Mortality risks in different subtypes of masked hypertension in the Spanish Ambulatory Blood Pressure Monitoring Registry

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ABSTRACT

Objective: We aimed to evaluate the risks of death and cardiovascular death of different subtypes of masked hypertension (MH), defined by either isolated daytime or nighttime blood pressure (BP) elevation, or both, compared with patients with normal both office and 24-hour BP.

Methods: We selected 4999 patients with MH (normal office BP and elevated 24-hour BP). They were divided in 3 different categories: isolated daytime MH (elevated daytime BP and normal nighttime BP, 800 patients), isolated nighttime MH (elevated nighttime BP and normal daytime BP, 1069 patients) and daytime and nighttime MH (elevation of both daytime and nighttime BP, 2989). All-cause and cardiovascular death (median follow-up 9.7 years) were assessed in each of these subtypes in comparison to 10006 patients with normal both office and 24-hour BP. Hazard ratios from Cox models after adjustment for clinical confounders were used for such comparisons.

Results: Compared to patients with normal both office and 24-hour BP, isolated daytime MH was not associated with an increased risk of death in models adjusted for clinical confounders (HR 1.07; 95%CI: 0.80-1.43). In contrast, isolated nighttime MH (HR: 1.39; 95%CI: 1.19-1.63) and daytime and nighttime MH (HR: 1.22; 95%CI: 1.08-1.37) had an increased risk of death in comparison to patients with BP in the normal range. Similar results were observed for cardiovascular death.

Conclusion: The risk of death in MH is not homogeneous and requires nocturnal BP elevation, either isolated or with daytime elevation. Isolated daytime MH is not associated with an increased risk of death.

Keywords: Masked hypertension; Isolated nocturnal hypertension; Ambulatory Blood Pressure Monitoring; Mortality

INTRODUCTION

The use of out-of-office blood pressure (BP) measurements has determined the existence of discrepancies in the diagnosis of about one third of individuals having both office and out-of-office BP measurements [1]. This is mainly due to the presence of new phenotypes, named “white-coat” and masked hypertension.

Masked hypertension (MH) is defined as having normal office BP (< 140/90 mm Hg), but elevated BP measured by home BP monitoring, or ambulatory BP monitoring (ABPM). Its prevalence ranges from 5% to 10% among the general hypertensive population, but from 15% to 30% among patients with normal office BP [2]. MH is associated with a high cardiovascular risk, with increased rates of cardiovascular events, and mortality [3,4].

On the other hand, nocturnal blood pressure is widely recognized as the most informative BP parameter related to cardiovascular risk and mortality [4,5]. We have previously reported that nocturnal systolic BP was 6 times more informative than office systolic BP in relation to mortality [4]. Moreover, the association between nocturnal BP and mortality was not affected by the level of daytime BP. In contrast, daytime BP was not associated with mortality after adjusting for nocturnal BP [4].

Mechanisms leading to masked hypertension are not fully understood and could be different among individuals. Smoking and increased job strain [6], leading to increased BP variability, are mostly related with daytime BP elevation. In contrast, sleep disturbances [7], and lack of normal nocturnal fall in BP due to different conditions [8] may be responsible for nocturnal BP elevation.

Based on these considerations, we sought to determine the association with mortality and cardiovascular mortality of different masked hypertension subtypes, defined as isolated increase in daytime BP (isolated daytime MH), isolated increase in

nighttime BP (isolated nighttime MH) or increase in both daytime and nighttime BP (daytime and nighttime MH) in patients with normal office BP who participated in the Spanish ABPM Registry, a prospective cohort study.

PATIENTS AND METHODS

Study Design

Details about Spanish ABPM Registry characteristics have been previously reported [4,8]. Patients untreated or treated for hypertension were required to be aged ≥18 years and to meet guideline-recommended indications for ABPM, which included suspected white-coat hypertension, refractory or resistant hypertension, assessment of drug treatment efficacy, high-risk hypertension, labile or borderline hypertension, and the study of circadian BP pattern. Patients were recruited from March 2004 to December 2014. The study was approved by the local institutional ethics committees, and informed consent was obtained from the participants.

BP Measurements

BP was measured at the office with a validated upper-arm cuff oscillometric device, after a 5-minute rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using the SpaceLabs 90207 automated oscillometric device (Snoqualmie, WA), programmed to register BP at 20-minute intervals for the day and at 30-min intervals for the night. Valid registries had to fulfil a series of pre-established criteria, including ≥70% of SBP and DBP successful readings during the daytime and nighttime periods, 24-hour duration, and at least one BP measurement per hour [4,8]. Daytime and nighttime periods were defined individually according to the patient's self-reported data of going-to-bed and getting-up times.

Study Variables

Variables collected for each patient based on the interviews and physical examination at the time of visit and on data drawn from clinical records were defined and measured in accordance with contemporary European guidelines [9-11]. These included

age, sex, weight, height, cardiovascular risk factors, such as smoking, diabetes mellitus, and dyslipidaemia, and history of cardiovascular disease (coronary heart disease, congestive heart failure, symptomatic peripheral artery disease, or cerebrovascular disease).

Mortality data

The date and cause of death were ascertained by a computerized search of the vital registry of the Spanish National Institute of Statistics (contract 20535 between the University of Barcelona and the National Institute of Statistics), which has been shown to be accurate and reliable with complete coverage [12]. Cause of death was determined by a nosologist from the death certificate and was coded according to the *International Statistical Classification of Diseases*, *Tenth Revision* (I00-I99 code for those of cardiovascular origin). For each study participant, follow-up was from the date of their recruitment visit in the blood pressure registry to the date of death or December 31, 2019.

Statistical Analysis

Data are presented as percentages for categorical variables and as mean ± SD for continuous variables. Differences in study variables among groups were assessed with the Pearson χ^2 for categorical variables and ANOVA for continuous variables.

Associations between subtypes of masked hypertension and risk of all-cause and cardiovascular death were summarized with hazard ratios and their 95% CI separately for each subtype in comparison to patients with blood pressure in the normal range (office BP < 140/90 mm Hg and 24-hour BP < 130/80 mm Hg), defined as the reference group. Hazard ratios were calculated by Cox models, adjusted for clinical confounders (age, sex, body mass index, smoking, diabetes, dyslipidaemia, antihypertensive treatment, and previous cardiovascular disease) The analysis was repeated separately in hypertension-treated and untreated patients.

The SPSS for Windows version 25.0 software (IBM, Armonk, New York) was used for statistical analysis.

RESULTS

Patient disposition and group definition

The mortality cohort from the Spanish Registry included 59 124 patients (59.4% treated with antihypertensive agents), from whom 15 005 (25.4%) had normal office blood pressure (< 140/90 mm Hg). Among them, ABPM revealed normal 24-hour BP (< 130/80 mm Hg) in 10006 (66.7%), defined as having blood pressure in the normal range (normotension or controlled hypertension), whilst 4999 (33.3%) had 24-hour BP ≥ 130 and/or ≥ 80 mmHg, and were classified as having MH. They were subsequently divided in 3 groups: isolated daytime MH (800 patients, 16% of MH), defined as having elevated daytime BP (≥ 135 and/or ≥ 85 mmHg), but normal nighttime BP (< 120/70 mm Hg); isolated nighttime MH (1069 patients; 21.4% of MH), defined as having elevated nighttime BP (≥ 120 and/or ≥ 70 mmHg), but normal daytime BP (<135/85 mm Hg), and combined daytime and nighttime MH (2989; 59.8% of MH), defined as having both elevated daytime and nighttime BP. A small group of MH (141 patients, 2.8% of MH) had normal both daytime and nighttime BP, even global values of 24-hour BP were elevated. They were excluded from the present analysis (Figure 1).

Table 1 shows clinical characteristics of the 3 different subtypes of MH patients, as well as patients with BP in the normal range. The group with isolated daytime MH was younger, more frequently smokers, and with lower proportions of diabetes, dyslipidaemia and previous cardiovascular disease, compared with those with isolated nocturnal MH or with combined daytime and nighttime MH. 24-hour BP was higher in patients with combined daytime and nighttime MH, while mean values were similar in groups with either isolated daytime or nighttime MH. Patients with isolated daytime MH were less frequently treated, and as a consequence, they show lower proportions of each antihypertensive drug class compared to the other two groups.

Compared with patients with BP in the normal range (normal values for both office and 24-hour BP), the group of patients with isolated daytime MH did not show an increased risk of all-cause death (HR: 1.07; 95%CI: 0.80-1.43) or cardiovascular death (HR: 0.99; 95%CI: 0.55-1.76), in the confounder-adjusted model. In contrast, isolated nighttime MH was associated with an increased risk in all-cause death (HR: 1.39; 95%CI: 1.19-1.63) and a borderline increased risk in cardiovascular death (HR: 1.33; 95%CI: 1.00-1.76). Patients with combined daytime and nighttime MH also had an increased risk in all-cause death (HR: 1.22; 95%CI: 1.08-1.37) and cardiovascular death (HR: 1.46; 95%CI: 1.19-1.78) (Table 2).

The same analysis was performed considering as the reference group only patients with normal BP at office and at all ambulatory periods (24-hour, daytime, and nighttime). Cox-regression models comparing subtypes of MH with this stricter normal BP reference group revealed similar results (Table S1).

When the risk of all-cause and cardiovascular death in subtypes of MH was estimated separately in untreated and treated patients, results went in the same direction, with higher hazard ratios in isolated nighttime MH and daytime and nighttime MH with respect to isolated daytime MH (Table 3). Hazard ratios for isolated nighttime MH and daytime and nighttime MH were numerically higher in the treated group, although interactions were not statistically significant.

DISCUSSION

The present study shows that the risk associated with MH may vary depending on the subtype of such condition. In particular, only MH patients with nocturnal BP elevation, either isolated or combined with daytime BP elevation show an increased risk of all-cause and cardiovascular mortality, after adjustment for clinical confounders. In contrast, the group of MH defined by an isolated daytime BP elevation with nighttime BP normal does not show an increased risk of mortality. These results emphasize both the importance of nocturnal BP as a risk carrier for mortality, and the evaluation of nighttime BP even in patients with a diagnosis of MH.

MH, the condition of normal office, but elevated out-of-office BP is recognized as a hypertension phenotype with high cardiovascular risk. We have previously reported that MH, as defined by 24-hour BP was associated with an increased risk in all-cause and cardiovascular mortality [4]. Moreover, previous smaller studies have also identified MH as a condition associated with increased risk of both mortality and cardiovascular events [3,13-16]. The risk has been confirmed independently of the criteria for definition of MH, either elevated daytime BP, 24-hour BP, or home BP.

In previous reports from the Spanish ABPM Registry examining the prevalence of MH, such prevalence was doubled when considering nocturnal BP elevation in comparison to only daytime elevation [17,18], thus emphasizing the need of including nocturnal BP for an adequate BP phenotype definition.

Previous studies have examined the risk of different MH subtypes (nighttime or daytime BP elevation) by using either home BP measurements or ABPM, with conflicting results. First, using data from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO), Asayama et al [19] reported increased hazard ratios for cardiovascular events and mortality for MH defined either by using

daytime or nighttime BP thresholds. In contrast, Coccina et al [20], reported that neither isolated daytime nor nighttime MUCH were associated with increased risk of cardiovascular events in comparison to normotensive individuals. These latter results, however, were based on small numbers of both patients and events.

In the opposite direction and similar to our results, Fujiwara et al [21] studied 2745 patients included in the Japan Morning Surge-Home Blood Pressure (J-HOP), who underwent nighttime home BP monitoring (3 times per night during 14 consecutive days). They concluded that masked nocturnal hypertension, but not masked daytime hypertension, was associated with an increased risk of cardiovascular events in comparison to controlled BP. As in the previous mentioned report, the number of cardiovascular events was relatively low (162).

Our results are also aligned with other previous reports demonstrating the superiority of nocturnal over daytime BP in the evaluation of cardiovascular risk [4,5,22,23]. Moreover, this increased risk also affects patients with isolated nocturnal hypertension, in some cases also fulfilling the criteria for definition of isolated nocturnal MH [24,25]. Reasons for the superiority of nighttime over daytime BP are probably based on a more standardized measurement during sleep, without important changes in body position and activity, as well as less variability. In this view, we have previously reported a higher regression dilution ratio of nighttime versus daytime SBP in patients who underwent 2 ABPM [4].

The prevalence of nocturnal MH increases in patients receiving antihypertensive treatment, whilst this does not affect the prevalence of MH defined by daytime BP [18]. As most patients receiving antihypertensive treatment take their medications in the morning, it is possible to speculate that such treatment will interfere more closely with daytime than nighttime risk. However, we have previously reported that in this cohort of patients,

the risk of mortality was not affected by time dosing of antihypertensive treatment [26], such results aligned with a previous clinical trial [27].

The weaknesses of the present study are those typical of observational studies, with results suggesting associations, but not causality. In addition, results are based on a single set of BP measurements (office and ABPM). It has been widely recognized that the reproducibility of BP phenotypes is low when two or more sets of measurements are performed [28,29]. Additionally, changes in treatment occurred during follow-up could also affect both BP phenotype definition and risk of mortality. Strengths of the study include the large number of patients (more than 15 000 with normal office BP and almost 5000 fulfilling criteria of MH) and a long follow-up of almost 10 years.

In conclusion, the risk of MH varies depending on the subtype, with only those with nighttime BP elevation (either isolated or combined with daytime elevation) having increased risk of mortality. In contrast, MH defined by isolated daytime BP elevation, with normal nocturnal values, does not have an increased risk in comparison to patients with normal BP. These results emphasize the importance of nocturnal BP in the assessment of risk and the need to include such parameter in an accurate evaluation of individuals. Although some guidelines recommend only daytime out-of-office BP evaluation (home BP monitoring or daytime ABPM) [30], it seems reasonable, as the most recent European guidelines recommend [31], the inclusion of the nighttime period (by 24-hour ABPM, or by nocturnal home BP monitoring, if available) in the out-of-office BP evaluation.

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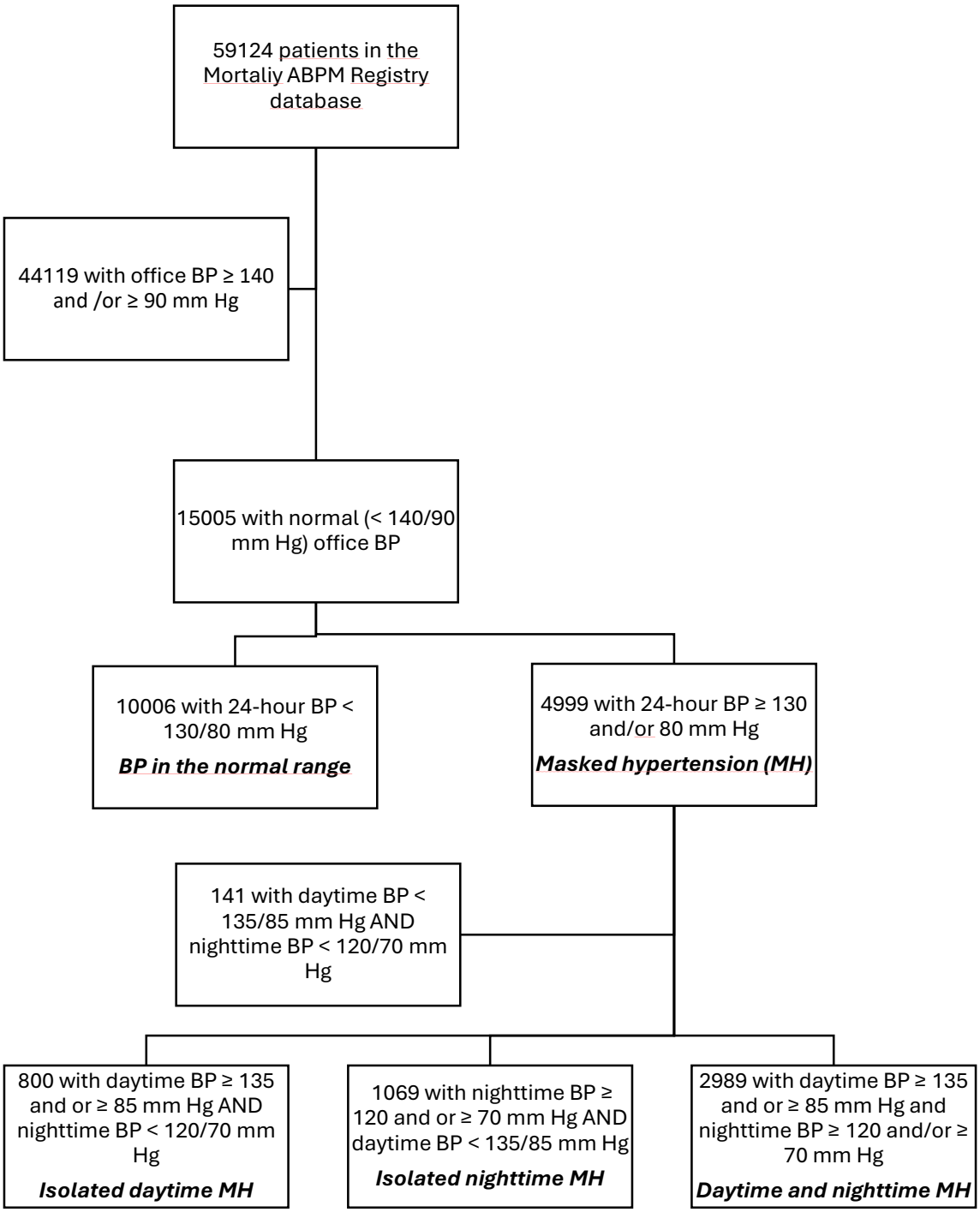

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361 **Figure 1. Flow chart of patients' disposition.**

Table 1. Demographic and clinical characteristics of the 3 different groups of patients with masked hypertension (MH)

Parameter	BP in the normal range N=10006	Isolated daytime MH N=800	Isolated nighttime MH N=1069	Daytime and nighttime MH N=2989	P value
Male sex, %	45.9	60.1	58.7	59.5	0.895
Age, y	58.1 ± 14.9	51.8 ± 13.6	60.6 ± 14.4	57.4 ± 14.3	<0.001
BMI, kg/m^2	28.6 ± 5.0	27.9 ± 4.2	28.7 ± 4.9	28.4 ± 4.6	<0.001
Current smoker, %	14.6	22.3	15.2	18.5	<0.001
Diabetes, %	16.8	12.5	21.2	18.6	<0.001
Dyslipidaemia, %	42.2	34.6	43.7	41.8	<0.001
Cardiovascular disease, %	12.1	5.4	14.3	10.6	<0.001
Blood pressure, mmHg					
Clinic systolic	125.8 ± 10.1	129.6 ± 7.3	128.1± 9.3	129.9 ± 8.0	<0.001
Clinic diastolic	76.2 ± 8.4	80.2 ± 6.9	77.2 ± 8.8	78.9 ± 8.1	<0.001
24-h systolic	116.3 ± 7.9	129.1 ± 6.3	128.8 ± 5.4	136.4 ± 9.1	<0.001
24-h diastolic	69.5 ± 6.7	79.7 ± 6.1	76.7 ± 6.7	82.2 ± 8.4	<0.001
Daytime systolic	119.1 ± 8.4	135.2 ± 7.1	129.1 ± 5.0	139.3 ± 8.9	<0.001
Daytime diastolic	72.3 ± 7.3	84.8 ± 6.9	77.8 ± 7.0	84.9 ± 9.0	<0.001
Nighttime systolic	108.9 ± 10.4	110.5 ± 6.3	127.3 ± 11.0	128.4 ± 12.8	<0.001
Nighttime diastolic	62.2 ± 7.3	64.3 ± 4.7	73.2 ± 7.5	74.5 ± 8.4	<0.001
Antihypertensive treatment, %	61.0	47.6	63.4	58.1	<0.001
Type of treatment, %					
Diuretics	28.5	18.8	28.0	26.2	<0.001
CCB	17.1	12.8	24.6	19.4	<0.001
Beta-blockers	16.0	9.9	14.5	13.7	<0.001
ACE inhibitors	19.1	15.1	20.9	18.2	0.007
ARB	31.6	22.1	31.6	31.6	<0.001
Alpha-blockers	3.2	1.5	7.4	4.4	<0.001
Others	0.9	0.6	1.1	0.9	0.858

Data expressed as mean ± SD, or %. BMI: body mass index; CCB: calcium channel blockers, ARB: angiotensin receptor blockers

Table 2. Number of deaths and hazard ratios (95% confidence interval) for different subtypes of masked hypertension (isolated daytime, isolated nighttime, and combined daytime and nighttime) in relation to all-cause and cardiovascular mortality

	Number of deaths (%)	Confounder-adjusted*	P value
All-cause mortality			
Blood pressure in the normal range N=10006	1074 (10.7%)	1.00 (ref)	
Isolated daytime masked hypertension N=800	48 (6.0%)	1.07 (0.80-1.43)	0.655
Isolated nighttime masked hypertension N=1069	189 (17.7%)	1.39 (1.19-1.63)	<0.001
Daytime and nighttime masked hypertension N=2989	364 (12.2%)	1.22 (1.08-1.37)	0.001
Cardiovascular mortality			
Blood pressure in the normal range N=10006	337 (3.4%)	1.00 (ref)	
Isolated daytime masked hypertension N=800	12 (1.5%)	0.99 (0.55-1.76)	0.962
Isolated nighttime masked hypertension N=1069	57 (5.3%)	1.33 (1.00-1.76)	0.052
Daytime and nighttime masked hypertension N=2989	137 (4.6%)	1.46 (1.19-1.78)	<0.001

Adjusted for age, sex, body mass index, smoking habit, diabetes, dyslipidaemia, previous cardiovascular disease, and treatment for hypertension

Table 3. Number of deaths and hazard ratios (95% confidence interval) for different subtypes of masked hypertension (isolated daytime, isolated nighttime, and combined daytime and nighttime) in relation to all-cause and cardiovascular mortality in patients with and without treatment for hypertension

	Untreated			Treated			
	Number of deaths (%)	Confounder-adjusted*	P value	Number of cardiovascular deaths (%)	Confounder-adjusted*	P value	Interaction p value
All-cause mortality							
Blood pressure in the normal range, N=3901	266 (6.8%)	1.00 (ref)		808 (13.2%)	1.00 (ref)		
Isolated daytime MH, N=419	15 (3.6%)	1.02 (0.60-1.72)	0.954	33 (8.7%)	1.09 (0.75-1.51)	0.725	0.901
Isolated nighttime MH, N=391	40 (10.2%)	1.18 (0.85-1.66)	0.326	149 (22.0%)	1.44 (1.20-1.71)	<0.001	0.433
Daytime and nighttime MH, N=1252	85 (6.8%)	1.10 (0.86-1.40)	0.468	279 (16.1%)	1.25 (1.09-1.44)	0.001	0.386
Cardiovascular mortality							
Controlled blood pressure, N=6105	66 (1.7%)	1.00 (ref)		271 (4.4%)	1.00 (ref)		
Isolated daytime MH, N=381	0 (0%)			12 (3.1%)	1.25 (0.70-2.24)	0.451	
Isolated nighttime MH, N=678	10 (2.6%)	1.20 (0.61-2.37)	0.602	47 (6.9%)	1.31 (0.96-1.79)	0.092	0.982
Daytime and nighttime MH, N=1737	23 (1.8%)	1.25 (0.77-2.01)	0.367	114 (6.6%)	1.50 (1.20-1.87)	<0.001	0.453

Adjusted for age, sex, body mass index, smoking habit, diabetes, dyslipidaemia, and previous cardiovascular disease. MH: Masked hypertension; MUCH: Masked uncontrolled hypertension