Blood pressure phenotypes based on ambulatory monitoring in a general middle-aged population

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Blood pressure phenotypes based on ambulatory monitoring in a general middle-aged population

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ABSTRACT

Background: Ambulatory blood pressure monitoring (ABPM) is increasingly recommended for clinical use, but more knowledge about the prevalence and variability in ABPM-derived phenotypes in the general population is needed. We describe these parameters in the community-based Swedish CArdioPulmonary biImage Study (SCAPIS) cohort.

Methods: We examined 5881 men and women aged 50–64 with 24-hour ABPM recordings using validated monitors. ABPM phenotypes were defined according to European guidelines. White coat hypertension was defined as elevated office BP (≥140/90 mmHg) with normal mean ambulatory BP (<135/85 mmHg in day-time, <120/70 mmHg in night-time, <130/80 mmHg over 24-h); and masked hypertension as normal office BP (<140/90 mmHg) with elevated mean ambulatory BP (≥135/85 mmHg in day-time, ≥120/70 mmHg in night-time, ≥130/80 mmHg over 24-h). Blood pressure variability was assessed using the coefficient of variation (CV), standard deviation (SD), and average real variability.

Results: Based on the ABPM recordings, 36.9% of participants had 24-h hypertension, 40.7% had day-time hypertension, and 37.6% nocturnal hypertension. Among participants treated with anti-hypertensive drugs, one in three had elevated office blood pressures, and more than half had elevated 24-h, day-time or nocturnal blood pressures. Among participants without anti-hypertensive drugs, only one in six had elevated office blood pressures, but one in three had elevated 24-h, day-time or nocturnal blood pressures. Men had higher 24-h blood pressures, more masked hypertension, but less white-coat hypertension than women. The prevalence of white-coat hypertension increased with age, but not the prevalence of masked hypertension. A positive association between blood pressure level and variability was observed, and within-person and between-person SD and CV were of similar magnitude. The variance in ABPM on repeated measurements was substantial.

Conclusions: In the middle-aged general population, masked hypertension is an underappreciated problem on the population level.

Introduction

High blood pressure (BP) is the strongest contributing cause of premature death globally [1]. Based on office BP measurements, the overall worldwide prevalence of hypertension in adults is 30–45% [2], with a global age-standardized prevalence of 24% in males and 20% in females [3], and a strong association with age [2,4].

The hypertension paradigm is challenged by recognising that BP is inherently hard to measure due to its substantial variability, with implications for both treatment decisions and treatment monitoring. Proposed solutions involve obtaining more BPs (e.g. through home or ambulatory BP assessments), or using other measures than BPs (such as global risk assessments) [5].

Ambulatory blood pressure monitoring (ABPM) captures risk of cardiovascular events better than office BP monitoring, and gives better clues to treatment strategies than home BP monitoring by informing on circadian patterns [6,7]. It has increasingly gained recommendation for clinical use [4], but more knowledge about prevalence, variability and
reproducibility of ABPM-derived phenotypes is needed to understand its limitations [8,9].

We aimed to investigate the variability and reproducibility of ABPM measures and prevalence of circadian BP traits in the large novel community-based Swedish CArdioPulmonary bioImage Study (SCAPIS).

**Method**

**Sample**

The SCAPIS study is a prospective community-based cohort comprising 30,000 men and women aged 50–64 years randomly selected from the Swedish population register (www.scapis.org). Participants were recruited to and examinations performed between 2013 and 2018 at six Swedish university hospitals (Gothenburg, Linkoping, Malmo/Lund, Stockholm, Umea, and Uppsala). Of the invited persons, 50% participated. All participants followed a core program consisting of at least two visits to the test centre, advanced imaging, a questionnaire including food-frequency (FFQ), basic biochemistry, anthropometry, electrocardiography, office BP, 7-day accelerometry, and lung function tests. Self-reported previous comorbidities and medications were recorded as yes, no, unwilling to answer, or unable to answer.

Twenty-four-hour ABPM was recorded in 5009 individuals at the SCAPIS-Uppsala site and 1299 individuals at the SCAPIS-Malmo/Lund site. After QC, valid ABPM registrations were available in 4729 participants at SCAPIS-Uppsala, and 1186 subjects at SCAPIS-Malmo/Lund. Among them, 34 participants had missing office BPs. Repeated measurements of ABPM were made within 6 weeks in 44 participants randomly selected among participants who had problems with ECG leads during the first examinations and thus needed to repeat the examinations. None of them repeated the examinations due to problems with the blood pressure readings (Supplementary Figure 1), and none of them changed blood pressure-lowering treatment regimen between the measurements, as validated by chart review.

The study was approved by the ethical review board in Umeå (# 2010-228-31 M) and all participants gave written informed consent.

**Biochemistry and physical examinations**

A venous blood sample (100 mL) was collected from participants after an overnight fast and was used for immediate analysis and stored in a biobank for later analysis (cholesterol, HDL, triglycerides, calculated LDL, plasma glucose, HbA1c, high-sensitivity C-reactive protein, and creatinine). If plasma glucose was \(\geq 7.0 \text{ mmol L}^{-1}\), a repeat sample was taken at the second visit to establish a potential diagnosis of diabetes [10]. Renal function was assessed as estimated glomerular filtration rate (eGFR) calculated by using the Revised Lund-Malmö Study equation (LM Revised) [11,12]. We chose this equation because LM Revised was more stable in terms of bias and accuracy across age and BMI groups than MDRD and CKD-EPI in a Swedish population [12].

Body weight was measured on a balance scale with participants dressed in light clothing without shoes. Body height, waist, and hip circumference were also measured according to current recommendations [13]. A 12-lead standard electrocardiogram was recorded in the supine position after a rest for 5 min. Office supine systolic and diastolic BPs were measured after 5 min rest twice in each arm, at least 1 min apart, with an automatic device (Omron M10-IT, Omron Health care Co, Kyoto, Japan) [14]. If the two results in the same arm differed by more than 10 mmHg, for either systolic or diastolic pressure, the measurement was repeated until two subsequent results within 10 mmHg was obtained, with a maximum of four attempts. The average of the two supine brachial blood pressures in the arm with the highest blood pressures were used [15]. The ankle-brachial index [16] was measured twice and bilaterally using a Doppler pulse sensor with the subject in a supine position. If the two results (from the same point of measurement) differed \(>10 \text{ mmHg}\), the measurement was repeated until two subsequent results were within \(\pm 10 \text{ mmHg}\) with a maximum of four attempts. If the difference was still \(>10 \text{ mmHg}\), the last two measurements were used. From the two stable registrations, the mean value was calculated. The SCORE-estimated 10-year risk of cardiovascular death was estimated based on sex, age, smoking, total cholesterol, and SBP according to updated risk charts for Sweden, as previously described [17].

**Ambulatory blood pressure measurement**

Blood pressure monitors (Labtech EC-3H/ABP, Labtech Ltd, Debrecen, Hungary) were applied in the morning of one day and removed in the morning the following day, after at least 24 h. New batteries were inserted before each registration. The applied standards related to the blood pressure measurement part of the EC-3H/ABP device was the following: EN
60601-1, EN 60601-1-2, EN 60601-1-6, EN 60601-1-11, EN 80601-2-30, EN 62304, ANSI/AAMI SP10, and EN ISO 10993-1. The validation according to AAMI SP10 for the EC-3H/ABP device is in the report nr. DEV-CE 2013/01 A [18]. A new registration was obtained if the initial registration was shorter or equal to 22 h, or if blood pressure monitoring or any ECG lead was interrupted for more than 2 h during the registration.

BP and heart rate were measured automatically every 30 min all day in the Malmö group and every 30 min during day-time and 90 min during night-time (in order to minimise the disturbance to a sleep registration) in the Uppsala group. Recordings with less than 10 day-time readings or less than five night-time readings in Lund or three night-time readings in Uppsala were discarded. Day-time and night-time readings in Lund or three night-time readings in Uppsala were discarded. Day-time and night-time were defined using narrow fixed clock-time periods [19] as 10:00–20:00 and 00:00–06:00, respectively. Narrow fixed clock-time intervals eliminate transition periods in mornings and evenings, during which the blood pressure changes rapidly [20].

Mean day-time BPs, mean night-time BPs, and mean 24-h BPs were calculated from ambulatory blood pressure records. In order to avoid an overestimation of mean 24-h BPs due to a higher number of readings per hour during day-time, we performed a time-weighted quantification of mean 24-h BP by taking account of the time interval between measurements [21].

**Blood pressure variability and diurnal pattern**

BP variability was evaluated as the coefficient of variation (CV), standard deviation (SD), and average real variability (ARV) in the 24-h, day-time and night-time BPs in 5881 participants. The within person 24-h SD and CV were calculated using time-weighted blood pressures [22]. ARV was calculated as the average of the absolute differences between consecutive blood pressure measurements [23].

The day-time-night-time difference in BPs was recorded [24]. Dipping was defined as a fall of >10% in systolic BP in the night compared to day-time readings; non-dipping conversely a nocturnal fall of <10% [25].

**Hypertension definitions using office and ambulatory blood pressure measurements**

In accordance with the European society of hypertension (ESH) guidelines, ambulatory hypertension was defined as a mean 24-h BP >130/80 mmHg, mean day-time BP >135/85 mmHg, and/or mean night-time BP >120/70 mmHg [6]. Office hypertension was defined as office BP >140/90 mmHg [26]. In the presence of an elevated office BP (≥140/90 mmHg), we defined participants with a normal mean ambulatory day-time BP (<135/85 mmHg) as having day-time white coat hypertension [4,27]; those with normal mean night-time BP (<120/70 mmHg) as having nocturnal white coat hypertension [26], and those with normal mean 24-h BP (<130/80 mmHg) as having 24-h white coat hypertension [26,28]. In the presence of a normal office BP (<140/90 mmHg), we defined those with an increased mean day-time BP (≥135/85 mmHg) as having day-time masked hypertension [26,28], those with an increased mean night-time BP (≥120/70 mmHg) as having nocturnal masked hypertension [26], and those with an increased mean 24-h BP (≥130/80 mmHg) as having 24-h masked hypertension [26,28]. Although ‘masked uncontrolled hypertension’ has been used for masked hypertension among individuals under anti-hypertensive treatment, we used ‘masked hypertension’ for individuals with or without anti-hypertensive treatment for consistency. Individuals with both elevated office and ABPM BPs were defined as having sustained hypertension, and those with both non-elevated office and ABPM BPs were defined as having sustained normotension [29].

**Statistical analysis**

All continuous baseline variables were presented using means (standard deviations) and categorical variables as n (%). We illustrated the data by three age groups (<55, 55–60, and ≥60 years), sex, and anti-hypertensive treatment. A time-weighted quantification of mean 24-h BP by taking account of the time interval between measurements was performed. Mixed linear regression models were used to evaluate the variance components for within-person and between-person SD and CV in 24-h, day-time, and night-time BPs. The long-term within-person BP reproducibility (between repeat ABPM measurements) was evaluated in 44 individuals who had at least 3 valid night-time and 10 day-time readings on two separate occasions at least one day apart. Reproducibility was assessed by calculating the average absolute differences within individuals with corresponding non-parametric bootstrap confidence intervals. The absolute difference is the difference between the two measurements; i.e. a −3 mm Hg difference and a +3 difference both count as a 3 mm Hg absolute difference. In order to find
clinical traits that could signal uncontrolled hypertension, multinomial logistic regression with a Benjamini-Hochberg correction for multiple testing, with a false discovery rate (FDR) of <5%, was used to investigate the associations of risk factors with hypertension phenotypes, controlling for age and sex, and stratified by hypertensive treatment. The results were presented as heatmaps showing p-values from the different models. A two-sided p-value < .05 was considered statistically significant. All statistical analyses were performed using R (version 4.0.1) and Stata (version 15, College Station, TX).

Results

Prevalence of hypertension phenotypes

Among the studied 5881 participants (3026 women), the mean age was 57.6 years. Baseline characteristics are shown in Table 1. The mean office BPs were 125/77 mmHg, men had higher office BPs than women, and office BPs were higher with higher age (Table 1). Self-reported comorbidities were also higher in men and with higher age, as was SCORE-estimated 10-year risk of cardiovascular death, which averaged 1.2% in the sample.

Line plots of hourly averages in 24-h BP stratified by age, sex, and anti-hypertensive treatment are presented in Figure 1, and distributions of 24-h, day-time and night-time SBP, DBP and dipping of SBP and DBP in Supplementary Figure 2. On ambulatory recordings, 36.9% had 24-h hypertension (≥130/80 mmHg), 40.7% had day-time hypertension (≥135/85 mmHg), and 37.6% had nocturnal hypertension (≥120/70 mmHg). Overall, 31.0% of participants had nocturnal non-dipping (Table 2).

Prevalence of uncontrolled hypertension

In this study, 3.4% of participants without anti-hypertensive drug treatment self-reported having hypertension, 15.6% had hypertension based on office BP recordings, and 1 in 3 had hypertension based on ABPM recordings. Compared to participants without anti-hypertensive treatment, persons with such drugs had more risk factors and more self-reported comorbidities (Table 3). Among participants treated with anti-hypertensive drugs, one in three had elevated office BP, and more than half had elevated 24-h, day-time or nocturnal BPs (Table 3). Among participants without anti-hypertensive drugs, only one in six had elevated office BP, but one in three had elevated 24-h, day-time or nocturnal BPs (Table 3). Compared to persons without anti-hypertensive drugs, those that used such drugs had more masked hypertension, less white-coat hypertension, and more nocturnal BP non-dipping (Table 3).

Variability of ambulatory blood pressure phenotypes

The variability of 24-h ambulatory BP phenotypes is presented in Table 4. Persons with higher mean systolic or diastolic BPs had higher ARV and SD, but lower CV (Figure 2). The between-person SDs and CVs of SBP/DBP for 24-h BP, day-time BP and night-time BP were similar to the within-person SDs and CVs (Table 4).

Reproducibility of ambulatory blood pressure phenotypes

The reproducibility between repeat ABPM measurements in 44 participants was presented in Figure 3. Among them, 11 participants were treated with anti-hypertensive drugs. The median time interval between the two ABPM measurements was 17 days (outer quartiles 10 and 22). The mean absolute difference was around 5-10 mmHg in 24-h, day-time and night-time blood pressures. The intraclass correlations (ICC) were 0.62, 0.60, 0.72 for SBP and 0.72, 0.66, 0.77 for DBP, on day, night and 24-h measurements.

Associations of clinical variables with hypertension phenotypes

In the search for clinical traits that could raise the suspicion of uncontrolled hypertension, we noted prominent overlaps in associations of clinical variables with more than one hypertension phenotype.

In persons without anti-hypertensive treatment, white-coat hypertension was associated with BMI, triglycerides, haemoglobin, glucose, total cholesterol,
Table 1. Baseline characteristics of 5881 middle-aged men and women with 24-hour ambulatory blood pressure recordings.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Age &lt;55 y/o</th>
<th>Age 55–60 y/o</th>
<th>Age ≥60 y/o</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 5881</td>
<td>N = 2855</td>
<td>N = 3026</td>
<td>N = 1930</td>
<td>N = 1894</td>
<td>N = 2057</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.6 (4.4)</td>
<td>57.6 (4.4)</td>
<td>57.6 (4.4)</td>
<td>52.5 (1.3)</td>
<td>57.5 (1.4)</td>
<td>62.6 (1.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>2855 (48.5)</td>
<td>2855 (100.0)</td>
<td>0 (0.0)</td>
<td>934 (48.4)</td>
<td>911 (48.1)</td>
<td>1010 (49.1)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>572 (10.1)</td>
<td>280 (10.3)</td>
<td>292 (10.0)</td>
<td>190 (10.3)</td>
<td>193 (10.6)</td>
<td>189 (9.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 (4.4)</td>
<td>27.6 (3.9)</td>
<td>26.6 (4.8)</td>
<td>26.9 (4.4)</td>
<td>27.2 (4.3)</td>
<td>27.1 (4.3)</td>
</tr>
<tr>
<td>Waist-hip ratio,</td>
<td>0.92 (0.09)</td>
<td>0.98 (0.07)</td>
<td>0.87 (0.07)</td>
<td>0.91 (0.09)</td>
<td>0.92 (0.08)</td>
<td>0.93 (0.09)</td>
</tr>
<tr>
<td>Ankle-brachial index, left</td>
<td>1.21 (0.10)</td>
<td>1.22 (0.09)</td>
<td>1.19 (0.10)</td>
<td>1.21 (0.10)</td>
<td>1.21 (0.09)</td>
<td>1.20 (0.10)</td>
</tr>
<tr>
<td>Ankle-brachial index, right</td>
<td>1.22 (0.10)</td>
<td>1.24 (0.10)</td>
<td>1.20 (0.10)</td>
<td>1.22 (0.10)</td>
<td>1.22 (0.10)</td>
<td>1.21 (0.11)</td>
</tr>
<tr>
<td>Office systolic blood pressure, mmHg</td>
<td>124.7 (16.1)</td>
<td>127.5 (14.7)</td>
<td>122.2 (17.0)</td>
<td>120.8 (14.9)</td>
<td>124.5 (16.1)</td>
<td>128.6 (16.4)</td>
</tr>
<tr>
<td>Office diastolic blood pressure, mmHg</td>
<td>76.6 (9.8)</td>
<td>77.5 (9.6)</td>
<td>75.8 (10.0)</td>
<td>75.28 (9.7)</td>
<td>76.85 (10.0)</td>
<td>77.69 (9.7)</td>
</tr>
<tr>
<td>ABPM systolic blood pressure, mmHg</td>
<td>76.3 (7.7)</td>
<td>78.0 (7.4)</td>
<td>74.7 (7.7)</td>
<td>76.3 (7.7)</td>
<td>76.7 (7.9)</td>
<td>75.9 (7.5)</td>
</tr>
<tr>
<td>ABPM diastolic blood pressure, mmHg</td>
<td>61.2 (9.5)</td>
<td>60.5 (9.8)</td>
<td>61.9 (9.1)</td>
<td>60.3 (9.2)</td>
<td>61.2 (9.5)</td>
<td>62.1 (9.5)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>61.2 (9.5)</td>
<td>60.5 (9.8)</td>
<td>61.9 (9.1)</td>
<td>60.3 (9.2)</td>
<td>61.2 (9.5)</td>
<td>62.1 (9.5)</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>175 (3.1)</td>
<td>125 (4.6)</td>
<td>50 (1.7)</td>
<td>33 (1.8)</td>
<td>35 (1.9)</td>
<td>55 (3.2)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1263 (22.6)</td>
<td>654 (24.3)</td>
<td>609 (21.1)</td>
<td>288 (15.8)</td>
<td>410 (22.9)</td>
<td>565 (28.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>259 (4.6)</td>
<td>148 (5.5)</td>
<td>111 (3.8)</td>
<td>48 (2.6)</td>
<td>86 (4.8)</td>
<td>125 (6.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>64 (1.1)</td>
<td>27 (1.0)</td>
<td>37 (1.3)</td>
<td>14 (0.8)</td>
<td>17 (0.9)</td>
<td>33 (1.7)</td>
</tr>
<tr>
<td>Sleep apnoea, n (%)</td>
<td>233 (4.2)</td>
<td>155 (5.8)</td>
<td>78 (2.7)</td>
<td>47 (2.6)</td>
<td>92 (5.1)</td>
<td>94 (4.8)</td>
</tr>
<tr>
<td>Self-reported comorbidity</td>
<td>1109 (19.9)</td>
<td>581 (20.4)</td>
<td>528 (17.4)</td>
<td>233 (12.1)</td>
<td>359 (19.0)</td>
<td>517 (25.1)</td>
</tr>
<tr>
<td>Antihypertensive medicine, n (%)</td>
<td>219 (3.7)</td>
<td>135 (4.7)</td>
<td>84 (2.8)</td>
<td>43 (2.2)</td>
<td>73 (3.9)</td>
<td>103 (5.0)</td>
</tr>
<tr>
<td>Antidiabetic medicine, n (%)</td>
<td>0.5 (1.1)</td>
<td>5.5 (1.1)</td>
<td>5.8 (1.1)</td>
<td>5.5 (1.0)</td>
<td>5.7 (1.1)</td>
<td>5.7 (1.1)</td>
</tr>
<tr>
<td>Low-density lipoproteins, mmol/L</td>
<td>3.6 (0.9)</td>
<td>3.6 (0.9)</td>
<td>3.5 (1.0)</td>
<td>3.5 (0.9)</td>
<td>3.6 (0.9)</td>
<td>3.6 (1.0)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.2 (4.2)</td>
<td>2.1 (3.8)</td>
<td>2.3 (4.5)</td>
<td>2.3 (4.5)</td>
<td>2.1 (2.8)</td>
<td>2.3 (4.7)</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>36.3 (6.5)</td>
<td>36.8 (7.4)</td>
<td>35.9 (5.3)</td>
<td>35.2 (5.6)</td>
<td>36.6 (7.1)</td>
<td>37.1 (6.7)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.9 (1.2)</td>
<td>6.1 (1.3)</td>
<td>5.7 (1.0)</td>
<td>5.8 (1.0)</td>
<td>5.9 (1.1)</td>
<td>6.1 (1.3)</td>
</tr>
<tr>
<td>Haemoglobin, g/L</td>
<td>141.9 (11.8)</td>
<td>149.6 (9.4)</td>
<td>134.7 (9.0)</td>
<td>141.9 (12.2)</td>
<td>141.7 (11.5)</td>
<td>142.2 (11.8)</td>
</tr>
<tr>
<td>Triacylglycerol, mmol/L</td>
<td>1.3 (0.8)</td>
<td>1.5 (0.9)</td>
<td>1.2 (0.6)</td>
<td>1.3 (0.0)</td>
<td>1.3 (0.9)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>SCORE-estimated 10-year risk of cardiovascular death, %</td>
<td>1.3 (1.2)</td>
<td>2.0 (1.3)</td>
<td>0.6 (0.7)</td>
<td>0.6 (0.6)</td>
<td>1.1 (0.9)</td>
<td>2.1 (1.4)</td>
</tr>
</tbody>
</table>

Missingness in medication usage is due to inability or unwillingness to report.
ABI, waist/hip ratio, and waist circumference (Supplementary Figure 3). Masked hypertension was associated with eGFR, BMI, triglycerides, haemoglobin, glucose, HbA1c, CRP, heart rate, waist/hip ratio, and waist circumference (Supplementary Figure 3). Sustained hypertension was associated with BMI, triglycerides, haemoglobin, fasting glucose, HbA1c, CRP, LDL and total cholesterol, heart rate, ABI, waist/hip ratio, and waist circumference (Supplementary Figure 3). Of note, sleep apnoea was associated with masked hypertension.
hypertension when defined based on night-time BPs but not based on 24-h or day-time BPs.

Patterns were quite different among users of anti-hypertensive drugs (Supplementary Figure 3). In these persons, sustained hypertension was associated with BMI, triglycerides, haemoglobin, LDL and total cholesterol, ABI, and waist circumference. Previous CVD was associated with sustained and masked hypertension in treated but not untreated persons. In contrast, most associations with white-coat hypertension or masked hypertension in untreated persons were not observed among anti-hypertensive drug users (Supplementary Figure 3).
Discussion

In this study of a large middle-aged general population sample, ambulatory 24-h blood pressure monitoring revealed important information. In persons drug treated for hypertension, BP was uncontrolled in one out of three using office BP measurements, and in more than half using ambulatory BP measurements. About one in four had masked hypertension among both treated and untreated persons, which is a higher prevalence than previously reported. Men had more masked hypertension but less white-coat hypertension than women.

Table 4. Short-term variability in 24-hour, day-time and night-time blood pressures.

<table>
<thead>
<tr>
<th></th>
<th>24-hour BP</th>
<th>Day-time BP</th>
<th>Night-time BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N = 5881$</td>
<td>$N = 5881$</td>
<td>$N = 5881$</td>
</tr>
<tr>
<td>Number of recordings, mean (SD)</td>
<td>39.4 (6.7)</td>
<td>20.0 (3.4)</td>
<td>6.3 (2.9)</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mmHg</td>
<td>123.7</td>
<td>130.0</td>
<td>112.3</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mmHg</td>
<td>76.4</td>
<td>82.0</td>
<td>66.4</td>
</tr>
<tr>
<td>Between-person SD of systolic blood pressure, mmHg</td>
<td>11.1</td>
<td>11.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Between-person SD of diastolic blood pressure, mmHg</td>
<td>7.4</td>
<td>8.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Within-person SD of systolic blood pressure, mmHg</td>
<td>11.9*</td>
<td>12.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Within-person SD of diastolic blood pressure, mmHg</td>
<td>9.5*</td>
<td>10.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Between-person CV of systolic blood pressure, %</td>
<td>3.8</td>
<td>3.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Between-person CV of diastolic blood pressure, %</td>
<td>4.2</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Within-person CV of systolic blood pressure, %</td>
<td>4.1*</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Within-person CV of diastolic blood pressure, %</td>
<td>5.4*</td>
<td>5.5</td>
<td>5.1</td>
</tr>
<tr>
<td>ARV of systolic blood pressure, mmHg</td>
<td>9.5</td>
<td>9.6</td>
<td>8.6</td>
</tr>
<tr>
<td>ARV of diastolic blood pressure, mmHg</td>
<td>7.4</td>
<td>7.5</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*Weighted SD: time-weighted average of day-time and night-time SDs.
BP: blood pressure; ARV: average real variability; SD: standard deviation; CV: coefficient of variation.

Figure 2. Blood pressure average real variability, standard deviation, and coefficient of variation against the mean systolic and diastolic blood pressure from 24-hour ambulatory blood-pressure recordings.
Underestimation of hypertension in the population

Office BP assessments have been reported to misdiagnose hypertension in the general population in 9–18% [30]. In classifying BP as controlled or uncontrolled accurately, office BP measurement agreed with 24-h ABPM in less than two out of the three cases [31]. Hence, misdiagnosis of hypertension status can occur in a substantial proportion of the population if classified purely with office BP assessments [30], rendering BP treatment decisions based solely on office BP measurements unacceptable [5]. ABPM has the potential to reduce misdiagnosis and save costs thanks to better-targeted treatment [32].

ABPM is a better predictor of cardiovascular events and end-organ damage than office BP [33,34], and several clinical care guidelines recognise the value of ABPM in clinical practice [35,36]. It sees limited use in clinical practice today, likely in part due to lack of evidence of improved risk discrimination [37].

Prevalence of masked hypertension and white-coat hypertension

One in three to four persons had masked hypertension, and a similar fraction had white-coat hypertension in the present study. Men were more likely than women to have masked hypertension. In contrast, white-coat hypertension was more frequent in women. The prevalence of white-coat hypertension increased with age, but not the prevalence of masked hypertension.

The prevalence of masked hypertension in the general population is around 1 in 3, with a wide range of prevalences reported [38–40], likely due to differences in populations, measurements, and definitions (e.g. 24-h, day-time, night-time) [41,42]. A third of persons using anti-hypertensive drugs has been reported to have masked uncontrolled hypertension [43,44], similar to the proportion in our study. In particular, masked hypertension (in anti-hypertensive treatment-naïve persons) and masked uncontrolled hypertension
(in persons on anti-hypertensive treatment) often go with nocturnal hypertension [45]. The high prevalence of masked hypertension in this and other communities implies a potentially sizeable public health opportunity [39,46].

The prevalence of white-coat hypertension in the community is similar to that of masked hypertension, in prior [26,38,40] and the present study. White-coat hypertension is linked to subsequent development of sustained hypertension, and has been associated with a slightly increased risk of cardiovascular morbidities in previous studies [40].

The latest American guidelines use lower BP cut-off values than other guidelines, hampering discussions of prevalences of these conditions [47].

Factors that should raise the suspicion of hypertension phenotypes

Traits associated with white-coat/masked/sustained hypertension were similar irrespectively of the method for diagnosis (using 24-h, day-time, or night-time records), but differed markedly between anti-hypertensive drug treated and untreated persons, with markedly more associations observed in the latter.

As in the present study, several risk factors have previously been associated with circadian hypertension phenotypes. For example, masked hypertension has been associated with age, higher BMI, smoking, excessive alcohol intake, and diabetes mellitus [39,48]; and nocturnal (hence masked) hypertension has been associated with sleep apnoea [48]. White-coat hypertension has previously been associated with age, obesity, and higher serum total cholesterol, triglycerides, and glucose [36,42]. Moreover, masked hypertension, rather than white-coat hypertension, was associated with eGFR. Masked hypertension has been associated with prognosis in non-dialysis CKD [49], and with risk of developing CKD [50].

Nocturnal hypertension and non-dipping

BP typically dips during the night by 10–20% [51]. Non-dipping (<10% decrease in BP at night) is associated with target organ damage and cardiovascular disease [52]. In the present cohort, the mean night-day blood pressure ratio on ABPM recordings was 0.87. Circa one in three were non-dippers, similar to previous observations in persons with hypertension [51]. Non-dipping was more common in older persons and those with anti-hypertensive treatment, similar to previous observations [45].

Blood pressure variability and measurement reproducibility

The long-term within-person BP reproducibility (between repeat ABPM measurements) was similar to that in previous studies among persons with hypertension, and on par with such variability in office BPs [8,9]. Such variability can be due to biological variability, e.g., differences in factors such as physical activity or sleeping hours, and to technical variability. The fact that variability was so large also in this study of the general population casts doubt on the superiority of ABPM over office BPs for treatment decisions and monitoring of treatment.

A positive association between BP level and short-term variability was observed in the present study, and within-person and between-person SD and CV were of similar magnitude. Short-term BP variability calculated by SD, CV, or ARV has been reported to be associated with subclinical organ damage and cardiovascular events [53]. The SD has been the most used parameter to assess short-term BP variability, but only reflects the dispersion of values around the mean without considering the order of BP measurements [54]. Hence, very different patterns of BP changes over time can yield the same SD [23]. ARV is the average of the absolute differences of consecutive measurements, thus reflecting the individual BP measurement order [54]. In our study, the higher the mean BP, the higher the SD and ARV. The reproducibility of BP variability measures is little known, as is their clinical utility.

Study strengths and limitations

This is one of the largest prospective community-based samples with 24-h ABPM globally, and the most contemporary; most 24-h ABPM studies have been based on clinical databases or multiple smaller and older cohorts. This study provides a detailed description of ABPM phenotypes in relatively healthy middle-aged persons, a target population for ABPM in current guidelines.

Some limitations are notable. The analysis used a cross-sectional design; longitudinal outcomes will only be available in the future. Anti-hypertensive drug treatment was recorded using a questionnaire, so recall bias with random misclassification is possible. The consistency of anti-hypertensive drug treatment between the two examinations in the reproducibility analyses was assured though manual chart review by one author (JS). Furthermore, we could not assess drug adherence, which may contribute to BP
phenotypes. The number of participants with repeated measurements of ABPM was small. We used narrow fixed clock-time intervals because of unavailability of awake and sleep time. The low frequency of nighttime BP measurements may affect variability measures somewhat. Lastly, generalisability to other ages, ethnicities and social circumstances than those included is unknown.

Conclusions

In the middle-aged general population, ABPM can identify important hypertension phenotypes. Masked hypertension is an underappreciated problem on the population level.

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Disclosure statement

Johan Sundström reports ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Eli Lilly, Boehringer, Bayer, Pfizer and AstraZeneca, outside the submitted work. All other authors report no conflicts of interest in connection with this study.

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