

The Metabolic Syndrome and the Carotid Artery Structure in Noninstitutionalized Elderly Subjects

The Three-City Study

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Background and Purpose—In contrast to the young adult population, limited data are presently available regarding the epidemiology of the metabolic syndrome (MetS) and its relationship with cardiovascular disease risk in the elderly. We have investigated the frequency of the MetS and its association with the carotid artery structure in an elderly free-living population.

Methods—The study population consists of 5585 French noninstitutionalized elderly men and women aged 65 to 85 years, free of diabetes, who participated in the multicenter Three City Study and who underwent ultrasound examination of the carotid arteries at baseline examination between March 1999 and March 2001. The MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria.

Results—The MetS was present in 12.1% of the study participants, with slightly higher rates in men. Subjects with the MetS had higher frequency of carotid plaques (odds ratio, 1.30; 95% CI, 1.09 to 1.55), higher intima-media thickness of the common carotid artery (odds ratio, 1.81; 95% CI, 1.37 to 2.41), and higher lumen diameter (odds ratio, 2.17; 95% CI, 1.61 to 2.94) (upper quintiles) after adjustment for other cardiovascular risk factors. This association was observed in both genders and in subjects without prevalent cardiovascular disease. Elevated blood pressure as defined in the MetS was the main determinant of the relations between the MetS and the carotid parameters, especially the lumen diameter.

Conclusions—The present data suggest that noninstitutionalized elderly subjects with the MetS have altered structure of the carotid arteries. (*Stroke*. 2007;38:893-899.)

Key Words: atherosclerosis ■ carotid artery abnormalities ■ elderly ■ epidemiology ■ metabolic syndrome

In industrialized countries, elderly subjects older than 65 years represent a growing part of the population that is at particular increased risk for cardiovascular disease.¹ Several large-scale observational studies have shown an inverse relationship between diet, physical activity, and cardiovascular disease in the elderly;^{2,3} recent preventive trials conducted in that population have suggested that treatment with lipid-lowering drugs had favorable risk/benefit.⁴ Therefore, identification of those elderly individuals who are at highest risk for cardiovascular disease and who could benefit from more effective and aggressive preventive strategy represent a major public health challenge.

In the adult population, the metabolic syndrome (MetS), a cluster of risk factors including impaired glucose tolerance, abdominal adiposity, dyslipidemia, and elevated blood pressure, is a frequent condition, found with a 10% to 30%

prevalence rate according to the population studied.⁵⁻⁸ Moreover, in that population, the MetS has been suggested to increase the risk of cardiovascular disease including coronary heart disease and ischemic stroke, independently of other cardiovascular disease risk factors.⁸⁻¹³ Current international guidelines recommend MetS screening for the identification of persons at high long-term risk of cardiovascular disease.¹⁴

Limited data are presently available regarding the epidemiology of the MetS in the elderly population. The frequency of the MetS has been estimated specifically in the elderly population in only 2 recent population based studies: according to the National Cholesterol Education Program Adult Treatment Panel III criteria, it was 28% in elderly Americans participating in the Cardiovascular Health Study,¹⁵ and 38% in a Chinese cross-sectional study including individuals with prevalent type 2 diabetes and cardiovascular disease.¹⁶ Other

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available frequency estimates of the MetS derived from studies of specific demographic subgroups (age and gender) and vary between 13% and 29%.^{17–19} However, these figure may not be applicable to elderly from countries at lower risk of cardiovascular disease such as France.

Moreover, the data of 3 prospective cohorts^{15,17,20} and 3 cross-sectional studies^{16,18,21} indicate that the MetS is associated with increased risk of cardiovascular disease in the elderly. Ultrasound examination of carotid arteries is a noninvasive sensitive method to detect presymptomatic alterations in the vasculature structure, a validated marker of atherosclerosis and increased risk of cardiovascular disease.²² In young adults, the MetS has been related to altered structure (and function) of carotid arteries.^{23–27} Whether the MetS is associated with such structural alterations in the elderly has not been investigated. One recent study found an association between the MetS and higher intima-media thickness of the common carotid artery (CCA-IMT), but this study had limited sample size and was restricted to women.¹⁹

The aim of the present study was to estimate the frequency of the MetS and to assess its relationship with various phenotypes of carotid artery structure in a large cohort of noninstitutionalized French elderly men and women aged older than 65 years.

Methods

Study Population

The subjects included in the present study were recruited into a large French multicenter prospective community study of coronary heart disease, vascular risk factors, and dementia, ie, the Three City Study. The study protocol has been described previously.²⁸ Briefly, subjects aged 65 years and older were selected from the electoral rolls of 3 cities, Bordeaux in the southwest, Dijon in the northeast, and Montpellier in the southeast, and then invited to participate in the study. The acceptance rate was 37%, yielding a study sample size of 9294 subjects (3469 men and 5645 women), respectively, 2104 in Bordeaux, 4931 in Dijon, and 2259 in Montpellier. The study protocol was approved by the Ethical Committee of the University hospital of Kremlin-Bicêtre, and each participant signed an informed consent.

Baseline Data Collection

Data were collected during a face-to-face interview using a standardized questionnaire administered by nurses. A wide range of information was collected including demographic characteristics, educational level, occupation, daily life habits such as smoking and alcohol consumption, functional evaluation, and depressive symptoms. Cognitive testing and screening for prevalent dementia were also performed by trained psychologists. History of cardiovascular disease was defined as the self-report of hospitalized myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or hospitalized stroke. Participants were also invited to bring to the study center all medications they have regularly used in the past month.

Baseline Examination

Participants underwent a standardized physical examination performed by technicians. Blood pressure was measured twice with a digital electronic tensiometer (sitting and lying) and the average of the 2 measurements was used in the statistical analyses. Height, weight, and waist measurement were estimated in a subject in a light dressing. A 12-lead ECG was recorded and resting pulse rate was measured. Blood samples were collected and centralized measurements of fasting total cholesterol, high-density lipoprotein cholesterol,

triglycerides and glucose levels were performed. Low-density lipoprotein cholesterol was calculated according to the Friedewald formula only for triglycerides values ≤ 4.5 g/L.

Ultrasound Examination

The ultrasound examination of the carotid arteries was proposed to participants aged younger than 85 years and who were able to come to the examination center. Because of cost constraints, ultrasound examination was not proposed to participants who were included in the study in the past 4 months of the recruitment. Ultrasound examination was thus performed at baseline examination in 73.7% ($n=6631$) of the study participants aged younger than 85 years. As reported previously, this subset of the population had a better cardiovascular risk profile compared with subjects who did not undergo ultrasound examination.²⁹ The protocol of carotid ultrasound examinations has been described in details recently.²⁹ Briefly, the same B-mode system (Ultramark 9 High Definition Imaging) with a 5- to 10-Mhz sounding was used in each center and a centralized reading was performed by 1 trained reader at the Reference Reading Center (Hopital Broussais, Paris) according to a standardized protocol. The examinations involved scanning of the CCAs, the carotid bifurcations, and the origin of the internal carotid arteries. The near and far walls of these arterial segments were scanned longitudinally and transversally to assess the presence of plaques, which was defined as previously reported.³⁰ For IMT and lumen diameter measurements, far and near walls of the right and left CCAs 2 to 3 cm of proximal to the bifurcation were imaged and frozen in end-diastole. The IMT was measured at site free of any discrete plaque along a 10-mm-long segment of the far wall of the CCA and defined as the distance between the lumen-intima interface and the media-adventitia interface. The mean of 75 measurements was automatically performed on each image and on each side. Lumen diameter was defined as the average of the distance between the 2 leading edges of far wall and near wall lumen-intima interfaces along at least a 0.5 cm of length using a computerized validated program. The reproducibility of the measures has been tested and the kappa coefficient for agreement between the 2 examiners was 0.78 for carotid plaques, whereas the mean absolute difference and correlation coefficient between repeated examinations were, respectively, 0.060 and 0.71 for CCA-IMT and, respectively, 0.16 mm and 0.91 for lumen diameter.

MetS

The MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria, which requires the presence of 3 or more alterations among the following: large waist circumference (>88 cm in women and >102 cm in men), elevated triglycerides (≥ 150 mg/dL), low high-density lipoprotein cholesterol (men <40 and women <50 mg/dL), elevated fasting glucose (≥ 110 mg/dL), and elevated systolic (≥ 130 mm Hg) or diastolic blood pressure (≥ 85 mm Hg), or use of antihypertensive medication.⁵

Statistical Analysis

Of the 6631 subjects who underwent ultrasound examination, 6504 had complete data on diabetic status as evaluated by fasting glycemia and/or current antidiabetic treatment. Of these, 9.6% ($n=626$) had type 2 diabetes, ie, a fasting glycemia ≥ 126 mg/dL or the use of antidiabetic treatment, and were excluded from the present analysis. Moreover, 297 subjects were further excluded because of incomplete data for the definition of the MetS. These latter subjects were 1 year younger, less frequently treated for hypertension or dyslipidemia, had less carotid plaques and lower lumen diameter, but they were more likely to be current smoker and to have higher CCA-IMT levels than the remaining 5585 subjects who represent the current study population.

Baseline characteristics of subjects with and without the MetS were compared using logistic and general linear regression models for categorical and continuous variables, respectively, with adjustment for age, gender, and the study center. The frequency of carotid

TABLE 1. Baseline Characteristics According to the Presence of the MetS as Defined by the National Cholesterol Education Program Adult Treatment Panel III Criteria: The Three City Study

	Total Cohort n=5585	MetS n=674	No MetS n=4911	<i>P</i> *
Age, y	73.5 (4.9)	73.9 (4.9)	73.5 (4.9)	0.024
Women	62.0	58.6	62.4	0.049
Bachelor degree or higher	38.7	33.8	39.4	<0.01
Current smokers	5.7	6.1	5.6	0.56
Alcohol, g/day	13.0 (14.9)	13.1 (15.6)	13.0 (14.8)	0.45
MMSE score	27.3 (2.1)	27.0 (2.3)	27.4 (2.0)	<0.01
Lipid-lowering drugs	29.7	33.1	29.2	0.026
BP-lowering drugs	48.1	67.7	45.5	<0.01
Current HRT user†	15.0	8.7	15.9	<0.01
History of CVD	8.4	12.5	7.8	<0.01
BMI, kg/m ²	25.4 (3.9)	29.3 (4.1)	24.9 (3.6)	<0.01
Waist, cm	87.8 (12.2)	99.9 (10.0)	86.1 (11.6)	<0.01
SBP, mm Hg	145.3 (21.6)	149.7 (19.4)	144.7 (21.8)	<0.01
DBP, mm Hg	81.4 (11.7)	84.2 (11.8)	81.1 (11.7)	<0.01
Fasting glycemia, mg/dL	88.2 (9.9)	95.6 (13.0)	87.4 (9.1)	<0.01
Total chol, mg/dL	226.3 (37.3)	226.7 (41.4)	226.3 (36.8)	0.45
HDL chol, mg/dL	63.7 (15.9)	47.2 (10.9)	65.0 (14.9)	<0.01
LDL chol, mg/dL	140.9 (32.5)	141.1 (34.8)	138.6 (31.6)	<0.01
TG, mg/dL	109.5 (51.4)	180.5 (64.5)	99.7 (40.6)	<0.01
Components of the MetS				<0.01
0	9.5	...	10.9	
1	52.6	...	59.8	
2	25.8	...	29.3	
3	9.0	74.6	...	
≥4	3.1	25.4	...	
Carotid plaques	45.3	53.2	44.2	<0.01
Carotid plaques, No. of sites				
0	54.7	46.8	55.8	<0.01
1	19.3	20.4	19.1	
>1	26.0	32.8	25.0	
Intima-media thickness, mm	0.71 (0.12)	0.73 (0.12)	0.71 (0.12)	<0.01
Lumen diameter, mm	6.20 (0.78)	6.4 (0.8)	6.2 (0.8)	<0.01

Data are % (n) and mean (SD) for categorical and continuous variables respectively; triglycerides were log-transformed for statistical analysis.

*Logistic regression and general linear regression model for categorical and continuous variables, respectively, adjusted for study centers, gender, and age.

†Analysis restricted to women.

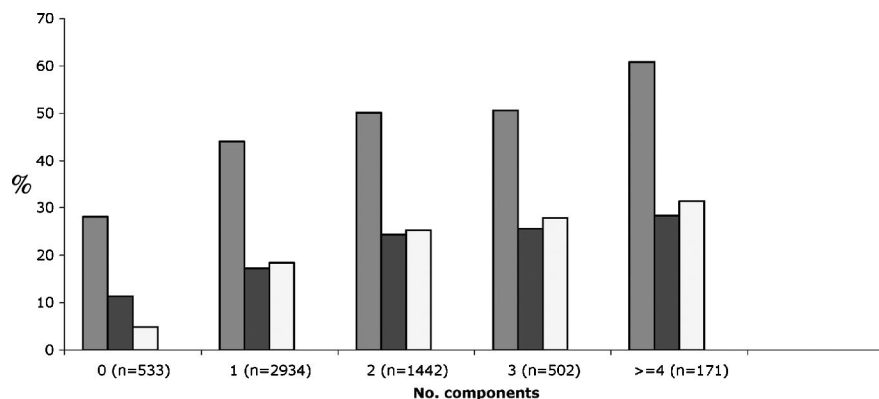
BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein; MMSE, Mini Mental State Examination; SBP, systolic blood pressure; TG, triglycerides.

plaques, higher CCA-IMT, and higher lumen diameter level (upper versus lower quintiles) associated with the MetS was estimated in separate logistic regression models. We have used quintiles of IMT and lumen diameter because we had no a priori hypothesis on the nature of their relationship (linear or not) with the MetS. Analyses were adjusted for age, study center, gender, smoking status, self-reported cardiovascular disease, and lipid-lowering medications. The individual components of the MetS were also entered in a logistic regression model adjusted for these same confounders to estimate their independent association with the carotid parameters. Analyses were performed on SAS 8.2 release (SAS Institute Inc).

Results

General Characteristics

The study sample consisted of 5585 subjects who were free of type 2 diabetes and who underwent ultrasound examination at baseline examination, respectively, 2124 men and 3461 women. The baseline characteristics of the cohort are reported in Table 1. According to the National Cholesterol Education Program Adult Treatment Panel III criteria, the MetS was present in 12.1% of the study participants, respec-



Frequency of plaques, high CCA-IMT level (upper quintile), and high carotid lumen diameter (upper quintile) according to the number of components of the metabolic syndrome in the total cohort. The Three City Study. Bars represent respectively carotid plaques (gray), high (5th quintile) intima-media thickness (dark gray), and high (5th quintile) lumen diameter (white). P for trend <0.001

tively, 11.2% in Dijon, 12.1% in Montpellier, and 14.1% in Bordeaux ($P=0.03$). High blood pressure was the most frequent component of the MetS (87%), followed by elevated waist circumference (26.8%), elevated triglycerides (16%), low high-density lipoprotein cholesterol (10.3%), and elevated fasting glycemia (3.8%). The prevalence and the number of carotid sites with plaques, the mean level of CCA-IMT, and lumen diameter were all significantly higher in those with the MetS as compared with controls. As displayed in Figure, the frequency of plaques, of CCA-IMT and carotid lumen diameter in the upper quintile of their distribution increased with the number of abnormalities of the MetS (P for trend <0.001).

Associations Between the MetS and Carotid Parameters

Table 2 indicates that subjects with the MetS had increased risk of having carotid plaques (33%), higher CCA-IMT (46%), and enlarged lumen diameter (62%) even after adjustment for age, study center, gender, smoking status, lipid-lowering treatment, and history of cardiovascular disease. There was a dose response between the MetS and the number of sites with carotid plaques (not shown). Consistent associations were seen in both genders and in subjects without history of cardiovascular disease. Association between the

MetS and higher lumen diameter was stronger in men than in women (P for interaction=0.041). There were no significant interactions with lipid-lowering treatment, antihypertensive treatment, or the study centers (not shown). When the 3 carotid parameters were considered as covariates in the same regression model, each parameter was associated with the MetS, after adjustment for the confounding variables (not shown).

Associations Between Individual Components of the MetS and Carotid Parameters

Table 3 shows the associations between the components of the MetS (considered in the same regression model) and the carotid parameters after adjustment for the study center, age, smoking status, and history of cardiovascular disease. Elevated blood pressure was consistently associated with the three carotid parameters, especially with higher lumen diameter, for which a 3-fold increased risk was observed. These associations were observed whether the subjects were or were not under antihypertensive treatment at baseline examination. Elevated waist circumference showed association with high CCA-IMT and lumen diameter, and elevated triglycerides with the presence of plaques and high CCA-IMT. Similar findings were observed for both sexes and in subjects without cardiovascular disease at baseline examination (not shown).

TABLE 2. Associations Between the MetS and Carotid Plaques, Intima-Media Thickness, and Carotid Lumen Diameter in Various Subgroups: The Three City Study

	Total Cohort, N=5585	Men, N=2124	Women, N=3461	No CVD, N=5116
Carotid plaques				
No MetS	1	1	1	1
MetS	1.33 (1.11–1.58)	1.34 (1.01–1.78)	1.32 (1.06–1.66)	1.37 (1.14–1.65)
High CCA-IMT*				
No MetS	1	1	1	1
MetS	1.46 (1.19–1.78)	1.51 (1.12–2.03)	1.43 (1.09–1.87)	1.38 (1.11–1.71)
High carotid lumen diameter*				
No MetS	1	1	1	1
MetS	1.61 (1.30–1.98)	1.33 (1.01–1.76)	2.01 (1.48–2.73)	1.58 (1.26–1.99)

Odds ratios were estimated by logistic regression model and were adjusted for age, study center, smoking status, lipid-lowering drug, and history of CVD.

*The lower quintiles were taken as the reference group. The fifth quintiles of CCA-IMT and lumen diameters refer to values ≥ 0.81 mm and 6.80 mm, respectively.

CCA indicates common carotid artery; IMT, intima-media thickness.

TABLE 3. Associations Between Individual Components of the MetS and Carotid Plaques, Intima-Media Thickness, Carotid Lumen Diameter in the Total Cohort: The Three City Study

	Carotid Plaques	High CCA-IMT* (5th Quintile)	High Lumen Diameter* (5th Quintile)
Elevated BP or on antihypertensive medication	1.72 (1.43–2.06)	1.51 (1.17–1.95)	3.06 (2.17–4.32)
Elevated waist	1.04 (0.90–1.19)	1.35 (1.16–1.58)	1.94 (1.64–2.30)
Elevated triglycerides	1.34 (1.14–1.58)	1.27 (1.05–1.54)	0.99 (0.81–1.21)
Elevated glycemia	1.21 (0.89–1.64)	0.94 (0.66–1.35)	1.04 (0.72–1.50)
Low HDL cholesterol	1.13 (0.93–1.38)	1.18 (0.94–1.48)	1.14 (0.89–1.45)

Odds ratios were estimated by logistic regression model; analysis was adjusted for the 5 components of the MetS and for age, study center, smoking status, and history of CVD.

*The lower quintiles were taken as reference for the estimation of the odds ratio.

Additional Analyses

Using the cut-off value of 100 mg/dL recently proposed to define impaired fasting glucose, the frequency estimates of impaired fasting glycemia and of the MetS were 12% and 15.5%, respectively. The recent AHA/NHLBI criteria additionally include specific treatment for low-plasma high-density lipoprotein or high-plasma triglycerides levels, mainly fibrates and nicotinic acid, in the definition of the MetS.³¹ In the current study, 13.2% were using fibrates and none was treated by nicotinic acid at baseline examination.³² Applying the AHA/NHLBI criteria to the present study yielded a frequency of the MetS of 25.6%. However, these modified definitions did not change the associations between the MetS, its components, and the carotid parameters. When CCA-IMT and lumen diameter were considered as continuous variables (instead of being in quintiles), positive associations with the MetS persisted: the adjusted means of CCA-IMT and lumen diameter were 0.74 mm versus 0.72 mm, and 6.56 mm versus 6.36 mm, in subjects with and without the MetS, respectively.

Discussion

In this large population-based study of noninstitutionalized French elderly individuals aged 65 years and older, the MetS as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria was present in 12% of the study participants. The MetS was associated with higher frequency of carotid plaques and increased level of CCA-IMT and lumen diameter, independently of established risk factors. Consistent results were observed in both genders and in subjects free of cardiovascular disease at baseline examination. In general, the MetS and its individual components including elevated blood pressure, elevated waist circumference, and elevated triglycerides showed comparable level of associations with the carotid parameters. However, association with higher lumen diameter was stronger for elevated blood pressure as compared with the MetS taken as a whole.

Prevalence of the MetS

Only 2 previous population-based studies have specifically estimated the frequency of the MetS in the elderly population.^{15–16} According to the NCEP/ATP III criteria, it was 28% in the Cardiovascular Health Study of elderly Americans initially nondiabetic and free of cardiovascular disease,¹⁵ and 38% in a Chinese cross-sectional study comprising subjects with type 2 diabetes and prevalent cardiovascular disease.¹⁶ Other frequency estimates of the MetS in the elderly derived from studies of specific demographic subgroups and vary from 29% in British women aged 60 to 79 years to 38% in elderly Americans aged 70 to 79 years.^{17–18} The present study complements these findings through a population-based study of larger sample size, conducted in a country at lower cardiovascular risk. The present frequency estimate of the MetS is much lower as compared with the above studies. However, it is similar to the 13% reported in a recent longitudinal Finnish study of initially nondiabetic elderly women aged 60 to 70 years,¹⁹ and is also comparable to previous estimates reported in young European and French populations.²⁵

MetS and Carotid Parameters

The associations found in the present study between the MetS and the carotid arteries structure are consistent with associations reported in younger populations.^{23–27} In one recent Finnish study of elderly women, higher IMT (mean IMT in the right carotid bifurcation) was associated with the MetS at baseline examination, and the mean increase in carotid IMT was greater among those in whom incident MetS developed during follow-up as compared with those in whom it did not.¹⁹ However, this study had a relatively small sample size ($n=101$) and was restricted to women. The Baltimore Longitudinal Study of Aging has also reported MetS (National Cholesterol Education Program Adult Treatment Panel III criteria) to be associated with increased CCA-IMT (right CCA at 1.5 cm from the bifurcation) and aortic stiffness in participants aged 21 to 96 years. However, the study was not focused on elderly and was also limited by sample size ($n=471$).³³

We observed independent associations between the MetS and carotid plaques, CCA-IMT, and lumen diameter, suggesting the implication of complementary mechanisms. Associations of the MetS with plaques and, to a lesser extent with IMT, may reflect a greater susceptibility to atherosclerosis. Enlargement of the carotid lumen diameter has been suggested to be an adaptive response to atherosclerosis and thickness of the arteries in some cases, and to mechanical stressors such as blood pressure in others.^{29,30} In the current study, the positive association between lumen diameter of the CCA and the MetS highly likely reflects an association with elevated blood pressure, an important risk factor of atherosclerosis and a factor that was the most frequent component of the MetS. Altogether, the present findings suggest that the MetS is associated with early markers of elevated risk of cardiovascular and cerebrovascular disease, ie, alterations of the carotid artery structure, a finding consistent with the results of 3 recent prospective studies

showing the MetS to increase cardiovascular disease risk in the elderly population.^{15,17,20}

Components of the MetS and Carotid Parameters

Whether the MetS exerts its effect on outcome beyond that of its components is currently debatable. Our data indicate that the effect of the MetS on the carotid arteries structure is comparable to that observed with some of its individual components, including elevated blood pressure, extended waist circumference, and elevated triglycerides. However, association with enlarged lumen diameter was particularly strong for elevated blood pressure as compared with the MetS taken as a whole. Consistent results have been observed in the Chinese study and in the British Women's Heart and Health Study, in which the MetS and its individual components had a similar level of association with prevalent cardiovascular disease.^{16,18} However, the present results are at variance from the Cardiovascular Health Study in which MetS remained associated with incident cardiovascular disease independently of its components.¹⁵ Therefore, at present, no firm conclusion can be drawn and further studies should investigate this question.

The current study has some limitations. As volunteers, the study participants may not be representative of the noninstitutionalized French elderly population, especially given the fact that the sample was restricted to subjects who were able to come to the study center. Therefore, it is highly likely that frequency estimates of the MetS and the observed associations with the carotid parameters were underestimated. The consistency of the current findings in other arterial beds should also be investigated. Being a cross-sectional study, the temporal sequence of the observed associations cannot be inferred. A further limitation has been the lack of longitudinal data on the progression of carotid arteries structure.

Conclusion

The present data suggest that in French noninstitutionalized elderly men and women older than 65 years, the MetS is associated with alterations of the carotid artery structure. Whether such alterations mediate the relationship between the MetS and cardiovascular disease in the elderly requires prospective evaluation.

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Disclosure

None.

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