Metabolic Syndrome and All-Cause and Cardiovascular Mortality in an Italian Elderly Population

The Progetto Veneto Anziani (Pro.V.A.) Study

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OBJECTIVE — The purpose of this study was to explore the association of metabolic syndrome and each of its components with all-cause and cardiovascular mortality in a general Italian elderly population.

RESEARCH DESIGN AND METHODS — Metabolic syndrome, diagnosed by National Cholesterol Education Program Adult Treatment Panel III criteria, all-cause mortality, and cardiovascular mortality, was evaluated in 2,910 subjects aged ≥65 years of the Progetto Veneto Anziani (Pro.V.A.) Study during a mean follow-up time of 4.4 years.

RESULTS — After multivariable adjustment, metabolic syndrome was associated with increased all-cause mortality in all subjects (hazard ratio 1.41 [95% CI 1.16–1.72], $P = 0.001$), among men (1.42 [1.06–1.89], $P = 0.017$), and among women (1.47 [1.13–1.91], $P = 0.004$). High glucose in all subjects (1.27 [1.02–1.59], $P = 0.037$) and in women (1.61 [1.16–2.24], $P = 0.005$) and low HDL cholesterol in women (1.48 [1.08–2.02], $P = 0.014$) were predictors of all-cause mortality, even independently of the interactions of different metabolic syndrome components. After multivariable adjustment, metabolic syndrome was also associated with increased cardiovascular mortality in all subjects (1.60 [1.17–2.19], $P = 0.003$), among men (1.66 [1.00–2.76], $P = 0.051$), and among women (1.60 [1.06–2.33], $P = 0.025$). High glucose (2.17 [1.28–3.68], $P = 0.004$) and low HDL cholesterol (1.78 [1.07–2.95], $P = 0.026$) among women predicted higher cardiovascular mortality.

CONCLUSIONS — In this general Italian elderly population, among metabolic syndrome components, all-cause mortality is better predicted by high glucose in all subjects and in women and by low HDL cholesterol in women, whereas cardiovascular mortality is better predicted by high glucose and low HDL cholesterol in women.

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M etabolic syndrome represents a cluster of metabolic abnormalities including central obesity, dyslipidemia, hyperglycemia, and high blood pressure, and it is an important predictor of all-cause and cardiovascular mortality (1–4). However, the majority of these data are derived from populations of different races and of middle-aged and young subjects, mostly men. Ford (2) suggested that the strength of the association between metabolic syndrome and all-cause and cardiovascular mortality may be higher in certain population subgroups, such as women and elderly subjects. However, in the Health, Aging, and Body Composition (Health ABC) study, no significant difference in mortality was observed among subjects aged 70–79 years with and without metabolic syndrome (5). In elderly Finns, metabolic syndrome predicted cardiovascular but not all-cause mortality (6). Also, in Italian elderly individuals metabolic syndrome was not independently associated with total mortality (7), whereas it increased the risk of cardiovascular mortality only in men (8).

The effects of metabolic syndrome in elderly individuals represent a crucial point because elderly populations worldwide are growing progressively, and the prevalence of metabolic syndrome increases with age, always with a higher rate in women than in men (7–10). In a longitudinal adult population–based cohort study, the increased risk of cardiovascular and all-cause mortality of subjects with metabolic syndrome was explained by high blood pressure and glucose levels, among components of the syndrome (11). In the Italian Longitudinal Study on Aging (ILSA), among metabolic syndrome features, low HDL cholesterol in men and high glucose in women were significant predictors of cardiovascular mortality (8).

Therefore, another important issue is whether metabolic syndrome as a whole is a better predictor of all-cause and cardiovascular mortality in comparison with its individual components (12). In the Cardiovascular Health Study (CHS), the total and cardiovascular mortality higher risk due to metabolic syndrome was confined to subjects having hypertension and/or high glucose (13). Lately, results from two prospective studies in elderly individuals showed that metabolic syndrome and its components have a strong association with type 2 diabetes but no association with incident cardiovascular events (14).

With this background, the objective of the present study was to explore the association of metabolic syndrome and each of its individual components with

all-cause and cardiovascular mortality in a general Italian elderly population.

RESEARCH DESIGN AND METHODS

The study population included 3,099 age- and sex-stratified subjects (1,245 men and 1,854 women) of the Progetto Veneto Anziani (Pro.V.A.) Study, an observational cohort study of the Italian population aged ≥65 years living in two geographical areas of northeastern Italy (Camposampiero and Rovigo) near the city of Padua in the Veneto region (15). The study population represented ~10% of the target population, which was randomly drawn from health district registries, including the entire resident population. The sampling frame included all subjects aged ≥65 years who were residents in one of the two study centers at the beginning of the cross-sectional phase; all subjects were 100% Caucasian. No exclusion criteria were used. The sampling strategy consisted of an age- (65–74, 75–84, and ≥85 years) and sex-stratified random sample designed to keep the male-to-female ratio at 2:3 and to oversample the oldest possible age-group. Oversampling was performed to provide stable estimates of conditions with low prevalence. The overall response rate to the visit clinic was 77% for men and 64% for women. Subjects living in the community and in nursing homes (3.5%) were included.

The baseline assessment was carried out from 1995 to 1997 as described elsewhere (15). This study includes information about mortality rates per person-years assessed for a mean ± SD of 4.4 ± 1.1 years of follow-up.

Lifestyle factors

Information on educational level, socioeconomic condition, physical activity, and smoking status was collected during an in-person interview. Educational level was verified by asking participants to quantify the total number of years of school attended; then the educational level was categorized as ≤5 versus >5 years of school. The socioeconomic condition was categorized as monthly income <500 € or >500 €. Physical activity was categorized as ≤4 or >4 h/week of at least moderate physical activity (brisk walking, biking, swimming, dancing, or physical exercising). Smoking status was categorized as "never," "former" (for at least 1 year in the past), and "current" smoking.

Clinical and laboratory data

BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured to the nearest 0.5 cm using a plastic tape measure while the subject was standing, and it was measured as the minimum abdominal circumference between the xiphoid process and the umbilicus. Blood pressure, measured using the Hypertension Detection Follow-up Program protocol (16), was the mean of three readings while the subject was supine. A venous blood sample was obtained from 99% of participants, after an overnight fast, for biochemical determinations, performed at the central laboratory of the city hospital by standard and quality-controlled procedures. LDL cholesterol was calculated by the Friedewald equation, except when triglycerides were >400 mg/dl.

Disease adjudication

As described (15,16), disease presence at baseline was determined by board-certified study physicians who examined all of the clinical information collected for each participant in the study, including disease history, self-reported symptoms by standardized questionnaires, Mini-Mental State Examination score, medical and hospital records, blood assays, physical examination, medication use, X-ray film readings, standardized electrocardiogram, and ankle/brachial index. Preexisting major diseases included any of the following: coronary heart diseases (angina and myocardial infarction), cardiovascular diseases (congestive heart failure, stroke, and peripheral artery disease), and major diseases (diabetes, chronic pulmonary and kidney diseases, cancer, and/or cognitive impairment).

Metabolic syndrome was identified by National Cholesterol Education Program Adult Treatment Panel III criteria (17). According to this definition, subjects with metabolic syndrome were identified by any combination of three or more of the following alterations: abdominal obesity (waist circumference >102 cm for men or >88 cm for women), elevated plasma triglycerides (≥150 mg/dl), low HDL cholesterol (≤40 mg/dl for men or ≤50 mg/dl for women), high blood pressure (≥130/≥85 mmHg) or antihypertensive treatment, or high fasting plasma glucose (≥110 mg/dl) or a previous physician diagnosis of diabetes or a fasting plasma glucose ≥126 mg/dl.

Mortality surveillance

Follow-up time was calculated as the time from baseline to death or censoring. A copy of the official death certificate of all deceased participants was obtained. The main cause of death reported in the death certificate was classified by expert nosologists according to ICD-9. Cardiovascular mortality was defined by codes from 390 to 459. Mortality rates were obtained by dividing the number of deaths occurring during the study by the accumulated number of person-years. Follow-up was complete for 99.3% of participants.

Statistical analysis

To generalize the Pro.V.A. sample to the general population of the two geographical areas, a set of weights was defined according to the sex and age distribution of the reference population (Italy, Census 1991) and to the sample fraction. Data are means ± SD for quantitative measures and frequency percentages for all discrete variables. Comparisons between means were evaluated using generalized linear models. Levene's test was performed to test the homoscedasticity of variances, and when its assumption was violated, Welch's ANOVA was used. The differential distribution of sex, smoking status, physical activity, socioeconomic status, selected diseases, and metabolic syndrome components was analyzed by χ^2 test.

The association of metabolic syndrome (present versus absent) and each of its components (individual and combined components as dichotomized variables) with all-cause and cardiovascular mortality was evaluated by Cox proportional hazards regression models, adjusted for age (as a continuous variable) and sex, including sequentially in the model potential explanatory and confounding variables as covariates (BMI, albumin, and LDL cholesterol were included as continuous variables). In the models testing the associations with all-cause and cardiovascular mortality of metabolic syndrome components all together as covariates, metabolic syndrome was introduced as a proxy for the interactions of individual factors. The assumption of proportionality was assessed through the analysis of Schoenfeld residuals of the covariates introduced in the models. Adjusted hazard ratios (HRs) and 95% CI were calculated to estimate the strength of the association. Subjects affected by prevalent cardiovascular disease at baseline (angina, myocardial infarc-

Table 1—*Demographic and clinical characteristics of the Pro.V.A. study population stratified by metabolic syndrome (weighted data)*

	Overall	MS−	MS+	P value*
Age (years)	74.0 ± 7.0	73.9 ± 7.0	74.3 ± 6.9	NS
Male sex (%)	38.9	46.4	26.8	0.000
BMI (kg/m^2)	27.8 ± 4.6	26.4 ± 4.0	30.1 ± 4.6	0.000
Waist circumference (cm)	97.0 ± 11.4	93.5 ± 10.6	102.7 ± 10.1	0.000
Systolic blood pressure (mmHg)	153 ± 21	152 ± 22	155 ± 19	0.000
Diastolic blood pressure (mmHg)	84 ± 11	84 ± 11	83 ± 10	NS
Triglycerides (mg/dl)	135 ± 74	108 ± 50	179 ± 86	0.000
Total cholesterol	232 ± 43	229 ± 41	237 ± 46	0.000
LDL cholesterol	146 ± 37	145 ± 36	149 ± 39	0.004
HDL cholesterol	59 ± 16	63 ± 15	52 ± 15	0.000
Plasma glucose	107 ± 35	96 ± 19	124 ± 46	0.000
Smoking status (%)				
Never	60.7	55.9	68.6	0.000
Former	29.3	32.4	24.2	
Current	10.0	11.7	7.2	
Albumin (g/l)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	NS
Physical activity ≤4 h/week (%)	75.5	72.6	80.1	0.000
Education ≤5 years (%)	83.7	81.7	87.0	0.000
Monthly income <500 € (%)	59.2	56.5	63.6	0.000
Prevalence rates of metabolic syndrome components (%)				
High blood pressure	89.6	85.4	96.5	0.000
High triglycerides	30.8	10.4	64.1	0.000
Low HDL cholesterol	19.1	4.9	42.1	0.000
Increased waist circumference	57.1	38.2	88.0	0.000
High glucose	28.2	9.9	58.0	0.000
Prevalence rates of (%)				
Coronary heart disease†	7.0	6.8	7.2	NS
Cardiovascular diseases‡	23.8	21.5	27.6	0.000
Other major diseases§	57.8	49.6	71.2	0.000

Data are means ± SD or %. *P values refer to comparison between those without metabolic syndrome (MS−) and with metabolic syndrome (MS+). †Angina and myocardial infarction. ‡Congestive heart failure, stroke, and peripheral artery disease. §Diabetes, chronic pulmonary and kidney diseases, cancer, and/or cognitive impairment.

tion, and stroke, n = 316) were excluded from the cardiovascular mortality analysis. All statistical analyses were performed using SPSS-X software (version 15.0; SPSS, Chicago, IL) and the SAS statistical package (version 9.1.3; SAS Institute, Cary, NC). P < 0.05 was considered significant.

RESULTS — Of the 3,099 subjects in the baseline cohort, information on metabolic syndrome diagnosis was available for 2,910 individuals (94%), and 1,135 of them (300 of 1,174 men and 835 of 1,736 women) were affected by metabolic syndrome (not weighted data). Compared with subjects without the syndrome, those affected by metabolic syndrome were more frequently women and had higher waist circumference, fasting plasma glucose, systolic blood pressure, triglycerides, BMI, and total and LDL cholesterol and lower HDL cholesterol levels (Table 1). Subjects with metabolic syn-

drome were less often former and current smokers, less educated, and less physically active and had lower monthly income than those without metabolic syndrome. Among different metabolic syndrome components, high blood pressure was the most common, followed in order by increased waist circumference, high triglycerides, high glucose, and low HDL cholesterol levels. Subjects with metabolic syndrome were more often affected by coronary heart, cardiovascular, and other major chronic diseases.

During 4.4 years of follow-up, 632 deaths occurred, 246 among subjects with metabolic syndrome (90 men and 156 women) and 386 among those without the syndrome (251 men and 135 women) (not weighted data). Women with metabolic syndrome consistently had a higher all-cause mortality rate than those without metabolic syndrome, whereas no significant difference in mor-

tality rate was observed among men (Table 2).

Cox proportional hazards regression models confirmed the differential effect by sex in the association between metabolic syndrome and all-cause mortality and revealed a significant sex by metabolic syndrome interaction (P = 0.000); therefore, models were also stratified by sex (Table 2). After adjustments for age and sex, the risk of all-cause mortality was higher among all subjects with metabolic syndrome. Confounding factors and diseases associated with increased mortality risk were sequentially included in the models, increasing the strength of the association between metabolic syndrome and all-cause mortality. Metabolic syndrome was significantly associated with increased all-cause mortality after adjustments for age, sex, smoking, physical activity, major diseases, BMI, albumin, and LDL cholesterol levels in all subjects (HR 1.41 [95% CI 1.16–1.72], P = 0.001),

Table 2—All-cause mortality associated with metabolic syndrome and its components in all subjects and stratified by sex

	Overall	P value	Men	P value	Women	P value
Deaths (%)						
MS−	17.5		22.9		12.8	
MS+	19.1		23.1		17.6	
Rate per 1,000 person-years*						
MS−	39.80		53.64		28.43	
MS+	44.27	0.000	54.93	0.603	40.50	0.000
Model						
Adjusted for age and sex	1.30 (1.11–1.54)	0.001	1.26 (0.99–1.60)†	0.064	1.33 (1.06–1.68)†	0.015
+ education and socioeconomic status	1.38 (1.14–1.64)	0.001	1.21 (0.93–1.57)	0.158	1.53 (1.18–2.00)	0.001
+ smoking and physical activity	1.35 (1.13–1.63)	0.001	1.20 (0.92–1.56)	0.172	1.51 (1.16–1.97)	0.003
+ major diseases and BMI	1.42 (1.15–1.75)	0.001	1.38 (1.01–1.87)	0.041	1.49 (1.10–1.99)	0.008
+ albumin and LDL cholesterol	1.41 (1.14–1.75)	0.001	1.41 (1.04–1.91)	0.029	1.48 (1.09–2.01)	0.013
All components together as covariates‡						
High blood pressure (versus not)	0.93 (0.71–1.23)	0.617	0.95 (0.65–1.38)§	0.786	1.03 (0.69–1.54)§	0.890
High triglycerides (versus not)	0.97 (0.77–1.23)	0.790	1.10 (0.79–1.52)§	0.576	0.83 (0.60–1.15)§	0.268
Low HDL cholesterol (versus not)	1.24 (0.97–1.58)	0.084	1.04 (0.70–1.54)§	0.860	1.48 (1.08–2.02)§	0.014
Increased waist circumference (versus not)	0.97 (0.74–1.26)	0.803	0.88 (0.60–1.30)§	0.528	1.13 (0.78–1.62)§	0.524
High glucose (versus not)	1.27 (1.02–1.59)	0.037	1.01 (0.74–1.38)§	0.959	1.61 (1.16–2.24)§	0.005

Data are HR (95% CI) computed by Cox proportional regression models unless indicated otherwise. *Mortality rate per 1,000 person-years weighted data. Major diseases include angina, myocardial infarction, congestive heart failure, stroke, peripheral artery disease, diabetes, chronic pulmonary and kidney diseases, cancer and/or cognitive impairment. †Model adjusted only for age. ‡Model adjusted for age, sex, smoking, physical activity, major diseases, BMI, albumin, LDL cholesterol, and metabolic syndrome (as proxy for the interactions of the individual factors). §Model adjusted for age, smoking, physical activity, major diseases, BMI, albumin, LDL cholesterol, and metabolic syndrome (as proxy for the interactions of the individual factors). MS−, without metabolic syndrome; MS+, with metabolic syndrome.

among men (1.42 [1.06−1.89], P = 0.017), and among women (1.47 [1.13−1.91], P = 0.004), respectively. Models including individual metabolic syndrome components did show a significant association between metabolic syndrome and all-cause mortality for low HDL cholesterol (1.34 [1.09−1.65], P = 0.005) and high glucose (1.37 [1.13−1.65], P = 0.001) in all subjects and particularly in women (low HDL cholesterol versus not 1.48 [1.14−1.92], P = 0.003; high glucose versus not 1.65 [1.27−2.15], P = 0.000), but not in men. In a model considering all metabolic syndrome components together as covariates and metabolic syndrome as a proxy for the interactions of individual factors, high glucose in all subjects and in women and low HDL cholesterol only in women were significant predictors of all-cause mortality (Table 2).

Subjects affected by angina, myocardial infarction, and stroke at baseline (n = 316) were excluded from the cardiovascular mortality analysis. During 4.4 years of follow-up, 230 cardiovascular deaths occurred, 96 in subjects with metabolic syndrome (29 men and 67 women) and 134 in subjects without the syndrome (73 men and 61 women) (not weighted data). Both men and women with metabolic syndrome had significant higher rates of cardiovascular mortality compared with subjects without the syndrome (Table 3).

The differential effect by sex in the association between metabolic syndrome and cardiovascular mortality was tested in the proportional hazards models, which revealed a substantial sex by metabolic syndrome interaction (P = 0.060); therefore, these models were also stratified by sex (Table 3). We found an increased risk of cardiovascular mortality among all subjects with metabolic syndrome after adjustment for age and sex. Confounding and cardiovascular risk factors were sequentially included in the models, increasing the strength of the association between metabolic syndrome and cardiovascular mortality. Metabolic syndrome was associated with increased cardiovascular mortality after adjustments for age, sex, smoking, LDL cholesterol, physical activity, and BMI in all subjects and also among men and women, respectively. After multivariable adjustment, including in the model the previous diagnosis of diabetes, metabolic syndrome was associated with increased risk of cardiovascular mortality in all subjects but not in men and women separately. Models including individual metabolic syndrome components showed a significant association between cardiovascular mortality and high glucose in all subjects (HR 1.59

[95% CI 1.18–2.13], P = 0.002). In the sex-stratified analysis, a significant association of cardiovascular mortality was found with high triglycerides (1.74 [1.08–2.78], P = 0.021) among men and with low HDL cholesterol (1.62 [1.07–2.45], P = 0.023) and high glucose (2.03 [1.36–3.02], P = 0.001) among women. In a model considering all metabolic syndrome components together as covariates and metabolic syndrome as a proxy for the interactions of individual factors, high glucose and low HDL cholesterol among women were significantly associated with an increased risk of cardiovascular mortality (Table 3).

CONCLUSIONS— In this general Italian elderly population, metabolic syndrome predicts all-cause and cardiovascular mortality in both men and women, but not all of its individual components significantly contribute to the increased risk of mortality. In fact, after a 4.4-year follow-up, all-cause mortality was significantly predicted by high glucose in all subjects and in women and by low HDL cholesterol only in women. Among metabolic syndrome components, high glucose and low HDL cholesterol in women also significantly predicted the risk of cardiovascular mortality.

Table 3—*Cardiovascular mortality associated with metabolic syndrome and its components in all subjects and stratified by sex*

	Overall	P value	Men	P value	Women	P value
Deaths (%)						
MS−	6.4		6.4		6.4	
MS+	8.0		7.5		8.1	
Rate per 1,000 person-years*						
MS−	14.45		14.84		14.13	
MS+	18.37	0.000	17.78	0.029	18.57	0.000
Model						
Adjusted for age and sex	1.36 (1.03–1.78)	0.029	1.51 (0.98–2.33)†	0.060	1.27 (0.90–1.79)†	0.183
+ smoking, LDL cholesterol, BMI, and physical activity	1.60 (1.17–2.19)	0.003	1.66 (1.00–2.76)	0.051	1.60 (1.06–2.33)	0.025
+ education and socioeconomic status	1.69 (1.19–2.39)	0.003	1.66 (0.89–3.11)	0.114	1.74 (1.08–2.80)	0.022
+ diabetes‡	1.51 (1.03–2.20)	0.033	1.86 (0.95–3.77)	0.072	1.31 (0.76–2.27)	0.337
All components together as covariates§						
High blood pressure (versus not)	0.99 (0.61–1.60)	0.969	0.85 (0.44–1.65)‖	0.627	1.51 (0.70–3.23)‖	0.290
High triglycerides (versus not)	0.87 (0.59–1.29)	0.493	1.37 (0.75–2.51)‖	0.312	0.66 (0.39–1.11)‖	0.115
Low HDL cholesterol (versus not)	1.19 (0.80–1.77)	0.385	0.77 (0.38–1.42)‖	0.473	1.78 (1.07–2.95)‖	0.026
Increased waist circumference (versus not)	0.98 (0.63–1.51)	0.914	0.71 (0.35–1.42)‖	0.328	1.26 (0.70–2.28)‖	0.439
High glucose (versus not)	1.39 (0.97–2.00)	0.075	0.87 (0.49–1.55)‖	0.634	2.17 (1.28–3.68)‖	0.004

Data are HR (95% CI) computed by Cox proportional regression models unless indicated otherwise. *Mortality rate per 1,000 person-years weighted data. †Model adjusted only for age. ‡Positive criteria for diabetes (previous physician diagnosis or fasting plasma glucose ≥26 mg/dl). §Model adjusted for age, sex, smoking, LDL cholesterol, BMI, physical activity, and metabolic syndrome (as proxy for the interactions of the individual factors). ‖Model adjusted for age, smoking, LDL cholesterol, BMI, physical activity, and metabolic syndrome (as proxy for the interactions of the individual factors).

Studies in American (5), Finnish (6), and Italian (7) elderly subjects demonstrated that metabolic syndrome was not an independent predictor of total mortality. However, the CHS recently demonstrated that metabolic syndrome predicted a 22% higher all-cause mortality in older adults and with the use of different criteria results were similar (13).

Our results clearly show that metabolic syndrome is an independent predictor of all-cause mortality in subjects overall, even after adjustment for important factors, such as educational level, socioeconomic condition, smoking status, physical activity, and several chronic major diseases known to be associated with mortality in elderly individuals. After adjustment for all of these factors, the increased risk of all-cause mortality in our elderly population was higher than that found in older adults of the CHS; however, our follow-up time was shorter. A longer follow-up could attenuate the effect of metabolic syndrome on mortality because of the interaction with other environmental and lifestyle factors and chronic diseases. However, not all individual components of metabolic syndrome contribute to the increased risk of total mortality, which is significantly predicted by high glucose in all subjects and by high glucose and low HDL cholesterol in women.

The differences between men and women can be explained by several factors: our study population includes a large cohort with a sex distribution (60% women) which reflects that of the Italian elderly population; the prevalence of metabolic syndrome after age 75 years decreases in men whereas it increases in women; women more frequently had two or more components of the metabolic syndrome compared with men; and women showed a higher prevalence of high triglycerides and low HDL cholesterol than men (10).

To our knowledge, no previous studies have demonstrated that, among metabolic syndrome features, low HDL cholesterol is an independent predictor of all-cause mortality in elderly subjects, even independently of the interaction of different metabolic syndrome components. In a previous report, low HDL cholesterol, combined with low albumin, was associated with the highest risk of all-cause mortality in older subjects (18). As with albumin, low HDL cholesterol seems to be a reliable marker for poor health status and chronic diseases, and its better prognostic value could be explained by impairment of the antioxidant and anti-inflammatory roles of HDL cholesterol (18,19).

Recently in the CHS, only high blood pressure and high glucose, among metabolic syndrome components, predicted higher mortality in older adults (13). Also, similar observations were reported in an Italian adult population (11). A possible reason that high blood pressure was not a predictor of mortality in our population is its overall high prevalence in our subjects.

We also confirmed the nonpredictive role of waist circumference and triglycerides. In our study, the waist circumference component is common in subjects without metabolic syndrome, and it is a matter of discussion whether overweight and/or modest adiposity is a risk factor in elderly individuals (20). Triglycerides may be nonpredictive because of their strong physiological relation with HDL cholesterol.

Regarding cardiovascular mortality among women, our findings confirm the strong impact of diabetes, even after adjustment for other cardiovascular risk factors (21). Moreover, a meta-analysis showed that women might have a greater cardiovascular disease risk associated with hyperglycemia than men even among subjects without diabetes, sug-

gesting that high glucose may abolish the protection on cardiovascular disease risk of women, particularly in elderly individuals (22). Moreover, there is accumulating evidence that later in life estrogen deficiency in association with aging processes might promote inflammation and vascular dysfunction, making women more vulnerable to atherosclerosis than men (23).

Our results confirm that low HDL cholesterol is a better cardiovascular mortality predictor than other lipid risk factors in older populations (24,25). The HDL cholesterol reduction results from modifications in HDL cholesterol composition and metabolism, which may impair the antiatherogenic properties of HDL cholesterol, making HDL cholesterol particles proinflammatory, less antioxidant, and less effective on reverse cholesterol transport (19). In addition, high triglycerides and low HDL cholesterol are associated with more atherogenic small, dense LDL particles (19).

A potential limitation of our study is that it included only elderly subjects without an age limit and therefore with a limited survival. Nevertheless, it has been postulated that the strength of the association between metabolic syndrome and all-cause and cardiovascular mortality may be higher in certain subgroups such as elderly subjects (2). Other potential limitations are the relative short follow-up period and the evaluation of only fatal events related to metabolic syndrome.

The strengths of our study are the large number of deaths due to old age and the cardiovascular mortality investigated in subjects without previous cardiovascular diseases. Other important features are the design based on community-dwelling Italian older adults, who are truly representative of a general elderly population, the thorough clinical diagnosis of diseases, and the assessment of several cardiovascular risk factors. Moreover, the Pro.V.A. Study collected extensive baseline data on educational level, socioeconomic conditions, and lifestyle factors that allowed us to adjust for several confounding variables.

In summary, our findings suggest the importance of considering individual risk factors rather than their combination in the metabolic syndrome in older individuals and that in elderly subjects clinicians should focus on simple fasting plasma glucose and HDL cholesterol measurements rather than on diagnosis of metabolic syndrome per se.

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