Metabolic Syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study

Daily Life Blood Pressure, Cardiac Damage, and Prognosis

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Abstract—The prevalence of the metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III criteria) and its relationships with daily life blood pressures, cardiac damage, and prognosis were determined in 2013 subjects from a Northern Italian population aged 25 to 74 years. Home blood pressure, 24-hour blood pressure, and left ventricular mass index (echocardiography) were also measured. Cardiovascular and noncardiovascular deaths were registered over 148 months. Metabolic syndrome was found in 16.2% of the sample, an office blood pressure elevation being the most frequent (95.4%) and the blood glucose abnormality the least frequent (31.5%) component. There was in metabolic syndrome a frequent elevation in home and/or 24-hour average blood pressure, as well as a greater left ventricular mass index and prevalence of left ventricular hypertrophy, which was manifest even when data were adjusted for between-group differences, including blood pressure. The adjusted risk of cardiovascular and all-cause mortality was greater in metabolic syndrome subjects (+71.0% and +37.0%; $P<0.05$), a further marked increase being observed with left ventricular hypertrophy or "in-office" and "out-of-office" blood pressure elevations. The increased risk was related to the blood pressure and the blood glucose component of metabolic syndrome, with no contribution of the remaining components. Thus, metabolic syndrome is common in a Mediterranean population in which it significantly increases the long-term risk of death. Cardiac abnormalities and increases in home and 24-hour blood pressure are common in metabolic syndrome, and their occurrence further enhances the risk. The contribution of metabolic syndrome components to the risk, however, is unbalanced and mainly related to blood pressure and glucose abnormalities. **(*Hypertension*. 2007;49:40-47.)**

Key Words: metabolic syndrome ■ blood pressure ■ cardiac hypertrophy ■ cardiovascular morbidity ■ cardiovascular mortality

In the last few years, growing attention has been devoted to a condition defined as metabolic syndrome (MS) based on the various clustering of alterations in glucose and lipid metabolism and blood pressure (BP). Several studies have shown that this syndrome has a high prevalence in many populations from various continents.[1–5] Cross-sectional and longitudinal studies have also shown that MS is associated with an increase in risk of cardiovascular (CV) disease and death,[5,6–15] posing the problem of which therapeutic interventions are needed to protect affected individuals.

In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study, we measured office, home, and ambulatory BP together with a number of metabolic and echocardiographic variables in a large sample of a population from an urban district in the northeast outskirts of Milan. Patients were then followed for >12 years during which information on the incidence of CV and all-cause deaths was obtained by collection of death certificates. This gave us a chance to obtain, in the context of a general population, information on several issues of clinical relevance on which previous information is limited or absent: first, the relationship that this condition has with BPs measured not only by the physician but also at home and over the 24 hours; second, whether in line with the reported greater prevalence of renal and vascular subclinical damage,[16–19] subjects with MS have an increased prevalence of cardiac subclinical damage compared with those without MS; third, the MS-associated risk of death over a time span longer than that provided by previous studies, as well as the contribution to this risk of "out-of-office" BP values and echocardiographic abnormalities.

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Methods

The methodology used in the PAMELA study is available in detail elsewhere.[20,21] An expanded Methods section is available in an online supplement available at http://www.hypertensionaha.org. Briefly, 3200 individuals were randomly selected from the residents of Monza (a town in the northeast area of the Milan province) to be representative of the local population for gender, age (25 to 74 years), and socioeconomic characteristics. The overall participation rate was 64%. All of the subjects gave their written consent to the study after being informed of its nature and purpose. The study protocol was approved by the Ethics Committee of one of the institutions involved (Centro Auxologico Italiano, Milan).

Entry Data

Participants were invited to come to the outpatient clinic of the local hospital (San Gerardo) in the morning of a working day (Monday through Friday) where several data were collected. Those relevant to the present study include the following: (1) 3 sphygmomanometric BP values with the patient in the sitting position; (2) 3 heart rate measurements (radial pulse), that is, 1 after each BP measurement; (3) a 24-hour ambulatory BP monitoring through an oscillometric device with the BP readings set at 20-minute intervals[20,21]; participants were sent home with instructions to hold the arm immobile at the time of the measurements, to keep a diary of daily activities and quality of night rest, and to return to the hospital for the device removal 24 hours later; (4) 2 home BP measurements (approximately at 7:00 AM and 7:00 PM) through a validated semiautomatic device[20,21]; (5) measurements of waist circumference, fasting venous plasma glucose, high-density lipoprotein (HDL) cholesterol and triglycerides; and (6) echocardiographic assessment of left ventricular mass indexed to the body surface area (LVMI) calculated by the Devereux formula.[22] Left ventricular hypertrophy (LVH) was defined as an LVMI >111 g/m^2 in men and >106 g/m^2 in women.[23]

Follow-Up

From the time of the medical visit to October 1, 2004, the survival state was ascertained by telephone interview, and a copy of the death certificate was obtained in all of the subjects who had died. The causes of death reported in the certificate were coded according to the *International Classification of Diseases, 10th Revision*.[24]

Data Analysis

The 3 office and the 2 home BP measurements were separately averaged. Ambulatory BP values were edited from artifacts according to preselected criteria[20,21,25] and averaged for the 24 hours, the daytime (7:00 AM to 11:00 PM), and the nighttime (11:00 PM to 7:00 AM). Averages were also calculated for the corresponding office, home, and 24-hour heart rate values. Diagnosis of MS was made according to the 2003 National Cholesterol Education Program Adult Treatment Panel III criteria,[2,26] that is, when ≥ 3 of 5 abnormalities were concomitantly present (increased waist circumference, impaired fasting glucose, BP elevation, reduced HDL cholesterol, and increased plasma triglyceride levels). Prevalence of MS was expressed as a percentage of the total sample, as well as of a variety of subgroups. Calculation was made of the number (%) of CV or all-cause death in subjects with and without MS using the whole population sample or excluding from the analysis subjects with diabetes (plasma glucose levels ≥ 126 mg/dL or antidiabetic treatment), hypertension (office BP ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic or antihypertensive treatment), or hypercholesterolemia (total serum cholesterol >200 mg/dL or hypolipidemic treatment). Data from subjects with and without MS were compared by the *t* test for unpaired observations. Kaplan–Meier survival curves were calculated for the 2 groups based on CV and all-cause death, with their comparison being made via the log-rank test. The risk of all-cause and CV death for subjects with MS was expressed as hazard ratio ($\pm$95% CI) versus those without MS using the Cox proportional hazard models. The likelihood ratio test was used to calculate the predictive value for CV and all-cause death of individual components and combined components of MS, using dichotomized data for each component. Calculation was also made of the addition to the risk associated with MS of LVH and elevations of home and 24-hour average BP. Home BP elevations were regarded to be values ≥ 122.1 mm Hg systolic or 77.7 mm Hg diastolic, whereas 24-hour BP elevations were regarded to be 118.7 mm Hg systolic or 75.3 mm Hg diastolic, that is, the values corresponding with office BP values ≥ 130 mm Hg systolic or 85 mm Hg diastolic in the asynthotic normal distribution of the BP values of the PAMELA population.[27] All of the statistical analyses were made before and after adjustment for age, gender, smoking habits, alcohol consumption, and history of CV events using ANOVA for continuous variables and for the categorical ones. LVMI data (mean values and LVH prevalence) were compared also after exclusion of patients with hypertension or adjustment for differences in 24-hour systolic BP. A $P<0.05$ was taken as the level of statistical significance. Throughout the text the symbol $\pm$ refers to the SD of the mean.

Results

Prevalence of MS

Table 1 shows the demographic, hemodynamic, and clinical characteristics of subjects with and without MS. There were 327 subjects with MS, which corresponded to 16.2% of the PAMELA population. Prevalence was slightly greater in men than in women (17.6% versus 14.8%). It was progressively greater from the younger to the older age group into which subjects were divided, the difference between the decade 25 to 34 years and the decade 65 to 74 years being $\approx$5 times (5.3% versus 27.2%). In the whole group of subjects with MS, a BP elevation was the most common component of the syndrome (95.4%) followed by high plasma levels of triglycerides (77.1%), low plasma levels of HDL cholesterol (72.2%), central obesity (58.5%), and impaired fasting glucose (31.5%). An impaired plasma glucose was the only component showing a clear cut increase in relative prevalence from the youngest to the oldest decades (5.3% to 30.8%).

BP, Heart Rate, LVMI, and LVH

Figure 1 (top left) shows that not only office, but also home and 24-hour average systolic and diastolic BPs were higher in subjects with than in those without MS, the differences being statistically significant before and after adjustment for age, gender, smoking, alcohol consumption, and previous CV events. Compared with those without MS, individuals with MS also had slightly higher office, home, and 24-hour average heart rate values (Figure 1, top right), whereas absolute and percentage nocturnal reductions in BP and heart rate were similar in the 2 groups (Figure 1, bottom). As shown in Figure 2, the MS group also had a greater LVMI in the whole sample, in men and women, and in subjects with different ages, the differences being statistically significant after adjustment for age, gender, smoking, alcohol consumption, and history of CV events. The difference in LVMI persisted when hypertensive subjects were excluded from either group, as well as when data were adjusted for 24-hour average systolic BP. This was the case also for the prevalence of LVH (Figure 2, bottom).

Prognostic Value of MS

The Kaplan–Meier curves of Figure 3 show that during an average follow-up of 148 months, subjects with MS had a much greater number of CV and all-cause fatal events than subjects without MS, the difference being statistically signif-

TABLE 1. Demographic, Hemodynamic, and Clinical Characteristics of Subjects Without (MS^-) and With (MS^+) MS in the PAMELA Population

Variable	MS^- (n=1686)	MS^+ (n=327)
Male prevalence, n (%)	841 (49.9)	180 (55.1)
Age, y	49.4±13.6	57.9±11.6*
Body mass index, kg/m^2	24.8±3.8	29.5±5.2*
Waist circumference, cm	83.4±11.3	97.4±11.4*
Office SBP/DBP, mm Hg	130.0±20.7/82.6±10.5	146.9±19.0*/90.3±9.3*
Office HR, bpm	70.7±10.1	72.7±10.1*
Home SBP/DBP, mm Hg	122.2±18.4/75.4±10.4	136.8±18.8*/82.5±9.6*
Home HR, bpm	72.3±9.9	74.4±11.7*
24 hours SBP/DBP, mm Hg	119.0±11.4/73.9±7.3	126.3±12.4*/77.0±8.0*
24 hours HR, bpm	75.4±8.3	76.3±9.4
LVMI, g/m^2	83.6±19.9	97.4±23.8*
Left ventricular hypertrophy, n (%)	152 (10.6)	69 (26.6)*
HDL cholesterol, mg/dL	58.1±15.0	42.4±11.0*
Total cholesterol, mg/dL	221.2±42.4	238.2±43.0*
Triglycerides, mg/dL	97.5±48.5	208.7±116.8*
Plasma glucose, mg/dL	87.0±11.3	109.9±39.9*
Smoking, n (%)	462 (27.4)	94 (28.8)
Alcohol consumption, n (%)	893 (53.1)	173 (52.9)
History CV event, n (%)	52 (3.1)	29 (8.9)*
Dead for CV cause, n (%)	41 (2.4)	24 (7.3)*
Dead for all-cause, n (%)	155 (9.2)	66 (20.2)*

Data are mean±SD and %. SBP indicates systolic BP; DBP, diastolic BP; HR, heart rate.
*$P<0.05$ vs MS^-.

icant. Over the follow-up period, the incidence of CV and all-cause death in subjects without MS was 2.4% and 9.2%, respectively. The corresponding figures in MS subjects were 7.3% and 20.2% ($P<0.0001$ for both). Compared with those without MS, subjects with MS had a greater hazard ratio for CV and all-cause death both before and after adjustment for between-group differences in age, gender, smoking, alcohol consumption, and history of CV events (Figure 4, top). In MS

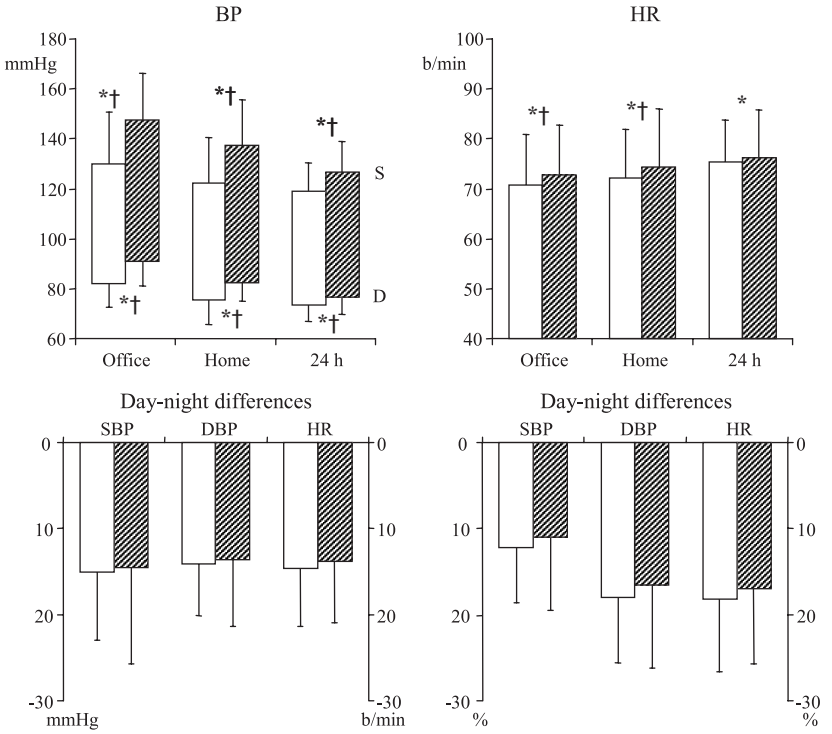

Figure 1. Top, office, home, and 24-hour average systolic (S) and diastolic (D) BP and heart rate (HR) values in subjects without (□) and with (▨) MS. Bottom, day–night differences in BP and HR in the same 2 groups, expressed as absolute (left) and percentage (%) values (right). Data from the whole population sample. Symbols (*$P<0.05$ for unadjusted data and †$P<0.05$ for data adjusted for age, gender, smoking, alcohol consumption, and previous cardiovascular events) refer to the statistical significance of the differences between groups.

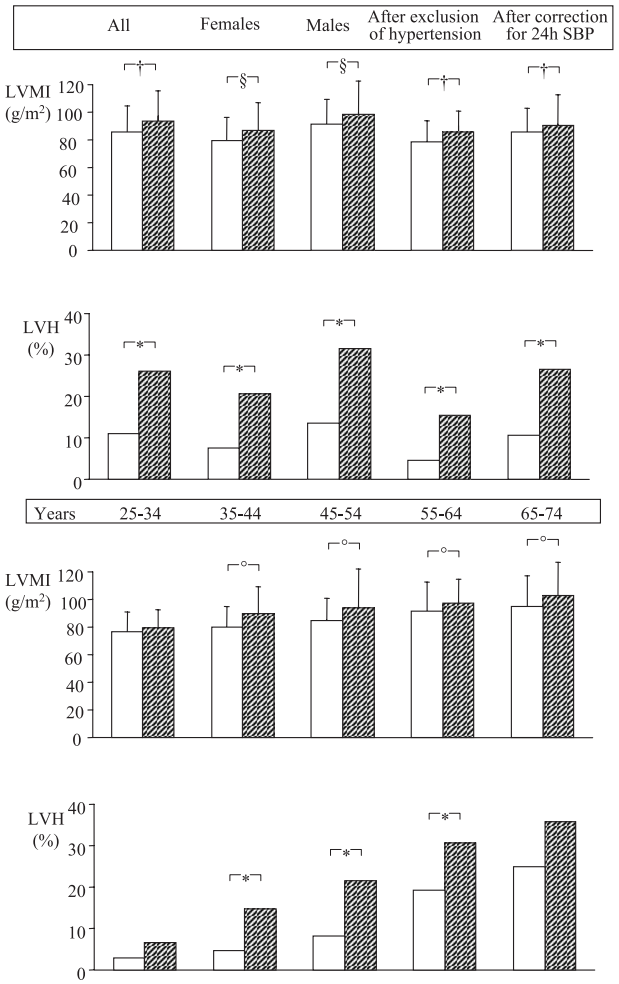

Figure 2. Top, LVMI in subjects without (□) and with (▨) MS in the whole population, men and women, and different ages (decades). Bottom, prevalence of LVH in the same groups as the top panels. Data are also shown after exclusion of hypertensive patients or adjustment for 24-hour systolic BP. Symbols refers to the statistical significance ($P<0.05$) of the difference between groups. Other symbols as in preceding figures or text.

subjects, the presence of LVH markedly increased the risk of CV and all-cause death. For CV death, this was the case also when there was an elevation (high normal or hypertensive values) in all 3 of the BPs (office, home, and 24-hour) as compared with MS subjects in which only 1 or 2 BPs were elevated (Figure 4, bottom).

Prognostic Impact of MS Components

Subjects with MS had a greater risk of fatal events than subjects without MS also when individuals affected by diabetes were excluded (17.9% versus 9.2%; $P<0.01$). This was the case also when exclusion involved hypertensive subjects (15.8% versus 5.0%; $P<0.01$) or hypercholesterolemic subjects (18.9% versus 6.7%; $P<0.01$). As shown in Table 2, after adjustment for age, gender, smoking, alcohol consumption, and previous CV events, an increase in waist circumference, an increase in plasma triglycerides, or a reduction in HDL cholesterol did not significantly predict the risk of CV or all-cause mortality of which the risk was significantly related only to each of the 2 remaining MS components, that is, office BP and blood glucose elevations. The waist circumference, plasma triglycerides, and HDL cholesterol components of MS did not contribute to the risk of death also when added to the BP and/or blood glucose components of which the combination, on the contrary, further increased the risk.

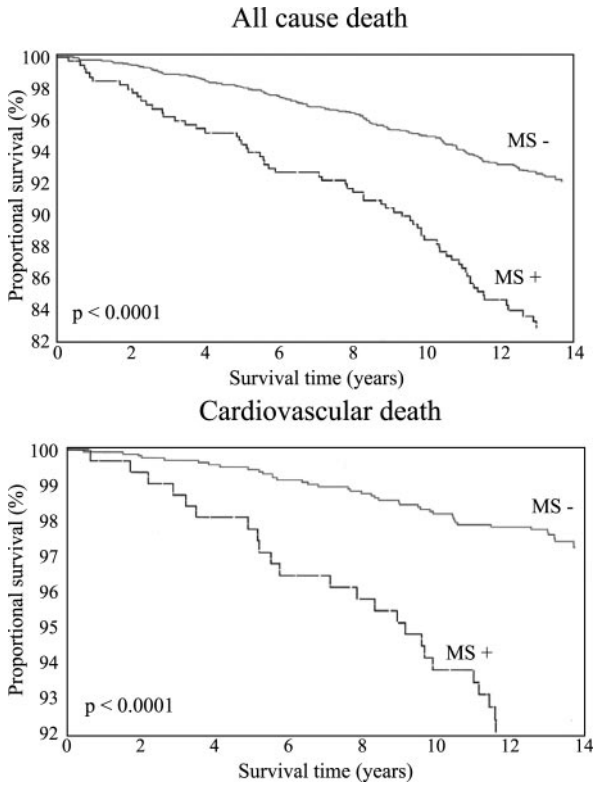

Figure 3. Kaplan–Meier survival curves for CV death and all-cause death in subjects without (MS−) and with (MS+) MS. *P* values refer to the difference between the curves. Other symbols as in preceding figures.

Discussion

The results of the PAMELA population study provide several new findings on MS, which will be discussed under separate headings.

Prevalence and Risk of MS

In the subjects of the PAMELA Study, MS was common, and its prevalence showed a steep age-related increase that peaked between the fifth and sixth decades. This allows us to conclude that what has been reported for other populations[1–8] is also true for an Italian population whose Mediterranean lifestyle, thus, does not provide protection from the clustering of MS components. Furthermore, and more importantly, in the PAMELA subjects, MS clearly increased the risk of CV mortality over a 12-year follow-up, with a negative impact also on all-cause mortality. Thus, detecting MS is clinically relevant also in populations with a low CV risk, such as the Mediterranean ones, because it allows detection of those in whom this favorable prognostic feature may be lost.

Cardiac Organ Damage

Several studies have shown that in hypertensive subjects with MS, LVH is more common than in hypertensive subjects

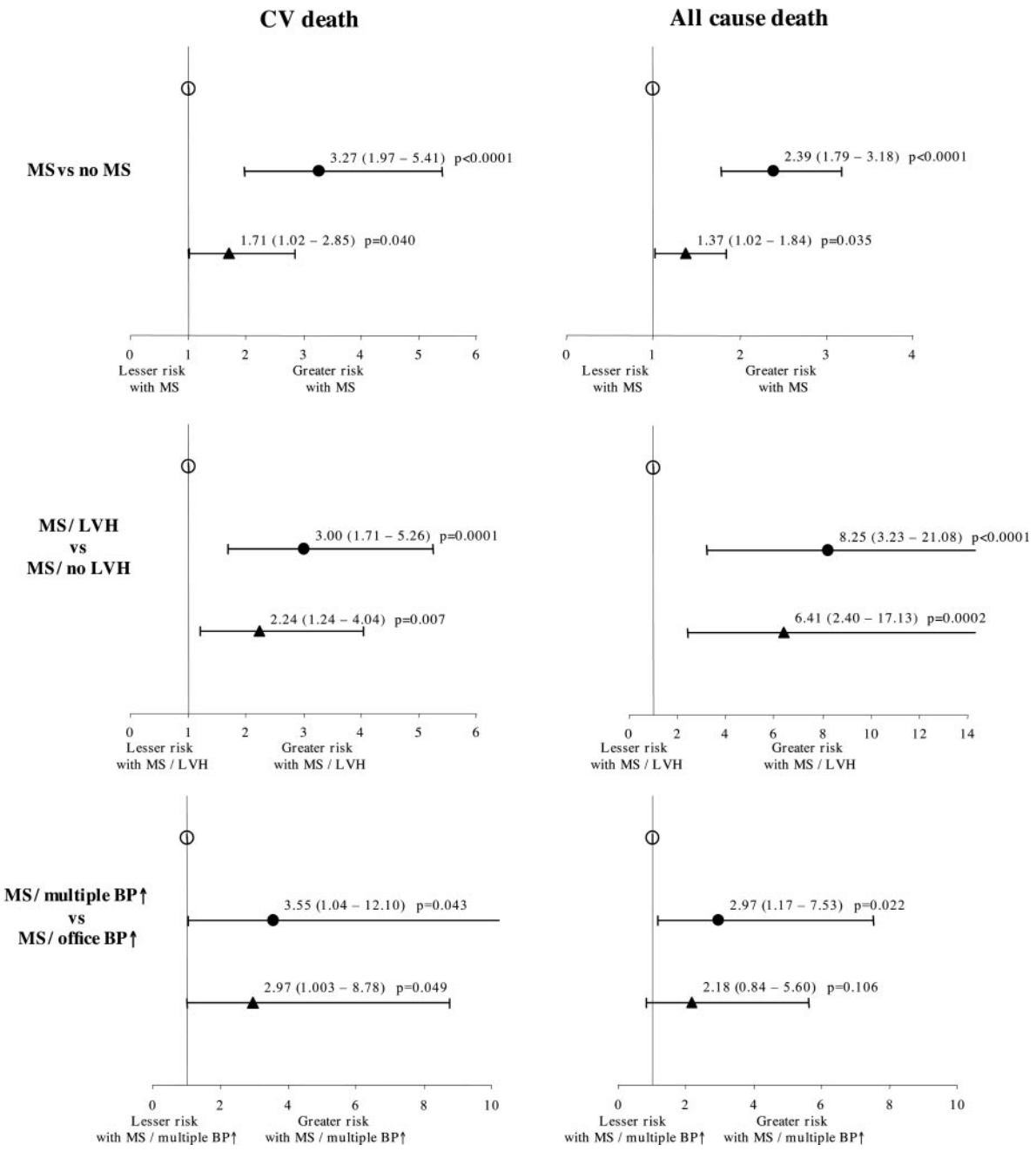

Figure 4. Top, hazard ratio (95% CIs) for CV death and all-cause death in subjects with MS (●) subjects without MS (▲) before and after adjustment for age, gender, smoking, alcohol consumption, and previous cardiovascular events. Middle, hazard ratio (95% CIs) for CV death and all cause death in subjects with MS without (▲) vs with left ventricular hypertrophy (●) before and after adjustment for above confounders. Bottom, hazard ratio (95% CIs) for CV and all cause death in subjects with MS with elevation in home and/or 24-h BP (●) before and after adjustment for above confounders vs elevation in only office BPs (▲).

without MS.[16–18,28–31] Our results extend these findings by showing that not just in hypertension but also in a general population MS is associated with an increased LVMI, as well as a more common occurrence of LVH. This is the case even when subjects with hypertension are excluded or adjustment is made for differences in the BP component that most importantly contributes to left ventricular growth, that is, 24-hour systolic BP.[23] Thus, in MS, alterations in cardiac structure are not inevitably linked to the occurrence of a BP elevation, a role being presumably played also by the metabolic and neural components of this condition. The most likely candidates are hyperinsulinemia and sympathetic activation, which have both been shown to favor cardiac muscle cell hypertrophy and connective tissue growth.[32–35]

Apart from mechanistic considerations, a greater prevalence of LVH in MS with or without hypertension has clinical implications, because LVH is known to increase the incidence of CV morbidity and mortality.[36] Furthermore, and more importantly, in our MS subjects, the presence of LVH markedly increased the risk of CV and all-cause mortality when compared with MS individuals without LVH. This implies that when MS is diagnosed, it may be advisable to

TABLE 2. Prediction of CV or All-Cause Death by MS Components and Their Combinations

	CV Mortality			All-Cause Mortality		
Type of Model	−2 Log L	LRT	*P*	−2 Log L	LRT	*P*
Model without covariates*	581.370			2179.099		
1 Covariate models*						
Waist circumference	581.029	0.341	0.5593	2177.910	1.189	0.2755
Triglycerides	580.508	0.862	0.3532	2175.603	3.496	0.0615
HDL cholesterol	581.369	0.001	0.9748	2178.431	0.668	0.4137
Glycemia	573.586	7.784	0.0053	2174.630	4.469	0.0345
BP	576.555	4.815	0.0282	2174.450	4.469	0.0311
2 Covariates models*						
BP+waist circumference	576.390	0.165	0.6846	2173.685	0.765	0.3818
BP+triglycerides	576.015	0.540	0.4624	2171.581	2.869	0.0903
BP+HDL cholesterol	576.552	0.003	0.9563	2173.776	0.674	0.4117
BP+glycemia	569.529	7.026	0.0080	2170.608	3.842	0.0500
Glycemia+ cholesterol	573.560	0.026	0.8719	2173.972	0.658	0.4173
Glycemia+triglycerides	573.485	0.101	0.7506	2172.533	2.097	0.1476
Glycemia+HDL cholesterol	573.395	0.191	0.6621	2173.428	1.202	0.2729
2 Covariates models with interaction*						
BP+glycemia	569.413	0.116	0.7334	2170.606	0.002	0.9643
3 Covariates models*						
BP+glycemia+waist circumference	569.528	0.001	0.9748	2170.235	0.373	0.5414
BP+glycemia+triglycerides	569.500	0.029	0.8648	2168.900	1.708	0.1912
BP+glycemia+HDL cholesterol	569.388	0.141	0.7073	2169.453	1.155	0.2825

LRT indicates likelihood ratio test.
*Data adjusted for age, gender, history of CV events, smoking, and alcohol consumption.

perform an echocardiogram because of the relatively high chance to find an LVH condition that makes the CV risk as particularly high. Under this circumstance, guidelines recommend the start of antihypertensive treatment even when BP is in the high normal range.[37]

Ambulatory and Home BPs

Our data show that an elevation in office BP, that is, an office BP in the high-normal or hypertensive range, was the most frequent component of MS. They further show that this elevation was accompanied by home and/or ambulatory BP values that were also frequently in their high-normal or hypertensive range. Interestingly, MS subjects in whom office, home, and 24-hour BPs were all elevated had a greater risk of CV death than those in whom the elevation did not include "in-" and "out-of-" office BPs. This means that in MS subjects, it may be important to also collect information on "out-of-office" BPs to more precisely estimate the degree of increase in CV risk and, thus, to more appropriately decide about the need for antihypertensive drugs.

Risk of MS Components and Their Combinations

An important finding of the present study is that not all MS components had a similar prognostic significance, because, when individually analyzed, only high-normal or hypertensive BP values and an impaired fasting glucose were associated with an increased risk of death, a further increase occurring with their combination. The 3 remaining components did not show an association with the risk when analyzed individually nor did they increase the risk further when combined or added to the BP and/or the blood glucose component. This is not agreement with previous reports that the CV risk shows a progressive increase from 1 to 5 components.[13,38] It seems, on the contrary, to provide support to the criticism that MS may represent a rather artificial "ensemble" of heterogeneous variables that lack an unifying pathophysiological core and of which the clinical significance may differ markedly. It also seems, however, to deny the rationale of a recent identification of MS principally based on visceral obesity,[39] which in the PAMELA subjects did not independently contribute to prognosis.

Other Results

Three other results should be mentioned. First, in MS, the elevation in ambulatory BP was not accompanied by an alteration in the circadian BP pattern, because the nighttime BP fall (as well as the nocturnal bradycardia) was not impaired in subjects with as compared with those without MS. Second, compared with subjects without, subjects with MS showed a small but significant increase in heart rate, not only when measurements were performed in the office, but also when they were performed at home and over the 24 hours. This may be because of the physical inactivity associated with the obesity state. It may also suggest that in MS there is an increase in cardiac sympathetic drive, in line with the increase that has been documented recently in the periph-

eral circulation via microneurographic assessment of sympathetic nerve firing.[40,41] Third, the cause of death by death certificates may not be entirely accurate. However, the data obtained for the much greater number of all-cause death were directionally always in line with those on CV death.

Perspectives

Our data provide evidence that MS has a high prevalence in a Mediterranean population in which it increases the long-term risk of CV and all-cause death. They also provide evidence that this condition is characterized by a high prevalence of LVH even in the absence of hypertension and that not only office but also home and ambulatory BP are frequently elevated, with both the subclinical cardiac damage and the "out-of-office" BP abnormalities further increasing the risk. They finally show that the contribution to the risk of various MS components is unbalanced and largely accounted for just by the BP and blood glucose abnormalities.

Disclosures

None.

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