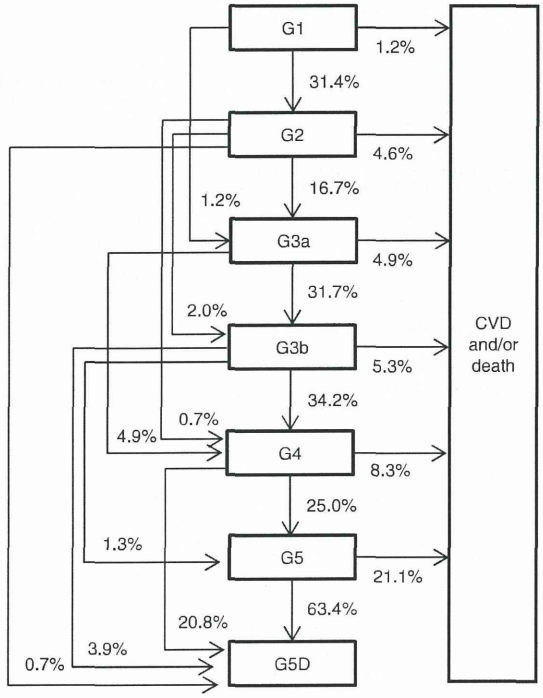

Fig. 3 CKD stage progression and incidence of CVD and/or death (after 3 years). The proportion progressing to the higher stages was 32.6, 20.0, 36.6, 39.5, and 45.8 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 0.7 % from stage G2, 3.9 % from stage G3b, 20.8 % from stage G4 and 63.4 % from stage G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from stages G1–5, respectively

63.4 % from stage G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from stages G1–5, respectively. The proportions of CKD stages that remained unchanged were 45.3, 58.7, 46.3, 32.9, 34.7, and 19.7 % for stages G1–5, respectively (data not shown).

As shown in Table 1, the annual eGFR decline was -3.17 ± 5.02 ml/min/1.73 m^2/year in all patients. The annual eGFR decline tended to be larger in the higher disease stages except stages G1 and G2 (−4.70, −2.44, −1.76, −2.90, −2.90 and −5.55 ml/min/1.73 m^2/year for stages G1–5) and higher with increases of proteinuria (−2.15, −2.47 and −4.60 ml/min/1.73 m^2/year for stages A1–3). During the 3-year follow-up period, 8.4 % of patients experienced a 50 % eGFR decline (0, 0.7, 2.4, 7.9, 26.4 and 23.9 % for stages G1–5).

Table 2 shows measured quality-adjustment weights by CKD stage—0.939 (95 % CI, 0.915–0.963), 0.915 (0.892–0.938), 0.894 (0.861–0.927), 0.882 (0.843–0.921), 0.834 (0.789–0.879) and 0.798 (0.757–0.839) for stages G1–5 and 0.912 (0.893–0.931), 0.901 (0.873–0.929) and 0.849 (0.824–0.874) for proteinuria stages A1–3, respectively. Quality-adjustment weights of all respondents decreased with decline of eGFR and increase of proteinuria. The weights at stages G4–5 were significantly lower than at stages G1–2 and the weights at stage A3 were significantly lower than at stages A1–2. The weights according to disease progression are shown in Table 3, and the weights of presence and absence of diabetes in each group are shown in Table 3. The weights were 0.907 (95 % CI 0.889–0.925) for the non-progressive group, 0.894 (0.874–0.914) for the progressive group, 0.842 (0.800–0.884) for the dialysis group and 0.617 (0.531–0.703) for the death group. The weights in the dialysis and death groups were significantly lower than in the non-progressive group. The presence of diabetes affected the quality adjustment weights in each group. The quality-adjustment weights of patients with events such as 50 % eGFR decline, dialysis, CVD, and/or death were also significantly lower than those without events in Table 4.

Table 1 Annual eGFR decline by CKD stage (total $n = 421$)

CKD stage		Proteinuria stage			
		A1	A2	A3	A1–3
GFR stage	n	173	82	166	421
G1	66	−4.16 ± 6.33	−6.31 ± 5.88	−6.20 ± 4.84	−4.70 ± 6.14
G2	118	−1.76 ± 3.23	−2.32 ± 2.68	−3.78 ± 4.49	−2.44 ± 3.52
G3a	72	−1.38 ± 2.32	−1.01 ± 2.46	−2.70 ± 4.70	−1.76 ± 3.34
G3b	61	−1.12 ± 2.09	−1.23 ± 3.23	−5.24 ± 7.69	−2.90 ± 5.70
G4	54	−0.01 ± 2.12	−2.18 ± 1.45	−4.03 ± 3.11	−2.90 ± 3.19
G5	50	0.45 ± 0	−0.57 ± 1.10	−6.00 ± 7.61	−5.55 ± 7.46
G1–5	421	−2.15 ± 4.25	−2.47 ± 3.63	−4.60 ± 5.94	−3.17 ± 5.02

A total of 421 patients had both eGFR and proteinuria measurement

The annual eGFR decline was -3.17 ± 5.02 ml/min/1.73 m^2/year in all patients (-3.33 ± 4.97 for males and -2.98 ± 5.08 for females)

The annual eGFR decline tended to be higher with increase of proteinuria

eGFR estimated glomerular filtration rate, *CKD* chronic kidney disease

Table 2 Quality-adjustment weights by CKD stage

CKD stage	*n*	Mean	95 % CI	*P* value
GFR stage				
G1	86	0.939	0.915–0.963	<0.001[a]
G2	150	0.915	0.892–0.938	
G3a	82	0.894	0.861–0.927	
G3b	76	0.882	0.843–0.921	
G4	72	0.834	0.789–0.879	
G5	71	0.798	0.757–0.839	
Proteinuria stage				
A1	214	0.912	0.893–0.931	<0.001[b]
A2	104	0.901	0.873–0.929	
A3	211	0.849	0.824–0.874	
All stages	537	0.885	0.871–0.899	

CKD chronic kidney disease, *CI* confidence interval, *GFR* glomerular filtration rate

[a] The weights at stages G4–5 were significantly lower than at stages G1–2 ($P < 0.001$)

[b] The weights at stage A3 were significantly lower than at stages A1–2 ($P < 0.001$)

Discussion

This study aimed to evaluate CKD progression and clinical outcomes among a hospital-based cohort of patients with CKD. The patients were under treatment by nephrologists, and received intensive care. During 12 months of follow-up, 32 cases (6.0 %) started renal replacement therapy, 11 CVD events (2.0 %) occurred, and 6 patients (1.1 %) died. These clinical outcomes were similar to the 12 months of observing 2,692 CKD outpatients by Nakayama et al. [17] where 113 patients (4.2 %) were introduced to renal replacement therapy, a total of 69 CVD events (2.6 %) occurred, and 24 patients (0.9 %) died. They also confirmed significant differences in the incidence of CVD events according to underlying renal disease. They concluded that patients with hypertensive nephropathy or diabetic nephropathy had a higher risk of a CVD event, while patients with primary renal disease had a lower risk.

In the present study, the annual eGFR decline was −3.17 ml/min/1.73 m^2/year (−3.33 for males and −2.98 for females) for the 3-year observation period. The rate of decline in kidney function was higher than the expected rate of −1.0 ml/min/1.73 m^2/year, which is widely considered to be the normal decline in kidney function with age [18]. This decline is also higher than the results from a hospital-based cohort of Japanese CKD patients (−1.01 ml/min/1.73 m^2/year, −1.18 for males, and −0.78 for females per year) [19]. Hanratty et al. [20] reported that in CKD patients who did not have diabetes or vascular disease, eGFR decline at −1.5 ml/min/1.73 m^2/year and diabetes at baseline was associated with an additional decline of

Table 3 Quality-adjustment weights according to the disease progression

Group		*n*	Mean	95 % CI	*P* value[a]
Quality-adjustment weights by each group					
Non-progressive group		245	0.907	0.889–0.925	
Progressive group		196	0.894	0.874–0.914	0.635
Dialysis group		64	0.842	0.800–0.884	0.009[b]
Death group		19	0.617	0.531–0.703	<0.001[c]
Group	Diabetes	*n*	Mean	95 % CI	*P* value[d]
Quality-adjustment weights by each group and with/without diabetes					
Non-progressive group	Presence	48	0.891	0.848–0.934	0.381
	Absence	197	0.911	0.891–0.931	
Progressive group	Presence	70	0.857	0.821–0.893	<0.05
	Absence	126	0.915	0.892–0.938	
Dialysis group	Presence	31	0.797	0.739–0.855	<0.05
	Absence	33	0.885	0.827–0.943	
Death group	Presence	9	0.660	0.554–0.766	0.368
	Absence	10	0.578	0.444–0.712	

CI confidence interval

[a] *P* value, each group versus the non-progressive group

[b] The weights in the dialysis group were significantly lower than in the non-progressive group ($P = 0.009$)

[c] The weight in the death group were significantly lower than in the non-progressive group ($P < 0.001$)

[d] *P* value, presence versus absence of diabetes

Table 4 Quality-adjustment weights by events (50 % eGFR decline, dialysis, CVD, and/or death)

Events	*n*	Mean	95 % CI	*P* value
Presence of 50 % eGFR decline, dialysis, CVD, and/or death	106	0.789	0.752–0.827	<0.001[a]
(a) Presence of 50 % eGFR decline and/or dialysis[b]	79	0.845	0.807–0.882	
(b) Presence of CVD, and/or death[b]	37	0.687	0.620–0.755	
Absence of all events	359	0.916	0.902–0.930	

eGFR estimated glomerular filtration rate, *CVD* cardiovascular disease, *CI* confidence interval

[a] *P* value, presence of 50 % eGFR decline, dialysis, CVD, and/or death versus absence of all events

[b] Some patients are overlapping between (a) and (b)

−1.38 ml/min/1.73 m^2/year, resulting in an overall decline of −2.9 ml/min/1.73 m^2/year. Therefore, the differences between results from previous studies and our study may be due to a difference in the primary kidney disease. In addition, the annual eGFR decline tended to be larger in the later disease stages except stages G1 and G2, and the 50 % eGFR decline also occurred in the later disease stages. The large eGFR decline in stage G1 might be due to the underlying renal disease such as vasculitis and collagen diseases, and that in stage G2 would be affected by the patient starting dialysis treatment who had a large eGFR decline. Kidney disease progressions were generally consistent with the results from a meta-analysis which showed lower eGFR is a risk factor for progressive CKD [21].

In this study, the rate of eGFR decline was higher with increase of proteinuria. This decline is similar to the results from a hospital-based study which showed the rate of eGFR decline for patients with ≥30 mg/g creatinine, urinary protein level was higher than those with <30 mg/g creatinine [19]. Thus, the higher level of proteinuria is associated with the progression of kidney dysfunction. In fact, proteinuria including higher albuminuria and lower eGFR are risk factors for ESKD, acute kidney injury and progressive CKD in both general and high-risk populations, independent of each other and of cardiovascular risk factors [21, 22]. The modified CKD classification based on this strong epidemiological evidence was defined by adding albuminuria stage, a subdivision of stage 3, and emphasizing clinical diagnosis [13].

With regard to another aim of this study, we demonstrated the HRQOL in terms of quality-adjustment weight using EQ-5D in CKD patients by the new CKD classification. This is the first report on such weights based on the association between eGFR and the level of proteinuria at baseline. It can be used in cost-effectiveness analysis with a preferred outcome measure, quality-adjusted life-years, of interventions for CKD. There are some studies about a relationship between CKD stage and HRQOL in patients with CKD before renal replacement therapy. Perlman et al. reported that patients with CKD had higher SF-36 scores (another generic questionnaire) than a large cohort of hemodialysis patients but lower scores than those reported for the USA adult population. They also identified associations between HRQOL and clinical indices such as hemoglobin or eGFR [7]. Mujais et al. conducted a prospective observational study for patients with CKD stages 3–5 by using the Kidney Disease Quality of Life (KDQOL) questionnaire and reported HRQOL was reduced in proportion to the severity grade of CKD. HRQOL scores are also influenced by age, gender, diabetes, history of cardiovascular co-morbidities, anemia and beta blocker usage [6]. Pagels et al. showed that CKD in its earlier stages has a negative impact on HRQOL. Co-existing conditions, such as inflammation and CVD were strong predictors of impaired HRQOL in CKD patients [9]. We already demonstrated that HRQOL decreases with progression of CKD stage and/or presence of anemia, undernutrition, hypertension, diabetes, or history of CVD as well as previous studies [12]. In addition, we showed that low HRQOL is possible to be a predictor of disease progression, initiation of dialysis therapy and death.

On the other hand, few studies are available about the relationship between proteinuria and HRQOL. Kelly et al. reported the HRQOL of advanced type 2 diabetic nephropathy patients using the KDQOL. They found that proteinuria profoundly impacted all major domains of HRQOL [15]. In our study, measured quality-adjustment weights by proteinuria stages were 0.912 for stage A1, 0.901 for stage A2, and 0.849 for stage A3 and the weights significantly decreased with increase of proteinuria. We also found a strong impact of proteinuria on HRQOL as well as eGFR, because the quality-adjustment weights decreased with increase of proteinuria in this study.

This study has several limitations. Firstly, we can neither exclude the possibility of sample selection nor implement a bias correction, because this is a single center study. Further epidemiologic studies are needed. Secondly, we could not evaluate the eGFR of a few patients who started dialysis treatment at other dialysis centers. Third, we assessed the quality-adjustment weights by different disease progression groups, but not the influence of disease progression on the changes of HRQOL.

In conclusion, the present study describes clinical outcomes including the progression of CKD stages, the rate of eGFR decline, and the incidence of CVD and/or death in a hospital-based cohort over a 3-year period. In addition, the quality-adjustment weights in CKD patients were associated with disease progression such as initiation of

dialysis treatment, incidence of CVD events and all-cause death, as well as the level of proteinuria of baseline.

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Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164: 659–63.
2. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
3. Japanese Society for Dialysis Therapy. An overview of regular dialysis treatment in Japan as of Dec 31, 2011. Tokyo: Japanese Society for Dialysis Treatment; 2012 (in Japanese).
4. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009;13:621–30.
5. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. Kidney Int. 2009;76(9):946–52.
6. Mujais SK, Story K, Brouillette J, et al. Health-related quality of life in CKD Patients: correlates and evolution over time. Clin J Am Soc Nephrol. 2009;4:1293–301.
7. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. Am J Kidney Dis. 2005;45:658–66.
8. Chow FY, Briganti EM, Kerr PG, et al. Health-related quality of life in Australian adults with renal insufficiency: a population-based study. Am J Kidney Dis. 2003;41:596–604.
9. Pagels AA, Söderkvist BK, Medin C, et al. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health Qual Life Outcomes. 2012;10:71.
10. Team Japanese EuroQol Translation. The development of the Japanese EuroQol instrument. J Health Care Soc. 1997;8:109–23 (in Japanese).
11. Tsuchiya A, Ikeda S, Ikegami N, et al. Estimating an EQ-5D population value set: the case of Japan. Health Econ. 2002;11: 341–53.
12. Tajima R, Kondo M, Kai H, et al. Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol. 2010;14:340–8.
13. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80:17–28.
14. Hemmelgarn BR, Zhang J, Manns B, et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006;69:2155–61.
15. Kelley K, Aricak OT, Light RP, et al. Proteinuria is a determinant of quality of life in diabetic nephropathy: modeling lagged effects with path analysis. Am J Nephrol. 2007;27:488–94.
16. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR: revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
17. Nakayama M, Sato T, Sato H, et al. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: Gonryo study. Clin Exp Nephrol. 2010;14:333–9.
18. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evidence, classification, and stratification. Am J Kidney Dis. 2002;39:S1–266.
19. Yamashita T, Yoshida T, Ogawa T, et al. Clinical outcomes in patients with chronic kidney disease: a 5-year retrospective cohort study at a University Hospital in Japan. Clin Exp Nephrol. 2011;15:831–40.
20. Hanratty R, Chonchol M, Miriam Dickinson L, et al. Incident chronic kidney disease and the rate of kidney function decline in individuals with hypertension. Nephrol Dial Transplant. 2010;25: 801–7.
21. Gansevoort RT, Matsushita K, van der Velde M, et al. Chronic Kidney Disease Prognosis Consortium: lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011;80:93–104.
22. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.

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ORIGINAL ARTICLE

U-shaped association between body mass index and proteinuria in a large Japanese general population sample

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Abstract

Background There is little data on the association between body mass index (BMI) and proteinuria.

Methods This was a cross-sectional cohort study assessing the association between BMI and proteinuria in a large Japanese population. Using a nationwide health check-up database of 212,251 Japanese aged >20 years with no pre-existing cardiovascular diseases (185,183 men, median age 66 years; 127,068 women, median age 65 years), we examined the association between BMI and proteinuria (≥1+ on dipstick).

Results Subjects were divided into 11 subgroups by BMI grading in 1 kg/m^2 intervals from 18.5–27.5 kg/m^2. A BMI of approximately 22 ± 0.5 kg/m^2 was considered optimal for Japanese; therefore, this subgroup was set as a reference when logistic analysis was applied. Age, waist circumference, height, weight, smoking and drinking habits, use of medications such as antihypertensive, antidiabetic, or antihyperlipidemic, as well as proteinuria, estimated glomerular filtration rate (eGFR), chemistry data, and blood pressure levels were significantly different between subgroups in both genders. The odds ratio for proteinuria showed a U-shape in men and women, even after adjustment for significant covariates such as age, waist circumference, systolic blood pressure, eGFR, fasting plasma glucose, triglyceride, low-density lipoprotein, antihypertensive use, antidiabetic use, antihyperlipidemic use, and lifestyle factors (smoking and drinking). Gender differences were also prominent—a BMI <20.4 kg/m^2 was significantly associated with proteinuria in men compared to a BMI <18.4 kg/m^2 in women. On the other hand, a BMI ≥ 25.5 kg/m^2 was also significantly associated with proteinuria in men compared to a BMI ≥ 22.5 kg/m^2 in women.

Conclusions We found that BMI levels were associated with proteinuria in a U-shaped manner and showed marked gender differences. Health guidance should not only focus

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on higher BMI subjects, but also on thin subjects, in terms of the prevention of chronic kidney disease.

Keywords Body mass index · Proteinuria · Odds ratio

Introduction

Body mass index (BMI) is a heuristic proxy for human body fat calculated from an individual's weight and height. According to the WHO criteria, a BMI between 18.5 and 25 kg/m^2 may be optimal; a BMI <18.5 kg/m^2 suggests the person is underweight; a BMI >25 kg/m^2 may indicate the person is overweight; and a BMI >30 kg/m^2 suggests the person is obese [1]. It is not difficult to anticipate a high prevalence of cardiovascular disease [2, 3], diabetes [3], hypertension [4], dyslipidemia [4], or proteinuria [5, 6] in higher BMI subjects; however, there is little published data about the association between proteinuria and BMI.

Chronic kidney disease (CKD) is now recognized as a major global public health issue [7, 8]. Persistent proteinuria is one of the major criteria of CKD [9]. Determination of the association between proteinuria and BMI is considered of value for health guidance. Therefore, we report here new findings concerning the independent association between proteinuria and BMI in both genders using a large Japanese national cohort.

Methods

Study design and population

This was a cross-sectional cohort study assessing the association between BMI and proteinuria in a large Japanese population. This study was performed as part of the prospective ongoing 'Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan' project. A new annual health check program 'The Specific Health Check and Guidance in Japan' was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population was Japanese citizens between the ages of 40 and 74 years. Local governments called for citizens to attend this annual health check under their own volition. Other details, such as the participants' area of residence, were reported previously [5, 10].

There was a total of 346,942 subjects [mean age 63.4 years; median age (interquartile range) 66.0 years (59.0–70.0); 41 % (n = 141,938) were men] for whom information on age, gender, blood pressure (BP), BMI, waist circumference, habitual smoking or drinking, use of anti-hypertensive, antidiabetic, and antihyperlipidemic drugs, and previous history of cardiovascular diseases (i.e., stroke and cardiac diseases such as angina and myocardial infarction) was available, as well as data on the serum creatinine level and dipstick urine test for proteinuria [11]. Individuals in certain regions participating in our project concomitantly underwent a regular health check-up for employees, which is legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years (n = 2,025).

Among the 346,942 subjects, 29,820 subjects with a previous history of cardiovascular disease, 243 subjects with CKD stage 5 (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2), and 47 subjects with both were excluded from the present analysis. Moreover, 88,101 subjects with insufficient blood sampling data of glucose and lipid parameters were excluded. Furthermore, out of 22,095 subjects with no waist circumference data, 5,568 subjects were already excluded for other reasons, and the remaining 16,527 subjects were excluded for lack of data. There were significant clinical and laboratory differences between subjects who were included in the present analysis (n = 212,251) and those who had missing data (n = 104,628); the numbers of both groups were large enough for even slight differences to be statistically significant (Supplementary Tables 1, 2).

This study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethical approval by the respective institutional review boards.

Baseline measurement

Blood samples were collected after an overnight fast and were assayed within 24 h with an automatic clinical chemical analyzer. All measurements were conducted locally rather than at a central laboratory, without calibration among different laboratories, despite the fact that standardized methods to measure laboratory data were recommended several years ago by the Japan Society of Clinical Chemistry and widely adopted.

Urinalysis by the dipstick method was performed manually by trained staff on a single spot urine specimen collected early in the morning after overnight fasting. Urine dipstick results were interpreted by the medical staff at each local medical institution and recorded as (−), (+), (1+), (2+), and (3+). In Japan, it has been recommended by the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dl. Proteinuria was defined as ≥1+. Because dipstick ± sometimes indicates microalbuminuria in the Japanese general population [12], taking changeable urine concentration or protein other than albumin contained in

urine into consideration, we adopted dipstick ≥1+ as reflecting positive urine protein.

eGFR was derived using the following equation [13]:

$$\text{eGFR}\ (\text{mL/min/1.73 m}^2) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094}\ (\text{if female} \times 0.739)$$

BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical check-up. In accordance with the recommendations of the Japanese Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs uncrossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement.

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habit (current smoker or not), and alcohol intake (daily drinker or not). The study physicians performed a physical examination of each subject and re-checked their medical history to improve the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m^2).

Statistical analysis

All statistical analyses were performed with SPSS version 20.0 J software (SPSS, Chicago, IL, USA). Data are expressed as median (25th–75th percentile). Clinical parameters and BP or metabolic values according to the level of BMI were compared using Kruskal–Wallis test, and categorical parameters were compared with the Chi-squared test.

We then used univariable and multivariable logistic regression analyses to examine the independent association between the level of BMI and proteinuria (≥1+). The subgroup with a BMI of 21.5–22.4 kg/m^2 was set as a reference for the BMI categorical variables. The reason for this was that a BMI of 22.2 kg/m^2 was reported to be associated with the lowest morbidity level in the Japanese population [14]. In the multivariable analysis, these associations were assessed with adjustments for age, waist circumference, systolic blood pressure (SBP), fasting plasma glucose (FPG) level, triglyceride (TG), low-density lipoprotein (LDL) cholesterol, eGFR, antihypertensive medication, antidiabetic medication, antihyperlipidemic medication, current smoking, and daily drinking. Statistical significance was defined as $P < 0.05$.

Results

Clinical characteristics of the study population (Tables 1, 2)

The median ages (interquartile range) of men (n = 85,183) and women (n = 127,068) were 66 (58–70) and 65 (59–70) years, respectively. The median BMI (interquartile range) of men and women were 23.6 (21.8–25.5) and 22.4 (20.4–24.7) kg/m^2, respectively. Participants were divided into 11 subgroups by BMI grading; gender differences in terms of their composition were prominent. Therefore, we analyzed the clinical characteristics of the participants by gender, as shown in Tables 1 and 2. Age, height, weight, waist circumference, smoking habit, drinking habit, use of antihypertensive, antidiabetic, or antihyperlipidemic medication, proteinuria, eGFR, chemistry data, and BP levels were significantly different between the groups in both men and women.

The waist circumference, body weight, SBP, FPG, TG, LDL, and the prevalence of using antihypertensive, antidiabetic, and antihyperlipidemic drugs increased with increasing BMI. In contrast, body height decreased with increasing BMI. The prevalence of proteiunuria was U-shaped in the crude data. The prevalence of current smokers was significantly higher in the lower BMI subgroups.

BMI and proteinuria

A BMI of approximately 22 kg/m^2 is considered as optimal for both Japanese men and women [14]; therefore, the subgroup of BMI_5 (BMI range 21.5–22.4 kg/m^2) was set as the reference for odds ratios (OR) and 95 % confidence intervals (CI) for proteinuria (dipstick ≥1+) were calculated after adjusting for age, waist circumference, SBP, eGFR, FPG, TG, LDL, antihypertensive, antidiabetic, and antihyperlipidemic medication, and lifestyle factors (drinking, smoking). Univariate and multivariate analyses are shown in Table 3 and Fig. 1. As shown in Fig. 1, the OR and CI for proteinuria were U-shaped for both men and women. Gender differences were prominent in that those with a BMI <20.4 kg/m^2 were significantly associated with proteinuria in men compared to a BMI <18.4 kg/m^2 in women. On the other hand, a BMI ≥25.5 kg/m^2 was also significantly associated with proteinuria in men compared to a BMI ≥22.5 kg/m^2 in women.

To examine whether age affects the association between BMI and proteinuria, ORs by age groups for proteinuria were calculated according to the degree of BMI after adjustment for waist circumference, SBP, FPG, TG, LDL, eGFR, antihypertensive medication, antidiabetic medication, antihyperlipidemic medication, current smoking and

Table 1 Characteristics of the study population (men)

	BMI_1	BMI_2	BMI_3	BMI_4	BMI_5	BMI_6	BMI_7
n	2,575	2,967	5,101	7,728	10,582	12,251	11,932
BMI, kg/m^2	17.7 (17.0–18.1)	19.0 (18.8–19.2)	20.0 (19.7–20.2)	21.0 (20.7–21.2)	22.0 (21.7–22.2)	23.0 (22.7–23.2)	23.9 (23.7–24.2)
BMI range	<18.5	18.5–19.4	19.5–20.4	20.5–21.4	21.5–22.4	22.5–23.4	23.5–24.4
Age, years	66 (59–70)	66 (59–70)	66 (58–70)	66 (59–70)	66 (59–70)	66 (59–70)	66 (59–70)
Waist circumference, cm	70.0 (67.0–73.0)	73.5 (71.0–76.5)	76.5 (73.5–79.0)	79.0 (76.0–82.0)	81.5 (78.8–84.0)	84.0 (81.0–86.5)	86.0 (83.0–88.7)
Height, cm	165.7 (161.2–170.0)	165.5 (161.0–169.7)	165.4 (161.2–169.8)	165.2 (161.0–169.5)	165.0 (160.9–169.5)	164.8 (160.7–169.0)	164.7 (160.6–168.9)
Weight, kg	48.0 (45.1–51.0)	52.0 (49.4–54.9)	54.8 (52.0–57.6)	57.4 (54.4–60.4)	60.0 (56.9–63.0)	62.4 (59.3–65.6)	65.0 (61.8–68.2)
SBP, mmHg	122 (110–134)	124 (112–136)	126 (114–138)	127 (116–138)	128 (118–140)	130 (120–140)	130 (120–140)
DBP, mmHg	73 (66–80)	74 (68–80)	76 (70–82)	76 (70–82)	78 (70–84))	78 (70–84)	80 (71–85)
Lifestyle							
Current smoker, *n* (%)	993 (38.6)	1,073 (36.2)	1,657 (32.5)	2,274 (29.4)	2,879 (27.2)	3,057 (25.0)	2,794 (23.4)
Daily drinker, *n* (%)	1,158 (45.0)	1,395 (47.0)	2,390 (46.9)	3,683 (47.7)	5,038 (47.6)	5,687 (46.4)	5,376 (45.1)
Drugs taken							
Antihypertensive, *n* (%)	343 (13.3)	478 (16.1)	950 (18.6)	1,636 (21.2)	2,624 (24.8)	3,441 (28.1)	3,822 (32.0)
Antidiabetic, *n* (%)	148 (5.7)	169 (5.7)	277 (5.4)	415 (5.4)	635 (6.0)	720 (5.9)	801 (6.7)
Antihyperlipidemic, *n* (%)	113 (4.4)	140 (4.7)	283 (5.5)	622 (8.0)	946 (8.9)	1,192 (9.7)	1,387 (11.6)
Chemistry data							
Proteinuria, *n* (%)	172 (6.7)	190 (6.4)	307 (6.0)	404 (5.2)	615 (5.8)	765 (6.2)	860 (7.2)
eGFR, ml/min/1.73 m^2	81.1 (72.1–89.8)	76.5 (66.0–87.3)	75.1 (66.3–86.1)	74.4 (65.1–85.7)	73.8 (64.9–85.0)	73.5 (64.3–84.7)	73.0 (63.8–84.0)
sCr, mg/dl	0.80 (0.70–0.82)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	0.80 (0.70–0.90)
FPG, mg/dl	92 (86–100)	93 (86–102)	93 (87–102)	94 (88–103)	95 (95–104)	96 (89–105)	97 (90–107)
TG, mg/dl	74 (58–100)	79 (61–110)	87 (65–122)	93 (69–132)	100 (73–143)	109 (78–154)	114 (83–163)
LDL, mg/dl	103 (85–123)	108 (89–128)	113 (94–132)	117 (98–136)	120 (101–140)	122 (103–142)	123 (104–143)

	BMI_8	BMI_9	BMI_10	BMI_11	Total	*P* value
n	10,135	7,622	5,354	8,936	85,183	
BMI, kg/m^2	24.9 (24.7–25.2)	25.9 (25.7–26.2)	26.9 (26.7–27.2)	28.9 (28.0–30.3)	23.6 (21.8–25.5)	
BMI range	24.5–25.4	25.5–26.4	26.5–27.4	≥27.5		
Age, years	66 (59–70)	66 (58–70)	65 (57–70)	63 (53–69)	66 (58–70)	<0.001
Waist circumference, cm	88.0 (85.0–91.0)	90.0 (87.0–93.0)	92.3 (89.5–95.3)	97.6 (94.0–102.0)	85.0 (80.0–90.0)	<0.001
Height, cm	164.5 (160.4–168.9)	164.0 (160.2–168.7)	164.3 (160.3–168.8)	164.9 (160.5–169.1)	164.9 (160.7–169.1)	<0.001
Weight, kg	67.5 (64.1–71.1)	70.0 (66.4–73.9)	72.7 (69.0–76.7))	79.2 (74.5–85.0)	64.0 (58.2–70.1)	<0.001
SBP, mmHg	131 (121–142)	132 (122–142)	133 (123–143)	134 (124–144)	130 (120–140)	<0.001
DBP, mmHg	80 (72–86)	80 (72–86))	80 (74–88)	80 (75–90)	79 (70–85)	<0.001
Lifestyle						
Current smoker, *n* (%)	2,338 (23.1)	1,708 (22.4)	1,263 (23.6)	2,209 (24.7)	22,245 (26.1)	<0.001
Daily drinker, *n* (%)	4,469 (44.1)	3,237 (42.5)	2,194 (41.0)	3,226 (36.1)	37,853 (44.4)	<0.001

Table 1 continued

	BMI_8	BMI_9	BMI_10	BMI_11	Total	*P* value
Drugs taken						
Antihypertensive, *n* (%)	3,489 (34.4)	2,837 (37.2)	2,071 (38.7)	3,908 (43.7)	25,599 (30.1)	<0.001
Antidiabetic, *n* (%)	672 (6.6)	531 (7.0)	436 (8.1)	943 (10.6)	5,747 (6.7)	<0.001
Antihyperlipidemic, *n* (%)	1,168 (11.5)	969 (12.7)	725 (13.5)	1,392 (15.6)	8,937 (10.5)	<0.001
Chemistry data						
Proteinuria, (%)	797 (7.9)	700 (9.2)	550 (10.3)	1,190 (13.3)	6,550 (7.7)	<0.001
eGFR, ml/min/1.73 m^2	72.9 (63.8–83.7)	72.6 (63.6–83.7)	72.9 (63.8–83.7)	73.5 (64.1–84.7)	73.5 (64.3–84.7)	<0.001
sCr, mg/dl	0.80 (0.74–0.90)	0.80 (0.75–0.90)	0.80 (0.80–0.90)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	<0.001
FPG, mg/dl	97 (91–108)	98 (91–108)	99 (92–110)	101 (93–114)	96 (90–106)	<0.001
TG, mg/dl	119 (86–172)	126 (90–179)	130 (94–184)	141 (101–201)	110 (78–159)	<0.001
LDL, mg/dl	124 (105–144)	125 (106–145)	125 (107–145)	126 (107–146)	121 (102–141)	<0.001

Data are expressed as median (interquartile range) or percentage. Differences were evaluated using Kruskal–Wallis test or Chi-squared test as appropriate

BMI body mass index, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

daily drinking. For the groups with the lowest BMI in both genders, there was a trend for the younger groups to have larger ORs for proteinuria; on the other hand, no clear age relationship was found in the group with the higher BMI (Fig. 3). The lowest BMI groups showed significant ORs relative to the reference, except for the 50−59 year age group in men; on the other hand, all age groups for the lowest BMI groups in women revealed significant ORs for proteinuria.

In terms of unhealthy habits, daily consumption of alcohol was a significant negative risk factor for proteinuria, especially in men; in contrast, current smoking was a positively related factor (Table 3; Fig. 2).

Discussion

The main findings of our study are that the association between BMI level and proteinuria showed a clear U-shape as well as remarkable gender differences. Many papers have revealed that a higher BMI is significantly associated with proteinuria [5, 6, 15]. The authors suggested that the pathophysiology included a high frequency of diabetes [3], hypertension [4], hyperlipidemia [4], and obesity-related glomerulopathy [16, 17]; however, this is not the main focus of this study. The two main issues that we identified and that should be focused on and discussed are (1) the high association with proteinuria, especially in women, among comparatively low BMI participants, and (2) the high association with proteinuria in the lowest BMI participants.

There was a significantly increased association with proteinuria even in comparatively low BMI participants in our cohort, especially women. There have been some discussions about whether the WHO criteria of overweight or obesity are unsuitable for Asians [18, 19]. The WHO proposed BMI criteria as $\geq$25 kg/m^2 overweight and $\geq$30 kg/m^2 obesity, mainly according to Caucasian data [1]. Asian people are reported to have a relatively high percentage of body fat compared to Caucasians with the same BMI [20, 21]. On the basis of Taiwanese data, revised definitions of overweight as $\geq$23 kg/m^2 and obesity as $\geq$25 kg/m^2 were proposed according to percent body fat data [21]. These observations are close to our findings of a strong association between proteinuria and subjects with a lower BMI than expected. The OR for proteinuria was significantly higher in both women and men (>23 kg/m^2 and >25 kg/m^2 BMI, respectively); this gender difference could have arisen from percent body fat being relatively high in women compared with that in men with the same BMI [18]. The accumulation of visceral adipose tissue (VAT) and that of subcutaneous adipose tissue (SAT) are basically different, with VAT being more biologically

Table 2 Characteristics of the study population (women)

	BMI_1	BMI_2	BMI_3	BMI_4	BMI_5	BMI_6	BMI_7
n	9,865	9,463	13,347	15,618	16,062	15,031	12,759
BMI, kg/m^2	17.6 (16.9–18.1)	19.0 (18.7–19.2)	20.0 (19.7–20.2)	21.0 (20.7–21.2)	22.0 (21.7–22.2)	22.9 (22.7–23.2)	23.9 (23.7–24.2)
BMI range	<18.5	18.5–19.4	19.5–20.4	20.5–21.4	21.5–22.4	22.5–23.4	23.5–24.4
Age, years	64 (57–69)	64 (56–69)	64 (58–69)	65 (59–69)	65 (60–70)	66 (61–70)	66 (61–70)
Waist circumference, cm	69.0 (65.0–73.0)	73.0 (69.2–77.0)	76.0 (72.0–80.0)	78.5 (74.5–82.5)	81.1 (77.2–85.0)	84.0 (80.0–87.5)	86.0 (82.0–89.5)
Height, cm	154.0 (150.1–158.0)	153.7 (150.0–157.6)	153.4 (149.5–157.2)	155.9 (149.0–156.6)	152.5 (148.7–156.2)	152.0 (148.2–155.7)	151.6 (148.0–155.3)
Weight, kg	41.3 (38.9–43.8)	45.0 (42.6–47.2)	47.0 (44.7–49.4)	49.0 (46.6–51.5)	51.0 (48.5–53.6)	53.3 (50.4–55.6)	55.0 (52.3–57.8)
SBP, mmHg	120 (108–130)	120 (110–132)	122 (110–134)	124 (113–136)	126 (116–138)	128 (118–140)	130 (120–140)
DBP, mmHg	70 (63–78)	71 (65–80)	72 (66–80)	73 (67–80)	74 (68–80)	76 (70–81)	76 (70–82)
Lifestyle							
Current smoker, (%)	903 (9.2)	749 (7.9)	913 (6.8)	913 (5.8)	879 (5.5)	720 (4.8)	593 (4.6)
Daily drinker, (%)	1,067 (10.8)	1,048 (11.1)	1,364 (10.2)	1,465 (9.4)	1,374 (8.6)	1,172 (7.8)	857 (6.7)
Drugs taken							
Antihypertensive, (%)	1,156 (11.7)	1,327 (14.0)	2,178 (16.3)	3,195 (20.5)	3,890 (24.2)	4,189 (27.9)	3,957 (31.0)
Antidiabetic, (%)	238 (2.4)	204 (2.2)	306 (2.3)	370 (2.4)	430 (2.7)	479 (3.2)	489 (3.8)
Antihyperlipidemic, (%)	1,254 (12.7)	1,419 (15.0)	2,234 (16.7)	3,008 (19.3)	3,469 (21.6)	3,463 (23.0)	3,090 (24.2)
Chemistry data							
Proteinuria, *n* (%)	359 (3.6)	251 (2.7)	359 (2.7)	419 (2.7)	442 (2.8)	526 (3.5)	487 (3.8)
eGFR, ml/min/1.73 m^2	75.7 (65.7–90.1)	75.3 (65.1–89.0)	75.3 (65.1–89.3)	75.0 (64.2–87.6)	74.7 (63.9–86.4)	74.7 (63.6–85.8)	74.4 (63.4–84.6)
sCr, mg/dl	0.60 (0.50–0.70)	0.60 (0.51–0.70)	0.60 (0.50–0.70)	0.60 (0.59–0.70)	0.60 (0.59–0.70)	0.60 (0.59–0.70)	0.60 (0.60–0.70)
FPG, mg/dl	88 (83–95)	89 (84–95)	90 (84–96)	90 (85–97)	91 (86–98)	92 (86–99)	93 (87–100)
TG, mg/dl	71 (55–93)	76 (58–101)	80 (61–109)	86 (65–117)	92 (69–126)	98 (73–134)	102 (76–140)
LDL, mg/dl	117 (99–137)	123 (103–142)	124 (105–145)	127 (108–147)	129 (110–150)	131 (112–151)	131 (112–152)

	BMI_8	BMI_9	BMI_10	BMI_11	Total	*P* value
n	10,174	7,501	5,407	11,841	127,068	
BMI, kg/m^2	24.9 (24.7–25.2)	25.9 (25.7–26.2)	26.9 (26.7–27.2)	29.2 (28.2–30.9)	22.4 (20.4–24.7)	
BMI range	24.5–25.4	25.5–26.4	26.5–27.4	≥27.5		
Age, years	66 (61–70)	66 (61–71)	66 (61–71)	66 (60–70)	65 (59–70)	<0.001
Waist circumference, cm	88.0 (84.3–91.8)	90.2 (86.5–94.0)	92.5 (88.5–96.0)	98.0 (93.0–103.0)	82.5 (76.0–89.0)	<0.001
Height, cm	151.3 (147.5–155.0)	151.1 (147.4–155.0)	150.9 (147.0–154.5)	150.5 (146.6–154.4)	152.2 (148.4–156.1)	<0.001
Weight, kg	57.0 (54.2–60.0)	59.2 (56.2–62.3)	61.3 (58.0–64.3)	67.7 (63.0–71.9)	52.0 (47.1–57.4)	<0.001
SBP, mmHg	130 (120–140)	131 (120–142)	132 (122–142)	134 (124–145)	128 (116–138)	<0.001
DBP, mmHg	77 (70–82)	78 (70–84)	78 (70–84)	80 (72–86)	75 (68–81)	<0.001
Lifestyle						
Current smoker, (%)	483 (4.7)	361 (4.8)	276 (5.1)	635 (5.4)	7,425 (5.8)	<0.001
Daily drinker, (%)	641 (6.3)	445 (5.9)	302 (5.6)	536 (4.5)	10,271 (8.1)	<0.001