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.
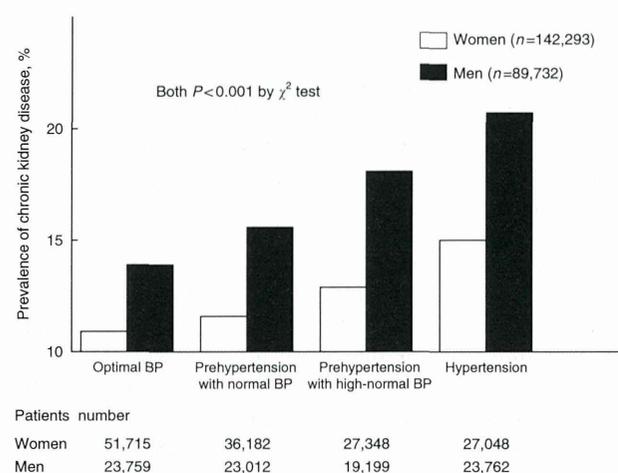

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined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

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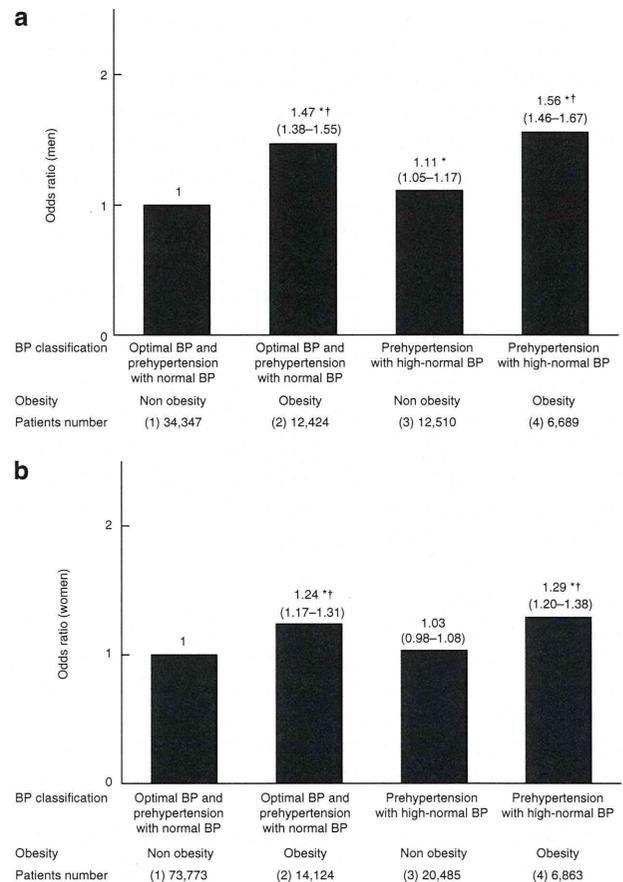
Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and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

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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 (≥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.

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.

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

Masahide Kondo · Kunihiro Yamagata · Shu-Ling Hoshi · Chie Saito ·
Koichi Asahi · Toshiki Moriyama · Kazuhiko Tsuruya · Hideaki Yoshida ·
Kunitoshi Iseki · Tsuyoshi Watanabe

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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M. Kondo (✉) · S.-L. Hoshi
Department of Health Care Policy and Management, Graduate School of Comprehensive Sciences, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8577, Japan
e-mail: mkondo@md.tsukuba.ac.jp

K. Yamagata · C. Saito
Department of Nephrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan

K. Asahi · T. Watanabe
Division of Nephrology and Hypertension, Fukushima Medical University, 1 Hikariga-oka, Fukushima 960-1295, Japan

T. Moriyama
Health Care Center, Osaka University, 1-17 Machikaneyama-cho, Toyonaka, Osaka 560-0043, Japan

K. Tsuruya
Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

H. Yoshida
Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-Ku, Sapporo, Hokkaido 060-8543, Japan

K. Iseki
Dialysis Unit, University Hospital of The Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan

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

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.

Table 1 Model assumptions

			Base-case value	Range tested in sensitivity analysis (%)	Source
Participant cohort					
Probability (%)					
Falling into sex and age stratum	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74	10.008, 9.280, 8.810, 9.783, 6.460, 5.721, 4.472	±50	[13]
	Female	40–44, 45-49, 50–54, 55–59, 60–64, 65–69, 70–74	6.291, 6.054, 6.137, 7.364, 6.836, 7.143, 5.643		
Falling into initial renal function stratum	−	Stage 1, stage 2, stage 3, stage 4, stage 5	11.660, 46.095, 28.627, 0.224, 0.029	±50	Japan Tokutei-Kenshin CKD Cohort 2008
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.866, 3.771, 3.214, 0.056, 0.008		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.325, 1.548, 1.779, 0.086, 0.013		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.385, 0.705, 0.095, 0.026		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.027, 0.104, 0.204, 0.053, 0.020		
Decision tree					
Probability (%)					
Seeking detailed examination after screened as further examination required			40.0	±50	[15, 16] and expert opinion
Either eGFR <50 ml/min/1.73 m^2 or having comorbidity among stage 3 patients (advanced stage 3)			83.5	±50	Japan Tokutei-Kenshin CKD Cohort 2008
Starting CKD treatment after detailed examination	−	Advanced stage 3, stage 4, stage 5	48.9, 82.2, 96.0	±50	Delphi method survey of expert committee
	±	Advanced stage 3, stage 4, stage 5	51.7, 83.9, 97.1		
	1+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	25.6, 31.1, 46.7, 71.7, 92.2, 98.0		
	2+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	62.2, 68.3, 78.9, 93.2, 97.1, 99.8		
	≥3+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	93.2, 94.3, 97.1, 97.7, 99.9, 99.9		
Markov model					
Probability (%)					
From (1) screened and/or examined to (2) ESRD with no treatment by initial renal function	−	Stage 1, stage 2, stage 3, stage 4, stage 5	0.001, 0.004, 0.016, 0.154, 1.743	±50	Calculated from Okinawa database [18]
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.019, 0.020, 0.036, 1.137, 5.628		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.036, 0.024, 0.303, 3.527, 15.802		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.305, 1.170, 10.939, 31.409		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.347, 0.933, 2.506, 13.824, 69.340		

Table 1 continued

				Base-case value	Range tested in sensitivity analysis (%)	Source
From (2) ESRD to (5) death by sex and age	Male		40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90	0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.044, 0.045, 0.047, 0.048, 0.050, 0.052, 0.054, 0.056, 0.058, 0.060, 0.062, 0.065, 0.068, 0.071, 0.074, 0.078, 0.081, 0.084, 0.088, 0.092, 0.097, 0.101, 0.105, 0.111, 0.117, 0.123, 0.129, 0.135, 0.142, 0.148, 0.155, 0.160, 0.166, 0.176, 0.186, 0.196, 0.202, 0.208, 0.226, 0.229, 0.245, 0.288, 0.257	±50	Calculated from Japanese dialysis patient registry [21]
	Female		40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90	0.029, 0.030, 0.031, 0.032, 0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.043, 0.045, 0.047, 0.049, 0.050, 0.052, 0.055, 0.057, 0.059, 0.062, 0.065, 0.068, 0.070, 0.074, 0.078, 0.080, 0.085, 0.089, 0.093, 0.097, 0.101, 0.105, 0.110, 0.115, 0.122, 0.127, 0.134, 0.138, 0.145, 0.151, 0.159, 0.162, 0.173, 0.185, 0.188, 0.198, 0.205, 0.219, 0.236		
From (1) screened and/or examined to (3) heart attack with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.005, 0.041, 0.076, 0.132, 0.126, 0.068	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.019, 0.078, 0.130, 0.234, 0.275, 0.372		
	≥1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.000, 0.000, 0.018, 0.033, 0.112, 0.077		
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.003, 0.010, 0.048, 0.079, 0.211, 0.224		
From (3) heart attack to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	2.8, 13.4, 13.0, 19.5, 33.7, 33.3	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	33.3, 0.0, 16.9, 25.0, 36.6, 45.8		
	2nd year	Male and female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	3.8, 3.8, 6.7, 19.5, 41.2, 100.0	±50	[24]
From (3) heart attack/(4) stroke to (2) ESRD				0.202	±50	[27]
From (1) screened and/or examined to (4) stroke with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.026, 0.139, 0.264, 0.477, 0.738, 0.769	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.050, 0.202, 0.357, 0.655, 1.052, 1.540		
		Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.014, 0.083, 0.124, 0.271, 0.508, 0.570		
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.034, 0.133, 0.187, 0.382, 0.699, 0.905		
From (4) stroke to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	19.1, 14.3, 9.9, 10.6, 12.7, 18.2	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	13.6, 14.0, 13.7, 6.8, 14.8, 18.1		
	2nd year	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	6.8, 8.2, 9.5, 12.6, 16.6, 23.3, 37.6, 61.9, 95.1, 100.0	±50	Calculated from Suzuki et al. [25, 26]
		Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	5.4, 6.4, 7.5, 9.0, 12.5, 18.4, 26.4, 40.1, 52.6, 71.7		

Table 1 continued

			Base-case value	Range tested in sensitivity analysis (%)	Source
From (1) screened and/or examined to (5) death by sex and age	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.002, 0.003, 0.004, 0.007, 0.010, 0.015, 0.024, 0.042, 0.070, 0.119, 0.196, 0.284, 0.397	±50	[28]
	Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.001, 0.001, 0.002, 0.003, 0.004, 0.006, 0.010, 0.019, 0.036, 0.070, 0.132, 0.213, 0.327		
Effectiveness of treatment (%)					
Reduction of transition probabilities from (1) screened and/or examined to (2) ESRD with treatment of CKD			42.1	±50	[20]
Reduction of transition probabilities from (1) screened and/or examined to (3) heart attack with treatment of CKD			71.0	±50	[23]
Reduction of transition probabilities from (1) screened and/or examined to (4) stroke with treatment of CKD			69.3	±50	[23]
Quality of life adjustment					
Utility weight					
(1) Screened and/or examined	Stage 1, stage 2, stage 3, stage 4, stage 5		0.940, 0.918, 0.883, 0.839, 0.798	±20	[31]
(2) ESRD			0.658	±20	[32]
(3) Heart attack			0.771		
(4) Stroke			0.714		
Costing					
Annual cost per person (¥)					
Screening	Dipstick test only, serum Cr assay only, dipstick test and serum Cr		267, 138, 342	±50	Survey of health checkup service providers
Detailed examination			25,000	±50	Expert opinion
CKD treatment	Stage 1, stage 2, stage 3, stage 4, stage 5		120,000, 147,000, 337,000, 793,000, 988,000	±50	Expert opinion
ESRD treatment			6,000,000	±50	[33]
Heart attack treatment	1st year, 2nd year		2,780,000, 179,000	±50	[34]
Stroke treatment	1st year, 2nd year		1,000,000, 179,000	±50	[34]