Introduction

Chronic kidney disease (CKD) is now recognized as a major global public health issue [1, 2]. Persistent proteinuria is one of the major criteria of CKD [3]. The prevalence of proteinuria among subjects with diabetes was reported to be high. For example, Ballard *et al.* [4] reported the incidence of proteinuria at initial diagnosis of type 2 diabetes and followed up ~20 years later as 8.2 and 24.6%, respectively, in 30-year-old and older US citizens. Parving *et al.* reported the prevalence of albuminuria among cases of type 2 diabetes as 13.8% in 66-year-old and older Danish individuals [5]. We also reported a rate of dipstick proteinuria of 11.3% among diabetes in a large Japanese cohort study [6].

In 1997 and 2009, the American Diabetes Association proposed the criterion for prediabetes of 100–125 mg/dL fasting plasma glucose (impaired fasting glucose, IFG) or 140–199 mg/dL OGT 2-h plasma glucose (impaired glucose tolerance, IGT) [7, 8]; subsequently, in 2011, an HbA1c level of 5.7–6.4% corresponding to the IFG was proposed [9]. There is a little data concerning the prevalence of proteinuria in prediabetes except our reported value of 5% for the same Japanese cohort [6].

Subjects with prediabetes were reported to have higher incidence of hypertension and obesity, and to be older than subjects with normal glucose tolerance [10, 11]. These variables are also independent risk factors for proteinuria [12]. After all, basic pathophysiology of prediabetes is thought to be insulin resistance [13]. Therefore, prediabetes is expected to be a risk factor for proteinuria; however, little data have been reported on this issue.

In a large national Japanese cohort, we examined the independent association of proteinuria with prediabetes, and further compared the association of prediabetes with proteinuria when it was defined by the recently proposed HbA1c criterion versus the standard impaired fasting glucose criterion.

Methods

Study design and population

This is a cross-sectional cohort study assessing the prediabetes with proteinuria in a large Japanese population. This study was performed as a 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 comprises Japanese citizens between the ages of 40 and 74 years. Local governments called for the citizen to attend this annual health check under their own volition. Other details such as the participants' area were reported previously [6].

There was a total of 346 942 subjects [mean age, 63.4 years, 41% (n = 141 938) were men] for whom information on age, gender, BP, body mass index (BMI), habitual smoking or drinking, use of anti-hypertensive 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 [14]. Individuals in certain regions participating in our project concomitantly underwent a regular health checkup 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 = 2025).

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. There was no clinical difference between subjects who were included in the present analysis (n = 228 778) and those who had missing data (n = 88 101).

The 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 fasting 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 starting several years ago, standardized methods to measure laboratory data have been recommended by the Japan Society of Clinical Chemistry and widely adopted.

The value for hemoglobin A1c (HbA1c) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following formula [15]:

$$\text{HbAlc}\,(\%) = \text{HbAlc}\,(\text{Japan Diabetes Society})\,(\%) + 0.4\%$$

Diabetes was defined in accordance with American Diabetes Association guidelines [9] as a fasting glucose concentration of 126 mg/dL or higher, HbA1c 6.5% or higher or self-reported use of anti-hyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL), HbA1c 5.7–6.4% or both [9].

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 in 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+ or more. Because dipstick +/− sometimes indicates microalbuminuria in the Japanese general population [16], taking changeable urine concentration or protein other than albumin contained in urine into consideration, we adopted dipstick 1+ or more as reflecting positive urine protein.

eGFR was derived using the following equation [17]:

$$\text{eGFR}\ (\text{mL/min/1.73 m}^2) = 194 \times \text{age}\ (\text{years})^{-0.287}$$

$$\times \text{serum creatinine}\ (\text{mg/dL})^{-1.094}\ (\text{if female} \times 0.739)$$

BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical checkup. According to the recommendations of the Japanese Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouscido01/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 rechecked 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 20.0J software (SPSS, Chicago, IL). Data are expressed as median (25th to 75th percentile). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using analysis of variance (ANOVA), and categorical parameters were compared with the chi-

squared test. We divided the study population into three groups (normal glucose tolerance, prediabetes and diabetes), and then the prediabetes population was subdivided into three subgroups [PD-A1c, fulfilled HbA1c criterion but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria] [9], according to the fasting glucose level or HbA1c level.

Next, we used multivariable logistic regression analysis to examine the independent association of prediabetes with proteinuria (≥1+) separately in subjects with normal glucose tolerance, prediabetes or diabetes. In the initial model (Model 1), these associations were assessed with adjustment for age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol. An extended model (Model 2) was used to assess whether there was an association of subtype of prediabetes with proteinuria (≥1+). Statistical significance was defined as $P < 0.05$.

Results

Clinical characteristics of the study population

The median age (interquartile range) of the 228 778 subjects was 66 (59–70) years, and 89 877 of the subjects (39.3%) were men. There were 27 913 subjects (12.2%) with diabetes and 100 214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes compared with those of subjects with normal glucose are shown in Table 1. Age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria, eGFR, chemistry data and blood pressure levels were significantly different between the groups. Subjects among prediabetes, 53.7, 21.7 and 24.5% subjects were divided into subclasses of PD-A1C, PD-IFG and PD-Both, respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1C criterion only. Clinical and laboratory data of subjects with subdivided prediabetes were shown in Table 2. Similar to Table 1, age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria, eGFR, chemistry data and blood pressure levels were significantly different between the groups. Especially, the prevalence of proteinuria in subjects with PD-IFG or PD-Both was higher than in subjects with PD-A1C.

Prediabetes and proteinuria

Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) (95% CI) for the increased risk of proteinuria (≥1+) in diabetes itself was 2.191 (2.081–2.307), and that in prediabetes was 1.093 (1.046–1.142), even after adjustment for significant covariates, such as age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol (both $P < 0.001$) (Table 3, Model 1).

Table 1. Characteristics of the study population overall

	Normal glucose tolerance (n = 100 651, 44.0%)	Prediabetes (n = 100 214, 43.8%)	Diabetes (n = 27 913, 12.2%)	Total (n = 228 778)	P-value
Age (years)	64 (56–69)	66 (60–70)	67 (61–71)	66 (59–70)	<0.01
Men, n (%)	35 174 (34.9%)	40 077 (40.0%)	14 626 (52.4%)	89 877 (39.3%)	<0.01
BMI (kg/m^2)	22.2 (20.3–24.3)	23.1 (21.1–25.3)	23.8 (21.7–26.2)	22.8 (20.8–25.0)	<0.01
Current smoker, n (%)	13 971 (13.9%)	12 960 (12.9%)	4 846 (17.4%)	31 777 (13.9%)	<0.01
Daily drinker, n (%)	21 521 (21.4%)	22 825 (22.8%)	7 162 (25.7%)	51 508 (22.5%)	<0.01
Proteinuria (≥1+), n (%)	3 913 (3.9)	5 013 (5.0)	3 164 (11.3)		<0.01
eGFR (mL/min/1.73 m^2)	74.4 (64.5–85.4)	74.1 (63.8–84.3)	74.4 (63.9–86.9)	74.4 (64.1–85.2)	<0.01
eGFR stage					<0.01
≥60 without proteinuria, n (%)	85 560 (85.0)	82 518 (82.3)	21 458 (76.9)	189 536 (82.8)	
≥60 with proteinuria, n (%)	3 052 (3.0)	3 634 (3.6)	2 320 (8.3)	9 006 (3.9)	
45–59, n (%)	11 035 (11.0)	12 832 (12.8)	3 531 (12.7)	27 398 (12.0)	
30–44, n (%)	912 (0.9)	1 095 (1.1)	510 (1.8)	2 517 (1.1)	
15–29, n (%)	92 (0.1)	135 (0.1)	94 (0.3)	321 (0.1)	
Antihypertensive drug, n (%)	21 410 (21.3%)	29 157 (29.1%)	11 101 (39.8%)	61 688 (27.0%)	<0.01
Antihyperlipidemic drug, n (%)	12 233 (12.2%)	17 440 (17.4%)	6 823 (24.4%)	36 496 (16.0%)	<0.01
Antihyperglycemic drug, n (%)	0 (%)	0 (%)	10 908 (39.1%)		
Chemistry data					
FPG (mg/dL)	89 (84–93)	98 (90–105)	125 (100–143)	93 (87–102)	<0.01
HbA1c (%)	5.4 (5.2–5.5)	5.8 (5.7–6.0)	6.6 (6.0–7.3)	5.6 (5.4–5.9)	<0.01
TG (mg/dL)	91 (67–127)	101 (74–142)	112 (79–162)	97 (71–138)	<0.01
LDL (mg/dL)	124 (105–144)	127 (108–148)	123 (104–145)	125 (106–146)	<0.01
HDL (mg/dL)	63 (53–75)	60 (51–72)	57 (48–68)	61 (51–73)	<0.01
BP parameters					
SBP (mmHg)	126 (114–136)	130 (120–140)	132 (122–144)	128 (118–140)	<0.01
DBP (mmHg)	75 (69–82)	78 (70–83)	78 (70–84)	76 (70–82)	<0.01

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square 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.

Table 2. Characteristics of the subjects with prediabetes

	PD-A1c ($n = 53\,838$, 53.7%)	PD-IFG ($n = 21\,794$, 21.7%)	PD-Both ($n = 24\,582$, 24.5%)	*P*-value
Age (years)	66 (60–70)	66 (59–70)	67 (61–71)	<0.01
Men, *n* (%)	16 620 (30.9%)	11 589 (53.2%)	11 868 (48.3%)	<0.01
BMI (kg/m^2)	22.6 (20.7–24.8)	23.3 (21.4–25.4)	23.9 (21.9–26.1)	<0.01
Current smoker, *n* (%)	6 402 (11.9%)	3 216 (14.8%)	3 342 (13.6%)	<0.01
Daily drinker, n (%)	9 145 (17.0%)	7 113 (32.6%)	6 567 (26.7%)	<0.01
Proteinuria (≥1+), *n* (%)	2 102 (3.9%)	1 329 (6.1%)	1 582 (6.4%)	<0.01
eGFR (mL/min/1.73 m^2)	74.1 (63.6–83.7)	74.1 (64.1–84.7)	73.8 (63.8–84.7)	<0.01
Antihypertensive drug, *n* (%)	13 800 (25.6%)	6 690 (30.7%)	8 667 (35.3%)	<0.01
Antihyperlipidemic drug, *n* (%)	10 159 (18.9%)	2 682 (12.3%)	4 559 (18.7%)	<0.01
Antihyperglycemic drug, *n* (%)	0 (%)	0 (%)	0 (%)	
Chemistry data				
FPG (mg/dL)	91 (86–95)	105 (102–110)	106 (102–112)	<0.01
HbA1C (%)	5.8 (5.7–6.0)	5.4 (5.3–5.5)	5.9 (5.8–6.1)	<0.01
TG (mg/dL)	97 (71–135)	104 (75–148)	110 (80–155)	<0.01
LDL (mg/dL)	128 (109–148)	124 (105–145)	129 (109–144)	<0.01
HDL (mg/dL)	61 (52–73)	60 (50–72)	58 (49–69)	<0.01
BP parameters				
SBP (mmHg)	128 (116–138)	130 (120–142)	132 (121–142)	<0.01
DBP (mmHg)	76 (70–82)	80 (70–85)	79 (70–84)	<0.01

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square test as appropriate.
PD-A1c, fulfilled HbA1c criterion (5.7–6.4%) but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion (100–125 mg/dL) but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria.
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.

Prediabetes subclass and proteinuria

According to univariable logistic regression analysis, not PD-A1C but PD-IFG and PD-Both were significant risk factors for proteinuria as well as diabetes. Next, multivariable logistic regression analysis was performed to examine the independent association with proteinuria, separately in subjects in prediabetes subclasses PD-A1c, PD-IFG and PD-Both, in addition to normal glucose tolerance or diabetes mellitus. Compared with subjects with normal glucose tolerance (as a reference), the OR (95% CI) for the increased risk of proteinuria (≥1+) in PD-IFG was 1.217 (1.140–1.300) and that in PD-Both was 1.249 (1.174–1.329) (both $P < 0.001$), but that in PD-A1c was not significant, even after adjustment for significant covariates, such as age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol (Table 3, Model 2 and Figure 1).

Discussion

The messages of this article are that prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and that subjects with prediabetes defined by using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Prediabetes and proteinuria

We showed that prediabetes was a significant risk factor associated with proteinuria independent of age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking) and lipid profile. Prediabetes is a risk factor not only for the development of diabetes but also for CVD occurrence [9, 18, 19]. Persistent proteinuria is one of the major criteria of CKD and promotes CVD [20–23]. Subjects having prediabetes with proteinuria are expected to be particularly susceptible to the development of CKD and/or CVD; therefore, these individuals should undergo medical intervention, such as lifestyle guidance and, if needed, medication.

We investigated 228 778 subjects who received a Japanese Tokutei Kenshin health checkup. Prediabetes was defined using the criterion of impaired fasting glucose level ($100 \leq \text{FPG} < 126$ mg/dL) or HbA1c level ($5.7 \leq \text{HbA1c} \leq 6.4\%$). According to these criteria, 100 214 (43.8%) subjects were judged as having prediabetes in our cohort. Clinical and laboratory data were significantly different among the groups of normal glucose tolerance, prediabetes and diabetes; however, because of the large number of participants, their clinical means, especially eGFRs, are unclear, and seem almost to be equal among groups (Table 1).

Why does this cohort exhibit so much prediabetes? A cohort study in the USA, the '1999 through 2006 National Health and Nutrition Examination Survey', (NHANES) revealed that 27.7% of participants had prediabetes, according to the ADA's IFG criterion [11]. Japanese data from a single facility revealed a rate of prediabetes of 33.5% among those undergoing an annual health checkup, according to the ADA criterion of IFG and/or IGT [24]. Possible reasons for the high level of prediabetes in our cohort are discussed. First, we can point out the age difference; mean age in the '1999 through 2006 NHANES was around 47 years of age, on the other hand, median age of our cohort was 66 years of age. Second, there are some possible biases toward the

Table 3. Results of the univariable and multivariable logistic regression analyses for proteinuria

	Unadjusted OR		Adjusted OR			
			Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
NGT (0 = no, 1 = yes)	1 (Reference)		1 (Reference)			
PD (0 = no, 1 = yes)	1.302 (1.247:1.359)	<0.001	1.093 (1.046:1.142)	<0.001		
DM (0 = no, 1 = yes)	3.161 (3.010:3.319)	<0.001	2.191 (2.081:2.307)	<0.001		
NGT (0 = no, 1 = yes)					1 (Reference)	
PD-A1c (0 = no, 1 = yes)	1.004 (0.952:1.060)	0.872			0.951 (0.900:1.005)	0.074
PD-IFG (0 = no, 1 = yes)	1.605 (1.506:1.712)	<0.001			1.217 (1.140:1.300)	<0.001
PD-Both (0 = no, 1 = yes)	1.7 (1.601:1.806)	<0.001			1.249 (1.174:1.329)	<0.001
DM (0 = no, 1 = yes)					2.207 (2.096:2.324)	<0.001
Age, +10 years	1.133 (1.111:157)	<0.001	0.910 (0.889:0.932)	<0.001	0.910 (0.889:0.932)	<0.001
Male, gender	2.061 (1.987:2.139)	<0.001	1.645 (1.576 :1.717)	<0.001	1.618 (1.550:1.689)	<0.001
BMI, +3 kg/m^2	1.134 (1.325:1.363)	<0.001	1.145 (1.127:1.164)	<0.001	1.141 (1.123:1.160)	<0.001
SBP, +10 mmHg	1.264 (1.252:1.277)	<0.001	1.173 (1.161:1.186)	<0.001	1.170 (1.157:1.183)	<0.001
Antihypertensives (0 = no, 1 = yes)	2.380 (2.295:2.472)	<0.001	1.709 (1.641:1.781)	<0.001	1.703 (1.634:1.774)	<0.001
Current smoker (0 = no, 1 = yes)	1.584 (1.512:1.659)	<0.001	1.420 (1.349:1.494)	<0.001	1.428 (1.356:1.503)	<0.001
Daily drinker (0 = no, 1 = yes)	1.325 (1.271:1.381)	<0.001	0.900 (0.859:0.943)	<0.001	0.892 (0.851:0.935)	<0.001
eGFR, +10 mL/min/1.73 m^2	0.829 (0.819:0.839)	<0.001	0.845 (0.834:0.855)	<0.001	0.844 (0.833:0.854)	<0.001
TG, +50 mg/dL	1.123 (1.114:1.132)	<0.001	1.043 (1.033:1.053)	<0.001	1.042 (1.032:1.052)	<0.001
LDL, +10 mg/dL	0.99 (0.984:0.996)	<0.001	0.998 (0.982:1.004)	0.545	0.998 (0.992:1.004)	0.508

NGT, normal glucose tolerance; PD, prediabetes; DM, diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low-density lipoprotein; SBP, systolic blood pressure.

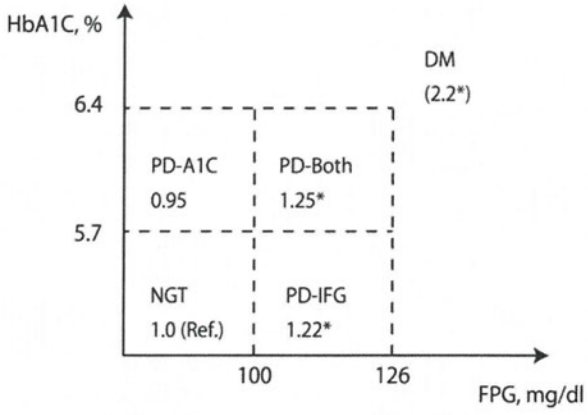

Fig. 1. OR for proteinuria according to subclass of prediabetes. The ORs of proteinuria in subjects with NGT, PD-A1c, PD-IFG, PD-Both or DM are shown. The analysis was adjusted for age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking), TG and LDL-C. *P < 0.001 versus NGT. NGT, normal glucose tolerance; PD, prediabetes; DM, diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low-density lipoprotein; SBP, systolic blood pressure.

participants who are particularly concerned about their physical condition or might be worried about their health status, such as the fact that many prediabetes subjects enrolled in this study under their own volition. Third, the actual number of subjects with prediabetes is increasing worldwide, especially in Asia. Increasing numbers of cases of prediabetes or diabetes itself have been reported not only in Japan, but also in India and China [25–27]. Dietary habits have also changed from the traditional style to a Western style, involving an increase in total calories, meat and fatty meals [28, 29]. Asians also exercise less now, associated with the spread of motorization [30]. A recent report stated that Asians tend to have much visceral fat tissue, in spite of a relatively low BMI score, compared with Caucasians [31–34]. Furthermore, genetically, Asians have a low insulin secretory ability [35–37]. These mechanisms of why Asians may be susceptible to diabetes are well summarized elsewhere [25].

Our study showed prediabetes was an independent risk factor for proteinuria, to diagnose prediabetes in a positive manner is meaningful for the measure to CKD in terms of prophylaxis transition to overt diabetes, renal function decrement or cardiovasucular disease.

In this study, the use of antihypertensive medication is one of the major risk factors associated with proteinuria (Table 3); however, the kind of antihypertensive drugs that patients used was unknown. The prevalence of ACE inhibitor or angiotensin II receptor antagonist users among cases of prediabetes, undiagnosed diabetes and diagnosed diabetes was reported in the USA to be lower than expected, at 8, 11 and 21%, respectively, in spite of these drugs being reported to have antiproteinuric effects or to delay CKD progression [11]. There are no data on the prevalence of the use of these drugs in patients with prediabetes in Japan. Longitudinal study is needed to clarify whether intervention using these drugs applied to prediabetes with proteinuria could prevent progression to CKD or to cardiovascular diseases.

Subclass of prediabetes and proteinuria

Subjects with prediabetes were classified into three groups: PD-A1c, PD-IFG and PD-Both, as defined above. The OR for proteinuria was significantly higher in subjects in the groups of PD-IFG and PD-Both than in PD-A1c, independent of age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking)

and lipid profile. Our data clearly revealed that the different groups, defined by different criteria, have different risks for proteinuria in the same category of prediabetes.

Insulin resistance is a principal pathophysiology of prediabetes as well as overt diabetes; however, two types of prediabetes, impaired fasting glucose or impaired glucose tolerance, are reported to be quite different in their causality of impaired glucose metabolism, such as hepatic insulin resistance or muscle insulin resistance [13]. There is a possibility that population of PD-A1c or PD-IFG has different bases of insulin resistance pathophysiology. However, we do not have sufficient data to support this idea yet.

A recent ADA statement indicated that HbA1c is a good marker to detect those at increased risk for diabetes (prediabetes) [9]; however, our data showed that HbA1c was not sufficient to identify subjects with prediabetes defined by impaired fasting glucose.

Limitations

This study is cross-sectional, so we were unable to infer causality for proteinuria. There might be some bias toward the participants who were particularly motivated to undergo a health examination. Many people were excluded because of missing data. Urine dipstick analyses were performed manually. This visual judgment is limitation. In particular, some of the dipstick-positive proteinuria could have been transient, and the presence of persisting proteinuria was not confirmed. Physiological proteinuria could not be ruled out because the dipstick test for detecting proteinuria was only carried out once. Urine-specific gravity and pH were not recorded; therefore, the effect of urine concentration on test performance was not assessed. Furthermore, a relatively high false-positive rate for proteinuria by judging isolated dipstick test results was reported [38]. Possible HbA1c value variability has also been mentioned. However, the effect of this should be minimal in this study because Japanese HbA1c assay CV has been reported to be low [39].

We could not rule out the presence of subjects who had not fasted and had plasma glucose levels above 100 mg/dL; therefore, these could have been counted among those actually having prediabetes. However, because participants were strictly instructed to attend a health checkup in a fasting state, we speculate that there were only a minimal number of nonfasting subjects.

Summary

We examined the association of prediabetes with proteinuria, and compared the risk of proteinuria among those classified prediabetes by two ADA prediabetes criteria, fasting plasma glucose and newer HbA1c, in a large (>200 000) Japanese database of health checkup data of adults with no pre-existing cardiovascular diseases. We found that prediabetes was a significant risk factor for proteinuria compared with completely normal glucose level, and subjects with prediabetes defined by using impaired fasting glucose were at significantly higher risk for proteinuria than those defined by HbA1c, only.

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Predicting outcomes after myocardial infarction by using the Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease study equation: results from the Korea Acute Myocardial Infarction Registry

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Abstract

Background. The presence of chronic kidney disease is an independent prognostic factor in patients with myocardial infarction (MI). We compared the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) study equation with regard to prognostic value in patients with MI.

Methods. This study analyzed a retrospective cohort of 11 050 consecutive patients who had MI and were

Prevalence of chronic kidney disease in China

Luxia Zhang and colleagues' well designed study (March 3, p 815)[1] calculates the overall prevalence of chronic kidney disease (CKD) in China to be 10·8%, and the prevalence of stages 1–5 to be 5·7%, 3·4%, 1·6%, 0·1%, and 0·03%, respectively. The proportion of CKD stage 3 was strikingly lower than for other countries.[2–4]

One reason for the difference could be the method of creatinine measurement and the equation used to estimate glomerular filtration rate (eGFR). A lower creatinine value or a systemic overestimation of GFR by the equation will result in eGFR distribution shifting to a higher value. We question whether there was a small change in the serum creatinine value after correction by regression between different study sites that caused a significant upshift in eGFR. If this was the case, Zhang and colleagues would have ended up with a higher proportion of individuals with an eGFR greater than 60 mL/min/1·73 m² and a lower prevalence of CKD stage 3.

In their study, only 56·6% of patients with CKD stage 5 and 34·3% of those with stage 4 had a urine albumin-to-creatinine ratio greater than 30 mg/g. The urine test is regarded as an important method by which to detect CKD.[5] We have seldom seen such a substantial proportion of patients with advanced stages of CKD and yet no albuminuria. If the high prevalence of albuminuria in rapidly developing rural areas reflects the rapid growth of lifestyle diseases such as hypertension and diabetes, the low prevalence of albuminuria in advanced stages of CKD is not relevant. It indicates that screening for proteinuria with urine albumin-to-creatinine ratio will miss a substantial proportion of patients with very low eGFR, and that the cheaper and less sensitive urine dipstick test will miss even more. This will complicate CKD screening and prevention.

We declare that we have no conflicts of interest.

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Chronic kidney disease (CKD) has become an important public health problem in China. Luxia Zhang and colleagues[1] shed new light on this issue by reporting that the overall prevalence of CKD is 10·8%, and that the number of patients with CKD in China is therefore about 119·5 million. However, all the markers of CKD were obtained from single measurements; therefore the reported prevalence of CKD might be an overestimate. Given the importance of excluding acute kidney injury, guidelines recommend that any patient with a reduced glomerular filtration rate (GFR) and no previous evidence of renal impairment should have a repeat estimated GFR (eGFR) within 2 weeks of the first.[2] For the diagnosis of microalbuminuria, two abnormal results from three specimens are required.[2]

Zhang and colleagues calculated eGFR with an equation adapted from the Modification of Diet in Renal Disease equations, which can underestimate GFR. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) four-level race GFR estimation equation significantly lessens bias. On the basis of the 201 million people older than 20 years in the USA in 2000, Levey and colleagues[3] used the CKD-EPI equation to give a CKD prevalence of 11·5% (23·2 million). They used repeated measurements, obtained about 2 weeks after the original examination. Both the CKD-EPI equation and the combination of the cystatin C and serum creatinine equations are useful for Chinese CKD patients.[4,5] However, the combination of the cystatin C and serum creatinine equations would be better.[5]

We declare that we have no conflicts of interest.

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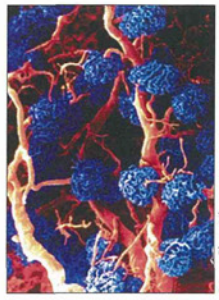
Luxia Zhang and colleagues[1] report the prevalence of chronic kidney disease (CKD) in a Chinese nationwide survey (n=47 204, mean age 50 years). Surprisingly, compared with our nationwide Japanese survey (n=232 025, mean age 62 years),[2] the mean estimated glomerular filtration rate (eGFR) in Zhang and colleagues' survey is much higher (101 *vs* 77 mL/min/1·73 m²), and the prevalence of CKD stage 3 and 4 is radically lower (1·7% *vs* 11·0%).

The difference in age between these surveys would not seem to account for these differences completely, since the 10-year odds ratio for an increase in low eGFR (<60 mL/min/1·73 m²) was 1·74 in Zhang and colleagues' survey. Glomerular hyperfiltration could have been more prevalent in Zhang and colleagues' survey than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in ours, which could have been due, at least partly, to the higher mean body-mass index (BMI) in Zhang and colleagues' survey than in ours (23·9 *vs* 22·6 kg/m²). Obesity induces haemodynamic changes in the glomerular hyperfiltration state, whose first clinical manifestation of renal injury seems to be increased albuminuria.[3] However, Zhang and colleagues paid little attention to obesity in their discussion. Moreover, we wonder why Zhang and colleagues did not enter BMI (or obesity) as a factor associated with indicators of CKD in their table 5.

Finally, we are interested in the sex difference in the risk of CKD. Women were at higher risk of CKD than were men in Zhang and colleagues' analysis; however, women are generally known to be at lower risk than men.[2,4] Zhang and colleagues should discuss this point.

We declare that we have no conflicts of interest.

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A reliable estimation of the world's major public health problems is important, especially for China, which is the largest developing country and is experiencing a huge transition in disease burden. Luxia Zhang and colleagues[1] deserve to be applauded for their survey on chronic kidney disease. However, we were puzzled by the size of one of the subpopulations.

As shown in Zhang and colleagues' table 1, the numbers of individuals with no indicators of kidney damage, with a low estimated glomerular filtration rate (eGFR <60 mL/min/1·73 m²), and with albuminuria were 41165, 1185, and 3517, respectively. However, the sum of these three subpopulations is 45 867—a little less than the total of 47 204 who were reported to have completed the survey. Indeed, the sum should absolutely not be less than 47 204 given that chronic kidney disease was defined as low eGFR, albuminuria, or both.

We did our own calculation on the basis of the data presented in table 2 and found that the number of participants with no indicators of kidney damage might be 42757 ([29 244–1877] + [16 775–1385]). Zhang and colleagues should thoroughly check their data again to ensure that their main finding is not undermined by the input of incorrect data.

We declare that we have no conflicts of interest.

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Two recent national representative surveys have presented the prevalence of diabetes in China. In 2010, Yang and colleagues[1] reported that the prevalence of diabetes was 9·7%, whereas the study by Luxia Zhang and colleagues[2] states that the prevalence is 4·9%. Both studies claimed to use randomly selected representative samples with response rates of 87·3% and 93%, respectively. In Yang and colleagues' study, an oral glucose-tolerance test (OGTT) was used to diagnose diabetes, whereas in Zhang and colleagues' study, the diagnosis was based only on fasting glucose and history of diabetes. Detailed comparisons between the two studies are needed. If both are correct, it means that half the cases of diabetes will be missed if OGTT is not done. This seems unlikely since, according to Yang and colleagues' study, "the prevalence of undiagnosed diabetes in which the 2-hour plasma glucose level in an OGTT test was 200 mg per decilitre or more but the fasting glucose level was less than 126 mg per decilitre was 2·9% among men and 2·6% among women".[1]

If the prevalence of diabetes was underestimated in Zhang and colleagues' study owing to selection bias, the prevalence of chronic kidney disease (CKD) will also be underestimated because those with diabetes have twice the normal risk of CKD.

These two studies have raised awareness of the burden of chronic diseases, which is a milestone for the prevention of such diseases in China. However, we need a correct estimate of the problem to plan prevention strategies.[3]

We declare that we have no conflicts of interest.

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Author's reply

Shang-Jyh Hwang and colleagues raise a question about the measurement of creatinine in our study. To ensure consistency of measurement, creatinine was measured in 40 samples both at the central laboratory in each province

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Blood Pressure Control in a Japanese Population With Chronic Kidney Disease: A Baseline Survey of a Nationwide Cohort

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BACKGROUND
Hypertension is a key risk factor for adverse renal outcomes in chronic kidney disease (CKD), and strict blood pressure control is recommended to halt its progression. This study assessed blood pressure control in the Japanese CKD population.

METHODS
We used a nationwide database of 250,130 subjects (aged 20–88), including 45,845 CKD subjects (18.3%), participated in an annual health check, "The Specific Health Check and Guidance in Japan," and examined the relationship between CKD status and blood pressure. Blood pressures were measured in sitting position by trained staff, and target blood pressure for CKD subjects was defined as systolic (SBP)/diastolic blood pressure (DBP) <130/80 mm Hg.

RESULTS
In total population, CKD subjects had a higher prevalence of hypertension (58.0% vs. 41.8%, $P < 0.001$) and a higher proportion with antihypertensive medication (42.4% vs. 26.7%, $P < 0.001$), compared with non-CKD subjects. The proportion of subjects achieving target blood pressure was significantly lower among total CKD subjects than among total non-CKD subjects (34.6% vs. 43.8%, $P \leq 0.001$). Among CKD subjects, these proportions were especially low in those with stage 4–5 (24.3–27.5%), those on antihypertensive medication (21.6%) and those with proteinuria ≥2± (21.3%). Logistic regression analysis showed that independent factors for high-blood pressure in CKD subjects were age, male gender, alcohol consumption, nonsmoking, diabetes, dyslipidemia, obesity, proteinuria, and antihypertensive medication.

CONCLUSIONS
Blood pressure control was inadequate in the majority of Japanese CKD subjects, despite antihypertensive treatment. More aggressive efforts to achieve target blood pressures among CKD subjects are recommended.

Keywords: *blood pressure; chronic kidney disease; epidemiology; hypertension*

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In recent years, chronic kidney disease (CKD) has received attention as a risk factor for end-stage renal disease, cardiovascular events, and all-cause mortality. Measures to prevent the development and progression of CKD are urgently required worldwide.

Various factors are associated with the development of CKD, including age, hypertension, diabetes, dyslipidemia, obesity, smoking, proteinuria, and hematuria.[1] Among these, the most prevalent and strongest risk factor for adverse renal outcomes is hypertension.[2] In the United States, the prevalence of hypertension is reported to be much higher in CKD subjects than in non-CKD subjects (50.9–70.9% vs. 21.9–48.3%).[3] In Japan, the prevalence of hypertension was documented to be 91.9% in a hospital-based CKD population[4] and 80.3% in high-risk CKD subjects.[5]

According to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High-Blood Pressure (JNC 7)[6] and the Japanese guidelines for CKD,[7] the target blood pressure for subjects with CKD is a systolic blood pressure (SBP) <130 mm Hg and diastolic blood pressure (DBP) <80 mm Hg. Furthermore, for those CKD subjects with proteinuria of 1 g/day or greater, tighter control of blood pressure (SBP <125 mm Hg, DBP <75 mm Hg) is recommended.[7]

Although the significance of blood pressure in the development of vascular disease, including CKD, is well-recognized,

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blood pressure control in patients with CKD is currently unsatisfactory. There are several reasons for this, including the fact that many hypertensive subjects do not receive antihypertensive medication, and that blood pressure control is poor due to insufficient treatment. A report based on the nationwide National Health and Nutrition Examination Survey (NHANES) survey in the United States indicated that within the hypertensive CKD population, the proportion of subjects using antihypertensive medication was 49.7–68.3%, and the majority (70.7–78.7%) of CKD subjects using antihypertensive medication did not achieve sufficient blood pressure control, with a low proportion of subjects (39.1–48.3%) achieving the target blood pressure.[8] Achievement of target blood pressure is affected by individual characteristics, including age, gender, and ethnicity.[9] However, there has been no study examining blood pressure control in the context of CKD in an Asian population.

To address this issue, a cross-sectional study was conducted using the nationwide annual health check database of "The Specific Health Check and Guidance in Japan".

METHODS

Study population. This study formed part of the 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 Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. This health check program includes all inhabitants over the age of 20 years in Japan, who are covered by national insurance. In 2009, the total number of subjects invited and participating were about 52 million and 21 million, respectively (response rate 40.5%).

In Japan there are 47 administrative districts (prefectures), each with a population of between 0.6 and 13 million. In this study, 13 prefectures (Yamagata, Miyagi, Fukushima, Niigata, Tokyo, Kanagawa, Ibaraki, Osaka, Okayama, Kochi, Fukuoka, Miyazaki, and Okinawa) that agreed with our study aim and were randomly distributed across Japan were selected. Data for these prefectures was obtained from the nationwide database, and data was collected on 278,017 men and 383,586 women (total population 676,905, aged from 20 to 101 years), who participated in the health checks in 2008 and 2009. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the institutional ethics committee.

In this health check, measurement of creatinine is optional and serum creatinine was not determined in half of the regions in Japan. Among the 676,905 participants, 426,775 were excluded from the present analysis because essential data, including blood pressure measurements, and data on proteinuria, and serum creatinine levels were incomplete. Therefore, data for 101,147 males and 148,983 females (a total of 250,130 subjects, aged 20 to 88 years) were used in the final statistical analyses. Comparison between those with and those without complete data did not show significant differences in baseline characteristics such as age, gender, or the proportion of subjects using antihypertensive medication.

Measurements. Subjects used a self-report questionnaire to document their medical history, current medications, smoking habit (smoker or nonsmoker), and alcohol intake (drinker or nondrinker). SBP and DBP were measured by trained staff, using a standard sphygmomanometer or an automated device, with subjects in the sitting position for at least 5 min before the measurement. Hypertension was defined as a SBP ≥140 mm Hg, or a DBP ≥90 mm Hg, or use of antihypertensive medication. Body mass index was calculated as weight (kg) divided by height squared (m^2). For both men and women, obesity was defined as a body mass index ≥25.0 kg/m^2. Plasma glucose levels were measured by the hexokinase enzymatic reference method. Subjects with diabetes were identified either by self-reported physical diagnosis, or by a fasting plasma glucose concentration ≥126 mg/dl, or a hemoglobin A_{1c} value ≥6.5%. Triglyceride and low-density lipoprotein cholesterol concentrations were measured by enzymatic methods. High-density lipoprotein cholesterol concentration was measured directly. Dyslipidemia was defined as a triglyceride concentration ≥150 mg/dl, or low-density lipoprotein cholesterol concentration ≥140 mg/dl, or high-density lipoprotein cholesterol concentration <40 mg/dl, or use of antilipidemic medication.

Dipstick urinalysis was performed on a single spot urine specimen, collected in the early morning after overnight fasting. The results of the urine test were recorded as (−), trace, (1+), (2+), or (3+). A positive proteinuria test was defined as (1+) or greater. Serum creatinine was measured by an enzymatic method and estimated glomerular filtration rate (eGFR) was obtained using the Japanese equation for eGFR.[10] In keeping with the universal definition, CKD was defined as proteinuria and/or reduced renal function (eGFR <60 ml/min/1.73 m^2), and was further categorized into five stages: stage 1, eGFR ≥90 ml/min/1.73 m^2 with proteinuria; stage 2, eGFR 60–89 with proteinuria; stage 3, eGFR 30–59; stage 4, eGFR 15–29; and stage 5, eGFR <15.[11] To investigate the relationship between CKD stage and blood pressure in detail, stage 3 was further divided into stage 3A (eGFR 45–59) and stage 3B (eGFR 30–44).

Statistical analyses. The unpaired *t*-test and one-factor analysis of variance were used to compare mean values, and the χ^2-test was used to evaluate differences in proportions. To examine the correlation between blood pressure and various parameters, including age, gender, alcohol consumption, smoking, diabetes, dyslipidemia, obesity, use of antihypertensive medication, eGFR, and proteinuria in subjects with CKD, a multiple linear regression analysis was performed. To examine the factors related to insufficient blood pressure control in subjects with CKD (SBP ≥130 mm Hg or DBP ≥80 mm Hg), multivariate logistic regression analyses that included age, gender, alcohol consumption, smoking, dyslipidemia, obesity, use of antihypertensive medication, renal function, and proteinuria, were performed. Continuous data are expressed as mean ± s.d.

All statistical analyses were performed using JMP version 8 software (SAS Institute Inc., Cary, NC). A significant difference was defined as $P < 0.05$.

RESULTS

Baseline characteristics of the participants

Among a total of 250,130 participants, there were 45,845 CKD subjects (18.3%) and 204,285 non-CKD subjects (81.7%). The CKD subjects were more likely to be males and older, had a higher prevalence of, diabetes, dyslipidemia and obesity, were more likely to have a past history of kidney or cardiovascular disease, and had a lower prevalence of smoking (**Table 1**).

Prevalence of hypertension in subjects with CKD

Blood pressure was first compared between CKD and non-CKD subjects. Hypertension was significantly more prevalent in CKD subjects than in non-CKD subjects (58.0% vs. 41.8%, $P < 0.001$) (**Figure 1**). Among the CKD subjects, the prevalence of hypertension was higher in males, the elderly, and in those with a higher grade of proteinuria. The prevalence of hypertension was also increased in the advanced stages of CKD: 60.3% in stage 1 ($n = 1,936$), 64.1% in stage 2 ($n = 8,061$), 56.0% in stage 3 ($n = 35,256$), 88.3% in stage 4 ($n = 461$), and 84.0% in stage 5 ($n = 131$) (P for trend < 0.001) (**Figure 1**).

Blood pressure was significantly higher in CKD subjects than in non-CKD subjects (SBP 132 ± 18 vs. 128 ± 17 mm Hg, $P < 0.001$; DBP 78 ± 11 vs. 76 ± 11 mm Hg, $P < 0.001$). CKD subjects in the advanced stages of disease had higher SBP and lower DBP, compared with those in the early stages of disease (**Figure 2**).

In the multiple regression analysis that included age, gender, alcohol consumption, smoking, diabetes, dyslipidemia, obesity, use of antihypertensive medication, eGFR and proteinuria, SBP was positively associated with all parameters except smoking. In contrast, DBP was positively associated with male gender, alcohol consumption, dyslipidemia, obesity, use of antihypertensive medication, eGFR and proteinuria, and negatively associated with age, smoking, and diabetes (**Table 2**).

Table 1 | Basal characteristics of the study participants

	Total population	Non-CKD population	CKD population
Number (%)	250,130	204,285 (81.7)	45,845 (18.3)
Age, years	63.6 ± 8.7	63.0 ± 9.0	66.3 ± 6.9*
Male gender, *n* (%)	101,147 (40.4)	77,349 (37.9)	23,798 (51.9)*
Hypertension, *n* (%)	112,002 (44.8)	85,396 (41.8)	26,606 (58.0)*
Using antihypertensive medication, *n* (%)	73,929 (29.6)	54,492 (26.7)	19,437 (42.4)*
Not using antihypertensive medication, *n* (%)	38,073 (15.2)	30,904 (15.1)	7,169 (15.6)*
Alcohol consumption, *n* (%)	113,317 (45.3)	92,438 (45.3)	20,879 (45.5)
Smoker, *n* (%)	34,185 (13.7)	28,356 (13.9)	5,829 (12.7)*
Diabetes, *n* (%)	34,403 (9.4)	17,119 (8.4)	6,284 (13.7)*
Dyslipidemia, *n* (%)	138,535 (55.4)	110,258 (54.0)	28,277 (61.7)*
Obesity, *n* (%)	63,899 (25.5)	48,903 (23.9)	14,996 (32.7)*
eGFR, ml/min/1.73 m^2	75.1 ± 16.2	78.9 ± 14.0	58.2 ± 14.3*
Systolic blood pressure, mm Hg	129 ± 17	128 ± 17	132 ± 18*
Diastolic blood pressure, mm Hg	76 ± 11	76 ± 11	78 ± 11*
Body mass index (kg/m^2)	23.1 ± 3.3	22.9 ± 3.3	23.8 ± 3.4*
Past history of kidney disease, *n* (%)	1,400 (0.6)	692 (0.3)	708 (1.5)*
Past history of CVD, *n* (%)	22,838 (9.1)	16,493 (8.1)	6,345 (13.8)*
Proteinuria ≥1+, *n* (%)	13,999 (5.6)	—	13,999 (30.5)

CVD, cardiovascular diseases; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*$P < 0.05$ by unpaired *t*-test, comparing non-CKD subjects with CKD subjects.

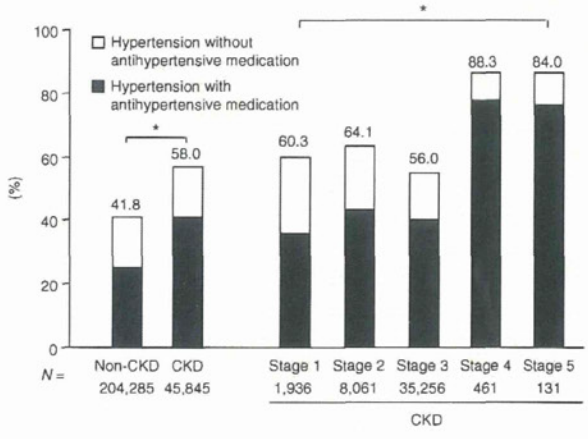

Figure 1 | The prevalence of hypertension in CKD and non-CKD subjects. *$P < 0.001$ by χ^2-test. CKD, chronic kidney disease.

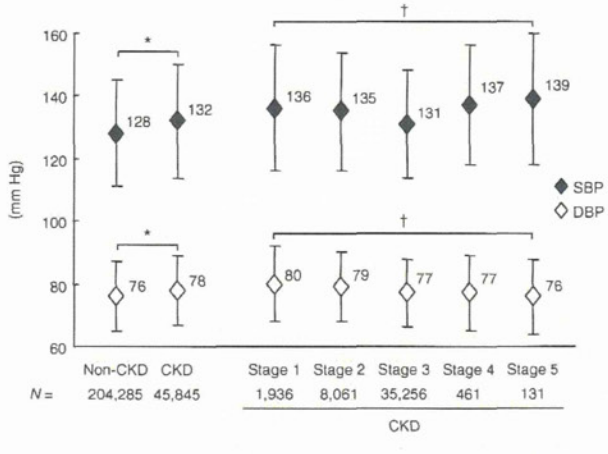

Figure 2 | Blood pressures levels in CKD and non-CKD subjects. *$P < 0.001$ by unpaired *t*-test, †$P < 0.001$ by analysis of variance. Data are mean ± s.d. CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 | Multivariate linear regression coefficients for the association of systolic and diastolic blood pressures with clinical parameters

	Systolic blood pressure		Diastolic blood pressure	
	Coefficient	*P* value	Coefficient	*P* value
Age	0.34	<0.001	−0.09	<0.001
Male gender	1.09	<0.001	2.38	<0.001
Alcohol consumption	1.81	<0.001	1.28	<0.001
Smoker	−0.8	0.001	−1.07	<0.001
Diabetes	2.23	<0.001	−1.68	<0.001
Dyslipidemia	1.57	<0.001	0.92	<0.001
Obesity	3.83	<0.001	2.59	<0.001
Use of antihypertensive medication	6.14	<0.001	2.26	<0.001
eGFR, ml/min/1.73 m^2	0.03	<0.001	0.01	0.022
Proteinuria, ≥1+	4.55	<0.001	1.73	<0.001

Adjusted for age, gender, alcohol consumption, smoking, diabetes, dyslipidemia, obesity, use of antihypertensive medication, eGFR, and proteinuria.
eGFR, estimated glomerular filtration rate.

The proportion of subjects using antihypertensive medication

Among the total population, the proportion of subjects using antihypertensive medication was higher in CKD subjects than in non-CKD subjects (42.4% vs. 26.7%, $P \leq 0.001$) (**Table 1**). In contrast, the proportion of subjects not using antihypertensive medication was almost identical in total CKD subjects (15.6%) and total non-CKD subjects (15.1%). Among those with hypertension, a higher proportion of CKD subjects than non-CKD subjects used antihypertensive medication (73.1% vs. 63.8%, $P \leq 0.001$). Among the CKD subjects, those proportions were especially high in subjects in the advanced stages of CKD (63.2–69.9% in stage 1–2, 74.1% in stage 3, and 86.3–90.4% in stage 4–5), and in the older population (57.6% in those <60 years, 69.4% in those between 60 and 64 years, 72.3% in those between 65 and 69 years, and 78.3% in those ≥70 years).

The proportion of subjects achieving the target blood pressure

The proportion of subjects achieving the target blood pressure (≤130/80 mm Hg) was significantly lower among CKD subjects than non-CKD subjects (34.6% vs. 43.8%, $P \leq 0.001$). Among CKD subjects, this proportion was especially low in those using antihypertensive treatment (21.6%) (**Table 3**).

Among the CKD population, a higher proportion of those who achieved the target blood pressure were in stage 3 (36.5%), and especially stage 3A (37.0%), than in the advanced stages (stage 4–5, 24.3–27.5%). In contrast, among CKD subjects using antihypertensive treatment, the proportion of those who achieved the target blood pressure was higher in stage 4–5 (23.9–27.4%) and lower in stages 1–2 (15.3–16.3%). Similarly, among the older population, attainment of target blood pressure was low for all subjects but high in those subjects using antihypertensive drugs. Lower proportions of subjects with a high grade of proteinuria, as well as males, achieved the target blood pressure, both among the total population, and the subpopulation receiving antihypertensive treatment (**Table 3**).

Table 3 | Blood pressure control in the CKD population

Variable (*n*)	BP <130/80 among total CKD subjects, *n* (%)	BP <130/80 among CKD subjects using antihypertensive medication, *n* (%)
CKD (45,845)	15,824 (34.6)	4,197 (21.6)
CKD		
Stage 1 (1,936)	562 (29.0)*	113 (15.3)*
Stage 2 (8,061)	2,255 (28.0)	588 (16.3)
Stage 3 (35,256)	12,877 (36.5)	3,382 (23.1)
Stage 3a (32,102)	11,879 (37.0)	2,880 (22.8)
Stage 3b (3,154)	998 (31.6)	502 (25.1)
Stage 4 (461)	112 (24.3)	88 (23.9)
Stage 5 (131)	36 (27.5)	26 (27.4)
Proteinuria		
−/± (31,846)	12,101 (38.0)*	3,031 (24.2)*
1+ (9,669)	2,816 (29.1)	798 (18.0)
≥ 2+ (4,330)	924 (21.3)	368 (14.9)
Gender		
Male (23,798)	7,139 (30.0)*	2,246 (20.6)*
Female (22,047)	8,709 (39.5)	1,951 (22.9)
Age, years		
<60 (6,283)	2,771 (44.1)*	287 (19.6)*
60–64 (7,470)	2,659 (35.6)	555 (21.4)
65–69 (14,606)	4,981 (34.1)	1,298 (21.1)
≥70 (17,486)	5,438 (31.1)	2,057 (22.8)

BP, blood pressure; CKD, chronic kidney disease.
*$P < 0.05$ across categories by χ^2-test.

For subjects with high-grade proteinuria (≥1 g/day), tighter control of blood pressure (<125/75 mm Hg) is recommended. In this study, no information was available on urinary protein and creatinine concentrations; therefore proteinuria ≥2+ by dipstick was used as a proxy for proteinuria ≥1 g/day. The proportions of CKD subjects achieving tighter blood pressure control were 14.4% for those with proteinuria ≥2±, 9.1% for those with proteinuria ≥2± who were receiving antihypertensive treatment, and 21.4% for those with proteinuria ≥2± who were not receiving antihypertensive treatment.

In addition, to investigate the factors associated with inadequate blood pressure control (SBP ≥130 mm Hg or DBP ≥80 mm Hg), logistic regression analysis was performed. Older age, male gender, alcohol consumption, being a nonsmoker, diabetes, dyslipidemia, obesity, use of antihypertensive treatment, and proteinuria were all independent factors predisposing to poor blood pressure control among subjects with CKD (**Table 4**).

Table 4 | Multiple logistic regression analysis of predictive factors associated with suboptimal blood pressure control (SBP ≥130 mm Hg or DBP ≥80 mm Hg) in subjects with CKD

	Odds ratio	95% CI	*P* value
Age (per 10 year increase)	1.21	1.17–1.24	<0.001
Male gender	1.25	1.20–1.31	<0.001
Alcohol consumption	1.27	1.21–1.32	<0.001
Smoker	0.86	0.81–0.92	<0.001
Diabetes	1.13	1.06–1.21	<0.001
Dyslipidemia	1.18	1.14–1.23	<0.001
Obesity	1.63	1.56–1.71	<0.001
Use of antihypertensive medication	2.36	2.26–2.47	<0.001
eGFR <60 ml/min/1.73 m^2	0.97	0.89–1.06	0.539
Proteinuria ≥ 1+	1.52	1.40–1.64	<0.001

CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

DISCUSSION

This study, which was based on a large-scale nationwide database of the Japanese population, revealed for the first time that blood pressure levels did not meet the target in the majority of subjects with CKD, and especially in those with advanced CKD and high-grade proteinuria. This poor blood pressure control may be partly attributable to inadequate use of medication.

This study showed that there was a higher prevalence of hypertension (58.0%), a higher proportion of subjects using antihypertensive treatment (42.4%), and a lower proportion of subjects achieving the target blood pressure (34.6%) among the total CKD population than among the total non-CKD population. Although the characteristics of the participants were different, these percentages were slightly better than those from the NHANES 1999–2006 study in the United States (63.9–80.5% prevalence of hypertension, 10.6–20.0% of subjects achieving the target blood pressure, and 49.7–68.3% receiving antihypertensive treatment).[8] Other studies in Western countries have documented the proportion of subjects among the CKD population that achieved target blood pressure as 12–46%.[12] Previous Japanese studies targeting a high-risk CKD population showed a much higher prevalence of hypertension; 91.9% in hospital-based CKD patients,[4] and 80.3% in a CKD population with past and family histories of hypertension, diabetes, and kidney disease.[5] This suggests that the prevalence of hypertension among subjects with CKD varies, depending on the characteristics of the study population. Overall, the severity of hypertension in this study appeared to be less than in previous studies.

Among the total population, the proportions of subjects not using antihypertensive medication was almost identical for all CKD subjects and all non-CKD subjects. In contrast, among subjects with hypertension, it was significantly lower in the CKD subjects than in the non-CKD subjects. Based on this observation, it might be speculated that the main reason for the high proportion of CKD subjects with inadequate blood pressure control appears to be under-treatment rather than nontreatment. Although there were high percentages of subjects receiving antihypertensive treatment among those with advanced CKD, those with proteinuria ≥2+, and among the older subjects, these groups had low proportions achieving target blood pressure. This suggests that intervention with antihypertensive medication is especially inadequate in these populations. In contrast, the proportion of CKD subjects in the early stages of disease that was using antihypertensive medication was lower, and the administration of antihypertensive treatment should be promoted in this group.

According to the CKD guidelines,[7] tighter control of blood pressure (<125/75 mm Hg) is recommended for subjects with proteinuria ≥2+. However, the proportion of these subjects with well controlled blood pressure was very low. Thus, meeting this target range of blood pressure does not appear to be feasible with current medications, and a more intense and comprehensive approach that includes the use of antihypertensive drugs is recommended. These findings suggest that different countermeasures need to be taken to achieve target blood pressure, depending on the status of subjects with CKD.

Of note, among CKD subjects with stage 3 disease, and especially those with stage 3A disease (eGFR 45–59ml/min/1.73 m^2), there was a relatively lower prevalence of hypertension and a higher proportion achieving target blood pressure control. This finding is in keeping with a Japanese report on a high-risk CKD population, which indicated that there was a lower proportion of subjects with high-blood pressure (≥140/90 mm Hg) among those with stage 3–4 disease than among those with stage 1–2 disease.[5] However, American studies have shown that blood pressure control deteriorates with advancing CKD stage, both in the general and high-risk populations.[9] Although differences in the backgrounds of participants may contribute to this discrepancy, it is possible that the effect of stage 3 CKD on blood pressure may differ, depending on the ethnicity of the population.

Multiple linear regression and logistic regression analyses suggested that multiple risk factors, including older age, gender, alcohol consumption, obesity, diabetes, and dyslipidemia, were associated with blood pressure and poor blood pressure control. This finding is consistent with a previous report that subjects with diabetes and high-grade albuminuria, among a cohort with chronic renal insufficiency, were likely to have inadequate blood pressure control.[13] These findings highlight the importance of lifestyle modifications in order to achieve target blood pressure.

Although a target blood pressure of <130/80 mm Hg is recommended for subjects with CKD, a recent study showed that the beneficial effect of intensive blood pressure control may be limited to CKD subjects with proteinuria.[14] Therefore, caution is required in applying this target blood pressure to CKD subjects without proteinuria.

The strengths of this study were the use of a large-scale nationwide database and the fact that the hypertensive status of this population reflected the current situation in the entire Japanese population. This study could provide useful clinical information for the treatment of subjects with CKD in Japan.

There are, however, several limitations to this study. First, single measurements of blood pressure, serum creatinine and proteinuria may have led to some misclassification of CKD and blood pressure categories. Such misclassification would probably have been nondifferential and would have biased the relationship toward the null. Therefore, there is a possibility that the observed relationship between blood pressure and CKD status may have been underestimated. Second, no detailed information was available on the antihypertensive treatments, such as the types of blood pressure-lowering drugs that were used. Third, blood pressure was measured in the morning after overnight fasting, and the values obtained in this study may differ from those measured in an outpatient clinic. Fourth, the response rate for this Specific Health Check and Guidance program was not high. This may have resulted in selection bias. Caution is required in generalizing these results to the entire Japanese population. Fifth, due to the cross-sectional nature of this study, we cannot infer the causality between blood pressure and related factors.

In conclusion, this study revealed that the majority of Japanese subjects with CKD had inadequate blood pressure control, despite using antihypertensive treatment. More aggressive efforts should be recommended in order to achieve target blood pressures in subjects with CKD.

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Association between prehypertension and chronic kidney disease in the Japanese general population

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The increased prevalence of chronic kidney disease (CKD) is a consequence of the accumulation of risk factors, one of which is hypertension. Here we assessed the prevalence of CKD according to blood pressure among 232,025 patients in a Japanese nationwide database with a focus on the prevalence and risk factors of CKD in prehypertension. Patients were stratified by blood pressure and included 75,474 with optimal blood pressure (less than 120/80 mm Hg); 59,194 with prehypertension and a normal blood pressure (120–129/80–84 mm Hg) or 46,547 patients with high-normal blood pressure (130–139/85–89 mm Hg); and 50,810 with hypertension (over 140/90 mm Hg without anti-hypertensive drugs). CKD was defined as an estimated glomerular filtration rate of stage 3 or lower or having proteinuria greater than 1+ by a dipstick method. The prevalence of CKD among patients with optimal blood pressure, prehypertension having normal or high-normal blood pressure, and hypertension was 13.9, 15.6, 18.1, and 20.7% in men, and 10.9, 11.6, 12.9, and 15.0% in women, with a significant difference between genders at each strata of blood pressure. In men, but not in women, whose blood pressure was high-normal, the CKD risk was significantly greater (odds ratio 1.11) than those with optimal blood pressure. Obesity (body mass index over 25) was significantly associated with an increased risk of CKD in both men and women (odds ratio 1.43 and 1.26, respectively), and there was an additive effect of obesity and pre-hypertension on CKD risk in men compared with men with optimal blood pressure. Thus, the prevalence of CKD increased with the severity of blood pressure. Prehypertension with high-normal blood pressure, particularly in conjunction with obesity, was found to be an independent risk factor of CKD in men.

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KEYWORDS: chronic kidney disease; high-normal blood pressure; obesity; prehypertension

Chronic kidney disease (CKD) is now recognized as a major global public health problem.[1,2] It is increasingly apparent that CKD is associated with increased risk of not only progression to renal failure but also excess cardiovascular morbidity and mortality in a manner independent of other known risk factors.[1,2]

CKD affects 10–15% of the adult population worldwide.[3,4] A recent Japanese survey demonstrated that the prevalence of CKD increased significantly in men, but not in women, from the 1970s to the 2000s in the general population.[5] The reasons are not well understood, but it is likely that the increased prevalence of CKD is a consequence of the accumulation of risk factors, such as hypertension or metabolic abnormalities including diabetes, dyslipidemia, and obesity, over the last three decades.[5] Furthermore, Japan is known to have a high incidence of end-stage renal disease, and the number of patients undergoing dialysis has been increasing.[6,7] The incidence and prevalence of end-stage renal disease are higher in men than in women in Japan.[8,9] Individuals with CKD have reduced life expectancy, and the social burden of CKD with or without end-stage renal disease is becoming greater. Accordingly, it should be a public health priority to identify CKD-prone high-risk subjects in the general population and to treat risk factors in the initial phase of CKD in order to prevent and delay the progression to renal failure. Such efforts would also help to prevent cardiovascular diseases.

Hypertension is well established as both a cause and consequence of CKD.[10–12] In Asian countries in particular, high blood pressure (BP) is the strongest risk factor for renal outcome.[10] A previous study in Japan demonstrated that there was a linear continuous association between BP and incidence of end-stage renal disease; even in subjects without hypertension (i.e., even in subjects with prehypertension: systolic BP/diastolic BP, 120–139/80–89 mm Hg), there was a greater risk of future development of end-stage renal disease compared with the risk in subjects with optimal BP (<120/80 mm Hg).[11] Given the evidence that the risk of end-stage renal disease is increased throughout the BP range, understanding the burden of CKD in subjects with prehypertension could help in promoting prevention and screening efforts for both CKD and prehypertension.[13] Recently, the National Health and Nutrition Examination Survey in the United States demonstrated that the prevalence of CKD among those with prehypertension was 17.3%, compared with 13.4% in those with optimal BP.[14] However, there has been no comparable analysis of a nationwide database in Japan.

Accordingly, in the present study, we examined the prevalence of CKD within BP classification using a large nationwide database of subjects recruited from the national health checkup system in Japan. In addition, we examined some clinical characteristics other than BP that are prone to increase risk of CKD.

RESULTS

Patient characteristics

By reviewing the data from the national health checkup program in Japan, we identified 346,942 subjects for whom all the clinical data required for the present analysis were available. A total of 84,854 subjects with a history of treatment with anti-hypertensive medications, 12,771 subjects with a previous history of cardiovascular diseases, and 17,049 subjects with both were excluded from the present analysis. Moreover, 243 subjects with CKD stage 5 (estimated glomerular filtration rate (eGFR) < 15 ml/min per 1.73 m^2) were excluded. Table 1 shows the clinical characteristics of all subjects included in the present study ($n = 232,025$, left column) or the clinical characteristics according to gender difference (right column).

BP classification

Among the study subjects, 75,474 subjects (32.5%) had optimal BP, 105,741 subjects (45.6%) had prehypertension (normal BP: 59,194 subjects, 25.5%; high-normal BP: 46,547 subjects, 20.1%), and 50,810 subjects (21.9%) had hypertension. As the prevalence of such BP classification differed between men and women, the clinical characteristics according to BP classification were described by gender (Table 2). In accordance with the severity of BP classification, significant increases of age and body mass index, and significant decrease in the prevalence of current smoking, were observed. Information about glucose and lipid parameters could be obtained in some subjects, although not all: according to the severity of BP classification, there were significant differences in the glucose and lipid parameters (Supplementary Table S1 online).

CKD and BP classification

A total of 32,692 subjects (14.1%) were diagnosed with CKD, and 8751 subjects (3.8%) had proteinuria (≥1+). There was a gender difference in the prevalence of CKD (17.0% in men versus 12.2% in women; $P<0.001$); accordingly, we determined the relationship between prevalence of CKD and BP classification separately for each gender (Table 2).

Table 1 | Characteristics of the study population overall (left column) or by gender (right column)

		Gender difference		
	Total subjects (n=232,025)	Women (n=142,293)	Men (n=89,732)	P-value
Age, years	61.8 ± 9.4	62.0 ± 9.1	61.4 ± 9.9	<0.001
Men, n (%)	89,732 (38.7)	—	89,732 (100)	<0.001
Body mass index, kg/m^2	22.6 ± 3.2	22.2 ± 3.2	23.4 ± 3.0	<0.001
Obesity, n (%)	58,061 (25.0)	29,358 (20.6)	28,703 (32.0)	<0.001
Current smoker, n (%)	36,058 (15.5)	9912 (7.0)	26,146 (29.1)	<0.001
Daily drinker, n (%)	50,495 (21.8)	12,471 (8.8)	38,024 (42.4)	<0.001
eGFR, ml/min per 1.73m^2	76.9 ± 16.0	76.9 ± 15.9	76.8 ± 16.3	0.57
CKD, n (%)	32,692 (14.1)	17,409 (12.2)	15,283 (17.0)	<0.001
Stage 1 and 2, n (%)	7041 (3.0)	3232 (2.3)	3809 (4.2)	<0.001
Stage 3, n (%)	25,547 (11.0)	14,117 (9.9)	11,430 (12.7)	
Stage 4, n (%)	104 (0.04)	60 (0.04)	44 (0.05)	
Proteinuria (≥1+), n (%)	8751 (3.8)	3948 (2.8)	4803 (5.4)	<0.001
BP measurement				
Systolic BP, mm Hg	126 ± 17	124 ± 17	128 ± 17	<0.001
Diastolic BP, mm Hg	75 ± 11	73 ± 10	77 ± 11	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data are expressed as the means ± SD or percentage. P-values were obtained by an unpaired t-test or χ^2-test between women and men. Statistical significance was defined as $P<0.05$. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2, and CKD was defined as eGFR < 60 ml/min per 1.73 m^2 and/or presence of proteinuria (≥1+). The proteinuria number in each column includes all stage 1/2 patients plus a few in stage 3/4.

Table 2 | Patient characteristics and BP values according to the BP classification by gender

	Women (*n*=142,293)					Men (*n*=89,732)				
	Optimal BP (*n*=51,715)	Prehypertension with normal BP (*n*=36,182)	Prehypertension with high-normal BP (*n*=27,348)	Hypertension (*n*=27,048)	*P*-value	Optimal BP (*n*=23,759)	Prehypertension with normal BP (*n*=23,012)	Prehypertension with high-normal BP (*n*=19,199)	Hypertension (*n*=23,762)	*P*-value
Age, years	58.8 ± 10.2	62.7 ± 8.4	64.4 ± 7.5	64.8 ± 7.2	<0.001	59.0 ± 10.7	61.0 ± 10.1	62.9 ± 9.3	63.0 ± 8.8	<0.001
Body mass index, kg/m^2	21.4 ± 2.9	22.2 ± 3.1	22.7 ± 3.2	23.2 ± 3.5	<0.001	22.5 ± 2.8	23.3 ± 2.9	23.6 ± 3.0	24.0 ± 3.1	<0.001
Obesity, *n* (%)	6775 (13.1)	7349 (20.3)	6863 (25.1)	8371 (30.9)	<0.001	5256 (22.1)	7168 (31.1)	6689 (34.8)	9590 (40.4)	<0.001
Current smoker, *n* (%)	4852 (9.4)	2234 (6.2)	1488 (5.4)	1338 (4.9)	<0.001	7953 (33.5)	6562 (28.5)	5071 (26.4)	6560 (27.6)	<0.001
Daily drinker, *n* (%)	4594 (8.9)	3120 (8.6)	2350 (8.6)	2407 (8.9)	0.33	8059 (33.9)	9428 (41.0)	8713 (45.4)	11,824 (49.8)	<0.001
eGFR, ml/min per 1.73m^2	77.8 ± 15.9	76.9 ± 15.9	76.1 ± 15.7	75.8 ± 15.8	<0.001	78.1 ± 16.5	77.0 ± 16.1	76.1 ± 16.0	76.0 ± 16.4	<0.001
CKD, *n* (%)	5619 (10.9)	4204 (11.6)	3540 (12.9)	4046 (15.0)	<0.001	3303 (13.9)	3582 (15.6)	3475 (18.1)	4923 (20.7)	<0.001
Stage 1 and 2, *n* (%)	864 (1.7)	672 (1.9)	650 (2.4)	1046 (3.9)	<0.001	729 (3.1)	799 (3.5)	814 (4.2)	1467 (6.2)	<0.001
Stage 3, *n* (%)	4774 (9.2)	3516 (9.7)	2874 (10.5)	2983 (11.0)	<0.001	2565 (10.8)	2775 (12.1)	2652 (13.8)	3438 (14.5)	<0.001
Stage 4, *n* (%)	11 (0.02)	16 (0.04)	16 (0.05)	17 (0.06)	<0.001	9 (0.03)	8 (0.03)	9 (0.04)	18 (0.07)	<0.001
Proteinuria (⩾1+), *n* (%)	1040 (2.0)	812 (2.2)	796 (2.9)	1300 (4.8)	<0.001	872 (3.7)	1003 (4.4)	1013 (5.3)	1915 (8.1)	<0.001
BP measurement										
Systolic BP, mm Hg	107 ± 8	123 ± 4	133 ± 4	149 ± 12	<0.001	109 ± 7	123 ± 4	132 ± 4	148 ± 13	<0.001
Diastolic BP, mm Hg	65 ± 7	73 ± 7	77 ± 7	85 ± 10	<0.001	67 ± 7	75 ± 6	79 ± 7	88 ± 10	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data are expressed as the means ± SD or percentage. Obesity was defined as body mass index (BMI) ⩾25 kg/m^2, and CKD was defined as eGFR <60 ml/min per 1.73 m^2 and/or presence of proteinuria (⩾1+). The proteinuria number in each column includes all stage 1/2 patients plus a few in stage 3/4.

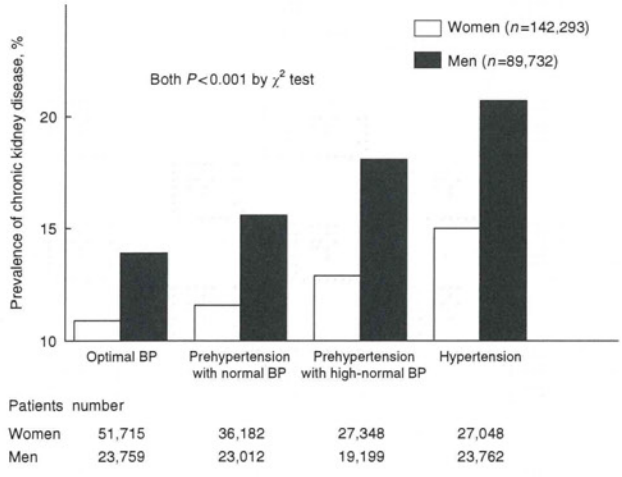

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and/or the presence of proteinuria (⩾1+).

The prevalence of CKD and/or proteinuria (⩾1+) paralleled the severity of BP classification in both genders (Figure 1). The gender difference of CKD became greater and more prominent with increasing severity of BP classification.

Using multiple logistic regression analysis, the odds ratio for the presence of CKD was estimated. Hypertension was significantly associated with CKD in both genders. In contrast, only in men, but not in women, prehypertension with high-normal BP was significantly associated with an increased risk of CKD even after adjustment for confounders, such as age, obesity, current smoking, and daily drinking (Table 3). We also reanalyzed the results of Table 3 after adjusting for serum glucose, triglyceride, high-density lipoprotein, and low-density lipoprotein levels: these factors had no influence on the association between prehypertension with high-normal BP and CKD in men (data not shown).

Lifestyle factors, obesity, and CKD

Obesity was positively associated with CKD in both genders, and eGFR was significantly decreased in the subjects with obesity compared with those without obesity (76.1 ± 16.2 versus 77.1 ± 16.0 ml/min per 1.73 m^2; $P<0.001$). When we reanalyzed the risk of CKD conferred by obesity in either the subjects with low eGFR (<60 ml/min per 1.73 m^2) or the subjects with proteinuria (⩾1+), the conclusion remained unchanged (data not shown). In contrast, daily drinking was inversely associated with CKD in both genders. Additional analysis of the subgroup of subjects for whom daily alcohol intake data were available ($n=70,416$ men and $n=75,416$ women) revealed that the inverse association between daily drinking and CKD was consistent regardless of the amount of daily intake (⩾23 g of ethanol or <23 g of ethanol) in men (odds ratio (95% confidence interval, CI): 0.77 (0.73–0.80) and 0.89 (0.84–0.95), respectively; both $P<0.001$); in women, the inverse association between daily drinking and CKD was found only in those with a daily intake of <23 g of ethanol (odds ratio (95% CI): 0.91 (0.84–0.99); $P=0.03$).

In women, current smoking status was positively associated with CKD. In contrast, among men, current smoking was inversely associated with CKD; that is, male current smokers had a significantly higher level of eGFR than current non-smokers (mean (95% CI) of eGFR: 79.0 (78.8–79.2) versus 75.9 (75.8–76.1) ml/min per 1.73 m^2; $P<0.001$). In contrast, there was no significant difference in eGFR between female current smokers and non-smokers (mean (95% CI) of eGFR: 77.0 (76.7–77.3) versus 76.9 (76.8–77.0) ml/min per 1.73 m^2; $P=0.45$). When we reanalyzed the association of current smoking with the presence

Table 3 | Odds ratio (95% confidence interval) for CKD by gender

	Women (n=142,293)		Men (n=89,732)	
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Age, 10 years	1.39 (1.37:1.42)	<0.001	1.82 (1.78:1.87)	<0.001
Obesity (0=no, 1=yes)	1.26 (1.22:1.31)	<0.001	1.43 (1.38:1.49)	<0.001
Current smoker (0=no, 1=yes)	1.34 (1.26:1.43)	<0.001	0.90 (0.86:0.94)	<0.001
Daily drinker (0=no, 1=yes)	0.92 (0.86:0.98)	0.006	0.78 (0.76:0.81)	<0.001
BP classification[a]				
Optimal BP	1 (Reference)		1 (Reference)	
Prehypertension with normal BP	0.95 (0.91:1.00)	0.03	1.01 (0.96:1.07)	0.60
Prehypertension with high-normal BP	1.02 (0.97:1.06)	0.54	1.11 (1.05:1.17)	<0.001
Hypertension	1.17 (1.12:1.23)	<0.001	1.32 (1.25:1.38)	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease.
Obesity was defined as body mass index (BMI) $\geq 25\,kg/m^2$. BP classification was defined as follows: optimal BP, systolic blood pressure (SBP) < 120 mm Hg and diastolic blood pressure (DBP) < 80 mm Hg; prehypertension with normal BP, SBP 120–129 mm Hg and/or 80–84 mm Hg; prehypertension with high-normal BP, SBP 130–139 mm Hg and/or DBP 85–89 mm Hg; hypertension, SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg. Statistical significance was defined as $P<0.05$.
[a]BP classification: Odds ratio was adjusted for age, obesity, current smoking, and daily drinking.

of proteinuria, there was a positive association between current smoking and proteinuria in both genders (odds ratio (95% CI): 1.47 (1.38–1.56) in men and odds ratio (95% CI): 1.89 (1.15–3.11) in women; both $P<0.001$).

Effect of obesity on the association between CKD and BP classification

Among subjects without hypertension ($n=181,215$), the risk of CKD conferred by prehypertension with high-normal BP increased when these conditions were accompanied by obesity ($\geq 25\,kg/m^2$) in men (Figure 2a), but not in women (Figure 2b). Accordingly, we examined whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk among subjects without hypertension. Using a multivariable logistic regression analysis, we showed that there was an additive effect, but not a synergistic one, of obesity and prehypertension with high-normal BP on CKD risk in men (data not shown). Furthermore, we also examined whether there was an interaction between obesity and hypertension ($\geq$ 140/90 mm Hg) on CKD risk among all subjects ($n=232,025$). The results showed that there was no synergistic interaction in either gender (data not shown).

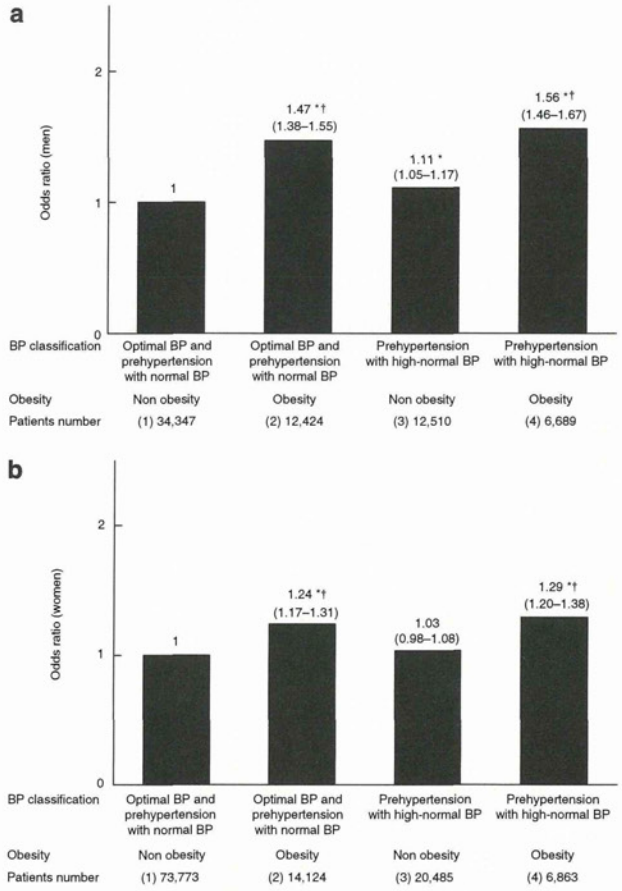

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and women (**b**). The analysis was adjusted for age, current smoking, and daily drinking. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2 and/or the presence of proteinuria ($\geq 1+$). *$P<0.001$ versus group (1) and †$P<0.001$ versus group (3).

DISCUSSION

Prehypertension and CKD

In this nationwide study of 232,025 Japanese aged 20 years or older, we have demonstrated the prevalence of CKD across the diagnostic spectrum of BP classification. In the present study, the prevalence of CKD was 17.0% in men and 12.2% in women. The prevalence was lower than a previous Japanese report,[5] because the present study excluded treated hypertensive patients. In particular, we focused on the prevalence of CKD among subjects with prehypertension (16.7% in men and 12.2% in women). The prevalence of CKD among subjects with prehypertension with high-normal BP was greater in men than in women (18.1% versus 12.9%), and prehypertension with high-normal BP was an

independent risk factor for CKD in men, but not in women, even after adjustment for confounders.

Evidence is accumulating that prehypertension, and particularly a high-normal BP range, is associated with a variety of cardiovascular diseases and cardiovascular-associated and all-cause mortality;[15–17] however, information about the association of prehypertension with CKD is scarce in Japan.[18] Much as in other previous reports worldwide,[14–16] older age, higher prevalence of men, and obesity or obesity-related metabolic abnormalities were more prevalent in subjects with prehypertension than those with optimal BP (Table 2). These characteristics could partly explain the cardiovascular risk of prehypertesion;[15–17] however, our data show that the association between CKD and prehypertension with high-normal BP in men is independent of these confounders.

The increased risk of CKD among prehypertensive subjects with high-normal BP was recognized only in men; this means that the parallel increase of CKD in accordance with the level of severity of BP begins at an earlier phase in men than in women. This gender difference cannot be fully explained by the gender differences in metabolic factors or BP itself. It is speculated that it may be related to gender-specific differences in glomerular structure, hemodynamic condition, activity of local cytokines and hormones, gene expression, and/or the effects of sex hormones on kidney cells.[9,19]

As shown in several previous reports,[10–12] hypertension ($\geqslant$140/90 mm Hg) is a clear risk factor for CKD in both the genders. In the present study, we excluded 84,854 subjects who had been treated with anti-hypertensive medication, and included 50,810 subjects who had never been treated with anti-hypertensive medication. This exclusion rate suggests that about a quarter of hypertensive subjects have not been treated for their condition. This proportion is substantially improved as compared with a previous report,[20] but more health promotion to increase awareness and treatment of hypertension is still considered necessary.

Obesity, BP, and CKD

Obesity is an independent risk factor for CKD both in men and women (Table 3). Intriguingly, our data indicate that the risk of CKD conferred by prehypertension with high-normal BP in men increased when these conditions were accompanied by obesity (Figure 2a). There was an additive effect of obesity and prehypertension with high-normal BP on CKD risk in men.

Obesity-associated glucose and lipid abnormalities could partly explain the increased risk of CKD in obesity.[21,22] However, our data show that the increased risk of CKD conferred by obesity was independent of these confounders, although there was some lack of data on glucose and lipid parameters. There remain several other possible explanations for the risk of obesity. First, unmeasured obesity-associated factors, such as insulin resistance, inflammatory and oxidative stress, and abnormal adipocytokine production, may be involved in the increased risk of CKD in obesity.[22,23] Second, obesity has a fairly consistent effect on renal hemodynamics, suggestive of glomerular hypertension.[24,25] At an early phase, obesity is associated with an elevated GFR with a less pronounced increase, or even a decrease, in effective renal plasma flow, resulting in an increased filtration rate. This alteration, that is, a predominant decrease in afferent rather than efferent glomerular tone in obese subjects, may confer enhanced renal susceptibility toward damage when BP increase is superimposed.[24,25] Obesity-induced hyperfiltration, if continued for a certain period, can cause a decline in GFR, which may be one of the reasons why our data showed that obese subjects had a lower eGFR than nonobese subjects in both genders.

Lifestyle factors and CKD

Lifestyle factors, such as smoking and drinking, are also important contributors to CKD.[26] In the present study, an inverse association between CKD and current smoking was found (Table 3), despite the fact that several previous studies have identified smoking as an important risk factor in the promotion and progression of renal dysfunction in healthy subjects or those with complications.[27,28] Our study is a cross-sectional study, and thus there may have been artifacts due to the observation of sick subjects after they have changed their lifestyles. However, the effects of smoking on eGFR are still controversial.[27,29,30] In fact, we observed that male current smokers had a higher eGFR than male non-smokers, whereas no such association was found in women. On the other hand, our present results agree with previous reports;[27,29] in that we found a positive association between smoking and proteinuria in both genders, suggesting the possibility that smoking causes endothelial dysfunction, partly through an inflammatory or oxidative pathway.[28,29] It was also unexpected that there was an inverse association between the BP increase and the prevalence of current smoking (Table 2); this may have been attributable to one of the following: (1) Some of the smokers in the hypertensive group may have had knowledge that they were hypertensive, and may have ceased to smoke on the advice of their physicians. (2) There may have been a so-called survival effect, as smokers who develop hypertension were more likely to have died and thus not to have been included in the cross-sectional study. (3) Daytime BP under daily activity would likely be more elevated in smokers compared with non-smokers, even when there is no difference in the clinical or office BP between them (i.e., masked hypertension is more prevalent in smokers).[31]

Evidence on the association between CKD and alcohol intake has been scarce. We found that subjects with a daily drinking habit had a lower likelihood of CKD compared with those who had no alcohol intake. We could not assess the kinds or total amount of alcohol; therefore, to discuss this issue is beyond the scope of the present research. Further investigation with prospective or lifestyle interventional studies, such as smoking cessation studies, are warranted to better elucidate the impact of smoking or drinking on renal outcomes.

Several limitations of our study should be mentioned. First, we cannot infer a cause–effect relationship based on our cross-sectional data. Second, only a single measurement of serum creatinine, as well as only a single assessment of proteinuria, is not fully accurate, and thus there may be an underestimation of the true association between CKD and BP level. Third, subjects who participated in the present survey were generally healthy individuals who were interested in their health; therefore, the prevalence of prehypertension/hypertension or CKD may have been underestimated. Finally, little is known about the cost-effectiveness of screening male subjects with prehypertension and high-normal BP range for CKD; therefore, an additional study is needed to identify the most appropriate populations to undergo CKD screening.

CONCLUSION

Using a nationwide Japanese database, we show an increased prevalence of CKD across the diagnostic spectrum of hypertension. Among men, even in the state of prehypertension, high-normal BP, particularly when in conjunction with obesity, was an independent risk factor for CKD. Considering the fact that the prevalence of CKD and the incidence of end-stage renal disease are increasing in Japanese men,[5,8,9] these data have important clinical implications; as CKD is often asymptomatic but progressive, more attention must be paid to men and women with hypertension or obesity and to men even with high-normal BP for the early detection and prevention of CKD, or to delay the progression to renal failure.

MATERIALS AND METHODS

Study population

The methods of the study are detailed in the Supplementary Information section online. Briefly, based on a recent survey that showed that obesity and metabolic syndrome are not uncommon in Japan (http://www-bm.mhlw.go.jp/houdou/2008/04/h0430-2.html), the Japanese government started a new health-care strategy that targeted early diagnosis and intervention for metabolic syndrome from 2008 (Specific Health Checkups and Guidance System (Tokutei-Kensin)). In this new health-care system, people diagnosed with metabolic syndrome are obligated to receive repeated lifestyle guidance over a 6-month period after an annual health examination.

Thirteen of the prefectures participating in this nationwide project (Yamagata, Miyagi, Fukushima, Niigata, Tokyo, Kanagawa, Ibaraki, Osaka, Okayama, Kochi, Fukuoka, Miyazaki, and Okinawa) agreed on our study purpose and were included in the present analysis. The population surveyed included a total of 346,942 subjects (41% ($n = 141{,}938$) were men) above 20 years of age, for whom all the data necessary for our research purposes were available—namely, information about age, gender, BP, body mass index, habitual smoking or drinking, use of anti-hypertensive drugs, previous history of cardiovascular diseases (i.e., cardiac disease and stroke), and data about the serum creatinine level and dipstick urine test for proteinuria. This study was granted ethics approval from the respective institutional review boards. Data were sent to an independent data center called the NPO Japan Clinical Research Support Unit, and verified by trained staff.

Baseline measurement

At the baseline examination, all subjects completed a self-administered questionnaire about lifestyle factors (current smoking status, daily drinking), and provided medical information on treatment with anti-hypertensive drugs and a previous history of cardiac disease or stroke. The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information.

According to the recommendations of the Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by trained observers using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs not crossed. Conversation and alcohol/caffeine consumption should also be avoided before measurement. Subjects were classified according to their BP level as follows: optimal BP (systolic BP/diastolic BP $< 120/80$ mm Hg), prehypertension[32] that comprises normal BP (systolic BP 120–129 mm Hg, diastolic BP 80–84 mm Hg or both) and high-normal BP (systolic BP 130–139 mm Hg, diastolic BP 85–89 mm Hg or both), and treated or untreated hypertension (systolic BP/diastolic BP $\geqslant 140/90$ mm Hg or usage of anti-hypertensive medication).[33]

Body height and weight were measured in light clothing without shoes, and the body mass index was calculated (kg/m^2). According to the Japan Society for the Study of Obesity,[34] obesity was defined as a body mass index $\geqslant 25$ kg/m^2.

Blood samples were collected after an overnight fast and were assayed within 24 h. For the purpose of our study, there were no missing data on the serum creatinine level, but there was a substantial lack of data on the glucose and lipid parameters (Supplementary Table S1 online). Freshly voided urine samples were tested by the dipstick methods in all subjects. Proteinuria was defined as 1+ or more.

Definition of CKD

Serum creatinine was assayed by an enzymatic method. eGFR was derived using the following equation:

$$\text{eGFR (ml/min per 1.73 m}^2) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094} \text{ (if women } \times 0.739).$$[35]

Details about this equation are also shown in the Supplementary Information section. CKD was defined as either the presence of proteinuria or eGFR < 60 ml/min per 1.73 m^2. The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines[36]: Stage 1 or 2 (eGFR $\geqslant 60$ ml/min per 1.73 m^2 and the presence of proteinuria), Stage 3 (eGFR 30–59 ml/min per 1.73 m^2), Stage 4 (eGFR 15–29 ml/min per 1.73 m^2), and Stage 5 (eGFR $<$ 15 ml/min per 1.73 m^2).

Statistical analysis

All statistical analyses were performed with the SPSS version 18.0J software (SPSS, Chicago, IL). The differences of patient characteristics and BP values according to the BP classification were assessed using analysis of variance, and categorical parameters were compared with the χ^2-test. As there is a significant gender difference in the prevalence of CKD, we examined the association between CKD and the severity of BP classification separately in men and women. The odds ratio and 95% CI of each BP classification group (optimal BP group (reference) versus prehypertension with normal BP, prehypertension with high-normal BP, and untreated hypertension group) were calculated for the presence of CKD by multiple