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ORIGINAL ARTICLE

# White-coat and masked hypertension are associated with albuminuria in a general population: the Hisayama Study

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**Epidemiological and clinical studies have investigated the influence of hypertension on chronic kidney disease (CKD), but limited data are available for the associations of white-coat hypertension (WCHT), masked hypertension (MHT) and sustained hypertension (SHT) with kidney dysfunction in general populations. We examined the associations of these types of hypertension with CKD (albuminuria and reduction in estimated glomerular filtration rate (eGFR)) in a cross-sectional survey of 2974 community-dwelling Japanese aged ⩾40 years. The types of hypertension were defined based on combined measurements of clinic and home blood pressures. Albuminuria was determined as urinary albumin–creatinine ratio (UACR) levels ⩾30.0 mg g$^{-1}$. The eGFR was calculated using the Japanese equation. The age- and sex-adjusted geometric mean of the UACR values was significantly higher in the subjects with WCHT (20.2 mg g$^{-1}$), MHT (19.6 mg g$^{-1}$) and SHT (31.6 mg g$^{-1}$) than in those with normotension (NT) (12.5 mg g$^{-1}$) (all $P<0.001$). Compared with NT, all types of hypertension were significantly associated with an increased likelihood of albuminuria (the age- and sex-adjusted prevalence of albuminuria; NT 14.1%, WCHT 26.3%, MHT 26.4% and SHT 43.3%; all $P<0.001$). These associations remained significant even after adjustment for other risk factors. However, the age- and sex-adjusted mean of eGFR and the prevalence of low eGFR (<60 ml min$^{-1}$ per 1.73 m$^2$) did not differ between NT and the three hypertension types. The associations of the types of hypertension with the likelihood of CKD were similar to those for albuminuria. Our findings suggest that WCHT, MHT and SHT are associated with albuminuria in the general Japanese population.**
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**Keywords:** albuminuria; chronic kidney disease; estimated glomerular filtration rate; masked hypertension; white-coat hypertension

## INTRODUCTION

Kidney disease is increasingly being recognized as a leading public health issue. Chronic kidney disease (CKD), usually defined by the presence of albuminuria and/or a low estimated glomerular filtration rate (eGFR), affects >10% of the population in many countries worldwide.[1–4] Growing evidence suggests that both albuminuria and low eGFR are independently associated with an increased risk of not only progressive kidney failure but also cardiovascular disease and mortality.[5–7] Better prevention and prognosis of CKD will thus require accurate knowledge of risk factors for albuminuria and low eGFR.

Based on combined measurements of clinic blood pressure (CBP) and home blood pressure (HBP), blood pressure (BP) status can be divided into normotension (NT), white-coat hypertension (WCHT), masked hypertension (MHT) and sustained hypertension (SHT).[8–13] Although a number of studies have investigated the influence of hypertension on albuminuria and reduction in eGFR, limited data are available regarding the associations of different types of hypertension, particularly WCHT, with albuminuria and eGFR.

In the present cross-sectional study, we evaluated the associations of WCHT, MHT and SHT with albuminuria and eGFR in a general Japanese population.

## METHODS

### Study population

The Hisayama Study is a population-based prospective cohort study of cardiovascular disease established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan.[13,14] According to the national census, the age and occupational distributions in Hisayama have been

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almost identical to those of all of Japan since the 1960s.[14] The present cross-sectional study was based on a screening survey conducted in 2007 and 2008. A total of 3384 residents aged ⩾40 years (78.2% of the total population of this age group) underwent a comprehensive assessment including HBP measurement. After the exclusion of 8 individuals who did not consent to participate in the study, 386 without HBP measurements for ⩾3 days and 16 without urine samples, a total of 2974 subjects (1295 men and 1679 women) were enrolled in the present study.

### BP measurement and classifications

Each subject's CBP was measured three times using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto, Japan) based on the cuff oscillometric method with an appropriately sized cuff on the right arm as he or she remained seated after rest for at least 5 min. The mean of the three measurements was used for the analysis.

Before the subjects started taking their HBP measurements, physicians and public health nurses taught the subjects how to measure their HBP accurately. The subjects were instructed to measure their HBP three times every morning before breakfast within 1 h of waking and after >5 min of rest in the sitting position for 4 weeks. Participants on BP-lowering medication were instructed to measure their HBP before taking their medication. The subjects were also instructed to place appropriately sized cuffs directly around their nondominant arms and to maintain the position of the cuff at the level of the heart. HBP measurements were performed using an automatic device (HEM-7080IC; Omron Healthcare) based on the cuff oscillometric method.[13] The device has a memory that allows the recording of 350 measurements, and a data output port that enables data extraction for the analysis. The mean value of all available daily averages was used in the present analysis (average days of HBP measurements: 25.0 days, s.d. 6.4).

Based on the combined measurements of CBP and HBP, irrespective of the use of antihypertensive medication, we divided the subjects into four groups: NT (CBP <140/90 mm Hg and HBP <135/85 mm Hg), WCHT (CBP ⩾140/90 mm Hg and HBP <135/85 mm Hg), MHT (CBP <140/90 mm Hg and HBP ⩾135/85 mm Hg) and SHT (CBP ⩾140/90 mm Hg and HBP ⩾135/85 mm Hg).[8–13]

### UACR and eGFR

A morning spot urine sample was obtained from each subject at the health examination visit. Urine creatinine and albumin were measured using a turbidimetric immunoassay method. The urinary albumin–creatinine ratio (UACR, in mg $g^{-1}$) was calculated by dividing the urinary albumin values by the urinary creatinine concentrations. Albuminuria was defined as UACR ⩾30.0 mg $g^{-1}$.[9,10,15] Serum creatinine (S-Cr) was measured by the enzymatic method. The eGFR of each subject was calculated using the following Japanese equation: eGFR (ml $min^{-1}$ per 1.73 $m^2$) = $194 \times Age^{-0.287} \times S\text{-}Cr^{-1.094}$ (if female × 0.739).[16] Low eGFR was defined as eGFR <60 ml $min^{-1}$ per 1.73 $m^2$. CKD was defined as the presence of albuminuria and/or low eGFR.[9,10,15]

### Other risk factor measurement

Each participant completed a self-administered questionnaire covering his or her medical history, including treatment for hypertension, diabetes mellitus, hyperlipidemia, prior cardiovascular disease, smoking habits, alcohol intake and regular exercise. Smoking habits and alcohol intake were classified into currently habitual or not. The subjects who reported engaging in sports or other forms of exertion ⩾3 times a week during their leisure time made up the regular exercise group. Body height and weight were measured in light clothing without shoes, and the body mass index (kg $m^{-2}$) was calculated. Serum total and high-density lipoprotein cholesterol levels were determined enzymatically. Blood glucose levels were measured by the hexokinase method. Diabetes was determined by medical history, plasma glucose levels (fasting glucose level ⩾7.0 mmol $l^{-1}$ or postprandial glucose level ⩾11.1 mmol $l^{-1}$) or a 75-g oral glucose tolerance test using the 1998 World Health Organization criteria.[17] History of cardiovascular disease was defined as any preexisting events of stroke or coronary heart disease, including myocardial infarction and coronary intervention. All cardiovascular events were adjudicated on the basis of physical examinations and a review of all available clinical information including medical records and imaging.

### Statistical analysis

We tested the differences in the mean values or the frequencies of risk factors across BP categories using general linear model or a logistic regression model. The UACR values were log-transformed to remove skewness, and geometrical means were reported by back transformation. The influence of BP categories on the adjusted means of the UACR and eGFR values was assessed using an analysis of covariance. We calculated the age- and sex-adjusted prevalences of albuminuria and low eGFR using the direct method. We assessed the age- and

**Table 1 Baseline characteristics of participants according to blood pressure categories**

| | *Normotension* | *White-coat HT* | *Masked HT* | *Sustained HT* |
|---|---|---|---|---|
| | (n = *1388*) | (n = *209*) | (n = *642*) | (n = *735*) |
| Age, years | 58.9±11.4 | 64.4±10.2* | 67.2±11.1* | 66.9±11.8* |
| Men, % | 37.0 | 39.7 | 50.0* | 51.3* |
| Clinic systolic blood pressure, mm Hg | 118.4±11.8 | 149.7±8.9* | 128.4±8.8* | 154.4±12.1* |
| Clinic diastolic blood pressure, mm Hg | 73.1±7.8 | 88.3±7.4* | 77.7±7.2* | 90.2±8.6* |
| Home systolic blood pressure, mm Hg | 117.6±10.1 | 126.2±6.6* | 144.8±11.0* | 151.3±13.3* |
| Home diastolic blood pressure, mm Hg | 71.6±6.9 | 74.7±6.7* | 83.0±8.2* | 85.1±9.6* |
| Days of home blood pressure measurement | 25.0±6.3 | 26.1±5.2 | 25.4±6.1 | 24.3±7.2 |
| Diabetes mellitus, % | 9.0 | 26.8* | 22.1* | 23.5* |
| Total cholesterol, mmol $l^{-1}$ | 5.45±0.93 | 5.58±0.99 | 5.29±0.91* | 5.45±0.86 |
| High-density lipoprotein cholesterol, mmol $l^{-1}$ | 1.80±0.46 | 1.72±0.47 | 1.68±0.43* | 1.67±0.46* |
| Body mass index, kg $m^{-2}$ | 22.2±3.0 | 24.0±4.1* | 23.5±3.2* | 24.2±3.7* |
| Current smoking, % | 19.4 | 8.1* | 20.3 | 19.9 |
| Current drinking, % | 47.2 | 39.2* | 52.0* | 51.2 |
| Regular exercise, % | 11.3 | 11.5 | 12.6 | 14.1 |
| Blood pressure-lowering medication, % | 13.5 | 35.6* | 49.7* | 48.7* |
| Lipid-lowering medication, % | 10.4 | 21.1* | 19.2* | 20.6* |
| History of cardiovascular disease, % | 3.4 | 6.2* | 8.1* | 7.1* |

Abbreviation: HT, hypertension.
All values are given as means±s.d. or as percentage.
*$P<0.05$ *vs.* normotension.

sex-adjusted or multivariable-adjusted odds ratios and their 95% confidence intervals (CIs) for the presence of albuminuria, low eGFR or all CKD using a multivariable logistic regression model. The subgroup analyses were performed for diabetes, BP-lowering medication and other possible risk factors. The interaction between BP categories and each subgroup was estimated by adding interaction terms to the relevant statistical model. All statistical analyses were performed using the SAS program package version 9.3 (SAS Institute, Cary, NC, USA). *P*-values of $<0.05$ were considered significant.

### Ethical considerations

The study protocol was approved by the Kyushu University institutional review board for clinical research, and the procedures followed were in accordance with national guidelines. All participants provided written informed consent.

## RESULTS

Among the 2974 subjects, there were 1388 (46.7%) with NT, 209 (7.0%) with WCHT, 642 (21.6%) with MHT and 735 (24.7%) with SHT. The mean values and the frequencies of cardiovascular risk factors are listed according to BP categories in Table 1. Compared with the NT group, the subjects with WCHT, MHT or SHT were significantly older and had higher CBP and HBP levels. The subjects with WCHT, MHT or SHT were more likely to have diabetes and receive BP- and lipid-lowering medications compared with the NT subjects. Average days of HBP measurement did not differ among the four groups. Supplementary Table S1 shows the distribution of drug classes among 940 subjects who were treated with BP-lowering medication. The proportions of users of renin–angiotensin system inhibitors were not significantly different among the BP categories.

For the total subjects, the geometric mean of UACR was 17.9 mg $g^{-1}$ (95% CI 17.2–18.7). The age- and sex-adjusted geometric mean of UACR was significantly higher in the WCHT (20.2 mg $g^{-1}$; 95% CI 17.5–23.4), MHT (19.6 mg $g^{-1}$; 18.0–21.3) and SHT groups (31.6 mg $g^{-1}$; 29.2–34.2) compared with the NT group (12.5 mg $g^{-1}$; 11.8–13.2) (all $P<0.001$). These associations remained significant even after adjustment for other cardiovascular risk factors, namely, age, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, regular exercise, BP-lowering medication, lipid-lowering medication and history of cardiovascular disease (Figure 1). The subjects with SHT had significantly higher UACR values compared with the subjects with WCHT or MHT (both $P<0.001$), whereas no significant difference was observed between the subjects with WCHT and those with MHT ($P>0.99$). The age- and sex-adjusted prevalence of albuminuria was significantly higher in all of the hypertension groups (including WCHT) than in the NT group (all $P<0.001$; Table 2). These associations remained significant even after adjusting for other cardiovascular risk factors. As shown in the multivariable analysis in Supplementary Table S2, the subjects with WCHT, MHT or SHT, as well as those with diabetes, BP-lowering medication or history of cardiovascular disease, had significantly higher likelihood of albuminuria.

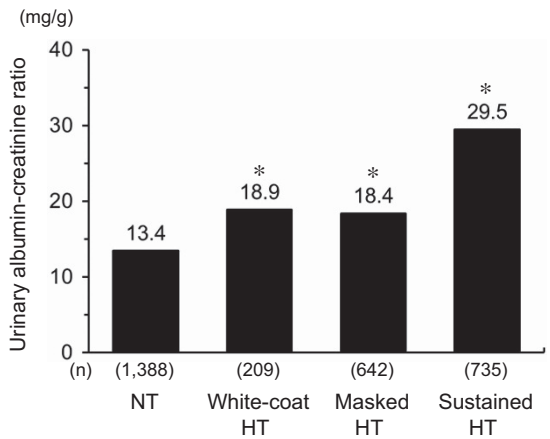


**Figure 1** Multivariable-adjusted geometric means of urinary albumin–creatinine ratio according to blood pressure categories. HT, hypertension; NT, normotension. *$P<0.001$ *vs.* normotension. Results were adjusted for age, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, exercise, blood pressure-lowering medication, lipid-lowering medication and history of cardiovascular disease.

In all subjects, the mean of eGFR was 71.2 ml $min^{-1}$ per 1.73 $m^2$ (s.d. 14.7). The adjusted mean of eGFR did not differ between the NT group and all three types of hypertension (the age- and sex-adjusted mean of eGFR; NT 70.7 ml $min^{-1}$ per 1.73 $m^2$ (95% CI 70.0–71.5), WCHT 70.2 ml $min^{-1}$ per 1.73 $m^2$ (68.4–72.0), MHT 72.2 ml $min^{-1}$ per 1.73 $m^2$ (71.1–73.2) and SHT 71.5 ml $min^{-1}$ per 1.73 $m^2$ (70.5–72.5)), and this association did not change after adjusting for other confounding factors (Figure 2). Similarly, the age- and sex-adjusted prevalence and multivariable-adjusted odds ratio of low eGFR did not differ between NT and any of the three types of hypertension (Table 2 and Supplementary Table S2).

When albuminuria and low eGFR were combined as CKD, the age- and sex-adjusted prevalence of CKD was significantly higher in all of the hypertension groups (including WCHT) than in the NT group (27.5% in the NT group, 41.7% in the WCHT group, 36.8% in the MHT group and 53.7% in the SHT group). These associations remained significant only in the WCHT and SHT groups after adjustment for other cardiovascular risk factors (the multivariable-adjusted odds ratio: 1.64 (95% CI 1.18–2.28) for WCHT, 1.20 (0.95–1.52) for MHT and 2.62 (2.10–3.27) for SHT; Table 2).

As diabetes is an important risk factor for albuminuria, we performed a subgroup analysis for diabetes (Table 3 and Supplementary Table S3). Although the associations of hypertension types with the geometric mean of UACR were stronger in the subjects with diabetes than in those without it ($P$ for interaction = 0.001), there were similar associations for the mean of eGFR ($P$ for interaction = 0.67), as well as the prevalence of albuminuria ($P$ for interaction = 0.90) and low eGFR ($P$ for interaction = 0.25) between the subjects with and without diabetes. Then, the subgroup analysis for BP-lowering medication status was conducted, as the medication could affect the classification of BP categories (Table 4 and Supplementary Table S4). There were also similar associations of WCHT, MHT and SHT with the mean values of UACR ($P$ for interaction = 0.28) and eGFR ($P$ for interaction = 0.62), as well as the prevalence of albuminuria ($P$ for interaction = 0.11) and low eGFR ($P$ for interaction = 0.40) between the subjects with and without BP-lowering medication. The results of the subgroup analyses for other possible risk factors are summarized in Supplementary Tables S5 and S6. The associations of BP categories with albuminuria were not substantially different between the subgroups (all $P$ for interaction $>0.1$; Supplementary Table S5). For low eGFR, a significant interaction was observed between subgroups of hypercholesterolemia ($P$ for interaction = 0.04; Supplementary Table S6). However, as there was no clear association of BP categories with low eGFR in either subgroup of hypercholesterolemia, the observed interaction might be because of the play of chance.

## DISCUSSION

The findings from the present population-based cross-sectional study provide good evidence of associations of all types of hypertension

**Table 2 Age- and sex-adjusted prevalence and adjusted odds ratios of albuminuria, low eGFR and CKD according to blood pressure categories**

| | *Normotension* | *White-coat HT* | *Masked HT* | *Sustained HT* |
|---|---|---|---|---|
| | (n = *1388*) | (n = *209*) | (n = *642*) | (n = *735*) |
| *Albuminuria* | | | | |
| No. of cases | 162 | 56 | 186 | 337 |
| Age- and sex-adjusted prevalence, % | 14.1 | 26.3 | 26.4 | 43.3 |
| Age- and sex-adjusted odds ratio (95% CI) | 1 (Reference) | 2.32 (1.63–3.31) | 2.28 (1.78–2.92) | 4.91 (3.92–6.16) |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.77 (1.22–2.57) | 1.74 (1.34–2.26) | 3.93 (3.08–5.01) |
| *Low eGFR* | | | | |
| No. of cases | 195 | 50 | 167 | 192 |
| Age- and sex-adjusted prevalence, % | 17.9 | 21.9 | 21.0 | 20.6 |
| Age- and sex-adjusted odds ratio (95% CI) | 1 (Reference) | 1.36 (0.93–1.98) | 1.13 (0.87–1.46) | 1.14 (0.88–1.46) |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.20 (0.81–1.76) | 0.98 (0.75–1.29) | 0.95 (0.73–1.24) |
| *Chronic kidney disease* | | | | |
| No. of cases | 315 | 91 | 267 | 429 |
| Age- and sex-adjusted prevalence, % | 27.5 | 41.7 | 36.8 | 53.7 |
| Age- and sex-adjusted odds ratio (95% CI) | 1 (Reference) | 2.05 (1.49–2.81) | 1.53 (1.23–1.90) | 3.34 (2.71–4.11) |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.64 (1.18–2.28) | 1.20 (0.95–1.52) | 2.62 (2.10–3.27) |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HT, hypertension.
Albuminuria is defined as urinary albumin–creatinine ratio $\geqslant$30.0 mg $g^{-1}$. Low eGFR is defined as eGFR $<$60 ml $min^{-1}$ per 1.73 $m^2$. CKD was defined as albuminuria and/or low eGFR.
[a]Adjusted for age, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, regular exercise, blood pressure-lowering medication, lipid-lowering medication and history of cardiovascular disease.

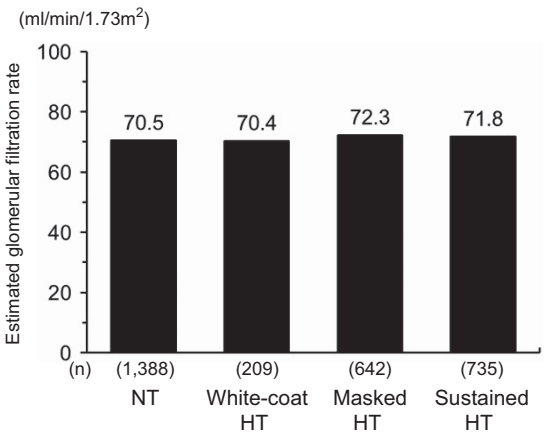


**Figure 2** Multivariable-adjusted means of estimated glomerular filtration rate according to blood pressure categories. HT, hypertension; NT, normotension. Results were adjusted for age, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, exercise, blood pressure-lowering medication, lipid-lowering medication and history of cardiovascular disease.

(including WCHT, defined by using CBP and HBP) with increased risks of albuminuria. These associations remained significant even after adjustment for potential confounding factors. On the other hand, there was no difference in eGFR between NT and all three types of hypertension.

Only a limited number of studies have evaluated the association of WCHT with albuminuria or proteinuria. Most previous studies failed to demonstrate a clear influence of WCHT on albuminuria or proteinuria, as they were hospital-based case/control or case-series studies, and their sample sizes were somewhat small.[18–20] However, a hospital-based study of 411 individuals from Denmark revealed a significant association between WCHT defined based on ambulatory blood pressure monitoring (ABPM) and albuminuria.[21] In addition, the Ohasama Study, a population-based study of 1023 individuals from a general Japanese population, showed a 2.62-fold increased prevalence of proteinuria in subjects with WCHT defined based on ABPM than in those with NT.[22] In the present large-scale population-based study, WCHT as well as MHT and SHT defined using HBP were clearly associated with an increased prevalence of albuminuria. On the basis of the totality of the current evidence, there seems to be a link between WCHT and albuminuria.

Regarding the influence of MHT and SHT on albuminuria or proteinuria, more consistent results were revealed by previous studies. A hospital-based study of 332 individuals from Japan showed a clear influence of MHT and SHT, defined using ABPM, on albuminuria.[20] The Ohasama Study also demonstrated a clear association of MHT and SHT, defined using ABPM, with proteinuria.[22] The present analysis confirmed the findings obtained from the previous studies and showed that both MHT and SHT were clearly associated with albuminuria. The evaluation of out-of-clinic BP is essential to detect individuals with MHT. Although ABPM can evaluate out-of-clinic BP more comprehensively than HBP measurement, HBP measurement is a more convenient and simple approach for out-of-clinic BP evaluation. The findings of the present study suggest that HBP as well as ABPM may be useful for screening individuals at higher risk of nephropathy.

In the present study, not only SHT and MHT but also WCHT were associated with a higher prevalence of albuminuria. Moreover, the prevalence of albuminuria in the WCHT group was similar to that in the MHT group. This finding is in accord with the result from the Ohasama Study.[22] Persistent high BP tends to cause endothelial dysfunction and subsequent albuminuria through the increment of shear stress and oxidative stress among subjects with SHT or MHT.[23] In addition, other risk factors for albuminuria, such as diabetes and obesity, are likely to accumulate in subjects with MHT as well as SHT.[11] On the other hand, a significant association of WCHT with albuminuria may be explained by sympathetic hyperactivity. Some clinical studies demonstrated that sympathetic hyperactivity occurred

**Table 3 Age- and sex-adjusted prevalence and adjusted odds ratios of albuminuria and low eGFR according to blood pressure categories among participants without and with diabetes mellitus**

| | *Normotension* | *White-coat HT* | *Masked HT* | *Sustained HT* |
|---|---|---|---|---|
| *Albuminuria* | | | | |
| No diabetes mellitus | | | | |
| No. of cases/participant | 127/1263 | 32/153 | 121/500 | 222/562 |
| Age- and sex-adjusted prevalence, % | 12.0 | 20.6 | 21.9 | 37.4 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.91 (1.22–2.98) | 1.85 (1.37–2.50) | 4.04 (3.06–5.32) |
| Diabetes mellitus | | | | |
| No. of cases/participant | 35/125 | 24/56 | 65/142 | 115/173 |
| Age- and sex-adjusted prevalence, % | 24.7 | 38.0 | 43.3 | 64.0 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.33 (0.65–2.72) | 1.41 (0.81–2.47) | 3.80 (2.19–6.60) |
| *Low eGFR* | | | | |
| No diabetes mellitus | | | | |
| No. of cases/participants | 172/1263 | 31/153 | 129/500 | 152/562 |
| Age- and sex-adjusted prevalence, % | 17.9 | 18.8 | 20.9 | 21.8 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 0.95 (0.60–1.51) | 0.98 (0.72–1.33) | 0.99 (0.74–1.34) |
| Diabetes mellitus | | | | |
| No. of cases/participants | 23/125 | 19/56 | 38/142 | 40/173 |
| Age- and sex-adjusted prevalence, % | 15.8 | 28.6 | 20.1 | 17.6 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.93 (0.84–4.42) | 1.02 (0.52–2.00) | 0.89 (0.45–1.75) |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hypertension.
Albuminuria is defined as urinary albumin–creatinine ratio $\geqslant 30.0$ mg $g^{-1}$. Low eGFR is defined as eGFR $<60$ ml $min^{-1}$ per 1.73 $m^2$.
[a]Adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, regular exercise, blood pressure-lowering medication, lipid-lowering medication and history of cardiovascular disease.

**Table 4 Age- and sex-adjusted prevalence and adjusted odds ratios of albuminuria and low eGFR according to blood pressure categories among participants without and with blood pressure-lowering medication**

| | *Normotension* | *White-coat HT* | *Masked HT* | *Sustained HT* |
|---|---|---|---|---|
| *Albuminuria* | | | | |
| No blood pressure-lowering medication | | | | |
| No. of cases/participant | 112/1200 | 32/134 | 64/323 | 142/377 |
| Age- and sex-adjusted prevalence, % | 11.8 | 27.0 | 18.6 | 36.0 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 2.42 (1.52–3.85) | 1.72 (1.20–2.46) | 4.57 (3.36–6.21) |
| Blood pressure-lowering medication | | | | |
| No. of cases/participant | 50/188 | 24/75 | 122/319 | 195/358 |
| Age- and sex-adjusted prevalence, % | 25.5 | 29.8 | 35.6 | 49.8 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.06 (0.57–1.98) | 1.54 (1.01–2.34) | 3.08 (2.04–4.66) |
| *Low eGFR* | | | | |
| No blood pressure-lowering medication | | | | |
| No. of cases/participant | 136/1200 | 29/134 | 65/323 | 70/377 |
| Age- and sex-adjusted prevalence, % | 15.7 | 23.8 | 19.0 | 17.9 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 1.43 (0.88–2.34) | 1.09 (0.75–1.57) | 0.96 (0.67–1.38) |
| Blood pressure-lowering medication | | | | |
| No. of cases/participant | 59/188 | 21/75 | 102/319 | 122/358 |
| Age- and sex-adjusted prevalence, % | 28.1 | 21.5 | 24.5 | 22.8 |
| Multivariable-adjusted odds ratio (95% CI)[a] | 1 (Reference) | 0.79 (0.41–1.50) | 0.80 (0.52–1.23) | 0.85 (0.56–1.30) |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hypertension.
Albuminuria is defined as urinary albumin–creatinine ratio $\geqslant 30.0$ mg $g^{-1}$. Low eGFR is defined as eGFR $<60$ ml $min^{-1}$ per 1.73 $m^2$.
[a]Adjusted for age, sex, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, smoking habits, alcohol intake, regular exercise, lipid-lowering medication and history of cardiovascular disease.

in subjects with WCHT,[24] and elevated levels of urinary norepinephrine and epinephrine, biomarkers for sympathetic activity, were associated with an increased urinary albumin excretion.[25] These findings suggest that not only MHT but also WCHT needs to be managed carefully for the prevention of albuminuria.

In the present analysis, however, we found no differences in eGFR between NT and all three types of hypertension. Our findings are in line with other cross-sectional studies that failed to reveal a clear influence of hypertension on the decrease in eGFR.[26–28] Although the eGFR decreases in the advanced stage of untreated hypertension, a slight increase in eGFR has been shown among subjects in the early stage of hypertension.[29–31] Furthermore, the speed of eGFR changes in the middle stage of hypertension has been reported to be much slower compared with that of the UACR change.[10] As our subjects were

recruited from a general population, and the prevalence of hypertension with advanced target organ damage was relatively low, the present study could not detect the association between hypertension and the decrease in eGFR. In contrast, the Ohasama Study showed a clear association of MHT and SHT with low eGFR.[22] The reasons for these different findings are unclear, but the discrepancy may be partially explained by different methods used for BP evaluation: the Ohasama Study defined BP categories based on ABPM that provided more comprehensive BP information than HBP measurements. In addition, the Ohasama Study was performed in 1992–1997, more than 10 years earlier than the present study. The association between hypertension and low eGFR might have been diminished with time as a result of recent changes in lifestyles (for example, the general reduction in salt intake)[32] and the spread of renin–angiotensin system inhibitors that might delay the progression of nephropathy.

To our knowledge, this is the largest population-based study to demonstrate a close association between WCHT and albuminuria. However, this study has several limitations. First, because of the cross-sectional nature of this study, we were not able to determine whether there is a causal association between WCHT and albuminuria. The possibility of reverse causality exists.[23] For example, a prospective study showed that a slight increase in urinary albumin excretion was associated with a higher risk of incident hypertension.[33] Future prospective studies are needed to confirm the causal association between hypertension types and the future risk of albuminuria. Second, the inclusion of participants on BP-lowering medication may have resulted in a misclassification of BP categories. However, our stratified analysis showed comparable influences of each type of hypertension on albuminuria between subjects with and without BP-lowering medication. Third, CBP was classified based on only three measurements on a single day. However, this source of variability would not account for the relation observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of the study findings.

In conclusion, WCHT as well as MHT and SHT were associated with albuminuria in the Japanese general population. As albuminuria is an established target organ damage of hypertension[9,10] and has been shown to be associated with cardiovascular disease and death irrespective of the eGFR levels,[6] subjects with WCHT may require lifestyle changes and a close follow-up of target organ damage as well as BP levels, as recommended by current guidelines for the management of hypertension.[9,10]

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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