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【 ORIGINAL ARTICLE 】

The Association between Anthropometric Indices of Obesity and Chronic Kidney Disease in Middle-aged Japanese Men and Women: A Cohort Study

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Abstract:

Objective This study investigated associations between three indices of obesity-the body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR)-and the incidence of chronic kidney disease (CKD).

Methods The employees of a company in Japan (1,725 men, 1,186 women; aged 35-55 years) had BMI, WC, and WHtR measured in health examinations. The incidence of CKD was determined at annual medical examinations over a six-year period. The hazard ratios for CKD were calculated using proportional hazard models, and the χ^2 statistic was used to compare the strengths of the associations.

Results The mean BMI (kg/m^2), WC (cm), and WHtR were 23.6, 84.3, and 0.49 for men and 22.3, 79.7, and 0.50 for women, respectively. The incidence of CKD (/1,000 person-years) was 18.1 for men and 8.4 for women. In men, positive linear associations were observed between the BMI, WC, and WHtR and the risk of CKD, even after adjusting for the presence of metabolic abnormalities (p for trend <0.001, 0.012, and 0.023, respectively). In women, a linear association was observed only between the WHtR and CKD, not the BMI or WC (p for trend =0.042, 0.057, and 0.186). The χ^2 statistics were the highest for the BMI in both men and women.

Conclusion The BMI, WC, and WHtR were linearly associated with the risk of CKD independently of metabolic abnormalities in men, while the associations were weaker or not significant in women. The BMI was the most strongly associated with the incidence of CKD in both men and women.

Key words: abdominal obesity, body mass index, epidemiology, cohort study, sex difference

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Introduction

Obesity is a risk factor for chronic kidney disease (CKD) (1, 2) and increases the risk of CKD directly by modulating the systemic circulation and glomerular hemodynamics (3-5) and indirectly via comorbid metabolic abnormalities, such as hypertension, diabetes mellitus, and dyslipidemia (6). An increase in the rate of CKD is associated with increases in medical care costs, cardiovascular diseases, and total deaths. As obesity increases, it is important from a public health perspective to elucidate the associations

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and mediators between obesity and CKD and to identify preventive measures.

Several reports describe sex differences in the association between obesity and CKD. In a previous cross-sectional study, we showed the presence of a sex difference in the association between obesity and CKD (7). Specifically, while obesity increased the risk of CKD in men, independently of metabolic abnormalities, obesity alone did not increase the risk in women. One observational study showed that obesity, determined by the body mass index (BMI), increases the risk of CKD by approximately 1.5-fold and that this association is comparable between men and women (8). In contrast, another study found that the risk of end-stage renal failure increased with an increasing BMI in men but not in women (9). In a meta-analysis of cohort studies that investigated the association between a decreased estimated glomerular filtration rate (eGFR) and indices of obesity, such as the BMI, waist circumference, and waist-to-height ratio (WHtR) (10), the risk of a decreased eGFR increased with these indices in both men and women. There was a sex difference in the risk of a decreased eGFR in those with a low BMI; specifically, the risk was higher in men with a low BMI than in those with a normal BMI, while this association was not observed in women.

Sex differences in the association between indices of obesity and CKD may be affected by the method of diagnosing obesity. Previously, we reported a sex difference in the association between obesity and metabolic abnormalities (11, 12). Metabolic abnormalities were associated more strongly with the waist circumference for men and with the BMI for women; because subcutaneous fat significantly affects waist circumference in women, it may be difficult to evaluate the visceral fat accumulation using the waist circumference. A similar association may be observed between obesity and CKD; however, which anthropometric index is best for determining the association with CKD or whether or not a sex difference exists in such association remains unclear.

Given the above, this observational study investigated how CKD is associated with the BMI, waist circumference, and WHtR and subsequently determined whether or not a sex difference exists in these associations.

Materials and Methods

Participants

The study participants were employees of a factory that produces zippers and aluminum sashes in Toyama Prefecture, Japan. Detailed information on the study population has been reported (13). The Industrial Safety and Health Law in Japan requires employers to provide annual health examinations for all employees. Of the 4,089 workers 35-55 years old (2,553 men and 1,536 women) who were employed in 2009, this study excluded 530 who did not take the 2009 baseline survey, 501 who had missing data at the baseline health examination (e.g., serum creatinine (sCr) and waist circumference), 96 who had already presented with CKD at the baseline survey, and 40 who were lost to follow-up after the baseline survey. Ultimately, 2,911 workers (1,725 men, 1,186 women) were included in the analysis.

Measurements

The baseline examination was carried out during annual medical examinations in 2009. Height was measured to the nearest 0.1 cm without shoes using a stadiometer. Weight was measured using a standard scale to the nearest 0.1 kg with participants wearing only light clothing and no shoes. The BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). The waist circumference was determined during minimal respiration in a standing position to the nearest 0.1 cm by measuring at the umbilical level. The height, weight, and waist circumference measurements followed the methods used in the National Health and Nutrition Survey in Japan (14), as defined by the Ministry of Health, Labour and Welfare. WHtR was calculated as waist circumference/height. Blood pressure was measured twice using an automatic manometer (BP 103i; Nippon Colin, Komaki, Japan) after a 5-min rest in a seated position. The mean of the measurements was used for the analysis. All measurements were carried out by trained staff.

Blood samples were obtained in the morning after overnight fasting. Plasma glucose levels were measured enzymatically using an Abbott glucose UV test (Abbott Laboratories, Chicago, USA). Hemoglobin A1c was measured by high-velocity liquid chromatography using a fully automated analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Total cholesterol and triglycerides were assessed using enzyme assays, and high-density lipoprotein cholesterol was measured using direct methods.

A questionnaire was used to identify voluntary health-related behaviors, such as smoking, alcohol consumption, and regular exercise (habitual exercise for at least 30 minutes more than twice a week). An additional self-administered questionnaire was used to collect medical history information on hypertension, dyslipidemia, and diabetes mellitus. The prevalence of high blood pressure, dyslipidemia, and high fasting plasma glucose was defined by the Japanese criteria for metabolic syndrome (15). *High blood pressure* was defined as a systolic blood pressure of at least 130 mmHg, a diastolic blood pressure of at least 85 mmHg, or using an antihypertensive drug. *Dyslipidemia* was defined as a serum triglyceride level of at least 150 mg/dL, high-density lipoprotein cholesterol not exceeding 40 mg/dL, or using a drug for hyperlipidemia. *High fasting plasma glucose* was defined as a fasting plasma glucose level of at least 110 mg/dL or medical treatment for diabetes.

The diagnosis of CKD

The incidence of CKD was determined during annual follow-up medical examinations from 2010 to 2015. Urinary proteins levels were examined using a dipstick test. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (16) with a Japanese coefficient of 0.813, where κ=0.7 for women and 0.9 for men, α=-0.329 for women and -0.411 for men, min (sCr/κ, 1) indicates the minimum of sCr/κ or 1, and max (sCr/κ, 1) indicates the maximum of sCr/κ or 1: eGFR (mL/min/1.73 m^2)=$0.813\times141\times\min(SCr/\kappa, 1)^{\alpha}\times\max(SCr/\kappa, 1)^{-1.209}\times 0.993^{Age}\times1.018$ (if a woman).

In accordance with the National Kidney Foundation guidelines (17), CKD was defined based on the presence of renal dysfunction, which was considered present if the eGFR was <60 mL/min/1.73 m^2 or if the participant had dipstick urinary protein scores of ≥1+.

Statistical analyses

The characteristics of the study participants were compared according to quartiles of each anthropometric variable. One-way analyses of variance were used to compare the continuous variables and the χ^2 test for categorical variables. We calculated the crude incidence rates and hazard ratios (HRs) for CKD according to the quartiles of each anthropometric variable. The Cox proportional hazard model was used to calculate the HRs. Adjustment for possible confounders was performed sequentially: for age (continuous) (Model 1); plus smoking status (never, ex-smoker, or current smoker), alcohol consumption (never drinker, consumed <20 g/day, consumed ≥20 g/day), and habitual regular exercise (no, yes) (Model 2); plus presence of high blood pressure (no, yes), dyslipidemia (no, yes), and high fasting plasma glucose (no, yes) (Model 3). After confirming the linear relationship in the quartile analysis, HRs were calculated to evaluate the risk of CKD for a one-standard deviation (SD) increase in each anthropometric index, and the strength of the relationships was compared using Wald χ^2 statistics.

Statistical analyses were performed using the Statistical Package for the Social Sciences software program (IBM SPSS Statistics, version 22.0; IBM, Armonk, USA). A p value <0.05 was deemed statistically significant.

Ethical considerations

Written informed consent was not obtained from the participants. The Occupational Safety and Health Committee of the subject company, which consisted of employee representatives, approved the design of the present study. Employees were informed of the study design and of their right to refuse to participate. Hence, participants who answered the questionnaire were considered to have consented to the survey. The company ensured that individuals were not identifiable by providing linkable anonymous data to the researchers. The Institutional Review Committee for Ethical Issues of Kanazawa Medical University approved the study. All procedures were performed in accordance with the Declaration of Helsinki.

Results

Table 1 (men) and 2 (women) show the baseline characteristics of the study participants according to the quartile of each anthropometric index. For both sexes, those in whom the BMI, waist circumference, and WHtR were all relatively high values had a significantly higher prevalence of metabolic abnormalities, such as high blood pressure, dyslipidemia, and high fasting plasma glucose, than those with relatively low values. The percentage of participants who had medical treatment for hypertension, dyslipidemia, and diabetes mellitus was 6.7%, 1.2%, 1.7% for men and 4.3%, 0.3%, 1.0% for women, respectively, and subjects in higher quartiles of obesity indices had a significantly higher prevalence of medical treatment for metabolic abnormalities than others (data not shown). These anthropometric indices were not associated with smoking status or exercise habits for either sex. In men, the percentage of drinkers differed among quartile groups for the BMI, waist circumference, and WHtR, whereas the percentage of never drinkers was high and the percentage of heavy drinkers low in the first and fourth quartiles.

During the study, 173 men and 56 women developed CKD, and the crude incidence rates (/1,000 person-years) were 18.1 for men and 8.4 for women. The CKD incidence and adjusted HRs were determined in the quartiles of each anthropometric index. In men, BMI was positively associated with the incident risk of CKD (Table 3, Model 1; p for trend <0.001), and the HRs [95% confidence interval (CI)] for the third and fourth quartiles relative to the lowest quartile were 1.81 (1.13-2.90) and 2.68 (1.72-2.19), respectively. The results were similar after adjusting for lifestyle factors (Table 3, Model 2). Furthermore, when adjusted for the presence of metabolic abnormalities (Model 3), the HR in Q 4 was extremely high [2.07 (1.30-2.32)], with a positive linear association between the BMI and incident risk of CKD (p for trend <0.001) (Figure). Waist circumference was significantly and positively associated with the risk of CKD after adjusting for age (Model 1) or lifestyle factors (Model 2) (p for trend =0.001, and <0.001, respectively), but the association was weakened after adjusting for metabolic abnormalities (Model 3; p for trend =0.023) (Figure). The association of the CKD risk with the WHtR was similar to that with the waist circumference (Table 3, Figure).

In women, a linear association was observed between the BMI and the risk of CKD after adjusting for age (Model 1) and lifestyle factors (Model 2) (Table 4), while the association was not significant (p for trend =0.057) after adjusting for metabolic abnormalities (Figure). The waist circumference was not significantly associated with the risk of CKD (Table 4, Figure), while the WHtR was associated with the risk of CKD even after adjusting for metabolic abnormalities (Model 3, Figure).

The incidence of CKD had or tended to have linear associations with anthropometric indices; therefore, we com-

Table 1. Baseline Characteristics of Male Participants according to the Quartile of Each Anthropometric Indices of Obesity.

Body mass index (kg/m², range)	Q1 <21.5	Q2 21.5-23.3	Q3 23.4-25.3	Q4 ≥25.4	p*
n	433	440	428	424	
Age (y)	44.5±6.4	45.5±6.3	45.7±6.3	45.2±6.3	0.038
Waist circumference (cm)	75.4±4.7	81.5±4.3	86.2±4.2	94.6±6.2	<0.001
Waist-to-height ratio	0.44±0.03	0.47±0.02	0.50±0.02	0.55±0.03	<0.001
Smoking status (%)					0.075
Nonsmoker	31.6	35.0	31.1	37.7	
Ex-smoker	20.1	22.5	24.5	24.3	
Current smoker	48.3	42.5	44.4	38.0	
Alcohol drinking (%)					0.035
Never	20.3	17.0	16.8	25.5	
Drinking <20g/day	41.8	43.4	42.3	39.9	
Drinking ≥20g/day	37.9	39.5	40.9	34.7	
Habitual Exercise - Yes (%)	42.0	45.7	46.3	46.2	0.541
Metabolic abnormalities (%)†					
High blood pressure	10.2	13.9	19.4	29.5	<0.001
Dyslipidemia	14.8	25.7	32.5	51.7	<0.001
High fasting plasma glucose	6.9	7.3	11.7	19.3	<0.001
Waist circumference (cm, range)	**Q1 <78.6**	**Q2 78.6-83.9**	**Q3 84.0-89.5**	**Q4 ≥89.6**	
n	436	428	430	431	
Age (y)	43.9±6.4	44.8±6.4	46.0±6.1	46.1±6.1	<0.001
Body mass index (kg/m²)	20.6±1.6	22.5±1.4	24.2±1.5	27.3±2.6	<0.001
Waist-to-height ratio	0.43±0.02	0.47±0.02	0.50±0.02	0.55±0.03	<0.001
Smoking status (%)					0.055
Nonsmoker	36.5	33.2	31.2	34.6	
Ex-smoker	18.6	20.8	26.7	25.3	
Current smoker	45.0	46.0	42.1	40.1	
Alcohol drinking (%)					<0.001
Never	23.2	17.1	14.2	25.1	
Drinking <20g/day	41.1	46.7	41.4	38.3	
Drinking ≥20g/day	35.8	36.2	44.4	36.7	
Habitual Exercise - Yes (%)	42.4	44.6	49.8	43.4	0.134
Metabolic abnormalities (%)†					
High blood pressure	7.1	14.3	20.2	31.1	<0.001
Dyslipidemia	13.8	25.7	35.3	49.4	<0.001
High fasting plasma glucose	6.2	5.8	13.3	19.7	<0.001
Waist-to-height ratio (range)	**Q1 <0.46**	**Q2 0.46-0.48**	**Q3 0.49-0.51**	**Q4 ≥0.52**	
n	450	439	418	418	
Age (y)	43.7±6.3	44.5±6.2	46.3±6.1	46.5±6.2	<0.001
Body mass index (kg/m²)	20.5±1.5	22.6±1.3	24.2±1.4	27.5±2.5	<0.001
Waist circumference (cm)	74.8±4.1	81.6±3.0	86.7±3.4	95.2±5.8	<0.001
Smoking status (%)					0.511
Nonsmoker	35.1	33.5	31.1	35.6	
Ex-smoker	20.0	23.0	24.4	24.2	
Current smoker	44.9	43.5	44.5	40.2	
Alcohol drinking (%)					0.020
Never	21.8	15.5	18.2	24.2	
Drinking <20g/day	43.8	44.4	41.4	37.6	
Drinking ≥20g/day	34.4	40.1	40.4	38.3	
Habitual Exercise - Yes (%)	44.9	44.9	47.4	43.1	0.663
Metabolic abnormalities (%)†					
High blood pressure	6.9	14.6	19.4	32.8	<0.001
Dyslipidemia	11.3	27.3	36.8	50.2	<0.001
High fasting plasma glucose	6.0	6.6	12.9	20.1	<0.001

Data are n, mean±standard deviation, or %.

*One-way analyses of variance for continuous variables and chi-squared test for categorical variables.

†Metabolic abnormalities were defined in accordance with the definition of metabolic syndrome for the Japanese population.

Table 2. Baseline Characteristics of Female Participants according to the Quartile of Each Anthropometric Indices of Obesity.

Body mass index (kg/m², range)	Q1 <19.9	Q2 19.9-21.6	Q3 21.7-23.8	Q4 ≥23.9	p*
n	307	300	286	293	
Age (y)	43.6±6.3	45.0±5.8	45.6±6.2	46.2±5.9	<0.001
Waist circumference (cm)	70.7±5.5	75.9±5.2	81.0±5.3	92.0±9.4	<0.001
Waist-to-height ratio	0.44±0.03	0.48±0.03	0.51±0.04	0.58±0.06	<0.001
Smoking status (%)					0.003
Nonsmoker	87.3	92.7	90.6	89.8	
Ex-smoker	4.9	3.3	3.5	0.3	
Current smoker	7.8	4.0	5.9	9.9	
Alcohol drinking (%)					0.003
Never	53.7	46.3	57.0	62.1	
Drinking <20g/day	41.0	48.0	38.1	36.2	
Drinking ≥20g/day	5.2	5.7	4.9	1.7	
Habitual Exercise - Yes (%)	32.9	32.3	31.8	32.8	0.992
Metabolic abnormalities (%)†					
High blood pressure	4.2	4.7	8.0	21.8	<0.001
Dyslipidemia	2.6	3.7	9.1	17.4	<0.001
High fasting plasma glucose	1.6	1.7	3.1	8.2	<0.001
Waist circumference (cm, range)	Q1 <72.7	Q2 72.7-78.5	Q3 78.6-85.3	Q4 ≥85.4	
n	300	293	298	295	
Age (y)	44.0±6.1	44.4±6.0	45.1±6.0	46.9±5.9	<0.001
Body mass index (kg/m²)	19.2±1.6	20.9±1.8	22.4±2.0	26.8±4.2	<0.001
Waist-to-height ratio	0.43±0.03	0.48±0.02	0.51±0.02	0.59±0.06	<0.001
Smoking status (%)					0.003
Nonsmoker	88.3	90.1	88.9	92.9	
Ex-smoker	4.0	5.5	2.7	0.0	
Current smoker	7.7	4.4	8.4	7.1	
Alcohol drinking (%)					0.001
Never	49.7	50.5	56.7	62.0	
Drinking <20g/day	44.3	42.7	39.6	36.9	
Drinking ≥20g/day	6.0	6.8	3.7	1.0	
Habitual Exercise - Yes (%)	31.7	37.9	32.9	27.5	0.060
Metabolic abnormalities (%)†					
High blood pressure	4.0	6.1	6.4	22.0	<0.001
Dyslipidemia	3.3	5.8	6.4	16.9	<0.001
High fasting plasma glucose	1.3	2.0	3.4	7.8	<0.001
Waist-to-height ratio (range)	Q1 <0.45	Q2 0.45-0.49	Q3 0.50-0.54	Q4 ≥0.55	
n	293	296	299	298	
Age (y)	43.6±6.1	43.9±5.8	45.5±6.1	47.3±5.7	<0.001
Body mass index (kg/m²)	19.1±1.5	20.7±1.6	22.5±1.9	26.9±4.1	<0.001
Waist circumference (cm)	68.6±3.8	75.8±3.1	81.4±3.3	92.8±8.4	<0.001
Smoking status (%)					0.006
Nonsmoker	88.1	88.5	91.6	91.9	
Ex-smoker	5.1	5.1	1.7	0.3	
Current smoker	6.8	6.4	6.7	7.7	
Alcohol drinking (%)					0.001
Never	49.8	51.7	55.5	61.7	
Drinking <20g/day	44.0	41.2	41.1	37.2	
Drinking ≥20g/day	6.1	7.1	3.3	1.0	
Habitual Exercise - Yes (%)	31.7	35.5	35.1	27.5	0.134
Metabolic abnormalities (%)†					
High blood pressure	4.8	4.4	6.7	22.5	<0.001
Dyslipidemia	2.7	3.4	8.4	17.8	<0.001
High fasting plasma glucose	2.0	1.4	2.7	8.4	<0.001

Data are n, mean±standard deviation, or %.

*One-way analyses of variance for continuous variables and chi-squared test for categorical variables.

†Metabolic abnormalities were defined in accordance with the definition of metabolic syndrome for the Japanese population.

Table 3. Incidence and Adjusted Hazard Ratios for CKD according to the Quartile of Each Anthropometric Indices of Obesity in Male Participants.

	Q1	Q2	Q3	Q4	p for trend
Body mass index					
n	433	440	428	424	
Incident case of CKD	27	28	49	69	
Person-years of follow-up	2,432	2,463	2,361	2,278	
Incidence (/1,000 person-year)	11.1	11.4	20.8	30.3	
HR (95% CI) Model 1	1.00 (reference)	0.99 (0.58-2.68)	1.81 (1.13-2.90)	2.68 (1.72-2.19)	<0.001
Model 2	1.00 (reference)	1.00 (0.59-2.69)	1.84 (1.15-2.94)	2.69 (1.72-2.21)	<0.001
Model 3	1.00 (reference)	0.96 (0.57-2.64)	1.63 (1.01-2.63)	2.07 (1.30-2.32)	<0.001
Waist circumference					
n	436	428	430	431	
Incident case of CKD	29	34	45	65	
Person-years of follow-up	2,446	2,380	2,386	2,323	
Incidence (/1,000 person-year)	11.9	14.3	18.9	28.0	
HR (95% CI) Model 1	1.00 (reference)	1.17 (0.72-2.93)	1.51 (0.94-2.41)	2.22 (1.43-2.45)	<0.001
Model 2	1.00 (reference)	1.19 (0.72-2.95)	1.57 (0.98-2.52)	2.25 (1.45-2.50)	<0.001
Model 3	1.00 (reference)	1.14 (0.69-2.88)	1.32 (0.81-2.13)	1.66 (1.04-2.65)	0.023
Waist-to-height ratio					
n	450	439	418	418	
Incident case of CKD	32	30	45	66	
Person-years of follow-up	2,514	2,484	2,299	2,237	
Incidence (/1,000 person-year)	12.7	12.1	19.6	29.5	
HR (95% CI) Model 1	1.00 (reference)	0.93 (0.56-2.53)	1.45 (0.92-2.29)	2.16 (1.41-2.32)	<0.001
Model 2	1.00 (reference)	0.95 (0.58-2.56)	1.48 (0.94-2.34)	2.20 (1.43-2.37)	<0.001
Model 3	1.00 (reference)	0.88 (0.53-2.46)	1.24 (0.77-2.99)	1.61 (1.01-2.54)	0.012

Model 1, adjusted for age; Model 2, adjusted for age, smoking status, alcohol consumption, regular exercise; Model 3, adjusted for the variables of model 2 plus presence of high blood pressure, dyslipidemia and high fasting plasma glucose at baseline.
CKD: chronic kidney disease, HR: hazard ratio, CI: confidence interval

pared the strength of the relationship between each anthropometric index and the incident risk of CKD (Table 5). Of the anthropometric indices of obesity, the BMI had the strongest relationship with the risk of CKD for both men (Model 3, Wald χ^2=18.5) and women (Wald χ^2=5.3). The strength of the relationship was similar for the waist circumference and WHtR in both men and women.

Discussion

This cohort study investigated the association between indices of obesity and incident risk of CKD. All three anthropometric indices (BMI, waist circumference, and WHtR) were significantly and linearly associated with the risk of CKD for men. The associations were significant even after adjusting for metabolic abnormalities, indicated that obesity was associated with the risk of CKD beyond metabolic abnormalities. However, compared with the findings in men, the associations of anthropometric indices of obesity were weaker or not significant for women. Of the three anthropometric indices of obesity, the BMI was the most strongly associated with CKD in both sexes.

Previous Western and Asian cohort studies have reported that the BMI is associated with the risk of CKD (1, 7-9, 11, 12, 18-23), consistent with our results. Many studies of the association between obesity and the risk of CKD have used the BMI as an index of obesity, whereas very few have used waist-related indices (7, 21). One of these, a cross-sectional study that investigated the association between CKD and obesity indices, demonstrated that the waist circumference had a stronger association with the prevalence of CKD than the BMI (7). We found that the three anthropometric indices of obesity were positively and linearly associated with the incidence of CKD in men, but the association was stronger with the BMI than with the waist circumference. Such discrepancies in the results may be due to differences in the study design (cross-sectional vs. cohort study). Furthermore, the finding that the association of CKD with the waist circumference was weakened after adjusting for metabolic abnormalities may be due to the stronger association of metabolic abnormalities with waist circumference than with the BMI in relatively lean Japanese men (11, 12).

A recent meta-analysis of cohort studies showed that the CKD risk is high even among those with a low BMI and that the association between the BMI and incidence of CKD is J-shaped (10); however, our results were linear, and an increased CKD risk was not evident in the low-BMI group. The mean BMI of our study participants was 23.6 kg/m^2 for men and 22.4 kg/m^2 for women, which was lower than the values reported in previous studies (10); our cohort may

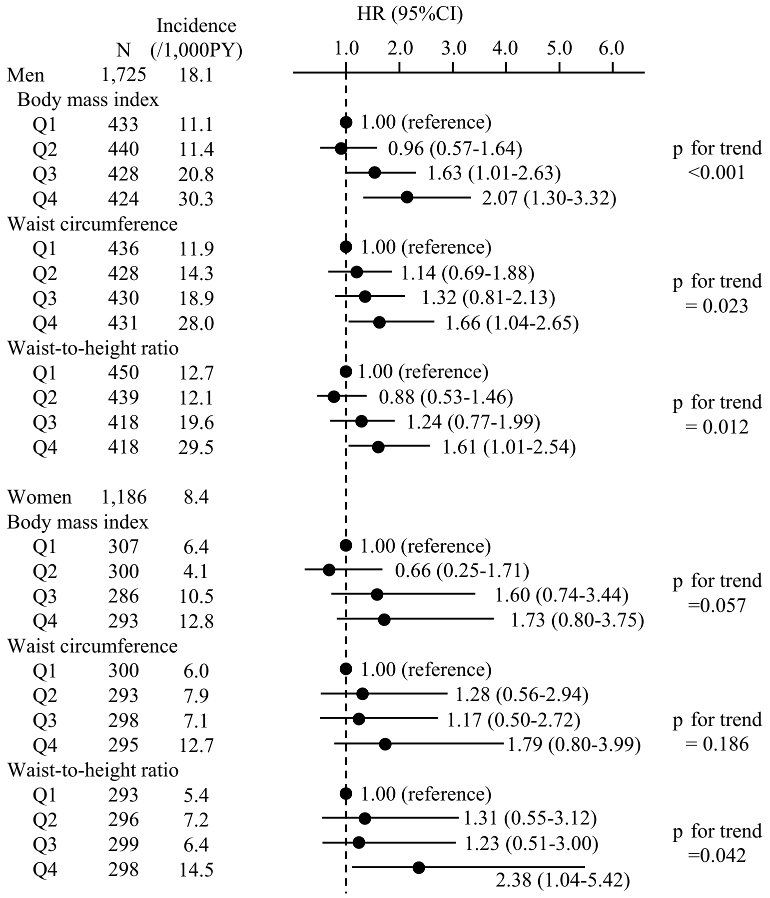

Figure. Adjusted hazard ratios of the incidence of CKD during the six-year follow-up according to the quartiles of the BMI, waist circumference, and waist-to-height ratio in Japanese men and women. The hazard ratios were calculated using Cox proportional hazard models adjusted for the age, smoking status, alcohol intake, habitual exercise, and presence of high blood pressure, dyslipidemia, and a high fasting plasma glucose level at the baseline examination. CKD: chronic kidney disease, HR: hazard ratio, CI: confidence interval

thus be suitable for detecting the risk of CKD in lean participants. Our study also examined a working population, which tends to be healthier than the general population, and high-risk people with a low BMI, such as those with malnutrition, hepatic disease, or cancer, are likely to be excluded from the workplace, which may affect the difference in the results.

The sex differences in the association between obesity indices and CKD remain unclear. We found that the associations between anthropometric indices of obesity and CKD were weaker for women than men. These results were similar to those of a cross-sectional study of a regional population that showed that obesity alone was not associated with the presence of CKD in women, in contrast to the findings in men (7). However, in our study, the HRs for the participants with higher obesity indices tended to be higher than in those with lower indices, although not to a significant degree, and the lower statistical power due to the smaller number of women or lower incidence of CKD in women may affect the results. The mean BMI of the women in our study was 22.4 kg/m^2 and relatively low, which may also be disadvantageous when examining the relationship between obesity and CKD. However, among the anthropometric indices of obesity, the BMI was the most strongly associated with the risk of CKD, and this result was the same in men. The results indicated that the BMI is a useful anthropometric index for obesity that can predict the risk of CKD, regardless of sex.

One of the strengths of this study is that the CKD incidence was definitively examined in annual health checkups in a relatively large working population and that a six-year follow-up was conducted. However, several limitations should also be noted. First, because this study included a working population, the study participants were younger than those in regional studies. The CKD incidence increases with age and is predicted to be higher in older individuals than in younger ones. However, our results are limited to CKD in middle-aged individuals. Second, the study population may have been healthier than the general population, since the participants were workers, due to the "healthy worker effect". Third, the presence of comorbidities that might affect the presence of obesity and the incidence of CKD, such as malnutrition, hepatic disease, or malignancy, were not evaluated in the study participants. However, the

Table 4. Incidence and Adjusted Hazard Ratios for CKD according to the Quartile of Each Anthropometric Indices of Obesity in Female Participants.

	Q1	Q2	Q3	Q4	p for trend
Body mass index					
n	307	300	286	293	
Incident case of CKD	11	7	17	21	
Person-year of follow-up	1,715	1,712	1,614	1,640	
Incidence (/1,000 person-year)	6.4	4.1	10.5	12.8	
HR (95% CI) Model 1	1.00 (reference)	0.62 (0.24-1.60)	1.58 (0.74-3.39)	1.90 (0.91-3.97)	0.018
Model 2	1.00 (reference)	0.65 (0.25-1.67)	1.59 (0.74-3.42)	1.96 (0.93-4.13)	0.018
Model 3	1.00 (reference)	0.66 (0.25-1.71)	1.60 (0.74-3.44)	1.73 (0.80-3.75)	0.057
Waist circumference					
n	300	293	298	295	
Incident case of CKD	10	13	12	21	
Person-year of follow-up	1,680	1,656	1,687	1,658	
Incidence (/1,000 person-year)	6.0	7.9	7.1	12.7	
HR (95% CI) Model 1	1.00 (reference)	1.31 (0.57-2.99)	1.19 (0.51-2.75)	2.02 (0.94-4.33)	0.081
Model 2	1.00 (reference)	1.30 (0.57-2.98)	1.19 (0.51-2.76)	2.09 (0.96-4.53)	0.073
Model 3	1.00 (reference)	1.28 (0.56-2.94)	1.17 (0.50-2.72)	1.79 (0.80-3.99)	0.186
Waist-to-height ratio					
n	293	296	299	298	
Incident case of CKD	9	12	11	24	
Person-year of follow-up	1,654	1,669	1,708	1,650	
Incidence (/1,000 person-year)	5.4	7.2	6.4	14.5	
HR (95% CI) Model 1	1.00 (reference)	1.32 (0.56-3.13)	1.16 (0.48-2.82)	2.56 (1.17-5.60)	0.017
Model 2	1.00 (reference)	1.30 (0.55-3.09)	1.22 (0.50-2.96)	2.68 (1.20-5.96)	0.014
Model 3	1.00 (reference)	1.31 (0.55-3.12)	1.23 (0.51-3.00)	2.38 (1.04-5.42)	0.042

Model 1, adjusted for age; Model 2, adjusted for age, smoking status, alcohol consumption, regular exercise; Model 3, adjusted for the variables of model 2 plus presence of high blood pressure, dyslipidemia and high fasting plasma glucose at baseline.
CKD: chronic kidney disease, HR: hazard ratio, CI: confidence interval

Table 5. Multivariate-adjusted Relationship between Each Anthropometric Indices and Incidence of CKD.

			Model 1			Model 3		
		SD	χ^2	HR (95%CI)	p	χ^2	HR (95%CI)	p
Men	Body mass index	3.1	39.8	1.53 (1.34-1.75)	<0.001	18.5	1.37 (1.19-1.58)	<0.001
	Waist circumference	8.5	22.1	1.41 (1.22-1.63)	<0.001	7.7	1.25 (1.07-1.45)	0.006
	Waist-to-height ratio	0.050	22.2	1.41 (1.22-1.63)	<0.001	7.6	1.25 (1.07-1.45)	0.006
Women	Body mass index	3.9	10.6	1.40 (1.14-1.71)	0.001	5.3	1.32 (1.04-1.66)	0.021
	Waist circumference	10.3	7.5	1.37 (1.10-1.72)	0.006	3.8	1.29 (1.00-1.65)	0.050
	Waist-to-height ratio	0.067	6.6	1.35 (1.07-1.70)	0.010	3.1	1.26 (0.97-1.62)	0.079

HRs are calculated for each anthropometric variable higher by 1 SD.
Model 1, adjusted for age; Model 3, adjusted for age, smoking status, alcohol consumption, regular exercise, presence of high blood pressure, dyslipidemia and high fasting plasma glucose at baseline.
CKD: chronic kidney disease, SD: standard deviation, χ^2: Wald χ^2 statistics, HR: hazard ratio, CI: confidence interval

impact of these comorbidities on the results may not be strong because the prevalence of these comorbidities in our study participants may have been low due again to the "healthy worker effect". Fourth, while we evaluated medical treatment of hypertension, dyslipidemia, and diabetes, we did not evaluate the use of medications that might affect the incidence of CKD, such as RAS inhibitors, SGLT-2 inhibitors, GLP1 analogues, and statins.

In conclusion, indices of obesity, namely the BMI, waist circumference, and WHtR, were associated with the incident risk of CKD in Japanese men. The associations were weaker for women than for men. Of the three anthropometric indices, the BMI was the most strongly associated with risk of CKD for both sexes. The BMI is a useful anthropometric index of obesity that can predict the risk of CKD.

The authors state that they have no Conflict of Interest (COI).

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