






ORIGINAL RESEARCH

# Blood Pressure and Chronic Kidney Disease Stratified by Gender and the Use of Antihypertensive Drugs

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**BACKGROUND:** The present study assessed the association between blood pressure (BP) and the risk of chronic kidney disease (CKD) according to gender and the use of antihypertensive drugs using data from a large-scale health checkup.

**METHODS AND RESULTS:** We conducted a retrospective cohort study using the JMDC database, which contains annual health checkup data of Japanese employees and their dependents aged <75 years. We included 154 692 participants (men, 69.68%; mean age, 44.74 years) without CKD. CKD was indicated by an estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup> or the presence of proteinuria. During the mean follow-up period of 4.78 years, new-onset CKD occurred in 14 888 participants. When the normal BP group (systolic/diastolic BP <120/<80 mm Hg) without treatment was used as a reference, the hazard ratios of the high BP (130–139/80–89 mm Hg) and grade 1 (140–159/90–99 mm Hg) and grade 2 or 3 hypertension (≥160/≥100 mm Hg) groups were 1.11 (95% CI, 1.06–1.17), 1.36 (95% CI, 1.28–1.45), and 1.76 (95% CI, 1.56–1.99) for untreated men, respectively. However, in treated men, even normal BP was associated with a 1.5-fold higher risk of CKD. The association between BP and the risk of CKD was weaker in untreated women than in untreated men. The risk of CKD in treated women with normal BP was similar to that of untreated women with normal BP.

**CONCLUSIONS:** Gender differences were found in the association between BP and CKD risk. Kidney function in treated individuals should be followed carefully, especially in men.

**Key Words:** blood pressure ■ chronic kidney disease ■ cohort study ■ database

Chronic kidney disease (CKD) has become a major global health burden in recent years.<sup>1</sup> Since damage sustained by kidneys cannot be reversed, priority should be given to the prevention of kidney disease by predicting CKD before the patient develops end-stage renal disease.

Blood pressure (BP) is a strong risk factor for CKD.<sup>2–9</sup> However, studies indicating this association have not involved stratification analysis by gender and the use of antihypertensive drugs. Individuals treated with antihypertensive drugs have a potentially higher cardiovascular disease risk compared with those not

prescribed antihypertensive drugs, regardless of BP.<sup>10</sup> This is because treated individuals have a long history of elevated BP. However, the degree to which the risk of CKD is increased in treated individuals compared with untreated individuals with the same BP has yet to be assessed. The association between BP and the risk of CKD could also be different based on the use of antihypertensive drugs. Although one study<sup>11</sup> indicated a positive association between BP and kidney dysfunction after stratification by the use of antihypertensive drugs, this study was only based on 2 specific health checkup data points and only had a 2-year follow-up

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## CLINICAL PERSPECTIVE

### What Is New?

- Our study is the first of its kind to demonstrate the risk of chronic kidney disease in blood pressure groups according to current guidelines after stratification for sex and the use of antihypertensive drugs in a large-scale Asian population.

### What Are the Clinical Implications?

- Blood pressure was significantly associated with an elevated risk of chronic kidney disease; however, the overall hazard ratio in treated individuals was higher versus that in those not taking antihypertensive drugs.
- Kidney function in treated individuals should be monitored more carefully versus that in untreated people.
- The association between blood pressure and the risk of chronic kidney disease was weaker in women versus that in men, and the risk of chronic kidney disease in women with controlled hypertension is similar to that in women with normal or high-normal blood pressure.

## Nonstandard Abbreviations and Acronyms

<b>BP</b>	blood pressure
<b>BMI</b>	body mass index
<b>CKD</b>	chronic kidney disease
<b>DM</b>	diabetes mellitus
<b>eGFR</b>	estimated glomerular filtration rate
<b>HR</b>	hazard ratio
<b>JSH</b>	Japanese Society of Hypertension

period.<sup>11</sup> Furthermore, the study<sup>11</sup> did not consider gender differences and defined BP by sextile of systolic BP and not by BP thresholds as recommended in hypertension guidelines.<sup>12–14</sup> Little information on gender differences in the association between BP and the risk of CKD is available.<sup>6</sup> Gender is an unmodifiable factor, unlike most other CKD risk factors. Also given gender differences in the progression of CKD<sup>15</sup>, gender must be considered as an important factor in studies of kidney disease.

To assess the association between BP and the risk of CKD after stratification by gender and the use of antihypertensive drugs, the present study conducted a longitudinal analysis based on multiple measurements of serum creatinine from a large-scale health checkup.

## METHODS

To comply with our contract with JMDC Inc., data and study materials will not be made available to other researchers.

### Study Design and Populations

We conducted a retrospective cohort study using the JMDC database. The JMDC database contains the annual health checkup data of Japanese employees and their dependents aged <75 years who are enrolled in the health insurance plans run primarily by large-scale enterprises.<sup>16–18</sup> As it is mandatory for individuals aged ≥75 years to be enrolled in the health insurance system (Later Elders Insurance), the JMDC database does not have data related to elderly people.

The JMDC database has data of 937 240 individuals aged ≥30 years who underwent a minimum of 1 annual health checkup between April 2008 and March 2017. We received data from 388 973 of these participants who had an annual health checkup ≥5 times between April 2008 and March 2017. Since the measurement of serum creatinine is not mandatory in Japanese annual health checkups, serum creatinine was only measured in 246 043 (63.25%) participants. We also excluded 2296 participants whose data did not include information relating to BP or the use of antihypertensive drugs, and 9 with an estimated glomerular filtration rate (eGFR) >200 mL/min per 1.73 m<sup>2</sup>, as they were considered outliers. After exclusion, follow-up data were available for 228,450 participants. Of those, 19,841 with CKD or kidney disease and 17,386 with a history of cardiovascular disease at baseline were excluded. Furthermore, we excluded 36,531 participants with an eGFR <70 mL/min per 1.73 m<sup>2</sup> as they already had a high risk of CKD (indicated in Figure S1). Finally, 154 692 participants were included in the present analyses.

Based on Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare, Japan, this retrospective study was exempted from obtaining approval of the institutional review board or ethics committee and individual informed consent since the JMDC data for this study are unlinkable anonymized data.

### Data Collection

The present data were collected at annual health checkups, which were conducted according to the guideline set out by the Japanese Ministry of Health, Labour and Welfare. Information regarding smoking status; alcohol consumption; use of antihypertensive, antidiabetic, and antidyslipidemia drugs; and history of cerebrovascular disease and ischemic heart disease was gathered by a self-administered questionnaire.

Diabetes mellitus (DM) was indicated by a fasting glucose level  $\geq 7.00$  mmol/L ( $\geq 126$  mg/dL), a random glucose level  $\geq 11.11$  mmol/L ( $\geq 200$  mg/dL), or the use of antidiabetic medications. Dyslipidemia was indicated by a low-density lipoprotein cholesterol  $\geq 3.62$  mmol/L ( $\geq 140$  mg/dL), high-density lipoprotein cholesterol  $< 1.03$  mmol/L (40 mg/dL), triglycerides  $\geq 1.69$  mmol/L (150 mg/dL), or use of antidyslipidemia medications.

### Definition of BP Category

The Japanese guidelines for annual health checks recommend measuring BP twice consecutively in a seated position.

As per the Japanese Society of Hypertension (JSH) 2019 guidelines,<sup>14</sup> we classified participants into 5 categories according to their systolic/diastolic BP: normal BP ( $< 120 / < 80$  mm Hg), high-normal BP (120–129/ $< 80$  mm Hg), high BP (130–139/ $80$ – $89$  mm Hg), grade 1 hypertension (140–159/ $90$ – $99$  mm Hg), and grade 2 or 3 hypertension ( $\geq 160 / \geq 100$  mm Hg). The BP thresholds stated in the JSH 2019 guidelines<sup>14</sup> are consistent with the US hypertension management guidelines,<sup>12</sup> where systolic/diastolic BP  $\geq 130 / \geq 80$  mm Hg is defined as hypertension.

### Outcome and Follow-Up

Serum creatinine was assayed enzymatically. An eGFR was calculated from the serum creatinine using a modified version of the equation used most commonly in Japan:  $\text{eGFR (mL/min per } 1.73 \text{ m}^2) = 194 \times (\text{serum creatinine})^{-1.094} \times \text{age}^{-0.287} (\times 0.739, \text{ for women}).$ <sup>19</sup> The presence of proteinuria was confirmed by a dipstick test that showed 1+ or above, which corresponds to urinary protein levels  $> 30$  mg/dL. CKD was indicated by an eGFR  $< 60$  mL/min per  $1.73 \text{ m}^2$  and/or the presence of proteinuria.

Baseline was considered as the first annual health checkup in the present data. The primary outcome was the new onset of CKD confirmed during the annual checkups.<sup>7</sup> The date of CKD incidence was defined as the midpoint between the most recent date the individual presented without CKD and the date on which CKD was first confirmed.<sup>7</sup> If a participant had  $> 1$  CKD event during the follow-up, only the first event contributed to the analysis. As for participants without CKD, the final follow-up date was the date of the final annual health checkup included in the present data. Therefore, the follow-up period was from baseline to the date of CKD incidence or final checkup.

### Statistical Analysis

We calculated age-standardized CKD rates by direct method using the population assumed to be the same proportion of individuals aged  $< 45$ , 45–59, and

$\geq 60$  years. The body mass index (BMI)-adjusted difference in eGFR at baseline between men and women was assessed by the ANCOVA separately by the BP category and the use of antihypertensive treatment. The Cox proportional hazard model was applied to assess the adjusted hazard ratios (HRs) for CKD incidence in BP groups. Then, dummy variables were created for the BP category and were included in the model at the same time. The untreated lowest BP group was set as a reference. The trend  $P$  values for the association between BP category and the risk for CKD were assessed in untreated or treated individuals separately. We also assessed the HR for antihypertensive treatment (untreated vs treated participants) in the model with systolic BP and covariates. Furthermore, the associations of BP category with the risk of an eGFR  $< 60$  mL/min per  $1.73 \text{ m}^2$  and the presence proteinuria were also assessed.

Interactions were assessed by the likelihood ratio test comparing a model, which included confounding factors and BP category, with a model further including appropriate interaction terms. For example, we defined 9 interaction terms (gender  $\times$  each BP group other than untreated normal BP) to assess the interaction between gender and the 10 BP categories on the risk of CKD. The likelihood ratio chi-square value was used to assess improvement in the goodness of fit.

We performed stratification analyses according to age, BMI, current smoking status, alcohol consumption, DM, dyslipidemia, eGFR, and the number of visits.

We also used restricted cubic splines with 3 knots to analyze the associations between systolic BP and the risk of CKD. Systolic BP of 110 mm Hg was treated as the reference value as it was the mean value in the normal BP group.

The covariates were age, BMI  $< 18.5 \text{ kg/m}^2$  and BMI  $\geq 25 \text{ kg/m}^2$  (to consider the U-shaped association), current smoking status, alcohol consumption, DM, dyslipidemia, and eGFR at baseline. The association between BP and CKD adjusted by linear and quadratic terms of BMI instead of BMI category was also assessed. We interpolated the missing BMI values ( $n=8$ ) from the regression slope on age. In participants with unknown smoking ( $n=10$ ) and drinking status ( $n=1863$ ), we set the design variable to the sex-specific mean of the codes (0, 1). For all multivariate analyses in the present study, we used these interpolated or design variables for missing values.

We stratified all analyses by gender, except for the analysis of the interaction effect of gender. Continuous variables were expressed as mean  $\pm$  SD. All data were analyzed using SAS software version 9.4 (SAS Institute Inc.). A  $P$  value  $< .05$  was considered statistically significant.

## RESULTS

### Baseline Characteristics

In total, 107 792 (69.68%) participants were men. The mean values for age, BMI, systolic BP, and diastolic BP were 44.74±7.43 years, 22.86±3.44 kg/m<sup>2</sup>, 120.22±15.21 mm Hg, and 74.42±11.05 mm Hg, respectively. Of the 144 385 untreated patients, the number of participants with normal BP, high-normal BP, high BP, grade 1 hypertension, and grade 2 or 3 hypertension was 69973 (48.46%), 22 826 (15.81%), 36 172 (25.05%), 12 887 (8.93%), and 2527 (1.75%), respectively. In treated participants, the number of participants with normal BP, high-normal BP, high BP, grade 1 hypertension, and grade 2 or 3 hypertension was 1251 (12.14%), 1141 (11.07%), 3803 (36.90%), 3231 (31.35%), and 881 (8.55%), respectively. The baseline characteristics according to the BP categories in untreated men and women and treated men and women are shown in Table 1 and Table 2. After adjusting for BMI, eGFR was significantly higher in women than men in the normal BP, high-normal BP, high BP, and

grade 1 hypertension groups among untreated participants and in the treated normal BP group ( $P \leq 0.016$ ) (Table S1).

### CKD Incidence Risk and BP Levels and the Use of Antihypertensive Drugs

During the mean follow-up period of 4.78 years (median, 4.82 years; interquartile range, 3.10–6.37 years), new-onset CKD occurred in 14 888 participants. The age-standardized CKD rate increased as BP increased (Table S2). The CKD rate ranged from 16.98 to 34.96 per 1000 patient-years in untreated men, 17.63 to 28.30 per 1000 patient-years in untreated women, 34.39 to 47.50 per 1000 patient-years in treated men, and 18.62–37.93 per 1000 patient-years in treated women (Table S2).

We calculated the HRs for BP categories, which was defined by BP and the use of hypertension treatment, with the untreated normal BP group as the reference group and adjusting for covariates including eGFR at baseline. The BP category was significantly associated with the risk of CKD in untreated and treated men (trend

**Table 1. Baseline Characteristics of Untreated Participants**

Strata	Variables	Category				
		Normal BP	High-Normal BP	High BP	Grade 1 Hypertension	Grade 2 or 3 Hypertension
Men	No.	39 877	16 968	29 644	11 008	2019
	Age, y	43.8±6.9	43.5±7.1	44.7±7.0	46.0±7.4	47.3±7.3
	BMI, kg/m <sup>2</sup>	22.3±2.7	23.3±3.0	23.9±3.2	24.7±3.7	25.3±4.1
	BMI <18.5 kg/m <sup>2</sup> , %	5.7	3.0	2.1	1.8	1.5
	BMI ≥25.0 kg/m <sup>2</sup> , %	15.3	25.1	32.3	41.2	48.2
	Current smoking, %	46.0	46.1	43.9	43.8	40.0
	Alcohol consumption, %	31.9	35.2	42.0	46.9	48.4
	Dyslipidemia, %	39.3	45.7	51.6	57.3	59.7
	DM, %	3.1	4.3	5.4	8.1	11.1
	eGFR, mL/min per 1.73 m <sup>2</sup>	84.7±10.9	85.4±11.2	84.6±11.0	84.8±11.4	84.8±11.8
Women	No.	30 096	5858	6528	1879	508
	Age, y	42.9±6.7	45.2±7.7	46.2±7.9	49.0±8.3	49.2±7.7
	BMI, kg/m <sup>2</sup>	20.7±2.7	22.1±3.4	22.7±3.8	23.7±4.5	24.4±4.8
	BMI <18.5 kg/m <sup>2</sup> , %	18.6	9.9	9.7	6.7	5.9
	BMI ≥25.0 kg/m <sup>2</sup> , %	6.9	17.7	22.9	32.0	36.8
	Current smoking, %	8.4	7.9	7.8	6.5	7.3
	Alcohol consumption, %	8.5	9.2	11.0	13.0	14.2
	Dyslipidemia, %	19.3	30.0	35.0	43.5	49.2
	DM, %	0.8	2.9	3.6	6.2	8.9
	eGFR, mL/min per 1.73 m <sup>2</sup>	86.2±12.5	86.1±12.5	85.7±12.1	85.7±12.2	85.3±12.5
Systolic BP, mm Hg	105.3±8.3	123.8±2.8	129.0±7.4	144.1±8.0	164.6±13.6	
Diastolic BP, mm Hg	63.8±7.1	71.3±5.5	80.5±5.6	87.6±7.0	99.4±9.9	

Data on body mass index (BMI), smoking status, and alcohol consumption were unavailable for 8, 9, and 1750 participants, respectively. BP indicates blood pressure; DM, diabetes mellitus; and eGFR, estimated glomerular filtration rate.

**Table 2. Baseline Characteristics of Treated Participants**

Strata	Variables	Category				
		Normal BP	High-Normal BP	High BP	Grade 1 Hypertension	Grade 2 or 3 Hypertension
Men	No.	960	845	3061	2679	731
	Age, y	52.1±7.5	52.8±8.2	51.1±7.3	50.7±7.5	49.9±7.3
	BMI, kg/m <sup>2</sup>	24.5±3.6	25±3.7	25.5±3.8	25.8±4.1	26.2±4.5
	BMI <18.5 kg/m <sup>2</sup> , %	2.1	1.4	0.8	0.9	1.1
	BMI ≥25.0 kg/m <sup>2</sup> , %	40.2	44.7	50.5	53.0	56.0
	Current smoking, %	42.0	38.6	37.1	36.8	39.2
	Alcohol consumption, %	44.9	51.0	49.6	52.5	50.3
	Dyslipidemia, %	59.1	58.8	60.9	63.3	65.5
	DM, %	18.6	21.5	19.3	19.1	20.5
	eGFR, mL/min per 1.73 m <sup>2</sup>	82.4±10.2	83.4±11.6	83.4±11.2	83.7±11.3	84.0±11.2
	Systolic BP, mm Hg	111.5±6.1	124.3±2.9	129.2±6.7	142.9±8.1	158.7±14.1
	Diastolic BP, mm Hg	70.6±5.9	73.6±4.6	82.8±4.6	89.9±6.0	101.4±8.5
	Women	No.	291	296	742	552
Age, y		53.7±7.7	55.5±7.7	53.2±8	54.0±8.7	54.3±8.4
BMI, kg/m <sup>2</sup>		23.3±3.7	24.2±4.5	24.4±4.2	24.9±4.8	25.7±5.2
BMI <18.5 kg/m <sup>2</sup> , %		3.8	2.7	3.4	4.5	3.3
BMI ≥25.0 kg/m <sup>2</sup> , %		25.8	33.4	38.3	42.0	45.3
Current smoking, %		12.7	9.5	5.8	4.5	6.0
Alcohol consumption, %		11.8	10.6	10.2	10.3	9.4
Dyslipidemia, %		60.5	60.1	53.1	55.8	58.7
DM, %		12.0	14.5	11.6	17.0	14.0
eGFR, mL/min per 1.73 m <sup>2</sup>		83.9±10.2	83.6±10.3	84.2±11.2	84.3±12.0	83.4±12.0
Systolic BP, mm Hg		110.8±6.2	124.3±3.0	130.7±6.5	144.6±7.2	165.0±12.6
Diastolic BP, mm Hg		69.2±6.3	71.7±5.9	81.0±5.5	86.5±7.9	99.0±9.3

Data on smoking status and alcohol consumption were unavailable for 1 and 113 participants, respectively. BMI indicates body mass index; BP, blood pressure; DM, diabetes mellitus; and eGFR, estimated glomerular filtration rate.

$P \leq 0.0023$ ) (Figure 1). However, the HRs in untreated men were lower than in the treated men (range of HR, 1.00–1.76 for untreated men vs 1.41–2.05 for treated men) (Figure 1). Although BP was significantly associated with the risk of CKD in women (trend  $P \leq 0.0011$ ), the association between BP and the risk of CKD was weaker in untreated women than in untreated men (Figure 2). Furthermore, in treated women, the HR of normal and high-normal BP was 0.98 and 0.95, respectively ( $P \geq 0.80$ ) (Figure 2). A significant interaction between gender and the 10 BP category with the risk of CKD was observed (interaction  $P < 0.0001$ ; likelihood ratio chi-square and degrees of freedom, 39.81 and 9, respectively). In the model used in Figure 1 and Figure 2, DM was also significantly associated with CKD (HR, 1.91 [95% CI, 1.79–2.03] for men and 1.35 [95% CI, 1.13–1.61] for women).

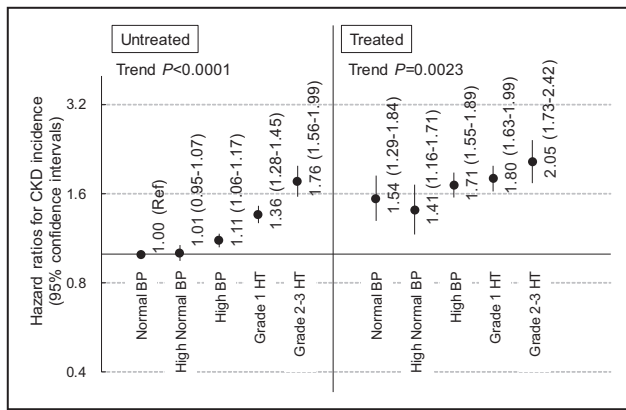
The covariates, systolic BP, and use of antihypertensive drugs were included in the same Cox model. When the untreated status was set as a reference, the HRs for the use of antihypertensive drugs were 1.44

(95% CI, 1.36–1.54) for men and 1.33 (95% CI, 1.15–1.54) for women. The interaction between gender and the use of antihypertensive drugs on the risk of CKD was also significant ( $P < 0.0001$ ).

### Sensitivity Analysis

We performed stratified analyses according to age (<50/≥50 years), BMI (<25/≥25 kg/m<sup>2</sup>), current smoking status, alcohol consumption, DM, and dyslipidemia (Table 3 and Table 4). The BP category was strongly associated with the risk of CKD in men without DM (Table 3) and women with a BMI of ≥25 kg/m<sup>2</sup> (Table 4) (interaction  $P \geq 0.051$ ). When women were stratified by an age of 50 years, the interaction between BMI of 25 kg/m<sup>2</sup> and BP category on the risk of CKD was observed in women aged <50 years ( $P$  for interaction=0.061) but not in women aged ≥50 years ( $P$  for interaction=0.77).

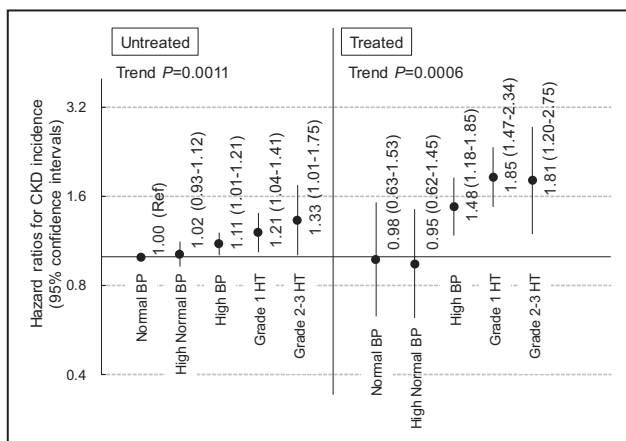
To consider the outcomes caused by the onset of proteinuria and an eGFR <60 mL/min per 1.73 m<sup>2</sup> separately, we assessed the HR for these outcomes



**Figure 1. Blood pressure (BP) and the risk of chronic kidney disease (CKD) incidence in men stratified by the use of antihypertensive treatment.** HR indicates hazard ratio. Covariates were age, body mass index <18.5 kg/m<sup>2</sup>, body mass index ≥25 kg/m<sup>2</sup>, current smoking status, alcohol consumption, diabetes mellitus, dyslipidemia, and estimated glomerular filtration rate at baseline.

instead of the CKD incidence. The untreated normal BP or high-normal BP group was used as the reference. The HR for proteinuria among men/women was 1.19/1.21 in the untreated high BP and hypertension group, 1.44/1.16 in the treated high BP and hypertension group, and 1.76/2.15 in the treated high BP and hypertension group (Table 5). The HRs for an eGFR <60 mL/min per 1.73 m<sup>2</sup> in men were 1.22 in untreated participants with high BP and hypertension, 1.83 in treated participants with normal and high-normal BP, and 1.90 for treated participants with high BP and hypertension. However, BP was not significantly associated with the risk of an eGFR <60 mL/min per 1.73 m<sup>2</sup> in women (P≥0.19) (Table 5).

The significant association between BP and the risk of CKD remained after adjusting for linear and



**Figure 2. Blood pressure (BP) and the risk of chronic kidney disease (CKD) incidence in women stratified by the use of antihypertensive treatment.** HR indicates hazard ratio.

quadratic terms of BMI instead of BMI category (trend P≤0.0052, Figure S2, and Figure S3). However, the HR in untreated women with grade 2 or 3 hypertension was not significant (HR, 1.29; 95% CI, 0.98–1.69) (Figure S3). In untreated participants, antihypertensive treatment was initiated in 3155 of 36 172 (8.72%) with high BP, 3233 of 12 887 (25.09%) with grade 1 hypertension, and 1339 of 2527 (52.99%) with grade 2 or 3 hypertension during the follow-up period. After excluding the 7727 participants who were treated during the follow-up, the HR of grade 2 or 3 hypertension in untreated men and untreated women increased to 2.34 and 1.47, respectively, when compared with the untreated normal BP group (Figure S4 and Figure S5).

The association between systolic BP and CKD risk was analyzed using restricted cubic splines. The risk of CKD was significant for SBP ≥130 mm Hg in untreated men, untreated women, and treated women, and for systolic BP ≥140 mm Hg in treated men (Figure S6).

## DISCUSSION

BP was significantly associated with an elevated risk of CKD in men, regardless of the use of antihypertensive drugs. This was also proven by the analysis using the cubic spline curve (Figure S6). The overall HR was higher in treated men than in untreated men. The association between BP and the risk of CKD in untreated women was weaker than in untreated men. The risk of CKD in treated women with normal or high-normal BP was almost the same as that in untreated women with the corresponding BP level.

The use of antihypertensive drugs was associated with an elevated risk of CKD in men, even in the normal and high-normal BP groups. It was found that treated men had a 1.44-fold higher risk of CKD than untreated men after adjusting for systolic BP. A meta-analysis based on 39 705 Japanese patients demonstrated that treated men had a 1.56-fold higher risk for total cardiovascular disease mortality than those who did not undergo antihypertensive treatment.<sup>10</sup> Longer duration of hypertension could contribute to the higher CKD risk in treated individuals.<sup>20</sup> Therefore, we should consider following treated men more carefully than untreated men, even when BP is well controlled.

In the untreated group, the association between BP and the risk of CKD in women was weaker than in men (Figure 2 and Figure S6). This may be caused by gender-related differences, such as estrogen production, which has been suggested to prevent atherosclerosis.<sup>21</sup> Our findings may raise the hypothesis that the deleterious effect of elevated BP on the kidneys may be weaker in women. However, no study has clarified the gender difference and the effect of intensive treatment on kidney protection. A recent meta-analysis based on randomized controlled trials

**Table 3. Stratification Analysis in Men**

Strata	No.	Events	HRs (95% CIs)				Interaction <i>P</i>
			Untreated		Treated		
			Normal and High-Normal BP	High BP and Grade 1–3 Hypertension	Normal and High-Normal BP	High BP and Grade 1–3 Hypertension	
Age <50 y	80 678	7690	1.00 (reference)	1.16 (1.10–1.22)	1.50 (1.22–1.84)	1.66 (1.51–1.83)	0.19
Age ≥50 y	27 114	2956	1.00 (reference)	1.30 (1.19–1.42)	1.52 (1.27–1.82)	1.94 (1.74–2.16)	
BMI <25 kg/m <sup>2</sup>	78 218	6612	1.00 (reference)	1.18 (1.12–1.24)	1.59 (1.32–1.91)	1.77 (1.59–1.97)	0.44
BMI ≥25 kg/m <sup>2</sup>	29 572	4034	1.00 (reference)	1.22 (1.13–1.31)	1.35 (1.11–1.64)	1.77 (1.60–1.95)	
Nonsmoking	59 832	5745	1.00 (reference)	1.21 (1.14–1.28)	1.43 (1.19–1.70)	1.70 (1.55–1.87)	0.37
Smoking	47 953	4901	1.00 (reference)	1.18 (1.11–1.26)	1.48 (1.21–1.81)	1.85 (1.66–2.06)	
Nondrinking	65 514	6635	1.00 (reference)	1.18 (1.12–1.25)	1.46 (1.22–1.74)	1.78 (1.62–1.95)	0.92
Drinking	40 946	3886	1.00 (reference)	1.21 (1.12–1.29)	1.44 (1.17–1.77)	1.72 (1.54–1.92)	
Non-DM	101 510	9416	1.00 (reference)	1.20 (1.15–1.25)	1.61 (1.39–1.88)	1.82 (1.69–1.97)	0.0017
DM	6282	1230	1.00 (reference)	1.11 (0.97–1.29)	1.06 (0.80–1.41)	1.50 (1.27–1.77)	
Nondyslipidemia	56 453	4826	1.00 (reference)	1.16 (1.09–1.24)	1.42 (1.13–1.77)	1.87 (1.66–2.09)	0.24
Dyslipidemia	51 339	5820	1.00 (reference)	1.22 (1.15–1.29)	1.49 (1.26–1.76)	1.72 (1.57–1.88)	
eGFR <90 mL/min per 1.73 m <sup>2</sup>	79 261	8217	1.00 (reference)	1.19 (1.14–1.25)	1.52 (1.31–1.76)	1.77 (1.64–1.92)	0.80
eGFR ≥90 mL/min per 1.73 m <sup>2</sup>	28 531	2429	1.00 (reference)	1.19 (1.09–1.30)	1.22 (0.90–1.66)	1.71 (1.47–1.99)	
Visits <5 times	50 004	4161	1.00 (reference)	1.26 (1.17–1.35)	1.45 (1.21–1.73)	1.74 (1.56–1.94)	0.11
Visits ≥5 times	57 788	6485	1.00 (reference)	1.20 (1.14–1.27)	1.46 (1.19–1.79)	1.84 (1.68–2.01)	

The data indicate the hazard ratios (HRs) for chronic kidney disease incidence when the normal/high-normal blood pressure (BP) group is treated as a reference. The model was adjusted by covariates indicated in the legend of Figure 1 (other than the factor used for stratification). Data on body mass index (BMI), smoking status, and alcohol consumption (drinking) were unavailable for 2, 7, and 1332 participants, respectively. DM indicates diabetes mellitus; and GFR, estimate glomerular filtration rate.

in adults without DM who had CKD did not find intensive antihypertensive treatment effective for the reduction of systolic/diastolic BP to <130/80 mm Hg for the prevention of kidney dysfunction.<sup>22</sup> In the present study, normal or high-normal BP with treatment that is well controlled, hypertension did not elevate the risk of CKD in women. Thus, appropriate antihypertensive treatment could be more effective for preventing kidney dysfunction in women with hypertension than in men with hypertension.

Several observational studies reported no significant gender differences in the association between BP and the risk of CKD.<sup>4,8,23</sup> However, an Iranian study with 3313 participants indicated a weaker association between BP and the risk of CKD in women than in men; this study did not consider the use of antihypertensive drugs.<sup>6</sup> The inconsistent results could be the result of the different age of the participants in the above studies<sup>4,8,23</sup> and those in the Iranian study<sup>6</sup> (≈60 years and 39.7 years, respectively). The mean age of the participants in our study was 44.74 years.

The association between BP and the increased risk of CKD was more remarkable in men without DM than in men with DM (Table 3). The deleterious effect of BP on the kidney could be more explicit in men without DM. BP was clearly associated with an elevated risk of CKD in women with a BMI of ≥25 kg/

m<sup>2</sup>, implying the synergistic effect of BP and being overweight on the risk of CKD (Table 4). One reason for being overweight in women could be reduced estrogens or increased testosterone, which increases the appetite and causes weight gain in women.<sup>24</sup> Estrogens have a renoprotective effect but testosterone adversely affects kidney function.<sup>15</sup> Estrogen levels are higher in nonobese women than in obese women, especially in the premenopausal group.<sup>25</sup> In the present study, the interaction between BMI and BP on the risk of CKD appears to remain only among women aged <50 years. Among overweight women in the present study, reduced estrogens or increased testosterone may have accelerated the deleterious effect of BP on the kidney. This hypothesis should be clarified by studies with data on sex hormones and menopause.

When CKD outcomes were classified as eGFR <60 mL/min per 1.73 m<sup>2</sup> and the presence of proteinuria, the BP category was significantly associated with both these suboutcomes in men. Meanwhile, in women, BP was associated with an elevated risk of proteinuria but not an eGFR <60 mL/min per 1.73 m<sup>2</sup> (Table 5). The present study was conducted based on multiple examinations after excluding participants with an eGFR <70 mL/min per 1.73 m<sup>2</sup>, which may have influenced the results. However, none of the previous

**Table 4. Stratification Analysis in Women**

Strata	No.	Events	HRs (95% CIs)				Interaction P
			Untreated		Treated		
			Normal and High-Normal BP	High BP and Grade 1–3 Hypertension	Normal and High-Normal BP	High BP and Grade 1–3 Hypertension	
Age <50 y	36 413	3594	1.00 (reference)	1.09 (1.00–1.19)	0.86 (0.50–1.48)	1.75 (1.41–2.16)	0.44
Age ≥50 y	10 487	648	1.00 (reference)	1.30 (1.09–1.56)	1.19 (0.80–1.75)	1.79 (1.40–2.29)	
BMI <25 kg/m <sup>2</sup>	40 740	3479	1.00 (reference)	1.06 (0.97–1.16)	1.01 (0.69–1.48)	1.61 (1.30–1.99)	0.051
BMI ≥25 kg/m <sup>2</sup>	6154	761	1.00 (reference)	1.36 (1.16–1.59)	0.93 (0.54–1.61)	1.81 (1.41–2.31)	
Nonsmoking	43 094	3858	1.00 (reference)	1.14 (1.05–1.24)	0.93 (0.66–1.30)	1.68 (1.43–1.97)	0.60
Smoking	3803	383	1.00 (reference)	1.03 (0.78–1.36)	1.05 (0.48–2.28)	1.19 (0.60–2.37)	
Nondrinking	42 087	3871	1.00 (reference)	1.15 (1.06–1.25)	0.93 (0.66–1.30)	1.70 (1.45–2.01)	0.37
Drinking	4282	326	1.00 (reference)	0.94 (0.72–1.23)	1.07 (0.43–2.64)	1.08 (0.59–1.99)	
Non-DM	45 807	4104	1.00 (reference)	1.13 (1.04–1.22)	0.90 (0.64–1.28)	1.55 (1.30–1.84)	0.44
DM	1093	138	1.00 (reference)	1.21 (0.80–1.86)	1.49 (0.70–3.18)	2.47 (1.54–3.96)	
Nondyslipidemia	34 844	3085	1.00 (reference)	1.09 (0.98–1.20)	0.97 (0.60–1.58)	1.24 (0.96–1.59)	0.092
Dyslipidemia	12 056	1157	1.00 (reference)	1.23 (1.08–1.41)	1.05 (0.69–1.57)	2.15 (1.74–2.65)	
eGFR <90 mL/min per 1.73 m <sup>2</sup>	34 339	3447	1.00 (reference)	1.12 (1.03–1.23)	0.97 (0.70–1.36)	1.51 (1.27–1.80)	0.41
eGFR ≥90 mL/min per 1.73 m <sup>2</sup>	12 561	795	1.00 (reference)	1.19 (0.99–1.43)	0.95 (0.42–2.16)	2.42 (1.70–3.46)	
Visits <5 times	23 322	1302	1.00 (reference)	1.29 (1.13–1.48)	1.21 (0.80–1.83)	1.67 (1.29–2.14)	0.13
Visits ≥5 times	23 578	2940	1.00 (reference)	1.05 (0.96–1.16)	0.78 (0.49–1.24)	1.65 (1.35–2.02)	

The data indicate the hazard ratios (HRs) for chronic kidney disease incidence when the normal/high-normal blood pressure (BP) group is treated as a reference. The model was adjusted by covariates indicated in the legend of Figure 1 (other than the factor used for stratification). Data on body mass index (BMI), smoking status, and alcohol consumption (drinking) were unavailable for 6, 3, and 531 participants, respectively. DM indicates diabetes mellitus; and eGFR, estimate glomerular filtration rate.

studies have considered this point. These exclusion criteria may have influenced the association between BP and the presence of proteinuria.

Approximately 50% of patients with grade 2 or 3 hypertension untreated at baseline had not been treated for 5 years in the present study. These findings may

**Table 5. HRs for the Incidence of Proteinuria or eGFR <60 mL/min per 1.73 m<sup>2</sup>**

Strata	Outcome	Variable	HRs (95% CIs)			
			Untreated		Treated	
			Normal and High-Normal BP	High BP and Grade 1–3 Hypertension	Normal and High-Normal BP	High BP and Grade 1–3 Hypertension
Men	Proteinuria	No. of events	3397	3432	167	814
		Incidence*, per 1000 patient-y	12.58	16.31	22.01	30.20
		HR† (95% CI)	1.00 (reference)	1.19 (1.14–1.25)	1.44 (1.23–1.69)	1.76 (1.62–1.92)
Men	eGFR <60 mL/min per 1.73 m <sup>2</sup>	No. of events	1348	1504	102	420
		Incidence*, per 1000 patient-y	5.43	7.19	11.99	13.97
		HR† (95% CI)	1.00 (reference)	1.22 (1.13–1.32)	1.83 (1.49–2.25)	1.90 (1.69–2.14)
Women	Proteinuria	No. of events	2060	574	25	128
		Incidence*, per 1000 patient-y	10.90	14.39	13.56	32.56
		HR† (95% CI)	1.00 (reference)	1.21 (1.10–1.33)	1.16 (0.77–1.73)	2.15 (1.77–2.61)
Women	eGFR <60 mL/min per 1.73 m <sup>2</sup>	No. of events	1172	345	20	74
		Incidence*, per 1000 patient-y	7.35	7.88	3.97	13.59
		HR† (95% CI)	1.00 (reference)	1.06 (0.94–1.21)	0.84 (0.53–1.32)	1.18 (0.92–1.52)

BP indicates blood pressure; and eGFR, estimated glomerular filtration rate.  
 \* The incidence rates were calculated after age standardization (<45/45–59/≥60 years) by the direct method.  
 † The hazard ratio (HR) was adjusted by covariates indicated in the legend of Figure 1.



link to issues regarding the insufficient treatment rate in Japanese patients with hypertension.<sup>14</sup> The HRs of grade 2 or 3 hypertension in untreated participants slightly increased after excluding those who were treated during the follow-up (Figure S4 and Figure S5), supporting the consensus that patients with hypertension who remain untreated have an increased risk of CKD.

The present study must be interpreted within the context of its potential limitations. First, the JMDC database predominantly includes young or middle-aged individuals who work in large enterprises. We received the data from adults who visited health checkups  $\geq 5$  times, whereas the original JMDC database has a larger sample size. The participants were more likely to have a stable income and could afford better health care than those in low-income areas. The present findings are not generalizable, especially to individuals aged  $\geq 75$  years, those in low-income areas, and unhealthy or patient populations. However, similar gender differences in the association between BP and CKD have been reported in an Iranian study while it did not consider the use of antihypertensive drugs.<sup>6</sup> Second, since the present study is observational, our findings cannot interpret the effect of intensive antihypertensive treatment on kidney protection. Third, the use of creatinine levels or the presence of proteinuria measured by only 1 measurement in each health checkup as an indication of CKD in the present study is considered a limitation. The current guidelines<sup>26</sup> define CKD as the presence of kidney damage or an eGFR  $< 60$  mL/min per  $1.73$  m<sup>2</sup> for  $\geq 3$  months. Therefore, acute kidney injury or dehydration might have been partly responsible for the incidence of CKD in the present study. The CKD outcomes in previous studies were defined in a similar manner.<sup>4,5,7,23,27,28</sup> CKD indicated by an eGFR  $< 60$  mL/min per  $1.73$  m<sup>2</sup> or the presence of proteinuria has been reported to be strongly associated with an elevated risk of cardiovascular disease. Fourth, we did not exclude type 1 DM since the present database does not have information on the type of DM. However, since the prevalence of type 1 DM in Asia is only 6.9 per 10 000 people,<sup>29</sup> the effect of type 1 DM on our findings is limited. Finally, the data from the annual health checkups did not include information regarding the type of antihypertensive treatment. For instance, dihydropyridine calcium channel blockers can decrease the tone of the afferent arteriole, increasing intraglomerular pressure and thus potentially increasing proteinuria. The difference in the antihypertensive drug type might have affected associations based on gender differences found in the present study. The BP change could also affect CKD risk.<sup>8</sup> Considering antihypertensive

treatment and BP change can improve the predictive value for CKD.

## Conclusions

BP was significantly associated with an elevated risk for CKD incidence, but the overall HR was higher in treated individuals than in those who did not undergo antihypertensive treatment. However, the risk of CKD in women with controlled hypertension was similar to untreated women with normal or high-normal BP, inconsistent with the trend in men. Kidney function in treated individuals should be followed carefully, especially in men. Future intervention studies assessing antihypertensive treatment on kidney dysfunction should focus on gender differences.

## ARTICLE INFORMATION

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### Supplementary Materials

Tables S1–S2

Figures S1–S6

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# **SUPPLEMENTAL MATERIAL**

**Table S1. BMI-adjusted difference in eGFR between men and women according to BP category and the use of antihypertensive treatment.**

BP group	BMI-adjusted eGFR at baseline (Standard Error)		<i>P</i>
	Men	Women	
Untreated normal BP	84.88 (0.06)	86.00 (0.07)	<0.0001
Untreated high normal BP	85.48 (0.09)	85.91 (0.15)	0.015
Untreated high BP	84.65 (0.07)	85.54 (0.14)	<0.0001
Untreated grade 1 HT	84.80 (0.11)	85.67 (0.27)	0.0026
Untreated grade 2–3 HT	84.80 (0.27)	85.38 (0.53)	0.33
Treated normal BP	82.33 (0.33)	84.01 (0.60)	0.016
Treated high normal BP	83.44 (0.39)	83.51 (0.66)	0.93
Treated high BP	83.43 (0.20)	84.22 (0.41)	0.088
Treated grade 1 HT	83.68 (0.22)	84.38 (0.49)	0.19
Treated grade 2–3 HT	84.01 (0.42)	83.40 (0.93)	0.55

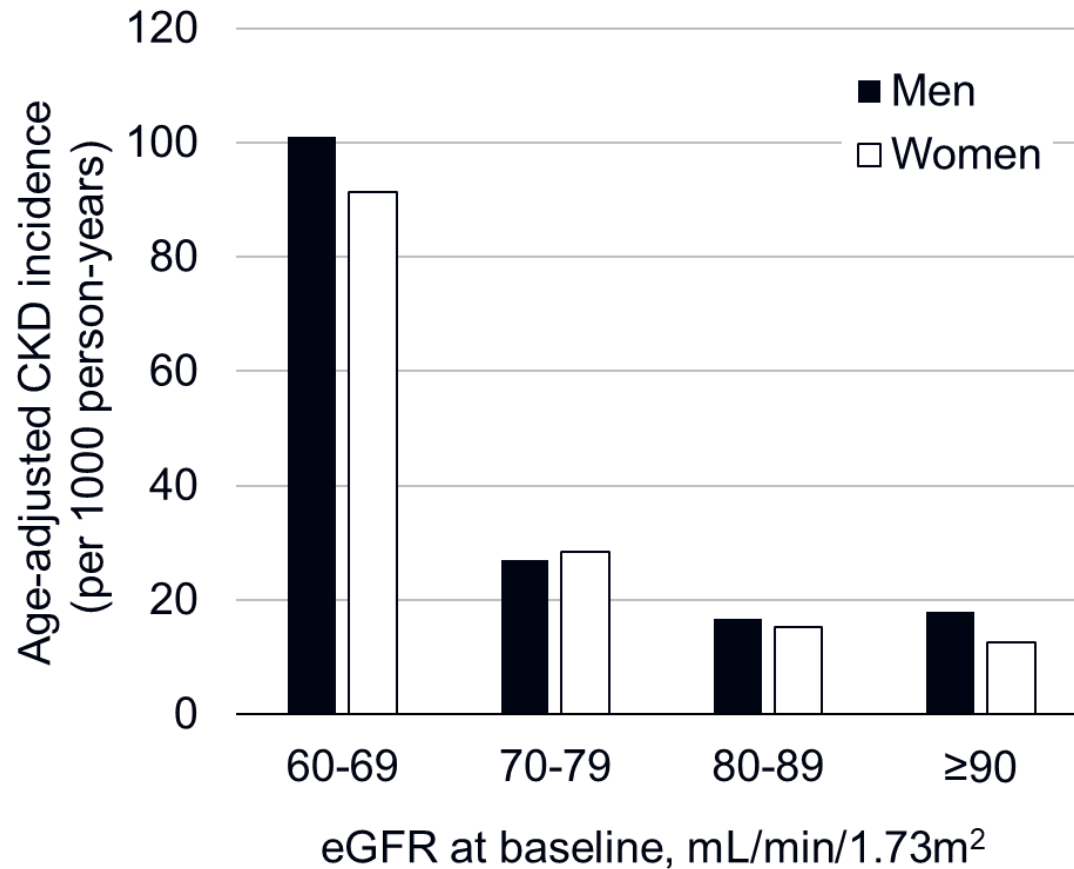
The analysis of covariance with model included BMI and men as independent variables. We performed the analysis in each BP group.

**Table S2. Number of CKD events and incidence rates in each BP-antihypertensive treatment group**

Strata	BP group	CKD events/ participants, n	Age-standardized CKD incidence, per 1000 person-year
Untreated men	Normal BP	3,124 / 39,877	16.98
	High Normal BP	1,449 / 16,968	18.02
	High BP	2,992 / 29,644	20.26
	Grade 1 HT	1,407 / 11,008	26.00
	Grade 2–3 HT	297 / 2,019	34.96
Treated men	Normal BP	130 / 960	35.76
	High Normal BP	108 / 845	34.39
	High BP	497 / 3,061	39.11
	Grade 1 HT	494 / 2,679	41.34
	Grade 2–3 HT	148 / 731	47.50
Untreated women	Normal BP	2,604 / 30,096	17.63
	High Normal BP	531 / 5,858	18.68
	High BP	639 / 6,528	20.68
	Grade 1 HT	184 / 1,879	23.37
	Grade 2–3 HT	54 / 508	28.30
Treated women	Normal BP	20 / 291	18.62
	High Normal BP	22 / 296	18.16
	High BP	85 / 742	28.05
	Grade 1 HT	80 / 552	35.85
	Grade 2–3 HT	23 / 150	37.93

The CKD incidence rates were calculated after age-standardization (<45/45–59/≥60 years) by the direct method. BP, blood pressure; HT, hypertension; CKD, chronic kidney disease.

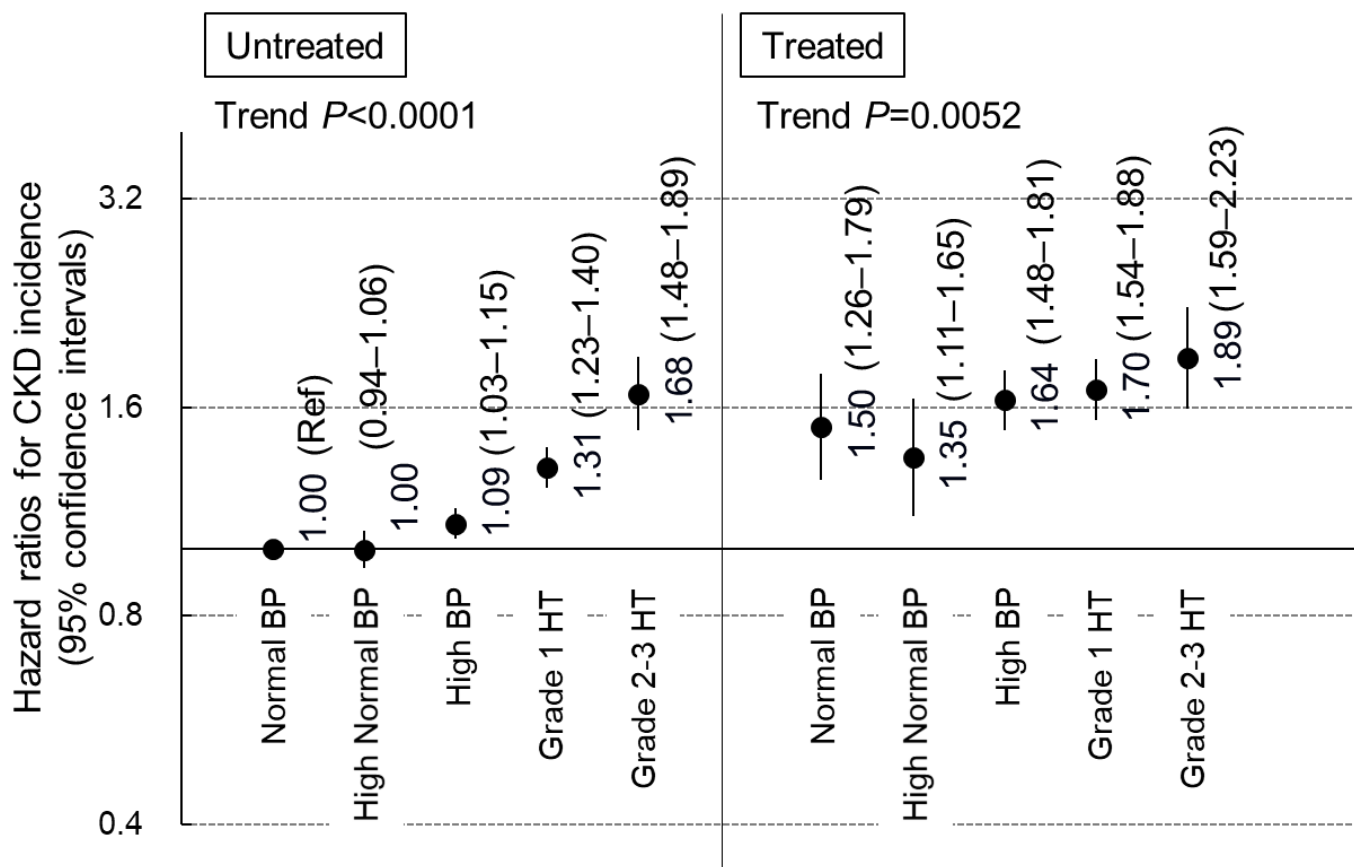
Figure S1. Baseline eGFR and age-adjusted CKD incidence.



We calculated the CKD incidence rates after age-standardization (<45/45–59/≥60 years) by the direct method. The participants with eGFR<70 mL/min/1.73 m<sup>2</sup> were excluded from the main analysis.

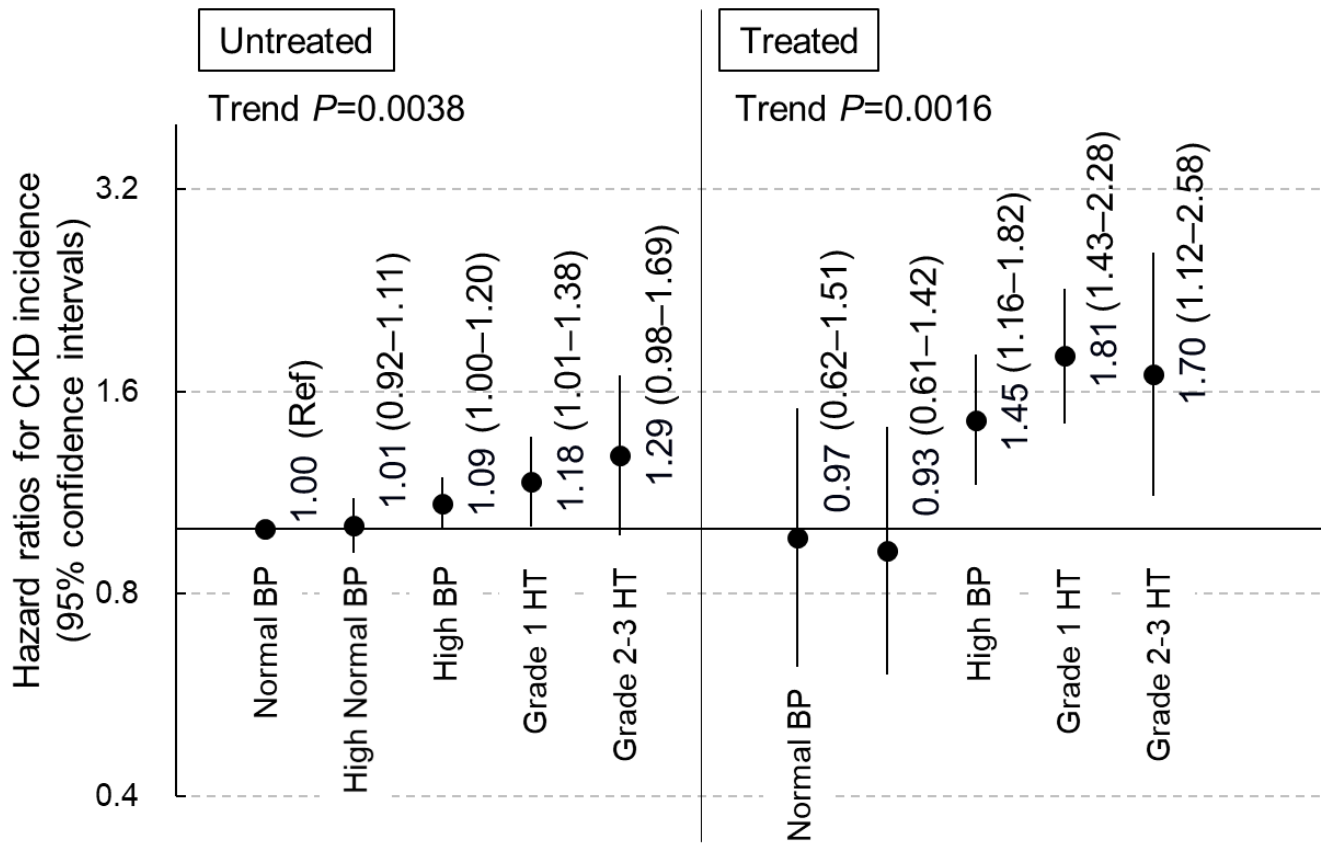
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Figure S2. BP and the risk of CKD incidence in men (BMI was included in the model as a continuous variable).



Covariates were age, linear and quadratic terms of BMI, current smoking status, alcohol consumption, diabetes mellitus, dyslipidemia, and eGFR at baseline. BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; HT, hypertension; eGFR, estimated glomerular filtration rate.

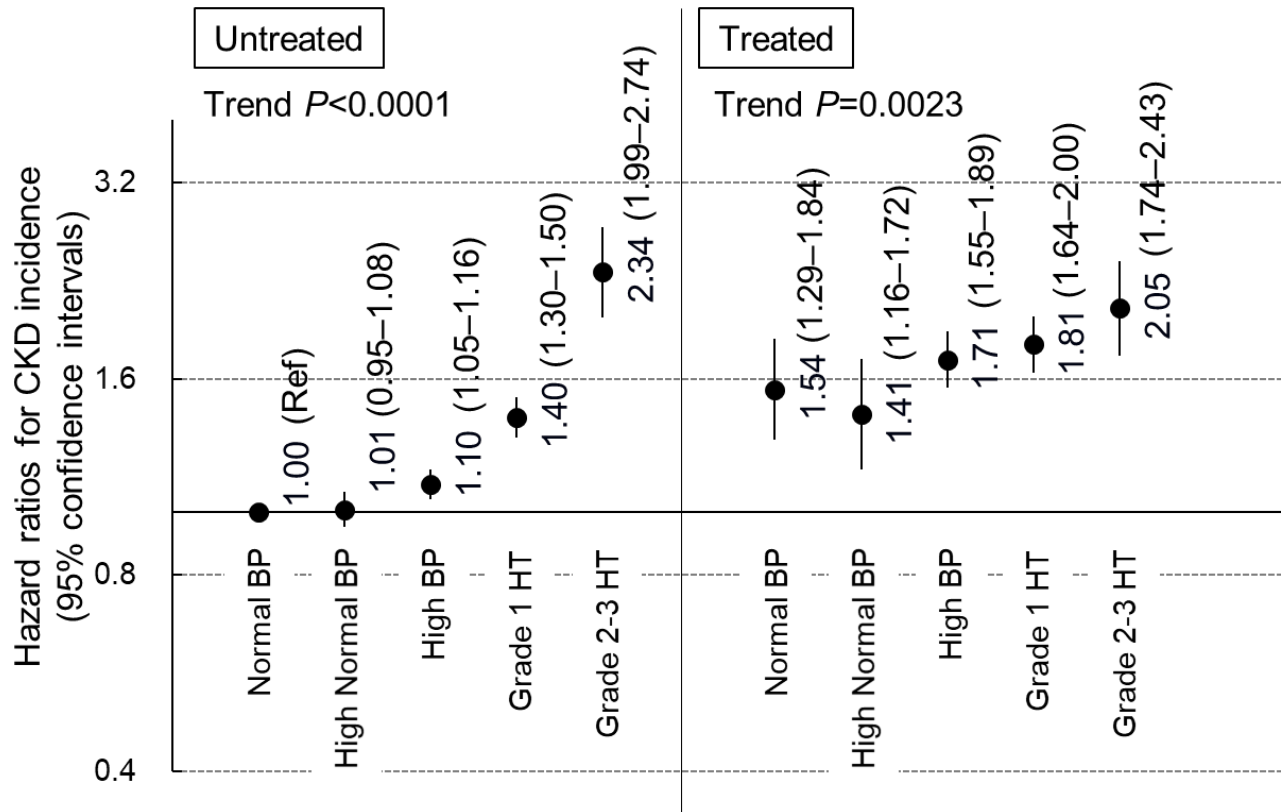
Figure S3. BP and the risk of CKD incidence in women (BMI was included in the model as a continuous variable).



Covariates and abbreviations are the same as indicated in Figure S2.

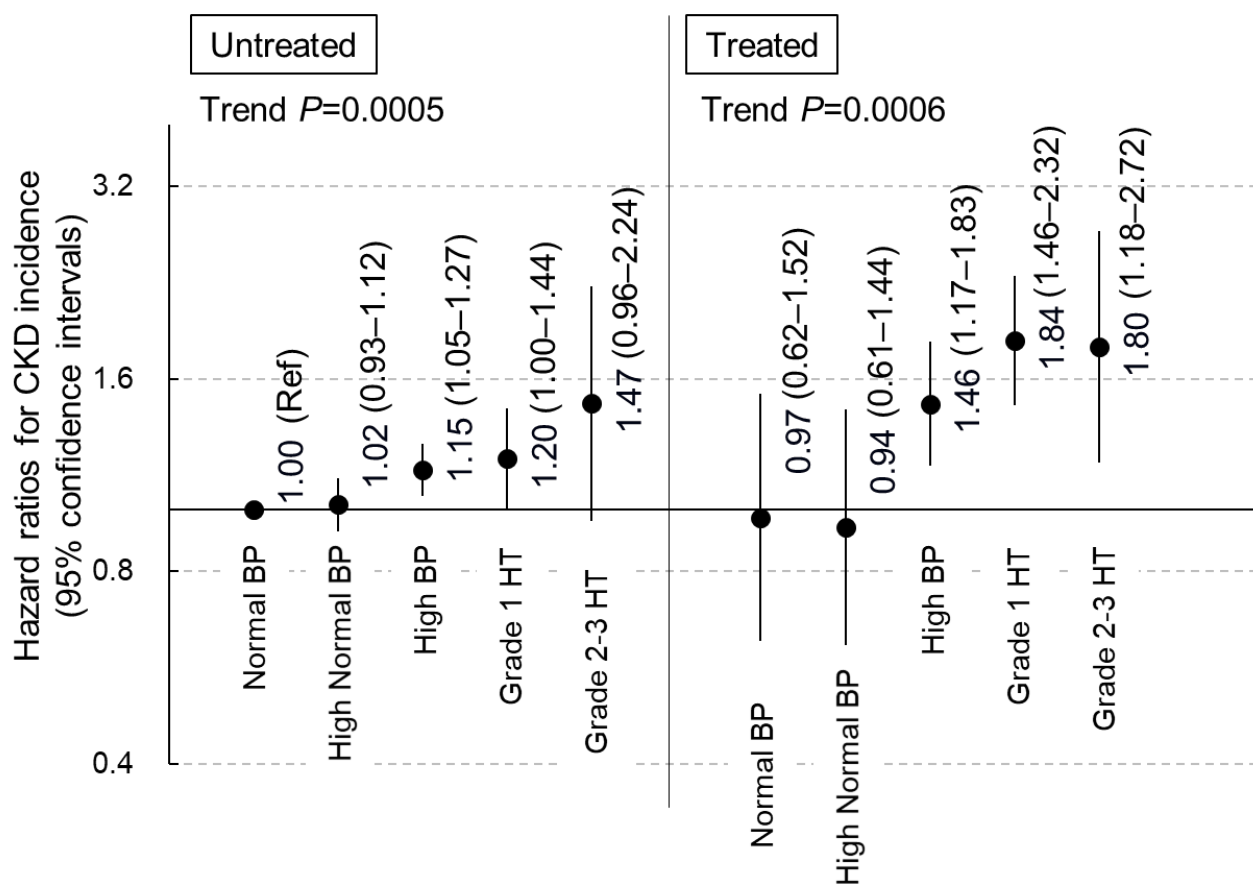


**Figure S4. BP and the risk of CKD incidence in men after excluding high BP or hypertensive participants who were untreated at baseline but treated during follow-up.**



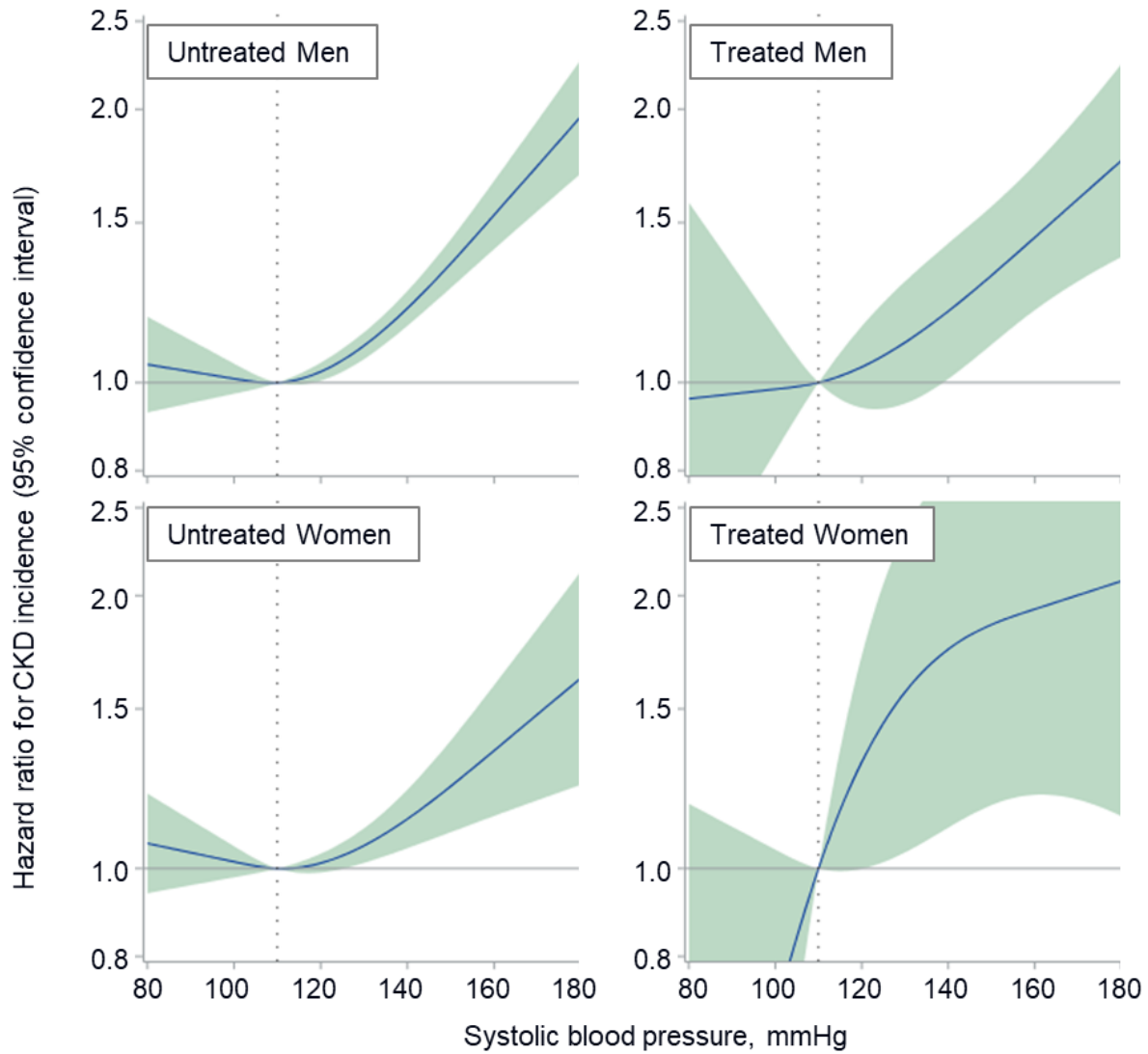
The untreated participants with high BP or hypertension at baseline and with antihypertensive treatment initiated during follow-up were excluded. Covariates were age, body mass index <18.5 kg/m<sup>2</sup>, body mass index ≥25 kg/m<sup>2</sup>, current smoking status, alcohol consumption, diabetes mellitus, dyslipidemia, and eGFR at baseline. BP, blood pressure; CKD, chronic kidney disease; HT, hypertension; eGFR, estimated glomerular filtration rate.

**Figure S5. BP and the risk of CKD incidence in women after excluding high BP or hypertensive participants who were untreated at baseline but treated during follow-up.**



The untreated participants with high BP or hypertension at baseline and with antihypertensive treatment initiated during follow-up were excluded. Covariates and abbreviations are the same as indicated in **Figure S4**.

**Figure S6. Restricted spline curves of hazard ratio stratified by sex and the use of antihypertensive treatment.**



The systolic BP of 110 mmHg, which was the mean value in the normal BP group, was treated as a reference. Hazard ratios were adjusted for the same covariates indicated in **Figure 1**. BP, blood pressure.