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Metabolic Syndrome and 16-year Cognitive Decline in Community-Dwelling Older Adults

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Abstract

PURPOSE—To determine whether metabolic syndrome is associated with accelerated cognitive decline in community-dwelling older adults.

METHODS—Longitudinal study of 993 adults (mean 66.8 ± 8.7 years) from the Rancho Bernardo Study. Metabolic syndrome components, defined by 2001 NCEP-ATP III criteria, were measured in 1984–87. Cognitive function was first assessed in 1988–92. Cognitive assessments were repeated approximately every four years, for a maximum 16-year follow-up. Mixed-effects models examined longitudinal rate of cognitive decline by metabolic syndrome status, controlling for factors plausibly associated with cognitive function (diabetes, inflammation).

RESULTS—Metabolic syndrome was more common in men than women (14% vs. 9%, $p=0.01$). In women, metabolic syndrome was associated with greater executive function and long term memory decline. These associations did not differ by inflammatory biomarker levels. Diabetes did not alter the association of metabolic syndrome with long-term recall but modified the association with executive function: metabolic syndrome was associated with accelerated executive function decline in diabetic women only. Metabolic syndrome was not related to rate of decline on any cognitive measure in men.

CONCLUSIONS—Metabolic syndrome was a risk factor for accelerated cognitive decline, but only in women. Prevention of metabolic syndrome may aid in maintenance of cognitive function with age.

Keywords

Aging; cognition; inflammation; diabetes; memory; executive function

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INTRODUCTION

With the aging population and high financial and personal costs of caring for cognitively impaired seniors, there is urgent need to better understand the influence of potentially modifiable risk factors on cognitive decline with aging. One prevalent risk factor is the metabolic syndrome, a cluster of cardiovascular risk factors including hyperglycemia, dyslipidemia, high blood pressure and central obesity.

Individual components of the metabolic syndrome have been linked to poor cognitive performance but emerging evidence suggests that metabolic syndrome as a whole is associated with poorer cognitive function (1). Results have not been entirely consistent, however (2–7), and there is controversy over whether inflammation (1) or hyperglycemia (8) underlie observed associations.

Because the relation between metabolic risk factors and cognitive ability may change with age and be influenced by neurodegenerative processes that begin years prior to cognitive symptoms, longitudinal studies with long follow-up are necessary to better understand how metabolic syndrome relates to cognition in aging. Here, we report the 16-year longitudinal association between metabolic syndrome and cognitive function in community-dwelling older participants of the Rancho Bernardo Study.

METHODS

Study Population

The Rancho Bernardo Study is a longitudinal, population-based study initiated in 1972–1974 (9). Surviving members have been followed to the present by annual mailed questionnaires and periodic clinic visits. The current analysis consists of 993 individuals (n=409 men and n=584 women; aged 42–89 years, mean 66.8 ± 8.7 years) who had metabolic syndrome components measured in 1984–87, and cognitive function first assessed in 1988–92 and in at least one subsequent research clinic visit. This study was approved by the Human Subjects Protection Program of the University of California, San Diego; all participants gave informed consent prior to each visit.

Data Collection

In 1984–87, a standardized questionnaire was used to obtain information on lifestyle and medical history, including physician-diagnosed type 2 diabetes. Medication use was validated by in-clinic examination of medications and prescriptions. Height, weight and waist circumferences were measured and body mass index (BMI; kg/m^2) calculated. Mood was assessed using the Beck Depression Inventory (BDI). Blood pressure was measured twice in rested, seated participants (10); the mean of the two readings were used in analyses.

Laboratory Methods

Blood samples were obtained after an overnight fast. Fasting and 2 hour post-challenge (75 g oral glucose tolerance test) glucose levels were measured using a glucose oxidase assay. Total cholesterol, triglycerides, and lipoprotein levels were measured in a Center for Disease Control certified laboratory (11, 12). Interleukin-6 (IL-6) was measured in a subsample of participants (339 men and 458 women) using a high-sensitivity amplified commercial ELISA with an alkaline phosphatase signal amplification system (R&D Systems, Minneapolis, MN). High-sensitivity C-reactive protein (CRP) was measured in the majority of participants (330 men and 446 women) with an automated, high-sensitivity immunonephelometry method (N Latex CRP mono, Dade Behring, Inc., Deerfield, Illinois). Individuals with CRP > 15 mg/liter (n=17) were excluded from inflammatory biomarker

analysis because these levels often reflect acute illness or trauma. IL-6 and CRP were log transformed prior to analyses.

Metabolic Syndrome and Diabetes

Metabolic syndrome was defined by 2001 NCEP-ATP III criteria (13) as presence of any three of the following: abdominal obesity (waist circumference >102 cm in men; >88 cm in women); triglycerides ≥150 mg/dL (1.7 mmol/L); HDL cholesterol levels <40mg/dL (1.04 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women; fasting glucose ≥110 mg/dL (6.1mmol/L); blood pressure ≥130/85 mmHg, or documented use of antihypertensive medication.

Diabetes was defined by fasting plasma glucose >126 mg/dL and/or 2-hour post-challenge plasma glucose >200mg/dL (14), documented use of diabetes medication, or self-reported physician-diagnosed diabetes.

Cognitive Function Tests

In 1988–92, a battery of standardized tests was administered, including the Mini-Mental State Examination (MMSE) (15), a measure of global cognitive function; the Trail-making Test, part B (Trails B) (16), a timed test of executive function; Verbal Category Fluency (17), a measure of semantic fluency; and long-term recall from the Buschke-Fuld Selective Reminding Test (18). Tests were repeated at roughly 4 year intervals, with a maximum of five assessments over 16 years.

Statistical Analyses

Chi-square or univariate analyses of variance were used to compare baseline demographic and clinical data between participants with and without metabolic syndrome. Analyses of covariance were used to compare baseline cognitive function scores in participants with and without metabolic syndrome, adjusting for age, education (some college: yes/no) and BDI. Analyses were sex-specific. Longitudinal data were examined with mixed-effects models (PROC-MIXED) using the categorization of metabolic syndrome status or number of metabolic syndrome components as exposure variables and repeated measures of cognitive function tests as outcomes, with separate models for each test. Mixed-effect models account for within-subject correlation between repeated measures and allow for incomplete outcome data. Follow-up time, measured in years since baseline was included as a random effect. This allows individual subject baseline levels (intercept) and rates of decline (slope) to vary randomly about the mean trajectory described by the fixed-effect terms. Baseline age, BDI, and education were included as fixed-effects, and a running count variable to address practice effects was included as a time-varying measure. Interaction terms of all covariates with time were included to allow the influence of each covariate to change over time. Metabolic syndrome status at baseline or number of metabolic syndrome components was individually added to the models as a fixed-effect term. Terms representing the interaction of metabolic syndrome status or number of components with time indicate the association of the exposure with change per year (slope) for each cognitive function score.

When significant effects were observed, secondary analyses evaluated the contribution of other factors plausibly associated with cognitive function. In separate models, the following covariates were included: BMI, CRP and IL-6; alcohol (categorized as daily intake, intake 3–4 times per week, 1–2 times per week, 1–2 times per month, less than monthly); tobacco habit (never, former, current smoker); physical activity (reported as engaging in strenuous physical activity ≥3 times per week); and prevalent CVD (defined as history of physician-diagnosed heart attack, angina pectoris, coronary artery revascularization, stroke and/or transient ischemic attack).

To determine whether observed associations were modified by inflammation (1) or diabetes (19) separate secondary models included interaction terms for CRP and diabetes status with metabolic syndrome or number of metabolic syndrome components. Stratified analyses were conducted as appropriate. These analyses adjusted for age, education, depressed mood, and number of cognitive assessments.

All statistical tests were two-tailed; $p < 0.01$ was considered statistically significant. Data were analyzed using SAS v9.1 (SAS Institute, Cary, NC) and SPSS v15.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline Metabolic Syndrome and Initial Cognitive Function

Table 1 shows sex-specific demographic and clinical data by metabolic syndrome status. Prevalence of metabolic syndrome was higher in men than women (13.9% versus 8.9%, respectively $\chi^2 = 6.23$; $p = .01$); overall prevalence of metabolic syndrome was 11% ($n=109$). Men and women with metabolic syndrome had an average of $3.3 (\pm 0.6)$ and $3.5 (\pm 0.7)$ components, respectively. Relative to those without metabolic syndrome, participants with metabolic syndrome had higher CRP levels and were more likely to have diabetes (40% of men and 35% of women with metabolic syndrome had diabetes; 9% of men and women without metabolic syndrome had diabetes). Overall prevalence of diabetes was 11.8% ($n = 117$).

Sex-specific BDI and cognitive function test scores at the initial cognitive assessment are shown in Table 2. After adjusting for age, education, and BDI, there were no differences in baseline cognitive function scores between participants with or without metabolic syndrome.

Association of Metabolic Syndrome with Longitudinal Cognitive Decline

On average, participants had 3.5 (range 2–5) cognitive function assessments; this did not differ by sex. Most participants (676, 68%) had cognitive function assessed three or more times. Those who attended all five visits (29% of study participants) were younger at baseline than those who attended 2, 3 or 4 visits (61 ± 6 ; 71 ± 8.3 ; 68.7 ± 8 and 66.5 ± 7.9 years respectively). Prevalence of the metabolic syndrome at baseline decreased with each follow-up visit, from 35% in participants who attended only 2 visits; 27.5% in those who attended 3 visits; 20.2% in those who attended 4 visits; and 17.4% in participants who attended 5 visits ($p=0.01$). The main reason for non-participation in follow-up visits was death (64%); more men than women died during follow-up (59% versus 44%).

Table 3 and Figure 1 show sex-specific associations of metabolic syndrome with cognitive decline for each test. Among women, metabolic syndrome status and higher number of metabolic syndrome components were associated with accelerated Trails B decline. Trails B score increased (indicating worse performance) by 2.27 seconds per year in women with metabolic syndrome compared to those without. Each additional component was associated with an increase of 0.61 seconds per year. Thus an individual with all five components would show 30 second slower performance time after 10 years than an individual without any metabolic syndrome components. Number of components was also associated with greater rate of memory decline in women: each additional component was associated with 0.12 decrease in recall score per year. In men, the metabolic syndrome was not associated with change in cognitive function over time. Adjusting for BMI, smoking, alcohol use, physical activity, or CVD did not change these results.

Adjusting for inflammation did not alter the association of metabolic syndrome with Trails B in women, but strengthened the association with recall: women with metabolic syndrome

showed a decrease in recall score of 0.46 points per year relative to those without ($p=.01$). Including CRP or IL-6 as interaction terms in the models revealed no significant main effects of inflammatory biomarkers or interactions of inflammatory biomarkers with metabolic syndrome status on cognitive decline.

Diabetes altered the association of metabolic syndrome with Trails B decline (p for interaction = .05). In models stratified by diabetes status, metabolic syndrome was associated with Trails B decline in women with diabetes ($p=.01$) but not in those without ($p=.029$). Women with both diabetes and metabolic syndrome showed an increase of 5.23 seconds per year relative to women with neither. Adjusting for fasting glucose level did not alter the interactive effect of diabetes and metabolic syndrome.

Secondary analyses examined the separate association of each individual metabolic syndrome component with Trails B and recall decline in women. For Trails B, the only component to show an association with cognitive decline was HDL. Low HDL was associated with an increase of 1.6 seconds per year ($p=.04$) after adjusting for age, education and BDI. For recall, only fasting glucose level was associated with rate of decline. Women with elevated glucose scored 0.34 points lower per year ($p=.02$) than those with normal glucose levels.

DISCUSSION

In this community-based study of older adults, metabolic syndrome predicted accelerated executive function (Trails B) and long-term verbal memory decline in women, but was not associated with rate of cognitive decline in men. The association of metabolic syndrome with cognitive function in women showed no interaction with inflammation. Diabetes, however, modified the association of metabolic syndrome with executive function decline, such that the detrimental influence of metabolic syndrome was only apparent in women with diabetes. In contrast, long-term memory declined more rapidly in women with metabolic syndrome independent of diabetes status.

These results are in general agreement with prior longitudinal studies that followed individuals for shorter periods (2 to 5 years). Those studies found that metabolic syndrome was associated with increased risk of clinically-defined cognitive impairment (20) or higher risk of cognitive decline (1, 21), with global function, memory, or executive abilities particularly affected. One small study, involving 101 older women, found that metabolic syndrome was associated with higher risk of global cognitive impairment and memory impairment 12 years later (2). In contrast, a study of nearly 600 individuals aged 85 years or older found less cognitive decline in individuals with metabolic syndrome, suggesting that metabolic syndrome may show a different relation to cognitive health among the very old (7).

High levels of inflammation increase the risk of developing diabetes and atherosclerosis, and have been proposed as a mechanism for adverse consequences of metabolic syndrome on cognition (22). Some studies reported that metabolic syndrome was associated with cognitive impairment primarily in individuals with high levels of inflammation (1, 8, 22–24), although others have not found inflammation to affect the association of metabolic syndrome with cognitive function (3, 5). Here, the association of metabolic syndrome with cognitive decline in women was strengthened after adjusting for IL-6 and CRP levels, suggesting that inflammation did not underlie the observed association of metabolic syndrome with cognitive decline.

Hyperglycemia has also been proposed as a main risk factor in the association of metabolic syndrome to cognitive impairment (8). Diabetes is a known risk factor for dementia and has

been associated with increased risk of cognitive impairment (19, 25). Here, similar to results reported in the French 3-city study (21), diabetes amplified the association between metabolic syndrome and executive function decline in women. Although diabetes did not modify the association of metabolic syndrome with memory decline, hyperglycemia was the only metabolic syndrome component associated with increased rate of memory decline. The magnitude of this association was similar to that observed for the metabolic syndrome as a whole suggesting that hyperglycemia may underlie the observed association between metabolic syndrome and memory decline in women.

In secondary analyses investigating the contribution of individual metabolic syndrome components to executive function decline in women, only HDL level showed a significant association with performance, but the magnitude of decline associated with low HDL was smaller than that for the metabolic syndrome as a whole (an increase in reaction time of 1.6 seconds per year for HDL relative to 2.78 seconds per year for metabolic syndrome). This suggests that, at least for executive function, the metabolic syndrome as a whole provides additional information on risk of decline than that provided by any individual component. The significant interaction of diabetes with metabolic syndrome further suggests that metabolic syndrome and diabetes have interactive as well as independent effects on cognitive function, and that effects vary by cognitive domain.

Sex differences in the association of cognitive function with metabolic syndrome have not been widely explored. Existing longitudinal studies have not explicitly investigated sex differences (1, 21), or have involved only women (2, 20). Cross-sectional studies have yielded conflicting results (3, 24). Sex differences in the influence of metabolic syndrome on cognitive decline observed here parallel our recent finding that increased Framingham cardiovascular risk score predicted accelerated cognitive decline in women, but not men (12). For reasons not fully understood, but that may relate, in part, to genetic differences (26, 27), women are more vulnerable than men to adverse cardiovascular effects of diabetes (28–30) and metabolic syndrome (31, 32). Metabolic syndrome is a stronger predictor of carotid atherosclerosis (33, 34), coronary heart disease, cardiovascular disease, and cardiovascular disease-related mortality in women than in men (31, 32). It is associated with increased risk of ischemic stroke in women, but not in men (35). Ischemic stroke risk is related to adverse changes in brain white matter, and such changes have been associated with impairments on cognitive tasks, such as the Trails B (36, 37).

Alternatively, selective attrition may underlie the lack of an observed association between metabolic syndrome and cognitive decline in men. Although men and women did not differ in number of repeated cognitive assessments, cognitive impairment could be associated with higher non-participation rates due to mortality in men than in women (38). A greater proportion of men died during follow up than women. Thus an association between cognitive decline and metabolic syndrome in men may have been missed due to selective vascular morbidity and mortality.

The major strength of this study is the population-based cohort with long follow-up and good longevity. Metabolic syndrome components and cognitive function were collected using standardized methods. Cognitive function was measured at least twice in all participants and at least three times in most, allowing us to assess the association of metabolic syndrome with trajectories of cognitive change. Cognitive tests assessed global function and specific cognitive domains including executive function, semantic fluency, and long-term recall. Finally, we were able to examine the role of major confounders, such as age, education level and depressed mood that may affect cognitive ability.

Study participants were white, middle class and 90% had at least a high school education. Although this limits generalizability, results are less confounded by differences in health literacy or access to health care. Prevalences of metabolic syndrome and diabetes in our sample were much lower than prevalence estimates based on a nationally representative sample, in which 54.4% of adults >60 years were estimated to meet NCEP-ATP III criteria for metabolic syndrome (39), and 26.9% of adults >65 years to meet criteria for diabetes (40). The lower prevalence of metabolic syndrome in our sample may have reduced our ability to detect associations of metabolic syndrome with cognitive decline, but is unlikely to have caused the observed associations. Other potential limitations include assessment of metabolic syndrome at baseline only, and the four-year interval between metabolic syndrome assessment and baseline cognitive function tests. Survivor bias, a potential limitation in all studies of aging, could have led to an underestimation of the true association between metabolic syndrome and cognitive function, but is unlikely to have caused it.

Conclusions

Metabolic syndrome is a well-known predictor of cardiovascular disease and diabetes (41, 42). This study adds to the emerging literature suggesting that metabolic syndrome is a risk factor for cognitive decline, particularly among women. It further suggests that diabetes may amplify the association of metabolic syndrome with cognitive decline, and that effects may vary by cognitive domain. The sex differences in the association of metabolic syndrome with cognitive decline observed here, although in need of replication, parallel known sex differences in cardiovascular risk associated with metabolic syndrome (31, 32) and diabetes (28–30). With the rapid growth in the size of the elderly population and the high prevalence of metabolic syndrome among older adults, even minor impairments in cognitive function associated with metabolic syndrome could have large public health impact. Prevention, early detection, and treatment of the cardiovascular risk factors embedded in the metabolic syndrome may aid in the maintenance of cognitive function, independence, and quality of life in old age.

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List of Abbreviations

BDI	Beck Depression Inventory
BMI	Body mass index
CRP	C-reactive protein
IL-6	Interleukin-6
MMSE	Mini Mental State Exam
Trails B	Trail Making Test, Part B from the Halstead-Reitan Test Battery

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Figure 1.

Modeled cognitive function test score trajectories by metabolic syndrome status for men and women. Plots are based on all model coefficients using sex-specific mean values for covariates (age, educational level, depression score, and number of cognitive assessments). Note that the y axis is reversed for the Trails B because increasing Trials B scores indicate poorer performance. Women with metabolic syndrome showed significantly greater longitudinal decline in Trails B performance relative to women without metabolic syndrome ($p=.01$). Rate of declining on long term recall significantly differed between women with and without metabolic syndrome after additionally controlling for inflammatory biomarkers. Rate of change did not differ significantly as a function of metabolic syndrome status in men. MMSE = Mini-Mental State Exam; Trails B = Trail Making Test Part B; Recall = Buschke-Fuld long-term recall.

Table 1

Clinical and demographic characteristics of participants by metabolic syndrome status.

	Men			Women		
	No MetS n=352 (86.1%)	MetS n=57 (13.9%)	No MetS n=532 (91.1%)	MetS n=52 (8.9%)		
	Mean (S.D.)	%	Mean (S.D.)	%	Mean (S.D.)	P value
Age	66.0 (8.5)		67.1 (9.0)		69.0 (7.3)	.14
Some college	82.1	73.7		65.6		48.1 .01
<i>MetS components</i>						
Waist Circumference (cm)	92.6 (7.7)	10.2	101.5 (10.7)	50.9	87.8 (8.5)	55.8 <.0001
Systolic BP (mmHg)	131.5 (17.8)	51.6	140.3 (18.0)	78.9	147.4 (25.1)	86.5 <.0001
Diastolic BP (mmHg)	77.9 (8.5)	22.2	81.7 (9.7)	35.1	77.9 (10.2)	17.3 .012
Fasting Glucose (mmol/l)	100.8 (18.1)	16.2	123.1 (27.5)	70.2	123.6 (56.1)	55.7 <.0001
Triglycerides (mmol/l)	109.8 (64.6)	16.2	214.6 (118.3)	80.7	221.2(95.8)	90.4 <.0001
HDL (mmol/l)	54.9 (13.8)	8.8	40.9 (8.1)	54.4	50.8 (13.4)	57.7 <.0001
Diabetes	--	8.8	--	40.4	--	34.6 <.001
BMI	25.68 (2.80)		28.68 (4.20)		27.36 (4.19)	<.0001
IL-6*	2.7 (2.31)	--	3.2 (2.29)	--	3.3 (1.9)	.001
CRP#	1.92 (2.1)	--	3.17 (2.8)	--	5.1 (4.0)	-- <.0001

S.D. = standard deviation; MetS= metabolic syndrome.

* IL-6 (interleukin-6) values were available for 339 men and 458 women

CRP (C-reactive protein) values were available for 330 men and 446 women; 4 men and 13 women were excluded due to CRP values > 15 mg/liter. IL-6 and CRP values were log transformed prior to analyses; raw means are displayed in the table.

P values for MetS components reflect univariate analyses of variance comparing mean levels of each component for No MetS vs. MetS for each sex separately. Chi square comparisons of the significance of the difference in percentage meeting the cut-off levels for No MetS vs. MetS were significant (at p< .001) for all MetS components except Diastolic blood pressure. The difference by MetS status in percentage with and without categorically-defined high diastolic blood pressure approached significance for men (p = .034) but did not differ for women (p=0.24).

Baseline mean (standard error of the mean) depression and cognitive function test scores by metabolic syndrome status for men and women.

Table 2

	Men			Women		
	No MetS	MetS	P value	No MetS	MetS	P value
BDI	4.2 (0.2)	5.4 (0.4)	.02	5.8 (0.2)	6.7 (0.6)	.15
MMSE	27.5 (0.1)	27.3 (0.2)	.51	27.6 (0.1)	27.8 (0.2)	.43
Trails B	107 (2.2)	107 (5.5)	.95	124 (2.2)	120 (7.0)	.55
Cat. Fluency	19.8 (0.2)	20.2 (0.6)	.54	18.1 (0.2)	17.3 (0.6)	.24
Recall	29.7 (0.6)	29.8 (1.5)	.93	36.0 (0.5)	36.5 (1.5)	.78

MetS= metabolic syndrome. BDI = Beck Depression Inventory; MMSE= Mini Mental State Examination. Trails B = The Trail-making Test, part B. Cat. Fluency = categorical fluency test; Recall: long-term verbal recall from Buschke-Fuld Selective Reminding Test, respectively. Higher scores on Trails B are indicative of worse performance. P values show significance of the No MetS vs. MetS comparison in men and women, separately.

Table 3

Sex-specific coefficients for rate of cognitive decline in mixed effects models for metabolic syndrome status (MetS) and number of metabolic syndrome components.

	MMSE	Trails B	Cat. Fluency	Recall
<u>Women</u>				
Time * MetS	0.00	2.27 *	0.02	-0.31
Time * Components	0.00	0.61 *	0.01	-0.12 *
<u>Men</u>				
Time * MetS	-0.05	0.99	0.03	0.08
Time * Components	-0.02	0.28	0.03	0.02

*
p 0.01;

**
p 0.001

MMSE = Mini Mental State Examination. Trails B = The Trail-making Test, part B. Cat. Fluency = categorical fluency test; BSTR, Buschke-Fuld long-term recall, respectively.

Time refers to follow-up time from baseline visit. Models also included age, education, baseline Beck Depression Inventory scores, a running count variable to address practice effects and interaction terms between each variable and follow up time.