

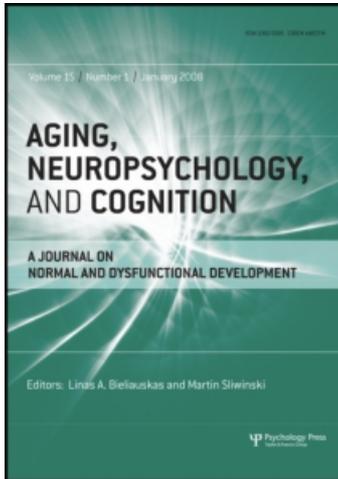
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### Metabolic Syndrome and Cognitive Function in Healthy Middle-Aged and Older Adults without Diabetes

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# Metabolic Syndrome and Cognitive Function in Healthy Middle-Aged and Older Adults without Diabetes

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## ABSTRACT

*Objective:* Few studies have addressed whether the metabolic syndrome (MetS) and its individual components are associated with cognitive function in middle-aged and older populations, as well as whether specific areas of cognition are more affected than others. We examined the cross-sectional association between MetS and six areas of cognitive function in healthy cognitively intact adults without diabetes ( $n = 853$ , mean age 61 years) randomized in two intervention trials. *Methods:* The National Cholesterol Education Program (NCEP) criteria were used to identify subjects with MetS. Cognitive function was assessed with a neuropsychological battery. A principal components analysis was used to extract five uncorrelated factors interpreted to represent five areas of cognition, and a measure of global cognition was calculated. *Results:* MetS was weakly but non-significantly associated with lower verbal learning ( $\beta = -.14$  [ $SE(\beta) = 0.09$ ],  $p = .15$ ). As the number of MetS criteria increased, scores on global cognition ( $p$  trend = .01), verbal learning ( $p$  trend = .06) and semantic memory ( $p$  trend = .04) decreased. Hypertension was the only MetS risk factor that was independently correlated with lower verbal learning ( $\beta = -.17$  [ $SE(\beta) = 0.08$ ],  $p = .04$ ), semantic memory ( $\beta = -.26$  [ $SE(\beta) = 0.08$ ],  $p = .001$ ) and global cognition ( $\beta = -.15$  [ $SE(\beta) = 0.07$ ],  $p = .04$ ). *Conclusion:* This study adds to the evidence of an association between MetS and lower cognitive function among healthy middle-aged and older adults without CVD and diabetes, as well as confirms the correlation between hypertension and lower cognition.

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**Keywords:** Metabolic syndrome; Cognitive function; Hypertension; Memory; Verbal learning; Global cognition.

## INTRODUCTION

Risk factors for cardiovascular disease (CVD) including hypertension and metabolic disturbances, such as diabetes, have been linked to the development of Alzheimer's disease (AD) and vascular dementia (VaD) (Biessels & Kappelle, 2005; Kumari, Brunner, & Fuhrer, 2000; Martins et al., 2006). Several population- and community-based studies of non-demented individuals have reported associations between these and other CVD risk factors and cognitive dysfunction or decline (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005; Kalmijn, van Boxtel, Verschuren, Jolles, & Launer, 2002; Robbins, Elias, Elias, & Budge, 2005), while others have not (Aleman, Muller, de Haan, & van der Schouw, 2005; Pavlik, Hyman, & Doody, 2005; Robbins, Elias, Budge, Brennan, & Elias, 2005). The metabolic syndrome (MetS), a clustering of risk factors that includes (1) abdominal obesity, (2) hypertriglyceridemia, (3) low levels of high density lipoprotein cholesterol (HDL-C), (4) hypertension, and (5) hyperglycemia, was defined to summarize a constellation of CVD risk factors (NCEP, 2001). MetS is associated with increased risk of CVD (Lakka et al., 2002) and diabetes (Reaven, 1988), and has also been linked to the incidence (Kalmijn et al., 2000) and prevalence of dementia (Hashizume, Suzuki, Hara, Komatsu, & Yamashita, 2006; Kalmijn et al., 2000) and prevalence of AD (Kuusisto et al., 1997; Vanhanen et al., 2006).

Whether MetS is correlated with cognitive dysfunction apart from each risk factor individually has been addressed by a limited number of studies (Dik et al., 2007; Geroldi et al., 2005; Komulainen et al., 2007; Xiong, Plassman, Helms, & Steffens, 2006; Yaffe et al., 2004, 2007). These studies found some evidence that MetS was associated with cognitive decline, but tended to focus on elderly populations (Dik et al., 2007; Geroldi et al., 2005; Komulainen et al., 2007; Xiong et al., 2006; Yaffe et al., 2004, 2007), and used measures that assessed limited areas of cognition (Geroldi et al., 2005; Xiong et al., 2006; Yaffe et al., 2004, 2007). Questions therefore remain as to whether MetS is associated with cognitive function in middle-aged and older populations, and with dysfunction in specific areas. Thus, we examined whether MetS was cross-sectionally associated with lower cognitive function in six areas among healthy cognitively intact women enrolled in the Women's Isoflavone Soy Health (WISH) Trial, and otherwise healthy cognitively intact men and women with elevated plasma homocysteine (Hcy) enrolled in the B-vitamin Atherosclerosis Intervention Trial (BVAIT) (<http://www.clinicaltrials.gov/>). We also investigated which MetS component factors are independently correlated with cognitive function. Study protocols

for both trials excluded diabetic persons from participation; thus this report is unique in that it focuses on MetS in a non-diabetic population.

## METHODS

### Study Participants

Healthy postmenopausal women who were randomized in WISH and otherwise healthy hyperhomocysteinemic adults who were randomized in BVAIT were the focus of the present study. Data obtained for participants at their baseline visit prior to randomization were used in the current analysis.

Briefly, postmenopausal women  $\geq 30$  years old were eligible for WISH; men and postmenopausal women  $\geq 40$  years old were eligible for BVAIT if they had Hcy  $\geq 8.5$   $\mu\text{mol/L}$ . Of 6372 individuals who were prescreened by telephone, 2884 met initial eligibility criteria for the trials and were invited for clinic screening. Exclusions were made for any clinical signs or symptoms of CVD ( $n = 165$ ), diabetes mellitus or fasting serum glucose  $\geq 126$  mg/dL ( $n = 137$ ), triglyceride (TG) levels  $\geq 500$  mg/dL ( $n = 3$ ), hypertension [systolic blood pressure (SBP)  $\geq 160$  mmHg and/or diastolic blood pressure (DBP)  $\geq 100$  mmHg] ( $n = 13$ ), untreated thyroid disease ( $n = 4$ ), creatinine clearance  $< 70$  mL/min or serum creatinine  $> 2.0$  mg/dL ( $n = 6$ ), a life threatening disease with prognosis  $< 5$  years ( $n = 124$ ), alcohol intake of  $> 5$  drinks per day/substance abuse ( $n = 4$ ), unwillingness to stop taking vitamin supplements ( $n = 626$ ) or current use of hormone therapy (WISH) ( $n = 15$ ). A total of 856 subjects were randomized (350 in WISH and 506 in BVAIT); all signed a written informed consent approved by the Institutional Review Board at the University of Southern California.

### Measurements

All subjects were administered a battery of cognitive tests (Lezak, Howieson, & Loring, 2004) in a standardized order by one trained psychometrist. The battery was designed to assess a broad array of cognitive abilities, with an emphasis on specific tasks used to detect age-associated change in middle-aged and elderly populations, particularly episodic memory and executive function, and included the following tests:

- Symbol Digit Modalities Test (SDMT)
- Trail Making Test Part B (Trails-B)
- Judgment of Line Orientation, Form H (JLO)
- Block Design [Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III)]
- Letter-Number Sequencing [Wechsler Memory Scale, 3rd edition (WMS-III)] (LNS)
- Category fluency (animal naming, 60 s) (Animals)

- Boston Naming Test, 30-item version (BNT)
- Shipley Institute of Living Scale Abstraction Subtest (Shipley)
- California Verbal Learning Test, 2nd edition (CVLT-II), immediate recall (IR) and delayed recall (DR)
- Logical Memory I and II (paragraph recall, IR and DR) (WMS-III)
- Faces I (IR) and II (DR) (WMS-III)

The Center for Epidemiologic Studies Depression Scale (CES-D) scale (Radloff, 1977) was used to assess mood. Of the randomized subjects, three did not have cognitive testing; 853 (99.6%) subjects were included in the present study.

Fasting total cholesterol (TC), HDL-C, LDL cholesterol (LDL-C) (computed with the Friedewald equation (Bachorik & Ross, 1995; Friedewald, Levy, & Fredrickson, 1972)) and TG were measured by enzymatic assay methodology and standardized to the CDC Lipid Standardization Program (Lipid Research Clinics Program, 1974). Fasting serum glucose levels were measured with spectrophotometry on an Olympus 5400 (Quest Diagnostics, West Hills, CA). Blood pressure, body height, weight and waist circumference (WC) were measured, and body mass index (BMI) was calculated ( $\text{kg}/\text{m}^2$ ). Smoking questionnaires were used to determine smoking status.

Study participants were identified as having MetS using a modified NCEP definition (Grundy et al., 2005; NCEP, 2001) if  $\geq 3$  of the following risk determinants were present: (1) abdominal obesity: WC  $>102$  cm ( $>40$  in) for men or  $>88$  cm ( $>35$  in) for women; (2) TG  $\geq 150$  mg/dL; (3) HDL-C  $<40$  mg/dL for men or  $<50$  mg/dL for women; (4) blood pressure  $\geq 130/\geq 85$  mmHg or current use of anti-hypertensive medications; and (5) fasting glucose level  $\geq 110$  mg/dL. Participants who did not meet  $\geq 3$  of the NCEP criteria were classified as not having MetS. Since both trials excluded diabetic persons, individuals identified with MetS in the present analysis represent MetS among non-diabetic populations.

### Statistical Analysis

We conducted  $\chi^2$ - or  $t$ -tests to assess whether baseline demographic and CVD risk factors significantly differed between study subjects with and without MetS. For subjects ( $n = 44$ ) who were unable to complete one or more tests in the neuropsychological battery, age-, gender- and education-specific mean values from the study population were imputed. Small reductions (averaging 3.7%) in variances of the tests resulted from imputations, which were made for  $<0.7\%$  of the total number of tests administered. There were no appreciable differences in results or conclusions if subjects with imputed values were excluded from analyses.

For data reduction purposes, a principal components analysis with an orthogonal varimax rotation was performed on the 14 cognitive tests in the

neuropsychological battery and consecutive uncorrelated factors were extracted. Following methods of Cattell (1966), a scree plot of successive eigenvalues was used to identify at what number of principal components the plot leveled off; this led to a decision to retain five factors. The five factors accounted for 72.4% of the total variance, and were interpreted by assigning a name to each that reflected high factor loadings of individual cognitive tests (i.e., loadings with an absolute value  $>0.45$ ). The resulting factors generally reflected cognitive abilities in areas of (1) executive function (high factor loadings on SDMT, Trails-B, LNS, JLO, Block Design and Shipley), (2) verbal learning (high factor loadings on CVLT- IR and DR), (3) logical memory (high factor loadings on paragraph recall – IR and DR), (4) visual episodic memory (high factor loadings on Faces I and II), and (5) semantic memory (high factor loadings on Animals and BNT). For each subject, a factor score for each of the five component factors was calculated. In addition, we created a measure of global cognition, which was calculated as the weighted sum of scores on each of the individual tests in the neuropsychological battery; weighting of each test was based on the sum of the inverse covariances of scores with other tests. The resulting measure was then divided by its standard deviation (*SD*) so as to interpret results per *SD* of global cognition and ensure a consistent interpretation of results with those of the five factors.

General linear models were used to examine the association between the presence of MetS (yes/no) (independent variable) and the six measures of cognition (dependent variables) adjusting for demographic characteristics that were significant univariate correlates of global cognition, including age ( $<54$ ,  $54-57$ ,  $58-62$ ,  $63-68$  and  $\geq 69$  years), race/ethnicity (indicator variables for Caucasian, African-American, Latino and Asian-American/Pacific Islander/Native American), highest educational level achieved (high school or less, some college, Bachelor's degree and graduate/professional degree), household income ( $<30,000$ ,  $30,000-49,999$ ,  $50,000-69,999$ ,  $70,000-99,999$  and  $\geq 100,000$  dollars/year), and for mood (CES-D total score  $0-3$ ,  $4-12$ ,  $13-19$  or  $\geq 20$ ). While gender was not a significant univariate correlate of global cognition in our study population, it was retained in regression models given its relationship with cognition reported in the literature (Butler, 1984; Overman, 2004). An indicator term for BVAIT or WISH was included in regression models to account for possible confounding due to study. Given recent reports of associations between use of medications such as statins (Bernick et al., 2005; Szwasz et al., 2007) or anti-hypertensives (Muldoon et al., 2002; Papademetriou, 2005) and lower incidence of cognitive decline or improved cognitive function, we additionally adjusted models for statin use (yes/no) and anti-hypertensive use (yes/no). Beta coefficients ( $\beta$ ) and their standard errors were estimated from regression models to assess the association between MetS and cognition. Separate models were run for each of the six

measures of cognition. For the variable expressing the presence/absence of MetS,  $\beta$  values represented average differences, in *SD* units, of the cognitive measure comparing subjects with MetS to those without MetS. To assess whether there was a trend in cognitive functioning with increasing number of MetS criteria, a term for the number of MetS criteria was tested in the regression models. The five MetS criteria were modeled individually to determine whether each criterion was a significant individual correlate of cognitive function, and together to determine whether each criterion was a significant independent correlate of cognitive function. Criteria were modeled both as continuous (divided by their *SD*) and categorical variables, using NCEP cut points to define categories (i.e., hypertensive versus non-hypertensive). Values of  $\beta$  were interpreted either as (1) the mean difference in the cognitive measure relative to subjects with a one *SD* lower value of the particular MetS criterion (criteria modeled continuously), or (2) the mean difference in the cognitive measure relative to subjects not meeting the particular MetS criterion (criteria modeled categorically). All analyses used SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

The mean (*SD*) age of the study population was 60.9 (8.8) years. The majority were women (63.9%), Caucasian (64.5%) and highly educated (59.6% with a Bachelor's or graduate degree). Nearly one-third (31.9%) was currently using medications for hypertension. A total of 112 (13.1%) of the study population fit the expanded NCEP definition for MetS. Of those, 75 (67%) met three criteria, 30 (26.8%) met four, and 7 (6.3%) met all five criteria. Among those with MetS, the most common criterion met was hypertriglyceridemia ( $n = 90$ , 80.4%), followed by hypertension ( $n = 86$ , 76.8%), abdominal obesity ( $n = 82$ , 73.2%), low HDL-C ( $n = 66$ , 58.9%) and hyperglycemia ( $n = 56$ , 50%). Subjects with MetS were more likely to be Hispanic and, as expected, have higher blood pressure, fasting glucose, TG and BMI and lower HDL-C compared to those without MetS (Table 1).

Participants with MetS had non-significantly lower scores on the verbal learning factor ( $\beta = -.14$  [ $SE(\beta) = 0.09$ ],  $p = .15$ ) compared to participants without MetS (Table 2). For each additional MetS criterion met, scores decreased by 6% of a *SD* on the measure of global cognition ( $\beta = -.06$  [ $SE(\beta) = 0.03$ ],  $p = .01$ ), by 5% of a *SD* on the verbal learning factor ( $\beta = -.05$  [ $SE(\beta) = 0.03$ ],  $p = .06$ ), and by 6% of a *SD* on the semantic factor ( $\beta = -.06$  [ $SE(\beta) = 0.03$ ],  $p = .04$ ). The MetS was not associated with executive function, logical memory or visual memory (Table 2).

Increases in SBP and TG were individually associated with lower semantic memory (Table 3). Lower global cognitive abilities were correlated with individual increases in TG ( $\beta = -.07$  [ $SE(\beta) = 0.03$ ],  $p = .02$ ). When

**TABLE 1.** Baseline characteristics for study subjects with cognitive testing ( $n = 853$ ) by the presence of the metabolic syndrome

Variable	With the metabolic syndrome* ( $n = 112, 13.1\%$ )	Without the metabolic syndrome* ( $n = 741, 86.9\%$ )	$p$ Value <sup>†</sup>
Age (years)	61.8 ± 8.2	60.8 ± 8.9	.28
Gender			.17
Male	47 (42.0%)	261 (35.2%)	
Female	65 (58.0%)	480 (64.8%)	
Race/Ethnicity			.009
Non-Hispanic White	64 (57.1%)	486 (65.6%)	
Non-Hispanic Black	15 (13.4%)	83 (11.2%)	
Hispanic	25 (22.3%)	87 (11.7%)	
Asian/Pacific Island/ Native American	8 (7.1%)	85 (11.5%)	
Educational level			.25
High school or less	16 (14.3%)	80 (10.8%)	
Some college	39 (34.8%)	210 (28.3%)	
Bachelor's degree	25 (22.3%)	192 (25.9%)	
Graduate/professional degree	32 (28.6%)	259 (34.9%)	
Household income			.23
Low	32 (28.6%)	165 (22.4%)	
Medium	15 (13.4%)	115 (15.6%)	
Moderate	24 (21.4%)	140 (19.0%)	
High	41 (36.6%)	317 (43.0%)	
Current/Former smoker	44 (39.3%)	290 (39.2%)	.98
Body-mass index (kg/m <sup>2</sup> )	32.6 ± 5.1	26.7 ± 4.7	<.0001
Blood pressure (mmHg)			
Systolic	132.4 ± 15.5	123.7 ± 16.6	<.0001
Diastolic	81.9 ± 10.2	77.9 ± 10.0	<.0001
Total cholesterol (mg/dL) <sup>‡</sup>	221.0 ± 32.9	220.7 ± 37.1	.92
LDL cholesterol (mg/dL) <sup>‡</sup>	136.1 ± 29.4	137.0 ± 34.5	.77
HDL cholesterol (mg/dL) <sup>§</sup>	46.3 ± 10.6	61.5 ± 16.0	<.0001
Triglycerides (mg/dL) <sup>§</sup>	194.5 ± 72.1	110.8 ± 57.9	<.0001
Glucose (mg/dL) <sup>  </sup>	109.3 ± 12.8	96.8 ± 9.2	<.0001
CES-D score <sup>‡</sup>	11.3 ± 9.2	11.8 ± 8.6	.51
Current use of anti-hypertensives	23 (20.5%)	102 (13.8%)	.06
Current use of statins	42 (37.5%)	120 (16.2%)	<.0001

\*Mean ± *SD* or number (%).

<sup>†</sup> $p$  Value for comparison of subjects with the metabolic syndrome to subjects without the metabolic syndrome.

<sup>‡</sup> $n = 851$ .

<sup>§</sup> $n = 852$ .

<sup>||</sup> $n = 848$ .

mutually adjusted as continuous variables, only increasing SBP was statistically significantly correlated with lower cognitive function (in semantic memory:  $\beta = -.08$  [ $SE(\beta) = 0.04$ ],  $p = .04$ ).

Using the NCEP-defined criteria for MetS, hypertension was individually associated with lower verbal learning ( $\beta = -.17$  [ $SE(\beta) = 0.08$ ],  $p = .04$ ),

**TABLE 2.** Beta coefficients from linear regression models\* of associations between the metabolic syndrome and six measures of cognition for 853 study subjects

Cognitive measure	Metabolic syndrome measure $\beta$ coefficient [ $SE(\beta)$ ], $p$ value			
	MetS ( $n = 112$ , 13.1%) vs. No MetS ( $n = 741$ , 86.9%)		Number of MetS criteria <sup>†</sup>	
Global cognition	-0.07 (0.08)	.40	-0.06 (0.03)	.01
Executive function	0.03 (0.09)	.74	-0.02 (0.03)	.54
Verbal learning	-0.14 (0.09)	.15	-0.05 (0.03)	.06
Logical memory	0.07 (0.10)	.52	-0.02 (0.03)	.52
Visual memory	-0.06 (0.10)	.57	-0.01 (0.03)	.94
Semantic memory	-0.12 (0.10)	.23	-0.06 (0.03)	.04

\*Adjusted for age, gender, race/ethnicity, education, income, study, CES-D score, statins or anti-hypertensive medication use.  
<sup>†</sup>Continuous variable ranging from 0 to 5.

**TABLE 3.** Beta coefficients from linear regression models\* of associations between components of the metabolic syndrome individually modeled as continuous variables and cognitive function for 853 study subjects

Metabolic syndrome component	Change in cognitive factor per $SD$ of component $[SE(\beta)]$ , $p$ value <sup>†</sup>					
	Verbal learning		Semantic memory		Global cognition	
SBP (17 mmHg)	0.03 (0.04)	.37	-0.08 (0.04)	.03	-0.01 (0.03)	.77
Glucose (11 mg/dL)	-0.01 (0.03)	.99	-0.05 (0.03)	.14	0.03 (0.03)	.38
HDL (16 mg/dL)	0.04 (0.04)	.21	0.01 (0.04)	.90	0.05 (0.03)	.11
Waist circumference (5 in)	-0.03 (0.04)	.40	0.06 (0.04)	.12	-0.03 (0.03)	.30
Triglycerides (66 mg/dL)	-0.03 (0.03)	.42	-0.07 (0.03)	.03	-0.07 (0.03)	.02

\*Adjusted for age, gender, race/ethnicity, education, income, study, CES-D score, statins or anti-hypertensive medication use.  
<sup>†</sup> $p$  Value for comparison per standard deviation.

semantic memory ( $\beta = -.28$  [ $SE(\beta) = 0.08$ ],  $p = .0006$ ) and global cognition ( $\beta = -.15$  [ $SE(\beta) = 0.07$ ],  $p = .04$ ). Hypertriglyceridemia and hyperglycemia were individually associated with lower semantic memory, and low HDL-C and hypertriglyceridemia were significantly individually associated with lower global cognition (Table 4). When all MetS criteria were mutually adjusted in regression models, hypertension was the only MetS risk factor that was consistently independently inversely associated with verbal learning, semantic memory and global cognition (Table 4). MetS criteria (modeled either as continuous or categorical variables) were not associated (either individually or independently) with executive function, logical memory or visual memory (results not shown).

**TABLE 4.** Beta coefficients from linear regression models\* of associations between individual NCEP metabolic syndrome characteristics (categorical variables) and cognitive function

Metabolic syndrome criteria	Verbal learning [SE(β)], <i>p</i> value <sup>†</sup>		Semantic memory [SE(β)], <i>p</i> value <sup>†</sup>		Global cognition [SE(β)], <i>p</i> value <sup>†</sup>	
	Individually modeled	Mutually adjusted	Individually modeled	Mutually adjusted	Individually modeled	Mutually adjusted
Hypertension	-0.17 (0.08)	.04	-0.28 (0.08)	.0006	-0.15 (0.07)	.04
Hyperglycemia	-0.05 (0.09)	.61	-0.18 (0.10)	.06	0.07 (0.08)	.43
Low HDL-C level	-0.12 (0.08)	.16	-0.07 (0.08)	.39	-0.16 (0.07)	.03
Abdominal obesity	-0.05 (0.08)	.47	0.16 (0.08)	.04	-0.05 (0.07)	.44
Hypertriglyceridemia	-0.04 (0.08)	.64	-0.15 (0.08)	.05	-0.17 (0.07)	.01

\* Adjusted for age, gender, race/ethnicity, education, income, study, CES-D score, statins or anti-hypertensive medication use.

<sup>†</sup> *p* Value for comparison of one category to reference category.

We explored whether gender modified the association between the MetS criteria and semantic memory. Mutually adjusted associations were several magnitudes higher in women for abdominal obesity ( $\beta = .34$  [ $SE(\beta) = 0.10$ ],  $p = .0005$ ) and hyperglycemia ( $\beta = -.32$  [ $SE(\beta) = 0.14$ ],  $p = .03$ ) than men ( $\beta = .05$  [ $SE(\beta) = 0.14$ ],  $p = .73$ , and ( $\beta = -.04$  [ $SE(\beta) = 0.14$ ],  $p = .78$ , respectively), but were not appreciably different for hypertension.

## CONCLUSIONS

This study provides evidence of an association between MetS and lower cognitive function among healthy, cognitively intact middle-aged and older men and women without CVD or diabetes. We found that non-diabetic adults with MetS tended to perform lower specifically on verbal learning tasks compared to those without MetS. A greater number of MetS criteria were also associated with lower scores on the verbal learning factor, supporting the validity of the association between MetS and this area of cognition. Granted the magnitude of the mean difference, about a fifth of an *SD*, is modest when applied to individuals. A similar trend with increasing number of MetS criteria and lower semantic memory and global cognition was also observed. Increases in blood pressure were individually and independently associated with lower semantic memory abilities. Hypertension was the only MetS risk factor that was an independent correlate of lower cognitive function in areas of verbal learning and semantic memory, as well as with global cognition. The average age of our study population was at least 10 years less than populations in previous studies of MetS and cognition (Dik et al., 2007; Geroldi et al., 2005; Komulainen et al., 2007; Xiong et al., 2006; Yaffe et al., 2004, 2007).

In contrast to a study (Komulainen et al., 2007) that reported that low HDL-C was the single MetS criteria independently associated with decreased memory function in elderly women, we found that hyperglycemia was an independent correlate of semantic memory among women in our study population. That study, however, examined baseline levels of HDL-C and memory assessed at a 12-year follow-up. Our study used baseline measures of both MetS criteria and cognition.

While higher blood pressure was not statistically significantly independently associated with lower verbal learning, hypertension was. One possible explanation of this finding is that the NCEP hypertension definition specifies a relevant threshold at which associations between elevations in blood pressure and cognition may be observed. To further investigate the role of hypertension in cognition, we assessed whether hypertension mediated the effect of MetS on verbal learning abilities. We found that hypertension attenuated the MetS–verbal learning association by approximately 50%, suggesting that a large proportion of this association is mediated by hypertension.

Results of this study suggest that the association between MetS, MetS components and cognition may be specific to certain areas of cognition, and specifically verbal learning and semantic memory may be more vulnerable to the metabolic disturbances clustered in MetS. Our finding that MetS is associated with verbal learning is consistent with the literature, in that MetS is a risk factor for diabetes (Reaven, 1988) and previous studies have reported associations between diabetes and decreased verbal memory (Strachan, Deary, Ewing, & Frier, 1997). The extension of these findings to a study population of non-diabetic persons makes our findings unique. Mechanisms by which hyperglycemia may lead to decreased cognitive function have been proposed. In animal studies, chronic hyperglycemia results in decreased acetylcholine synthesis and loss of cortical neurons (Kumari et al., 2000). Cholinergic transmission is known to be important for learning and memory, and the cerebral cortex is thought to be where memory is 'stored' in the brain (Kandel, Schwartz, & Jessell, 2000). Hypertension, which has been consistently linked (Elias & Robbins, 1991; Elias, Elias, & Wolf, 2000) to decline in cognitive functioning, may act by accelerating arteriosclerosis in the cerebral microvasculature, leading to brain lacunar infarctions and or white matter lesions (Kumari et al., 2000).

Previous studies examining the association between MetS or its components and cognition have used one (Geroldi et al., 2005; Xiong et al., 2006; Yaffe et al., 2004) or at most a few (Komulainen et al., 2007; Yaffe et al., 2007) neuropsychological instruments to assess cognitive function, usually the Mini-Mental State Examination (MMSE) or a derivative. The MMSE was originally designed to evaluate mental status in elderly individuals and to screen for cognitive impairment or dementia (Feher et al., 1992; Tombaugh & McIntyre, 1992). While a popular measure in epidemiological studies for its brevity and ease of administration, the MMSE does not provide a wide range of scores with which to assess variability in cognitively intact populations, nor does it allow for a comprehensive examination of different areas of cognition. A strength of the current study is the neuropsychological battery that allowed for an assessment of a broad range of cognitive abilities. Furthermore, our approach to calculating cognitive factor scores using a principal components analysis ensures that the cognitive outcomes (except for the global cognition score) examined in this study were uncorrelated. In addition, we controlled for a number of demographic factors known to be associated with cognitive function in order to minimize their contribution to the observed associations.

Nevertheless, the effects observed in this population were small. For verbal learning, the decrease in cognitive performance associated with the presence of MetS corresponds to approximately 14% of *SD* in the factor score, which is still within the range of what is considered a clinically 'normal' level of cognitive functioning (Elwood, 1995; Norman, Evans, Miller, & Heaton, 2000; Paolo, Troster, & Ryan, 1997).

This study is limited by small numbers of adults >80 years old. Thus we may have been underpowered to assess cognition at lower bounds of normal given the inverse association between age and cognition. In addition, the study's findings may not generalize to elderly adults. Furthermore, given the BVAIT selection criteria for subjects with Hcy  $\geq 8.5$   $\mu\text{mol/L}$ , it is possible that results from this study may not be generalizable to populations with lower Hcy. Limitations of the cross-sectional design are that we do not have information on duration of specific conditions, and moreover, are unable to address directionality of associations. Finally, the study population was comprised of healthy, well-educated volunteers for two clinical trials, and probably does not represent the entire range of cognitive abilities prevalent in the general population. Therefore, it is possible that we may have underestimated the true association between MetS and cognition.

In conclusion, this study adds to the evidence that MetS and its component factors are associated with lower cognitive functioning, specifically with lower verbal learning, semantic memory and global cognition in healthy, cognitively intact middle-aged and older adults without CVD or diabetes. Results from this study also suggest that individual components of MetS, particularly hypertension, may be at least as important a contributor to cognition as the MetS symptom cluster.

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## REFERENCES

- Aleman, A., Muller, M., de Haan, E. H., & van der Schouw, Y. T. (2005). Vascular risk factors and cognitive function in a sample of independently living men. *Neurobiology of Aging*, *26*(4), 485–490.
- Bachorik, P. S., & Ross, J. W. (1995). National Cholesterol Education Program recommendations for measurement of low-density lipoprotein cholesterol: Executive summary. The National Cholesterol Education Program Working Group on Lipoprotein Measurement. *Clinical Chemistry*, *41*(10), 1414–1420.
- Bernick, C., Katz, R., Smith, N. L., Rapp, S., Bhadelia, R., Carlson, M., et al. (2005). Statins and cognitive function in the elderly: The Cardiovascular Health Study. *Neurology*, *65*(9), 1388–1394.
- Bieless, G. J., & Kappelle, L. J. (2005). Increased risk of Alzheimer's disease in Type II diabetes: Insulin resistance of the brain or insulin-induced amyloid pathology? *Biochemical Society Transactions*, *33*(Pt 5), 1041–1044.

- Butler, S. (1984). Sex differences in human cerebral function. *Progress in Brain Research*, 61, 443–455.
- Cattell, R. B. (1966). The scree test for the number of factors. *Multivariate Behavioral Research*, 1, 245–276.
- Dik, M. G., Jonker, C., Comijs, H. C., Deeg, D. J., Kok, A., Yaffe, K., et al. (2007). Contribution of metabolic syndrome components to cognition in older persons. *Diabetes Care*, 30(10), 2655–2660.
- Elias, M. F., & Robbins, M. A. (1991). Cardiovascular disease, hypertension and cognitive function. In A. P. Shapiro & A. Baum (Eds), *Behavioral aspects of cardiovascular disease*. Hillsdale, NJ: Lawrence Erlbaum.
- Elias, M. F., Elias, P. K., & Wolf, P. A. (2000). Comparative effects of age and blood pressure on neuropsychological test performance: The Framingham Study. In S. B. Manuck, R. Jennings, B. S. Rabin, & A. Baum (Eds), *Behavior, health and aging* (pp. 199–223). Mahwah, NJ: Lawrence Erlbaum Associates.
- Elias, M. F., Elias, P. K., Sullivan, L. M., Wolf, P. A., & D'Agostino, R. B. (2005). Obesity, diabetes and cognitive deficit: The Framingham Heart Study. *Neurobiology of Aging*, 26(Suppl. 1), 11–16.
- Elwood, R. W. (1995). The California Verbal Learning Test: Psychometric characteristics and clinical application. *Neuropsychology Review*, 5(3), 173–201.
- Feher, E. P., Mahurin, R. K., Doody, R. S., Cooke, N., Sims, J., & Pirozzolo, F. J. (1992). Establishing the limits of the Mini-Mental State. Examination of 'subtests'. *Archives in Neurology*, 49(1), 87–92.
- Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, 18(6), 499–502.
- Geroldi, C., Frisoni, G. B., Paolisso, G., Bandinelli, S., Lamponi, M., Abbatecola, A. M., et al. (2005). Insulin resistance in cognitive impairment: The InCHIANTI study. *Archives in Neurology*, 62(7), 1067–1072.
- Grundey, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., et al. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*, 112(17), 2735–2752.
- Hashizume, K., Suzuki, S., Hara, M., Komatsu, A., & Yamashita, K. (2006). Metabolic syndrome and age-related dementia: Endocrinological aspects of adaptation to aging. *Mechanisms of Ageing and Development*, 127(6), 507–510.
- Kalmijn, S., Foley, D., White, L., Burchfiel, C. M., Curb, J. D., Petrovitch, H., et al. (2000). Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arteriosclerosis and Thrombosis, Vascular Biology*, 20(10), 2255–2260.
- Kalmijn, S., van Boxtel, M. P., Verschuren, M. W., Jolles, J., & Launer, L. J. (2002). Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *American Journal of Epidemiology*, 156(10), 936–944.
- Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). *Principles of neural science* (4th ed.). New York: McGraw-Hill.
- Komulainen, P., Lakka, T. A., Kivipelto, M., Hassinen, M., Helkala, E. L., Haapala, I., et al. (2007). Metabolic syndrome and cognitive function: A population-based follow-up study in elderly women. *Dementia and Geriatric Cognitive Disorders*, 23(1), 29–34.
- Kumari, M., Brunner, E., & Fuhrer, R. (2000). Minireview: Mechanisms by which the metabolic syndrome and diabetes impair memory. *Journal of Gerontology A Biological Science and Medical Science*, 55(5), B228–232.

- Kuusisto, J., Koivisto, K., Mykkanen, L., Helkala, E. L., Vanhanen, M., Hanninen, T., et al. (1997). Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: Cross sectional population based study. *British Medical Journal*, *315*(7115), 1045–1049.
- Lakka, H. M., Laaksonen, D. E., Lakka, T. A., Niskanen, L. K., Kumpusalo, E., Tuomilehto, J., et al. (2002). The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *Journal of the American Medical Association*, *288*(21), 2709–2716.
- Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological assessment* (4th ed.). New York: Oxford University Press.
- Lipid Research Clinics Program. (May, 1974). *The Manual of Laboratory Operations: Lipid and Lipoprotein Analysis*. (Vol. 1). Bethesda, MD: National Heart and Lung Institute.
- Martins, I. J., Hone, E., Foster, J. K., Sunram-Lea, S. I., Gnjec, A., Fuller, S. J., et al. (2006). Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Molecular Psychiatry*, *11*(8), 721–736.
- Muldoon, M. F., Waldstein, S. R., Ryan, C. M., Jennings, J. R., Polefrone, J. M., Shapiro, A. P., et al. (2002). Effects of six anti-hypertensive medications on cognitive performance. *Journal of Hypertension*, *20*(8), 1643–1652.
- NCEP (2001). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Journal of American Medical Association*, *285*(19), 2486–2497.
- Norman, M. A., Evans, J. D., Miller, W. S., & Heaton, R. K. (2000). Demographically corrected norms for the California Verbal Learning Test. *Journal of Clinical and Experimental Neuropsychology*, *22*(1), 80–94.
- Overman, W. H. (2004). Sex differences in early childhood, adolescence, and adulthood on cognitive tasks that rely on orbital prefrontal cortex. *Brain and Cognition*, *55*(1), 134–147.
- Paolo, A. M., Troster, A. I., & Ryan, J. J. (1997). California Verbal Learning Test: Normative data for the elderly. *Journal of Clinical and Experimental Neuropsychology*, *19*(2), 220–234.
- Papademetriou, V. (2005). Hypertension and cognitive function. Blood pressure regulation and cognitive function: A review of the literature. *Geriatrics*, *60*(1), 20–22, 24.
- Pavlik, V. N., Hyman, D. J., & Doody, R. (2005). Cardiovascular risk factors and cognitive function in adults 30–59 years of age (NHANES III). *Neuroepidemiology*, *24*(1–2), 42–50.
- Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*, 385–401.
- Reaven, G. M. (1988). Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*, *37*(12), 1595–1607.
- Robbins, M. A., Elias, M. F., Budge, M. M., Brennan, S. L., & Elias, P. K. (2005). Homocysteine, type 2 diabetes mellitus, and cognitive performance: The Maine-Syracuse Study. *Clinical and Chemical Laboratory Medicine*, *43*(10), 1101–1106.
- Robbins, M. A., Elias, M. F., Elias, P. K., & Budge, M. M. (2005). Blood pressure and cognitive function in an African-American and a Caucasian-American sample: The Maine-Syracuse Study. *Psychosomatic Medicine*, *67*(5), 707–714.
- Strachan, M. W., Deary, I. J., Ewing, F. M., & Frier, B. M. (1997). Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care*, *20*(3), 438–445.
- Szwast, S. J., Hendrie, H. C., Lane, K. A., Gao, S., Taylor, S. E., Unverzagt, F., et al. (2007). Association of statin use with cognitive decline in elderly African Americans. *Neurology*, *69*(19), 1873–1880.

- Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatric Society*, 40(9), 922–935.
- Vanhanen, M., Koivisto, K., Moilanen, L., Helkala, E. L., Hanninen, T., Soininen, H., et al. (2006). Association of metabolic syndrome with Alzheimer disease: A population-based study. *Neurology*, 67(5), 843–847.
- Xiong, G. L., Plassman, B. L., Helms, M. J., & Steffens, D. C. (2006). Vascular risk factors and cognitive decline among elderly male twins. *Neurology*, 67(9), 1586–1591.
- Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E. M., Harris, T., Shorr, R. I., et al. (2004). The metabolic syndrome, inflammation, and risk of cognitive decline. *Journal of the American Medical Association*, 292(18), 2237–2242.
- Yaffe, K., Haan, M., Blackwell, T., Cherkasova, E., Whitmer, R. A., & West, N. (2007). Metabolic syndrome and cognitive decline in elderly Latinos: Findings from the Sacramento Area Latino Study of Aging study. *Journal of the American Geriatric Society*, 55(5), 758–762.