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ORIGINAL CONTRIBUTION

Metabolic syndrome and quality of life in the elderly: age and gender differences

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Abstract
Purpose The metabolic syndrome (MetS) is highly prevalent in Western older populations. MetS is an intriguing entity, because it includes potentially reversible risk factors. Some studies have suggested an inverse correlation between MetS and health-related quality of life (HRQoL), but data regarding older subjects are scanty and conflicting. The aim of this study was to assess the association between HRQoL and MetS in older, unselected community-dwelling subjects.
Methods We analyzed data of 356 subjects aged 75+ living in Tuscania (Italy). HRQoL was assessed using the Health Utilities Index, Mark 3. Diagnosis of MetS was defined according to the National Cholesterol Education Program's ATP-III criteria.
Results MetS was reported by 137 (38%) participants. According to linear regression analysis, MetS was associated with significantly better HRQoL in men ($B = 0.19$ 95% CI = 0.06–0.32; $p = 0.006$), but not in women. Also, when the regression model was analyzed in men, MetS was associated with better HRQoL ($B = 0.17$, 95% CI = 0.01–0.32; $p = 0.035$) only among participants aged 80+. No significant associations were found in men between HRQoL and any of the single components of MetS.
Conclusions MetS is not associated with worse HRQoL among community-dwelling elderly; it is associated with significantly better HRQoL among the oldest men.

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Introduction

The metabolic syndrome (MetS) is defined by abdominal adiposity, elevated triglyceride level, low high-density lipoprotein cholesterol level, high blood pressure, and high fasting blood glucose [1]. This syndrome is increasingly being recognized in geriatric populations [2]; the pathophysiological pathway seems to involve hyperinsulinemia, which is strongly associated with obesity. The mechanisms that link obesity with hyperinsulinemia, in turn, are thought to involve primarily insulin resistance, which is chiefly attributed to adipose tissue inflammation and dysfunction with ensuing release of inflammatory cytokines [3]. Not surprisingly, MetS has been associated with increased risk of diabetes and accelerated atherosclerosis, as well as with its complications, including stroke and myocardial infarction [4, 5]. Thus, recognition and treatment of the above-mentioned components of MetS are recommended for prevention at the individual, as well as population levels [6].

On the other hand, it is acknowledged that health-related quality of life (HRQoL) as perceived by the patient should be considered the main outcome of any health interventions. Studies so far conducted generally found an association of MetS, as well as its components, with worse HRQoL [7]; in some studies, however, MetS has been found to be associated with reduced HRQoL in women, but not in men [8, 9]. However, these studies generally enrolled selected, middle-aged populations, often with no mention of comorbidity. Little is known about elderly populations, especially the oldest [10]. This issue is relevant for the

implementation of preventive services at the population level, as oldest age subjects, among whom the components of MetS are most prevalent, are steeply increasing in Western countries. Also, it has been found that the cost-effectiveness of preventive interventions for type II diabetes mellitus is strongly dependent upon the HRQoL perceived by subjects with MetS [6].

The aim of the present study was to evaluate the association of MetS with self-assessed quality of life in an unselected, community-dwelling older population, and to ascertain whether such an association varies according to sex and age.

Methods

Participants

This study involved 356 subjects aged ≥75 years who were living in Tuscania (Italy) on January 1st, 2004. All 387 inhabitants of this town aged 75+ had been enrolled in a study of the genetic determinants of health status in six Italian towns and were visited by the study researchers between January 1st and June 1st, 2004. For the present study, we excluded 31 of 387 subjects because of missing data for the study variables. All participants underwent ambulatory or home visits by the study physicians, who performed physical examination, electrocardiography, Doppler echocardiography, ultrasonographic bone densitometry, and collected medical history and blood samples for serum chemistry and genomic analyses. Also, they completed a questionnaire that included participants' data on socioeconomic status and lifestyle habits. Appointments dedicated to blood sample collection were given early in the morning.

The Institutional Review Board approved the protocol of the present study, and all patients provided written informed consent.

Covariates

Education was expressed as years of school attendance. Alcohol consumption was defined by consuming at least two drinks per week. Drinks were recorded as wine units (100 mL), because this beverage represents by far the major form of alcohol consumption in Italy, independently of any seasonal variations [11]. A conversion table was used for other alcoholic beverages; each liter of wine was assumed to contain 80 g of alcohol [12].

Smoking was calculated as total lifetime pack years for current, as well as former smokers. Income was expressed as perceived adequate or inadequate by the participant.

Functional ability was estimated using the Katz' activities of daily living (ADLs) [13], and the Lawton and Brody scale for instrumental activities of daily living (IADLs) [14]. We adopted the same scoring for women and men (i.e., 0–8) for the IADLs because men had a median number of preserved instrumental activities of 7. This figure is higher than the maximum score of 5 that has been sometimes adopted for men; furthermore, it was not different from that reported by older female participants (median = 7). Depressive symptoms were evaluated using the validated 30-item Italian version of the Geriatric Depression Scale (GDS) [15], a self-reported scale based upon yes-or-no questions regarding mood over the previous week. A cutoff of 11 is generally adopted to diagnose depression. The test yields 84% sensitivity and 95% specificity for the diagnosis of depression [16]. Cognitive performance was assessed using the Hodkinson abbreviated mental test (AMT) [17], which has been validated for detection of cognitive impairment in older, including Italian, populations [18]. A major advantage of this scale is represented by the lack of written items, which are known to bias the assessment of cognitive function in older populations with prevalent illiteracy, such as that of the present study.

Participants' diagnoses and drug treatments were obtained by their general practitioners and further confirmed by the study physicians, who received specific training and whose concordance had been tested (Cohen's Kappa >0.80 for all the five proposed dummy cases).

All drugs assumed by participants were coded according to the Anatomical Therapeutic and Chemical codes. Diagnoses were coded according to the International Classification of Diseases, ninth edition, Clinical Modification codes [19]. Comorbidity was quantified using the Charlson comorbidity index score by adding scores assigned to specific diagnoses [20].

Blood samples were obtained after overnight fast; the processed specimens were aliquoted into cryovials, frozen at −70 °C, and shipped to the Department of Experimental Pathology, University of Bologna. Serum creatinine was measured by a standard creatinine Jaffe method (Roche Diagnostics, Mannheim, Germany). Hemoglobin was measured using the hematology automated Autoanalyzer DASIT SE 9000 (Sysmex Corporation, Kobe, Japan). Albumin was measured using an agarose electrophoretic technique (Hydragel Protein(E) 15/30; Sebia, Issy-les-Moulineaux, France). Sodium was measured by indirect ion-selective electrode (ISE) method (DXC600, Beckman Coulter, Brea, USA).

Measurements of high-sensitivity C-reactive protein were performed in duplicate by enzyme-linked immunosorbent assay (ELISA). These objective tests were analyzed as potential confounders of the association between

MetS and HRQoL, because they reflected relevant conditions that might be affected by MetS and might influence HRQoL, namely renal function (serum creatinine), nutritional status (albumin, hemoglobin), hydration status (sodium), and subclinical inflammation (high-sensitivity C-reactive protein).

Perceived quality of life

Perceived health-related quality of life was assessed using the Health Utilities Index, Mark 3 (HUI3) [21]. This tool calculates self-assessed, preference-based quality of life using a 15-item questionnaire. The HUI3 explores eight domains, namely vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. A overall "utility" score is calculated as the value of a single function that composition is based upon preference weights for 243 health states obtained from representative populations from several countries. HUI3 scores range from −0.36 to 1.00. Higher scores indicate better quality of life; the value of 1 corresponds to the best conceivable health status and zero to instant death, negative scores representing states considered worse than death. The utility scores calculated by this multi-attribute health-status classification system allow to measure the overall HRQL for patients, which is also used in formal cost-utility and cost-effectiveness analyses.

Metabolic syndrome

The metabolic syndrome was defined according to the National Cholesterol Education Program's ATP-III criteria, adding use of hypolipemic, hypoglycemic, and antihypertensive medications, as already done in several previous studies; the diagnosis of the metabolic syndrome was established as the presence of three or more of the following features: waist circumference >88 cm in women and >102 cm in men; fasting serum triglycerides ≥150 mg/dL; serum HDL <50 mg/dL in women and <40 mg/dL in men; blood pressure ≥130/85 mmHg; fasting blood glucose levels ≥110 mg/dL [1]. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest (normally umbilical level). Blood pressure was recorded using a standard mercury sphygmomanometer.

All blood pressure measurements were performed in supine position by three measurements, separated by 2-min intervals; the average of the last two measures was used in the analyses. HDL cholesterol and triglycerides concentrations were determined using commercial enzymatic tests (Roche Diagnostics, Mannheim, Germany). Serum glucose levels were determined by enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany).

Statistical analyses

Data of continuous variables are presented as mean values ± standard deviation (SD). Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS for Windows version 13.0, 2004, SPSS Inc., Chicago, IL); differences were considered significant at the $p < 0.05$ level. Analysis of variance (ANOVA) for normally distributed variables according to MetS was performed by ANOVA comparisons; otherwise, the non-parametric Kruskal–Wallis H test was adopted. Chi-square analysis was used for dichotomous variables. Serum C-reactive protein levels were analyzed after log transformation; smoking and the Health Utilities Index score were not transformed because the tests for linearity and deviation from linearity indicated that the association of these variables with MetS had significant F ratio for linearity ($p < 0.02$ for both variables), but not for nonlinear components ($p > 0.5$ for both variables).

Linear regression analysis was used to estimate the association of variables of interest, including MetS, with the HUI3 score. To assess independent correlates of HRQoL, which might confound the association between the HUI3 score and MetS, groups of variables (demographics, comorbid conditions, medications, and objective tests, as depicted in Table 1) were first examined using separate age- and sex-adjusted regression models (Table 2, left columns). Those variables, significant at the $p < 0.050$ level in these initial models, were simultaneously entered into a summary model (Table 2, right columns). The summary model was anyway adjusted for age and sex, as generally recommended for more conservative analyses. The same fully adjusted regression model was analyzed after stratifying for sex (Table 3). Also, the fully adjusted regression model was analyzed in logistic regression analysis considering a HUI3 score above or below the median value, among male participants (Table 4).

Analyses of the interaction term "MetS*consumption of alcohol", "MetS*use of angiotensin-converting enzyme inhibitors", and "MetS*use of benzodiazepines" were also performed to assess whether the association of MetS with a HUI3 score above the median value varied according to consumption of alcohol, use of angiotensin-converting enzyme inhibitors, or benzodiazepines, also after stratifying for sex.

In addition, the association between the HUI3 score and MetS was assessed in men after stratifying for age < or ≥80 years (i.e., the median age of the study sample), using the fully adjusted linear regression model (Table 5). Analysis of the interaction term "MetS*age" was performed using the fully adjusted logistic regression model to ascertain whether the association between MetS and HUI3 varied according to age. Also, the fully adjusted linear

Table 1 Characteristics of participants according to diagnosis of the metabolic syndrome

	Participants with metabolic syndrome ($n = 137$) n (%) or mean ± SD	Participants without metabolic syndrome ($n = 219$) n (%) or mean ± SD	p
Demographics and lifestyle habits			
Age (years)	79 ± 5	79 ± 6	0.973α
Sex (female)	88 (64%)	106 (48%)	0.004β
Education (years)	4 ± 3	5 ± 3	0.101α
Current alcohol consumption	94 (69%)	155 (72%)	0.004β
Smoking[a]	3,909 ± 7,781	5,437 ± 10,845	0.128γ
Income[b]	101 (75%)	171 (81%)	0.221β
Comorbid conditions			
Chronic pulmonary disease	39 (28%)	53 (24%)	0.456β
Heart failure	25 (18%)	41 (19%)	0.890β
Arthritis	113 (82%)	164 (76%)	0.184β
Stroke	15 (11%)	31 (14%)	0.419β
Renal disease	9 (7%)	7 (3%)	0.189β
Depression[c]	71(53%)	92 (44%)	0.123β
Hepatic disease	7 (5%)	7 (3%)	0.410β
Cancer	16 (12%)	18 (8%)	0.355β
Charlson comorbidity score index	2 ± 2	1 ± 1	0.017α
Medications			
SSRI[d]	6 (4%)	7 (3%)	0.573β
Beta-blockers	10 (7%)	7 (3%)	0.123β
Corticosteroids	6 (4%)	8 (4%)	0.783β
ACE-inhibitors[e]	55 (40%)	51 (23%)	0.001β
Loop diuretics	33 (24%)	36 (16%)	0.098β
Benzodiazepines	37 (27%)	36 (16%)	0.021β
NSAIDS[f]	8 (6%)	17 (8%)	0.531β
Aspirin	35 (25%)	38 (17%)	0.079 β
Objective tests			
Serum creatinine (mg/dL)	1.1 ± 0.3	1.0 ± 0.3	0.056α
Serum albumin (g/dL)	4.2 ± 0.7	4.1 ± 0.5	0.216α
Hemoglobin (g/dL)	14.1 ± 1.6	14.2 ± 1.7	0.913α
Serum sodium (mEq/L)	143 ± 3	144 ± 3	0.325α
C-reactive protein (mg/dL)	0.98 ± 2.02	0.63 ± 1.27	0.087γ
Activities of daily living	5 ± 1	5 ± 1	0.723α
IADLs[g]	6 ± 2	6 ± 2	0.930α
Hodkinson abbreviated mental test	8 ± 2	7 ± 2	0.146α
Quality of life[h]	0.31 ± 0.45	0.30 ± 0.47	0.405α

[a] Total lifetime pack years

[b] Perceived as adequate

[c] Defined by a Geriatric Depression score >11

[d] Selective serotonin reuptake inhibitors

[e] Angiotensin-converting enzyme inhibitors

[f] Nonsteroidal antiinflammatory agents

[g] Instrumental activities of daily living

[h] Measured using the Health Utilities Index—Mark 3

α ANOVA comparison

β Chi-square analysis

γ Nonparametric Kruskal–Wallis H test

Table 2 Association (*B* coefficients, and 95% confidence intervals, CI) of perceived quality of life with the variables of interest according to the initial (age- and sex-adjusted), and the summary linear (fully adjusted) regression models

	Age- and sex-adjusted models			Summary model		
	B	95% CI	*p*	*B*	95% CI	*p*
Demographics and lifestyle habits						
Age (years)	0.03	0.02 to 0.04	<0.0001	0.04	0.03 to 0.05	<0.0001
Sex (female)	−0.07	−0.17 to 0.04	0.235	−0.12	−0.21 to −0.03	0.006
Education (years)	0.02	0.01 to 0.03	0.014	0.01	−0.01 to 0.02	0.433
Current alcohol consumption	−0.07	−0.13 to −0.01	0.025	−0.029	−0.08 to 0.02	0.285
Smoking[a]	0.01	−0.03 to 0.08	0.863			
Income[b]	−0.08	−0.20 to 0.03	0.151			
Comorbid conditions						
Chronic pulmonary disease	−0.12	−0.24 to −0.01	0.043	−0.06	−0.16 to 0.03	0.161
Heart failure	0.05	−0.09 to 0.18	0.513			
Arthritis	−0.01	−0.12 to 0.10	0.900			
Stroke	0.08	−0.08 to 0.24	0.320			
Renal disease	−0.11	−0.35 to 0.14	0.382			
Depression[c]	−0.27	−0.35 to −0.17	<0.0001	−0.14	−0.23 to −0.05	0.002
Hepatic disease	−0.11	−0.35 to 0.12	0.349			
Cancer	−0.18	−0.37 to 0.01	0.053			
Charlson comorbidity score index	−0.01	−0.06 to 0.04	0.638			
Medications						
SSRI[d]	0.06	−0.19 to 0.31	0.642			
Beta-blockers	0.02	−0.19 to 0.23	0.842			
Corticosteroids	−0.31	−0.55 to −0.08	0.009	−0.19	−0.41 to 0.03	0.085
ACE-I[e]	0.24	0.07 to 0.40	0.005	0.12	−0.02 to 0.26	0.082
Loop diuretics	−0.03	−0.15 to 0.09	0.638			
Benzodiazepines	0.02	−1.01 to 0.14	0.731			
NSAIDS[f]	−0.02	−0.20 to 0.17	0.846			
Aspirin	−0.05	−0.17 to 0.06	0.389			
Objective tests						
Serum creatinine (mg/dL)	0.01	−0.11 to 0.14	0.824			
Serum albumin (g/dL)	−0.06	−0.17 to 0.04	0.243			
Hemoglobin (g/dL)	0.01	−0.02 to 0.05	0.510			
Serum sodium (mEq/L)	0.01	−0.01 to 0.02	0.624			
C-reactive protein (mg/dL)[g]	0.01	−0.05 to 0.05	0.943			
ADL[h]	0.05	−0.00 to 0.11	0.065			
IADL[i]	0.05	0.02 to 0.08	0.003	0.08	0.06 to 0.10	<0.0001
Hodkinson abbreviated mental test	0.02	−0.02 to 0.05	0.298			
Metabolic syndrome	0.13	0.02 to 0.25	0.026	0.07	−0.01 to 0.15	0.072

All the covariates were entered simultaneously into the regression models

[a] Total lifetime pack years

[b] Perceived as adequate

[c] 30-item Geriatric Depression score >11

[d] Selective serotonin reuptake inhibitors

[e] Angiotensin-converting enzyme inhibitors

[f] Nonsteroidal antiinflammatory agents

[g] High-sensitivity, log-transformed

[h] Activities of daily living

[i] Instrumental activities of daily living

Table 3 Association (*B* coefficients, and 95% confidence intervals, CI) between perceived quality of life and the metabolic syndrome according to the fully adjusted linear regression model, in women and men

	Women			Men		
	B	95% CI	*p*	*B*	95% CI	*p*
Age (each year)	0.04	0.03 to 0.05	<0.0001	0.04	0.03 to 0.05	<0.0001
Education (each year)	0.01	−0.01 to 0.03	0.102	−0.01	−0.01 to 0.02	0.943
Current alcohol consumption	−0.04	−0.10 to 0.02	0.194	−0.01	−0.13 to 0.10	0.828
Chronic pulmonary disease	−0.14	−0.27 to −0.02	0.025	0.01	−0.14 to 0.14	0.995
Diagnosis of depression[a]	−0.15	−0.27 to −0.04	0.007	−0.09	−0.24 to 0.05	0.185
Corticosteroids	−0.07	−0.33 to 0.19	0.612	−0.27	−0.68 to 0.12	0.176
ACE-I[b]	0.10	−0.06 to 0.25	0.219	0.12	−0.14 to 0.39	0.368
IADL[c]	0.08	0.06 to 0.11	<0.0001	0.08	0.05 to 0.11	<0.0001
Metabolic syndrome	−0.01	−0.11 to 0.09	0.811	0.19	0.06 to 0.32	0.006

All the covariates were entered simultaneously into the regression models

[a] 30-item Geriatric Depression score >11

[b] Angiotensin-converting enzyme inhibitors

[c] Instrumental activities of daily living

Table 4 Association (odds ratios, OR, and 95% confidence intervals, CI) between perceived quality of life above the median value (≥0.31) and the metabolic syndrome according to logistic regression in men

	OR	95% CI	*p*
Age (each year)	1.19	1.09–1.30	<0.0001
Education (each year)	1.00	0.87–1.15	0.976
Current alcohol consumption	1.14	0.50–2.58	0.760
Chronic pulmonary disease	1.00	0.40–2.50	0.993
Diagnosis of depression[a]	0.38	0.15–1.00	0.040
Corticosteroids	0.43	0.03–5.65	0.520
ACE-I[b]	0.39	0.14–1.13	0.083
IADL[c]	1.57	1.28–1.92	<0.0001
Metabolic syndrome	3.34	1.28–8.70	0.013

All the covariates were entered simultaneously into the regression model

[a] 30-item Geriatric Depression score >11

[b] Angiotensin-converting enzyme inhibitors

[c] Instrumental activities of daily living

regression model was analyzed among men, also after stratifying for age < or ≥80 years, by entering the single components of MetS (Table 6). Eventually, the variance inflation factors and condition index were calculated among men, to assess collinearity between the single components of MetS (Table 7).

Results

The main characteristics of participants according to the presence of MetS are depicted in Table 1. Excluded participants did not differ significantly from those included in the study by age, sex, or prevalent MetS.

MetS was found in 137/356 (38%) participants. Overall, participants with MetS, as compared with remaining subjects, showed no differences in the HUI3 score (Table 1). However, men aged 80+ with MetS, as compared with age-matched participants without MetS, had better quality of life scores (0.57 ± 0.34 vs. 0.39 ± 0.44; $p = 0.018$). MetS was more common in women (88/194) than in men (49/162; Fisher's exact test $p = 0.004$). C-reactive protein levels did not differ among men and women (0.70 ± 1.36 vs. 0.83 ± 1.82; $p = 0.523$).

Main characteristics of participants with and without MetS

Participants with MetS, as compared with other participants, reported less frequent consumption of alcohol ($p = 0.004$), and a more prevalent use of angiotensin-converting enzyme inhibitors ($p = 0.001$) and benzodiazepines ($p = 0.021$). Noticeably, participants with MetS had higher Charlson comorbidity score, as compared with remaining subjects ($p = 0.017$).

Multivariable analyses

Results of the initial age- and sex-adjusted regression models for demographics and lifestyle habits, comorbid conditions, medications, and objective tests, groups of variables are depicted in the left ("age- and sex-adjusted") columns of Table 2.

In the initial linear regression models, age, sex, MetS, education level, current alcohol consumption, diagnosis of

Table 5 Association (*B* coefficients, and 95% confidence intervals, CI) between the perceived quality of life score and the metabolic syndrome according to the fully adjusted linear regression model in men, after stratifying for age

	Age <80 years ($n = 85$)			Age ≥80 years ($n = 69$)		
	B	95% CI	*p*	*B*	95% CI	*p*
Age (each year)	0.09	0.07 to 0.11	<0.0001	−0.01	−0.04 to 0.01	0.231
Education (each year)	0.01	−0.02 to 0.03	0.673	−0.01	−0.02 to 0.02	0.941
Current alcohol consumption	−0.01	−0.15 to 0.14	0.945	−0.06	−0.20 to 0.09	0.444
Chronic pulmonary disease	0.04	−0.15 to 0.22	0.698	0.03	−0.13 to 0.19	0.710
Diagnosis of depression[a]	−0.20	−0.39 to −0.01	0.035	−0.15	−0.31 to 0.01	0.064
Corticosteroids	−0.20	−0.65 to 0.26	0.393	0.39	−0.21 to 0.99	0.203
ACE-I[b]	0.15	−0.20 to 0.49	0.397	0.09	−0.23 to 0.42	0.559
IADL[c]	0.06	0.02 to 0.09	0.005	0.06	0.03 to 0.09	0.000
Metabolic syndrome	0.16	−0.02 to 0.35	0.081	0.17	0.01 to 0.32	0.035

All the covariates were entered simultaneously into the regression models

[a] 30-item Geriatric Depression score >11

[b] Angiotensin-converting enzyme inhibitors

[c] Instrumental activities of daily living

Table 6 Association (*B* coefficients, and 95% confidence intervals, CI) between the individual components of the metabolic syndrome and perceived quality of life, according to the fully adjusted linear regression model, among men

	All men ($n = 162$)			Age <80 ($n = 93$)			Age ≥80 ($n = 69$)		
	B	95% CI	*p*	*B*	95% CI	*p*	*B*	95% CI	*p*
Abdominal obesity	0.10	−0.04 to 0.24	0.174	0.01	−0.19 to 0.20	0.955	0.15	−0.01 to 0.31	0.072
Hypertriglyceridemia	0.09	−0.05 to 0.23	0.218	0.18	−0.03 to 0.39	0.099	0.05	−0.10 to 0.21	0.497
Low HDL–cholesterol	0.08	−0.08 to 0.25	0.331	0.01	−0.21 to 0.22	0.968	−0.05	−0.28 to 0.18	0.677
High blood pressure	0.01	−0.15 to 0.17	0.903	−0.02	−0.22 to 0.18	0.847	0.06	−0.16 to 0.27	0.598
High fasting blood glucose	0.06	−0.08 to 0.20	0.421	−0.02	−0.20 to 0.17	0.860	−0.01	−0.18 to 0.17	0.958

All the covariates were entered simultaneously into the models

Adjusted for age, education level, alcohol consumption, chronic pulmonary disease, diagnosis of depression, use of corticosteroids and angiotensin-converting enzyme inhibitors, and instrumental activities of daily living

Table 7 Collinearity diagnostics (variance inflation factors (VIF), and condition index) between the individual components of the metabolic syndrome and perceived quality of life, among men

	All men ($n = 162$)		Age <80 ($n = 93$)		Age ≥80 ($n = 69$)	
	VIF	Condition index	VIF	Condition index	VIF	Condition index
Abdominal obesity	1.11	2.10	1.22	2.07	1.10	2.15
Hypertriglyceridemia	1.08	2.45	1.19	2.26	1.04	2.40
Low HDL–cholesterol	1.06	2.61	1.08	2.65	1.09	2.72
High blood pressure	1.05	2.65	1.11	2.84	1.04	2.80
High fasting blood glucose	1.03	5.78	1.02	5.15	1.08	7.00

chronic pulmonary disease and depression, use of corticosteroids and angiotensin-converting enzyme inhibitors, and the instrumental activities of daily living score were all associated with the HUI3 score at a $p < 0.050$ level (Table 2). After simultaneously adjusting for all these potential confounders in the summary model (Table 2, right columns), MetS was not statistically associated with the HUI3 score in the whole population ($B = 0.07$, 95% CI = −0.01–0.15; $p = 0.072$). When this fully adjusted regression model was analyzed after stratifying for sex, MetS was associated with higher HUI3 score ($B = 0.19$, 95% CI = 0.06–0.32; $p = 0.006$) in men (Table 3); no

significant associations were found ($B = -0.01$, 95% CI = −0.11–0.09; $p = 0.811$) in women (Table 3). Also, logistic regression modeling showed that MetS was associated with an HUI3 score above the median value in men (OR = 3.34; 95% CI = 1.28–8.70; $p = 0.013$) (Table 4).

Analyses of the interaction term indicated that consumption of alcohol did not affect the association between MetS and a HUI3 score above the median value in the whole population ($p = 0.468$), as well as in men ($p = 0.915$). Also, use of angiotensin-converting enzyme inhibitors did not affect such an association in the whole population ($p = 0.586$), as well as in men ($p = 0.216$). Eventually, use of benzodiazepines did not affect the association in the whole population ($p = 0.635$), as well as in men ($p = 0.276$).

Also, when the fully adjusted linear regression model was analyzed in men aged ≥ 80 (Table 5), MetS was statistically associated with the HUI3 score ($B = 0.17$, 95% CI = 0.01–0.32; $p = 0.035$); no significant association was found in younger men ($B = 0.16$, 95% CI = −0.02–0.35; $p = 0.081$). Analysis of the interaction term confirmed ($p = 0.006$) that the association of MetS with HUI3 varied according to age. Also, no significant associations were found in men between the HUI3 score and any of the single components of MetS, even after stratifying for age below or above 80 years (Table 6). Eventually, collinearity diagnostics indicated that no collinearity was in men between the HUI3 score and any of the single components of MetS (Table 7).

Discussion

The results of the present study indicate that MetS is not associated with worse HRQoL in community-dwelling elderly; in addition, MetS is associated with significantly better HRQoL among the oldest male subjects (Table 5).

Due to the aging of populations, the prevalence of MetS is increasing in Western countries [22]. In keeping with the hypothesized pathophysiology, which is chiefly based upon obesity-related insulin resistance with consequent hyperinsulinemia, this condition is associated with increased risk of diabetes, as well as accelerated atherosclerosis with ensuing complications, including peripheral vascular disease, stroke, and myocardial infarction [4, 5]. Such complications are known to affect HRQoL, in addition to survival and functional ability [23]. Knowledge of the effects of diseases and treatments on patients' HRQoL is crucial for clinical decision making, as well as for resource allocation, as any interventions in the field of health and social functioning must have self-assessed, preference-based quality of life as the main outcome [6]. As stated by the Panel on Cost-Effectiveness in Health and Medicine conveyed by the US Public Health Service in 1993, HRQoL should be assessed using comprehensive, generic classification systems including preferences for a wide range of health states, based upon time-trade-off measurements, and generating "utilities" that can be used for cost-effectiveness calculations [24]. The Health Utilities Index Mark 3, which has been adopted in the present study, is among the classification systems approved by the Panel and is widely used in clinical studies, cost-effectiveness studies, and in population health surveys. Thus, our results are of interest for clinicians and decision makers, also because the cost-effectiveness ratio of preventive interventions for diabetes and cardiovascular disease in subjects with MetS has been found to depend heavily upon utilities that patients attribute to their health state [6].

Several studies have investigated the association between MetS and perceived HRQoL, as well as the possible confounders of such an association, such as gender [7–10]. Regarding the first issue, most previous studies, which involved selected populations of young- to middle-aged subjects, have indicated a reduced HRQoL among subjects with MetS [7–10]. Indeed, most of these studies adopted the SF-36 scale to measure HRQoL. This scale is objective, so it is not conceived, nor suitable, to assess the impact of pathological conditions (such as MetS) or treatments on self-assessed, preference-based HRQoL. Also, this scale yields separate scores for general and mental health; in some cases, MetS can show divergent associations with physical and mental HRQoL scores [25]. The issue of gender-related differences in the association of MetS with HRQoL is more complex, because results of previous studies are often conflicting. Intriguingly, some studies found that MetS was associated with reduced HRQoL among women, but not men; in general, among subjects with MetS, men referred higher HRQoL than women [8, 9]. Thus, the sex-related differences in the association between MetS and HRQoL in the present study add to existing evidence in this field. The determinants of such gender-related differences are unclear; according to some studies, it might be related to a stronger association of MetS with subclinical inflammation in women, as compared with men [26, 27]. Inflammation, in turn, might be associated through several pathophysiologic pathways to decreased HRQoL. However, in the present study, high-sensitivity C-reactive protein among participants with MetS did not differ according to sex. Rather, in our population, MetS has been found to be associated with depressive symptoms among women, but not in men [28]. This might contribute to the differences observed between sexes in the association of MetS with HRQoL, as affective status is included among the dimensions explored by the HUI3. Indeed, the most remarkable finding of this study, that was conducted in a whole, unselected older population,

beyond the lack of any significant overall association between MetS and HRQoL (Table 2), is the increased HRQoL among the oldest male participants with MetS (Table 3). These results might be included in the setting of the so-called "reverse epidemiology". This term refers to repeated observations of established risk factors in the general population having a paradoxically opposite predictive pattern in selected populations; for instance, obesity, increased serum cholesterol concentration, and higher blood pressure have been associated with decreased morbidity and mortality in subjects with heart failure or end-stage renal disease, as well as in older subjects [29]. In all these populations, that are characterized by a common condition of "frailty", the presence of obesity, hypertension, or high serum cholesterol levels are thought to reflect the absence of more powerful risk factors (such as malnutrition) that most commonly, and in a shorter term, might affect their health status and survival [29]. Therefore, frailty might represent the common determinant of the lack of association between MetS with a worse HRQoL, as well as with the selective association between MetS and better HRQoL in the present study. Participants in the present study were markedly older than those enrolled in previous studies; furthermore, the subgroup of subjects in whom MetS was associated with better HRQoL was beyond the life expectancy (around 77 years) of Italian men in 2004. Thus, the association of MetS with increased health-related HRQoL among the oldest male, as well as the loss of the predictive pattern of MetS for decreased HRQoL in the remaining participants, is likely to reflect the absence of competitive risk factors, such as hepatic dysfunction, malnutrition, or cachexia from chronic conditions. In particular, such competitive risk factors might have affected increased short-term mortality, while MetS might yield its effects on survival only over a longer time course. Therefore, selective survival might represent the key to understand our, as well as other similar findings of a reverse epidemiology.

The lack of association between HRQoL and the single components of MetS (Table 6) might reflect insufficient statistical power of the single items; indeed, in the multivariable analysis, the B coefficients of the single components seem to diverge, especially after stratifying for age. Of notice, no collinearity was found among the components of MetS (Table 7). Thus, our results support the current view that the clinical significance of MetS exceeds the arithmetic sum of its individual components.

An ineludible limitation of this study is represented by its cross-sectional design, which does not allow ascertaining any cause-effect relationship. However, independently of any underlying factors, the neutral or inverse association on MetS with HRQoL casts doubts on the routine screening and treatment of MetS beyond the age of 75 and suggests the need of a thorough revision of preventive interventions in the oldest age segments of populations [29]. In particular, the HUI3 score that we adopted to measure HRQoL has straight economical implications; according to the results of the present study, the cost-effectiveness ratio of interventions aiming at reversing MetS would be less favorable, or even unacceptable, in older populations.

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