Contribution of the metabolic syndrome to sudden death risk in asymptomatic men: the Paris Prospective Study I

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Aims To compare the risk of sudden death and non-sudden death from myocardial infarction associated with the metabolic syndrome (MetS) in asymptomatic men.

Methods and results The mortality status of 6678 middle-aged men from the Paris Prospective Study I, who were free of diabetes and coronary heart disease (CHD) at the baseline examination, has been investigated over 21 years of follow-up. The sagittal abdominal diameter was substituted for waist circumference, and HDL cholesterol was unavailable. The presence of three abnormalities and the presence of abdominal adiposity plus at least two abnormalities defined the MetS, using the NCEP-ATP III and IDF criteria, respectively.

Frequency estimate of the MetS was 14.4 and 16.7%, using the NCEP-ATP III and IDF criteria, respectively. The MetS increased the risk of sudden death and non-sudden death by 68% [95% confidence interval (CI) 1.05–2.70] and 38% (95% CI 0.95–2.01), respectively, after adjustment for other CHD risk factors (P for the comparison of the hazard ratios = 0.25). Hazards ratio using the IDF criteria were 2.02 (95% CI 1.30–3.14) and 1.69 (95% CI 1.20–2.38), respectively, (P = 0.26).

Conclusion In healthy middle-aged men, the MetS increased the risk of sudden death and, to a lesser extent, the risk of non-sudden death over 21 years independent of CHD risk factors.

KEYWORDS Epidemiology; Sudden cardiac death; Risk factors; Metabolic syndrome

Introduction Sudden death is a major contributor to coronary heart disease (CHD) mortality, and epidemiological data suggest that half of the victims have no physician-diagnosed CHD at the time of death.1,2 Thus, the possibility of early identification of those subjects in the population at increased risk of sudden death using simple markers represents a major challenge.

Although traditional CHD risk factors (age, smoking, blood pressure, and total cholesterol) have been associated with both sudden and non-sudden death in the population,1 some risk factors have been suggested to be preferentially associated with sudden death. Using a systematic comparison of risk factors for sudden death and non-sudden death from myocardial infarction in the Paris Prospective Study I, we have reported specific associations with sudden death for type 2 diabetes and circulating free fatty acid level, and a strong (but not specific) association for the sagittal abdominal diameter, an anthropometric marker of abdominal adiposity.3–5 These risk factors may cluster in the metabolic syndrome (MetS), which additionally includes dyslipidaemia and elevated blood pressure.6,7 The MetS is a frequent clinical condition, with prevalence estimates varying between 10 and 30% according to population characteristics and definitions of the MetS.6–18 Cohort studies have shown the MetS to be associated with total and cardiovascular mortality14,17 and more strongly with CHD mortality.14–17 However, the association between the MetS and sudden death has never been evaluated. In addition, the extent to which the MetS is preferentially associated with sudden death as opposed to non-sudden death is not known.

To address these two questions, we used data from the Paris Prospective Study I,19 a large prospective cohort of healthy asymptomatic men whose mortality has been followed up for more than 20 years.

Methods

Population The Paris Prospective Study I is a prospective study of 7746 native Frenchmen employed by the Paris Civil Service, who were 43–52 years of age at the baseline examination, between 1967 and 1972. Details of the recruitment, design, and procedures have been described elsewhere.19

Clinical examination Subjects underwent ECG and physical examinations conducted by a physician, provided blood samples for laboratory tests, and
Definition of the metabolic syndrome

International Diabetes Federation criteria
Recently, an International Diabetes Federation (IDF) consensus proposed a new definition of the MetS, in which the presence of abdominal adiposity (with ethnic-specific cut-offs) was a prerequisite, and the threshold for elevated glycaemia was lowered to 100 mg/dL.\(^2\) The MetS is present in subjects with abdominal adiposity and two or more abnormalities among the following: elevated triglycerides (\(\geq 150 \text{ mg/dL}\)), low HDL cholesterol (men \(< 40 \text{ mg/dL}\) and women \(< 50 \text{ mg/dL}\)), elevated fasting glucose (\(\geq 110 \text{ mg/dL}\)) and elevated systolic (\(\geq 130 \text{ mmHg}\)) or diastolic blood pressure (\(\geq 85 \text{ mmHg}\)), or use of antihypertensive medications.

However, waist circumference and HDL cholesterol were not measured at the baseline examination of the study, which took place more than 30 years ago. We have substituted the SADx for the waist circumference, and on the basis of previous findings from the Paris Prospective Study I, the highest quintile of the SADx (\(\geq 24 \text{ cm}\)) was used as a marker of elevated abdominal adiposity.\(^5\) Accordingly, the MetS was defined in the following analyses by the presence of three among the four possible abnormalities (abdominal adiposity, elevated blood pressure, fasting glycaemia, and triglycerides).

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Follow-up and ascertainment of CHD deaths
The administrative department (Town Hall) provided annually a list of deceased subjects, until participant retirement. All available data on the causes of death were collected from specific inquiries (hospital medical records, general practitioners identified by relatives). After retirement, causes of death were obtained from death certificates. An independent medical committee assigned causes of death using standardized conditions by the same three trained technicians and the methods have been previously reported.\(^2\) The sagittal abdominal diameter, which is the antero-posterior diameter of the abdomen in the sagittal plane, was measured with sliding callipers below the xyphoid level (SADx) and recorded to the nearest centimetre.\(^5\)

Study population
We excluded from the analysis men with a diagnosis of ischaemic heart disease (myocardial infarction or angina) established at entry from personal medical history, clinical examination, or ECG (\(n = 312\)); those with known diabetes on the basis of self-reported physician-diagnosis or the use of oral hypoglycaemic treatment (\(n = 113\)); those with a fasting glycaemia \(\geq 126 \text{ mg/dL} \text{ (n = 223)}\); and those with missing data on fasting glycaemia (\(n = 65\)). Moreover, on 1 January 1994, the vital status could not be obtained for 355 subjects (4.6%). Of note, there were no major differences between the baseline characteristics of these 355 subjects and of the remaining 6678 men who were free of ischaemic heart disease and/or diabetes at baseline, whose mortality status was known, and who represent the study population of the current study.

Statistical analysis
Descriptive data are presented as mean (standard deviation) and in percent (n) for continuous and categorical variables, respectively. Pearson \(\chi^2\) and ANOVA tests were used to compare the distribution of categorical and continuous variables, respectively, between the groups. Cox proportional hazards model was used to estimate the hazards ratios (HRs) and their 95% confidence intervals (CI) of sudden death and non-sudden death associated with the MetS, considering men who remained alive or had died of other causes during follow-up as the reference group. HR of sudden death and non-sudden death associated with the MetS were then compared by a \(z\)-test on the regression coefficients. HRs were adjusted for risk factors not in the definition of the MetS, including age, mean number of cigarettes smoked daily in past 5 years, sporting activity, total cholesterol, parental history of sudden death, and fatal myocardial infarction (MI). We also estimated the HRs of mortality associated with individual components of the MetS in separate Cox models adjusted for these risk factors. In these latter models, men without the component under investigation were the reference group. The proportionality assumption of the hazards was verified using a graphical method. The linearity assumption of the Cox model was assessed and satisfied for each quantitative variable by comparing the likelihood of one model containing the variable as quantitative (in its ordinal form) with another model with the variable categorized in dummy variables. All analyses were performed on SAS, release 8.2 (SAS Institute Inc., Cary, NC, USA).

Results
Of the 6678 men who were free of ischaemic disease and diabetes at baseline, 14.4% (\(n = 963\)) had the MetS according to the NCEP III criteria. Among them, 84.0% (\(n = 809\)) and 16.0% (\(n = 154\)) had three and four components of the MetS, respectively. Using the IDF criteria, the prevalence of the MetS increased to 16.7% (\(n = 1111\)). Men with the MetS were more likely to be smokers, less likely to play sport, and had higher mean BMI, resting heart rate, and total cholesterol (Table 1). Parental history of sudden death or fatal MI were equally frequent in the two groups. Comparisons based on the IDF criteria of the MetS yielded similar results (not shown).

Mortality has been followed up for 21.2 years on average (± 5.5), during which 1915 deaths have been registered, including 315 from CHD. Among these, there were 105 sudden deaths and 180 non-sudden deaths from myocardial infarction (the remaining 30 deaths being due to other coronary causes). Table 2 describes the baseline characteristics of men who died from sudden death, non-sudden death from myocardial infarction, or who died from other causes or who remained alive during follow-up (\(n = 6393\),...
HR observed with the IDF criteria were slightly higher but were of the same order of magnitude than that found with the NCEP criteria. Of note, the HR of the MetS for non-sudden death remained statistically significant in multivariable analysis (Table 3). Analysis based on the individual components of the MetS (NCEP criteria) (Table 3) indicates that clear and statistically significant associations were observed only with elevated abdominal adiposity as defined by a SADx over 24 cm (upper quintile). Besides, the magnitude of the HRs associated with SADx was comparable with that observed with the MetS taken as a whole. Accordingly, although higher, the HR of elevated SADx for sudden death (2.26; 95% CI 1.49–3.44) was not statistically different from that for non-sudden death (1.60; 95% CI 1.16–2.19) (P = 0.67).

Compared with men free of any component of the MetS, the risk of mortality for each cause (adjusted for CHD risk factors) increased stepwise with the number of components (P for linear trend <0.0001). This increase in risk was not statistically different between sudden death and non-sudden death (P for comparison of trend = 0.83). Consistent results were obtained using the IDF criteria (not shown).

Additional analyses

Given the unavailability of HDL cholesterol in the study, we performed subanalysis, with the MetS defined by the presence of at least two abnormalities (NCEP-ATP III criteria) or by the presence of abdominal adiposity plus at least one abnormality (IDF criteria). Using these two definitions, the frequency of the MetS was 43.0 and 22.6% with the NCEP-ATP III and IDF criteria, respectively. For the control group). The prevalences of the MetS at baseline in these groups were, respectively, 25.7, 20.6, and 14.1% using the NCEP criteria, and 30.5, 26.8, and 16.2% with the IDF criteria. Elevated blood pressure was the most frequent abnormality of the MetS, with a prevalence rate of 78.0–86.1% according to the group. Focusing on sudden and non-sudden death, elevated SADx and elevated fasting glycaemia tended to be more frequent in men who died from sudden death; elevated blood pressure and elevated triglycerides were equally frequent in both groups. Moreover, men who died of sudden death were more likely to have two or more components of the MetS than men who died from non-sudden death.

Univariate analysis, men with the MetS at baseline examination (NCEP III criteria) had a 90% increased risk of CHD mortality: there was a more than a two-fold increased risk of sudden death and a lower (65%) but not statistically different (P = 0.18) increased risk of non-sudden death (Table 3). After adjustment for age, cigarette consumption, total cholesterol, parental history of sudden death or fatal MI, and sport activity, increased mortality risks associated with the MetS were 56% (HR 1.56; 95% CI 1.18–2.06), 68% (HR 1.68; 95% CI 1.05–2.70), and 38% (HR 1.38; 95% CI 0.95–2.01), respectively, for CHD mortality, sudden death, and non-sudden death. Although marginally not statistically significant, the HR of the MetS for non-sudden death was not different to the HR observed for sudden death (P = 0.25).
prospective analyses, the pattern of association remained similar to that with the initial definition of the MetS. Although HR were practically unchanged with the IDF criteria, with the use of the NCEP-ATP III criteria, the HRs were higher, especially for sudden coronary death (2.03 vs. 1.68) (not shown). We have also explored the consequences of including diabetes as a separate group (from the MetS) in the analysis. Diabetes was defined by a fasting glycaemia greater or equal to 126 mg/dL or the use of oral hypoglycaemic medications. An additional group of 336 diabetic men (4.8%) was included, and the frequencies of the MetS were 14.8 and 16.9% according to the NCEP-ATP III and IDF criteria, respectively. In the multivariable Cox regression analysis, after additional adjustment for diabetes, HRs of the MetS for CHD mortality, sudden and non-sudden coronary death were mostly unchanged. Diabetes was associated with a more than two-fold increased risk of sudden death (HRNCEP-ATPIII = 2.11; 95% CI 1.12–3.95 and HRIDF = 2.10; 95% CI 1.12–3.93) but not with CHD mortality, nor with non-sudden death.

**Discussion**

In this population of healthy middle-aged men initially free of diabetes and ischaemic heart disease, the MetS as defined by modified NCEP criteria, conferred on average a 68% increased risk of sudden death and a lower (38%) but not statistically different increased risk of non-sudden death over 21 years, after adjustment for other CHD risk factors. Elevated abdominal adiposity was the only component of the MetS that was clearly associated with mortality risks, and these were comparable with that observed with the MetS. Consistent figures were observed using the IDF criteria for the definition of the MetS.

**Definition of the MetS**

In this study, the prevalence and HR estimates for the MetS should be interpreted keeping in mind that a modified definition of the syndrome has been used. Baseline examinations of the current study were performed more than 30 years ago when HDL cholesterol and waist circumferences measurements were not used routinely. Waist circumference has been replaced by the SADx to estimate abdominal adiposity, and previous studies have indicated that both measures are highly correlated and that the SADx is the anthropometric measure most correlated to abdominal adiposity. Accordingly, our definition of the MetS (at least three among four abnormalities) only covers part of the full spectrum of the possible combinations (at least three abnormalities among five). It is thus likely that estimates of both the prevalence of the MetS and HRs of mortality associated with the MetS were underestimated.

**Previous studies**

**Prevalence of the MetS**

Despite the limitations cited earlier, the current prevalence estimate of the MetS as defined by modified NCEP criteria (14.4%) is concordant with the range reported in European populations. Higher prevalences have been estimated in US men, ranging from 18–35% according to the ethnic group. Moreover, the present study is one of the few that describe prevalence of the MetS according to the IDF criteria. Using this definition, there was an 11.5% relative increase in the prevalence, comparable with what has been recently described in the NHANES III survey.

**Mortality risks**

The present figures of CHD mortality risk associated with the MetS (NCEP criteria) are consistent with most previous prospective studies. For instance, in the Kuopio Heart Study and NHANES II, the MetS was associated with a two-fold increased risk in CHD mortality. In the WOSCOPS study of moderately hypercholesterolaemic men assigned to pravastatin or placebo, the presence of the MetS was associated with a 30% increased risk of definite CHD death or non-fatal MI, after adjustment for classical CHD risk factors and C-reactive protein. We are unaware of previous studies assessing the mortality risks associated with the MetS as defined by the IDF criteria. In the current study, figures and levels of associations were similar to that observed with the MetS as defined by the NCEP criteria.

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**Table 3** Hazards ratios and 95% CIs of mortality associated with the presence of the MetS—The Paris Prospective Study I

<table>
<thead>
<tr>
<th>Component of the MetS</th>
<th>CHD mortality (n = 315)</th>
<th>Sudden death (n = 105)</th>
<th>Non-sudden death (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.90 (1.46–2.46)</td>
<td>2.15 (1.39–3.33)</td>
<td>1.65 (1.15–2.37)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.56 (1.18–2.06)</td>
<td>1.68 (1.05–2.70)</td>
<td>1.38 (0.95–2.01)</td>
</tr>
<tr>
<td>IDF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>2.14 (1.67–2.73)</td>
<td>2.29 (1.51–3.47)</td>
<td>1.91 (1.37–2.66)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.88 (1.46–2.43)</td>
<td>2.02 (1.30–3.14)</td>
<td>1.69 (1.20–2.38)</td>
</tr>
<tr>
<td>Components of the MetS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SADx &gt; 24 cm</td>
<td>1.87 (1.47–2.37)</td>
<td>2.26 (1.49–3.44)</td>
<td>1.60 (1.16–2.19)</td>
</tr>
<tr>
<td>BP &gt; 130/85 mmHg or HTN medications</td>
<td>1.46 (1.05–2.04)</td>
<td>1.46 (0.80–2.66)</td>
<td>1.41 (0.92–2.16)</td>
</tr>
<tr>
<td>FG ≥ 110 mg/dL</td>
<td>1.16 (0.88–1.54)</td>
<td>1.37 (0.86–2.18)</td>
<td>1.08 (0.74–1.57)</td>
</tr>
<tr>
<td>TG ≥ 150 mg/dL</td>
<td>1.26 (0.97–1.64)</td>
<td>1.05 (0.66–1.67)</td>
<td>1.36 (0.97–1.90)</td>
</tr>
</tbody>
</table>

Hazards ratios and their 95% CIs were estimated by Cox proportional hazards model.

*Risk factors adjustment comprised age, cigarette consumption, total cholesterol, parental history of sudden death or fatal MI, and sports activity.
However, previous studies have not reported data on the relationship between the MetS and sudden death.

MetS and sudden death

In this study, the MetS was more prevalent in the sudden death than in the non-sudden death group. Some abnormalities of the MetS, including elevated blood pressure and elevated triglycerides, were equally frequent in both groups, whereas others, comprising elevated abdominal adiposity and elevated fasting glycaemia, were more prevalent in the sudden death group. This is consistent with our hypothesis that there may be risk factors for the development of atherosclerosis that are common to sudden and non-sudden death (blood pressure, possibly triglycerides, in addition to LDL and total cholesterol, tobacco), and risk factors that are more likely to be involved in pro-arrhythmogenic mechanisms and sudden death (abdominal adiposity and type 2 diabetes). However, the increased risk of sudden death and non-sudden death associated with the MetS was not statistically different. This may be partly explained by the very high prevalence of elevated blood pressure as defined in the MetS, which may mask the specific effect of elevated fasting glycaemia and abdominal adiposity on sudden death risk.

Whether the MetS predicts mortality risk beyond its individual components questions the clinical utility of the MetS. In the current study, elevated abdominal adiposity was the only component that significantly increased CHD mortality risks including sudden death and non-sudden death. In addition, associations observed were of the same order of magnitude as those of the MetS taken as a whole. From a public health perspective, to screen subjects at risk factors that are more likely to be involved in pro-arrhythmogenic mechanisms and sudden death (abdominal adiposity and type 2 diabetes). The public health perspective, to screen subjects at greater risk of CHD mortality, the routine measurement of abdominal adiposity may be easier and less time consuming than the search for the coexistence of several risk factors, as defined in the MetS. The lack of statistically significant associations between elevated blood pressure and sudden death or non-sudden death in one hand, and between elevated fasting glycaemia and sudden death on the other hand, were surprising, given previous observations in this cohort.

The current thresholds used to define high blood pressure as defined in the MetS may not be applicable to a study initiated more than 30 years ago. Accordingly, when we employed a cut-off value of 160/90 mmHg, significant associations were observed with both outcomes (not shown). Moreover, in the definition of the MetS, components are dichotomized, which does not take into account the graded and more specific relationship that has been observed particularly between elevated fasting glycaemia and sudden death risk.

Sensitivity and robustness analyses

Consistent associations of the MetS with CHD mortality risk were found when the iliac circumference (highest quintile ≥ 99 cm) or BMI (≥ 30 kg/m²) was used to define elevated abdominal adiposity or when the lower threshold of impaired fasting glycaemia (100 mg/dL) recently proposed by the NCEP III criteria was employed.

Inclusion of diabetes as a separate group in the regression analysis yielded similar patterns of association between the MetS and mortality.

Limitations

Our study has some limitations that need to be underlined. Owing to the unavailability of the HDL cholesterol in the present study, the cluster of metabolic risk factors we described is more likely to reflect a MetS profile than the MetS per se. It is highly likely that both the prevalence of the MetS and the level of association between the MetS and CHD mortality risks were underestimated in the current study. No information was available on lipid-lowering treatment at the baseline examination so that this could not be included in the definition of the MetS. Change in the therapy during follow-up was not available, but may have modified the relationship between the MetS and sudden death. The present study included only white middle-aged-men and we have no data on the elderly, women, or non-caucasians.

In conclusion, the present data support that the MetS is associated with a 68% increase in the risk of sudden death, independently of CHD risk factors, in middle-aged men initially free of diabetes and ischaemic cardiac disease. However, the MetS may not discriminate subjects from the general population who are at increased risk of sudden death vs. non-sudden death. The assessment of a differential association between the MetS and sudden and non-sudden death in the general population should be replicated in more recent studies, which include the five core criteria of the MetS as defined in the NCEP-ATP III or IDF criteria.

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Conflict of interest: none declared.

References


