

Incident Left Ventricular Hypertrophy in Masked Hypertension

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Abstract—In the PAMELA study (Pressioni Arteriose Monitorate e Loro Associazioni), clinical variables, an echocardiogram, as well as office and ambulatory blood pressure (ABP) were simultaneously measured at baseline and after a 10-year follow-up. The study design allowed us to assess the value of masked hypertension (MH) as a predictor of new-onset left ventricular hypertrophy (LVH). The present analysis included 803 participants without LVH at baseline (left ventricular mass index <115 g/m² in men and <100 g/m² in women). Based on office and 24-hour mean ABP values, subjects were divided into 3 groups: normal subjects (normotensive, office blood pressure [BP] <140/90 mmHg and 24-hour mean ABP <130/80 mmHg), MH (office BP, normal, and 24-hour mean ABP, elevated), and sustained hypertension (office and 24-hour BP, both elevated). At entry, 57 of 803 subjects fulfilled diagnostic criteria for MH (7.1%); 182 participants developed LVH (22.6%). Compared with subjects with normal in-office and out-of-office BP, the risk of new-onset LVH was greater in MH (odds ratio, 2.22; CI, 1.11–4.46, $P=0.0250$) after adjustment for potential confounders. This was also the case for the absolute increase of left ventricular mass index. Our study provides a new piece of evidence that MH, identified by office and ABP values, is associated with an increased risk of new-onset LVH. Moreover, our findings convey the notion that office BP may inaccurately estimate the risk of incident LVH in the general population. (*Hypertension*. 2019;74:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.12887.) • [Online Data Supplement](#)

Key Words: blood pressure ■ follow-up studies ■ humans ■ masked hypertension ■ risk



Hypertension adversely affects left ventricular (LV) structure and function by inducing a wide array of abnormalities, including myocyte hypertrophy, fibrosis, and alterations of both LV contractility and relaxation.^{1,2} LV hypertrophy (LVH)—the cardinal biomarker of subclinical cardiac damage—is the result of LV exposure to pressure overload combined with a variety of nonmodifiable and modifiable cardiovascular risk factors.^{3–5}

Although elevated blood pressure (BP) is regarded as the most important trigger of LVH development, BP load assessed by standard office measurements accounts for only 20% to 25% of the observed LV mass variance.⁶ Several lines of evidence have shown that BP measured outside the medical environment is more closely associated to subclinical organ damage, including LVH, compared with traditional measurements in the physician's office.^{7,8}

In the last few decades, the use of combined office and out-of-office (ambulatory or home) BP measurements has provided an accurate information on the association of different BP patterns, that is, sustained hypertension (SH), white coat hypertension, and masked hypertension (MH; normal office and elevated out-of-office BP) with LVH.^{9,10} In particular, a

consistent body of evidence by cross-sectional studies and their meta-analysis supports the view that in MH individuals, both LV mass (LVM) and LVH prevalence are increased compared with individuals with normal office and out-of-office BP.^{11–14} Unfortunately, with the exception of a small study on Chinese adolescents, in which persistent MH was associated with the development of greater LVM values compared with no persistent MH or normotension,¹⁵ this cross-sectional evidence has never been complemented by longitudinal studies on the long-term risk of MH for incident LVH. Thus, the question about the independent role of this condition in the development of subclinical cardiac damage remains unanswered. Also unanswered is the question about whether the risk of incident LVH in MH subjects compared with patients with SH, that is, with in-office and out-of-office BP elevation, is similar or different.

We have addressed this issue in the PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) population, taking advantage of the fact that an echocardiographic examination, office BP measurements, and ambulatory BP (ABP) measurements were obtained in all participants at baseline and 10 years later.

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Methods

Data to verify study outcomes are available on request to the corresponding author from qualified clinical researchers with approval by an institutional review board.

The PAMELA study was performed in 3200 subjects representative of the population of Monza (a town near Milan, Italy) for sex, age (25–74 years), and other characteristics. Participation rate was 64%, and data of 2051 subjects were available. Demographic and clinical characteristics of participants and nonparticipants, as assessed by phone interviews, were similar.

As described in detail elsewhere,¹⁶ after an informed consent, participants were invited to attend the outpatient clinic of S. Gerardo Hospital of Monza in the morning of a working day (Monday to Friday), after an overnight fast and abstinence from alcohol and smoking since the previous day. Data collection included medical history, weight, height, office BP, ABP, standard blood examinations, and LVM as assessed by echocardiography. Office BP was measured 3× with the subject in the sitting position, using a mercury sphygmomanometer and taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. To measure ABP, subjects were fitted with an ABP-monitoring device (Spacelabs 90207; Issaquah, WA) set to obtain automated BP and heart rate oscillometric readings every 20 minutes over 24 hours. The subjects were asked to pursue their normal activities during the monitoring period with the precaution of holding the arm still at time of BP readings, going to bed not later than 11:00 PM and arising not before 7:00 AM.

Participants with normal office BP values at entry (<140/90 mmHg, mean of 3 values, see below) were divided into 2 groups: true normotensives and MHs, based on 24-hour mean BP values in the normal or elevated range according to the hypertension

guidelines,^{17,18} that is, <130 mmHg or ≥130 mmHg systolic and 80 mmHg diastolic BP, respectively. As in the PAMELA population, the corresponding cutoff dividing normotension from hypertension in 24-hour mean ABP values was 125/79 mmHg,¹⁶ subjects were divided into true normotensives and MHs also according to this more restrictive cutoff. Data were compared with a third group of subjects, that is, those with elevated both office and 24-hour mean BP, the latter again according to guidelines and PAMELA normal criteria.

Echocardiography

Echocardiographic data were collected according to standard procedures, as previously reported.⁶ In brief, M-mode and 2-dimensional echo examinations were performed with a commercially available instrument (Acuson 128 CF; computer sonography). End-diastolic (d) and end-systolic (s) LV internal diameters (LVID), interventricular septum (IVS), and posterior wall (PW) thickness were measured off-line from 2-dimensionally guided M-mode tracings recorded at 50 to 100 cm/s speed, during at least 3 consecutive cycles. LVM was estimated by using the corrected American Society of Echocardiography method: $0.8 \times (1.04 \times [(IVSd + LVIDd + PWTd)^3 - LVIDd^3]) + 0.6$ ¹⁹ and normalized to body surface area. Echocardiographic tracings were obtained by 2 skilled operators and read by a third independent observer: intraobserver coefficient of variation was 0.6% for LVIDd, 3.1% for IVSd thickness, and 3.2% for posterior wall thickness diastole thickness. LVH was defined as LVM index (LVMI) equal to or higher than 115 g/m² in men and 100 g/m² in women.⁶ This was based on data from sex-specific upper normal limits (mean+1.96 SD) for LVMI in 675 healthy individuals (284 men and 391 women) with sustained normal BP, as assessed by in-office and out-of-office BP measurements.⁶

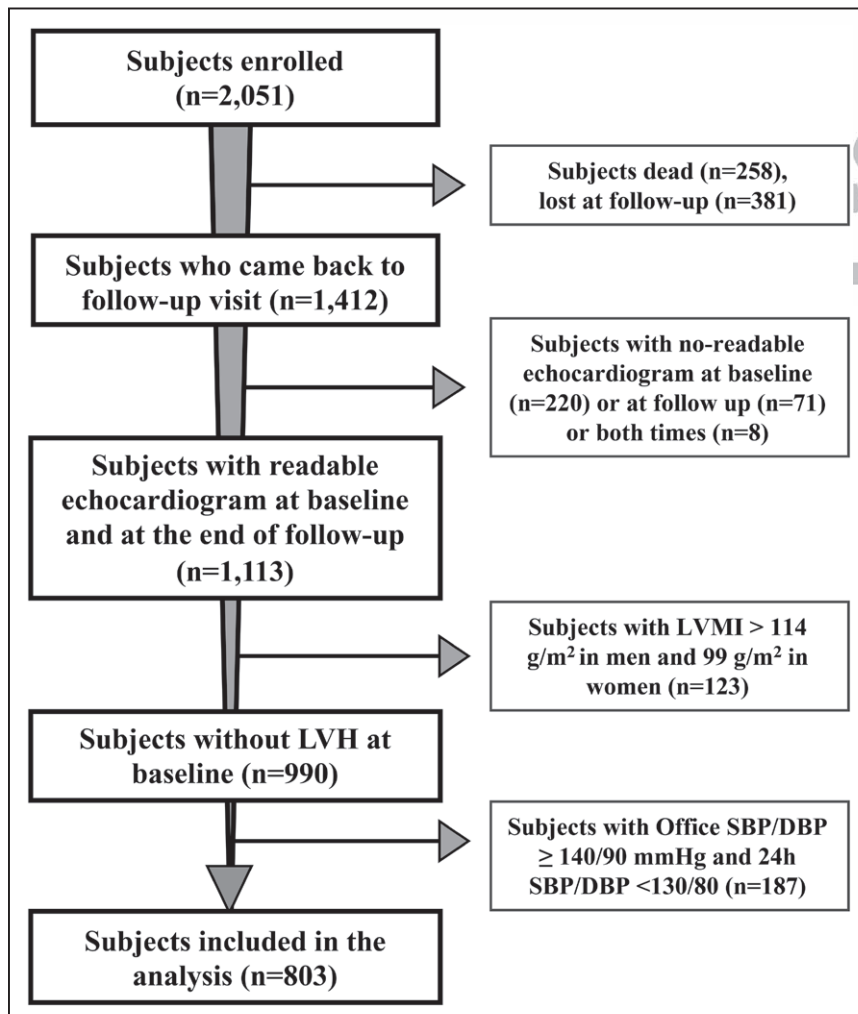


Figure 1. Flowchart reporting the selection of the study population sample included in the present analysis. DBP indicates diastolic blood pressure; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; and SBP, systolic blood pressure.

Follow-Up

All participants were followed from the time of the initial medical visit (from 1990 to 1993) to September 30, 2003. Participants were contacted from 2001 to 2003 (after a total time interval of 10.7 ± 0.61 years), and survivors ($n=1843$) willing to be reexamined were asked to attend the San Gerardo Hospital for a second echocardiographic examination, as well as for recollection of clinical data. As shown in the flowchart, a total of 1412 subjects agreed to be reexamined, and 1113 of them had a valuable echocardiogram. A total of 310 were also excluded from the analysis because 123 of them had LVH at baseline and 187 had white coat hypertension, the final population, thus, including 803 individuals (Figure 1).

Data Analysis

In each subject, the 3 office BP measurements were averaged. ABP readings were also averaged after editing for artifacts and analyzed to obtain 24-hour mean (\pm SD) systolic/diastolic BP. The same procedure was applied to heart rate. The incidence (%) of LVH was calculated as the presence of LVH at the second examination in subjects with normal LVMI at baseline. Values are expressed as means \pm SD or percentages. Comparisons between groups were performed by *t* test or ANOVA with Bonferroni correction (mean values) and by χ^2 test or Fisher exact test (prevalence). Trend was tested by linear regression model (mean values) or Cochran-Armitage trend test (prevalence). Logistic regression was used to estimate the odds ratio of new-onset LVH in MH patients, having the group with normal office and ABP as reference. Models were as follows: (1) unadjusted model; (2) model adjusted for age, sex, baseline LVMI, body mass index (BMI) change, antihypertensive drugs, clinic systolic BP change, and 24-hour systolic BP change; and (3) model adjusted for age, sex, baseline LVMI, BMI change, antihypertensive drugs, clinic diastolic BP change, and 24-hour diastolic BP change. Logistic model was also used to calculate odds ratio trend. Calculations were extended to LVMI changes during follow-up and to the group of patients with SH

but no LVH at entry. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed by SAS System (version 9.4; SAS Institute, Inc, Cary, NC).

Results

The present analysis included 803 participants with no LVH at baseline and a measurable LVMI at the follow-up examination performed 10 years later. In this population sample, the prevalence of MH at the initial evaluation was 7.1%. The Table reports clinical data at entry and at the end of follow-up period. At baseline, subjects with MH showed a greater male prevalence, age, body surface area, BMI, office and 24-hour heart rate, office and 24-hour mean systolic/diastolic BP, and LVMI compared with subjects with true normotension (normal office and ABP). Baseline blood glucose, total serum cholesterol, serum creatinine, and prevalence of antihypertensive drug treatment were similar in the 2 groups. These differences were even more evident between the true normotension and the SH group, in which antihypertensive drug treatment was more frequent. At the end of the follow-up period, the percentage of subjects treated with antihypertensive drugs was significantly increased in all 3 groups. This trend was associated with a parallel increase in BMI values.

New-Onset LVH and LVMI Increase

A total of 182 of 803 subjects with normal LVMI at the initial evaluation developed LVH (22.6%) during follow-up. A similar incidence (23.5%) was found when LVH was defined according to European Society of Hypertension/European

Table. Entry and Follow-Up Demographic and Clinical Characteristics of the Participants of the PAMELA Population Who Were Classified Into 3 Groups (ie, NT, MH, and SH) by Office and 24-h Ambulatory Blood Pressure

Variable	NT		MH		SH		P_{trend}	
	Baseline	10 y later	Baseline	10 y later	Baseline	10 y later	Baseline	10 y later
No. of subjects	625		57		121			
Male prevalence, %	44.3*†		70.2		70.2		<0.0001	
Age, y	43.2 \pm 12.1*†	53.9 \pm 11.9*†	48.1 \pm 11.6†	58.8 \pm 11.6†	55.1 \pm 10.9	65.5 \pm 10.5	<0.0001	<0.0001
BSA, m ²	1.71 \pm 0.18*†	1.8 \pm 0.2*†	1.81 \pm 0.2	1.9 \pm 0.2	1.80 \pm 0.18	1.8 \pm 0.2	<0.0001	0.0001
BMI, kg/m ²	24 \pm 3.4*†	25.6 \pm 4*†	26.3 \pm 3.7	27.9 \pm 3.9†	26.4 \pm 3.6	27.5 \pm 3.7	<0.0001	<0.0001
SBP office, mm Hg	117.6 \pm 10.1*†	127.7 \pm 18.1*†	126.7 \pm 7.1†	136.4 \pm 17.6†	151 \pm 17.5	152.9 \pm 22.1	<0.0001	<0.0001
DBP office, mm Hg	76.9 \pm 6.8*†	80.8 \pm 9.7*†	82.5 \pm 4.5†	85.3 \pm 9.7	94.9 \pm 7.5	89.1 \pm 11.2	<0.0001	<0.0001
HR office, bpm	69.7 \pm 8.6†	73.2 \pm 9.9	70 \pm 9	73.5 \pm 11.1	73.3 \pm 10.6	74.8 \pm 12.4	0.0002	0.1122
SBP, 24 h; mm Hg	113.2 \pm 6.8*†	119.2 \pm 10.1*†	127.6 \pm 5.5†	128.6 \pm 10.1	133.1 \pm 9.2	132.5 \pm 11.9	<0.0001	<0.0001
DBP, 24 h; mm Hg	70.6 \pm 4.9*†	73.4 \pm 7.1*†	81.6 \pm 4.6	79.2 \pm 8.3	83.4 \pm 4.9	78.9 \pm 7.7	<0.0001	<0.0001
HR, 24 h; bpm	75.6 \pm 7.9*	73.4 \pm 8.6	80.2 \pm 8.9	74.9 \pm 10	77.1 \pm 9.2	72.9 \pm 9.9	0.0085	0.8058
Antihypertensive drugs, %	4.0†	13.1*†	7.0†	35.1†	30	72.7	<0.0001	<0.0001
LVMI, g/m ²	77.1 \pm 14.1*†	88.7 \pm 20.3*†	83.3 \pm 14.2†	102 \pm 21.5	88.8 \pm 13.4	109.4 \pm 24.4	<0.0001	<0.0001
Serum cholesterol, mg/dL	212 \pm 40.8*†	201.9 \pm 33.9	225.8 \pm 44.1	207.8 \pm 39.2	228.2 \pm 40.2	206.5 \pm 40.1	<0.0001	0.1300
Blood glucose, mg/dL	85.3 \pm 12.8*†	89.3 \pm 16.8*†	93.6 \pm 28.9	97.3 \pm 21.1†	96.9 \pm 24	109.4 \pm 41.8	<0.0001	<0.0001
Serum creatinine, mg/dL	0.86 \pm 0.15†	0.89 \pm 0.18†	0.88 \pm 0.14	0.92 \pm 0.25	0.92 \pm 0.17	0.97 \pm 0.24	0.0002	<0.0001

BMI indicates body mass index; BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; MH, masked hypertensive; NT, normotensive; PAMELA, Pressioni Arteriose Monitorate e Loro Associazioni; SBP, systolic blood pressure; and SH, sustained hypertensives.

* $P < 0.05$ vs MH.

† $P < 0.05$ vs SH.

Society of Cardiology guidelines.¹⁸ As shown in Table S1 in the [online-only Data Supplement](#), subjects who developed LVH exhibited a number of baseline differences compared with those who did not, that is, older age, greater male prevalence, greater LVMI, higher office and 24-hour mean BP values, more frequent antihypertensive drug treatment, and worse metabolic risk profile.

During the 10 years of follow-up, office systolic and diastolic BP increased by $8.7\pm 13.2/5.3\pm 12.2$, $7.8\pm 13.1/3.6\pm 12$, and $1.7\pm 13.3/-5.7\pm 12.1$ mmHg in true normotensive, MH, and SH subjects, respectively. The corresponding 24-hour BP changes were $5.3\pm 7.8/4\pm 8.5$, $1\pm 8.3/-2.7\pm 9.8$, and $-0.3\pm 8.5/-5.3\pm 9.1$ mmHg, respectively.

In MH subjects, LVMI consistently increased by 60%, and the cumulative LVH incidence in this group was $\approx 2\times$ greater compared with normotensive subjects (35.1% versus 16.6%). In SH, a further slight increase in both LVH incidence and LVMI increment was observed (Figure 2A and 2B). As shown in Figure 3, the unadjusted risk of incident LVH was significantly greater in MH subjects compared with true normotensives, a small further increase being observed in SH. This was also the case after adjustment of data for potential demographic and clinical confounders, including prevalence

of antihypertensive treatment or the extent of both office and 24-hour mean systolic or diastolic BP and BMI change during the follow-up period. Similar differences were observed after analysis of data based on the lower 24-hour BP cutoff value ($\geq 125/79$ mmHg; see Methods). As expected, a higher prevalence of MH (12.5%) was obtained by the application of this more restrictive criterion for definition of normal ABP values; also in this larger group of MH subjects, the fully adjusted risk of incident LVH was significantly higher than in normotensives (Figure 4).

Discussion

The most important result of the present analysis of the PAMELA population is that MH individuals at entry showed a much greater incidence of new-onset LVH over a 10-year follow-up compared with individuals with normal office and ABP values at entry (35.5% versus 16.6%). Of note, the risk of developing this subclinical cardiac damage in MH subjects was still more than doubled compared with control subjects after adjustment for relevant confounders, and was not lower than that associated to SH. This allows to conclude that individuals of the general population exhibiting normal office but elevated ABP, that is, a MH condition, have an increased long-term risk

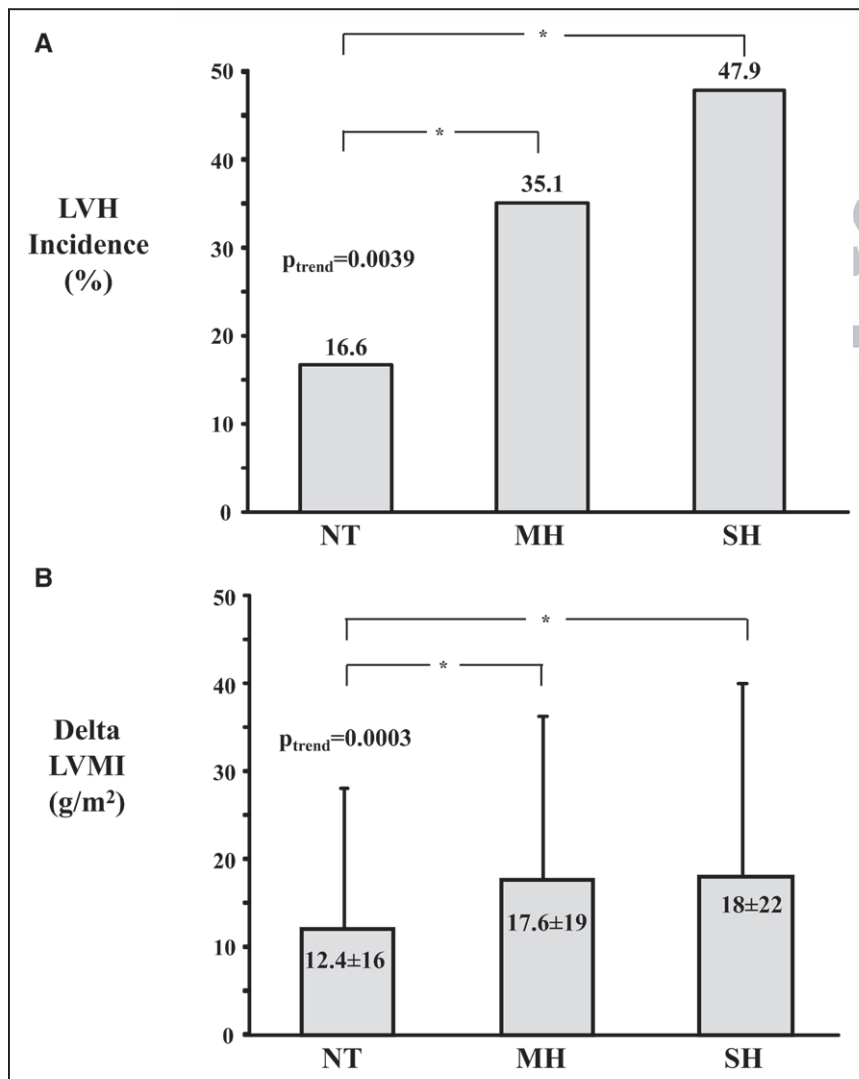


Figure 2. Incidence rates of new-onset left ventricular hypertrophy (LVH) according to sex-specific cutoff values of LV mass index (LVMI) in normotensives (NT), masked hypertensives (MH), and sustained hypertensives (SH) during a 10-y follow-up period. * $P < 0.05$. Average increase of LVMI in NT, MH, and SH during a 10-y follow-up period. * $P < 0.05$ adjusted for age, sex, and baseline LVMI.



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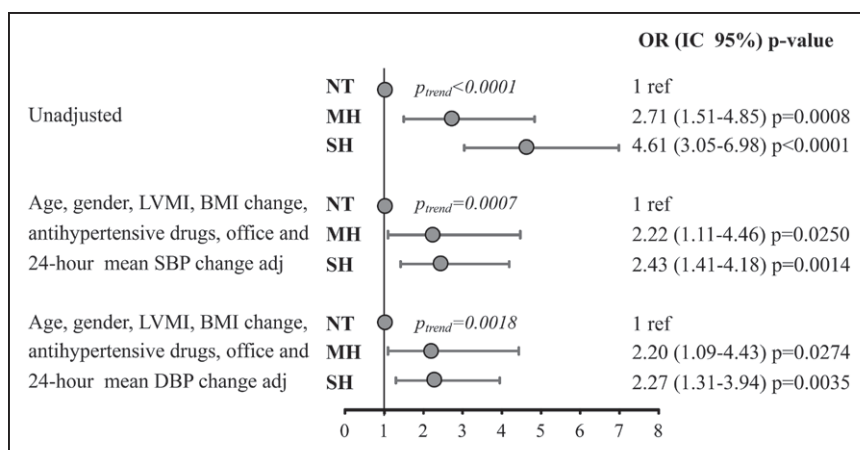


Figure 3. Odds ratio (OR) and 95% CI, for new-onset left ventricular hypertrophy (LVH) during a 10-y follow-up period in normotensives (NT), masked hypertensives (MH), and sustained hypertensives (SH). Data are shown as follows: (1) unadjusted model; (2) model adjusted (adj) for age, sex, baseline left ventricular mass index (LVMI), body mass index (BMI) change, antihypertensive drugs, clinic systolic blood pressure (SBP) change, and 24-h SBP change; and (3) model adjusted for age, sex, baseline LVMI, BMI change, antihypertensive drugs, clinic diastolic blood pressure (DBP) change, and 24-h DBP change.

of developing LVH. Because LVH is independently associated with a higher risk of cardiovascular outcomes,^{20,21} this finding may explain the relationship of MH with an increased risk of cardiovascular morbid and fatal events.²²

Several additional results of our study deserve to be mentioned. First, the higher risk of new-onset LVH in MH individuals compared with true normotensives was even more evident in the larger MH sample defined according to the more restrictive ABP upper normal limits.

Second, compared with the control population, MH also exhibited a greater absolute 10-year increase in LVMI values; thus, it is unlikely that the greater risk of new-onset LVH in MH was related to the higher LVMI values at entry, already close to cutoff value for LVH definition. As the relationship of LVMI with outcomes is known to persist down to low LVMI values,²⁰ also LVMI increases below the LVH threshold are clinically relevant.

Third, the increased risk of new-onset LVH, as well as the magnitude of LVMI increments observed in MH individuals, was only slightly lower than that observed in individuals with SH. This is in line with previous outcome-based observations,^{23,24} as well as with the 2018 European Society of Hypertension/European Society of Cardiology hypertension guidelines, considering this as a reason for implementing antihypertensive treatment.¹⁸

Fourth, the common notion that LVMI progressively increases from young adulthood to the middle and old age is largely based on cross-sectional comparisons of subjects with different ages, rather than on longitudinal studies documenting the rate of age-related progression from normal cardiac morphology to LVH in individuals during long follow-ups.²⁵ For this reason, the extent of the dynamic LVMI changes across adult life span and the progression to LVH may have been underestimated, to date. In a community-based cohort of middle aged to older adults belonging to the Framingham Heart Study, progression from normal geometry/concentric remodeling to eccentric/concentric hypertrophy during a 4-year follow-up was infrequent (4%–8%).²⁶ This was the case also in an Asian community-based cohort of women aged >65 years, in which only 10% of subjects developed LVH at the second echocardiographic examination during a 5-year follow-up.²⁷ At variance from these reports, our longer term study supports the view that a relatively large fraction of normotensive subjects from a general population-based

sample (≈1 of 5 subjects) may progress to LVH and develop an echocardiographic phenotype of adverse prognostic significance.²⁸ The incidence of new LVH in the PAMELA normotensive population was even higher than that observed in the CARDIA study (Coronary Artery Risk Development in Young Adults), in which LVMI changes were assessed after 20 years in participants aged 23 to 35 years at the initial evaluation.²⁹ In that population, the prevalence of LVH increased by ≈13%, the difference being probably related to the older age of participants included in our study (mean age, 50 years).

Finally, previous studies addressing the determinants of new-onset LVH in the community (or in hypertensive cohorts) have shown that this condition is promoted by a complex interplay of modifiable and nonmodifiable factors.³⁰ In all reports, aging was found to be a key predictor of new-onset LVH, as a likely result of long-term exposure to factors promoting LVM increase.

In this context, our observation that LVH incidence was markedly increased in subjects with MH over the 10-year follow-up emphasizes the role of 24-hour ABP values on LVH development, these values likely reflecting the integrated pressure load on LV over the circadian cycle. In previous studies,

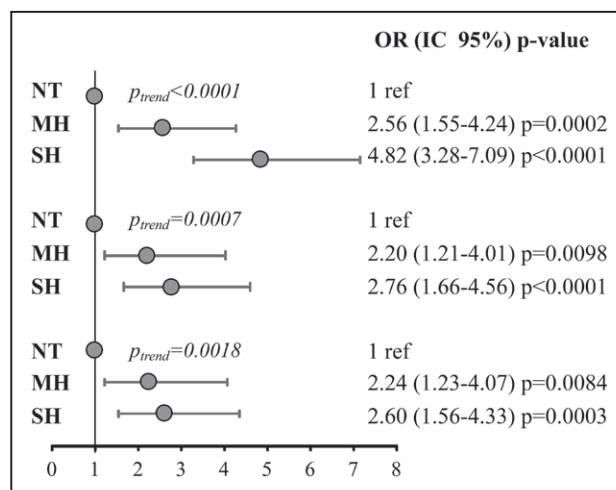


Figure 4. Odds ratio (OR) for new-onset left ventricular hypertrophy (LVH) during a 10-y follow-up period in subjects with normotension (NT), masked hypertension (MH), and sustained hypertension (SH). Data are shown unadjusted and adjusted as described for Figure 3. MH was defined by a 24-h mean blood pressure ≥125/79 mmHg. SBP indicates systolic blood pressure.

including a large meta-analysis of 12 studies for a total of 4884 patients,¹² this relationship was only inferred by the closer cross-sectional association of LVM and LVH with ABP compared with office BP.

MH is a BP phenotype characterized by a cluster of cardiovascular risk factors, which likely play a role in LV remodeling toward LVH, in addition to elevated out-of-office BP.³¹ Furthermore, our observation that LVH was more frequent among MH subjects who developed SH suggests that multiple BP features may complement ABP in the development of LVH.

Our study has strengths and limitations. Strengths are the standardized longitudinal data collection, long-term follow-up, evaluation of multiple risk factors, echocardiographic examination, and quality of office and ABP measurements in the whole sample. As for the limitations, our findings refer to a Mediterranean population, and extrapolation to populations with different demographic and clinical characteristics should be done with caution. Furthermore, participants on antihypertensive therapy were not excluded from our study to reflect real-world conditions at population level.

In conclusion, our study shows that MH carries an increased risk of new-onset LVH, independently of confounders. To available evidence, our findings add the notion that this condition represents a risk for the development of a prognostically adverse cardiac damage.

Perspectives

The present study also reinforces the notion that BP status only assessed by in-office measurements is inaccurate in assessing total cardiovascular risk and in particular in estimating the long-term risk of incident LVH in the general population.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The evidence of an association between masked hypertension (MH) and left ventricular hypertrophy (LVH) has never been complemented by longitudinal studies on the long-term risk of MH for incident LVH, leaving the question of the independent role of this condition for the development of this marker of cardiac damage unanswered. Also unanswered is the question whether the risk of incident LVH in MH subjects is similar or different from that of patients with sustained hypertension.

What Is Relevant?

- Our study shows that MH carries an increased risk of new-onset LVH, independently of confounders, adding to the available evidence that this condition represents a risk for the development of prognostically adverse cardiac damage.

Summary

Our findings provide a new piece of evidence that MH, identified by office and ambulatory blood pressure values, is associated with a marked increase in the risk of new-onset LVH in the general population.



Hypertension