ORIGINAL ARTICLE

Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study

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Masked hypertension (MHT) is considered to be associated with organ damage, whereas the association of white-coat hypertension (WCHT) with organ damage remains controversial. Using home blood pressure measurements, we have previously reported that MHT is associated with a risk of chronic kidney disease (CKD) compared with sustained normal blood pressure (SNBP), although WCHT was not significantly related to CKD in a general Japanese population. The objective of this study was to examine CKD risk associated with WCHT and MHT as determined by ambulatory blood pressure (ABP) monitoring. Among 1023 residents in the general Japanese population of Ohasama, ABP and casual blood pressure (CBP) levels were recorded and blood and urine samples were collected. CKD was defined as a positive proteinuria and/or estimated glomerular filtration rate $<60\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$. Participants were categorized into four groups using daytime ABP of 140/85 mm Hg and CBP of 140/90 mm Hg as cutoff points: SNBP, 60.0%; WCHT, 15.4%; MHT, 15.0%; and sustained hypertension (SHT), 9.6%. Odds ratios (ORs) for prevalence of CKD were calculated using a multiple logistic regression model. Compared with SNBP, risk of CKD was significantly higher in SHT (OR, 2.81; 95% confidence interval (CI), 1.66–4.75; $P=0.0001$), MHT (OR, 2.29; 95% CI, 1.45–3.63; $P=0.0004$) and WCHT (OR, 1.67; 95% CI, 1.03–2.71; $P=0.0368$). CKD was significantly associated with MHT and WCHT on the basis of ABP monitoring compared with SNBP in the general Japanese population.

INTRODUCTION

Ambulatory blood pressure (ABP) has recently been the focus of large amounts of research, and the utility and usefulness of this technique have been recognized and established in the diagnosis and management of hypertension.[1–3] ABP is also considered as a useful tool for detecting overall blood pressure (BP) load, nighttime BP level and circadian and short-term variations in BP. These parameters contribute to the diagnosis and treatment of hypertension.[4–6] The measurement of ABP has enabled us to identify a subgroup of individuals with white-coat hypertension (WCHT), showing persistent hypertensive casual BP (CBP) but normal ABP, and a subgroup of individuals with masked hypertension (MHT), showing normal CBP but hypertensive ABP. MHT is reported to be associated strongly with high risk of

morbidity and mortality from cardiovascular disease (CVD).[7] Conversely, controversy remains about whether WCHT is a benign condition[8] or linked to an increased risk of target-organ damage and CVD.[9,10]

Chronic kidney disease (CKD) is now considered as a major public health issue. The prevalence of end-stage renal disease is increasing in Japan, and is currently more than 2000 per million population. In 2007, the number of patients with end-stage renal disease on chronic hemodialysis exceeded 275 119.[11] Moreover, a recent study showed that CKD, defined as an estimated glomerular filtration rate (eGFR) of $<60\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$, has been increasing in Japan. Prevalence of stage 3–5 CKD was estimated as 19.1 million among the general Japanese adult population of 103.2 million.[12] On the other hand,

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prevalence of stage 4–5 CKD was estimated as 200 000 after excluding patients on dialysis. Early detection and appropriate intervention for CKD are thus necessary to prevent further increases in the number of patients with end-stage renal disease. Hypertension is a key risk factor for progression of CKD. To prevent progression of CKD, strict BP control is considered essential. In a recent study, we demonstrated that CKD risk of WCHT based on home BP (HBP) was no different from that of sustained normal blood pressure (SNBP).[13]

Although several clinical studies have reported associations between ABP and CKD,[14,15] only limited information is available from the general population. The objective of this study was to examine CKD risk associated with WCHT and MHT, as determined by ABP monitoring.

METHODS
Design
This cross-sectional study is a part of the Ohasama study, a BP measurement project conducted in the rural community of Ohasama in Iwate Prefecture, Japan. Ohasama had a total population of 7496 in 1992. The socioeconomic and demographic characteristics of this region and details of this project have been described previously.[16] This project was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Study population
Among the 7496 residents of Ohasama, 3076 were eligible for annual health checkups in 1992.[13] Of the 2013 residents who participated in checkups from 1992 to 1997, data on serum creatinine levels, dipstick test for spot urine and confounding factors were unavailable for 214 subjects. Of the remaining 1799 individuals, ABP measurements were recorded in 1073 participants. A total of 27 participants were excluded because of missing data from ABP monitoring, that is, fewer than 14 measurements during the day or fewer than seven measurements during the night based on the guidelines of the European Society of Hypertension.[17] This study population thus consisted of 1023 individuals, representing 33% of the total eligible population. All participants provided written, informed consent to participate in the study, which was approved by the Institutional Review Board of Tohoku University School of Medicine.

ABP monitoring
ABP was monitored using an ABPM 630 (Nippon Colin, Komaki, Japan), a fully automatic device that uses the cuff-oscillometric method to measure BP. The device was preset to measure BP every 30 min. All devices were validated[18] and satisfied the criteria outlined by the Association for the Advancement of Medical Instrumentation.[19] Each ABP monitoring device was attached by well-trained public health nurses who visited the participants on a weekday morning and detached the device the next morning.[16] Participants were asked to report their daily activities, including the times at which they went to bed and awoke. Normal daily activities were allowed and participants were instructed to keep the nondominant arm still and relaxed to the side during measurements. A nondipper was defined as a patient showing a ratio of nighttime to daytime ambulatory systolic BP > 0.9.

CBP measurement
CBP was measured twice by nurses or technicians at local medical centers using a semiautomatic BP measuring device (USM-700F; UEDA Electronic Works, Tokyo, Japan) based on the microphone method with subjects in a seated position after resting for 2 min, and the average of the two readings was used in this analysis. The device has been validated previously[20] and meets the criteria of the Association for the Advancement of Medical Instrumentation.[19]

Data collection
Information on smoking status, habitual drinking, use of antihypertensive medications at baseline, as well as history of cardiovascular disease (CVD),

diabetes mellitus or hypercholesterolemia, was verified on the basis of the medical charts of the Ohasama Hospital and a questionnaire administered during annual health checkups. History of CVD was defined as disease of the circulatory system, stroke or transient ischemia attack. Subjects treated with lipid-lowering drugs or with levels of serum total cholesterol ⩾220 mg per 100 ml were considered to have hypercholesterolemia. Subjects receiving treatment with antihyperglycemic agents or with fasting serum glucose level ⩾126 mg per 100 ml or casual glucose level ⩾200 mg per 100 ml were defined as having diabetes mellitus.

Measurement of eGFR and proteinuria
Serum creatinine (Scr) was measured using the Jaffé method. Kidney function was estimated by the calculated glomerular filtration rate using a modified three-variable equation based on insulin clearance for Japanese as follows: eGFR (ml min^{-1} per 1.73 m^2)=194×(Scr in enzymatic method)$^{-1.094}$×age$^{-0.287}$ (×0.739, if female).[21] We used the following equation to convert the level of Scr from the Jaffé method to that for the enzymatic method (Scr in enzymatic method=Scr in Jaffé method−0.2). After adjustment, mean Scr (± s.d.) was 0.67 ± 0.16 mg per 100 ml. Proteinuria was diagnosed with a dipstick test for spot urine (Urohemabonbix 5G08C; Bayer Medical, Tokyo, Japan). Proteinuria was considered to be present for a dipstick result of 1+ or more, which corresponds to a urinary protein level >30 mg per 100 ml. CKD was defined as a composite result of eGFR <60 ml min^{-1} per 1.73 m^2 and/or positive proteinuria.

Diagnostic criteria for hypertension at each measurement
The criterion for hypertension in CBP was defined as 140/90 mm Hg on the basis of the cutoff values from several guidelines.[17,22] With ABP, the results of the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) study were applied as diagnostic criteria for hypertension as follows: 24-h hypertension, 130/80 mm Hg; daytime hypertension, 140/85 mm Hg; and nighttime hypertension, 120/70 mm Hg.[23]

In addition, participants were categorized into four groups on the basis of daytime ABP and CBP: sustained hypertension (SHT), with daytime ABP ⩾140/85 mm Hg and CBP ⩾140/90 mm Hg; MHT, with daytime ABP ⩾140/85 mm Hg and CBP <140/90 mm Hg; WCHT, with daytime ABP <140/85 mm Hg and CBP ⩾140/90 mm Hg; or SNBP, with daytime ABP <140/85 mm Hg and CBP <140/90 mm Hg.

Statistical analysis
Continuous variables are expressed as means ± s.d. Discrete variables are presented as numbers and percentages. Statistical differences in means among groups were analyzed using one-way analysis of variance (ANOVA) or χ^2-test as appropriate. A multivariate logistic regression model was used to examine associations between CKD and clinical parameters, and we incorporated the following clinical variables into the model as independent variables: age, gender, current smoking status, current habitual drinking status, body mass index, diabetes mellitus, hypercholesterolemia, history of CVD and use of any antihypertensive medications. To compare the association of different BP indices in CBP and ABP with CKD, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for a 1–s.d. elevation in each BP index. The likelihood ratio of the χ^2-value was used as a measure of improvement in the goodness of fit between models containing each single CBP or ABP index and models containing two BP indices. Data were analyzed using SAS version 9.1 software (SAS Institute, Cary, NC, USA).

RESULTS
Comparison of characteristics among four groups
The characteristics of subjects as classified by daytime ABP and CBP into four groups are presented in Table 1. Of the 1023 study subjects, 216 (21.1%) were receiving antihypertensive medication. Among them, 63.4% were prescribed with calcium channel blockers, 26.4% with diuretics, 11.5% with angiotensin-converting enzyme inhibitors, 2.3% with α-blockers and 5.9% with other drugs. Compared with

Table 1 Clinical characteristics in four blood pressure groups

Variable	SNBP (N=614)	WCHT (N=158)	MHT (N=153)	SHT (N=98)	P (adjusted)
Age (year)	65.6 ± 8.5	69.0 ± 8.0[†]	68.4 ± 7.2[†]	68.4 ± 7.8[†]	<0.0001
Gender (%female)	76.7	63.9[†]	71.8	59.1[†]	0.0003
BMI (kg m^{-2})	23.0 ± 2.9	23.5 ± 3.2	23.5 ± 3.2	24.1 ± 2.7[†]	0.0038
Serum creatinine (mg per 100 ml)	0.85 ± 0.14	0.89 ± 0.18[†]	0.87 ± 0.16	0.92 ± 0.22[†]	<0.0001
Proteinuria (%)	3.1	7.6	8.5[†]	14.2[†]	<0.0001
Estimated GFR (ml min^{-1} per 1.73 m^2)	77.9 ± 16.9	75.3 ± 17.1	74.6 ± 16.3	73.3 ± 17.5	0.0142
Estimated GFR <60 ml min^{-1} per 1.73 m^2 (%)	8.6	15.1	20.2[†]	22.4[†]	<0.0001
CKD (%)	10.9	19.6	24.8	28.5	<0.0001
Current smoker (%)	8.6	12.6	12.4	13.2	NS
Current drinker (%)	16.9	22.1	16.3	29.5[†]	0.0139
Diabetes mellitus (%)	12.3	12.0	13.0	15.3	NS
Hypercholesterolemia (%)	29.4	36.7	35.2	38.7	NS
History of cardiovascular disease (%)	3.1	7.0	7.2	6.1	0.0450
Antihypertensive therapy (%)	12.5	27.2[†]	30.7[†]	28.5[†]	<0.0001
Casual SBP (mm Hg)	120.9 ± 11.9	149.6 ± 10.8[†]	125.6 ± 9.4[†,§]	150.5 ± 10.7[†]	<0.0001
Casual DBP (mm Hg)	68.1 ± 8.7	81.8 ± 9.8[†]	69.8 ± 8.0[†,§]	80.1 ± 10.6[†]	<0.0001
24 h SBP (mm Hg)	118.5 ± 9.0	124.4 ± 7.8[†]	140.0 ± 8.6[†,§]	140.9 ± 8.3[†,§]	<0.0001
24 h DBP (mm Hg)	69.1 ± 5.5	71.0 ± 5.1[†]	80.5 ± 5.5[†,§]	79.6 ± 6.0[†,§]	<0.0001
Daytime SBP (mm Hg)	123.6 ± 9.5	128.9 ± 7.5[†]	147.8 ± 7.8[†,§]	148.9 ± 7.9[†,§]	<0.0001
Daytime DBP (mm Hg)	72.8 ± 6.0	74.6 ± 5.3[†]	86.0 ± 5.3[†,§]	85.1 ± 6.4[†,§]	<0.0001
Nighttime SBP (mm Hg)	108.8 ± 11.5	116.0 ± 12.3[†]	125.6 ± 13.8[†,§]	127.0 ± 12.5[†,§]	<0.0001
Nighttime DBP (mm Hg)	62.0 ± 6.4	64.4 ± 6.9[†]	70.4 ± 8.0[†,§]	70.0 ± 7.2[†,§]	<0.0001
Nighttime/daytime SBP	0.88 ± 0.07	0.90 ± 0.08[†]	0.84 ± 0.08[†,§]	0.85 ± 0.07[†,§]	<0.0001
Nighttime/daytime DBP	0.85 ± 0.07	0.86 ± 0.08	0.81 ± 0.07[†,§]	0.82 ± 0.06[†,§]	<0.0001
Non-dipper (%)	39.0	46.2	28.1[§]	22.4[†,§]	<0.0001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; NS, no significance; PP, pulse pressure; SBP, systemic blood pressure; SNBP, sustained normal blood pressure, WCHT, white-coat hypertension.
Values are expressed as percentages or means ± s.d. adjusted by age, sex and BMI.
[†]$P<0.05$ *vs.* SNBP group, [§]$P<0.05$ *vs.* WCHT group.

SNBP, prevalence of proteinuria was significantly higher in MHT and SHT. ABP levels in MHT were similar to those in SHT. Subjects with MHT and SHT were more likely to be prescribed with anti-hypertensive drugs and to show cardiovascular complications. Scr was significantly higher in SHT and WCHT than in SNBP. In addition, we performed a stratified analysis between the genders; however, there was no significant difference with regard to the prevalence of positive proteinuria, eGFR <60 ml min^{-1} per 1.73 m^2 and CKD between them.

Adjusted ORs for CKD among four BP groups
Adjusted ORs for the presence of proteinuria were significantly higher in SHT, MHT and WCHT groups than in the SNBP group (Figure 1a). Adjusted ORs for the presence of eGFR <60 ml min^{-1} per 1.73 m^2 in SHT and MHT groups were significantly higher than that in the SNBP group (Figure 1b). In addition, adjusted ORs for the presence of CKD were significantly higher in SHT, MHT and WCHT groups than in the SNBP group (Figure 1c).

Furthermore, there is also a possibility that, using a 140 mm Hg threshold for daytime ABP, prevalence of ambulatory hypertension is underestimated. Therefore, we performed a reanalysis with the use of the 135/85 mm Hg threshold for daytime ABP. As a result, prevalence

of WCHT was decreased from 15.4 to 12.0%, whereas that of MHT was increased from 15.0 to 22.4%, respectively. Using 135/85 mm Hg threshold for daytime ABP, adjusted ORs for the presence of proteinuria in the WCHT group (OR, 3.27; 95% CI, 1.44–7.40; $P<0.01$) and the MHT group (OR, 2.57; 95% CI, 1.23–5.38; $P=0.01$) were significantly higher than that in the SNBP group, which were similar to the results in the case of 140/85 mm Hg threshold. Regarding the OR for eGFR <60 ml min^{-1} per 1.73 m^2 or CKD, results similar to those of 140/85 mm Hg threshold were observed.

When the WCHT group was subdivided into two groups (WCHT-1 (those with lower systolic daytime ABP) and WCHT-2 (those with higher systolic daytime ABP)) around the median systolic daytime ABP (130.6 mm Hg), CBP was significantly higher in the WCHT-1 and WCHT-2 groups than in the SNBP group (Table 2). Daytime, nighttime and 24-h ABP measurements were significantly higher in the WCHT-2 group than in the SNBP group, although there were no significant differences in ABP values between the WCHT-1 and SNBP groups (Table 2). The systolic ABP in the WCHT-2 group was also significantly higher than that in the WCHT-1 group (Table 2).

The adjusted OR for proteinuria was significantly higher in the WCHT-2 group compared with the SNBP group (OR, 2.73; $P=0.04$).
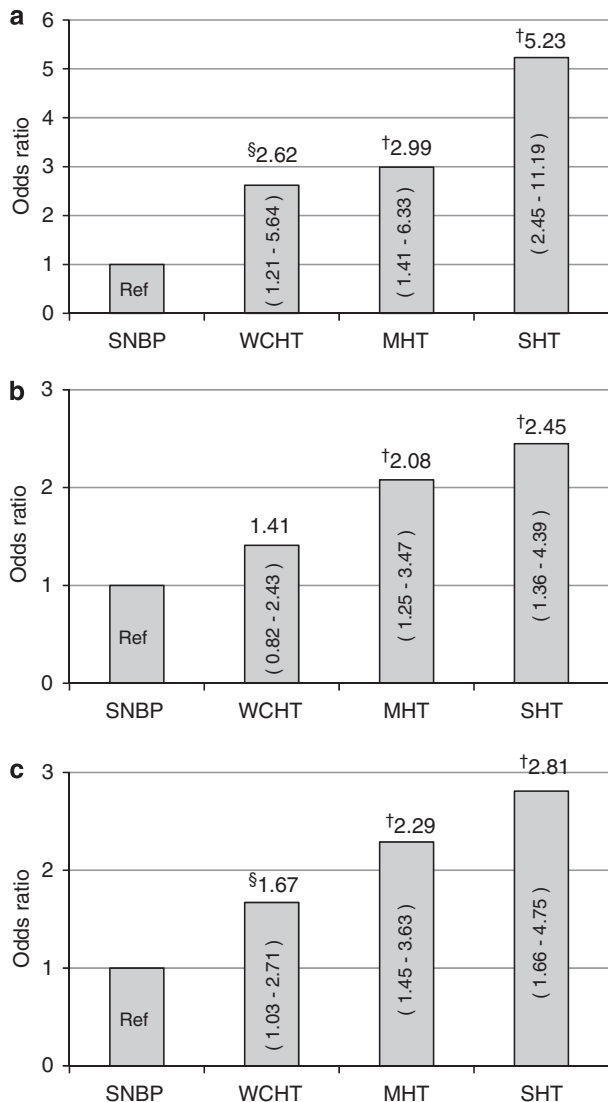
Figure 1 Odds ratios and 95% confidence intervals for the presence of (**a**) proteinuria, (**b**) estimated glomerular filtration rate $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and (**c**) chronic kidney disease (CKD) associated with combinations of groups with and without hypertension in daytime ambulatory blood pressure (ABP) and casual blood pressure (CBP), adjusted for age, gender, body mass index, smoking status, alcohol intake, antihypertensive medication, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. $^{§}P<0.03$ vs. reference; $^{†}P<0.01$ vs. reference. MHT, masked hypertension; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.

Corresponding OR in the WCHT-1 group was almost significantly higher than that in the SNBP group (OR, 2.51; $P=0.06$) (Figure 2a). Adjusted OR for CKD also tended to be higher in the WCHT-1 (OR, 1.54; $P=0.19$) and WCHT-2 groups (OR, 1.81; $P=0.06$) than in the SNBP group (Figure 2b). On the other hand, when we conducted logistic regression analysis treating the WCHT-1 group as the reference category, adjusted ORs in the WCHT-2 group for the presence of proteinuria (OR, 1.09; 95% CI, 0.33–3.60; $P=0.89$) and CKD (OR, 1.18; 95% CI, 0.53–2.64; $P=0.69$) were almost similar to those in the WCHT-1 group without any significant differences. No significant differences in adjusted ORs of eGFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD were seen between WCHT and SNBP.

Table 2 Comparison of CBP and ABP in the SNBP and subdivided WCHT groups

	SNBP (N=614)	WCHT-1 (N=79)	WCHT-2 (N=79)
Systolic CBP (mm Hg)	121 ± 12	149 ± 10[†]	151 ± 12[†]
Diastolic CBP (mm Hg)	68 ± 9	83 ± 9[†]	81 ± 11[†]
Systolic daytime ABP (mm Hg)	124 ± 10	123 ± 6	135 ± 3[†,‡]
Diastolic daytime ABP (mm Hg)	73 ± 6	72 ± 5	77 ± 4[†]
Systolic nighttime ABP (mm Hg)	109 ± 12	112 ± 13	120 ± 10[†,‡]
Diastolic nighttime ABP (mm Hg)	62 ± 6	63 ± 8	66 ± 6[†]
Systolic 24 h ABP (mm Hg)	118 ± 10	119 ± 7	130 ± 4[†,‡]
Diastolic 24 h ABP (mm Hg)	69 ± 6	69 ± 5	73 ± 4[†,‡]

Abbreviations: ABP, ambulatory blood pressure; CBP, casual blood pressure; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.
[†]$P<0.05$ vs. SNBP group, [‡]$P<0.05$ vs. WCHT-1 group. Values are expressed as means ± s.d.

The adjusted OR for CKD was significantly higher in the MHT and SHT groups than in the SNBP group, in spite of antihypertensive treatment (Figure 3). When subjects with and without medication were analyzed separately, similar results were obtained (data not shown).

When nighttime ABP was further added into logistic regression models, the adjusted OR for the presence of proteinuria in the WCHT group remained significantly higher than that in the SNBP group ($P=0.03$), whereas the adjusted OR in the MHT group was not significantly different ($P=0.09$). Similarly, after adjustment of nighttime ABP, the significance for proteinuria of WCHT on the basis of higher daytime systolic ABP disappeared ($P=0.08$).

Association of ABP and CBP as continuous variables with risk of proteinuria, estimated GFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD
For systolic BP, daytime, nighttime and 24-h ABPs were significantly associated with prevalence of proteinuria, eGFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD, whereas no such associations were observed for systolic CBP in Table 3. For diastolic BP, ABP and CBP were similarly associated with prevalence of proteinuria, eGFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD in Table 3.

DISCUSSION
In this study, we demonstrated that MHT, WCHT and SHT were significantly associated with higher risks of proteinuria and CKD compared with SNBP on the basis of ABP monitoring in the general population.

We have already reported that risk of cardiovascular mortality and stroke morbidity is significantly higher in subjects with MHT than in those with SNBP.[7] We have also previously reported that MHT on the basis of HBP is significantly associated with creatinine clearance $<60\,\mathrm{ml\,min}^{-1}$ with proteinuria when compared with SNBP in the general population.[13] Consistent with those findings, this study demonstrated that individuals with MHT on the basis of ABP showed a higher prevalence of proteinuria, eGFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD.

In this study, we compared the 140/85 mm Hg threshold with the 135/85 mm Hg threshold of daytime ABP, which is proposed by the Japanese, American and European hypertension guidelines. As a result, adjusted ORs for proteinuria, eGFR $<60\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ and CKD showed almost similar results; therefore, it is considered that the difference in threshold of daytime ABP did not have a significant impact on CKD risk.
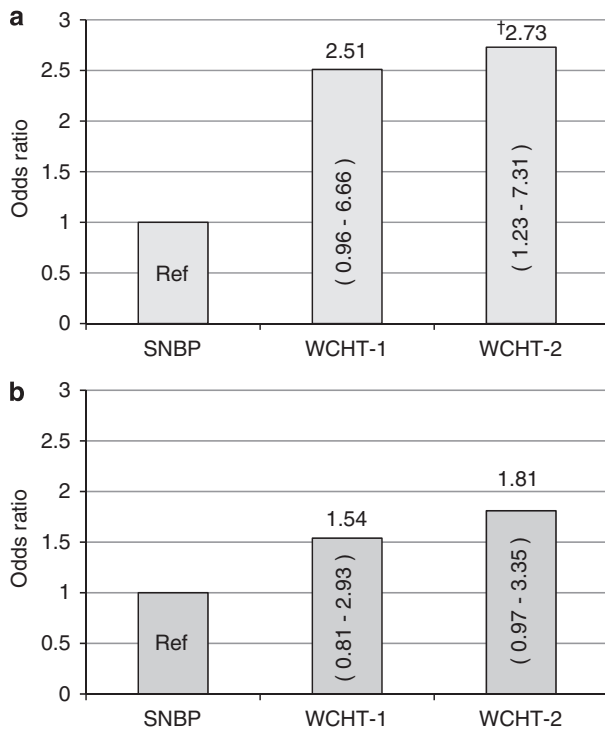
Figure 2 Odds ratios and 95% confidence intervals for the presence of (a) proteinuria and (b) chronic kidney disease (CKD) associated with the comparison of the sustained normal blood pressure (SNBP) group, adjusted for age, gender, body mass index, smoking status, alcohol intake, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. [†]$P<0.05$ vs. reference. WCHT, white-coat hypertension.
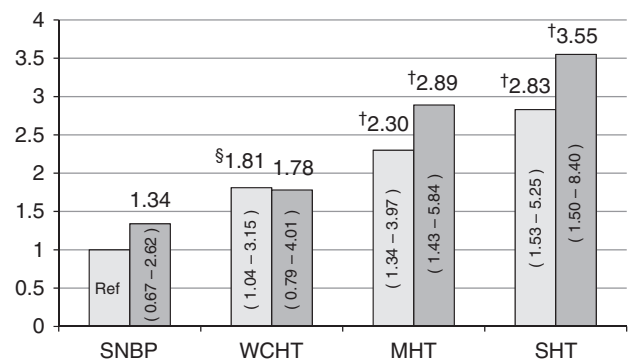

Figure 3 Odds ratios and 95% confidence intervals for the presence of chronic kidney disease (CKD) in the presence or absence of antihypertensive treatment, adjusted for age, gender, body mass index, smoking status, alcohol intake, history of cardiovascular disease, history of diabetes mellitus and hypercholesterolemia. ▢ Antihypertensive medication (−), ▪ antihypertensive medication (+). [§]$P<0.05$ vs. reference; [†]$P<0.01$ vs. reference. MHT, masked hypertension; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension.

In the previous study, we reported that treated individuals with optimal BP had a higher stroke risk than untreated ones with optimal BP.[24] Therefore, in this study, we thought that it is necessary to verify whether there is a residual CKD risk in treated hypertensive patients; hence we added Figure 3. As a result, among SHT, MHT groups, ORs for CKD in the treated hypertensive population were shown to be higher than in untreated hypertensive patients.

When we included nighttime ABP into the multivariate logistic regression model, MHT was no longer associated with CKD. MHT is considered to be mediated mainly by nondipper and riser status, and thus by nocturnal elevation of BP.[25] Nocturnal BP may represent a common mechanism related to risk of CKD in subjects with MHT defined by daytime ABP.[25]

WCHT has recently been reported to be associated with a higher risk of coronary artery disease when compared with subjects without WCHT.[26] In our 8-year follow-up study, WCHT was a significant predictor for the development of HBP hypertension.[10] In addition, one-third of patients with nondialytic CKD of stage 3–5 reportedly show WCHT.[27] In this study, WCHT with a relatively higher daytime ABP showed increased risk of proteinuria. This result is different from that of the previous study on the basis of HBP. This might be partly because ABP includes a comprehensive BP information, that is, an average daily BP load, a component of short-term variability of BP, BP in the morning and circadian variation of BP more than HBP. These results indicate that WCHT is not innocent, but is a condition warranting a follow-up. Individuals with WCHT should receive careful long-term follow-up.

In our study, when we subdivided the WCHT group into two groups, the daytime ABP was almost similar between the WCHT group with lower systolic daytime ABP and the SNBP group, whereas adjusted OR for the presence of proteinuria and CKD tended to be higher in the WCHT group with lower systolic daytime ABP than in the SNBP group. On the other hand, even though systolic ABP in the WCHT group with higher systolic daytime ABP was significantly higher than that in the WCHT group with lower systolic daytime ABP, there was no difference in the adjusted ORs for the presence of proteinuria and CKD between the subdivided WCHT groups. However, CBP was almost similar between these two groups. These results suggest a possibility that the risk in the WCHT group might be largely attributable to the higher CBP rather than to the higher ABP levels.

It has been documented that sympathetic hyperactivity occurs in WCHT.[28] It is also reported that sympathetic activity is increased in patients with CKD.[29] In addition, sympathetic nerve activity is shown to be related to kidney injury, especially proteinuria.[30] However, there is no conclusion about whether sympathetic activity itself leads to kidney injury or whether an increased sympathetic nerve system is derived as a result of development of kidney injury. In the previous study, it was examined that sympathetic blocking agents inhibited albuminuria and glomerulosclerosis without lowering blood pressure[31]. In clinical research, it was shown that sympathetic blocking agents decrease urine albumin excretion in normotensive diabetes patients.[32] These reports indicate that it is possible that inhibition on sympathetic nerve activity would alleviate kidney injury. These pathophysiological conditions of WCHT and CKD might suggest a relationship between WCHT and kidney injury.

WCHT was significantly related to the prevalence of proteinuria, but this association was less marked for the prevalence of eGFR $<60\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$. It is possible that the underlying mechanisms might thus differ between proteinuria and decreased eGFR. WCHT may reflect a phasic component of BP, whereas SHT and MHT may be associated with tonic load of BP, suggesting that proteinuria may be associated with phasic BP changes, and that decreased eGFR may be related to the tonic load under high BP. Estimated GFR of females is smaller than that of males. The

Table 3 Comparison of adjusted odds ratio for each condition of renal disorder (per elevation of 1–s.d. of the BP indices)

Models	Proteinuria			eGFR< 60 ml min^{-1} per 1.73 m^2			CKD		
BP variables	Odds ratio (95% CI)	P-value	LR	Odds ratio (95% CI)	P-value	LR	Odds ratio (95% CI)	P-value	LR
Systolic BP									
Casual+24 h									
Casual	1.27 (0.97–1.69)	NS	2.9	1.09 (0.89–1.34)	NS	0.7	0.98 (0.74–2.29)	NS	2.3
24 h	1.66 (1.25–2.20)	0.0004	12.4	1.28 (1.04–1.58)	0.0193	5.5	1.36 (1.13–1.64)	0.0011	10.7
Casual+daytime									
Casual	1.30 (0.98–1.72)	NS	3.2	1.09 (0.89–1.34)	NS	0.7	1.16 (0.97–1.39)	NS	2.5
Daytime	1.54 (1.16–2.04)	0.0030	8.8	1.29 (1.05–1.59)	0.0164	5.8	1.34 (1.11–1.61)	0.0021	9.5
Casual+nighttime									
Casual	1.30 (0.98–1.71)	NS	3.4	1.12 (0.91–1.37)	NS	1.1	1.17 (0.98–1.41)	NS	3.0
Nighttime	1.65 (1.25–2.18)	0.0005	12.3	1.19 (0.97–1.46)	NS	2.8	1.30 (1.09–1.57)	0.0042	8.2
Diastolic BP									
Casual+24 h									
Casual	1.22 (0.93–1.66)	NS	2.0	1.25 (1.03–1.52)	0.0269	4.9	1.30 (1.09–1.56)	0.0035	8.5
24 h	1.39 (1.06–1.82)	0.0181	5.6	1.27 (1.04–1.56)	0.0223	5.2	1.37 (1.06–1.52)	0.0105	6.6
Casual+daytime									
Casual	1.25 (0.95–1.64)	NS	2.4	1.25 (1.03–1.53)	0.0265	4.9	1.31 (1.10–1.56)	0.0030	8.8
Daytime	1.31 (0.99–1.73)	NS	3.6	1.28 (1.04–1.58)	0.0182	5.6	1.26 (1.05–1.51)	0.0149	5.9
Casual+nighttime									
Casual	1.22 (0.93–1.61)	NS	2.0	1.26 (1.04–1.53)	0.0205	5.4	1.31 (1.10–1.57)	0.0027	9.0
Nighttime	1.41 (1.08–1.84)	0.0116	6.4	1.19 (0.97–1.45)	NS	2.8	1.24 (1.03–1.48)	0.0205	5.4

Abbreviations: BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; LR, likelihood ratio; NS, not significant.

percentage of females in the WCHT group of this study was significantly lower than that of the SNBP group (Table 1). Therefore, we imagine that if the proportion of females in the WCHT group had been similar to that in the SNBP group, the percentage of 'subjects with eGFR <60' in the WCHT group might have been significantly higher than that in the SNBP group.

This study should be interpreted within the context of its potential limitations. First, the level of CBP and the prevalence of hypertension in CBP are overestimated because of the use of single-visit clinic BP measurements. Second, proteinuria was diagnosed in this study using a semiquantitative dipstick test for spot urine, with results of ⩾30 mg per 100 ml representing a positive finding. This approach does not allow subjects with microalbuminuria and overt proteinuria to be distinguished. Third, serum creatinine was measured using the Jaffé method, and this value was corrected to obtain an equivalent value for the enzymatic method using a modified equation. Finally, this study was cross-sectional in design and thus cannot provide any insights into causal relationships between BP parameters and CKD.

This study demonstrated that WCHT, as well as MHT, is an independent risk factor for prevalence of proteinuria and CKD. In the earlier stage of CKD, evaluation of albuminuria and renal function, as well as therapeutic intervention, may be important to prevent future development and progression of CVD, in addition to the development and progression of CKD.[33–35] These results thus revealed that CKD is significantly related to MHT and WCHT on the basis of ABP monitoring in the general population. Further prospective studies are needed to clarify the role of ABP measurements in predicting future occurrence of CKD and associated disorders in the general population.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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