Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

# Metabolic syndrome and mortality in the elderly: A time-dependent association

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ARTICLE INFO

*Article history:*
Received 22 June 2012
Received in revised form
1 November 2012
Accepted 8 November 2012
Published on line 30 November 2012

*Keywords:*
Metabolic syndrome
All-cause mortality
Cause-specific mortality
Blue Mountains Eye Study
Time-dependent

ABSTRACT

*Aims:* To evaluate the association between metabolic syndrome (MetS) components and mortality over time.

*Methods:* 3086 residents aged ≥49 years were followed in the Blue Mountains Eye Study, Australia. MetS components as defined by the International Diabetes Federation criteria were measured at baseline (1992–1994), 5-year (1997–1999) and 10-year (2002–2004). Using Cox proportional hazards and competing risks models with MetS as a time-dependent covariate, we estimated the effects of MetS on all-cause and cause-specific mortality. Time-dependent receiver-operating-characteristic curve, integrated-discrimination-improvement and net-reclassification-improvement tests assessed predicting abilities of individual and combined MetS components.

*Results:* Effect of MetS on mortality increased with time: all cause: 2-year: adjusted hazard ratio 0.96 [95% confidence interval 0.69–1.34]; 5-year: 1.06 [0.84–1.32]; 10-year: 1.23 [1.01–1.51]; and CHD: 2-year: 0.46 [0.20–1.03]; 5-year: 0.70 [0.41–1.21]; 10-year: 1.62 [1.02–2.59]. Conversely, MetS was associated with an increased risk of cancer death at 2-year only: 1.62 [1.01–2.62]; but not 5-year: 1.30 [0.94–1.81] or 10-year: 0.90 [0.57–1.44]. The discrimination analyses showed that different MetS components were associated with different causes of death.

*Conclusions:* The long-term effect of MetS on all-cause and CHD mortality in an older population was detected using time-dependent models while simulating the real scenarios of MetS changes over time.



## 1. Introduction

Metabolic syndrome (MetS) was first described in the 1920s as the clustering of hypertension, hyperglycemia and gout [1], with current definitions, namely European Group for the Study of Insulin Resistance (EGIR), World Health Organisation (WHO), Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-3), and the International Diabetes Federation (IDF) [2], including components of obesity,

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0168-8227/$ – see front matter 
http://dx.doi.org/10.1016/j.diabres.2012.11.005

insulin resistance, dyslipidemia and hypertension [1]. In middle-age populations, the adverse effect of Mets on morbidity and mortality has been established [3–5], but the utility of MetS in predicting mortality amongst the elderly is doubtful. First, underweight elderly populations may be predisposed to an increased risk of mortality [6,7]. Secondly, some MetS components, namely hypertriglyceridemia and diastolic blood pressure (BP), are not clearly related to poor health outcomes later in life [8,9]. Furthermore, the cut-off point for individual MetS components may not be appropriate for predicting mortality in the elderly population, since these distributions were often characterized in middle-age populations [10].

While many studies have examined the relationship between MetS and mortality, there are still key unanswered questions. First, the relationship between MetS with all-cause and cause-specific mortality remains unclear. Some studies showed MetS to be a predictor of all-cause [11,12] and coronary heart disease (CHD) mortality [11–13], whereas other studies demonstrated no effects of MetS on all-cause [14,15], CHD [14,15] or cardiovascular disease (CVD) [12,14,15] deaths in the elderly. Although MetS was found to predict cancer death in some studies [13,16], this relationship was not evident in one study [12].

Second, individual MetS components may have different effects on mortality. While hypertension [17], hyperglycemia [11,13,17,18], low HDL [11,13,18] and high triglyceride levels [12] have been shown to predict all-cause and CVD-death, there is inconsistency with regards to which of these MetS components better predicts mortality. Third, it remains unclear whether MetS as a whole or its individual components provide a better prediction of all-cause and cause-specific mortality [19,20]. Finally, no studies have clarified whether earlier or most updated status of MetS best predicts all-cause and cause-specific mortality.

In this study, we evaluated the effect of MetS and its components on subsequent all-cause and cause-specific mortality in an older Australian population. We fully utilized the information on MetS collected at baseline, 5-year and 10-year visits to unravel the relationship between MetS and mortality, and to determine whether this association changes with time.

## 2. Materials and methods

### 2.1. Study design

The Blue Mountains Eye Study (BMES) is a population-based cohort study of vision, common eye diseases and other health outcomes of a suburban population in the west of Sydney, Australia [21]. Between 1992 and 1994, non-institutionalised permanent residents aged 49 years and older were invited to participate in this study, and were requested to return for follow-up examinations at 5-year (1997–1999) and 10-year (2002–2004). We included 3086 participants at baseline who had complete information for the study factors. The BMES was approved by the Human Research Ethics Committee of the University of Sydney and conducted according to the Helsinki Declaration. Written informed consent was obtained from all participants at each examination. Recruitment details have been previously described [21].

### 2.2. Exposure measurements

At each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, smoking status, eye and general medical history including hypertension, diabetes, and pre-existing diseases (namely, cancer, angina, acute myocardial infarction (AMI), stroke and chronic lung disease) as well as medication used. Height, weight and seated BP [22] were measured. Fasting pathology tests, including total cholesterol, HDL cholesterol and triglycerides [23] and fasting plasma glucose (FPG) [24], were also measured within a month of each interview.

### 2.3. Definition of metabolic syndrome

It has been reported that EGIR, WHO and ATP-3 definitions for MetS were not as successful in predicting diabetes and cardiovascular disease as compared to IDF definition [2]. Thus, in this study, we define MetS based on the IDF criteria. This is a diagnostic tool for both research purpose and clinical practice and can be used relatively easily in any country by any physician to identify patients at increased risk of developing health related outcomes. Moreover, studies have suggested that the IDF criteria is more reliable for diagnosing MetS in predictive model for coronary clinical status in type 2 diabetes populations [2,25].

MetS was defined according to the IDF criteria [2] as obesity (i.e. body mass index (BMI) $>30\ kg/m^2$) plus any two of the following four factors: serum triglyceride level $\geq 1.7$ mmol/L or specific treatment for this lipid abnormality; serum HDL cholesterol $<1.03$ mmol/L in men and $<1.29$ mmol/L in women, or specific treatment for this lipid abnormality; systolic BP $\geq 130$ mmHg or diastolic BP $\geq 85$ mmHg, or treatment of previously diagnosed hypertension; or FPG $\geq 5.6$ mmol/L, or previous diagnosis or specific treatment for type 2 diabetes.

### 2.4. Mortality

Deaths occurring between the baseline examination (1992–1994) and 31 December 2007 were confirmed by matching the demographic information of the participants with the Australian National Death Index (NDI), using probabilistic record linkage [26]. The causes of death were provided by the NDI using the International Classification of Diseases (ICD) 9th revision and the International Statistical Classification of Diseases, 10th revision. For example, ICD-9 codes 430.0–438.9 and ICD-10 codes 160.0–169.9 were classified as stroke-related deaths, whereas ICD-9 codes 410.0-9, 411.0-8, 412, 414.0-9, and ICD-10 codes 121.0-9, 122.0-9, 123.0-8, 124.0-9, 125.0-9 were classified as cardiovascular related deaths. The sensitivity and specificity of the Australian NDI have been estimated as 93.7% and 100% for all deaths, and 92.5% and 89.6% respectively, for cardiovascular deaths [26].