# Metabolic Syndrome

## Prevalence and prediction of mortality in elderly individuals

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**OBJECTIVE** — Little is known about the prevalence of the metabolic syndrome among elderly people in Italy, its association with all-cause mortality, and whether measurement of serum C-reactive protein (CRP) and interleukin (IL)-6 affects this association.

**RESEARCH DESIGN AND METHODS** — The baseline prevalence of metabolic syndrome, diagnosed according to the National Cholesterol Education Program (NCEP) criteria, and all-cause mortality at 4 years were recorded in an Italian population-based cohort (981 subjects, 55% women, aged 65–97 years). A Cox model adjusted for sociodemographic, lifestyle, and medical variables was used to investigate *1*) whether metabolic syndrome was a predictor of mortality and *2*) how the association was affected by baseline high CRP (>3 mg/l) and IL-6 (>1.33 pg/ml).

**RESULTS** — Overall, metabolic syndrome prevalence was 27.2% [95% CI 24.0–30.5] and higher in women (33.3% [28.7–38.0]) than in men (19.6% [15.5–24.2]). During follow-up, 137 deaths occurred. Using the no metabolic syndrome/no high IL-6 group as the reference, mortality was not associated with the metabolic syndrome alone (multivariable-adjusted hazard ratio 1.24 [0.60–2.59]), only weakly associated with high IL-6 alone (1.66 [1.04–2.63]), but strongly associated with the concurrent presence of metabolic syndrome and high IL-6 (3.26 [2.00–5.33]). High CRP was not a mortality predictor (0.83 [0.58–1.20]) nor did it affect the association of the other variables with mortality.

**CONCLUSIONS** — Metabolic syndrome by NCEP criteria is highly prevalent in the Italian elderly population. It is not itself associated with mortality but may improve the usefulness of IL-6 as a mortality predictor in older age.

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The concept of the metabolic syndrome as a condition that included increased risk for cardiovascular disease, diabetes, and all-cause mortality has existed for at least eight decades, but internationally recognized diagnostic criteria appeared only in 1998 (1,2). The most recent metabolic syndrome definition was provided by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (3). Other definitions were proposed by the World Health Organization and the European Group for the Study of Insulin Resistance (1), but they include laboratory measurements too complex for clinical or epidemiological use.

Knowledge about the prevalence of metabolic syndrome among elderly people in Italy is important for health care planning, since metabolic syndrome prevalence is consistently shown to increase with age (4), but this issue was reported on in only two population-based studies (5,6).

Metabolic syndrome is a proinflammatory condition (3), and measurement of peripheral inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-6 improves the ability to the predict the risk of cardiovascular events and diabetes with occurrence of the metabolic syndrome (7,8). CRP and IL-6 are also associated with increased risk of all-cause mortality in older age (9–11), but the role of metabolic syndrome as a mortality predictor in the elderly is still questioned (2,12,13). It is also not known whether this predictive power may be improved by concurrent measurement of inflammatory markers. In this article, we investigate the prevalence of metabolic syndrome by NCEP criteria in an elderly Italian population and its association with risk of 4-year all-cause mortality and whether measurement of serum CRP or IL-6 provided additional prognostic information for the association.

## RESEARCH DESIGN AND METHODS

— The Conselice Study of Brain Ageing (CSBA) is a population-based prospective survey with the main aim of exploring dementia epidemiology and risk factors in the elderly (14). After approval by our institutional review board, written informed consent was obtained from all participants. Briefly, in 1999–2000, 1,016 (75%) of the 1,353 individuals aged ≥65 years residing in the Conselice municipality (Emilia Romagna region, Northern Italy) underwent the baseline examination including *1*) a standardized personal interview for collection of sociodemographic, lifestyle, and medical information, *2*) a medical examination, and *3*) venous blood sampling. Data on vital status at the second examination in 2003–2004 (mean follow-up 3.8 ± 0.8 years) were collected for the entire baseline cohort. Official death records with dates and causes of death were available for all deceased participants. Data for diagnosis of metabolic syndrome were available for 981 individuals (96.5% of the baseline cohort). Measurement of inflammatory proteins was not performed for 11 of these subjects.

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**Abbreviations:** CRP, C-reactive protein; IL, interleukin; NCEP, National Cholesterol Education Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Table 1—*Characteristics of the study population***

| Characteristics | Men | Women | *P* value |
|---|---|---|---|
| *n* | 438 | 543 | |
| Age (years) | 73.9 ± 6.8 (65–94) | 75.2 ± 7.1 (65–97) | <0.001 |
| Education ≤3 years | 110 (25.1) | 232 (42.7) | <0.001 |
| Active lifestyle | 193 (44.1) | 356 (65.6) | <0.001 |
| Smoking status | | | |
| Current smokers | 57 (13.0) | 34 (6.2) | <0.001 |
| Ex-smokers | 241 (55.0) | 56 (10.3) | |
| Never smokers | 140 (32.0) | 453 (83.4) | |
| Preexisting major diseases | 229 (50.3) | 221 (40.7) | <0.001 |
| Albumin (g/l) | 4.7 ± 0.3 | 4.6 ± 0.3 | <0.001 |
| Components of the metabolic syndrome | | | |
| Obesity | 141 (32.2) | 334 (61.5) | <0.001 |
| Hypertriglyceridemia | 100 (23.6) | 128 (22.8) | 0.785 |
| Low HDL cholesterol | 36 (8.2) | 107 (19.7) | <0.001 |
| Hypertension | 376 (85.8) | 464 (85.4) | 0.031 |
| Abnormal glucose metabolism | 92 (21.0) | 105 (19.3) | 0.517 |
| Serum CRP* | 0.3 (0.2–0.4) | 0.3 (0.2–0.5) | 0.235† |
| Serum IL-6* | 1.28 (0.29–8.71) | 1.36 (0.42–8.60) | 0.615† |
| High serum CRP (>3 mg/l)* | 213 (48.6) | 296 (54.5) | 0.067 |
| High serum IL-6 (>1.33 pg/ml)* | 214 (49.3) | 273 (50.3) | 0.615 |

Data are means ± SD (range), *n* (%), or median (interquartile range). Interquartile range spans from the 25th to the 75th percentile. *Data missing for four men and seven women. †Analyses performed on log-transformed values.

## Metabolic syndrome

According to NCEP criteria (3), the metabolic syndrome was defined as the presence of at least three of the following: *1*) waist measurement >88 cm for women and >102 cm for men, *2*) hypertriglyceridemia (≥1.69 mmol/l), *3*) low HDL cholesterol (<1.03 mmol/l in men and <1.29 mmol/l in women), *4*) hypertension (systolic, ≥130 mmHg; diastolic, ≥85 mmHg using the average of two seated measurements or currently using an antihypertensive medication), and *5*) fasting serum glucose ≥6.1 mmol/l or currently using antidiabetes medication.

## Laboratory measurements

Fasting venous blood samples were rapidly sent for processing. Serum total and HDL cholesterol, triglycerides, albumin, and glucose were measured in fresh blood by enzymatic assay (Roche Diagnostics, Monza, Italy) on a Hitachi 917 system autoanalyzer (Boehringer Mannheim, Mannheim, Germany). Serum CRP was measured in fresh blood using the N-high sensitivity CRP assay with a latex-enhanced immunonephelometric assay on a BN II analyser (Dade Behring, Milan,

**Table 2—*Age- and sex-specific prevalence of the metabolic syndrome in the Conselice Study of Brain Ageing population***

| Age classes | *n* | Cases | Prevalence | Metabolic syndrome |
|---|---|---|---|---|
| All | | | | |
| 65–69 years | 275 | 81 | 29.4 (23.3–35.9) | 1.00 |
| 70–74 years | 270 | 75 | 27.8 (21.7–34.2) | 0.90 (0.62–1.31) |
| 75–79 years | 200 | 49 | 24.5 (17.8–31.9) | 0.77 (0.51–1.17) |
| ≥80 years | 236 | 62 | 26.3 (19.9–33.1) | 0.85 (0.57–1.24) |
| All | 981 | 267 | 27.2 (24.0–30.5) | |
| Men | | | | |
| 65–69 years | 136 | 29 | 21.3 (13.8–30.1) | 1 |
| 70–74 years | 130 | 42 | 25.4 (17.1–34.8) | 1.19 (0.67–2.12) |
| 75–79 years | 80 | 37 | 15.0 (7.0–25.9) | 0.64 (0.26–1.14) |
| ≥80 years | 92 | 50 | 13.0 (6.0–22.7) | 0.55 (0.31–1.34) |
| All | 438 | 86 | 19.6 (15.5–24.2) | |
| Women | | | | |
| 65–69 years | 139 | 52 | 37.4 (28.1–47.0) | 1 |
| 70–74 years | 140 | 42 | 30.0 (21.4–39.3) | 0.72 (0.44–1.19) |
| 75–79 years | 120 | 37 | 30.8 (21.5–41.0) | 0.75 (0.44–1.26) |
| ≥80 years | 144 | 50 | 34.7 (25.8–25.8) | 0.87 (0.53–1.42) |
| All | 543 | 181 | 33.3 (28.7–38.0) | |

Data are reported prevalence [% (95% CI)]. Metabolic syndrome across age-groups using the youngest age-group as the reference is reported as OR (95% CI).

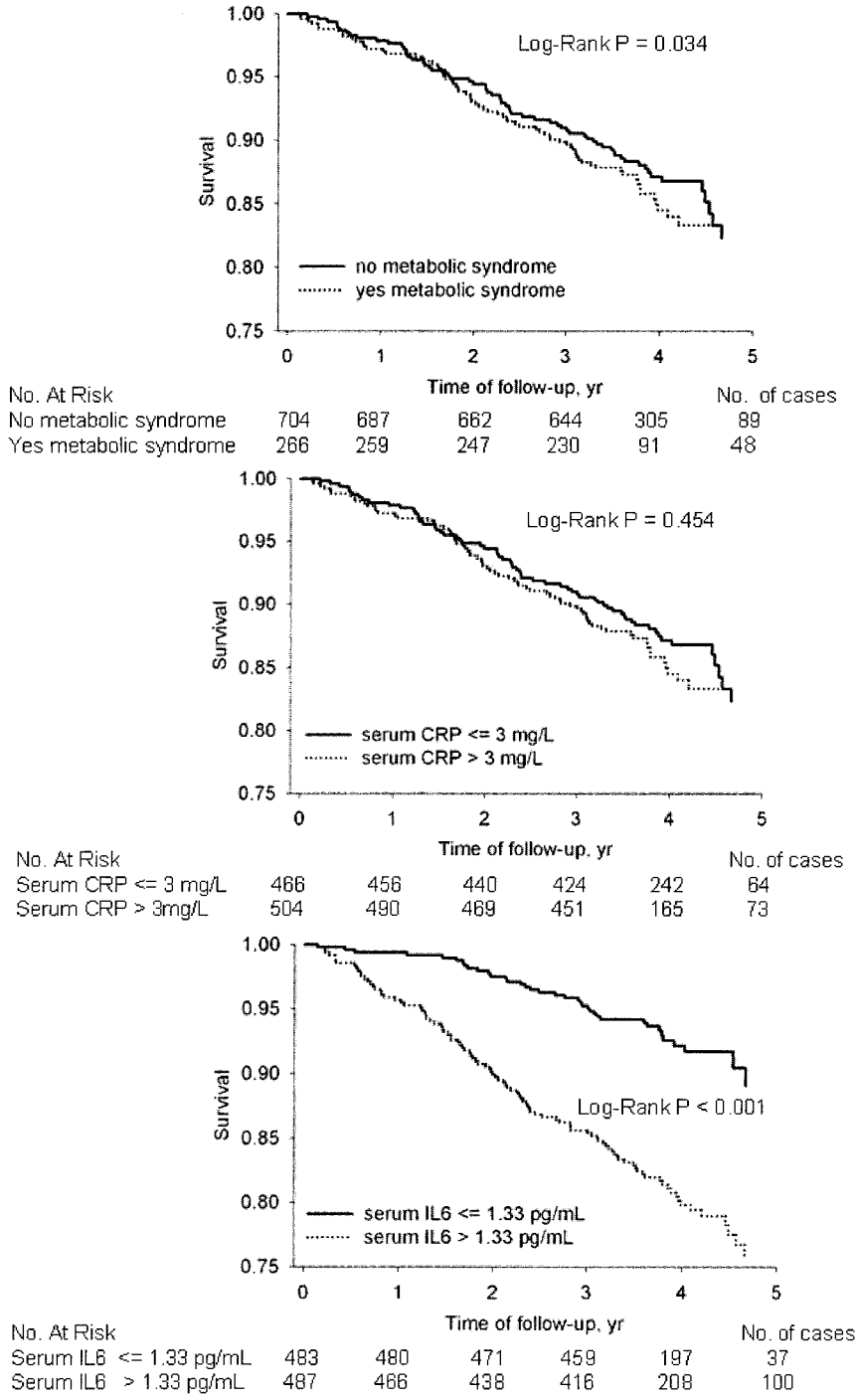



**Figure 1—** *Unadjusted all-cause mortality risk by metabolic syndrome, serum CRP, and serum IL-6.*

Italy). The assay has a detection limit of 0.175 mg/dl and intra- and interassay coefficients of variation (CVs) <3%. Serum IL-6 was measured on frozen samples stored at −70°C (maximum duration of storage up to 48 months) using a high-sensitivity ELISA kit (R&D Systems, Minneapolis, MN). The assay has a detection limit of 0.10 pg/ml and intra- and interassay CVs <4%.

### Sociodemographic, lifestyle, and medical information

Covariates included in the study are age, sex, education (categorized as ≤ or >3 years of formal education because of the poor educational background of the sample population), physical activity (sedentary versus active lifestyle; the latter defined as performing at least moderate physical activity for ≥4 h/week), and preexisting major diseases associated with both increased mortality risk and inflammation (10,15) (any of the following: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver and kidney disease, diabetes, or cancer). Except for dementia, diagnosed through a standardized workup (14), the other diagnoses were based on self-report and information from the participant's general practitioner. BMI (calculated as weight in kilograms divided by the square of the height in meters) was also considered because, in elderly individuals, it is an index of both fat and lean mass, and underweight is an acknowledged mortality risk factor in older age (16,17).

### Statistical analysis

CRP and IL-6 had very skewed distributions and were analyzed both as log-transformed and categorical variables (16). Median values from the whole cohort were used for defining "high" CRP (>3 mg/l) and IL-6 (>1.33 pg/ml) serum levels.

$\chi^2$ and *t* tests were used for comparisons between groups. Pearson's coefficient was used as a correlation measure. The 95% CIs for sex-specific metabolic syndrome prevalence rates (cases per 100 populations) across four age ranges (65–69, 70–74, 75–79, and ≥80 years) were calculated from the binomial distribution. The associations of metabolic syndrome with age and inflammatory markers were investigated with logistic regression. The associations of metabolic syndrome and inflammatory markers with all-cause mortality were investigated with Cox proportional hazards regression. A first model was adjusted for age, sex, education, smoking, physical activity, albumin, and preexisting diseases. A second model was additionally adjusted for BMI. The 95% CI was calculated for both odds ratios (ORs) and hazard ratios. The log-rank test was used to compare survival curves across categories of interest. All models were tested for interactions. Statistical analyses were performed using SYSTAT10 (SPSS, Chicago, IL).

## RESULTS

### Prevalence of the metabolic syndrome

Table 1 shows the cohort characteristics. Table 2 provides details on the prevalence of metabolic syndrome by age and sex.

**Table 3—*Risk of all-cause mortality associated with metabolic syndrome, serum CRP, and serum IL-6***

| Risk factor | Deaths | Unadjusted | Model 1 | Model 1 + BMI |
|---|---|---|---|---|
| Metabolic syndrome | | | | |
| No ($n$ = 704) | 89 (12.6) | 1.00 | 1.00 | 1 |
| Yes ($n$ = 266) | 48 (18.0) | 1.46 (1.03–2.70) | 1.79 (1.23–2.58) | 2.29 (1.51–3.46) |
| Serum CRP (mg/l) | | | | |
| ≤3.0 ($n$ = 466) | 64 (13.7) | 1.00 | 1.00 | 1 |
| >3.0 ($n$ = 504) | 73 (14.5) | 1.14 (0.47–2.77) | 0.83 (0.58–1.0) | 1.12 (0.77–1.63) |
| Per SD (0.27) of log-transformed serum CRP | | 1.11 (0.96–1.27) | 1.12 (0.96–1.31) | 1.12 (0.96–1.32) |
| Serum IL-6 (pg/ml) | | | | |
| = 1.33 ($n$ = 446) | 37 (7.7) | 1.00 | 1.00 | 1.00 |
| >1.33 ($n$ = 387) | 100 (20.5) | 2.77 (1.91–4.05) | 1.96 (1.33–2.89) | 1.99 (1.34–2.95) |
| Per SD (1.63) of log-transformed serum IL-6 | | 1.27 (1.10–1.46) | 1.26 (1.10–1.46) | 1.22 (1.05–1.42) |
| Stratified by metabolic syndrome and serum IL-6 | | | | |
| No metabolic syndrome/IL-6 ≤1.33 pg/ml ($n$ = 354) | 27 (7.6) | 1.00 | 1.00 | 1 |
| Yes metabolic syndrome/IL-6 ≤1.33 pg/ml ($n$ = 129) | 10 (7.7) | 1.01 (0.49–2.08) | 1.24 (0.60–2.59) | 1.61 (0.76–3.39) |
| No metabolic syndrome/IL-6 >1.33 pg/ml ($n$ = 350) | 62 (17.7) | 2.37 (1.50–3.72) | 1.66 (1.04–2.63) | 1.68 (1.05–2.69) |
| Yes metabolic syndrome/IL-6 >1.33 pg/ml ($n$ = 137) | 38 (27.7) | 3.90 (2.38–6.38) | 3.26 (2.00–5.33) | 4.38 (2.53–7.57) |

Data are $n$ (%) or hazard ratios (95% CI). Multivariable-adjusted hazard ratios from model 1 are adjusted for all three main risk factors along with age, sex, education, albumin, smoking, physical activity, and preexisting diseases.

Prevalence did not vary with age in women (OR for 1-year increment of age 0.99 [95% CI 0.97–1.02]), whereas it tended to decrease in men (0.97 [0.93–1.00]), especially after age 74. No association between age and prevalence of individual metabolic syndrome components was found in either sex, except for an inverse relationship with hypertriglyceridemia and hypertension observed in men ($P < 0.05$ for both). At all ages, women were more likely than men to have metabolic syndrome (OR 2.05 [1.51–2.77]).

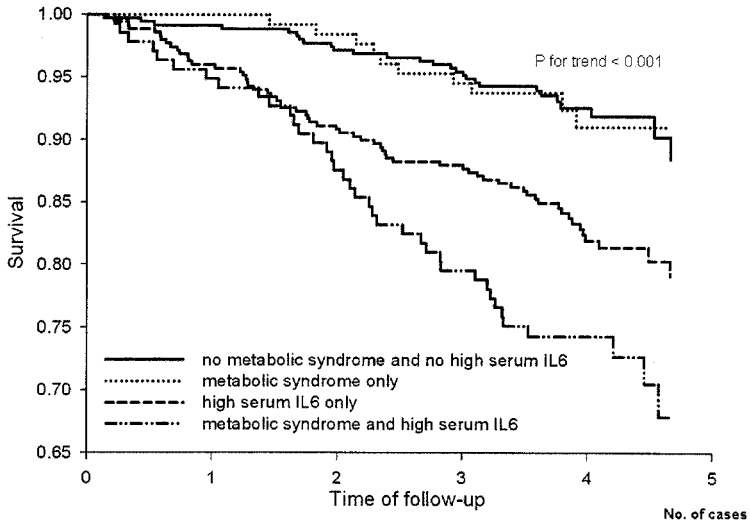
### Metabolic syndrome, inflammatory markers, and all-cause mortality

Among the 970 participants with measurement of serum inflammatory markers, CRP was weakly associated with IL-6 ($r$ = 0.080, $P$ = 0.012). High CRP was more frequent in those with ($n$ = 166, 62.4%, multivariable-adjusted OR 1.85 [1.36–2.50]) than in those without metabolic syndrome ($n$ = 338, 48%). High IL-6 prevalence did not differ between those with ($n$ = 137, 51.4%, multivariable-adjusted OR 1.09 [0.82–1.46]) and without metabolic syndrome ($n$ = 350, 49.7%). All metabolic syndrome components were associated with high CRP ($P < 0.05$) except for hypertension, whereas only low LDL was associated with high IL-6 ($P$ = 0.01). Among subjects with metabolic syndrome, the prevalence of single metabolic syndrome components did not differ by IL-6 level.

There were 137 deaths (54.7% in women) during 3,727 person-years of follow-up (32% from cardio- or cerebrovascular disease and 30% from cancer). As shown in Fig. 1 and Table 3, mortality risk was associated with metabolic syndrome and high IL-6 but not high CRP. Age, poor education, sedentary lifestyle, low albumin level, preexisting diseases, and low BMI were also significant mortality predictors ($P$ at least <0.05), whereas sex was not. Inclusion of BMI in the multivariable-adjusted models strengthened the associations of metabolic syndrome with mortality. Whatever the model used, the interaction term high IL-6 multiplied by metabolic syndrome was not significant ($P > 0.30$) but caused the significant metabolic syndrome effect to disappear ($P > 0.50$) with a CV >30%. Therefore, according to Hosmer and Lemeshow (18), analyses were repeated, stratifying the cohort according to the presence or absence of metabolic syndrome and high IL-6. As shown in Table 3 (bottom) and Fig. 2, using the no metabolic syndrome/no high IL-6 group as the reference, all-cause mortality was not associated with metabolic syndrome alone and only weakly associated with high IL-6 alone, whereas the yes metabolic syndrome/yes high IL-6 group had a risk from three- to fourfold greater than the reference group, depending on whether the models included or did not include BMI. Mortality risk for this group was also significantly higher than that for high IL-6 alone (for all models, $P < 0.05$ as calculated from the final model estimates [17]). Additional controls for alcohol consumption, use of nonsteroidal anti-inflammatory drugs, statins, and cause of death did not change the results (data not shown).

**CONCLUSIONS** — Prevalence of the metabolic syndrome by NCEP criteria in this elderly Italian cohort was ~27%. Our estimates are lower than those reported for the U.S. elderly population (~40%) (1) but confirm and extend the findings from the only two other Italian population-based studies including elderly individuals and using standardized metabolic syndrome definitions. In the Bruneck Study (5) (888 individuals aged 40–79 years), prevalence of the metabolic syndrome by World Health Organization criteria was higher at age >60 (42.8%) than in younger subjects (27%), and also higher than by NCEP criteria in the overall sample (31.7 vs. 17.8%); NCEP age-specific prevalence estimates were not provided. In the Lucca Cuore Study (6) (2,100 individuals aged ≥20 years), metabolic syndrome prevalence by NCEP criteria was ~25% among the 70-year-old subjects, but elderly subjects represented only 17% of the total sample. Neither the Bruneck nor the Lucca Cuore Study provided specific prevalence estimates for subjects aged >80 years.

In contrast with the lack of sex-related differences in metabolic syndrome prevalence reported in previous Italian studies (5,6), but in agreement with a large meta-analysis of European studies




| No. At Risk | | | | | | No. of cases |
|---|---|---|---|---|---|---|
| No metabolic syndrome/ no high IL6 | 354 | 351 | 344 | 337 | 141 | 27 |
| Yes metabolic syndrome/no high IL6 | 129 | 129 | 127 | 121 | 67 | 10 |
| No metabolic syndrome/yes high IL6 | 350 | 336 | 318 | 307 | 151 | 62 |
| Yes metabolic syndrome/yes high IL6 | 137 | 130 | 120 | 109 | 47 | 36 |

**Figure 2—** *Unadjusted all-cause mortality risk stratified by metabolic syndrome and serum IL-6.*

(12), we found a higher metabolic syndrome prevalence in elderly women than men. Our sample was larger and older than the other Italian cohorts, and the sex-related difference might appear only in samples including a substantial number of older subjects because of the trend for a decreasing metabolic syndrome prevalence after age 75 observed in men. This decrease might in turn reflect a selection bias consequent to sex-related differences in cardiovascular mortality.

Our results are the first evidence that, in elderly individuals, metabolic syndrome is not an independent mortality predictor but might increase the prognostic value of the known association between IL-6 and all-cause mortality. Previous literature data about all-cause mortality risk associated with metabolic syndrome are conflicting (2,12), with no association reported in the only study including elderly individuals (13).

IL-6 is the main stimulant for CRP production (19), yet in the present study metabolic syndrome was associated only with high CRP. This association has already been clearly defined (7), whereas data about the association with IL-6 are few and inconsistent (20,21). Because of its shorter half-life and greater diurnal variation (18), IL-6 is considered weaker and less reliable than CRP as a peripheral marker of inflammation. In the present study, however, only IL-6 was associated with mortality. This finding agrees with previous studies showing that, in elderly individuals, IL-6 can predict several chronic diseases and all-cause mortality independently of (9) and even better than CRP (22,23).

Adjustment for BMI did not substantially change the results but tended to increase the strength of the association of metabolic syndrome and IL-6 with mortality. In the elderly population, the health harms of obesity measured as increased BMI are very controversial (17), but low BMI as a parameter of malnutrition is an established mortality risk factor (16). As in this cohort, BMI was inversely associated with mortality; its inclusion in the models might decrease the variability related to poor nutritional status.

Although our study was population based and had a good response rate, it also has several limitations. First, the NCEP criteria are not the only standardized definition for metabolic syndrome. In elderly subjects, however, they predict clinically significant outcomes better than metabolic syndrome by other criteria (24). Second, our results are based on single-time measurements of inflammatory markers. Third, a longer follow-up time may be required to assess the effect of the study variables on mortality. Finally, for analyses treating them as categorical variables, inflammatory markers were dichotomized at their median value. The threshold used for CRP corresponds to a significantly increased cardiovascular risk (7), but no clinical meaning can be associated to the IL-6 threshold, thus limiting the interpretation of our results. In summary, metabolic syndrome defined by NCEP criteria is highly prevalent in this Italian elderly cohort, and although it is not by itself independently associated with mortality, it might improve the usefulness of IL-6 as a mortality predictor in older age.

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