renal failure, stage 3 was further divided into stages 3A (eGFR 45–59) and 3B (eGFR 30–44).

Statistical analyses

Unpaired *t* tests were used to compare mean values, and chi-square tests were used to evaluate differences in proportions. The trend in proportions was examined by chi-square test. To examine the factors associated with CVD (stroke and heart disease), unadjusted and adjusted multivariate logistic regression analyses were performed, including age, gender, alcohol consumption, smoking, hypertension, diabetes, metabolic syndrome, proteinuria, renal insufficiency and past history of renal failure as independent variables. Continuous data are expressed as mean ± SD. All statistical analyses were performed using JMP version 8 software (SAS Institute Inc., Cary, NC). Differences were regarded as significant when *P* values were <0.05.

Results

Characteristics of subjects in the general population with a past history of renal failure

Among the 250,130 participants, there were 650 men and 750 women with a past history of renal failure (a total of 1,400 subjects, 0.6% of all participants, 1.5% of the subjects with CKD). Subjects with a history of renal failure were more likely to be older, to be male, obese, and have CKD, hypertension, diabetes, metabolic syndrome, hematuria (≥1+), proteinuria (≥1+), a past history of CVD (stroke and heart disease), to have received treatment for hypertension, diabetes or dyslipidemia, and less likely to be smokers compared with the 248,730 subjects without a history of renal failure (Table 1). The subjects with a history of renal failure were mostly aged over 40 years (mean age 64.5 years); as percentages of all participants, 0.1% were <40 years, 0.5% were 40–49 years, 0.5% were 50–59 years, 0.5% were 60–69 years and 0.7% were ≥70 years.

The association between CKD and a past history of renal failure

The prevalence of a history of renal failure was higher in the CKD population than in the population without CKD (1.5 vs. 0.3%, $P < 0.001$) and increased with progression of the stage of CKD: 0.9% in stage 1, 1.0% in stage 2, 1.3% in stage 3 (0.9% in stage 3A and 5.4% in stage 3B), and 23.2% in stage 4 and 43.5% in stage 5 (*P* for trend <0.001) (Fig. 1).

The distribution of eGFR in subjects with a history of renal failure and subjects with other common disorders was

Table 1 The characteristics of participants with and without past history of renal failure

	Past history of renal failure		
	(+)	(−)	*P* value
Number (%)	1,400 (0.6%)	248,730 (99.4%)	
Age (years)	64.5 ± 8.2	63.6 ± 8.7	<0.001
Male (%)	46.4	40.4	<0.001
Serum creatinine (mg/dl)	1.16 ± 1.27	0.72 ± 0.22	<0.001
eGFR (ml/min/1.73 m^2)	60.6 ± 23.6	75.2 ± 16.1	<0.001
CKD (%)	50.6	18.2	<0.001
Hypertension (%)	60.8	44.7	<0.001
Diabetes (%)	15.4	9.3	<0.001
Dyslipidemia (%)	57.4	55.4	0.123
Drinker (%)	37.6	45.4	<0.001
Smoker (%)	13.1	13.7	0.515
Obesity (%)	29.5	25.5	<0.001
Metabolic syndrome (%)	13.7	11.2	0.002
Hematuria ≥1+ (%)	27.9	17.1	<0.001
Proteinuria ≥1+ (%)	25.6	5.5	<0.001
Past history of CVD (%)	31.9	9.0	<0.001
Past history of stroke (%)	19.6	3.5	<0.001
Past history of heart disease (%)	24.9	6.1	<0.001
Treatment in hypertension (%)	49.3	29.5	<0.001
Treatment in diabetes (%)	11.5	5.2	<0.001
Treatment in dyslipidaemia (%)	23.4	17.2	<0.001

Mean ± SD

eGFR estimated glomerular filtration rate, *CKD* chronic kidney disease, *CVD* cardiovascular disease (stroke and heart disease)

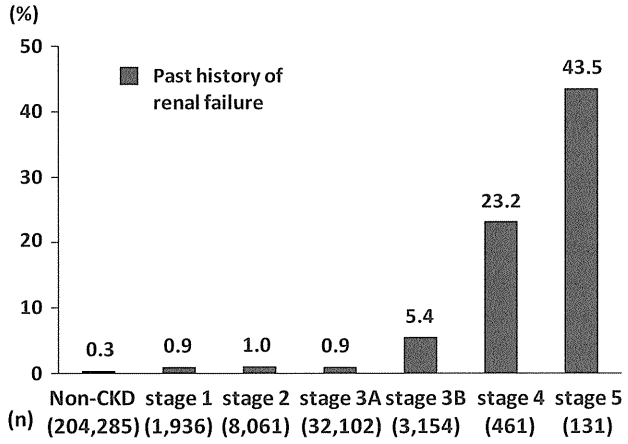

Fig. 1 The prevalence of a history of renal failure according to stage of CKD. *CKD* chronic kidney disease

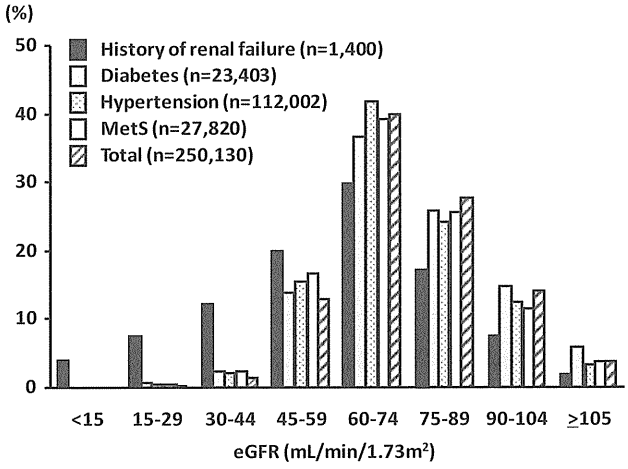

Fig. 2 The distribution of eGFR in subjects with a history of renal failure and subjects with other common disorders. *eGFR* estimated glomerular filtration rate, *MetS* metabolic syndrome

examined. The eGFR distribution was shifted to the low range in subjects with a history of renal failure, as compared to those with hypertension, metabolic syndrome or diabetes (Fig. 2). The prevalence of proteinuria (≥1+) was higher in subjects with a history of renal failure (25.6%), as compared with the total population (5.5%), those with metabolic syndrome (13.0%), those with hypertension (8.5%) and those with diabetes (14.4%). Furthermore, high grade proteinuria (≥2+) was frequently observed in subjects with a history of renal failure.

The prevalence of CKD in subjects with various disorders was investigated. Subjects with a history of renal failure had a higher prevalence of CKD (50.5%) as compared with the total population (18.3%), those with metabolic syndrome (22.6%), those with hypertension (23.8%) and those with diabetes (26.9%) (Fig. 3). Although the prevalence of early stages of CKD (stages 1–3A) was

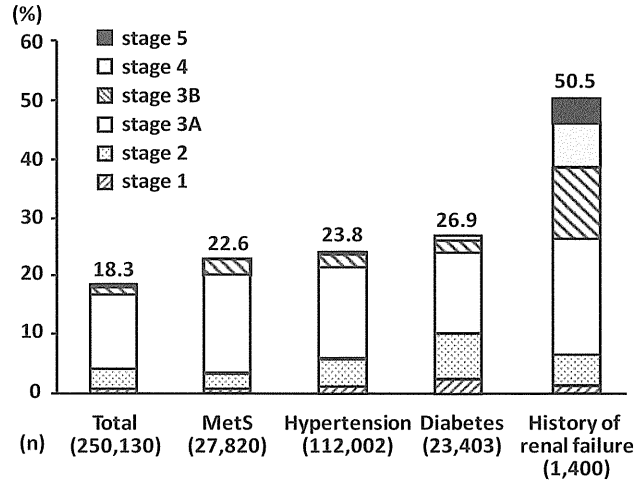

Fig. 3 The proportion of CKD stages. *MetS* metabolic syndrome

similar between subjects with different disorders (20.0–26.7%), the prevalence of advanced CKD (stages 3B–5) was much higher in subjects with a history of renal failure (23.8%), compared to those with other disorders (2.6–3.1%).

In addition, the significance of a history of renal failure among the population with CKD was investigated. Among the total of 45,845 subjects with CKD, there were 406 men and 302 women with a history of renal failure (a total of 708 subjects). As compared with the 45,137 subjects without a history of renal failure, subjects with a history of renal failure were more likely to be male, to have a lower eGFR (44.6 ± 20.3 vs. 58.4 ± 14.1 ml/min/1.73 m^2, $P < 0.001$) and a higher prevalence of hypertension, diabetes, hematuria (≥1+), proteinuria (≥1+), a history of CVD (stroke and heart disease), to have received treatment for hypertension, diabetes or dyslipidemia, and were less likely to consume alcohol (Table 2). The proportion of subjects with optimal blood pressure control for CKD (<130/80 mmHg) did not differ significantly between those with or without a history of renal failure (34.1 vs. 34.6%, $P = 0.833$).

The association between a past history of cardiovascular disease and renal failure

Finally, the relationship between a past history of CVD (stroke and heart disease) and renal failure was examined. The subjects with a history of renal failure had a higher prevalence of CVD (31.9%) as compared with the total population (9.1%), those with metabolic syndrome (12.1%), those with hypertension (13.7%) and those with diabetes (14.8%) (Fig. 4). Logistic regression analyses showed that a past history of CVD was independently associated with proteinuria, renal insufficiency (eGFR

Table 2 The characteristics of participants with and without past history of renal failure among CKD population

	Past history of renal failure		
	(+)	(−)	*P* value
Number (%)	708 (1.5%)	45,137 (98.5%)	
Age (years)	66.3 ± 6.7	66.3 ± 6.9	0.83
Male (%)	57.3	51.8	0.004
Systolic BP (mmHg)	132.4 ± 18.5	131.9 ± 17.7	0.454
Diastolic BP (mmHg)	76.8 ± 11.0	77.6 ± 10.8	0.079
Serum creatinine (mg/dl)	1.63 ± 1.65	0.93 ± 0.38	<0.001
eGFR (ml/min/1.73 m^2)	44.6 ± 20.3	58.4 ± 14.1	<0.001
Hypertension (%)	75	57.8	<0.001
Diabetes (%)	19.2	13.6	<0.001
Dyslipidemia (%)	59.2	61.7	0.168
Drinker (%)	34.6	45.7	<0.001
Smoker (%)	10.7	12.8	0.111
Obesity (%)	31.8	32.7	0.595
Metabolic syndrome (%)	17.1	17.4	0.841
Hematuria ≥1+ (%)	35.9	20.5	<0.001
Proteinuria ≥1+ (%)	50.7	30.2	<0.001
BP <130/80 (mmHg)	34.1	34.6	0.833
Past history of CVD (%)	29.2	13.6	<0.001
Past history of stroke (%)	12.9	5.7	<0.001
Past history of heart disease (%)	21.5	9.2	<0.001
Treatment in hypertension (%)	66	42	<0.001
Treatment in diabetes (%)	15.1	8.2	<0.001
Treatment in dyslipidemia (%)	26.1	21.4	0.003

Mean ± SD

CKD chronic kidney disease, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease

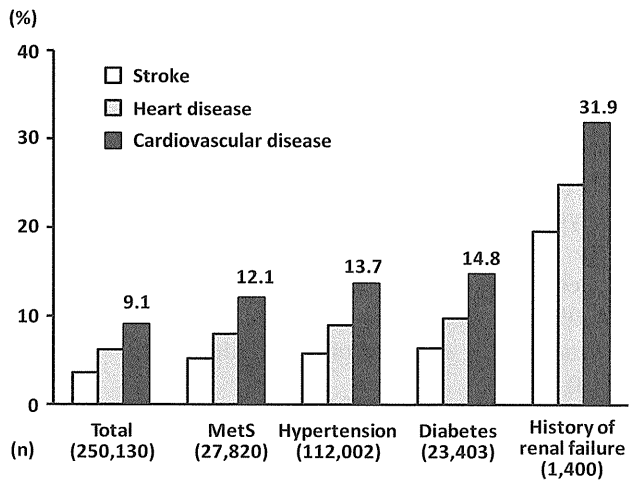

Fig. 4 The prevalence of a history of cardiovascular disease. *CVD* cardiovascular disease (stroke and heart disease), *MetS* metabolic syndrome

<60 ml/min/1.73 m^2) and a history of renal failure, both in unadjusted and adjusted models. In the adjusted model that included possible confounders, the odds ratio (OR) for CVD and a history of renal failure [OR 3.68, 95% confidence interval (CI) 3.26–4.15] was greater than those for CVD and proteinuria (OR 1.16, 95% CI 1.10–1.22) or CVD and eGFR <60 ml/min/1.73 m^2 (OR 1.32, 95% CI 1.27–1.36) (Table 3).

Discussion

This study showed, for the first time, that the proportion of subjects who had a past history of renal failure was low at health checkup; however, they had a high prevalence of advanced stages of CKD, a history of cardiovascular events and risk factors for atherosclerosis.

Several studies reported that the prevalence of a previous diagnosis of renal failure in the general population, irrespective of severity and time course (acute or chronic), was 2.0% in the United States [10] and 3.3% in Italy [11]. Other studies documented a higher prevalence of family history of kidney disease (17–24%) [4] or end-stage renal disease (9.5%) [5]. The present study, which focused on severe kidney disease (renal failure or requirement for dialysis therapy), showed that the prevalence (0.6%) was much less than those reported in previous studies and was closer to the prevalence of acute kidney disease, as identified in the International Classification of Diseases (ICD) [12]. Although the prevalence of a history of kidney disease varies, depending on the criteria used, our finding

Table 3 Factors related with the past history of cardiovascular diseases

	Unadjusted		Adjusted[a]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Proteinuria (≥1+)	1.75 (1.67–1.84)	<0.001	1.16 (1.10–1.22)	<0.001
eGFR <60 (ml/min/1.73 m^2)	1.87 (1.81–1.93)	<0.001	1.32 (1.27–1.36)	<0.001
Past history of renal failure	4.74 (4.23–5.31)	<0.001	3.68 (3.26–4.15)	<0.001

OR odds ratio, *eGFR* estimated glomerular filtration rate

[a] Adjusted with age, gender, drinking, smoking, hypertension, diabetes and metabolic syndrome

showed that the number of subjects with a past history of renal failure, who might require further examination for advanced CKD and CVD, is small and could be easily identified at health checkup.

Subjects with a history of renal failure were not only likely to have CKD, but also to have CVD and multiple risk factors for atherosclerosis, including male gender, hypertension and metabolic syndrome. Therefore, these subjects should be regarded as a high-risk population both for end-stage renal disease and CVD. However, a history of renal failure was not emphasized in health checkups in Japan, and blood pressure was optimally controlled (<130/80 mmHg) [13] in only one-third of these subjects. An Italian study reported that the evaluation and treatment of kidney disease by general physicians was likely to be suboptimal [14, 15]. These findings suggest that the management of a majority of subjects with CKD may be inadequate, and that aggressive evaluation and treatment of kidney disease should be encouraged.

Of note, a history of renal failure was independently associated with cardiovascular events, with a greater odds ratio than those for other renal indices such as proteinuria and renal insufficiency. Due to the cross-sectional nature of this study, it is not possible to infer a causal relationship; however, there is a possibility that renal failure might directly affect the development of cardiovascular events, or vice versa. The causal relationship between these factors should be clarified by a longitudinal investigation.

This study had several strengths. First, we focused on information regarding a past history of renal failure that was readily obtained at health checkup and shows a strong association with advanced CKD and CVD. Currently, the measurement of serum creatinine is not mandatory at health checkup, mainly due to the low cost-effectiveness. Consequently, serum creatinine is not determined in more than half of participants. This causes advanced CKD subjects without urine abnormalities to be overlooked. Although the past history of renal failure cannot cover the whole population of CKD and CVD, it could be a help to find occult subjects with advanced stages of CKD without extra effort and cost. Second, we utilized a large nationwide database that reflects the current health status of the entire Japanese population. This enabled us to analyze the characteristics of the target population in detail and to obtain useful clinical information for the detection of individuals at high-risk of CKD and CVD. In previous reports the incidence rate of end-stage renal disease among individuals with AKI was 2.6–2.8 per 100 person-years [16, 17]. In a referred CKD cohort 44.9% of CKD patients had at least one AKI episode [18]. Consistent with these reports that acute kidney injury is the risk factor of end-stage renal disease, half of the subjects with a history of renal failure had CKD in this study. However, it is of interest that the other half of them showed no sign of CKD. This indicates that the population with a history of renal failure is heterogeneous and should be treated individually.

This study also had some limitations that should be noted. First, the single measurements of clinical parameters may have led to some misclassification of comorbidities, including CKD. Such misclassification would probably have been non-differential and would have biased the relationship toward null. Therefore, there is a possibility that the strength of the observed relationship between a history of renal failure and various parameters may have been underestimated. Second, there was no detailed information available on the cause and clinical course of kidney disease. The observed relationship may be affected by the etiology and treatment of kidney disease. Third, there may have been a selection bias in that the study population was comprised of relatively healthy local inhabitants. Therefore, caution is required in generalizing these findings to other populations.

In conclusion this study showed that a past history of renal failure was strongly associated with current CKD and CVD. Information on past history of renal failure could be utilized for the efficient detection of high-risk individuals for end-stage renal disease and CVD at health checkup.

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Conflict of interest None of the authors has a conflict of interest to declare.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
2. Kiberd BA, Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. BMJ. 1995;311:1595–9.
3. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA. 2003;290:3101–14.
4. Jolly SE, Burrows NR, Chen SC, Li S, Jurkovitz CT, Narva AS, et al. Racial and ethnic differences in albuminuria in individuals with estimated GFR greater than 60 mL/min/1.73 m^2: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2010;55:S15–22.
5. McClellan W, Speckman R, McClure L, Howard V, Campbell RC, Cushman M, et al. Prevalence and characteristics of a family history of end-stage renal disease among adults in the United States population: Reasons for Geographic and Racial Differences in Stroke (REGARDS) renal cohort study. J Am Soc Nephrol. 2007;18:1344–52.
6. Brown WW, Peters RM, Ohmit SE, Keane WF, Collins A, Chen SC, et al. Early detection of kidney disease in community settings: the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2003;42:22–35.
7. Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome (in Japanese). Nippon Naika Gakkai Zasshi. 2005;94:794–809.
8. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
9. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
10. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. J Am Soc Nephrol. 2005;16:180–8.
11. Cirillo M, Laurenzi M, Mancini M, Zanchetti A, Lombardi C, De Santo NG. Low glomerular filtration in the population: prevalence, associated disorders, and awareness. Kidney Int. 2006;70:800–6.
12. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21:1757–64.
13. Japanese Society of Nephrology. Evidence-based practice guideline for the treatment of CKD. Clin Exp Nephrol. 2009;13:537–66.
14. Minutolo R, De Nicola L, Mazzaglia G, Postorino M, Cricelli C, Mantovani LG, et al. Detection and awareness of moderate to advanced CKD by primary care practitioners: a cross-sectional study from Italy. Am J Kidney Dis. 2008;52:444–53.
15. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010;55:441–51.
16. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20:223–8.
17. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA. 2009;302:1179–85.
18. Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrol Dial Transplant. 2010;25:2203–9.

see commentary on page 229

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.

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.

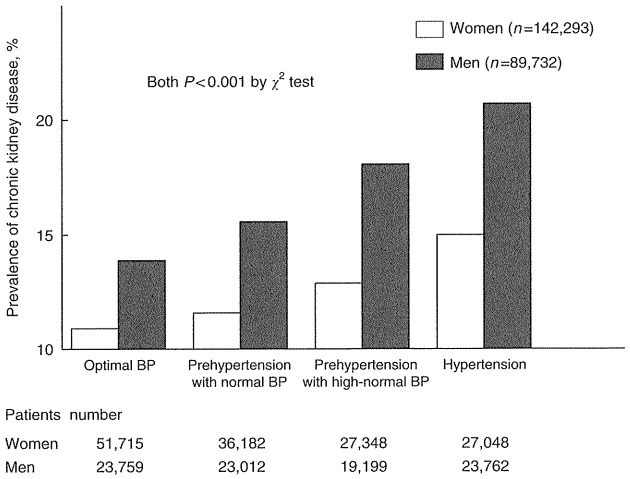

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined 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) $\geqslant$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 $\geqslant$140 mm Hg and/or DBP $\geqslant$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 ($\geqslant$25 kg/m^2) in men (Figure 2a), but not in women (Figure 2b). Accordingly, we examined whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk among subjects without hypertension. Using a multivariable logistic regression analysis, we showed that there was an additive effect, but not a synergistic one, of obesity and prehypertension with high-normal BP on CKD risk in men (data not shown). Furthermore, we also examined whether there was an interaction between obesity and hypertension ($\geqslant$140/90 mm Hg) on CKD risk among all subjects ($n=232,025$). The results showed that there was no synergistic interaction in either gender (data not shown).

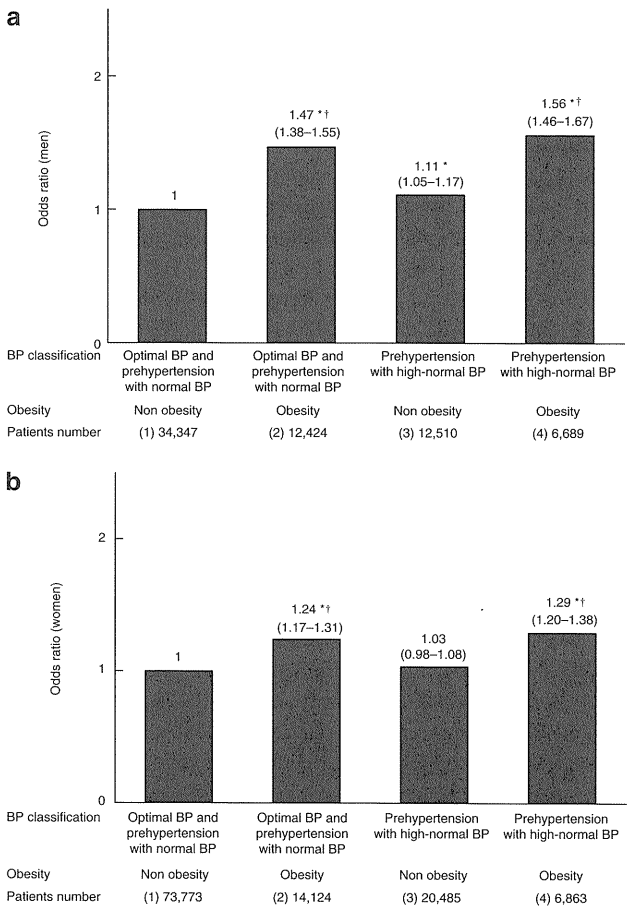

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and 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 ($\geqslant$1+). *$P<0.001$ versus group (1) and $^{\dagger}P<0.001$ 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

logistic regression analysis. Finally, we used a multivariable logistic regression analysis to examine the effect of obesity on the association between CKD and BP classification, as well as whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk. Statistical significance was defined as $P<0.05$.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Table S1. Glucose and lipid parameters according the BP classification by gender.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Levey AS, Atkins R, Coresh J *et al.* Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; **72**: 247–259.
2. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation* 2007; **116**: 85–97.
3. Imai E, Horio M, Watanabe T *et al.* Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol* 2009; **13**: 621–630.
4. Hall YN, Hsu CY, Iribarren C *et al.* The conundrum of increased burden of end-stage renal disease in Asians. *Kidney Int* 2005; **68**: 2310–2316.
5. Nagata M, Ninomiya T, Doi Y *et al.* Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: the Hisayama Study. *Nephrol Dial Transplant* 2010; **25**: 2557–2564.
6. Nakai S, Masakane I, Akiba T *et al.* Overview of regular dialysis treatment in Japan as of 31 December 2006. *Ther Apher Dial* 2008; **12**: 428–456.
7. Imai E, Matsuo S, Makino H *et al.* Chronic Kidney Disease Japan Cohort study: baseline characteristics and factors associated with causative diseases and renal function. *Clin Exp Nephrol* 2010; **14**: 558–570.
8. Iseki K, Iseki C, Ikemiya Y *et al.* Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996; **49**: 800–805.
9. Iseki K. Gender differences in chronic kidney disease. *Kidney Int* 2008; **74**: 415–417.
10. O'Seaghdha CM, Perkovic V, Lam TH *et al.* Blood pressure is a major risk factor for renal death: an analysis of 560 352 participants from the Asia-Pacific region. *Hypertension* 2009; **54**: 509–515.
11. Iseki K, Ikemiya Y, Kinjo K *et al.* Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int* 2004; **65**: 1870–1876.
12. Yamagata K, Ishida K, Sairenchi T *et al.* Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; **71**: 159–166.
13. Kiberd B. The chronic kidney disease epidemic: stepping back and looking forward. *J Am Soc Nephrol* 2006; **17**: 2967–2973.
14. Crews DC, Plantinga LC, Miller 3rd ER *et al.* Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension* 2010; **55**: 1102–1109.
15. Pimenta E, Oparil S. Medscape. Prehypertension: epidemiology, consequences and treatment. *Nat Rev Nephrol* 2001; **6**: 21–30.
16. Ishikawa Y, Ishikawa J, Ishikawa S *et al.* Prehypertension and the risk for cardiovascular disease in the Japanese general population: the Jichi Medical School Cohort Study. *J Hypertens* 2010; **28**: 1630–1637.
17. Kalaitzidis RG, Bakris GL. Prehypertension: is it relevant for nephrologists? *Kidney Int* 2010; **77**: 194–200.
18. Ninomiya T, Kubo M, Doi Y *et al.* Prehypertension increases the risk for renal arteriosclerosis in autopsies: the Hisayama Study. *J Am Soc Nephrol* 2007; **18**: 2135–2142.
19. Iseki K, Iseki C, Ikemiya Y *et al.* Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996; **49**: 800–805.
20. Tanaka T, Okamura T, Yamagata Z *et al.* Awareness and treatment of hypertension and hypercholesterolemia in Japanese workers: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. *Hypertens Res* 2007; **30**: 921–928.
21. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol* 2007; **2**: 550–562.
22. Guarnieri G, Zanetti M, Vinci P *et al.* Metabolic syndrome and chronic kidney disease. *J Ren Nutr* 2010; **20**(5 Suppl): S19–S23.
23. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004; **15**: 2792–2800.
24. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension* 1995; **26**: 610–615.
25. Krikken JA, Bakker SJ, Navis GJ. Role of renal haemodynamics in the renal risks of overweight. *Nephrol Dial Transplant* 2009; **24**: 1708–1711.
26. Appel LJ. Lifestyle modification as a means to prevent and treat high blood pressure. *J Am Soc Nephrol* 2003; **14**(7 Suppl 2): S99–S102.
27. Ishizaka N, Ishizaka Y, Toda E *et al.* Association between cigarette smoking and chronic kidney disease in Japanese men. *Hypertens Res* 2008; **31**: 485–492.
28. Orth SR. Effects of smoking on systemic and intrarenal hemodynamics: influence on renal function. *J Am Soc Nephrol* 2004; **15**(Suppl 1): S58–S63.
29. Sauriasari R, Sakano N, Wang DH *et al.* C-reactive protein is associated with cigarette smoking-induced hyperfiltration and proteinuria in an apparently healthy population. *Hypertens Res* 2010; **33**: 1129–1136.
30. Shankar A, Klein R, Klein BE. The association among smoking, heavy drinking, and chronic kidney disease. *Am J Epidemiol* 2006; **164**: 263–271.
31. Mann SJ, James GD, Wang RS *et al.* Elevation of ambulatory systolic blood pressure in hypertensive smokers. A case-control study. *JAMA* 1991; **265**: 2226–2228.
32. Chobanian AV, Bakris GL, Black HR *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
33. Ogihara T, Kikuchi K, Matsuoka H *et al.* The Japanese society of hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
34. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–992.
35. Matsuo S, Imai E, Horio M *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
36. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(2 Suppl 1): S1–S266.

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ORIGINAL ARTICLE

Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among participants of the Specific Health Check and Guidance System in Japan 2008

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Abstract
Background Estimated glomerular filtration rate (eGFR) and albuminuria (proteinuria) are both important determinants of the risk of cardiovascular disease (CVD), end-stage renal disease (ESRD), and mortality. Few studies, however, have examined the risk factor profiles based on eGFR and proteinuria among the general population.
Methods Data of the newly developed nationwide screening program of the Specific Health Check-up and Guidance System (Tokutei-Kensin) initiated in 2008 were used in this study. The aim of this screening, targeting people 40–74 years of age, was to detect those with metabolic syndrome and to offer those services regarding lifestyle modifications that will lead to the reduction of diabetes mellitus (DM) and DM-related ESRD. Individual records of 580,000 participants in 69 cities and towns and 3 union cohorts throughout Japan were anonymously provided and included in the present study.
Results Details of 332,174 participants (57.3% of the total) with both serum creatinine and dipstick urine test data were analyzed. Mean (SD) age was 63.6 (8.3) years and 40.6% were men. The mean (SD) eGFR was 75.0 (16.2) ml/min/1.73 m^2 and 5.4% had proteinuria. The prevalence of chronic kidney disease (CKD) stage 3, 4, and 5 was 14.2%, 0.2%, and 0.07%, respectively. The prevalence of DM, hypertension, and history of stroke and heart disease was correlated with the combination of eGFR and degree of proteinuria.
Conclusion The findings of the present study indicate that CKD and risk factors for CVD are quite common among middle-aged Japanese. CKD classification based on eGFR and proteinuria may be useful for predicting CVD, mortality rate, and ESRD in the Japanese population.

Keywords eGFR · CKD · Screening · Proteinuria · Epidemiology

Introduction

Chronic kidney disease (CKD) is a common condition and is a risk factor for developing cardiovascular disease (CVD) and end-stage renal disease (ESRD) [1]. Both the prevalence and incidence of treated ESRD are very high in Japan [2]. Furthermore, the incidence and prevalence continue to increase, despite several preventive strategies aimed at early detection and treatment of CKD. Japan has a long history of universal screening, a program that might facilitate the early detection of CKD [3]. A higher mean age at the start of dialysis can be interpreted as delaying the progression of CKD, but it may also simply reflect the increase in the elderly population and longevity. Dipstick proteinuria is a strong predictor of developing ESRD in a setting of community-based screening [4]. Delayed visits to the nephrology clinic result in an inevitable initiation of

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dialysis with a short duration of follow-ups [5, 6]. Such 'late referral' negatively impacts survival after dialysis is initiated. Preliminary results of the Japanese Society Dialysis Therapy support the notion that the longer the duration of pre-ESRD treatment, the better the survival. Because CKD remains asymptomatic until the late stages, effective strategies for the early detection and treatment of CKD are necessary.

The increasing prevalence of obesity and diabetes mellitus (DM) has become the leading cause of ESRD. A specific nationwide health check-up and guidance system, called Tokutei-Kenshin, was initiated in April 2008 in Japan (The Ministry of Health, Labour and Welfare; http://www-admin@.mhlw.go.jp). The aim of this project is to detect metabolic syndrome and if confirmed, to provide individual instruction to modify lifestyle and the necessary treatment. The target population comprises Japanese citizens between the ages of 40–74 years. Data on the prevalence of risk factors for developing CKD, ESRD, and CVD are limited to the Japanese population. In the present study, we examined the demographics of participants of the newly developed screening system in Japan. Risk factor profiles were examined according to the new CKD classification based on the combination of estimated glomerular filtration rate (eGFR) and dipstick proteinuria findings [7]. Results of dipstick proteinuria were categorized into three groups: (−) and (±), 1+, and ≥2+. The present study provides the baseline characteristics for the future outcome study as the unique identification number was set by the government.

Methods

Individual records for 580,000 participants in 12 communities or prefectures were anonymously provided and included in this analysis. Among these participants, subjects with data for both serum creatinine and dipstick proteinuria were selected for this study. A test was mandatory for dipstick proteinuria, but not for serum creatinine. Therefore, rates of measurement of serum creatinine differ among cohorts or prefectures. Databases included in this study were from Yamagata, Miyagi, Fukushima, Ibaraki, Tokyo, Kanagawa, Niigata, Osaka, Okayama, Kochi, Fukuoka, Miyazaki and Okinawa, and ethical approval was obtained from the respective institute review boards. Data were sent to a data center called the NPO Japan Clinical Research Support Unit to be verified. Outliers were deleted through winsorization and accounted for 0.01–0.1% of the total. Eligible participants visited a pre-assigned clinic or hospital and responded to a questionnaire regarding past history of stroke, cardiac disease, kidney disease, lifestyle habits such as smoking, alcohol intake, walking, etc., and medications for hypertension, DM, and dyslipidemia. Screening participants are eligible for public support for the standard health checks, such as measurement of height, weight, waist circumference, blood pressure, fasting blood glucose, hemoglobin A1c, triglyceride, serum high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, glutamyl oxaloacetic transaminase, glutamate pyruvate transaminase, gamma-glutamyl transpeptidase, hemoglobin, uric acid, serum creatinine, dipstick urine test for proteinuria, hematuria, and glucosuria. Proteinuria was coded as (−), (±), (1+), (2+), and (3+). Serum creatinine was measured using the enzymatic method. Glomerular filtration rate was calculated using the formula of the Japanese Society of Nephrology [8]. Reference levels for triglyceride, HDL cholesterol, LDL cholesterol, uric acid, fasting blood glucose, and hemoglobin A1c were set at 150, 40, 7, 110 mg/dl, and 6.1%, respectively. Blood pressure was measured in all cohorts using a standard sphygmomanometer. Hypertension was defined as ≥140/90 mmHg or on antihypertensive medication. DM was defined as hemoglobin A1c ≥6.1% or on medication for DM. Obesity was defined as body mass index (BMI) ≥25 kg/m^2.

Statistical analysis

Data were analyzed with SAS/STAT software (version 6.03, SAS Institute, Tokyo, Japan). Student's *t* test and the Chi-squared test were performed to compare the significance of discrete variables. A *P* value of less than 0.05 was considered statistically significant in all analyses.

Results

Demographics of the screened subjects are summarized in Table 1. The prevalence of CKD (i.e., eGFR <60 ml/min/1.73 m^2) was as high as 14.2%. Compared to national statistics, smoking rates were lower in both men and women than in the general population. Those with low eGFR comprised 14.2% and proteinuria was distributed as follows: negative and ± 94.55%, 1+ 3.75%, and ≥2+ 1.7%.

The prevalence of obesity, DM, and hypertension is summarized based on the results of eGFR and proteinuria in Table 2. The prevalence of obesity, DM, and hypertension increased in relation to the degree of proteinuria in each eGFR group. Higher levels of proteinuria together with lower levels of eGFR were associated with an increased prevalence of hypertension (Fig. 1).

History of stroke, heart disease, and CVD (either stroke or heart disease) is summarized in Table 3. The prevalence of CVD was highest (25.2%) in those with proteinuria of (1+) and an eGFR of 15–29 ml/min/1.73 m^2, and the prevalence was lowest (6.1%) in those negative and ± for

Table 1 Demographics of the screened cohorts. Screening was performed during April 1, 2008 to March 31, 2009

Number of participants	332,174		
Men (%)	134,751 (40.6)		
Age (years)	63.6 (8.3), 40–74		
Body height (cm)	157.2 (8.5)	Men 164.6 (6.3)[#]	Women 152.2 (5.7)
Body weight (kg)	57.6 (10.5)	Men 64.5 (9.5)[#]	Women 52.8 (8.3)
Body mass index (kg/m^2)	23.2 (3.3)	Men 23.8 (3.1)[#]	Women 22.8 (3.5)
Waist circumference (cm)	84.1 (9.2)	Men 85.7 (8.3)[#]	Women 83 (9.5)
Systolic blood pressure (mmHg)	128.9 (17.4)		
Diastolic blood pressure (mmHg)	76.3 (10.7)		
Fasting blood glucose (mg/dl)	98.2 (21.5)		
Hemoglobin A1c (%)	5.3 (0.7)		
Triglyceride (mg/dl)	122.5 (84.0)		
HDL cholesterol (mg/dl)	62.1 (16.3)		
LDL cholesterol (mg/dl)	125.9 (30.6)		
Hemoglobin (g/dl)	13.6 (1.4)		
Serum creatinine (mg/dl)	0.7 (0.2)	Men 0.8 (0.3)[#]	Women 0.6 (0.2)
eGFR (ml/min/1.73 m^2)	75.0 (16.2)		
<15	240 (0.07%)		
15–29	655 (0.20%)		
30–44	4,300 (1.29%)		
45–59	42,975 (12.94%)		
60–89	225,081 (67.76%)		
≥90	58,923 (17.74%)		
Serum uric acid (mg/dl)	5.2 (1.4)	Men 6.0 (1.3)[#]	Women 4.7 (1.1)
Glucosuria[a]	2.30%		
Proteinuria[a]	5.40%		
Hematuria[a]	7.50%		
Past history (%)			
Stroke	3.30		
Cardiac disease	6.00		
Kidney disease	0.70		
Medication (%)			
Anti-hypertensive drugs	28.80		
Lipid lowering drugs	15.80		
Insulin or hypoglycemic drugs	5.20		
Lifestyle (%)			
Smoking	13.50	Men 25.2%[#] Women 5.5%	
Drinking	44.30	Men 65.2%[#] Women 30.0%	

Data are mean (SD)

[a] Positive urine test denote ≥1+ by dipstick

[#] $P < 0.01$ (vs women)

proteinuria and having an eGFR ≥90 ml/min/1.73 m^2. The combination of higher levels of proteinuria and lower levels of eGFR was associated with an increased prevalence of a history of CVD (Fig. 2).

Mean (SD) levels of BMI and smoking rate are summarized in Table 4. Both BMI and smoking rate were higher in men than in women. The smoking rate tended to decrease in the lower eGFR category.

Discussion

The target population of this screening in Japan comprised participants from 40 to 74 years of age, and the expected turnout was approximately 58 million. In the 2008 screening, the actual participation rate remained low, 20–30%, probably because of the lack of preparation for implementing this new system. The total number of participants in the present study was approximately 0.58 million; therefore, our analysis included at least 1% of the target population in Japan.

The results revealed the current health status among the general Japanese population. The proportion of the population comprising elderly people is high in Japan and its rate of increase is currently the highest in the world. The proportion of those with a low GFR (<60 ml/min/1.73 m^2), regardless of proteinuria, increases with aging. Fortunately, the rate of decline of the GFR in the Japanese is relatively low, 0.36 ml/min/1.73 m^2/year [9]. Elderly people are at risk for CVD and death. Effective strategies to establish a health check and guidance system are necessary to better accommodate the future burden of medical and social costs due to the aging population. Based on the findings of the present study, we propose that a cost–benefit analysis be performed on programs designed for the early detection and treatment of CKD, including education regarding lifestyle modification.

CVD is a recently recognized risk factor for CKD and ESRD [7]. The prevalence of CVD in CKD stage 5 is

Table 2 Prevalence of obesity, DM, and hypertension based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Number (%)	Obesity (%)	DM (%)	Hypertension (%)
<15	Minus, ±	101 (0.03)	22.8	10.2	50.5#
	1+	35 (0.01)	28.6	17.6	88.6*
	≥2+	103 (0.03)	31.1	32.0*	92.2*
15–29	Minus, ±	251 (0.08)	29.1	25.2*	81.1*
	1+	119 (0.04)	31.1	22.7*	85.5*
	≥2+	285 (0.09)	40.3*	38.4*	91.9*
30–44	Minus, ±	3,194 (0.96)	35.8*	13.9*	68.2*
	1+	504 (0.15)	43.8*	24.9*	83.3*
	≥2+	579 (0.17)	46.5*	33.9*	85.9*
45–59	Minus, ±	39,265 (11.82)	30.7*	9.3*	52.7*
	1+	2,408 (0.72)	42.2*	19.6*	71.6*
	≥2+	1,326 (0.40)	49.5*	31.1*	80.2*
60–89	Minus, ±	214,768 (64.66)	25.4*	8.4*	43.3*
	1+	7,579 (2.28)	38.5*	19.3*	62.1*
	≥2+	2,703 (0.81)	46.5*	31.1*	72.0*
≥90	Minus, ±	56,495 (17.01)	24.3	10.6	39.8
	1+	1,812 (0.55)	37.9*	26.5*	57.4*
	≥2+	647 (0.19)	46.5*	36.4*	72.0*

Total number of participants was 332,174. Parentheses are the percentage to the total participants in each column. Obesity, BMI ≥25 kg/m^2; DM, HbA1c ≥6.1% or on treatment; hypertension, 140/90 mmHg or on treatment

* $P < 0.0001$, #$P < 0.05$ (vs. reference value of eGFR ≥90 and proteinuria minus or ±)

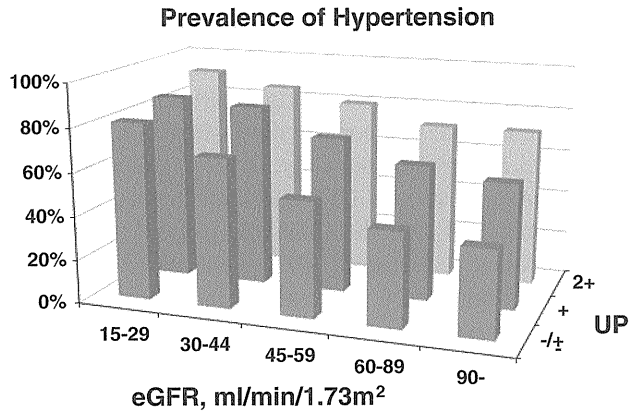

Fig. 1 Prevalence of hypertension by the combination of eGFR and proteinuria. Prevalence of hypertension was significantly ($P < 0.0001$) higher in every column except those with eGFR 15–29 and proteinuria minus or (±) ($P < 0.05$) when compared to the reference value of eGFR ≥90 and proteinuria minus or (±)

Table 3 Prevalence of history of stroke and heart disease based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Stroke	Heart Disease	CVD
<15	Minus, ±	4.0	6.9	10.9*
	1+	5.7	17.1*	22.9
	≥2+	8.7*	12.6	19.4#
15–29	Minus, ±	13.9*	15.9*	25.1*
	1+	15.1*	15.1*	25.2*
	≥2+	11.6*	13.7*	22.5*
30–44	Minus, ±	8.6*	13.1*	19.2*
	1+	9.9*	16.1*	22.4*
	≥2+	10.5*	16.4*	23.7*
45–59	Minus, ±	4.8*	8.5*	12.3*
	1+	6.9*	11.7*	16.2*
	≥2+	8.3*	13.1*	19.2*
60–89	Minus, ±	3.0*	5.6*	8.1*
	1+	4.7*	7.3*	11.1*
	≥2+	5.8*	9.3*	13.8*
≥90	Minus, ±	2.4	4.1	6.1
	1+	3.5†	6.0*	8.8*
	≥2+	4.5†	4.6	8.5†

Total number of participants was 332,174. Cardiovascular disease (CVD) denotes stroke and/or heart disease

* $P < 0.0001$, †$P < 0.02$, #$P < 0.05$ (vs reference value of eGFR ≥90 and proteinuria minus or ±)

approximately 25%; similar to the prevalent dialysis population. Ethnic variations in CVD incidence and subtype are well described in the general population [10, 11]. The stroke mortality rate is high in Japan; however, in the present study, the prevalence of stroke was lower than that of cardiac disease (Table 1). The reasons for this finding are not clear, but many people with stroke are unable to participate in this type of screening program.

Metabolic syndrome is an important risk factor for developing CKD [12], and for DM and hypertension, which are the main causes of ESRD [13]. We previously reported the significance of obesity in the risk for ESRD. Recent societal changes in lifestyle related to motorized transportation and high-calorie intake may have contributed to the

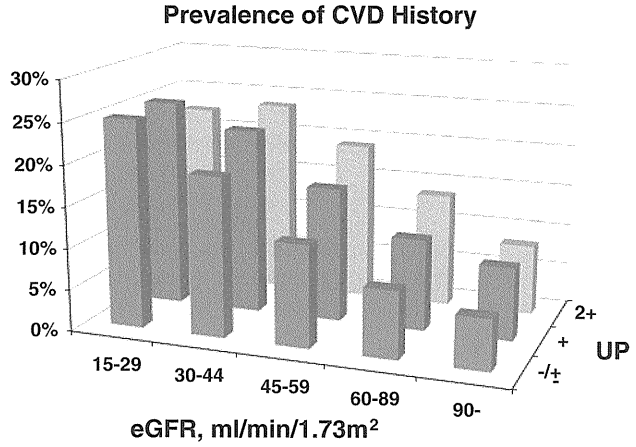

Fig. 2 Prevalence of history of cardiovascular disease (*CVD*) by the combination of eGFR and proteinuria. Prevalence of CVD was significantly ($P < 0.0001$) higher in every column except those with eGFR 15–29; not significant for proteinuria (+), and $P < 0.05$ for proteinuria ≥2+, when compared to the reference value of eGFR ≥90 and proteinuria minus or (±). *P* value was <0.02 for those with eGFR ≥90 and proteinuria ≥2+

Table 4 Mean (SD) levels of body mass index (BMI) and smoking rate in each sex based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Men		Women	
		BMI (kg/m^2)	Smoker (%)	BMI (kg/m^2)	Smoker (%)
<15	Minus, ±	24.1 (2.6)	5.4	22.2 (3.0)	10.9
	1+	24.2 (2.4)	12.5	22.0 (3.4)	5.3
	≥2+	23.3 (2.8)	22.2	24.5 (4.7)	2.5
15–29	Minus, ±	23.6 (3.1)	15.0	23.6 (4.1)	8.0
	1+	24.5 (3.4)	7.0	23.5 (3.8)	6.5
	≥2+	24.2 (3.1)	18.4	25.3 (4.7)	6.0
30–44	Minus, ±	24.3 (2.9)	15.3	23.7 (3.8)	4.4
	1+	24.8 (3.5)	19.5	24.2 (4.5)	6.6
	≥2+	25.2 (3.2)	19.5	24.9 (4.4)	5.9
45–59	Minus, ±	24.1 (2.8)	15.8	23.2 (3.4)	3.9
	1+	24.7 (3.0)	20.6	24.2 (4.2)	5.7
	≥2+	25.2 (3.5)	24.9	25.1 (4.4)	5.7
60–89	Minus, ±	23.7 (3.0)	24.4	22.7 (3.4)	5.1
	1+	24.5 (3.4)	29.4	23.9 (4.3)	6.8
	≥2+	25.1 (3.8)	31.2	24.8 (4.8)	8.1
≥90	Minus, ±	23.4 (3.4)	38.8	22.7 (3.6)	7.2
	1+	24.2 (4.0)	46.5	24.2 (4.5)	8.3
	≥2+	25.0 (4.2)	39.5	25.0 (5.0)	9.4

Total number of participants was 332,174

SD standard deviation

increased prevalence of obesity. Although the prevalence of obesity (BMI ≥30 kg/m^2) is lower in Japan than in the USA [14], complications begin to increase in the Japanese after reaching a BMI of 25 kg/m^2.

Microalbuminuria is suspected when the dipstick test results for proteinuria are (±) and/or 1+ [15]. Routine measurement of microalbuminuria is not feasible for the universal screening of CKD, as the cost is much higher than that of a dipstick urine test for proteinuria. Japan has a long history of universal screening, including dipstick urine testing for both proteinuria and hematuria. A positive proteinuria test result has a strong predictive value for the development of ESRD.

The strengths of the present study are: the number of participants was sufficiently large. It is the first nationwide targeted screening program aimed at determining the prevalence of metabolic syndrome in Japan. People diagnosed with metabolic syndrome are entitled to receive instruction to modify their lifestyles and therefore the risk factors for CKD and CVD can be modified accordingly. The prevalence of metabolic syndrome and obesity, particularly in men, is increasing; therefore, the prevalence of CKD is increasing in Japan [16].The combined eGFR and dipstick proteinuria test results indicate that the prevalence of risk factors for CKD and CVD increasing. Future follow-up studies will provide the predictive value of this CKD stratification on CVD, ESRD, and mortality.

The present study has several limitations. It is a cross-sectional study. Single tests for dipstick proteinuria and serum creatinine might cause misclassification of the true prevalence of CKD. To confirm the existence of CKD, the test should be repeated annually, at least 3 months apart. The current estimation of GFR used in this study is precise (<60 ml/min/1.73 m^2); therefore, the proportion of those with moderately decreased GFR (<45 ml/min/1.73 m^2) seems to be high, 1.56%. We selected patients with data for both serum creatinine and dipstick urine test, which comprised approximately two-thirds of the total participants. A cost–benefit analysis on the best combination of screening tests remains to be performed in Japan. Details of CVD, such as subtype of stroke and heart disease, are not clear. Risk factors may differ among diseases. Information of past medical history, medications, and lifestyle were obtained from a questionnaire, which has not yet been validated. Finally, the elderly population, those aged ≥75 years, was not considered in the present screening. It remains to be determined whether or not risk stratification based on both eGFR and proteinuria is applicable in this age group. CKD also has a role in medical problems commonly seen in elderly people, such as malignancies, pneumonia, sepsis, dementia, and bone fractures.

In conclusion, the risk profiles of CKD and CVD are indicated by the new CKD classification based on eGFR and proteinuria levels in the newly developed screening system used in Japan. Although CKD stratification based on the combined eGFR and proteinuria results seems to be a useful predictor of CVD and mortality in the general

population in Japan, the validity of this finding has yet to be demonstrated in outcome studies, and would be useful for the international comparison of the incidence of ESRD [17].

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Conflict of Interest None.

References

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.
2. An overview of regular dialysis treatment in Japan as of December 31, 2008. Japanese Society for Dialysis Therapy, Tokyo, Japan; 2009.
3. Jungers P, Zingraff J, Albouze P, Chauveau P, Page B, Hannedouche T, et al. Late referral to maintenance dialysis: detrimental consequences. Nephrol Dial Transplant. 1993;3:1089–93.
4. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
5. Iseki K for the Okinawa Dialysis Study (OKIDS) Group. Analysis of referral pattern and survival in chronic dialysis patients in Okinawa, Japan (1993–1997). Clin Exp Nephrol. 2002;6:43–8.
6. Sunagawa H, Iseki K, Nishime K, Uehara H, Toma S, Kinjo K, et al. Epidemiologic analysis of diabetic patients on chronic dialysis. Nephron. 1996;74:361–6.
7. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
8. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
9. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;1:433–41.
10. Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KA, Topol EJ. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopiodogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. Am Heart J. 2009;157:658–65.
11. Markus HS, Khan U, Birns J, Evans A, Kalra L, Rudd AG, et al. Differences in stroke subtypes between black and white patients with stroke: the South London Ethnicity and Stroke Study. Circulation. 2007;116:2157–64.
12. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71:159–66.
13. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65:1870–6.
14. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol. 2006;17:1453–9.
15. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. Clin Exp Nephrol. 2007;11:51–5.
16. Nagata T, Ninomiya T, Doi Y, Yonemoto K, Kubo M, Hata J, et al. Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: the Hisayama Study. Nephrol Dial Transplant. 2010;25:2557–64.
17. Caskey FJ, Cramer A, Elliott RF, Stel VS, Covic A, Cusumano A, et al. Global variation in renal replacement therapy for end-stage renal disease. Nephrol Dial Transplant. 2011; Epub.

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ORIGINAL ARTICLE

Cost-effectiveness of chronic kidney disease mass screening test in Japan

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Abstract
Background Chronic kidney disease (CKD) is a significant public health problem. Strategy for its early detection is still controversial. This study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, and Japan's health checkup reform.
Methods Cost-effectiveness analysis was carried out to compare test modalities in the context of reforming Japan's mandatory annual health checkup for adults. A decision tree and Markov model with societal perspective were constructed to compare dipstick test to check proteinuria only, serum creatinine (Cr) assay only, or both.
Results Incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as ¥1,139,399/QALY (US $12,660/QALY) for dipstick test only, ¥8,122,492/QALY (US $90,250/QALY) for serum Cr assay only and ¥8,235,431/QALY (US $91,505/QALY) for both. ICERs associated with the reform were calculated as ¥9,325,663/QALY (US $103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test, and ¥9,001,414/QALY (US $100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion.
Conclusions Taking a threshold to judge cost-effectiveness according to World Health Organization's recommendation, i.e. three times gross domestic product per capita of ¥11.5 million/QALY (US $128 thousand/QALY), a policy that mandates serum Cr assay is cost-effective. The choice of continuing the current policy which mandates dipstick test only is also cost-effective. Our results suggest that a population strategy for CKD detection such as mass screening using dipstick test and/or serum Cr assay can be justified as an efficient use of health care resources in a

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population with high prevalence of the disease such as in Japan and Asian countries.

Keywords Chronic kidney disease · Cost-effectiveness · Dipstick test · Mass screening · Proteinuria · Serum creatinine

Introduction

A consensus has been established that chronic kidney disease (CKD) is a worldwide public health problem [1, 2]. The effectiveness of its early detection and treatment to prevent progression to end-stage renal disease (ESRD) and premature death from cardiovascular disease has become widely accepted [3], while the strategy of its screening is still under debate [4]. Whereas high-risk strategies such as routine screening for diabetes patients and as a part of initial evaluation of hypertension patients are pursued in Western countries [5, 6], some argue that population strategies, such as mass screening, could be adopted in Asian countries where CKD prevalence is high [7].

Japan has a long history of mass screening programme for kidney diseases targeting school children and adults since the 1970s. Both urinalysis and measurement of serum creatinine (Cr) level have been mandated to detect glomerulonephritis in annual health checkup provided by workplace and community for adults aged ≥40 years old since 1992 [8]. However, glomerulonephritis was replaced as the leading cause of ESRD by diabetic nephropathy in 1998, and the focus of mass screening policy for adults was shifted to control of lifestyle-related diseases. In 2008, the Japanese government launched a programme, Specific Health Checkup (SHC) and Specific Counselling Guidance, focusing on metabolic syndrome in order to control lifestyle-related diseases, targeting all adults between the ages of 40 and 74 years [9]. This is a combined programme of mass screening followed by health education or referral to physicians. During the process of this development of SHC, different types of screening test for kidney diseases were discussed in the health policy arena [10]. Abandonment of dipstick test to check proteinuria was initially proposed by the Ministry of Health, Labour and Welfare, which was opposed by nephrologists who emphasised the significance of CKD. As a consequence, serum Cr assay was alternatively dropped and dipstick test remained in the list of mandatory test items [11]. However, those found with proteinuria in SHC are not included in the health education programme nor referred to physicians in the following Specific Counselling Guidance that particularly targets metabolic syndrome. At the time, much attention was paid to a report from the USA which suggested the cost-ineffectiveness of mass screening for proteinuria [12], which encouraged the government to abandon dipstick test in their initial proposal.

From the viewpoint of CKD control, the current SHC and Specific Counselling Guidance are not adequate. Therefore, to present evidence regarding CKD screening test for the revision of SHC, which is due in 5 years from its start in 2008, the Japanese Society of Nephrology set up the Task Force for the Validation of Urine Examination as a Universal Screening. Since cost-effectiveness analysis provides crucial information for organising public health programmes such as mass screening, the task force conducted an economic evaluation as a part of their mission. This paper presents the value for money of CKD screening test demonstrated by the task force. The results have implications for CKD screening programmes not only in Japan but also for other populations with high prevalence of CKD such as in Asian countries.

Methods

We conducted cost-effectiveness analysis of CKD screening test in SHC with a decision tree and Markov modelling from societal perspective in Japan. In modelling, we carried out a deliberate literature survey to find the best available evidence from Japan, while reports from overseas were excluded. The PubMed database and Igaku Chuo Zasshi (Japana Centra Revuo Medicina), a Japanese medical literature database, were accessed with combinations of relevant terms such as CKD, health checkup etc. Additionally, we re-analysed our databases and carried out surveys where applicable.

Participant cohort

We assume that uptake of SHC does not change regardless of the choice of the test used for CKD screening, so we model a cohort of participants in SHC. Since the sex and age distribution of participants affects outcomes, we run our economic model by sex and age strata. Probabilities of falling into a sex and age stratum are adopted from a nationwide complete count report of SHC in 2008 [13]. Each value is shown in Table 1, and we estimate outcomes based on the prognosis of participants by initial renal function. We also run our economic model for 25 initial renal function strata defined by the combination of five levels of dipstick test results and five stages of CKD according to estimated glomerular filtration rate (eGFR) derived from serum Cr level. Probabilities of falling into an initial renal function stratum are calculated from the Japan Tokutei-Kenshin CKD Cohort 2008, which is a large cohort for the evaluation of SHC. Each value is shown in Table 1.