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 m^2 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]

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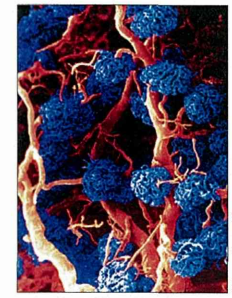

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Luxia Zhang and colleagues[1] report the prevalence of chronic kidney disease (CKD) in a Chinese nationwide survey (n=47 204, mean age 50 years). Surprisingly, compared with our nationwide Japanese survey (n=232 025, mean age 62 years),[2] the mean estimated glomerular filtration rate (eGFR) in Zhang and colleagues' survey is much higher (101 *vs* 77 mL/min/1·73 m^2), 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 m^2) 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/m^2). 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 m^2), and with albuminuria were 41 165, 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 42 757 ([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.

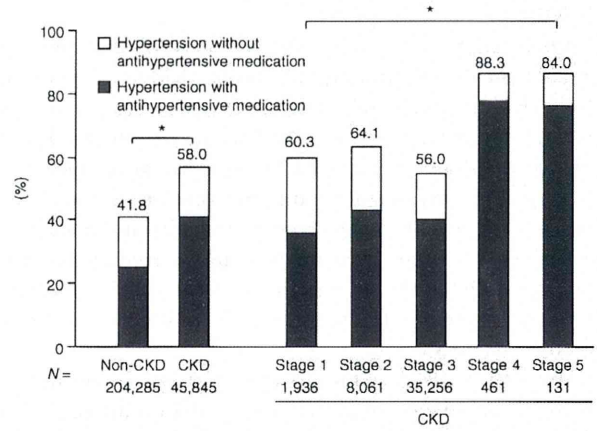

Figure 1 | The prevalence of hypertension in CKD and non-CKD subjects. *$P < 0.001$ by χ^2-test. CKD, chronic kidney disease.

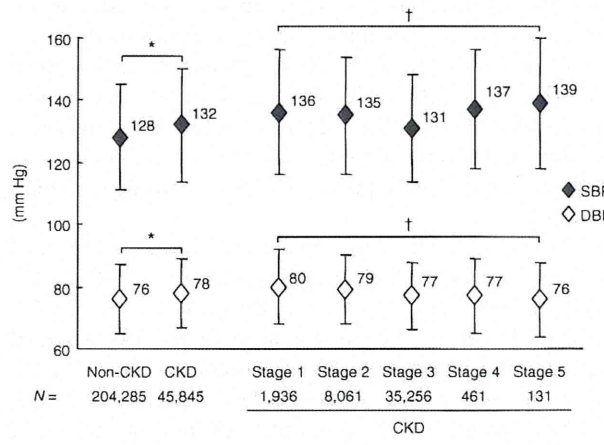

Figure 2 | Blood pressures levels in CKD and non-CKD subjects. *$P < 0.001$ by unpaired *t*-test, †$P < 0.001$ by analysis of variance. Data are mean ± s.d. CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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

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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.