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Job Stress Strengthens the Link between Metabolic Risk Factors and Renal Dysfunction in Adult Men

Shinobu Tsurugano,[1] Mutsuhiro Nakao,[1,2] Takeaki Takeuchi,[1,2] Kyoko Nomura[1,2] and Eiji Yano[1]

[1]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[2]Division of Psychosomatic Medicine, Teikyo University Hospital, Tokyo, Japan

Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease. The metabolic risk factors obesity, hypertension, diabetes, and dyslipidemia are closely associated with renal dysfunction. As psychosocial stress affects these risk factors, here, we examined relationships between metabolic risk factors and renal function, and their association with job stress. The participants were 1,231 Japanese male office workers attending annual health examinations. The estimated glomerular filtration rate (eGFR) was determined using the equation recommended by the Japanese Society for Nephrology: eGFR (mL/min/1.73 m^2) = 194× age$^{-0.287}$ × Cr$^{-1.094}$. Job stress was measured using the Job Content Questionnaire based on the job demand-control model. The job strain index equaled the job demand scores divided by the job control scores. The participants were classified into four ordinal groups of job strain index, based on previous studies (*i.e.*, ≤ 0.4 the lowest, 0.4-0.5 lower, 0.5-0.6 higher, or ≥ 0.6 the highest). A significant correlation was found between lowered eGFR and each of the metabolic risk factors waist circumference, systolic and diastolic blood pressure, and total cholesterol ($p < 0.001$). Furthermore, job stress had an interactive effect on the relationships between eGFR and systolic and diastolic blood pressure, and triglycerides, depending on the job strain index (highest vs. lowest) ($p < 0.05$). The highly stressed workers exhibited a close association of eGFR with metabolic risk factors like hypertension and dyslipidemia. Therefore, intensive management may be important for preventing the progression of renal dysfunction and cardiovascular complications in those experiencing stress.

Keywords: chronic kidney disease; estimated glomerular filtration rate; job strain; metabolic syndrome; renal function
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In recent years, chronic kidney disease (CKD) has gained attention and the urgent need to address CKD has been recognized. Not only is CKD a predictor for end-stage renal disease, but numerous epidemiological studies have indicated that CKD is an important risk factor for the onset and mortality of people with cardiovascular disease (CVD) (Go et al. 2004; Fox et al. 2004). Using a glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2 as an indicator of CKD, a survey of the Japanese general population estimated that 19.3 million people (18.7% of the adult population) met this criterion (Imai et al. 2007), making it more prevalent than in the US and Europe (Coresh et al. 2003; Hallan et al. 2006).

Metabolic syndrome (MS) is an important risk factor for the onset of CKD. In recent epidemiological studies, the presence of a greater number of risk factors associated with MS resulted in a higher cumulative CKD onset ratio. There are several reports showing that each of the criteria for the diagnosis of MS were independent risk factors for proteinuria (Ramirez et al. 2002; Chen et al. 2004; Yamagata et al. 2007). Because MS and CKD are among the leading causes of CVD, there is an urgent need to identify the pathological mechanisms linking MS and CKD to CVD. Both MS and CKD are expected to significantly influence the life expectancy and medical expenses of the Japanese people (Ninomiya et al. 2006; Yamagata et al. 2007, 2008). Because middle-aged or older workers constitute the main workforce of Japanese industries, early detection of cardiovascular diseases among these age groups is also essential from the perspective of industrial medicine.

In recent years, psychosocial stress has become a serious problem concomitant with poor health. Psychosocial stress has been closely associated with diseases such as CVD, hypertension, and depression; and job stress seems to be a particularly important risk factor for the onset of CVD and increased death rates in employees (Karasek et al.

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Correspondence: Shinobu Tsurugano, Department of Hygiene and Public Health, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan.
e-mail: turugano-tky@umin.ac.jp

1981; Theorell et al. 1998; Tsutsumi et al. 2006). The demand-control model proposed by Karasek has been widely used as a quantitative method to measure job stress (Karasek et al. 1981). Based on this model, high job demand and low job control have been reported to contribute to deteriorating health (Karasek et al. 1981; Theorell et al. 1998; Steptoe and Willemsen 2004; Nomura et al. 2005; Tsutsumi et al. 2006). However, there are no studies linking impaired renal function and metabolic risk factors with job stress. The purpose of this study was to assess the relationship between each of metabolic risk factors and eGFR and to further clarify the role of job stress in the development of MS and reduced eGFR in Japanese men.

Methods

Participants

The participants were 1433 white-collar employees working in Tokyo, Japan, who underwent mandatory annual health examinations in 2007. One hundred eighty three females were excluded because they were a relatively small group, and 19 males were excluded because they failed to attend a medical examination. The remaining 1231 men, who were 20-67 years old, were included as participants. Written informed consent was obtained from all of the participants before starting the study. The study protocol was approved by the health and safety committee of the company. This research was performed in accordance with the Declaration of Helsinki as well as the theoretical principles on the conduct of epidemiological research of the Japanese Ministry of Education, Culture, Sports, Science and Technology, as well as those of the Japanese Ministry of Health, Labor and Welfare (Nakao et al. 2004).

Data measurements

Medical history, current therapeutic regime, and information regarding tobacco and alcohol consumption as well as exercise habits were included in the survey questionnaire (Nomura et al. 2009; Takeuchi et al. 2009). This information was subsequently confirmed in an interview with a physician. Participants were asked whether they smoked, how much they smoked (cigarettes/day), and how long they had been smoking. To identify the daily consumption of alcohol, participants were asked whether they drank alcohol, and if so, the type, volume, and frequency of alcohol intake. Participants were also asked about their frequency of exercise per week.

Evidence of proteinuria was determined by urinalysis in the early morning using the Ames dipstick test. The results were categorized as ±, 1+, 2+, and 3+. Body mass index (BMI) was calculated by weight (kg)/height^2 (m). The waist circumference was measured by a trained person at the level of the iliac crest. Resting blood pressure was measured manually using a sphygmomanometer. Fasting blood samples were collected in the early morning. Serum creatinine, total cholesterol, uric acid, triglycerides, and serum glucose were measured using enzymatic methods. HDL cholesterol was measured directly, and hemoglobin A_{1c} was measured by the latex agglutination method. All serum sample analyses were performed in one laboratory (SRL, Tokyo, Japan).

MS was determined using the criteria of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) modified by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) applying a cut-off value appropriate to Asian males (Grundy et al. 2004). MS was diagnosed when three or more of the following were present: waist circumference ≥ 90 cm, systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85 mmHg, triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL, and fasting blood glucose ≥ 100 mg/dL.

The eGFR was determined using the new 3-variable Japanese equation by the Japanese Society for Nephrology (Matsuo et al. 2009): eGFR (mL/min/1.73 m^2) = 194 × age$^{-0.287}$ × Cr$^{-1.094}$. The estimate of renal function was performed according to the guidelines by the Kidney Disease Outcome Quality Initiative (K/DOQI) (National Kidney Fundation 2002). CKD was diagnosed if the eGFR was < 60 mL/min/1.73 m^2, or proteinuria was > 1+ (Kopple 2001; Yamagata et al. 2008). Participants with eGFR < 60 mL/min/1.73 m^2 were considered as the low eGFR group, while those with eGFR ≥ 60 mL/min/1.73 m^2 were considered as the high eGFR group.

Measurement of perceived job stress

The measurement of perceived job stress was evaluated using a Japanese version of the Job Content Questionnaire (Kawakami et al. 1995). Prior research has confirmed the reliability and validity of the questionnaire for Japanese employees (Kawakami and Fujigaki 1996). Job demand was evaluated by required execution speed, task difficulty, work volume, time allowed for performance, and competing demands. Job control was evaluated by the requirement to learn new things of highly repetitive nature, creativity, skill required, the ability to make decisions, and the influence on group decision-making processes. The job strain index was defined by dividing the job demand scores by the job control scores. Because the job strain index has been used as a risk indicator for cardio and cerebrovascular diseases more than an indicator of demand or control (Sokejima and Kagamimori 1998; Yoshimasu 2001), the job strain index was used in this research. The participants were divided into groups based on a job strain index from our previous studies (Nishikitani et al. 2005, 2006). A job strain index value below 0.4 was classified as the lowest group, 0.4 or below 0.5 as lower, 0.5 or below 0.6 as higher and 0.6 or above as the highest.

Statistical Analysis

Statistical analysis was performed with SAS version 9.1 for Windows. All of the differences were subjected to two-tailed tests and the significance level was set at 5%. Because all the data distributions of the continuous variables (age; BMI; waist circumference; systolic and diastolic blood pressures; total cholesterol; triglycerides, HDL cholesterol; fasting blood sugar; hemoglobin A_{1c}; uric acid; creatinine; eGFR; the number of cigarettes smoked by smokers per day; the amount of alcohol consumed by drinkers per day; and scores on job demand, job control, and job strain) were assumed not to be normal ($p > 0.05$, Shapiro-Wilk test), the Wilcoxon rank-sum test was used to compare the two (high or low) eGFR levels (cut-off: 60 mL/min/1.73 m^2). The chi-square test or the Fisher's exact test was performed to compare categorical variables between the two groups. The step-wise method of multiple logistic regression analysis was performed with the two levels of eGFR as dependent variables and waist circumference, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, blood glucose, hemoglobin A_1c, and job strain index as the independent variables. We didn't included age to independent variables since it is a factor obviously associated with eGFR. Inclusion and exclusion criteria were $p < 0.20$ (SAS Institute Inc. 1999). Odds ratios and 95%

confidence intervals were estimated for selected independent variables described above.

We used Spearman's correlation analysis to analyze the relationship between eGFR and each metabolic risk factor. To further examine the impact of job stress on this relationship, we grouped job stress into the four levels of the job strain index (lowest, lower, higher, and highest). SAS GLM procedures were then performed in the lowest group and the highest group. eGFR was the dependent variable and the following three parameters were explanatory variables: 1) each independent variable, 2) job-stress group (the lowest or highest), and 3) the interaction of each independent variable and the job-stress group. The two groups with the lowest and highest job strain index were selected to assess the interaction of the job strain index on the relationship between eGFR and each independent variable. Because eGFR was adjusted by age, the explanatory variable of age was not included in the GLM analysis.

Results

Factors related to renal dysfunction

The mean ± standard deviation of eGFR was 77.8 ± 12.4 mL/min/1.73 m^2 and 6.7% of the participants (n = 82) fell into the low eGFR group (< 60 mL/min/1.73 m^2). The number of those with proteinuria was 72 in the high eGFR group, and the prevalence of CKD (stage 1-3) turned to be 12.5% (n = 154) according to the categories provided by the K/DOQI. When eGFR was dichotomized, age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, fasting blood glucose, hemoglobin A_{1c}, uric acid, creatinine, and prevalence of MS were all significantly greater in the low eGFR group than in the high group (Table 1). The proportion of smokers, as well as the number of cigarettes smoked per

Table 1. Physical and physiological characteristics of the 1,231 participants and the association of renal dysfunction.

	Total (n = 1,231)	eGFR, mL/min/1.73 m^2		
		eGFR ≥ 60 (n = 1,149)	eGFR < 60 (n = 82)	p-Value
Age, years	42.5 ± 10.4 [20-67]	41.9 ± 10.2	51.2 ± 8.7	< 0.0001
Body mass index, kg/m^2	24.2 ± 3.4 [16.6-47.2]	24.1 ± 3.4	24.8 ± 2.6	0.0018
Waist circumference, cm[a]	85.1 ± 8.9 [59.3-133.4]	84.9 ± 9.0	87.6 ± 7.4	0.0004
Systolic blood pressure, mmHg	124.4 ± 13.6 [84-184]	124.1 ± 13.6	127.9 ± 13.0	0.0008
Diastolic blood pressure, mmHg	78.4 ± 9.8 [50-112]	78.1 ± 9.9	81.3 ± 8.8	< 0.0001
Total cholesterol, mg/dL	201.4 ± 35.4 [73-406]	200.0 ± 34.9	221.0 ± 36.4	< 0.0001
Triglyceride, mg/dL	131.9 ± 98.1 [21-1429]	120.6 ± 96.1	148.5 ± 87.4	0.0004
HDL cholesterol, mg/dL	56.3 ± 13.6 [22-115]	56.4 ± 13.7	54.2 ± 12.1	0.129
Fasting blood sugar, mg/dL	95.1 ± 20.6 [68-380]	94.8 ± 20.7	99.2 ± 19.6	0.0008
Hemoglobin A_{1c}, %	5.2 ± 0.7 [2.7-11.8]	5.2 ± 0.7	5.4 ± 0.7	< 0.0001
Uric acid, mg/dL	6.0 ± 1.2 [0.6-10.2]	6.0 ± 1.2	6.5 ± 1.0	< 0.0001
Creatinine, mg/mL	0.83 ± 0.11 [0.47-1.33]	0.8 ± 0.1	1.1 ± 0.1	<0.0001
estimated GFR, mL/min/1.73 m^2	77.8 ± 12.4 [41.2-149]	79.8 ± 11.2	55.3 ± 4.3	< 0.0001
Proteinuria, n (%)	84 (6.8)	72 (6.3)	12 (14.6)	< 0.0001
Metabolic syndrome, n (%) (n = 1,216)	177 (14.5)	157 (13.8)	20 (24.7)	0.005
Current smoking, n (%) (n = 1,227)	491 (40.0)	472 (41.3)	19 (23.2)	0.004
Tobacco consumption, cigarettes/day	19.6 ± 11.2 [1-60]	19.8 ± 10.8	16.1 ± 9.2	0.008
Drinking habit, n (%) (n = 1,216)	995 (81.8)	935 (82.2)	60 (75.0)	0.170
Alcohol consumption, g/ethanol/day	16.3 ± 11.4 [3.3-52.6]	16.5 ± 12.5	16.1 ± 10.1	0.610
Exercise, n (%) (n = 1,192)	682 (57.2)	643 (57.4)	39 (50.7)	0.410
Job Content Questionnaire (n = 1,226)				
Demand (12-48)	32.4 ± 5.0	32.4 ± 5.0	31.4 ± 4.9	0.068
Control (24-96)	69.3 ± 8.3	69.2 ± 8.2	69.8 ± 8.2	0.560
Job strain,† ratio	0.47 ± 0.0	0.47 ± 0.1	0.45 ± 0.1	0.100
<0.4, n (%)	215 (17.5)	192 (16.8)	16 (19.8)	
0.4-0.5, n (%)	568 (46.1)	527 (46.1)	41 (50.5)	
0.5-0.6, n (%)	348 (28.3)	328 (28.7)	20 (24.7)	
>0.6, n (%)	100 (8.1)	96 (8.4)	4 (5.0)	

eGFR: estimated glomerular filteration rate. Values are the "mean ±S.D. [range]" or "number and percentage".

†Job strain: the ratio of job demand versus job control. The participants were classified into four groups based on our previous studies. A job strain index value below 0.4 was classified as the lowest group, 0.4 or below 0.5 as lower, 0.5 or below 0.6 as higher and 0.6 or above as the highest.

Table 2. Factors associated with renal dysfunction (eGFR <60 mL/min/1.73 m^2): results of stepwise-method multiple logistic regression analysis[a].

Selected variables	Odds ratio [95% confidence intervals]
1. Total cholesterol, mg/dL	1.010 [1.005, 1.016] (p < 0.0001)
2. HDL cholesterol, mg/dL	0.998 [0.996, 0.999] (p = 0.0321)
3. Diastolic blood pressure, mmHg	1.003 [1.002, 1.005] (p = 0.0234)

eGFR, estimated glomerular filtration rate.
[a]Both entry and exclusion criteria were p <0.20.

Table 3. Correlation between participant variables and eGFR based on job stress.

Independent variables	Correlation to eGFR (n = 1,231) Spearman's correlation r	p-value	Correlation with eGFR according to job stress[a]: Individual Spearman's correlation coefficient, r — Lowest (n = 215)	Lower (n = 518)	Higher (n = 348)	Highest (n = 100)	p-value, lowest vs. highest[b]
Obesity-related							
Body mass index, kg/m^2	−0.126	< 0.001	−0.119	−0.130**	−0.106*	−0.228*	0.828
Waist circumstance, cm	−0.136	< 0.001	−0.097	−0.160**	−0.099	−0.239*	0.569
Hypertension-related							
Systolic blood pressure, mmHg	−0.095	< 0.001	−0.084	−0.025	−0.140**	−0.329**	**0.039**
Diastolic blood pressure, mmHg	−0.113	< 0.001	−0.023	−0.108*	−0.108*	−0.303**	**0.036**
Dyslipidemia-related							
Serum total cholesterol, mg/dL	−0.179	< 0.001	−0.154*	−0.163**	−0.167**	−0.316**	0.059
Serum triglyceride, mg/dL	−0.028	0.330	0.072	−0.037	−0.001	−0.253*	**0.006**
Serum HDL cholesterol, mg/dL	0.003	0.921	−0.028	0.015	−0.028	0.181	0.162
Diabetes-related							
Fasting blood glucose, mg/dL	−0.078	0.006	−0.040	−0.071	−0.088	−0.129	0.277
Hemoglobin A_1c, %	−0.061	0.033	−0.011	−0.077	−0.081	−0.017	0.748
Metabolic syndrome (MS)[c]	−0.067	0.020	0.004	−0.052	−0.098	−0.178	0.173
Number of MS components	−0.108	< 0.001	−0.019	−0.120**	−0.084	−0.294**	**0.047**
Lifestyle							
Current smoking[c]	0.208	< 0.001	0.130	0.246**	0.186**	0.166	0.755
Drinking[c]	0.052	0.070	0.066	0.048	0.032	0.108	0.517
Exercise[c]	−0.080	0.006	−0.119	0.004	−0.157**	−0.066	0.617

eGFR, estimated glomerular filtration rate.
[a]The participants were classified into four groups based on our previous studies. A job strain index value below 0.4 was classified as the lowest group, 0.4 or below 0.5 as lower, 0.5 or below 0.6 as higher and 0.6 or above as the highest. *p < 0.05 and **p < 0.01, Spearman's correlation analysis.
[b]The GLM procedures were performed to assess the group differences in the correlations between eGFR and each independent variable; two extreme groups with the lowest and highest job-stress were selected. eGFR was adopted as an dependent variable and the following three parameters as explanatory variables: each independent variable, job-stress group (the lowest or highest), interaction of each independent variable and job-stress group. p-Values indicate the interaction effects of the job-stress groups on the relationship between each independent variable and eGFR.
[c]MS, current smoking, drinking and exercise are categorical variables. The grouping criteria for each variable are: "being diagnosis as MS or not" for MS, "currently smoking or not" for current smoking, "drinking or not" for drinking and "having no exercise habit, 1-2days as week and over 3 days a week" for exercise.

day, was significantly smaller in the lower eGFR group than in the higher group. No significant difference was found between the two groups in terms of HDL cholesterol, drinking habits, and scores on the Job Content Questionnaire.

The logistic regression analysis indicated that serum levels of total cholesterol, HDL cholesterol and diastolic blood pressure were significantly and independently associated with the low eGFR group (Table 2). When the presence of CKD was a dependent variable in the multiple logistic regression analysis, the selected independent variables remained unchanged; total cholesterol (odds ratio: 1.108, 95% confidence interval: 1.062-1.156), HDL choles-

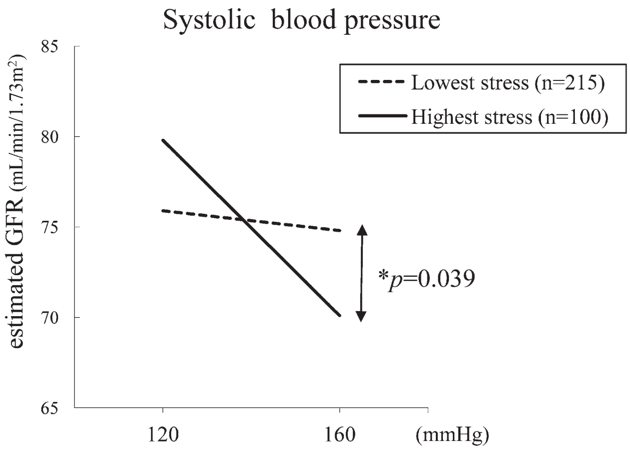

Fig. 1. Effects of job stress on the association between systolic blood pressure and eGFR.
eGFR, estimated glomerular filtration rate.
*p-Values indicate the interaction effects of the job-stress groups on the relationship between systolic blood pressure and eGFR as described in Table 3. The intersection of the two regression lines was 135.6 mmHg, 75.6 mL/min/1.73 m^2.

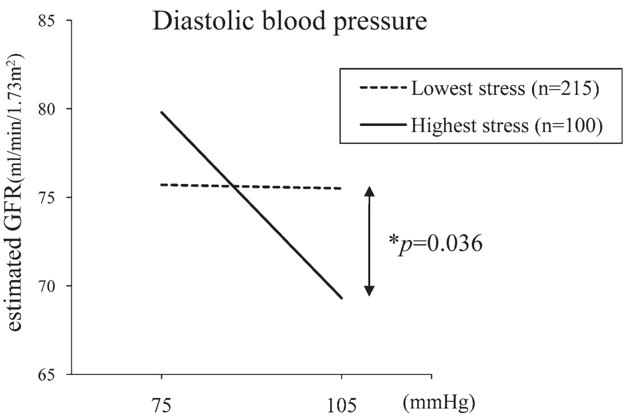

Fig. 2. Effects of job stress on the association between diastolic blood pressure and eGFR.
eGFR, estimated glomerular filtration rate.
*p-Values indicate the interaction effects of the job-stress groups on the relationship between diastolic blood pressure and eGFR as described in Table 3. The intersection of the two regression lines was 87.0 mmHg, 75.6 mL/min/1.73 m^2.

terol (0.926, 0.866-0.989) and diastolic blood pressure (1.056, 1.024-1.087). The job strain index was not significant in either high or low eGFR groups in the logistic regression model (data not shown).

Effects of perceived job stress on the relationship between renal dysfunction and metabolic risk factors

A significant negative correlation was found between eGFR and BMI, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, fasting blood glucose, hemoglobin A_{1c}, the number of MS compo-

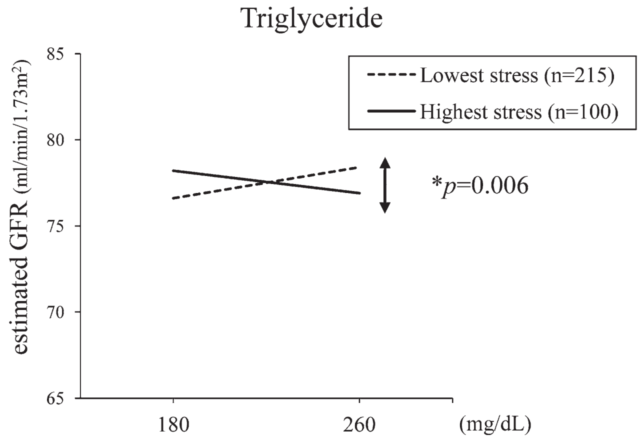

Fig. 3. Effects of job stress on the association between serum triglyceride levels and eGFR.
eGFR, estimated glomerular filtration rate.
*p-Values indicate the interaction effects of the job-stress groups on the relationship between triglyceride and eGFR as described in Table 3. The intersection of the two regression lines was 221.0 mg/dL mmHg, 77.5 mL/min/1.73 m^2.

nents, and exercise habits (Table 3). Smoking habits and eGFR were positively correlated. When the effects of job strain index on the relationship of eGFR were analyzed, there was a significant interaction between eGFR and systolic blood pressure, diastolic blood pressure, and triglyceride groups, with the highest and lowest job stress. Figs. 1-3 show the association between eGFR and systolic and diastolic blood pressure in each of the highest and lowest groups of the job strain index.

Discussion

In this study, a significant negative correlation was observed in male workers between eGFR and a variety of metabolic risk factors, such as waist circumference, systolic and diastolic blood pressures, and fasting blood glucose. Although the job strain index was not significantly related to eGFR, there were significant interaction effects of the job strain index for the relationships of eGFR to systolic and diastolic blood pressure and to serum triglycerides. These results suggested that workers who were under severe job stress exhibited a close negative correlation of eGFR with metabolic risk factors like hypertension and dyslipidemia.

Until date, there have been no reports of a direct relationship between the onset and development of CKD and psychosocial stress; however, job stress is a well known risk factor for both CVD and metabolic factors (Karasek et al. 1981; Sokejima and Kagamimori 1998; Theorell et al. 1998; Yoshimasu et al. 2001; Steptoe and Willemsen 2004; Nomura et al. 2005; Tsutsumi et al. 2006). For example, the relationship between job stress and hypertension has been reported to be stronger in older workers than in younger ones, and more apparent in blue-collar workers than in white-collar workers (Theorell et al. 1998). Our study cohort consisted of white-collar, young, or middle-

aged employees. We found a clear dose-response relationship between some metabolic risk factors and renal dysfunction and the degree of job strain. Hence, these types of studies should be extended to include working and non-working Japanese people.

While aging is the most significant cause for reduced renal function, healthy adults rarely develop CKD (eGFR < 60 mL/min/1.73 m^2) solely because of advancing age (Imai et al. 2008). Among disease conditions, hypertension is the most important risk factor for CKD, and high blood pressure increases the risk for proteinuria (Ramirez et al. 2002; Chen et al. 2004; Yamagata et al. 2007). Moreover, hypertension is a strong risk factor for end-stage renal disease and high normal blood pressure may be a predictive factor for CKD (Klag et al. 1996; Segura et al. 2004). In general, the rate of reduction in eGFR of males is shorter compared with females (Eriksen and Ingebretsen 2006). Thus, the management of blood pressure is important for preventing CKD among middle-aged men (Iseki et al. 2007). In the present study, eGFR was significantly associated with higher serum levels of total cholesterol and lower serum levels of HDL levels, and job stress evaluated by job strain index had significant interaction effects on the relationship between eGFR and serum levels of triglyceride. Hypertriglyceridemia and hypo-HDL cholesterolemia have also been reported as risk factors for the development of proteinuria and increased serum creatinine (Weiner et al. 2008). Despite this, the effects of job stress on dyslipidemia are not as clear as that for hypertension. Although the literature is limited, it has been reported that job stress is associated with overeating contributes to the development of hyperlipidemia (Hellerstedt and Jeffery 1997). A higher consumption of meat was more likely to be observed in those suffering from job stress (Tsutsumi et al. 2003), and the proportion of fatty food to the overall calorie intake tended to be high under such stressed conditions. However, according to a previous study of more than 15,000 Japanese male workers, no significant correlation was observed between job stress and fat intake (Kawakami et al. 2006). There may also be a significant influence of sociocultural elements that affect eating behavior, and this may be related to job stress. Another Japanese study reported that workers who perceived low stress and good support in the workplace had many opportunities to eat out with their peers, resulting in a tendency to consume more high-calorie, high-fat food (Tsutsumi et al. 1998).

It is known that smoking is related to proteinuria and is a factor in the development of CKD (Weiner et al. 2008). In this study, we found a positive relationship between renal function and smoking. In agreement with our results, previous studies revealed that current smokers had a significantly higher creatinine clearance than nonsmokers, and they had a marked risk for macroalbuminuria, which leads to the hypothesis of smoking-induced hyperfiltration (Halimi et al. 2000; Orth and Hallan 2008). In the present study, the number of current smokers in the > 50 age group (n = 353) was significantly lower than in the < 50 age group (n = 871) (34.2% vs. 42.5%, p = 0.008, chi-squared test, missing data = 7). Because people who never smoked and former smokers were regarded as non-smokers, we may have overlooked the cumulative effects of smoking in former smokers. For example, it may be that some of the workers aged ≥ 50 years stopped smoking for health reasons due to renal dysfunction.

The following points need to be considered as study limitations. (i) Because this study was cross-sectional, we were unable to show a direct causal effect for the correlation of job stress with metabolic risk factors and reduced renal function. (ii) A study targeting an employed population may be biased. Employees encountering job stress-related health problems could change to a lower stress position or employees could retire due to job stress-related health problems and be excluded from surveys. These factors could have underestimated the impact of job strain in this study. This possible selection bias could explain why we found no correlation between renal function and smoking in contrast to other studies (Halimi et al. 2000; Weiner et al. 2008; Orth and Hallan 2008). (iii) In this study, information on the working environment of the participants, such as their job duties, positions, or salaries could not be obtained. All the participants in the study are white-collar workers at one company and many of the work-related factors mentioned above are determined by age, which does not suggest a big impact on the analysis results. Still, the lack of available information on the participants' home environments, such as their marital status or family members, may have introduced a confounding bias. (iv) The Job Content Questionnaire inquires objectively about job stress, but does not include questions regarding the perception of daily life stress or ability to cope with stress (Nomura et al. 2007). Moreover, considering the influence of age on responses to a psychosocial questionnaire, relatively older Japanese workers may be reluctant to express psychosocial stress compared with younger ones (Iwata et al. 1998). Hence, in relation to job stress, it is important to consider an evaluation method that gathers multifaceted information on the responders and their cultural characteristics. (v) The information on job stress and lifestyle habits was self-reported, which may have introduced a bias (Rostrup and Ekeberg 1992). In the company where this study was conducted, most of the study participants receive an annual medical examination and, thus, may be more aware of health problems based on previous results. Because of this, there is a possibility that they may select a negative response to their own psychosocial situation and lifestyle habits, and this may introduce a bias toward job stress and outcomes. Therefore, it is necessary to use objective interview methods to increase the reliability of the results in the future. (vi) The mutual interaction effects of job stress on renal function and metabolic risk factors were nothing more than a modulatory effect. The mechanism relating stress results and an increased risk of CVD could not be eluci-

dated in this study. Because healthy behavior is adversely affected by stress from smoking, reduced exercise, and drinking, it was assumed to result in a risk for CVD via secondary effects (Lallukka et al. 2008). In a recent study, job stress was reported to reduce heart rate variability and increase early morning cortisol secretion (Chandola et al. 2008). It was suggested that direct autonomic nervous system involvement and altered cortisol levels could lead to CVD.

A multi-institutional research study with a large sample size will be required to determine whether job stress is an independent risk factor for reduced renal function.

Conclusions

Our study suggested that job stress may be a contributing factor for reduced renal function, mediated by metabolic risk factors like hypertension and dyslipidemia. Since 2008, the diagnosis and evaluation of MS has become obligatory in Japan. Instruction on behavior modification for improving lifestyle habits is necessary in those with metabolic risk factors, but an evaluation of stress levels in workers and intensive stress management are important considerations for the prevention of CKD and CVD.

Conflict of Interest

The authors declare that they have no competing interests.

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