The metabolic syndrome: similar deleterious impact on all-cause mortality in hypertensive and normotensive subjects

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Objectives **Few data are available on the impact of the metabolic syndrome on all-cause mortality risk according to the presence of hypertension. Our aim was to evaluate the 5-year impact of the metabolic syndrome, according to blood pressure status, on all-cause mortality risk in a large French population.**

Methods **The study population included 39 998 men and 20 756 women with no personal history of cardiovascular disease, who had a health check-up at the IPC Center (Paris, France) between 1999 and 2002, and who were followed up for 4.7 ± 1.2 years. The metabolic syndrome was defined according to the National Cholesterol Educational Program classification (2001). Cox regression models were used to evaluate risk of all-cause mortality after adjustment for age, sex, classical risk factors and socioeconomic categories. Subjects were classified according to blood pressure status: hypertensive subject (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment) and normotensive subject.**

Results **The risk of all-cause mortality associated with the metabolic syndrome was 1.50 (1.24–1.82) [hazard ratio (HR) (95% confidence interval)]. The risk of all-cause mortality associated with the presence of hypertension was 1.60 (1.38–1.85). During the 4.7 years of follow-up, the impact of the metabolic syndrome was similar among normotensive and hypertensive subjects [HR: 1.09 (0.68–1.75) and 1.40 (1.13–1.74), respectively, *P* for interaction = 0.35].**

Conclusion **The findings from this study show that, in a large middle-aged French population, the metabolic syndrome has the same deleterious impact on all-cause mortality in hypertensive subjects and normotensive subjects. *J Hypertens* 26:1223–1228 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2008, **26**:1223–1228

Keywords: arterial hypertension, blood pressure, epidemiology, metabolic syndrome, mortality, waist circumference

Abbreviations: CNAM, Caisse Nationale d'Assurance Maladie; CPAM-Paris, Caisse Primaire d'Assurance Maladie de Paris; DBP, diastolic blood pressure; ESC-ESH, European Society of Cardiology-European Society of Hypertension; HDL, high-density lipoprotein; INSERM, Institut National de la Santé et de la Recherche Médicale; IPC, Investigations Préventives et Cliniques; LDL, low-density lipoprotein; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; NCEP-ATP III, the third report of the National Cholesterol Educational Program's; SBP, systolic blood pressure

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Received 26 June 2007 **Revised** 4 February 2008
Accepted 19 February 2008

Introduction

Described by Reaven in 1988 [1], the metabolic syndrome (MetS) is defined as an association of risk factors expressing a metabolic disorder linked to insulin resistance and increased inflammation. The definition of MetS has evolved from Reaven's description into the National Cholesterol Education Program's (NCEP) definition, elaborated in 2001 [2], and two recent definitions [3,4]. A large number of studies have shown the increased risk of all-cause mortality and cardiovascular mortality associated with MetS; the risk is nearly two times higher than without MetS [5,6]. Regardless of the definition chosen, elevated blood pressure (BP) is a component, which is always included. Schillaci *et al.* [7] showed that in hypertension, MetS is associated with twice the risk of long-term cardiovascular mortality during a maximum follow-up of 10.4 years. In that study, the definition of MetS included body mass index rather than abdominal fat measurement, and the population was composed only of hypertensive subjects. No analysis was carried out among normotensive subjects.

The primary objective of the present study was to examine the short-term impact of MetS, as defined by the original NCEP 2001 classification, on all-cause mortality in hypertensive subjects compared with normotensive subjects, in a large French population.

Methods

Study population

Subjects were examined at the IPC (Investigations Préventives et Cliniques) Center (Paris-France). This medical center, which is subsidized by the French national healthcare system (Sécurité Sociale-CNAMTS),

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offers all working and retired individuals and their families a free medical examination every 5 years. It carries out approximately 25 000 examinations per year for people living in the Paris area.

Our study population was composed of all subjects aged 40 years and over who had a health check-up at the IPC Center between January 1999 and December 2002. The population included 39 998 (52.6 ± 8.3 years) men and 20 756 (54.7 ± 9.2 years) women with no known history of cardiovascular disease.

Supine BP was measured in the right arm using a manual mercury sphygmomanometer, after a 10-min rest period. The first and the fifth Korotkoff phases were used to define systolic blood pressure (SBP) and diastolic blood pressure (DBP). The mean of three measurements was considered as the BP value. Pulse pressure (SBP–DBP) was also determined. Waist circumference was measured using an inelastic tape placed midway between the lower ribs and iliac crests on the mid-axillary line. Standard biological parameters [enzymatic method, automat HITACHI 917 (HITACHI, Tokyo, Japan); colorimetric method for albumin dosage and hematology, ABX Pentra 120 (HORIBA ABX, Montpellier, France)] were measured under fasting conditions; high-density lipoprotein (HDL) cholesterol was measured by direct enzymatic method with cyclodextrin. All clinical and biological parameters were evaluated on the same day of the examination.

The IPC Center received authorization from the Comité National d'Informatique et des Libertés (CNIL) to conduct these analyses. All subjects gave their informed consent at the time of the examination.

Follow-up

For each screened subject, vital status was obtained from the French National Institute of Statistics and Economic Studies (Institut National de Statistiques et d'Etudes Economiques, INSEE, France). To validate this procedure, a random sample of 250 subjects was taken and data were compared with those found in city hall registries. A discordance was found in only two cases (<1%). Based on the results of this validation, we considered that we had a complete follow-up for the entire study population.

The study population was followed up from 1999 until December 2005. Mean follow-up was 4.7 ± 1.2 years. During this period, 1.54% ($n = 621$) of men and 1.02% ($n = 215$) of women died.

Data analyses

Definitions

The MetS definition used to evaluate the impact on mortality was taken from the NCEP–ATP (Adult Treatment Panel) III (2001) [3], and requires the association of three out of the five following criteria: abdominal obesity with waist circumference more than 102 cm in men and more than 88 cm in women, triglycerides at least 150 mg/dl, HDL cholesterol less than 40 mg/dl in men and less than 50 mg/dl in women, SBP at least 130 mmHg or DBP at least 85 mmHg, fasting glucose at least 110 mg/dl.

Hypertension was defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg or antihypertensive treatment. To assess the prevalence of each MetS component according to BP levels, the European Society of Cardiology–European Society of Hypertension (ESC–ESH) 2007 classification of hypertension was used [8] and is as follows:

Optimal: SBP less than 120 mmHg and DBP less than 80 mmHg
Normal: SBP 120–129 mmHg and/or DBP 80–84 mmHg
Normal high: SBP 130–139 mmHg and/or DBP 85–89 mmHg
Grade 1: SBP 140–159 mmHg and/or DBP 90–99 mmHg
Grade 2: SBP 160–179 mmHg and/or DBP 100–109 mmHg
Grade 3: SBP at least 180 mmHg and/or DBP at least 110 mmHg

Statistical analyses

Descriptive analyses were carried out separately in men and women. As the relationship between MetS and all-cause mortality was similar in both sexes (P for interaction = 0.70), all subjects were grouped together for mortality analyses. The impact of MetS on all-cause mortality was studied using Cox regression models including age, sex, current smoking status, calculated low-density lipoprotein (LDL)–cholesterol levels, diabetes, declared physical activity, and socioeconomic categories. Cox regression models were used to assess the risk [hazard ratio (HR) and 95% confidence interval (CI)] of all-cause mortality associated with the presence of MetS and combinations of at least three specific MetS components. The impact of MetS on all-cause mortality was evaluated by comparing subjects with MetS with subjects without MetS (≤ 2 MetS components). The impact of combinations of at least three MetS components on all-cause mortality was compared with subjects with no MetS components. Kaplan–Meyer survival curves were studied in the following four subgroups of subjects:

(1) Without MetS [MetS (−)] and without hypertension [hypertension (−)]
(2) With MetS [MetS (+)] and hypertension (−)
(3) MetS (−) and hypertension [hypertension (+)]
(4) MetS (+) and hypertension (+)

The impact of MetS on all-cause mortality among hypertensive subjects, compared with normotensive subjects,

Table 1 Age-adjusted mean (SEM) for principal clinical and biological parameters, according to blood pressure (BP) status and metabolic syndrome (MetS), in men and women

	Normotensive subjects		Hypertensive subjects	
	No MetS	MetS	No MetS	MetS
Men	$n=20\,731$	1181	14596	3490
Age (years)	50.7 (7.7)	52.0 (7.7)	54.7 (8.6)	54.7 (8.1)
BMI (kg/m^2)	24.9 (0.1)	28.9 (0.1)***	26.1 (0.1)	29.8 (0.1)***
Waist circumference (cm)	89.7 (0.1)	101.5 (0.3)***	92.7 (0.1)	104.0 (0.1)***
SBP (mmHg)	124.0 (0.1)	131.1 (0.4)***	152.1 (0.1)	155.9 (0.2)***
DBP (mmHg)	75.4 (0.1)	80.1 (0.3)***	91.0 (0.1)	93.4 (0.1)***
HR (bpm)	60.4 (0.1)	65.1 (0.3)***	65.1 (0.1)	68.6 (0.2)***
Cholesterol (g/l)	2.19 (0.01)	2.31 (0.01)***	2.25 (0.01)	2.34 (0.01)***
Glycemia (g/l)	0.98 (0.01)	1.15 (0.01)***	1.00 (0.01)	1.18 (0.01)***
Triglycerides (g/l)	1.00 (0.01)	2.13 (0.02)***	1.07 (0.01)	2.02 (0.01)***
HDL cholesterol (g/l)	0.59 (0.01)	0.43 (0.01)***	0.60 (0.01)	0.47 (0.01)***
Percentage of physical activity (*n*)	46.6 (9660)	39.0 (461)***	50.3 (7337)	41.8 (1459)***
Percentage of current smokers (*n*)	28.9 (5999)	35.5 (419)***	22.9 (3344)	28.7 (1000)***
Percentage of white-collar workers (*n*)	56.2 (11639)	48.6 (574)***	52.1 (7602)	46.5 (1622)***
Women	$n=12\,305$	360	6891	1200
Age (years)	52.3 (8.5)	55.1 (8.8)***	58.4 (9.1)	58.3 (9.1)***
BMI (kg/m^2)	23.4 (0.1)	29.9 (0.2)***	25.1 (0.1)	30.8 (0.1)***
Waist circumference (cm)	76.4 (0.1)	94.9 (0.5)***	80.3 (0.1)	95.7 (0.3)***
SBP (mmHg)	121.4 (0.1)	130.1 (0.7)***	152.2 (0.2)	156.1 (0.4)***
DBP (mmHg)	72.1 (0.1)	77.4 (0.5)***	87.0 (0.1)	88.9 (0.3)***
HR (bpm)	64.5 (0.1)	69.0 (0.5)***	67.3 (0.1)	70.5 (0.3)***
Cholesterol (g/l)	2.20 (0.01)	2.31 (0.02)***	2.22 (0.01)	2.33 (0.01)***
Glycemia (g/l)	0.93 (0.01)	1.15 (0.01)***	0.95 (0.01)	1.11 (0.01)***
Triglycerides (g/l)	0.78 (0.01)	1.66 (0.01)***	0.84 (0.01)	1.61 (0.01)***
HDL cholesterol (g/l)	0.74 (0.01)	0.51 (0.01)***	0.74 (0.01)	0.53 (0.01)***
Percentage of physical activity (*n*)	45.4 (5592)	35.0 (126)***	48.2 (3323)	37.2 (446)***
Percentage of current smokers (*n*)	21.2 (2613)	25.6 (92) (NS)	12.0 (828)	13.4 (161) (NS)
Percentage of white-collar workers (*n*)	26.3 (3229)	16.4 (59)***	21.7 (1495)	16.3 (195)***

DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; SBP, systolic blood pressure. MetS versus no MetS. *** $P<0.0001$.

was assessed as the interaction between BP status and the impact of MetS on mortality.

All statistical analyses were carried out using the SAS statistical software package (version 8.02) (SAS Institute, Cary, North Carolina, USA).

Results

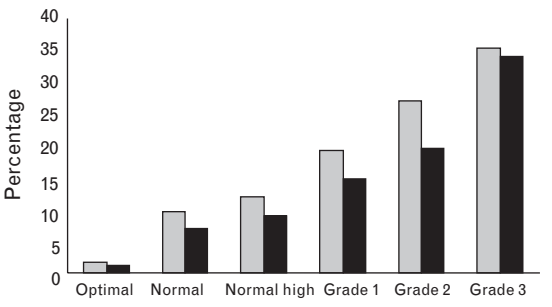
Table 1 shows the clinical and major biological characteristics of subjects according to BP status and MetS, in men and women.

The prevalence of hypertension was 45.2% ($n=18\,086$) in men and 39.0% ($n=8091$) in women. The prevalence of MetS was 11.7% ($n=4671$) in men, 7.5% ($n=1560$) in women and 10.3% ($n=6231$) for the entire population. According to BP status, the prevalence of MetS was 5.4% ($n=1181$) among normotensive men and 2.8% ($n=360$) among normotensive women, and rose to 19.3% ($n=3490$) for hypertensive men and 14.8% ($n=1200$) for hypertensive women.

Figure 1 shows the prevalence of MetS according to BP classes. The prevalence of MetS increased in both sexes as BP levels increased. For the grade 2 class, it reached 27% in men and 20% in women. Figure 2 shows the prevalence of MetS components other than BP; prevalence increased with grade of hypertension in both sexes, and with high waist circumference especially in women.

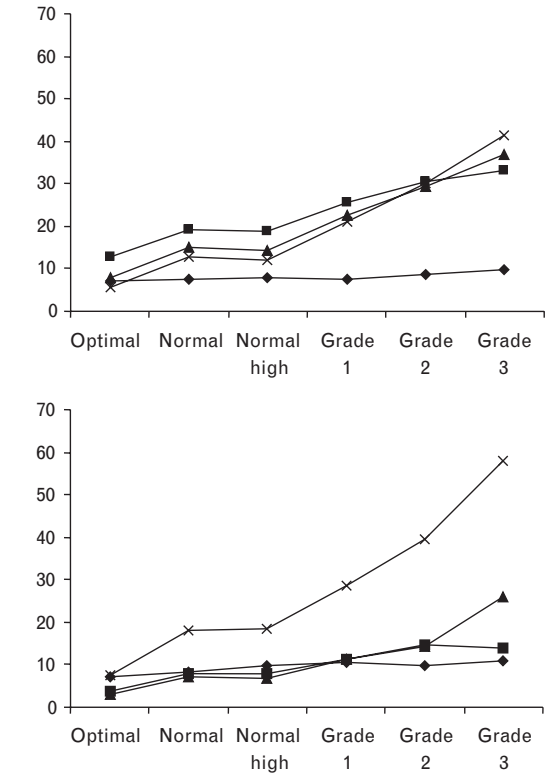
Figure 3 represents Kaplan–Meyer survival curves; the logrank test comparing all survival probability curves is statistically significant ($P<0.0001$). The presence of hypertension (curves 3 and 4) is associated with the most deleterious impact on mortality. The presence of MetS (curves 2 and 4) adds a deleterious effect on mortality. This nonadjusted analysis shows that the additive effect of MetS was slightly higher among hypertensive subjects (curve 3 versus curve 4) than among normotensive subjects (curve 1 versus curve 2).

Fig. 1



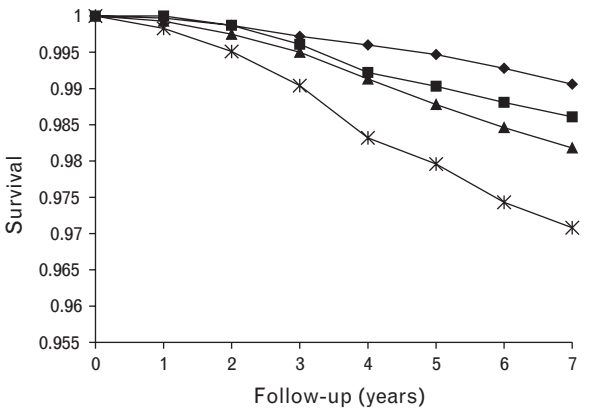
Prevalence of metabolic syndrome (MetS) [National Cholesterol Education Program's (NCEP 2001)] according to the European Society of Cardiology–European Society of Hypertension (ESC–ESH) 2007 classification for blood pressure in men and women. There was no statistical difference between sexes. Men [□]; women [■].

Fig. 2



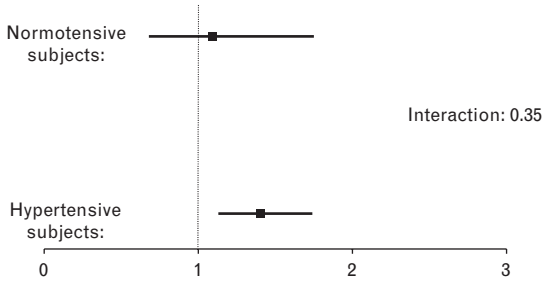
Prevalence of each metabolic syndrome (MetS) component other than blood pressure, according to the European Society of Cardiology–European Society of Hypertension (ESC–ESH) 2007 classification for blood pressure in men (upper panel) and women (lower panel). HDL, high-density lipoprotein. HDL (%) [◆]; Triglycerides (%) [■]; Glycemia (%) [▲]; Waist circumference (%) [✳].

Fig. 3



Kaplan–Meyer survival curves according to four subgroups: metabolic syndrome (MetS) (–) and hypertension (HTN) (–) [◆]; MetS (+) and HTN (–) [■]; MetS (–) and HTN (+) [▲]; MetS (+) and HTN (+) [✳]. (Log rank analysis: $P < 0.0001$).

Fig. 4



Hazard ratio (95% confidence interval) for all-cause mortality in subjects with metabolic syndrome (MetS) versus no MetS, according to blood pressure status (normotensive subjects; hypertensive subjects) during a follow-up of 4.7 years.

After adjustment for age, sex, current smoking status, calculated LDL cholesterol levels, diabetes, declared physical activity and socioeconomic categories, the risk of all-cause mortality associated with the presence of hypertension was 1.60 (1.38–1.85) [HR and 95% CI]. According to the presence of MetS, the risk was 1.50 (1.24–1.82). Compared to no MetS, the presence of MetS slightly increased the risk of all-cause mortality among normotensive subjects [HR (95% CI) = 1.09 (0.68–1.75)] and it increased the risk among hypertensive subjects by 40% [(HR (95% CI) = 1.40 (1.13–1.74)]; no significant interaction ($P = 0.35$) was found according to the BP groups (Fig. 4). These results suggest that the impact of MetS components on all-cause mortality is similar among hypertensive and normotensive subjects. Similar results were also observed for all possible combinations of at least three MetS components (data not shown).

Interestingly, based on the presence of MetS, a similar trend for all-cause mortality risk was found in subjects with high normal BP: HR = 1.50 (1.18–1.91), and in subjects with normal BP: HR = 1.27 (0.92–1.76). The interaction was not significant: $P = 0.41$.

Discussion

Prevalence of metabolic syndrome and its components

Compared to older definitions that include insulinemia, or to the two most recent definitions with different thresholds for certain parameters or with the required presence of one variable [3,4], the ATP III (NCEP) definition [2] was chosen because it has been repeatedly validated in terms of the impact on mortality. The prevalence of MetS in our study was lower than in other populations such as in Quebec [9], in northern European countries [10], or in North America, particularly in hypertensive subjects [11]. Based on the ATP III–NCEP criteria, the French prevalence of MetS appears to be lower than that observed in other European countries [12], but closer to those in the population-based Multinational Monitoring of Trends and Determinants in

Cardiovascular Diseases (MONICA) study in France [13]. The point deserves large and more detailed comparisons of prevalence of MetS components between France, Europe or other countries. Ethnicity cannot be studied in France for ethical reasons but its interaction in such a result should be analyzed. We, however, found that the prevalence of MetS increased with BP levels as defined in the ESH–ESC 2007 classification. It increased three-fold in the normotensive groups and doubled in the hypertensive groups. Although the prevalence of MetS in the hypertensive group was lower than in the Italian hypertensive population [5], the prevalence of MetS in hypertensive subjects with grade 2 and grade 3 was similar to the Italian study. It is important to note that increases in the prevalence of MetS components, previously observed [14,15], were not similar in men and women. In men, the prevalence of high glycemia, high waist circumference, and high triglycerides increased more than the prevalence of low HDL cholesterol, whereas in women the main increase was observed for high waist circumference, with a three-fold increase according to BP levels, compared with normotensive subjects.

Relationship between metabolic syndrome, blood pressure, and mortality

In our study, the relationship between MetS and all-cause mortality was similar in both sexes, as shown by the lack of any significant interaction. This point was recently discussed in two meta-analyses including studies with longer follow-ups, showing a higher impact on mortality in women than in men [5,6], as was previously suggested for cardiovascular mortality in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study [16]. As in numerous studies [17–33], our study showed that the observed total mortality risk with MetS was nearly twice as high as without MetS, despite a relatively short follow-up period of 5 years. We also found that the adjusted all-cause mortality risk associated with hypertension was approximately twice as high as in normotensive subjects during this follow-up.

The increased risk of all-cause mortality associated with MetS was not statistically different in hypertensive and normotensive subjects. Consequently, the main result of this study is that MetS is associated with a similar excess risk of all-cause mortality in both populations.

The hazard ratios showed that mortality risk in the presence of MetS was not statistically significant among normotensive subjects but was significant among hypertensive subjects. This lack of significance is undoubtedly due to the lack of statistical power because of the low prevalence of MetS in our normotensive population: 4.5% ($n = 1541$) versus 17.9% ($n = 4690$) in hypertensive subjects. The analysis of interaction, however, showed a nonsignificant difference between the hazard ratio values of the two groups, which is the primary result of this study. Consequently, the impact of MetS in the entire population, both normotensive and hypertensive subjects together, could be analyzed and the results showed that MetS was associated with an increase in mortality.

MetS does not seem to increase the risk of mortality associated with hypertension during a 5-year follow-up period. Although insulin resistance and inflammation appear to play a critical role in the pathophysiological clinical consequences of MetS [34–36], they do not appear to play an additional short-term prognostic role in hypertension. This result is clearly independent of the role of increased BP on the prevalence of all other MetS components and on the higher prevalence of MetS in hypertension, according to BP levels.

Limitations of the study

The study population was composed of volunteers for a standard health checkup. The fact that these individuals were volunteers suggests that they were particularly concerned about their health and consequently their health-related behavior. This could explain the relatively low prevalence of MetS found among this particular population by comparison to the French cohort MONICA [10]. As the follow-up period was short and the number of deaths relatively low, an analysis that would take into account causes of mortality, particularly cardiovascular disease (CVD) and coronary heart disease (CHD) mortality, was not carried out.

Conclusion

It is a well established fact that MetS is a risk marker in the general population, and in hypertensive subjects. We have shown that for a short follow-up period, the impact of MetS on all-cause mortality in hypertensive subjects was no different from that observed in normotensive subjects. During a mean follow-up of 4.7 years, no significant statistical difference was found between all-cause mortality associated with MetS in these two groups. This cannot be due to low statistical power given the large number of subjects that were followed up, and given the larger prevalence of MetS in hypertensive subjects than in normotensive subjects. These results indicate that MetS is associated with all-cause mortality risk regardless of BP status. During a 4.7-year follow-up, MetS does not appear to have any additional effect on the functional and structural cardiac and vascular alterations associated with hypertension, at least in terms of prognostic consequences.

In conclusion, in a large middle-aged French population, MetS and hypertension were both associated with an increase in risk of all-cause mortality after a 4.7-year follow-up. The major result of this study is that the impact of MetS on all-cause mortality is similar in both normotensive and hypertensive subjects.

Acknowledgements

The present study was made possible with the help of the Caisse Nationale d'Assurance Maladie (CNAM), the Caisse Primaire d'Assurance Maladie de Paris (CPAM-Paris), and the Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France.

There are no conflicts of interest.

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