lifestyle modification, dietary education, and testing for type 2 DM [15].

The prevalence of dialysis patients in Okinawa is around 3,000 per million population, which is higher than the national average of 2,300 per million population [8]. The reasons for such a high prevalence of dialysis might be both the high acceptance for dialysis therapy and higher incidence and prevalence of CKD. Severe obesity (BMI $\geq$ 30 kg/m^2), DM, hypertension, and dyslipidemia have prediction rates for CKD of 6.9, 7.0, 28.7, and 31.6 %, respectively. These comorbid conditions and the smoking rate are higher in Okinawa than in other parts of Japan. The prevalence of smoking was rather low in the higher quartile of medical costs than in the lowest quartile (Table 2). Medical costs were slightly higher among smokers (median 787) than non-smokers (median 721).

Medical costs increase with age, and eGFR decreases with age. It would be difficult to dissect the effect of normal aging processes on medical costs. Unfortunately, we have no information regarding the population of those aged 75 and over. Subjects with a low eGFR and proteinuria are at risk of developing acute kidney injury and have a high mortality rate. Prolonging life by dialysis, both acute and chronic, may substantially raise medical costs. In this regard, advanced directives on life support are needed.

There are multiple explanations to account for the high cost among subjects with a low eGFR and/or proteinuria. Patients with CKD have a higher risk of morbidity resulting from cardiovascular disease [2], anemia, and infection than non-CKD subjects; therefore, medical costs will eventually increase. Medical costs may be an imperfect proxy for complications related to CKD. A small fraction of subjects had a high eGFR ($\geq$120) and had higher medical costs. Hyperfiltration could be an early marker of DM nephropathy, malnutrition, and other conditions [16]. Although not included in this study, medications such as renin-angiotensin inhibitors, erythropoiesis stimulating agents, and antibiotics are often prescribed in general and in nephrology practice.

Strength of the study

To our knowledge, this is the first study to examine medical costs based on eGFR and proteinuria. Screenees are eligible for conventional clinical care and are different from the cohorts of referral populations, recruited cohorts, or clinical-trial participants; therefore. these results are probably generalizable, at least in Japan. The identification was perfect as both screening and analysis of the receipt score were performed by the same association. Screenees received medical services while they were partly, but not 100 %, covered by insurance. The disenrollment rate was rather low (14.6 %) during the 2-year study period. The reasons for this are not clear, but disenrollment could be a result of death, job loss, transfer to other parts of Japan, etc. In general, subjects not eligible for the Japan Health Insurance Association are rather economically handicapped; therefore, these subjects may have contracted medical problems after disenrollment [2]. In Japan, several other types of Health Insurance Associations exist for government workers and employees of big companies that adopt similar reimbursement policies.

Limitations of the study

First, serum creatinine testing and a dipstick urine test were performed only once; therefore, the classification based on eGFR and proteinuria may be misleading. The purpose of this study, however, was not to determine the prevalence of CKD, but rather to investigate the trends in medical costs based on eGFR and proteinuria. Second, as usual in such a health check program, participants were self-selected as they were interested in their health status [1]. The prevalence of CKD is dependent on socioeconomic status. The participants in this cohort were relatively wealthy and would not be entirely representative of the general population of Okinawa, Japan [17]. All of the participants were employed at the time of screening and responded to the invitation for screening. The prevalence of CKD and proteinuria was 5.7 and 5.0 %, respectively (Table 1). Third, the receipt score denotes the total amount of medical expenditure invested in each subject and is summarized monthly from all medical facilities in Okinawa area. The criteria for receipt points may differ by country, but the receipt point is a proxy of medical costs resulting from morbidity at least partly related to CKD. This, however, does not necessarily relate to the total cost of treatment. Other than the cost for medication and dental services, indirect costs such as transportation and supportive care must also be considered. In addition, job loss will eventually follow the development of CKD, and these subjects will not be able to afford adequate treatment. Further study is necessary to dissect the details of medical costs in relation to cardiovascular disease.

In conclusion, we analyzed the medical costs by eGFR and proteinuria. In the elderly population, aged 65 years and older, the difference in medical costs decreased in contrast to the younger age group. Insurance policies and reimbursement systems are different in each country [10], but our findings indicate the power of a single determination of serum creatinine and dipstick proteinuria for the prediction of medical costs, which is an important social and economic concern [14]. It is noteworthy that the medical cost increases abruptly at stage 3b and above, supporting the recent classification of CKD by KDIGO [3].

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Conflict of interest We declare that we have no conflict of interest.

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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

Table 2 continued

	BMI_8	BMI_9	BMI_10	BMI_11	Total	*P* value
Drugs taken						
Antihypertensive, (%)	3,538 (34.8)	2,923 (39.0)	2,298 (42.5)	5,720 (48.3)	34,371 (27.0)	<0.001
Antidiabetic, (%)	475 (4.7)	430 (5.7)	342 (6.3)	1,159 (9.8)	4,922 (3.9)	<0.001
Antihyperlipidemic, (%)	2,540 (25.0)	2,008 (26.8)	1,388 (25.7)	3,234 (27.3)	27,107 (21.3)	<0.001
Chemistry data						
Proteinuria, (%)	422 (4.1)	344 (4.6)	343 (6.3)	1,008 (8.5)	4,960 (3.9)	<0.001
eGFR, ml/min/1.73 m^2	74.4 (63.4–86.7)	74.4 (63.4–85.8)	74.4 (63.1–85.2)	74.4 (63.4–89.0)	74.7 (63.9–88.9)	<0.001
sCr, mg/dl	0.60 (0.56–0.70)	0.60 (0.60–0.70)	0.60 (0.59–0.70)	0.60 (0.50–0.70)	0.60 (0.53–0.70)	<0.001
FPG, mg/dl	94 (88–101)	95 (89–103)	95 (89–103)	97 (90–107)	92 (86–99)	<0.001
TG, mg/dl	106 (78–145)	108 (82–147)	112 (84–153)	118 (88–159)	93 (69–129)	<0.001
LDL, mg/dl	132 (113–153)	133 (113–153)	133 (113–153)	132 (114–153)	128 (109–149)	<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

active [22]. VAT is reported to have a higher association with proteinuria; however, this has not been found consistently [23]. Our study did not assess SAT or VAT condition; therefore, we cannot shed any further light on this issue.

A new finding in this study is that the subjects with a BMI <20.4 kg/m^2 in men and <18.4 kg/m^2 in women were significantly associated with proteinuria; however, the reason for this is not clear. Few papers have described an association between lowest BMI subjects and proteinuria [24]. According to our data, there was no strong association by univariate analysis, but significant associations were found between the lowest BMI subjects and proteinuria by multivariate analysis in both genders. Therefore, lowest BMI is not thought to have a strong influence on the presence of proteinuria, but it has significant power. There was no definitive explanation, but we would like to put forward some suggestions for consideration as to why these subjects had a significant association with proteinuria.

Firstly, postural proteinuria is thought to be related to renal ptosis or wandering kidney, which is often found in thinner people [25]. This condition might be included in subjects with the lowest BMI. Secondly, another risk of low BMI on proteinuria could be related to age. The OR for proteinuria was analyzed for age groups—in younger subjects, a larger OR was particularly prominent in the subjects with the lowest BMI; on the other hand, no clear age relationship was found in the higher BMI group. This suggested the possibility of more glomerulonephritis than nephrosclerosis or more postural proteinuria in the lowest BMI subjects. Thirdly, we could see that current smokers were more prevalent in the lower BMI groups in both genders, and causal relationships between cigarette smoking and proteinuria have been reported via the hyperfiltration mechanism [26].

Some epidemiological studies revealed that subjects with chronic lung disease or with malignancies were frequently seen among those with a lower BMI [27, 28]. In addition, a significant relationship between the presence of proteinuria and chronic obstructive lung disease has been reported [29], and its cause was speculated to be endovascular dysfunction [30]. In our study, the presence of lung disease or malignancies was not surveyed, so we could not clarify this issue; therefore, we were unable to rule out the contribution of lung diseases or malignancies to the presence of proteinuria, especially in view of the high frequency of smoking in the lower BMI participants.

Overall mortality analysis showed a U-shape with high mortality in both lower and higher BMI subjects [28]; however, because our study was cross-sectional, mortality analysis was not feasible. Other considered

Table 3 Univariate and multivariate logistic analyses for proteinuria

	Univariate			Multivariate		
	OR	95 % CI		OR	95 % CI	
		Lowest	Highest		Lowest	Highest
Men						
BMI subgroup (kg/m^2)						
≤18.4	1.160	0.974	1.382	1.756	1.455	2.118
8.5–19.5	1.109	0.937	1.312	1.429	1.199	1.703
19.5–20.4	1.038	0.901	1.195	1.261	1.090	1.459
20.5–21.4	0.894	0.786	1.017	0.980	0.858	1.118
21.5–22.4	1 (reference)			1 (reference)		
22.5–23.4	1.079	0.967	1.204	0.978	0.875	1.095
23.5–24.4	1.259	1.131	1.401	1.034	0.925	1.156
24.5–25.4	1.383	1.240	1.542	1.066	0.950	1.197
25.5–26.4	1.639	1.464	1.834	1.187	1.050	1.342
26.5–27.4	1.855	1.646	2.092	1.234	1.079	1.410
≥27.5	2.490	2.249	2.756	1.422	1.245	1.624
Age, +10 years	1.151	1.120	1.182	0.952	0.922	0.984
Waist circumference, +10 cm	1.393	1.355	1.432	1.113	1.064	1.165
SBP, +10 mmHg	1.246	1.229	1.264	1.176	1.158	1.194
FPG, + 10 mg/dl	1.134	1.126	1.142	1.109	1.099	1.118
TG, +50 mg/dl	1.075	1.064	1.086	1.029	1.017	1.042
LDL, +10 mg/dl	1.004	0.994	1.011	1.003	0.995	1.012
eGFR, +10 ml/min/1.73 m^2	0.822	0.809	0.836	0.822	0.808	0.837
Antihypertensive	2.316	2.201	2.436	1.731	1.635	1.833
Antidiabetic	2.773	2.576	2.985	1.481	1.357	1.615
Antihyperlipidemic	1.645	1.533	1.766	1.112	1.031	1.201
Current smoking	1.217	1.151	1.286	1.433	1.350	1.521
Daily drinking	0.950	0.903	1.000	0.899	0.852	0.949
Women						
BMI subgroup (kg/m^2)						
≤18.4	1.335	1.158	1.538	1.717	1.473	2.002
18.5–19.5	0.963	0.823	1.127	1.168	0.993	1.374
19.5–20.4	0.977	0.848	1.125	1.132	0.980	1.308
20.5–21.4	0.974	0.851	1.116	1.047	0.913	1.201
21.5–22.4	1 (reference)			1 (reference)		
22.5–23.4	1.282	1.127	1.457	1.205	1.059	1.372
23.5–24.4	1.402	1.230	1.599	1.259	1.101	1.439
24.5–25.4	1.529	1.335	1.752	1.275	1.108	1.467
25.5–26.4	1.699	1.471	1.961	1.334	1.147	1.550
26.5–27.4	2.394	2.071	2.766	1.799	1.541	2.099
≥27.5	3.288	2.933	3.687	2.203	1.917	2.532
Age, +10 years	1.129	1.093	1.167	0.869	0.837	0.902
Waist circumference, +10 cm	1.338	1.303	1.374	0.989	0.948	1.032
SBP, +10 mmHg	1.261	1.242	1.280	1.179	1.160	1.199
FPG, + 10 mg/dl	1.156	1.145	1.167	1.112	1.100	1.125
TG, +50 mg/dl	1.156	1.137	1.175	1.066	1.046	1.087
LDL, +10 mg/dl	1.012	1.002	1.021	0.999	0.990	1.009
eGFR, +10 ml/min/1.73 m^2	0.843	0.828	0.859	0.847	0.831	0.864
Antihypertensive	2.304	2.176	2.440	1.608	1.507	1.716