Contribution of Metabolic Syndrome Components to Cognition in Older Individuals

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OBJECTIVE — Recent evidence suggests that the metabolic syndrome and inflammation affect cognitive decline in old age and that they reinforce each other. However, it is not known what the roles of the individual components of the metabolic syndrome on cognition are.

RESEARCH DESIGN AND METHODS — The sample consisted of 1,183 participants in the Longitudinal Aging Study Amsterdam who were aged 65–88 years. Metabolic syndrome (U.S. National Cholesterol Education Program definition) and its individual components and the inflammatory markers C-reactive protein (CRP) and α_1-antichymotrypsin (ACT) were assessed. Cognitive assessments included general cognition (Mini-Mental State Examination), memory (verbal learning test), fluid intelligence (Raven's Matrices), and information processing speed (coding task).

RESULTS — Of the sample, 36.3% had metabolic syndrome. Metabolic syndrome 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* values, indicating differences in scores between both groups, ranging from −0.38 to −1.21). There was a significant interaction between metabolic syndrome and inflammation on cognition ($P < 0.01$–0.09). Metabolic syndrome was negatively associated with cognition in subjects with high inflammation (highest tertile for both CRP and ACT; *B* values ranging from −0.86 to −1.94, $P < 0.05$), whereas an association was absent in subjects with low inflammation (*B* values ranging from −0.10 to −0.70).

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

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

Recent evidence suggests that metabolic syndrome 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 and may be considered as a primary causal pathway of Alzheimer's disease (11). In addition, metabolic syndrome often co-occurs with an increased inflammatory response, although it is not known whether metabolic syndrome leads to increased inflammation or vice versa (12).

The question arises whether metabolic syndrome has a 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 metabolic syndrome on heart diseases and diabetes is greater than that of the sum of its components (3,13), but it is not known how this association accounts for cognitive function as outcome.

Therefore, in the present study, our aim was to investigate the association between metabolic syndrome and its individual components with cognition and to determine whether this association is modified by inflammation. We hypothesized that *1*) metabolic syndrome and its individual components are associated with cognition and *2*) the link between metabolic syndrome and cognition is modified by chronic inflammation. We test these hypotheses on different cognitive domains, which is a novel aspect compared with the previous study on this topic (4).

RESEARCH DESIGN AND METHODS

— 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 55–85 years), stratified by age and sex according to expected 5-year mortality, was drawn from population registries. Respondents were interviewed at home in a main and a medical interview, in which

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Abbreviations: ACT, α_1-antichymotrypsin; Apo, apolipoprotein; CRP, C-reactive protein; CVD, cardiovascular disease; ELISA, enzyme-linked immunosorbent assay; MMSE, Mini-Mental State Examination.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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. In total, 3,107 predominantly Caucasian (>99%) subjects were enrolled in the baseline examination in 1992/1993.

The analytical 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. 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 metabolic syndrome. Both cognition and metabolic syndrome were determined at the same measurement. Of the 1,720 eligible respondents, 1,509 took part in the interview and blood samples were obtained for 1,321. Metabolic syndrome could be determined for 1,279 respondents; 96 participants had missing data for any cognitive test, leaving 1,183 participants in this study (68.8% of 1,720). An additional 31 participants had missing data for the inflammatory markers. Respondents included in this study were significantly younger, were more often men, had higher education, 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 1 minute. The mean score for three trials was used in the analyses (range 1.0–42.7).

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

Fluid intelligence, the ability to deal with essentially new problems, was measured with Raven's Colored Progressive Matrices. The respondent was presented with an incomplete design and six alternatives from which the one that best completes the design had to be chosen. Every correctly solved item on 2 sets of 12 items each resulted in 1 point (range 1–24).

Overall cognitive function was measured with the Mini-Mental State Examination, 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

Metabolic syndrome was defined as the presence of three 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; and fructosamine ≥0.247 mmol/l or antidiabetes medication. This is the definition established by the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (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 before blood sampling allowed respondents to take tea and dry toast but no dairy products, we could not 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 using a standard mercury sphygmomanometer with the subject in a sitting position. Waist circumference was determined as the average of two measurements calculated to the nearest 0.1 cm midway between the lower rib margin and the ilial crest after a normal expiration. A history of pharmacological medication was obtained using the drug inventory method (identification of prescription drugs taken in the previous 2 weeks).

Fructosamine was determined by a colorimetric test, and HDL cholesterol and triglycerides were determined 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 VU University Medical Center in 2005.

Inflammatory markers

The inflammatory markers α_1-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, the Netherlands) (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 monoclonal antibody against CRP (CLB anti–CRP-2) was used as the detecting antibody. ACT was measured with an ELISA in which specific monoclonal antibodies against ACT were used. Results were expressed as micrograms per milliliter for CRP, and percentage of pooled normal human plasma for ACT. This plasma pool contained 100% ACT, which is ~300 mg/l. The intra- and interassay 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 5–18 years). Apolipoprotein (apo) E phenotypes (ε4 or non-ε4 carriers) were deter-

Table 1—*Characteristics of the study sample by metabolic syndrome status*

	No metabolic syndrome	Metabolic syndrome	*P* value
n	754	429	
Age (years)	74.9 ± 6.4	75.3 ± 6.4	0.28
Men (%)	52.4	41.7	<0.001
Education (years)	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)	2.6 (1.2–6.0)	3.9 (2.0–7.1)	<0.001
ACT (% normal human plasma)	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)	143 (86–213)	144 (77–210)	0.37
Depression score	6 (3–12)	6 (2–11)	0.52
Stroke (%)	5.4	12.3	<0.001
Myocardial infarction (%)	7.4	9.8	0.16
Diabetes (%)	4.4	17.7	<0.001
Information processing speed*	24.0 ± 7.2	22.1 ± 7.0	<0.001
Immediate recall†	8.5 ± 2.5	8.0 ± 2.5	0.001
Delayed recall‡	6.0 ± 2.9	5.7 ± 2.9	0.053
Fluid intelligence§	18.0 ± 3.9	16.8 ± 4.1	<0.001
MMSE‖	28 (26–29)	27 (26–29)	<0.001

n = 1,183. Data are means ± SD, %, or median (interquartile range). *P* value of χ^2 tests for dichotomous variables, independent *t* test for continuous variables, and Mann-Whitney *U* tests for skewed distributed variables. *Range = 1.0–42.7; †range = 2–15; ‡range = 0–15; §range = 1–24; ‖range = 16–30 (higher scores indicate better performance).

mined 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. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale. Stroke, myocardial infarction, and diabetes were assessed using algorithms in which information obtained from general practitioners, inspection of medicine bottles, and self-report were combined. Self-reported diabetes 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 were 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) metabolic syndrome with cognition were analyzed 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 exclusion of subjects with diabetes, stroke, and myocardial infarction because a possible link between metabolic syndrome and cognition may be explained by these diseases. The independent roles of the individual components of metabolic syndrome on cognition were analyzed by including each component both separately and together in a regression model. On the basis of previous findings (4), we tested whether the association between metabolic syndrome and cognition differed by level of inflammation by including the interaction term "metabolic syndrome × inflammation (CRP and ACT continuously)" in the models. In addition, interactions between metabolic syndrome 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 owing to the multiplication of the measurement error. Because of their skewed distribution, the inflammatory markers were log-transformed before analyses.

RESULTS — The prevalence of metabolic syndrome among the 1,183 participants aged 65–88 years was 36.3%. The prevalences of the individual components of metabolic syndrome were 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 metabolic syndrome, 21.3% of the subjects met three, 11.9% met four, and 3.0% met five of the NCEP criteria.

Subjects with metabolic syndrome were more often women, had lower education, consumed less alcohol, and had higher prevalences of stroke and diabetes. Furthermore, they scored significantly lower on all cognition tests ($P < 0.001$), with borderline significance on delayed recall ($P = 0.053$) (Table 1). After full adjustment, metabolic syndrome remained significantly associated with lower cognitive performance (all $P < 0.05$), except for delayed recall ($P = 0.12$) (Table 2). Subjects with metabolic syndrome performed 0.84 points lower on information processing speed to 0.24 points lower on delayed recall compared with subjects without metabolic syndrome, as indicated by the *B* values. After exclusion of diabetic patients ($n = 109$, with a median [interquartile range] disease duration of 6.8 [3.5–20.2] years), the association between metabolic syndrome 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 myocardial infarction ($n = 77$) produced almost identical results (data not shown).

Investigating the individual components of metabolic syndrome in relation to cognition revealed that hyperglycemia

Table 2—*Associations between the metabolic syndrome and its individual components with cognitive function*

	Total study sample						Study sample without diabetic patients	
Adjusted *B**	Metabolic syndrome	Abdominal obesity	High triglycerides	Low HDL cholesterol	Hypertension	Hyperglycemia	Metabolic syndrome	Hyperglycemia
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* values, 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. †$P < 0.05$; ‡$P < 0.01$.

was significantly associated with all cognition measures, also after full adjustment (*B* values ranging from −0.38 to −1.21, all $P < 0.05$). Low HDL cholesterol was significantly associated with information processing speed and with fluid intelligence ($B = -0.71$ 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 studied fructosamine levels (in millimoles per liter) continuously. In adjusted regression analyses, fructosamine was significantly associated with cognition ($B = -4.57$ to -9.51; $P < 0.05$) but lost significance on information processing speed and fluid intelligence after exclusion of diabetic patients ($B = -7.38$, $P = 0.27$ and $B = -4.35$, $P = 0.27$, respectively). 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* values ranged from −0.37 on the 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. Thus, hyperglycemia is shown to be the most important component of metabolic syndrome in relation to cognitive function. Adding the metabolic syndrome variable to the models with the individual components showed that metabolic syndrome was not significant and that hyperglycemia remained significantly associated with information processing speed and with immediate recall ($B = -1.18$, $P < 0.01$ and -0.39, $P = 0.02$). The hyperglycemia component was significantly associated with HDL cholesterol ($\chi^2 = 10.8$, degrees of freedom [df] = 1, $P = 0.001$) and with triglycerides ($\chi^2 = 4.6$, df = 1, $P = 0.03$) but not with hypertension ($\chi^2 = 2.6$, df = 1, $P = 0.11$) and abdominal obesity ($\chi^2 = 0.15$, df = 1, $P = 0.70$). There were no interactions between hyperglycemia and any other component of metabolic syndrome 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 metabolic syndrome and CRP (adjusted models) were significant on all cognitive functions: on information processing speed ($P = 0.01$), on immediate and delayed recall ($P < 0.01$ and $P = 0.09$), on fluid intelligence ($P = 0.01$), and on MMSE ($P = 0.01$). Interactions with ACT (adjusted models) were significant on two of five tests: on delayed recall ($P = 0.03$) and on fluid intelligence ($P = 0.001$). Interactions between metabolic syndrome 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 the highest tertile for both CRP and ACT) inflammation versus others. After full adjustment, metabolic syndrome was significantly negatively associated with cognition in subjects with high inflammation, with *B* values that were 2.8–10.4 times higher than those in subjects with low inflammation (Table 3). After exclusion of diabetic patients ($n = 98$), interactions between metabolic syndrome and CRP and ACT remained significant. Strengths of the associations between metabolic syndrome and cognition in subjects with high inflammation were slightly lower though (borderline) significant after exclusion of diabetic patients (Table 3). The interaction between hyperglycemia and inflammation was not significant on any cognitive test ($P > 0.10$).

CONCLUSIONS — In this study, we found that subjects with metabolic syndrome showed poorer cognitive performance than subjects without metabolic syndrome, especially those with high levels of inflammation. Hyperglycemia was the main contributor of the association of metabolic syndrome with cognition. This finding was consistent for the different cognitive tests, suggesting that it affects all cognitive domains that were measured. However, metabolic syndrome and hyperglycemia were more strongly associated with information processing speed and fluid intelligence, both including perceptual speed, rather than with memory (delayed recall). This finding is consistent with studies on diabetes, showing that diabetes may affect perceptual speed more than other cognitive domains (see ref. 18 for review). These functions are mainly

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*

	Inflammation status			
	Others		High†	
Adjusted*	*B*	*P* value	*B*	*P* value
Total study sample (*n*)	962		190	
Information 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		173	
Information 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* values, which indicate the differences in cognitive scores between subjects with and without the metabolic syndrome, separately for those with high inflammation and others. *Adjusted for age, sex, education, smoking, and alcohol use. †High inflammation is defined as the highest tertile on both CRP and ACT.

performed in fronto-subcortical brain structures, which have also been shown to be predominantly associated with diabetes and glucose intolerance (19).

So far, only one previous study among high-functioning older individuals has investigated the association between metabolic syndrome 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 metabolic syndrome may reflect an underlying atherosclerotic process, and either this atherosclerosis or inflammation or both contribute to cognitive decline. Concordantly, such an interaction between metabolic syndrome and inflammation has also been found for cardiovascular diseases (CVDs) and diabetes (20).

Whether inflammation leads to metabolic syndrome or vice versa is an interesting question, which remains to be answered. Most likely, inflammation and metabolic syndrome 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 metabolic syndrome, and evidence that inflammation should be added as a component in the definition of the syndrome is increasing (20). Our study shows that older individuals with both inflammation and metabolic syndrome are worse off with regard to cognition than are those with either metabolic syndrome or inflammation. This observation is supported by a prior study as well (4). Whether the pathway goes from inflammation to metabolic syndrome 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 metabolic syndrome 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 CVDs and atherosclerosis. This hypothesis is supported by the cognitive profile of impairment on perceptual speed that we found, 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. Third, hyperglycemia may affect cognition through diabetes, 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 suggests that the effects of hyperglycemia and diabetes may occur via toxic advanced glycosylated end products that are formed in the brain or via hypofunction of insulin-degrading enzyme, which may lower amyloid degradation (23,24).

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

The novelty and strengths of our study are that we studied the contribution of the individual components of metabolic syndrome 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 an increased risk for cardiovascular diseases and which may also be predictive of development of metabolic syndrome (20). ACT is an inflammatory marker more specific for Alzheimer's disease and previously was shown to be especially important in cognitive decline and dementia (5,6). Third, 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 metabolic syndrome. 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 cutoff we used was shown to have maximal effectiveness in discriminating subjects with impaired glucose tolerance from subjects with normal glucose tolerance (16).

In summary, this study shows that metabolic syndrome is associated with cognition, mainly in subjects with high inflammation. Hyperglycemia was the main contributor of the association with cognition.

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