All-Cause Mortality Associated With Specific Combinations of the Metabolic Syndrome According to Recent Definitions

Louis Guize, md[1,2]
Frédérique Thomas, phd[1]
Bruno Pannier, md[1,3]
Kathy Bean, ma, mph[1]
Bertrand Jego, mba[1]
Athanase Benetos, md, phd[1,4]

OBJECTIVE — The aim was to evaluate the impact of specific component combinations of the metabolic syndrome on all-cause mortality risk in a large French cohort.

RESEARCH DESIGN AND METHODS — The population was composed of 39,998 men (aged 52.6 ± 8.3 years) and 20,756 women (aged 54.7 ± 9.2 years) who were examined at the Investigations Préventives et Cliniques Center from 1999 to 2002. Mean follow-up was 3.57 ± 1.12 years. Metabolic syndrome was defined according to three definitions: the National Cholesterol Educational Program (NCEP 2001), the revised NCEP (NCEP-R; American Heart Association/National Heart, Lung, and Blood Institute 2005), and the International Diabetes Federation (IDF 2005). Subjects with metabolic syndrome were compared with subjects without metabolic syndrome and with subjects with no metabolic syndrome components using Cox regression models.

RESULTS — The prevalence of metabolic syndrome increased from 10.3% (NCEP) to 17.7% (NCEP-R) and 23.4% (IDF). After adjustment for age, sex, classical risk factors, and socioprofessional categories, and compared with subjects without metabolic syndrome, the risk of all-cause mortality was 1.79 (95% CI 1.35–2.38), 1.46 (1.14–1.88), and 1.32 (1.04–1.67) with the NCEP, NCEP-R, and IDF definitions, respectively. Among the combinations significantly associated with all-cause mortality, the following three-component combinations and the four-component combination were more highly significant than other combinations ($P < 0.05$): elevated waist circumference plus elevated glucose, plus either elevated blood pressure or elevated triglycerides, and the combination of all four of these.

CONCLUSIONS — In a large middle-aged French population, four specific components of metabolic syndrome are associated with a much higher mortality risk. These results may have a significant impact on detecting high-risk subjects suffering from metabolic disorders and underline the fact that metabolic syndrome is a nonhomogeneous syndrome.

Diabetes Care **30**:2381–2387, 2007

Described by Reaven in 1988 (1), the metabolic syndrome, defined as a constellation of several cardiometabolic risk factors, has been the focal point of a large number of studies that have attempted to elucidate the pathophysiological and epidemiological aspects of this syndrome.

Recently, several expert groups have developed simple diagnostic criteria to be used in clinical practice to identify subjects with a metabolic syndrome profile (2). Until very recently, the principle definitions used to define metabolic syndrome were those established by the World Health Organization and the Third Report of the National Cholesterol Educational Program's Adult Treatment Panel (NCEP) (3). Because criteria included in the NCEP definition could easily be recorded, a large number of studies used this definition when examining different epidemiological aspects of the metabolic syndrome.

New criteria for identifying subjects with metabolic syndrome were published in 2005 by the International Diabetes Federation (IDF) (4) and by the American Heart Association/National Heart, Lung, and Blood Institute (revised NCEP [NCEP-R]) (2). The IDF definition, which requires abdominal obesity as one of the criteria for identifying subjects with metabolic syndrome, is in agreement with findings from studies that have shown the prognostic importance of the association of overweight and other cardiometabolic risk factors (5,6).

The existing definitions are based on different expert opinions, but few longitudinal epidemiological studies have shown the impact of all these classifications on mortality. Recently, a few studies have suggested that the IDF definition is similar to the NCEP definition for women aged >60 years with coronary heart disease (CHD) (7), is not associated with CHD mortality and morbidity in a Chinese population (8), or is similar to the NCEP and NCEP-R definitions for the impact on all-cause mortality (9) and for the impact on cardiovascular mortality in European men but not in women (10).

The required presence of three of the five metabolic syndrome components in order to establish a diagnosis of metabolic syndrome is the common feature of these three classifications. Using these definitions, many studies have shown that metabolic syndrome is associated with an excess risk of all-cause and cardiovascular disease (CVD) mortality (11). Two meta-analyses, which included all of these studies, recently summarized the relationship between metabolic syndrome and mortality (12,13). However, the impact of metabolic syndrome varies greatly from one study to the next. This variation could be due to population characteristics, the definition used, and length of follow-up.

•••

Interestingly, to date, no study has clearly shown whether the risk of mortality is similar for the different component combinations of metabolic syndrome, although some have suggested that the impact of specific associations could be particularly deleterious (14,15). It appears that specific associations are more highly linked to cardiovascular morbidity than others (16), especially those associated with metabolic disorders in diabetic patients (17). Grundy et al. (2) showed that metabolic syndrome is still not clearly defined and that the role of each component as a predictor of mortality has not been clearly established.

The primary objective of this study was to address the impact of different three-component and four-component combinations of the metabolic syndrome according to the NCEP, NCEP-R, and IDF definitions on all-cause mortality in a large French population composed of 60,754 men and women.

RESEARCH DESIGN AND METHODS
— Subjects were examined at the Investigations Préventives et Cliniques (IPC) Center (Paris, France). This medical center, which is subsidized by the French national health care system (Sécurité Sociale-CNAMTS), offers all working and retired individuals and their families a free medical examination every 5 years. It is one of the largest medical centers of this kind in France, carrying out ~25,000 health examinations per year for people living in the Paris area.

Our study population was composed of 39,998 men (aged 52.6 ± 8.3 years) and 20,756 women (aged 54.7 ± 9.2 years), all aged ≥40 years, who had a health checkup at the IPC Center between January 1999 and December 2002. To focus on primary prevention, subjects with previous CVD were excluded.

Supine blood pressure was measured in the right arm using a manual mercury sphygmomanometer, after a 10-min rest. 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 blood pressure value. 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; colorimetric method for albumin dosage and hematology; ABX, Pentra 120) were measured under fasting conditions; HDL cholesterol was measured by direct enzymatic array with cyclo-dextrin. A resting electrocardiogram was recorded. Tobacco consumption (never smoker, ex-smoker, or current smoker), physical activity (regular physical activity: yes or no), personal medical history, current medications, and alcohol consumption were assessed using a self-administered questionnaire. 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 to conduct these analyses. All subjects gave 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). To validate this procedure, we took a random sample of 250 subjects and compared our data 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 until March 2004; the mean follow-up was 3.6 ± 1.1 years. During this period, 0.68% (*n* = 271) of men and 0.42% (*n* = 87) of women died.

Data analyses
Definitions. Three different definitions of the metabolic syndrome were used to evaluate the impact on mortality. The first definition was the NCEP definition (3), which requires at least three of the following criteria: *1*) waist circumference >102 cm in men and >88 cm in women (W), *2*) triglycerides ≥150 mg/dl (TG), *3*) HDL cholesterol <40 mg/dl in men and <50 mg/dl in women (HDL), *4*) SBP ≥130 mmHg or DBP ≥85 mmHg (blood pressure), and *5*) fasting glucose ≥110 mg/dl (G).

The second definition was the American Heart Association/National Heart, Lung, and Blood Institute 2005 (NCEP-R) definition (2), which requires at least three of the following criteria: *1*) waist circumference ≥102 cm in men and ≥88 cm in women (W), *2*) triglycerides ≥150 mg/dl or a specific treatment for elevated triglycerides (TG), *3*) HDL cholesterol <40 mg/dl in men and <50 mg/dl in women or a specific treatment for reduced HDL cholesterol (HDL), *4*) SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive treatment (blood pressure), and *5*) fasting glucose ≥100 mg/dl or drug treatment for elevated glucose (G).

The third definition (IDF definition) (4) requires the presence of abdominal obesity defined as waist circumference ≥94 cm in men and ≥80 cm in women for Europids (W) and at least two of the following criteria: *1*) triglycerides ≥150 mg/l or a specific treatment for lipid abnormalities (TG), *2*) HDL cholesterol <40 mg/dl in men and <50 mg/dl in women or a specific treatment for lipid abnormalities (HDL), *3*) SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive treatment (blood pressure), and *4*) fasting glucose ≥100 mg/dl or diabetes (G).

Statistical analyses
Descriptive analyses were carried out separately in men and women. As the relationship between metabolic syndrome 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 metabolic syndrome on all-cause mortality was studied using Cox regression analysis including age, sex, current smoking status, LDL cholesterol levels, declared physical activity, and socioprofessional category in the second model. Cox regression models were used to assess the risk (hazard ratio [HR] and 95% CI) of all-cause mortality in the presence of metabolic syndrome and its components; at least three of the five metabolic syndrome components on all-cause mortality were evaluated.

Three different analyses were conducted in order to clarify the relationship between all-cause mortality and metabolic syndrome, metabolic syndrome's components, and specific associations of at least three metabolic syndrome components. The impact of metabolic syndrome on all-cause mortality was evaluated by comparison to the reference group, which was defined as subjects without metabolic syndrome (two or less metabolic syndrome components). Mortality associated with each metabolic syndrome component and combinations of these components (2–4) was compared with the group with no metabolic syndrome components. All-cause mortality, associated with specific combinations of three or four components, was compared with other

Table 1—*Number and prevalence (%) of one metabolic syndrome component, two metabolic syndrome components, and the metabolic syndrome according to the three definitions: NCEP, NCEP-R, and IDF*

Definition	NCEP	NCEP-R	IDF
One component			
Elevated BP	37,137 (61.1)	37,652 (62.0)	37,652 (62.0)
Elevated W	9,461 (15.6)	9,461 (15.6)	25,796 (42.5)
Elevated TG	9,614 (15.8)	13,559 (22.3)	13,559 (22.3)
Reduced HDL C	4,836 (8.0)	4,836 (8.0)	4,836 (8.0)
Elevated G	7,924 (13.0)	23,818 (39.2)	23,818 (39.2)
Two components			
BP+W	7,141 (11.8)	7,706 (12.7)	19,222 (31.6)
BP+TG	7,237 (11.9)	10,126 (16.7)	10,126 (16.7)
BP+HDL	3,115 (5.1)	3,176 (5.2)	3,176 (5.2)
BP+G	6,164 (10.2)	6,250 (10.3)	6,250 (10.3)
W+TG	2,871 (4.7)	2,871 (4.7)	8,335 (13.7)
W+HDL	1,550 (2.6)	1,540 (2.5)	3,146 (5.2)
W+G	2,265 (3.7)	5,019 (8.3)	12,263 (20.2)
TG+HDL	2,243 (3.7)	2,429 (4.0)	2,429 (4.0)
TG+G	2,311 (3.8)	6,984 (11.5)	6,984 (11.5)
HDL+G	964 (1.6)	2,236 (3.7)	2,236 (3.7)
MetS (three or more components)	6,231 (10.3)	10,774 (17.7)	14,226 (23.4)

BP, increased blood pressure; G, increased glycemia; HDL C, HDL cholesterol; MetS, metabolic syndrome; TG, increased triglycerides; W, increased waist circumference.

subjects with the metabolic syndrome defined without these components.

All statistical analyses were carried out using the SAS statistical software package (version 8.02; SAS Institute, Cary, NC).

RESULTS — Mean age was 52.6 ± 8.3 years in men and 54.7 ± 9.2 years in women. The percentage of subjects who had a regular physical activity was 47.3 and 45.7% in men and women, respectively. The percentage of current smokers and never smokers was 26.9 and 41.6%, respectively, in men and 17.8 and 67.0%, respectively, in women. In this population, 42.5% of the men and 15.5% of the women were "white-collar" workers. Mean LDL cholesterol was 1.42 ± 0.35 g/l in men and 1.32 ± 0.36 g/l in women.

The baseline age for subjects who died during follow-up was 57.0 ± 9.7 years for men and 62.7 ± 10.1 years for women versus 52.5 ± 8.3 years for men and 54.7 ± 9.2 years for women among survivors ($P < 0.0001$). Mean age at death was 59.1 ± 9.7 years for men and 64.7 ± 10.0 years for women versus mean age at the end of the follow-up period for survivors, which was 56.1 ± 8.4 years and 58.3 ± 9.3 years, respectively. After adjustment for age, a number of variables differed significantly between subjects who had died during the follow-up pe-

riod and those who had not. Subjects (both men and women) who had died had higher blood pressure, pulse pressure, heart rate, alcohol and tobacco consumption, prevalence of hypertension, obesity and diabetes, and test scores for stress and depression ($P < 0.01$). Men who had died also had less physical activity (data not shown).

The prevalence of metabolic syndrome according to the IDF, NCEP-R, and NCEP definitions was 26.0% ($n = 10,412$), 20.0% ($n = 7,981$), and 11.7% ($n = 4,671$), respectively, in men and 18.4% ($n = 3,814$), 13.5% ($n = 2,793$), and 7.5% ($n = 1,560$), respectively, in women. Regardless of the definition used, the prevalence of metabolic syndrome was higher among men than among women and increased with age (data not shown). The prevalence of each metabolic syndrome component and combinations of two components is shown in Table 1. Regardless of the definition, elevated blood pressure was the most prevalent metabolic syndrome component. The least prevalent was reduced HDL cholesterol. Taking into account the different thresholds, the component for which the greatest difference was found between the three definitions was increased glycemia, which represented 13% of the subjects with the NCEP- and 39.2% with the

NCEP-R– and IDF-defined metabolic syndrome.

When compared with subjects with no metabolic syndrome (two or less metabolic syndrome components) after adjustment for age, sex, current smoking status, LDL cholesterol, declared physical activity, and socioprofessional category, the risk (HR) of all-cause mortality associated with the presence of metabolic syndrome was 1.79 (95% CI 1.35–2.38), 1.46 (1.14–1.88), and 1.32 (1.04–1.67) for the NCEP, NCEP-R, and IDF definitions, respectively.

Regardless of the definition, the presence of only one component was not significantly associated with increased risk of all-cause mortality during the 3.5-year follow-up. Among combinations of two metabolic syndrome components, BP+W, BP+G, and W+TG were significantly associated with an increased risk of all-cause mortality for the NCEP and NCEP-R definitions. The W+G combination was significantly associated with an increased risk of all-cause mortality for NCEP and IDF definitions. BP+W, BP+G, W+G, and W+TG were significantly associated with an increased risk of all-cause mortality for the NCEP definition, as were BP+W, BP+G, and W+TG for the NCEP-R definition. The only combination significantly associated with an increased risk of all-cause mortality for the IDF definition was W+G.

Figure 1 shows the all-cause mortality risk associated with different combinations of at least three metabolic syndrome components according to the three different definitions, compared with subjects with no metabolic syndrome components, after adjustment for age, sex, current smoking status, LDL cholesterol, declared physical activity, and socioprofessional category. The number of subjects per combination and the percentage of subjects with strictly three components in each group are shown in this figure. For all three definitions, subjects who had combinations of W+G, plus BP or TG, regardless of the additional metabolic syndrome components, had a statistically significant higher risk of all-cause mortality than subjects with no metabolic syndrome components. A statistically significant high risk of all-cause mortality was also found for the following associations: TG+BP+G and W+TG+BP for the NCEP definition, TG+HDL+G for the NCEP-R definition, and W+TG+BP for the IDF definition. For all three definitions, only one four-component combi-
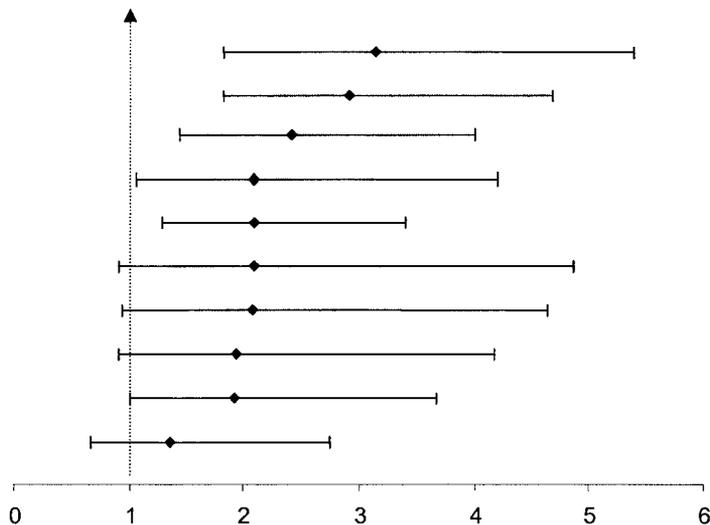
A NCEP

W+TG+G	943	6.8%
W+BP+G	1974	51.0%
TG+HDL+G	603	11.3%
TG+BP+G	1946	44.7%
W+TG+BP	2442	48.0%
W+HDL+G	452	6.0%
W+TG+HDL	837	13.0%
W+HDL+BP	1232	33.8%
HDL+BP+G	765	18.6%
TG+HDL+BP	1607	42.7%
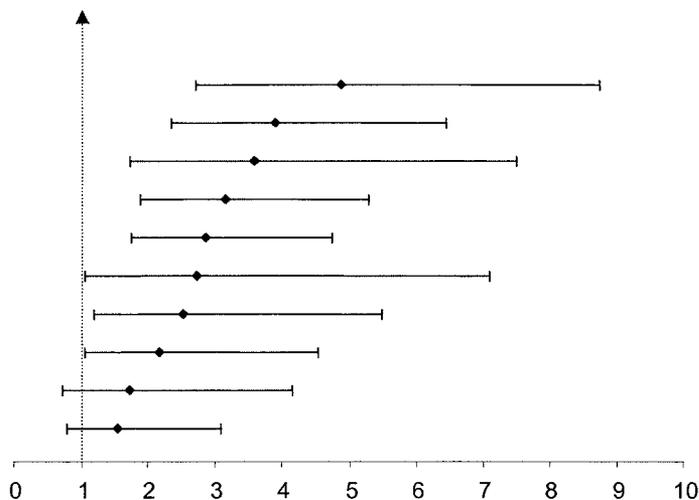
B NCEP-R

W+TG+G	2235	8.7%
W+BP+G	4271	47.8%
W+TG+BP	3142	29.1%
TG+HDL+G	1316	16.6%
TG+BP+G	5573	54.9%
W+HDL+G	881	7.6%
W+TG+HDL	896	9.0%
W+HDL+BP	1232	18.6%
HDL+BP+G	1662	22.7%
TG+HDL+BP	1746	26.4%

C IDF

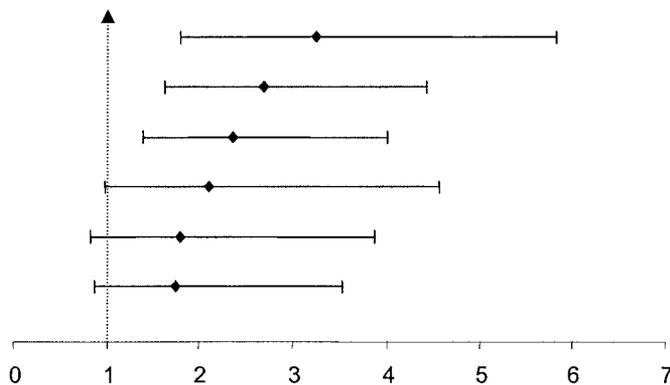|		
W+TG+G	4631	12.0%
W+ BP+G	9777	55.5%
W+TG+BP	6721	34.2%
W+HDL+G	1612	9.2%
W+TG+HDL	1748	12.5%
W+HDL+BP	2299	21.4%

Figure 1—*HR (95% CI) for all-cause mortality, adjusted for age, sex, current smoking status, LDL cholesterol levels, declared physical activity, and socioprofessional category associated with the presence of three-component combinations of metabolic syndrome according to the three definitions: NCEP (A), NCEP-R (B), and IDF (C). The columns depict the number of subjects included in each subgroup and the percentage of subjects with strictly three components. The reference group is composed of subjects with no metabolic syndrome components.*

nation of metabolic syndrome (W+TG+G+BP) was associated with a significant increase in all-cause mortality risk in comparison with subjects with no metabolic syndrome components, regardless of the additional metabolic syndrome components involved: HR 4.56 (95% CI 2.53–8.53) for the NCEP definition, 3.04 (1.74–5.31) for the NCEP-R definition, and 3.32 (1.87–5.90) for the IDF definition.

Specific combinations of three or four components were compared with metabolic syndrome defined without these components: the relative risk was statistically significant for W+BP+G and W+TG+G only. HR for W+BP+G was 2.10 (95% CI 1.27–3.47) for the NCEP definition, 1.98 (1.31–3.00) for the NCEP-R definition, and 1.78 (1.11–2.84) for the IDF definition. HR for W+TG+G was 2.10 (1.21–3.63) for the NCEP definition, 1.79 (1.15–2.76) for the NCEP-R definition, and 1.45 (0.97–2.17) for the IDF definition.

CONCLUSIONS

Influence of the metabolic syndrome definition on prevalence
Our results, obtained from a large French population, confirm the impact of the choice of the definition used to identify metabolic syndrome on its prevalence. Regardless of the definition, the prevalence found in France was lower than in North America and in other European countries; it varied from 11.7% in men and 7.5% in women according to the NCEP definition to 26.0% in men and 18.4% in women according to the IDF definition. This discrepancy was already noted in the MONICA Study (18), in a French population. The NCEP-R definition remains intermediary, as in other studies (9). Clearly, prevalence increases ~50% when the IDF definition is used, compared with the NCEP definition. In addition, Lorenzo et al. (19) compared the prevalence in different populations and showed that the impact of the different definitions on prevalence might depend on the characteristics of the population studied.

Relationship between metabolic syndrome, as defined by the different definitions, and mortality
Numerous studies have shown the increased risk of all-cause mortality and cardiovascular mortality associated with metabolic syndrome; the risk is nearly two times higher than without metabolic syndrome (11,20–30).

In a recent study, we showed that metabolic syndrome was characterized by altered levels of clinical and biological characteristics known as cardiovascular risk markers or risk factors (31). One point of interest of the present analysis is that despite a shorter follow-up period than in other studies, the impact of metabolic syndrome on all-cause mortality was confirmed with similar intensity. Another point is that the results observed in the present study showed a higher risk of all-cause mortality with the NCEP 2001 definition compared with the other two definitions, confirming the results found by Katzmarzyk et al. (9), Lawlor et al. (7), and Wang et al. (8).

The interest of specific component combinations
The most important result of this study is that the risk of short-term all-cause mortality among subjects with metabolic syndrome is different depending on the components involved.

As shown in Fig. 1, in comparison with subjects without metabolic syndrome components, not all combinations are associated with the risk of all-cause mortality. W+G+BP or TG, regardless of the definition; TG+BP+G and W+TG+BP for the NCEP definition; TG+HDL+G for the NCEP-R definition; and W+TG+BP for the IDF definition are associated with short-term mortality risk.

When compared with other associations of metabolic syndrome components, metabolic syndrome defined by the presence of high waist circumference, high glucose levels, and high triglycerides and/or high blood pressure was significantly associated with a high risk of all-cause mortality, regardless of the other additional metabolic syndrome component(s) involved. This result was observed for all definitions.

Few studies have evaluated the effect of specific combinations of risk factors on morbidity and mortality. Wilson et al. (16), using the Framingham offspring study data, after evaluation of the different combinations of metabolic syndrome components, found that few differences in impact on incidence of CVD and type 2 diabetes were present between associations of three components. The difference observed between that study and the present report could be explained by the

characteristics of the population, the definition of metabolic syndrome used, and the nature of analyzed events. The Framingham population was characterized by a higher prevalence of elevated waist circumference and a higher prevalence of reduced HDL cholesterol. Furthermore, the threshold for elevated glucose levels varied from 110 mg/dl in our study to 100 mg/dl in the study by Wilson et al. (16). Lemieux et al. (14) suggested that simultaneous measurement of waist circumference and fasting triglycerides contributed to a better identification of high-risk patients. In their analysis, Katzmarzyk et al. (9) observed a significant increase in CVD mortality when elevated waist circumference was associated with two or three risk factors. Protopsaltis et al. (17) showed that in diabetic patients without known CHD, the triad consisting of diabetes, hypertension, and low HDL (or the combination of diabetes, hypertension, low HDL, and high triglyceride levels) was associated with greater risks of developing a CHD event. In a previous study, we reported that subjects with impaired fasting glucose presented an elevated risk of cardiovascular mortality and all-cause mortality when associated with elevated SBP (32). Our results suggest that metabolic syndrome is not a homogenous syndrome, from a pathophysiological standpoint. Focusing on determining a more accurate definition of metabolic syndrome, based on robust clinical outcomes, appears necessary. Interestingly, the three highest risk combinations are based on the consequences of increased deposit of abdominal fat, which is undoubtedly the primary factor involved in the underlying mechanism of the metabolic syndrome. The relationship between metabolic syndrome and abdominal obesity appears to play a critical role in the clinical consequences of metabolic syndrome in terms of insulin resistance and inflammation (33). Different links between visceral adipose tissue metabolism, its secreted factors, and mortality are now major fields of research.

The findings of this study require further confirmation in other populations, based on geographic origin, lifestyle, underlying diseases, and different global mortality risk. These findings, however, do clearly indicate that metabolic syndrome needs to be more clearly defined and that attention should be focused on the combination of factors that are mostly associated with short- and long-term mortality risk.

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 low prevalence of metabolic syndrome found among this particular population. In the cohort from the French population-based study MONICA, the prevalence of metabolic syndrome was higher: 22.5% in men and 16.5% in women for the 3,441 subjects included (16). Our data, however, according to the NCEP definition, are similar to those from the DESIR Study (34) and to a somewhat lesser degree to the MONICA Study, which regroups three French geographical regions and is more representative of France. However, the strength of the association between metabolic syndrome and all-cause mortality was similar to the one that was observed in other populations, suggesting a representative characteristic of metabolic syndrome in our population. As is common practice in the majority of epidemiological studies, the classification of metabolic syndrome was established using a single measure for each parameter, and diagnosis of metabolic syndrome was not confirmed with another evaluation. During this short follow-up, we were not able to show any difference in the relationship between metabolic syndrome and all-cause mortality based on sex, as was recently mentioned in two meta-analyses (11,12). The duration of the study was undoubtedly not long enough to observe significant differences.

Because the follow-up period was short and the number of deaths relatively low, an analysis that would take into account causes of mortality, particularly CVD and CHD mortality, was not carried out.

In conclusion, in a French middle-aged population, the presence of metabolic syndrome identified using all three definitions was associated with an excess risk of all-cause mortality after <4 years of follow-up. Among all the possible three-component and four-component combinations, three were significantly more highly associated with all-cause mortality; all of these associations included increased abdominal fat deposit assessed by waist circumference and increased glycemia, with either elevated triglycerides or elevated blood pressure. This main result suggests the heterogeneity of metabolic syndrome regarding short-term all-cause mortality.

These results have a strong impact on identifying a category of high-risk subjects suffering from metabolic disorders and on preventing short-term increase in all-cause mortality through the use of dedicated intervention strategies.

References

1. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
2. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–2752, 2005
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
4. Alberti KG, Zimmet P, Shaw J; for the IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
5. Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A: Cardiovascular mortality in overweight subjects: the key role of associated risk factors. *Hypertension* 46:654–659, 2005
6. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF: Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 355:763–778, 2006
7. Lawlor DA, Smith G, Ebrahim S: Does the new International Diabetes Federation definition of metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study. *Diabetologia* 49:41–48, 2006
8. Wang JJ, Li HB, Kinnunen L, Hu G, Jarvinen TM, Miettinen ME, Yuan S, Tuomilehto J: How well does the metabolic syndrome defined by five definitions predict incident diabetes and incident coronary heart disease in a Chinese population? *Atherosclerosis* 192:161–168, 2006
9. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair S: The importance of waist circumference in the definition of metabolic syndrome. *Diabetes Care* 29:404–409, 2006
10. The DECODE Study Group; Qiao Q: Comparison of different definitions of the metabolic syndrome in relation to cardiovascular mortality in European men and women. *Diabetologia* 49:2837–2846, 2006
11. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28:1769–1778, 2005
12. Galassi A, Reynolds K, He J: Metabolic syndrome and risk of cardiovascular disease: a meta analysis. *Am J Med* 19:812–819, 2006
13. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM: Metabolic syndrome and risk of incident cardiovascular events and death. *J Am Coll Cardiol* 49:403–414, 2007
14. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Despres JP: Hypertriglyceridemic waist: a marker of the atherogenic metabolic metabolic triad (hyperinsulinemia; hyperlipoprotein B; small, dense LDL) in men? *Circulation* 102:179–184, 2000
15. Tanko LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C: Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation* 111:1883–1890, 2005
16. Wilson PWF, D'Agostino RB, Parise H, Sullivan L, Meigs JB: Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 112:3066–3072, 2005
17. Protopsaltis I, Nikolopoulos G, Dimou E, Brestas P, Kokkoris S, Korantzopoulos P, Melidonis A: Metabolic syndrome and its components as predictors of all-cause mortality and coronary heart disease in type 2 diabetic patients. *Atherosclerosis.* 2006 Oct 23; [Epub ahead of print]
18. Dallongeville J, Grupposo MC, Cottel D, Ferrieres J, Arveiler D, Bingham A, Ruidavets JB, Haas B, Ducimetiere P, Amouyel P: Association between the metabolic syndrome and parental history of premature cardiovascular disease. *Eur Heart J* 27:722–728, 2006
19. Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, Gonzalez-Sanchez JL, Seclen S, Villena A, Gonzalez-Villalpando C, Williams K, Haffner SM: Geographic variations of the International Diabetes Federation and the National Cholesterol

Education Program-Adult Treatment Panel III definitions of the metabolic syndrome in nondiabetic subjects. *Diabetes Care* 29:685–691, 2006

20. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001

21. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002

22. Resnick HE, Jones K, Ruotolo G, Jain AK, Henderson J, Lu W, Howard BV; Strong Heart Study: Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians: the Strong Heart Study. *Diabetes Care* 26:861–867, 2003

23. Marroquin OC, Kip KE, Kelley DE, Johnson BD, Shaw LJ, Bairey Merz CN, Sharaf BL, Pepine CJ, Sopko G, Reis SE; Women's Ischemia Syndrome Evaluation Investigators: Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation* 109:714–721, 2004

24. Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE: Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation* 109:706–713, 2004

25. Schillaci G, Pirro M, Vaudo G, Gemelli F, Marchesi S, Porcellati C, Mannarino E: Prognostic value of the metabolic syndrome in essential hypertension. *J Am Coll Cardiol* 43:1817–1822, 2004

26. Trevisan M, Liu J, Bahsas FB, Menotti A: Syndrome X and mortality: a population-based study: Risk Factor and Life Expectancy Research Group. *Am J Epidemiol* 148:958–966, 1998

27. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 110:1245–1250, 2004

28. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G: The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities Study. *Diabetes Care* 28:385–390, 2005

29. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ: Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 112:666–673, 2005

30. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K; DECODE Study Group: Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 164:1066–1076, 2004

31. Pannier B, Thomas F, Eschwège E, Bean K, Benetos A, Leochmach Y, Danchin N, Guize L: Cardiovascular risk markers associated with the metabolic syndrome in a large French population: the Symfonie study. *Diabete Metab* 32:467–474, 2006

32. Henry P, Thomas F, Benetos A, Guize L: Impaired fasting glucose, blood pressure and cardiovascular disease mortality. *Hypertension* 40:458–463, 2002

33. Langenberg C, Bergstrom J, Scheidt-Nave C, Pfeilschifter J, Barrett-Connor E: Cardiovascular death and the metabolic syndrome: role of adiposity-signaling hormones and inflammatory markers. *Diabetes Care* 29:1363–1369, 2006

34. Balkau B, Vernay M, Mhamdi L, Novak M, Arondel D, Vol S, Tichet J, Eschwege E; D.E.S.I.R. Study Group: The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome: the French D.E.S.I.R. study. *Diabetes Metab* 29:526–532, 2003