

Setting Thresholds to Varying Blood Pressure Monitoring Intervals Differentially Affects Risk Estimates Associated With White-Coat and Masked Hypertension in the Population

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Abstract—Outcome-driven recommendations about time intervals during which ambulatory blood pressure should be measured to diagnose white-coat or masked hypertension are lacking. We cross-classified 8237 untreated participants (mean age, 50.7 years; 48.4% women) enrolled in 12 population studies, using $\geq 140/\geq 90$, $\geq 130/\geq 80$, $\geq 135/\geq 85$, and $\geq 120/\geq 70$ mmHg as hypertension thresholds for conventional, 24-hour, daytime, and nighttime blood pressure. White-coat hypertension was hypertension on conventional measurement with ambulatory normotension, the opposite condition being masked hypertension. Intervals used for classification of participants were daytime, nighttime, and 24 hours, first considered separately, and next combined as 24 hours plus daytime or plus nighttime, or plus both. Depending on time intervals chosen, white-coat and masked hypertension frequencies ranged from 6.3% to 12.5% and from 9.7% to 19.6%, respectively. During 91 046 person-years, 729 participants experienced a cardiovascular event. In multivariable analyses with normotension during all intervals of the day as reference, hazard ratios associated with white-coat hypertension progressively weakened considering daytime only (1.38; $P=0.033$), nighttime only (1.43; $P=0.0074$), 24 hours only (1.21; $P=0.20$), 24 hours plus daytime (1.24; $P=0.18$), 24 hours plus nighttime (1.15; $P=0.39$), and 24 hours plus daytime and nighttime (1.16; $P=0.41$). The hazard ratios comparing masked hypertension with normotension were all significant ($P<0.0001$), ranging from 1.76 to 2.03. In conclusion, identification of truly low-risk white-coat hypertension requires setting thresholds simultaneously to 24 hours, daytime, and nighttime blood pressure. Although any time interval suffices to diagnose masked hypertension, as proposed in current guidelines, full 24-hour recordings remain standard in clinical practice. (*Hypertension*. 2014;64:935-942.) • [Online Data Supplement](#)

Key Words: ambulatory blood pressure monitoring ■ cardiovascular risk ■ masked hypertension ■ population science ■ white-coat hypertension

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Ambulatory blood pressure should be offered to those with elevated conventional blood pressure.^{1,2} White-coat hypertension is a condition, characterized by an elevated blood pressure on conventional office measurement, but a normal ambulatory blood pressure outside the medical environment. Conversely, masked hypertension is a normal blood pressure on conventional measurement accompanied by an elevated blood pressure on ambulatory monitoring.

To define white-coat and masked hypertension, guidelines¹⁻⁵ and previous studies^{6,7} have applied varying thresholds during different periods of the day, which have included systolic/diastolic blood pressure thresholds of $\geq 130/\geq 80$ mmHg for the 24-hour blood pressure, $\geq 135/\geq 85$ mmHg for the daytime or awake blood pressure, and $\geq 120/\geq 70$ mmHg for the nighttime or asleep blood pressure.^{2,4,5} There is no firm recommendation on how to maximize discrimination of risk among patients with white-coat and masked hypertension by applying the aforementioned thresholds to 24-hour, daytime, or nighttime blood pressure levels or combinations of these intervals.² To address this issue, we did a participant-level meta-analysis among 8237 people recruited from 12 populations and enrolled in the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO). We determined the long-term outcome associated with white-coat hypertension and masked as defined from ambulatory blood pressure thresholds applied during varying periods of the day.

Methods

Study Population

Previous publications have described the construction of the IDACO database in detail.⁸ Studies qualified for inclusion if they involved a random population sample, if baseline information on the conventional and ambulatory blood pressures and cardiovascular 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 database⁸ currently includes 12 752 people representing 12 randomly recruited population cohorts⁹⁻¹⁸ with validated information on outcome. Exclusion criteria were as follows: (1) age <18 years (n=303), (2) conventional blood pressure unavailable (n=248), (3) nighttime blood pressure not recorded (n=1391),¹⁰ (4) being on antihypertensive drug treatment at baseline (n=2152), and (5) ambulatory blood pressure recordings not complying with predefined⁸ quality standards, including <10 daytime or <5 nighttime readings (n=421). The number of participants statistically analyzed was 8237 (Figure S1 in the online-only Data Supplement).

Cross-Classification Based on Conventional and Ambulatory Blood Pressure

Previous publications^{19,20} and the expanded Methods available in the online-only Data Supplement provide detailed information on conventional and ambulatory blood pressure measurement and on the anthropometric and biochemical measurements performed at baseline.

Conventional hypertension was a conventional blood pressure of 140 mmHg systolic or 90 mmHg diastolic or more.⁵ Ambulatory hypertension was a 24-hour level of 130 mmHg systolic or 80 mmHg diastolic or more; for the daytime blood pressure these thresholds were 135 and 85 mmHg and for the nighttime blood pressure 120 and 70 mmHg, respectively.⁵ Normotension and sustained hypertension were consistently normal or elevated levels on both conventional and ambulatory blood pressures (Figure S2). White-coat hypertension was defined as conventional hypertension in the presence of a normal ambulatory blood pressure. Masked hypertension

was defined as ambulatory hypertension in participants with a normal conventional blood pressure. When systolic or diastolic blood pressure was in a different category (normotensive versus hypertensive), we considered the participant as hypertensive. Table S1 lists the thresholds and intervals used for the cross-classification of participants. For ambulatory time intervals including nested periods (24 hours \pm daytime \pm nighttime), the interval with the highest blood pressure classification (normotensive versus hypertensive) determined the ambulatory blood pressure status.

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 previous publications.^{19,20} Outcomes were coded according to the *International Classification of Diseases (ICD)*. Fatal and nonfatal stroke (*ICD-Eighth/Ninth Revision* [8/9] 430-434 and 436, *ICD-10* I60-I64 and I67-I68) did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease (*ICD-8* 411-412, *ICD-9* 411 and 414, and *ICD-10* I20, I24-I25), sudden death (*ICD-8* 427.2 and 795, *ICD-9* 427.5 and 798, and *ICD-10* I46 and R96), nonfatal myocardial infarction (*ICD-8/9* 410 and *ICD-10* I21-I22), and coronary revascularization. Cardiac events comprised coronary end points and fatal and nonfatal heart failure (*ICD-8* 428, 427.1, 427.2, and 429; *ICD-9* 429 and *ICD-10* I50 and J81). The diagnosis of heart failure required admission to hospital in the 3 cohorts.⁹⁻¹¹ In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate. However, in all cases the event was validated against hospital files or records held by family doctors. The cardiovascular end point included all aforementioned end points plus cardiovascular mortality (*ICD-8* 390-448, *ICD-9* 390.0-459.9, and *ICD-10* I00 to I79 and R96). In all outcome analyses, we only considered the first event within each category.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute Inc, Cary, NC). We compared mean values and proportions using the standard normal *z* test for large samples or ANOVA and the χ^2 -statistic, respectively. We used McNemar-Bowker test for the pairwise comparison of proportions. After stratification for cohort and sex, we interpolated missing values of body mass index (n=8) and total serum cholesterol (n=611) from the regression slope on age. In participants with unknown smoking (n=22), drinking (n=384), history of cardiovascular disease (n=1), or diabetes mellitus (n=3), we set the design variable to the cohort- and sex-specific mean of the codes (0, 1). Statistical significance was an α -level of ≤ 0.05 on 2-sided tests.

We calculated incidence rates in each category while standardizing by the direct method for sex and age (<40, 40-59, and ≥ 60 years). We used stratified Cox models to account for the heterogeneity of baseline hazards among cohorts and adjusted for sex, age, body mass index, smoking and drinking, total cholesterol, history of cardiovascular disease, and diabetes mellitus. Unless otherwise indicated, we used normotension as the reference group (hazard ratio, 1).

Results

Baseline Characteristics

Of 8237 participants, 3986 (48.4%) were women, 2438 (29.7%) were current smokers, 455 (5.5%) had diabetes mellitus, and 650 (7.9%) had a history of cardiovascular disease. Age averaged 50.7 (SD, 15.8) years. In all participants, the conventional blood pressure averaged 128.8 (21.6) mmHg systolic and 78.6 (11.3) mmHg diastolic. The corresponding ambulatory blood pressure levels were 122.1 (13.6) and 73.1 (8.2) mmHg in 24-hour, 128.5 (14.5) and 78.3 (8.9) mmHg in daytime recordings, and 111.0 (14.5) and 64.0 (9.0) mmHg in nighttime, respectively. The median (5th-95th percentile interval) numbers of readings averaged to estimate the 24-hour,

daytime, and nighttime blood pressure were 55 (35–82), 28 (15–42), and 11 (6–13), respectively.

Table 1 lists the baseline characteristics by 4 categories according to the cross-classification of conventional and 24-hour ambulatory blood pressure. The differences across the 4 categories were significant for all variables listed ($P < 0.0001$).

Prevalence of White-Coat, Masked, and Sustained Hypertension

Based on the cross-classification between conventional and 24-hour ambulatory blood pressure (Table 1), 4988 participants (60.6%) were normotensive and 881 (10.7%), 800 (9.7%), and 1568 (19.0%) had white-coat, masked, and sustained hypertension, respectively. Using different time intervals during which ambulatory blood pressure thresholds were applied substantially affected the estimates of prevalence (Table 2). They ranged from 50.7% to 60.6% for normotension, from 6.3% to 12.5% for white-coat hypertension, from 9.7% to 19.6% for masked hypertension, and from 17.3% to 23.5% for sustained hypertension. The prevalence of normotension and white-coat hypertension was lowest and the prevalence of masked and sustained hypertension was highest

based on thresholds set simultaneously to the 24-hour and the daytime and nighttime blood pressures (Table 2). Table 3 summarizes reclassification rates of participants with white-coat and masked hypertension from the commonly used definitions based on daytime, nighttime, or 24-hour ambulatory blood pressure to one of the other definitions.

Incidence of Events

In the overall study population, median follow-up was 11.1 years (5th–95th percentile interval, 2.5–18.2 years). During 91 046 person-years of follow-up, 906 participants died (10.0 per 1000 person-years) and 729 participants experienced a fatal or nonfatal cardiovascular event (8.2 per 1000 person-years). Considering cause-specific first cardiovascular events, the incidence of cardiac events and stroke amounted to 473 and 242, respectively. More details on the incidence of end points are available in the Results in the online-only Data Supplement.

Risk of a Cardiovascular Event Associated With White-Coat Hypertension

Table 4 provides risk estimates by varying time intervals during which the ambulatory blood pressure thresholds were

Table 1. Baseline Characteristics of 8237 Untreated Participants Cross-Classified by Conventional and 24-Hour Ambulatory Blood Pressure

Characteristics	Normotension	White-Coat Hypertension	Masked Hypertension	Sustained Hypertension
No. of characteristics (%)	4988	881	800	1568
Women	2767 (55.5)	404 (45.9)*	293 (36.6)*	522 (33.3)
Current smoking	1544 (31.0)	168 (19.2)*	298 (37.3)*	428 (27.4)*
Drinking alcohol	2304 (47.5)	381 (46.6)	458 (60.3)*	923 (64.6)†
Diabetes mellitus	182 (3.6)	67 (7.6)*	57 (7.1)	149 (9.5)
Previous cardiovascular diseases	237 (4.8)	126 (14.3)*	54 (6.8)*	233 (14.9)*
Ethnicity (white)	4171 (83.6)	662 (75.3)*	641 (80.1)†	1294 (82.6)
Mean characteristic (SD)				
Age, y	45.7 (15.1)	59.3 (13.8)*	52.8 (14.0)*	60.8 (12.4)*
Body mass index, kg/m ²	24.3 (3.8)	26.0 (4.1)*	25.7 (4.0)	26.9 (4.4)*
Total serum cholesterol, mmol/L	5.44 (1.15)	5.80 (1.26)*	5.68 (1.18)†	5.86 (1.16)*
Blood pressure				
Conventional systolic, mm Hg	117.0 (11.3)	148.4 (15.0)*	126.2 (8.9)*	156.7 (20.9)*
Conventional diastolic, mm Hg	73.2 (7.9)	85.6 (9.4)*	78.7 (7.3)*	91.7 (10.4)*
24-h systolic, mm Hg	114.7 (7.7)	121.4 (6.1)*	132.7 (7.7)*	140.8 (12.0)*
24-h diastolic, mm Hg	69.3 (5.3)	71.7 (5.2)*	79.9 (5.8)*	82.6 (8.3)*
Daytime systolic, mm Hg	121.0 (9.1)	128.0 (8.3)*	139.1 (10.0)*	147.2 (12.9)*
Daytime diastolic, mm Hg	74.5 (6.3)	76.8 (7.0)*	84.9 (7.0)*	87.5 (9.4)*
Nighttime systolic, mm Hg	104.1 (8.8)	109.7 (8.8)*	120.9 (10.7)*	128.8 (15.3)*
Nighttime diastolic, mm Hg	60.2 (6.3)	62.8 (6.3)*	70.5 (7.4)*	73.4 (9.5)*

Values are number of participants (%) or arithmetic mean (SD). Thresholds for hypertension were $\geq 140/\geq 90$ and $\geq 130/\geq 80$ mm Hg on conventional and 24-hour ambulatory measurement, respectively. Normotension and sustained hypertension were consistently normal or elevated blood pressure on both conventional and 24-hour ambulatory measurement. White-coat hypertension had a raised conventional blood pressure and normal 24-hour blood pressure. Masked hypertension had an elevated 24-hour ambulatory blood pressure with normal conventional blood pressure. If for a type of measurement, systolic and diastolic blood pressures were in a different category, participants were classified as hypertensive. Smoking, drinking, diabetes mellitus, history of cardiovascular disease, body mass index, and cholesterol were unavailable in 22, 384, 3, 1, 8, and 611 participants, respectively.

Significance of the difference with the left adjacent column: * $P < 0.001$ and † $P < 0.05$.

Table 2. Prevalence of Blood Pressure Categories According to Intervals of Ambulatory Monitoring

Intervals Used to Categorize the Ambulatory Blood Pressure	White-coat Hypertension		Masked Hypertension	
	Normotension	Hypertension	Normotension	Hypertension
Daytime only	4683 (56.9)	747 (9.1)	1105 (13.4)	1702 (20.7)
Nighttime only	4806 (58.3)	1027 (12.5)	982 (11.9)	1422 (17.3)
24 h only	4988 (60.6)	881 (10.7)	800 (9.7)	1568 (19.0)
24 h plus daytime	4551 (55.3)	642 (7.8)	1237 (15.0)	1807 (21.9)
24 h plus nighttime	4572 (55.5)	724 (8.8)	1216 (14.8)	1725 (20.9)
24 h plus daytime and nighttime	4176 (50.7)	515 (6.3)	1612 (19.6)	1934 (23.5)

Values are number of participants (%). Normotension and sustained hypertension had consistently normal or elevated blood pressure levels on both conventional and ambulatory measurement. White-coat hypertension was defined as conventional hypertension in the presence of a normal ambulatory blood pressure. Masked hypertension was defined as ambulatory hypertension in participants with a normal conventional blood pressure. When systolic or diastolic blood pressure was in a different category (normotensive vs hypertensive), participant were classified as hypertensive. For ambulatory time intervals including nested periods (24 hours±daytime±nighttime), the interval with the highest blood pressure classification (normotensive vs hypertensive) determined the ambulatory blood pressure status.

applied. Although accounting for cohort, sex, age, body mass index, smoking, drinking, total serum cholesterol, history of cardiovascular disease, and diabetes mellitus (Table 4), white-coat hypertension based on daytime blood pressure compared with daytime normotension as well as that based on nighttime blood pressure compared with nighttime normotension carried significantly elevated risks of 30% ($P\leq 0.048$). Defining white-coat hypertension based on the 24-hour blood pressure with or without accounting for the daytime or nighttime blood pressure or both weakened the risk compared with normotension during the same periods to a nonsignificant level ranging from 27% ($P=0.097$) for 24-hour plus daytime blood pressure to 9% ($P=0.55$) for 24-hour plus nighttime blood pressure. Irrespective of the ambulatory blood pressure time intervals used to cross-classify participants, the linear trend in the hazard ratios from normotension over white-coat and masked

hypertension to sustained hypertension was consistently significant ($P<0.0001$).

In Table 4, the normotensive reference group differed according to the time intervals considered. In a further step of the analysis, we applied the most stringent definition of normotension as unique reference (Figure 1). This definition required that the conventional blood pressure was normal and that the 24-hour, daytime, and nighttime ambulatory blood pressures were within normal limits. The hazard ratios for white-coat hypertension versus normotension weakened from 1.38 for daytime only to 1.16 for 24 hours plus daytime and nighttime. Conversely, applying the most stringent definition of hypertension (Figure 2) showed that the risk of white-coat hypertension was consistently lower than that of sustained hypertension ($P<0.0001$) with hazard ratios decreasing from 0.57 for daytime to 0.45 for 24 hours plus daytime and nighttime.

Risk of a Cardiovascular Event Associated With Masked Hypertension

In multivariable-adjusted analyses (Table 4), the risk associated with masked hypertension compared with normotension was always highly significant ($P\leq 0.0001$) with estimates of excess risk ranging from 61% to 81%. Applying the most stringent definition of normotension (Figure 1) confirmed that the hazard ratios comparing masked hypertension with normotension were all significant ($P<0.0001$), between 1.76 and 2.03. Conversely, applying the most stringent definition of hypertension (Figure 2) showed that the risk of masked hypertension was lower than that of sustained hypertension ($P\leq 0.0074$). The hazard ratios were essentially similar, from 0.61 to 0.70.

Risk of Other End Points Associated With White-Coat and Masked Hypertension

Results for total and cardiovascular mortality, fatal and non-fatal cardiac events, and stroke—equivalent to those given for the composite cardiovascular end point in Table 4—are provided in Table S2. In analyses with normotension as reference and adjusted as before, white-coat hypertension did not confer a formally significantly elevated risk ($P\geq 0.051$) except for the risk of stroke based on a nighttime-derived definition of white-coat hypertension ($P=0.0065$).

Table 3. Reclassification of White-Coat and Masked Hypertensive Participants

Time Intervals Used for Reclassification	White-Coat Hypertension			Masked Hypertension		
	Original Intervals	Maintaining White-Coat Hypertension	Reclassified to Sustained Hypertension	Original Intervals	Maintaining Masked Hypertension	Reclassified to Normotension
From daytime to 24 h	747	642 (85.9)	105 (14.1)	1105	668 (60.5)	437 (39.5)
From nighttime to 24 h	1027	724 (70.5)	303 (29.5)	982	566 (57.6)	416 (42.4)
From daytime to 24 h plus daytime and nighttime	747	515 (68.9)	232 (31.1)	1105	1105 (100)	0
From nighttime to 24 h plus daytime and nighttime	1027	515 (50.1)	512 (49.9)	982	982 (100)	0
From 24 h to 24 h plus daytime and nighttime	881	515 (58.5)	366 (41.5)	800	800 (100)	0

Values are number of participants (reclassification rates, %) of white-coat and masked hypertensive participants from the commonly used definitions based on daytime, nighttime, or 24-hour ambulatory blood pressure to one of the other definitions. The McNemar–Bowker test for symmetry along the diagonal of the matrix was significant for all rows ($P<0.0001$).

Table 4. Risk of Cardiovascular End Point by Intervals of Ambulatory Monitoring

Blood Pressure Cross-Classification	E/R, n	Rate (SE)	Hazard Ratio (95% CI)	P Value
Daytime				
Normotension	203/4683	6.0 (0.4)	1.00	...
White-coat hypertension	92/747	9.7 (1.2)	1.30 (1.00–1.69)	0.048
Masked hypertension	105/1105	8.8 (0.9)	1.61 (1.27–2.05)	0.0001
Sustained hypertension	329/1702	13.7 (0.8)	2.14 (1.76–2.60)	<0.0001
Nighttime				
Normotension	209/4806	5.9 (0.4)	1.00	...
White-coat hypertension	121/1027	8.7 (0.9)	1.30 (1.03–1.64)	0.031
Masked hypertension	99/982	9.6 (1.0)	1.71 (1.34–2.18)	<0.0001
Sustained hypertension	300/1422	15.4 (0.9)	2.40 (1.97–2.93)	<0.0001
24 h				
Normotension	219/4988	5.9 (0.4)	1.00	...
White-coat hypertension	98/881	8.3 (1.0)	1.20 (0.93–1.54)	0.16
Masked hypertension	89/800	10.1 (1.1)	1.81 (1.41–2.32)	<0.0001
Sustained hypertension	323/1568	15.0 (0.9)	2.31 (1.91–2.80)	<0.0001
24 h plus daytime				
Normotension	187/4551	5.7 (0.4)	1.00	...
White-coat hypertension	74/642	9.0 (1.2)	1.27 (0.96–1.69)	0.097
Masked hypertension	121/1237	9.1 (0.8)	1.72 (1.36–2.17)	<0.0001
Sustained hypertension	347/1807	13.7 (0.8)	2.23 (1.83–2.72)	<0.0001
24 h plus nighttime				
Normotension	189/4572	5.7 (0.4)	1.00	...
White-coat hypertension	70/724	7.3 (1.1)	1.09 (0.82–1.45)	0.55
Masked hypertension	119/1216	9.2 (0.9)	1.67 (1.32–2.11)	<0.0001
Sustained hypertension	351/1725	14.8 (0.8)	2.35 (1.93–2.87)	<0.0001
24 h plus daytime and nighttime				
Normotension	159/4176	5.5 (0.5)	1.00	...
White-coat hypertension	50/515	7.7 (1.3)	1.13 (0.81–1.57)	0.47
Masked hypertension	149/1612	8.8 (0.7)	1.70 (1.35–2.14)	<0.0001
Sustained hypertension	371/1934	13.8 (0.8)	2.34 (1.90–2.88)	<0.0001

Definition of the blood pressure cross-classifications is given in the Methods and in the footnote to Table 2. Rates (SE) of events per 1000 person-year were standardized by the direct method for sex and age. Hazard ratios (95% CI) express the risk compared with normotension and were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, history of cardiovascular disease, and cohort. CI indicates confidence interval; and E/R, events/participants at risk.

Masked hypertension was a significant predictor ($P \leq 0.023$) of all end points with the exception of all-cause mortality if the diagnosis was derived from the daytime blood pressure, 24-hour blood pressure, or 24-hour plus daytime blood pressure ($P \geq 0.059$).

Discussion

Current guidelines for ambulatory blood pressure monitoring or for the management of hypertension do not provide outcome-driven evidence for defining the time windows during which the ambulatory blood pressure should be measured to define white-coat and masked hypertension in an accurate manner. Depending on the definition, frequencies

of white-coat and masked hypertension ranged from 6.3% to 12.5% and from 9.7% to 19.6%, respectively. Furthermore, the risk associated with white-coat hypertension decreased when a more stringent definition of ambulatory normotension was used. Finally, ambulatory hypertension during any time interval predicted an ≈ 2 -fold higher cardiovascular risk in patients with masked hypertension.

During the past decade, European guidelines^{5,21,22} have proposed changing or twin thresholds for ambulatory hypertension without providing any solid justification in terms of outcome data. The 2003 guideline only recommended a threshold for the 24-hour ambulatory blood pressure of $\geq 125/\geq 80$ mmHg.²¹ The 2007 guideline proposed as thresholds for the 24-hour, daytime, and nighttime blood pressure levels of ≥ 125 to $130/\geq 80$, ≥ 130 to $135/\geq 85$, and $\geq 120/\geq 70$ mmHg, respectively.²² The 2013 guideline⁵ removed the ambiguity in the thresholds for the 24-hour and daytime blood pressure, recommending $\geq 130/\geq 80$ and $\geq 135/\geq 85$ mmHg, respectively, whereas keeping the nighttime threshold at $\geq 120/\geq 70$ mmHg. In a 2007 analysis of the IDACO database,⁶ we determined thresholds for the ambulatory blood pressure, which yielded 10-year cardiovascular risks similar to those associated with optimal (120/80 mmHg), normal (130/85 mmHg), and high (140/90 mmHg) blood pressure on conventional measurement. After rounding, approximate thresholds for an optimal ambulatory blood pressure amounted to 115/75 mmHg for 24 hours, 120/80 mmHg for daytime, and 100/65 mmHg for nighttime. Rounded thresholds for a normal ambulatory blood pressure were 125/75, 130/85, and 110/70 mmHg, respectively, and those for ambulatory hypertension were 130/80, 140/85, and 120/70 mmHg.

Whether white-coat hypertension substantially elevates cardiovascular risk continues to divide expert opinion. In a meta-analysis of summary statistics from 4 prospective cohorts, the pooled hazard ratio for stroke associated with white-coat hypertension defined by a daytime blood pressure threshold of 130/80 mmHg became comparable with that in ambulatory hypertension group by the ninth year of follow-up.²³ However, the median follow-up of the 4 cohorts was only 5.4 years, and the pooled hazard ratio was not adjusted.²³ The risk in white-coat hypertension was not significantly different from that in normotension when multivariable-adjusted models were applied.^{12,24,25} In the meta-analysis by Pierdomenico and Cuccurullo,²⁵ 5 of the 7 eligible studies applied a daytime blood pressure threshold of 135/85 mmHg, whereas 2 other studies either applied a daytime threshold ranging from 131 to 136 mmHg²⁶ or a 24-hour blood pressure cut off of 130/80 mmHg.²⁷ In a previous IDACO publication,²⁸ we included both treated and untreated participants. In this analysis, we classified treated people according to the achieved ambulatory blood pressure.²⁸ Compared with normotension, the risk of all cardiovascular and cause-specific cardiovascular complications was not increased, irrespective of whether we used 130/80 or 135/85 mmHg as cutoff threshold for the daytime blood pressure ($0.63 \geq P \geq 0.09$).²⁸ Subsequently, Franklin et al,²⁴ using the IDACO database, reported that in treated subjects with isolated systolic hypertension, the cardiovascular risk was similar in elevated conventional and normal daytime systolic blood pressure as compared with those with normal

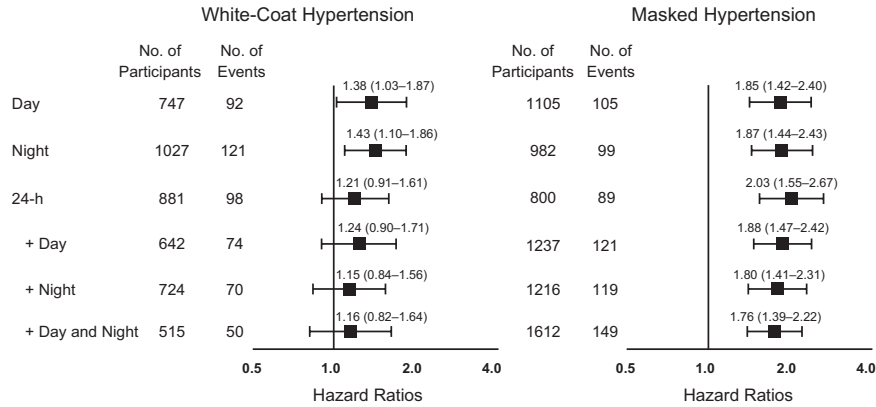


Figure 1. Risk of a cardiovascular end point associated with white-coat and masked hypertension vs stringently defined normotension defined by various intervals of ambulatory monitoring. Definition of the blood pressure cross-classifications is given in the Methods and in the footnote to Table 2. In this analysis, we applied the most stringent definition of normotension as unique reference in which the conventional blood pressure was normal and that the ambulatory blood pressure was within normal limits for 24 hours plus daytime and nighttime. Hazard ratios express the risk compared with normotension and were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, history of cardiovascular disease, and cohort. Horizontal bars denote the 95% confidence interval of the hazard ratios.

conventional and normal daytime blood pressure ($P=0.57$). However, both treated patients with isolated systolic hypertension and white-coat hypertension and treated participants with normal blood pressure had an ≈ 2 -fold increased cardiovascular risk when compared with untreated normotensive people.²⁴ Summarizing the evidence of previous studies,²⁶ it is clear that the long-term white-coat hypertension carries an increased risk and that the prognostic meaning of white-coat hypertension differs among treated and untreated subjects. What our current study adds to the knowledge on white-coat hypertension²⁶ is that to identify the low-risk subjects among untreated people with white-coat hypertension, full 24-hour ambulatory recordings are required and the most stringent definition of ambulatory normotension, with thresholds applied to the whole ambulatory recording including daytime and nighttime, has to be applied. Although in our study the risk of white-coat hypertension, as defined using the most stringent definition, was not significantly different from the risk in

sustained normotension, we cannot definitely exclude that this definition of white-coat hypertension is not associated with increased risk. Further analyses in large population cohorts applying the same stringent definition of white-coat hypertension are needed to confirm our findings.

In contrast to white-coat hypertension,^{12,26,27,29-31} the current literature by and large supports the view that masked hypertension carries a risk only slightly lower than or equal to sustained hypertension,^{28,32} irrespective of treatment status. The Finn-Home Study Investigators³³ are in agreement with IDACO findings,²⁸ demonstrating that high-normal systolic and diastolic conventional blood pressure, older age, greater body mass index, current smoking, and diabetes mellitus are independent determinants of masked hypertension. Similarly, Franklin et al³² reported that among people not being treated for hypertension, the prevalence of masked hypertension, using a daytime ambulatory threshold of 135/85 mm Hg, was higher in diabetic than in nondiabetic participants (18.1% versus 13.8%). Moreover,

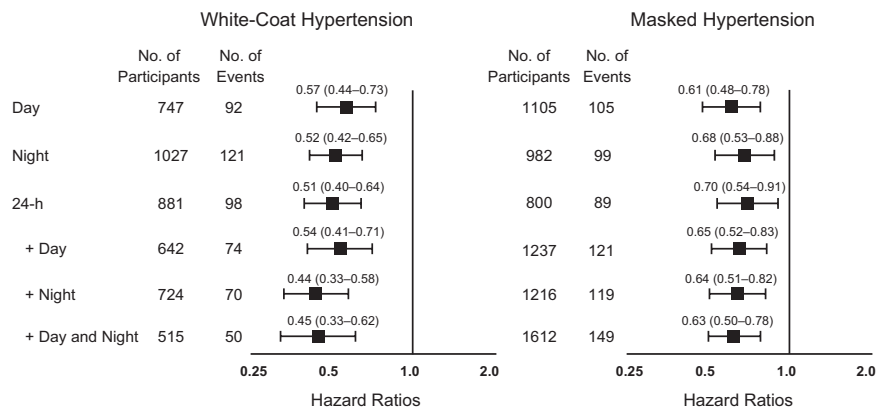


Figure 2. Risk of a cardiovascular end point associated with white-coat and masked hypertension vs stringently defined hypertension defined by various intervals of ambulatory monitoring. Definition of the blood pressure cross-classifications is given in the Methods and in the footnote to Table 2. In this analysis, we applied the most stringent definition of hypertension as unique reference in which the conventional blood pressure was over the threshold and that the ambulatory blood pressure was over the thresholds for 24 hours plus daytime and nighttime. Hazard ratios express the risk compared with hypertension and were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, history of cardiovascular disease, and cohort. Horizontal bars denote the 95% confidence interval of the hazard ratios.

we previously reported that masked hypertension, as diagnosed by ambulatory³⁴ or home³⁵ blood pressure monitoring, leads to an ≈2-fold increase in the risk of cardiovascular events or stroke in people with an optimal or normal conventional blood pressure. What our current study adds to the knowledge on blood pressure is that ambulatory hypertension during any part of the day reliably identifies this high-risk condition.

Our current study must be interpreted within the context of some potential limitations. First, conventional blood pressure was the average of only 2 readings obtained at a single examination, which might not have been sufficient to remove the white-coat effect. Second, we have no information on anti-hypertensive drug treatment after the baseline visit at enrolment. Third, the current IDACO participants were recruited from 12 geographically areas with different life styles and healthcare delivery systems. Study protocols and definition of events were cohort specific. However, we accounted for these differences in methodology among cohorts by including center as stratification variable in the Cox proportional hazard models. Finally, ambulatory blood pressure monitoring was not standardized in terms of device type and intervals between readings. However, using a single SAS macro ensured that the time-weighted mean values during all periods of the day were calculated identically across cohorts.

Our current study has important clinical implications and may inform future guidelines. From a clinical point of view, our findings highlight that to identify individuals at low risk of cardiovascular complications among untreated participants with white-coat hypertension, full 24-hour ambulatory recordings are necessary with thresholds set during the whole recording period including daytime and nighttime. Conversely, to diagnose masked hypertension, ambulatory hypertension during any period of the day might be sufficient with a slight difference in the predictive accuracy. Furthermore, among 8237 untreated IDACO participants, 747 (9.1%) and 881 (10.7%) had white-coat hypertension based on the 24-hour or daytime blood pressure according to the current guidelines,^{2,5} but only 515 (6.3%) had the low-risk variant as defined in our current report.

Perspectives

To identify patients with white-coat hypertension with a cardiovascular risk similar to that of normotensive people, one needs full 24-hour ambulatory recordings with thresholds set to all recording intervals, including daytime and nighttime. The definition in current guidelines of truly low-risk white-coat hypertension is therefore not precise enough. To diagnose masked hypertension, ambulatory hypertension during any period of the day is sufficient with a slight difference in predictive accuracy. Current guidelines therefore accurately cover the definition of masked hypertension. The difference between white-coat and masked hypertension in terms of time intervals during which blood pressure must be monitored is unexpected and novel. Our findings might inform expert committees writing guidelines so that arbitrary definitions are replaced by outcome-driven standards.

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Disclosures

None.

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Novelty and Significance

What Is New?

- In 8237 untreated participants, we generated outcome-driven proposals about the time intervals during which the ambulatory blood pressure should be measured to diagnose truly low-risk white-coat hypertension and masked hypertension. White-coat hypertension was hypertension on conventional measurement with ambulatory normotension, the opposite condition being masked hypertension. Intervals used for classification of participants were daytime, nighttime, and 24 hours, first considered separately, and next combined as 24 hours plus daytime or plus nighttime or plus both.

What Is Relevant?

- To identify patients with white-coat hypertension who have a cardiovascular risk similar to that of normotensive people, one needs full 24-hour ambulatory recordings with thresholds set to all recording intervals, including daytime and nighttime.

- To diagnose masked hypertension, ambulatory hypertension during any period of the day is sufficient with only a slight increase in predictive accuracy, if the ambulatory blood pressure is consistently elevated for most of the day.

Summary

The difference between white-coat and masked hypertension in terms of time intervals during which blood pressure must be monitored was unexpected. These findings might inform guidelines so that outcome-driven standards replace arbitrary definitions and so that the management of white-coat hypertension is differentiated, based on the time interval of blood pressure monitoring used for its diagnosis.



Supplementary Material

Setting Thresholds to Varying Blood Pressure Monitoring Intervals Differentially Affects Risk Estimates Associated with White-Coat and Masked Hypertension in the Population

Short title: White-Coat vs. Masked Hypertension

Kei Asayama, Lutgarde Thijs, Yan Li, Yu-Mei Gu, Azusa Hara, Yan-Ping Liu, Zhenyu Zhang, Fang-Fei Wei, Inés Lujambio, Luis J. Mena, José Boggia, Tine W. Hansen, Kristina Björklund-Bodegård, Kyoko Nomura, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Katarzyna Stolarz-Skrzypek, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Leonella Luzardo, Kalina Kawecka-Jaszcz, Edgardo Sandoya, Jan Filipovský, Gladys E. Maestre, Jiguang Wang, Yutaka Imai, Stanley S. Franklin, Eoin O'Brien, Jan A. Staessen,
on behalf of the International Database
on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators

This Online Data Supplement has been provided by the authors to give readers additional information about the work.

Expanded Methods

Study Population

Analyzed participants were 1823 residents from Copenhagen, Denmark;¹ 851 inhabitants from Ohasama, Japan;² 1175 subjects from Noorderkempen, Belgium;³ 713 older men from Uppsala, Sweden;⁴ 1188 subjects from Montevideo, Uruguay;⁵ 299 villagers from the Jingning County, China;⁶ 930 employees of the Irish Allied Bank, Dublin, Ireland;⁷ 204 subjects from Novosibirsk, the Russian Federation;⁸ 133 from Pilsen, Czech Republic;⁹ 266 from Padova, Italy;⁹ 244 from Kraków, Poland;⁹ and 411 from Maracaibo, Venezuela.¹⁰ Participants recruited in Kraków, Novosibirsk, Padova, and Pilsen took part in the European Project on Genes in Hypertension (EPOGH).⁹

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,^{1,6,7,9} with validated auscultatory (Elquest USM-700F2) or oscillometric (Omron HEM-705CP⁵ or Dinamap 8100¹⁰) devices, using the appropriate cuff size, with participants in the sitting^{1-3,5,6,8-10} or supine⁴ position. Conventional blood pressure was the average of two consecutive readings in one occasion¹⁻⁹ except in participants from Maracaibo,¹⁰ who were characterized by a single reading.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30 minute intervals throughout the whole day,^{2,7} or at intervals ranging from 15 minutes^{1,10} to 30 minutes⁴ during daytime and from 30 minutes^{1,10} to 60 minutes at night.⁴ The devices implemented an auscultatory algorithm (SunTech Accutracker II) in Uppsala⁴ or an oscillometric technique (SpaceLabs 90202, SpaceLabs 90207, Colin ABPM 630, and Takeda TM-2421) in the other cohorts.^{1-3,5-10}

The same SAS macro processed all ambulatory recordings, which generally remained unedited. The Ohasama recordings were edited sparsely according to previously published criteria.¹¹ Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. While accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10 AM to 8 PM in people from Europe^{1,3,4,7-9} and South America,^{5,10} and from 8 AM h to 6 PM in those from Asia.^{2,6} The corresponding nighttime intervals ranged from midnight to 6 AM^{1,3-5,7-10} and from 10 PM to 4 AM.^{2,6} These fixed time intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.^{6,12}

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking habits. Body mass index was body weight in kilograms divided by height in meters squared. Biochemical measurements included serum cholesterol and blood glucose. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L, a random blood glucose concentration of at least 11.1 mmol/L,¹³ a self-reported diagnosis, or diabetes documented in practice or hospital records.

Cross-Classification Based on Systolic and Diastolic Conventional and Ambulatory Blood Pressure

Conventional systolic hypertension was a conventional systolic blood pressure of at least 140 mm Hg. Conventional diastolic hypertension was a conventional diastolic blood pressure 90 mm Hg or more. Ambulatory hypertension was a 24-h level of 130 mm Hg systolic and/or 80 mm Hg diastolic or more; for the daytime blood pressure these thresholds were 135 mm Hg and/or 85 mm Hg and for the nighttime blood pressure 120 mm Hg and/or 70 mm Hg, respectively.⁵ Normotension and sustained hypertension were consistently normal or elevated levels on both conventional and ambulatory blood pressures (Figure S2). White-coat hypertension was defined as conventional hypertension in the presence of a normal ambulatory blood pressure. Masked hypertension was defined as ambulatory hypertension in participants with a normal conventional blood pressure. When systolic or diastolic blood pressure were in a different category (normotensive vs. hypertensive), we considered the participant as hypertensive. For ambulatory time intervals including nested periods (24 hours \pm daytime \pm nighttime), the interval with the highest blood pressure classification (normotensive vs. hypertensive) determined the ambulatory blood pressure status.

Sensitivity Analysis Based on Multiple Imputation

To ascertain that the simple interpolation method used to impute missing covariates did not weaken or inflate the associations, we repeated the analyses using a Markov single-chain Monte Carlo imputation model including all the covariates entered in the Cox model.¹⁴

Supplementary Results

Incidence of Events

In the overall study population, median follow-up was 11.1 years (5th to 95th percentile interval, 2.5 to 18.2 years). Across cohorts, median follow-up ranged from 2.5 years (2.3 to 2.6) in Jingning to 17.6 years (16.4 to 18.2) in Dublin. During 91,046 person-years of follow-up, 906 participants died (10.0 per 1000 person-years) and 729 experienced a fatal or nonfatal cardiovascular event (8.2 per 1000 person-years). Mortality included 339 cardiovascular deaths. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 75 and 190, respectively. Cardiac events consisted of 213 fatal and 301 nonfatal events, including 89 fatal and 141 nonfatal cases of acute myocardial infarction, 121 deaths from ischemic heart disease, 57 sudden deaths, 34 fatal and 139 nonfatal cases of heart failure, and 71 cases of surgical or percutaneous coronary revascularization.

The sensitivity analysis based on the Markov single-chain Monte Carlo imputation model did not materially change our results (Table S3).

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Table S1. Thresholds and Intervals Used for Cross-Classification of Participants

Blood Pressure Cross-Classification	Conventional Pressure	Ambulatory Blood Pressure		
		24-h	Day	Night
Normotension				
Daytime	<140/<90	...	<135/<85	...
Nighttime	<140/<90	<120/<70
24 hours	<140/<90	<130/<80
+ Day	<140/<90	<130/<80	<135/<85	...
+ Night	<140/<90	<130/<80	...	<120/<70
+ Day + Night	<140/<90	<130/<80	<135/<85	<120/<70
White-coat hypertension				
Daytime	≥140/≥90	...	<135/<85	...
Nighttime	≥140/≥90	<120/<70
24 hours	≥140/≥90	<130/<80
+ Day	≥140/≥90	<130/<80	<135/<85	...
+ Night	≥140/≥90	<130/<80	...	<120/<70
+ Day and Night	≥140/≥90	<130/<80	<135/<85	<120/<70
Masked hypertension				
Daytime	<140/<90	...	≥135/≥85	...
Nighttime	<140/<90	≥120/≥70
24 hours	<140/<90	≥130/≥80
+ Day	<140/<90	≥130/≥80	≥135/≥85	...
+ Night	<140/<90	≥130/≥80	...	≥120/≥70
+ Day and Night	<140/<90	≥130/≥80	≥135/≥85	≥120/≥70
Sustained hypertension				
Daytime	≥140/≥90	...	≥135/≥85	...
Nighttime	≥140/≥90	≥120/≥70
24 hours	≥140/≥90	≥130/≥80
+ Day	≥140/≥90	≥130/≥80	≥135/≥85	...
+ Night	≥140/≥90	≥130/≥80	...	≥120/≥70
+ Day and Night	≥140/≥90	≥130/≥80	≥135/≥85	≥120/≥70

An ellipsis indicates that the time interval was not used in the cross-classification. Numbers are blood pressure thresholds in mm Hg. For normotension and white-coat hypertension, all blood pressure thresholds in a row should be satisfied. For masked and sustained hypertension, the criterion for the conventional blood pressure should be satisfied and the ambulatory blood pressure should be elevated during at least one interval.

Table S2. Risk of Fatal Endpoints and Cardiac and Cerebrovascular Events by Intervals of Ambulatory Monitoring (Starts)

Blood Pressure Cross-Classification	Total Mortality	Cardiovascular Mortality	Cardiac Events	Stroke
Number of endpoints	906	339	473	242
Daytime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	1.17 (0.94–1.47)	1.07 (0.72–1.59)	1.27 (0.92–1.76)	1.60 (1.00–2.58)
Masked hypertension	1.23 (0.99–1.51)	1.66 (1.15–2.39)†	1.53 (1.12–2.08)†	1.84 (1.21–2.79)†
Sustained hypertension	1.37 (1.15–1.62)‡	2.06 (1.55–2.74)‡	1.88 (1.47–2.39)‡	3.20 (2.27–4.51)‡
Nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.99 (0.81–1.22)	1.22 (0.86–1.73)	1.24 (0.93–1.65)	1.76 (1.17–2.65)†
Masked hypertension	1.29 (1.04–1.59)*	1.93 (1.34–2.76)‡	1.51 (1.10–2.06)*	1.97 (1.30–2.99)†
Sustained hypertension	1.59 (1.34–1.89)‡	2.38 (1.77–3.19)‡	2.02 (1.58–2.59)‡	3.53 (2.50–5.00)‡
24 hours				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	1.00 (0.81–1.24)	1.04 (0.71–1.52)	1.12 (0.82–1.54)	1.51 (0.98–2.35)
Masked hypertension	1.25 (0.99–1.56)	1.93 (1.32–2.81)‡	1.73 (1.26–2.38)‡	1.94 (1.26–2.98)†
Sustained hypertension	1.47 (1.24–1.74)‡	2.24 (1.69–2.97)‡	2.05 (1.61–2.60)‡	3.37 (2.41–4.71)‡

Table S2. Risk of Fatal Endpoints and Cardiac and Cerebrovascular Events by Intervals of Ambulatory Monitoring (Continues)

	Total Mortality	Cardiovascular Mortality	Cardiac Events	Stroke
24 hours plus daytime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	1.11 (0.87–1.41)	1.01 (0.65–1.55)	1.24 (0.87–1.76)	1.63 (0.99–2.67)
Masked hypertension	1.21 (0.99–1.48)	1.73 (1.22–2.47)†	1.74 (1.30–2.34)‡	1.69 (1.12–2.55)*
Sustained hypertension	1.39 (1.17–1.64)‡	2.14 (1.60–2.86)‡	2.03 (1.59–2.61)‡	3.05 (2.16–4.31)‡
24 hours plus nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.87 (0.68–1.12)	0.93 (0.60–1.45)	1.05 (0.74–1.50)	1.42 (0.86–2.33)
Masked hypertension	1.27 (1.04–1.55)*	1.99 (1.41–2.82)‡	1.55 (1.15–2.09)†	1.88 (1.25–2.82)†
Sustained hypertension	1.54 (1.30–1.82)‡	2.41 (1.79–3.24)‡	2.04 (1.59–2.61)‡	3.49 (2.46–4.95)‡
24 hours plus daytime and nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.97 (0.74–1.28)	0.86 (0.51–1.44)	1.14 (0.76–1.70)	1.49 (0.83–2.65)
Masked hypertension	1.25 (1.03–1.52)*	1.91 (1.36–2.70)‡	1.68 (1.26–2.25)‡	1.80 (1.20–2.69)†
Sustained hypertension	1.46 (1.23–1.74)‡	2.37 (1.74–3.23)‡	2.10 (1.62–2.72)‡	3.32 (2.30–4.78)‡

Definition of the blood pressure cross-classifications are given in the Methods and in the footnote to Table 2. Hazard ratios (95% confidence interval) express the risk compared to normotension and were adjusted for cohort, sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, and history of cardiovascular disease. Significance of the hazard ratios: * $P < 0.05$; † $P < 0.01$; and ‡ $P < 0.001$.

Table S3. Risk of Cardiovascular Endpoint by Intervals of Ambulatory Monitoring Applying the Markov Single-Chain Monte Carlo Imputation Method.

Blood Pressure Cross-Classification	Number E / R	Rate (SE)	Hazard Ratio (95% CI)	P
Daytime				
Normotension	203 / 4683	6.0 (0.4)	1.00	
White-coat hypertension	92 / 747	9.7 (1.2)	1.30 (1.00–1.70)	0.048
Masked hypertension	105 / 1105	8.8 (0.9)	1.61 (1.27–2.05)	0.0001
Sustained hypertension	329 / 1702	13.7 (0.8)	2.13 (1.76–2.59)	<0.0001
Nighttime				
Normotension	209 / 4806	5.9 (0.4)	1.00	
White-coat hypertension	121 / 1027	8.7 (0.9)	1.30 (1.02–1.64)	0.031
Masked hypertension	99 / 982	9.6 (1.0)	1.71 (1.34–2.18)	<0.0001
Sustained hypertension	300 / 1422	15.4 (0.9)	2.39 (1.96–2.92)	<0.0001
24 hours				
Normotension	219 / 4988	5.9 (0.4)	1.00	
White-coat hypertension	98 / 881	8.3 (1.0)	1.20 (0.93–1.54)	0.16
Masked hypertension	89 / 800	10.1 (1.1)	1.81 (1.41–2.32)	<0.0001
Sustained hypertension	323 / 1568	15.0 (0.9)	2.30 (1.90–2.79)	<0.0001
24 hours plus daytime				
Normotension	187 / 4551	5.7 (0.4)	1.00	
White-coat hypertension	74 / 642	9.0 (1.2)	1.27 (0.96–1.69)	0.096
Masked hypertension	121 / 1237	9.1 (0.8)	1.72 (1.36–2.17)	<0.0001
Sustained hypertension	347 / 1807	13.7 (0.8)	2.23 (1.83–2.71)	<0.0001
24 hours plus nighttime				
Normotension	189 / 4572	5.7 (0.4)	1.00	
White-coat hypertension	70 / 724	7.3 (1.1)	1.09 (0.82–1.45)	0.55
Masked hypertension	119 / 1216	9.2 (0.9)	1.67 (1.32–2.11)	<0.0001
Sustained hypertension	351 / 1725	14.8 (0.8)	2.35 (1.92–2.86)	<0.0001
24 hours plus daytime and nighttime				
Normotension	159 / 4176	5.5 (0.5)	1.00	
White-coat hypertension	50 / 515	7.7 (1.3)	1.13 (0.81–1.57)	0.47
Masked hypertension	149 / 1612	8.8 (0.7)	1.70 (1.35–2.14)	<0.0001
Sustained hypertension	371 / 1934	13.8 (0.8)	2.33 (1.90–2.87)	<0.0001

Number E / R indicate the number of events / participants at risk. Definition of the blood pressure cross-classifications are given in the Methods and in the footnote to Table 2. Rates (SE) of events per 1000 person-year were standardized by the direct method for sex and age. Hazard ratios (95% confidence interval) express the risk compared to normotension and were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes, history of cardiovascular disease, and cohort.

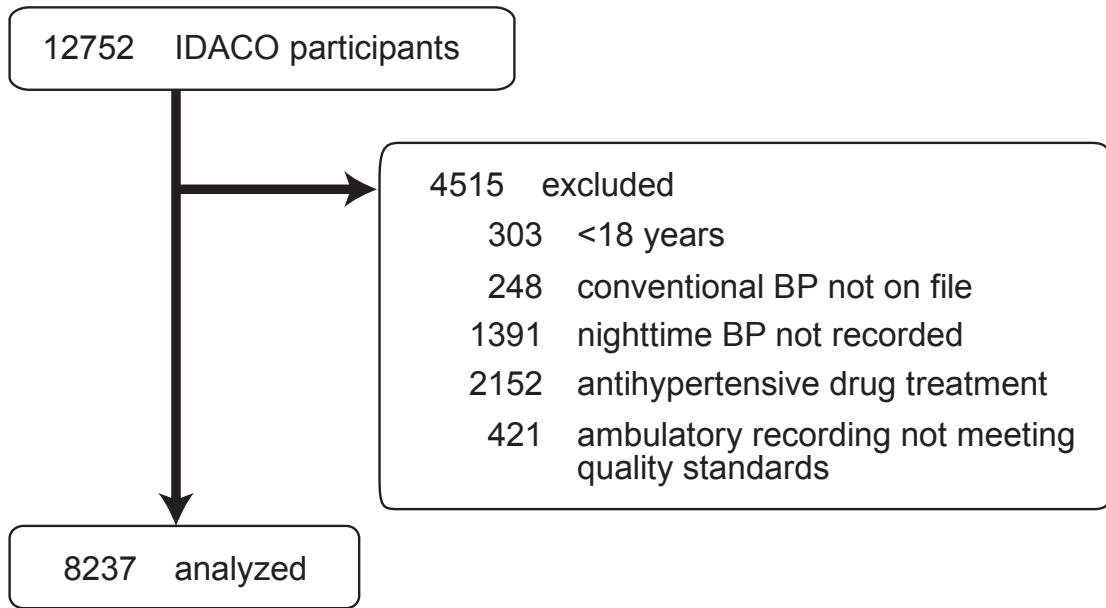


Figure S1. Flow chart of the study participants. BP denotes blood pressure.

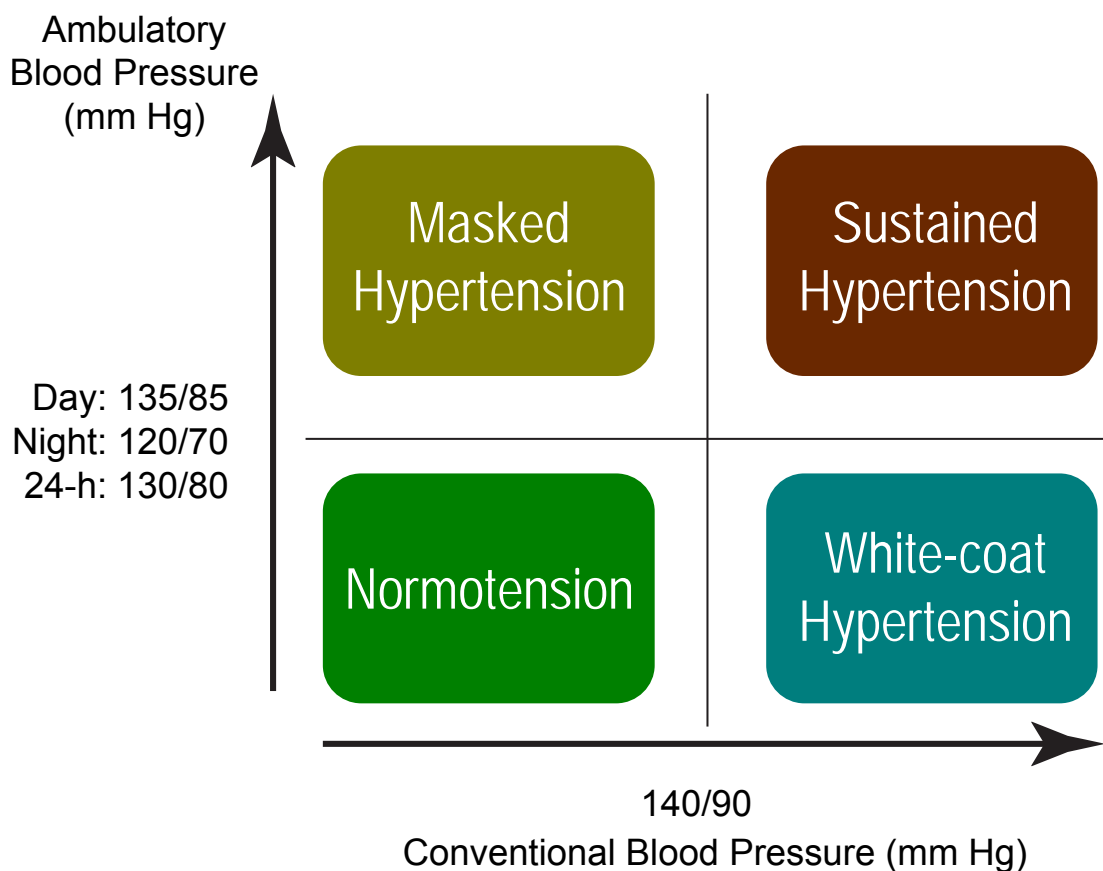


Figure S2. Cross-classification of office and ambulatory blood pressure categories.

Office hypertension was a blood pressure at least 140 mm Hg systolic and/or 90 mm Hg diastolic. Ambulatory hypertension was a 24-h level of 130 mm Hg systolic and/or 80 mm Hg diastolic or more; for the daytime blood pressure these thresholds were 135 mm Hg and 85 mm Hg and for the nighttime blood pressure 120 mm Hg and 70 mm Hg, respectively. If for a type of blood pressure measurement, systolic and diastolic blood pressure were in different categories, participants were classified as hypertensive.

Setting Thresholds to Varying Blood Pressure Monitoring Intervals Differentially Affects Risk Estimates Associated With White-Coat and Masked Hypertension in the Population

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on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators

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Supplementary Material

Setting Thresholds to Varying Blood Pressure Monitoring Intervals Differentially Affects Risk Estimates Associated with White-Coat and Masked Hypertension in the Population

Short title: White-Coat vs. Masked Hypertension

Kei Asayama, Lutgarde Thijs, Yan Li, Yu-Mei Gu, Azusa Hara, Yan-Ping Liu, Zhenyu Zhang, Fang-Fei Wei, Inés Lujambio, Luis J. Mena, José Boggia, Tine W. Hansen, Kristina Björklund-Bodegård, Kyoko Nomura, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Katarzyna Stolarz-Skrzypek, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Leonella Luzardo, Kalina Kawecka-Jaszcz, Edgardo Sandoya, Jan Filipovský, Gladys E. Maestre, Jiguang Wang, Yutaka Imai, Stanley S. Franklin, Eoin O'Brien, Jan A. Staessen,
on behalf of the International Database
on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators

This Online Data Supplement has been provided by the authors to give readers additional information about the work.

Expanded Methods

Study Population

Analyzed participants were 1823 residents from Copenhagen, Denmark;¹ 851 inhabitants from Ohasama, Japan;² 1175 subjects from Noorderkempen, Belgium;³ 713 older men from Uppsala, Sweden;⁴ 1188 subjects from Montevideo, Uruguay;⁵ 299 villagers from the Jingning County, China;⁶ 930 employees of the Irish Allied Bank, Dublin, Ireland;⁷ 204 subjects from Novosibirsk, the Russian Federation;⁸ 133 from Pilsen, Czech Republic;⁹ 266 from Padova, Italy;⁹ 244 from Kraków, Poland;⁹ and 411 from Maracaibo, Venezuela.¹⁰ Participants recruited in Kraków, Novosibirsk, Padova, and Pilsen took part in the European Project on Genes in Hypertension (EPOGH).⁹

Blood Pressure Measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,^{1,6,7,9} with validated auscultatory (Elquest USM-700F2) or oscillometric (Omron HEM-705CP⁵ or Dinamap 8100¹⁰) devices, using the appropriate cuff size, with participants in the sitting^{1-3,5,6,8-10} or supine⁴ position. Conventional blood pressure was the average of two consecutive readings in one occasion¹⁻⁹ except in participants from Maracaibo,¹⁰ who were characterized by a single reading.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30 minute intervals throughout the whole day,^{2,7} or at intervals ranging from 15 minutes^{1,10} to 30 minutes⁴ during daytime and from 30 minutes^{1,10} to 60 minutes at night.⁴ The devices implemented an auscultatory algorithm (SunTech Accutracker II) in Uppsala⁴ or an oscillometric technique (SpaceLabs 90202, SpaceLabs 90207, Colin ABPM 630, and Takeda TM-2421) in the other cohorts.^{1-3,5-10}

The same SAS macro processed all ambulatory recordings, which generally remained unedited. The Ohasama recordings were edited sparsely according to previously published criteria.¹¹ Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. While accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10 AM to 8 PM in people from Europe^{1,3,4,7-9} and South America,^{5,10} and from 8 AM to 6 PM in those from Asia.^{2,6} The corresponding nighttime intervals ranged from midnight to 6 AM^{1,3-5,7-10} and from 10 PM to 4 AM.^{2,6} These fixed time intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.^{6,12}

Other Measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking habits. Body mass index was body weight in kilograms divided by height in meters squared. Biochemical measurements included serum cholesterol and blood glucose. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L, a random blood glucose concentration of at least 11.1 mmol/L,¹³ a self-reported diagnosis, or diabetes documented in practice or hospital records.

Cross-Classification Based on Systolic and Diastolic Conventional and Ambulatory Blood Pressure

Conventional systolic hypertension was a conventional systolic blood pressure of at least 140 mm Hg. Conventional diastolic hypertension was a conventional diastolic blood pressure 90 mm Hg or more. Ambulatory hypertension was a 24-h level of 130 mm Hg systolic and/or 80 mm Hg diastolic or more; for the daytime blood pressure these thresholds were 135 mm Hg and/or 85 mm Hg and for the nighttime blood pressure 120 mm Hg and/or 70 mm Hg, respectively.⁵ Normotension and sustained hypertension were consistently normal or elevated levels on both conventional and ambulatory blood pressures (Figure S2). White-coat hypertension was defined as conventional hypertension in the presence of a normal ambulatory blood pressure. Masked hypertension was defined as ambulatory hypertension in participants with a normal conventional blood pressure. When systolic or diastolic blood pressure were in a different category (normotensive vs. hypertensive), we considered the participant as hypertensive. For ambulatory time intervals including nested periods (24 hours \pm daytime \pm nighttime), the interval with the highest blood pressure classification (normotensive vs. hypertensive) determined the ambulatory blood pressure status.

Sensitivity Analysis Based on Multiple Imputation

To ascertain that the simple interpolation method used to impute missing covariates did not weaken or inflate the associations, we repeated the analyses using a Markov single-chain Monte Carlo imputation model including all the covariates entered in the Cox model.¹⁴

Supplementary Results

Incidence of Events

In the overall study population, median follow-up was 11.1 years (5th to 95th percentile interval, 2.5 to 18.2 years). Across cohorts, median follow-up ranged from 2.5 years (2.3 to 2.6) in Jingning to 17.6 years (16.4 to 18.2) in Dublin. During 91,046 person-years of follow-up, 906 participants died (10.0 per 1000 person-years) and 729 experienced a fatal or nonfatal cardiovascular event (8.2 per 1000 person-years). Mortality included 339 cardiovascular deaths. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 75 and 190, respectively. Cardiac events consisted of 213 fatal and 301 nonfatal events, including 89 fatal and 141 nonfatal cases of acute myocardial infarction, 121 deaths from ischemic heart disease, 57 sudden deaths, 34 fatal and 139 nonfatal cases of heart failure, and 71 cases of surgical or percutaneous coronary revascularization.

The sensitivity analysis based on the Markov single-chain Monte Carlo imputation model did not materially change our results (Table S3).

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Daytime	<140/<90	...	<135/<85	...
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+ Night	<140/<90	<130/<80	...	<120/<70
+ Day + Night	<140/<90	<130/<80	<135/<85	<120/<70
White-coat hypertension				
Daytime	≥140/≥90	...	<135/<85	...
Nighttime	≥140/≥90	<120/<70
24 hours	≥140/≥90	<130/<80
+ Day	≥140/≥90	<130/<80	<135/<85	...
+ Night	≥140/≥90	<130/<80	...	<120/<70
+ Day and Night	≥140/≥90	<130/<80	<135/<85	<120/<70
Masked hypertension				
Daytime	<140/<90	...	≥135/≥85	...
Nighttime	<140/<90	≥120/≥70
24 hours	<140/<90	≥130/≥80
+ Day	<140/<90	≥130/≥80	≥135/≥85	...
+ Night	<140/<90	≥130/≥80	...	≥120/≥70
+ Day and Night	<140/<90	≥130/≥80	≥135/≥85	≥120/≥70
Sustained hypertension				
Daytime	≥140/≥90	...	≥135/≥85	...
Nighttime	≥140/≥90	≥120/≥70
24 hours	≥140/≥90	≥130/≥80
+ Day	≥140/≥90	≥130/≥80	≥135/≥85	...
+ Night	≥140/≥90	≥130/≥80	...	≥120/≥70
+ Day and Night	≥140/≥90	≥130/≥80	≥135/≥85	≥120/≥70

An ellipsis indicates that the time interval was not used in the cross-classification. Numbers are blood pressure thresholds in mm Hg. For normotension and white-coat hypertension, all blood pressure thresholds in a row should be satisfied. For masked and sustained hypertension, the criterion for the conventional blood pressure should be satisfied and the ambulatory blood pressure should be elevated during at least one interval.

Table S2. Risk of Fatal Endpoints and Cardiac and Cerebrovascular Events by Intervals of Ambulatory Monitoring (Starts)

Blood Pressure Cross-Classification	Total Mortality	Cardiovascular Mortality	Cardiac Events	Stroke
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Masked hypertension	1.23 (0.99–1.51)	1.66 (1.15–2.39)†	1.53 (1.12–2.08)†	1.84 (1.21–2.79)†
Sustained hypertension	1.37 (1.15–1.62)‡	2.06 (1.55–2.74)‡	1.88 (1.47–2.39)‡	3.20 (2.27–4.51)‡
Nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.99 (0.81–1.22)	1.22 (0.86–1.73)	1.24 (0.93–1.65)	1.76 (1.17–2.65)†
Masked hypertension	1.29 (1.04–1.59)*	1.93 (1.34–2.76)‡	1.51 (1.10–2.06)*	1.97 (1.30–2.99)†
Sustained hypertension	1.59 (1.34–1.89)‡	2.38 (1.77–3.19)‡	2.02 (1.58–2.59)‡	3.53 (2.50–5.00)‡
24 hours				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	1.00 (0.81–1.24)	1.04 (0.71–1.52)	1.12 (0.82–1.54)	1.51 (0.98–2.35)
Masked hypertension	1.25 (0.99–1.56)	1.93 (1.32–2.81)‡	1.73 (1.26–2.38)‡	1.94 (1.26–2.98)†
Sustained hypertension	1.47 (1.24–1.74)‡	2.24 (1.69–2.97)‡	2.05 (1.61–2.60)‡	3.37 (2.41–4.71)‡

Table S2. Risk of Fatal Endpoints and Cardiac and Cerebrovascular Events by Intervals of Ambulatory Monitoring (Continues)

	Total Mortality	Cardiovascular Mortality	Cardiac Events	Stroke
24 hours plus daytime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	1.11 (0.87–1.41)	1.01 (0.65–1.55)	1.24 (0.87–1.76)	1.63 (0.99–2.67)
Masked hypertension	1.21 (0.99–1.48)	1.73 (1.22–2.47)†	1.74 (1.30–2.34)‡	1.69 (1.12–2.55)*
Sustained hypertension	1.39 (1.17–1.64)‡	2.14 (1.60–2.86)‡	2.03 (1.59–2.61)‡	3.05 (2.16–4.31)‡
24 hours plus nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.87 (0.68–1.12)	0.93 (0.60–1.45)	1.05 (0.74–1.50)	1.42 (0.86–2.33)
Masked hypertension	1.27 (1.04–1.55)*	1.99 (1.41–2.82)‡	1.55 (1.15–2.09)†	1.88 (1.25–2.82)†
Sustained hypertension	1.54 (1.30–1.82)‡	2.41 (1.79–3.24)‡	2.04 (1.59–2.61)‡	3.49 (2.46–4.95)‡
24 hours plus daytime and nighttime				
Normotension	1.00	1.00	1.00	1.00
White-coat hypertension	0.97 (0.74–1.28)	0.86 (0.51–1.44)	1.14 (0.76–1.70)	1.49 (0.83–2.65)
Masked hypertension	1.25 (1.03–1.52)*	1.91 (1.36–2.70)‡	1.68 (1.26–2.25)‡	1.80 (1.20–2.69)†
Sustained hypertension	1.46 (1.23–1.74)‡	2.37 (1.74–3.23)‡	2.10 (1.62–2.72)‡	3.32 (2.30–4.78)‡

Definition of the blood pressure cross-classifications are given in the Methods and in the footnote to Table 2. Hazard ratios (95% confidence interval) express the risk compared to normotension and were adjusted for cohort, sex, age, body mass index, smoking, drinking, total cholesterol, diabetes mellitus, and history of cardiovascular disease. Significance of the hazard ratios: * $P < 0.05$; † $P < 0.01$; and ‡ $P < 0.001$.

Table S3. Risk of Cardiovascular Endpoint by Intervals of Ambulatory Monitoring Applying the Markov Single-Chain Monte Carlo Imputation Method.

Blood Pressure Cross-Classification	Number E / R	Rate (SE)	Hazard Ratio (95% CI)	P
Daytime				
Normotension	203 / 4683	6.0 (0.4)	1.00	
White-coat hypertension	92 / 747	9.7 (1.2)	1.30 (1.00–1.70)	0.048
Masked hypertension	105 / 1105	8.8 (0.9)	1.61 (1.27–2.05)	0.0001
Sustained hypertension	329 / 1702	13.7 (0.8)	2.13 (1.76–2.59)	<0.0001
Nighttime				
Normotension	209 / 4806	5.9 (0.4)	1.00	
White-coat hypertension	121 / 1027	8.7 (0.9)	1.30 (1.02–1.64)	0.031
Masked hypertension	99 / 982	9.6 (1.0)	1.71 (1.34–2.18)	<0.0001
Sustained hypertension	300 / 1422	15.4 (0.9)	2.39 (1.96–2.92)	<0.0001
24 hours				
Normotension	219 / 4988	5.9 (0.4)	1.00	
White-coat hypertension	98 / 881	8.3 (1.0)	1.20 (0.93–1.54)	0.16
Masked hypertension	89 / 800	10.1 (1.1)	1.81 (1.41–2.32)	<0.0001
Sustained hypertension	323 / 1568	15.0 (0.9)	2.30 (1.90–2.79)	<0.0001
24 hours plus daytime				
Normotension	187 / 4551	5.7 (0.4)	1.00	
White-coat hypertension	74 / 642	9.0 (1.2)	1.27 (0.96–1.69)	0.096
Masked hypertension	121 / 1237	9.1 (0.8)	1.72 (1.36–2.17)	<0.0001
Sustained hypertension	347 / 1807	13.7 (0.8)	2.23 (1.83–2.71)	<0.0001
24 hours plus nighttime				
Normotension	189 / 4572	5.7 (0.4)	1.00	
White-coat hypertension	70 / 724	7.3 (1.1)	1.09 (0.82–1.45)	0.55
Masked hypertension	119 / 1216	9.2 (0.9)	1.67 (1.32–2.11)	<0.0001
Sustained hypertension	351 / 1725	14.8 (0.8)	2.35 (1.92–2.86)	<0.0001
24 hours plus daytime and nighttime				
Normotension	159 / 4176	5.5 (0.5)	1.00	
White-coat hypertension	50 / 515	7.7 (1.3)	1.13 (0.81–1.57)	0.47
Masked hypertension	149 / 1612	8.8 (0.7)	1.70 (1.35–2.14)	<0.0001
Sustained hypertension	371 / 1934	13.8 (0.8)	2.33 (1.90–2.87)	<0.0001

Number E / R indicate the number of events / participants at risk. Definition of the blood pressure cross-classifications are given in the Methods and in the footnote to Table 2. Rates (SE) of events per 1000 person-year were standardized by the direct method for sex and age. Hazard ratios (95% confidence interval) express the risk compared to normotension and were adjusted for sex, age, body mass index, smoking, drinking, total cholesterol, diabetes, history of cardiovascular disease, and cohort.

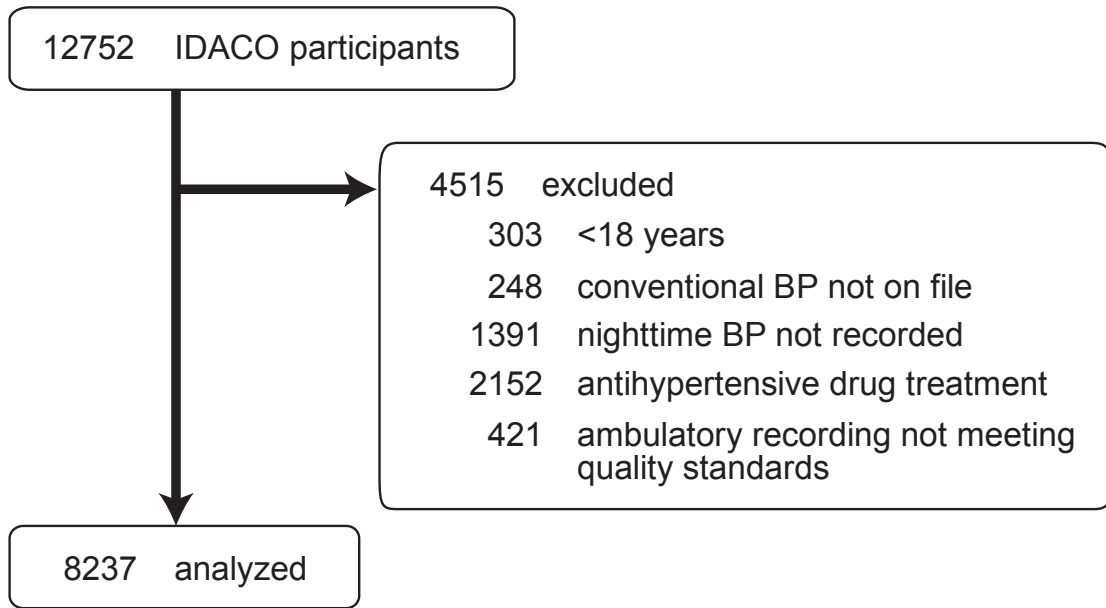


Figure S1. Flow chart of the study participants. BP denotes blood pressure.

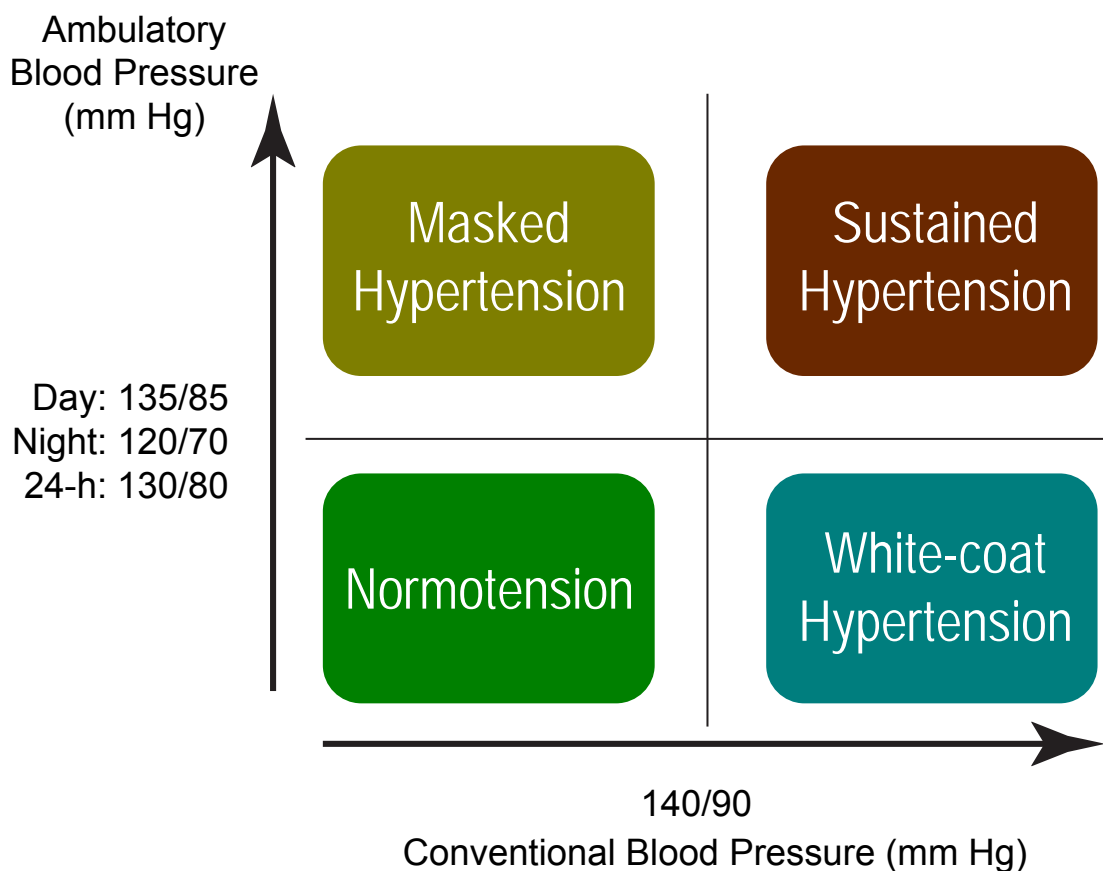


Figure S2. Cross-classification of office and ambulatory blood pressure categories.

Office hypertension was a blood pressure at least 140 mm Hg systolic and/or 90 mm Hg diastolic. Ambulatory hypertension was a 24-h level of 130 mm Hg systolic and/or 80 mm Hg diastolic or more; for the daytime blood pressure these thresholds were 135 mm Hg and 85 mm Hg and for the nighttime blood pressure 120 mm Hg and 70 mm Hg, respectively. If for a type of blood pressure measurement, systolic and diastolic blood pressure were in different categories, participants were classified as hypertensive.