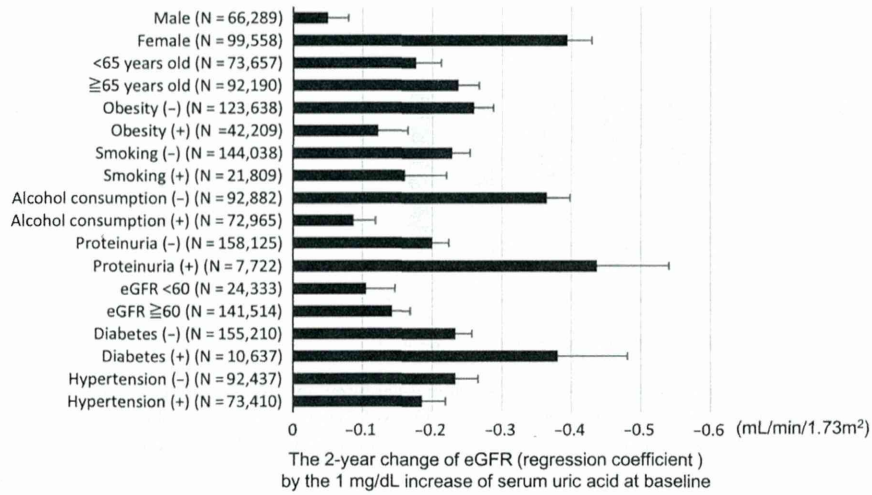

FIGURE 2: The 2-year change in eGFR by the 1 mg/dL increase of serum uric acid at baseline. eGFR, estimated glomerular filtration rate. Adjusted for gender, age, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking, alcohol consumption and proteinuria. Mean ± SE.

Table 2. OR of serum uric acid level categories for incidental renal insufficiency

Category	Unadjusted			Adjusted[a]		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.229	1.141–1.324	<0.001	0.995	0.920–1.077	0.909
Q3 (M 5.7–6.2, F 4.4–4.8)	1.576	1.466–1.696	<0.001	1.048	0.971–1.132	0.231
Q4 (M 6.3–7.0, F 4.9–5.4)	1.921	1.789–2.063	<0.001	1.104	1.024–1.191	0.010
Q5 (M ≥ 7.1, F ≥ 5.5)	2.399	2.236–2.575	<0.001	1.203	1.115–1.299	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.739	1.645–1.837	<0.001	1.117	1.051–1.187	<0.001
Uric acid (per 1 mg/dL increase)	1.280	1.260–1.300	<0.001	1.056	1.035–1.078	<0.001

OR, odds ratio; CI, confidence interval; M, males; F, females.
[a]Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR and proteinuria.

Table 3. Adjusted OR of serum uric acid level categories for incidental renal insufficiency by gender.

Category	Males			Females		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.007	0.896–1.133	0.904	0.985	0.886–1.096	0.784
Q3 (M 5.7–6.2, F 4.4–4.8)	1.113	0.992–1.248	0.067	1.013	0.913–1.125	0.806
Q4 (M 6.3–7.0, F 4.9–5.4)	1.183	1.059–1.323	0.003	1.065	0.960–1.182	0.237
Q5 (M ≥ 7.1, F ≥ 5.5)	1.243	1.107–1.397	<0.001	1.216	1.098–1.348	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.134	1.045–1.230	0.003	1.136	1.036–1.245	0.007
Uric acid (per 1 mg/dL increase)	1.056	1.027–1.087	<0.001	1.076	1.043–1.109	<0.001

Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, proteinuria and eGFR.
OR, odds ratio; CI, confidence interval; M, males; F, females.

function could be modulated by the characteristics of the studied population.

Previous studies showed conflicting results on the association between uric acid levels and kidney disease, and this could be due to the insufficient statistical power resulting from a small sample size, the difference in characteristics of subjects and the analytical methods used [5]. In this study, we had a very large sample size to allow for subgroup

analyses with sufficient statistical power, different classifications of uric acid levels (hyperuricemia, quintiles and the 1 mg/dL increase in uric acid), to include various correction factors and end points (GFR decrease and incidental renal insufficiency). Therefore, the findings obtained in this study appear to be robust.

Our study showed that the decline of renal function was significantly more rapid with the increased uric acid levels (≥5.7 mg/dL in males and ≥4.4 mg/dL in females), and the OR for incidental renal insufficiency was significantly increased with uric acid levels of ≥6.3 mg/dL in males and ≥5.5 mg/dL in females. This indicates that a slight increase within the normal range of serum uric acid might be a risk for renal function deterioration. This is consistent with the previous observation that cardiovascular mortality in females increases with serum uric acid levels of ≥5.5 mg/dL [1]. Together with previous observations, our finding suggests that the risk for reduced renal function might increase with increased serum uric acid levels, even within the normal range.

Although it is difficult to explain the mechanism of how uric acid causes renal function deterioration, a series of experimental studies provide a possible assumption that mild elevation of uric acid induces oxidative stress and endothelial dysfunction, resulting in the development of glomerular hypertension and arteriolosclerosis [15]. This assumption is supported by the clinical observations that uric acid levels are associated with renal arteriolopathy in biopsy specimens [16] and that an increase of uric acid (≥7 mg/dL for men, ≥6 mg/dL for women) was independent predictor for the development of albuminuria in a community-based population [17].

There was an interaction between uric acid and several clinical parameters such as eGFR, gender, age, BMI, triglycerides, HDL-C, presence of proteinuria and alcohol consumption. This indicates that the characteristics of the studied population might modulate the association between uric acid levels and renal changes. Its effect seems to be stronger in females, those with diabetes and proteinuria and those who do not drink alcohol. In females, serum uric acid levels are lower than males, because of estrogenic compounds that enhance the renal urate excretion [18], and after menopause serum uric acid is increased [19], suggesting an important role of estrogenic hormones in the regulation of uric acid. The estrogenic compounds are also known to have a vascular protective property. Therefore, it is speculated that the increase in uric acid in females is induced by the combination of the decrease of the protective estrogenic compounds and the overproduction of uric acid. This might enhance the effect of uric acid on renal function in females. Hyperuricemia increases intraglomerular pressure [20] and urinary albumin excretion [21]. Diabetes also develops glomerular hypertension and albuminuria, and massive proteinuria is a risk for ESKD [22]. Therefore, it is speculated that hyperuricemia and diabetes synergistically promote kidney injury by inducing glomerular hypertension and proteinuria. Several studies disclosed that regular light-to-moderate drinking appears to protect against incident hypertension and cardiovascular events [23]. Such protective effect of alcohol consumption might attenuate the aggravating effect of uric acid on renal function. The precise mechanism of how these factors interact with uric acid warrants a further research.

Interestingly, there was a positive association between uric acid levels and the change in eGFR in the unadjusted model that became inverse in the eGFR- and multivariate-adjusted models. A significant interaction between uric acid levels and renal function was detected. The baseline GFR was reported to be negatively correlated with GFR changes in the diabetic population [24]. Similarly, in this study, the baseline GFR shows a significant negative correlation with uric acid at baseline and GFR change. This indicates that subjects with high eGFR at baseline is likely to show a low uric acid at baseline and a rapid decline of eGFR. This observation suggests that eGFR at baseline should be regarded as a confounding factor to evaluate the independent effect of uric acid on renal function. Some previous studies did not include baseline eGFR in their multivariate-adjusted models, which may explain the conflicting results observed.

The increase in uric acid was associated with a slow decline of eGFR, but a high incidence of renal insufficiency in the unadjusted model. One of the possible explanations for these contrasting results between the eGFR change and incident renal insufficiency is the difference in baseline eGFR among the quartiles. The subjects with high uric acid are likely to show low eGFR at baseline and to fall into a category of renal insufficiency with a small decline of eGFR. On the other hand, the subjects with low uric acid are likely to show high eGFR at baseline and not to develop renal insufficiency even with a relatively large decline of eGFR.

The strength of this study is the large number of nationwide samples that were prospectively followed. This adds reliability to our results, even in the subgroup analyses. However, this study has several limitations. First, the serum uric acid levels were measured only at the baseline. Therefore, the changes in serum uric acid levels during the follow-up period that might have an independent effect on renal outcome [25] were not evaluated. Second, the eGFR was evaluated only twice (at baseline and 2 years). These parameters are known to show day-to-day variations. Measuring them twice only might, therefore, underestimate the association between uric acid levels and renal outcomes. Third, renal function was estimated by using the Japanese equation for eGFR, not inulin clearance. Fourth, we have no information on uric acid-lowering medication use in this population.

In conclusion, our study showed that serum uric acid levels are an independent factor for a more rapid decline in renal function in a community-based population and that a slight increase in uric acid levels within the normal range might be a risk for a decline in renal function. To understand the effect of serum uric acid levels on the progression of renal disease, clinical trials of uric acid-lowering therapy are required.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

This study was supported by the Health and Labor Sciences Research Grant for 'the Study on the appropriate states of Specific Health Checkups and Specific Health Guidance for prevention of CKD progression and the design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health Checkups' from the Ministry of Health, Labour and Welfare of Japan.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 31.3.2014; Accepted in revised form: 27.6.2014

Original Article

New-onset hypertension and risk for chronic kidney disease in the Japanese general population

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See editorial comment on page 2351

Objectives: Our aims were to assess the progression rate of normotension and prehypertension to hypertension in Japan, and the effect of the new-onset hypertension on chronic kidney disease (CKD).

Methods: This was a nationwide study of 45 378 Japanese aged 40–74 years (mean age 60 years, 37% men) without hypertension or cardiovascular disease at baseline. At baseline and 3-year follow-up, blood pressure (BP) and kidney function were assessed. CKD was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73 m^2 or the presence of proteinuria (≥1+ by a dipstick).

Results: At 3-year follow-up, the incidence rates of hypertension among participants with optimal BP (<120/80 mmHg, $n = 18\,724$), normal BP (120–129/80–84 mmHg, $n = 15\,017$) and high-normal BP (130–139/85–89 mmHg, $n = 11\,637$) were 8, 23, and 39% in men, and 6, 20, and 37% in women, respectively. Among those without CKD at baseline ($n = 42\,625$), 2142 participants (5%) had developed CKD during follow-up. Irrespective of the baseline BP classifications, participants with new-onset hypertension had a higher risk for proteinuria [odds ratio (95% confidence interval) 1.7 (1.3–2.3) in men and 1.6 (1.2–2.2) in women], but not for eGFR below 60 ml/min per 1.73 m^2, compared with those who maintained optimal BP during follow-up. Men who remained in the high-normal BP range during follow-up showed higher risk for proteinuria [odds ratio (95% confidence interval) 1.6 (1.1–2.3)], but not for eGFR below 60 ml/min per 1.73 m^2.

Conclusions: This nationwide longitudinal study suggests that, over 3 years of follow-up, women and men with new-onset hypertension and men with high-normal BP were at higher risk of newly developing proteinuria.

Keywords: chronic kidney disease, high-normal blood pressure, new-onset hypertension, prehypertension, proteinuria

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbAlc, hemoglobin Alc; HDL, high-density lipoprotein; LDL, low-density lipoprotein

INTRODUCTION

Prehypertension, defined as SBP of 120–139 mmHg or DBP of 80–89 mmHg [1], is associated with a higher risk for future development of hypertension and cardiovascular disease (CVD) compared with optimal blood pressure (BP) (<120/80 mmHg) among the general population [2–4]. Prehypertension is highly prevalent in Asia, existing in 30–45% of the general population [5–7]. Nevertheless, less is known about the progression rate of prehypertension to hypertension in Japan and the effects of the new-onset hypertension on chronic kidney disease (CKD).

Longitudinal associations between prehypertension and CKD have been shown [8–12]. However, none of these studies provided information on BP during follow-up, which is a concern, since nearly half of prehypertension cases eventually progress to hypertension [1,2,4–6]. It remains uncertain whether the longitudinal association of prehypertension with CKD could be confounded by the BP values during follow-up.

Using a large nationwide database of participants recruited from the national health check-up system in

Journal of Hypertension 2014, 32:2371–2377

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Received 3 March 2014 **Revised** 16 July 2014 **Accepted** 16 July 2014

J Hypertens 32:2371–2377

DOI:10.1097/HJH.0000000000000344

Japan, we assessed the progression rate of normotension and prehypertension to hypertension at 3-year follow-up, and the effect of the new-onset hypertension on CKD.

METHODS

Study population

The study was performed as a part of the prospective ongoing project 'Design of the comprehensive healthcare system for CKD based on the individual risk assessment by Specific Health Checkups' [7]. A new annual health check program, 'The Specific Health Check and Guidance System in Japan' was started by the Japanese government in 2008. The target population was the Japanese general population between the ages of 40 and 74 years. The details are described in the Supplementary data (http://links.lww. com/HJH/A397). In Japan, there are 47 administrative divisions (prefectures). Twenty-seven of the prefectures (Hokkaido, Yamagata, Miyagi, Fukushima, Niigata, Fukui, Ishikawa, Nagano, Tochigi, Tokyo, Chiba, Saitama, Kanagawa, Ibaraki, Osaka, Hyogo, Gifu, Okayama, Kochi, Tokushima, Fukuoka, Miyazaki, Kumamoto, Oita, Saga, Nagasaki, and Okinawa) agreed with the aims of this study and performed a prospective data collection from individuals who agreed to participate in this project. Data were sent to an independent data center, the NPO Japan Clinical Research Support Unit, after anonymization in a linkable fashion, and verified by trained staff (K.I.).

Until July 2013, from 13 prefectures (Hokkaido, Fukui, Ishikawa, Nagano, Tochigi, Chiba, Saitama, Hyogo, Gifu, Tokushima, Kumamoto, Nagasaki, and Okinawa), we obtained data of 85 826 participants (mean age ± SD, 62.1 ± 7.6 years; 41.0% men) for whom information on age, sex, BMI, estimated glomerular filtration rate (eGFR), and dipstick urine test results were obtained both at baseline (2008) and at 3-year follow-up (2011).

For the present analysis, we excluded 40 448 participants who had baseline hypertension ($n = 38\,229$) or self-reported pre-existing CVD (i.e. stroke and coronary artery disease) ($n = 6096$). The included participants ($n = 45\,378$) were younger (mean age 60.4 vs. 64.0 years), and had a lower proportion of men (37.2 vs. 45.2%) and higher mean eGFR (78.1 vs. 74.9 ml/min per 1.73 m^2; all $P < 0.001$) than those not included (Supplementary Table S1, http://links.lww.com/HJH/A397).

The study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for epidemiological research (1 December 2008, 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

Body height and weight were measured in light clothing without shoes, and BMI was calculated (kg/m^2). Obesity was defined as a BMI at least 25 kg/m^2 [13]. Among 45 378 included participants, although there were substantial missing data, smoking (current smoker or not) ($n = 45\,117$) and drinking (daily drinking or not) ($n = 39\,656$) status was assessed at baseline.

Blood pressure measurement and blood and urine sampling were performed at each local medical institution. 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 the medical staff using a standard sphygmomanometer or an automated device on the right arm after the participants had rested for 5 min in a seated position. Participants were classified into one of the following groups according to their BP levels [1]: optimal BP (SBP/DBP <120/80 mmHg), normal BP (SBP 120–129 mmHg, DBP 80–84 mmHg or both), high-normal BP (SBP 130–139 mmHg, DBP 85–89 mmHg or both), and hypertension (SBP/DBP ≥140/90 mmHg and/or use of antihypertensive medications).

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; calibration across different laboratories was not tested, but standardized methods for the measurement of laboratory data, recommend by the Japan Society of Clinical Chemistry, have been adopted widely in Japan. In some cases but not all, hemoglobin Alc (HbAlc; $n = 42\,561$), triglycerides ($n = 42\,607$), low-density lipoprotein (LDL; $n = 42\,611$), and high-density lipoprotein (HDL; $n = 42\,624$) were assessed both at baseline and at 3-year follow-up. The value for HbAlc was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following formula: HbAlc (%) = HbAlc (Japan Diabetes Society) (%) + 0.4%.

Definition of chronic kidney disease

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early 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 is a widely adopted policy of the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick tests should be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dl. We defined proteinuria as 1+ or more. Serum creatinine was assayed by an enzymatic method. eGFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for Japanese as follows: [14]

$$144 \times \min(\mathrm{Cr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Cr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018 \text{ (if female)} \times 0.813 \text{ (Japanese coefficient)}$$

where κ is 0.7 in women and 0.9 in men; α is −0.329 in women and −0.411 in men.

Details about the equation are shown in the Supplementary data (http://links.lww.com/HJH/A397). CKD was defined as the presence of proteinuria and/or eGFR below 60 ml/min per 1.73 m^2.

Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, Illinois, USA). Differences in participant characteristics by BP classification and sex were assessed by analysis of variance (ANOVA) or the chi-square test. At first, in all participants ($n = 45\,378$), we estimated the progression rate of normotension and prehypertension to hypertension at 3-year follow-up. Next, excluding participants with eGFR below 60 ml/min per 1.73 m^2 or proteinuria at baseline ($n = 42\,625$), we calculated the risk of newly developed CKD for each BP classification. Using multiple logistic regression analysis including age and BMI as adjusted factors, the odds ratio (OR) and 95% confidence interval (CI) of risk for CKD, proteinuria, and low eGFR (<60 ml/min per 1.73 m^2) at 3-year follow-up were estimated for each BP classification. In separate analyses, we included current smoking and daily drinking at follow-up, and changes of BMI, HbAlc, triglycerides, HDL-cholesterol, and LDL-cholesterol levels during follow-up as adjusted factors; the sample size was reduced ($n = 12\,284$ in men and $n = 21\,069$ in women) due to missing data on covariates. A two-sided P value less than 0.05 was defined as significant.

RESULTS

Study population

Table 1 shows clinical characteristics of the included participants according to BP classification within each sex. In accordance with the severity of BP classification, higher age and BMI, less prevalent current smoking, higher levels of HbAlc and triglycerides, lower eGFR, and higher prevalent proteinuria were observed both in men and women.

Incidence rate of hypertension at 3-year follow-up

At 3-year follow-up, 8816 participants (19% of the entire population) had developed hypertension, defined as BP at least 140/90 mmHg ($n = 5568$) or use of antihypertensive medications ($n = 3248$). The incidence rates of hypertension developing from optimal BP (<120/80 mmHg), normal BP, and high-normal BP at baseline are shown in Fig. 1a.

Incidence rate of newly developed chronic kidney disease at 3-year follow-up

Among 42 625 participants without CKD at baseline, 2142 participants (5%) had new-onset CKD at 3-year follow-up; these included individuals with eGFR below 60 ml/min per 1.73 m^2 ($n = 1277$), proteinuria ($n = 801$), and both ($n = 64$). The incidence rate of CKD according to BP classification at baseline is shown in Fig. 1b. Using multiple logistic regression analyses including age and BMI as adjusted factors, the ORs for developing CKD among each BP classification at baseline were calculated (Figure S1, http://links.lww.com/HJH/A397). In men ($n = 15\,443$), high-normal BP at baseline was associated with a higher risk of CKD [OR (95% CI) 1.2 (1.0–1.4); $P < 0.05$]. When we assessed the endpoint as proteinuria or eGFR below 60 ml/min per 1.73 m^2 separately, high-normal BP in men was associated with a higher risk of proteinuria [OR (95% CI) 1.5 (1.1–1.9); $P < 0.01$], but not of eGFR below 60 ml/min per 1.73 m^2 [OR (95% CI) 1.0 (0.8–1.3); $P = 0.83$].

Progression to hypertension and risk for chronic kidney disease

Participants without CKD at baseline were divided into six groups according to BP classification at baseline and at 3-year follow-up. Since the risk for developing CKD with normal BP at baseline was similar to that with optimal BP (Figure S1, http://links.lww.com/HJH/A397), we combined normal BP and optimal BP into a single BP category and defined it as the reference. The changes in BMI, glucose, and lipid parameters during follow-up among the six groups are shown in Supplementary Table S2 and S3 (http://links.lww.com/HJH/A397).

TABLE 1. Baseline characteristics according to blood pressure classification within each sex ($n = 45\,378$)

	Men				Women			
	Optimal BP ($n = 6028$)	Normal BP ($n = 6032$)	High-normal BP ($n = 4841$)	P	Optimal BP ($n = 12\,696$)	Normal BP ($n = 8985$)	High-normal BP ($n = 6796$)	P
Age (years)	58.6 ± 9.1	60.0 ± 8.8	61.6 ± 8.2	<0.001	58.9 ± 8.6	61.5 ± 7.4	62.9 ± 6.6	<0.001
BMI (kg/m^2)	22.8 ± 2.8	23.6 ± 2.8	23.9 ± 2.9	<0.001	21.8 ± 2.9	22.7 ± 3.0	23.1 ± 3.2	<0.001
Obesity (%)	19.7	28.9	32.5	<0.001	13.3	20.3	24.6	<0.001
Current smoker[a] (%)	34.0	28.0	26.0	<0.001	7.9	6.1	5.9	<0.001
Daily drinker[b] (%)	31.5	37.4	40.5	<0.001	5.7	5.8	4.9	0.05
SBP (mmHg)	108.9 ± 7.1	122.5 ± 4.3	132.3 ± 4.4	<0.001	107.4 ± 7.9	122.9 ± 4.0	132.7 ± 3.9	<0.001
DBP (mmHg)	67.3 ± 6.5	75.4 ± 6.1	79.5 ± 6.5	<0.001	65.5 ± 6.8	73.7 ± 6.5	77.9 ± 6.7	<0.001
HbAlc[c] (%)	5.22 ± 0.6	5.27 ± 0.7	5.30 ± 0.7	<0.001	5.18 ± 0.4	5.24 ± 0.5	5.26 ± 0.5	<0.001
High-density lipoprotein (mg/dl)	57.1 ± 14.4	57.5 ± 14.8	56.9 ± 14.9	0.13	66.7 ± 15.2	65.0 ± 15.2	64.9 ± 15.4	<0.001
Low-density lipoprotein[d] (mg/dl)	121.5 ± 29.1	122.8 ± 29.3	122.9 ± 29.9	0.02	126.3 ± 29.8	130.8 ± 29.9	132.6 ± 30.0	<0.001
Triglycerides[e] (mg/dl)	118.0 ± 80.6	129.8 ± 88.5	136.9 ± 98.3	<0.001	97.0 ± 56.2	106.4 ± 62.6	110.2 ± 62.7	<0.001
eGFR (ml/min per 1.73 m^2)	78.1 ± 9.6	77.1 ± 9.8	76.0 ± 9.6	<0.001	79.8 ± 9.0	78.3 ± 8.6	77.5 ± 8.4	<0.001
CKD (%)	7.5	8.9	9.7	<0.001	4.0	4.7	5.4	<0.001
Proteinuria (%)	3.3	4.0	4.4	0.005	1.7	1.9	2.4	0.007
eGFR <60 ml/min per 1.73 m^2 (%)	4.5	5.4	5.9	<0.01	2.5	2.9	3.2	<0.05

Data are expressed as the mean ± SD or percentage. P values were obtained by ANOVA or chi-square test among optimal BP, normal BP, and high-normal BP within each sex. BP classification was defined as follows: optimal BP, SBP below 120 mmHg and DBP below 80 mmHg; normal BP, SBP 120–129 mmHg and/or 80–84 mmHg; high-normal BP, SBP 130–139 mmHg and/or DBP 85–89 mmHg. Obesity was defined as BMI at least 25kg/m^2. Some clinical characteristics were not obtained from all participants, and the sample size is shown by superscript alphabets: a, $n = 45\,117$; b, $n = 39\,656$; c, $n = 45\,323$; d, $n = 45\,370$; e, $n = 45\,370$. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbAlc, hemoglobin Alc.

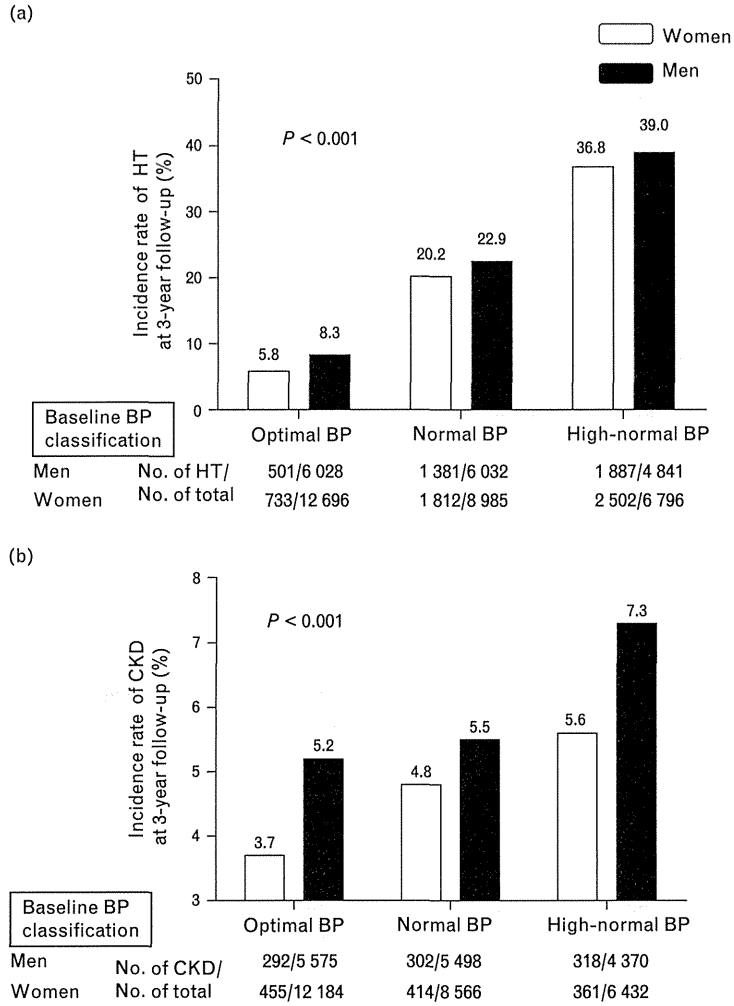

FIGURE 1 Incidence rate of hypertension and chronic kidney disease at 3-year follow-up. (a) Shows the incidence rate of hypertension at 3-year follow-up in all participants ($n = 45\,378$). (b) Shows the incidence rate of CKD in those without CKD at baseline ($n = 42\,625$). The percentages are shown stratified by BP classification and sex. *P* values were obtained by the chi-square test within each sex. BP, blood pressure; CKD, chronic kidney disease.

Data from logistic regression models suggest that among men, those who developed hypertension during follow-up and those remaining in the high-normal BP category had a higher risk for proteinuria and eGFR below 60 ml/min per 1.73 m^2 (model 1 in Table 2). Adjustment for baseline age and BMI attenuated the associations, but new-onset hypertension and high-normal BP remained significantly associated with a higher risk of proteinuria, but not of eGFR below 60 ml/min per 1.73 m^2 (model 2, Table 2). Among women, those who developed hypertension during follow-up had a higher risk of proteinuria after adjustment for age and BMI (model 2 in Table 2). The results were similar when we excluded those who used antihypertensive medications at follow-up (data not shown).

In model 2 in Table 2, we further adjusted for current smoking and daily drinking at follow-up and for changes in BMI, HbAlc, triglycerides, HDL cholesterol, and LDL cholesterol levels during follow-up. Although the sample size was reduced ($n = 12\,284$ men and $n = 21\,069$ women), the risk for proteinuria remained significant in those who developed hypertension from optimal and normal BP [OR (95% CI) 1.9 (1.4–2.7) in men and 1.9 (1.3–2.6) in women; both $P < 0.001$], and those who developed hypertension from high-normal BP [OR (95% CI) 1.8 (1.3–2.5) in men and 1.9 (1.3–2.6) in women; both $P < 0.01$]. The risk of proteinuria for men remaining in the high-normal BP category during follow-up was also significant [OR (95% CI) 1.9 (1.3–2.8); $P = 0.001$] even after adjustments for lifestyle factors and for glucose and lipid metabolic factors.

DISCUSSION

In this nationwide study of 45 378 Japanese aged 40–74 years with no hypertension or CVD at baseline, we calculated a 19% incidence rate of new-onset hypertension at 3-year follow-up. Among those without CKD at baseline

TABLE 2. Sex-specific unadjusted and multivariable-adjusted odds ratio (95% confidence interval) for risk of proteinuria and estimated glomerular filtration rate below 60 ml/min per 1.73 m^2 by blood pressure classification

BP at baseline	Optimal-normal BP			High-normal BP		
BP at 3-year follow-up	Optimal-normal BP	High-normal BP	Hypertension	Optimal-normal BP	High-normal BP	Hypertension
Men (*n*)	7817	1611	1645	1620	1076	1674
Event number (proteinuria, *n*)	164	35	62	45	39	65
OR (95% CI) of proteinuria						
Model 1 (unadjusted)	Reference	1.0 (0.72–1.5)	1.8 (1.4–2.5)***	1.3 (0.95–1.9)	1.8 (1.2–2.5)**	1.9 (1.4–2.5)***
Model 2	Reference	0.99 (0.7–1.4)	1.7 (1.3–2.3)***	1.2 (0.9–1.7)	1.6 (1.1–2.3)**	1.7 (1.3–2.3)***
Event number (eGFR <60 ml/min per 1.73 m^2, *n*)	237	42	73	73	39	70
OR (95% CI) of eGFR <60 ml/min per 1.73 m^2						
Model 1 (unadjusted)	Reference	0.9 (0.6–1.2)	1.5 (1.1–1.9)**	1.5 (1.2–2.0)**	1.2 (0.9–1.7)	1.4 (1.1–1.8)*
Model 2	Reference	0.8 (0.5–1.1)	1.2 (0.9–1.6)	1.3 (0.96–1.6)	0.98 (0.7–1.4)	1.1 (0.8–1.4)
Women (*n*)	15770	2606	2374	2514	1573	2345
Event number (proteinuria, *n*)	225	50	56	38	30	56
OR (95% CI) of proteinuria						
Model 1 (unadjusted)	Reference	1.4 (0.99–1.8)	1.7 (1.2–2.2)**	1.1 (0.8–1.5)	1.3 (0.9–2.0)	1.7 (1.3–2.3)**
Model 2	Reference	1.3 (0.96–1.8)	1.6 (1.2–2.2)**	1.0 (0.7–1.5)	1.3 (0.9–1.9)	1.6 (1.2–2.1)**
Event number (eGFR <60 ml/min per 1.73 m^2, *n*)	378	88	94	88	55	104
OR (95% CI) of eGFR<60 ml/min per 1.73 m^2						
Model 1 (unadjusted)	Reference	1.4 (1.1–1.8)**	1.7 (1.3–2.1)***	1.5 (1.2–1.9)**	1.5 (1.1–2.0)**	1.9 (1.5–2.4)***
Model 2	Reference	1.1 (0.8–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.99 (0.7–1.3)	1.2 (0.9–1.5)

Sex-specific unadjusted and adjusted ORs (95% CI) for risk of proteinuria and eGFR below 60 ml/min per 1.73 m^2 with each BP classification are shown. BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio. As adjusted factors, model 2 includes age and BMI at baseline. Statistical significance was defined as $P < 0.05$.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

($n = 42\,625$), the incidence rate of new-onset CKD was 5%. In both men and women, new-onset hypertension was associated with a higher risk for proteinuria compared with optimal and normal BP. Men remaining in high-normal BP for over 3 years of follow-up had a higher risk for proteinuria compared to those with optimal and normal BP.

Longitudinal associations between baseline BP and risk for kidney disease have been suggested [15–17], but little evidence exists on whether the associations could be modified by BP values during follow-up. Vupputuri *et al.* [18] suggested that among 722 treated hypertensive men with eGFR at least 60 ml/min per 1.73 m^2 at baseline (70% African American), increase in SBP was associated with greater decline in kidney function (defined as a rise in serum creatinine $\geq$0.6 mg/dl) during a median follow-up of 7 years. Among 43 305 hypertensive patients without CKD at baseline (46% were men, 54% were Caucasians, and mean age 60 years), Hanratty *et al.* [19] reported that time-varying SBP was associated with greater decline in eGFR during a median follow-up of 44 months. Neither study assessed proteinuria as an outcome. Both studies recruited hypertensive patients [18,19], suggesting that some renal structural and functional alterations might already have been present at baseline.

In the present study, new-onset hypertension was associated with a higher risk for proteinuria, but not for eGFR below 60 ml/min per 1.73 m^2. Proteinuria is a sign of glomerular hypertension, impaired glomerular permeability, and dysfunction of the glomerular barrier and endothelial cells [20,21]. These changes often precede any detectable decline in renal filtration function [20–22]. Since we evaluated the incident hypertension only once, without information on the interim period, we cannot clarify reverse causality in the association between new-onset hypertension and proteinuria. However, we excluded those who had hypertension, proteinuria, lower eGFR (60 ml/min per 1.73 m^2) and pre-existing CVD at baseline, so it is unlikely that proteinuria without accompanying lower eGFR could have preceded the development of hypertension over this short-term follow-up period.

In addition to high BP, proteinuria is associated with obesity, glucose and lipid metabolic abnormalities, and a number of nontraditional risk factors (e.g. high C-reactive protein and adiponectin) [20–24]. We observed that both men and women who had new-onset hypertension showed the highest increase in BMI during follow-up (Supplementary Table S2 and S3, http://links.lww.com/HJH/A397). Although our analyses were adjusted for changes in BMI as well as glucose and lipid parameters during follow-up, potentially confounding factors remained, including inflammation, adipocytokines, and sleep-disordered breathing.

High-normal BP in men only, even those who did not develop hypertension during follow-up, constituted a higher risk for proteinuria. The reasons for the sex difference are unclear, but the parallel increase of proteinuria in accordance with BP severity might begin at an earlier phase in men than in women [25]. Results from prior studies on longitudinal associations between prehypertension and CKD risk [not limited to end-stage renal disease (ESRD)] in the general population are inconsistent [8–12]. Most studies did not exclude CKD at baseline, defined based on both eGFR and proteinuria. Three prospective studies from the United States (8093 men; aged 40–84 years; 14 years of follow-up) [9], Norway (17 375 healthy Caucasians; mean age 42 years; 53% men; median follow-up of 7 years) [11], and Iran (3313 participants; aged over 20 years; 44% men; mean follow-up of 10 years) [12] failed to show a risk for CKD in individuals with prehypertension. These

studies defined CKD as eGFR below 60 ml/min per 1.73 m^2. A study in a Japanese population demonstrated that prehypertension with normal and high-normal BP was associated with a 1.5-fold higher risk for CKD than optimal BP over 6.5 years of follow-up, although the sample size was small ($n = 2150$) and BP values at follow-up were not considered as confounders [8]. Our study complements and extends these prior studies by showing that men remaining in the high-normal BP category even over a relatively shorter period (i.e. 3 years) were at higher risk for proteinuria.

The major strengths of this study are that it was a nationwide survey with a large sample size, incorporating complete information on BP, eGFR, and proteinuria at both baseline and follow-up. However, there were limitations. First, a single measure of BP, eGFR, and proteinuria might not be accurate. In particular, some dipstick-positive proteinuria findings might be transient. These factors could have led to underestimation of the true association between BP and proteinuria. Second, the participants were generally healthy individuals undergoing health check-ups, so our results might underestimate the incidence of new-onset hypertension from normotension and prehypertension and the effect on CKD. Third, we could not assess how many people had an annual health check but declined to participate in this project, and we could not calculate the percentage of the baseline population from which we were able to gather follow-up data. There is potential bias in the study participants chosen for the analysis. Last, we could not assess what kinds of antihypertensive drugs had been prescribed in treated hypertensive patients. The use of such agents, particularly renin–angiotensin–aldosterone inhibitors, is potentially confounding [26], although our conclusions remained unchanged when we analyzed our data excluding the participants on antihypertensive medications at follow-up.

In conclusion, this Japanese nationwide survey demonstrated that, over 3 years of follow-up, women and men with new-onset hypertension and men with high-normal BP were at higher risk of newly developing proteinuria. Taken together with evidence of a rapidly increasing number of patients with CKD in Japan [27], our findings have important clinical implications. CKD is often asymptomatic but progressive, and thus we need to pay attention to patients who develop hypertension and to men remaining in the high-normal BP category in order to detect CKD as early as possible and to prevent its adverse consequences, such as CVD and ESRD.

ACKNOWLEDGEMENTS

Sources of funding: This work was supported by Health and Labor Sciences Research Grants for 'Research on the Positioning of Chronic Kidney Disease (CKD) in Specific Health Check and Guidance in Japan', 'Study on the Appropriate States of Specific Health Checkups and Specific Health Guidance for Prevention of CKD Progression', and 'Design of a Comprehensive Healthcare System for CKD Based on the Individual Risk Assessment by Specific Health Checkups' from the Ministry of Health, Labor and Welfare of Japan.

Conflicts of interest

Y.Y. received grants from the Manpei Suzuki International Prize for Diabetes Research.

None of the other authors has any potential conflict of interest to disclose.

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Reviewers' Summary Evaluations

Reviewer 1

This is a very large epidemiological study addressing the probability of new onset hypertension over time in Japanese participants with normal BP or prehypertension at baseline. The study also examines the relationship between changes in BP over time and the probability of developing new onset proteinuria or a decrease in GFR.

Reviewer 2

This study shows that even within three years after new-onset of hypertension, there is an increased risk of developing proteinuria. The strength of the study is the nationwide, population-based design, and the methods used are well reported. Also, the results are of particular importance as the study is performed in a Japanese population.