

# Metabolic Syndrome, Brain Magnetic Resonance Imaging, and Cognition

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**OBJECTIVE** — We explored cognitive impairment in metabolic syndrome in relation to brain magnetic resonance imaging (MRI) findings.

**RESEARCH DESIGN AND METHODS** — We studied 819 participants free of clinical stroke and dementia of the population-based Austrian Stroke Prevention Study who had undergone brain MRI, neuropsychological testing, and a risk factor assessment relevant to National Cholesterol Education Program Adult Treatment Panel III criteria-defined metabolic syndrome. High-sensitivity C-reactive protein (hs-CRP) was also determined.

**RESULTS** — Of 819 subjects, 232 (28.3%) had metabolic syndrome. They performed worse than those without metabolic syndrome on cognitive tests assessing memory and executive functioning after adjustment for possible confounders. Stratification by sex demonstrated that metabolic syndrome was related to cognitive dysfunction in men but not in women. Only in men was an increasing number of metabolic syndrome components associated with worse cognitive performance. MRI showed no significant differences in focal ischemic lesions and brain volume between subjects with and without metabolic syndrome, and MRI abnormalities failed to explain impaired cognition. Cognitive performance was most affected in male subjects with metabolic syndrome who also had high hs-CRP levels.

**CONCLUSIONS** — Metabolic syndrome exerts detrimental effects on memory and executive functioning in community-dwelling subjects who have not had a clinical stroke or do not have dementia. Men are more affected than women, particularly if they have high inflammatory markers. MRI-detected brain abnormalities do not play a crucial role in these relationships.

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**M**etabolic syndrome is a cluster of cardiovascular risk factors, including abdominal obesity, atherogenic dyslipidemia, raised blood pressure, and insulin resistance and glucose intolerance (1). It has been associated with cognitive dysfunction (2,3) and Alzheimer's disease (4), but data are discordant (5–7). Negative associations were reported with memory, processing speed, and fluid intelligence (3). Impaired cog-

nition was linked to high-level inflammation (2).

Although components of the metabolic syndrome have been individually related to cognitive outcomes, the mechanisms affecting cognition in metabolic syndrome are undetermined. Factors related to peripheral hyperinsulinemia are probably highly relevant. Peripheral hyperinsulinemia downregulates blood-brain barrier insulin receptors and

subsequently reduces insulin transport to the brain followed by decreased acetylcholine neurotransmission and cerebral blood flow (8). In addition, hyperglycemia itself contributes to neuronal apoptosis via increased generation of free radicals, enhanced glycation end products, and elevated lipid peroxidation (8). Interactive effects between hyperglycemia and components of metabolic syndrome such as arterial hypertension have been reported (9). Another possible mechanism are vascular lesions as a sequela of components of metabolic syndrome including hypertension, impaired glucose tolerance, and dyslipidemia. Previous magnetic resonance imaging (MRI) studies described higher rates of silent brain infarcts (10) and leukoaraiosis (11). A diffusion tensor imaging study found evidence for ultrastructural tissue damage in frontal and temporal lobes (12). These studies did not include cognitive testing and thus cannot imply the higher frequency of brain lesions to be responsible for metabolic syndrome-related cognitive dysfunction.

We evaluated both cognitive function and brain MRI-detected lesions in a large cohort of community-dwelling subjects. We hypothesize that individuals with metabolic syndrome have global and domain-specific cognitive dysfunction, a higher frequency of brain abnormalities, and a cognitive status that relates to brain MRI findings.

## RESEARCH DESIGN AND METHODS

The Austrian Stroke Prevention Study (ASPS) is a prospective study on the effects of vascular risk factors on brain structure and function in cognitively normal middle-aged and elderly inhabitants of Graz, Austria; details have been previously described (13,14). Briefly, 2,007 participants were randomly selected from the official community register, and all participants were free of stroke and dementia. The study protocol was approved by the responsible ethics committee.

In a first study panel between 1991 and 1994, 509 subjects randomly selected from the entire cohort underwent an extended diagnostic work-up including brain MRI and cognitive testing. To

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enlarge the cohort with imaging and neuropsychological assessments, an additional 567 individuals were randomly selected in a second panel between 1999 and 2003. They underwent identical imaging and cognitive test procedures. Participants of the first and second panels were pooled, which resulted in a total of 1,076 individuals with brain MRI and neuropsychological evaluation. The long diagnostic periods resulted from limited research-devoted time slots at the MRI center. All clinical examinations were repeated with MRI scanning and neuropsychological testing. Clinical history, blood tests, MRI, and cognitive assessments were always done in 1 day. A total of 819 subjects had a complete risk factor assessment necessary to determine metabolic syndrome and thus created the current study cohort.

### Risk factors and definition of metabolic syndrome

Risk factors were determined based on history and measurements at the examination, as previously described (13). Hypertension was considered a history of hypertension with repeated blood pressure readings  $\geq 140/90$  mmHg, treatment for hypertension, or readings at the examination exceeding the limit. Diabetes was coded present if an individual was treated for diabetes at the time of examination or if the fasting blood glucose level at the examination exceeded 126 mg/dl. History of coronary heart disease was determined according to the Rose questionnaire, atrial fibrillation was diagnosed based on electrocardiogram findings, and peripheral artery disease was diagnosed based on history. Study participants were asked whether they were previous and/or current smokers or habitual daily drinkers as well as about their physical activity at leisure time; the amount of activity was graded into none (no physical activity), mild (daily walk), and moderate to intensive (daily sports). Waist circumference was measured to define central obesity. A lipid status was determined with standardized measurements for each study participant after a 12-h fasting. High-sensitivity C-reactive protein (hs-CRP) was measured with a particle-enhanced immunoturbidimetric assay, with a detection limit of 0.1 mg/l. We defined a high level of inflammation as hs-CRP levels above the median of hs-CRP distribution ( $>1.9$  mg/l) in our cohort.

Metabolic syndrome was defined according to National Cholesterol Educa-

tion Program Adult Treatment Panel III criteria and revised American Heart Association/National Heart, Lung, and Blood Institute criteria (1). Participants were considered to have metabolic syndrome if they met three or more of the following criteria: 1) waist circumference  $>102$  cm in men and  $>88$  cm in women, 2) fasting serum triglycerides  $\geq 150$  mg/dl or treatment for hypertriglyceridemia, 3) serum HDL cholesterol  $<40$  mg/dl in men and  $<50$  mg/dl in women or treatment for low HDL cholesterol, 4) blood pressure  $\geq 130/85$  mmHg or use of antihypertensive drugs, 5) fasting blood glucose levels  $\geq 110$  mg/dl or use of antidiabetes drugs.

### Neuropsychological testing

A test battery assessing memory and learning abilities, psychomotor skills, and executive functions was administrated as described previously (13,14). To assess learning ability and intermediate memory recall, one test called Bäumler's Lern und Gedächtnistest was used. Psychomotor skills were evaluated by one test called the Purdue's Pegboard Test. Executive functions were assessed by three tests: the Wisconsin Card Sorting Test, part B of the Trail Making Test, and Digit Span Backwards, which is part of the Wechsler Adult Intelligence Scale, revised. We used summary measures of cognitive function by converting individual test results to z-scores and computing the average of the scores within each cognitive domain. Z-scores were not adjusted for age, sex, and education. For assessment of depressive mood we applied the "Eigenschaftswörterliste" of W. Janke, G. Debus (1978) Die Eigenschaftswörterliste (EWL); Handanweisung, Göttingen: Hogrefe, a validated multidimensional tool consisting of a list of given adjectives describing the emotional status of a test person at the time of the interview.

### MRI

All scans were obtained on a 1.5-Tesla scanner (Philips Medical Systems, Eindhoven, The Netherlands) with protocols described previously (13). White matter lesion (WML) volume, lacunes, thromboembolic infarcts, and brain volume were determined in each study participant.

### WML volume

The scans were analyzed by two experienced investigators (C.E. and R.S.). They first graded WMLs according to our scheme (15), then marked and outlined each WML on a transparency that was

overlaid on the proton density scans. They were blinded to clinical data of study participants. Independently from this visual analysis, lesion load measurements were done on proton density-weighted images on an UltraSPARC workstation (Sun Microsystems, Santa Clara, CA) by a trained operator using DISPImage (16). The trained operator used a hardcopy overlaid by the transparency, with all lesions outlined by the experienced readers as reference, and segmented all lesions on the computer image. Lesion areas were then provided by the semiautomated thresholding algorithm implemented in DISPImage. The total lesion volume ( $\text{cm}^3$ ) was calculated by multiplying the total lesion area by slice thickness.

### Lacunes and thromboembolic infarcts

Lacunes were defined as focal lesions that involved the basal ganglia, internal capsule, thalamus, or brain stem, not exceeding a maximum diameter of 15 mm. The presence of silent thromboembolic infarcts was also recorded.

### Brain volume

Brain volume was calculated from the T<sub>2</sub>-weighted spin echo sequence using the fully automated structural image evaluation of atrophy (Sienax, part of the FMRIB Software Library; <http://www.fmrib.ox.ac.uk/fsl>). Brain parenchyma percentage was estimated from the ratio of parenchymal volume to the total volume given by the outer surface of the brain. To determine the measurement errors in our dataset, 20 participants were scanned and rescanned after shortly leaving the scanner. The median relative error for Sienax was 1.2%.

### Data analysis

Significant differences in means of normally distributed continuous variables were tested by ANOVA and significant differences of nonnormally distributed variables by the Mann-Whitney *U* test. Difference in proportions was assessed by  $\chi^2$  statistics.

Linear regression analysis was performed to estimate the association between metabolic syndrome and the z-scores of the specific cognitive domains. Different models were assessed. Model 1 included age and sex plus subjects' characteristics that were different across the metabolic syndrome, including years of education, leisure physical activity, and

coronary heart disease. Although significantly more common in patients with metabolic syndrome, hypertension and diabetes were not used as covariates because all subjects with hypertension and diabetes were included in our definition of metabolic syndrome. Depressive mood was considered as a covariate based on its significant relationship to cognitive functioning. Model 2 investigated to what extent the associations between metabolic syndrome and cognition were mediated by MRI findings and thus included all covariates of model 1 plus presence of lacunes, silent infarcts, WML volume, and brain parenchymal fraction. The relationship between metabolic syndrome and vascular lesions and brain atrophy was determined by multivariate regression analyses using model 1 covariates.

Multicollinearity between MRI variables was assessed using the variance inflation factor (VIF). Usually, VIF values >10 are suggestive of multicollinearity and merit further investigation. The mean VIF for MRI variables in our study was 1.04 (range 1.01–1.08). Because data from the literature suggest possible sex differences in metabolic syndrome (6,17), we also stratified our analyses by sex.

Hs-CRP measurements were available in only a subset of our cohort, thus we did not include this factor in the primary model but performed a subanalysis in 541 subjects with hs-CRP measurement to assess whether inflammation plays a causal role in the association between metabolic syndrome and cognition. This subanalysis was done with and without additional adjustment for nonsteroidal anti-inflammatory drugs or acetylsalicylic acid use. Interactions of hs-CRP and metabolic syndrome with cognitive functioning were tested by including the respective interaction term in the multivariate linear regression models. All analyses were done using Stata (Stata Statistical Software, release 6; StataCorp, College Station, TX).

**RESULTS**— A total of 232 (28.3%) study participants had metabolic syndrome. There were 157 (67.6%) subjects with three, 55 (23.7%) with four, and 20 (8.6%) with five components of metabolic syndrome. The characteristics of the study cohort are shown in Table 1. Subjects with metabolic syndrome had lower educational status, less leisure physical activity, more coronary heart disease, higher frequencies of each component of metabolic syndrome, and higher hs-CRP.

Table 2 shows that subjects with met-

**Table 1—Characteristics of the study cohort (n = 819) by the absence or presence of metabolic syndrome**

Variable	No metabolic syndrome	Metabolic syndrome	P
<i>n</i>	587	232	
Demographic characteristics			
Age (years)	64.8 ± 8.1	65.1 ± 7.2	0.64*
Women	318 (54.1)	138 (59.5)	0.16†
Years of education	10 (9–13)	10 (9–10)	<0.002‡
Risk factors			
Smoking status			0.44†
Never	361 (61.5)	133 (57.3)	
Former	163 (27.8)	68 (29.3)	
Current	63 (10.7)	31 (13.4)	
Daily alcohol consumption	75 (16.4)	36 (19.8)	0.30†
Physical activity at leisure time			0.008†
None	31 (5.3)	26 (11.2)	
Mild	189 (32.2)	76 (32.7)	
Moderate to intensive	367 (62.5)	130 (56.1)	
Hypertension	391 (66.6)	202 (87.1)	<0.001†
History of coronary heart disease	183 (31.2)	89 (38.9)	0.051†
Diabetes	15 (2.6)	56 (24.2)	<0.001†
Atrial fibrillation	12 (2.0)	4 (1.7)	0.77†
Peripheral arterial disease	5 (0.9)	5 (2.3)	0.13†
Depressive mood	1 (0–2)	1 (0–2)	0.92‡
hs-CRP (mg/l)§	1.7 (0.8–3.2)	2.5 (1.4–5.1)	<0.001‡
Components of metabolic syndrome			
Abdominal obesity	149 (25.3)	176 (75.8)	<0.001‡
Triglycerides ≥150 mg/dl	76 (12.9)	172 (74.1)	<0.001†
Low HDL cholesterol	64 (10.9)	133 (57.3)	<0.001†
Fasting glucose ≥110 mg/dl	25 (4.2)	84 (36.2)	<0.001†
Blood pressure ≥130/85 mmHg	467 (79.5)	226 (97.4)	<0.001†

Data are means ± SD, *n* (%), or median (interquartile range). \*ANOVA test. † $\chi^2$  test. ‡Mann-Whitney *U* test. §Measurement of hs-CRP only available in 541 subjects.

abolic syndrome performed worse on all cognitive tests, with significant differences in memory and executive functions, but there existed no significant differences in MRI findings between subjects with and without metabolic syndrome. Metabolic syndrome and MRI findings were also not significantly associated in multivariate regression analyses (data not shown).

When using linear regression analysis with adjustment for age, sex, years of education, depressive mood, coronary heart disease, and physical activity at leisure time (Table 3, model 1), the inverse associations between metabolic syndrome and memory, as well as executive functions, remained significant. The results were virtually unchanged following adjustment for MRI findings (Table 3, model 2). Stratification by sex demonstrated that the significant relationship between metabolic syndrome and impaired memory and executive functioning existed only in men but not in women (Table 3).

Figure 1 displays the relationship between the number of components of metabolic syndrome and performance on tests of memory and executive functioning. In men, with more components of metabolic syndrome present, memory (one component:  $\beta = -0.38$ ; two components:  $\beta = -0.52$ ; three components:  $\beta = -0.64$ ; more than three components:  $\beta = -0.71$ ; *P* for trend <0.001) and executive functions (one component:  $\beta = -0.99$ ; two components:  $\beta = -1.02$ ; three components:  $\beta = -1.55$ ; more than three components:  $\beta = -1.90$ ; *P* for trend = 0.010) were more impaired. No such relationship existed in women.

A multivariate regression analysis adjusted for model 1 and 2 covariates showed that men, but not women, with metabolic syndrome who had high hs-CRP levels (i.e., >1.9 mg/l) performed significantly worse on tests of memory ( $\beta = -0.44$ ; 95% CI [-0.94 to 0.04]; *P* = 0.074) and executive functions ( $\beta =$

Table 2—Cognitive performance and brain MRI findings in the sample (n = 819) by the absence or presence of metabolic syndrome

Variable	No metabolic syndrome	Metabolic syndrome	P
n	587	232	
Neuropsychological test results			
Mini Mental State Examination	27.5 ± 1.5 (22–30)	27.4 ± 1.5 (22–30)	0.58*
Memory	0.06 ± 1.0 (−1.91 to 4.38)	−0.17 ± 0.9 (−1.98 to 3.32)	<0.001*
Psychomotor skills	0.06 ± 0.8 (−3.00 to 2.56)	0.01 ± 0.9 (−2.17 to 2.93)	0.46*
Executive functions	0.49 ± 3.0 (−18.23 to 5.44)	−0.32 ± 3.1 (−16.04 to 5.21)	<0.001*
Brain MRI findings			
WML volume in cm <sup>3</sup>	0.9 (0.2–3.1)	0.9 (0.2–2.4)	0.89†
Lacunae	32 (5.4)	15 (6.4)	0.56‡
Silent infarcts	16 (2.7)	10 (4.3)	0.24‡
Normalized brain percentage	0.78 ± 0.03 (0.67–0.87)	0.78 ± 0.04 (0.68–0.86)	0.38*

Data are means ± SD (range), n (%), or median (interquartile range). \*ANOVA test. †Mann-Whitney U test. ‡χ<sup>2</sup> test.

−2.21; 95% CI [−3.81 to −0.62]; P = 0.007) than their male counterparts with low hs-CRP (memory: β = −0.05; 95% CI [−0.45 to 0.33]; P = 0.774; executive functions: β = 0.48; 95% CI [−0.74 to 1.7]; P = 0.437). After adjustment for nonsteroidal anti-inflammatory drugs or aspirin usage in the model, the results remained almost identical (data not shown). The interaction between hs-CRP and metabolic syndrome was significant for executive functions (β = −2.79; 95% CI [−4.67 to −0.92]; P = 0.004) and showed a nonsignificant trend for memory (β = −0.56; 95% CI [−1.17 to 0.04]; P = 0.068).

**CONCLUSIONS**— Middle-aged and elderly community-dwelling subjects with metabolic syndrome performed worse on tasks assessing memory and executive functions than their counterparts without metabolic syndrome. This was

seen in men but not in women, and the more components of metabolic syndrome were present, the more impaired was cognitive functioning. Focal and diffuse brain lesions failed to explain the association between metabolic syndrome and cognition. Men with metabolic syndrome and high inflammatory markers had more severe cognitive deficits.

Previous studies (2,3) described cognitive dysfunction in patients with metabolic syndrome. Most used gross measures of cognition for patients' assessment (2). The Longitudinal Aging Study Amsterdam also applied comprehensive neuropsychological testing and, similar to us, also found memory and processing speed deficits in metabolic syndrome patients (3). This pattern favors both cortical and subcortical brain damage as the underlying cause (18). Our finding that metabolic syndrome affects cognition, particularly in men, is novel. So far, only

few studies stratified their analyses by sex, and they yielded conflicting results. Vanhanen et al (4) found more Alzheimer's disease in metabolic syndrome patients, and, after stratification by sex, this association existed predominantly in women. By contrast, Laudisio et al. (6) reported that female patients performed cognitively better than male patients. So far, sex-specific differences in risk factor-related biological mechanisms leading to cognitive decline remained widely unexplored. We can only speculate on the causes for more pronounced cognitive deficits in men than in women with metabolic syndrome. Central nervous insulin resistance may play a role. It is assumed to be a common denominator of metabolic disorders and cognitive dysfunctions by exerting detrimental effects on cholinergic and glutamatergic pathways which establish neuronal plasticity (19).

Women have less insulin resistance

Table 3—Relationship between metabolic syndrome and cognition: multivariate regression analysis

	Model 1*								
	Total sample (n = 819)†			Men (n = 363)			Women (n = 456)		
	β	P	95% CI	β	P	95% CI	β	P	95% CI
Memory	−0.14	0.034	−0.27 to −0.01	−0.27	0.013	−0.49 to −0.05	−0.06	0.444	−0.22 to 0.09
Psychomotor skills	−0.03	0.593	−0.14 to 0.08	−0.09	0.280	−0.26 to 0.07	0.03	0.670	−0.11 to 0.17
Executive functions	−0.58	0.010	−1.02 to −0.14	−0.80	0.033	−1.54 to −0.06	−0.39	0.162	−0.94 to 0.15
	Model 2*								
	Total sample (n = 819)†			Men (n = 363)			Women (n = 456)		
	β	P	95% CI	β	P	95% CI	β	P	95% CI
Memory	−0.12	0.090	−0.27 to 0.02	−0.25	0.050	−0.51 to 0.00	−0.04	0.645	−0.23 to 0.14
Psychomotor skills	−0.006	0.920	−0.13 to 0.11	0.02	0.842	−0.18 to 0.22	−0.003	0.961	−0.16 to 0.15
Executive functions	−0.65	0.010	−1.14 to −0.15	−0.94	0.023	−1.74 to −0.13	−0.44	0.165	−1.07 to 0.18

\*Model 1: adjusted for age, years of education, depressive mood, coronary heart disease, and physical activity at leisure time. Model 2: model 1 plus adjustment for WML volume, presence of lacunae, silent infarcts, and brain parenchymal fraction. †Total sample: additionally adjusted for sex.



cognitive functioning irrespectively of their possible role in the etiology of vascular and primary degeneration. Increased hs-CRP levels may well reflect lifetime overreactivity of the innate immune system to various exogenous and endogenous stimuli. This overreactivity may be genetically determined and confer the increased risk for developing both metabolic syndrome and cognitive impairment in later life. Consequently, the interactive association observed here of metabolic syndrome and hs-CRP with cognitive functions is of particular interest. In this context it is also noteworthy that elevated levels of inflammatory markers have been repeatedly linked to an increased risk of dementia (23). Intriguingly, the Honolulu Asia Aging Study reported increased hs-CRP levels 25 years prior to the occurrence of dementia (24). Similar data come from the Rotterdam Study (25).

A strength of our study is the simultaneous assessment of cognitive function and brain MRI in a large cohort of community-dwelling subjects who were prospectively examined using a standardized protocol. An important limitation of this study is its cross-sectional design, which does not permit to deduce a cause-and-effect relationship. Other limitations include missing measurements of hippocampal volume due to lack of coronal MRI sequences and missing information on duration of metabolic syndrome. The cognitive deficits observed in our study are subtle and clinically covert. Their predictive implications require long-term longitudinal evaluation. Sex-specific effects associated with proinflammatory markers and the lack of significant associations with MRI abnormalities ought to be considered in future studies on mechanisms of cognitive impairment in metabolic syndrome.

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