Blood Pressure Variability in Elderly Persons With White-Coat and Masked Hypertension Compared to Those With Normotension and Sustained Hypertension

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BACKGROUND
The relationship between blood pressure (BP) measured, its variability, and risk of cardiovascular events is well established; however, it is not well known whether there is a difference of variability between the four categories of BP status obtained by the comparison of office and home BP measurements: normotension and masked, white-coat, and sustained hypertension. Here, we assessed BP variability (BPV) according to BP status in the elderly.

METHODS
The study population consisted of 1,701 individuals aged ≥73 years drawn from the general population. Office and home BP measurements were obtained with the same device. At home, 18 measures were taken (3 in the morning, 3 in the evening, for 3 consecutive days). BP statuses were defined according to European Society of Hypertension recommendations. To assess BPV, seven indexes were defined (e.g., standard deviation of the 18 measures, day-to-day variability, triplet-to-triplet variability, and coefficient of variation).

RESULTS
Subjects with white-coat hypertension and normotension had similar BPV, and the variability among those with masked hypertension was very close to that in those with sustained hypertension. Overall, BPV was much higher in subjects with masked hypertension than in those with white-coat hypertension, in both treated and untreated groups.

CONCLUSIONS
In elderly individuals, the short-term variability of BP is similar in masked and sustained hypertension and higher than in normotension and white-coat hypertension. This result suggests the hypothesis that BPV among persons with masked hypertension may contribute to the elevated cardiovascular risk observed in this BP pattern.

Keywords: blood pressure; variability; elderly; home blood pressure measurement; hypertension.

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Numerous studies have demonstrated the relationship between office blood pressure (BP) and risk of cardiovascular events,[1–4] which has been described as continuous, consistent, and independent of other risk factors.[5,6] Office BP is also associated with total and cardiovascular mortality, especially in elderly patients.[7] These undisputed findings suggest that patients with "white-coat" hypertension with elevated office BP would show higher cardiovascular risk than individuals with masked hypertension with normal office BP. However, several studies have reported that persons with masked hypertension show cardiovascular risk similar to that of those with sustained hypertension, while persons with white-coat hypertension have a lower cardiovascular risk that is similar to or slightly higher than that of normotensive patients.[2,8-12] Although out-of-office BP level has also been reported to be associated with cardiovascular risk, there is no clear explanation for this difference in cardiovascular risk between persons with white-coat hypertension and those with masked hypertension. It is plausible that the unexpected risks in persons with white-coat or masked hypertension could be due to BP variability (BPV). Indeed, recent studies have shown that clinical misjudgment of BP status may partly stem from BPV,[13] and that intervisit and home BPV are involved in the progression of organ damage and in triggering vascular events.[14–16] However, it is not well known whether BPV differs according to BP pattern.

Therefore, the present study aimed to compare home BPV between BP categories in a large population-based sample of elderly individuals.

METHODS

Study sample

Details of the study design and entry criteria for the 3C-HBPM Study have been published elsewhere.[17,18]

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The participants in the present study were part of the 3C-Study, which evaluated the risk of dementia attributable to vascular factors in a population-based cohort of the elderly.[17]

To summarize, participants were randomly selected from the electoral rolls between 1999 and 2000. To be eligible for the study, subjects were required to be 65 years or older and noninstitutionalized. The study protocol was approved by the Ethics Committee of Kremlin-Bicêtre University Hospital, and each participant signed an informed consent form. At the end of the fourth follow-up exam and at the beginning of the fifth follow-up exam, we performed an ancillary study of home blood pressure measurement (HBPM) in 1,814 participants aged 73 years or more (participation rate = 87%).

BP measurements

Participants were asked to measure their home BP for three consecutive days, six times per day: three times in the morning (less than 1 hour after awakening and before taking any drug) and three times in the evening (close to bedtime). In total, 18 measures were taken, as six triplet (three consecutive) measures. BP measurement had to be performed according the following protocol: three measurements at 2-minute intervals, after at least 5 minutes of rest in a seated position, with an adjustable sized cuff placed on the left arm and using a validated digital electronic device (OMRON M6, OMRON Healthcare, Kyoto, Japan).[19] BP was also measured at the beginning of the interview at the study center by trained examiners, using the same device and following the same protocol: three BP measures were performed, each separated by 2 minutes.

Definition of BP categories

Following the recommendations of the European Society of Hypertension, subjects were classified into four categories: (1) normotension (NT): office BP <140/90 mm Hg and home BP <135/85 mm Hg; (2) white-coat hypertension (WCHT): office BP ≥140/90 mm Hg and home BP <135/85 mm Hg; (3) masked hypertension (MHT): office BP <140/90 mm Hg and home BP ≥135/85 mm Hg; (4) sustained hypertension (SH): office BP ≥140/90 mm Hg and home BP ≥135/85 mm Hg.[20,21]

Definition of BP variability

To define BPV, we used home BP standard deviation (SD). Several indexes were defined with both systolic and diastolic measures, including (i) SD of all 18 BP measurements (SD_{total}); (ii) day-to-day variability (SD_{day}); (iii) triplet-to-triplet variability ($SD_{between\text{-}triplet}$); (iv) within-triplet range variability ($SD_{intra\text{-}triplet}$).

We also calculated (a) coefficient of variation (CV), defined as the SD_{total} divided by BP level; (b) BP range, obtained by subtracting the lowest BP value from the highest BP value; and (c) absolute difference between morning and evening BP levels.

Other data and measurements

Sociodemographic and medical data were collected during the baseline visit by trained interviewers. Age was used as a continuous variable and as a three-group variable based on tertile divisions (≤76 years, 76–80 years, and >80 years). Height and weight were measured, and body mass index (BMI) was computed as the weight divided by the square of the height. Normal weight was defined as a BMI <25 kg/m², overweight as a BMI of 25–30 kg/m², and obesity as a BMI ≥30 kg/m². Two educational levels were defined: high (12 or more years of formal education), and low (<12 years of formal education). Cognition level was assessed with the Mini-Mental State Examination (MMSE), which is a summed score evaluating various dimensions of cognition (memory, calculation, orientation in space and time, language, and word recognition). Test scores range from 0 to 30; higher scores indicate better cognitive status.[22,23] MMSE was used as a three-group variable: high cognition level (MMSE score ≥28), moderate cognition level (MMSE score 23–28), and low cognition level (MMSE score ≤23). Depression was assessed with the Center for the Epidemiologic Study–Depression (CES-D) scale, a 20-item self-administered instrument that provides total scores ranging from 0 to 60[24] and that has been validated for use in studies that included elderly individuals.[25–27] The CES-D rates the frequency of reported depressive symptoms experienced in the past week (i.e., depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, and sleep disturbance). The CES-D scores were considered dichotomously (yes/no) using recommended cutoff values. Clinically significant depressive symptoms were defined as CES-D scores of ≥17 in men, and ≥23 in women.[27] Participants were classified as having a history of cardiovascular events if they had experienced a stroke, bypass, angioplasty, myocardial infarction, angina, or heart surgery. Blood samples were collected and assayed for fasting cholesterol, triglycerides, and glucose levels. Diabetes mellitus was defined as either a current intake of glucose-lowering drugs or fasting glycemia of ≥7 mmol/l. Hypercholesterolemia was defined as either a current use of lipid-lowering therapy or fasting total cholesterol of ≥6.2 mmol/l. All prescription and over-the-counter drugs used during the preceding month were recorded. To avoid misreporting, participants were asked to show all of their medical prescriptions and drug packages.

Statistical analysis

Statistical analyses were performed using data from the 1,701 participants who had complete home and office measurements.

BPV indexes were assessed and compared between BP categories using analysis of variance (ANOVA) adjusted for age, sex, and antihypertensive treatment intake, as well as ANOVA adjusted for age, sex, BMI, antihypertensive treatment intake, past history of cardiovascular events, diabetes, and hypercholesterolemia.

Analyses were also stratified on the basis of antihypertensive intake. Statistical analyses were performed using SAS statistical

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software version 9.2 (SAS Institute, Cary, NC). *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

Sample description

In the overall sample, mean age was 79.0 (4.0) years; 34% of participants (n = 570) were older than 80 years, and 60% (n = 1,019) were women. Mean (SD) home BP was 141.9 (16.7)/73.4 (8.8) mm Hg. About 60% (n = 1,013) of the participants were using antihypertensive medication. Twenty-four percent (n = 401) were normotensive and 47% (n = 795) had sustained hypertension. WCHT and MHT were observed in 13% (n = 226) and 16% (n = 279) of the sample, respectively.

Table 1 shows participant characteristics by BP status. Compared to NT participants, those with WCHT, MHT, or SH were older and more frequently took antihypertensive treatment. Female sex was less frequent in participants with MHT and SH compared to normotensive subjects. BMI was higher in subjects with MHT and SH than in those with NT. Between these four groups, we found no differences in cardiovascular event history, smoking status, hypercholesterolemia, or depressive symptoms.

BP variability

Table 2 shows the home BPV indexes according to BP categories. SD_{total} was 9.9 mm Hg in NT subjects, 10.6 mm Hg in those with WCHT, 12.3 mm Hg in those with MHT, and 12.5 mm Hg in those with SH. Systolic and diastolic BPV indexes were higher in individuals with SH and MHT than in those with NT and WCHT. Participants with NT had the lowest BPV indexes, and those with SH had the highest.

Individuals with WCHT displayed slightly higher systolic BPV indexes compared to NT. A minority of the defined indexes differed significantly between these two categories. Diastolic BPV indexes did not differ between WCHT and NT or between MHT and SH. All of the BPV indexes were higher in MHT than in WCHT, with most of the indexes significantly differing between these two BP categories. Participants with MHT had slightly lower BPV indexes compared to those with SH, but none of the BPV indexes statistically differed between these two types of hypertension.

As shown in Table 3, the results did not change after multiple adjustments. Multiadjusted SD_{total} was 10.9 mm Hg in NT, 11.4 mm Hg in WCHT, 13.1 mm Hg in MHT, and 13.3 mm Hg in SH subjects. Multiadjusted BPV indexes were similar between individuals with NT and WCHT, and

Table 1. Baseline characteristics of participants by blood pressure status

	BP status			
	NT n = 401	WCHT n = 226	MHT n = 279	SH n = 795
Age, years	78.3 (3.7)	79 (4.2)*	79.6 (4.0)*	79.2 (4.0)*
Age >80 years, % (n)	25.2 (101)	31.9 (72)	39.8 (111)*	36 (286)*
Female, % (n)	68.8 (276)	64.6 (146)	58.8 (164)*	54.5 (433)*
SBP office, mm Hg	125.9 (9.8)	150.9 (10.1)*	129.5 (8.0)*	159.2 (15)*
DBP office, mm Hg	70.0 (7.3)	78.0 (8.5)*	69.4 (8.2)	79.9 (10.0)*
SBP home, mm Hg	123.9 (8.1)	127.9 (6.1)*	146.7 (9.4)*	153.2 (13)*
DBP home, mm Hg	68.0 (6.2)	68.5 (6.2)	75.1 (7.8)*	77.0 (8.9)*
BMI, kg/m²	24.9 (3.8)	24.9 (3.5)	25.6 (3.6)*	25.8 (3.7)*
Obesity[a], % (n)	9.5 (38)	8.4 (19)	10.4 (29)*	13.1 (104)*
Cardiovascular events[b], % (n)	3.8 (15)	6.7 (15)	4.3 (12)	5.0 (40)
Diabetes[c], % (n)	3.6 (14)	5.4 (12)	9.4 (26)*	9.6 (75)
Hypercholesterolemia[d], % (n)	35.6 (142)	33.9 (76)	39.8 (111)	42 (334)*
Depressive symptom[e], % (n)	11.8 (47)	10 (22)	13.7 (38)	12.3 (98)
High education level[f] ≥12 y, % (n)	40.9 (164)	32.3 (73)*	36.2 (101)	36.7 (292)
BP-lowering medication, % (n)	46.4 (185)	59.4 (133)*	63.8 (178)*	65 (517)*
Current smoker, % (n)	3.3 (13)	3.1 (7)	2.9 (8)	4 (32)
MMSE score	27.4 (2.3)	27 (2.2)	27 (2.0)*	27.1 (2.2)*

Continuous variables are shown as mean (SD).

Abbreviations: BMI, body mass index; BP, blood pressure; MHT, masked hypertension; MMSE, Mini-Mental State Examination; NT, normotension; SH, sustained hypertension; WCHT, white-coat hypertension.

[a]BMI ≥30 kg/m². [b]Past history of stroke, bypass, angioplasty, myocardial infarction, angina, or heart surgery. [c]Blood sugar ≥7 mmol/l or hypoglycemic medication. [d]Cholesterol ≥6.2 mmol/l or hypocholesterolemic medication. [e]Center for Epidemiological Studies–Depression scale total of ≥17 for men and ≥23 for women. [f]Twelve or more years of formal education. *P < 0.05, χ^2 test for categorical variables and variance analysis for continuous variables.

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Table 2. Home blood pressure variability indexes according to blood pressure status

	Blood pressure category				*P* value*		
	NT	WCHT	MHT	SH	WCHT vs. NT	WCHT vs. MH	MHT vs. SH
SBP							
SD_{total}	9.9 (3.4)	10.6 (3.7)	12.3 (4.7)	12.5 (4.4)	0.04	<0.001	0.36
SD_{day}	4.7 (3.0)	5.4 (3.5)	6.1 (3.8)	6.2 (4.0)	0.04	0.04	0.60
$SD_{between\text{-}triplet}$	8.0 (3.6)	9.0 (4.2)	10.4 (5.4)	10.7 (4.9)	0.01	<0.01	0.22
$SD_{intra\text{-}triplet}$	6.4 (3.5)	6.4 (2.8)	7.0 (3.6)	7.0 (3.5)	0.92	0.02	0.96
CV	0.08 (0.03)	0.08 (0.03)	0.08 (0.03)	0.08 (0.03)	0.32	0.75	0.42
Range	35.4 (12.2)	37.2 (12.1)	43.2 (15.3)	44.0 (14.6)	0.20	<0.001	0.31
[Morning – Evening]	8.4 (6.7)	9.1 (7.4)	10.7 (9.4)	11.6 (9.0)	0.33	0.05	0.14
DBP							
SD_{total}	5.6 (2.7)	5.8 (2.3)	6.4 (3.2)	6.4 (2.7)	0.67	0.03	0.90
SD_{day}	2.8 (1.7)	2.9 (1.8)	3.0 (1.9)	3.1 (1.9)	0.99	0.60	0.51
$SD_{between\text{-}triplet}$	4.7 (2.2)	5.0 (2.2)	5.3 (2.7)	5.4 (2.5)	0.13	0.21	0.74
$SD_{intra\text{-}triplet}$	4.2 (4.2)	4.0 (3.6)	4.8 (4.8)	4.4 (3.8)	0.25	0.03	0.25
CV	0.08 (0.04)	0.08 (0.03)	0.09 (0.04)	0.08 (0.03)	0.80	0.97	0.36
Range	21.0 (11.3)	21.2 (9.9)	23.7 (12.9)	23.3 (11.1)	0.84	0.02	0.66
[Morning – Evening]	4.7 (3.8)	5.3 (4.1)	5.6 (4.6)	5.9 (4.5)	0.09	0.57	0.40

Data are shown as crude mean (SD).

Abbreviations: CV, coefficient of variation; DBP, diastolic blood pressure; MHT, masked hypertension; NT, normotension; SBP, systolic blood pressure; SD_{total}, SD of all 18 blood pressure measurements; SD_{day}, day-to-day variability; $SD_{between\text{-}triplet}$, triplet-to-triplet variability; $SD_{intra\text{-}triplet}$, within-triplet range variability; SH, sustained hypertension; WCHT, white-coat hypertension.

**P* value adjusted with age, sex, and antihypertensive treatment.

between those with MHT and SH. The most significant differences were observed between subjects with WCHT and MHT. Participants with MHT showed a multiadjusted SD_{total} that was 15% higher than that of participants with WCHT.

Figure 1 shows SD_{total} systolic indexes stratified by antihypertensive treatment. In both treated and untreated strata, WCHT values were similar to those of NT, and MHT values were similar to those of SH. In treated and untreated subgroups, this BPV index was substantially higher in individuals with MHT than in those with WCHT. Similar results were observed with other BPV indexes (data not shown).

DISCUSSION

The important issue identified in this study is that, in the elderly, home BPV was similar between NT subjects and those with WCHT, and between subjects with MHT and those with SH. BPV was growing from NT and WCHT participants to MHT and SH participants. Considering the demonstrated correlation between BPV and cardiovascular risk,[14–16] our results are entirely consistent with previous studies that have reported cardiovascular risk to increase with hypertensive conditions in the following order: NT, WCHT, MHT, and SH.[2,8-12] Importantly, BPV indexes did not change after multiple adjustments and remained higher in MHT and SH than in NT and WCHT. Moreover, BPV remained consistent in treated/untreated subgroups, confirming the robustness of these results.

BPV is correlated with BP level; thus, we cannot exclude the possibility that the high BPV observed in masked hypertensives was partly due to their high home BP level. However, the home BP level of masked hypertensives was lower than that of sustained hypertensives; therefore, if BP level was the only explanation for this high variability, they would be expected to consequently have a lower BPV compared to subjects with SH. Yet, they displayed BPV similar to that of sustained hypertensives, suggesting that the high BPV observed in masked hypertensives is more than a simple reflection of their high BP level.

Strengths of this study include its large sample size, the community-based setting, and the age range of our participants, which has been seldom studied. We used replication of multiple sitting BP measurements using the same oscillometric device in both the clinic and home environment, which limited classification bias. This method enabled the definition of several BPV indexes, in addition to SD_{total}, which described different kinds of variability (e.g. between triplets, between days). This is important to note that all indexes were higher in participants with MHT and SH than in those with NT and WCHT, except CV, which did not increase from NT and WCHT participants to MHT and SH participants. It is possible the fact that BP levels were used to define CV and also BP category generated an overadjustment that removed any difference regarding CV.

As BP level is associated with BPV, adjustment for BP level should be performed when assessing BPV. However, in the particular case of assessing BPV in BP categories, such an adjustment was not appropriate. Indeed, categories were defined using home and office BP levels, and it would not be relevant to adjust for BP level, because BP levels had been used

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Table 3. Multiadjusted home blood pressure variability indexes according to blood pressure status

	Blood pressure categories				*P* value*		
	NT	WCHT	MHT	SH	WCHT vs. NT	WCHT vs. MH	MHT vs. SH
SBP							
SD_{total}	10.9 (0.4)	11.4 (0.5)	13.1 (0.4)	13.3 (0.4)	0.06	<0.0001	0.38
SD_{day}	5.2 (0.4)	5.7 (0.4)	6.4 (0.4)	6.5 (0.4)	0.05	0.07	0.67
$SD_{between\text{-}triplet}$	9.1 (0.5)	9.9 (0.5)	11.2 (0.5)	11.6 (0.4)	0.01	0.005	0.22
$SD_{intra\text{-}triplet}$	6.9 (0.4)	6.8 (0.4)	7.4 (0.4)	7.4 (0.3)	0.89	0.04	0.98
CV	0.086 (0.003)	0.088 (0.003)	0.088 (0.003)	0.087(0.003)	0.39	0.83	0.39
Range	38.5 (1.4)	39.6 (1.5)	45.3 (1.5)	46.4 (1.3)	0.26	<0.0001	0.29
[Morning – Evening]	10.0 (0.9)	10.3 (0.9)	11.8 (0.9)	12.7 (0.8)	0.38	0.05	0.12
DBP							
SD_{total}	6.0 (0.3)	6.1 (0.3)	6.6 (0.3)	6.6 (0.3)	0.81	0.06	0.92
SD_{day}	2.8 (0.2)	2.8 (0.2)	2.9 (0.2)	3.0 (0.2)	0.81	0.94	0.61
$SD_{between\text{-}triplet}$	5 (0.3)	5.2 (0.3)	5.4 (0.3)	5.5 (0.2)	0.18	0.33	0.72
$SD_{intra\text{-}triplet}$	4.8 (0.4)	4.4 (0.5)	5.2 (0.4)	4.9 (0.4)	0.19	0.04	0.27
CV	0.089 (0.004)	0.089 (0.004)	0.089 (0.004)	0.086 (0.003)	0.96	0.85	0.35
Range	22.8 (1.2)	22.4 (1.3)	24.9 (1.2)	24.5 (1.1)	0.63	0.02	0.69
[Morning – Evening]	5.2 (0.5)	5.6 (0.5)	5.7 (0.5)	6.0 (0.4)	0.17	0.62	0.36

Data are shown as adjusted mean (SD) for age, sex, antihypertensive treatment, body mass index, past history of cardiovascular events, diabetes, hypercholesterolemia.

Abbreviations: CV, coefficient of variation; DBP, diastolic blood pressure; MHT, masked hypertension; NT, normotension; SBP, systolic blood pressure; SD_{total}, SD of all 18 blood pressure measurements; SD_{day}, day-to-day variability; $SD_{between\text{-}triplet}$, triplet-to-triplet variability; $SD_{intra\text{-}triplet}$, within-triplet range variability; SH, sustained hypertension; WCHT, white-coat hypertension.

**P* value adjusted with age, sex, antihypertensive treatment, body mass index, past history of cardiovascular events, diabetes, and hypercholesterolemia.

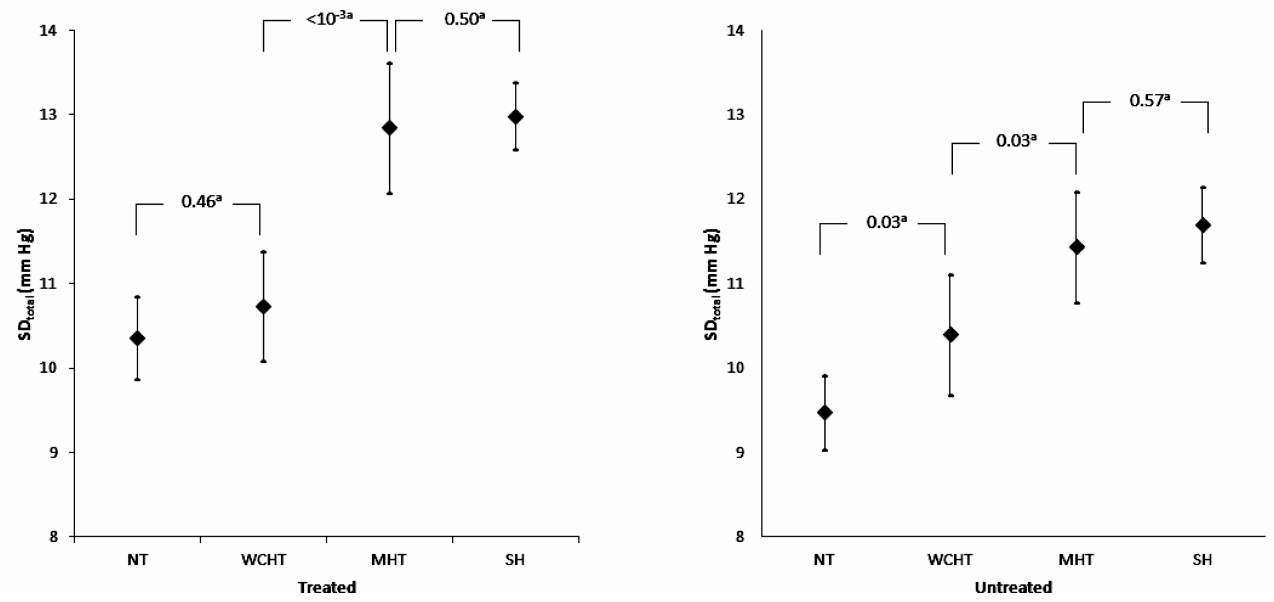

Figure 1. Standard deviation (SD) of all 18 systolic blood pressure measurements (SD_{total}) according to blood pressure status in strata of antihypertensive treatment. Mean ± 95% confidence interval. Abbreviations: NT, normotension; MHT, masked hypertension; SH, sustained hypertension; WCHT, white-coat hypertension. [a]*P* value adjusted for age, sex, body mass index, past history of cardiovascular events, diabetes, and hypercholesterolemia.

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to stratify and create BP categories. The effect of stratification is exactly to remove bias, and such an adjustment would likely result in an overadjustment, effectively resulting in bias.

We did not discard the first day of BP measurement, which might have affected the reliability of the reported BPV due to the instability of these measures. However, our results did not change after reassessment of BPV indexes excluding the values obtained on the first day of measurement.

In conclusion, among the elderly members of the general population, the BPV observed in MHT participants was similar to that observed in SH participants and higher than the BPV observed in WCHT and NT participants. This result suggests the hypothesis that the high BPV may contribute to the elevated CV risk observed in masked hypertensives.

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DISCLOSURE

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