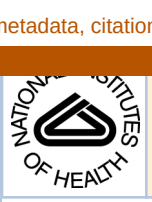

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Metabolic Syndrome and Cognitive Decline in Early Alzheimer's Disease and Healthy Older Adults

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Abstract

Metabolic syndrome (MetS) is a cluster of risk factors (i.e., abdominal obesity, hypertension, dyslipidemia, glucose and insulin dysregulation) that is associated with cardiovascular disease, diabetes, and dementia. Recent studies addressing the association of MetS with cognitive performance and risk for dementia report mixed results. An important step in clarifying these conflicting results is determining whether cognition is influenced by the effects of individual MetS components versus the additive effects of multiple components. We assessed the effect of MetS on cognitive performance and decline over two years in 75 cases of early Alzheimer's disease (AD) and 73 healthy older adult controls in the Brain Aging Project. Using factor analytic techniques, we compared the effect of a combined MetS factor to the effect of individual MetS components on change in attention, verbal memory, and mental status. In healthy controls, a combined MetS factor did not significantly predict cognitive performance, though higher insulin predicted poorer cognitive performance outcomes. In the AD group, higher scores on a combined MetS factor predicted *better* cognitive outcomes. Our findings suggest that MetS does not have the same association with cognitive decline in healthy older adults and those with early AD. We suggest that individual MetS components should not be evaluated in isolation and that careful methodological approaches are needed to understand the timing and non-linear relationships among these components over time.

Keywords

Alzheimer's disease; cognitive decline; factor analysis; metabolic syndrome

INTRODUCTION

Alzheimer's disease (AD) research has increasingly focused on methods of early detection and prevention. Modifiable risk factors for cognitive decline and dementia are the targets for

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earlier interventions to delay or prevent the disease process. Lifestyle factors in mid- and late-life, such as diet and exercise, are related to several biological mechanisms assumed to play a role in the development of AD including obesity, diabetes, and chronic inflammation [1–4]. Metabolic syndrome (MetS) is a cluster of risk factors including abdominal obesity, hypertension, lipid abnormalities, and impaired metabolism of glucose and insulin that is associated with cardiovascular disease, diabetes, and dementia [5–10].

Recent studies addressing the association of MetS with cognitive performance and risk for dementia report mixed results. In several studies, individuals meeting National Cholesterol Education Program (NCEP) criteria for MetS have had poorer cognitive performance [11–14], while other studies showed no association with dementia and cognitive performance [15–18] or even reduced risk of AD and decelerated cognitive decline in individuals over age 75 [12, 19]. A recent review by Crichton et al. evaluated evidence from 19 studies regarding the relationship between MetS, cognition, and risk for dementia [20]. They concluded that clarifying the meaning of mixed findings requires researchers to address several methodological limitations by including new approaches to measurement of MetS and cognitive performance, and explicitly evaluating the effects of individual MetS components versus a combined or additive effect. We offer the additional hypothesis that the relationship between MetS and cognitive performance depends on cognitive disease status and may be better reflected in changes over time than at a single point in time. In the following paragraphs, we introduce each of these issues and describe our approach for addressing them in the current investigation.

The NCEP defines MetS as meeting cutoffs for three of more of the following risk determinants: waist circumference >102 cm for males, or >88 cm for females, triglyceride levels ≤ to 150 mg/dL, HDL cholesterol <40 mg/dL for males, or <50 mg/dL for females, blood pressure ≤130/85 or current use of antihypertensive medications, and fasting glucose ≤110 mg/dL. To clarify whether individual MetS markers increase or decrease risk for cognitive decline, Crichton et al. [20] recommend using precise levels of biomarkers instead of categorical (yes/no) cutoffs that are typically used such as the NCEP criteria. Cutoffs are somewhat arbitrary as individuals just above or just below the cutoffs may be more alike than different. Furthermore, standardized cutoff scores do not reflect elevations from an individual's own baseline biomarker levels. To address this in the present study, we report a comparison of results using cutoffs for NCEP criteria to results using continuous biomarker levels.

A wide variety of cognitive tests has been used to evaluate the effect of MetS on cognitive performance. Because individual cognitive tests often measure multiple cognitive domains, they are frequently categorized differently across studies. Thus, it is very difficult to compare results across studies regarding which cognitive domains are affected by MetS. To address this limitation and evaluate the specific cognitive abilities most influenced by MetS, Crichton et al. [20] recommend using factor analysis of tests of cognitive performance. This approach improves measurement accuracy by using multiple measures of cognitive abilities. Factor analytic techniques aggregate common variance across multiple subtests and attenuate error idiosyncratic to the individual tests. Factor scores yield more sensitive and specific estimates of cognitive ability than do traditional analyses of raw scores or scaled score composites because they are purer indices of ability [21]. Following the recommendations of Crichton et al. [20], we used a factor analytic model of cognitive performance scores.

A key question that remains unresolved is whether one or two individual components of MetS drive the relationship with cognitive outcomes, or whether these individual components are additive or interact in some way [20]. Though the majority of studies report

only the effects of individual MetS components, a few studies report that a greater number of abnormal MetS components is associated with poorer cognitive performance [13, 15]. For example, Gatto and colleagues [15] reported that meeting cutoffs for an increasing number of individual MetS components was associated with a trend for poorer cognitive performance, though Cavalieri et al. [13] found this relationship only in men. In the current report, we directly tested competing hypotheses about the additive effect of the hypothesized metabolic syndrome versus the effect of individual components. Following the recommendations of Crichton et al. [20], we used a factor analytic model to represent the combined influence of MetS components on cognitive performance and decline. This approach estimates the relative contribution of each item to the overall factor and combines them according to their relative weight. We then compared these results to the traditional method of testing individual MetS items in a multiple regression framework.

No published studies have examined whether MetS components cluster together in the same fashion in healthy older adults and those with AD, although there may be reason to suspect they are different. Higher insulin and higher blood pressure may predict better cognitive performance in individuals with dementing illness [22, 23], the opposite of what is expected in healthy older adults. Losses in body mass preceding dementia diagnosis [24, 25] also reflects a counterintuitive process compared with the risks associated with high body mass index in healthy middle-aged adults. Higher levels of cholesterol in late life may be associated with reduced risk for dementia, in contrast to mid-life studies reporting that high cholesterol increases risk for dementia [26]. Changes in the pattern of MetS clustering could indicate a clinically relevant change in the process of conversion to dementia. Few previous studies of MetS and cognition have used longitudinal designs [12, 27, 28], preventing conclusions from being drawn regarding the role of MetS in cognitive decline over time or conversion to dementia. To address this limitation of the existing literature, the current study reports the comparison of these relationships in healthy older adult controls and individuals with early AD over a two year follow up.

Our study aimed to address gaps in the literature by 1) comparing the effects of individual MetS components versus a combined MetS factor on cognitive performance, 2) assessing the comparability of the MetS factor in healthy older adults and individuals with early AD, and 3) assessing the effect of MetS on change in cognitive performance over a two year follow up. To explain conflicting reports that metabolic syndrome increases, decreases, or has no impact on cognitive decline and risk for dementia, we hypothesized that the relationship between MetS components and cognitive performance depends on disease status.

MATERIALS AND METHODS

Sample and recruitment

Data used in the present analyses were collected from participants enrolled in the longitudinal Brain Aging Project at the University of Kansas Alzheimer and Memory Program who had tests of markers of metabolic syndrome and completed standardized neuropsychological testing at baseline and two years later. All study procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved in compliance of the ethical standards of the University of Kansas Medical Center Institutional Review Board. Informed consent was obtained for all participants prior to enrollment into the study. Clinical assessment included dementia diagnosis and staging, cognitive testing, and collection of MetS biomarker data, as previously described [29]. Briefly, dementia status of the participant was based on an in-depth clinical evaluation and interview with the participant and a study partner with whom they had regular contact. Participants were classified as having AD if they met established diagnostic criteria: gradual and progressive

impairment in memory and at least one other cognitive or functional domain [30]. The clinical evaluation included the Clinical Dementia Rating (CDR) [31]. The CDR evaluates cognitive function in each of six categories (memory, orientation, judgment and problem solving, performance in community affairs, home and hobbies, and personal care) without reference to psychometric performance or results of previous evaluations. CDR 0 indicates no dementia, and CDR 0.5, 1, 2, or 3 correspond to very mild, mild, moderate, and severe dementia. Our method of diagnostic classifica-tion follows the recommendations of Morris et al. [32] and Storandt et al. [33]. These methods have a diagnostic accuracy for AD of 93% and have been shown to be accurate in identifying the subset of individuals meeting criteria for mild cognitive impairment (MCI) who have early-stage AD [32, 34]. Although some of our participants may have met classification criteria for MCI, we only enrolled individuals who demonstrated intra-individual decline and interference with daily function consistent with a clinical diagnosis of AD.

All healthy older adult controls ($n = 73$ at baseline) were without evidence of functional cognitive impairment (CDR 0) at both time points. At baseline, AD participants ($n = 75$) had very mild or mild dementia (CDR 0.5 or 1). On average, AD patients demonstrated one-third of a point increase in CDR stage (increased severity) two years later. AD participants were recruited largely by media appeals and from a referral-based memory clinic. All healthy older adult control participants were recruited by self-referral in response to media coverage and word of mouth. Study exclusions at baseline include diabetes mellitus (clinical diagnosis, use of an anti-diabetic agent, or 2-hour post-load serum glucose) and unstable ischemic heart disease within the last 2 years as previously described [29]. As MetS is a pre-morbid condition rather than a clinical diagnosis, its definition should not include individuals with established diabetes [35].

Clinical assessment

A trained psychometrician administered a standard psychometric battery [29] that included the Mini-Mental State Exam (MMSE), Wechsler Memory Scale [WMS]–Revised Logical Memory I and II, Free and Cued Selective Reminding Task, Wechsler Adult Intelligence Scale [WAIS] letter–number sequencing, digit symbol, and Stroop Color–Word Test (color reading). Higher scores indicate better performance.

Biomarker collection included traditional measures of MetS: systolic and diastolic blood pressure, glucose and insulin area under the curve, triglycerides, HDL cholesterol, body mass index (BMI), and waist circumference. Body mass was measured by scale and height was measured using a standard stadiometer. BMI was determined by dividing total body mass (in kg) by the square of height (in meters). The average of three measures of waist circumference was used (in cm). Blood pressure was assessed using the average of two measurements using a manual cuff on the left arm. Laboratory assessments included a 14-sample intravenous glucose tolerance test (IVGTT) performed at 8 : 30 AM after a 12-hour overnight fast. An intravenous glucose bolus of 0.3 g/kg body weight was delivered and blood samples were drawn over three hours [29]. The total areas-under-the-curve (AUC) for insulin and glucose were determined by the trapezoidal rule [36]. Serum insulin was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 1.3 mU/L. Fasting venous blood samples were assessed using commercial enzymatic assays for total cholesterol and high density lipoprotein cholesterol (Diagnostic Chemicals, Ltd.) and triglycerides (Roche Diagnostic Systems). APOE genotyping results were obtained using restriction enzyme isotyping.

Statistical analysis

Cognitive test scores and individual MetS components were standardized relative to the mean of the baseline healthy older adult controls [37]. Therefore, scores for individuals with early AD represent the distance between the raw score and the mean of a healthy older adult control in units of the standard deviation (SD = 1). When scores for early AD patients are negative it indicates they are below the mean for healthy older adult controls. When positive, they are above the mean for healthy older adult controls. Thus, all indices of change can be interpreted relative to a cognitively normal aging process. As several of the MetS variables were non-normally distributed, we followed standard practice for correction of skewed distributions that violate assumptions of normality by using logarithmic transformation for insulin, glucose, BMI, and triglycerides. For descriptive purposes, we calculated the percent of cases and controls meeting NCEP criteria for metabolic syndrome [38].

Confirmatory factor analysis

We conducted confirmatory factor analysis (CFA) using Mplus [39] to evaluate the factor structures of MetS components and tests of cognitive performance. This approach offers improved measurement accuracy by aggregating common variance across multiple subtests and attenuating error idiosyncratic to the individual items. In accordance with guidelines for proper execution of CFA techniques, we applied theoretical reasoning and well-established clinical observation to the practice of selecting variables to include, testing models, and interpreting the results [40].

Goodness-of-fit was evaluated based on root mean square error of approximation (RMSEA) which is a measure of discrepancy between predicted and observed model values; values closer to 0 indicate better fit (preferred values <0.09). We also report the comparative fit index which estimates the relative fit of a model compared to an alternative model (CFI, >0.90 indicates good fit). We used full information maximum likelihood algorithm to account for missing data.

We used multiple-group tests of invariance to determine whether the cognitive and MetS factors differed between the early AD and healthy older adult groups. Tests of measurement invariance evaluate the degree to which measurements conducted in different groups of people (or at different points in time) reflect measurement of the same attributes [41]. The test of *weak invariance* is the least restrictive. Good fit indicates that the groups share the same factor structure and the same factor loadings. The test of *strong invariance* requires all assumptions for *weak* as well as the same item intercepts across groups. We evaluated changes in goodness-of-fit indices using a table of significant change in chi-square and using a change in RMSEA >0.01 as an indicator of significant change based on the research of Cheung and Rensvold recommending this as an appropriate cutoff point for testing measurement invariance [42].

Step one: Factor analysis of metabolic syndrome

We hypothesized that a single common factor would best describe the relationship among components of MetS: systolic and diastolic blood pressure, glucose and insulin area under the curve, triglycerides, HDL cholesterol (reverse scored), BMI, and waist circumference. For these analyses, we used the full continuous ranges of each variable rather than the dichotomous NCEP cutoffs. We allowed correlated error terms for BMI with waist circumference and systolic with diastolic blood pressure. We then conducted multiple group tests of invariance as described above to determine whether the MetS factor differed between the early AD and healthy older adult groups.

Step two: Factor analysis of cognitive performance

We used a subset of six cognitive indices from a larger cognitive battery. We hypothesized a two factor structure (attention and verbal memory) with cognitive tests loading on each factor. We allowed correlated error terms for logical memory tests I & II (immediate & delayed).

Factor analysis was used to evaluate what individual tests had in common, rather than what they did not share. This common quality is reflected in the cognitive factor scores that were used in our statistical analyses. The factor weights estimated from the factor analysis were converted to cognitive factor scores that were used in subsequent analyses. Rather than assuming that all cognitive tests were equal contributors to the domains of verbal memory or attention, factor analysis was used to estimate the relative importance and measurement error associated with each individual cognitive test. These estimates (factor weights) were used to create a weighted factor score combining individual tests together into a single score. For example, a factor score for verbal memory contains the scores for each individual test weighted by its relative contribution to verbal memory and adjusted for the measurement error associated with each test. These cognitive domains have been shown to be sensitive to AD-related changes over time [43]. We used multiple-group tests of invariance, as described above, to determine whether the cognitive performance factors differed between the early AD and healthy older adult groups and whether the factors were identical at baseline and at the two year follow up.

Step three: Predicting cognitive performance from the combined MetS factor

To estimate the effect of the combined MetS factor we used structural equation models (SEM) in which the MetS factor predicted cognitive factor scores for attention and verbal memory, MMSE, and change in each. We used SEM to test the relationships between the factor analytically derived scores for cognitive performance and MetS that could not be tested in a traditional regression model. Change in cognitive scores was assessed by subtracting the baseline score from the follow up score. Although this method does not in itself account for the relationship between baseline cognition and amount of change, cognitive scores were standardized to the mean performance on healthy older adult controls at baseline. All models were adjusted for age in years, gender, number of years of education, and APOE $\varepsilon 4$ carrier status.

Step four: Predicting cognitive performance from individual MetS components

To address the issue of individual versus additive effects of metabolic syndrome components, we conducted multiple regression analysis to determine whether individual MetS components were better predictors of cognitive scores than a MetS factor. We estimated the effects of individual metabolic syndrome components on cognitive performance at baseline and follow up and two year change adjusting for age, gender, years of education, and APOE $\varepsilon 4$ carrier status. All MetS components were entered into the equation simultaneously. Separate analyses were conducted for healthy older adult controls and individuals with early AD. Regression coefficients were estimated using bootstrap estimation (5,000 resamples) and 95% confidence intervals. For comparison purposes, we also evaluated the differences between those with MetS and without as defined by the NCEP-III criteria. We used *t*-tests to evaluate mean differences in cognitive factors scores and mental status for those meeting NCEP-III criteria for MetS and those not meeting the criteria. In an exploratory analysis to examine the role of APOE $\varepsilon 4$ carrier status, we conducted these regressions again dividing the sample into carriers and non-carriers.

RESULTS

Table 1 summarizes characteristics for healthy older adult controls and individuals with early AD. Prevalence of MetS according to NCEP ATP-III criteria [43] was 33% ($n = 24$) in the healthy older adult control group and 33% ($n = 25$) in the early AD group. Prevalence did not differ statistically between the groups ($p = 0.86$).

Step one: Factor analysis of metabolic syndrome

The one factor model fit the data in both groups (Controls $X^2/df = 22/18$; CFI = 0.97; RMSEA = 0.06 and Early AD $X^2/df = 27/18$; CFI 0.94; RMSEA = 0.08). While all the measures loaded adequately on the factor in the healthy older adult controls group, two items did not load in the early AD group: systolic blood pressure and glucose (Table 2). We tested invariance of this structure in the two groups and found the groups were equivalent at the level of strong invariance with the exception that the intercept for systolic blood pressure could not be equated between the two groups (Table 2). This is reflected in the significant mean difference in systolic blood pressure between the groups in Table 1.

Step two: Factor analysis of cognitive performance

A two factor model of cognitive performance (attention and verbal memory) provided a good fit to the data ($X^2/df = 7/7$, CFI = 0.99, RMSEA = 0.03). The healthy control and early AD groups were equivalent at the level of strong invariance with the exception that the intercept for digit symbol differed between the two (Table 3). This particular test may differ in the two groups because the digit symbol test is highly sensitive to neuropsychological dysfunction [44]. An identical factor structure fit the cognitive data at the two year follow up ($X^2/df = 42/20$, CFI = 0.98, RMSEA = 0.09).

Step three: Predicting cognitive performance from the combined MetS factor

Using SEM, we used the MetS factor to predict cognitive factor scores for attention and verbal memory, MMSE, and change in each. All models were adjusted for age, gender, education, and APOE $\varepsilon 4$ carrier status (Table 4). In the healthy older adult controls, a combined MetS factor at baseline did not predict cognitive performance or change in cognitive performance. In the early AD group, a higher combined MetS factor score at baseline was associated with better cognitive performance on attention and verbal memory at the two-year follow up and a trend for better MMSE score at the two year follow up. Although higher combined MetS was statistically associated with shallower declines in cognitive performance before adjusting for APOE $\varepsilon 4$ carrier status, the relationship was no longer significant once carrier status was added to the model. A higher combined MetS factor score indicates higher levels of the individual indicators weighted by their individual contributions to the shared factor variance.

Step four: Predicting cognitive performance from individual MetS components

Using multiple regression analysis, we used the individual MetS components to predict cognitive factor scores for attention and verbal memory, MMSE, and change in each. All models were adjusted for age, gender, education, and APOE $\varepsilon 4$ carrier status (Table 5). In the healthy older adult controls, higher insulin at baseline predicted greater declines in verbal memory and a trend for greater declines in attention over the two year follow up. Higher HDL cholesterol was associated with greater declines in attention and a trend for declines in verbal memory over two years. Note that HDL is reverse scored such that a higher HDL level indicates lower HDL (“worse”) levels to be in the same direction as the other components. In the group with early AD, higher insulin at baseline predicted a trend toward better performance on attention at baseline and better verbal memory performance at

follow up. Higher baseline levels of glucose predicted greater declines in attention over the 2 year follow up.

We conducted analyses to further examine the role of APOE ε4 carrier status on the relationship between individual MetS components and cognitive performance. In the healthy older adult controls, the relationship between higher insulin and greater cognitive decline was confirmed in non ε4 carriers (verbal memory β = −0.599, $p = 0.022$; attention β = −0.511, $p = 0.033$) whereas it was not found in ε4 carriers (β = 0.324, $p = 0.592$; attention β = 0.301, $p = 0.845$). Lower HDL cholesterol was associated with worse baseline MMSE performance only among non ε4 carriers (β = −0.511, $p = 0.027$) not in e4 carriers (β = −0.452, $p = 0.109$). By contrast in the early AD group, higher levels of insulin at baseline were associated with better baseline attention in ε4 carriers (β = 0.629, $p = 0.005$), but not in non ε4 carriers (β = −0.253, $p = 0.553$). In early AD patients, decline in attention was predicted by higher baseline levels of glucose (β = −0.425, $p = 0.030$) and higher triglycerides (β = −0.549, $p = 0.035$) only among carriers, not among non-carriers (glucose β = −0.078, $p = 0.877$; triglyc-erides β = −0.070, $p = 0.853$).

Individuals with and without MetS, as defined by the NCEP-III cutoff scores, did not differ in their cognitive performance on verbal memory at baseline (AD $t = 0.25$, $p = 0.80$; Control $t = -0.21$, $p = 0.83$) or follow up (AD $t = 1.17$, $p = 0.25$; Control $t = -0.08$, $p = 0.94$) attention at baseline (AD $t = 0.71$, $p = 0.48$; Control $t = 0.60$, $p = 0.55$), or follow up (AD $t = 0.66$, $p = 0.51$; Control $t = -0.03$, $p = 0.98$) or MMSE at baseline (AD $t = 0.03$, $p = 0.98$; Control $t = 0.09$, $p = 0.93$) or follow up (AD $t = -0.01$, $p = 0.99$; Control $t = 0.46$, $p = 0.65$). An increasing number of components for which NCEP criteria were met was associated with a non-significant trend for poorer baseline attention performance in healthy controls (β = −0.217, $p = 0.066$), but did not show this trend for any other cognitive measure, or at follow up in the healthy controls (β range −0.155 to 0.163, all $p > 0.191$). In those with early AD, a higher number of NCEP criteria met was associated with a trend for less steep declines in attention over two years (β = 0.223, $p = 0.087$), which became stronger after adjusting for APOE ε4 carrier status (β = 0.261, $p = 0.052$). This trend was not found for other cognitive measures, or at other time points (β range −0.071 to 0.077, all $p > 0.590$).

DISCUSSION

Our findings suggest that MetS may not have the same association with cognitive decline in healthy older adults and those with early AD. In healthy older adult controls, MetS did not predict cognitive decline, while in those with early AD a higher MetS score predicted better cognitive performance and less cognitive decline. Past research has shown that in adults over age 75, MetS is associated with better cognitive performance and reduced risk of dementia, contrary to the findings at younger ages [12, 19]. If the relationship between MetS and cognitive function is not linear, timing of measurement would be an essential feature of understanding this relationship. In mid-life, elevated levels of biomarkers may be causal indicators of the onset of a disease process, whereas, in old age, biomarkers are more likely signs of disease rather than causal indicators. After disease processes have developed for decades, systems are dysregulated and fail to maintain homeostasis. This dysregulation may be reflected in biomarker levels that are higher than or lower than normal levels [44]. This does not necessarily imply that hypertension or diabetes are healthy conditions in old age, merely that low or dysregulated levels of blood pressure or insulin may also indicate poor cognitive function. Similarly, with early AD patients, biomarkers may reflect a dysregulation that is a sign of disease, not a cause of disease. For example, systolic blood pressure levels were significantly higher in the early AD group. Glucose and systolic blood pressure did not cluster together with the other indicators of MetS in early AD as they did in the healthy older adult controls. Thus, elevation in glucose and systolic blood pressure is

uncorrelated with elevation in the other MetS indicators in this group. This supports the notion that these indicators function as signs of dysregulation of systems in early AD.

The typical approach to measuring MetS uses cutoff scores that do not reflect changes in these biomarker values that occur with age or disease status. Using this approach to measure the relationship between MetS and cognitive function may not adequately reflect the non-linear relationship and lack of uniformity across groups. Using continuous measures allows a better understanding of the shape and distribution of change over time. Furthermore, the typical approach gives equal weight to each individual component without evaluating whether some may play a more prominent role. A factor analytic approach estimates the relative contribution of each individual indicator and weights them accordingly. Using the traditional NCEP criteria (i.e., sum of the items meeting yes/no cutoffs) we did not find a relationship between MetS and cognitive performance in either group, which is similar to several previous studies [15–18]. When we used factor analysis, we found a relationship between elevated levels of MetS markers and better cognitive performance in early AD, a key contribution of the present research.

When evaluating the effects of individual MetS components, insulin was the most consistent predictor of cognitive performance and decline in both groups, but in opposite directions. In healthy controls, higher insulin predicted more rapid declines in attention and verbal memory over two years. By contrast in those with early AD, higher insulin predicted better cognitive performance. In our sample, insulin was likely driving the relationship between the combined MetS factor and cognitive performance in early AD. The finding that insulin is independently associated with cognitive performance is consistent with numerous previous studies suggesting that insulin resistance, even in non-diabetics, is associated with risk of cognitive decline, dementia, and brain atrophy [22, 45–48]. In individuals with AD, insulin has been associated with cognitive outcomes in the opposite direction from what is expected in healthy older adults [22, 23]. AD patients with type 2 diabetes may have slower rates of cognitive decline than non-diabetic AD patients [49]. Insulin signaling may affect brain health in a disease specific manner or insulin signaling may be affected by changes in the AD brain. It remains unclear whether altered insulin signaling contributes to the development and progression of AD or whether insulin regulation changes are the result of AD brain changes. Pilot trials of intranasal administration of insulin suggest promise for improvement of cognitive symptoms and modulation of amyloid-β in individuals with amnestic MCI and AD [50, 51].

While insulin was the strongest and most consistent individual component, our findings suggest that individual MetS components should not be evaluated in isolation. The relationship between insulin and cognitive outcomes was dependent on APOE carrier status, suggesting that insulin is not acting alone but interacts with other components [52–54]. Several other indicators were independently associated with cognitive performance including cholesterol, blood pressure, glucose, and body mass index and not always in a linear direction. Similar to previous research [15], we found that an increasing number of individual MetS components was associated with a trend for worse performance in one cognitive domain for healthy controls, but uniquely, we found a trend for less steep declines in attention in early AD that was strengthened by adjusting for APOE carrier status. Though our approach allowed assessment of the combined effect of multiple components simultaneously, data with a longer follow up period are needed to further evaluate the timing and potential multiple interactions between individual MetS components.

Declines in verbal memory and attention are some of the earliest cognitive changes in AD, often occurring a year or more before diagnosis [43, 55]. As such, measures of these cognitive domains are useful for distinguishing between healthy aging and early stages of

dementia [37, 56]. Several other studies have reported associations between MetS and cognitive performance in these particular domains [12–14, 57]. A comprehensive review of studies suggests that attention and verbal memory were among the domains most frequently assessed and the most frequently associated with MetS [20].

Insulin and glucose were the two individual MetS components most strongly associated with verbal memory and attention in the present study. Poor verbal memory is the cognitive domain most consistently associated with diabetes in large epidemiological studies [58, 59]. In non-diabetics, verbal memory and attention have been shown to be impaired during an oral glucose challenge with a magnitude similar to impairment seen in diabetics [60].

In our early AD group, higher insulin predicted better verbal memory at the two year follow up, while higher glucose predicted more rapid declines in attention over two years. Previous research suggests that both increases and decreases in glucose can alter cognitive function [44]. Hyperinsulinemia may be a compensatory process to maintain normal glucose concentrations and often precedes overt diabetes [44]. Our failure to confirm several other studies that demonstrate a positive association between NCEP defined MetS and cognitive performance in healthy older adults [12–14, 27, 28, 57, 61] may be due to our exclusion of diabetics. Only two other published studies have evaluated the role of MetS in cognitive performance or dementia risk among healthy older adults without diabetes [15, 16]. Neither study found an association between NCEP defined MetS and cognitive performance or risk of dementia. Among three studies finding no association of NCEP defined MetS with dementia risk [16–18], two reported that hyperin-sulinemia was associated with higher risk of dementia including AD, vascular dementia, and MCI [16, 17] lending support to our finding that high insulin levels were associated with poor cognitive performance in healthy older adult controls. In contrast to our find-ings, Gatto and colleagues reported that hypertension was the only MetS risk factor independently associated with cognitive performance in their study which also excluded diabetics. Differences in our results may be related to differences in the rates of hypertension in the two samples, or differences in cognitive domains assessed. Further research comparing individuals with and without diabetes is needed to clarify the role of individual MetS components and cognitive performance.

Several limitations of our study should be noted. Our relatively small sample size limits our ability to detect relationships, though the factor analytic techniques we used allow estimation of measurement error that might otherwise obscure results. Failing to detect a significant relationship is more likely in this case (i.e., Type 2 error) than finding a relationship that is not truly present (i.e., Type 1 error). It is also possible that our findings are due to idiosyncrasies of the sample, thus replication in other samples is needed to lend support to these findings. Finally, our study did not include moderate or late stage AD, thus we cannot draw conclusions regarding metabolic features in later stages of the disease.

Our study offers unique contributions, particularly in our methodological approach and inclusion of APOE ε4 carrier status. We compared several approaches to measurement of MetS including traditional cutoff scores, continuous measures, and a combined MetS factor score. We compared the clustering of MetS components in individuals with and without early AD using multiple group tests of invariance. Finally, no previous studies have compared cases and controls longitudinally to evaluate the differential influence of MetS on cognitive decline across groups. Our findings are consistent with the few previous longitudinal studies of MetS and cognitive performance, of which all three reported that elevated glucose or diabetes was related to poorer cognitive outcomes [12, 27, 28].

Our results have several implications for clinical practice. First, they suggest consideration of multiple systems in combination rather than in isolation when evaluating risk for disease and cognitive decline. Second, they imply that understanding the meaning of biomarker levels may require consideration of change relative to the patient's own previous levels (e.g., mid-life or premorbid levels). This knowledge may add value over and above the exclusive use of standard cutoff criteria for hypertension, hyperlipidemia, obesity, and diabetes and help improve detection of pre-clinical stages of disease and simultaneous dysregulation of multiple systems. Finally, knowledge of an individual's APOE genotype may allow for more individualized assessment of risk associated with MetS and cognitive decline.

Regardless of whether MetS components are independent or interactive, each component (body mass, blood pressure, cholesterol, insulin regulation) is mod-ifiable with health behaviors and lifestyle choices. For patients seeking to maintain cognitive function and reduce risk of myriad chronic illnesses, diet and exercise for example may be effective preventive strategies, especially in mid-life or stages prior to disease onset, to prevent systems dysregulation that has already begun by the earliest stages of dementia. Understanding the individual and combined influences of MetS on cognitive performance requires a careful methodological approach. In combining individual components, it should not be assumed that each contributes equally. Attention to timing of measurement is needed to capture the non-linear changes in MetS and its relationship to cognitive outcomes. Further research using long term follow up is needed to explore the timing and interactions of individual components over age and with the progression of disease.

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Table 1

Baseline and follow up participant characteristics by Alzheimer's disease (AD) status

	Healthy controls (*n* = 73)	**Early AD (*n* = 75)**	***p*-value**	**Healthy controls (*n* = 66)**	**Early AD (*n* = 58)**	***p*-value**
	Baseline mean	Baseline mean		2 Year follow up	2 Year follow up	
Age, years	74.2	75.2	0.39	75.6	77.5	0.12
Females, *n* (%)	42 (58)	45 (60)	0.87	35 (53)	33 (57)	0.72
Mini-mental status examination	29.4	26.1	<0.001	29.2	22.4	<0.001
Body mass index kg/m^2	26.4	25.4	0.10	26.2	25.9	0.71
Waist circumference cm	88.5	86.2	0.26	93.7	94.7	0.66
Systolic blood pressure	130.0	140.1	<0.001	130.3	135.0	0.16
Diastolic blood pressure	71.7	75.2	0.04	71.5	73.0	0.42
Triglycerides mg/dL	112.0	118.0	0.55	–	–	–
High density lipoprotein mg/dL	55.9	53.9	0.82	–	–	–
Glucose area under the curve	22749.1	23074.2	0.59	21937.0	23155.0	0.06
Insulin area under the curve	2520.5	2831.0	0.22	3924.0	4564.6	0.07
AOPE *ε*4 carrier, *n* (%)	19 (26)	32 (43)	<0.001	–	–	–
Meets NCEP criteria for MetS *n* (%)	24 (33)	25 (33)	0.86	–	–	–

–indicates data not available at 2 year follow up.

Table 2

Factor analysis of metabolic syndrome and multiple group tests of invariance

	Healthy controls	*p*-value	Early AD	*p*-value
	Standardized loading (λ)		Standardized loading (λ)	
Systolic blood pressure	0.45	<0.001	0.22	0.10
Diastolic blood pressure	0.25	0.06	0.25	0.05
Log insulin (AUC)	0.71	<0.001	0.63	<0.001
Log glucose (AUC)	0.31	0.01	0.05	0.74
Log body mass index	0.77	<0.001	0.73	<0.001
Waist circumference	0.59	<0.001	0.75	<0.001
Log triglycerides	0.71	<0.001	0.31	<0.05
HDL cholesterol	0.48	<0.001	0.67	<0.001
Model	x^2/df	RMSEA	RMSEA 90% CI	Constraint tenable?
Weak invariance (factor loadings)	69.3/45	0.09	0.04–0.12	Yes
Strong invariance (item intercepts)	97.8/52	0.11	0.08–0.14	No
Free estimation of systolic BP intercept	86.5/51	0.10	0.06–0.13	Yes

AUC, area under the curve; HDL, high density lipoprotein; CI, confidence interval. Standardized loadings (λ) reflect the strength of the relationship of each item with the shared MetS factor. Similar to a correlation coefficient (range 0.00–1.00), a higher number indicates a stronger association.

Table 3

Factor analysis of cognitive performance and multiple group tests of invariance

	Healthy controls	*p*-value	Early AD	*p*-value
	Standardized loading (λ)		Standardized loading (λ)	
Attention				
Digit symbol	0.70	<0.001	0.87	<0.001
Letter number sequencing	0.66	<0.001	0.69	<0.001
Stroop interference	0.68	<0.001	0.88	<0.001
Verbal memory				
Logical memory	0.55	<0.001	0.76	<0.001
Delayed logical memory	0.55	<0.001	0.80	<0.001
Selective reminding task	0.72	<0.001	0.72	<0.001
Correlation attention, verbal memory	0.75	<0.001	0.40	<0.01
Model	x^2/df CFI	RMSEA	RMSEA 90% CI	Constraint tenable?
Weak invariance (factor loadings)	29.8/18 0.97	0.09	0.02–0.15	Yes
Strong invariance (item intercepts equal)	39.1/22 0.95	0.10	0.05–0.15	No
Free estimation of digit symbol intercept	33.5/21 0.97	0.09	0.02–0.13	Yes

Standardized loadings (λ) reflect the strength of the relationship of each item with the shared cognitive factor. Similar to a correlation coefficient (range 0.00–1.00), a higher number indicates a stronger association.

Table 4

Standardized regression coefficients (β (*p*-value)) predicting cognitive performance

	Healthy controls			Early AD		
	Attention	**Verbal memory**	**MMSE**	**Attention**	**Verbal memory**	**MMSE**
Baseline						
Combined MetS factor	−0.086 (0.431)	−0.053 (0.631)	−0.016 (0.899)	0.303 (0.081)	0.249 (0.148)	0.222 (0.203)
Age	**−0.518 (<0.001)**	**−0.464 (<0.001)**	**−0.286 (0.006)**	−0.192 (0.090)	−0.169 (0.136)	0.069 (0.546)
Gender	**−0.237 (0.017)**	**−0.293 (0.004)**	−0.131 (0.250)	−0.263 (0.091)	0.047 (0.759)	−0.031 (0.844)
Years of education	0.030 (0.764)	0.113 (0.268)	0.184 (0.102)	**0.299 (0.007)**	0.045 (0.693)	0.117 (0.298)
APOE ε4 carrier status	−0.173 (0.070)	−0.133 (0.175)	0.157 (0.154)	−0.178 (0.112)	**−0.258 (0.020)**	**−0.248 (0.025)**
Follow up						
Combined MetS factor	−0.136 (0.228)	−0.110 (0.325)	0.066 (0.630)	**0.399 (0.031)**	**0.375 (0.018)**	0.366 (0.056)
Age	**−0.584 (<0.001)**	**−0.589 (<0.001)**	−0.194 (0.114)	−0.142 (0.282)	−0.222 (0.054)	0.004 (0.977)
Gender	−0.066 (0.545)	−0.044 (0.684)	−0.226 (0.067)	0.047 (0.763)	0.247 (0.069)	0.184 (0.236)
Years of education	0.009 (0.934)	0.001 (0.990)	0.114 (0.350)	−0.013 (0.926)	0.106 (0.366)	−0.060 (0.653)
APOE ε4 carrier status	−0.149 (0.124)	−0.169 (0.081)	0.173 (0.126)	−0.116 (0.363)	−0.189 (0.092)	0.052 (0.675)
2-year change						
Combined MetS factor	−0.125 (0.362)	−0.112 (0.404)	0.067 (0.633)	0.091 (0.684)	0.150 (0.390)	0.271 (0.173)
Age	0.047 (0.712)	−0.097 (0.437)	−0.053 (0.683)	−0.020 (0.874)	−0.134 (0.314)	−0.002 (0.989)
Gender	0.171 (0.184)	**0.280 (0.024)**	−0.189 (0.139)	**0.395 (0.011)**	0.204 (0.157)	0.244 (0.118)
Years of education	0.083 (0.510)	−0.062 (0.617)	0.047 (0.711)	**−0.289 (0.015)**	0.153 (0.237)	−0.112 (0.385)
APOE ε4 carrier status	0.128 (0.272)	0.021 (0.854)	0.122 (0.301)	−0.036 (0.766)	−0.122 (0.340)	0.178 (0.147)

1. Standardized coefficients (β) indicate the strength of the association between each variable, adjusting for covariates. 2. Change is calculated by subtracting the score at Baseline from the score at Follow Up.

Table 5

Standardized regression coefficients (β (*p*-value)) predicting cognitive performance from individual MetS components

	Healthy controls			Early AD		
	Attention	**Verbal memory**	**MMSE**	**Attention**	**Verbal memory**	**MMSE**
Baseline						
Systolic blood pressure	−0.252 (0.158)	−0.103 (0.561)	0.199 (0.283)	−0.299 (0.106)	−0.062 (0.720)	−0.110 (0.548)
Diastolic blood pressure	0.278 (0.136)	0.204 (0.270)	−0.330 (0.087)	0.144 (0.409)	−0.075 (0.653)	−0.035 (0.843)
Body mass index	0.185 (0.472)	0.114 (0.656)	0.181 (0.499)	−0.196 (0.453)	0.121 (0.629)	−0.042 (0.874)
Waist circumference	−0.197 (0.516)	−0.340 (0.263)	−0.297 (0.346)	0.266 (0.355)	−0.058 (0.833)	0.016 (0.957)
Insulin (AUC)	0.015 (0.934)	0.122 (0.516)	−0.035 (0.857)	0.326 (0.064)	0.231 (0.167)	0.082 (0.636)
Glucose (AUC)	−0.075 (0.599)	0.065 (0.650)	0.192 (0.202)	0.111 (0.465)	−0.232 (0.117)	−0.093 (0.541)
Triglycerides	−0.017 (0.929)	0.046 (0.810)	0.185 (0.344)	0.057 (0.734)	0.088 (0.581)	0.177 (0.293)
HDL cholesterol	−0.098 (0.579)	−0.187 (0.293)	−0.339 (0.069)	0.042 (0.829)	0.086 (0.648)	0.247 (0.216)
Age	−0.249 (0.111)	−0.279 (0.075)	−0.173 (0.282)	−0.071 (0.640)	−0.095 (0.516)	0.069 (0.655)
Gender	−0.136 (0.554)	−0.105 (0.647)	0.139 (0.555)	−0.170 (0.379)	0.262 (0.161)	0.052 (0.790)
Education (years)	0.082 (0.563)	0.177 (0.215)	0.170 (0.252)	**0.311 (0.047)**	−0.004 (0.977)	0.145 (0.345)
APOE carrier status	−0.110 (0.407)	−0.068 (0.606)	**0.375 (0.009)**	−0.092 (0.537)	**−0.289 (0.049)**	−0.237 (0.118)
Follow up						
Systolic blood pressure	−0.233 (0.184)	−0.234 (0.191)	−0.015 (0.937)	−0.247 (0.237)	−0.273 (0.126)	−0.169 (0.413)
Diastolic blood pressure	0.335 (0.063)	0.320 (0.081)	−0.145 (0.430)	0.136 (0.487)	−0.026 (0.875)	0.076 (0.694)
Body mass index	0.233 (0.384)	0.274 (0.316)	0.545 (0.055)	0.106 (0.693)	0.207 (0.368)	−0.151 (0.575)
Waist circumference	−0.047 (0.879)	−0.057 (0.857)	−0.337 (0.296)	0.004 (0.988)	0.035 (0.882)	0.240 (0.387)
Insulin (AUC)	−0.362 (0.062)	−0.327 (0.097)	0.064 (0.751)	0.313 (0.106)	**0.328 (0.048)**	0.161 (0.397)
Glucose (AUC)	0.033 (0.822)	0.028 (0.850)	0.261 (0.098)	−0.120 (0.480)	−0.169 (0.242)	−0.131 (0.438)
Triglycerides	−0.174 (0.369)	−0.183 (0.355)	−0.106 (0.589)	−0.111 (0.554)	−0.052 (0.743)	0.014 (0.939)
HDL cholesterol	0.204 (0.242)	0.163 (0.358)	**−0.379 (0.046)**	0.056 (0.790)	−0.032 (0.856)	0.107 (0.610)
Age	**−0.407 (0.015)**	**−0.398 (0.019)**	−0.074 (0.661)	0.000 (0.998)	−0.012 (0.936)	0.148 (0.385)
Gender	−0.127 (0.581)	−0.077 (0.743)	0.042 (0.859)	0.197 (0.339)	**0.403 (0.025)**	0.312 (0.132)
Education (years)	0.222 (0.129)	0.184 (0.216)	0.155 (0.308)	−0.161 (0.327)	0.080 (0.565)	−0.185 (0.261)
APOE carrier status	−0.078 (0.558)	−0.119 (0.383)	0.281 (0.051)	−0.208 (0.227)	−0.185 (0.208)	0.005 (0.975)
2 year change						
Systolic blood pressure	−0.176 (0.335)	−0.328 (0.104)	−0.048 (0.805)	0.059 (0.737)	−0.166 (0.407)	0.160 (0.403)

	Healthy controls			Early AD		
	Attention	**Verbal memory**	**MMSE**	**Attention**	**Verbal memory**	**MMSE**
Diastolic blood pressure	−0.116 (0.529)	0.020 (0.922)	−0.149 (0.460)	−0.021 (0.901)	−0.059 (0.754)	−0.141 (0.439)
Body mass index	−0.029 (0.917)	0.136 (0.654)	0.138 (0.625)	0.315 (0.177)	0.201 (0.439)	0.211 (0.441)
Waist circumference	0.337 (0.302)	0.415 (0.245)	−0.060 (0.856)	−0.185 (0.437)	0.213 (0.427)	0.136 (0.650)
Insulin (AUC)	−0.379 (0.062)	**−0.444 (0.046)**	−0.306 (0.145)	0.070 (0.664)	0.086 (0.638)	−0.186 (0.306)
Glucose (AUC)	0.191 (0.211)	−0.048 (0.771)	−0.074 (0.639)	**−0.335 (0.026)**	0.036 (0.827)	−0.195 (0.223)
Triglycerides	−0.079 (0.696)	−0.146 (0.509)	0.062 (0.765)	−0.217 (0.180)	−0.338 (0.067)	−0.113 (0.517)
HDL cholesterol	0.359 (0.053)	0.361 (0.074)	−0.032 (0.867)	0.101 (0.576)	−0.035 (0.863)	0.099 (0.630)
Age	0.227 (0.179)	0.142 (0.437)	−0.105 (0.537)	−0.003 (0.984)	−0.014 (0.932)	0.206 (0.202)
Gender	−0.226 (0.350)	−0.102 (0.698)	0.255 (0.309)	**0.458 (0.013)**	0.135 (0.495)	−0.202 (0.922)
Education (years)	0.302 (0.051)	0.083 (0.611)	0.029 (0.854)	**−0.492 (0.001)**	0.179 (0.260)	−0.016 (0.921)
APOE carrier status	0.164 (0.244)	0.036 (0.813)	0.153 (0.296)	−0.286 (0.056)	−0.031 (0.850)	−0.080 (0.610)