Target Organ Damage in "White Coat Hypertension" and "Masked Hypertension"

Vasilios Kotsis[1], Stella Stabouli[2,3], Savvas Toumanidis[2], Christos Papamichael[2], John Lekakis[2], George Germanidis[1], Apostolos Hatzitolios[1], Zoe Rizos[4], Michael Sion[1] and Nikos Zakopoulos[2]

BACKGROUND

In this study we investigated (i) the prevalence of white coat hypertension (WCH) and masked hypertension (MH) in patients who had never been treated earlier with antihypertensive medication, and (ii) the association of these conditions with target organ damage.

METHODS

A total of 1,535 consecutive patients underwent office blood pressure (BP) measurements, 24-h ambulatory BP monitoring (ABPM), echocardiography, and ultrasonography of the carotid arteries. Subjects who showed normotension or hypertension on the basis of both office and ambulatory BP (ABP) measurement were characterized as having confirmed normotension or confirmed hypertension, respectively. WCH was defined as office hypertension with ambulatory normotension, and MH as office normotension with ambulatory hypertension.

RESULTS

WCH was found in 17.9% and MH in 14.5% of the subjects. The prevalence of WCH was significantly higher in subjects with obesity, while the prevalence of MH was significantly higher in normal-weight subjects. The confirmed hypertensive subjects as well as the masked hypertensive subjects had significantly higher left ventricular mass (LVM) (corrected for body surface area) and carotid intima media thickness (cIMT) than the confirmed normotensive subjects did (108.9 ± 30.6, 107.1 ± 29.1 vs. 101.4 ± 29.9 g/m^2 and 0.68 ± 0.16, 0.68 ± 0.21 vs. 0.63 ± 0.15 mm, respectively, $P < 0.005$). White coat hypertensive subjects did not have a significantly higher LVM index than confirmed normotensive subjects (101.5 ± 25.9 vs. 101.4 ± 29.9 g/m^2); they tended to have higher cIMT than the confirmed normotensive subjects, but the difference was not statistically significant (0.67 ± 0.15 vs. 0.63 ± 0.15 mm).

CONCLUSIONS

WCH and MH are common conditions in patients who visit hypertension outpatient clinics. Confirmed hypertension and MH are accompanied by increased LVM index and cIMT, even after adjusting for other risk factors.

Am J Hypertens 2008; **21**:393-399 © 2008 American Journal of Hypertension, Ltd.

The introduction of ambulatory blood pressure monitoring (ABPM) in clinical practice has opened new perspectives on the evaluation of hypertensive individuals. In addition to normotensive and hypertensive patients, two more groups of patients, referred to as white coat hypertensive patients and masked hypertensive patients, were recognized by using both traditional clinic blood pressure (CBP) measurements and ABPM.[1]

White coat hypertension (WCH) is a condition characterized by persistently elevated office blood pressure (BP) levels and persistently normal 24-h or daytime ambulatory BP (ABP).[1,2] The prevalence of WCH varied in different studies, depending on the definition used to define ambulatory hypertension.[3] The clinical importance of using different upper normal limits of ABP is related with the potential cardiovascular risk faced by WCH patients. The impact of WCH on target organ damage, and the prognostic significance of WCH hypertension are issues that are being debated, with some authors suggesting that WCH is an innocent phenomenon whereas others report that it is associated with increased cardiovascular morbidity.[4–13] Masked hypertension (MH) is a clinical condition that applies to patients whose CBP is normal, but ABP is elevated.[14] These patients particularly benefit from ABPM as they cannot be easily diagnosed by routine methods. MH has been associated with target organ damage in both adults and children.[15–20]

Few studies have assessed these conditions in untreated populations, and most of these studies included only small numbers of subjects. In this study we investigated the prevalence of WCH and MH, and the associations of these conditions with target organ damage, in a large population that had never received antihypertensive treatment earlier. We hypothesized that these conditions, especially MH, could be associated with increased target organ damage, given that ABP has a higher predictive power in assessing the risk of target organ damage.

[1]Department of Medicine, Aristotle University, Thessaloniki, Greece; [2]Department of Clinical Therapeutics, National and Kapodestrial University, Athens, Greece; [3]Department of Paediatrics, National and Kapodestrial University, Athens, Greece; [4]University of Toronto, Toronto, Ontario, Canada. Correspondence: Vasilios Kotsis (bkotsis@med.uoa.gr)

Received 22 August 2007; first decision 20 September 2007; accepted 16 January 2008; advance online publication 21 February 2008. doi:10.1038/ajh.2008.15

METHODS

Study population. Study subjects were recruited from patients referred to two hypertension centers: Hypertension Center of the Department of Clinical Therapeutics in Athens, and Hypertension Center of the 3rd Department of Internal Medicine in Thessaloniki, from 2000–2006. The subjects were either those who had been referred to us for possible hypertension from their primary health care providers (60%), or who visited our hospital outpatient clinic for a routine BP check up. All patients who visit our centers undergo 24-h ABPM as a routine procedure. In order to be considered for further analysis, the inclusion criteria for the subjects were: (i) they had never been treated earlier with antihypertensive medication; (ii) they were taking no medication with the potential to raise BP (prednisone or NSAIDs); (iii) they showed no clinical signs or laboratory evidence of secondary causes of hypertension; and (iv) they had no history of coronary artery disease or heart failure. Finally, the study population consisted of a total of 1,535 patients. All patients gave their informed consent to participate in the study. The institutional review board approved the human research protocol. Body weight was measured with the subjects wearing light clothing without shoes. Patients were characterized as "normal weight" if their BMI was between 18.5 and 24.9, "overweight" if their BMI was between 25 and 29.9, and "obese" if their BMI was >30. Fasting serum glucose, fasting serum total cholesterol, and triglycerides were measured in all the subjects. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or being under medication for diabetes mellitus (9.1% of the population).

CBP measurements. A physician measured CBP three times in each subject, using a mercury sphygmomanometer with the appropriate size of cuff, before the fitting of the ABP monitors. During the measurement process the participant remained seated for 10 min with the arm comfortably placed at heart level. Three additional sphygmomanometric sitting BP measurements were performed after the removal of the ABP device. CBP was calculated as the average of the six BP measurements.

ABPM. All the subjects underwent 24-h ABPM on a normal working day. The Spacelabs 90217 ABP monitor (Spacelabs, Redmond, WA) was used. The procedure for reading and analyzing the ABP data has been described earlier.[5–7] Shift workers and other patients who did not rest or sleep ($n = 12$) at night were excluded from the analysis, while 1% of our patients reported taking a daytime nap. Confirmed normotensive subjects were defined as those with measurements of the clinic systolic BP (CSBP) <140 mm Hg and clinic diastolic BP (CDBP) <90 mm Hg, and the 24-h ABP systolic <125 mm Hg and diastolic BP <80 mm Hg. Confirmed hypertensive subjects were defined as those with CSBP ≥140 mm Hg and/or CDBP ≥90 mm Hg and 24-h ABP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg. WCH subjects were defined as those with CSBP ≥140 mm Hg and/or CDBP ≥90 mm Hg and 24-h ABP systolic <125 mm Hg and diastolic <80 mm Hg. MH subjects were defined as those with CSBP <140 mm Hg and CDBP <90 mm Hg and 24-h ABP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg.[21]

Echocardiography. All subjects underwent standard two-dimensional M-mode echocardiograms within a week of the BP measurements, with a Sigma-1C echocardiograph (Kontron Instruments, Everett, MA). Left ventricle dimensions were measured using the guidelines of the American Society of Echocardiography.[22] Numbers were randomly assigned to all echocardiograms, blinding all patient identification. Two experts in echocardiography, blinded as to the BP status of each patient, read each echocardiogram. The average of mean measurements provided by the two investigators for each echocardiogram was used in all calculations. Left ventricular mass (LVM) was calculated according to an anatomically validated formula,[23] and indexed for height$^{2.7}$. The κ statistics of agreement between the investigators was $\kappa = 0.95$, which suggests a high agreement between echocardiogram readings.

Ultrasound measurements (cIMT). Within a week of recording the BP measurements, all the participants were subjected to ultrasound examination while in the supine position with the head slightly elevated. The scans were performed with a high-resolution Ultrasound-Doppler system (Acuson 128 XP, Mountain View, CA) using a 7 MHz linear transducer. Both carotid arteries were scanned longitudinally in order to visualize the intima-media complex in the far wall of the artery. The best images of the far wall that could be obtained were used for determining the maximal intima media thickness (IMT) of the common and internal carotid arteries. The methods of reading and analyzing the data have been described earlier.[7,24] Measurements were made on frozen images, magnified to standard size, online. The IMT value was defined as the mean of the right and left IMTs of the common carotid arteries (MCCA), or the IMT of internal carotid arteries (MICA), calculated from 10 measurements on each side, taken within 10 mm proximal to the carotid bifurcation. The lumen/intima leading edge (I line) to media/adventitia leading edge (M line) method was used.[25] The mean cIMT was calculated as (MCCA + MICA)/2.[24] Various scanning angles (anterior, lateral, and posterior) were applied during each examination to identify maximal IMT. If plaque lay at an IMT measurement point, the IMT was measured and scanned from other angles. Therefore mean cIMT did not include values obtained at sites of plaque lesions. The reproducibility of mean cIMT measurements was assessed in 60 individuals and showed 5.9% intraobserver and 7.3% interobserver coefficient between the two measurements. These findings are comparable with reproducibility data from other studies.[25]

Statistical analysis. The SPSS (SPSS, Chicago, IL) statistical package was used for analyzing the data. Standard descriptive statistics, two-tailed Student's *t*-test and χ^2-test were used where appropriate to compare the characteristics of the groups. The results are expressed as percentages or mean values ± s.d.

Multiple comparisons between subgroups were performed using one-way analysis of variance Post Hoc Tukey analysis. The non-parametric Kruskal–Wallis test was also used where appropriate. Analysis of covariance (ANCOVA) was carried out with dependent variables in the full factorial models LVM and mean cIMT, with fixed factor being the four BP groups and covariates being age and BMI with weighted least squares regression by gender. The estimated marginal mean values were used for adjusting the LVM and cIMT mean values for age, BMI, and gender. Pairwise comparisons based on estimated marginal mean values were also used, with Bonferroni adjustment, for multiple comparisons.

RESULTS

General characteristics of the subjects

Confirmed normotension was found in 34.3% of the study population, WCH in 17.9%, MH in 14.5%, and confirmed hypertension in 33.3%. Demographic data of the four groups are listed in Table 1 as mean values ± s.d.

Confirmed normotensive subjects were younger than those with WCH ($P < 0.001$) and those with confirmed hypertension ($P < 0.001$), but not younger than the ones with MH. Subjects with MH were younger than those with confirmed hypertension ($P < 0.05$), but not younger than those with WCH. Confirmed normotensive subjects also had significantly lower fasting serum glucose than those with confirmed hypertension ($P < 0.001$), significantly lower triglycerides than those with MH ($P < 0.05$), and significantly higher high-density lipoprotein than those with MH ($P < 0.05$). Confirmed normotensive subjects had significantly lower BMI in comparison with WCH subjects ($P < 0.001$) and confirmed hypertensive subjects ($P < 0.001$), but not in comparison with MH subjects.

The prevalence rates of confirmed normotension, WCH, MH, and confirmed hypertension in normal-weight, overweight, and obese subjects are reported in Table 2. Women were more likely to have confirmed normotension (55.2% of the group, $P < 0.001$) or WCH (62.7% of the group, $P < 0.001$), whereas men were more likely to have either MH (60.9% of the group, $P < 0.001$) or confirmed hypertension (56% of the group, $P < 0.001$).

Clinic and ambulatory BP measurements

Subjects with MH had significantly higher CSBP and CDBP than those with confirmed normotension ($P < 0.0001$). Those with WCH had significantly higher 24-h SBP and DBP than those with confirmed normotension ($P < 0.0001$). Importantly, although those with MH had elevated 24-h SBP and DBP

Table 1 | Characteristics of the study population

Variables	Confirmed normotensives (*N* = 528)	White coat hypertensives (*N* = 274)	Masked hypertensives (*N* = 222)	Confirmed hypertensives (*N* = 511)
Age (years)	48.7 ± 17.2*,**	52.3 ± 14.1*	50.5 ± 15.9***	53.4 ± 12.7**,***
Sex (male %)	44.8*,**,***	37.3*,†,††	60.9**,†	56***,††
Current smoking (%)	32.7*,**	32.1***,†	41.1*,***	35.6**,†
Pack-years	25.7 ± 22.1*,**	27.4 ± 21.7	33.7 ± 26.3*	39.1 ± 27.6**
BMI (kg/m^2)	26.4 ± 5.2*,**	28.7 ± 5.2*	26.8 ± 3.9	28.1 ± 4.7**
Clinic SBP (mm Hg)	123 ± 12*,**,***	154 ± 13*,†,††	129 ± 10**,†,†††	159 ± 17***,††,†††
Clinic DBP (mm Hg)	79 ± 9*,**,***	95 ± 10*,†,††	83 ± 8**,†,†††	97 ± 11***,††,†††
24 h SBP (mm Hg)	115 ± 9*,**,***	120 ± 7*,†,††	135 ± 10**,†,†††	143 ± 15***,††,†††
24 h DBP (mm Hg)	70 ± 7*,**,***	72 ± 6*,†,††	83 ± 8**,†,†††	86 ± 10***,††,†††
Daytime SBP (mm Hg)	118 ± 10*,**,***	124 ± 7*,†,††	138 ± 10**,†,†††	146 ± 15***,††,†††
Daytime DBP (mm Hg)	73 ± 7*,**,***	76 ± 6*,†,††	86 ± 9**,†,†††	89 ± 10***,††,†††
Nighttime SBP (mm Hg)	108 ± 10*,**,***	111 ± 8*,†,††	129 ± 13**,†,†††	136 ± 18***,††,†††
Nighttime DBP (mm Hg)	64 ± 7*,**	65 ± 6***,†	78 ± 9*,***,††	80 ± 11**,†,††
Glucose (mg/dl)	97.7 ± 23.3*	99.7 ± 22.2	99.6 ± 27.7	104.3 ± 35.4*
Total cholesterol (mg/dl)	217.3 ± 43.9	221.3 ± 47.8	221.3 ± 45.8	222.7 ± 42.2
Triglycerides (mg/dl)	119.5 ± 67.1*	127.5 ± 69.9	137.6 ± 78.3*	126.5 ± 75.8
HDL (mg/dl)	54.1 ± 15.1*	52.7 ± 13.9	50.4 ± 12.55*	52.4 ± 13.5
LDL (mg/dl)	140.9 ± 36.7	148.4 ± 44.1	146.5 ± 39.1	147.3 ± 36.6

Values represents mean ± s.d.
HYP, confirmed hypertensives; MH, masked hypertensives; NORM, confirmed normotensives; WCH, white coat hypertensives.
Age: *$P < 0.001$ NORM vs. WCH, **$P < 0.001$ NORM vs. HYP, and ***$P < 0.05$ MH vs. HYP; Sex: *$P < 0.001$ NORM vs. WCH, **$P < 0.001$ NORM vs. MH, ***$P < 0.001$ NORM vs. HYP, †$P < 0.001$ WCH vs. MH, and ††$P < 0.001$ WCH vs. HYP; Current smoking: *$P < 0.001$ NORM vs. MH, **$P < 0.05$ NORM vs. HYP, ***$P < 0.05$ WCH vs. MH, and †$P < 0.05$ WCH vs. HYP; Pack-years: *$P < 0.05$ NORM vs. MH and **$P < 0.001$ NORM vs. HYP; BMI: *$P < 0.001$ NORM vs. WCH, **$P < 0.001$ NORM vs. HYP; Clinic SBP, Clinic DBP, Mean 24 h SBP, Mean 24 h DBP, Daytime SBP, Daytime DBP, and Nighttime SBP: *$P < 0.001$ NORM vs. WCH, **$P < 0.001$ NORM vs. MH,***$P < 0.001$ NORM vs. HYP, †$P < 0.001$ WCH vs. MH, ††$P < 0.001$ WCH vs. HYP, and †††$P < 0.001$ MH vs. HYP; Nighttime DBP: *$P < 0.001$ NORM vs. MH, **$P < 0.001$ NORM vs. HYP, ***$P < 0.001$ WCH vs. MH, †$P < 0.001$ WCH vs. HYP, and ††$P < 0.001$ MH vs. HYP; Glucose: *$P < 0.001$ NORM vs. HYP; Triglycerides and HDL: *$P < 0.05$ NORM vs. MH.

Table 2 | Prevalence of weight status according to confirmed normotension, white coat, masked, and confirmed hypertension

Groups	Confirmed normotension	White coat hypertension	Masked hypertension	Confirmed hypertension
Normal Weight ($N = 484$)	220 (45.5%)*,**,***	70 (14.5%)*,†	71 (14.7%)**,††	123 (25.4%)***,†,††
Overweight ($N = 668$)	207 (31.0%)*,**	107 (16.0%)*,***	110 (16.5%)**,†††	244 (36.5%)***,†††
Obese ($N = 383$)	101 (26.4%)*,**	97 (25.3%)***	41 (10.7%)*,***,†††	144 (37.6%)**,†††

HYP, confirmed hypertensives; MH, masked hypertensives; NORM, confirmed normotensives; WCH, white coat hypertensives.
Normal weight: *$P < 0.01$ NORM vs. WCH, **$P < 0.01$ NORM vs. MH, ***$P < 0.01$ NORM vs. HYP, †$P < 0.01$ WCH vs. HYP, ††$P < 0.01$ MH vs. HYP; Overweight: *$P < 0.01$ NORM vs. WCH, **$P < 0.01$ NORM vs. MH, ***$P < 0.01$ WCH vs. HYP, †††$P < 0.01$ MH vs. HYP; Obese: *$P < 0.01$ NORM vs. MH, **$P < 0.01$ NORM vs. HYP, ***$P < 0.01$ WCH vs. MH, †††$P < 0.01$ MH vs. HYP.

within the hypertensive range, these values were significantly lower than the corresponding values in subjects with confirmed hypertension ($P < 0.0001$). None of the patients in the MH group showed a combination of abnormal daytime BP and normal 24-h BP, 20% of them had normal daytime BP with abnormal 24-h BP, and 80% showed abnormal BP both in the daytime and in the 24-h monitoring.

Echocardiographic measurements of left ventricle

LVM indexed for height$^{2.7}$ was positively related to CSBP (Pearson's correlation coefficient $r = 0.18$, $P < 0.0001$) and CDBP (Pearson's correlation coefficient $r = 0.10$, $P < 0.001$). The 24-h SBP (Pearson's correlation coefficient $r = 0.25$, $P < 0.0001$) and the 24-h DBP (Pearson's correlation coefficient $r = 0.14$, $P < 0.0001$) were also positively associated with LVM indexed for height$^{2.7}$. In an ANCOVA model, LVM/height$^{2.7}$ was inserted as the dependent variable, BMI and age were inserted as covariates, and sex (male/female), diabetes mellitus (no/yes) and current smoking (no/yes) were inserted as fixed factors (Table 3). The predictors in the model were BMI, age, and sex with the model's adjusted $R^2 = 0.23$. Current smoking and diabetes mellitus were excluded. The addition of 24-h SBP in the model increased the adjusted R^2 to 0.25, but the further addition of CSBP did not increase R^2 beyond 0.25. The 24-h SBP was a predictor in the model, whereas CSBP was not (Table 3). On the other hand, the addition of 24-h SBP in a model that already included CSBP increased the R^2 from 0.23 to 0.25. Similar results were found for 24-h DBP and CDBP. Another ANCOVA model, with dependent variable being LVM/height$^{2.7}$, fixed factor being the four BP groups, and covariates being age and BMI with weighted Least Squares Regression by gender, revealed that LVM/height$^{2.7}$ was significantly associated with: age, BMI, MH vs. confirmed normotension, MH vs. WCH, confirmed hypertension vs. confirmed normotension, and confirmed hypertension vs. WCH (Table 3). 95% Confidence interval for the estimated marginal mean values were 39.3–41.7 g/m$^{2.7}$ for those with confirmed normotension, 37.9–41.1 g/m$^{2.7}$ for those with WCH, 39.6–43.6 g/m$^{2.7}$ for those with MH, and 41.1–43.4 g/m$^{2.7}$ for those with confirmed hypertension, after adjusting for age, BMI, and gender. On the basis of estimated marginal mean values, the mean differences between subjects with masked and confirmed hypertension vs. those with WCH and confirmed normotension were significant at the 0.05 level, after Bonferroni's adjustment for multiple comparisons. LVM indexed for height$^{2.7}$ for subjects with confirmed normotension, WCH, MH, and confirmed hypertension, after adjusting for age, BMI, and sex are showed in Figure 1.

Table 3 | ANCOVA analysis for LVM/height$^{2.7}$

LVM/height$^{2.7}$	B (95% CI)	*P*
Model 1		
BMI	0.86 (0.71 to 1.02)	0.001
Age	0.24 (0.19 to 0.29)	0.001
Sex (male-female)	3.1 (0.34 to 5.2)	0.05
Diabetes mellitus (no/yes)	−0.51 (−8.72 to 7.69)	0.90
Current smoking (no/yes)	−1.1 (−2.01 to 2.47)	0.82
+24 h SBP	0.09 (0.04 to 0.13)	0.001
+CSBP	0.01 (−0.03 to 0.05)	0.52
Model 2		
BMI	0.92 (0.77 to 1.08)	0.0001
Age	0.25 (0.18 to 0.28)	0.0001
NORM vs. MH	−1.63 (−3.93 to −0.67)	0.01
WCH vs. MH	−2.42 (−4.98 to −0.13)	0.01
NORM vs. HYP	−1.74 (−3.39 to −0.08)	0.01
WCH vs. HYP	−2.70 (−4.67 to −0.76)	0.01

CI, confidence interval; CSBP, clinic systolic blood pressure; HYP, confirmed hypertensives; MH, masked hypertensives; NORM, confirmed normotensives; WCH, white coat hypertensives.

IMT of carotid arteries

cIMT was positively related to CSBP (Pearson's correlation coefficient $r = 0.15$, $P < 0.0001$) and 24-h SBP (Pearson's correlation coefficient $r = 0.18$, $P < 0.0001$). CDBP and 24-h DBP were not related to cIMT. A model of ANCOVA (Table 4) with dependent variable being the mean cIMT, covariates being age and BMI, and fixed factors being sex (male/female), diabetes mellitus (no/yes), and current smoking (no/yes), revealed that cIMT was significantly associated with age, BMI, sex, and diabetes, but not with current smoking, the model's R^2 being 0.29. The addition of 24-h SBP in the model increased the R^2 to 0.31, but further addition of CSBP did not increase R^2 beyond 0.31. On the other hand, the addition of 24-h SBP in a model that already included CSBP increased the R^2 from 0.29 to 0.31. Another model of ANCOVA with dependent variable being the mean cIMT, fixed factor being the four BP groups and diabetes mellitus (no/yes), and covariates being age and BMI with weighted least squares regression by gender (Table 4) revealed that cIMT was significantly

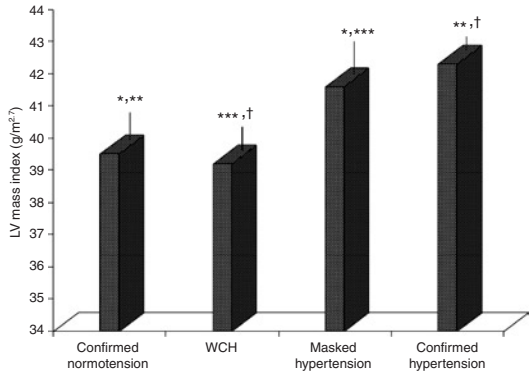

Figure 1 | Left ventricular mass index in subjects with confirmed normotension, those with white coat hypertension, those with masked hypertension, and those with confirmed hypertension, after adjusting for age, BMI, and gender. *$P < 0.05$ for confirmed normotension vs. masked hypertension, **$P < 0.05$ for confirmed normotension vs. confirmed hypertension, ***$P < 0.05$ for white coat hypertension vs. masked hypertension, †$P < 0.05$ for white coat hypertension vs. confirmed hypertension.

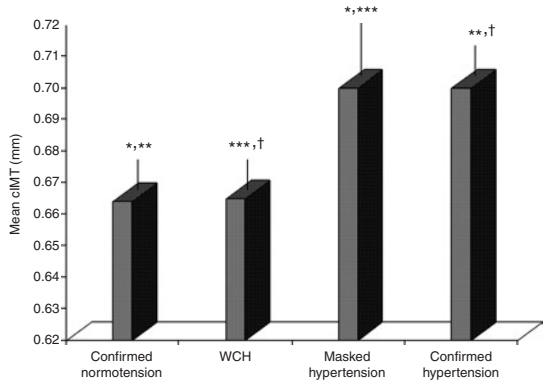

Figure 2 | Carotid intima media thickness (cIMT) in subjects with confirmed normotension, those with white coat hypertension, those with masked hypertension, and those with confirmed hypertension, after adjusting for age, BMI, diabetes mellitus, and gender. *$P < 0.05$ for confirmed normotension vs. masked hypertension, **$P < 0.05$ for confirmed normotension vs. confirmed hypertension, ***$P < 0.05$ for white coat hypertension vs. masked hypertension, †$P < 0.05$ for white coat hypertension vs. confirmed hypertension.

Table 4 | ANCOVA analysis for mean cIMT

Mean cIMT	B (95% CI)	*P*
Model 1		
BMI	0.004 (0.001 to 0.006)	0.001
Age	0.005 (0.005 to 0.006)	0.001
Sex (male-female)	0.072 (0.052 to 0.092)	0.001
Diabetes mellitus (no/yes)	−0.055 (−0.091 to −0.019)	0.01
Current smoking (no/yes)	−0.006 (−0.027 to 0.015)	0.58
+24 h SBP	0.001 (0.0001 to 0.002)	0.001
+CSBP	0.0001 (0.0001 to 0.001)	0.47
Model 2		
BMI	0.003 (0.001 to 0.006)	0.001
Age	0.005 (0.004 to 0.006)	0.001
Diabetes mellitus (no-yes)	−0.07 (−0.114 to −0.039)	0.001
NORM vs. MH	−0.033 (−0.057 to −0.008)	0.001
WCH vs. MH	−0.032 (−0.057 to −0.05)	0.01
NORM vs. HYP	−0.030 (−0.058 to −0.008)	0.001
WCH vs. HYP	−0.030 (−0.058 to −0.05)	0.01

CI, confidence interval; CSBP, clinic systolic blood pressure; HYP, confirmed hypertensives; MH, masked hypertensives; NORM, confirmed normotensives; WCH, white coat hypertensives.

associated with age, BMI, diabetes, MH vs. confirmed normotension, MH vs. WCH, confirmed hypertension vs. confirmed normotension, and confirmed hypertension vs. WCH. The 95% confidence intervals for the estimated marginal mean values were 0.64–0.68 mm for subjects with confirmed normotension, 0.64–0.69 mm for WCH, 0.68–0.73 mm for MH and 0.67–0.72 mm for those with confirmed hypertension, after adjusting for age, BMI, diabetes mellitus, and gender. On the basis of estimated marginal means, the mean differences between subjects with MH and confirmed hypertension vs. those with WCH and confirmed normotension were significant at the 0.05 level, after Bonferroni's adjustment for multiple comparisons. The cIMT for subjects with confirmed normotension, those with WCH, those with MH and those with confirmed hypertension, after adjusting for age, BMI, diabetes, and gender are showed in **Figure 2**.

DISCUSSION

The clinical significance of WCH and MH lies in a potentially increased risk of occurrence of cardiovascular events. In this study, which included untreated hypertensive as well as normotensive patients, the prevalence of WCH and MH was found to be 17.9 and 14.5%, respectively. Moreover, this study provides data on the extent of target organ damage in what is, to our knowledge, the largest untreated population with the aforementioned conditions to be studied to date.

Subjects with MH exhibited more extensive target organ damage, increased LVM indices, and cIMT than normotensives did, as expected given that ABP is better able to predict target organ damage. It is interesting that the values of the LVM indices were similar in subjects with MH and those with confirmed hypertension, thereby implying that MH represents an equivalent risk for cardiovascular disease. These findings represent refinements of data from earlier studies in both adults and children.[15–18] Longitudinal studies showed that subjects with MH have increased cardiovascular morbidity.[19] In the Ohasama study, the risk of cardiovascular mortality and stroke was greater for those with MH and those with confirmed hypertension than for those with confirmed normotension and WCH patients.[20]

WCH possibly represents an intermediate group, as regards risk for target organ damage, between those with confirmed normotension and those with hypertension. Several investigators have explored the effect of WCH on target organ damage, and the results have been controversial.[4–10] In our study population, WCH subjects did not demonstrate statistically significant differences in target organ damage when com-

pared with subjects with normotension. We found that WCH subjects had significantly higher ABP values than confirmed normotensive subjects, thereby implying that WCH subjects may have an increased risk of becoming confirmed hypertensive patients, and may require close follow-up especially in the presence of comorbidities.

While WCH is more frequently found in elderly patients, MH is less prevalent with increasing age. This can be explained by the fact that ABP increases less with age than CBP does.[26] It is interesting that both WCH and MH had almost the same prevalence in the normal-weight group as in the overweight group, whereas in obese subjects the prevalence of MH was significantly lower. As we have earlier shown, increasing BMI has a greater association with office BP than with ABP.[27,28] Also, current smokers were more likely to have abnormal ABP. It has earlier been reported that the nicotine in cigarette smoke has the effect of raising BP acutely.[29] We also found that a large number of MH subjects had normal daytime BP and abnormal 24-h BP, thereby suggesting that high nighttime BP is an important factor in identifying subjects with MH. A further important finding was that subjects with MH exhibited higher CBP than those with confirmed normotension did, thereby suggesting that MH subjects tend to have high normal CBP. In agreement with data from earlier studies, we found that subjects with MH were more likely to be smokers, belong to the male sex, and have higher levels of triglycerides and lower levels of high-density lipoprotein when compared with confirmed normotensive subjects, and this indicates an adverse cardiovascular profile for MH subjects.[16,30]

This is a cross-sectional study, and therefore conclusions regarding the associations demonstrated for WCH and MH are limited. Follow-up visits could have provided evidence of attenuation of these conditions or of changes in them, and insights into how these changes influence target organ damage and cardiovascular prognosis. Another possible limitation may include bias as a result of subject selection and limits in generalizing the findings to different ethnic populations.

The association of BP with health outcomes is likely to be a continuum, at least in the range of values near the established thresholds. Any thresholds for diagnosis/treatment are a little arbitrary if the impact of BP is a continuum. The WCH and MH groups (in this untreated population) would be expected to fall somewhere between the consistently normal and the consistently hypertensive. BP has a high intra-individual (in the same person) variability. The 24-h values are less subject to this variability (because they represent the mean value of a larger number of readings), whereas the CBP (even multiple CBPs) will vary more. Thus the masked will be a little closer to the consistently elevated whereas the white coat, also in the "middle" will be a little closer to the consistently normotensive.

In summary, WCH represents a subgroup of patients that exhibit abnormal CBP measurements although their 24-h BP is normal. Close follow-up with ABPM and repeated examinations for target organ damage will facilitate the estimation of cardiovascular risk in such patients, and guide optimal therapeutic decisions. For MH subjects, the risk for target organ damage is probably similar to that for confirmed hypertensive subjects. The MH group may have higher CBPs than the confirmed normotensive group, and could be classified as "prehypertensive" subjects. MH subjects probably have the greater risk for cardiovascular morbidity and mortality because they are not aware of their real BP situation, and hypertension might be underdiagnosed. Although cost-effectiveness studies are not available, the current evidence may suggest that male non-obese smoking prehypertensive subjects could selectively undergo ABPM. MH subjects need to be treated for hypertension, and probably for reversal of target organ damage.

Disclosure: The authors declared no conflict of interest.

1. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142–161.
2. Angeli F, Verdecchia P, Gattobigio R, Sardone M, Reboldi G. White-coat hypertension in adults. *Blood Press Monit* 2005; 10:301–305.
3. Verdecchia P, Schillaci G, Boldrini F, Zampi I, Porcellati C. Variability between current definitions of "normal" ambulatory blood pressure. Implications in the assessment of white coat hypertension. *Hypertension* 1992; 20:555–562.
4. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) Study). *Circulation* 2001; 104:1385–1392.
5. Zakopoulos NA, Kotsis VT, Pitiriga VCh, Toumanidis ST, Lekakis JP, Nanas SN, Vemmos KN, Stamatelopoulos SF, Moulopoulos SD. White-coat effect in normotension and hypertension. *Blood Press Monit* 2002; 7:271–276.
6. Pitiriga VC, Kotsis VT, Papamichail CM, Alexandrou ME, Lekakis JP, Kokolakis N, Petrocheilou-Paschou VD, Zakopoulos NA. High prevalence of Chlamydia pneumoniae antibodies in white-coat hypertensives. *Atherosclerosis* 2003; 167:231–235.
7. Zakopoulos N, Papamichael C, Papaconstantinou H, Dubbins PA, Burrell CJ, Lekakis J, Stamatelopoulos S, Moulopoulos S. Isolated clinic hypertension is not an innocent phenomenon: effect on the carotid artery structure. *Am J Hypertens* 1999; 12:245–250.
8. Palatini P, Mormino P, Santonastaso M, Mos L, Dal Follo M, Zanata G, Pessina AC. Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension: results from the HARVEST study. *Hypertension* 1998; 31:57–63.
9. Cavallini MC, Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Is white coat hypertension associated with arterial disease or left ventricular hypertrophy? *Hypertension* 1995; 26:413–419.
10. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol* 2001; 38:238–245.
11. Verdecchia P, Reboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, Imai Y, Ohkubo T, Kario K. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension* 2005; 45:203–208.
12. Gustavsen PH, Hoegholm A, Bang LE, Kristensen KS. White coat hypertension is a cardiovascular risk factor: a 10-year follow-up study. *J Hum Hypertens* 2003; 17:811–817.
13. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; 47:846–853.
14. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002; 40:795–796.
15. Tomiyama M, Horio T, Yoshii M, Takiuchi S, Kamide K, Nakamura S, Yoshihara F, Nakahama H, Inenaga T, Kawano Y. Masked hypertension and target organ damage in treated hypertensive patients. *Am J Hypertens* 2006; 19:880–886.
16. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999; 131:564–572.

17. Hernandez del-Rey R, Armario P, Martin-Baranera M, Sanchez P, Almendros MC, Coca A, Pardell H. Cardiac damage in hypertensive patients with inverse white coat hypertension. Hospitalet study. *Blood Press* 2003; 12:89–96.
18. Stabouli S, Kotsis V, Toumanidis S, Papamichael C, Constantopoulos A, Zakopoulos N. White-coat and masked hypertension in children: association with target-organ damage. *Pediatr Nephrol* 2005; 20:1151–1155.
19. Bjorklund K, Lind L, Zethelius B, Andren B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation* 2003; 107:1297–1302.
20. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; 46:508–515.
21. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21:1011–1053.
22. Sahn PS, De Maria A, Kisslo J, Weyman A. The Committee on the M-mode standardization of the American Society of Echocardiography results of a survey of echocardiographic measurements. *Circulation* 1978; 58:1072–1083.
23. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy. Comparison to necropsy findings. *Am J Cardiol* 1986; 57:450–458.
24. Kotsis V, Pitiriga V, Stabouli S, Papamichael C, Toumanidis S, Rokas S, Zakopoulos N. Carotid artery intima-media thickness could predict the presence of coronary artery lesions. *Am J Hypertens* 2005; 18:601–606.
25. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infraction: the Rotterdam Study. *Circulation* 1997; 96:1432–1437.
26. Kotsis V, Stabouli S, Pitiriga V, Toumanidis S, Papamichael C, Zakopoulos N. Ambulatory blood pressure monitoring and target organ damage: effects of age and sex. *Blood Press Monit* 2006; 11:9–15.
27. Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, Zakopoulos N. Impact of Obesity on 24-Hour Ambulatory Blood Pressure and Hypertension. *Hypertension* 2005; 45:602–607.
28. Stabouli S, Kotsis V, Papamichael C, Constantopoulos A, Zakopoulos N. Adolescent obesity is associated with high ambulatory blood pressure and increased carotid intimal-medial thickness. *J Pediatr* 2005; 147:651–656.
29. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Battistelli M, Gattobigio R, Sacchi N, Porcellati C. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. *J Hypertens* 1995; 13:1209–1215.
30. Mallion JM, Clerson P, Bobrie G, Genes N, Vaisse B, Chatellier G. Predictive factors for masked hypertension within a population of controlled hypertensives. *J Hypertens* 2006; 24:2365–2370.