All-Cause and Cardiovascular Mortality Using the Different Definitions of Metabolic Syndrome

Athanase Benetos, MD, PhD[a,b,*], Frédérique Thomas, PhD[a], Bruno Pannier, MD[a], Kathy Bean, MA, MPH[a], Bertrand Jégo, MBA[a], and Louis Guize, MD[a,c]

The aim of the present study was to assess the risk of all-cause and cardiovascular disease (CVD) mortality in subjects identified as having metabolic syndrome (MS) using either the recent International Diabetes Federation (IDF) definition or the revised National Cholesterol Educational Program (NCEP-R) definition, but not the original NCEP (2001) definition. The study population was composed of 84,730 men and women without CVD aged ≥40 years who had a health checkup at the IPC Center. Follow-up for mortality was 4.7 ±1.7 years. Prevalences of MS were 9.6%, 21.6%, and 16.5% according to the NCEP, IDF, and NCEP-R definitions, respectively. Compared with subjects without MS, risks of all-cause mortality associated with MS were 1.63 (95% confidence interval [CI] 1.38 to 1.93) with the NCEP, 1.25 (95% CI 1.09 to 1.45) with the IDF, and 1.32 (95% CI 1.13 to 1.53) with the NCEP-R, and risks of CVD mortality were 2.05 (95% CI 1.28 to 3.28), 1.77 (95% CI 1.18 to 2.64), and 1.64 (95% CI 1.08 to 2.50), respectively. In subjects with MS detected using the IDF and NCEP-R definitions, but not the NCEP definition, risks of all-cause mortality were 1.07 (95% CI 0.89 to 1.28) and 0.92 (95% CI 0.73 to 1.18) and 1.42 (95% CI 0.86 to 2.34) and 1.07 (95% CI 0.55 to 2.09) for CVD mortality, respectively. In conclusion, in a large French population, the recent definitions of MS almost double the prevalence compared with the original definition. Subjects identified as having MS using only the recent definitions and not the original definition did not have higher rates of all-cause and CVD mortality compared with subjects without MS during follow-up. **(Am J Cardiol 2008;102:188–191)**

Using the original National Cholesterol Educational Program (NCEP)[1] definition, many studies have shown that metabolic syndrome (MS) was associated with excess risk of all-cause and cardiovascular disease (CVD) mortality and increased risk of type 2 diabetes mellitus.[2–4] Recently, the International Diabetes Federation (IDF)[5] published its definition for MS and the original NCEP definition has been revised (NCEP-R).[6] The NCEP-R and IDF definitions generally identify a substantially larger number of subjects with MS compared with the original NCEP definition. Katzmarzyk et al[7] found a 50% higher prevalence of MS using the IDF definition compared with the NCEP definition. However, it is not known whether subjects identified using only the recent definitions and not the original definition are also at higher risk of all-cause and CVD mortality. The aim of the present analysis was to assess the risk of all-cause and CVD mortality in subjects identified as having MS using either the recent IDF or NCEP-R definition, but not the original NCEP (2001) definition.

Methods

Subjects were examined at the Centre d'Investigations Préventives et Cliniques (IPC Center), a medical center subsidized by the French national health care system (Sécurité Sociale-CNAM) that offers all working and retired persons and their families a free medical examination every 5 years.[8]

Our study population was composed of all subjects aged ≥40 years who had a health checkup from January 1999 to December 2004. The population included 57,076 men and 29,618 women. For the purpose of this study, 1,282 men and 682 women with previous CVD (data derived from questionnaires and electrocardiograms) were excluded, leaving 84,730 subjects (55,794 men and 28,936 women) for the analyses. Table 1 lists the main clinical characteristics of this population.

Supine blood pressure (BP) was measured in the right arm using a manual mercury sphygmomanometer after a 10-minute rest period. The first and fifth Korotkoff phases were used to define systolic BP and diastolic BP. Height and weight were recorded by a nurse. Waist circumference was measured using an inelastic tape placed midway between the lower ribs and iliac crests on the midaxillary line. Standard biologic parameters (enzymatic method, automat Hitachi 917, Hitachi, Tokyo, Japan) were measured under fasting conditions. Tobacco use, physical activity, personal medical history, and current medications were assessed using a self-administered questionnaire. All clinical and bio-

[a]Centre d'Investigations Préventives et Cliniques (IPC Center), Paris; [b]CHU de Nancy, University of Nancy, Vandoeuvre lès Nancy; and [c]University of Paris-Descartes, Paris, France. Manuscript received January 31, 2008; revised manuscript received and accepted March 4, 2008.

*Corresponding author: Tel: +333-8315-3322; fax: +333-8315-7668.
E-mail address: a.benetos@chu-nancy.fr (A. Benetos).

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Table 1
Main clinical characteristics of the population and mortality data during the 4.7-year follow-up period

	Men	Women	All
No. of subjects	55,794	28,936	84,730
Age (yrs)	52.1 ± 8.2	54.2 ± 9.1	52.8 ± 8.6
Body mass index (kg/m^2)	25.9 ± 3.5	24.5 ± 4.4	25.4 ± 3.9
Waist circumference (cm)	91.6 ± 9.9	75.5 ± 11.0	87.1 ± 12.0
Systolic BP (mm Hg)	136.2 ± 18.6	132.7 ± 20.8	135.0 ± 19.5
Dystolic BP (mm Hg)	82.3 ± 1.5	77.8 ± 1.6	80.7 ± 11.7
Heart rate (beats/min)	63.1 ± 10.2	65.2 ± 9.9	63.8 ± 10.2
Total cholesterol (g/L)	2.21 ± 0.39	2.20 ± 0.39	2.21 ± 0.39
High-density lipoprotein cholesterol (g/L)	0.58 ± 0.14	0.72 ± 0.17	0.63 ± 0.17
Triglycerides (g/L)	1.14 ± 0.69	0.87 ± 0.44	1.04 ± 0.64
Glycemia (g/L)	1.10 ± 0.18	0.95 ± 0.15	0.99 ± 0.17
Total mortality	695 (1.25%)	234 (0.81%)	929 (1.10%)
Cancer mortality	284 (0.51%)	110 (0.38%)	394 (0.47%)
Total CVD mortality	76 (0.14%)	28 (0.10%)	104 (0.12%)
Stroke mortality	19 (0.03%)	13 (0.04%)	32 (0.04%)
Coronary heart disease mortality	31 (0.06%)	8 (0.03%)	39 (0.05%)

Values expressed as mean ± SD or number (percent).

logic evaluations and electrocardiograms were performed on the same day. The IPC Center received authorization from the Comité National d'Informatique et des Libertés to conduct these analyses. All subjects gave their informed consent at the time of the examination.

For each screened subject, vital status was obtained from the Institut National de Statistiques et d'Etudes Economiques (Paris, France). Causes of death obtained from death certificates were provided by the Department of Mortality Studies at the Institut National de la Santé et de la Recherche Médicale (Unit SC8). Causes of death were codified according to the *International Classification of Diseases, 10th Revision*. Deaths before 2002 were recoded using the 10th revision, and CVD-related deaths were coded according to chapter IX (I 10 to I 82). Validation of this procedure has been detailed in a previous publication.[8] Based on results of the validation of this procedure, we considered that we had complete follow-up for the entire study population.

Because of the absence of an interaction between gender and MS for all-cause mortality, men and women were grouped together for the present analysis. For each definition, the impact of MS on all-cause mortality was studied using Cox regression analysis including age, gender, current tobacco use, low-density lipoprotein cholesterol, physical activity, and socioeconomic categories. To evaluate the risk of mortality according to the IDF definition compared with the original NCEP definition, Cox analyses were performed in the 4 subgroups of (1) the absence of MS according to the NCEP definition (NCEP$^-$) and the IDF definition (IDF$^-$), (2) NCEP$^-$ and the presence of MS according to the IDF definition (IDF$^+$), (3) NCEP$^+$ IDF$^-$, and (4) NCEP$^+$ IDF$^+$. In the group NCEP$^+$ IDF$^-$, the risk of CVD mortality could not be estimated (only 2 CVD deaths were observed in this group). Similar subgroup analyses were carried out for the NCEP-R definition compared with the original NCEP definition as (1) NCEP$^-$ NCEP-R$^-$, (2) NCEP$^-$ NCEP-R$^+$, and (3) NCEP$^+$ NCEP-R$^+$. The NCEP$^+$ NCEP-R$^-$ group had no subjects because all NCEP$^+$ subjects were also NCEP-R$^+$.

All statistical analyses were carried out using the SAS statistical software package (version 8.02; SAS Institute, Cary, North Carolina) for (Windows Microsoft Corp., Redmond, Washington).

Table 2
Prevalence of metabolic syndrome (MS) and adjusted all-cause and cardiovascular disease (CVD) mortality risk in subjects with MS compared with subjects without MS according to each definition

Definition	Prevalence (%)	All-Cause Mortality	CVD Mortality
NCEP	9.6 (n = 8,160)	1.63 (1.38–1.93)	2.05 (1.28–3.28)
IDF	21.6 (n = 18,258)	1.25 (1.09–1.45)	1.77 (1.18–2.64)
NCEP-R	16.5 (n = 14,014)	1.32 (1.13–1.53)	1.64 (1.08–2.50)

Values expressed as hazard ratio (95% confidence interval). Adjusted for age, gender, tobacco, physical activity, low-density lipoprotein cholesterol, and socioprofessional category.

Results

The study population was followed up until December 2005. Mean follow-up was 4.7 ±1.7 years. Table 1 lists the main clinical characteristics of the population. The prevalence of MS was higher using the IDF and NCEP-R definitions compared with the classic NCEP definition (Table 2), and subjects with MS were at increased risk of total and CVD mortality compared with subjects without MS (Table 2).

Table 3 lists the risks of all-cause and CVD mortality according to the presence or absence of MS when the NCEP and IDF definitions were combined (NCEP$^-$ IDF$^-$ was the reference group). This analysis showed that the risk of all-cause mortality in subjects classified as having MS based on the IDF definition, but not the original NCEP definition, did not increase compared with the reference group. Conversely, the risk of mortality increased significantly in the 2 groups of subjects classified as having MS according to both definitions (NCEP$^+$ IDF$^+$) or only according to the NCEP definition (NCEP$^+$ IDF$^-$). The risk of CVD mortality in subjects classified as having MS based on only the IDF definition did not increase significantly compared with the reference group. The risk in the group with MS according to both criteria increased by 136%. The hazard ratio in the NCEP$^+$ IDF$^-$ group was not assessed because of lack of statistical power (low number of subjects [n = 1,200] and CVD deaths [n = 2] in this group).

Table 3 lists the risks of all-cause and CVD mortality according to the presence or absence of MS using the NCEP and NCEP-R definitions (NCEP$^-$ NCEP-R$^-$ was the reference group). This analysis showed that subjects classified as having MS when using only the NCEP-R definition (NCEP$^-$ NCEP-R$^+$) did not show a trend for increased risk of all-cause mortality compared with subjects without MS. Conversely, the NCEP$^+$ NCEP-R$^+$ subgroup showed a 60% increase in all-cause mortality risk. Analysis of the risk of CVD mortality also showed that subjects classified as having MS when using only the NCEP-R definition, but not the original NCEP definition (NCEP$^-$ NCEP-R$^+$), were not at increased risk compared with subjects without MS. CVD risk was more than twice as high in the NCEP$^+$ NCEP-R$^+$ group.

Table 3
Adjusted risk of all-cause and cardiovascular disease (CVD) mortality in the presence or absence of metabolic syndrome (MS) by combining the NCEP and IDF definitions and NCEP and NCEP-R definitions

	NCEP$^-$ IDF$^-$	NCEP$^-$ IDF$^+$	NCEP$^+$ IDF$^-$	NCEP$^+$ IDF$^+$
No. of subjects	65,272	11,298	1,200	6,960
All-cause mortality	Reference group	1.07 (0.89–1.28)	1.86 (1.25–2.76)	1.62 (1.34–1.95)
CVD mortality	Reference group	1.42 (0.86–2.34)	Not estimated*	2.36 (1.42–3.92)
	NCEP$^-$ NCEP-R$^-$	NCEP$^-$ NCEP-R$^+$		NCEP$^+$ NCEP-R$^+$
No. of subjects	70,716	5,854		8,160
All-cause mortality	Reference group	0.92 (0.73–1.18)		1.61 (1.36–1.92)
CVD mortality	Reference group	1.07 (0.55–2.09)		2.08 (1.29–3.36)

Values expressed as hazard ratio (95% confidence interval). Adjusted for age, gender, tobacco, physical activity, low-density lipoprotein cholesterol, and socioprofessional category.

* Low number of CVD deaths in this group.

To clarify whether the observed results were related to the presence of treated subjects, the same analyses as those listed in Table 3 were carried out after exclusion of all subjects with specific treatment for lipid abnormalities, hypertension, and diabetes (n = 6,953). These analyses provided results similar to those observed for the entire population, such as the lack of a significant increase in total and CVD mortality in the groups identified as having MS using only IDF and NCEP-R criteria, but not the original NCEP classification (data not shown).

Discussion

Our results obtained from a large French middle-aged population without previous CVD confirmed the impact of the choice of the definition of MS on its prevalence, as shown in several North American and European studies.[3,7,9,10] In our study, use of the IDF and NCEP-R definitions dramatically increased the prevalence of MS from approximately 10% according to the NCEP definition to >21% according to the IDF definition and >16% according to the NCEP-R definition.

In the present study, we found that subjects identified as having MS using the 2 recent definitions, but not the original NCEP definition, were not at higher risk of all-cause and CVD mortality.

CVD risk according to combinations of different metabolic disorders is of major clinical interest. In a recent study, we showed that obesity in the absence of associated risk factors was not associated with increased CVD risk.[8] More recently, we examined the role of the different combinations of 3 MS components on the risk of mortality.[11] In a population of subjects who underwent coronary angiography, Saely et al[12] observed a significantly higher risk of vascular events with the original NCEP definition than with the IDF definition.

Several other recent studies have shown that patients with MS identified using the various classifications were at high risk of CVD mortality.[7,13–15] The present study also confirmed these results because subjects with MS showed increased risk of all-cause and CVD mortality. The originality of our study was that it combined the original NCEP and more recent definitions to identify subjects with MS. Using this approach, we showed that increased risk according to the IDF and NCEP-R classifications depended almost exclusively on the presence of subjects already identified as having MS using the original NCEP classification.

The difference between the original NCEP and IDF definitions is that the IDF definition requires that every subject have increased waist circumference, establishes regional-specific cut-off values for waist circumference, proposes lower cut-off values for fasting glucose, and includes treatment for BP, lipids, glucose, or the specific cut-off point.[5] In our study, subjects identified using only the IDF definition showed a slight, but not significant, increase in risk of all-cause and CVD mortality during the 5-year follow-up. Conversely, the mandatory presence of high waist circumference as 1 of the MS components in the IDF definition excludes some subjects from being classified as having MS and creates a small group of subjects classified as having MS using only the NCEP definition. In our study, this group had 1,200 subjects, which corresponded to 1.4% of the total studied population. This group, identified in our study as IDF$^-$ NCEP$^+$, showed a high risk of all-cause mortality. However, because of the lack of statistical power, the risk of CVD mortality was not evaluated in this group.

The increase in MS subjects when the NCEP-R classification was used (16.5% vs 9.6%) was caused by decreasing the cut-off value for fasting glucose and including treatment for BP, lipids, glucose, or the specific cut-off point.[6] Subjects with MS according to the original NCEP definition were a subgroup of MS subjects identified using the more recent NCEP-R definition. Our study clearly showed that the increased risk of both all-cause and CVD mortality observed in subjects with MS according to the NCEP-R definition was caused exclusively by the subgroup of subjects classified as having MS using the NCEP definition. This was mainly caused by lowering the cut-off value for fasting glucose because after exclusion of all subjects with hypolipemic, antihypertensive, or antidiabetic treatment from the analyses, the NCEP$^-$ NECP-R$^+$ group remained at low risk. These data suggested that subjects with metabolic disorders or high BP controlled with drug treatment and subjects with a moderate increase in glycemia may not be at higher risk than subjects without these risk factors. It can be suggested that subjects identified as having MS using the more recent definitions may have a higher degree of insulin

resistance than subjects without MS, and long-term follow-up is needed to identify their CVD risk.

The follow-up of approximately 5 years was shorter than in other studies,[16] and it is possible that subjects identified using only the 2 recent definitions may have increased long-term mortality. In addition, these results concerned all-cause and CVD mortality in a relatively low-risk population because subjects with a history of significant CVD were eliminated from this analysis. It is therefore possible that the 2 recent definitions have utility for higher risk populations or subgroups.

The present study is the first to show that the 2 recent definitions may not identify additional high-risk subjects compared with the original NCEP definition, leading us to question the value of the recent definitions. Although it is important to detect high-risk patients, it is also important not to overextend risk criteria to not include non–high-risk subjects.

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Appendix: NECP, IDF, and NCEP-R definitions of MS

NCEP[1]: Requires the association of 3 of the 5 criteria of (1) abdominal obesity with waist circumference >102 cm in men and > 88 cm in women, (2) triglycerides ≥150 mg/dl, (3) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women, (4) systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg, and (5) fasting glucose ≥110 mg/dl.

IDF[5]: Includes as mandatory the presence of abdominal obesity defined as waist circumference ≥94 cm in men and ≥80 cm in women and the presence of 2 of the 4 criteria of (1) triglycerides ≥150 mg/dl or a specific treatment for lipid abnormalities, (2) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women or a specific treatment for lipid abnormalities, (3) systolic BP ≥130 mm Hg or diastolic BP ≥8 5 mm Hg or antihypertensive treatment, and (4) fasting glucose ≥100 mg/dl or diabetes.

NCEP-R[6]: Requires the association of 3 of the 5 criteria of (1) abdominal obesity with waist circumference ≥102 cm in men and ≥88 cm in women, (2) triglycerides ≥150 mg/dl or a specific treatment for lipid abnormalities, (3) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women or a specific treatment for lipid abnormalities, (4) systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or antihypertensive treatment, and (5) fasting glucose ≥100 mg/dl or drug treatment for increased glucose.

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