

Original article

The metabolic syndrome defined by modified International Diabetes Federation criteria and mortality: A 9-year follow-up of the aged in Finland

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Abstract

Aim. – The aim of this study was to investigate the relationship between the metabolic syndrome (MetS) and mortality in the aged population.

Methods. – In this prospective population-based study with a 9-year follow-up, the participants were all residents of the municipality of Lieto, Finland, aged 64 and over in 1998–99 ($n = 1529$). Altogether, 1260 (82%) were included in the study. Cox proportional-hazard models were used to estimate hazard ratios (HRs) for all-cause, cardiovascular (CVD), coronary heart disease (CHD) and cerebrovascular (CV) mortality as predicted by MetS (defined by modified International Diabetes Federation criteria).

Results. – At baseline, 17% of the men and 21% of the women had MetS. During the 9-year follow-up, 422 deaths occurred. After multivariable adjustment, no significant differences were found between subjects with and without MetS for all-cause, CVD, CHD or CV mortality in all study participants or by gender. On evaluating MetS components separately, elevated blood pressure was found to predict lower all-cause mortality in all participants [HR: 0.65; 95% confidence interval (CI): 0.47–0.89], and lower CHD mortality in men (HR: 0.42; 95% CI: 0.18–0.97). In women, high triglyceride levels predicted lower all-cause mortality (HR: 0.67; 95% CI: 0.47–0.95), whereas low HDL cholesterol predicted higher all-cause (HR: 1.61; 95% CI: 1.15–2.24) and CV (HR: 2.44; 95% CI: 1.05–5.67) mortality.

Conclusion. – These findings suggest that MetS does not predict mortality later in life and, of the separate components of MetS, only low HDL cholesterol is predictive of mortality in women. Also, even markedly higher blood pressure values than those included in the criteria for MetS fail to predict mortality in this age group.

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Keywords: Metabolic syndrome; Mortality; Population-based study; Elderly; Aged; Finland

Résumé

Syndrome métabolique (défini par les critères révisés de l'IDF) et mortalité : suivi durant neuf ans de sujets âgés finlandais.

Objectif. – L'objectif de cette étude était d'examiner les relations éventuelles entre syndrome métabolique (SMET) et mortalité chez les sujets âgés.

Méthodes. – Étude prospective en population avec suivi de neuf ans. Tous les sujets étaient résidents de la commune de Lieto en Finlande et âgés de 64 ans ou plus en 1998–1999 ($n = 1529$). Au total, 1260 sujets (82 %) ont participé à l'étude. Le risque relatif (RR) de mortalité toutes causes confondues et de mortalité cardiovasculaire, coronaire et vasculaire cérébrale a été calculé grâce au modèle proportionnel de Cox en fonction de l'existence ou non d'un SMET (défini selon les critères révisés de la Fédération internationale du diabète).

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Résultats. – À l'inclusion, 17 % des hommes et 21 % des femmes étaient atteints de SMET. Pendant le suivi de neuf ans, 422 sujets sont décédés. L'ajustement multivarié n'a révélé aucune différence importante liée au SMET entre les sujets des deux sexes quant à la mortalité cardiovasculaire, coronaire et vasculaire cérébrale et la mortalité toutes causes confondues. L'évaluation de chacun des composants du SMET a montré que l'hypertension artérielle était associée à une mortalité toutes causes confondues plus basse pour l'ensemble de la population étudiée (RR 0,65 ; intervalle de confiance à 95 % 0,47–0,89) et à une mortalité coronaire plus basse chez les hommes (RR 0,42 ; IC 95 % 0,18–0,97). Chez les femmes, l'hyperglycémie était associée à une mortalité toutes causes confondues plus basse (RR 0,67 ; IC à 95 % 0,47–0,95), tandis que des concentrations basses de HDLc étaient associées à une mortalité toutes causes confondues et à une mortalité vasculaire cérébrale plus élevées (respectivement RR 1,61 ; IC à 95 % 1,15–2,24) et (RR 2,44 ; IC à 95 % 1,05–5,67).

Conclusion. – Ces résultats suggèrent que le SMET est dépourvu de valeur pronostique de mortalité dans les phases ultérieures de la vie. Parmi les composants individuels du SMET, seules des concentrations basses de HDLc sont associées à la mortalité chez les femmes. Même des valeurs de pression artérielle plus élevées que les critères du SMET sont dépourvues de valeur pronostique de la mortalité dans cette tranche d'âge.

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Mots clés : Syndrome métabolique ; Mortalité ; Étude en population ; Personnes âgées ; Valeur pronostique ; Finlande

1. Introduction

The metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors, including visceral obesity, dyslipidaemia, hyperglycaemia and hypertension, that has become one of the major public-health challenges worldwide [1]. Yet, the relationship between MetS and mortality among the aged is uncertain because of several factors. First, the association between some risk factors, such as adiposity and mortality, diminish with increasing age [2,3]. Second, the dichotomization of the components of MetS and the selected cutoff points may not be optimal for identifying those aged patients who are at higher risk, as they are based on distributions found in middle-aged populations [4,5]. Third, there are competing risks from non-cardiovascular disease mortality in the older population [6] and, fourth, MetS as a combined measure may be less important than its constituent components [5,7,8].

For this reason, the present study was carried out to determine whether or not the MetS and/or its individual components, as defined by modified criteria of the International Diabetes Federation (IDF), can predict all-cause, cardiovascular, coronary heart disease and cerebrovascular mortality in an older-aged Finnish cohort over 9 years of follow-up.

2. Methods

2.1. Baseline measurements

The present study was part of a longitudinal epidemiological study (described in detail elsewhere [9,10]) carried out in the municipality of Lieto in southwestern Finland, and was designed to investigate the prevalence, risk factors and prognosis of cardiovascular, respiratory and other common diseases in an unselected Finnish population aged 64 years and over. All persons born in or prior to 1933 ($n = 1529$) were asked to participate between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or failed to respond, leaving a total of 1260 (82%) study participants (533 men and 727 women) [10].

At entry to the study, the participants' weight and height were measured, and their body mass index (BMI), measured as kg/m^2 , was calculated. Blood pressure was measured in a sitting

position using the standard cuff method and a mercury sphygmomanometer. Systolic blood pressure was determined using Korotkoff phase 1, and diastolic blood pressure with Korotkoff phase 4 or 5. Two values were recorded (to within 2 mmHg accuracy) 5 min apart, and the mean of the two measurements used in the analyses. Blood samples were drawn after an overnight fast at the health centre and analyzed by the Central Laboratory of Turku University Hospital. Diabetes was defined based on previous diagnosis (E10–E14) in the medical records and/or treatment with antidiabetic agents (ATC code A10), and/or a fasting serum glucose level ≥ 7 mmol/L measured at this time [11].

2.2. Confounding factors

Data on current smoking status (1 = no, 2 = yes) and frequency of exercise (1 = 1 to 7 days a week, 2 = less than once a week or not at all) were collected by interview. Cardiovascular disease (CVD) at baseline comprised ICD-10 codes I10–I15 (hypertension), I20–I25 (ischaemic heart disease), I50 (heart failure), I60–I66 (I60, subarachnoid haemorrhage; I61, intracerebral haemorrhage; I62, other non-traumatic intracranial haemorrhage; I63, cerebral infarction; I64, stroke not specified as haemorrhage or infarction; I65, occlusion and stenosis of precerebral arteries not resulting in cerebral infarction; I66, occlusion and stenosis of cerebral arteries not resulting in cerebral infarction), and I69 (sequelae of cerebrovascular disease), I71 (aortic aneurysm and dissection) and I74 (arterial embolism and thrombosis).

2.3. Definition of the metabolic syndrome

To identify those participants with the metabolic syndrome (MetS), the IDF definition [12,13] was used: $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ [in which case, central obesity can be assumed and waist circumference (WC) need not be measured] plus any two of the following four factors: (1) raised triglycerides (≥ 1.7 mmol/L) or specific treatment for this lipid abnormality (C10AB); (2) reduced high-density lipoprotein (HDL) cholesterol (1.03 mmol/L for men; 1.29 mmol/L for women) or specific treatment for this lipid abnormality (C10AC); (3) raised blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or treatment for

previously diagnosed hypertension (C02, 03, 07–09); and (4) elevated fasting plasma glucose (≥ 5.6 mmol/L) or previously diagnosed type 2 diabetes. As the present study did not measure WC, modified IDF criteria were used wherein BMI ≥ 30 kg/m² assumed central obesity. Altogether, 238 (19%) participants fulfilled the criteria for MetS, 61 (26%) of whom were diagnosed with type 2 diabetes and 156 (66%) with CVD.

2.4. Outcome measures

Data for the study participants who had died prior to 1 January 2008 were obtained from the official Finnish Cause of Death Registry using their unique personal identification numbers. Deaths recorded as resulting from ICD-10 codes I10–I15, I20–I25, I50, I60–I66, I69, I71 and I74 were classified as CVD deaths. Coronary heart disease (CHD) deaths were defined as those resulting from codes I20–I25 and I50, whereas codes I60–I66 and I69 were considered cerebrovascular (CV) deaths.

2.5. Ethics

The present study was conducted according to the guidelines of the Declaration of Helsinki. The ethics committee of the Hospital District of Varsinais-Suomi approved the study protocol. All participants gave their informed consent.

2.6. Statistical analyses

At baseline, differences between participants with and without MetS were assessed using the Chi² test, Fisher's exact test or two-sample *t* test, and the Kolmogorov-Smirnov test was used to determine normality of distributions. Because of the skewed distributions, triglyceride was log-transformed and glucose was square (x^2)-transformed for the statistical analyses.

Hazard ratios (HRs) and their 95% confidence intervals (CI) for all-cause, CVD, CHD and CV mortality were calculated using Cox proportional-hazard models. Follow-up times were calculated from baseline measurements either at the end of the follow-up period or upon the participant's death. Analyses

were adjusted for the following confounding factors: gender; age; smoking status; frequency of exercise; occurrence of CVD; and low-density lipoprotein (LDL) cholesterol. The associations between MetS and each of its individual components and mortality were analyzed by adjusting confounding factors and, in the analyses of the separate components, by other components of MetS as well. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.1 software for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

The mean age of participants was 73.5 (\pm SD 6.8) years, and those with MetS were younger than their healthy counterparts (Table S1; see the supplementary material associated with this article online). Also, CVD was more common among participants with MetS than in those without it.

3.2. Prevalence of MetS

At baseline, 17 and 21% of the male and female participants, respectively, had MetS. Elevated blood pressure was the most commonly found component of MetS, followed by high levels of triglycerides and fasting glucose (Table 1). Being overweight, and having low HDL cholesterol and hypertension were more commonly seen in women than in men, whereas raised fasting plasma glucose levels were more common in men than in women.

3.3. Mortality

During the 9 years of follow-up, 422 deaths occurred (198 men, 224 women). A total of 181 individuals died because of CVD (81 men and 100 women), including 116 deaths due to CHD (59 and 57, respectively) and 47 deaths (15 and 32, respectively) due to CV disease. After multivariable adjustment, no

Table 1
Baseline prevalence of the metabolic syndrome and its components in 1260 aged individuals by gender.

Characteristics	Men (<i>n</i> = 533) [<i>n</i> (%)]	Women (<i>n</i> = 727) [<i>n</i> (%)]	<i>P</i> ^b
The metabolic syndrome ^a	89 (17)	149 (21)	0.094
Obesity (body mass index ≥ 30 k/m ²)	104 (20)	190 (26)	0.007
High triglyceride level (≥ 1.7 mmol/L or specific treatment for this lipid abnormality)	154 (29)	237 (33)	0.175
Low HDL-cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women, or specific treatment for this lipid abnormality)	117 (22)	203 (28)	0.018
Elevated blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment for previously diagnosed hypertension)	475 (89)	677 (94)	0.006
Elevated fasting plasma glucose (≥ 5.6 mmol/L or previously diagnosed type 2 diabetes)	302 (57)	352 (49)	0.004

^a As defined by the International Diabetes Federation.

^b By Chi² test.

Table 2
Hazard ratios (HRs) for the metabolic syndrome, as defined by the International Diabetes Federation for all-cause, cardiovascular, coronary heart disease and cerebrovascular mortality during the 9-year follow-up study.

Mortality	All ^a		Men ^b		Women ^b	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
All-cause (<i>n</i> = 422)	0.90 (0.69–1.17)	0.436	1.12 (0.77–1.63)	0.543	0.73 (0.50–1.08)	0.118
Cardiovascular ^c (<i>n</i> = 181)	1.07 (0.74–1.56)	0.713	1.35 (0.80–2.29)	0.268	0.88 (0.51–1.51)	0.638
Coronary heart disease (<i>n</i> = 116)	1.35 (0.86–2.10)	0.190	1.73 (0.94–3.17)	0.077	1.06 (0.54–2.08)	0.872
Cerebrovascular (<i>n</i> = 47)	0.60 (0.25–1.44)	0.255	0.35 (0.08–1.62)	0.179	0.71 (0.25–2.06)	0.530

An HR > 1 indicates higher mortality with vs without MetS.

^a Adjusted for age, gender, current smoking status, frequency of exercise, cardiovascular disease and LDL cholesterol.

^b Adjusted for current age, smoking, frequency of exercise, cardiovascular disease and LDL cholesterol.

^c Includes coronary heart disease and cerebrovascular deaths, as well as deaths due to other complications of raised blood pressure (*n* = 11) and aortic aneurysms (*n* = 7).

significant differences were found between participants with and without MetS in terms of all-cause, CVD, CHD or CV mortality in all study subjects or by gender (Table 2).

The HRs (95% CI) for the individual components of MetS for all-cause, CVD, CHD and CV mortality in all study subjects and by gender are shown in Table S2 (see the supplementary material associated with this article online). In women, high triglyceride levels predicted lower all-cause mortality, whereas low HDL-cholesterol levels predicted higher all-cause and CV mortality. Raised blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment for previously diagnosed hypertension) predicted lower all-cause mortality among all participants and lower CHD mortality in men. Additional analyses for elevated blood pressure showed that using even higher blood pressure cutoff points was predictive of lower all-cause mortality in all participants ($\geq 150/90$ mmHg and $\geq 170/100$ mmHg) and in women ($\geq 150/90$ mmHg).

4. Discussion

In the present population-based 9-year follow-up study of older-aged Finns living in southwestern Finland, MetS (defined by modified IDF criteria) was common (in 17% of men and in 21% of women), but was not predictive of all-cause, CVD, CHD or CV mortality. In an earlier study by Hildrum et al. [14], MetS as defined by the IDF was also not associated with increased mortality rates after the age of 60 years. However, in two previous studies conducted in an older population (≥ 65 years), MetS (defined by the IDF) was associated with an increased risk of all-cause mortality in an aged US population free of prevalent CVD [5], and with CVD and CHD mortality in an aged non-diabetic Finnish population [7]. In addition, in an observational cohort study of the Italian population [15], MetS diagnosed by the National Cholesterol Education Program–Adult Treatment Panel (ATP)-III criteria was also associated with increased all-cause mortality among subjects aged 65 years or older.

There are several possible reasons for this inconsistency of results. The prevalence of MetS was considerably lower in our present study than in the previous Finnish population-based, 13-year follow-up study of slightly younger, non-diabetic, individuals living in eastern Finland [7]. The different prevalences

of MetS may be due to the geographical differences in health-related behaviour, risk-factor profiles and CVD mortality in subjects living in western and eastern Finland found during the 1970s [16,17] and at present [18], favouring those living in western Finland. It has also been reported that MetS defined by IDF criteria does not predict mortality outcomes compared with those defined by ATP-III criteria [19,20].

In addition, the association of MetS and its constituent components with mortality may be stronger in younger subjects than in older ones [3,12]. The prevalence of MetS was also higher in the 15-year follow-up US study of a multiracial CVD-free population of the same age [5] as the population in our present study.

Furthermore, in our study, BMI was used as the sole measure of obesity, as WC was not measured, and this might be behind the different findings. Central obesity, as assessed by WC, has been considered a pivotal and essential component of MetS in the new IDF definition. Yet, if the BMI is ≥ 30 kg/m², then central obesity can be assumed and the WC does not need to be measured [12,13]. Altogether, 19% of the participants in our study fulfilled the MetS criteria of a BMI ≥ 30 kg/m² plus two of the four other criteria. However, using BMI instead of WC may have led to underestimation of the prevalence of MetS in the present study, as there may have been subjects fulfilling the criterion of central obesity (WC 94 cm in men and 80 cm in women) among those whose BMI was < 30 kg/m². On the other hand, the DECODE Study Group [21] found that MetS (defined by the IDF) predicted CVD mortality regardless of the presence or absence of abdominal adiposity in a European population aged 30–89 years. According to that study, the inclusion of abdominal adiposity as a prerequisite will exclude those non-obese individuals with an increased risk of CVD mortality. Also, BMI is correlated with fat mass [22,23] and, as such, could underestimate adiposity in older people, as lean body mass is replaced by fat on ageing [22,24,25], a change that is especially pronounced in women [25]. Women also have significantly greater amounts of total body fat than do men with the equivalent BMI [22,23]. Therefore, the BMI describes different characteristics in men compared with women.

In addition, in the present study, participants with diabetes or CVD at baseline were not excluded in the case definition of MetS, as has otherwise been suggested, as they offer no

additional understanding of risk or current treatment recommendations [26]. On the other hand, it has been shown that MetS significantly predicted all-cause and CVD mortality in a community-based sample of men, and in subgroup samples without diabetes or clinically evident CVD at baseline [27]. However, Huang et al. [28] found that the relative risk of CVD mortality among those with MetS did not statistically significantly change after excluding those with diabetes or CVD at baseline.

Of the separate components of MetS, low HDL cholesterol predicted higher all-cause and CV mortality in women, and there was also a trend towards higher CVD and CHD mortality in women with low HDL cholesterol. In a study by Zambon et al. [15], low HDL cholesterol predicted higher CVD mortality among women aged 65 years or older. Also, the results of a previous prospective study indicated a strong inverse association between HDL cholesterol and both CVD and CHD mortality in all age groups [28], an effect that has been found to be stronger in women than in men [29,30]. In a prospective study by Mazza et al. [31], HDL cholesterol was an inverse predictor of CHD mortality among aged women, but not among men. Thus, it appears that the inverse relationship between HDL cholesterol and mortality is maintained with increasing age – at least in women.

Elevated triglycerides are an important CHD risk factor, especially in women [32–34]. In the present study, high triglyceride levels (≥ 1.7 mmol/L) predicted lower all-cause mortality in women. A similar trend was found for CVD, CHD and CV mortality among both men and women. However, low triglyceride levels in the aged may be a sign of frailty syndrome or illness, or it could be that the selected cutoff point is not optimal for identifying those older individuals who are at higher risk [4,5].

Elevated blood pressure predicted lower all-cause mortality among all participants and lower CHD mortality in men. Almost all of our study subjects fulfilled the criterion of raised blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment for previously diagnosed hypertension). In the aged, low blood pressure is considered a marker of deteriorating health, the presence of serious disease, approaching frailty, poor vitality or imminent death [35–38]. Low blood pressure is also an indicator of subclinical, non-cardiovascular, comorbid conditions [39]. This is why additional analyses were conducted for raised blood pressure using higher cutoff points ($\geq 150/90$ mmHg and $\geq 170/100$ mmHg), and even these higher blood pressure values were predictive of lower all-cause mortality. Thus, it appears that the association of elevated blood pressure and mortality diminishes with increasing age. In addition, the selected cutoff points for the components of MetS, such as elevated blood pressure, are not optimal for identifying those older individuals who are at higher risk [4,5].

The strengths of the present study were its population-based design and high participation rate, as almost the entire older-aged population living in Lieto were included. BMI measurements relied on clinical anthropometric assessment, and information on CVD and type 2 diabetes was based on several sources, including laboratory measurements, clinical examinations, medical records and medication use. Another study strength was

the large number of deaths ($n = 422$), thereby ensuring adequate power for the statistical analyses of all-cause mortality. Also, the mortality rates were adjusted for confounding variables at baseline, which was important because statistically significant differences were found especially in the occurrence of CVD between those with and without MetS.

In conclusion, our present study findings suggest that MetS does not predict mortality later in life. This may be due to our selection of an older population, and the strong inverse association of traditional cardiovascular risk factors with frailty and other latent diseases [40]. Of the various components of MetS, only low HDL cholesterol was predictive of mortality in women. Raised or even markedly higher blood pressure values than those used in the criteria for MetS did not predict mortality in this older-aged population. The results of our study suggest that confounding factors, such as frailty syndrome and other diseases, have less of an effect on HDL cholesterol than on triglycerides or blood pressure. HDL cholesterol may, therefore, be useful for evaluating CVD risk profiles in elderly women.

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Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

Appendix A. Supplementary material

Supplementary material (Tables S1 and S2) associated with this article can be found at <http://www.sciencedirect.com>, at doi:10.1016/j.diabet.2010.05.002

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