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The metabolic syndrome and 10-year cognitive and functional decline in very old men. A population-based study

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ABSTRACT

Objectives: To describe longitudinal relationships of metabolic syndrome (MetS) to cognitive decline and functional disability in a sample of older non-institutionalized men.
Methods: data from 1991 to 2000 of the Italian cohorts of the Finland, Italy, the Netherlands, Elderly (FINE) study, were used. Global cognitive function and functional disability, defined as limitations in mobility, basic (ADLs) and instrumental activities of daily living (IADLs) were screened in 1991 and 2000. MetS was defined according to the NCEP ATP-III criteria.
Results: The study sample consisted of 195 men, baseline age 76.1 ± 3.1 years. Baseline MetS was prospectively associated with greater 10-year cognitive and functional decline in ADLs and IADLs. After multiple adjustment including age, education, marital status, ApoE ε4 allele, cerebrovascular disease and initial cognitive and depressive status, MetS predicted cognitive decline (B = −1.684, 95%CI = −2.202 to −1.167, $p < 0.001$) and risk of IADLs (OR = 1.09, 95% CI = 1.01–1.20, p = 0.048) and ADLs disability (OR = 1.35, 95%CI = 1.12–1.62, $p < 0.001$). Interestingly, such associations were not attributable to individual altered components of MetS nor to their sum. Incident disability in ADLs and IADLs were not explained by parallel decline in cognitive function.
Conclusions: MetS as an entity was associated with accelerated cognitive and functional decline in a population-based sample of very old men.

1. Introduction

Cognitive impairment, functional disability, and late-onset depression are major determinants of loss of healthy life in older people (Carriere et al., 2014; Kim & Feldman, 2015; Pan et al., 2012; Yaffe et al., 2007). As life expectancy grows fast, their prevalence within the general population will increase exponentially over the forthcoming years. Thus, identification of preventable and modifiable risk factors for such conditions is a major challenge. In this context the metabolic syndrome (MetS) is of particular interest. The MetS is a clustering of major cardiovascular (CV) risk factors including atherogenic dyslipidemia, hypertension, altered glucose homeostasis and abdominal obesity (Grundy, 2008). In parallel with the increasing prevalence of obesity, physical inactivity and poor dietary patterns, MetS has mounted to epidemic proportions in Westernized Countries, affecting around 25% of people in the general adult population and up to 40% of those ages 65 years and more (Grundy, 2008; National Cholesterol Education Program, 2001). MetS might predict risk of chronic disorders other than CV diseases (Carriere et al., 2014; Gorelick et al., 2011; Kim & Feldman, 2015; Pan et al., 2012; Viscogliosi, Chiriac, Andreozzi, & Ettorre, 2015a; Yaffe et al., 2007). Several pieces of evidence indicate a detrimental effect of MetS on global and domain-specific cognitive function (Kim et al., 2015; Siervo, Harrison, Jagger, Robinson, & Stephan, 2014; Viscogliosi et al., 2015a; Viscogliosi, Chiriac, Andreozzi, & Ettorre, 2015b; Yaffe et al., 2007). It has also been suggested, however, that there may be no association among oldest old individuals (Liu et al., 2013; Siervo et al., 2014). Instead, evidence of an association between MetS and loss of functional independency, defined as limitations in mobility, basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs), is currently very limited (Blazer, Hybels,& Fillenbaum, 2006; Carriere et al., 2014; Penninx et al., 2009; Stenholm et al., 2010), with most of population-based studies focusing on decline in mobility only (Blazer et al., 2006; Penninx et al., 2009; Stenholm et al., 2010). Furthermore it remains unclear whether, if any, the longitudinal relationship of MetS to functional decline is independent of concomitant impairment in cognitive

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function. The aims of the present study were: to describe 10-year relationships of MetS to functional and cognitive decline in a sample of very old men; to assess whether the association with functional decline was not attributable to cognitive decline; to assess whether such associations were attributable to MetS as an entity rather than driven by specific altered MetS components and/or MetS severity, i.e. the sum of MetS components. For our purposes, we used data from the Italian cohorts of the population-based Finland, Italy, The Netherlands, Elderly (FINE) study.

2. Materials and methods

2.1. Study population

The FINE study started in 1985 as a continuation of the Seven Countries Study, focusing on older men born between 1900 and 1920 (Giampaoli et al., 1999; Menotti et al., 2001). The Italian survey was conducted in two rural areas in central Italy (Montegiorgio and Crevalcore). The ethics committee of the National Institute of Health approved the study protocol; written informed consent was obtained from all participants. For the purposes of this study we considered data collected in 1991 as baseline and those in 2000 as endpoint. More information about the FINE study, its populations and variables collection are better described elsewhere (Giampaoli et al., 1999; Menotti et al., 2001).

2.2. Baseline covariates

Information on prevalence of coronary heart disease (myocardial infarction and angina), cerebrovascular disease (stroke and transient ischemic attack), diabetes mellitus, chronic obstructive pulmonary disease (COPD) and osteoarthritis was collected using standardized questionnaires and clinical examination, and verified by written information from general practitioners or hospital discharge diagnoses. MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria (National Cholesterol Education Program, 2001), as the presence of three or more of: adverse blood pressure (systolic $\geq$ 130 mmHg or diastolic $\geq$85 mmHg and/or antihypertensive treatment); adverse fasting serum triglycerides ($\geq$ 150 mg/dl); adverse fasting plasma glycemia ($\geq$110 mg/dl and/or diabetes history and/or antidiabetic medications); adverse serum HDL-cholesterol (<40 mg/dl); abdominal obesity (waist circumference >102 cm). Depressive symptoms were assessed using the Zung self-rated depression scale, whose details are described elsewhere (Zung, 1965). This is a 20-item scale exploring different dimensions of depression. Comprehensive scores range 25–100, the higher the score the higher the depression severity. Baseline depressive symptoms level was used as confounding variable. Unfortunately, we were unable to analyze trajectories of depressive symptoms from 1991 to 2000, as depressive symptoms were not assessed in 2000.

2.3. Disability and cognitive function

A self-administered short form of the World Health Organization (WHO) scale (Giampaoli et al., 1999), was administered to assess functional disability. Three domains were assessed: mobility (4 items: moving outdoors, climbing stairs, walking at least 400 m, carrying heavy objects), activities of daily living (ADLs) (6 items: walking from one room to the other, self-feeding, getting in and out of bed alone, using the toilet, washing and taking a bath, dressing and undressing) and instrumental activities of daily living (IADLs) (3 items: cooking own food, doing light housework, doing heavy housework). Level of difficulty in performing each activity was coded as: 1) unable to perform; 2) some help needed; 3) with difficulty but without help; 4) without any difficulty. Categories 1 and 2 identified disability in the specific tasks. Global cognitive function was evaluated using the Folstein's Mini-mental State Examination (MMSE) test, the best validated instrument to screen global cognitive function in older people (Folstein, Folstein, & McHugh, 1975). MMSE score ranges from 0 to 30, the lower the score the greater the cognitive impairment.

2.4. Outcomes of interest

10-year incidence of disability in mobility, ADLs and IADLs was defined as being dependent in one or more indicator of activity limitation in 2000, in the absence of such limitation at baseline. Cognitive decline was expressed as a continuous variable, defined as 10-year change in MMSE score, calculated as the difference between MMSE score in 2000 and baseline score.

2.5. Statistical analysis

All analyses were performed via Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) version 20.0 for Windows. Baseline characteristics of participants were compared according to the presence of MetS using the Student's unpaired *t*-test or $\chi 2$-test as appropriate. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Univariate associations between baseline variables with cognitive decline and incident disability were explored by regression models adjusted for baseline age of participants, education and marital status. In particular, marital status was forced as covariate due to the great impact of such variable on late-life wellness (Hoppmann & Gerstorf, 2009). Further, multiple regression models were constructed to assess whether MetS independently predicted longitudinal changes in MMSE score and incident disability. We further assessed the extent to which any prospective association of MetS was driven by the sum of its components. Statistical significance was set at 2-sided *p*-values at $\leq$0.05.

3. Results

427 men were studied in 1991 as part of the Italian survey. 11 were not considered because they gave no information on disability status or cognitive function. Of the 416 subjects considered in 1991, 195 were re-examined in 2000: 165 had died and 56 missed the interview in 2000. Men who died or were lost to follow up had similar prevalence of MetS as compared with our study population (27.1% vs 24.6%, $\chi 2 = 0.36$, $p = 0.661$). As shown by Table 1, participants with baseline MetS (n = 48, 24.6% of the sample) were less educated and had greater depressive symptoms when compared to those without. No differences were observed in cognitive function and disability status. Overall, 10-year incidence of ADLs and IADLs disability were respectively 67.2% and 68.0%. Incidence of IADLs disability was assessed in 138 participants, that were those free of such limitation at baseline. Since almost all participants (96.0%) presented mobility limitations in 2000, incident disability in mobility was not analyzed. 10-year MMSE points loss was significantly greater in participants with MetS. Table 2 shows univariate logistic models controlled for age, education and marital status. Both MetS and the number of its components were associated with cognitive decline, IADLs and ADLs disability, whereas none of the individual components of MetS was. Table 3 shows proportion of cognitive decline and incident disability in ADLs and IADLs by baseline MetS status. Multiple logistic models predicting decline in cognition, ADLs and IADLs were constructed entering variables showing significant associations with at least one of the three outcomes by univariate models. As shown by Table 3, baseline MetS significantly predicted greater risk of cognitive decline, IADLs and ADLs disability. Of note,