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Short report

The role of frailty in explaining the association between the metabolic syndrome and mortality in older adults

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ABSTRACT

The association between the metabolic syndrome (MetS) and adverse outcomes in older adults may be explained by other health conditions. This study examined the role of frailty in explaining the association between MetS and mortality, independent of comorbidity. Data were used from 1247 men and women aged ≥65 years of the Longitudinal Aging Study Amsterdam. MetS was assessed using the definition of the US National Cholesterol Education Program. Frailty was measured by the frailty phenotype. Mortality was monitored from 1995 until 2015. Associations of MetS with 19-year all-cause mortality were assessed using Cox proportional hazard models. MetS was present in 37% of the participants. In a model adjusted for age, sex and educational level hazard ratios of mortality were significantly higher in people with MetS (HR = 1.23, 95% CI = 1.08–1.40). After adjusting for frailty the association of MetS with mortality reduced, but remained statistically significant (HR = 1.15, 95% CI = 1.01–1.31). The presence of chronic diseases (cardiovascular diseases and diabetes) explained a larger part of the relationship between MetS and mortality (HR = 1.12, 95% CI = 0.98–1.28). These results show that physical frailty has a smaller contribution to the explanation of the association between MetS and 19-year all-cause mortality than the presence of chronic diseases.

1. Introduction

The metabolic syndrome (MetS) is a combination of risk factors for type 2 diabetes and cardiovascular events. A large body of evidence relates MetS with the risk of premature death (Scuteri et al., 2005; Wang et al., 2007). Gaining insight into pathways leading from MetS to mortality is imperative for the development of preventive strategies. Previous research showed that diseases, and in particular cardiovascular disease, play an important role in the association between MetS and mortality (Mozaffarian et al., 2008). Another factor that may be important is physical frailty. Frailty is a condition that involves physiological alterations leading to an increased vulnerability to external stressors (Fried et al., 2001; Clegg et al., 2013). A greater degree of frailty is related to a higher mortality risk and other adverse outcomes (Dent et al., 2016). Older individuals with MetS and diseases such as type 2 diabetes, cardiovascular disease or obesity are more often frail (Blaum et al., 2005; Hubbard et al., 2010; Viscogliosi, 2016). Furthermore, MetS has recently been linked to incident frailty (Viscogliosi et al., 2016). However, the role of frailty in the relationship between MetS and mortality is unknown. If frailty is a mediating factor in the pathway from MetS to mortality, it may be an important marker for identifying high-risk individuals.

The purpose of this study was to examine the role of frailty in explaining the association between MetS and all-cause mortality in a cohort of community-dwelling older adults, and to investigate whether its contribution to the explanation is independent of comorbidity.

2. Methods

2.1. Study sample

Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing study on physical, emotional, cognitive, and social functioning of older adults in the Netherlands. Details on cohort sampling and data collection have been described elsewhere (Hoogendijk et al., 2016a). In short, a nationally representative survey was conducted in 1992–1993 among 3107 respondents aged 55–84 years. Follow-up measurements are collected approximately every three years. Data are collected in a main interview and a medical interview by trained interviewers who visit the respondents at home. In 1995–1996, the medical interview was followed by the collection of blood samples. All participants signed an informed consent. The study received approval by the medical ethics committee of the VU University Medical Center.

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For the current study, we used data from the second LASA measurement wave (1995–1996). Of 1722 respondents aged ≥65 years with valid data from the main interview, 1509 participated in the subsequent medical interview (87.6%). We excluded participants with no blood sample ($N = 181$), and missing data on MetS or frailty items ($N = 81$). This resulted in an analytic sample of 1247 respondents.

2.2. Metabolic syndrome

MetS was measured at baseline, and was defined as the presence of three or more of the following criteria: triglycerides 1.7 mmol/l (150 mg/dl); HDL cholesterol <1.0 mmol/l (40 mg/dl) for men and <1.3 mmol/l (50 mg/dl) for women; blood pressure 160/90 mm Hg or antihypertensive medication; waist circumference > 102 cm for men and >88 cm for women; and fructosamine 0.247 mmol/l or antidiabetic medication. This is the definition established by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (JAMA, 2001), with an increased cut-off for blood pressure, adjusted for an older population. Fructosamine was used instead of glucose because we could not guarantee fasting blood samples.

2.3. Frailty

Frailty was assessed at baseline using the criteria of the frailty phenotype: weight loss, weak grip strength, exhaustion, slow gait speed and low physical activity (Fried et al., 2001). We used the original variables and cut-offs, except for gait speed and physical activity. For those measures the lowest quintile approach was used (Saum et al., 2012). This slightly modified frailty phenotype has been successfully applied before in LASA (Hoogendijk et al., 2016a; Hoogendijk et al., 2014; Hoogendijk et al., 2016b). Weight loss was present if a participant lost 5% or more body weight in the previous 3-years (i.e., current weight compared with the weight in the previous LASA measurement wave). Body weight was measured using a calibrated bathroom scale, with the participants wearing underclothing only. Grip strength was assessed with a handheld dynamometer (Takei TKK 5001, Takei Scientific Instruments, Tokyo, Japan). It was measured in a standing posture with the elbow extended (or seated when the participant was not able to stand). The sum of the highest values of two measurements on each hand was used, and original cut-off points stratified by sex and body mass index were applied to indicate weak grip strength. Exhaustion was measured using two items from the Center for Epidemiologic Studies Depression Scale (CES-D). Gait speed was assessed by recording the time taken (in seconds) to walk 3 m, turn around, and walk the 3 m back as quickly as possible. Slow gait was defined by the lowest quintile, stratified by sex and height. Finally, low physical activity was defined by the lowest quintile of average time spent on physical activities per day during two weeks before the interview, based on the LASA Physical Activity Questionnaire (LAPAQ). Participants were considered frail if three or more criteria were present (Fried et al., 2001).

2.4. Chronic diseases

Seven major chronic diseases were assessed at baseline by self-report. Respondents were asked whether they currently or previously had one of the following chronic diseases: cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, chronic nonspecific lung disease (asthma and chronic obstructive pulmonary disease), cancer, and arthritis (rheumatoid arthritis or osteoarthritis).

2.5. Covariates

Covariates included age (in years), sex and educational level (9-category scale).

2.6. Mortality

All-cause mortality status was retrieved from registers of the municipalities where respondents were living. All deaths that occurred between the baseline measurement and July 1, 2015, were recorded (99.8% ascertainment for the current sample).

2.7. Statistical analyses

First, we tabulated baseline characteristics according to MetS status. Differences between groups were determined using Chi square tests and *t*-tests. Second, to evaluate the association of MetS, frailty and chronic diseases with 19-year all-cause mortality, Cox proportional hazard models were fitted, adjusted for age, sex and educational level. Survivors were censored at the end of the follow-up (July 1, 2015). Interaction effects of MetS with frailty and chronic diseases were tested, but there were no signs of effect modification. Finally, to study the association of MetS with mortality and the role of potential mediators, we fitted four models. Model 1 adjusted for socio-demographics: age, sex and educational level. In Models 2 and 3, the degree of frailty and chronic diseases were separately introduced into the first model. Model 4 included all variables of the previous models. To examine the role of frailty, a percentage reduction in hazard ratio (HR) from Model 3 was computed by (HR model 3 − HR model 4) / (HR model 3–1) × 100. We performed the data analysis using IBM SPSS Statistics 23 (SPSS Inc. Chicago, Illinois), and all p-values are 2-sided.

3. Results

Among 1247 LASA respondents, 462 (37%) had MetS at baseline, and 146 (11.7%) were defined as frail. The presence of MetS was significantly associated with female gender, lower education level, frailty, and chronic diseases (Table 1). During 19 years of follow-up, 982 persons died (78.7%). The median survival time was 11.6 years. The presence of MetS was significantly associated with 19 year all-cause mortality risk (HR = 1.23, 95% CI = 1.08–1.40) (Table 2). Since frailty, cardiovascular diseases and diabetes were significantly associated with both MetS and mortality (results not shown), they were considered as mediators.

Table 1
Baseline characteristics by metabolic syndrome status.

Baseline characteristics	Total $N = 1247$	No MetS $N = 785$	MetS $N = 462$	p-value[a]
Age (years), 65–88, mean (SD)	75.4 (6.5)	75.2 (6.5)	75.6 (6.5)	0.25
Sex, % women	51.3	47.6	57.6	0.001
Educational level, 1–9				
Low (1–2), %	41.2	36.7	48.9	<0.001
Medium (3–4), %	30.6	31.8	28.4	
High (5–9), %	28.2	31.5	22.7	
MetS components				
High triglycerides, %	31.2	10.6	66.4	<0.001
Low HDL cholesterol, %	35.9	12.8	75.5	<0.001
Hypertension, %	63.5	50.3	85.9	<0.001
Abdominal obesity, %	52.3	35.0	81.6	<0.001
Hyperglycemia, %	25.1	14.6	42.9	<0.001
Frailty status, % frail	11.7	8.8	16.7	<0.001
Chronic diseases				
Cardiac disease, %	26.7	22.7	33.5	<0.001
Peripheral atherosclerosis, %	12.5	9.7	17.3	<0.001
Stroke, %	7.3	5.0	11.3	<0.001
Diabetes, %	8.0	3.4	15.8	<0.001
Lung disease, %	15.1	15.9	13.9	0.35
Cancer, %	12.0	11.5	13.0	0.43
Arthritis, %	47.6	46.1	50.0	0.19
Number of diseases, 0–7, mean (SD)	1.3 (1.1)	1.1 (1.0)	1.5 (1.2)	<0.001

[a] Chi square test and *t*-tests.