Metabolic Syndrome and Onset of Depressive Symptoms in the Elderly

Findings from the Three-City Study

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OBJECTIVE—Given the increasing prevalence of both metabolic syndrome (MetS) and depressive symptoms during old age, we aimed to examine prospectively the association between MetS and the onset of depressive symptoms according to different age-groups in a large, general elderly population.

RESEARCH DESIGN AND METHODS—This was a prospective cohort study of 4,446 men and women aged 65–91 years who were free of depression or depressive symptoms at baseline (the Three-City Study, France). MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria. New onset of depressive symptoms (the Center for Epidemiologic Studies Depression Scale score ≥16 and use of antidepressant treatment) was assessed at 2- and 4-year follow-ups.

RESULTS—After adjusting for a large range of potential confounders, we observed MetS to be associated with 1.73-fold (95% CI 1.02–2.95) odds for new-onset depressive symptoms in the youngest age-group (65–70 years at baseline), independently of cardiovascular diseases. No such association was seen in older age-groups.

CONCLUSIONS—Our findings suggest that the link between MetS and depressive symptoms evidenced until now in middle-aged people can be extended to older adults but not to the oldest ones. Additional research is needed to examine if a better management of MetS prevents depressive symptoms in people aged 65–70 years.

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Although depression has long been shown to be associated with the development of metabolic syndrome (MetS) (1), more recent evidence of a bidirectional association has been reported in young (2) and middle-aged women (3,4) and older men (5), suggesting a more complex etiological pathway than has previously been considered. We recently have confirmed the association between MetS and depressive symptoms in a larger, middle-aged population (6), suggesting that better management of MetS might reduce the incidence of depressive symptoms in those within the age range of 40–60 years. The adverse consequences of depression on quality of life in older adults (7), combined with the increasing prevalence of MetS (8) during old age, raised interest in establishing whether MetS continues to increase the risk of depressive symptoms in older people. Any potential association benefits from a biologically plausible hypothesis. Research suggests that the etiology of late-onset depression is linked to vascular causes, such as diseases of the blood vessels and circulation (9). There also are clear associations between diabetes and neurodegenerative disease and, within these diseases, depression and other mood disorders can be an early and observable feature. Thus, our objective was to prospectively assess the association between MetS and onset of depressive symptoms according to different age-groups in the elderly by using data from a large, general-population cohort.

RESEARCH DESIGN AND METHODS

The Three-City Study (3C study) is an ongoing multisite cohort study of community-dwelling people aged ≥65 years recruited from the electoral rolls of three French cities (Bordeaux, Montpellier, and Dijon) from 1999 to 2001 (n = 9,294) (10). Participants were interviewed by trained staff and underwent a number of clinical examinations at baseline and at 2 and 4 years. The study protocol was approved by the ethics committee of the University Hospital of Bicêtre (Paris, France), and written informed consent was obtained from each participant. Participants with dementia (n = 500), those who presented with depressive symptoms (n = 2,066), or those who reported past or current major depressive disorder episodes (n = 540) at baseline were excluded. Of these 6,188 participants, the present analyses were carried out in the 4,446 participants who had complete data on MetS, had all covariates measured at baseline, and had at least one assessment of depressive symptoms available at the 4-year follow-up.

Data collection

Assessment of MetS. The MetS was defined at baseline, using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria (11), based on the presence of three or more of the following: waist circumference: men >102 cm and women >88 cm;

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serum triglycerides: ≥1.7 mmol/L; HDL cholesterol: men <1.04 mmol/L and women < 1.29 mmol/L; systolic blood pressure: ≥130 mmHg and diastolic blood pressure 85 mmHg; fasting glucose: ≥6.1 mmol/L, or presence of type 2 diabetes. As data on the established diagnosis of type 2 diabetes by a practitioner were not available, the use of antidiabetes treatment was considered as a proxy. Details of procedures regarding waist circumference, blood pressure, fasting blood glucose, HDL cholesterol, and triglyceride measurements have been previously described (12).

Assessment of depression and depressive symptoms at baseline and over the follow-up. At each wave, depressive symptomatology was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), which has been validated in the general population (13). Depressive symptomatology refers to any symptoms of depression reported by subjects on the CES-D, with the higher number of symptoms representing greater severity. A cutoff point of 16 on the CES-D provides a categorical division of symptoms, with higher scores corresponding to clinically significant levels of depressive symptomatology warranting clinical intervention (13). Subjects with low levels of depressive symptomatology are referred to as a low-symptom group. In longitudinal analyses, incident depressive symptoms were identified from this low-symptom group who were not treated by antidepressants at baseline but who subsequently had incident depressive symptoms or began an antidepressant treatment during the follow-up. To strengthen the assumption that participants included in the present analyses were free of depressive symptoms, we also excluded subjects with lifetime major depressive episodes according to the DSM-IV criteria by using the Mini International Neuropsychiatry Interview, a standardized psychiatric examination validated in the general population (14).

Assessment of covariates at baseline. Sociodemographic variables consisted of sex, age, study center, marital status (living alone, married, or cohabitating), and educational level (no formal education, primary school or lower secondary education, or higher secondary education or university degree). The health behaviors considered were smoking status (nonsmoker, former smoker, or current smoker) and alcohol consumption (nondrinker; moderate drinker, defined by three glasses or less per day for men and two glasses or less per day for women; or heavy drinker, defined by three or more glasses per day for men and two or more glasses per day for women). Health status was ascertained using BMI categories (normal: BMI <25 kg/m^2, overweight: 25 ≤ BMI < 30 kg/m^2, obese: BMI ≥30 kg/m^2). Cognitive impairment was defined as having a score <24 on the Mini-Mental State Examination (MMSE); disability was evaluated using the Instrumental Activities of Daily Living (IADL) scale (score >0); treatment of MetS was determined by the use of lipid-lowering drugs; and treatment of hypertension was determined by the use of hypotensor, angiotensor, β-blockers, diuretics, and lipid-lowering drugs. An inventory of all drugs (prescription and over-the-counter drugs) used during the preceding month was included in a standardized interview. Medical prescriptions and, where feasible, the medications themselves were checked by the interviewer. In addition, self-reported history of cardiovascular or cerebrovascular disease (CVD) (angina pectoris, myocardial infarction, coronary balloon dilation or artery bypass, stroke, or peripheral artery disease surgery) at baseline and incident CVD (including stroke) over the follow-up also was considered.

Statistical analyses

A Student *t* test (for continuous variables) and the χ^2 test (for categorical variables) were used to compare characteristics of participants according to *1*) the presence of new-onset depression based on the CES-D and *2*) MetS status at baseline. Logistic regression models were performed to assess the association between MetS, its components, and onset of depression based on the CES-D. The statistically significant interaction found between age and MetS in new-onset depressive symptoms (Wald test $P = 0.03$) led us to conduct these analyses separately within each age-quartile group. The following were mean ages (SDs) for each group: age-group 1: 67.9 (1.04); age-group 2: 71.1 (1.0); age-group 3: 74.7 (1.1); and age-group 4: 79.9 (2.5). These analyses were adjusted for age at baseline (by year), sex, study center, education, marital status, smoking habits, alcohol consumption, BMI categories, cognitive impairment, disability, MetS treatment, and self-reported history of CVD at baseline. Furthermore, to explore whether any association between MetS and depression based on the CES-D could be driven by CVD, we repeated the analyses after excluding participants who self-reported a history of CVD at baseline or who developed incident CVD over the follow-up. All analyses were conducted using SAS software (version 9.2; SAS Institute).

RESULTS—Over the 4-year follow-up, 827 (18.6%) new cases of depression based on the CES-D were observed. Characteristics of the population as a function of incident CES-D depressive symptoms over the 4-year follow-up are detailed in Table 1. Overall, the prevalence of MetS was 12.9% (n = 574) at baseline. Compared with MetS-free participants, those with MetS were more likely to be men ($P = 0.002$), to be former smokers ($P < 10^{-4}$), to be in higher BMI categories ($P < 10^{-4}$), to have less education ($P = 0.002$), to have more disabilities ($P = 0.02$), to have more cognitive deficits ($P = 0.002$), to report a history of CVD ($P = 0.0003$), and to develop CVD during the study ($P = 0.009$) (Supplementary Table 1).

The results of Table 1 show that the incidence of depressive symptoms increased significantly across age-groups ($P < 0.0001$). Table 2 shows the association of MetS with the incidence of depressive symptoms by age-groups categorized according to quartile distribution. In age-group 1 (first quartile), participants with MetS were more likely to develop depressive symptoms (odds ratio 1.73 [95% CI 1.02–2.95]) compared with participants without MetS at baseline, after adjusting for a large range of sociodemographic characteristics (sex, study center, educational attainment, and marital status), health behaviors (smoking and alcohol consumption), and health-status factors (MetS treatment, cognitive deficit, disability, BMI, and self-reported history of CVD at baseline). In older age-groups, there was no statistically significant association between MetS and new onset of depressive symptoms.

To assess the robustness of this finding, we performed analyses in age-groups that were categorized a priori (aged 65–70 years, n = 1,300; aged 70–75 years, n = 1,558; aged 75–80 years, n = 1,164; and aged 80–91 years, n = 424). These analyses confirmed the main analysis by showing that MetS was associated with a 1.8-fold odds ratio for new-onset depressive symptoms in elderly subjects aged 65–70 years (odds ratio 1.82 [95% CI 1.12–2.95]), but no association was found for older participants (Supplementary Table 2).

Table 1—*Characteristics of 4,446 3C study participants according to the onset of new CES-D depression cases over the 4-year follow-up*

	Cumulative onset of depressive symptoms*		
	No (%)	Yes (%)	*P*
n	3,619	827	
Age-quartile groups			$<10^{-4}$
65.0–69.4	26.0	20.8	
69.4–72.8	25.6	22.1	
72.8–76.8	24.6	26.7	
76.8–91.1	23.8	30.3	
Sex			$<10^{-4}$
Men	49.3	27.8	
Women	50.7	72.2	
Marital status			$<10^{-4}$
Living alone	29.5	37.0	
Married or cohabiting	70.5	63.0	
Education			$<10^{-4}$
No qualification/primary	29.6	37.0	
Lower secondary	29.6	31.1	
Higher secondary or higher	40.9	32.9	
Smoking habit			$<10^{-4}$
Never smoker	57.0	65.1	
Former smoker	37.7	30.1	
Current smoker	5.3	4.8	
Alcohol consumption			0.0004
Nondrinker	16.5	20.2	
Moderate	63.2	64.8	
Regular	20.3	15.0	
BMI categories			0.02
Normal	45.6	49.0	
Overweight	42.3	37.1	
Obesity	12.1	13.9	
Cognitive deficit (MMSE <24)			0.14
No	96.9	95.9	
Yes	3.1	4.1	
Use of antihypertensive drugs			0.04
No	56.9	53.1	
Yes	43.1	46.9	
Use of lipid-lowering drugs			0.21
No	67.9	70.1	
Yes	32.1	29.9	
Disability (assessed by the IADL scale)			$<10^{-4}$
No	96.0	92.3	
Yes	4.0	7.1	
Self-report history of stroke and CVD			0.005
No	85.7	81.9	
Yes	14.3	18.1	

*Onset of depression based on the CES-D over the 4-year follow-up was defined by reporting incident CES-D depression (defined by a CES-D score ≥16 or use of antidepressive drugs) over the 4-year follow-up, after excluding participants with prevalent CES-D depression at baseline and those who reported past or actual major depressives episodes.

The MetS is defined as a clustering of five metabolic disorders, including elevated abdominal obesity, low HDL cholesterol, high triglycerides, high blood pressure, and high fasting glucose or type 2 diabetes. We performed an analysis to examine which specific MetS components were associated with new onset of depressive symptoms over the 4-year follow-up, especially in age-group 1. Of five MetS components, only the low HDL cholesterol component was significantly associated with new onset of depressive symptoms in that age-group.

The evidence of an association between CVD and depression (15), combined with the fact that MetS is an establish risk factor for CVD (8), led us to explore whether the association between the MetS and new-onset depression would be driven by CVD. Analyses were rerun after excluding participants who *1*) reported a history of CVD at baseline (n = 666) and *2*) developed CVD during the 4-year follow-up (n = 201). The age-dependent association was largely replicated, with MetS retaining its observed association with a higher odds of new-onset depression in age-group 1, after excluding participants with a self-reported history of CVD (odds ratio 1.85 [95% CI 1.04–3.27]) and after additionally excluding participants with incident cases of CVD during the follow-up (odds ratio 2.06 [1.15–3.67]).

CONCLUSIONS—To our knowledge, this is the first study to report the association between MetS and the onset of depressive symptoms across different age-groups in a prospective, multicentric, elderly general-population cohort. MetS was associated with an almost doubling of the odds for new-onset depressive symptoms in the age-group 65–70 years, even in subjects without apparent CVD pathologies, whereas for older age-groups the association was not significant.

Several cross-sectional studies have shown an association between the MetS and depression in young adults (16) and middle-aged populations (17–19). Although in several studies the assumption has been that depression predicts the MetS, depression also could be a consequence of the MetS. To date, this direction of the association has been prospectively investigated in the middle-aged population (3,4,6), and a "two-way street" between depression and the MetS is now evidenced. Our observation of an elevated risk of developing depressive symptoms in both pre-elderly men and women with MetS is consistent with a previous report (6) carried out in a large, middle-aged British population that included men and women. Another prospective study (3) carried out in the middle-aged population has suggested a sex-specific association by finding an association in women but not in men and was in accordance with a previous study (4) reporting an association between MetS and depressive symptoms in a cohort of middle-age women. The absence of a relationship in men may, however, result from the lack of

Table 2—*Association of MetS and each of its components with onset of depressive symptoms over the 4-year follow-up by age-quartile group*

Age-groups	Without MetS or components [*n* (% depressed)]	With MetS or components, [*n* (% depressed)]	Odds ratio (95% CI)*	*P*
Overall MetS				
65.0–69.4	989 (14.8)	123 (21.1)	1.73 (1.02–2.95)	0.04
69.4–72.8	963 (16.4)	148 (16.9)	1.18 (0.70– 1.97)	0.58
72.8–76.8	960 (19.8)	152 (20.4)	0.94 (0.57–1.52)	0.81
76.8–91.1	960 (22.9)	151 (20.5)	0.89 (0.56–1.42)	0.63
Central obesity component†				
65.0–69.4	863 (14.6)	249 (18.5)	1.18 (0.80–1.75)†	0.40
69.4–72.8	821 (16.0)	290 (17.9)	1.00 (0.68–1.46)†	0.99
72.8–76.8	801 (19.5)	311 (20.9)	0.98 (0.69–1.38)†	0.91
76.8–91.1	770 (22.5)	341 (22.9)	0.86 (0.62–1.19)†	0.37
High triglyceride component				
65.0–69.4	933 (15.4)	179 (15.6)	1.14 (0.71–1.84)	0.58
69.4–72.8	916 (16.5)	195 (16.4)	1.11 (0.71–1.74)	0.63
72.8–76.8	947 (19.4)	165 (22.4)	1.18 (0.77–1.80)	0.45
76.8–91.1	943 (22.7)	168 (22.0)	0.99 (0.65–1.50)	0.95
Low HDL cholesterol component				
65.0–69.4	1,025 (14.8)	87 (23.0)	1.81 (1.04–3.17)	0.03
69.4–72.8	998 (16.5)	113 (15.9)	1.03 (0.59–1.80)	0.91
72.8–76.8	1,009 (19.4)	103 (24.3)	1.23 (0.74–2.03)	0.42
76.8–91.1	1,021 (22.1)	90 (27.8)	1.37 (0.82–2.29)	0.22
Hypertension component				
65.0–69.4	274 (18.6)	838 (14.4)	0.88 (0.60–1.30)	0.53
69.4–72.8	229 (21.8)	882 (15.1)	0.70 (0.47–1.03)	0.07
72.8–76.8	193 (26.9)	919 (18.4)	0.63 (0.43–0.92)	0.02
76.8–91.1	175 (25.7)	936 (22.0)	0.91 (0.61–1.33)	0.62
High fasting blood glucose component				
65.0–69.4	991 (15.3)	121 (16.5)	1.25 (0.70– 2.21)	0.45
69.4–72.8	982 (15.8)	129 (21.7)	1.80 (1.10– 2.96)	0.02
72.8–76.8	973 (20.1)	139 (18.0)	0.88 (0.54– 1.45)	0.63

*Odds ratio adjusted for age at baseline (by year), sex, study center, MetS treatment (use of lipid-lowering drugs or antihypertensive drugs), educational attainment, marital status, smoking, alcohol consumption, cognitive deficit (MMSE <24), disability (assessed by the IADL scale), BMI, and self-reported history of CVD (including stroke) at baseline. The reference (odds ratio = 1) corresponded to the subjects without MetS (or MetS components) for each age-group and conditions. †BMI categories were not included in this model.

statistical power as a result of the lower prevalence of MetS combined with the lower incidence of depressive symptoms in men compared with women. In our study, no evidence of an interaction with sex was found in the MetS/depressive symptoms relationship. Our results are in line with those reported by Almeida et al. (5), which was a study carried out on a large cohort of Australian older men (12,216 men aged 65–84 years), indicating that MetS was associated with an increase in the risk of incident depression.

MetS has gained clinical currency as a robust predictor of cardiovascular morbidity (8), which may consequently raise the prevalence of "vascular depression" (9). It is therefore crucial to determine whether the association between the MetS and depressive symptoms is not driven by depressive symptoms generated by manifest CVD. To our knowledge, very few studies have investigated this question (20). The present data provide evidence that the observed MetS/depression association may be independent of past, current, and incident CVDs and thus constitutes a novel finding.

Regarding the specific components of MetS, our data showed that the low HDL cholesterol component was associated with increased odds of new-onset depressive symptoms in those aged 65–70 years. Corresponding associations in that age-group were not observed for other MetS components. These data are in agreement with recent findings on the importance of dyslipidemia in the etiology of late-life depression (21) and also may imply that the association observed between MetS and depressive symptoms may be partially driven by HDL cholesterol in the pre-elderly participants. Additional work is needed to assess whether a better management of HDL cholesterol would reduce the incidence of depressive symptoms in this age-group.

The reason why MetS would predict new-onset depressive symptoms until age 70 years but not after remains unclear. MetS, as an entity, is an empirical concept (8), and it is possible that its clinical utility is less relevant in late-elderly subjects than in young elders. Another explanation would be that the MetS/depression relationship in older-aged subjects is masked by the higher disability, morbidity, and mortality rate associated with older age, because poor health is associated with both the MetS (12) and late-onset depression (14) in our previous work carried out in the 3C study and other cohorts. Finally, our results also

may reflect the fact that the late onset of late-life depression (after age 70 years) did not share the same etiology, and therefore the same risk factors, as the onset of depressive symptoms in middle-aged and pre- and "young" elderly subjects (7). Additional work is needed to further investigate whether the MetS/depressive symptoms relationship is different before and after age 70 years.

The longitudinal and multicentric design and the large sample size, which included >4,000 elderly subjects from the general population, constitute the major strengths of this investigation. Furthermore, to strengthen the assumption that participants included in the present analyses are free of depressive symptoms, we made the choice to also exclude all participants who were diagnosed at baseline as having current or past major depressive episodes based on the MINI Psychiatric Interview, which was administered in the entire 3C study cohort only at baseline. The limitations of the present report included, first, the classification of the clinical level of depression using the CES-D. This instrument has, however, been validated in the elderly general population, with a cutoff point of 16, which corresponds to clinically significant levels of depressive symptomatology and warrants clinical intervention (13). A second drawback involves reliance on the NCEP-ATP III in defining MetS, whereas other definitions also exist (8). However, the NCEP-ATP III is the most widely used definition, thus allowing us to compare our results with other studies. Furthermore, as the diagnosis of type 2 diabetes by a general practitioner was not assessed in the 3C study at baseline, we considered participants who reported the use of antidiabetes drugs as having type 2 diabetes to compute MetS according to NCEP-ATP III criteria. Third, the design of our study, an observational epidemiological study with MetS only assessed at baseline, does not permit us to conclude that there is a causal link between MetS and depressive symptoms. Furthermore, the description of factors associated with the MetS condition suggests that participants with MetS at baseline constitute a vulnerable population and thus the possibility that unmeasured confounders may partly explain the observed associations remains. However, our results were robust to adjustments for a large range of sociodemographic, health behavior, and health status factors, making it less probable that they were attributable to confounding or obtained by chance. Additional investigation is needed to establish MetS as an etiological factor for depression in pre-elderly subjects; especially, it remains to be shown whether a better management of MetS or its reversion is associated with lower incidence of depressive symptoms.

Despite these limitations, by exploring MetS/depressive symptoms across different age-groups in the elderly, our findings suggest that the MetS/depressive symptoms link evidenced until now in middle-aged subjects can probably be extended to young elderly populations but not to the oldest ones. At this stage, it is too early to present MetS as a predictor of depression, but under the hypothesis that prevention and treatment of MetS may be important for the prevention of depressive symptoms in middle age (6), results of our study would suggest that such intervention studies also would be justified in order to prevent depressive symptoms in populations between 65 and 70 years of age.

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T.N.A. conducted the statistical analyses and cowrote the initial and final drafts and is the guarantor. T.N.A. had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analysis. M.-L.A. contributed to the design of the 3C study and cowrote the final draft. I.J. and C.R. cowrote the final draft. P.B.-G. and C.D. contributed to the design of the 3C study and cowrote the final draft. M.K. cowrote the final draft. C.B. and K.R. contributed to the design of the 3C study and cowrote the final draft.

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