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Running title: Metabolic Syndrome and depression in elderly

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ABSTRACT

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 onset of depressive symptoms according to different age-groups in a large general elderly population.

Research Design and Methods: Prospective cohort study of 4446 men and women aged 65 to 91 and free of depression or depressive symptoms at baseline (the Three-City study, France). MetS was defined using the NCEP-ATP III criteria. New onset of depressive symptoms (the Center for Epidemiologic Studies Depression Scale (CES-D) 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 a 1.73-fold (95% CI: 1.02-2.95) odds for new-onset depressive symptoms in the youngest age group (65 to 70 at baseline), independently of cardiovascular diseases. No such association was seen in older age groups.

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

Keywords: Depressive symptoms; metabolic syndrome; elderly; prospective study

While depression has long shown to be associated with the development of metabolic syndrome (MetS) [1], more recent evidence of a "bi-directional" 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 have recently confirmed the association between MetS and depressive symptoms in a larger middle-aged population [6], suggesting that a better management of MetS might reduce the incidence of depressive symptoms in the 40-60 years age range. The adverse consequences of depression on quality of life in older adults [7] combined to the increasing prevalence of MetS [8] during old age, raised the interest in establishing whether MetS continues to increase the risk of depressive symptoms in older persons. 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 are also 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 assess prospectively 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

Study population

The Three-City Study (3C) is an ongoing multisite cohort study of community-dwelling persons aged 65 years or older and recruited from electoral rolls of three French cities (Bordeaux, Montpellier and Dijon) from 1999 to 2001 (N=9294) [10]. Participants were interviewed by trained staff and underwent a number of clinical examinations at baseline, two and four years. 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. Participants with dementia (n=500), those who presented depressive symptoms (n=2066) or who reported past or current major depressive disorders episodes (n=540) at baseline were excluded. Of these 6188 participants, the present analyses were carried out on the 4446 participants who had complete data on MetS, and all covariates measured at baseline and with at least one assessment of depressive symptoms available at 4-year follow-up.

Data Collection

Assessment of metabolic syndrome

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 3 or more of the following; waist circumference: men >102 cm, women >88 cm; serum triglycerides:≥ 1.7 mmol/L; HDL cholesterol: men <1.04 mmol/L, women < 1.29 mmol/L; systolic blood pressure:≥130 mmHg, diastolic blood pressure 85 mmHg systolic ; fasting glucose:≥6.1 mmol/L or presence of type 2 diabetes. As data on established diagnosis of type 2 diabetes by a practitioner were not available, the use of anti-diabetic treatment was considered as a proxy. Details of procedures regarding waist circumference, blood pressure, fasting blood glucose, HDL-cholesterol, and triglycerides measurements have been described previously [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 scale which has been validated in general population [13]. Depressive symptomatology refers to any symptoms of depression reported by subjects on the CES-D, with the higher number of symptoms being considered to represent greater severity. A cut-off 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 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 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.

Socio-demographic variables consisted of sex, age, study center, marital status (living alone /married or cohabited), educational level (no formal education or primary school / lower secondary education /higher secondary education or university degree), *Health behaviors* considered were smoking status (non /former /current smoker), alcohol consumption (no drinker /moderate defined by 3 (2) glasses or less per day for men (women) /high: > 3 (2) glasses per day for men (women)). *Health status* was ascertained BMI categories (normal: BMI <25 kg/m² /overweight: 25≤BMI<30 kg/m^2 / obesity: BMI≥30 kg/m²), cognitive impairment defined as having score below 24 on the Mini-Mental State Examination (MMSE), disability (evaluated using the instrumental activities of daily living (IADL) scale, (score>0)), and MetS treatment (lipid lowering drugs and treatment of hypertension including hypotensor, angiotensor, beta-blocker and diuretics, 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-report history of

cardio- 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 was also considered.

Statistical analyses

Student's *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 of CES-D depression 2) MetS status at baseline. Logistic regression models were performed to assess the association between MetS, its components and onset of CES-D depression. The statistically significant interaction found between age and MetS on new-onset depressive symptoms (Wald test p=0.03) led us to conduct these analyses separately within each age-quartile group. The mean age (SD) for each group was: age-group1: 67.9 (1.04); age-group2: 71.1 (1.0); age-group3: 74.7 (1.1); age-group4: 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, self-report history of CVD at baseline. Furthermore, to explore whether any association between MetS and CES-D depression could be driven by CVD, we repeated the analyses after excluding participants who self-reported 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 CES-D depression 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 the

MetS was 12.9% (n=574) at baseline. Compared to MetS-free participants, those with MetS were more likely to be men (p=0.002), former smokers ($p<10^{-4}$), in higher BMI categories ($p<10^{-4}$), to have less education (p=0.002), more disability (p=0.02) and more cognitive deficit (p=0.002) and to report history of CVD (p=0.0003) and to develop CVD during the study (p=0.009) (Appendix-Table-A).

Results of table 1 show that incidence of depressive symptoms increased significantly across age groups ($p < 0.0001$). Table 2 shows the association of MetS with incidence of depressive symptoms by age-groups categorized according to quartile distribution. In age-group1 (first quartile), participants with MetS were more likely to develop depressive symptoms (OR=1.73; 95% CI=1.02; 2.95) compared to participants without MetS at baseline, after adjusting for a large range of socio-demographic characteristics (sex, study center, educational attainment, marital status), health behaviors (smoking, alcohol consumption) and health status factors (MetS treatment, cognitive deficit, disability, BMI, self-report 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 which age-groups were categorized a priori: [65-70[, (n=1300); [70-75[, (n=1558); [75-80[, (n=1164); [80-91], (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 aged 65 to 70 (OR=1.82; 95% CI=1.12, 2.95), but no association was found for older participants (Appendix-Table-B).

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/ 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-group1. Of the five MetS components, only 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 to 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 re-run after excluding participants firstly who reported a history of CVD at baseline (n=666) and then those who 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-group1, after excluding participants with self-reported history of CVD (OR=1.85;95% CI=1.04, 3.27) and after further excluding participants with incident cases of CVD during the follow-up (OR=2.06; 95% CI=1.15, 3.67).

CONCLUSION

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 age-group 65 to 70, even in subjects without apparent cardio- or cerebro-vascular pathologies, while 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 could also be a consequence of the MetS. To date, this direction of the association has been prospectively investigated in 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 carried out in a large middle aged British population including men and women [6]. Another prospective study carried in middle-aged population has suggested a sex-specific association by finding an association in women but not in men [3] and was in accordance with a previous study reporting an association between MetS and depressive symptoms in a cohort of middle-age women [4]. The absence of relationship in men may however, result from the lack of statistical power due to lower prevalence of MetS combined to the lower incidence of depressive symptoms in men compared to 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. 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 [5].

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 has investigated this question [20]. The present data provide evidence that MetS-depression association observed may be independent of past and current and incident cardio- and cerebro-vascular diseases and thus constitutes a novel finding.

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

The reason why MetS would predict new onset of depressive symptoms until 70 years old 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 than in young elders. Another explanation would be that the MetS-depression relationship in older aged is masked by the higher disability, morbidity and mortality rate associated with older age, as poor health is associated with both the MetS [12] and late onset of depression [14] in our previous work carried on the Three-City Study and other cohorts. Finally, our results may also reflect the fact that late onset of late-life depression (after 70 years old) did not share the same etiology- and therefore the same risk factors - as onset of depressive symptoms in middle aged, pre- and "young"- elderly [7]. Further work is needed to further investigating whether MetS-depressive symptoms relationship is different before and after 70 years old.

The longitudinal and multicentric design and the large sample size including more than 4000 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 Three-city cohort only at baseline. The limitations of the present report included, first, the classification of clinical level of depression using CES-D. This instrument has however been validated in elderly general population, a cut-off point of 16 corresponding to clinically significant levels of depressive symptomatology warranting clinical intervention [13]. A second drawback involves reliance on the NCEP-ATP III in defining MetS while other definitions also exist [8]. However, the NCEP-ATP III is the most widely used definition, thus allowing comparison of our results with other studies. Furthermore as the diagnosis of type 2 diabetes by a general practitioner was not assessed in the Three-city Study at baseline, we considered participants who reported the use of anti-diabetic 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 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 socio-demographic, health behavior and health status factors making less probable that they were attributable to confounding or obtained by chance. Further investigation is needed to establish MetS as an etiological factor for depression in pre-elderly; 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 the 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 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 would also be justified in order to prevent depressive symptoms in populations between 65 to 70 years of age.

Author contribution

TNA conducted the statistical analyses and co-wrote the initial and final drafts, and is guarantor; MLA, PBG, CD, CB and KR contributed to the design of the 3C study; MLA, IJ, CR, PBG, CD, MK, CB and KR co-wrote the final draft.

TNA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Authors have no conflicts of interest to declare

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TABLES

Table 1: Characteristics of the 4446 of the Three-City Study participants according to the onset of new CES-D depression cases over the 4-year of follow-up.

		Cumulative onset of depressive symptoms *		
		No (%) (N=3619)	Yes (%) (N=827)	p
Age-quartile groups	[65.0-69.4]	26.0	20.8	$<10^{-4}$
	]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	Men	49.3	27.8	$<10^{-4}$
	Women	50.7	72.2	
Marital status	Living Alone	29.5	37.0	$<10^{-4}$
	Married or cohabiting	70.5	63.0	
Education	No qualification/primary	29.6	37.0	$<10^{-4}$
	Lower secondary	29.6	31.1	
	≥ Higher secondary	40.9	32.9	
Smoking habit	Never smoker	57.0	65.1	$<10^{-4}$
	Former smoker	37.7	30.1	
	Current smoker	5.3	4.8	
Alcohol consumption	No drink	16.5	20.2	0.0004
	Moderate	63.2	64.8	
	Regular	20.3	15.0	
BMI categories	Normal	45.6	49.0	0.02

	Overweight	42.3	37.1	
	Obesity	12.1	13.9	
Cognitive deficit (MMSE <24)	No	96.9	95.9	0.14
	Yes	3.1	4.1	
Use of anti-hypertensive drugs	No	56.9	53.1	0.04
	Yes	43.1	46.9	
Use of lipids lowering drugs	No	67.9	70.1	0.21
	Yes	32.1	29.9	
Disability (assessed by IADL scale)	No	96.0	92.3	$<10^{-4}$
	Yes	4.0	7.1	
self-report history of stroke and CVD	No	85.7	81.9	0.005
	Yes	14.3	18.1	

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

MMSE: Mini Mental state Examination, IADL: Instrumental Activities of Daily Living, BMI: Body Mass Index, CVD: cardiovascular diseases

Table 2: Association of metabolic syndrome and each of its components with onset of depressive symptoms over the 4-year follow-up by age quartile group.

Age group	Without MetS or components (n, % depressed)	With MetS or components (n, % depressed)	OR (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 TG 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]	1025 (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]	1009 (19.4)	103 (24.3)	1.23 (0.74;2.03)	0.42
[76.8-91.1]	1021 (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 FBG 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, anti-hypertensive drugs), educational attainment, marital status, smoking, alcohol consumption, cognitive deficit (MMSE<24), disability (assessed by IADL scale), BMI, self-report history of CVD (incl. stroke) at baseline. The reference (OR=1) corresponded to the subjects without MetS (or MetS components), for each age group and conditions.

† BMI categories were not included in this model