

**Title : METABOLIC SYNDROME, ITS COMPONENTS AND MORTALITY IN THE ELDERLY**

**Short Title :** *MetS & mortality in the elderly*

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Table in online appendix.

**Precis:** FPG-component potentiates the excess mortality risk associated with lipid abnormality, suggesting a causal impact of the multi-component MetS on mortality in the elderly

## ABSTRACT

**Context and Objective:** The metabolic syndrome (MetS) has been shown to predict mortality in the middle-aged, but less is known on the impact of MetS and its components on mortality risk in the elderly. Our objectives were (1) to examine the association of MetS with the risk of all-cause and cause specific mortality in a French elderly community-dweller cohort; (2) to determine the main components driving these associations.

**Participants and Methods:** Prospective analyses were carried out on 7118 men and women aged 65 and over from the Three-City cohort. Association between MetS (defined using the NCEP-ATP III criteria) and mortality risk over the 7-year follow-up was assessed using Cox proportional hazards models.

**Results:** After adjusting for socio-demographic variables, health behaviors and health status, a 50 % increased risk for all-cause mortality was observed in participants with MetS at baseline compared to those without, hazard ratio 1.54 (95% CI 1.24, 1.92). Elevated fasting blood glucose (FBG), high triglycerides and low HDL-cholesterol were the major contributors to this association, acting synergistically on mortality risk. For coronary heart disease mortality and cancer mortality, the hazard ratios associated with MetS were 2.21 (95% CI: 1.07, 4.55) and 1.49 (95% CI: 1.04, 2.14), respectively.

**Conclusions:** By showing that an elevated FBG potentiates the excess mortality risk associated with lipid abnormality, our study supports the status of MetS as a risk factor for mortality in the elderly. Our findings emphasize the importance of MetS screening and managing dyslipidemia and hyperglycemia in older persons in general practice.

68 INTRODUCTION

69           The role of metabolic syndrome (MetS), defined as a cluster of metabolic abnormalities  
70 including obesity, hyperglycemia, dyslipidemia and hypertension, has been evidenced in the middle-  
71 age and pre-elderly (1-7). Its role in mortality of the elderly has been less explored and led to mixed  
72 results (8-12).

73           As MetS is comprised of multiple components, it remains unclear whether the relation  
74 between MetS and mortality in the elderly is attributable to the MetS as a whole, or driven by some  
75 specific MetS components. Furthermore, while elevated risk factor levels are common and  
76 increasingly treated in older populations, it is also important to determine whether the use of  
77 hypertensive, anti-diabetic and lipids lowering drugs modifies the association between MetS and  
78 mortality. To increase understanding on these issues, we aimed to investigate the association of MetS  
79 and each of its components with the risk of overall mortality and cause specific mortality over 7-year  
80 follow-up, in a large general elderly population by 1) assessing the impact of medication on the MetS-  
81 mortality risk 2) investigating whether the association is fully driven by some of the MetS  
82 components, or alternatively whether there is synergistic effect between the MetS components on  
83 mortality risk.

## PARTICIPANTS AND METHODS

Data came from the French multicentre prospective Three-Cities-Study including originally 9294 community-dwelling persons aged 65 years or older recruited from electoral rolls of three French cities from 1999 to 2001 (13). The study protocol was approved by the ethics committee of the University-Hospital of Bicêtre, France, and written informed consent was obtained from each participant. The present analyses were conducted on 7118 participants with complete data on mortality status, MetS, or any other covariates.

MetS was defined using the National Cholesterol Education Program Adult treatment Panel III criteria (14) based on the presence of 3 or more of the following: waist circumference: men (women) >102 (88) cm; serum triglycerides (TG):  $\geq 1.7$  mmol/L; HDL cholesterol: men (women) <1.04 (1.29) mmol/L; systolic/diastolic blood pressure:  $\geq 130$  mmHg /  $\geq 85$  mmHg ; fasting blood glucose (FBG):  $\geq 6.1$  mmol/L or presence of type 2 diabetes (assessed by the use of anti-diabetic treatment). Procedures of MetS components have been previously described (13). Mortality and cause of death were ascertained over the 7 years after the baseline examination. Information on the exact date and cause of death was obtained respectively from death registries and medical records (based on the International Classification of Diseases, version 10, ICD-10) (15). Mortality from cardiovascular disease (CVD) (ICD-10: I and R960 codes) coronary heart disease (CHD) (ICD-10: I20-25 and R960), stroke (ICD-10: I60-69), cancer (ICD-10: C) were analyzed (16).

The associations of MetS and its components with the risk of mortality were determined by Cox proportional hazards regression in which age (in years) during the study was used as the time axis, with left truncation at age of study entry. In addition to age, analyses were adjusted for sex, educational level (no or primary school/lower secondary/higher secondary /university degree), occupational grade (high grade/office-based /manual worker or housewife) and study center (model 1) and then additionally for marital status (living alone/married), smoking status (non/former/current smoker), alcohol consumption (no/moderate defined by  $\leq 3$  (2) glasses per day for men (women) /high: > 3(2) glasses per day for men (women)), dietary habits (intakes of fish : <1 /, 1-3 /  $\geq 4$  per week;

110 consumption of fruits and vegetables ( $<1$  /  $\geq 1$  per day), self-report history of vascular diseases, cancer  
111 and depression, BMI categories (normal:  $\text{BMI} < 25 \text{ kg/m}^2$  / overweight:  $25 \leq \text{BMI} < 30 \text{ kg/m}^2$  / obesity:  
112  $\text{BMI} \geq 30 \text{ kg/m}^2$ ), and cognitive impairment (Mini-Mental State Examination score  $< 24$ ) (model 2). All  
113 analyses were conducted using SAS software, version 9 (SAS Institute).  
114

## RESULTS

Characteristics of the 7118 participants included in the present analyses according to the presence of MetS are described in Table 1.

*Association between MetS and all-cause and cause-specific mortality risk.* Among participants who died over the 7-year follow-up ( $n=575$ , 8.1%), a higher prevalence of MetS was observed (21.2 % vs. 13.2% in participants still alive at the end of follow-up). After adjustment for potential confounders having MetS at baseline was associated with 55% increase in the risk of all cause mortality (HR=1.55, 95 % CI: 1.25-1.92). After taking into account the use of anti-diabetic, anti-hypertensive and lipids lowering drugs, MetS remained significantly associated with mortality risk (HR=1.49, 95 % CI: 1.19-1.86) (Online appendix). The mortality risk was even higher among participants with MetS and treated, compared to those without MetS and without MetS treatment (HR=1.96, 95% CI: 1.49; 2.57).

Regarding the cause specific mortality, MetS was significantly associated with mortality from cancer ( $n=218$ , HR=1.50, 95% CI: 1.04-2.15) and with mortality from CVD ( $n=133$ , HR=1.73, 95% CI: 1.12; 2.67) and CHD ( $n=43$ , HR =2.19, 95% CI: 1.06; 4.50) but not with mortality by stroke ( $n=27$ , HR=1.43, 95% CI: 0.50; 4.11).

*Association between MetS components and all cause mortality risk.* Of the five components, only high triglyceride (HR=1.31, 95% CI: 1.07-1.60), low HDL-cholesterol (HR=1.38, 95% CI: 1.09-1.76) and elevated FBG levels (HR=1.58, 95% CI: 1.29-1.95) were associated with significantly increased risk of all cause mortality after controlling for all potential confounders. After controlling for MetS status, the number of MetS components was not significantly associated with the risk of mortality (HR=1.13, 95% CI: 0.98; 1.29).

To examine whether the components of the MetS had an independent effect on mortality, we included all the 5 components of the MetS simultaneously in a model. A significant association with mortality was found for the elevated FBG component (HR=1.47, 95 % CI: 1.14-1.90) but not for the other MetS components. To assess whether the impact of FPG criteria on mortality risk is due to the elevated blood glucose or to the diabetic status (assessed by the use of anti-diabetic drugs), we performed a new analysis in which elevated blood glucose and use of anti-diabetic drugs were introduced separately in the same model. Our results showed that the significant association of FPG component of the MetS

was due to the anti-diabetic drugs (HR=1.96, 95 %CI:1.46-2.62) rather than the elevated blood glucose (HR=1.11, 95 %CI:0.85-1.46).

Furthermore, to assess whether the MetS - mortality risk association was mainly driven by the FBG, component, we examined the association between MetS and mortality risk after excluding the 875 participants with the elevated FBG component. MetS remained statistically associated with an increased risk of mortality (HR=1.58, 95%CI, 1.17-2.14). To examine the impact of MetS component on the MetS-mortality risk and to assess in which extent they would have a synergistic effect on mortality risk, we calculated the percent attenuation of the association after adding each individual component separately to a model already including MetS (Table 2). Elevated FBG attenuates the MetS-mortality risk by 37.7 %, while low HDL-cholesterol and high triglycerides attenuate it by 10.8% and 3.7% respectively). The percent of attenuation by including both elevated FBG and one of the lipid abnormalities was higher than the sum of the percent attenuation of each of these components alone, suggesting that elevated FBG potentiates the lipid abnormality risk of mortality (Table2). To further investigate this synergistic effect , we used a backward elimination approach that removed all of the 5-, 4-, 3-, and 2-way interaction terms with  $P > 0.05$  from a saturated model that included all of the MetS components and their interaction terms. Non-significant main effects were retained when interactions were significant.. A significant interaction ( $p=0.03$ ) was found between elevated FBG, high triglyceride and low HDL cholesterol. To quantify specifically the combined effects of these three components on all-cause mortality risk, a unique variable combining elevated FBG, high triglyceride, and low HDL cholesterol components was constructed we showed that participants with all these three components ( $n=113$ ) were at a greater risk of all cause mortality (HR=2.66, 95%CI:1.71-4.13) compared to those with none of these components.



## CONCLUSION

The present study, carried out over 7-year follow-up, in a large elderly general population provides an empirical argument to support MetS as a risk factor for all-cause mortality in the elderly. by showing evidence that specific components of MetS acted synergistically such that having elevated fasting blood glucose potentiates the impact of high triglyceride and low HDL-cholesterol on mortality risk. This predictive role of MetS on mortality risk was found to be independent of treatment for hypertension, dyslipidemia and hyperglycemia

The observed 50% excess risk of all-cause mortality associated with the MetS is in accordance with other prospective epidemiological studies conducted in Finnish (11), US (9) and Italian (12) elderly populations. Our findings on MetS components are also consistent with previous reports carried out on middle-aged or elderly population, suggesting the predictive association of elevated FBG (1-3, 5, 7, 9, 11, 12) and high triglyceride components (2, 7) with mortality risk. The supremacy of FPG over other MetS components in predicting mortality has been investigated, and our results suggest that the increased risk of mortality is associated with diabetes status (assessed by use of anti-diabetic drugs) but not with the elevated fasting blood glucose. In some studies, hypertension has been postulated to be a strong predictor of mortality (2, 3, 5, 9) whereas other studies emphasize the consistent association between obesity measures and mortality risk (17). We did not find an increased mortality risk associated with either condition. The overall high prevalence of hypertension in the elderly may be one explanation. There is also evidence that obesity is less marked a risk factor for mortality at older ages and among those with chronic conditions. Indeed, meta-analysis combining data from 40 cohort studies and including more than 250,152 patients with coronary artery disease, sustained the “obesity paradox” by showing that higher body mass index has been associated with reduced rather than increased mortality (18).

Several limitations should be noted: 1/ the limited number of CVD, CHD and stroke mortality events precluded any analyses on the impacts of MetS components on cause specific mortality risk. 2/ MetS was defined using the NCEP (ATPIII) criteria while other definitions also exist (19). 3/ in spite of extensive adjustments for a large range of socio-demographic, socio-economic and health

factors, with observational data the possibility remains that unmeasured confounders may partly explain part of the associations between MetS, its components and overall mortality.

Although the concept of MetS has been increasingly used by researchers and clinicians to identify individual predisposed to cardiovascular morbidity and mortality, the fact remains that MetS as an entity is an empirical concept (19) whose clinical utility is often challenged (20). In the present longitudinal and multicentre study, carried out in a large sample size of elderly subjects from the general population, the FPG component potentiates the excess mortality risk associated with lipid abnormality. Our finding strongly supports a causal impact of the multi-component MetS on mortality risk in the elderly and suggests that assessing MetS in clinical practice and ensuring the optimal management of the hyperglycemia or dyslipidemia in older subjects by the medical practitioner may help to delay age-related morbidity and mortality.

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210 co-wrote the initial and final drafts, and is guarantor. MK, MLA, TM, PBG, CT, JT, KR, and CB co-  
211 wrote the final draft. MK AND MLA participated equally to the work

212 FOOTNOTES

213 Abbreviations: 3C, Three City Study; BMI, body mass index; CI, confidence interval; CHD, coronary  
214 heart diseases; CVD, cardio-vascular diseases; FBG, fasting blood glucose; HDL, high density  
215 lipoprotein; HR, hazard Ratio ; ICD, International Classification of Diseases; MMSE, mini-mental  
216 state examination ; MetS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education  
217 program Adult Treatment Panel III;

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