Contribution of Metabolic Syndrome Components to Cognition in Older Persons

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Running title: Metabolic syndrome components and cognition

OBJECTIVE

Recent evidence suggests that the metabolic syndrome (MetS) and inflammation affect cognitive decline in old age, and that they reinforce each other. It is unknown what the role of the individual components of MetS on cognition is.

RESEARCH DESIGN AND METHODS

The sample consisted of 1,183 participants of the Longitudinal Aging Study Amsterdam (LASA), aged 65 to 88 years. MetS (US National Cholesterol Education Program definition) and its individual components, and the inflammatory markers C-reactive protein (CRP) and α1-antichymotrypsin (ACT) were assessed. Cognitive assessments included general cognition (MMSE), memory (verbal learning test), fluid intelligence (Raven's matrices), and information processing speed (coding task).

RESULTS

36.3% of the sample had MetS. MetS was significantly associated with all cognitive measures ($p<0.05$). Of the individual components, hyperglycemia was most strongly and significantly associated with cognitive function (multivariate adjusted models; B's, indicating differences in scores between both groups, ranging from -0.38 to –1.21). There was a significant interaction between MetS and inflammation on cognition ($p<0.01$ to 0.09). MetS was negatively associated with cognition in subjects with high inflammation (highest tertile on both CRP and ACT; B's range from -0.86 to -1.94, $p<0.05$), whereas an association was absent in subjects with low inflammation (B's range -0.10 to -0.70).

CONCLUSIONS

Subjects with MetS showed poorer cognitive performance than subjects without MetS, especially in those with high levels of inflammation. Hyperglycemia was the main contributor of the association of MetS with cognition.

The metabolic syndrome (MetS) identifies the clustering of hypertension, abdominal obesity, dyslipidaemia, and hyperglycaemia. It is very common, especially among older persons, with a prevalence of 45% at ages 60 years and over (1). MetS has been shown to increase the risk of diabetes mellitus and cardiovascular disease. The concept, that was introduced as syndrome X in 1988 (2), has since then been subject to a large amount of research, and an even larger amount of discussion about its validity and utility (3).

Recent evidence suggests that MetS also affects cognitive decline in old age, especially among those with high levels of inflammation (4). An increased inflammatory response has been associated with cognitive decline (5-10) and Alzheimer's disease (AD), and may be considered as a primary causal pathway of AD (11). In addition, MetS often co-occurs with an increased inflammatory response, although it is unknown whether MetS leads to increased inflammation or vice versa (12).

The question arises whether MetS has higher predictive value than the sum of its individual components, and what the role of its individual components is. There is no evidence that the risk of MetS on heart diseases and diabetes mellitus is higher than that of the sum of its components (3,13), but it is unknown how this accounts for cognitive function as outcome.

Therefore, the present study aims to investigate the association between MetS and its individual components with cognition, and whether this association is modified by inflammation. We hypothesize that: 1) MetS and its individual components are associated with cognition; 2) the link between MetS and cognition is modified by chronic inflammation. We test these hypotheses on different cognitive domains, which is a novel aspect compared to the previous study on this topic (4).

RESEARCH DESIGN AND METHODS

Study population

Study subjects participated in the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in the aging population in the Netherlands. The sampling and data collection procedures have been described in more detail elsewhere (14). Briefly, a sample of older men and women (aged 55 to 85 years), stratified by age and sex according to expected five-year mortality, was drawn from population registries. Respondents were interviewed at home in a main and a medical interview, in which structured questionnaires were completed and tests were performed. Informed consent was obtained from all respondents and the study was approved by the Medical Ethics Committee of the VU University Medical Center (VUmc). In total, 3,107 predominantly Caucasian (>99%) subjects were enrolled in the baseline examination in 1992/1993.

The analytic sample for the present study consisted of subjects who participated in the medical interview of the second data collection (1995/1996), which was restricted to subjects who were aged 65 years and older. Loss-to-follow up of the original cohort was mainly because of mortality (14%). More subjects with cognitive impairments were lost-to-follow up, although the sample included enough subjects who performed in the lower ranges of cognition to detect associations with MetS. Both cognition and MetS were determined at the same measurement. Of the 1,720 eligible respondents, 1,509 took part in the interview, and for 1,321 blood samples were obtained. MetS could be determined for 1,279 respondents and 96 participants had missing data on any cognitive test, leaving 1,183 participants in this study (68.8% of 1,720). An additional 31 participants had missing data on the inflammatory markers. Respondents included in this study were significantly younger, more often men, higher educated, and had better cognitive scores (all $p<0.05$) than the 537 subjects not included in this study.

Cognitive performance

Information processing speed was measured with a letter substitution task, the Alphabet Coding Task-15. The respondent had to name the missing characters corresponding to the characters in the upper boxes (using the substitution key) as quickly and accurately as possible. The score consisted of the number of completed characters within one minute. The mean score for three trials was used in the analyses (range, 1.0 to 42.7).

Memory was measured with the Auditory Verbal Learning Test (AVLT). Fifteen words were read aloud, after which the respondents recalled as many words as possible (immediate recall, maximum score of three trials; range, 2 to 15). Delayed recall (range, 0 to 15) was measured after approximately 20 minutes.

Fluid intelligence, the ability to deal with essentially new problems, was measured with Raven's Coloured Progressive Matrices (RCPM). The respondent was presented with an incomplete design and six alternatives among which one must be chosen that best completes the design. Every correctly solved item on two sets of 12 items each resulted in 1 point (range, 1 to 24).

Overall cognitive function was measured with the MMSE, a 23-item global cognitive function test, which includes questions on orientation in time and place, attention, language, memory and visual construction. Actual scores ranged from 16 to 30, with a higher score indicating better performance.

The tests have been described in more detail elsewhere (4). The Spearman correlation between immediate and delayed recall on the memory test was 0.80 ($p<0.01$). All other tests correlated between 0.32 (Raven's matrices X delayed recall) and 0.56 (Raven's matrices X coding task; all $p<0.01$).

Metabolic syndrome

MetS was defined as a presence of 3 or more of the following criteria: triglycerides ≥ 1.7 mmol/L (150 mg/dl); HDL cholesterol < 1.0 mmol/L (40 mg/dl) for men and <1.3 mmol/L (50 mg/dl) for women; blood pressure ≥ 160/90 mmHg or antihypertensive medication; waist circumference > 102 cm for men and > 88 cm for women; fructosamine ≥ 0.247 mmol/L or antidiabetic medication. This is the definition established by the US National Cholesterol Education Program (NCEP)-ATP3 (15), with an increased cutoff for blood pressure, adjusted for an older population. Furthermore, the cutoff of 0.247 mmol/L for fructosamine corresponds to the cutoff of 6.1 mmol/L for fasting plasma glucose in terms of sensitivity and specificity in discriminating subjects with glucose intolerance from subjects with normal glucose tolerance (16). Because the instructions prior to blood sampling allowed respondents to take tea and dry toast, but no dairy products, we cannot guarantee fasting blood samples. Fructosamine is little affected by eating, unlike the plasma glucose level. Therefore, we used serum fructosamine as a proxy for plasma glucose.

Assessment of components of the metabolic syndrome

Blood pressure was measured in sitting position using a standard mercury sphygmomanometer. Waist circumference was calculated as the average of two measurements measured to the nearest 0.1 cm midway between the lower rib margin and the iliacrest following a normal expiration. History of pharmacological medication was obtained using the drug inventory method (identification of prescription drugs taken in the previous two weeks).

Fructosamine was determined by a colorimetric test, and HDL cholesterol and triglycerides by an enzymatic colorimetric test (Roche diagnostics, Mannheim, Germany). The interassay coefficient of variation was <2.8% for fructosamine and triglycerides, and <6.4% for HDL cholesterol. All laboratory analyses (HDL cholesterol, triglycerides, and fructosamine) were performed in EDTA plasma samples stored at –80° C, at the Department of Clinical Chemistry of the VUmc in 2005.

Inflammatory markers

The inflammatory markers α1-antichymotrypsin (ACT) and C-reactive protein (CRP) have been shown to be associated with cognitive decline and dementia (5,6,10). Serum levels of CRP and ACT were determined using sensitive regular immunoassays (ELISA) developed and performed at Sanquin Research, Amsterdam (5). CRP levels were measured with a sandwich-type ELISA in which polyclonal rabbit anti-CRP antibodies were used as catching antibodies and a biotinylated mAb against CRP (CLB anti–CRP-2) as the detecting antibody. ACT was measured with an ELISA in which specific mAbs against ACT were used. Results were expressed as μg/mL for CRP, and % of pooled normal human plasma (%NHP) for ACT. This plasma pool contained 100% ACT, which is ~300 mg/L. The intra- and inter-assay coefficient of variation was <5%. The detection limit was 0.8 ng/mL for CRP. High inflammation was defined as serum levels of both CRP and ACT in the highest tertile.

Putative confounders and effect modifiers

Data on age and sex were derived from the population registries at baseline. Education was assessed by asking the respondent for the highest educational level completed, which was converted into total number of years of education (range, 5 to 18 years). ApoE phenotypes (ε4 or non-ε4 carriers) were determined by isoelectric focusing of delipidated plasma samples, followed by immunoblotting. Smoking status was categorized as never, former and current smoker. Alcohol consumption was categorized as none, moderate and high intake. Physical activity was assessed with the LASA Physical Activity Questionnaire (LAPAQ). Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D). Stroke, myocardial infarction (MI), and diabetes mellitus were assessed using algorithms in which information obtained from general practitioners, inspection of medicine bottles, and self-report were combined. Self-reported diabetes mellitus has been shown to be in good concordance with the general practitioner's report (kappa = 0.85) (17).

Data analyses

Characteristics of the study sample were presented by metabolic syndrome status, and compared using χ^2 tests for dichotomous variables or independent t tests for continuous variables. Skewed distributed variables were compared using Mann-Whitney U tests.

Associations of (components of) MetS with cognition were analysed with linear regression analyses, both unadjusted and adjusted for age, sex, education, smoking, and alcohol use. The categorical variables smoking and alcohol were included in the regression models as dummies. The analyses were repeated after excluding subjects with diabetes mellitus, stroke, and MI because a possible link between MetS and cognition may be explained by these diseases. The independent role of the individual components of MetS on cognition were analysed by including each component both separately and together in a regression model. Based on previous findings (4), we tested whether the association between MetS and cognition differed by level of inflammation by including the interaction term 'MetS*inflammation (either CRP and ACT continuously)' in the models. In addition, interactions between MetS and ApoE were tested. All analyses were tested at the 0.05 level of significance, except for the interaction terms for which a level of significance of 0.10 was tolerated, because of the multiplication of the measurement error. Because of their skewed distribution, the inflammatory markers were ln-transformed before analyses.

RESULTS

The prevalence of MetS among the 1,183 participants aged 65-88 years was 36.3%. The prevalence of the individual components of MetS was: 51.7% for abdominal obesity, 62.8% for hypertension, 31.2% for high triglycerides, 35.5% for low HDL cholesterol, and 24.1% for hyperglycemia. With regard to MetS, 21.3% met three, 11.9% met four, and 3.0% met five of the NCEP criteria.

Subjects with MetS were more often women, lower educated, consumed less alcohol, and had higher prevalences of stroke and diabetes mellitus. Furthermore, they scored significantly lower on all cognition tests ($p<0.001$), with borderline significance on DR ($p=0.053$; Table 1). After full adjustment, MetS remained significantly associated with lower cognitive performance (all $p<0.05$), except for delayed recall ($p=0.12$; Table 2). Subjects with MetS performed 0.84 points lower on information processing speed to 0.24 points lower on delayed recall compared to subjects without MetS, as indicated by the B's. After exclusion of diabetic patients (N=109, with a median (IR) disease duration of 6.8 (3.5-20.2) years), the association between MetS and cognition remained significant and became stronger and borderline significant on delayed recall (B=-0.31, $p=0.065$; Table 2). Also, additional exclusion of subjects with stroke (N=79), and MI (N=77) revealed almost identical results (data not shown).

Investigating the individual components of MetS in relation to cognition revealed that hyperglycemia was significantly associated with all cognition measures, also after full adjustment (B's range from –0.38 to –1.21, all $p<0.05$). Low HDL cholesterol was significantly associated with information processing speed, and with fluid intelligence (B's= –0.71 and –0.48, $p<0.05$). Abdominal obesity, high triglycerides, and high blood pressure were not significantly associated with any cognitive measure. After exclusion of diabetic patients, associations between hyperglycemia and cognition became slightly weaker ($0.03<p<0.10$; Table 2). To additionally assess whether hyperglycemia is quantitatively related to cognitive dysfunction, we have studied fructosamine levels (in mmol/L) continuously. In adjusted regression analyses, fructosamine was significantly associated with cognition (B's = -4.57 to –9.51; $p<0.05$), but lost significance on information processing speed and fluid intelligence after exclusion of diabetic patients (B=-7.38; $p=0.27$, respectively B=-4.35; $p=0.27$). After exclusion of subjects with hyperglycemia (N=276), the association between fructosamine and cognition lost significance on all cognitive tests ($0.06<p<0.53$). These results suggest that the observed lower cognition can be fully attributed to hyperglycemia.

Combining all components together in one regression model showed that hyperglycemia was most strongly and significantly associated with all cognition tasks (fully adjusted; B's ranged from –0.37 on MMSE to –1.19 on information processing speed); none of the other components remained significantly associated. This finding was supported by analysis of continuous variables for the individual components in the models, showing that fructosamine was significantly associated with all cognitive tests (fully adjusted models, $p<0.05$), whereas the other components were not. This reveals that hyperglycemia is the most important component of MetS in relation to cognitive function. Adding the MetS variable to the models with the individual components showed that MetS was not significant, and that hyperglycemia remained significantly associated with information processing speed, and with immediate recall (B's = –1.18, $p<0.01$, and –0.39, $p=0.02$). The hyperglycemia component was significantly associated with HDL-cholesterol ($X^2=10.8$, df=1, p=0.001) and with triglycerides (X^2=4.6, df=1, p=0.03), but not with hypertension (X^2=2.6, df=1, p=0.11) and abdominal obesity (X^2=0.15, df=1, p=0.70). There were no interactions between hyperglycemia and any other component of MetS on cognition (all p>0.10).

In adjusted models, CRP and ACT were not significantly associated with cognition (all p>0.05). Adding hyperglycemia to the models showed that hyperglycemia was significantly associated with cognition (p<0.02), but CRP and ACT were not. Also, CRP and ACT did not change the strength of the associations between hyperglycemia and cognition. Interactions between MetS and CRP (adjusted models) were significant on all cognitive functions: on information processing speed (p=0.01), immediate and delayed recall (p<0.01 and p=0.09), fluid intelligence (p=0.01), and MMSE (p = 0.01). Interactions with ACT (adjusted models) were significant on 2 out of 5 tests: on delayed recall (p=0.03), and on fluid intelligence (p=0.001). Interactions between MetS and ApoE were not significant (all p>0.10). To illustrate the influence of inflammation, further analyses were stratified for subjects with high (defined as highest tertile on both CRP and ACT) inflammation versus others. After full adjustment, MetS was significantly negatively associated with cognition in subjects with high inflammation, with B’s that were 2.8 to 10.4 times higher than those in subjects with low inflammation (Table 3). After exclusion of diabetic patients (N=98), interactions between MetS and CRP and ACT remained significant. Strengths of the associations between MetS and cognition in subjects with high inflammation were slightly lower though (borderline) significant after exclusion of diabetic patients (Table 3, lower part). The interaction between hyperglycemia and inflammation was not significant on any cognitive test (p>0.10).

CONCLUSIONS

This study found that subjects with MetS showed poorer cognitive performance than subjects without MetS, especially in those with high levels of inflammation. Hyperglycemia was the main contributor of the association of MetS with cognition. This was consistently found for the different cognitive tests, suggesting that it affects all cognitive domains that were measured. However, MetS and hyperglycemia were more strongly associated with information processing speed and fluid intelligence, both including perceptual speed, rather than with memory (delayed recall). This is consistent with studies on diabetes mellitus, showing that diabetes may affect perceptual speed more than other cognitive domains (see (18) for review). These functions are mainly performed in fronto-subcortical brain structures, which have also been shown to be predominantly associated with diabetes mellitus and glucose intolerance (19).

So far, one previous study among high-functioning elders has investigated the association between MetS and cognitive status (4). Our findings are in line with that study, showing an association with cognition primarily in those with high inflammation. The association between inflammation and MetS may reflect an underlying atherosclerotic process, and either this atherosclerosis or inflammation or both contribute to cognitive decline. Concordantly, such an interaction between MetS and inflammation has also been found for cardiovascular diseases (CVD) and diabetes mellitus (20).

Whether inflammation leads to MetS or vice versa is an interesting question, which remains to be answered. Most likely, inflammation and MetS are related in a circular process, with inflammation leading to the syndrome, and the syndrome leading to inflammation, causing a downward vicious circle (12). Inflammation may also be seen as part of MetS and evidence is increasing that inflammation should be added as a component in the definition of the syndrome (20). Our study shows that older people with both inflammation and MetS are worse off with regard to cognition compared to those with either MetS or inflammation. This is supported by a prior study as well (4). Whether the pathway goes from inflammation to MetS to cognitive decline or vice versa needs to be examined in a longitudinal design with multiple measurements of both determinants and outcomes.

There are several possible explanations for the finding that hyperglycemia was the main contributor of the association between MetS and cognition. First, hyperglycemia may have direct negative effects on cognitive function (21), whereas such direct effects have not been found for the other components. Second, hyperglycemia may affect cognition through cardiovascular diseases (CVD) and atherosclerosis. This is supported by the found cognitive profile of impairment on perceptual speed suggesting involvement of the fronto-subcortical circuit, which is mainly associated with vascular components. Although hyperglycemia remained associated with cognition after exclusion of subjects with stroke in our study, we could not sufficiently adjust for subclinical CVD. Thirdly, hyperglycemia may affect cognition through diabetes mellitus, which has repeatedly been associated with cognitive decline and dementia (18,22). Associations between hyperglycemia and cognition were slightly lower after exclusion of subjects with diabetes, which is not surprising as diabetes is at the extreme end of the hyperglycemia spectrum. Evidence from experimental studies suggest that the effects of hyperglycemia and diabetes may be via toxic advanced glycosylated end-products (AGEs) that are formed in the brain or via hypofunction of Insulin-Degrading Enzyme (IDE), which may lower amyloid degradation (23,24).

The lack of association between hyperglycemia and hypertension and abdominal obesity components might suggest that MetS is not always a coherent concept, which has been suggested before by others who have described different factors underlying the concept of the MetS (25,26). Also, low power or selective survival may explain some of rather weak associations between hyperglycemia and some components of the MetS in our older population.

The novelty and strengths of our study are that we studied the contribution of the individual components of MetS to cognition, and that we used a broad cognitive test battery shown to be sensitive to early cognitive decline. Second, subjects with high inflammation were identified by two inflammatory markers: CRP and ACT. CRP is a widely used marker of inflammation which is strongly associated with increased risk for cardiovascular diseases, and which may also be predictive of development of MetS (20). ACT is an inflammatory marker more specific for AD, and previously shown to be especially important to cognitive decline and dementia (5,6). Thirdly, the multidisciplinary design of our study allows careful adjustment for potential confounders including demographics, lifestyle, and chronic diseases.

This study also has a few limitations. First, our findings are based on cross-sectional data. Although it is likely that metabolic syndrome will lead to cognition loss and not vice versa, analysis of longitudinal data of both determinants and outcomes is needed to distinguish the acute and chronic effects of hyperglycemia on cognition, and to get insight into the chicken-egg conundrum as to inflammation and MetS. Second, hyperglycemia was measured by serum fructosamine as a proxy for fasting glucose. Because we could not fully guarantee that the blood samples were fasting, we used fructosamine which is little affected by eating. The used cut-off was shown to have maximal effectiveness in discriminating subjects with impaired glucose tolerance from subjects with normal glucose tolerance (16).

In conclusion, this study showed that MetS is associated with cognition, mainly in subjects with high inflammation. Hyperglycemia was the main contributor of the association with cognition.

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Table 1. Characteristics of the study sample by metabolic syndrome status (N=1,183)

	No metabolic syndrome (N=754)	Metabolic syndrome (N=429)	P-value
Age, yr (mean, SD)	74.9 (6.4)	75.3 (6.4)	0.28
Men (%)	52.4	41.7	<0.001
Education, yr (median, IR)	9 (6-11)	9 (6-10)	<0.001
ApoE4 (%)	25.4	27.8	0.36
Abdominal obesity (%)	34.7	81.3	
High triglycerides (%)	10.8	67.4	
Low HDL cholesterol (%)	12.6	76.1	
Hyperglycemia (%)	13.9	42.0	
Hypertension (%)	49.8	85.5	
CRP, μg/mL (median, IR)	2.6 (1.2-6.0)	3.9 (2.0-7.1)	<0.001
ACT, % NHP (median, IR)	152.0 (129.8-179.0)	158.5 (135.0-182.0)	0.08
Smoking status (%)			
Never	33.4	38.0	0.17
Former	47.5	46.4	
Current	19.1	15.6	
Alcohol consumption (%)			
None	18.8	29.4	<0.001
Middle	70.2	62.7	
High	11.0	7.9	
Physical activity, min/day (median, IR)	143 (86-213)	144 (77-210)	0.37
Depression score (median, IR)	6 (3-12)	6 (2-11)	0.52
Stroke (%)	5.4	12.3	<0.001
Myocardial infarction (%)	7.4	9.8	0.16
Diabetes mellitus (%)	4.4	17.7	<0.001
Info processing speed (mean, SD)[*]	24.0 (7.2)	22.1 (7.0)	<0.001
Immediate recall (mean, SD)[†]	8.5 (2.5)	8.0 (2.5)	0.001
Delayed recall (mean, SD)[‡]	6.0 (2.9)	5.7 (2.9)	0.053
Fluid intelligence (mean, SD)[§]	18.0 (3.9)	16.8 (4.1)	<0.001
MMSE (median, IR)[‖]	28 (26-29)	27 (26-29)	<0.001

P value of χ^2 tests for dichotomous variables, independent *t* tests for continuous variables, and Mann-Whitney *U* tests for skewed distributed variables (median, IR presented).

IR = Interquartile Range; MMSE = Mini-Mental State Examination.

[*] Range = 1.0-42.7; [†] Range = 2-15; [‡] Range = 0-15; [§] Range = 1-24; [‖] Range = 16-30. Higher scores indicating better performance.

Table 2. Associations between the metabolic syndrome and its individual components with cognitive function [*]

	Total study sample						Study sample without diabetic patients	
	Metabolic syndrome	Abdominal obesity	High triglycerides	Low HDL cholesterol	Hypertension	Hyper-glycemia	Metabolic syndrome	Hyper-glycemia
Adjusted B [**]								
Info processing speed	-0.84 [†]	-0.63	-0.56	-0.71 [†]	-0.11	-1.21 [‡]	-0.80 [†]	-0.78
Immediate recall	-0.39 [‡]	-0.19	-0.21	-0.28	-0.09	-0.46 [‡]	-0.43 [‡]	-0.39 [†]
Delayed recall	-0.24	-0.14	-0.07	-0.17	-0.05	-0.40 [†]	-0.31	-0.37
Fluid intelligence	-0.63 [‡]	0.04	-0.38	-0.48 [†]	-0.26	-0.62 [‡]	-0.48 [†]	-0.10
MMSE	-0.32 [†]	0.00	-0.15	-0.09	-0.06	-0.38 [†]	-0.34 [†]	-0.31

[*] Data are presented as adjusted *B*'s, which indicate the differences in cognitive scores between subjects with the metabolic syndrome and its individual components and those without these determinants.

[**] Adjusted for age, sex, education, smoking, and alcohol use.

[†] $p < 0.05$

[‡] $p < 0.01$

Table 3. Associations between the metabolic syndrome and cognitive function by inflammation status, in the total study sample, and after exclusion of subjects with diabetes mellitus [*]

	Inflammation status			
	Others		High[**]	
Adjusted [†]	*B*	*P-value*	*B*	*P-value*
Total study sample		N=962		N=190
Info processing speed	-0.70	0.07	-1.94	0.03
Immediate recall	-0.23	0.13	-1.14	0.001
Delayed recall	-0.10	0.55	-1.04	<0.01
Fluid intelligence	-0.36	0.11	-1.93	0.001
MMSE	-0.24	0.09	-0.86	0.01
Diabetic patients excluded		N=881		N=173
Info processing speed	-0.72	0.09	-1.48	0.12
Immediate recall	-0.29	0.06	-1.14	<0.01
Delayed recall	-0.17	0.35	-0.93	0.02
Fluid intelligence	-0.28	0.25	-1.50	0.01
MMSE	-0.31	0.04	-0.61	0.08

[*] Data are presented as adjusted *B*'s, which indicate the differences in cognitive scores between subjects with and without the metabolic syndrome, separately for those with high inflammation and others.

[**] High inflammation defined as highest tertile on both C-reactive protein and α1-antichymotrypsin.

[†] Adjusted for age, sex, education, smoking, and alcohol use.