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

Yuichiro Yano[1], Shouichi Fujimoto[2], Yuji Sato[1], Tsuneo Konta[3], Kunitoshi Iseki[4], Toshiki Moriyama[4], Kunihiro Yamagata[4], Kazuhiko Tsuruya[4], Hideaki Yoshida[4], Koichi Asahi[4], Issei Kurahashi[5], Yasuo Ohashi[5] and Tsuyoshi Watanabe[4]

[1]Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; [2]Dialysis Division, University of Miyazaki Hospital, Miyazaki, Japan; [3]Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan; [4]Steering Committee for the 'Research on the positioning of chronic kidney disease (CKD) in Specific Health Check and Guidance in Japan', Japan and [5]Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan

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

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

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

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

Correspondence: *Shouichi Fujimoto, Dialysis Division, University of Miyazaki Hospital, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan. E-mail: fujimos@fc.miyazaki-u.ac.jp*

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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.

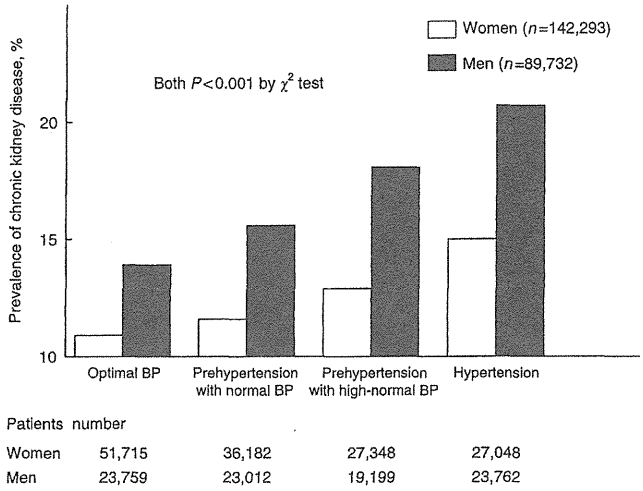

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined 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) ≥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 (≥140/90 mm Hg) on CKD risk among all subjects ($n=232,025$). The results showed that there was no synergistic interaction in either gender (data not shown).

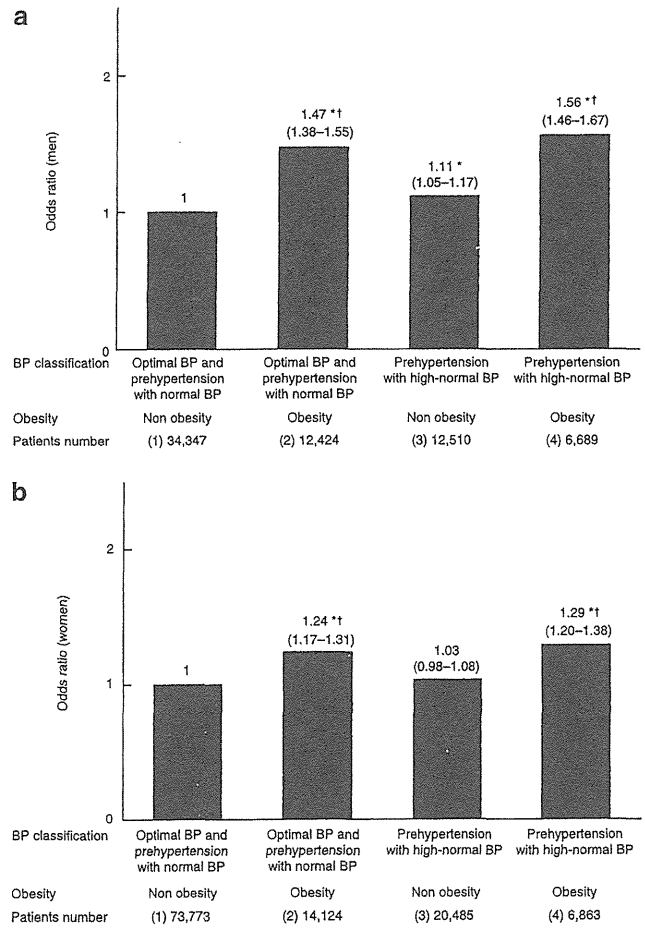

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and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

DISCUSSION

Prehypertension and CKD

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

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

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

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

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

Obesity, BP, and CKD

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

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

Lifestyle factors and CKD

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

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

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

CONCLUSION

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

MATERIALS AND METHODS

Study population

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

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

Baseline measurement

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

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

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

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

Definition of CKD

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

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

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

Statistical analysis

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

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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Association of High Pulse Pressure With Proteinuria in Subjects With Diabetes, Prediabetes, or Normal Glucose Tolerance in a Large Japanese General Population Sample

YUICHIRO YANO, MD[1]
YUJI SATO, MD, PHD[2]
SHOUICHI FUJIMOTO, MD, PHD[3]
TSUNEO KONTA, MD, PHD[4]
KUNITOSHI ISEKI, MD, PHD[5]
TOSHIKI MORIYAMA, MD, PHD[5]
KUNIHIRO YAMAGATA, MD, PHD[5]
KAZUHIKO TSURUYA, MD, PHD[5]
HIDEAKI YOSHIDA, MD, PHD[5]
KOICHI ASAHI, MD, PHD[5]
ISSEI KURAHASHI, MD, PHD[6]
YASUO OHASHI, MD, PHD[7]
TSUYOSHI WATANABE, MD, PHD[5]

OBJECTIVE—To examine whether there is a difference in the association between high pulse pressure and proteinuria, independent of other blood pressure (BP) indices, such as systolic or diastolic BP, among subjects with diabetes, prediabetes, or normal glucose tolerance.

RESEARCH DESIGN AND METHODS—Using a nationwide health checkup database of 228,778 Japanese aged ≥20 years (mean 63.2 years; 39.3% men; none had pre-existing cardiovascular disease), we examined the association between high pulse pressure, defined as the highest quintile of pulse pressure (≥63 mmHg, n = 40,511), and proteinuria (≥1+ on dipstick, n = 12,090) separately in subjects with diabetes (n = 27,913), prediabetes (n = 100,214), and normal glucose tolerance (n = 100,651).

RESULTS—The prevalence of proteinuria was different among subjects with diabetes, prediabetes, and normal glucose tolerance (11.3 vs. 5.0 vs. 3.9%, respectively; $P < 0.001$). In subjects with diabetes, but not those with prediabetes or normal glucose tolerance, high pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (odds ratio 1.15 [95% CI 1.04–1.28]) or diastolic or mean BP (all $P < 0.01$). In patients with diabetes, a +1 SD increase of pulse pressure (+13 mmHg) was associated with proteinuria, even after adjustment for systolic BP (1.07 [1.00–1.13]) or diastolic or mean BP (all $P < 0.05$).

CONCLUSIONS—Among the Japanese general population, there was a significant difference in the association between high pulse pressure and proteinuria among subjects with diabetes, prediabetes, and normal glucose tolerance. Only in diabetes was high pulse pressure associated with proteinuria independent of systolic, diastolic, or mean BP levels.

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From the [1]Divisions of Community and Family Medicine, University of Miyazaki, Miyazaki, Japan; [2]Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; the [3]Dialysis Division, University of Miyazaki Hospital, Miyazaki, Japan; the [4]Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan; the [5]Steering Committee for the "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan," Tokyo, Japan; the [6]Department of Planning, Information, and Management, University of Tokyo, Tokyo, Japan; and the [7]Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan.
Corresponding author: Shouichi Fujimoto, fujimos@fc.miyazaki-u.ac.jp.
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In the systemic circulation, the kidney has unique features: vascular resistance in the glomerular afferent arterioles is low, and the myogenic response of the glomerular arterioles is insensitive to changes in the other BP indices of systolic blood pressure (BP), including pulse pressure (1–3). These characteristics suggest that pressure pulsatility may contribute to barotrauma-induced renal microvascular injury, and in turn causes glomerular ultrastructural changes (e.g., podocyte loss and glomerular basement membrane thickness) (1–6).

In fact, several cross-sectional studies performed in general or hypertensive populations have demonstrated a significant association between pulse pressure and albuminuria (7,8), and some longitudinal studies have underscored the importance of pulse pressure as a risk factor for increased albuminuria in general or hypertensive populations (9,10); however, few studies have directly examined the impact of high pulse pressure on albuminuria with adjustment for other BP components, such as systolic BP, diastolic BP, and/or mean BP levels. Since renal autoregulation is particularly impaired in patients with diabetes (1–3,11–13), we hypothesized that the association between high pulse pressure and albuminuria would be more prominent in patients with diabetes than in subjects without diabetes (14–16); as of yet, however, there have been no studies examining this hypothesis directly in a large database. Furthermore, the association of pulse pressure with albuminuria has never been explored in prediabetics, who are classified as being at an intermediate stage between normal glucose tolerance and diabetes (17), but prediabetics have been shown to have a significantly increased risk of developing not only diabetes but also cardiovascular disease (18).

In the current study, therefore, we examined the association of high pulse pressure with proteinuria separately in each of subjects with diabetes, prediabetes, and normal glucose tolerance, using a large nationwide

database of subjects recruited from the national health checkup system in Japan.

RESEARCH DESIGN AND METHODS

Study 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. In Japan, there are 47 administrative divisions (prefectures), and 13 of these prefectures (Yamagata, Miyagi, Fukushima, and Niigata from the Tohoku region in northeastern Japan; Tokyo, Kanagawa, and Ibaraki from the Kanto region in central Japan; Osaka, Okayama, and Kochi from the Kansai, Tyugoku, or Shikoku region in western Japan; and Fukuoka, Miyazaki, and Okinawa from the Kyushu region in southern Japan), which were randomly distributed across Japan, agreed with the aims of this study and performed data collection prospectively from 2008 to 2009. Data were sent to an independent data center, the nonprofit organization Japan Clinical Research Support Unit after anonymization in a linkable fashion, and verified by trained staff (K.I. and Y.O.). After that, the database was locked with a security password, which contained the participant's information managed by a research ID number but did not contain the participant's name, and was sent to each investigator on a recordable compact disc.

There were a total of 346,942 subjects (mean age, 63.4 years; 41% [n = 141,938] men) for whom information on age, sex, BP, BMI, habitual smoking or drinking, use of antihypertensive drugs, and previous history of cardiovascular diseases (i.e., stroke and cardiac diseases such as angina and myocardial infarction) were available, as well as data on the serum creatinine level and dipstick urine test for proteinuria (19). Some of the regions participating in our project (i.e., Okinawa and Osaka) concomitantly performed regular health checkups for employees as legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years (n = 2,025). Among the 346,942 subjects, 29,820 subjects with a previous history of cardiovascular disease, 243 subjects with chronic kidney disease stage 5 (estimated glomerular filtration rate [eGFR] $<$15 mL/min/1.73m^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. Supplementary Table 1 shows the differences in clinical characteristics 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 Ethical Guidelines for Epidemiological Research (1 November 2007, Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor, and Welfare of Japan). Ethical approval from the respective institutional review boards was also granted.

Baseline measurement

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habits (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). 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 the subject had rested for 5 min in a seated position with the legs not crossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement. Pulse pressure was calculated as systolic BP − diastolic BP, and mean BP was calculated as diastolic BP + (pulse pressure/3).

Blood samples were collected after an overnight fast 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 beginning several years ago, standardized methods to measure laboratory data were recommended and widely adopted by the activity of the Japan Society of Clinical Chemistry.

The value for hemoglobin A_{1c} (HbA_{1c}) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following equation (20): HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%.

Diabetes was defined in accordance with American Diabetes Association guidelines (17) as a fasting glucose concentration of 126 mg/dL or higher, HbA_{1c} 6.5% or higher, or self-reported use of antihyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) or HbA_{1c} 5·7–6·4%, or both (17).

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early morning after overnight fasting. Urine dipstick results are interpreted by the medical staff in each local medical institution and recorded as −, ±, 1+, 2+, and 3+. In Japan, it is recommended and widely adopted by the activity of the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick tests be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dL. In the current study, proteinuria was defined as 1+ or more. eGFR was derived using the following equation (21): eGFR (mL/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × serum creatinine (mg/dL)$^{-1.094}$ (if women ×0.739).

Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Data were expressed as the means ± SD (age, BMI, eGFR, and BP values) or median and interquartile range (glucose and lipid parameters). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using ANOVA, and categorical parameters were compared with the χ^2 test. We subdivided the study population according to the quintiles of pulse pressure, and the prevalence of proteinuria (≥1+) was compared by χ^2 test among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The highest quintile of pulse pressure (≥63 mmHg, n = 40,511) was defined as the high pulse pressure group in the present analysis.

Next, we used a multivariable logistic regression analysis to examine the independent

association of high pulse pressure with proteinuria (≥1+) separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. In the initial model (Model 1), these associations were assessed with adjustment for age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and eGFR. Extended models were used to assess whether the association of high pulse pressure with proteinuria (≥1+) was attenuated by the potential confounding effects of glucose and lipid parameters (Model 2) and systolic BP (Model 3). In addition, to minimize the influence of systolic BP in the association between pulse pressure and proteinuria, we examined the association only in patients with diabetes whose systolic BP was within the normal BP range (i.e., <130 mmHg) (22). Finally, we examined the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes by a multivariable logistic regression analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics of the study population

The mean age ± SD of the 228,778 subjects was 63.2 ± 8.9 years, and 89,877 of the subjects (39.3%) were men. There were 27,913 subjects (12.2% of the total subject population) with diabetes, of whom 10,980 subjects (39.1%) were taking antihyperglycemic medications. There were 100,214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes are shown in Table 1. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) for the increased risk of proteinuria (≥ 1+) in diabetes itself was 2.14 (95% CI 2.03–2.25), and that in prediabetes was 1.10 (1.05–1.14), even after adjustment for significant covariates, such as age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and systolic BP level (both $P < 0.001$).

Pulse pressure and proteinuria

Clinical characteristics and metabolic or BP parameters according to the quintile of pulse pressure are shown in Supplementary Table 2. The increasing prevalence of proteinuria (≥1+) in accordance with the increasing pulse pressure was more prominent in subjects with diabetes than those without diabetes (Fig. 1). Supplementary Table 3 shows the prevalence of proteinuria subdivided by the dipstick positive scale according to the quintile of pulse pressure with or without diabetes.

Next, a multivariable logistic regression analysis was performed to examine the independent association between the highest quintile of pulse pressure and proteinuria, separately in subjects with diabetes, prediabetes, and normal glucose tolerance. In patients with diabetes, the highest quintile of pulse pressure (≥63 mmHg) was positively associated with proteinuria, independently of significant covariates, including systolic BP (Models 1–3 in Table 2). When we examined the association between pulse pressure and proteinuria only in patients with diabetes whose systolic BP was within the normal range (i.e., <130 mmHg, n = 11,074 [39.7%]), the highest quintile of pulse pressure still remained significantly associated with proteinuria (OR 1.46 [95% CI 1.03–2.08]; $P = 0.04$, respectively), even after adjustment for significant covariates, as shown in Model 2 in Table 2. When diastolic BP or mean BP was entered into Model 3 in Table 3 in place of systolic BP, the association between the highest quintile of pulse pressure and proteinuria still remained significant (1.61 [1.49–1.75] and 1.42 [1.31–1.55]; both $P < 0.001$, respectively). In contrast, the highest quintile of pulse pressure in subjects with prediabetes or normal glucose tolerance was not associated with proteinuria independently of systolic BP (Model 3 in Table 2). When

Table 1—*Characteristics of the study population according to the presence of diabetes or prediabetes*

	Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)	P value
Age (years)	65.2 ± 7.3	64.2 ± 7.9	61.6 ± 9.8	<0.001
Men, n (%)	14,626 (52.4)	40,077 (40.0)	35,174 (34.9)	<0.001
BMI (kg/m^2)	24.1 ± 3.7	23.3 ± 3.3	22.5 ± 3.1	<0.001
Current smoker, n (%)	4,846 (17.4)	12,960 (12.9)	13,971 (13.9)	<0.001
Daily drinker, n (%)	7,162 (25.7)	22,825 (22.8)	21,521 (21.4)	<0.001
eGFR (mL/min/1.73 m^2)	76.2 ± 17.8	74.7 ± 15.6	76.1 ± 15.9	<0.001
Proteinuria (≥1+), n (%)	3,164 (11.3)	5,013 (5.0)	3,913 (3.9)	<0.001
Glucose and lipid parameters				
Fasting glucose (mg/dL)*	125.0 (100.0–143.0)	98.0 (90.0–105.0)	89.0 (84.0–93.0)	<0.001
HbA_{1c} (%)*	6.2 (5.6–6.9)	5.4 (5.3–5.6)	5.0 (4.8–5.1)	<0.001
Triglycerides (mg/dL)*	112.0 (79.0–162.0)	101.0 (74.0–142.0)	91.0 (67.0–127.0)	<0.001
LDL (mg/dL)*	123.0 (104.0–145.0)	127.0 (108.0–148.0)	124.0 (105.0–144.0)	<0.001
HDL (mg/dL)*	57.0 (48.0–68.0)	60.0 (51.0–72.0)	63.0 (53.0–75.0)	<0.001
Antihypertensive drugs, n (%)	11,101 (39.8)	29,157 (29.1)	21,410 (21.3)	<0.001
Antihyperlipidemic drugs, n (%)	6,823 (24.4)	17,440 (17.4)	12,233 (12.2)	<0.001
Antihyperglycemic drugs, n (%)	10,980 (39.1)	0 (0)	0 (0)	<0.001
BP parameters				
Systolic BP (mmHg)	133.4 ± 17.5	129.7 ± 17.0	125.7 ± 17.2	<0.001
Diastolic BP (mmHg)	77.1 ± 10.8	76.8 ± 10.5	75.1 ± 10.7	<0.001
Pulse pressure (mmHg)	56.2 ± 13.4	52.9 ± 12.4	50.6 ± 12.2	<0.001

Data are expressed as the means ± SD or percentage. P values were obtained by ANOVA or χ^2 test. *Variables with skewed distribution are expressed as median (interquartile range).

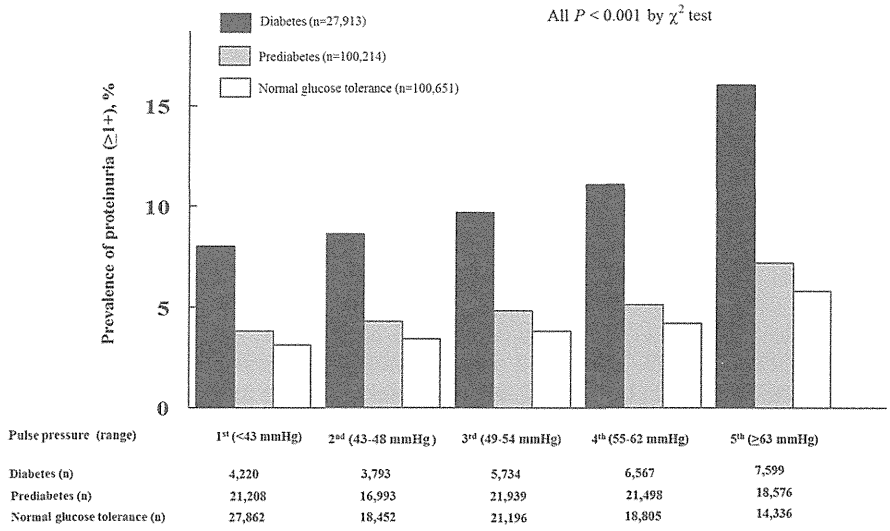

Figure 1—*Prevalence of proteinuria according to the quintile of pulse pressure in subjects with diabetes, prediabetes, or normal glucose tolerance. The prevalence of proteinuria (≥1+) was calculated among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The* P *value was obtained by a* χ^2 *test among each group of the quintiles of pulse pressure.*

we examined the risk of the highest quintile of pulse pressure on proteinuria among subjects without antihypertensive medications (n = 167,110), the conclusion remained unchanged (Model 4 in Table 2). Use of antihyperglycemic or antihyperlipidemic drugs did not influence any of the above results (data not shown). In contrast, systolic BP, used as an adjusted factor in Model 3 in Table 2, showed significant associations with proteinuria in subjects with diabetes, prediabetes, and normal glucose tolerance (data not shown).

Finally, we analyzed the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes. We found that a +1 SD increase of pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (Table 3), diastolic BP, or mean BP (data not shown).

CONCLUSIONS—In this nationwide study of 228,778 Japanese people (mean age 63.2 years) who had no known cardiovascular disease, we demonstrated for the first time that there was a significant difference in the association between the highest quintile of pulse pressure (≥63 mmHg) and proteinuria (≥1+ on dipstick) among subjects with diabetes, prediabetes, and normal glucose tolerance. The cross-sectional design of the current study did not allow us to elucidate the pathophysiological pathway linking high pulse pressure and proteinuria (≥1+). However, there are some possible explanations for the observed association.

Pulse pressure, proteinuria, and patients with diabetes

Since the glomerular afferent arterioles provide relatively low resistance, the glomerulus is susceptible to barotrauma if the pulse pressure is elevated (1–6). In fact, prior studies have demonstrated an association of high pulse pressure with microalbuminuria even in subjects without diabetes (7,8). In the current study, we examined the possible association of high pulse pressure and proteinuria (≥1+), i.e., macroalbuminuria, and found that this association was not significant independently of systolic BP in subjects without diabetes. In contrast, systolic BP was significantly associated with proteinuria in these subjects. Although the usefulness of the urine dipstick test for risk stratification of renal and cardiovascular disease has been recognized, this method is a less sensitive measure of albuminuria compared with the measurement of urinary albumin excretion (23–26). Accordingly, we cannot deny the possibility of an association between high pulse pressure and microalbuminuria in subjects without diabetes.

Table 2—*OR for the highest quintile of pulse pressure in the association of proteinuria (≥1+) according to the presence of diabetes or prediabetes*

Model	Adjusted covariates	OR (95% CI)		
Overall (n = 228,778)		Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)
Model 1	Age + sex + BMI + current smoking + daily drinking + antihypertensive medications + eGFR	1.72 (1.59–1.87)‡	1.45 (1.35–1.55)‡	1.48 (1.37–1.61)‡
Model 2	Model 1 + fasting glucose + triglycerides + HDL + LDL	1.63 (1.50–1.77)‡	1.41 (1.31–1.50)‡	1.48 (1.36–1.60)‡
Model 3	Model 2 + systolic BP	1.16 (1.05–1.29)†	0.97 (0.89–1.05)	1.08 (0.98–1.20)
Subjects without antihypertensive medications (n = 167,110)		Diabetes (n = 16,812)	Prediabetes (n = 71,057)	Normal glucose tolerance (n = 79,241)
Model 4	Age + sex + BMI + current smoking + daily drinking + eGFR + fasting glucose + triglycerides + HDL + LDL + systolic BP	1.21 (1.03–1.43)*	1.09 (0.97–1.23)	1.13 (0.98–1.29)

OR (95% CI) of proteinuria (≥1+) was calculated for highest quintile of pulse pressure (≥63 mmHg, n = 40,511) vs. lower quintiles of pulse pressure (<63 mmHg) in each model. Statistical significance was defined as $P < 0.05$. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$.

Table 3—*OR (95% CI) for proteinuria in diabetes* (n = 27,913)

Model	OR (95% CI)	*P* value
Age (+9 years)*	0.94 (0.89–1.00)	0.04
Sex (0, men; 1, women)	0.55 (0.50–0.60)	<0.001
BMI (+3 kg/m^2)*	1.18 (1.14–1.22)	<0.001
Current smoking (0, no; 1, yes)	1.49 (1.35–1.65)	<0.001
Daily drinking (0, no; 1, yes)	0.90 (0.82–0.99)	0.04
Antihypertensive medications (0, no; 1, yes)	0.59 (0.54–0.64)	<0.001
eGFR (+16 mL/min/1.73 m^2)*	0.76 (0.73–0.79)	<0.001
Fasting glucose (+21 mg/dL)*	1.20 (1.18–1.22)	<0.001
Triglycerides (+78 mg/dL)*	1.06 (1.03–1.09)	<0.001
LDL (+30 mg/dL)*	1.07 (1.03–1.11)	<0.001
HDL (+16 mg/dL)*	1.02 (0.98–1.07)	0.39
Systolic BP (+17 mmHg)*	1.27 (1.20–1.36)	<0.001
Pulse pressure (+13 mmHg)*	1.08 (1.01–1.14)	0.02

Statistical significance was defined as $P < 0.05$. *The OR (95% CI) of proteinuria (≥1+) was calculated for a +1 SD increase of each indicated variable as well as dichromatic variables.

In spite of the strict collinearity between systolic BP and pulse pressure, the OR of high pulse pressure to proteinuria was reduced but remained significant even after adjustment for systolic BP in patients with diabetes (Table 2). Table 3 also shows that a +1 SD increase of systolic BP and a +1 SD increase of pulse pressure were associated with proteinuria independently of each other, with the OR of the systolic BP increase on proteinuria being higher than that of the pulse pressure increase. These findings indicate that high systolic BP showed a confirmed association with proteinuria and is an important confounder explaining the association between high pulse pressure and proteinuria; however, even after adjustment for systolic BP, the pulsatile component of BP itself was still significantly associated with proteinuria in patients with diabetes. Intriguingly, even in the patients with diabetes who were within the normal range of systolic BP values, high pulse pressure was associated with proteinuria. Some possible explanations for these findings exist. First, since renal autoregulation is impaired in diabetes (1–3,11–13), it may be possible that when pulse pressure is elevated, more barotrauma-induced glomerular ultrastructural changes leading to albuminuria occur in subjects with diabetes than in those without diabetes (1–5). Second, much as in the previous reports (27,28), higher pulse pressure was observed in diabetes than nondiabetes (Table 1), suggesting the possibility that diabetes accelerates aortic and large arterial stiffness (29). Aortic stiffness itself has a potential etiologic role in the causation and progression of renal dysfunction (30–32), because loss of the damping of ventricular ejection in the stiffened aortae could lead to an increase in the transmission of these pressure changes to the renal microcirculation. In the current study, however, we did not use any measure of vascular stiffness more direct than pulse pressure, such as pulse wave velocity, and thus the potential efficacy of such measures will need to be investigated in the future. Third, overt proteinuria in patients with diabetes, which is observed in long-standing diabetes, together with hypertension and increased arterial stiffness, is a surrogate marker not only for renal structural damages but also generalized vascular damages (3,6,24,25). Therefore, we speculate that patients with diabetes with proteinuria are likely to have systemic vasculopathy, and as a consequence, they have high pulse pressure. Lastly, since the current study is a cross-sectional analysis, we have to pay attention to another possibility that diabetic renal disease indicated by greater proteinuria raises systolic BP as well as pulse pressure rather than the reverse in patients with diabetes.

Pulse pressure, proteinuria, and prediabetes

The current study provided the first examination of the association of pulse pressure with proteinuria in prediabetes using a large sample size. Understanding such risk estimates is important, given the increases in the prevalence of prediabetes that have occurred in many populations in conjunction with the increasing prevalence of obesity, particularly in Asian populations (33,34). In the current study, the prevalence of prediabetes was substantially high (44%). Another Japanese study performed in healthy Japanese people (n = 6,636, mean age 50 years) demonstrated that the prevalence of prediabetes was 32% (35). This survey was performed between 1997 and 2003, and since the prevalence of diabetes in Asian populations has increased rapidly in recent years (33,34), the high prevalence of prediabetes in the current study was not entirely unexpected.

Several limitations of our study should be mentioned. First, single-measurement readings of BP, fasting glucose or HbA_{1c}, and proteinuria cannot be considered fully accurate. In particular, some of the dipstick-positive proteinuria could have been transient, and thus could not be taken as definitive evidence of the presence of persisting proteinuria. These factors may introduce a source of variability that could have led to a tendency to underestimate the true association between pulse pressure and proteinuria. Second, we could not separate diabetes into type 1 or type 2 diabetes. However, the incidence of type 1 diabetes is extremely low (approximately two cases/year/100,000 individuals), and Japan has one of the lowest incidence rates of type 1 diabetes in the world (36). Third, we could not assess the diabetes- and atherosclerosis-related information, such as the duration of diabetes and the presence of diabetes complications (e.g., neuropathy), which would be informative and extend the knowledge achieved in the current study. Lastly, we could not assess what kinds of antihypertensive drugs had been prescribed in treated hypertensive subjects. Some antihypertensive drugs (e.g., angiotensin receptor blockers or angiotensin enzyme–converting inhibitors) have more favorable effects on vascular and renal protection (37). Therefore, their use was potentially confounding, although our conclusions remained unchanged when we analyzed our data while excluding the subjects with antihypertensive medications.

In conclusion, among the Japanese general population, high pulse pressure, particularly in individuals with diabetes, was associated with proteinuria, and this information has the potential to supplement other BP indices. To confirm our findings, a prospective study as well as interventions that examine whether or not reduction of pulse pressure can enhance nephron-protective benefits in diabetes will be required.

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Y.Y. and Y.S. analyzed data. S.F. designed the study, collected data, and wrote the manuscript. T.K. and K.I. designed the study and collected data. T.M., K.Y., K.T., H.Y., K.A., I.K., Y.O., and T.W. designed the study, collected data, supervised the study, and revised the manuscript. S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ORIGINAL ARTICLE

Annual incidence of persistent proteinuria in the general population from Ibaraki annual urinalysis study

Kei Nagai · Chie Saito · Fumiyo Watanabe · Reiko Ohkubo · Chihiro Sato · Tetsuya Kawamura · Kensuke Uchida · Akira Hiwatashi · Hirayasu Kai · Kumiko Ishida · Toshimi Sairenchi · Kunihiro Yamagata

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Abstract
Background For a definitive diagnosis of chronic kidney disease, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. However, most previous reports were based on single-screening data.
Patients and methods The subjects in this study were participants in an annual health examination held in Ibaraki, Japan, between 1993 and 2003. The follow-up duration with serial urinalysis for 3 years of patients who were negative for proteinuria in the initial year was 330,614 person-years in males and 687,381 person-years in females among 81,854 male and 155,256 female subjects. We evaluated the incidence and risk factor for the incidence of proteinuria and persistent proteinuria.
Result The annual incidence of proteinuria and persistent proteinuria was 1.31 and 0.33 % in males and 0.68 and 0.14 % in females. Among the subjects without hypertension and diabetes, the annual incidence was 0.81 and 0.16 % in males and 0.37 and 0.06 % in females, respectively. Risk analysis indicated that hypertension in males [hazard ratio (HR) 2.052] and females (2.477), diabetes in males (3.532) and females (3.534) and reduced renal function in males (3.097) and females (2.827) were significant positive risks for development of persistent proteinuria.
Conclusion By annual urinalysis screening of the general population, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year. Subjects with diabetes, hypertension and reduced renal function had a 2 or 3 times higher risk for the incidence of persistent proteinuria in both males and females.

Keywords Urinalysis · Chronic kidney disease · Persistent proteinuria · Risk factors

Introduction

At present, it is considered that the worldwide population of patients with end-stage renal disease (ESRD) will continue to increase as a result of more patients requiring renal replacement therapy (RRT). Moreover, we know that chronic kidney disease (CKD) is a risk factor of not only progression to ESRD, but also the development of cardiovascular diseases (CVD) [1–3]. Therefore, we should promote reducing the incidence of CKD to save quality of life in the general population and economic loss due to the increasing number of ESRD patients.

In Japan, annual urinalysis screening programs were introduced for every schoolchild in 1973, for every working adult in 1972, and for residents >40 years of age in 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan [4]. However, Boulware et al. [5] reported that annual urinalysis screening for proteinuria is not cost-effective unless selectively directed toward a high-risk group such as older persons and persons with hypertension, or conducted at an infrequent interval. However, Kondo et al. [6] reported that

K. Nagai · C. Saito · F. Watanabe · R. Ohkubo · C. Sato · T. Kawamura · K. Uchida · A. Hiwatashi · H. Kai · K. Yamagata (✉)
Department of Nephrology, Faculty of Medicine, University of Tsukuba, 1-1-1 Ten-oudai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: k-yamaga@md.tsukuba.ac.jp

K. Ishida
Ibaraki Prefectural Government, Tsukuba, Japan

T. Sairenchi
Department of Public Health, Dokkyo Medical University, Tochigi, Japan

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annual screening of proteinuria with dipsticks was cost-effective for the Japanese population. One reason for the opposite views on urinalysis screening comes from the difference in the prevalence of proteinuria among races [7–9]. In particular, the prevalence of proteinuria is high in the Japanese general population [4, 10] and in Asians generally [7]. Chronic glomerulonephritis (CGN) has been found to be a more frequent underlying renal disease for ESRD in Asians than in Caucasians [11, 12]. Most CGN patients have no symptoms at the early stage of the disease, and the only method for early detection is urinalysis [13]. The reduced number of new ESRD patients with CGN might be caused by early detection and early referral to nephrologists due to the annual urinalysis screening program in Japan [14, 15]. Proteinuria also accelerates a decline in the glomerular filtration rate (GFR) [16], and proteinuria is the strongest predictor of CKD stage progression [17].

Therefore, to explain the effectiveness of annual urinalysis screening, we had to elucidate the annual incidence of proteinuria and persistent proteinuria in the general population and focus on people without high risk of proteinuria such as hypertension and diabetes. To date, however, because most previous reports were based on single-screening data, we had no precise evidence of the incidence of persistent proteinuria for a period of more than 3 months, which is a required for a definitive diagnosis of CKD in the general population.

In this study, from the result of the annual health examination held in Ibaraki, Japan, we estimated the annual incidence of proteinuria and persistent proteinuria among the Japanese general population and among the population with or without diabetes, hypertension or reduced renal function. This analysis might provide clues for future screening policy for urinary abnormalities to reduce the number of CKD patients.

Subjects and methods

The participants in the annual health examination held in Ibaraki, Japan between 1993 and 2003 comprised 152,569 males and 267,594 females (age range 40–98 years (median 61 years). Among them, 63,728 males and 103,381 females did not receive serial urinalysis for 3 years, 5,174 males and 4,368 females had proteinuria at their initial urinalysis, and 1,813 males and 4,589 females had missing data. The prevalence of proteinuria in our subjects, i.e., a positive result for proteinuria in their first urine examination, was 3.4 % (5,174/152,569) in males and 1.6 % (4,368/267,594) in females. After we excluded those subjects, the study population comprised 81,854 male and 155,256 female subjects.

To diagnose persistent proteinuria, data obtained with an interval of >3 months is required by definition [18]. The incidence of persistent proteinuria in this study was defined as positive for proteinuria by consecutive annual urinalysis. The subjects were followed up until persistent proteinuria was recorded during the 10-year follow-up duration; their follow-up duration was 330,614 person-years in males and 687,381 person-years in females (Fig. 1).

We defined diabetes as subjects who were taking oral hypoglycemic or insulin treatment, subjects with fasting blood sugar ≥126 mg/dl or random blood sugar ≥200 mg/dl. Subjects having systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medication were defined as hypertensive [19]. Estimated GFR (eGFR) was calculated from the simplified equation developed from the MDRD study [20] as follows: $\text{eGFR (ml/min/1.73 m}^2) = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for female subjects})$ without adjusting for Japanese covariant factors and we separated the subjects to normal renal function (eGFR ≥60 ml/min/1.73 m^2) and reduced renal function (eGFR <60 ml/min/1.73 m^2). These co-morbid conditions of the initial year were applied for the analysis.

Hypercholesterolemia was defined as total cholesterol (T-Cho) ≥220 mg/dl, low high-density lipoprotein cholesterol (HDL-C) as ≤35 mg/dl, and hypertriglyceridemia was defined as triglycerides (TG) ≥250 mg/dl.

Alcohol intake was defined as total alcohol consumption in grams per day calculated from questions on the number of glasses of wine, beer, fortified wines, sake, and liqueurs/

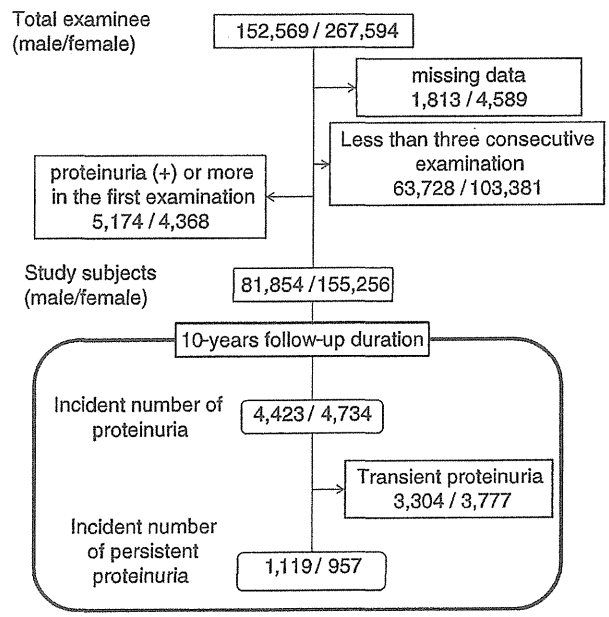

Fig. 1 Number of examinee and study subjects and their male:female ratio are shown

spirits per day. One glass of any alcoholic beverage was assumed to contain 10 g of alcohol. The total alcohol consumption was then classified into four categories—no alcohol consumption, occasional alcohol consumption, <20 g/day, and >20 g/day. Smoking habits were classified into three categories—non-smoker, previous smoker or current smoker.

Proteinuria was tested using dipstick (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan). A test result of '1+' or more was defined as positive. Serum creatinine concentration was measured by a modified Jaffe method (Creatinine-HR; Wako Pure Chemicals Industries, Ltd., Osaka, Japan) using an autoanalyzer (Hitachi 7350; Hitachi Ltd., Tokyo, Japan or RX-20; JEOL Ltd., Tokyo, Japan). Measurements of blood glucose, T-Cho, TG, and HDL-C were measured using an autoanalyzer (Hitachi 7350; Hitachi Ltd).

Statistical methods

To compare males and females and to compare subjects with presence and absence of hypertension, diabetes or reduced renal function, we applied the chi-squared test. The primary outcome for the analysis was the development of persistent proteinuria during the follow-up period. Variables were age, diabetes, hypertension and renal function (eGFR <60 ml/min), hypercholesterolemia (−, +), low HDL-C (−, +), hypertriglyceridemia (<150 mg/dl, 150−299 mg/dl, ≥300 mg/dl), obesity (−, +), cigarette smoking (never, previous smoker and current smoker with <1 pack/day and >1 pack/day), alcohol consumption (never, occasional drinker, alcohol consumption <20 g/day and alcohol consumption ≥20 g/day). Hazard ratios of proteinuria and persistent proteinuria development by sex were estimated by using Cox regression model after confirming the proportionality in each model (SAS software, version 8.3, SAS Institute Inc., CA, USA). A p value of <0.05 was considered statistically significant.

Result

Table 1 shows baseline characteristics of the study subjects. Male subjects were significantly older, more frequently with hypertension and diabetes, and less frequently with reduced renal function.

During the entire observation period, 4,423 male and 4,734 female subjects were newly positive for proteinuria and the annual incidence of proteinuria was 1.31 % in males and 0.689 % in females (Fig. 2a). Among them, 1,119 males and 957 females had continued to be positive for proteinuria. Consequently, the incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females (Fig. 2a); 74.7 % (3,304/4,423) in males and 79.8 % (3,777/4,734) in females had transient proteinuria.

From the above results, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year in our study subjects. The incidence of proteinuria and the incidence of persistent proteinuria were both significantly higher in males.

When separating the subjects by co-morbid conditions, the annual incidence of proteinuria among the subjects without hypertension and diabetes was 0.83 % in males and 0.37 % in females (Fig. 2b). Moreover, the annual incidence of persistent proteinuria was 0.16 and 0.06 %, respectively, and 1 out of 632 male subjects and 1 out of 1,626 female subjects developed persistent proteinuria every year.

The annual incidence of proteinuria and persistent proteinuria in the subjects with hypertension, diabetes or reduced renal function was significantly higher than the incidence without each condition. Meanwhile, the annual incidence of persistent proteinuria in males with each co-morbid condition was significantly higher than the incidence without it (Fig. 3a). In females, the annual incidence of proteinuria was highest in subjects with diabetes followed by reduced renal function and hypertension and each of them was also significantly higher than the incidence without each condition (Fig. 3b).

We then analyzed the risk factors for the incidence of proteinuria and persistent proteinuria. Significant risk factors for the incidence of proteinuria were age, hypertension, diabetes, reduced renal function, obesity, low HDL-C, hypertriglyceridemia, and heavy smoker (current smoker >1 pack/day) in male subjects. In females, we found the same trend in risk factors for the incidence of persistent proteinuria as in males except for low HDL, hypertriglyceridemia and alcohol consumption (Table 2). Low HDL was not a significant risk for the incidence of persistent proteinuria in females, whereas hypertriglyceridemia (≥300 mg/dl) was a higher risk factor in females than in males. For smoking habit, a significant risk for incidence of persistent proteinuria was observed in both previous and current smoker in males.

Discussion

Diabetic nephropathy, CGN, and hypertensive nephropathy are three universal major primary renal diseases leading to ESRD. For the purpose of early detection of diabetic nephropathy or hypertensive nephropathy, selective screening of patients with diabetes or hypertension might be preferable. However, we should take into account that the prevalence and incidence of ESRD due to CGN are

Table 1 Baseline characteristics of the subjects divided by sex

	Males		Females	
Subjects in the study (*N*)	81,854		155,256	
Age[a]	60.2	9.7	56.8	10.2*
Follow-up duration (person-years)	330,614		687,381	
Non-hypertensive, non-diabetic[b]	36,567	44.7 %	89,360	57.6 %*
Non-hypertensive, diabetic[b]	2,410	2.9 %	2,171	1.4 %*
Hypertensive, non-diabetic[b]	39,115	47.8 %	60,301	38.8 %*
Hypertensive, diabetic[b]	3,762	4.6 %	3,424	2.2 %*
GFR <60 ml/min/ 1.73 m^2 [b]	4,272	5.20 %	9,643	6.2 %*
Total cholesterol (mg/dl[a])	196.5	34.1	209.9	35.2*
HDL-C (mg/dl[a])	52.8	14.6	58.4	14.5*
TG (mg/dl[a])	151.6	100.4	131	78.4*
Body mass index[a]	23.4	2.9	23.4	3.2
Smoking				
Current[b]	38,847	47.5 %	9036	5.9 %*
Previous[b]	24,103	29.4 %	1,219	0.8 %*
Alcohol consumption				
Occasional[b]	12,019	14.7 %	13,857	8.9 %*
Ethanol <20 g/day[b]	39,135	47.8 %	6,854	4.4 %*
Ethanol >20 g/day[b]	4,468	5.5 %	192	0.1 %*

* $p < 0.05$

[a] Mean, SD

[b] *N* (%)

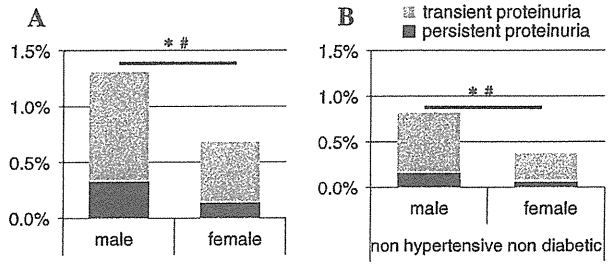

Fig. 2 The annual incidence of proteinuria and persistent proteinuria. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria, respectively. A total of *stacked bars* mean annual incidence of proteinuria. The incidence of proteinuria and persistent proteinuria in males and females with any comorbid conditions (a) or without hypertension and diabetes (b) was demonstrated. Statistical significant value between males and females was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

different among races and geographic areas [4, 21–25]. Moreover, early detection of asymptomatic CGN without hypertension or diabetes strongly depends on urinalysis performed when screening the general population.

For a definitive diagnosis of CKD, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. To date, there has been no report on the annual incidence of persistent proteinuria in the general population.

In the present study, the incidence of persistent proteinuria in the general population was one-quarter of the incidence of proteinuria with an estimated 3,298 cases per million per year (1 patient per 303 person-years) in males and 1,379 cases per million per year (1 patient per 725 person-years) in females.

Previously, Brantsma et al. reported that the annual incidence of microalbuminuria was 1.02 % in both genders [26]. By using urine dipsticks we found an annual incidence of proteinuria of 1.20 % in males and 0.64 % in females. Furthermore, the incidences of proteinuria in our study were 37–81 times higher than in previous reported incidences in the non-hypertensive and non-diabetic population [0.01 % (0.001–0.1 %)] [5, 27]. In Japan, because of the high annual incidence of proteinuria among the non-hypertensive and non-diabetic population including CGN, frequent universal urinalysis screening might be preferable. As well as the incidence of proteinuria, the incidence of persistent proteinuria was higher in subjects with hypertension, diabetes or reduced renal function than in subjects without these conditions in both genders. Among incident proteinuria, 74.7 % of males and 79.8 % of females had transient proteinuria. Using 24-h urinary albumin excretion, albuminuria was diminished in 27.8 % of the subjects for a median follow-up duration of 4.2 years [26]. Using dipstick urinalysis, we have higher false positive results due to urine concentration or other non-pathological conditions. However, it is important to know aging, hypertension, diabetes, reduced renal function, obesity, dyslipidemia and smoking habit were strong risk factors for developing persistent proteinuria in both males and females. Further studies are needed to confirm the effect of controlling those factors on the incidence of both proteinuria and persistent proteinuria in a large population.

Our study has the advantage of a large sample size and availability of serial data. Moreover, this is the first report to show the incidence of persistent proteinuria in a community-based frequent follow-up study. However, it also has several limitations. Firstly, the participants of this study were from a community-based general population, but there was a lack of subjects aged <40 years old. Secondly, there was no data about detailed underlying renal diseases in our subjects.

In conclusion, our study aimed to determine the incidence of persistent proteinuria and its risk factors, and this is the first report to show the incidence of persistent proteinuria in the general population. As a result, the annual incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females. The incidence of persistent proteinuria among the hypertensive, diabetic or reduced renal function

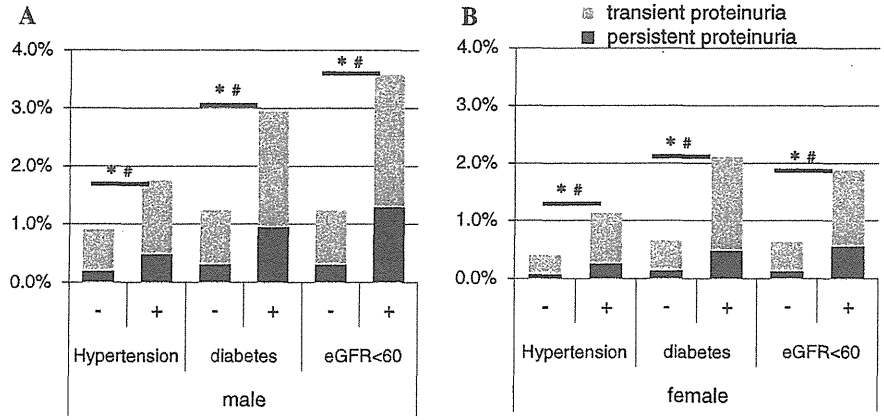

Fig. 3 The different annual incidence between the presence and absence of co-morbid conditions. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria. A total of *stacked bars* mean annual incidence of proteinuria. Every co-morbid condition was significantly higher than without it (**a**, **b**). In any condition >20 % in males (**a**) and >16 % in females (**b**) with proteinuria in the 2nd year had persistent positive results for proteinuria. Statistical significant value between presence and absence of co-morbid conditions was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

Table 2 Multivariate analysis of predictors for developing persistent proteinuria

Predictors at first year	Male			Female		
	HR	95 % CI	*p*	HR	95 % CI	*p*
Age	1.03	1.022–1.04	<0.0001*	1.024	1.016–1.032	<0.0001*
Non-hypertensive, non-diabetic	1.00					
Non-hypertensive, diabetic	3.532	2.627–4.75	<0.0001*	3.534	2.338–5.341	<0.0001*
Hypertensive, non-diabetic	2.052	1.761–2.39	<0.0001*	2.477	2.116–2.898	<0.0001*
Hypertensive, diabetic	5.216	4.239–6.42	<0.0001*	5.62	4.315–7.319	<0.0001*
GFR <60 ml/min/1.73 m^2	3.097	2.637–3.64	<0.0001*	2.827	2.392–3.340	<0.0001*
Body mass index >25	1.511	1.332–1.71	<0.0001*	1.649	1.446–1.880	<0.0001*
Total cholesterol ≥220 mg/dl	1.075	0.934–1.24	0.3105	1.103	0.968–1.258	0.1401
HDL-C <35 mg/dl	1.387	1.144–1.68	0.0009*	1.008	0.729–1.393	0.9609
TG 150–299 mg/dl	1.25	1.096–1.43	0.0009*	1.449	1.261–1.666	<0.0001*
TG >300 mg/dl	1.249	0.992–1.57	0.0583	1.815	1.41–2.336	<0.0001*
Previous smoking	1.26	1.07–1.49	0.0058	1.537	0.765–3.091	0.2273
Current smoking <1 pack/day	1.48	1.09–2.02	0.0134*	1.419	0.934–2.157	0.1014
Current smoking >1 pack/day	1.44	1.23–1.7	<0.001*	1.44	0.97–2.137	0.0707
Occasional drinker	0.99	0.82–1.19	0.891	0.816	0.603–1.104	0.1879
Ethanol <20 g/day	0.85	0.74–0.97	0.0195*	1.012	0.71–1.442	0.9486
Ethanol >20 g/day	0.91	0.68–1.21	0.5067			

95 % CI 95 % confidence interval

* $p < 0.05$

population was much higher than among the normal population. By annual urinalysis screening of the general population, we detected that 1 out of 303 male subjects and 1 out of 725 female subjects developed CKD due to persistent proteinuria every year in Japan.

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Conflict of interest None declared.

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