897	206/162/143	544/448/320	451/384/319	107/136/115	<0.001
Sleep duration, h	6.3±0.9	4.9±0.4	6.0±0.1*	7.0±0.1*,†	8.1±0.3*,†,‡	<0.001
<i>Women</i>						
Subjects	6,722	1,197	2,965	2,034	526	–
Age, years	42.1±8.5	43.6±8.4	42.2±8.3*	41.4±8.5*,†	40.4±8.9*,†	<0.001
BMI	21.0±3.0	21.4±3.2	21.1±3.0*	20.9±2.8*	20.8±2.9*	<0.001
SBP, mm Hg	109.9±14.4	110.1±14.8	110.2±14.4	109.4±14.2	110.0±14.7	0.304
DBP, mm Hg	68.1±9.7	68.1±10.0	68.3±9.6	67.8±9.4	67.9±9.9	0.383
Fasting plasma glucose, mmol/L	5.0±0.5	5.1±0.5	5.0±0.6	5.0±0.5	5.0±0.5*	0.011
Triglycerides, mmol/L	0.7±0.4	0.7±0.4	0.7±0.4	0.7±0.5*	0.7±0.4	0.165
HDL cholesterol, mmol/L	1.6±0.4	1.7±0.4	1.6±0.4*	1.6±0.4*	1.6±0.4*	<0.001
Uric acid, μmol/L	229.4±49.3	232.8±49.6	230.4±48.9	226.6±50.6*,†	227.4±45.0	0.003
Creatinine, μmol/L	61.1±9.6	60.2±9.3	61.3±9.6*	61.2±9.8*	61.0±9.8	0.005
eGFR, mL/min/1.73 m ²	76.3±14.6	76.5±14.2	75.8±14.5	76.5±15.0	77.4±14.8	0.068
Ratio of ex-/current smokers	468/511	106/120	183/222	141/121	38/48	<0.001
Exercisers	1,019	153	481	316	69	0.020
Light/moderate/heavy alcohol consumption	418/192/88	73/42/24	197/80/29	122/54/22	26/16/13	0.042
Sleep duration, h	6.3±0.9	4.9±0.4	6.0±0.1*	7.0±0.1*,†	8.1±0.3*,†,‡	<0.001

Data are expressed as numbers or means ± SD unless otherwise stated. Comparisons were performed using one-way ANOVA and Tukey's honestly significant difference test for continuous variables and the χ^2 test for categorical variables. DBP, diastolic blood pressure; SBP, systolic blood pressure. * $p < 0.05$ vs. the <6-h group. † $p < 0.05$ vs. the 6 to <7 h group. ‡ $p < 0.05$ vs. the 7 to <8 h group.

Fig. 2. Scatter plot and linear regression analysis of the correlation between sleep duration and change in Cr. Change in Cr was defined as a percentage: (Cr of the follow-up examination – Cr of the baseline examination)/Cr of the baseline examination/follow-up duration (years). There was a correlation between change in Cr and sleep duration in men ($r = 0.0316$ and $p = 0.006$). On the other hand, there was no correlation between change in Cr and sleep duration in women ($r = 0.004$, $p = 0.757$).

Fig. 3. Kaplan-Meier curves for freedom of CKD progression according to sleep duration. A log-rank test was used to assess differences among groups. To correct for family-wise error, we performed a Bonferroni correction and $p < 0.0083$ was considered statistically significant in the log-rank test. A shorter sleep duration was associated with a significantly lower development of CKD in men (<6 h group vs. 6–7 h, 7–8 h, and ≥ 8 h groups: $p < 0.0083$; 6–7 h group vs. 7–8 h group: $p < 0.0083$). There was no association between sleep duration and incident CKD in women ($p = 0.894$).

Table 2. HR for incident CKD

	HR (95% CI)	p
<i>Men</i>		
Age (years)	1.06 (1.05–1.06)	<0.001
BMI	1.04 (1.02–1.05)	<0.001
Uric acid (10 µmol/L)	1.003 (1.002–1.003)	<0.001
Creatinine (µmol/L)	1.07 (1.07–1.08)	<0.001
Triglycerides (mmol/L)	1.14 (1.10–1.17)	<0.001
HDL cholesterol (mmol/L)	0.72 (0.61–0.84)	<0.001
SBP (mm Hg)	1.01 (1.003–1.010)	0.0001
Fasting plasma glucose (mmol/L)	1.05 (0.98–1.11)	0.161
Exerciser	1.22 (1.07–1.38)	0.004
Alcohol consumption	1.04 (1.02–1.07)	0.0007
Ex-smoker	1.24 (1.10–1.42)	0.0013
Current smoker	1.02 (0.90–1.15)	0.807
Sleep duration		
<6 h group	0.54 (0.45–0.64)	<0.001
6 to <7 h group	0.73 (0.66–0.82)	<0.001
7 to <8 h group	1.00 (reference)	–
≥8 h group	0.93 (0.78–1.11)	0.433
<i>Women</i>		
Age (years)	1.09 (1.08–1.10)	<0.001
BMI	1.08 (1.05–1.10)	<0.001
Uric acid (10 µmol/L)	1.007 (1.006–1.009)	<0.001
Creatinine (µmol/L)	1.07 (1.06–1.08)	<0.001
Triglycerides (mmol/L)	1.64 (1.44–1.85)	<0.001
HDL cholesterol (mmol/L)	0.94 (0.76–1.16)	0.550
SBP (mm Hg)	1.02 (1.015–1.025)	<0.001
Fasting plasma glucose (mmol/L)	1.22 (1.11–1.34)	<0.001
Exerciser	1.55 (1.30–1.86)	<0.001
Alcohol consumption	0.96 (0.92–1.00)	0.044
Ex-smoker	0.93 (0.67–1.31)	0.691
Current smoker	1.17 (0.89–1.55)	0.245
Sleep duration		
<6 h group	0.89 (0.71–1.10)	0.273
6 to <7 h group	1.16 (0.97–1.38)	0.103
7 to <8 h group	1.00 (reference)	–
≥8 h group	1.08 (0.81–1.45)	0.584

“No exercise habit” and “nonsmoker” were set as references for lifestyle factors.

CKD [13]. A strength of the present study is that we researched the longitudinal association between sleep duration and incident CKD in a large-scale cohort study of apparently healthy Japanese individuals. The reason why the result of this study is different from those of prior meta-analyses may stem from the characteristics of Japanese. The average sleep time of Japanese people is shorter than that of other ethnic groups [27], and this distinction can result in different study results.

Regarding with the association between sleep duration and mortality, it was reported that the mortality rate was lowest in individuals who regularly sleep 7 h [28]. The authors of that study indicated a U-shaped curve between sleep length and subsequent mortality [28]. Later investigations showed that both short and long sleep durations were associated with mortality [29, 30].

Short sleep duration was also reported to be associated with the risk of hypertension [9], type 2 diabetes [10, 11], obesity [12], and cardiovascular disease [15, 16], but another recent

meta-analysis including a meta-regression showed that a long sleep duration was associated with mortality, incident diabetes, cardiovascular disease, stroke, coronary heart disease, and obesity [31].

In CKD patients, neurological and cognitive impairments can be seen [32] and altered sleep habits are considered as one of the behavioral manifestations of brain changes in CKD. These have not been clarified, but in our present study, neurological changes may have had an influence on the sleep habit of the participants with incident CKD. In addition, sleep disturbances are associated with cognitive dysfunctions [33]. In fact, recent studies have revealed that even early CKD stages can be accompanied by cognitive dysfunctions [34], and thus sleep duration might be an early sign of CKD.

The precise mechanisms underlying how a short sleep duration affects incident CKD are not known, but some possibilities are as follows. A short sleep duration is associated with reduced leptin levels and elevated ghrelin levels [35]. Ghrelin, which has an anti-inflammatory effect [36], has a protective effect against renal fibrotic changes through the inhibition of angiotensin II-induced upregulation of transforming growth factor- β and plasminogen activator inhibitor-1 [37]. Moreover, leptin is associated with the progression of kidney diseases [38, 39]. Together these findings suggest that each sleep habit could affect incident CKD occurrence. Therefore, routine screening of renal function for patients with a sleep disturbance should be considered.

Some limitations of our study should be considered. First, the study population might have been comprised of mostly or only health-conscious individuals who undergo multiple health examinations, and this could have resulted in selection bias. Second, we defined proteinuria by dipstick testing, and thus the level of proteinuria was not quantified. We could not discuss urine occult blood, which could affect the amount of urine protein. However, the dipstick test is a useful tool, and it has been reported that most patients with a dipstick test result $\geq 1+$ have micro- or macroalbuminuria [24]. In addition, the presence of proteinuria shown by dipstick testing was reported to be a useful maker for future end-stage renal disease [40]. Third, our sleep duration data were based on a self-administered questionnaire, and the reliability of such self-reporting is a study limitation, although previous investigations of sleep duration have also been based on questionnaire responses [9–11, 18]. We did not evaluate the quality of the subjects' sleep. Lastly, the generalizability of our research to non-Japanese populations is uncertain.

In conclusion, our analyses of 14,474 subjects showed that the risk of incident CKD is lowest for those who sleep < 6 h in apparently healthy men. That is why physicians should take note of altered sleep duration appropriately as an early sign of CKD, which would result in delaying the development of CKD.

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Statement of Ethics

All of the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee of the institute at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all of the individual participants included in this study. This study was approved by the Medical Ethics Committee of the Asahi University Hospital.

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Author Contributions

H.N. contributed to the design of this work and analysis of the data and wrote this paper. Y.H. contributed to the conception and design of this work, analysis and interpretation of the data, and drafting of the Discussion. T.O. contributed to interpretation of the data and drafting of the Discussion. A.O. and T.K. contributed to the conception and design of this work, acquisition of data, and revision of the Discussion. M.H. contributed to the conception this work, acquisition and interpretation of data, and revision of the Discussion. M.F. contributed to the conception of this work, interpretation of data, and revision of the Discussion. M.H. is the guarantor of this work and, as such, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of the version to be published and agree to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

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