Metabolic syndrome, its components, and mortality in the elderly.

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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.

MESH Keywords Aged ; Aged, 80 and over ; Blood Glucose ; Cholesterol, LDL ; blood ; Coronary Disease ; blood ; etiology ; mortality ; Female ; Health Behavior ; Health Status ; Humans ; Male ; Metabolic Syndrome X ; blood ; complications ; mortality ; Neoplasms ; blood ; etiology ; mortality ; Proportional Hazards Models ; Prospective Studies ; Risk ; Risk Factors ; Triglycerides ; blood

Author Keywords Metabolic syndrome ; Mortality ; Elderly ; Multi-centric prospective cohort

Introduction

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

As MetS is comprised of multiple components, it remains unclear whether the relation between MetS and mortality in the elderly is attributable to the MetS as a whole, or driven by some specific MetS components. Furthermore, while elevated risk factor levels are common and increasingly treated in older populations, it is also important to determine whether the use of hypertensive, anti-diabetic and lipids lowering drugs modifies the association between MetS and mortality. To increase understanding on these issues, we aimed to investigate the association of MetS and each of its components with the risk of overall mortality and cause specific mortality over 7-year

follow-up, in a large general elderly population by 1) assessing the impact of medication on the MetS-mortality risk 2) investigating whether the association is fully driven by some of the MetS components, or alternatively whether there is synergistic effect between the MetS components on 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): ≥1.7 mmol/L; HDL cholesterol: men (women) <1.04 (1.29) mmol/L; systolic/diastolic blood pressure: ≥130 mmHg/≥85 mmHg; fasting blood glucose (FBG): ≥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 ≤ 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/≥4 per week; consumption of fruits and vegetables (<1/≥1 per day), self-report history of vascular diseases, cancer and depression, BMI categories (normal: BMI <25 kg/m^2 /overweight: 25≤BMI<30 kg/m^2 /obesity: BMI≥30 kg/m^2), and cognitive impairment (Mini-Mental State Examination score < 24) (model 2). All analyses were conducted using SAS software, version 9 (SAS Institute).

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 perfumed 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 (Table 2). 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.

Ackowledgements:

Financial support : This work was carried out with the financial support of the « ANR- Agence Nationale de la Recherche - The French National Research Agency » under the « Programme National de Recherche en Alimentation et nutrition humaine », project « COGINUT ANR-06-PNRA-005». The 3C Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche

Médicale (INSERM), Victor-Segalen Bordeaux-2 University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux d'Aquitaine et Bourgogne, Fondation de France and Ministry of Research – INSERM Programme 'Cohortes et collections de données biologiques'. Mika Kivimäki is supported by the Academy of Finland, Finland, the BUPA Foundation, the UK, and the National Heart, Lung, and Blood Institute (R01HL036310-20A2) and the National Institute on Aging (R01AG034454-01), NIH, US.

Footnotes:

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The funders had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosure Statement: The authors have nothing to disclose.

Contributors: KR, PBG, CT, CB, MLA designed the study; TNA conducted the statistical analyses and co-wrote the initial and final drafts, and is guarantor. MK, MLA, TM, PBG, CT, JT, KR, and CB co-wrote the final draft. MK AND MLA participated equally to the work

Abbreviations

3C : Three City Study

BMI : body mass index

CI : confidence interval

CHD : coronary heart diseases

CVD : cardio-vascular diseases

FBG : fasting blood glucose

HDL : high density lipoprotein

HR : hazard Ratio

ICD : International Classification of Diseases

MMSE : mini-mental state examination

MetS : metabolic syndrome

NCEP-ATPIII : National Cholesterol Education program Adult Treatment Panel III

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Table 1
Characteristics of the 7118 Three City Study participants according to the presence of the metabolic syndrome at baseline.

		Metabolic Syndrome *		
		No (N=6134) % or m (SD)	**Yes (N=984) % or m (SD)**	**P**
Age (year)	(year)	73.5 (4.9)	73.8 (4.8)	0.10
Sex	Women	61.3	54.0	$<10^{-4}$
Marital status	Married/cohabited	66.0	65.0	0.53
Education	No qualification/primary school	32.0	37.1	0.002
	Lower secondary school	29.6	30.6	
	Higher secondary school	13.8	11.4	
	University degree	24.6	20.9	
Former occupational grade	Manual worker +housewife	29.5	34.6	
	Office based	50.4	46.8	$<10^{-4}$
	High grade	20.1	18.6	
Smoking habit	Never smoke	62.3	54.7	
	Former smoker	32.2	39.9	$<10^{-4}$
	Current smoker	5.5	5.4	
Alcohol intake *	No drinks	19.5	22.2	0.08
	Moderate: ≤ 3 (2) men (women)	63.2	59.8	
	High > 3 (2) men (women)	17.3	18.0	
Fruits and vegetables intake	Regular: (≥1/day)	93.4	92.4	0.29
Fish consumption	Rarely: <1/week	10.6	12.8	0.13
	Regular 1–3/ week	83.4	81.6	
	Often ≥ 4/ week	6.0	5.6	
	Normal	52.7	14.2	
BMI	Overweight	38.7	48.4	$<10^{-4}$
	Obesity	8.6	37.4	
Cognitive impairment in Mini Mental State Examination (score<24)		5.0	8.6	$<10^{-4}$
History of ischemic vascular diseases or stroke		15.4	21.3	$<10^{-4}$
History of cancer		0.5	0.3	0.43
History of depression		21.4	20.9	0.76
Use of anti-hypertensive drugs		41.5	64.1	$<10^{-4}$
Use of anti-diabetic drugs		2.9	26.9	$<10^{-4}$
Use of lipids lowering drugs		30.3	39.1	$<10^{-4}$
Metabolic syndrome components				
Central obesity criteria		20.2	76.2	$<10^{-4}$

High Triglycerides criteria	7.8	71.5	$<10^{-4}$
Low HDL Cholesterol criteria	4.4	44.2	<10-4
Hypertension criteria	76.4	94.3	<10-4
Elevated Fasting Blood Glucose criteria	5.5	54.7	<10-4

* Defined using the National Cholesterol Education Program (NCEP) criteria ([8]).

Table 2

Contribution of the lipid and glucose components of the metabolic syndrome (MetS)* to the association between MetS and mortality risk

	β	SE	Reduction in effect (%)‡
MetS basic model†	0.427	0.115	Ref.
MetS basic model additionally adjusted for			
High triglyceride component	0.411	0.139	3.7
Low HDL-C component	0.381	0.140	10.8
Elevated Glucose component	0.266	0.129	37.7
High triglycerides and Low HDL-C components	0.366	0.149	14.3
High triglycerides and Elevated glucose components	0.156	0.165	63.5
Low HDL-C and Elevated glucose components	0.189	0.145	55.7
High triglycerides, Low HDL-C and Elevated glucose components	0.094	0.175	78.0

* Defined using the National Cholesterol Education Program (NCEP) criteria ([8]).

† The effect of MetS on all-cause mortality adjusted for sex, age, centre, education level, occupational grade, marital status, smoking status, alcohol intake, dietary intakes (fruits, vegetables and fish), BMI categories, cognitive impairment, and history of vascular pathologies, cancer and depression

‡ To assess the weight of individual MetS components in the association with mortality, we calculated the percent attenuation in the MetS –all cause mortality association after adding each individual component separately to a model already including MetS. The percent attenuation in the association between the MetS and mortality risk was determined using the formula $\% = \{[(\beta_x - \beta_{x \text{ adjusted for w}})/\beta_x]\} \times 100$, where β is the coefficient estimated from the proportional hazards regression model.

Online Appendix

Association between MetS and risk of all-cause mortality over the 7-year of follow-up:

		Mortality risk		
		HR*	**95 % CI**	**p**
Metabolic syndrome	Yes vs. no	1.55	1.25; 1.92	$<10^{-4}$
Sex	Women vs. men	0.45	0.36; 0.57	$<10^{-4}$
Educational Achievement	Lower secondary vs. no or primary school	0.69	0.53; 0.89	0.005
	Higher secondary vs. no or primary school	0.98	0.77; 1.24	0.83
	University degree vs. no or primary school	0.74	0.55; 1.00	0.05
Study center	Bordeaux vs. Montpellier	1.04	0.81; 1.35	0.71
	Dijon vs. Montpellier	0.99	0.80; 1.23	0.92
Former occupational grade	high grade vs. office-based	0.92	0.78; 1.11	0.39
	high grade vs. manual worker/housewife	0.55	0.41; 0.72	$<10^{-4}$
Living alone	Yes vs; no	1.09	0.89; 1.33	0.39
Alcohol consumption	Moderate vs. no drink	0.80	0.64; 1.00	0.05
	High vs. no drink	0.79	0.59; 1.05	0.10
Smoking status	Former vs no	1.02	0.83;1.25	0.87
	Current vs. no	1.51	1.07;2.15	0.02
Fish Consumption	1–3 per week vs. <1	0.91	0.70;1.17	0.46
	≥4 per week vs. <1	1.08	0.72; 1.61	0.72
Fruit and Veg. consumption	≥1 per day vs. <1	0.90	0.67; 1.22	0.50
BMI categories	Overweight vs. normal	0.99	0.82; 1.19	0.88
	Obese vs. normal	0.99	0.76; 1.31	0.97
self-report history of vascular diseases	Yes vs. no	1.83	1.52; 2.19	$<10^{-4}$
Cognitive deficit	Yes vs. no	1.33	0.97; 1.81	0.07
self-report history of cancer	Yes vs. no	1.48	0.65; 3.37	0.35
self-report history of depression	Yes vs; no	1.07	0.86; 1.32	0.55

Results from the multivariate 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.

* HR were adjusted for all variables listed in the table.