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

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

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

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

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

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

RESULTS

Patient characteristics

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

BP classification

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

CKD and BP classification

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

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

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

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

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

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

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

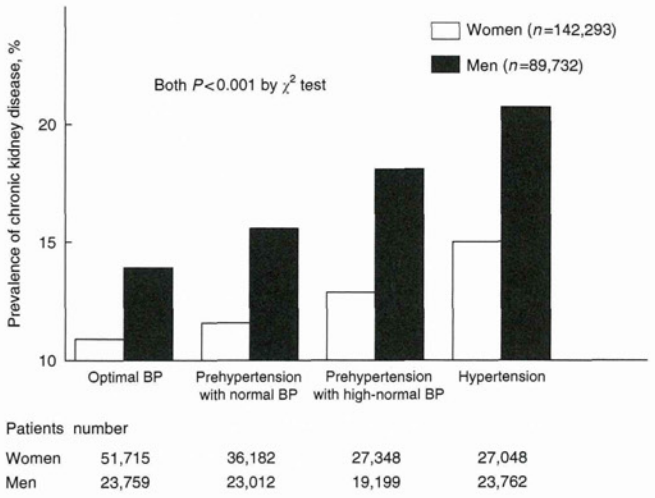

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined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

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

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

Lifestyle factors, obesity, and CKD

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

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

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

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

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

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

Effect of obesity on the association between CKD and BP classification

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

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

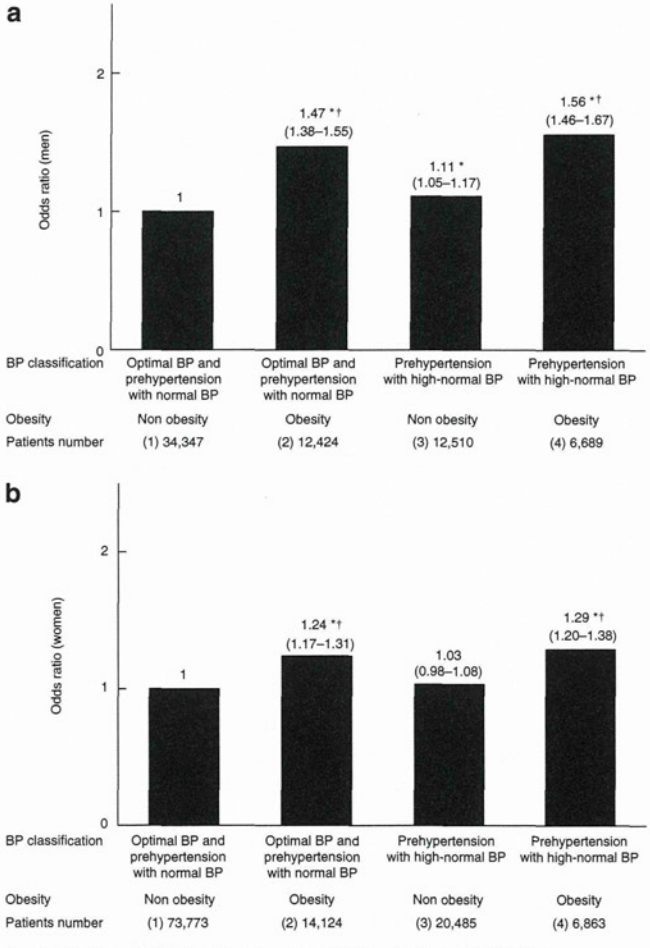

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and 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).

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.

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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

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Original Article

Glycohemoglobin not as predictive as fasting glucose as a measure of prediabetes in predicting proteinuria

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Abstract

Background. There is little data on the assessment of prediabetes with proteinuria.

Methods. This is a cross-sectional cohort study assessing prediabetes with proteinuria in a large Japanese population. Using a nationwide health checkup database of 228 778 Japanese aged ≥20 years (median 66 years; 39.3% were men; none had pre-existing cardiovascular disease), we examined the association between prediabetes and proteinuria (≥1+ on dipstick) separately in prediabetes subjects diagnosed with the new hemoglobin A1c (HbA1c) criterion only (PD-A1c), the impaired fasting plasma glucose only (PD-IFG) and fulfilling both criteria (PD-Both).

Results. According to the American Diabetes Association's (ADA's) criterion of 5.7–6.4% HbA1c and/or 100–125 mg/dL fasting plasma glucose, 43.8% of the subjects were judged as having prediabetes. Prediabetes subjects were divided into subclasses of PD-A1c (53.7%), PD-IFG (21.7%) and PD-Both (24.5%), respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1c criterion only. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) [95% confidence interval (95% CI)] for the increased risk of proteinuria (≥1+) in diabetes itself was 2.191 (2.081–2.307) and in whole prediabetes was 1.093 (1.046–1.142); when prediabetes was subdivided, the OR for proteinuria in PD-IFG was 1.217 (1.140–1.300) and that in PD-Both was 1.249 (1.174–1.329), but that in PD-A1c was not significant, even after adjustment for significant covariates, such as age, sex, body mass index, systolic blood pressure, antihypertensive medication, eGFR, lifestyle and lipid profile.

Conclusions. Prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and subjects with prediabetes defined using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Keywords: odds ratio; prediabetes; proteinuria

Introduction

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

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

Subjects with prediabetes were reported to have higher incidence of hypertension and obesity, and to be older

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

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

Methods

Study design and population

This is a cross-sectional cohort study assessing the prediabetes with proteinuria in a large Japanese population. This study was performed as a part of the prospective ongoing 'Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan' project. A new annual health check program, 'The Specific Health Check and Guidance in Japan', was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprises Japanese citizens between the ages of 40 and 74 years. Local governments called for the citizen to attend this annual health check under their own volition. Other details such as the participants' area were reported previously [6].

There was a total of 346 942 subjects [mean age, 63.4 years, 41% (n = 141 938) were men] for whom information on age, gender, BP, body mass index (BMI), habitual smoking or drinking, use of anti-hypertensive drugs and previous history of cardiovascular diseases (i.e. stroke and cardiac diseases such as angina and myocardial infarction) was available, as well as data on the serum creatinine level and dipstick urine test for proteinuria [14]. Individuals in certain regions participating in our project concomitantly underwent a regular health checkup for employees, which is legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years (n = 2025).

Among the 346 942 subjects, 29 820 subjects with a previous history of cardiovascular disease, 243 subjects with CKD stage 5 (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2) and 47 subjects with both were excluded from the present analysis. Moreover, 88 101 subjects with insufficient blood sampling data of glucose and lipid parameters were excluded. There was no clinical difference between subjects who were included in the present analysis (n = 228 778) and those who had missing data (n = 88 101).

The study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethical approval by the respective institutional review boards.

Baseline measurement

Blood samples were collected after an overnight fasting and were assayed within 24 h with an automatic clinical chemical analyzer. All measurements were conducted locally rather than at a central laboratory, without calibration among different laboratories, despite the fact that starting several years ago, standardized methods to measure laboratory data have been recommended by the Japan Society of Clinical Chemistry and widely adopted.

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

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

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

Urinalysis by the dipstick method was performed manually by trained staff on a single spot urine specimen collected early in the morning after overnight fasting. Urine dipstick results were interpreted by the medical staff in each local medical institution and recorded as (−), (+), (1+), (2+) and (3+). In Japan, it has been recommended by the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dL. Proteinuria was defined as 1+ or more. Because dipstick +/− sometimes indicates microalbuminuria in the Japanese general population [16], taking changeable urine concentration or protein other than albumin contained in urine into consideration, we adopted dipstick 1+ or more as reflecting positive urine protein.

eGFR was derived using the following equation [17]:

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

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

BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical checkup. According to the recommendations of the Japanese Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs uncrossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement.

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habit (current smoker or not) and alcohol intake (daily drinker or not). The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m^2).

Statistical analysis

All statistical analyses were performed with SPSS version 20.0J software (SPSS, Chicago, IL). Data are expressed as median (25th to 75th percentile). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using analysis of variance (ANOVA), and categorical parameters were compared with the chi-squared test. We divided the study population into three groups (normal glucose tolerance, prediabetes and diabetes), and then the prediabetes population was subdivided into three subgroups [PD-A1c, fulfilled HbA1c criterion but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria] [9], according to the fasting glucose level or HbA1c level.

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

Results

Clinical characteristics of the study population

The median age (interquartile range) of the 228 778 subjects was 66 (59–70) years, and 89 877 of the subjects (39.3%) were men. There were 27 913 subjects (12.2%) with diabetes and 100 214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes compared with those of subjects with normal glucose are shown in Table 1. Age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria,

Table 1. Characteristics of the study population overall

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

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square test as appropriate.
BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

eGFR, chemistry data and blood pressure levels were significantly different between the groups. Subjects among prediabetes, 53.7, 21.7 and 24.5% subjects were divided into subclasses of PD-A1C, PD-IFG and PD-Both, respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1C criterion only. Clinical and laboratory data of subjects with subdivided prediabetes were shown in Table 2. Similar to Table 1, age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria, eGFR, chemistry data and blood pressure levels were significantly different between the groups. Especially, the prevalence of proteinuria in subjects with PD-IFG or PD-Both was higher than in subjects with PD-A1C.

Prediabetes and proteinuria

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

Prediabetes subclass and proteinuria

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

Discussion

The messages of this article are that prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and that subjects with

Table 2. Characteristics of the subjects with prediabetes

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

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square test as appropriate.
PD-A1c, fulfilled HbA1c criterion (5.7–6.4%) but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion (100–125 mg/dL) but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria.
BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

prediabetes defined by using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Prediabetes and proteinuria

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

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

Why does this cohort exhibit so much prediabetes? A cohort study in the USA, the '1999 through 2006 National Health and Nutrition Examination Survey', (NHANES) revealed that 27.7% of participants had prediabetes, according to the ADA's IFG criterion [11]. Japanese data from a single facility revealed a rate of prediabetes of 33.5% among those undergoing an annual health checkup, according to the ADA criterion of IFG and/or IGT [24]. Possible reasons for the high level of prediabetes in our cohort are discussed. First, we can point out the age difference; mean age in the '1999 through 2006 NHANES was around 47 years of age, on the other hand, median age of our cohort was 66 years of age. Second, there are some possible biases toward the participants who are particularly concerned about their physical condition or might be worried about their health status, such as the fact that many prediabetes subjects enrolled in this study under their own volition. Third, the actual number of subjects with prediabetes is increasing worldwide, especially in Asia. Increasing numbers of cases of prediabetes or diabetes itself have been reported not only in Japan, but also in India and China [25–27]. Dietary habits have also changed from the traditional style to a Western style, involving an increase in total calories, meat and fatty meals [28, 29]. Asians also exercise less now, associated with the spread of motorization [30]. A recent report stated that Asians tend to have much visceral fat tissue, in spite of a relatively low BMI score, compared with Caucasians [31–34]. Furthermore, genetically, Asians have a low insulin secretory ability [35–37]. These mechanisms of why Asians may be susceptible to diabetes are well summarized elsewhere [25].

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

In this study, the use of antihypertensive medication is one of the major risk factors associated with proteinuria

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

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

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

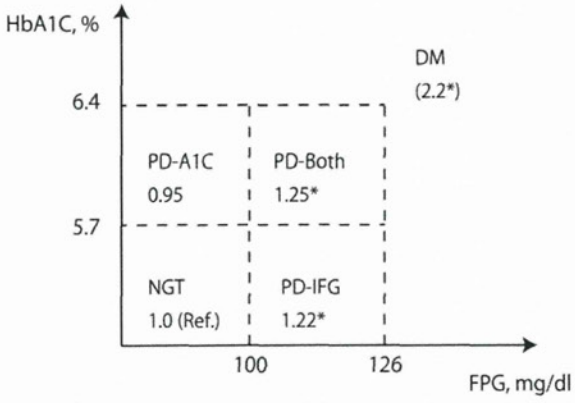

Fig. 1. OR for proteinuria according to subclass of prediabetes. The ORs of proteinuria in subjects with NGT, PD-A1c, PD-IFG, PD-Both or DM are shown. The analysis was adjusted for age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking), TG and LDL-C. *P < 0.001 versus NGT.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

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

Subclass of prediabetes and proteinuria

Subjects with prediabetes were classified into three groups: PD-A1c, PD-IFG and PD-Both, as defined above. The OR for proteinuria was significantly higher in subjects in the groups of PD-IFG and PD-Both than in PD-A1c, independent of age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking) and lipid profile. Our data clearly revealed that the different groups, defined by different criteria, have different risks for proteinuria in the same category of prediabetes.

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

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

Limitations

This study is cross-sectional, so we were unable to infer causality for proteinuria. There might be some bias toward the participants who were particularly motivated to undergo a health examination. Many people were

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

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

Summary

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

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ORIGINAL ARTICLE

Weight gain after 20 years of age is associated with prevalence of chronic kidney disease

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Abstract
Background Weight gain after maturity is a risk factor for diabetes, coronary heart disease, and stroke, even in individuals with a normal body mass index; however, there is little information about the influence of weight gain after maturity on chronic kidney disease (CKD). Therefore, we examined the association between weight gain after 20 years of age and the prevalence of CKD.
Methods A cross-sectional study was performed on 28,151 women and 21,110 men aged between 40 and 59 years who participated in the specific health check and guidance system of Japan in 2008. We compared prevalence of CKD between participants with and without weight gain of at least 10 kg after 20 years of age. Multivariate logistic regression models and stratified analyses were used to adjust for possible confounding factors.
Results The prevalence of CKD among participants with weight gain was significantly higher than among those without weight gain both in women (11.8 vs 8.3%, $p < 0.0001$) and in men (12.2 vs 9.2%, $p < 0.0001$). After adjustment for age, smoking, regular exercise, alcohol intake, history of kidney disease, hypertension, diabetes, and hypercholesterolemia, the odds ratio (95% confidence interval) for CKD was 1.24 (1.14–1.36) in women and 1.15 (1.05–1.26) in men with weight gain of at least 10 kg after the age of 20 years. Even in participants without metabolic syndrome, weight gain was independently associated with CKD in both genders.
Conclusions Weight gain after 20 years of age is associated with CKD among Japanese, even those without metabolic syndrome.

Keywords Weight gain · Chronic kidney disease · Obesity · General population · Cross-sectional study

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Introduction

The prevalence of obesity in Japan has increased over the past several decades [1], and is a worldwide public health problem of growing importance. Obesity is an established risk factor for several chronic diseases, including hypertension and diabetes mellitus. Even in individuals with a normal body mass index (BMI), weight gain after maturity is an important risk factor for diabetes [2, 3], coronary heart disease [4, 5], and stroke [6].

Obesity has also been recognized as a risk factor for chronic kidney disease (CKD). Weight gain has been reported to be associated with the incidence of CKD among Korean men, even when BMI remained within the normal range [7]. However, information is lacking about the influence of weight gain after maturity on CKD among

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women, because previous studies of the association between obesity and CKD defined obesity by the BMI or waist circumference [8, 9]. An increase of weight after maturity largely reflects increased fat mass, so such an increase may be more closely associated with the risk of CKD, especially among participants with a normal BMI or waist circumference. The average BMI of Asian populations is lower than that of non-Asian populations, although the tendency for abdominal obesity might be greater than in non-Asian populations [10]. Weight gain after maturity might be a basis for recommendations on lifestyle modification, and it may be especially attractive to use this measure for Asian populations. Measures such as weight and weight gain are also attractive from a public education perspective, because they are much easier for the general population to understand than BMI and can be measured more accurately than waist circumference.

In this study, we examined the effect of weight gain after maturity on the prevalence of CKD among Japanese. We hypothesized that the prevalence of CKD might be associated with weight gain after maturity, even for individuals within the normal range of BMI or waist circumference.

Methods

Study population

We used data from 68 areas of 7 prefectures obtained by the Japanese specific health check and guidance system (SHC) in 2008; the SHC has been described elsewhere [11]. In brief, participants answered a self-administered questionnaire that covered their medical history, smoking habits, alcohol intake, and exercise pattern. Trained staff then measured the height, weight, blood pressure, and waist circumference of each participant, after which serum and spot urine samples were collected. We only included participants aged between 40 and 59 years in this study, because previous reports have indicated that metabolic syndrome was a risk factor for CKD only for younger participants ($\leq$60 years) among men [12, 13] and because body weight might decrease due to comorbidities >60 years. Participants with missing information were also excluded. All of the participants remained anonymous and the study was conducted according to Japanese privacy protection laws and the ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture and the Ministry of Health, Labor and Welfare in 2005.

Proteinuria and CKD

Proteinuria was defined by a dipstick urinalysis score of $\geq$1+ proteinuria (equivalent to $\geq$30 mg/dl) because of poor discrimination between negative and trace positive dipstick readings [14]. The primary endpoint was the prevalence of CKD, which was defined as $\geq$1+ proteinuria on urinalysis, a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 as calculated by using the estimated GFR (eGFR) formula shown below for Japanese [15], or both [16].

$$\text{eGFR} = 194 \times (\text{serum creatinine}^{-1.094}) \times (\text{age}^{-0.287}) \times (0.739 \text{ for females}).$$

Weight gain, obesity, and metabolic syndrome

Information about weight gain was collected from the self-administered questionnaire, which included the following item: "Have you gained more than 10 kg since 20 years of age?" Participants answered yes or no. Using BMI values (calculated as weight in kilograms/(height in meters)^2), the subjects were categorized as non-obese (<25 kg/m^2) or obese ($\geq$25 kg/m^2). Using waist circumference measured at the umbilicus, they were categorized as having abdominal obesity ($\geq$90 cm for women and $\geq$85 cm for men) or not (<90 cm for women and $\leq$85 cm for men) according to the definition of the metabolic syndrome in the SHC [11]. The SHC definition of the metabolic syndrome is not the same as that used by the World Health Organization or the Japanese Society of Internal Medicine [17, 18]. Instead, metabolic syndrome is defined as abdominal obesity (waist circumference $\geq$90 cm in women and $\geq$85 cm in men) and/or obese (BMI $\geq$25 kg/m^2) plus any two of the following three categories: (1) fasting blood glucose $\geq$100 mg/dl, hemoglobin A_{1c} $\geq$5.2%, use of insulin, and/or oral antidiabetic medication; (2) triglycerides $\geq$150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, and/or the use of cholesterol-lowering medication; or (3) blood pressure $\geq$130/85 mmHg and/or use of antihypertensive medication.

Covariates

Information about current smoking, alcohol, and exercise habits, a history of stroke, heart disease, CKD, or dialysis, and use of medication for diabetes mellitus, hypertension, or hypercholesterolemia was collected from the questionnaire. Diabetes mellitus was defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose $\geq$126 mg/dl, or both. Hypertension was defined as the use of antihypertensive medication, a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg, or both. Hypercholesterolemia was defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level $\geq$140 mg/dl, or both.

Statistical analysis

We analyzed the data separately by gender, because previous reports have indicated that the influence of BMI or

metabolic syndrome on CKD differs between men and women [12, 13, 19]. We used the Chi-squared test, Student's *t* test, and the Mann–Whitney *U* test to assess differences among the characteristics of the study participants in relation to weight gain. We conducted multivariate analyses using logistic regression models. The data were initially adjusted for age alone, and then for multiple covariates. In the multivariate models, we included the following covariates that might confound the relationship between weight and CKD: age, current smoking, regular exercise, alcohol intake, a history of kidney disease, and current hypertension, diabetes, and hypercholesterolemia. Because hypertension, diabetes, and hypercholesterolemia are likely to be intermediate factors on the pathway between weight gain and CKD, we did not adjust for these variables in the primary analyses, but we added them sequentially to multivariate models in the secondary analyses. We also performed analyses stratified by presence or absence of metabolic syndrome, abdominal obesity, and obesity or non-obesity. We compared the sensitivity and specificity of weight gain, BMI, and waist circumference for identifying CKD. We calculated 95% confidence intervals (CI) using Wilson's method [20]. A p value of <0.05 was considered to indicate statistical significance and all tests were two-tailed. All statistical analyses were performed with the SPSS for Windows statistical package (Version 18.0; SPSS, Chicago, IL, USA).

Results

A total of 189,709 residents and workers of the target districts aged between 40 and 59 years participated in the SHC. Among them, complete data were available for 28,151 women (27.1%) and 21,111 men (24.6% of participants in this age range). There were no differences between the included and excluded subjects with regard to characteristics such as age, BMI, and waist circumference. Among the 28,151 women and 21,111 men, 8,494 women (30.2%) and 10,485 men (49.7%) answered that their weight had increased by at least 10 kg since 20 years of age.

Table 1 Clinical characteristics of 28,151 women stratified by weight gain after 20 years of age

Variable	Weight gain		*p* value
	<10 kg (n = 19,657)	≥10 kg (n = 8,494)	
Age [years; mean (SD)]	51.9 (5.9)	52.4 (5.7)	<0.0001
BMI [kg/m^2; mean (SD)]	20.9 (2.5)	25.9 (3.6)	<0.0001
Waist circumference [cm; mean (SD)]	76.5 (7.8)	88.7 (9.1)	<0.0001
Current smoker (%)	13.2	13.3	0.73
Regular exercise, yes (%)	26.8	25.0	0.002
Alcohol intake (%)			
Every day	14.1	10.8	<0.0001
Sometimes	26.7	24.2	
Never	59.3	65.0	
History of stroke (%)	1.0	1.6	<0.0001
History of cardiac disease (%)	1.8	2.9	<0.0001
History of kidney disease (%)	0.4	0.5	0.24
Systolic blood pressure [mmHg; mean (SD)]	118.1 (16.8)	125.7 (17.5)	<0.0001
Diastolic blood pressure [mmHg; mean (SD)]	71.9 (11.0)	76.6 (11.2)	<0.0001
Antihypertensive medication, yes (%)	9.2	20.9	<0.0001
Fasting blood glucose [mg/dl; mean (SD)]	90.3 (15.3)	97.2 (21.3)	<0.0001
Hemoglobin A_{1c} [%; mean (SD)]	5.1 (0.5)	5.3 (0.7)	<0.0001
Antidiabetic medication, yes (%)	1.3	3.5	<0.0001
Low-density lipoprotein cholesterol [mg/dl; mean (SD)]	122.8 (31.7)	134.5 (32.4)	<0.0001
Medication for hypercholesterolemia, yes (%)	6.8	12.3	<0.0001
Triglycerides [mg/dl; median (IQR)]	77 (57, 107)	108 (77, 155)	<0.0001
High-density lipoprotein cholesterol [mg/dl; mean (SD)]	71.4 (16.5)	61.5 (14.4)	<0.0001
Creatinine [mg/dl; mean (SD)]	0.61 (0.15)	0.61 (0.13)	0.66
eGFR [ml/min/1.73 m^2; mean (SD)]	82.4 (16.2)	82.5 (16.8)	0.71
Proteinuria[a] (%)	2.9	5.6	<0.0001
Chronic kidney disease[b] (%)	8.3	11.8	<0.0001

SD standard deviation, *IQR* interquartile range

[a] Defined as the presence of ≥1+ proteinuria on urinalysis

[b] Defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2 or as proteinuria on urinalysis

Table 2 Clinical characteristics of 21,110 men stratified by weight gain after 20 years of age

Variable	Weight gain		*p* value
	<10 kg (n = 10,625)	≥10 kg (n = 10,485)	
Age [years; mean (SD)]	50.9 (6.0)	51.3 (5.8)	0.31
BMI [kg/m^2; mean (SD)]	22.3 (2.6)	26.0 (3.1)	<0.0001
Waist circumference [cm; mean (SD)]	80.7 (7.1)	90.5 (7.9)	<0.0001
Current smoker (%)	40.1	37.5	<0.0001
Regular exercise, yes (%)	31.6	27.6	<0.0001
Alcohol intake (%)			
Every day	44.2	39.9	<0.0001
Sometimes	27.6	30.7	
Never	28.2	29.4	
History of stroke (%)	1.9	2.1	0.24
History of cardiac disease (%)	2.7	3.5	<0.0001
History of kidney disease (%)	0.3	0.5	0.06
Systolic blood pressure [mmHg; mean (SD)]	123.1 (16.6)	127.9 (16.1)	<0.0001
Diastolic blood pressure [mmHg; mean (SD)]	72.6 (11.5)	80.5 (11.3)	<0.0001
Antihypertensive medication, yes (%)	11.7	19.9	<0.0001
Fasting blood glucose [mg/dl; mean (SD)]	98.1 (26.2)	102.7 (26.5)	<0.0001
Hemoglobin A_{1c} [%; mean (SD)]	5.2 (0.8)	5.4 (0.8)	<0.0001
Antidiabetic medication, yes (%)	3.5	4.4	0.0001
Low-density lipoprotein cholesterol [mg/dl; mean (SD)]	119.6 (31.4)	129.8 (31.9)	<0.0001
Medication for hypercholesterolemia, yes (%)	4.8	9.0	<0.0001
Triglycerides [mg/dl; median (IQR)]	103 (73, 156)	142 (99, 211)	<0.0001
High-density lipoprotein cholesterol [mg/dl; mean (SD)]	61.0 (16.4)	53.0 (13.1)	<0.0001
Creatinine [mg/dl; mean (SD)]	0.80 (0.26)	0.83 (0.37)	<0.0001
eGFR [ml/min/1.73 m^2; mean (SD)]	83.4 (17.0)	80.6 (16.2)	<0.0001
Proteinuria[a] (%)	5.9	8.2	<0.0001
Chronic kidney disease[b] (%)	9.2	12.2	<0.0001

SD standard deviation, *IQR* interquartile range

[a] Defined as the presence of ≥1+ proteinuria on urinalysis

[b] Defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2 or as proteinuria on urinalysis

Clinical characteristics of the participants stratified by weight gain status are listed in Tables 1 and 2. As expected, both women and men with at least 10 kg of weight gain had a higher BMI, larger waist circumference, higher blood pressure, higher blood glucose, and higher low-density lipoprotein cholesterol and triglyceride levels. They were also more likely to have a history of cardiac disease, lower alcohol consumption, and less physical activity in both genders. The prevalence of CKD among the participants with weight gain was significantly higher than among those without weight gain both in women (11.8 vs 8.3%, $p \leq 0.0001$) and in men (12.2 vs 9.2%, $p \leq 0.0001$). The prevalence of proteinuria among the participants with weight gain was also significantly higher than among those without weight gain both in women (5.6 vs 2.9%, $p \leq 0.0001$) and in men (8.2 vs 5.9%, $p \leq 0.0001$).

In the age-adjusted analysis, the odds ratios for CKD increased along with increasing age in both genders (Tables 3, 4). Multivariate analysis revealed that weight gain was significantly associated with the prevalence of CKD, even after adjusting for hypertension, diabetes, and hypercholesterolemia. Thus, weight gain was independently associated with CKD in both genders. When the participants with a history of kidney disease were excluded, the results of the models also remained similar (Appendix). When proteinuria was replaced by the prevalence of CKD, multivariate analysis revealed that weight gain was significantly associated with proteinuria, even after adjusting for hypertension, diabetes, and hypercholesterolemia [the odds ratio (95% CI) 1.43 (1.25–1.63) in women and 1.16 (1.04–1.30) in men].

Stratified analysis showed that weight gain was independently associated with the prevalence of CKD among the subgroup without metabolic syndrome in both genders (Table 5). Among women, weight gain was also independently associated with the prevalence of CKD in the subgroup without abdominal obesity (waist circumference ≤90 cm).

The sensitivity and specificity of weight gain, BMI, and waist circumference for identifying CKD are shown in Table 6. Weight gain among women showed highest sensitivity (38%), but lowest specificity (71%), among the

Table 3 Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among women

Variable	Age-adjusted (95% CI)	Model 1[a] Odds ratio (95% CI)	Model 2[b] Odds ratio (95% CI)
Weight gain after 20 years			
<10 kg (ref)	1.00	1.00	1.00
≥10 kg	1.43 (1.32–1.56)	1.43 (1.31–1.55)	1.24 (1.14–1.36)
Age			
40–44 (ref)	1.00	1.00	1.00
45–49	1.22 (1.02–1.46)	1.21 (1.01–1.45)	1.14 (0.95–1.37)
50–54	2.06 (1.76–2.42)	2.04 (1.74–2.39)	1.82 (1.54–2.13)
55–59	2.40 (2.07–2.78)	2.35 (2.03–2.73)	1.99 (1.71–2.32)
Current smoker			
No (ref)		1.00	1.00
Yes		1.05 (0.93–1.19)	1.05 (0.93–1.19)
Regular exercise			
No (ref)		1.00	1.00
Yes		0.88 (0.81–0.96)	0.88 (0.81–0.97)
Alcohol intake			
Every day (ref)		1.00	1.00
Sometimes		1.07 (0.92–1.23)	1.07 (0.92–1.24)
Little or never		1.14 (1.00–1.30)	1.15 (1.00–1.31)
History of kidney disease			
No (ref)		1.00	1.00
Yes		3.34 (2.18–5.13)	3.07 (1.99–4.72)
Hypertension[c]			
No (ref)			1.00
Yes			1.57 (1.43–1.72)
Diabetes mellitus[d]			
No (ref)			1.00
Yes			1.47 (1.26–1.71)
Hypercholesterolemia[e]			
No (ref)			1.00
Yes			1.16 (1.06–1.26)

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, history of kidney disease, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

three variables, while weight gain showed middle-level sensitivity (57%) and specificity (51%) among men.

Discussion

The present study demonstrated that weight gain of at least 10 kg after 20 years of age was independently associated with the prevalence of CKD. This association was recognized even in the subgroup of participants without metabolic syndrome in both genders. The present study also showed that weight gain was independently associated with the prevalence of CKD in the subgroup of women without abdominal obesity (waist circumference ≤90 cm). These results suggest that using the assessment of weight gain for prevention of obesity may protect individuals who are within the current guidelines from potentially avoidable risks related with obesity to CKD, particularly for women.

Obesity is not only indirectly associated with CKD through various risk factors, such as hypertension and diabetes, but has also been recognized to directly influence the development of kidney dysfunction [9, 21–24]. Although the exact mechanism by which obesity is associated with CKD has not yet been elucidated, intra-abdominal fat mass plays a key role in metabolic syndrome. Weight gain after maturity largely reflects an increased fat mass, and thus may be a more direct (i.e., better) predictor of CKD than BMI or waist circumference. In addition, because the median BMI of Asians is lower than that of non-Asians [10], weight gain may be a more effective predictor of CKD in Asian populations. In fact, weight gain has been reported to be associated with the incidence of CKD among Korean men, even when BMI remained within the normal range [7].

Table 4 Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among men

Variable	Age-adjusted (95% CI)	Model 1[a] Odds ratio (95% CI)	Model 2[b] Odds ratio (95% CI)
Weight gain after 20 years			
<10 kg (ref)	1.00	1.00	1.00
≥10 kg	1.37 (1.26–1.49)	1.34 (1.23–1.47)	1.15 (1.05–1.26)
Age			
40–44 (ref)	1.00	1.00	1.00
45–49	1.30 (1.11–1.52)	1.31 (1.12–1.53)	1.20 (1.02–1.40)
50–54	1.44 (1.24–1.67)	1.47 (1.27–1.71)	1.22 (1.05–1.42)
55–59	1.83 (1.60–2.09)	1.87 (1.63–2.15)	1.43 (1.27–1.64)
Current smoker			
No (ref)		1.00	1.00
Yes		1.05 (0.96–1.15)	1.05 (0.96–1.15)
Regular exercise			
No (ref)		1.00	1.00
Yes		1.05 (0.96–1.16)	1.04 (0.94–1.14)
Alcohol intake			
Every day (ref)		1.00	1.00
Sometimes		1.21 (1.08–1.35)	1.24 (1.11–1.39)
Little or never		1.40 (1.26–1.56)	1.48 (1.33–1.65)
History of kidney disease			
No (ref)		1.00	1.00
Yes		9.43 (6.05–14.69)	8.11 (5.15–12.77)
Hypertension[c]			
No (ref)			1.00
Yes			2.07 (1.88–2.27)
Diabetes mellitus[d]			
No (ref)			1.00
Yes			2.00 (1.78–2.25)
Hypercholesterolemia[e]			
No (ref)			1.00
Yes			1.24 (1.13–1.37)

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, history of kidney disease, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

The present study also found weight gain was independently associated with the prevalence of CKD among both genders, even individuals without metabolic syndrome. To our knowledge, this is the first study to demonstrate a relationship between weight gain after maturity and CKD among women.

The present study also showed that weight gain among women had the highest sensitivity, but the lowest specificity, for CKD among the three measurements used to evaluate obesity. It is theoretically desirable for a screening test to be both highly sensitive and highly specific, but it is difficult to achieve this because of a trade-off between sensitivity and specificity. For public health activities aimed at preventing obesity, a test with high sensitivity may be more useful than one with high specificity. Thus, using the assessment of weight gain for prevention of obesity and CKD is attractive from a public health perspective, particularly for women.

Several studies revealed that the clinical implication of CKD and obesity or metabolic syndrome may be different according to gender. [12, 13, 19] Menopausal status has been suggested to be one of the candidates in determining the gender differences, because metabolic syndrome was a risk factor for CKD in postmenopausal women, but not in premenopausal women [13]. Because the mean age at menopause was reported to be 48.3 years and 80% of females had their menopause between 45 and 54 years of age in Japan [25], our study must include both premenopausal and postmenopausal women. Some differences between men and women in this study might be associated with menopausal status, whereas the information regarding menopausal status of participants was lacking in this study.