Abstract

Objective: To investigate the association of sleep duration and shift work with development of chronic kidney disease (CKD) in Japanese workers.

Methods: A total of 3600 participants without CKD were followed for an average of 4.4 years. The Cox proportional-hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of CKD associated with sleep duration and shift work.

Results: Sleep duration and shift work showed no significant association with the risk of CKD. However, when the results were stratified by shift work status, short sleep duration was associated with a significantly higher risk of CKD among shift workers (HR = 3.60; 95% CI: 1.52–10.68).

Conclusions: Short sleep duration was a risk factor for early CKD but only among shift workers.

Introduction

Chronic kidney disease (CKD) has become a public health concern worldwide because of its association with an increased prevalence of end-stage renal disease (ESRD) [1-3]. In addition, several epidemiological observations and clinical studies have documented a strong association between CKD and accelerated cardiovascular disease (CVD), resulting in increased morbidity and mortality [1, 4]. Recent studies have confirmed that even the earlier stage of CKD constitutes a significant risk factor for cardiovascular events and death [5, 6]; however, CKD is asymptomatic in its earlier stages. Therefore, to slow the progression of CKD, it is essential to develop better strategies for early detection and intervention using modifiable lifestyle factors.

It is widely accepted that sleep is an essential part of a healthy lifestyle; however, approximately 20% of the adult population in western countries and Japan experiences sleep disturbances [7, 8]. In addition, growing evidence indicates that short sleep duration is associated with an increased risk of mortality [9, 10], CVD [11-14], hypertension [15, 16], and metabolic disorders such as type 2 diabetes mellitus [17, 18], insulin resistance [19], and obesity [20]. However, research on the impact of sleep disturbances on earlier stages of CKD is limited. Although a previous retrospective study suggested that short sleep duration may be a modifiable risk factor for proteinuria [21], which is an important risk

factor for ESRD, it remains unclear whether sleep duration is a predictive factor for CKD.

With the rapid progress of a 24-hour-a-day society, shift work and related health problems have become common [22, 23]. Epidemiological studies have reported that shift workers are at a significantly increased risk of developing several vascular events, including ischemic stroke [24], ischemic heart disease [25], type 2 diabetes [26], and metabolic syndrome [27]. A previous cross-sectional study reported that an association of night shift work with decreased renal function in police officers [28]. However, to the best of our knowledge, no prospective study has reported an association between shift work and risk of CKD. In addition, shift workers are known to sleep less than day workers [22]. Recent reviews focused on the potential health effects of shift work suggested that sleep disturbances induced by shift work contribute to development of CVD and metabolic disorders [29, 30]. However, there is no study focusing on the effect of shift work in relation to sleep duration and CKD. Therefore, in the present study, we examined the association of sleep duration and shift work with CKD among Japanese civil servants. We also assessed whether shift work acts as an effect modifier in the association between sleep duration and incident CKD.

Methods

Study design and population

This prospective occupational study was conducted in Sapporo, Hokkaido Prefecture, Japan. A total of 10,423 local government employees aged 35–62 years who underwent annual health check-ups between April 2003 and March 2004 were contacted. Of these, 5,013 (response rate = 48.1%) returned a self-administered questionnaire after completing the check-up. The questionnaire included questions regarding sleep duration, medical history, family history, smoking, alcohol consumption, exercise frequency, educational background, and occupational factors. A total of 1,203 participants were excluded on account of the following reasons: those aged ≥59 years, because they were due for retirement during the follow-up period (n = 156); those for whom data on exposure or relevant covariates was missing (n = 231); those under medical treatment for hypertension, diabetes mellitus, dyslipidemia, or renal disease (n = 665); or those with a history of coronary disease or stroke (n = 71). In order to examine the predictors of earlier stages of kidney disease, those with a baseline estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (calculated by the simplified Japanese GFR inference formula equation [31]) were also excluded (n = 80). Follow-up annual health check-ups took place from 2004 to 2008. After excluding 210 (5.5%) participants who

never received check-ups even once during the follow-up periods, a total of 3600 participants (2798 men and 802 women) were included for longitudinal analysis. All participants provided written informed consent, and the study protocol was approved by the institutional ethical board for epidemiological studies of Hokkaido University Graduate School of Medicine.

Assessment of sleep duration and shift work

Information on sleep was obtained from the self-administered questionnaire. Sleep duration was assessed by the question "On average, how long, in hours and minutes, do you normally sleep?" The responses were then categorized into ≤5 h, 6-7 h, and ≥8 h, because previous studies have suggested that individuals with a sleep duration of ≤5 h are at a significantly higher risk of proteinuria [21], whereas those with a sleep duration of 6–7 h are at the lowest risk of cardiometabolic disease [32]. Because of the small number of participants, we chose to combine participants with a sleep duration of 8h and ≥9 h into a single group (≥8 h).

Information regarding shift work was collected from the self-administered questionnaires at baseline, which included the following question: "Do you work in shifts?" The possible responses were "Yes, without night shifts," "Yes, with night shifts,"

or “No.” Night shift was defined as work schedule from 22:00 to 05:00. Because the number of participants without night shifts was small, we categorized shift work into 2 categories: “Yes” and “No.”

Assessment of renal function and follow-up

Creatinine levels were measured using an enzymatic assay (Kanto Kagaku, Tokyo, Japan). Kidney function was assessed in terms of eGFR, which was calculated using the simplified Japanese GFR inference formula developed by the Japanese Society of Nephrology [31]: GFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × age$^{-0.287}$ (× 0.739 if female). Onset of CKD was defined as an eGFR of <60 mL/min/1.73 m^2 after the first health check-up and confirmed annually. For participants who had more than one CKD event during the follow-up period, only the first event was included for statistical analyses. The date of onset of CKD was defined as the intermediate day between the first CKD event and the last eGFR measurement.

Assessment of covariates

Anthropometric measurements (height and body weight) at the health check-ups were assessed using a standardized protocol. Body mass index (BMI) was calculated as

weight/height (kg/m^2). Systolic and diastolic blood pressure (SBP and DBP, respectively) was measured using an automated sphygmomanometer (USM-700G Si; Ueda Avancer Corp., Tokyo, Japan) placed on the arm of a seated participant who had rested in the sitting position for a few minutes before measurement. Blood samples were drawn after a 12-h fast from the antecubital vein of seated participants with minimal tourniquet use. Specimens were collected in siliconized glass vacuum tubes containing sodium fluoride for analysis of blood glucose levels, which were measured by an amperometric method (Arkray, Kyoto, Japan). Enzymatic assays were used to measure levels of total cholesterol (TC) (Wako, Osaka, Japan), triglycerides (TG) (Daiichi Pure Chemicals, Tokyo, Japan), and uric acid (UA) (Daiichi Pure Chemicals, Tokyo, Japan). C-reactive protein (CRP) levels were measured by nephelometry with a latex particle-enhanced immunoassay (N Latex CRP Ⅱ; Dade Behring, Tokyo, Japan), which could detect 0.004 mg/dL of CRP. Undetectable CRP values were recorded as 0.002 mg/dL. Urine dipstick tests were interpreted and categorized as negative or ≥1+.

Educational background was categorized as “high school or less” or “more than high school.” Frequency of leisure time exercise (with perspiration) was categorized as “rarely or never,” “1–2 times/week,” or “≥3 times/week.” Smoking status was categorized as “non-smoker” (never smoked), “ex-smoker,” or “current smoker.” The

average daily alcohol consumption, based on the alcohol concentration of each beverage type (g/day, ethanol equivalent), was estimated according to the frequency and amount of consumption and was categorized into the following 4 categories: non-drinkers, <30 g/day, 30–59 g/day, and ≥60 g/day. Working hours were calculated as the average number of working hours, including overtime, per week during the previous month. Occupational stress was assessed using the demand–control model (DCM) [33, 34]. The Japanese version of the DCM consists of 5 questions on psychological demands (job demands, time pressures, and conflicting demands) and 6 questions on decision latitude (influence or control over work, job variety, and opportunities for learning new skills). Each question has 4 frequency-based response categories ranging from "never" (1 point) to "always" (4 points). Job strain was defined as the ratio of demand to job control [34].

Statistical analysis

The Cox proportional-hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of CKD associated with sleep duration and shift work using the following 2 models: (1) adjusted for age, sex, and eGFR at baseline and (2) adjusted for model 1 variables plus SBP, BMI, TC, TG, fasting glucose, UA,

CRP, proteinuria ≥1+, family history of renal disease, lifestyle factors (smoking, exercise, and alcohol consumption), educational background, working hours, and job strain. In addition, to assess whether the association between sleep duration and CKD was modified by shift work, we stratified the analyses by shift work.

All analyses were performed using JMP software version 10.0.0 for Windows (SAS Institute, Cary, NC, USA). A two-tailed probability (*P*) value of <0.05 was considered statistically significant.

Results

Over an average follow-up period of 4.4 years, a total of 182 cases of CKD (148 in men and 34 in women) were identified. The mean age of the study cohort was 47.0 ± 6.7 years. Mean eGFR and sleep duration at baseline were 84.3 ± 13.1 mL/min/1.73 m^2 and 6.6 ± 0.9 h, respectively. Baseline characteristics according to sleep duration categories are presented in Table 1. Compared with participants reporting a sleep duration of 6–7 h, those with a sleep duration of ≤5 h and ≥8 h were more likely to be shift workers. Short sleep duration was associated with younger age; female gender; lower SBP, DBP, TG, fasting glucose, UA, and CRP levels; higher possibility of being non-smoker and non-drinker; more exercise; higher levels of education; longer working hours; and higher job strain. Table 2 shows baseline characteristics according to shift work. Compared with participants without shift work, those with shift work were more likely to be young, males, non-smokers and non-drinkers, less educated, and engaged in more exercise, with longer working hours, and higher job strain.

The results of longitudinal multivariate analyses using Cox proportional hazards models to examine the impact of sleep duration and shift work on CKD are presented in Table 3. Neither sleep duration nor shift work was associated with the risk of CKD. The results of stratification by shift work are presented in Table 4. In model 1, compared

with participants reporting a sleep duration of 6–7 h, those reporting a sleep duration ≤5 h had a significantly increased risk of CKD among shift workers (HR = 3.60; 95% CI = 1.38–8.41); in contrast, no association was observed among non-shift workers (HR =0.52; 95% CI = 0.20–1.12). After adjustment for potential confounders, a significant association between short sleep duration and CKD was confined to shift workers (HR = 4.22; 95% CI = 1.52–10.68).

Discussion

The results of the present study showed no significant association of sleep duration and shift work with the risk of CKD. However, short sleep duration was associated with a significantly higher risk of CKD in shift workers but not in non-shift workers.

Only few studies have examined the effects of sleep duration on earlier stages of CKD [21, 35]. Previous studies have indicated an association between sleep duration of ≤5 h and proteinuria, even among non-shift workers. In contrast to the results of these previous studies, a significant association between short sleep duration and CKD was confined to shift workers in the present study. There are several possible explanations for this disparity. The first is the difference in the distribution of sleep duration. Compared with previous studies [21], the participants in our study reported a longer average sleep duration, with only a small proportion of participants reporting a short sleep duration; this possibly reduce the effect of sleep duration on the incidence of CKD. The second reason is that the definition of CKD was based on eGFR, which could be affected by several factors, including muscle mass and protein intake [31]. In addition, eGFR can decrease regardless of the presence of renal disorders [36]. Previous studies have assessed proteinuria using dipstick tests. Proteinuria is a useful marker of decreased renal function and rapid progression of

kidney damage [37]; however, the dipstick urine test for proteinuria has low sensitivity [38]. In the present study, we used eGFR to quantitatively evaluate renal dysfunction. This difference in the definition of CKD may have influenced these conflicting results.

Our results indicated that shift work acted as an effect modifier in the association between sleep duration and CKD. Epidemiological studies have reported that shortened sleep duration is the most common health-related problem of shift work and most shift workers suffer from disruptions in circadian rhythms [22, 23]. Recent reviews have hypothesized that sleep disturbances induced by shift work contribute to the development of CVD and other metabolic disorders [29, 39]. Some prospective studies have investigated the impact of shift work on the association between sleep duration and health outcomes; however, the results have been conflicting [15, 40]. For example, the Nurses' Health Study investigated the effects of short sleep duration on hypertension and found that shift work did not act as an effect modifier [15], whereas another study indicated that shift work enhanced the association between short sleep duration and obesity [40]. It is not clear why the conflicting results were found, but they may be related to differences in the methods used for assessment of outcomes or participants. Shift work is related not only to insufficient sleep, but also to lifestyle factors and job strain [41,

[42]. In the present study, we considered these factors and found that the risk of CKD in shift workers with short sleep duration was significantly increased even after adjusting for lifestyle factors such as smoking status, alcohol consumption, exercise, and job strain. Our results indicated that the interaction of shift work and short sleep duration may promote the development of CKD. Because this is the first study to investigate the association of risk for CKD with sleep duration and shift work, more studies are needed to confirm or refute these findings.

The possible reasons for the increased risk of CKD in shift workers with short sleep duration remain unknown. Shift work has been shown to disrupt circadian rhythms [43]. Experimental data have suggested a role of altered circadian organization in the development of severe renal diseases, such as proteinuria, tubular dilation, and cellular apoptosis [44]. It is possible that disturbances in circadian rhythms induced by shift work may enhance the association between sleep duration and CKD. In addition, it has also been proposed that shift work could result in stress [45], leading to metabolic disturbances that involve increased secretion of glucocorticoids and catecholamines as well as activation of the sympathetic nervous system [46]. It is possible that these factors may increase the progression of renal dysfunction.

The pathophysiology of sleep duration and the underlying mechanisms of association

with CKD remain unknown. A plausible biological mechanism is activation of the sympathetic nervous system. Disturbed sleep induces activation of the sympathetic nervous system, higher evening cortisol levels, and attenuation of the sleep-induced decrease in blood pressure (referred to as non-dipping), which could lead to kidney dysfunction [47-50]. A previous prospective study also indicated non-dipping as a risk factor for decreased renal function among non-CKD patients [51]. In addition, mechanisms that promote inflammation could possibly mediate the link between short sleep duration and renal dysfunction [52, 53]. However, in the present study, levels of CRP, marker of inflammation were not associated with a higher risk of CKD. Another possible mechanism is objective sleep apnea (OSA). A limited small study suggested that OSA influences renal hemodynamics [54] and that treatment with continuous positive airway pressure improves this effect [55]. However, further research is necessary to better elucidate the association between sleep disturbance and CKD.

The strengths of our study include its prospective design and detailed information on potential confounders. However, this study had some limitations as well. First, our sleep duration measure relied on a self-administered questionnaire, which could be susceptible to misclassification, particularly with respect to sleep duration on weekends. The daily average sleep duration of Japanese workers is reportedly 7 h on weekdays, 7.5

h on Saturdays, and 8 h on Sundays [56]. The differences in sleep duration between weekdays and weekends may have influenced the results of our study. In addition, sleep duration was only evaluated once at the beginning of the follow-up period; therefore, we could not examine the possible effects of time-dependent changes in sleeping habits. Assessment of self-reported exposures may result in some misclassification. However, in many similar epidemiological studies, a self-reported measure was used to assess sleep duration and shift work. Moreover, because the outcome was assessed prospectively using blood samples, any misclassification is likely to be non-differential with respect to CKD. Second, we did not have any information on whether workers were engaged in fixed or rotating shift work. One previous study reported that fixed shift work (working mainly at night and the same time every day) was not associated with ischemic heart disease [25]. Further research is needed to assess the effect of patterns of shift work. ~~However, we were unable to assess the effect of fixed shift work because rotating shifts are common among Japanese civil servants.~~ Third, the outcome variable of serum creatinine levels was measured once a year and we used eGFR to define CKD without measurement of urinary albumin excretion. However, annual health examinations are common in Japan and this approach has been used in several previous studies [57, 58]. Fourth, the response rate of our study was rather low (48.1%), so

our participants may not necessarily be representative of civil servants in general in Japan. However, because the average sleep duration in our study did not differ from that of middle-aged Japanese people in general [56], we believe that our results are minimally affected by the low response rate. In addition, only 5% of participants were lost to follow-up, which strengthens our findings.

In conclusion, short sleep duration was significantly associated with an increased risk of CKD in shift workers. Additional large prospective studies are needed to confirm this finding and to investigate the possible biological mechanisms underlying this association.

Reference

1. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med.* 2004;164:659-663.

2. Collins AJ, Foley RN, Herzog C, et al. US Renal Data System 2012 Annual Data Report. *Am J Kidney Dis.* 2013;61:A7, e1-476.

3. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis.* 2003;42:677-684.

4. Ninomiya T, Kiyohara Y, Kubo M, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. *Kidney Int.* 2005;68:228-236.

5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296-1305.

6. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol.* 2003;41:1364-1372.

7. US-Sleep-Foundation. *Sleep in America* poll-Summariy of findings. http://www.sleepfoundation.org/sites/default/files/2005_summary_of_findings.pdf2005.

8. Doi Y, Minowa M, Okawa M, Uchiyama M. Prevalence of sleep disturbance and hypnotic medication use in relation to sociodemographic factors in the general Japanese adult population. *J Epidemiol.* 2000;10:79-86.

9. Tamakoshi A, Ohno Y. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. *Sleep.* 2004;27:51-54.

10. Heslop P, Smith GD, Metcalfe C, Macleod J, Hart C. Sleep duration and mortality: The effect of short or long sleep duration on cardiovascular and all-cause mortality in working men and women. *Sleep Med.* 2002;3:305-314.

11. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med.* 2003;163:205-209.

12. Ikehara S, Iso H, Date C, et al. Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: the JACC study. *Sleep.* 2009;32:295-301.

13. Chandola T, Ferrie JE, Perski A, Akbaraly T, Marmot MG. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep

disturbance: a prospective study from the Whitehall II cohort. *Sleep.* 2010;33:739-744.

14. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, van den Berg JF, Verschuren WM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. *Sleep.* 2011;34:1487-1492.

15. Gangwisch JE, Feskanich D, Malaspina D, Shen S, Forman JP. Sleep duration and risk for hypertension in women: results from the nurses' health study. *Am J Hypertens.* 2013;26:903-911.

16. Bansil P, Kuklina EV, Merritt RK, Yoon PW. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens (Greenwich).* 2011;13:739-743.

17. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care.* 2005;28:2762-2767.

18. Beihl DA, Liese AD, Haffner SM. Sleep duration as a risk factor for incident type 2 diabetes in a multiethnic cohort. *Ann Epidemiol.* 2009;19:351-357.

19. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol (1985).* 2005;99:2008-2019.

20. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity (Silver Spring).* 2008;16:643-653.

21. Yamamoto R, Nagasawa Y, Iwatani H, et al. Self-reported sleep duration and prediction of proteinuria: a retrospective cohort study. *Am J Kidney Dis.* 2012;59:343-355.

22. Ohayon MM, Smolensky MH, Roth T. Consequences of shiftworking on sleep duration, sleepiness, and sleep attacks. *Chronobiol Int.* 2010;27:575-589.

23. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep.* 2004;27:1453-1462.

24. Brown DL, Feskanich D, Sanchez BN, Rexrode KM, Schernhammer ES, Lisabeth LD. Rotating night shift work and the risk of ischemic stroke. *Am J Epidemiol.* 2009;169:1370-1377.

25. Fujino Y, Iso H, Tamakoshi A, et al. A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. *Am J Epidemiol.*

2006;164:128-135.

26. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med.* 2011;8:e1001141.

27. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. Rotating shift work and the metabolic syndrome: a prospective study. *Int J Epidemiol.* 2009;38:848-854.

28. Charles LE, Gu JK, Fekedulegn D, Andrew ME, Violanti JM, Burchfiel CM. Association between shiftwork and glomerular filtration rate in police officers. *J Occup Environ Med.* 2013;55:1323-1328.

29. Puttonen S, Harma M, Hublin C. Shift work and cardiovascular disease - pathways from circadian stress to morbidity. *Scand J Work Environ Health.* 2010;36:96-108.

30. Vyas MV, Garg AX, Iansavichus AV, et al. Shift work and vascular events: systematic review and meta-analysis. *Bmj.* 2012;345:e4800.

31. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* 2009;53:982-992.

32. Knutson KL. Sleep duration and cardiometabolic risk: a review of the

epidemiologic evidence. *Best Pract Res Clin Endocrinol Metab.* 2010;24:731-743.

33. Sugisawa A, Uehata T, Pin H, et al. [Mental health, work environment, and health practices among middle-aged male workers]. *Sangyo Igaku.* 1993;35:7-18.

34. Tsutsumi A, Kayaba K, Tsutsumi K, Igarashi M. Association between job strain and prevalence of hypertension: a cross sectional analysis in a Japanese working population with a wide range of occupations: the Jichi Medical School cohort study. *Occup Environ Med.* 2001;58:367-373.

35. Fujibayashi K, Fukuda H, Yokokawa H, et al. Associations between healthy lifestyle behaviors and proteinuria and the estimated glomerular filtration rate (eGFR). *J Atheroscler Thromb.* 2012;19:932-940.

36. Nickolas TL, Barasch J, Devarajan P. Biomarkers in acute and chronic kidney disease. *Curr Opin Nephrol Hypertens.* 2008;17:127-132.

37. Zandi-Nejad K, Eddy AA, Glassock RJ, Brenner BM. Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidney Int Suppl.* 2004:S76-89.

38. Kawashima M, Wada K, Ohta H, Moriya R, Aizawa Y. Evaluation of validity of

the urine dipstick test for identification of reduced glomerular filtration rate in Japanese male workers aged 40 years and over. *J Occup Health.* 2012;54:176-180.

39. Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC. Shift work and chronic disease: the epidemiological evidence. *Occup Med (Lond).* 2011;61:78-89.

40. Itani O, Kaneita Y, Murata A, Yokoyama E, Ohida T. Association of onset of obesity with sleep duration and shift work among Japanese adults. *Sleep Med.* 2011;12:341-345.

41. Frost P, Kolstad HA, Bonde JP. Shift work and the risk of ischemic heart disease - a systematic review of the epidemiologic evidence. *Scand J Work Environ Health.* 2009;35:163-179.

42. Tenkanen L, Sjöblom T, Härmä M. Joint effect of shift work and adverse life-style factors on the risk of coronary heart disease. *Scand J Work Environ Health.* 1998;24:351-357.

43. Rajaratnam SM, Howard ME, Grunstein RR. Sleep loss and circadian disruption in shift work: health burden and management. *Med J Aust.* 2013;199:S11-15.

44. Martino TA, Oudit GY, Herzenberg AM, et al. Circadian rhythm disorganization

produces profound cardiovascular and renal disease in hamsters. *Am J Physiol Regul Integr Comp Physiol.* 2008;294:R1675-1683.

45. Härmä M. Workhours in relation to work stress, recovery and health. *Scand J Work Environ Health.* 2006;32:502-514.

46. Tsatsoulis A, Fountoulakis S. The protective role of exercise on stress system dysregulation and comorbidities. *Ann N Y Acad Sci.* 2006;1083:196-213.

47. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep.* 2006;29:1009-1014.

48. Basta M, Chrousos GP, Vela-Bueno A, Vgontzas AN. CHRONIC INSOMNIA AND STRESS SYSTEM. *Sleep Med Clin.* 2007;2:279-291.

49. Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep.* 1997;20:865-870.

50. 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;60:823-833.

51. Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. *Arch Intern Med.* 2006;166:846-852.

52. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol.* 2004;43:678-683.

53. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis.* 2009;51:294-302.

54. Chou YT, Lee PH, Yang CT, et al. Obstructive sleep apnea: a stand-alone risk factor for chronic kidney disease. *Nephrol Dial Transplant.* 2011;26:2244-2250.

55. Kinebuchi S, Kazama JJ, Satoh M, et al. Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond).* 2004;107:317-322.

56. Institute. NBCR. National Time Use Survey 2005 Report. Tokyo: Japan Broadcast Publishing Co., Ltd.; 2006.

57. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol.* 2009;13:621-630.

58. Iseki K, Asahi K, Moriyama T, et al. Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among participants of the Specific Health Check and Guidance System in Japan 2008. *Clin Exp Nephrol.*

2012;16:244-249.

Table 1. Association of demographic and clinical characteristics with sleep duration at baseline

	Baseline Sleep Duration		
	≤5 h (n = 295)	6–7 h (n = 2619)	≥8 h (n = 686)
Shift work			
No	196 (66.4)	2033 (77.6)	495 (72.2)
Yes	99 (33.6)	586 (22.4)	191 (27.8)
Age	44.9 ± 6.8	47.0 ± 6.4	48.3 ± 6.4
Sex (male)	198 (67.1)	2001 (76.4)	599 (87.3)
SBP (mmHg)	112.7± 15.1	115.5 ± 15.6	117.8 ± 15.8
DBP (mmHg)	68.4 ± 10.2	71.0 ±11.3	73.1 ±11.1
BMI	23.1 ± 3.3	23.3 ± 3.0	23.3 ± 2.9
Total cholesterol (mg/dL)	206.3 ± 33.2	207.4 ± 32.2	208.8 ± 35.4
Triglyceride (mg/dL)[a]	92.1 (86.2–98.4)	95.2 (93.2–97.2)	103.4 (99.2–108.0)
Fasting glucose (mg/dL)	90.3 ± 11.9	92.1 ± 15.7	94.2 ± 18.0
Uric acid (mg/dL)	5.4± 1.2	5.5 ± 1.3	5.7 ± 1.2
CRP (mg/dL)[a]	0.037 (0.032–0.042)	0.040 (0.039–0.042)	0.042 (0.039–0.046)
eGFR (mL/min/1.73 m^2)	86.0 ± 14.5	84.1 ± 12.8	84.1 ± 13.2
Proteinuria			
≥1+	4 (1.4)	34 (1.3)	16 (2.3)
Family history of renal disease	7 (2.4)	77 (2.4)	18 (2.6)
Frequency of exercise			
Rarely or never	169 (57.5)	1533 (58.6)	355 (51.8)
1-2 times/week	71 (24.2)	722 (27.6)	214 (31.2)
3 times/week or more	54 (18.3)	361 (13.8)	117 (17.0)
Smoking status			
Non-smoker	108 (36.6)	906 (34.6)	170 (24.8)
Ex-smoker	43 (14.6)	582 (22.2)	185 (27.0)
Current	144 (48.8)	1131 (43.2)	331 (48.2)
Alcohol consumption (g/day)			
Non-drinker	103 (35.8)	813 (31.2)	184 (26.9)
1-29	119 (40.6)	957 (36.7)	197 (28.8)
30-59	36 (12.3)	498 (19.1)	168 (24.6)
≥60	33 (11.3)	338 (13.0)	135 (19.7)
Educational background			
high school or less	141 (47.8)	1393 (53.2)	427 (62.2)
more than high school	154 (52.2)	1266 (46.8)	259 (37.8)
Working hours (h/week)	49.7 ± 11.6	44.9 ± 8.2	43.6 ± 7.2
Job strain			
Low	68 (23.1)	851 (32.7)	259 (38.0)
Medium	93 (31.6)	890 (34.2)	216 (31.7)
High	133 (45.3)	863 (33.1)	207 (30.3)

Variables are presented as mean ± standard deviation (SD), geometric mean (interquartile range), or number (percentage).

[a] Log-transformed data were analyzed, and median (interquartile range) were back-transformed.

Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

Table 2. Association of demographic and clinical characteristics with shift work at baseline

	Non-shift worker (n =2724)	Shift worker (n = 876)
Age	47.4 ± 6.6	46.1 ± 6.5
Sex (male)	2063 (75.7)	735 (83.9)
SBP (mmHg)	115.3 ± 15.8	116.9 ± 15.0
DBP (mmHg)	71.0 ± 11.3	71.7 ± 11.1
BMI	23.1 ± 2.9	23.6 ± 3.2
Total cholesterol (mg/dL)	208.4 ± 33.2	205.1 ± 32.5
Triglyceride (mg/dL)[a]	92.5 (65.0–137.0)	98.0 (67.2–145.7)
Fasting glucose (mg/dL)	92.5 ± 16.7	91.7 ± 13.1
Uric acid (mg/dL)	5.5 ± 1.2	5.6 ± 1.3
CRP (mg/dL)[a]	0.036 (0.019–0.073)	0.041 (0.020–0.086)
eGFR (mL/min/1.73 m^2)	84.0 ± 13.1	85.1 ± 13.0
Proteinuria		
≥1+	40 (1.5)	14 (1.6)
Family history of renal disease	83 (3.1)	19 (2.2)
Frequency of exercise		
Rarely or never	1620 (59.5)	437 (50.0)
1-2 times/week	756 (27.8)	251 (28.7)
3 times/week or more	346 (12.7)	186 (21.3)
Smoking status		
Non-smoker	983 (36.1)	201 (23.0)
Ex-smoker	1136 (41.7)	470 (53.6)
Current	605 (22.2)	205 (23.4)
Alcohol consumption (g/day)		
Non-drinker	389 (14.3)	117 (13.4)
1-29	514 (19.0)	188 (21.5)
30-59	954 (35.2)	319 (36.6)
≥60	853 (31.5)	249 (28.5)
Educational background		
high school or less	1344 (49.3)	617 (70.4)
more than high school	1380 (50.7)	259 (29.6)
Working hours (h/week)	43.8 ± 7.2	48.8 ± 10.9
Job strain		
Low	945 (34.8)	233 (26.9)
Medium	927 (34.2)	272 (31.4)
High	841 (31.0)	362 (41.7)

Variables are presented as mean ± standard deviation (SD), geometric mean (interquartile range), or number (percentage).

[a] Log-transformed data were analyzed, and median (interquartile range) were back-transformed.

Table 3. HR (95% CI) for incidence of CKD (eGFR <60 mL/min/1.73 m^2) according to sleep duration and shift work

	Person-years	No. of cases	Model 1	Model 2
Sleep Duration				
≥8 h	2,948	37	1.00 (0.68–1.43)	1.06 (0.72–1.54)
6–7 h	11,699	131	1.00	1.00
≤5 h	1,343	14	1.01 (0.52–1.85)	0.99 (0.53–1.73)
Shift work				
(–)	11,993	146	1.00	1.00
(+)	3,997	36	0.96 (0.66–1.38)	1.01 (0.67–1.50)

Model 1: age, sex, and eGFR at baseline

Model 2: Model1 + SBP, BMI, TC, TG, fasting glucose, UA, CRP, proteinuria ≥ 1+, family history of renal disease, smoking, alcohol, exercise, education, work hours, and job strain

Table 4. HR (95% CI) for incidence of CKD (eGFR <60 mL/min/1.73 m^2) according to sleep duration stratified by shift work

	Person-years	No. of cases	Model 1	Model 2
Non-shift worker				
	2,108			
≥8 h		28	0.86 (0.55–1.29)	0.95 (0.60–1.45)
6–7 h	8,918	111	1.00	1.00
≤5 h	904	7	0.58 (0.24–1.17)	0.52 (0.20–1.12)
Shift worker				
≥8 h	840	9	1.69 (0.72–3.71)	1.77 (0.70–4.29)
6–7 h	2,718	20	1.00	1.00
≤5 h	439	7	3.60 (1.38–8.41)	4.22 (1.52–10.68)

Model 1: age, sex, and eGFR at baseline

Model 2: Model1 + SBP, BMI, TC, TG, fasting glucose, UA, CRP, proteinuria ≥ 1+, family history of renal disease, smoking, alcohol, exercise, education, work hours, and job strain