METABOLIC SYNDROME AND DISABILITY: FINDINGS FROM THE PROSPECTIVE THREE-CITY STUDY

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ABSTRACT

Background: Metabolic syndrome (MetS) is a potentially reversible cause of disability in the elderly. The published literature suggests that the MetS-disability association is likely to be complex, dependent on factors such as co-existing risk factors and may vary for each of the specific MetS components and more evidence is needed to understand the specific MetS functional consequences.

Methods: Prospective analyses included data from 6141 participants (60.9% women) aged 65 and over from the Three-City cohort. Mixed logistic models were used to determine associations between MetS (NCEP-ATP III criteria) and 7-year incident disability measured as social restriction, mobility limitations (Rosow and Breslau scale), and limitations in instrumental and basic activities of daily living (IADL and ADL).

Results: MetS was associated with incident social restriction (odds ratio (OR)=1.55, 95% CI: 1.14-2.09), limited mobility (OR=1.52, 95% CI: 1.21-1.90), and IADL limitations (OR=1.62, 95% CI: 1.24-2.10) after adjustment for a range of potential socio-demographic, health behaviour and health status confounders at baseline. These associations were independent of chronic conditions, including cardiovascular disease and dementia. There was evidence of associations between MetS components; central obesity, high triglycerides and elevated fasting glucose and incidence of limitations in mobility and IADL.

Conclusions: Our results suggest that the increased risk of mobility and IADL limitations in the elderly associated with MetS is over and above that associated with its components.

A worldwide increase in the number of disabled elderly people is expected in the coming decades (1). This has led to considerable public health concern about the predicted social and economic burden associated with the growing disabled population and a need for improved prevention. With chronic disease being the leading cause of disability, current research is seeking to identify early-stage markers and potentially reversible risk factors for these disorders to inform implementation of prevention programmer prior to onset of the disability. In this context, metabolic syndrome (MetS) is of particular interest (2) as it represents a cluster of metabolic and vascular abnormalities which increase the risk of a range of common chronic cerebrovascular, cardiovascular and neurological disorders known to be associated with disability. MetS may thus constitute an "early warning signal" for potentially disabling disorders. Importantly, all its components (central obesity, hyperglycemia, dyslipidemia and hypertension) are highly amenable to therapeutic intervention.

To date, research in this area is very limited. To our knowledge only five studies have assessed the association between MetS and onset of disability (3-7). Of these, three focused on the association between MetS and mobility limitation only (4, 5, 7). The other two studies investigated the association of MetS with limitations in instrumental activities of daily living (IADLs) and basic activities of daily living (ADLs). While the first study showed that MetS was associated with a higher rate of ADL limitations and poorer health-related quality of life (6), the second reported that participants with MetS (but without type 2 diabetes) showed a 3-year decline in activities requiring strength and mobility but not ordinary daily activities (3). The association between MetS and disability is likely to be complex and dependent on factors such as MetS severity and co-existing risk factors, and may vary for each of the specific MetS components. Furthermore, any study of disability needs to be prospective and take into account multiple potential confounding factors, most notably co-morbidity, if robust associations that can indicate causal processes are to be identified.

Accordingly, the aim of this study was to examine longitudinally the association between MetS and incident disability using multiple measures of limitation within a large elderly population, the Three City Study (3C) study. Our secondary aim was to examine whether associations observed between MetS and limitations were attributable to MetS overall or driven by a specific component. An advantage of the 3C dataset is the opportunity to take into account a large range of potential confounders and a sufficiently long prospective follow-up.

METHODS

Study Design and Participants

The Three City Study (3C) is an ongoing multisite cohort study of 9294 community-dwelling persons aged 65 years or older and recruited from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier) from 1999 to 2001 (8). The ethics committee of the University-Hospital of Bicêtre, France, approved the study protocol and written informed consent was obtained from each participant. Participants underwent a standardized evaluation with face-to-face interviews and clinical examinations were undertaken at baseline and at 2, 4 and 7 years in a study center or during home visits.

Outcome of Interest

Three complementary activity limitation indicators were measured at baseline and repeated at each follow-up; mobility, IADLs and ADLs. Mobility was assessed using the Rosow and Breslau scale (9) which assesses ability to do heavy housework, walk half a mile and climb stairs. The Lawton–Brody IADL scale was used to assess an individual's ability to use the telephone, manage medication and money, use public or private transport, shop, and, for women only, prepare meals and do housework and laundry (10). For ADLs, participants were asked whether they needed help for any task included in the Katz ADL scale: bathing, dressing, transferring from bed to chair, toileting, and eating (11). For each domain of disability, participants indicating inability to perform one or more activities without help were considered as having limitations: moderate limitation for mobility limitation and more severe limitation for IADL or ADL limitations.

Social restriction: confinement to bed, home, or outings restricted to the local neighbourhood assessed using the International Classification of Functioning, Disability and Health (12) was considered as the fourth outcome .

Explanatory Variables

MetS was defined using the National Cholesterol Education program Adult Treatment Panel III (NCEP ATP III) criteria (13), 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; high density lipoprotein (HDL) cholesterol: men <1.04 mmol/L, women < 1.29 mmol/L; systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or treatment of hypertension; fasting blood glucose (FBG) ≥5.6 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. Waist circumference was measured between the lower rib margin and the iliac crest following normal expiration. Details of procedures for measuring blood pressure, fasting blood glucose, HDL-cholesterol, and triglycerides have been previously described (14).

Covariates at baseline

Socio-demographic variables were sex, age, study center, marital status, educational attainment and household income. *Health behaviors* included smoking status and alcohol consumption. *Health status* was ascertained by self-reported history of cardiovascular disease (CVD) (including stroke, angina pectoris, myocardial infarction and cardiac and vascular surgery), self-reported history of respiratory disease (asthma attacks during the last year or chronic bronchitis), use of lipid lowering drugs, body mass index (BMI) categories (normal: BMI <25 kg/m² /overweight: 25≤BMI<30 kg/m^2 / obesity: BMI≥30 kg/m²) and current depressive symptoms assessed by the Center for Epidemiologic Studies-Depression scale (CES-D) with a cut-off point of ≥ 16, or a current major depressive episode diagnosed by the Mini International Neuropsychiatric Interview algorithms (15). Aging-related impairments

also taken into account were visual impairment, defined as having a corrected near visual acuity (Parinaud scale) of more than 4, or difficulties recognizing a familiar face at 4 meters; hearing impairment defined as deafness or only able to hear a conversation when a single person speaks loudly; and cognitive impairment defined as having a score below 24 on the Mini-Mental State Examination (MMSE). Finally, presence of allele ε4 of the apolipoprotein E genotype (APOEε4) was included as covariate as it has been found to be associated with moderate activity limitation (16).

Statistical Analyses

The χ^2 test was used to compare the categorical characteristics of participants according to the presence of MetS at baseline. For each indicator of activity limitation, longitudinal associations according to MetS status, each of its components and the severity of MetS (assessed as the sum of MetS components at baseline and analysed as a continuous variable, range 0-5) at baseline were examined in participants free of that limitation at baseline. Thus the sample size was 3497 for mobility, 5764 for IADL, 6125 for ADL and 5893 for social restriction. In longitudinal studies the within-person responses (i.e. the repeated evaluations of the limitations) are correlated. This correlation was accounted for by using a mixed logistic model (17). In brief, this model has four basic advantages: (i) the evolution of limitations within the individual over time are taken into account, including possible reversion to the normal (non-disabled) state; (ii) participants with incomplete responses across time are included in the analysis; (iii) participants do not have to be evaluated at the same time points; (iv) the model allows within-participant dependency to vary from one participant to another, via random effects. The SAS procedure NLMIXED was used to estimate the parameters (version 9.2).

The association of MetS and its components with incident activity limitations and social restriction during follow up was first minimally adjusted for sex, center, age, time and interaction time * age (*Model 1*). Multivariate odds ratios (OR) and their 95% confidence interval (95 % CI) were additionally adjusted for income, education level, marital status, alcohol intake, smoking status, BMI, CVD, use of lipid lowering drugs, respiratory disease, depressive symptoms, and cognitive, visual and hearing impairments and APOEε4 genotype (*Model 2*). Models did not account for time-varying covariates as most covariates were only assessed at baseline. Interactions between MetS and the covariates on regarding the disability outcomes were not found to be statistically significant at $p < 0.05$.

In supplementary analyses, we further explored the extent to which any associations between MetS and indicators of disability are driven by specific MetS components. In these analyses associations between MetS and indicators of the disability were adjusted successively for each of the MetS components. To assess the weight of individual MetS components in the MetS-disability indicator association, we calculated the percent attenuation of this association after adding each individual component separately to a model already including MetS. The percent attenuation in the association was determined using the formula $[(\beta_{MetS} - \beta_{MetS\ adjusted\ for\ component})/\beta_{MetS}] \times 100$, where βs are the coefficients estimated from the mixed logistic model.

RESULTS

Of the 9080 dementia-free participants included at baseline, 877 missed all follow-up evaluations of disability outcomes (of whom 410 died), 1029 had missing data for at least one component of MetS and a further 1033 had missing data for covariates assessed at baseline. These participants were excluded from the present analyses which were thus conducted on 6141 participants (2404 men and 3737 women). Compared with participants included, those excluded were more likely to be older, have lower education and existing limitations in mobility and daily activities. They were also more likely to have depressive symptoms, have a history of CVD or cognitive, visual or hearing impairment ($p<0.0001$ for each comparison) and to have MetS ($p=0.007$).

In the 6141 participants included in this study, the prevalence of MetS at baseline was 17.3%. The characteristics of these participants, as a function of MetS status, are presented in Table 1. Compared to participants without MetS, those with MetS were more likely to be male, older, have low educational attainment, lower alcohol intake and be ex-smokers. MetS was also associated with a higher prevalence of depressive symptoms, cognitive impairment, respiratory disease and CVD as well as higher BMI and use of lipid lowering agents. With the exception of ADL, participants with MetS were more likely to report limitations at baseline.

The association between MetS status at baseline and incidence of disability over the 7 years of follow-up for each disability indicator was assessed by performing analyses in participants without limitations on the individual scales at baseline. Overall the incidence (at least one follow-up visit with limitations) was 14.9%, 63.5%, 21.3% and 2.6% for social restrictions, mobility, IADL and ADL respectively and the reversibility rate (percentage of participants with incident limitations who reversed to normal state at a subsequent visit) was16.3%, 29.1%, 16.4% and 12.6% respectively. Table 2 shows the crude rates of social

restriction and mobility and activity limitations by follow-up visit as a function of baseline MetS. After adjustment for sex, center, age, time and the interaction between age and time, participants with MetS at baseline had double the odds of developing limitations in mobility, IADL and ADL and nearly triple the odds of developing social restrictions (Model 1) compared to participants without MetS. Further adjustment for socio-economic factors (income, education, living alone), health behaviors (alcohol, smoking) and health factors (BMI, cognitive, hearing and visual impairment, depressive symptoms, lipid lowering treatment, respiratory disease, CVD and APOEε4 genotype) substantially attenuated these associations (Model 2) although they remained statistically significant except for the ADL scale (social restrictions: Odds ratio[OR]=1.55, 95% CI: 1.14-2.09; mobility limitations: OR=1.52, 95% CI: 1.21-1.90 and limitations in IADL: OR=1.62, 95% CI: 1.24-2.10), (Table2). Similar results were obtained when considering the severity of MetS - assessed by the number of MetS components at baseline – as a predictor of future disability (Table 3).

Multivariate analyses of associations between each component of MetS and onset of limitations in IADL, mobility and social restriction showed that of the five criteria, central obesity and high triglyceride levels were associated with all three disability outcomes (Figure 1). The elevated blood glucose component was only associated with the onset of mobility and IADL limitations; the low HDL-cholesterol component was only associated with onset of mobility limitations; and the high blood pressure component with the onset of limitations in IADL.

Further analyses in which MetS as a whole was adjusted successively for each of its components were performed to assess the extent to which specific MetS components may drive the overall MetS-activity limitation association (Appendix-Table A). Except for the MetS-social restriction association which was no longer statistically significant after adjustment for central obesity, these analyses showed that MetS remained significantly

associated with social restriction, mobility and IADL limitations regardless of the component adjusted for in the analyses. These models also showed an independent effect of central obesity (p=0.03) and high blood pressure (p=0.05) on limitations in IADL. The central obesity component was also found to be independently associated with social restriction (p=0.002). The percentage by which the MetS-limitation associations were attenuated by adjustment for the individual MetS components was calculated in additional analyses (Appendix-Table B). On all scales the percentage attenuation achieved when including central obesity and elevated blood glucose together was slightly higher than the sum of the percentage attenuation achieved by each component alone, suggesting that central obesity may potentiate the impact of elevated blood glucose on limitations.

To explore whether associations between MetS and incident limitations could be driven by CVD, dementia or type 2 diabetes, we re-ran the analyses after excluding 1) participants with prevalent CVD at baseline and those who developed CVD over the follow-up (Appendix-Table C) and 2) incident cases of dementia (Appendix-Table D); and 3) participants with type 2 diabetes (assessed by using treatment for type 2 diabetes) (Appendix-Table E). This had little effect on the associations.

DISCUSSION

This study of a large cohort of community-dwelling elderly participants shows that MetS increased the odds of developing social restrictions and limitations in mobility and IADL over a 7-year follow-up by at least 50%. Our analysis took into account a range of socio-demographic variables, health behaviors and health status factors such as depression, and cognitive, visual and hearing impairment; and we confirmed that the association was not mediated by CVD and dementia, which also increase with aging and are associated with disability. Of the five MetS components, central obesity and high triglycerides were significantly associated with the incidence of limitations assessed by all three scales. In addition, elevated fasting glucose was associated with mobility and IADL limitations, while low HDL-cholesterol was associated with mobility, and high blood pressure with IADL. However, MetS overall increased the odds of moderate mobility limitations, and more severe limitations measured by IADL.

Our results on the association between MetS and mobility restriction are in line with previous longitudinal studies carried out in the elderly (3-5, 7). Although the definition of mobility limitation and the prevalence of MetS varies between studies (from 29% to more than 45%) an increase in the rate of mobility limitations associated with MetS is reported by all. The study that failed to observe this association was limited to non-obese men (7). Our findings, carried out in an elderly cohort with a lower prevalence of MetS (17.3%) and longer follow-up, bring additional evidence to the existing literature by showing that MetS increased the odds of social and mobility restrictions by over 50%.

Several studies that focus on the determinants of disability evaluated mobility limitations as they are common at advanced age and highly predictive of more severe and rapid progression to disability (4, 5, 7). Furthermore, mobility difficulties at older ages constitute a stage early enough in the disablement process to be amenable to intervention (18).

However, to examine the predictive link between MetS and overall disability in old age, it is important to use scales that not only assess mobility difficulties, but also limitations in more complex activities of daily living, usually assessed with IADL and ADL scales. Epidemiological observations are scarce regarding the association between MetS and ADL/IADL limitations. One cross-sectional study has reported in a stroke-free population that MetS was associated with a 2-fold increased prevalence of dependence as measured by ADL and IADL (6). Only one study has investigated this association prospectively (3). This study, carried out on a cohort of older Mexican Americans, failed to observe an association between MetS and progression of ADL/IADL limitations in participants without type 2 diabetes. Our study is the first to provide evidence of an association between MetS and incidence of limitations in IADL over a 7-year follow-up. This association was found to be independent of elevated fasting blood glucose, anti-diabetic drugs, or other MetS components suggesting that MetS may constitute an independent predictor of limitation. While a significant association was observed between MetS and incidence of limitations in ADL in sex and age adjusted analyses, this association was lost after controlling for health behaviour and health status.

Further studies prospectively assessing associations between MetS and incidence of limitations in ADL are needed, as the present study, with less than 3% incident ADL cases over the 7-year follow-up, may not be sufficiently powered. Future work is needed to establish whether MetS plays a role at all stages of the disability process. This would suggest that detecting and managing metabolic disorders at an early stage might be beneficial to delay disability onset among the high number who would otherwise end up with mobility or activity limitations

We assessed whether components of MetS were associated with the onset of disability-related limitations. Our findings are concordant with those previously reported in

literature as we observed that central obesity (19, 20), high blood pressure (5, 21) and elevated fasting glucose (22) increased the odds of new-onset IADL limitations, and that central obesity was associated with mobility limitations (23, 24) independently of having MetS. In terms of designing efficient intervention strategies, it is important to determine whether the MetS-health outcome association is driven by all or only some of its components. Our findings show that MetS remains significantly associated with new onset limitations after adjustment for each of its components, making it less probable that the observed predictive effect of MetS on the disability process is completely driven by a single component. Furthermore we show that the percentage attenuation of the MetS-limitation association achieved when including its two leading components - central obesity and elevated fasting glucose - was rather higher than the sum of the percentage attenuation achieved by each component alone. This suggests that central obesity may potentiate the effect of elevated fasting blood glucose, a finding that reinforces the clinical utility of the MetS concept (2).

The MetS-limitations association is biologically plausible with possible underlying pathophysiological mechanisms including chronic inflammatory processes (and their catabolic consequences on muscle) (25), hyperglycemia-related mechanisms (5) (fatigue, headache, oxidative stress), and obesity-related mechanism (26) (pain, osteoarthritis, reduced physical activity). All these mechanisms contribute to muscle mass decrease and impaired muscle strength predisposing individuals to limitations involving physical activity (27).

Our study was subject to a number of limitations. First, disability outcomes were self-reported which may have led to over-reporting in participants who suffered from metabolic (e.g. obesity) or vascular (e.g. hypertension) disorders. However, this may be counter-balanced by the fact that participants included in the present study were less likely to report limitations compared to those excluded. Second, in spite of adjustments for a large number of potential confounding factors - measures of physical health (comorbidity, sensory

impairments, and health behaviors), cognitive impairment, and depression - the possibility remains that unmeasured confounders, such as physical activity at baseline, may still explain part of the associations between MetS or its components and the incidence of limitations. On the other hand, possible over-adjustment may have occurred when several factors were added to the models, such as BMI, as these would dilute the influence of MetS components. A third drawback concerns the NCEP (ATPIII)(13) definition of MetS as other definitions have also been proposed (2, 28). However, the NCEP ATP III criteria remain the most widely used, allowing comparison of our results with other studies. The prevalence of MetS in our study (17.3 %) is about half that commonly observed in the US population (29, 30). The Three-city study participants - all volunteers - have been shown to be healthier, with higher socio-economic status compared to the general population of French elderly; a factor that may limit the generalizability of our findings. Finally, a large number of participants were excluded from the present study due to existing high rates of both MetS and disability. However, this is more likely to have weakened the associations presented rather than negate the results.

Despite these limitations, the present prospective study with a multicenter design, based on a large community sample permitted a detailed evaluation of the onset of limitations over 7 years. The use of a number of validated scales exploring the major domains of dependency corresponding to levels of disability severity, allowed us to show that MetS is associated with a 50% increase in the odds of developing social restriction and limitations in mobility, and a 62% increased in the odds of difficulties with instrumental activities of daily living. Our findings suggest that MetS increased both the onset and severity of disability at older ages. Additional analyses are needed to assess whether the screening of MetS in clinical practice and the optimal management of obesity and hyperglycemia in older participants by the medical practitioner may help to reduce age-related disability and delay the loss of autonomy with its subsequent risk of institutionalization.

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Author contributions:

IC researched data, conducted the statistical analyses and co-wrote the final drafts and is the guarantor. KP researched data and contributed to the discussion and reviewed/edited the manuscript. MLA researched data and contributed to the discussion and reviewed/edited the manuscript. VG researched data. CB researched data and reviewed/edited the manuscript. PBG researched data and reviewed/edited the manuscript. KB contributed to the discussion and reviewed/edited the manuscript. MK contributed to the discussion and reviewed/edited the manuscript. KR researched data and contributed to the discussion and reviewed/edited the manuscript. TNA researched data and wrote the first draft and the final draft.

IC is the guarantor of this work and, as such, 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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FIGURE LEGENDS

FIGURE 1. Fully adjusted odds ratio and 95% CI of limitations by metabolic syndrome component

Legend: Black bar: social restriction, grey bar: Rosow and Breslau mobility scale, dotted bar: IADL limitations

Footnotes: adjusted for sex, center, age, time, interaction time * age, income, education level, marital status, alcohol intake, smoking status, BMI, CVD, respiratory diseases, depressive symptoms, use of lipid lowering drugs, and cognitive, visual, hearing impairment and APOEε4 genotype.

TABLES

Table 1. Characteristics of the 6141 participants according to Metabolic syndrome* status at baseline

	No MetS N=5078		MetS N=1063		Chi2
	N	%	N	%	P-value
Sex: women	3128	61.6	609	57.3	0.009
Age					
65-69	1354	26.7	228	21.5	0.004
70-74	1739	34.2	399	37.5	
75-80	1383	27.2	297	27.9	
80+	602	11.9	139	13.1	
Center					
Bordeaux	1087	21.4	273	25.7	0.003
Dijon	2775	54.7	570	53.6	
Montpellier	1216	23.9	220	20.7	
MetS components					
Central obesity	944	18.6	831	78.2	<0.0001
High TG	389	7.7	630	59.3	<0.0001
Low HDL cholesterol	196	3.9	471	44.3	<0.0001
High BP	3996	78.7	1024	96.3	<0.0001
Elevated FBG	468	9.2	670	63.0	<0.0001
Social restriction	171	3.4	76	7.2	<0.0001
Mobility limitations	2047	40.8	564	53.1	<0.0001
IADL limitations	276	5.4	97	9.1	<0.0001
ADL limitations	11	0.2	3	0.3	0.72†

	No MetS		MetS		
	N=5078		N=1063		Chi2
	N	%	N	%	P-value
Education: ≤ 5 years	1145	22.6	291	27.4	0.0007
High income (≥1525€ per month)	3500	68.9	648	60.9	<0.0001
Living alone	1713	33.7	379	35.7	0.23
Alcohol					
0	944	18.6	239	22.5	0.001
1-36 g/day	3717	73.2	719	67.6	
> 36g/day	417	8.2	105	9.9	
Smoking					
Never	3145	61.9	604	56.8	0.002
Former	1653	32.6	405	38.1	
Current	280	5.5	54	5.1	
BMI					
Normal	2739	53.9	140	13.2	<0.0001
Overweight	1941	38.2	503	47.3	
Obese	398	7.8	420	39.5	
Cognitive impairment	186	3.7	64	6.0	0.0004
Visual impairment	358	7.0	91	8.5	0.09
Hearing impairment	303	6.0	79	7.4	0.07
Respiratory disease	266	5.2	79	7.4	0.005
CVD	727	14.3	216	20.3	<0.0001
Depressive symptoms	1099	21.6	283	26.6	0.0004
Lipid lowering treatment	1560	30.7	414	39.0	<0.0001

	No MetS		MetS		
	N=5078		N=1063		Chi2
	N	%	N	%	P-value
APOE4	1021	20.1	211	19.9	0.85

MetS: metabolic syndrome; TG: triglycerides; BP: blood pressure; FBG: fasting blood glucose; IADL: instrumental activities of daily living; ADL: basic activities of daily living; BMI: body mass index; CVD Cardiovascular diseases (including stroke); APOEε4: (having at least one ε4 allele).

*MetS defined according the National Cholesterol Education program Adult Treatment Panel III (NCEP ATP III) criteria (13)
† Fisher's exact test

Table 2. Incident cases of limitations by baseline metabolic syndrome and adjusted risk of limitations

	No at baseline	Follow-up			Model 1			Model 2		
		2 years	4 years	7 years						
		%	%	%	OR*	95%CI	p-value	OR†	95%CI	p-value
Social restriction										
Baseline MetS	N=5893	N=5713	N=5179	N=4243						
No		3.5	5.3	12.0	1			1		
Yes		6.5	8.5	22.0	2.83	2.13-3.75	<0.0001	1.55	1.14-2.09	0.006
Mobility										
Baseline MetS	N=3497	N=3344	N=3112	N=2624						
No		33.1	37.9	49.5	1			1		
Yes		44.0	45.5	60.2	1.90	1.54-2.35	<0.0001	1.52	1.21-1.90	0.0003
IADL										
Baseline MetS	N=5764	N=5575	N=5063	N=4150						
No		4.7	7.6	18.5	1			1		

Yes		9.0	10.5	30.5	2.55	1.98-3.27	<0.0001	1.62	1.24-2.10	0.0003
ADL										
Baseline MetS	N=6125	N=5927	N=5367	N=4349						
No		0.6	1.0	1.8	1			1		
Yes		0.8	1.4	2.9	2.00	1.07-3.77	0.03	0.91	0.48-1.74	0.79

MetS: metabolic syndrome; IADL: instrumental activities of daily living; ADL: basic activities of daily living

* adjusted for center, baseline age, time, baseline interaction age x time and sex
† adjusted for center, baseline age, time, baseline interaction age x time, sex, education, income, living alone, alcohol, BMI, smoking, cognitive impairment, visual impairment, hearing impairment, depressive symptoms, respiratory disease, CVD, lipid lowering treatment and APOEε4 genotype.

Table 3. Associations between baseline number of metabolic syndrome components and risk of limitation incidence

	Model 1			Model 2		
	OR*	95%CI	p-value	OR†	95%CI	p-value
Social restriction						
No. of MetS components	1.62	1.45-1.81	<0.0001	1.24	1.10-1.40	0.0005
Mobility						
No. of MetS components	1.29	1.20-1.39	<0.0001	1.18	1.09-1.29	<0.0001
IADL						
No. of MetS components	1.52	1.38-1.67	<0.0001	1.27	1.14-1.41	<0.0001
ADL						
No. of MetS components	1.39	1.09-1.77	0.007	0.97	0.74-1.26	0.80

MetS: metabolic syndrome; IADL: instrumental activities of daily living; ADL: basic activities of daily living

* adjusted for center, baseline age, time, baseline interaction age x time and sex
† adjusted for center, baseline age, time, baseline interaction age x time, sex, education, income, living alone, alcohol, BMI, smoking, cognitive impairment, visual impairment, hearing impairment, depressive symptoms, respiratory disease, CVD, lipid lowering treatment and APOEε4 genotype.