JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 19, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.08.035

ORIGINAL INVESTIGATIONS

The Cardiovascular Risk of White-Coat Hypertension

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ABSTRACT

BACKGROUND The role of white-coat hypertension (WCH) and the white-coat-effect (WCE) in development of cardiovascular disease (CVD) risk remains poorly understood.

OBJECTIVES Using data from the population-based, 11-cohort IDACO (International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes), this study compared daytime ambulatory blood pressure monitoring with conventional blood pressure measurements in 653 untreated subjects with WCH and 653 normotensive control subjects.

METHODS European Society Hypertension guidelines were used as a 5-stage risk score. Low risk was defined as 0 to 2 risk factors, and high risk was defined as ≥3 to 5 risk factors, diabetes, and/or history of prior CVD events. Age- and cohort-matching was done between 653 untreated subjects with WCH and 653 normotensive control subjects.

RESULTS In a stepwise linear regression model, systolic WCE increased by 3.8 mm Hg (95% confidence interval [CI]: 3.1 to 4.6 mm Hg) per 10-year increase in age, and was similar in low- and high-risk subjects with or without prior CVD events. Over a median 10.6-year follow-up, incidence of new CVD events was higher in 159 high-risk subjects with WCH compared with 159 cohort- and age-matched high-risk normotensive subjects (adjusted hazard ratio [HR]: 2.06; 95% CI: 1.10 to 3.84; $p = 0.023$). The HR was not significant for 494 participants with low-risk WCH and age-matched low-risk normotensive subjects. Subgroup analysis by age showed that an association between WCH and incident CVD events is limited to older (age ≥60 years) high-risk WCH subjects; the adjusted HR was 2.19 (95% CI: 1.09 to 4.37; $p = 0.027$) in the older high-risk group and 0.88 (95% CI: 0.51 to 1.53; $p = 0.66$) in the older low-risk group (p for interaction $= 0.044$).

CONCLUSIONS WCE size is related to aging, not to CVD risk. CVD risk in most persons with WCH is comparable to age- and risk-adjusted normotensive control subjects. (J Am Coll Cardiol 2016;68:2033–43) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ABPM = ambulatory blood pressure monitoring

BP = blood pressure

CVD = cardiovascular disease

ESC = European Society of Cardiology

ESH = European Society of Hypertension

ICD = International Classification of Diseases

WCE = white-coat effect

WCH = white-coat hypertension

It has been 32 years since Thomas Pickering's original description of white-coat hypertension (WCH), and yet there is still controversy as to the presence and extent of increased cardiovascular disease (CVD) risk in persons with this very common condition (1-3). Recent studies suggest that the incidence of WCH increases with the aging of the population (4,5). Moreover, WCH and the white-coat effect (WCE) are not identical. WCH exists if the office blood pressure (BP) is high (i.e., an office BP of ≥140 systolic and/or ≥90 mm Hg diastolic) and ambulatory blood pressure monitoring (ABPM) is normal (i.e., awake daytime ABPM <135/85 mm Hg) in a patient who is not receiving antihypertensive medication. The WCE is defined as the rise in BP that occurs in the medical environment, regardless of the daytime ABPM level or the use of antihypertensive drugs (6,7).

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Few of the studies addressing the question of possible increased CVD risk in persons with WCH were population-based. Furthermore, many older studies had an insufficient number of persons with WCH and/or short follow-up periods. Therefore, there was a relatively low incidence of subsequent CVD events and, hence, limited statistical power. In contrast, the current IDACO (International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes) study includes a large number of people residing in the community from 11 countries, with standard protocols for conventional BP measurement and ABPM, a majority free of antihypertensive drug treatment, and a median follow-up of 10.6 years (8).

To address the association of WCH with CVD risk, we recognized 2 barriers to overcome that have been largely overlooked in past studies. First, because age itself is such a strong risk factor, age-matching of persons with WCH should be made to their normotensive comparator group; this is superior to age-adjusting. Second, because CVD risk varies considerably among subjects, we must subdivide persons with WCH into low- versus high-risk CVD groups in a standardized manner.

METHODS

STUDY POPULATION. A previous publication described the construction of the IDACO database in

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Manuscript received May 10, 2016; revised manuscript received August 3, 2016, accepted August 9, 2016.

detail (8). Studies qualified for inclusion if they involved a random population sample, if baseline information on conventional BP, ABPM, and CVD risk factors was available, and if subsequent follow-up included both fatal and nonfatal outcomes. All studies received ethical approval and adhered to the principles of the Declaration of Helsinki, and participants gave written informed consent.

The IDACO database currently includes 12,752 people, representing 12 randomly recruited population cohorts with validated information on outcome. We discarded 1 cohort (9) (n = 604) because the large number of subjects with WCH (38.1%) and the low number of normotensive participants (16.3%) did not allow matching the WCH subjects with normotensive participants by age (see the Statistical Methods section). In the remaining 12,148 participants, we applied the following exclusion criteria: 1) age <18 years (n = 303); 2) conventional BP unavailable (n = 248); 3) taking antihypertensive drug treatment at baseline (n = 2,156); 4) <10 daytime ambulatory BP recordings available (n = 131); and 5) missing information on 1 or more risk factors (n = 728). A total of 8,582 subjects remained, of whom 5,137 were normotensive and 653 had WCH.

COLLECTION OF BASELINE DATA. We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking and drinking habits. Conventional BP was the mean of 2 consecutive readings. We programmed portable monitors to obtain ambulatory BP readings at 30-min intervals throughout the whole day, or at intervals ranging from 15 to 30 min during the daytime and from 30 to 60 min at night. Body mass index was calculated as body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was defined as the use of antidiabetic drugs, a fasting glucose of at least 7.0 mmol/l, a random glucose of at least 11.1 mmol/l, a self-reported diagnosis, or diabetes documented in practice or hospital records.

CROSS-CLASSIFICATION ON THE BASIS OF CONVENTIONAL AND AMBULATORY BP. Conventional hypertension was a BP of at least 140 mm Hg systolic and/or 90 mm Hg diastolic. Ambulatory hypertension was a daytime level of ≥135 mm Hg systolic and/or ≥85 mm Hg diastolic. When systolic and diastolic BPs were in different categories (normotensive vs. hypertensive), the participant was considered as hypertensive. Sustained normotension was a consistently normal level on both conventional BP and ABPM. WCH was defined as conventional hypertension in the presence of a normal daytime ABPM. The WCE was calculated as the systolic or diastolic conventional BP minus the daytime ABPM.

CONTROL OF CONFOUNDING BY AGE MATCHING. Because of the 12-year mean age difference between the WCH and normotensive subjects, and because of the huge risk associated with age, we used a greedy algorithm to match the 653 WCH subjects by cohort and age (within 5 years) with 653 normotensive participants. Indeed, in case of insufficient overlap in the confounding variable between the 2 groups to be compared, matching might be more efficient than adjustment. In contrast to adjustment techniques, matching does not require any assumptions about the relation between outcome and age.

ASCERTAINMENT OF RISK. We used the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines as the basis for assigning a risk score to each subject (10). The purpose of the study was to compare WCH participants with normotensive subjects having a similar number of risk factors other than BP; therefore, BP was not included in the risk score. In addition, we matched WCH and normotensive subjects by age, rather than including age in the risk score, because age differences would otherwise bias our comparisons of CVD risk between WCH subjects and their normotensive comparators. The ESH/ESC risk score restricted to the available data in IDACO defines the following risk categories: 1) no risk factor; 2) 1 to 2 risk factors; 3) ≥3 risk factors; 4) diabetes without risk factors; and 5) history of CVD events or diabetes with other risk factors (10). We took into account the following risk factors: male sex; current smoking; dyslipidemia, defined as total cholesterol >4.9 mmol/l; and obesity, defined as body mass index >30 kg/m^2. Subjects were classified into low-risk (risk categories 1 and 2) or high-risk (risk categories 3, 4, and 5) groups (10).

ASCERTAINMENT OF EVENTS. We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in detail in a previous publication (8). Outcomes were coded according to the International Classification of Diseases (ICD). The cardiovascular endpoint included: cardiovascular mortality (ICD-8 390 to 448, ICD-9 390 to 459, and ICD-10 I00 to I79); sudden death (ICD-8 795, ICD9 798, and ICD-10 R96); nonfatal stroke (ICD-8/9 430 to 434 and 436, ICD-10 I60 to I64 and I67 to I68); nonfatal myocardial infarction (ICD-8/9 410, and ICD-10 I21 to I22); coronary revascularization and nonfatal heart failure (ICD-8 428, 427.1, 427.2, 429 and 5191; ICD-9 429 and

TABLE 1 Baseline Characteristics of 653 Subjects With WCH and 653 Cohort- and Age-Matched Normotensive Subjects

	Low Risk		High Risk	
	Normotension (n = 494)	WCH (n = 494)	Normotension (n = 159)	WCH (n = 159)
Women	278 (56.3)	245 (49.6)*	27 (17.0)	26 (16.4)
Ethnicity (Caucasian)	413 (83.6)	414 (83.8)	137 (86.2)	137 (86.2)
Current smoking	82 (16.6)	46 (9.3)†	95 (59.8)	79 (49.7)
Drinking alcohol	197 (43.2)	206 (45.1)	78 (54.6)	86 (61.4)
Diabetes mellitus	0 (0.0)	0 (0.0)	30 (18.9)	36 (22.6)
Body mass index ≥30 kg/m^2	25 (5.1)	44 (8.9)*	29 (18.2)	49 (30.8)*
Total cholesterol >4.9 mmol/l	329 (66.6)	353 (71.5)	139 (87.4)	143 (89.9)
History of CVD events	0 (0.0)	0 (0.0)	38 (23.9)	40 (25.2)
ESH/ESC risk group				
No risk factors	269 (54.4)	249 (50.4)	0 (0.0)	0 (0.0)
1–2 risk factors	225 (45.6)	245 (49.6)	0 (0.0)	0 (0.0)
≥3 risk factors	0 (0.0)	0 (0.0)	93 (58.5)	85 (53.5)
Diabetes	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
History of CVD or DM with risk factor(s)	0 (0.0)	0 (0.0)	65 (40.9)	74 (46.5)
Mean characteristics				
Age, yrs	56.2 ± 15.0	56.2 ± 15.0	59.5 ± 12.9	59.5 ± 12.9
Body mass index, kg/m^2	24.5 ± 3.6	25.5 ± 3.9†	25.9 ± 4.0	27.6 ± 4.2†
Total serum cholesterol, mmol/l	5.51 ± 1.13	5.74 ± 1.24‡	5.85 ± 1.00	5.98 ± 1.01
Blood pressure, mm Hg				
Conventional systolic	119.7 ± 11.5	144.6 (11.9)†	122.7 ± 9.2	147.4 ± 13.4†
Conventional diastolic	73.6 ± 7.9	86.5 ± 8.8†	75.1 ± 7.8	86.5 ± 9.2†
24-h systolic	115.4 ± 7.5	121.3 ± 7.2†	117.4 ± 7.5	121.8 ± 6.4†
24-h diastolic	68.9 ± 5.4	72.0 ± 5.4†	70.6 ± 5.9	71.9 ± 5.9
Daytime systolic	120.7 ± 7.7	125.8 ± 6.8†	122.4 ± 7.7	126.0 ± 5.8†
Daytime diastolic	73.3 ± 5.6	76.1 ± 5.9†	74.7 ± 6.2	75.7 ± 6.1
Nighttime systolic	105.6 ± 9.9	111.4 ± 11.5†	108.5 ± 10.8	111.0 ± 10.6*
Nighttime diastolic	61.2 ± 6.9	64.1 ± 7.5†	63.2 ± 7.3	64.0 ± 8.3

Values are n (%) or arithmetic mean ± SD. Thresholds for hypertension were ≥140/≥90 mm Hg and ≥135/≥85 mm Hg on conventional and daytime ABPM, respectively. Normotension was normal BP on both conventional and daytime ABPM. WCH was a raised conventional BP and normal daytime ABPM. Subjects in the first and second ESH/ESC risk groups were classified as low risk. Subjects in the 3 upper ESH/ESC risk groups were classified as high risk. Information on alcohol intake was unavailable in 54 normotensive and 56 WCH participants. The ABPM was not recorded during night-time in 72 normotensive and 75 WCH subjects. Significance of the difference between normotensive participants and subjects with WCH: *p ≤ 0.05; †p ≤ 0.001; ‡p ≤ 0.01.

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; ESH = European Society of Hypertension; ESC = European Society of Cardiology; WCH = white-coat hypertension.

5184; and ICD10 I50 and J81). We only considered the first event within each category.

STATISTICAL ANALYSIS. For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina). Between-group comparisons of means and proportions were tested using the Student *t* test and Fisher exact test, respectively. We searched for covariates associated with the WCE using single and stepwise multiple linear regression analyses, with cohort entered as a random effect and with p values for explanatory variables to enter and stay in the model set at 0.15 and 0.05. We used Kaplan-Meier survival function estimates and the Cox proportional hazards model to compare the incidence of CVD morbidity and mortality between WCH participants and their cohort- and age-matched normotensive comparators. We took correlations within matched pairs into account by including "pair" as a random effect in the models. We adjusted for sex, body mass index, smoking and drinking, total serum cholesterol, and history of CVD and diabetes mellitus.

RESULTS

CHARACTERISTICS OF PARTICIPANTS. The clinical characteristics of the 5,137 normotensive subjects and the 653 WCH participants are provided in Online Table 1. Online Figure 1 illustrates their age distributions. The overall prevalence of WCH among subjects with a normal daytime ABPM was 11.3%, with a variation by cohort from 3.6% (11) to 35.4% (12). Compared with the sustained normotensive group, subjects with WCH were older by 11.9 years, had a 14.7% greater male prevalence, had a significant increase in CVD risk factors, and had a higher prevalence of diabetes and prior CVD events.

Table 1 shows the baseline characteristics of the 653 WCH participants and their cohort- and age-matched normotensive control subjects, divided into low-risk (n = 494) and high-risk (n = 159) groups. By definition, the high-risk WCH group included more ($p < 0.001$) men (83.6%) than the low-risk WCH group (50.4%). Online Figure 2 illustrates equal age distributions in the participants with WCH and their age-matched normotensive comparators. Mean ages were 56.2 and 59.5 years in the low- and high-risk groups, respectively. Body mass index and the daytime, night-time, and 24-h systolic BP values were significantly higher ($p < 0.05$) in the WCH subjects as compared with the normotensive control subjects in both the low- and high-risk groups. The same tendency was present for diastolic BP. In contrast, all of the daytime, night-time, and 24-h readings were similar in low- and high-risk WCH subjects. BP variability, as assessed by the daytime and 24-h SD and coefficient of variability, was significantly higher in the high-risk WCH subjects as compared with the high-risk normotensive subjects (Online Table 2).

Online Table 3 provides the WCE and CVD risk factors according to sex and age in the 653 subjects with WCH. Importantly, the magnitude of the WCE was estimated to increase from 9.4 mm Hg at age 30 years to 25.0 mm Hg at age 70 years ($p < 0.0001$) (Online Figure 3), but was independent of sex.

TABLE 2 Factors Correlating With the WCE in 653 Subjects With WCH

	Systolic WCE, mm Hg (95% CI)		Diastolic WCE, mm Hg (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Female (0,1)	0.28 (−1.74 to 2.31)	NS	1.03 (−0.32 to 2.38)	NS
Age (+10 yrs)	3.89 (3.16 to 4.62)*	3.83 (3.10 to 4.56)*	−0.64 (−1.17 to −0.12)†	−0.63 (−1.14 to −0.12)†
Body mass index (+5 kg/m^2)	−0.61 (−1.80 to 0.57)	NS	1.88 (1.10 to 2.66)*	1.87 (1.09 to 2.64)*
Obesity (0,1)	−2.17 (−4.85 to 0.51)	NS	1.55 (−0.25 to 3.34)	NS
Smoking (0,1)	−1.30 (−3.65 to 1.05)	NS	−0.80 (−2.38 to 0.78)	NS
Drinking alcohol (0,1)	−1.79 (−4.01 to 0.43)	NS	−0.19 (−1.67 to 1.29)	NS
History of CVD events (0,1)	5.62 (1.79 to 9.45)‡	NS	−0.24 (−2.83 to 2.35)	NS
Diabetes (0,1)	5.32 (1.18 to 9.46)†	3.88 (0.02 to 7.74)†	1.08 (−1.70 to 3.87)	NS
High risk (0,1)	1.84 (−0.31 to 3.98)	NS	0.44 (−1.00 to 1.88)	NS
Serum cholesterol (+1 mmol/l)	1.16 (0.33 to 1.98)‡	NS	0.01 (−0.55 to 0.56)	NS

Values are unadjusted and mutually adjusted regression coefficients (95% CI) obtained from a mixed linear regression model including cohort as a random effect. These coefficients estimate the change in the WCE associated with the indicated change in the independent variables. The adjusted analysis was a stepwise linear regression model that included all the factors. The p values to enter and stay in the model were set at 0.15 and 0.05, respectively. The WCE was calculated as the conventional BP minus the daytime ABPM. Obesity is body mass index >30 kg/m^2. NS indicates not significant. For the definition of high risk, see the Methods section. *$p < 0.0001$; †$p < 0.05$; ‡$p < 0.01$.

CI = confidence interval; WCE = white-coat effect; other abbreviations as in Table 1.

FACTORS CORRELATING WITH THE WCE. Table 2 shows the correlates of the WCE in the 653 subjects with WCH. The systolic WCE increased by 3.83 mm Hg (95% confidence interval [CI]: 3.10 to 4.56 mm Hg; $p < 0.0001$) per 10-year increase in age, and was 3.88 mm Hg (95% CI: 0.02 to 7.74 mm Hg; $p = 0.049$) higher in diabetic than in nondiabetic subjects. The proportion of variance in the systolic WCE accounted for by age amounted to 13.9%. Diabetes explained an additional 0.3% of the variance. The diastolic WCE decreased by 0.63 mm Hg (95% CI: 0.12 to 1.14 mm Hg; $p < 0.05$) per 10-year increase in age, but increased by 1.87 mm Hg (95% CI: 1.09 to 2.64 mm Hg; $p < 0.0001$) per 5-kg/m^2 increase in body mass index. Age and body mass index explained 3.9% of the variance in the diastolic WCE. After adjustment for age, none of the other CVD risk factors were associated with the size of the WCE in this cross-sectional analysis. In particular, the WCE was similar in 494 low-risk and 159 high-risk subjects ($p \geq 0.82$), and in subjects with ($n = 40$) and without ($n = 613$) a history of cardiovascular complications ($p \geq 0.12$).

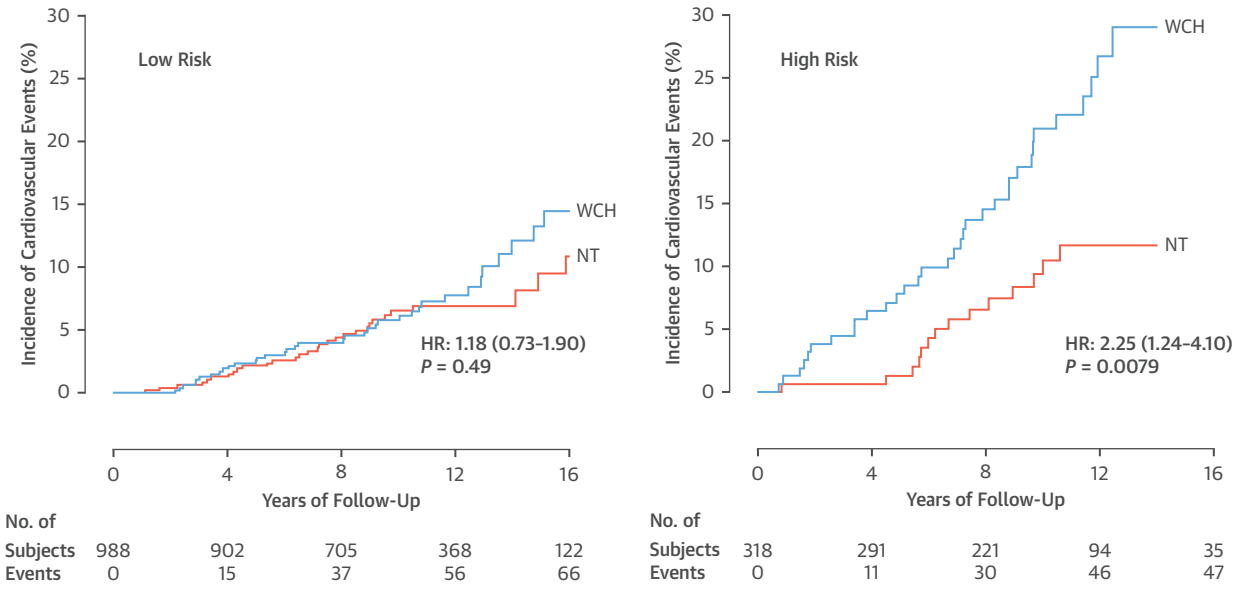
PROGNOSTIC VALUE OF WCH BY RISK SCORE. The 653 subjects with WCH and their normotensive control subjects were followed up for a total of 6,817 years (median: 10.8 years; 5th to 95th percentile interval: 2.6 to 17.8 years) and 6,855 years (median: 10.5 years; 5th to 95th percentile interval: 2.5 to 18.1 years), respectively. During this period, 70 participants with WCH and 48 normotensive control subjects experienced a fatal or nonfatal CVD event.

Figure 1 shows the Kaplan-Meier cumulative incidence of CVD events in the 653 subjects with WCH and their cohort and age-matched normotensive control subjects, broken down by low (left panel) and high (right panel) CVD risk. After adjusting for covariates, the incidence of CVD events over a median follow-up of 10.6 years was significantly higher in the high-risk subjects with WCH as compared with the cohort- and age-matched high-risk normotensive subjects (hazard ratio [HR]: 2.06; 95% CI: 1.10 to 3.84; $p = 0.023$). In contrast, low-risk subjects with WCH and normotensive participants having <3 CVD risk factors were at similar long-term CVD risk (HR: 1.06; 95% CI: 0.66 to 1.72; $p = 0.80$). The unadjusted HR tended to be higher in the high-risk group as compared with the low-risk group ($p = 0.074$), whereas the adjusted HR was not significantly different between the 2 groups ($p = 0.14$). Sensitivity analyses, in which we excluded 1 cohort at a time, produced consistent results (Online Table 4).

SUBGROUP ANALYSIS OF WCH BY AGE. Online Table 5 shows baseline characteristics of 311 younger (<60 years of age) subjects with WCH and their age-matched normotensive control subjects, subdivided into low-risk ($n = 244$) and high-risk ($n = 67$) groups, respectively. In this younger subgroup (47.6% of total WCH), the incidence of new CVD events over a median of 10.6 years follow-up was low (12 events, representing 17% of the CVD events in the total WCH population), without any tendency for increased risk as compared with their cohort- and age-matched normotensive control subjects, either in the low-risk group ($p = 0.32$) or in the high-risk group ($p = 0.41$).

Table 3 shows the baseline characteristics of the 342 older subjects with WCH (≥60 years of age and representing 52.4% of total WCH) and their age-matched normotensive control subjects, subdivided

FIGURE 1 Kaplan-Meier Cumulative Incidence of CVD Events in 653 Subjects With WCH and Their Cohort- and Age-Matched (Within 5 Years) Normotensive Control Subjects



The analysis is broken down according to low (**left**, n = 494) and high (**right**, n = 159) cardiovascular disease (CVD) risk. Definitions of the blood pressure cross-classifications are given in the Methods section and in the footnote to Table 1. The number of incident CVD events in the white-coat hypertension (WCH) and normotensive (NT) groups totaled 37 and 32 in the low-risk group and 33 and 16 in the high-risk group, respectively. The **numbers below the horizontal axes** are the number of subjects experiencing a CVD event and the number of subjects still in follow-up at 4-year intervals. HR is the unadjusted hazard ratio estimating the relative event rate in subjects with WCH versus the normotensive participants. The HR tended to be higher in the WCH group compared with the normotensive group (p for interaction = 0.074).

into low-risk (n = 250) and high-risk (n = 92) groups, respectively. The older high-risk WCH subjects represented 14.1% of the total WCH population. The high-normal daytime ABPM category (systolic BP of 125 to 134 mm Hg and diastolic BP of 80 to 84 mm Hg) occurred in 45.6% of older high-risk normotensive subjects versus 80.4% of the high-risk WCH population ($p < 0.0001$). However, all ABPM values were below hypertensive BP levels, as defined by guidelines for both subjects with WCH and their age-matched normotensive comparators.

During follow-up, 58 of the 342 older participants with WCH experienced a new CVD event, corresponding to 82.8% of the new CVD events in the total WCH population. A total of 41 new CVD events occurred in the 342 cohort- and age-matched normotensive control subjects.

Figure 2 shows the Kaplan-Meier cumulative incidence of new CVD events in the older WCH and normotensive subjects, broken down by low (left panel) and high (right panel) CVD risk. After adjusting for covariates, older low-risk subjects with WCH (n = 250) and their cohort- and age-matched low-risk normotensive control subjects were at similar long-term CVD risk (HR: 0.88; 95% CI: 0.51 to 1.53; p = 0.66). In contrast, the incidence of CVD events after a median follow-up of 10.6 years was significantly higher in the 92 older high-risk subjects with WCH (30 new CVD events) as compared with their high-risk and age-matched normotensive comparators (12 new CVD events; HR: 2.19; 95% CI: 1.09 to 4.37; p = 0.027). Both the unadjusted (p = 0.016) and adjusted (p = 0.044) HRs were significantly higher in the high-risk group as compared with the low-risk group.

DISCUSSION

The novel findings of the present study can be summarized as follows:

1. After accounting for age, the size of the WCE was not influenced by the severity of CVD risk or the presence of past CVD events.
2. There was no significant difference in the number of new CVD events during a median follow-up of 10.6 years between all low-risk subjects with WCH and their age-matched low-risk normotensive control subjects, as well as high-risk subjects <60 years of age and their high-risk normotensive

TABLE 3 Baseline Characteristics of 342 Older (Age ≥60 Years) Subjects With WCH and 342 Cohort- and Age-Matched Normotensive Subjects

	Low Risk		High Risk	
	Normotension (n = 250)	WCH (n = 250)	Normotension (n = 92)	WCH (n = 92)
Women	118 (47.2)	112 (44.8)	15 (16.3)	9 (9.8)
Ethnicity (Caucasian)	208 (83.2)	208 (83.2)	75 (81.5)	75 (81.5)
Current smoking	43 (17.2)	18 (7.2)*	47 (51.1)	42 (45.6)
Drinking alcohol	110 (51.4)	112 (52.6)	43 (55.8)	49 (67.1)
Diabetes	0 (0.0)	0 (0.0)	23 (25.0)	28 (30.4)
Body mass index ≥30 kg/m^2	10 (4.0)	12 (4.8)	11 (12.0)	21 (22.8)
Total cholesterol >4.9 mmol/l	188 (75.2)	205 (82.0)	80 (87.0)	82 (89.1)
History of CVD	0 (0.0)	0 (0.0)	29 (31.5)	28 (30.4)
ESH/ESC risk group				
No risk factors	112 (44.8)	114 (45.6)	0 (0.0)	0 (0.0)
1–2 risk factors	138 (55.2)	136 (54.4)	0 (0.0)	0 (0.0)
≥3 risk factors	0 (0.0)	0 (0.0)	42 (45.6)	38 (41.3)
Diabetes	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
History of CVD events or diabetes with risk factor(s)	0 (0.0)	0 (0.0)	49 (53.3)	54 (58.7)
Mean characteristics				
Age, yrs	68.2 ± 5.1	68.2 ± 5.1	68.7 ± 4.6	68.7 ± 4.6
Body mass index, kg/m^2	24.6 ± 3.5	25.1 ± 3.4	25.6 ± 3.9	26.7 ± 3.5†
Total serum cholesterol, mmol/l	5.78 ± 1.15	6.10 ± 1.25‡	5.88 ± 1.04	5.93 ± 0.98
Blood pressure, mm Hg				
Conventional systolic	123.0 ± 10.8	149.3 ± 10.8*	124.0 ± 9.5	152.6 ± 12.7*
Conventional diastolic	74.2 ± 7.6	83.9 ± 9.1*	74.3 ± 7.8	84.7 ± 9.3*
24-h systolic	116.8 ± 7.5	122.3 ± 7.5*	118.2 ± 7.7	123.1 ± 6.4*
24-h diastolic	68.9 ± 5.3	70.9 ± 5.7*	69.9 ± 6.0	71.2 ± 6.0
Daytime systolic	121.9 ± 7.9	126.1 ± 6.8*	122.3 ± 8.0	127.5 ± 5.24*
Daytime diastolic	72.7 ± 5.5	74.0 ± 6.1†	73.3 ± 6.3	74.9 ± 6.3
WCE systolic	1.1 ± 11.6	23.3 ± 11.8*	1.7 ± 9.8	25.1 ± 13.2*
WCE diastolic	1.4 ± 7.9	9.9 ± 8.4*	1.0 ± 7.0	9.8 ± 8.0*
Daytime ambulatory BP category				
Optimal: <115/<75 mm Hg	44 (17.6)	16 (6.4)	16 (17.4)	2 (2.2)
Normal: 115–124/75–79 mm Hg	100 (40.0)	68 (27.2) *	34 (37.0)	16 (17.4) *
High-normal: 125–134/80–84 mm Hg	106 (42.4)	166 (66.4)	42 (45.6)	74 (80.4)
Incidence of CVD events				
n (%)	29 (11.6)	28 (11.2)	12 (13.0)	30 (32.6)‡
Rate (SE)§	11.3 (3.0)	11.3 (3.0)	13.3 (3.8)	36.0 (6.4)‡

Values are n (%) or arithmetic mean ± SD. Alcohol intake was missing in 34 high-risk subjects and 73 low-risk subjects. Significance of the difference between normotensive subjects and participants with WCH: *p < 0.001; †p < 0.05; and ‡p < 0.01. §Rate (SE) is expressed as number of events/1,000 subject-years.

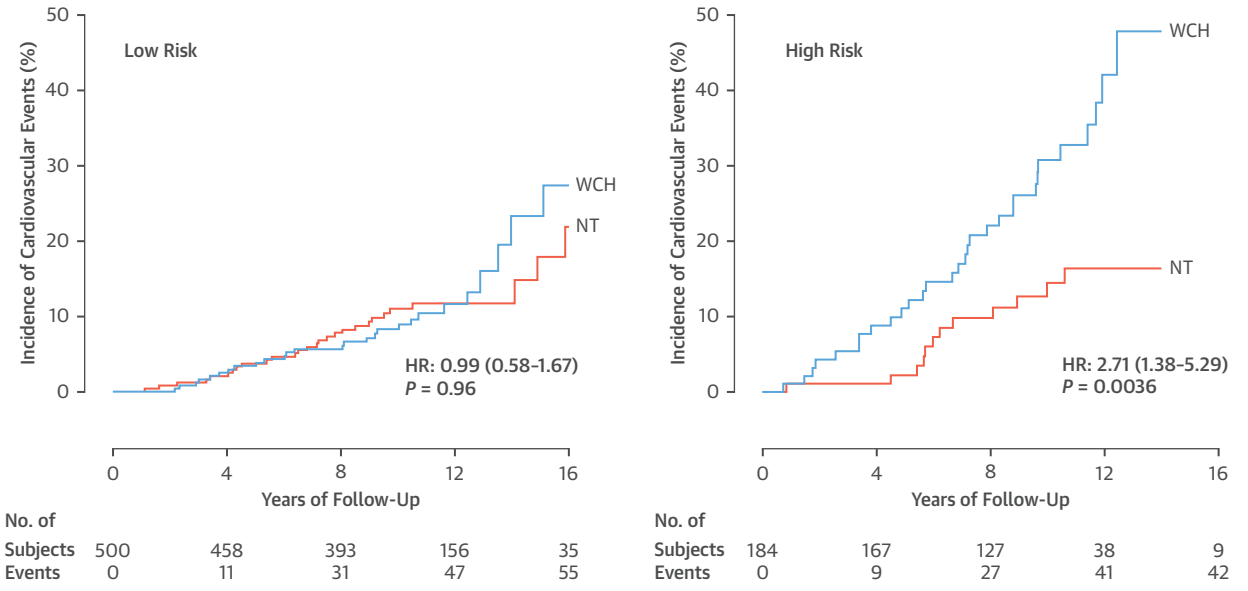
Abbreviations as in Table 1.

control subjects; together, they made up 86% of the entire WCH population.

3. In contrast, there were significantly more new CVD events in the high-risk, older WCH subjects (≥60 years of age with mean age of 67.8 years) than in their high-risk, cohort- and age-matched normotensive control subjects. This potentially involved a maximum of 14% of the entire WCH population, with new CVD events occurring at a median age of 75.4 years. In actuality, there were 70 new CVD events in persons with WCH versus 48 in the age-matched normotensive control subjects during the 10.6-year follow-up; that is, there was an excess of 22 new CVD events in elderly persons with WCH, representing 3.4% of the 653-person WCH population in this IDACO study.

NEUROGENIC FACTORS THAT REGULATE THE WCE. Mancia et al. (13) first described the WCE in detail in 1983 with a technique that used cuff versus intra-arterial bedside measurements of BP. The pathogenesis of the WCE is thought to be an alerting reaction working through reflex activation of the sympathetic nervous system (14). Our study showed that the size of the WCE is independent of CVD risk. This finding supports Verdecchia et al. (7), who found

FIGURE 2 Kaplan-Meier Cumulative Incidence of Cardiovascular Events in 342 Older (Age ≥60 Years) Subjects With WCH and Their Cohort- and Age-Matched (Within 5 Years) Normotensive Control Subjects

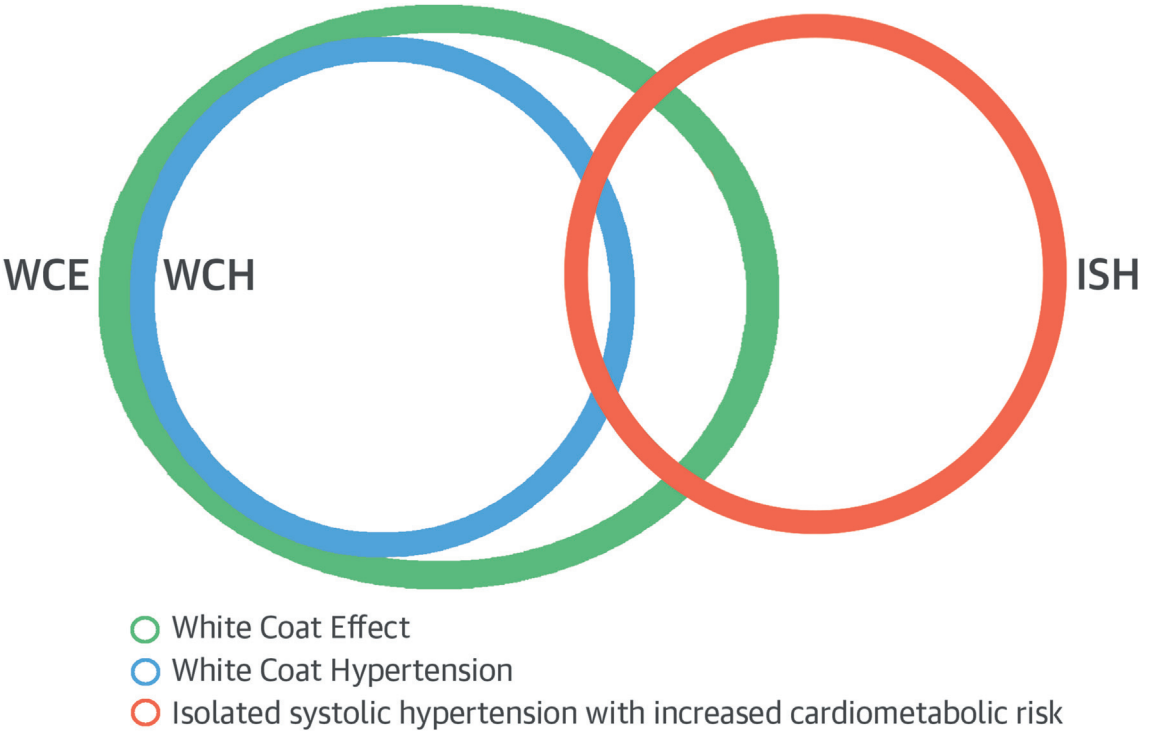


The analysis is broken down by low (**left**, n = 250) and high (**right**, n = 92) CVD risk. Definitions of the blood pressure cross-classifications are given in the Methods section and in the footnote to **Table 1**. The characteristics of the subjects considered in this figure are provided in Online Table 5. The number of new CVD events in the WCH and normotensive groups totaled 28 and 29 in the low-risk group and 30 and 12 in the high-risk group, respectively. The **numbers below the horizontal axes** are the number of subjects experiencing a new CVD event and the number of subjects still in follow-up at 4-year intervals. HR is the unadjusted hazard ratio estimating the relative event rate in subjects with WCH versus the normotensive participants. The HR was higher in the WCH group compared with the normotensive group (p for interaction = 0.016). Abbreviations as in **Figure 1**.

no association between the size of WCE and the presence of left ventricular hypertrophy. Because the WCE increases with aging and stiffening of conduit arteries, this suggests that a decrease in baroreceptor sensitivity plays a major role in this phenomenon (15). Thus, psychic stress produces wider swings in BP in older versus younger subjects with stimulation of the sympathetic nervous system and, hence, larger increases in the WCE. Indeed, the WCE in older, treatment-naïve persons with isolated systolic hypertension in a prior IDACO study exceeded daytime ABPM by a mean of 20 mm Hg systolic and/or 10 mm Hg diastolic (16).

THE RELATIONSHIP BETWEEN CVD RISK AND WCH. There are 3 possible relationships between WCH and future CVD events. First, if there was no relationship between WCH and future CVD events, the number of future CVD events would be identical in both WCH subjects and in their age-matched normotensive control subjects; this pattern was not observed in the present analysis. Second, if there were an intrinsic relationship between the presence of WCH and the development of new CVD events, one would expect high rates of new CVD events in WCH, in excess of what was noted in their age-matched normotensive control subjects; furthermore, the new CVD events would be spread over a wider age range during the 10.6-year follow-up. This pattern was not observed in the current study. Third, if there were an extrinsic relationship, one would observe a unique pattern of new CVD events occurring in WCH as compared to their age-matched normotensive control subjects. Indeed, we noted that the new CVD events, in excess of those that occurred in age-matched control subjects, were confined entirely to a small number of elderly persons with WCH and a high cardiometabolic burden. Importantly, this was an excess of 22 new CVD events in subjects with WCH (3.4% of the entire WCH population) versus new CVD events occurring in the age-matched normotensive control subjects (70 new events vs. 48 new events, respectively), resulting in an HR favoring new CVD events in WCH (HR: 2.19; 95% CI: 1.09 to 4.37; p = 0.027) after full adjustment. In contrast, the number of new CVD events in 96.6% of persons with WCH matched those that occurred in their normotensive control subjects

CENTRAL ILLUSTRATION **Relationship Between WCH and Cardiometabolic Risk, as Shown by a Venn Diagram**



Franklin, S.S. et al. J Am Coll Cardiol. 2016;68(19):2033–43.

There is an extrinsic relationship between WCH and ISH: 1) both may share an increase in WCE; 2) both are present predominantly in the elderly; and 3) both may show a small overlap in diagnosis by ambulatory blood pressure monitoring. ISH = isolated systolic hypertension; WCE = white-coat effect; WCH = white-coat hypertension.

during the 10.6-year follow-up of this study. These findings support an extrinsic relationship between WCH and increased future CVD events, but the cause is undetermined.

Therefore, we put forward the following hypothesis to explain these findings. In addition to the association of advanced age with increased magnitude of WCE and increased frequency of WCH, as noted in the present study, there is an increased prevalence of new-onset isolated systolic hypertension occurring in older subjects with high cardiometabolic burden (16). Lending support to that contention, Vasan et al. (17), using the Framingham Heart Study database, showed a 49% progression from high-normal BP to hypertension over a duration of 4 years in persons 65 years of age and older who were obese and continued to gain weight. We postulate that a few of these persons with isolated systolic hypertension are inadvertently diagnosed as having WCH by ABPM (**Central Illustration**). The isolated systolic hypertension hypothesis is consistent with demographic factors, but conclusive proof of concept has yet to be established. Not surprisingly, a single ABPM may not always detect systolic hypertension in an elderly person who otherwise would be diagnosed with WCH in the presence of increased WCE. Indeed, multiple BP readings are necessary to accurately stage CVD risk because small changes in BP from visit to visit can shift readings back and forth between high-normal systolic BP (not detected by ABPM) and systolic hypertension (detected by ABPM and frequently by home BP monitoring). Therefore, the accurate detection of systolic hypertension depends greatly on the frequency and method of BP measurement, as has been emphasized by Mancia et al. (18). Importantly, in support of the current study, there are 4 large observational cohort studies of long duration and 2 extensive meta-analyses that showed minimal or no increased CVD risk in untreated subjects with WCH compared with their normotensive comparators (16,19–23).

ERRORS IN THE DIAGNOSIS OF WCH. ABPM is the gold standard for defining WCH risk; home BP monitoring and ABPM are not interchangeable methods for detecting WCH risk. Indeed, home BP monitoring in the presence of isolated nocturnal hypertension would falsely diagnose WCH in the presence of high WCE, whereas the true diagnosis is sustained hypertension. Furthermore, the conventional office BP measurement cannot detect either WCH or masked hypertension. In a previous IDACO study of older persons with isolated systolic hypertension where the prevalence of WCH and masked hypertension were high, we showed that the exclusive use of conventional office BP measurement to diagnose hypertension would result in failure to recognize WCH and masked hypertension in over two-thirds of subjects (16). Reliance on the conventional office BP measurement could therefore result in the overtreatment of many persons with low-risk WCH and the underdiagnosis of and failure to treat patients with high-risk masked hypertension. Importantly, the use of the conventional office measurement of BP in older persons with large WCE would result in the frequent excessive treatment of elderly patients with true isolated systolic hypertension and erroneous treatment of persons with true WCH. Therefore, new treatment guidelines should emphasize the need to use ABPM, supplemented by home BP measurements, to correctly diagnose high-risk systolic hypertension and to exclude low-risk WCH. Perhaps, as recently suggested by Myers and Stergiou (24), it is time to change the nomenclature from WCH to "white-coat phenomenon" to "remove the stigma of hypertension."

STUDY STRENGTHS AND LIMITATIONS. Specifically, IDACO studies are limited to a single ABPM procedure and 2 conventional office BP readings taken at the same setting. One strength of our study favoring an extrinsic, rather than intrinsic, relationship between WCH and new CVD events was the small number of CVD events, involving only 3.4% of the entire WCH population, and which significantly separated the older high-risk WCH population from the older high-risk normotensive population. On the one hand, it is reassuring that WCH subjects had baseline normal daytime, night-time, and 24-h BP readings; furthermore, these ABPM values were similar in the low- and high-risk WCH groups. On the other hand, the absence of home BP monitoring may have failed to identify a few older persons with isolated systolic hypertension and increased WCE, and therefore, may have falsely increased the incidence of new CVD events in the majority of subjects with true WCH. Indeed, the small increase in BMI and in daytime, night-time, and 24-h ABPM in subjects with WCH versus normotensive control subjects (although all within normal limits) may have occurred because of the inadvertent inclusion of a small number of subjects with systolic hypertension who were misdiagnosed as having WCH at baseline. Another matter of concern is that we do not have information on antihypertensive drug intake after the baseline visit. As the diagnosis of hypertension is often on the basis of conventional BP, the start of antihypertensive drug treatment during follow-up in some subjects with WCH might have lowered the incidence of CVD events in the WCH group. However, it is unlikely that this would have altered the pattern of CVD events in high- versus low-risk subjects with WCH and their age-matched normotensive comparators. Finally, the risk score, as defined in the current paper, includes only a subset of the risk factors suggested by the ESC/ESH (10). This might have diluted the true differences between subjects with low and high cardiometabolic burden.

CONCLUSIONS

Using the 11-country IDACO database with a median follow-up of 10.6 years, our analysis showed that: 1) after accounting for age, the size of the WCE was not influenced by the severity of CVD risk or the presence of past CVD events; 2) the event rate of new CVD events, after accounting for equal event rates in the WCH and the age-matched normotensive comparative group, was entirely confined to an excess of 22 new CVD events in persons thought to have WCH (3.4% of the entire WCH population) who were ≥60 years of age at baseline and had high cardiometabolic burden; and 3) we hypothesize that this represented a small number of elderly persons with isolated systolic hypertension and high WCE who were mistakenly diagnosed as having WCH on the basis of a single ABPM. Therefore, we concluded that the great majority of persons with WCH are not destined to transition to a higher-risk state when compared with their normotensive control subjects. Furthermore, a single 24-h ABPM may not distinguish a few subjects with systolic hypertension and increased WCE from those subjects with high-normal BP and increased WCE. Multiple BP readings are necessary to accurately stage CVD risk because small changes in BP from visit to visit can shift readings back and forth between high-normal BP and systolic hypertension, especially in older persons.

ACKNOWLEDGMENTS The authors thank Mrs. Renilde Wolfs and Mrs. Vera De Leebeeck (Studies Coordinating Centre, Leuven, Belgium) for their expert clerical assistance.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Metabolic abnormalities in a small proportion of patients incorrectly thought to have WCH, rather than those with true WCH, largely account for the risk of adverse cardiovascular events attributed to WCH.

TRANSLATIONAL OUTLOOK: Further studies using carefully defined criteria for diagnosis of WCH are needed to determine its actual risk implications.

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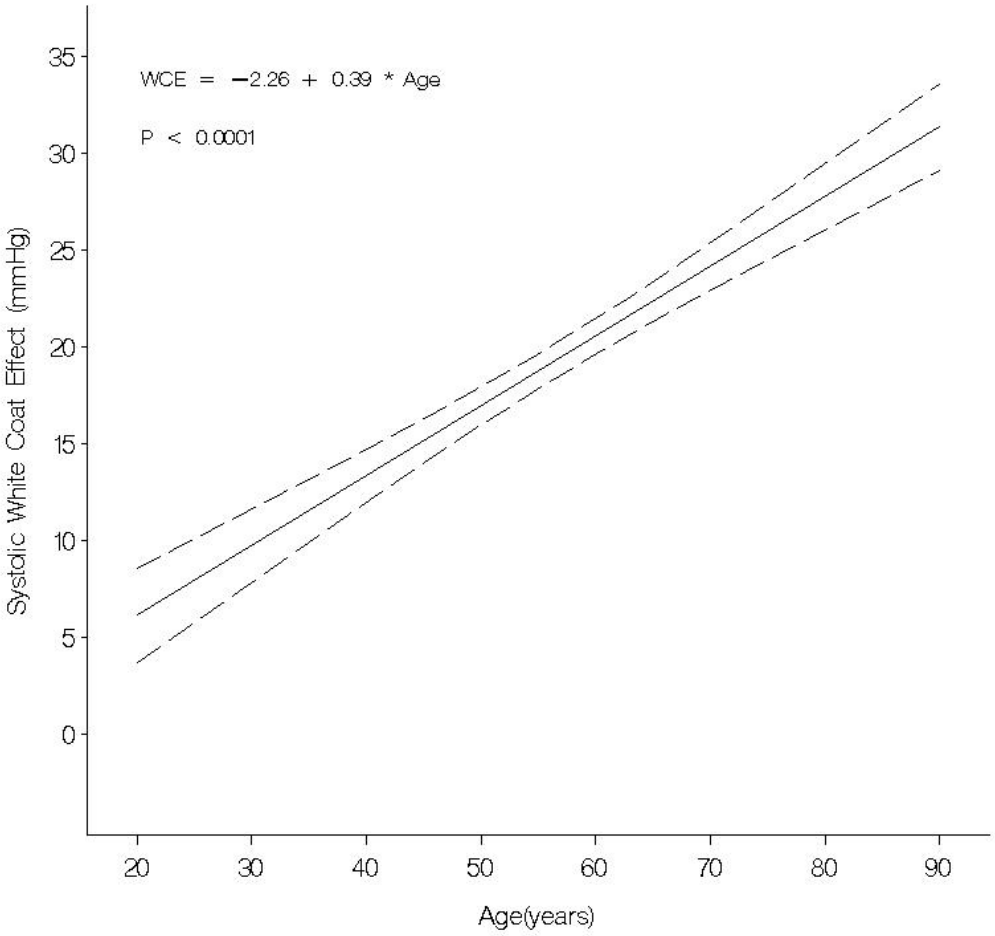
KEY WORDS ambulatory blood pressure monitoring, cardiovascular disease, epidemiology, white-coat effect

APPENDIX For supplemental tables and figures, please see the online version of this article.

Online Figure 2. Histogram of the age distribution in 653 subjects with WCH (right panel) and their cohort and age matched normotensive controls (left panel).



Online Figure 3. The association between the white coat effect in systolic blood pressure and age in 653 subjects with white coat hypertension.