Prevalence, Causes, and Consequences of Masked Hypertension: A Meta-analysis

Willem J. Verberk\textsuperscript{1,2}, Alphons G.H. Kessels\textsuperscript{3} and Peter W. de Leeuw\textsuperscript{1,2}

BACKGROUND
Masked hypertension (MH) is a relatively newly detected condition of which little is known. More information about MH may help to improve overall antihypertensive health care. We aimed to investigate the prevalence, potential causes, and associated consequences of MH.

METHODS
We searched published literature using MEDLINE, EMBASE, and the Cochrane database completed with references cited in reviews and original study articles. We restricted our research to articles written in the English, German, French, and Spanish language. Studies were included only when the prevalence of MH was reported, office blood pressure (BP) values were given, and methods of BP measurements were described in detail. All data were extracted independently by two readers with a standardized protocol and data-collection form.

RESULTS
The prevalence of MH averaged 16.8% (95% confidence interval 13.0–20.5%). The MH prevalence was 7% for children and 19% for adults. MH prevalences did not differ significantly when determined with self or ambulatory BP measurement (21.1% vs. 16.8%; \(P = 0.42\)). Subjects with MH had significantly higher left ventricular mass index (LVMI) values than normotensives (110 vs. 98 g/m\(^2\); \(P < 0.01\)) but similar values as sustained hypertensives (109 g/m\(^2\)). In addition, patients with MH were more often smokers than normotensives (mean difference 18%; \(P < 0.03\)).

CONCLUSIONS
MH strikes about a quarter of the patients who were initially classified as normotensives (based on office BP measurements) and of treated hypertensives. Patients with MH seem to have a similar cardiovascular risk as sustained hypertensives but they may remain undetected. The presence of MH seems to be a matter of a coincidentally low office BP value not related to certain subject characteristics although the chance of its presence may be increased by smoking and antihypertensive treatment.


The widespread use of both self blood pressure measurements (SBPms) and ambulatory blood pressure monitoring (ABPms) has revealed two major forms of discrepancy between office blood pressure measurements (OBPms) and these out-of-office measurements. The first of these, white-coat hypertension (WC), has been extensively studied. WC can lead to unnecessary drug prescription but overall causes less harm for patients than sustained hypertension.\(^1\) The second form of discrepancy has only recently become a matter of interest. In this situation, BP is low when measured in the physician’s office but higher outside. This condition is commonly called masked hypertension (MH) but has also been labeled as: “isolated home hypertension”, “isolated ambulatory hypertension”, “reverse white-coat hypertension”, and “white-coat normotension”.\(^2\)

Several observations suggest that MH is not an innocent phenomenon but has (almost) similar risks for future cardiovascular events as sustained hypertensive patients have. This makes it essential to get more insight into the possible causes and consequences of MH so that adequate measures can be taken. In this article, we aimed at pooling data from studies that dealt with the subject of MH to estimate its prevalence and to assess any relationship with certain subject characteristics and target organ damage.

METHODS
We searched MEDLINE using the medical subject headings “prevalence”, “masked hypertension”, “isolated home hypertension”, “isolated ambulatory hypertension”, “reverse white-coat effect”, “reverse white-coat hypertension”, and “white-coat normotension”. We searched for additional studies manually using references cited in reviews and original study articles. We also interrogated the Cochrane and EMBASE database. We restricted our research to articles written in the English, French, German, and Spanish language. Eligibility criteria for inclusion were (i) studies had to report the prevalence of MH, or provide enough information to calculate this; (ii) BP values as measured in the office had to be available or could be retrieved; (iii) methods of BP measurement were described in sufficient
detail. A total of 252 papers were retrieved, of which 52 were identified as potentially eligible for the present analysis. Of these, 28 papers met the inclusion criteria and were used for the analysis. When studies clearly distinguished between certain patient groups (e.g., normotensives, hypertensives, random), treatment status intervention (untreated, treated, or both) or age, we considered such groups as different patient groups. All data were extracted independently by two readers (W.J.V. and P.W.L.), with a standardized protocol and data-collection form.

Statistical analysis. Analyses were performed with meta-analysis regression using the command “metareg” in Stata version 9.2 (StataCorp, College Station, TX). In studies that specified patient characteristics among patients with normotension (NT), masked hypertension (MH), white-coat hypertension (WC) and hypertension (HT) we pooled the results weighted with inverse variances (direct pooling) and investigated whether these differences were modified by age and sex. Heterogeneity was tested using I² statistics.

In an additional analysis we determined the odds ratios for smoking in these four groups using patients with MH as the reference group. To this end, we performed a logistic regression using subject categories (NT, MH, WC, and HT) and study centre as independent variable and smoking status (yes or no) as the dependent variable. For LVMI we did the same using linear regression.

RESULTS

Studies were performed among patients who, based on OBPM values, initially were classified as normotensives (6 studies), hypertensives (19 studies), or as hypertensives and NTs (11 studies). Seven studies were performed among children with mean ages from 10 to 15 years. In 12 studies subjects were treated for their hypertension, in 17 studies subjects were untreated, and in 7 studies both treated and untreated subjects were examined (Table 1). To ascertain the prevalence of MH, 28 studies followed the European Society of Hypertension guidelines: OBPM <140 and 90 mm Hg and SBPM (or daytime ABPM) ≥135 and/or 85 mm Hg for systolic and diastolic blood pressures (BPs), respectively and the 95th percentile threshold for normal BP in children. The total number of participants from all studies was 25,605 and ranged from 23 to 4,939 per study; mean age ranged from 10 to 72 years. The prevalence of MH among studies varied from 1 to 61%. The average prevalence from all studies weighted for the number of subjects was 16.8% (95% confidence interval 13.0–20.5%). The prevalence of MH was based on OBPM and SBPM data in 10 studies and on OBPM and ABPM data in 26 studies. The heterogeneity test showed that the proportion variation due to heterogeneity was 1 and did not decrease after including patient characteristics such as sex, age, body mass index (BMI), and smoking.

Figure 1 shows the MH prevalences of subjects <20 years of age and adults which were 6.8 ± 3.8 and 19.4 ± 3.8%, respectively.

For further analyses studies with adults (≥20 years) and children (<20 years) were separated. Analyses of studies with the adults did not show any relationship between the prevalence of MH and either smoking, type 2 diabetes mellitus or treatment status. Neither in adults nor in children the prevalence of MH was related to age, male gender, or BMI and was not influenced by the method of BP measurement (number of office and/or self-measurements, body position or device used).

The rest of the analyses were restricted to the adult population (≥20 years). In addition, to prevent bias caused by different threshold values, we only included studies that used 140 mm Hg for systolic BP as threshold values for OBPM and a threshold of 135 mm Hg systolic for SBPM or daytime ABPM. We also included one study that used 125/79 mm Hg as a threshold value for 24-h ABPM systolic and diastolic BP as this is also in accordance with the European Society of Hypertension guidelines. In total this comprised 20 studies.

Figure 2 shows the average prevalence of MH in adults separated for the clinical condition to which the study populations were initially classified (NT, HT, or both) and treatment status (treated, untreated, or both). The results indicate that subjects who were initially classified as normotensive (mean OBPM values 115/72 mm Hg) had the highest MH prevalences from all groups, whereas treated hypertensive patients (mean OBPM values 145/82 mm Hg) had the second highest prevalence of MH.

The group of treated hypertensive patients displayed a significant inverse relationship between MH prevalence and both systolic and diastolic OBPM values (r = −0.12, P < 0.03; r = 0.25, P < 0.05). This relationship could not be found in the remaining five groups (NT, NT + HT untreated, NT + HT untreated and treated, HT untreated, and HT untreated and treated).

When the diagnosis was based upon SBPM, MH prevalences seemed to be somewhat higher than when it was determined with ABPM but this difference was not statistically significant (21.1% vs. 16.8%; P = 0.42).

LVMI

Some studies specified LVMI among normotensives, masked hypertensives, white-coat hypertensives, and sustained hypertensives. These studies demonstrated that patients with MH have, on average, a significantly higher LVMI than normotensives but similar LVMI as sustained hypertensives (Figure 3). In addition, age significantly increased the LVMI difference between patients with MH and NT with 0.39 g/m² (P = 0.035).
## Table 1 | Characteristics of studies to masked hypertension

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The classifications such as those indicated under “Pop” were based on office blood pressure measurement (OBPM).

ABPM, ambulatory blood pressure measurement; Dia, diastolic blood pressure; DM, diabetes mellitus type 2; HT, subjects with hypertension; MH, subjects with masked hypertension; n, number of subjects; NT, subjects with normotension; Pop, population; SBPM, self blood pressure measurement; Sys, systolic blood pressure; Tr, treated; Untr, untreated; WC, subjects with white-coat hypertension. *OBPM–dayABPMl > −10 mm Hg; †95th percentile; ‡ABPM > OBPM; —, not specified.
Masked Hypertension

STATE OF THE ART

smoking

Studies that specified the percentage of smokers among normotensives, masked hypertensives, white-coat hypertensives, and sustained hypertensives showed that subjects with MH were more often smokers than normotensive and hypertensive subjects (Figure 4). For other subject characteristics that were specified for different groups such as BMI, age, percentage of treated patients, and patients with type 2 diabetes mellitus, this did not differ significantly between these four groups (data not shown).

DISCUSSION

The present analyses show that the prevalence of MH is on average 17% and highest among patients who were initially classified as normotensive (24%) and in those who were treated (22%). The diagnosis of MH may be based on either ABPM or SBPM as both methods yield almost similar prevalences of the condition (21.1% vs. 16.8%; \( P = 0.42 \)).

The occurrence of MH bears no relationship with age, gender, BMI, the percentages of smokers, patients with type 2 diabetes mellitus, or treatment status. However, analysis among studies that specified LVMI for each diagnostics group (NT, HT, MH, WC) separately, reveals that LVMI in patients with MH is significantly higher than that in normotensives but similar to that in sustained hypertensives. In addition, studies that specified the prevalence of smokers for each of the four groups separately showed that patients with MH were more often smokers than normotensive and white-coat hypertensive subjects.

The results of this study should be interpreted within the context of its limitations. Although several studies have addressed the prevalence of MH, the heterogeneity among the studies with respect to subjects, methodology, BP levels, and cut-off points may have led to large differences in prevalence and makes it difficult to interpret and to compare the data. In particular, SBPM-based studies were combined with those using ABPM. Although the results of Stergiou et al. have shown that...
both methods are appropriate for detecting MH, there is some discrepancy that could have influenced the results. The study of Ishikawa et al. was based on a population who was, according to their office BP measurements, normotensive with treatment. For this reason there were only two possibilities after ABPM was performed, either normotensive or masked hypertensive. Although the exclusion of hypertensive and white-coat hypertensive patients has led to an overestimation of MH prevalence, we choose to include these patients to illustrate that the prevalence of MH in treated hypertensive patients may be high.

Based on the results of this article one may be inclined to think that children have lower MH prevalences than adults have. However, the criteria of office hypertension and MH in children differ markedly from that in adults so that the MH prevalences cannot be compared between children and adults.

In this article we excluded studies that used threshold values which deviated consistently from those recommended by the European Society of Hypertension. Although analyses with and without these studies did not lead to different conclusions, it cannot be excluded that omitting these data has introduced some bias. Finally, for interpretation of the analysis of the LVMI it should be realized that this measure is inhomogeneous and thus could have led to different values between studies.

One of the first studies that dealt with the subject of MH was performed by Høegholm et al. They found that 5 from 159 subjects who were newly referred from primary health care to the hypertension clinic were considered normotensive by office measurements but hypertensive when evaluated by ambulatory BP measurement.

Some studies have investigated whether certain patient characteristics or habits are linked to MH which could help the physician to be more alert when a patient fits into that profile. For instance, MH populations have higher percentages of males, smokers, alcohol consumers, and antihypertensive drug users than truly normotensive populations. However, as there is large heterogeneity among studies, these results should be interpreted with caution. Recently, Ben-Dov et al. found an increased prevalence of masked BP elevations in treated diabetic subjects. This finding may be explained by hyperglycemia and accompanying metabolic abnormalities or by the lower sensitivity of clinic BP measurements in diabetic patients. Even more recently, Wang et al. showed in a population study of 694 Chinese subjects that the risk of MH increased with age (OR, 1.40) and BMI (OR, 1.12) and that women were less likely to have MH than men (OR, 0.39).

Our analysis confirmed that patients with MH are more often smokers. The reason for the association may be the fact that smoking increases BP, an effect that is absent during OBPM as patients commonly do not smoke in the hospital or at the general practitioner’s practice. Another important finding of this study was that subjects with MH have LVMI values that are higher than those in normotensive subjects but similar to those in hypertensive patients. This suggests that MH is associated with similar risks for developing cardiovascular events as sustained hypertension. As a matter of fact, the risk may even be higher as subjects with MH may remain undetected and devoid of antihypertensive treatment. The results of this study seem to confirm earlier findings from several studies. In addition, Fagard et al. performed a meta-analysis with seven studies, involving 11,502 participants. They found that, during an average follow-up period of 8 years, overall adjusted hazard rates for the incidence of cardiovascular events were 1.12 (95% confidence interval 0.84–1.50) for WC ($P < 0.59$), 2.00 (1.58–2.52) for MH ($P < 0.001$), and 2.28 (1.87–2.78) for HT ($P < 0.001$) as compared to sustained normotensive patients.

Accordingly, patients with MH probably are true hypertensives and it is questionable, therefore, whether MH should be considered as a separate entity. In fact the condition may just result from a coincidently low OBPM value at one particular occasion. In fact the condition may just result from a coincidently low OBPM value at one particular occasion. However, a recent study of Ben-Dov et al. among 25 patients with MH showed a reproducibility of 72%.

The results of this study indicate that MH is a commonly occurring phenomenon that could be found in any patient. A study by Sega et al. showed that patients with MH had a cardiovascular risk profile that lay in between normotensive and hypertensive subjects. Clement et al. have shown that patients who are seemingly well treated on the basis of OBPM, still have exaggerated risk when their ABPM is high. All these observations argue against the notion that MH is an innocuous condition. Patients with BP values close to the threshold for normal BP have a greater chance of being diagnosed as having MH than patients with higher BP levels, which may explain that LVMI and albuminuria levels are still somewhat lower than in sustained hypertension. This finding was partly confirmed in the present analysis where a significant relationship was found between MH prevalence and OBPM values in treated hypertensive patients.

There is some debate about whether one can speak of MH when a patient is being treated and thus has already been diagnosed with hypertension. However, this study demonstrated that treated patients in particular often show an MH effect. As the lack of treatment effect may be masked when BP is normal in the office and elevated outside, the physician should be aware of this phenomenon in these patients. Therefore, it seems reasonable to consider MH as a characteristic feature which is independent of treatment status. In addition, the high MH prevalence among treated hypertensives suggests that it may even be caused by treatment as, for instance, patients could have taken their medication before the OBPM and/or the drug may have a short-lasting effect.
From the results of the present analyses we conclude that the prevalence of MH can be very high, particularly in subjects who have initially been classified as normotensive based on earlier office measurements and in treated hypertensive patients, where it seems to strike almost a quarter of the population. Because there is no single cause for MH except that it occurs more frequently in smokers and in those on treatment, the presence of MH mainly seems to be a matter of a coincidently low office BP value that can be found in any patient. For that reason SBPM as a cheaper alternative to ABPM may help in detecting MH and thus help improve antihypertensive treatment.

Disclosure: The authors declared no conflict of interest.


