Cardiovascular risk markers associated with the metabolic syndrome in a large French population: the SYMFONIE study

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SUMMARY

Objective: The SYMFONIE study was designed to analyze the clinical and biological characteristics, and the cardiovascular risk markers, in men and women with the metabolic syndrome compared to control subjects.

Research Design and Methods: The study population included 101,697 men and women, 18 to 80 years of age, who had a health checkup at the Centre d'Investigations Preventives et Cliniques (Paris, France) between 1997 to 2002. The metabolic syndrome was defined according to the ATPIII-NCEP 2001 criteria.

Results: Out of the 66,202 men (47.4±11.8 years) and 35,495 women (48.5±13.6 years) included in this population, 6761 men (10.2%) and 2155 women (6.1%) presented the metabolic syndrome. Among subjects ≤40 years of age, the prevalence of the metabolic syndrome was 5.0% in men and 2.2% in women, and rose to 14.1% and 12.0%, respectively, among men and women >70 years of age. After adjustment for age, patients with the metabolic syndrome presented higher pulse pressure (systolic minus diastolic blood pressure), higher heart rate, lower vital respiratory capacity, lower physical activity, an increase in inflammatory status assessed through leukocyte count and dental inflammation, hepatic abnormalities, and increased levels of stress and depression.

Conclusion: In this large French population, the prevalence of the metabolic syndrome is lower than in North American and northern European populations. Patients with the metabolic syndrome present several additional hemodynamic, inflammatory and psychological risk markers which could contribute to the poor cardiovascular prognosis of these subjects.

Key-words: Epidemiology · Metabolic syndrome · Inflammation · Pulse pressure · Heart rate · Psychosocial factors · Hepatic abnormalities.

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RÉSUMÉ

Facteurs de risque cardiovasculaire associés au syndrome métabolique dans une importante population française : l'étude Symfonie

Objectif : L'étude SYMFONIE a pour but d'étudier les caractéristiques cliniques et biologiques, ainsi que les facteurs de risque cardiovasculaire, chez des hommes et des femmes porteurs du syndrome métabolique comparés à des sujets témoins.

Population et méthodes : La population de l'étude était composée de 101 697 hommes et femmes, âgés de 18 à 80 ans, qui ont eu un bilan de santé standard au Centre d'Investigation Préventives et Cliniques (Paris, France) entre 1997 et 2002. Le syndrome métabolique a été défini selon les critères ATPIII-NCEP (2001).

Résultats : Parmi les 66 202 hommes (47,4 ± 11,8 ans) et 35 495 femmes (48,5 ± 13,6 ans), 6 716 hommes (10,2 %) et 2 155 femmes (6,1 %) présentaient un syndrome métabolique. Parmi les sujets de moins de 40 ans, la prévalence du syndrome métabolique était de 5,0 % chez les hommes et 2,2 % chez les femmes, pour atteindre respectivement 14,1 % et 12,0 % chez les hommes et les femmes de plus de 70 ans. Après ajustement sur l'âge, les patients avec le syndrome métabolique présentaient un pression pulsée (pression artérielle systolique-pression artérielle diastolique) plus élevée, une fréquence cardiaque plus haute, une capacité respiratoire plus faible, une activité physique moins importante, une augmentation de l'état inflammatoire évalué à partir du nombre de leucocytes et de l'état dentaire, une augmentation des anomalies hépatiques, et une augmentation de l'état de stress et de dépression.

Conclusion : Dans une importante cohorte française, la prévalence du syndrome métabolique est plus faible qu'en Amérique du Nord ou que dans les populations d'Europe du Nord. Les patients avec le syndrome métabolique présentent une augmentation de plusieurs facteurs hémodynamiques, inflammatoires et psychologiques qui pourraient expliquer leur risque cardiovasculaire élevé.

Mots-clés : Épidémiologie · Syndrome métabolique · Inflammation · Pression pulsée · Fréquence cardiaque · Facteurs psychologiques · Anomalies hépatiques.

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The Metabolic Syndrome (MetS) is defined as an association of risk factors which are an expression of a fundamental metabolic disorder known as insulin resistance. The definition of MetS has evolved from Reaven's description in 1988 to the National Cholesterol Education Program's (NCEP) definition, elaborated in 2001 [1], and which is widely used because it relates to clinical and biological variables used by general practionners. We used this definition to examine our large population that had a health checkup at the Centre d'Investigations Préventives et Cliniques (IPC Center) between January 1997 and December 2002. Numerous studies worldwide have confirmed that this definition is associated with increased risk of death. The classification of dysmetabolic patients based on the NCEP is associated with a well established increased risk of mortality, up to three times greater, as has been shown in different populations from northern Europe [2], Europe [3-4] and the U.S.A [5]. In France, few studies have focused on the prevalence of MetS [6], particularly among patients over 65 years of age. The aim of the present study, the SYMFONIE study (Syndrome Métabolique en France, ObservatioN, Intervention et Epidémiologie), was to assess the clinical and biological characteristics of men and women living in the Paris area, who suffered from MetS as defined by the NCEP guidelines. This study examined the prevalence and components of MetS, based on the NCEP 2001, among subjects who had a health examination at the IPC Center.

Research design and methods

Population

Subjects were examined at the IPC Center. This medical center, which is subsidized by the French national health care system (Sécurité Sociale-CNAM), provides all working and retired persons and their families with a free medical examination every five years. It is one of the largest medical centers of this kind in France, having carried out approximately 20-25 thousand examinations per year since 1970 for people living in the Paris area.

Our study population was composed of all subjects who had a health checkup between January 1997 and December 2002 and for whom all five of the criteria that define MetS were collected. The population included 66,202 men (47.4±11.8 years) and 35,495 women (48.5±13.6 years).

Supine blood pressure (BP) was measured in the right arm using a manual mercury sphygmomanometer, after a 10-minute-rest period. The first and the fifth Korotkoff phases were used to define systolic blood pressure (SBP) and diastolic blood pressure (DBP). The mean of three measurements was considered as the BP value. Pulse pressure (SBP-DBP) was also determined. Height (using a wall-mounted stadiometer) and weight (using calibrated scales) were recorded by a nurse. Waist perimeter was measured in the standing position by a trained nurse, using a tape measure placed at the smallest trunk circumference. Standard biological parameters were measured under fasting conditions and analyzed with an enzymatic method (automat HITACHI 917) or a colorimetric method for albumin dosage and hematology (ABX, Pentra 120). Resting electrocardiogram (ECG), provided heart rate measurements. Tobacco consumption (non smokers, ex-smokers, current smokers), physical activity (more than 2 hours of regular physical activity by week), personal medical history, and alcohol consumption (never, occasionally, several time per week, and daily) were assessed using a self-administered questionnaire [7]. Stress and depression scores were assessed with a validated self-administered questionnaire. The depression questionnaire was developed and validated by Pichot et al. [8] and the Stress questionnaire by Cohen et al. [9]. The score for depression corresponds to the sum of the answers to 13 dichotomic questions and the score for stress corresponds to the sum of the answers to 4 multiple choice questions (appendix). Respiratory capacity was measured in a sitting position with a Spyro analyser spirometer (ST200, Fukuda Sangyo) and a dental examination was performed by a dentist. All clinical and biological parameters were evaluated on the same day of the examination.

The IPC Center received authorization from the Comité National d'Informatique et des Libertés (CNIL) to conduct these analyses. All subjects gave their informed consent at the time of the examination.

Data analyses

The definition used for MetS was taken from the ATPIII, NCEP (2001) [1] and requires the association of three out of the five following criteria:

– abdominal (androïd) obesity with waist circumference >102 cm for men and >88 cm for women;
– high blood pressure with SBP ≥130 mmHg and/or DBP ≥85 mmHg and/or ongoing antihypertensive treatment;
– triglycerides ≥1.50 g/l;
– HDL cholesterol <0.40 g/l in men and <0.50 g/l in women;
– fasting glycaemia ≥1.10 g/l.

The prevalence of MetS was also calculated in different subgroups in which diabetes was defined as fasting glycaemia ≥1.26 g/l (7.0 mmol/l and/or anti-diabetic drugs), hypertension was defined as SBP >140 mmHg and/or DBP >90 mmHg and/or antihypertensive treatment, and obesity was defined as BMI≥30 kg/m^2.

Analyses were carried out separately in men and women. For quantitative parameters, multivariate analyses including age were used to compare subjects with MetS to those without MetS. Chi-square tests were used to compare the two groups for qualitative parameters. Logistic regression analyses were carried out to assess the risk [Odds-Ratio(OR)] of each of the MetS components in subjects with MetS

compared to subjects without MetS. All statistical analyses were carried out using the SAS statistical software package (version 8.02) [SAS institute, Cary, North Carolina, USA].

Results

Mean age in patients with MetS, by comparison with subjects without MetS, was higher for men (52±10 vs. 47±12 years, P<0.0001) and for women (55±12 vs. 48±14 years, P<0.0001). Consequently, all of the analyses were adjusted for age. All of the variables involved in the definition of the metabolic syndrome were higher in patients with MetS (data not shown).

The prevalence of MetS was 10.2% (n=6761) in men and 6.1% (n=2155) in women. In our study population, 30.7% of men and 45.4% of women were free of MetS components. A single abnormality was observed in 40.0% of men and 35.9% in women and two abnormalities were observed in 19.1% of men and 12.6% of women. As shown in figure 1 for men and figure 2 for women, the prevalence of MetS and its components increased with age. Among subjects ≤40 years of age, the prevalence of MetS was 5.0% among men and 2.2% among women, and rose to 9.9% and 5.2% at 41-50 years, 13.6% and 7.6% at 51-60 years, 15.1% and 10.0% at 61-70 years, and 14.1% and 12.0% >70 years of age, respectively, among men and women. High blood pressure clearly increases in prevalence with age in both genders. High blood pressure was the component most frequently found in both genders (58.5% in men, 44.6% in women), followed by high triglycerides (18.9% in men, 7.2% in women) and high waist circumference (12.1% in men, 14.7% in women).

In order to assess the impact of the different components which make up MetS, in patients with MetS compared to those without, a logistic regression analysis, after adjustment for age (figure 3), showed that the presence of elevated triglycerides [OR: 27.4 (95% CI 25.7-29.2) in men and 35.7 (32.1-39.7) in women], elevated waist circumference [OR: 19.9 (95% CI 18.8-21.2) in men and 40.8 (36.1-46.0) in women] and low HDL cholesterol [OR: 17.0 (95% CI 15.9-18.1) in men and 27.9 (25.0-31.1) in women] were the strongest determinants of the presence of MetS, stronger than the presence of high BP and high glycemic levels.

Clinical and biological characteristics of patients with MetS are presented in table I. Among the clinical parameters, other than those which define MetS, BMI, pulse pressure (PP) and HR increased in the presence of MetS. Vital capacity ratio (observed value/theoritical value), a marker of global health, was lower among men and women with MetS. Total cholesterol, leucocytes, globulin, gamma-glutamyl transpeptidase (Gamma-GT), and transaminase ALAT and ASAT were significantly higher among both men and women with MetS. To clarify the links between

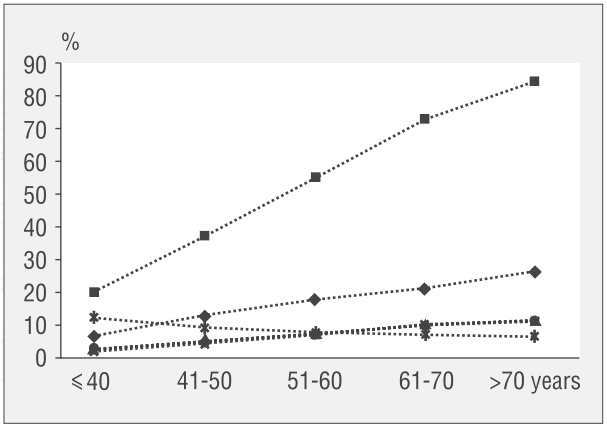

Figure 2
Prevalence of MetS and its components according to age in women.
◆Elevated waist circumference (%); ■ Elevated blood pressure (%); ▲ Elevated glucose level (%); ✕Elevated triglycerides (%); ✳ Low HDL-cholesterol (%);● METS (%).

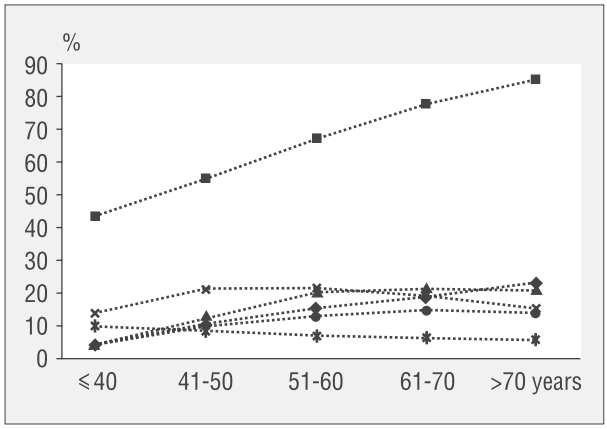

Figure 1
Prevalence of MetS and its components according to age in men.
◆ Elevated waist circumference (%); ■ Elevated blood pressure (%) ; ▲ Elevated glucose level (%) ; ✕ Elevated triglycerides (%) ; ✳ Low HDL-cholesterol (%) ;● METS (%)

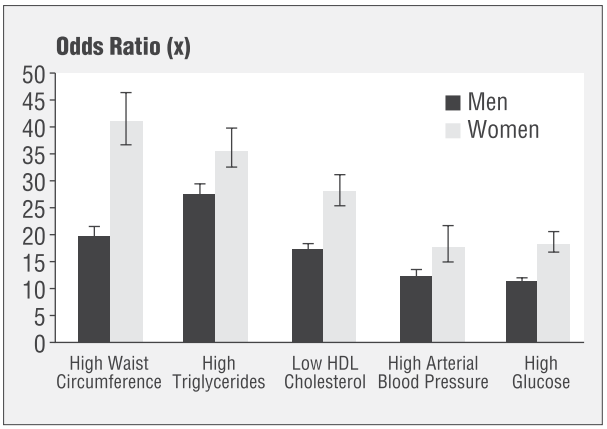

Figure 3
Age-adjusted Odds ratio of MetS components, comparing subjects with MetS to subjects without MetS (black bars=Men; white bars=Women).

Table I
Age-adjusted means (SEM) for clinical and biological parameters according to gender and MetS.

	Without MetS	With MetS	P*
Men			
BMI (kg/m^2)	25.0 (0.1)	29.4 (0.1)	<0.0001
PP (mmHg)	53.1 (0.1)	58.5 (0.1)	<0.0001
Vital capacity ratio†	0.94 (0.01)	0.88 (0.01)	<0.0001
HR (bpm)	62.1 (0.1)	67.5 (0.1)	<0.0001
Cholesterol (g/l)	2.2 (0.01)	2.3 (0.01)	<0.0001
Albumin (g/l)	43.6 (0.1)	43.8 (0.1)	<0.0001
Globulin (g/l)	31.6 (0.1)	32.8 (0.1)	<0.0001
Haemoglobin (g/100ml)	15.0 (0.1)	15.4 (0.1)	<0.0001
Leucocytes (Giga/l)	6.7 (0.01)	7.4 (0.04)	<0.001
Gamma-Gt (UI/l)	35.2 (0.2)	59.3 (0.7)	<0.0001
Alat (UI/l)	33.8 (0.1)	50.4 (0.4)	<0.0001
Asat (UI/l)	28.0 (0.1)	32.6 (0.2)	<0.0001
Women			
BMI (kg/m^2)	23.5 (0.1)	30.5 (0.1)	<0.0001
PP (mmHg)	52.2 (0.1)	60.5 (0.3)	<0.0001
Vital capacity ratio**	1.07 (0.03)	0.86 (0.10)	<0.04
HR (bpm)	65.2 (0.1)	70.3 (0.2)	<0.0001
Cholesterol (g/l)	2.2 (0.01)	2.3 (0.01)	<0.0001
Albumin (g/l)	42.3 (0.1)	42.2 (0.1)	<0.0001
Globulin (g/l)	32.4 (0.02)	34.9 (0.09)	<0.0001
Haemoglobin (g/100ml)	13.4 (0.1)	13.7 (0.1)	<0.0001
Leucocytes (Giga/l)	6.75 (0.02)	7.65 (0.06)	<0.0001
Gamma-Gt (UI/l)	19.8 (0.2)	39.7 (0.8)	<0.0001
Alat (UI/l)	21.5 (0.1)	30.8 (0.4)	<0.0001
Asat (UI/l)	22.9 (0.07)	25.9 (0.28)	<0.0001

*P: Without MetS vs with MetS; **Observed/theoretical values ratio; BMI: body mass index; PP: pulse pressure; HR: heart rate

MetS and hepatic biological markers, an analysis which took into account alcohol consumption was carried out (figure 4). We showed that Gamma-GT, ALAT and ASAT were higher in the presence of MetS, in both genders, regardless of the levels of alcohol consumption. In men and women, the elevation of Gamma-GT with alcohol consumption increased more substantially in the presence of MetS (P for interaction <0.0001).

The stress and depression scores obtained from a self-administered questionnaire were significantly higher in both men and women with MetS (table II). The percentage of patients with the highest scores for depression (higher than 6), as well as the percentage of those treated for anxiety or depression, was greater in the presence of MetS.

Comparison of dental health status showed a statistically significant increase in the dental inflammatory process in the presence of MetS. Dental plaque increased from 69.7% to 74.1% in men (P<0.0001) and from 59.5% to 66.3% in women (P<0.0001). Gingivitis increased from 12.1% to 17.5% in men (P<0.0001) and from 10.2% to 13.9% in women (P<0.0001).

As for lifestyle habits, tobacco consumption was similar in men with or without MetS (32.3% vs. 30.3%, NS). However, the percentage of men who never smoked was higher among those without MetS (43.6% vs. 32.8%, P<0.001). No relationship was found between tobacco and MetS among women. In both genders, subjects with MetS were significantly more sedentary. Among subjects with MetS, 41.5% of the men and 35.6% of the women declared having a regular physical activity as compared to 48.9% of the men and 45.6% of the women without MetS (P<0.001 in both genders). Men with MetS were somewhat more likely to live alone than men without Mets (16.3% vs. 20.5%, P=0.02); no difference was found for women.

A study of the prevalence of MetS in different subgroups was also conducted. Among subjects with diabetes (3.5% of men and 1.8% of women), the prevalence of MetS was 54.0% and 55.8%, respectively, in men and women. The prevalence of MetS observed among non-diabetic subjects was 8.7% and 5.1%, respectively. Among subjects with hypertension (38.2% of men and 29.8%women), the prevalence of MetS was 19.1% and 14.9% in men and women, respectively. The prevalence of MetS among normotensive subjects was 1.7% and 2.3%, respectively. Among obese subjects (10% of men and 9% of women), the prevalence of MetS was 44.7% and 34.4% in men and women, respectively, compared to 6.4% and 3.2% among non-obese subjects.

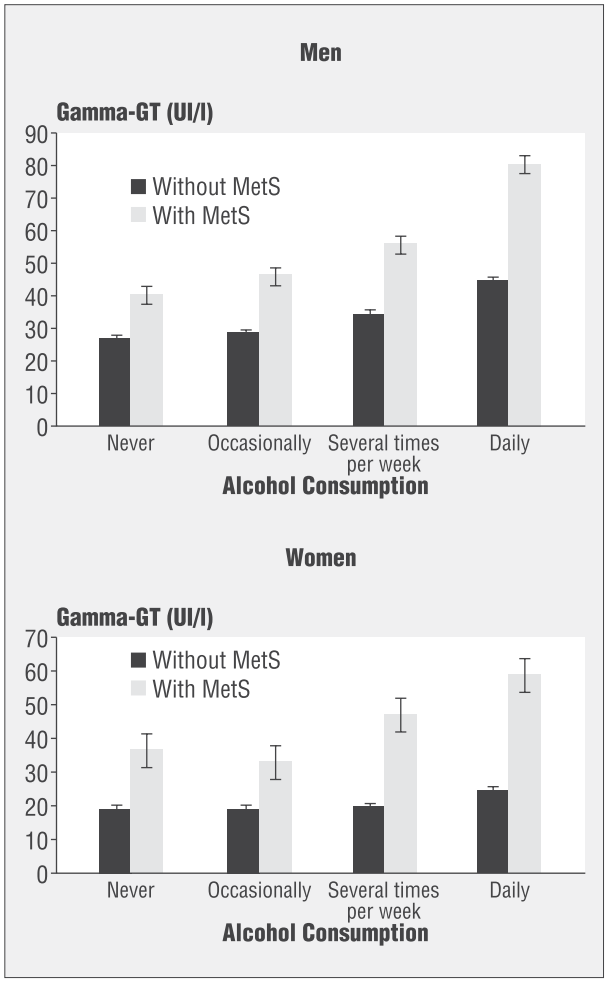

Figure 4
Plasma level for Gamma-GT according to MetS status and alcohol consumption in men (upper panel) and women (lower panel); (black bars=without MetS; white bars=with MetS). (P for interaction <0.0001)

Discussion

Our results indicate an increased level of risk markers observed in subjects with MetS, such as increased pulse pressure, increased heart rate, decreased vital capacity ratio, and the presence of increased inflammatory indexes such as leukocyte count, globulin level, gingivitis, tarter and plaque, and hepatic biological alterations. In addition, these patients had increased levels of stress and depression. Few data on the prevalence of MetS are available for the French population, particularly after 60 years of age. In the DESIR study [6], which used the same definition for MetS as we did, the prevalence of MetS in France was 9.7% in men and 6.6% in women before 64 years. Our findings are similar to these results and show that the prevalence of MetS, which is approximately 50% lower in young and middle aged women compared to men of the same age (≤60 years), reaches similar levels in both genders after the age of 70 years. Recently, Bauduceau et al. [10], in a population of 2045 men, found that 9% of the subjects presented at least 3 of the 5 NCEP-ATPIII criteria defining MetS, with a large contribution of elevated blood pressure and dyslipidaemia. These results were consistent with our observations.

The prevalence of MetS in the world depends on the definition used and the population studied. The WHO definition includes insulin resistance along with the association of metabolic factors as does the European Group for the Study of Insulin Resistance (EGIR) definition, but their

Table II
Psychosocial factors expressed as stress and depression scores; age-adjusted means (SEM) in men and women according to MetS status.

	Men		Women	
	Without MetS	**With MetS**	**Without MetS**	**With MetS**
Stress score	3.48 (0.01)	3.75 (0.04)***	4.56 (0.02)	5.26 (0.07)***
Depression score*	1.27 (0.01)	1.47 (0.03)***	2.29 (0.02)	2.98 (0.07)***
% score >6*	10.1 (n=6372)	13.0 (n=389)***	5.75 (n=1824)	8.78 (n=331)***
% of treated patients**	4.7	6.0***	12.1	15.8***

*Score for depression; **treatment for anxiety/depression; ***P<0.0001

actual application appears difficult from an epidemiological point of view. The ATP III (NCEP) definition we have chosen is adapted to our large epidemiological study. The Quebec study found a prevalence of more than 30% [11], a study of northern European countries found a prevalence up to 39% in men and 22% in women [12], and the NHANES II survey program found 26% in North America [5]. Numerous discussions have already been had regarding the validity of the thresholds set for each item depending on the studied population. The WHO has already suggested different levels of waist circumference for Asians, adjusted to the population, in order to study the relationship between BMI and risk [13]. Based on the ATP III-NCEP criteria used for this study, the French prevalence of MetS appears significantly lower than in Anglo-Saxon populations. However, this prevalence seems closer, although lower, to that which was observed in other European countries, such as in the DECODE study which used a modified WHO definition [4].

In addition to the cardiovascular risk factors included in the definition, subjects with MetS, in the present study, presented two additional haemodynamic risk markers. After adjustment for age, they had higher pulse pressure [(PP), +5 mmHg on average in men and + 8 mmHg in women] and an increased HR (+5 bpm on average in both genders) when compared with subjects without MetS. Previous studies have suggested that increased HR is associated with metabolic disorders and this could be related to the fact that high sympathetic activity may be involved in insulin resistance [14]. In the present study, the increase in PP in patients with MetS corroborates results showing high arterial stiffness in patients with MetS [15]. Since both PP and HR are significant determinants of CV morbidity and mortality [16-18], they may contribute to the higher risk in patients with MetS.

Dental inflammatory status was shown to be an independent cardiovascular risk marker [19-20]. The relationship between dentition status and general inflammatory status, usually assessed with a test for C-reactive protein (CRP), was established in patients with coronary heart disease [21]. However, the relationship between periodontal microbial status and CRP was not statistically significant in the INVEST study, although the white blood cell count was statistically related to periodontal microbial status, and the periodontal microbial status was linked to arterial atherosclerosis [22]. In our study, we did not measure CRP levels, however the clinical evaluation of dentition status, coupled with leukocyte count and globulin level, may provide a complementary approach to evaluating the general inflammatory status in patients with MetS. Markers, such as white blood cell counts, were previously observed in MetS in the NHANES cohort [23].

Patients with MetS presented lower pulmonary function, as assessed with relative respiratory capacity, than control subjects. It is a well established fact that pulmonary function is considered an indirect measurement of health status, at least among the elderly [24]. The final major variable related to higher cardiovascular risk status was the score for anxiety and depression which was higher in subjects with MetS. In the INTERHEART study [25], a specific score, including a combination of depression, stress at work or at home, financial stress and life events, was a clear indicator of cardiovascular risk, particularly for the occurrence of myocardial infarction. Although the score calculations are not similar, we could speculate that our psychosocial evaluation, mainly a depression score, might reflect a similar psychological situation. In this cross-sectional study however, the respective roles of these risk markers in the prognosis of MetS patients cannot be assessed, but the accumulation of these factors, most of which are modifiable, are particularly noticeable in these high risk patients. These markers are usually underestimated in epidemiological studies which tend to focus on the impact of medical strategy on classical risk factors. An interventional study that focuses on "correcting" these markers is needed. The combination of risk factors and markers creates an extremely high risk condition for the metabolic syndrome.

Non-alcoholic steatohepatitis (NASH) has been established in MetS [26] from a histopathological description. Although NASH could be considered as a part of the metabolic syndrome, we have shown that MetS is associated with biological alterations of the liver independently from alcohol consumption. Furthermore, in the presence of MetS, alcohol consumption is associated with increased biological changes in the liver. Unfortunately, in our population, we were unable to assess liver steatosis which appears to be associated with MetS [27].

In conclusion, in this large French population, based on the ATP III-NCEP 2001 definition, our study confirmed the low prevalence of MetS in France, even among the elderly. Mortality data associated with MetS in France and in this cohort is not currently available, however this cross-sectional study clearly demonstrates that numerous, well-established risk markers are present in patients with MetS, putting them at a statistically high risk for cardiovascular mortality. Further studies are needed in order to examine the benefits of treating these modifiable risk factors.

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APPENDIX

Depression

— Right now, my life seems empty (Y/N).
— I have a hard time getting rid of the bad thoughts that run through my head (Y/N).
— I don't have any energy (I'm listless) (Y/N)
— I feel incapable of doing the least little thing (Y/N)
— I am disappointed and disgusted with myself (Y/N)
— I have to force myself to do anything.
— I have a difficult time doing the things I used to do.
— I'm sad these days.
— My mind is not as clear as it usually is.
— I don't enjoy doing the things I like or that interest me as much as before.
— My memory doesn't seem as good as it usually is.
— I feel hopeless about the future.
— These days, I feel less happy than most people.

Stress

During the past month, how many times...

Only one answer per question

1. Did you feel it was difficult to control the important things in your life?

   never
   almost never
   sometimes
   quite often

2. Did you feel confident in your abilities to handle your personal problems?

   never
   almost never
   sometimes
   quite often

3. Did you feel as though things were going to way you wanted them to?

   never
   almost never
   sometimes
   quite often

4. Did it seem that problems kept adding up to such an extent that you could not control them?

   never
   almost never
   sometimes
   quite often