

ORIGINAL ARTICLE

Blood pressure components and risk for chronic kidney disease in middle-aged Japanese men: The Kansai Healthcare Study

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It is unclear which blood pressure (BP) components (that is, systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP) and mean arterial pressure (MAP)) are superior predictors of chronic kidney disease (CKD). Furthermore it is unclear whether the combination of SBP+DBP or PP+MAP is superior to any of these four individual BP components in predicting CKD. We enrolled 9928 Japanese men aged 40–55 years who had a normal estimated glomerular filtration rate (eGFR), no proteinuria and no history of cardiovascular disease and were not taking any antihypertensive medications at baseline. CKD was defined as an eGFR of $<60 \text{ ml min}^{-1}$ per 1.73 m^2 using the modified diet in renal disease equation. Δ Akaike's information criterion (Δ AIC) was used to compare the BP components-added model to the model without them in a Cox proportional hazards model. During the 52 428 person-years of follow-up, there were 434 cases of CKD. Of all four BP components, the model including DBP- or MAP-alone had the highest values of Δ AIC (10.2 and 9.85, respectively). The PP-alone model had the lowest Δ AIC value (-1.48). The combination models including SBP+DBP (Δ AIC 8.42) or PP+MAP (8.42) were not superior to the models including DBP- or MAP-alone. These findings suggested that, of the four BP components, both DBP and MAP were the most useful predictors for subsequent incidence of CKD, but PP was not an important predictor. The combination model, including SBP+DBP or PP+MAP, was not superior to the models including DBP- or MAP-alone for predicting CKD.

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INTRODUCTION

Hypertension is a well-known risk factor for cardiovascular diseases,^{1,2} and it has also been associated with the incidence of chronic kidney disease (CKD).^{3–7} Some epidemiological studies have focused on which blood pressure (BP) components are superior as predictors of cardiovascular diseases, including systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP) and mean arterial pressure (MAP).^{8–17} However, the BP components that are the most important risks factor for CKD are currently unknown.

A number of epidemiological studies have examined the association between hypertension, defined by SBP and DBP, and the risk of CKD.^{3–7} BP is also divided into two other components: MAP, which reflects a steady component, and PP, which reflects a pulsatile component.^{18–21} PP is mainly determined by ventricular ejection, arterial stiffness and the timing of the reflected waves, and it increases with advancing age.^{18–21} MAP mainly depends on cardiac output and peripheral vascular resistance.^{18–21} Only two prospective studies have

examined associations between these four BP components and the incidence of reduced kidney function.^{22,23} One study focused on only subjects over the age of 65 with isolated systolic hypertension and did not include subjects with diastolic hypertension or normotension.²² The other study used data based on self-reported BP information.²³ No prospective cohort study using both normotensive and hypertensive subjects has examined the relationship of directly measured BP components, such as SBP, DBP, PP and MAP, to the incidence of CKD (defined by low estimated glomerular filtration rate (eGFR)).

We therefore examined the effects of SBP, DBP, PP and MAP on the onset of CKD, as defined by an eGFR of $<60 \text{ ml min}^{-1}$ per 1.73 m^2 in middle-aged Japanese men. Our specific purposes were: (1) to examine which BP components (that is, SBP, DBP, PP and MAP) were superior predictors of CKD and (2) to examine whether it was more helpful to use combined BP components (that is, SBP+DBP or PP+MAP) to predict the risk of CKD instead of any one of the four single BP components.

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METHODS

Study sample

The Kansai Healthcare Study was an ongoing cohort investigation designed to examine risk factors for cardiometabolic diseases. The details of the study have been described previously.^{24–26} Between April 2000 and March 2001, 12 647 male employees of a company in Kansai, Japan, aged 40–55 years at entry and considered to be involved in sedentary jobs were enrolled in this study. All employees in this company aged 40 years or older undergo annual medical checkups. The protocol for this research was reviewed by the Human Subjects Review Committee at Osaka City University.

Eligibility criteria for inclusion in the study were as follows: an eGFR of 60 ml min⁻¹ per 1.73 m² or higher; dipstick-negative proteinuria; no history of cardiovascular diseases; and not taking oral antihypertensive medications at baseline. A total of 10 666 Japanese men were included in this study. Of them, we excluded 349 men who had missing covariate information at baseline. We also excluded 389 participants because they did not undergo annual checkups during the follow-up period. Thus, the analytic cohort consisted of 9928 men.

Data collection and measurements

The clinical examination consisted of the following: medical history; physical examination; anthropometric measurements; self-reported questionnaires on lifestyle characteristics, such as regular leisure-time physical activity, smoking habit and daily alcohol consumption; measurements of fasting plasma glucose and serum creatinine; and dipstick urinalysis. Trained nurses took all of the measurements. Blood samples were drawn after an overnight 12-h fast, and plasma glucose was measured. Diabetes was diagnosed if the fasting plasma glucose level was ≥ 126 mg dl⁻¹ or if participants were taking oral hypoglycemic medications or insulin according to the American Diabetes Association criteria.²⁷ Serum creatinine was measured enzymatically using a Hitachi 7350 automatic chemistry analyzer (Hitachi, Tokyo, Japan). Serum creatinine at baseline was also measured by the Jaffe method in 1930 subjects. We recalibrated the values of the Jaffe method to the values of the enzymatic method using the following formula: serum creatinine (mg dl⁻¹, enzymatic method) = 1.02 × serum creatinine (mg dl⁻¹, Jaffe method) 0.25 ($r=0.9996$). We calculated eGFR using the Modification of Diet in Renal Disease (MDRD) Study equation for Japanese men,²⁸ which was validated by the standard inulin clearance techniques, as follows: $eGFR=194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$. The serum creatinine in the equation was the value measured by the enzymatic method. CKD was defined as an eGFR < 60 ml min⁻¹ per 1.73 m². CKD was diagnosed based on the eGFR level at baseline and each annual follow-up examination. Dipstick urinalysis was occasionally performed on fresh and mid-stream urine. The results of the dipstick urinalysis were interpreted as negative, ±, 1+, 2+, 3+ or 4+. Proteinuria was defined as 1+ or higher at baseline. Body mass index was calculated as weight in kg divided by height in m².

After a 5-min rest period in a quiet room, SBP and DBP were measured in a sitting position on the right arm with an automatic sphygmomanometer (BP-203RV; Omron Colin, Tokyo, Japan, and Udex-super; ELK Osaka, Japan). The Spearman's correlation between the former device and a standard mercury sphygmomanometer was 0.985 for SBP and 0.976 for DBP. The Spearman's correlation between the latter device and a standard mercury sphygmomanometer was 0.997 for SBP and 0.976 for DBP. BP was measured once or twice at an interval of a few minutes. If the initial reading showed hypertension, BP was measured again, and the subject's BP was defined as the lower of the two readings after the second measurement. Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg.¹ PP was defined as SBP minus DBP. MAP was calculated as DBP plus one-third PP.

Questions about alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. The types of beverage included beer, sake (rice wine), whiskey and shochu (a type of brandy). The units of alcohol consumed were expressed as 'go', or the equivalent of 23.0 g of ethanol, and were converted to daily alcohol consumption (in g of ethanol per day). One go is 180 ml of sake, which corresponds to one bottle (663 ml) of beer, two single shots (75 ml) of whisky, or a half go (90 ml) of shochu. Regarding smoking habits, participants were classified as non-smokers, past smokers or current smokers. The single-item questionnaire regarding leisure-time physical activity had three possible answers: rarely,

sometimes and regular (that is, at least once weekly). Participants were classified as engaging in regular leisure-time physical activity at least once weekly or less than once weekly. The validity of this questionnaire has been described in detail previously.²⁴

Statistical analysis

We used unpaired *t*-tests for continuous variables or χ^2 -tests for categorical variables to examine the difference between participants who developed CKD and those who did not. We used Cox proportional hazards models to investigate the association between BP components and the incidence of CKD. Follow-up of each subject was continued until diagnosis of CKD or until 31 March 2007, whichever came first. The proportional hazards assumption was confirmed by a log-minus-log plot. Nonlinear effects of continuous independent variables were evaluated by categorizing a continuous variable into multiple dichotomous variables of equal units and visually assessing a scatter plot of each variable's coefficient in the Cox proportional hazards models against the median value of each class of dichotomous variables.²⁹ The presence of an effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. We calculated the 95% confidence interval for each hazard ratio.

In the Cox proportional hazards models, Δ Akaike's information criterion (Δ AIC) and the $\Delta\chi^2$ of likelihood ratio test were used as a measure of the improvement of goodness of fit to compare the two models, one of which was nested within the other. We used Δ AIC to evaluate which BP components were superior predictors of the risk for the incidence of CKD and whether the models including combined BP components (that is, SBP+DBP or PP+MAP) outperformed models including any one of the four single BP components for predicting the incidence of CKD because AIC can be used to compare non-nested models. An absolute Δ AIC value of ≤ 2 indicates no meaningful difference of goodness of fit between the methods. An absolute Δ AIC value of > 2 indicates a meaningful difference of goodness of fit between the methods.³⁰ A larger decrease in AIC can be interpreted as a better fit. In models including combined BP components (SBP+DBP or PP+MAP), we assessed multicollinearity by inspecting the changes in the coefficient and standard error of each BP component variable caused by the addition of the other.³¹ The linear trends in risks of quartiles of all BP components were evaluated by entering indicators for each categorical level of exposure using the median value for each category.

All *P* values were two-tailed and considered statistically significant if the values were < 0.05 . All statistical analyses were performed using PASW Statistics, version 17.0 (SPSS, Chicago, IL, USA).

RESULTS

The baseline characteristics of the study participants are shown in Table 1. During the 52 428 person-years of follow-up (a median follow-up of 6.0 years), there were 434 incident cases of CKD. Participants who developed CKD had higher mean values of SBP, DBP and MAP than those who did not (Table 1). There was no significant difference in PP between the groups. The group of participants who developed CKD also had a higher proportion of hypertension, a higher mean body mass index and a lower mean eGFR at baseline (Table 1).

In the Cox proportional hazards models, all continuous variables, except eGFR, in the models (presented in Tables 2 and 3) fulfilled the linearity assumption. To account for the nonlinearity of eGFR, we fit a model using categorized eGFR (60.0–69.9, 70.0–79.9, 80.0–89.9, ≥ 90.0 ml min⁻¹ per 1.73 m²) in all models presented in Tables 2 and 3. Therefore, the following variables were included in the base model: age, body mass index, diabetes status (non-diabetes or diabetes), daily alcohol consumption, regular leisure-time physical activity (yes/no), smoking habit (non-smokers, past smokers, or current smokers), and categorized eGFR (60.0–69.9, 70.0–79.9, 80.0–89.9, ≥ 90.0 ml min⁻¹ per 1.73 m²). We examined the significance of the interaction terms SBP × DBP and PP × MAP in all models

Table 1 Baseline characteristics of study participants according to whether CKD developed during the follow-up period

| Characteristics | CKD (-) | CKD (+) | P value |
|--|--------------|--------------|---------|
| <i>n</i> | 9494 | 434 | |
| Age, years | 47.8 ± 4.2 | 48.6 ± 4.1 | <0.001 |
| Body mass index, kg m ⁻² | 23.3 ± 2.9 | 23.9 ± 2.9 | <0.001 |
| Systolic blood pressure, mm Hg | 127.9 ± 17.9 | 130.9 ± 18.3 | 0.001 |
| Diastolic blood pressure, mm Hg | 79.7 ± 11.9 | 82.5 ± 11.5 | <0.001 |
| Pulse pressure, mm Hg | 48.1 ± 12.6 | 48.5 ± 13.1 | 0.626 |
| Mean arterial pressure, mm Hg | 95.8 ± 12.9 | 98.6 ± 12.7 | <0.001 |
| Hypertension, % | 2722 (28.7) | 158 (36.4) | 0.001 |
| Fasting plasma glucose, mg dl ⁻¹ | 101.3 ± 21.0 | 99.2 ± 17.1 | 0.036 |
| Diabetes, % | 653 (6.9) | 19 (4.4) | 0.043 |
| Alcohol consumption, g ethanol per day | 25.6 ± 22.0 | 21.3 ± 20.0 | <0.001 |
| Drinking habits, % | 8105 (85.4) | 357 (82.3) | 0.074 |
| Regular leisure-time physical activity, % | 1704 (17.9) | 91 (21.0) | 0.110 |
| Current smoker, % | 5600 (59.0) | 199 (45.9) | <0.001 |
| Serum creatinine, mg dl ⁻¹ | 0.82 ± 0.13 | 0.98 ± 0.12 | <0.001 |
| eGFR, ml min ⁻¹ per 1.73 m ² | 86.2 ± 14.2 | 69.7 ± 9.8 | <0.001 |

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. Data are mean ± s.d. or n (%).

Table 2 Comparison of four blood pressure components and their combinations in predicting the incidence of chronic kidney disease

| Model 1 | Model 2 | ΔAIC | Likelihood ratio | |
|--|----------------------------|-------|------------------|---------|
| | | | Δχ ² | P value |
| <i>The effects of adding each BP component to base model</i> | | | | |
| Base ^a | Base ^a +SBP | 5.56 | 7.56 | 0.006 |
| Base ^a | Base ^a +DBP | 10.2 | 12.19 | <0.001 |
| Base ^a | Base ^a +PP | -1.48 | 0.52 | 0.471 |
| Base ^a | Base ^a +MAP | 9.85 | 11.85 | 0.001 |
| Base ^a | Base ^a +SBP+DBP | 8.42 | 12.43 | 0.002 |
| Base ^a | Base ^a +PP+MAP | 8.42 | 12.43 | 0.002 |
| <i>The effects of adding the second BP component to each model</i> | | | | |
| Base ^a +SBP | Base ^a +SBP+DBP | 2.87 | 4.87 | 0.027 |
| Base ^a +DBP | Base ^a +DBP+SBP | -1.76 | 0.24 | 0.625 |
| Base ^a +PP | Base ^a +PP+MAP | 9.91 | 11.91 | 0.001 |
| Base ^a +MAP | Base ^a +MAP+PP | -1.42 | 0.58 | 0.447 |

Abbreviations: AIC indicates Akaike's information criterion; CKD, chronic kidney disease; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

Likelihood ratio Δχ² statistics and ΔAIC for chronic kidney disease outcomes were calculated by comparing model 2 to model 1. ΔAIC was used to evaluate which blood pressure components or combined BP components, SBP, DBP, PP, MAP, SBP+DBP or PP+MAP, were superior as the risk for incident CKD. Higher value of ΔAIC indicates better model fit and predictive utility. Likelihood ratio Δχ² statistics and its P values were used as a measure of the improvement of goodness of fit to compare the fit between model 1 and model 2, one of which was nested within the other.

^aBase model includes age, body mass index, diabetes status (non-diabetes or diabetes), daily alcohol consumption, regular leisure-time physical activity (yes/no), smoking habits (non-smokers, past smokers or current smokers) and estimated glomerular filtration rate categories (60.0–69.9, 70.0–79.9, 80.0–89.9, ≥90.0 ml min⁻¹ per 1.73 m²) at baseline, but no BP component.

including these two BP components (Tables 2 and 3). None of these interactions were significant. In all models presented in Tables 2 and 3, the proportional hazards assumption was confirmed by a log-minus-log plot, and all independent variables met the assumption.

To examine which BP components or combined BP components (that is, SBP, DBP, PP, MAP, SBP+DBP or PP+MAP) were superior predictors of incident CKD, ΔAIC was calculated as the AIC of the

Table 3 Comparison of four blood pressure components and their combinations in predicting the incidence of chronic kidney disease

| Model ^a | Hazard ratio (95% CI) | P value |
|---|-----------------------|---------|
| <i>Continuous analysis</i> | | |
| Multiple-adjusted models including a single BP component | | |
| SBP, per 1 s.d. | 1.14 (1.04–1.26) | 0.005 |
| DBP, per 1 s.d. | 1.20 (1.08–1.32) | <0.001 |
| PP, per 1 s.d. | 1.04 (0.94–1.14) | 0.469 |
| MAP, per 1 s.d. | 1.19 (1.08–1.31) | <0.001 |
| Multiple-adjusted models including combined two BP components | | |
| SBP and DBP | | |
| SBP, per 1 s.d. | 1.03 (0.91–1.18) | 0.624 |
| DBP, per 1 s.d. | 1.17 (1.02–1.34) | 0.028 |
| PP and MAP | | |
| PP, per 1 s.d. | 0.96 (0.87–1.06) | 0.448 |
| MAP, per 1 s.d. | 1.21 (1.09–1.35) | 0.001 |
| <i>Categorical analysis</i> | | |
| Multiple-adjusted models including a single BP component | | |
| SBP, mm Hg | | |
| Quartile 1 (-116) | 1.00 (reference) | |
| Quartile 2 (117–126) | 1.23 (0.92–1.65) | 0.156 |
| Quartile 3 (127–138) | 1.41 (1.07–1.88) | 0.017 |
| Quartile 4 (139-) | 1.51 (1.13–2.02) | 0.005 |
| P for trend | 0.004 | |
| DBP, mm Hg | | |
| Quartile 1 (-71) | 1.00 (reference) | |
| Quartile 2 (72–80) | 1.25 (0.92–1.68) | 0.149 |
| Quartile 3 (81–87) | 1.45 (1.08–1.96) | 0.015 |
| Quartile 4 (88-) | 1.75 (1.30–2.37) | <0.001 |
| P for trend | <0.001 | |
| PP, mm Hg | | |
| Quartile 1 (-40) | 1.00 (reference) | |
| Quartile 2 (41–47) | 0.84 (0.64–1.10) | 0.197 |
| Quartile 3 (48–55) | 0.93 (0.71–1.21) | 0.582 |
| Quartile 4 (56-) | 1.05 (0.81–1.35) | 0.734 |
| P for trend | 0.606 | |
| MAP, mm Hg | | |
| Quartile 1 (-86.7) | 1.00 (reference) | |
| Quartile 2 (86.8–95.2) | 1.20 (0.89–1.63) | 0.231 |
| Quartile 3 (95.3–103.7) | 1.37 (1.02–1.83) | 0.038 |
| Quartile 4 (103.8-) | 1.65 (1.23–2.22) | 0.001 |
| P for trend | <0.001 | |
| Multiple-adjusted models including combined two BP components | | |
| SBP and DBP | | |
| SBP, mm Hg | | |
| Quartile 1 (-116) | 1.00 (reference) | |
| Quartile 2 (117–126) | 1.12 (0.82–1.52) | 0.490 |
| Quartile 3 (127–138) | 1.18 (0.86–1.63) | 0.303 |
| Quartile 4 (139-) | 1.15 (0.81–1.64) | 0.445 |
| P for trend | 0.493 | |
| DBP, mm Hg | | |
| Quartile 1 (-71) | 1.00 (reference) | |
| Quartile 2 (72–80) | 1.20 (0.87–1.64) | 0.266 |
| Quartile 3 (81–87) | 1.35 (0.96–1.88) | 0.081 |
| Quartile 4 (88-) | 1.60 (1.11–2.32) | 0.012 |
| P for trend | 0.009 | |
| PP and MAP | | |
| PP, mm Hg | | |
| Quartile 1 (-40) | 1.00 (reference) | |
| Quartile 2 (41–47) | 0.80 (0.61–1.05) | 0.102 |

Table 3 (Continued)

| Model ^a | Hazard ratio (95% CI) | P value |
|-------------------------|--------------------------|---------|
| Quartile 3 (48–55) | 0.87 (0.66–1.13) | 0.292 |
| Quartile 4 (56–) | 0.90 (0.69–1.18) | 0.447 |
| P for trend | 0.560 | |
| MAP, mm Hg | | |
| Quartile 1 (–86.7) | 1.00 (reference) | |
| Quartile 2 (86.8–95.2) | 1.22 (0.90–1.66) | 0.193 |
| Quartile 3 (95.3–103.7) | 1.40 (1.04–1.89) | 0.027 |
| Quartile 4 (103.8–) | 1.70 (1.24–2.31) | 0.001 |
| P for trend | <0.001 | |

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; s.d., standard deviation; 95% CI, 95% confidence interval.
^aAdjusted for age, body mass index, diabetes status (non-diabetes or diabetes), daily alcohol consumption, regular leisure-time physical activity (yes/no), smoking habits (non-smokers, past smokers or current smokers) and estimated glomerular filtration rate categories (60.0–69.9, 70.0–79.9, 80.0–89.9, ≥ 90.0 ml min⁻¹ per 1.73 m²) at baseline.

model that did not include any BP components in model 1 (Table 2) minus the AIC of the model that included any one BP component or combined BP components in model 2 (Table 2). Of all of the models including each BP component, those including DBP- or MAP-alone had the strongest utility for the prediction of incident CKD (Δ AIC: 10.2 and 9.85, respectively). By contrast, PP had no utility for predicting the incidence of CKD (Δ AIC=–1.48). Furthermore, the model containing both SBP and DBP (Δ AIC=8.42) was not superior to the DBP-alone model (Δ AIC=10.2) in predicting the incidence of CKD. The model containing both MAP and PP (Δ AIC=8.42) was also not superior to the MAP-alone model (Δ AIC=9.85) in predicting the incidence of CKD.

The Δ AIC and the $\Delta\chi^2$ of the likelihood ratio test were used as measures of the improvement of goodness of fit to compare the two models, one of which was nested within the other (Table 2). When SBP was added to the DBP model, the model fit was not improved (Δ AIC=–1.76, likelihood ratio test, $P=0.625$). However, when DBP was added to the SBP model, the model fit was improved (Δ AIC=2.87, likelihood ratio test, $P=0.027$). Therefore, combining SBP with DBP provided no additional information to the DBP-alone model for predicting the incidence of CKD. When PP was added to the MAP model, the model fit was not improved (Δ AIC=–1.42, likelihood ratio test, $P=0.447$), but when MAP was added to the PP model, the model fit was improved (Δ AIC=9.91, likelihood ratio test, $P=0.001$). Combining PP and MAP provided no additional information to the MAP-alone model for predicting the incidence of CKD.

The multiple-adjusted hazard ratios of each BP component for the incidence of CKD are shown in Table 3 and presented by 1 s.d. increase and by the quartile of each BP component. DBP and MAP had the highest hazard ratios by 1 s.d. increase for the incidence of CKD. When SBP and DBP were included simultaneously in the model, DBP, but not SBP, was associated with an increased risk of CKD. When PP and MAP were included simultaneously in the model, MAP, but not PP, was associated with an increased risk of CKD.

DISCUSSION

These prospective data demonstrate that of all of the four BP components, DBP and MAP were the most useful predictors for risk of subsequent incidence of CKD. Neither combination model (SBP+DBP or PP+MAP) was superior to either the DBP-alone or the MAP-alone model for predicting the incidence of CKD. Models

including SBP+DBP or PP+MAP had similar predictive values for the incidence of CKD. These findings were independent of age, body mass index, diabetes status, daily alcohol consumption, regular leisure-time physical activity, smoking habit and baseline eGFR.

A limited number of prospective studies have investigated the associations between the four BP components SBP, DBP, PP, and MAP and the risk of reduced kidney function.^{22,23} Young *et al.*²² showed in the Systolic Hypertension in the Elderly Program that SBP was associated with the highest risk of decline of kidney function as defined by an increase in serum creatinine to ≥ 0.4 mg dl⁻¹ at follow-up compared with the baseline level. As this study focused on an older population with high SBP and low DBP and did not include subjects with DBP ≥ 90 mm Hg, it had a great advantage in that it could examine the effect of SBP and PP on the risk of decline of kidney function. However, it was unable to examine the effects of DBP and MAP on the risk of decline of kidney function. Schaeffner *et al.*²³ also reported in the Physicians' Health Study that SBP and PP were stronger predictors of the risk of eGFR falling to < 60 ml min⁻¹ per 1.73 m². Their results were based on self-reported information, and direct measurements of BP, serum creatinine and proteinuria at baseline were not performed. Although the authors commented that self-reported SBP and DBP were highly correlated with measured SBP ($r=0.72$) and DBP ($r=0.60$), the correlation between PP and MAP calculated by self-reported SBP and DBP and PP and MAP calculated using the measured SBP and DBP must be lower than that between self-reported SBP and DBP and measured SBP and DBP. It was therefore difficult to compare the four BP components in the context of the risk of low eGFR using self-reported BP.

In the present study, we did not identify why DBP or MAP increased the risk of CKD. Two large-scale, collaborative cohort studies and other recent cohort studies have reported that DBP has a strong or stronger relationship to the incidence of coronary heart disease than SBP until \sim age 50,^{8,11,12,32,33} thereafter, SBP and PP, but not DBP, were more influential.^{8,12,33–35} MAP was strongly related to the risk of coronary heart disease over a wide age range.^{8,12} For stroke, most prospective studies have reported that SBP is the most powerful risk factor, although these studies did not examine the effect of BP components on age-specific stroke incidence.^{15–17,35–38} Recently, three large-scale collaborative cohort studies and several large-scale cohort studies have examined BP components in relation to the risk of stroke by age group.^{8,11–14} These studies have reported that the relation of DBP to stroke incidence was as strong as or stronger than that of SBP until \sim age 60–65,^{8,11–14,39} thereafter, the relation of SBP to stroke incidence was stronger than that of DBP.^{8,12–14,35} In addition, MAP was strongly related to stroke risk over a wide age range.^{8,11–14} However, PP was not associated with the risk of stroke after adjusting for MAP in both middle-aged and older subjects.^{13,14} These results suggest that each BP component might have a different role in organ damage at different ages. As our cohort was composed of subjects 40–55 years of age, our findings that both DBP and MAP were associated with an increased risk for kidney dysfunction were consistent with the results of previous reports of cardiovascular diseases in the middle-aged population.^{8,11–14,33,39} Further investigation is warranted to elucidate the age-specific hemodynamic mechanism of the initiation of CKD.

Our study has several limitations. First, the results might be biased because GFR was not directly measured. However, because direct measurement of GFR is cumbersome and expensive, this limitation is common in large cohort studies. Using the modification of diet in renal disease formula to estimate renal function should be permitted.⁴⁰ Second, our study was based on the measurement of office

BP at a single visit, not self-monitored BP, which may lead to a misclassification of BP levels. BP was measured once if the initial reading did not show hypertension, but was measured twice if hypertension was detected; this may also have led to a misclassification of BP levels. Third, because all participants were registered employees of the same company and from a single ethnic group, our results may not be representative of the general population. Instead, it may apply to middle-aged Japanese-American men and possibly other Asian-American and native Asian men. The results of the present study might underestimate the real associations between BP components and CKD because of the healthy worker effect.⁴¹ Fourth, the inclusion of some participants who started to take antihypertensive medication during the follow-up period may have contributed to an underestimate of the relationship between BP components and CKD risk. Fifth, calculated values of PP and MAP were used in place of the invasive measurement because it is not practical in a large-scale cohort study to use invasive measurement techniques. Any error that occurred as a result of these indirect measures, however, is likely to be random, as opposed to systematic, thereby biasing study results toward null values.⁴² Therefore, this might lead to an attenuation of the observed association between the BP components and the outcome.

These results provide evidence that both DBP and MAP are most predictive of the incidence of CKD in middle-aged Japanese men. Our findings supplement the many reports of the effects of BP components on cardiovascular disease and suggest that each BP component may have a different role in organ damage at different ages. Future clinical research is needed to examine whether DBP- and/or MAP-lowering therapy is effective in preventing or delaying the incidence of CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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