THE RELATIONSHIP BETWEEN DURATION OF METABOLIC SYNDROME AND COGNITIVE FUNCTIONING

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DEDICATION

For Ryen,

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THE RELATIONSHIP BETWEEN DURATION OF METABOLIC SYNDROME AND COGNITIVE FUNCTIONING

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The metabolic syndrome is defined by ≥ 3 of the following: Elevated blood glucose, triglycerides, waist circumference, and blood pressure as well as low levels of high-density lipoprotein. Research has linked cardiovascular risk factors composing metabolic syndrome with decrements in cognition, which may relate to prolonged metabolic syndrome presence. This project aimed to determine the relationship between metabolic syndrome status over time and cognitive performance, whether this relationship varies by cognitive domain, and assess if metabolic syndrome status across time predicts later cognitive impairment, with further exploration of age, race, gender, income, education, exercise, alcohol, and smoking effects in a

racially diverse sample. Subjects included 1,314 individuals for whom archival Dallas Heart Study data for metabolic syndrome were available across two time points, including baseline and follow-up 2-9 years later as well as brief cognitive testing at follow-up, with 137 individuals who had additional cognitive testing and consensus diagnosis of cognitive impairment as part of the University of Texas Southwestern Alzheimer's Disease Center Dallas Heart/Brain Aging Study. Total Montreal Cognitive Assessment score means were compared with 3 levels of metabolic syndrome status: Presence at 1) baseline and follow-up, 2) only at baseline, and 3) absent at both time points within the overall sample. Comparisons were made within homogenous subsamples grouped by age, gender, race, exercise, and education performed with inclusion of those who met metabolic syndrome criteria at baseline but not follow-up. Covariates included age, education, income, gender, race, smoking, cardio-respiratory fitness, and alcohol consumption when significant ($p < .15$). The relationship between duration of the syndrome and cognitive functioning was modest, but significant among African American women, African Americans with at least 12 years of education, and men ≥ age 55. Follow-up analyses found that presence of metabolic syndrome at follow-up was related to cognition among African Americans ≥ age 55. Conclusion: Though effects are small, African American race may place an individual at risk of cognitive effects of metabolic syndrome independent of other demographic and lifestyle factors, particularly for women, and reversing the syndrome may mitigate associated decrements in cognitive functioning among some groups.

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LIST OF DEFINITIONS

MetS – Metabolic Syndrome

HDL – High Density Lipoprotein

DHS – Dallas Heart Study

DHS-1 – Dallas Heart Study Phase I

DHS-2 – Dallas Heart Study Phase II

DHBAS – Dallas Heart/ Brain Aging Study

ADC – Alzheimer's Disease Center

CVD – Cardiovascular Disease

MoCA – Montreal Cognitive Assessment

NHBLA-AHA – National Heart Lung Blood Institute/American Heart Association

NHANES – National Health and Nutrition Examination Survey

WHO – World Health Organization

NCP ATP-III – National Cholesterol Education Program Adult Treatment Panel III

IDF – International Diabetes Federation

EGIR – International Diabetes Federation

SECTION ONE
Introduction

The Metabolic Syndrome (MetS) is a constellation of frequently co-occurring metabolic abnormalities that increase the risk of developing atherosclerotic cardiovascular disease (CVD). Though different definitions of the syndrome exist, most define MetS by the presence of three or more of the following factors: Elevated blood glucose levels, elevated triglycerides, increased waist circumference, elevated blood pressure, and low levels of high-density lipoprotein (HDL). The combined presence of these factors can increase risk of CVD, measured by incident coronary heart disease, stroke, or congestive heart failure, by 20% to 30% (McNeill et. al., 2006). There are immense costs attributed to MetS end-points, including direct and indirect costs for treating diabetes mellitus, myocardial infarction, stroke/transient ischemic attack, and coronary heart disease (McNeill et al., 2006), and the costs are anticipated to increase as the world's population ages and as obesity becomes more prevalent. MetS can identify CVD risk in individuals who exhibit abnormal metabolic processes below levels established for clinical disorders related to specific MetS factors (e.g., hypertension, diabetes, hypercholesterolemia; Prabhakaren, & Anand, 2004). At sub-threshold levels, the components of MetS are considered reversible through lifestyle modifications and medication use. As such, identification of MetS represents a practical means to target treatment for individuals at risk for CVD, and may provide an avenue to combat the high rates of morbidity and mortality associated with CVD.

In addition to increased risk of CVD and related health complications, the syndrome has been linked to decrements in cognitive functioning in a number of investigations (Yaffe, Weston,

Blackwell & Kreuder, 2009;Yaffe et al., 2004; Gatto et al., 2008; Vanhanen et al., 2006; Razay, Vreugdenhil, & Wilcock, 2007; Kalmijn et al., 2000). A growing body of research indicates that the presence of MetS places an individual at risk of cognitive decline (Yates, Sweat, Yau, Turchiano, & Convit, 2012; Reijmer et al., 2011; Ho, Niti, Yap, Kua, & Ng, 2008), and it has been associated with decrements across multiple cognitive domains (Abbatecola et al., 2004; Watari et al., 2008; Boeka & Lokken, 2008; Bokura, Nagai, Ogura, Kobayashi, & Yamaguchi, 2011). Functional deficits in the elderly have also been linked to MetS (Martinho et al., 2013; Borowiak & Kostka, 2006; Garster, Palta, Sweitzer, Kaplan, & Fryback, 2009), and it may play a role in the development of dementia syndromes (Panza et al., 2011; Fillit, Nash, Rundek, & Zuckerman, 2008; Milionis, Florentin, & Giannopoulos, 2008; Solfrizzi et al., 2011). Though several studies report poorer cognitive performance in relation to MetS, findings have been mixed, as some studies have found no association between MetS and cognitive functioning (Panza et al., 2011), and at least one report found better cognitive performance among individuals with MetS in a sample over the age of 85 (Van den Berg, Biessels, de Craen, Gusseko, & Westendorp 2007).

Factors that may contribute to such discrepant findings include demographic characteristics (i.e., age, gender, and ethnicity), employment of different criteria for MetS, variability in measurement methods for each component, the manner in which cognitive functioning is assessed, and study design. With regard to study design, many investigations have been cross-sectional and unable to account for the length of time that an individual has met criteria for MetS. Longitudinal studies are better suited to address this issue but most, with a few exceptions, have assessed MetS only at baseline and measured cognition at multiple time points

(Panza et al., 2011). Such a design allows for examination of cognitive decline risk and prevalence of MetS, but is insufficient to analyze the relationship of prolonged exposure to MetS components with cognitive functioning. The length of time that a person satisfies criteria for MetS is important, as many of the underlying mechanisms that contribute to MetS, and the associated metabolic consequences of MetS, are hypothesized to impact cognitive functioning through gradual processes (Schuur et al., 2010). Studies that have examined the association over time between MetS presence and cognitive function have found that those meeting criteria for MetS at two or more time points exhibited poorer cognitive performance compared to those who met the criteria at one or fewer visits (Akbaraly et al., 2010). Such investigations have also reported that some individuals exhibit variability across time with respect to meeting MetS criteria, and groups that exhibit this variability (i.e., fulfill MetS criteria at one out of three time points) perform similarly to groups that have never met criteria during the study period (Akbaraly et al., 2010). The few studies that have utilized a longitudinal approach to examine cognitive functioning while accounting for the duration of MetS have typically been conducted with samples that have limited generalizability, such as with convenience or all-female samples (Akbaraly et al., 2010; Langenberg, Kuh, Wadsworth, Brunner, & Hardy, 2007).

Since decrements in cognitive functioning may be attributable to the prolonged presence of MetS (Akbaraly et al., 2010), individuals who meet MetS criteria over the course of several years would be expected to show poorer cognitive performance than individuals who developed the syndrome more recently. This study aims to expand upon past research by determining whether the presence of MetS across time is related to poorer cognitive performance in a large, racially diverse sample of community-dwelling volunteers.

Definitions of Metabolic Syndrome

The concept of MetS was first developed to identify individuals at increased risk of developing CVD due to the presence of several cardiovascular risk factors that were often observed together (Reaven, 2008). Initially, impairment in glucose regulation was conceptualized as the driving force for the syndrome. While the importance of impaired glucose regulation continues to be emphasized in some definitions of the syndrome, this is likely an oversimplification of the complex processes and component interactions that are involved in MetS (Sarti & Gallagher, 2006).

MetS criteria have been proposed by several groups, including the World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III), and the International Diabetes Federation (IDF), as well as the European Group for the Study of Insulin Resistance (EGIR). These organizations have operationalized the syndrome in distinct ways (Sarti & Gallagher, 2006; Han & Lean, 2006; Reaven, 2008). The WHO continues to emphasize the role of insulin dysregulation, requiring the presence of impaired glucose regulation, diabetes, or insulin resistance. In addition to insulin dysregulation, any two of the remaining criteria are required: elevated blood pressure, triglycerides, body mass index (BMI) or waist-to-hip ratio, and microalbuminaria or decreased HDL levels (Alberti et al., 2009). The NCEP ATP-III criteria do not necessitate any single component, but rather three or more of the following: elevated blood pressure (≥130/85 mmHg), elevated triglycerides (≥150 mg/dl), elevated fasting blood glucose (≥110 mg/dl), increased waist circumference (>102 cm for

men and >88 cm for women), and low levels of HDL cholesterol (<40 mg/dl). The National Lung and Blood Institute/ American Heart Association (NHLBI/AHA) revised the NCEP ATP-III criteria in 2005, lowering the fasting blood glucose threshold to 100 mg/dl and adding prescription medication use as qualifying for the respective blood glucose, triglyceride, and blood pressure components. The IDF establishes increased waist circumference, at lower levels than NCEP ATP-III, as a requirement plus two or more components that are consistent with the remaining revised NCEP ATP-III criteria (Alberti, Zimmet, & Shaw, 2006). The EGIR definition also requires hyperinsulinemia, similar to the WHO, but excludes those with diabetes (Sarti & Gallagher, 2006).

These various definitions identify different patient populations in epidemiological studies (McNeill et al., 2006), varying as a function of the specific components and associated assessment techniques outlined by each criterion (Assmann et al., 2007). A comparison between NCEP ATP-III and WHO criteria found that 17.8% of the Bruneck study sample met NCEP ATP-III MetS criteria, yet the prevalence of MetS was 34.1% in this sample when the WHO classification was employed (Bonora et al., 2003). Another comparison of definitions found that the NCEP ATP-III criteria was associated with a higher percentage of adverse cardiac events over ten years (10.7%), compared to the IDF criteria (5.5%), even though concordance was high between the two definitions (Assmann et al., 2007). Both definitions identified individuals at risk of CVD at higher rates than those observed in individuals without the syndrome (3.4%). The study also compared MetS rates between a German and American sample, which included Dallas Heart Study (DHS) and National Health and Nutrition Examination Survey (NHANES) participants, finding increased prevalence rates with use of the ATP-III criteria in Americans

while MetS rates were higher in the German sample according to the IDF definition (Assmann et al., 2007). In the United States, NCEP ATP-III is the most commonly used criteria (Yates et al., 2012).

Despite these differences, there is a large overlap between the definitions of MetS. In fact, with the exception of classifications that include albuminuria, all identify a similar constellation of factors as comprising MetS. These similar components are elevated blood pressure, glucose dysregulation, dyslipidemia, and abdominal obesity.

The Relationship between Metabolic Syndrome and Cognition

Research findings regarding the relationship between MetS and cognition have been varied, yet numerous studies report associations between MetS, its component processes, and multiple cognitive domains. A criticism of MetS concept is that it does not confer a greater risk of CVD than that conveyed by its individual components, and this criticism has also been raised regarding associations with cognitive decrements. However, a recent review reported that several large epidemiological studies found that MetS was a useful construct in conveying CVD risk above its individual factors, and that the syndrome has utility in the identification of dementia and pre-dementia syndromes that surpasses the risk attributable to the individual components (Panza et al., 2011). Such investigations support the utility of MetS in the identification of those at risk for CVD and cognitive decline.

Many studies have found increased risk of poor cognitive performance associated with the syndrome. Yaffe et al. (2004) found that in an elderly sample of 2,632 African American and

Caucasian individuals the presence of MetS at baseline was associated with poorer performance on the Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987) and Delayed Word-List Recall (DelRec; Gonzalez, Mungas, & Reed, 2001) after five years. In a subsequent investigation in a sample of 1,624 Latinos, age 60 and older, Yaffe et al. (2007) again examined MetS at baseline finding the occurrence of the syndrome placed an individual at risk of developing cognitive impairment, again measured by the 3MS and DelRec, over a three year follow-up period.

Studies examining sex differences in the relationship between MetS and cognition report conflicting results. One such study included 819 community-dwelling men and women with a mean age of 65, and found that the presence of MetS was associated with poorer memory and executive functioning performance. The number of MetS components was inversely related to cognitive functioning, but these findings were only significant for men (Cavalieri, et al., 2010). Yet another study found women, but not men, to be at risk for decline in memory and executive functioning (McEvoy et al., 2012).

Some investigations have observed executive function deficits in individuals with MetS, while other cognitive domains, such as language, remain relatively intact, though such findings have not been universal. Cavaliere et al. (2010) found memory and executive functioning deficits associated with MetS in men, and reported an inverse relationship between number of MetS components present and cognitive performance.

A cross-sectional analysis found deficits in executive functions were associated with MetS in a community dwelling, racially diverse, rural sample of 395 participants. In this investigation, individuals who met criteria for the revised NCEP ATP-III guidelines performed

more poorly on an aggregate of executive function tasks derived from performance on the Executive Function Interview (EXIT25), Trail Making Test- B (TMT-B), phonemic verbal fluency (FAS), and Clock drawing task, after controlling for age and education (Falkowski, Atchison, Debutte-Smith, Weiner, & O'Bryant, 2014). This study found that the syndrome was associated with poorer performance, but an additive effect was not observed (i.e., more components were not associated with poorer performance on EF tasks).

Extensive research has supported the association that MetS components and related processes have with cognition. Dyslipidemia, elevated blood pressure, obesity, and elevated blood glucose/insulin insensitivity have all been linked with poor cognitive outcomes. A study focusing on the individual components of MetS and cognition in a sample of 1,183 individuals, with 36.3% prevalence of MetS, reported that performance on the MMSE, Alphabet Coding Task-15, Auditory Verbal Learning Test, and Raven's Colored Progressive Matrices were associated with all five components of MetS, with hyperglycemia exhibiting the highest association (Dik et al., 2007). The investigators also reported that the associations were strongest for individuals with high levels of inflammation (i.e., C-reactive protein and α1-antichymotrypsin) (Dik et al., 2007). However, other studies have found an increased risk of cognitive decline for those with MetS independent of inflammatory markers (McEvoy, et al. 2012). Considering the vast research that has tied MetS factors to cognition, a review of each component and its relation with cognition is appropriate.

Insulin and Blood Glucose

Insulin is a hormone that serves a multitude of complicated functions in the body and is best known for its role in providing energy to cells by allowing glucose to transfer from the blood stream, through cell walls, and into the cell. Although 30% of individuals with MetS have normal sensitivity to insulin, many of the components are related to insulin resistance (Han & Lean, 2006).

Cognition has been linked to glucose regulation. Studies examining individuals with elevated fasting glucose and impaired glucose tolerance have found lower levels of cognitive functioning, though larger deficits are observed in individuals with diabetes mellitus (Panza et al., 2011). One study examining the association between insulin resistance and cognitive functioning found a significant relationship using performance on TMT-A and TMT-B among an Italian population aged 24-91, after excluding those with dementia or diabetes mellitus (Abbatecola et al., 2004). Poor performance on executive function tasks has also been linked with the presence of diabetes (Lowe, Tranel, Wallace, & Welty, 1994; Hewer, Mussell, Rist, Kulzer, & Bergis, 2003). Elevated fasting blood glucose has been found to augment the relationship between decline of executive functioning in women and MetS, such that female participants meeting criteria for MetS with elevated levels of fasting blood glucose were at heightened risk of decline of executive functions compared to women with MetS but with lower levels of blood glucose (McEvoy, et al., 2012). Other studies have connected insulin dysregulation with dementia (Kerola, Kettunen, & Niemen, 2011).

Blood Pressure

Of the five MetS components, elevated blood pressure poses the greatest risk of CVD (McNeill et. al., 2006; Weiner et. al., 2011). Substantial evidence exists in support of the relationship between blood pressure and cognitive functioning (Robbins, Elias, Elias, & Budge, 2005; Kerola, Kettunen, & Nieminen, 2011), particularly the role hypertension in mid-life may have in the development of dementia later in life (Panza, et al., 2011). Importantly, this relationship is modifiable through treatment with antihypertensive medications (Panza et al., 2011). EF has been linked with this syndrome component in several investigations, as decrements in EF have been found to correlate with elevations in blood pressure (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998, Waldstein et al., 1996; Elias et al., 1997). Most cases of hypertension are idiopathic, but elevated blood pressure may be brought about by increased insulin concentration through renal tubular reabsorption of sodium (Han & Lean, 2006), highlighting the complex ways in which MetS factors can be related.

Abdominal Obesity

In comparison to hypertension and blood glucose, relatively few studies have investigated the relationship between obesity and cognition, but those that have suggest that being either overweight or underweight, as measured by BMI, may place an individual at risk for cognitive decline. The increased risk at both high and low BMI levels may be related to the presence of disease or malnourishment at low levels and attributable to cardiovascular related processes at higher levels (Panza et al., 2011). In one investigation of obese individuals with an average body mass index of 51.2 k/m2 (ranging from 35.0-80.0 k/m2), subjects were administered cognitive

testing prior to undergoing bariatric surgery. This group showed decrements on cognitive tests of executive functions even after adjusting for co-morbidity, diabetes mellitus, and hypertension (Boeka & Lokken, 2008).

Abdominal obesity is associated with a diet that is high in calories and fat and a sedentary lifestyle. Though not in itself a specific metabolic process, excess adiposity can result in a series of processes closely related to other MetS components (Barter et al., 2007). Specifically, adiposity distributed along the midsection signifies an irregular pattern of deposition and can be related to insulin dysregulation. Abdominal adipose tissue can be differentiated as visceral, within the abdominal cavity, or subcutaneous. Animal studies have found that visceral adipose tissue is more resistant to insulin (Farin, Abbassi, & Reaven, 2006; Després & Lemieux, 2006) and that insulin resistance can be reversed through surgical removal of visceral adipose tissue in animal models (Barzilai et al., 1999).

Given that the distinction between visceral and subcutaneous adiposity is impractical in most treatment settings, waist circumference is considered a closer approximation of this distinction than BMI (Mendelson, 2008). However, the association between fat deposition and total body fat in relation to CVD risk is not fully understood, as both may place an individual at heightened risk of developing different metabolic risk factors (Grundy et al. 2005: Vega et al., 2006). Since increased abdominal girth includes both subcutaneous and visceral adiposity, waist circumference is used in many definitions of MetS. The metabolic consequences of abdominal obesity have been linked with a cascade of processes, including insensitivity to insulin, altered free fatty acid metabolism, decreased adipokine release, and increased epicardial and muscle fat deposits (Mendelson, 2008).

Excessive adiposity can also contribute to alterations in liver functioning, including increased production of very low density lipoprotein (Mendelson, 2008). In addition, adipose cells are less sensitive to insulin than other cell types. This indicates that the mere presence of excess abdominal adipose tissue, particularly when deposited viscerally, can lead to higher blood levels of insulin and the development of insulin resistance (Mendelson, 2008). However, there is evidence suggesting the relationship between obesity and other metabolic abnormalities, such as increased blood pressure and fasting blood glucose, may be augmented by dyslipidemia (Barter et al., 2007). Obese persons without dyslipidemia show much lower rates of elevations in blood pressure and blood glucose than their obese counterparts with elevated levels of triglycerides and low levels of HDL cholesterol (Barter et al., 2007).

Dyslipidemia

The association between dyslipidemia and cognition is less clear. Some reports found higher levels of cholesterol were associated with poorer cognitive performance while others suggest the opposite, as studies across the lifespan have been inconsistent (Kerola, Kettunen, & Nieminen, 2011). It has been suggested that these discrepancies, particularly with regard to the development of dementia syndromes, may be related to the effect of dyslipidemia in the production of the protein beta amyloid, which can increase in the presence of altered lipid metabolism. Interestingly, the onset of dementia is often preceded by weight loss and malnutrition which can reduce cholesterol levels (Kerola, Kettunen, & Niemen, 2011).

Dyslipidemia is related to both elevations in triglycerides and decreased HDL levels. Some studies have linked low levels of HDL with the development of cognitive impairment over

a 12-year period of observation, with one investigation reporting a 46% increase in risk of memory impairment (1 SD below the mean of the sample) with low HDL levels among women, though the sample size was small (n=101) (Komulainen et al., 2007).

Possible Underlying Mechanisms

Metabolic abnormalities, including midlife obesity, insulin resistance, hyperglycemia, and hypertension, may cause disease states in old age, possibly via factors that alter the autonomic regulation of arterial pressure and glucose metabolism (Novak 2012). Such changes can increase oxidative stress and inflammation, which in turn can produce changes in neurovascular coupling that can bring about microvascular disease (Novak 2012).
MetS has also been linked with reduction in cerebral blood flow. An investigation of 75 individuals found that MetS and cerebral blood flow were both associated with lower memory scores, and that the correlation between MetS and memory deficits was partially mediated by cerebral blood flow (Birdsill et al.,2013).

Central nervous system insulin resistance may underlie cognitive deficits, as elevations in insulin levels in the blood may adversely impact the glutamatergic and cholinergic pathways, damaging cortical and subcortical connections (Cavalieri et al., 2010). In addition to changes brought about in vascular reactivity, neuroinflammation, oxidative stress, and alterations in lipid metabolism in the brain may also play a role (Yates et al., 2012). Stroke is also one potential endpoint of Mets, which increases the likelihood of cognitive deficits related to damage to downstream structures. The relationship between MetS and cognitive functioning is complex, as

components can lead to alterations in brain metabolism and may contribute to neuronal changes and cognitive dysfunction through multiple mechanisms (Panza et al., 2011; Panza, et al., 2010).

Metabolic Syndrome and Cognition Over Time

As discussed above, several studies have reported a relationship between the presence of MetS at baseline and cognitive decline at follow-up (Yaffe et al., 2007; Yaffe et al., 2009). Fewer studies have examined the relationship between the duration of MetS and its relationship to cognition. One such study examined the presence of MetS across three time points over a 10-year period in a convenience sample of all white London-based office staff, aged 35-55, that included 4,150 individuals with cognitive testing at the third time point (Akbaraly et al., 2010). There was no difference between participants who had never met MetS criteria during the study period and those who met criteria at only one time point. However, the presence of MetS at two or three time points was associated with poorer performance on follow-up testing, which included assessments of short-term verbal memory, verbal and mathematical reasoning, and vocabulary (Akbaraly et al. 2010). This suggests that it is not merely the presence of the syndrome that is related to lower cognitive performance, but rather, prolonged exposure.

MetS has also been related to cognitive decline in all female samples. Once such study compared cognitive performance between subjects with or without MetS at two time points, 12 years apart, in an all-female Finish sample of 101 women ages 60-70. Over the 12 years, the prevalence of MetS increased from 13% to 49%. Although there was no association between MetS at baseline or follow-up with cognitive performance as reflected by the MMSE and on a

processing speed composite (derived from the Stroop Test and Letter-Digit Substitution Test), there was a positive relationship between the number of MetS factors present and risk of cognitive decline (Komulainen et al., 2007).

Metabolic Syndrome and Demographic Variables

MetS has long been associated with a number of lifestyle variables, including physical inactivity, excessive consumption of high-fat foods, smoking, and consumption of large quantities of alcohol (Han & Lean, 2006). Furthermore, populations that are disadvantaged (Han & Lean, 2006), such as those located in rural settings or impoverished environments, often exhibit higher prevalence rates of MetS. Gallo et al. (2007) found that socioeconomic position was related directly and indirectly to several components of the syndrome, suggesting low educational attainment and income may contribute to MetS components through lifestyle factors. Another investigation of the link between childhood socioeconomic status and subsequent development of MetS found that associations between adult socioeconomic status and MetS were explained by childhood socioeconomic measures (Langenberg et al., 2006). Although these variables are known to be related to MetS as well as cognitive functioning, few investigators have accounted for such demographic factors.

Summary

MetS is defined by the presence of ≥3 of the following: High blood glucose levels, triglycerides, waist circumference, blood pressure, and low HDL levels. Researchers have linked the cardiovascular risk factors that compose MetS with decrements in cognitive functioning in a number of studies (Abbatecola et al., 2004; Watari et al., 2008; Boeka & Lokken, 2008; Newman, et al. 2005; Roriz-Cruz et al. 2007). Investigations of the relationship between these cardiovascular risk factors and cognition have found impairment in various cognitive domains (Yates et al., 2012; Segura et al., 2009). A fuller understanding of the association between abnormal metabolic processes and cognitive performance could have important implications as it may provide an avenue to mitigate cognitive decline (Yaffe et al., 2009) and enhance interventions to reduce the prevalence of cardiovascular disease (Hall et al., 2008). The directionality of the effect of this association is relevant, however, as decreased cognitive function may place an individual at risk for developing cardiovascular risk factors. Conversely, structural damage to fronto-subcortical structures caused by abnormal metabolic processes may directly result in cognitive impairment (Segura et al., 2009; Roriz-Cruz, et al., 2007; Schuur et al., 2010). Interventions designed to reduce an individual's risk of either cognitive decline or cardiovascular disease may be more effective when taking this relationship into account.

Since metabolic processes related to MetS may contribute to cognitive efficiencies across time, decrements in cognitive functioning may be attributable to the length of exposure to MetS (Akbaraly et al., 2010). Thus, individuals meeting criteria for the syndrome over a longer duration would be expected to show greater cognitive deficits than individuals who develop

MetS more recently or those who have never met criteria for the syndrome. Additionally, cognitive domains may show differential impairment associated with the prolonged presence of MetS, such as executive functions and memory, as specific cognitive abilities may have neural substrates that are more susceptible to adverse effects brought about by MetS and related processes (Segura et al., 2009; Roriz-Cruz et al., 2007; Schuur et al., 2010). Such domains would be expected to show greater impairments than other cognitive domains with respect to the duration of the cardiovascular risk factors composing MetS. This study aims to expand upon past research by determining if the length of exposure to MetS is related to poorer cognitive performance in a large, racially diverse sample of community dwelling volunteers that was oversampled for African Americans and stratified to be representative of Dallas County residents.

Hypotheses

Overall Aim: To investigate the relationship between MetS status over time and cognitive functioning.

Aim 1: To investigate the impact of prolonged exposure to MetS on cognitive performance.

Hypothesis 1: Individuals meeting criteria for MetS at baseline and follow-up will exhibit significantly lower performance on a brief measure of cognitive functioning than individuals meeting criteria only at follow-up. Individuals who do not meet criteria for MetS at either baseline or follow-up will show the highest cognitive performance relative to the other groups.

Aim 2: To determine if the association between status of MetS across time and cognitive functioning varies by cognitive domain.

Hypothesis 2: The effect size for the relationship between subsections of the MoCA (i.e., designed to assess executive functions, attention, and memory) and duration of MetS will be greater than the effect size for the relationship between MetS status over time and other domains assessed by the MoCA (naming, orientation, and language).

Aim 3: To determine if prolonged exposure to MetS and baseline cognitive screening is useful in predicting later cognitive impairment.

Hypothesis 3: Prolonged exposure to MetS will be a significant predictor of cognitive impairment after accounting for relevant demographic variables, including age, education, and race, as well as baseline cognitive testing.

Exploratory Aim 1: To determine if the relationship between duration of MetS and cognitive functioning is attenuated after accounting for demographic and lifestyle factors that have been associated with MetS. Specifically, this association will be examined in relation to age, gender, race/ethnicity, levels of cardio-respiratory fitness, self report of exercise level, alcohol consumption, smoking status, income, and education.

Exploratory Aim 2: To determine if the presence of specific metabolic components over time is differentially related to cognitive functioning.

Exploratory Aim 3: To determine whether the prevalence of MetS at DHS-1 among the sample at large is related to cognitive performance on the MoCA at DHS-2 and to determine if MetS presence at DHS-2 is related to concurrent MoCA performance.

Exploratory Aim 4: To explore whether performance on select neuropsychological tests is related to prolonged MetS presence among the DHBAS subsample

Methodology

Method

This study used archival data from two databases, the Dallas Heart Study (DHS) and the UT Southwestern Alzheimer's Disease Center Database. The DHS is a longitudinal project, funded by UT-STAR and NIH/NCATS Grant UL1RR024982, developed to investigate cardiovascular risk factors in a stratified, multi-racial, population-based sample. Procedures for data collection have been described elsewhere (Victor et al., 2004). The Dallas Heart Brain and Aging Study (DHBAS) is a subset of DHS participants who are seen at the UT Southwestern Alzheimer's Disease Center (ADC) where neuropsychological assessment is performed on a yearly basis. Funding for the DHBAS is provided by NIA AG12300.

Participants

The DHS sample included 3,402 individuals with available data from DHS-1 and DHS-2. Of this sample, 1,192 were missing information on all MetS components at either DHS-1 or DHS-2. Sixty two individuals were subsequently excluded due to history of stroke. Of the remaining 2,210 participants, 1,314 individuals had data for MetS at both DHS-1 and DHS-2, a valid MoCA score at DHS-2, and data on age, education, race, gender, income, alcohol consumption, cardio-respiratory fitness, and smoking (all from DHS-2).

The DHBAS subset consisted of 137 participants over the age of 55 at DHBAS enrollment, for whom there were metabolic data from DHS-1 and DHS-2, in addition to a more extensive neuropsychological battery, gathered 3 to 4 years subsequent to DHS-2, as well as information on consensus diagnosis of cognitively normal, mild cognitive impairment and

dementia. Participants were included in analysis 1 and 2 if data for MetS from DHS-1 and DHS-2, a valid Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) score (including item-level data available for Hypothesis 2) from DHS-2 were obtained, and data on relevant covariates were present (n = 1,314). Hypothesis 3 included all participants in the DHBAS subset with information regarding MetS at DHS-1 and DHS-2, a valid MoCA score from DHS-2, data for the neuropsychological testing, and consensus diagnosis made at DHBAS. Exclusionary criterion was history of stroke (n = 62).

Measures

Cognition

Cognition at DHS-2 was measured with the Montreal Cognitive Assessment (MoCA; Nasreddine et. al., 2005). The MoCA is a 30-point global cognitive screening instrument that was selected for use in the DHS for its brevity of administration (approximately 10 to 15 minutes) and sensitivity to gross cognitive status. It was constructed to briefly assess aspects of attention, visuospatial abilities, executive functions, language, memory, and orientation. The range of scores for each area varies by domain: visuospatial/executive abilities (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), orientation (6 points), and verbal memory (5 points), see Appendix A. Higher scores indicate more intact cognitive function. The one point adjustment for education was not used because it was shown to reduce the reliability of the measure when used in the DHS database (Rossetti, Lacritz, Cullum, & Weiner, 2011) and education was used as a covariate when indicated.

Other investigators have examined the MoCA in the DHS sample, finding that MoCA scores are inversely related to Framingham Coronary and Stroke Risk scores (Weiner, Hynan, Rossetti, Warren, & Cullum, 2011). An evaluation of the psychometric properties of the MoCA in the DHS sample, in comparison with a clinical sample, found the measure to correlate with education and exhibited an alpha coefficient of .63 among DHS participants, while the alpha coefficient was .75 among clinical patients. This suggests that, although the MoCA may be a practical tool in large-scale population-based studies, the measure has greatest internal consistency in clinical populations suspected of having cognitive impairment (Bernstein, Lacritz, Barlow, Weiner, & DeFina, 2011). Normative data by age and education have also been published for the MoCA utilizing the DHS database (Rossetti et al., 2011).

The larger neuropsychological battery administered to DHBAS participants includes the MoCA, Trail Making Tests A and B (TMT-A and TMT-B; Reitan, 1979), Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), Controlled Oral Word Association Test (COWAT), California Verbal Learning Test-Second Edition (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), Block Design (BD), Digit Symbol subtest (DS), from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery (Morris et al., 1989), as well as selected subtests of the Wechsler Memory Scale-Revised (WMS-R) [Digits Span Forward (DF), Digits Span Backward (DB), Logical Memory I Story A (LM1-A), Logical Memory II Story A (LM2-A), Visual Reproduction I (VR1), and Visual Reproduction II (VR2); Wechsler, 1987].

TMT-A is a measure of sequencing and processing speed, and is scored in seconds to completion. TMT-B adds a set-shifting component and is also measured in seconds. The WCST assesses problem solving and mental flexibility by having participants sort cards according to a changing principle. The BNT measures confrontation naming. Verbal Fluency required participants to generate words according to a phonemic (FAS) or categorical rule (Animals) for one minute. CVLT measures verbal learning and memory, with scores representing the number of words recalled from a word list across five learning trials and after a long delay. LM1 assesses immediate recall of a short story and LM2 is a measure of delayed recall of a short story. Similarly, VR1 assesses immediate recall of visual details and VR2 assesses visual memory of those details following a delay.

Metabolic Syndrome Variables

The presence of the MetS was based on criteria established by National Institutes of Health National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP-ATP-III) at DHS-1 and DHS-2. NCEP-ATP-III criteria includes abdominal obesity (waist circumference > 102 cm for men and ≥ 88 cm for women), triglyceride levels ≥ 150mg/dl, high density lipoprotein (HDL) levels < 40mg/dl for men and < 50mg/dl for women, systolic blood pressure ≥ 130 or diastolic pressure ≥ 85, and fasting plasma glucose levels ≥ 100 mg/dl (Grundy et al., 2005). The presence of any three of these components was sufficient for the diagnosis of MetS. Self report of medication for treatment of hypertension, diabetes, low HDL, and high triglyceride levels was considered as meeting the respective component. Self report of diabetes medication, including insulin, counted as the plasma glucose component. Use of fibrates or

niacin counted as both low HDL and high triglyceride components. DHS-1 data were obtained from up to three visits (range; < 1 to 2 years), and blood pressure readings from the initial patient visit, when available, were used for MetS diagnosis to limit potential treatment affects. To reduce loss of data, a gender specific BMI regression approach was adopted to estimate waist circumference if unavailable for DHS-1.

Statistical Analysis

Demographic variables were examined with analysis of variance (ANOVA) for continuous variables and chi-square for nominal variables across levels of MetS status. Demographic variables included age (in years), education (in years), race (African American, non-Hispanic White, Hispanic, and other), gender, income (the following 10 levels ; [1] < $16,000, [2] $16,000 to $19,999, [3] $20,000 to $24,999, [4] $25,000 to $29,999, [5] $30,000 to $34,999, [6] $35,000 to $39,999, [7] $40,000 to $49,999, [8] $50,000 to $74,999, [9] $75,000 to $99,999, and [10] ≥ $100,000), smoking status (current smoker, past smoker, and never smoked), alcohol consumption (lifetime abstainer, recent abstainer, and current drinker) and $VO_{2\,max}$ which is a measure of cardio-respiratory fitness estimated based on Hellerstein's formula (Givoni & Goldman, 1971) as:

$$VO_{2max} = VO_2 / (1.41 * \% \text{ Maximal Heart Rate}) - 42.$$

Additional exercise and fitness related variables were self-reports of the amount of physical activity engaged in on a weekly basis and peak treadmill speed. Self report of weekly physical activity was calculated based on answers provided on the Mesa Physical Activity Questionnaire, which allowed each participant to report the number of hours and minutes each day engaged in various light,

moderate, or vigorous physical activity in a typical week, and converts this amount into metabolic equivalent of task scores based on values for each activity presented in the 2011 Compendium of Physical Activity (Ainsworth et al., 2011). Peak speed was based on the maximum output an individual was able to produce during a treadmill test.

Data were examined to determine if the assumptions of multivariate analysis were met, including the assumption of homogeneity of variances. Differences in demographic characteristics between levels of MetS were examined with chi-square analyses for categorical variables and ANOVA for continuous variables. Demographic variables included age in years, education in years, race (African American, non-Hispanic White, Hispanic, and other), gender, income, smoking status (current smoker, past smoker, and never smoked) alcohol consumption (lifetime abstainer, recent abstainer, and current drinker) and cardio-respiratory fitness ($VO_{2\ max}$) which were included as potential covariates in each initial Analysis of Covariance Analysis (ANCOVA) procedure and remained in the model as covariates if significant at $p < .15$. Significant findings were further explored with comparisons between each level of the independent variable.

Hypothesis 1

To evaluate the relationship between status of MetS at two time points (approximately eight years apart) and cognitive performance at time 2, total MoCA scores were compared using Analysis of Covariance (ANCOVA) with three levels of the independent variable: [1] those meeting criteria for MetS at DHS-1 and DHS-2, [2] those meeting criteria at DHS-2 only, [3] and those not meeting MetS criteria at either DHS-1 or DHS-2. A similar process was employed to examine the

effect of MetS status over time with an ANCOVA with four levels of MetS, adding those that improved (met criteria at DHS-1 but not at DHS-2) to the three levels described above to the model.

Hypothesis 2

To examine the relationship between cognitive domains assessed by the MoCA and prolonged presence of MetS, subsections of the MoCA were first analyzed for dimensionality using factor analysis performed using both principal components and maximum likelihood estimation procedures. Factor structure was determined through several processes, including examination of the scree plot, interpretability of the factor solution, amount of variance accounted for by each factor, and eigenvalues. Forcing the extraction of two factors was also conducted and both orthogonal and oblique rotation methods were examined. The MoCA was divided into subsections based on face validity and each subsection was compared across status of MetS in Multivariate Analysis of Covariance (MANCOVA), as well as separate ANCOVA, including relevant covariates. These analyses were performed on the MoCA by dividing items in two ways. First, the MoCA was divided in the following two sections: [1A] visuospatial/executive (5 points), attention (6 points), and memory (5 points), totaling 16 points and [1B] language (3 points), orientation (6 points), naming (3 points), and abstraction (2 points) which totals 14 points. The MoCA was then also divided as follows, [2A] executive (1 points), attention (6 points), memory (5 points), and abstraction (2 points) summed for a total of 14 points and [2B] language (3 point), orientation (6 points), naming (3 points), and visuouspatial (4 points) for a total of 16 points. Specific items comprising each composite are presented in Appendix A. MoCA subsection differences were further explored in homogenous groups by age

(those age 55 and older, those under the age of 55) race (African American, Caucasian), gender (male, female), as well as African American age 55 or older, and males and females age 55 or older.

Hypothesis 3

The DHBAS subsample of individuals with more extensive testing was categorized into normal or impaired based on consensus diagnosis made by a team of neurologists and neuropsychologists. The sample was dichotomized such that the unimpaired group consisted of normal controls (n = 42) and the impaired group (n = 60) was comprised of participants with diagnosis of MCI (n = 54) or Alzheimer disease (n = 6). Individuals diagnosed with another type of dementia (n = 8) were excluded from this analysis. Age, gender, education, race, and DHS-2 MoCA performance, along with MetS status (which was dichotomized into either those meeting criteria for MetS at both time points (n = 29) or those meeting criteria at no time point (n = 73)) were entered into a model of logistic regression predicting cognitive impairment diagnosis at DHBAS (those meeting MetS criteria at only one time point were excluded from analyses). The DHBAS sample was also categorized into impaired groups based on performance on neuropsychological test results. Specifically, individuals who performed 1 or more standard deviations below the mean on age and education corrected scores on two or more neuropsychological tests comprised the impaired group (n = 57), while those with performance on one or fewer tests falling in this range (below one standard deviation below age corrected scores, additional demographic corrections, including age and race were used when available) composed the normal group (n = 50). Variables that were used to determine

impairment include: TMT-A (time to completion) and TMT-B (time to completion), WCST (perseverative errors), BNT (items correctly identified on a 30-item version that was prorated for 60-items and used to generate corrected score based on race, age, and education), FAS (number of words generated), Animals (number of animals generated), CVLT (total words recalled across learning trails and after a delay), WAIS-R BD (total score), DS subtest (total score), WMS-R DS (number of digits recalled forward and backward), WMS-R LM1 (percent of verbal details retained after a delay), and WMS-R VR1 (percent of visual details recalled after a delay).

Exploratory Hypotheses

Differences in MoCA performance by MetS status over time were examined in homogenous subsamples, based on gender, age, race, education level, self report of exercise, and cardio-respiratory fitness. The following subgroup analyses were all performed with 3 or 4 levels of MetS status for the independent variable in ANCOVAs, with total MoCA score as the dependent variable. Specifically, MoCA differences between MetS status groups was examined in those ≥ age 55 with 3 levels of MetS status (n = 377), as well as with four levels of MetS status (n = 429) controlling for education. This analysis was repeated including additional covariates. MoCA total scores were compared across MetS status in those < 55 with four levels of MetS status (n = 885). MoCA total scores were also examined by MetS status over time among men (n = 581) and women (n = 733), as well as among African American (n = 300), non Hispanic White (n = 476), and Hispanic participants (n = 217), while accounting for significant covariates.

To investigate effects within gender groups additional analyses examined MoCA scores between MetS groups in women ≥ 55 (n = 241) and men over the age of 55 (n = 188). MetS status over time was used to compare MoCA total scores in African American participants ≥ 55 (n = 184) and further explored with independent ANCOVAs among African American men ≥ 55 (n = 76) and African American women ≥ 55 (n = 108). MetS status and total MoCA scores were also examined using an ANCOVA among White participants ≥ 55 (n = 190) with similar procedures performed in White men over the age ≥ 55 (n = 87) and White women ≥ 55 (n = 103).

MoCA total scores were explored across MetS status (with four levels) using an ANCOVA among those with 12 years of education or more (n = 1143), as well as in those with less than 12 years of education (n = 171). Further exploration of group differences were conducted comparing MoCA means across MetS status groups in men with 12 or more years of education (n = 514), and women with 12 or more years of education (n =629). Racial differences were explored among those with at least 12 years of education, as an ANCOVA with four levels of MetS status and MoCA scores entered as the dependant variable was performed on African American participants (n = 533) and a comparable ANCOVA was run on Caucasian participants (n = 457).

Groups were dichotomized based on self report of exercise, with MoCA scores examined by MetS status among those reporting no weekly physical activity and a separate ANCOVA investigating this relationship among participants reporting any weekly physical activity. The sample was also grouped based on a median split of VO_{2max} scores, using ANCOVA to investigate MetS groups on MoCA performance for those at or above the median versus those falling below the median.

The individual components of MetS were examined with respect to cognitive functioning by coding each variable as either present at DSH-1 and DHS-2, present at DHS-2 but absent at DHS-1, present at DHS-1 but absent at DHS-2, and absent at both DHS-1 and DHS-2. Each variable was then examined individually in an ANCOVA, covarying for age and education, with MoCA scores entered as the dependant variable to determine if exposure to specific syndrome components over time is associated with lower cognitive performance on the MoCA. Significant findings were followed with analyses that included additional covariates in the model if $p < .15$.

MetS syndrome status over time was further explored for stability of the syndrome over time using the McNemar test. This was also performed among individuals ≥ age 55, as well as for those under the age of 55. To determine whether point prevalence of the syndrome was associated with MoCA scores, rather than MetS status at two time points, MoCA scores were examined with respect to prevalence at DHS-1 and at DHS-2 with an ANCOVA controlling for significant covariates in the overall sample. In these analyses the sample was dichotomized as either meeting MetS criteria at DHS-1 or not and a parallel procedure was conducted to examine the effects of prevalence of MetS at DHS-2 (dichotomized as either present or absent at DHS-2 among the entire DHS sample). MetS status at DHS-1 and DHS-2 were also examined separately in homogenous subgroups, including those ≥ age 55 as well as those under the age of 55. An ANCOVA examined differences in MoCA performance by MetS presence at DHS-1 in African Americans, with a similar analysis examining differences for MetS at DHS-2. MetS presence at DHS-2 was also investigated among Caucasians. An ANCOVA was performed to investigate MoCA score differences attributable to MetS at DHS-2 among

African American participants ≥ age 55. Differences between MoCA scores by MetS status at DHS-2 were also examined in men ≥ age 55 and women ≥ age 55 in separate ANCOVAs.

Select cognitive measures were examined for differences in performance based on MetS status (with four levels) and age and education corrected scores on individual tasks in the DHBAS sample, while controlling for relevant demographic/lifestyle variables. Specifically, performance on TMT-A, TMT-B, Animals, FAS, CVLT total learning, and CVLT long delay free recall were explored.

Results

Demographic Variables and Characteristics

Subjects were characterized into groups with respect to duration of MetS, resulting in 707 who did not meet criteria at DHS-1 or DHS-2, 209 who did not meet criteria at DHS-1 but did have the syndrome at DHS-2, 125 who met criteria at DHS-1 but not at DHS-2, and 237 who met criteria for the syndrome at both DHS-1 and DHS-2. Demographic characteristics of the sample obtained from DHS-2, which was concurrent with the MoCA, are presented in Table 1, and self - report of weekly exercise and cardio-respiratory fitness data are presented in Table 2. Those without MetS at either phase of the study were younger ($F(3, 1313) = 17.6$, $p < .001$) and had higher levels of education ($F(3, 1313) = 6.0$, $p < .001$) than the rest of the sample. Those without the syndrome at either time point exhibited higher MoCA scores than those meeting criteria at both time points or meeting criteria at DHS-2 only ($F(3, 1313) = 14.6$, $p < .001$). Increased fitness (VO_{2max} derived from a treadmill test; $F(3, 1313) = 38.9$, $p < .001$) was seen in those without MetS at both time points in comparison to all other groups and those that improved had higher fitness levels than individuals who met MetS criteria at both DHS-1 and DHS-2. Higher peak treadmill speed ($F(3, 1313) = 27.5$, $p < .001$) was observed in those without MetS at DHS-1 or DHS-2 compared to those who had the syndrome at both time points or only at DHS-2. Significant differences were also observed for MoCA scores ($F(3, 1313) = 6.4$, $p < .001$), as those without the syndrome at both time points exhibited higher MoCA scores than those meeting MetS criteria at DHS-1 and DHS-2 or those meeting criteria only at DHS-2.

Demographic characteristics of the DHBAS subsample are presented in Table 3. Of the DHBAS subsample, those without the syndrome at either DHS-1 or DHS-2 had higher MoCA score means ($F(3, 136) = 3.28$, $p = .023$) and completed more years of education ($F(3, 136) = 2.86$, $p = .040$). There was not a significant difference in age between the four groups ($F(3, 136) = 1.42$, $p = .241$).

Hypothesis 1

In order to test the hypothesis that MetS status over time is related to MoCA performance a series of ANCOVAs were performed. Significant covariates included in the initial ANCOVA investigating the relationship between MetS status with three levels of the independent variable; MetS absence (not present at either time point), MetS incidence (present only at DHS-2), and presence at both time points over time (present at DHS-1 and DHS-2) and MoCA scores in the sample at large, were age, education, race, gender, income, alcohol consumption, ($p = .001$) and cardio-respiratory fitness ($p = .077$). Education demonstrated the largest effect (partial eta squared = .152, which is considered large). In this model, MetS was not significant after accounting for these covariate factors [$F(2, 1188) = .50$, $p = .607$; Demographically Corrected means; absent MetS M = 23.8, incident MetS M = 23.5, prolonged MetS M = 23.7]. A subsequent ANCOVA including the MetS group that improved (n=125), forming four levels of MetS status, was also not significant ($F(3, 1313) = .36$, p = .783, demographically corrected means; absent MetS M = 23.7, improved MetS M = 23.7, incident MetS M = 23.5, prolonged MetS M = 23.6), and covariates were the same as the previous model.

Hypothesis 2

Examination of the factor structure of MoCA subsections performed with extraction techniques of principal components and maximum likelihood found that the subcomponents loaded onto a single factor. The one dimensional factor structure was consistent across different approaches, including examination of the eigenvalues greater than one and referring to the scree plot. Forcing the extraction of two factors, and subsequently rotating them, with various rotation methods did not greatly improve the amount of variance accounted for by the factors, and resulted in some subsections loading onto both factors, reducing the interpretability of the results. Due to the unitary factor structure, groupings of MoCA subsections were not generated based on factor analysis results to examine the effects of MetS status on various cognitive domains in subsequent analyses, but were instead grouped based on face validity of specific items.

MoCA subsections were grouped to compare cognitive domains ([1A] and [1B] described in Appendix B), which resulted in a non-significant MANCOVA for the impact of MetS status (with three levels of MetS status) after covarying age, education, cardio-respiratory fitness, gender, race, alcohol consumption, and income ($F(2, 1188) = .531$, $p = .71$). ANCOVAs for each subsection were also not significant ([1B.] language section, $F(2, 1188) = 1.0$, $p = .368$, [1A.] executive section $F(3, 1188) = .06$, $p = .943$). A subsequent MANCOVA, including those that improved at the fourth level of MetS status, was also not significant ($F(3, 1313) = .35$, $p = .910$). Separate ANCOVAs also did not reach significance after covarying for age and education across MoCA subscores ([1A] executive section, $F(3, 1313) = .05$, $p = .984$; [1B] language section, $F(3, 1313) = .66$, $p = .574$).

The alternate method of dividing the MoCA into two sections composed of [2A] executive, abstraction, attention, and memory tasks and the other consisting of [2B] language, naming, visuospatial and orientation tasks (presented in Appendix B) found that the MANCOVA was not significant ($F(2, 1188) = .28$, $p = .893$), and the follow-up ANCOVAs were also non-significant ([2A]executive $F(2, 1188) = .18$, $p = .839$, and [2B] language $F(2, 1188) = .48$, $p = .618$) after the effects of income, race, age, education, gender, and cardio-respiratory fitness, were taken into account. Inclusion of the MetS group that improved did not significantly change the results (MANCOVA; ($F(3, 1313) = .23$, $p = .968$), Follow-up ANCOVAs; ([2A] executive $F(3, 1313) = .18$, $p = .908$), and [2B] language $F(3, 1313) = .31$, $p = .815$).

ANCOVAs examining the relationship between MetS status (with four levels) and the on the MoCA subsections [1A] and [1B] found that MetS status was not related to composite [1A] ($F(3, 428) = 1.02$, $p = .384$), after controlling for education, gender, race, and income and the relationship was also not significant for the composite [1B] (F (3, 428) = .99, $p = .398$) when accounting for education, race, income, and alcohol consumption. Individual ANCOVAs analyzing the relationship between MetS status (with four levels) with MoCA composites [2A] and [2B] among individuals ≥ age 55 found the composite of executive, abstraction, attention, and memory sections [2A] of the MoCA was non-significant ($F(3, 428) = .71$, $p = 0.546$), with race, income, alcohol consumption, and gender entered as covariates, and the sum of the orientation, language, naming, and visuospatial sections [2B] also was not significant ($F(3, 428) = 1.63$, $p = .182$), controlling for education, race, and income. Results for African American participants ≥ age 55, found no relationship between MetS status and the executive composite [2A] ($F(3, 183) = .93$, $p = .430$), after covarying for education and income, and the composite

comprised of orientation and visuospatial sections [2B], was also not significant ($F(2, 275) = .77$, $p = .454$).

Hypothesis 3

Table 4 presents information regarding clinical consensus diagnosis and impairment rates among the DHBAS sample. The logistic regression model predicting impairment based on consensus diagnosis in the DHBAS subsample that included age, education, race, and DHS-2 MoCA scores was not significant for the effect of MetS ($p = .528$). Significant predictors in the model included MoCA total score ($p < .001$, odds ratio= .628), and age ($p = .042$, odds ratio = 1.11). In a model using MetS status to predict impaired performance on 2 or more neuropsychological assessments found baseline MoCA score and age were significant predictors of impairment ($p < .001$, odds ratio.653, and $p = .02$, odds ratio = 1.12 respectively), while MetS status was not ($p = .156$).

Exploratory Hypotheses

For the subsequent analyses, demographically corrected means and standard deviations as well as significant covariates for each model are presented in Tables 5, 6, 7, and 8.

Gender

With regard to gender differences, the relationship between MoCA means and MetS status was not significant for men ($F(3, 580) = .60$, $p = .615$). MetS group differences were also

not significant among women ($F(3, 732) = .56$, $p = .640$), when including significant covariates in the model presented in Table 5.

Race

There were no significant differences in MoCA scores based on MetS status for African Americans ($F(3, 593) = 2.1$, $p = .098$). Significant covariates are presented in Table 5. The relationship was also not significant among White participants ($F(3, 475) = 1.2$, $p = .329$) after accounting for relevant covariates (presented in Table 5). An ANCOVA among Hispanic individuals was not significant ($F(3, 216) = 1.1$, $p = .373$).

Age

In those age ≥ age 55, a preliminary ANCOVA found significant group differences in MoCA scores by MetS status with three levels after accounting for education as a covariate ($F(2, 376) = 3.3$, $p = .037$) with a partial eta squared of .017. Follow-up comparisons found those without the syndrome at either time point performed significantly better on the MoCA than the those with MetS only at DHS-2 and those with MetS at DHS-1 and DHS-2, which were not significantly different from each other (education corrected means: absent MetS M = 23.6, incident MetS M = 22.6, prolonged MetS M = 22.5). Follow-up analysis with inclusion of the group that improved (n = 52) yielded non-significant results ($F(3, 428) = 2.3$, $p = .074$, education corrected means: absent MetS M = 23.5, improved MetS = 23.3, incident MetS M = 22.7, prolonged MetS M = 22.6). Additional demographic factors were examined as possible covariates, and inclusion of the variables (see Table 6) resulted in a non-significant ANCOVA

examining MetS and MoCA scores in those ≥ age 55, ($F(3, 428) = 1.4$, $p = .256$). Among those under the age of 55, MetS status was not related to cognitive performance ($F(3, 884) = .22$, $p = .883$) after accounting for relevant covariates listed in Table 6 (all at or below $p < .01$).

Individuals ≥ age 55 were further grouped into homogenous subsamples based on race and gender, as described previously, to explore the effects of these demographic variables. These analyses included those that improved over time (had MetS at DHS-1 but not DHS-2). Among women ≥ age 55, there were no significant group differences in MoCA scores based on MetS status ($F(3, 240) = 1.0$, $p = .387$). However, MoCA means were significantly different among men ≥ age 55 ($F(3, 187) = 3.1$, $p = .027$) with a partial eta squared of .050, which is considered medium. Follow-up comparison found the group without MetS performed better on the MoCA than those that meeting criteria at only DHS-1 or meeting criteria at DHS-1 and DHS-2 (significant covariates and means are presented in Table 6).

The relationship between cognition and MetS status over time was not significant for African American participants ≥ age 55 ($F(3, 183) = 2.2$, $p = .090$). Relevant covariates included in the model are presented in Table 6. Dividing African Americans ≥ age 55 by gender found no association between MetS and cognition for African American men ≥ age 55 with four levels of MetS status ($F(3,75) = .87$, $p = .457$), while an ANCOVA among African American females ≥ age 55 was significant ($F(3, 108) = 2.9$, $p = .037$), after controlling for education ($p = .001$), and income ($p = .022$), with a small to medium effect size of MetS status (partial eta squared = .079). Follow-up comparisons found the group that improved performed significantly better than those with MetS at DHS-2 only as well as those meeting criteria for MetS at both DHS-1 and DHS-2 (see Table 6).

There were non-significant mean differences between MoCA scores and duration of MetS in non-Hispanic white participants ≥ age 55 ($F(3, 189) = .76$, $p = .517$), after accounting for education. An ANCOVA among White males ≥ age 55 was also not significant ($F(3, 86) = 1.361$, $p = .261$), after accounting for education. Results were similar for white females ≥ age 55 ($F(3, 102) = .19$, $p = .904$). Means, standard deviations, and significant covariates for both analyses are presented in Table 6.

Education

MoCA performance was also examined with respect to duration of MetS and across homogenous groups based on education. Among those with 12 years of schooling or more, MetS status was not significant ($F(3, 1142) = .92$, $p = .429$), after controlling for significant covariates listed in Table 7. When accounting for demographic factors (see Table 7) there were no groups differences in MoCA scores based on MetS duration in individuals with 11 years of schooling or less, ($F(3, 170) = .33$, $p = .807$). An ANCOVA among men with at least 12 years of education found no effect of MetS status over time on MoCA scores, ($F(3, 513) = .15$, $p = .932$). There was a non-significant result for women who completed 12 years of education or more ($F(3, 628) = .91$, $p = .436$) after accounting for relevant covariates presented in Table 7.

Significant differences in MoCA scores by MetS status were observed among African Americans with 12 or more years of education ($F(3, 532) = 3.3$, $p = .020$) after controlling for demographic/lifestyle factors, listed in Table 7, with a small effect size (partial eta squared = .019). Those that improved performed significantly better on the MoCA than all other groups. Such differences did not exist for Whites ($F(3, 456) = 1.7$, $p = .178$).

Exercise and Fitness

Mean MoCA total scores were not significantly different between MetS status groups among individuals who reported no intentional exercise each week ($F(3, 307) = .08$, $p = .97$). Demographic variables included as covariates are listed in Table 8. MoCA scores were not significantly different among those who reported engaging in any intentional physical activity each week ($F(3, 976) = .73$, $p = .536$), after controlling for numerous lifestyle and demographic factors (see Table 8). Dividing the sample based on median VO_{2max} scores found that among those with cardio-respiratory fitness levels equal to or above the median, MetS status groupings did not produce statistically significant differences in MoCA scores ($F(3, 656) = .41$, $p = .750$). Similarly, the relationship was not significant for individuals with cardiovascular fitness levels below the median $VO_{2max\ score}$ ($F(3, 656) = .63$, $p = .596$). Relevant covariates for these analyses are presented in Table 8.

Metabolic Syndrome Components

Information from initial ANCOVAs, controlling for age and education, investigating each component in isolation is presented in Table 9. Presence of the triglyceride component over time was significant after covarying for age and education in an ANCOVA with four levels of the independent variable ($F(3, 1307) = 3.5$, $p = .015$), partial eta squared = .008; however, this relationship did not occur in the expected direction, as the group composed of individuals meeting criteria for the presence of the triglyceride component at follow-up and base-line performed better on the MoCA after accounting for age and education than the group never meeting the triglyceride component. Yet, this relationship was no longer significant after

accounting for gender, race, income, cardio-respiratory fitness, and alcohol consumption, in addition to age and education ($F(3, 1307) = 2.0$, $p = .112$).

Presence of the blood pressure component over time was significant ($F(3, 1313) = 7.2$, $p < .001$) with a partial eta squared of .016 (see Table 9), after covarying for age and education. The absence of the blood pressure component at baseline and follow-up was associated with significantly higher MoCA scores than the presence of this component at both time points. Entering additional covariates into the model including race, gender, income, cardio-respiratory fitness, and alcohol consumption, however, rendered the relationship not significant ($F(3, 1312) = 1.0$, $p = .386$).

Presence of the elevated blood glucose component over time was significant in an ANCOVA ($F(2, 1298) = 2.7$, $p = .046$), partial eta square = .006, after controlling for age and education (see Table 9) as individuals without the glucose component at DHS-1 and DHS-2 exhibited significantly higher MoCA scores than those meeting criteria for the glucose component at both DHS-1 and 2; however, when including alcohol consumption, income, race, cardio-respiratory fitness, and gender, the glucose component was no longer significant ($F(3, 1298) = 1.7$, $p = .163$). No other component reached significance after accounting for age and education, as duration of HDL was not significantly related to MoCA scores after adjusting for age and education ($F(3, 1311) = .92$, $p = .433$), and duration of the waist circumference component was also not significant after accounting for age and education, ($F(2, 1307) = .96$, $p = .412$). Means are presented in Table 9.

Metabolic Syndrome Prevalence

A McNemar test was performed to determine the stability of MetS criteria across baseline and follow-up visits, which was significant, suggesting the construct is not stable across time ($p < .001$). The McNemar test was also significant when performed on those ≥ age 55, as well as when performed on participants under the age of 55, indicating MetS is not stable across time among these age groups.

Presence of MetS at DHS-1 was not significantly associated with MoCA score means after accounting for race, income, education, gender, alcohol consumption, cardio-respiratory fitness, and age ($F(1, 1313) = .001$, $p = .971$) and neither was presence of the syndrome at DHS-2 when controlling for these same factors ($F(1, 1313) = .82$, $p = .364$). Additional analyses examining the presence of MetS at DHS-1 and DHS-2 among participants ≥ age 55 found that prevalence of MetS at DHS-1 was not significant ($F(1, 428) = 1.3$, $p = .263$) with education, income, gender, race, and alcohol consumption entered as covariates in the model. Results were also non-significant for prevalence of MetS at DHS-2 after controlling for race, income, education, gender, and alcohol consumption ($F(1, 428) = 3.7$, $p = .056$), though there was a trend such that presence of the syndrome was related to lower MoCA performance (MetS M = 22.1, SD = 4.4, No MetS M = 23.8, SD = 3.6). Prevalence of MetS at DHS-1 was not related to MoCA scores in those under the age 55 after controlling for education, gender, race, alcohol consumption, income, age, and fitness ($F(1, 884) = .30$, $p = .585$), and neither was prevalence of MetS at DHS-2 ($F(1, 884) = .03$, $p = .870$), after accounting for these same demographic/lifestyle variables.

Exploring racial differences in the impact of MetS prevalence at either DHS-1 or DHS-2 found the relationship with MoCA scores was not significant among African Americans at DHS-1 ($F(1, 593) = .66$, $p = .417$), controlling for education, income, gender, race, age, and fitness, and the relationship between MetS prevalence at DHS-2 and MoCA scores was also not significant ($F(1, 593) = 3.62$, $p = .058$; MetS M = 21.8, SD = 3.9, No MetS M = 22.7, SD = 3.7) when controlling for income, education, gender, and age. The presence of MetS at DHS-1 among Caucasians was not significant ($F(1, 475) = .30$, $p = .586$) after controlling for age and education. MetS at DHS-2 was also not significantly related to MoCA scores among White participants ($F(1, 475) = .08$, $p = .778$) when accounting for the impact of age and education. The relationship between MetS prevalence at DHS-2 and MoCA scores was not significant among men ($F(1, 580) = .68$, $p = .411$), with significant covariates including education, race, alcohol consumption, and income. The relationship among women was also not significant after controlling for age, gender, race, alcohol consumption and income ($F(1, 732) = .69$, $p = .405$).

Among cohesive subgroups, presence of MetS at DHS-2 was significant among African Americans ≥ age 55 independent of education ($F(1, 183) = 6.1$, $p = .014$), with a partial eta squared of .033 (representing a small effect), as higher MoCA score means were related to absence of the syndrome in this group (MetS M = 20.0, SD = 4.0, No MetS M = 21.9, SD = 3.4). The relationship among white participants ≥ age 55 was not significant ($F(1, 189) = 1.2$, $p = .277$) after controlling for education.

Gender differences were examined among those ≥ age 55, and the relationship between MetS status at DHS-2 was not related to MoCA scores for men after covarying for education, race, and income ($F(1, 187) = 1.5$, $p = .227$), and this relationship also did not exist for women

($F(1, 240) = 1.5$, $p = .218$), when accounting for education, race, income, and cardio-respiratory fitness.

Select DHBAS Subtest Analyses

ANCOVAs were also performed to identify differences on demographically adjusted scores on several neuropsychological tests administered as part of the DHBAS. The relationship between TMT-A performance and MetS status was not significant ($F(1, 106) = 3.6$, $p = .062$). Age, education, and race corrected TMT-B scores were not significantly related to MetS status (F (1, 96) = 3.1, $p = .082$). Performance on FAS was significantly related to MetS (F (1, 99) = 14.0, $p < .001$), with those without the syndrome at either time point exhibiting significantly higher age and educated corrected scores than those that met criteria for MetS at both time points. Demographically adjusted means are presented in Table 10. Age corrected scores on CVLT learning trial were significantly related to MetS status ($F(1, 101) = 5.0$, $p = .027$), partial eta squared = .048 (no covariates were significant). Those with the syndrome at both time points had lower scores compared to without the syndrome at both times points. CVLT delayed recall performance was also significantly related to MetS status ($F(1, 102) = 3.9$, $p = .050$), as those without the syndrome at both time points performed better than those with MetS at DHS-1 and 2. No significant groups differences were observed on age, education, and race corrected scores on Animal verbal fluency by MetS status across time ($F(1, 106) = 2.5$, $p = .119$).

Discussion

Contrary to Hypothesis 1, there was no relationship between duration of MetS and cognitive functioning after controlling for relevant covariates among the sample at large. Rather, the relationship between cognitive functioning and duration of MetS was wholly accounted for by demographic factors, such as age, education, gender, race/ethnicity, income, as well as life style variables including alcohol consumption, smoking, and cardio-respiratory fitness, when such factors were included as covariates.. The depth of information available in the DHS database allowed for thorough examination of the relationship between MetS and cognitive functioning in the context of several demographic factors which have often been associated with both the syndrome and cognitive functioning in past studies. Yet, such an approach masked the relationship that existed among homogenous groups within the larger DHS sample.

In the DHS sample, divisions based on race, age, gender, and education uncovered significant associations between duration of MetS and MoCA scores among various groups. In particular, higher MoCA means were seen with improvement in MetS status during the span of the study among African American females age 55 and older, even after controlling for significant covariates (smoking and education) and among African American participants with 12 or more years of education (p = .041), as well as men over the age of 55 (p = . 027). Additional trends were observed in some older African American subgroups. These findings suggest that certain segments of the population may be more at risk of decrements in cognition related to MetS than others, particularly elderly individuals and African American women.

Gender differences existed, even among racial groups, in those 55 years and older for the relationship between MetS and cognition, as presence of the syndrome was associated with poorer cognitive functioning in African American females independent of relevant demographic factors, while such a relationship was not observed for African American men. A relationship did, however, exist among men over the age of 55, yet remission of the syndrome was associated with even poorer cognitive functioning. Numerous other studies have found gender effects of MetS (Panza et al., 2011; Schuur et. al., 2010), though few have looked specifically at sex differences longitudinally. One such study found that the syndrome at baseline was associated with cognitive decline in women but not men (McEvoy, et. al., 2012). It has been proposed that genetic susceptibility to adverse outcomes related to MetS may exist for women and not men, potentially contributing to gender-specific declines and impairments in cognition for women with MetS (McEvoy, et. al., 2012). The current results suggest that men may not benefit cognitively from reversal of the syndrome.

Differences by racial group were also observed. There were trends and significant differences between MetS and cognitive functioning among older African Americans that were not observed in non-Hispanic Whites. Past research has found elevations in blood pressure, a component of MetS consistently related to poorer cognition, are more strongly related to cognition for African Americans than for Caucasians, even though blood pressure was related to cognitive functioning in both groups across the lifespan (Robbins, Elias, Elias, & Budge, 2005).

In-depth examination of demographic variables in the current study may help explain variability in research on the relationship between MetS and cognition. Combining participants into groups that are diverse with regard to demographic factors, such as age, race, income,

education, or life style factors such as smoking, and alcohol use, may obscure the subtle effects that exist between MetS and cognition due to pronounced between group differences. Additionally, covarying for these differences may leave the issue unaddressed, since entering variables as covariates does not allow for examination of the ways in which relationships may change at different values of these factors. The impact of MetS on cognition may be most observable in midlife, since early or late in life other factors may play a much greater role, such as disease processes. Past studies that have covaried for factors such as race, age, and gender may have missed important differences that exist between these groups with regard to the association between MetS and cognition functioning.

Somewhat related to this issue was the extent to which the demographic factors that were examined as covariates in the current sample differed across segments of the study sample. Age, education, smoking, alcohol consumption, gender, income, cardio-respiratory fitness, and race/ethnicity were all included in various models as covariates due to reaching significance (at least at $p < .15$); however, most demographic factors varied widely with respect to their significance levels when included in different analyses. This indicates that factors influencing the relationship between MetS and cognitive functioning may exert different effects on the association depending on the sample being studied, which may partly explain discrepancies found in the literature.

Failing to account for these factors might, depending on sample characteristics, result in considerably divergent results. For example, the preliminary analysis investigating duration of MetS and cognition in those age 55 or over in the current study was initially significant after controlling for education (age was not a significant covariate in this analyses, likely due to the

truncated age range). Including age and education as covariates is standard practice for studies of MetS and cognition due to consistent findings supporting the relationship between age and education with the syndrome and cognition. Yet, inclusion of other factors that have been demonstrated to relate with the syndrome as well as cognitive performance, resulted in a non-significant finding in those 55 and older. Most other studies have not attempted to account for the extent of covariates that were included in the current study, which were significant to varying degrees depending on characteristics of the subsample, though some have (Crane et al., 2013; Gatto et. al., 2008; Schuur et. al., 2010). Past research that has found an effect of MetS on cognition, but failed to account for these other variables, may be making attributions to the syndrome that are better accounted for by demographic and lifestyle factors. The effects of MetS are hypothesized to produce small changes in cognition through indirect processes, and are not expected account for substantial variance in cognitive performance. Consistent with this, most effect sizes between MetS and cognitive functioning were quite small, particularly when compared with other variables such as age and education. Such other variables exerted substantially more effect on cognition than MetS, with less variance accounted for by metabolic processes.

Investigations that have controlled for demographic variables by entering them as covariates in analyses examining MetS and cognitive performance may have limited the ability to identify such relationships among certain groups. Covarying for demographic variables may mask effects that exist within cohesive subgroups since the dynamic processes that underlie the syndrome may exert differential effects as a function of the population studied. Past research suggests that the prevalence of MetS varies widely based on the sample under investigation and

that medical conditions related to MetS may convey different levels of CVD risk for various populations. For instance, hypertension is related to the MetS, and CVD risk associated with elevations in blood pressure can change as a function of race, age, and gender. Since the deleterious effects of hypertension on cardiovascular health differs in conjunction with demographic factors, it is possible that the impact of MetS on cognition may vary in a similar manner, and be dependent on gender, race/ethnicity, education, and age, as well as interactions between these variables and other factors. Supporting examples include Laudisio et al. (2008), who reported that the prevalence of MetS was related to improved cognitive performance in elderly individuals, however, follow-up analyses found that this association was mostly driven by a stronger relationship among those over the age 80, and the impact of abdominal obesity and low HDLs were most pronounced. Furthermore, the above relationship existed for women but not men. Deceleration in cognitive decline associated with the syndrome among elderly individuals over the age of 85 has been reported by other investigations, giving further support of this relationship (Van den Berg et al., 2007). The authors surmised that some components of the syndrome may be protective against cognitive decline in old age. Alternatively, the relationship may have been mediated by survival effects (Laudisio et. al. 2008; Van den Berg et al., 2007). Whatever the underlying mechanism, the study highlights the potential for complex changes in the relationship between MetS and cognition that can vary due to age and gender, which may extend to other factors.

The current investigation also set out to examine the effect that duration of MetS may have on various cognitive domains. Specifically, the hypothesis that duration of MetS would be more strongly related to particular subsections of the MoCA, such as those involving executive

functioning, attention, and memory, than other cognitive domains was tested. Since the factor structure of the MoCA was found to be unidimensional using factor analysis, the MoCA was divided into subsections based on face valid items and past research that indicated MetS has been more consistently linked with specific domains. The results found that Hypothesis 2 was not supported, as the duration of the MetS was not related to either subsection after accounting for relevant demographic characteristics when examined across the entire DHS sample.

An extensive body of research exists associating MetS to the development of later cognitive impairment and dementia syndromes (Crane et al., 2013; Yates et. al., 2012; Kerola, Kettunen, & Niemen, 2011; Onyike, 2006; Muller et al., 2009; Viera et al., 2011); however, such a relationship was not found in the current investigation. Hypothesis 3 of the present study was not supported, as MetS duration was not useful in predicting future cognitive impairment at follow-up when the DHBAS sample was dichotomized based on consensus diagnosis, though education and MoCA scores at DHS-2 were significant predictors. Potential explanations for the discrepant findings are that the DHBAS subsample was quite small, which may have limited the power of the analyses. Also this group is composed of individuals who volunteered to be followed yearly with more extensive neuropsychological testing. These volunteers may differ from the larger sample, which was specifically designed to represent the greater Dallas area, in ways that may impact the relationship between duration of MetS and future cognitive impairment. These potential confounding factors may have also contributed to the negative results when performing a logistic regression to predict impairment on neuropsychological testing by the presence of the syndrome at DHS 1 and DHS 2.

Multiple exploratory analyses were conducted to gain a deeper understanding of the relationship between cognitive functioning and MetS among homogenous groups within the larger DHS sample, several of which are discussed above. Additional analyses examining the specific components of the syndrome over time were conducted. Of the components, prolonged exposure to elevations in blood glucose and increased blood pressure were associated with poorer cognition after adjusting for age and education. This relationship was such that prolonged exposure to either component was associated with poorer total MoCA scores, however, these relationships were not significant after including additional variables as covariates in the analysis, such as race, gender, income, cardio-respiratory fitness, and alcohol consumption. Curiously, an initial relationship was observed with prolonged levels of elevated triglycerides, such that individuals who met criteria for the triglyceride component at two time points performed significantly better than those who did not meet criteria at either time point, after controlling for age and education. Although this relationship was no longer significant after accounting for additional demographic and lifestyle variables in a subsequent analysis, it raises the possibility that inclusion of this component in MetS criteria used in Hypothesis 1 and 2 may have contributed to the negative findings. These series of analyses highlight the importance of controlling for numerous demographic variables when examining the relationship between cardiovascular risk factors, as studies that do not account such factors may be attributing lowered cognitive performance to these cardiovascular risk factors rather than other variables that may account for performance differences.

This project focused on identifying the impact that duration of MetS may have on cognitive functioning, with the underlying assumption that having the syndrome over two time

points would be associated with poorer cognitive performance. Since those without the syndrome tended to perform similarly to those that improved over time while means for those that met criteria at follow-up were closer in approximation to individuals meeting criteria at both time points in several analyses, the impact of prevalence of MetS at DHS-1 and DHS-2 as well as the stability of the syndrome were examined. The presence of MetS was not significantly related to MoCA scores at either DHS-1 or DHS-2 after controlling for various demographic factors; however, a trend existed such that, among individuals age 55 and over, those without MetS at DHS-2 scored higher on the MoCA than their peers with the syndrome. Analyses performed within subgroups found a significant association between presence of MetS at DHS-2 and cognition among African Americans 55 years old and older after controlling for relevant covariates. There are several potential explanations for this finding. The power was increased when the four groups were combined into two, reducing the number of comparisons from three to one while increasing the sample size of both groups, which may have accounted for the positive findings in relation to MetS prevalence at DHS-2. It is also possible that mere presence of the syndrome, particularly in mid-life, is more strongly related to cognition than prolonged presence of the syndrome. It should be noted that concurrent MoCA scores were not available for DHS-1, so further exploration of the possible effect of point prevalence was not possible. Nevertheless, such results suggest that presence of MetS exerts more of an effect on cognitive functioning than the presence of the syndrome across time, at least among older African Americans.

The stability of MetS over time was also examined. A McNemar analysis found considerable variability among individuals with respect to meeting MetS criteria across time,

indicating that the syndrome is a dynamic construct and MetS status may oscillate in some individuals. Considering the dynamic nature of the syndrome observed in the current investigation in conjunction with the finding that concurrent presence of the syndrome may be more impactful with regard to cognitive performance deficits than prolonged exposure, reversing the syndrome may result in small improvements in cognition among some populations, such as African American women, particularly those over the age of 55. Past research does support this, as some studies have found that reversing blood pressure, treating dyslipidemia, and controlling diabetes through medication and lifestyle modifications are associated with improvements in cognitive functioning, though the research does not approach the substantial support for such interventions reducing cardiovascular risk (Grodstein, 2007).

Further exploratory analyses examined the effect of duration of MetS on additional neuropsychological assessments among the DHBAS subsample and prolonged presence of the syndrome was found to be related to lower performance on FAS, CVLT total learning, and CVLT delay, see Table 10, with small to medium effect sizes. Though not significant, those meeting criteria for MetS at both time points exhibited lower mean scores compared to those without the syndrome at DHS-1 and 2 on the other assessments examined, including Animals, TMT-A, and TMT-B. This suggests that processing speed, verbal fluency, and verbal learning and memory, may be susceptible to deleterious cognitive effects associated with the syndrome.

Many of the analyses performed did not result in significant findings. Yet significant results and trends in the data were observed in gender and racial subgroups over the age of 55. In the DHS sample, the relationship between cognition and MetS existed for older African American women. Such findings are consistent with some past investigations into cardiovascular

risk factors and cognition, as African American women may be at heightened risk for the negative cognitive outcomes linked with the syndrome, the group with the highest prevalence of all-cause dementia (Heyman et al., 1991). One study found such differences in dementia risk were not associated with being male in a White and African American sample (Green et al., 2002). Furthermore, remitted MetS was associated with reduction of cognitive effects to the same level as in persons who never had the MetS in some subsamples, particularly African American females, suggesting that its cognitive effects may be reversible, thus reducing susceptibility to the effects of potentially dementing illnesses and delaying their clinical onset. This is made pertinent by past research suggesting that cognitive impairment is a major source of disability in elders, and often heralds the development of dementia due to vascular causes or Alzheimer disease, which occurs most frequently in older African American women (Heyman et al., 1991). The MetS is a common reversible disorder with a small, but distinct effect on cognition that is independent of its duration in certain demographic groups. Other studies have found that risk of CVD is not equal across populations and it is possible that negative cognitive effects related to exposure to the syndrome may vary widely as a function of sample characteristics. This may account for a large part of the discrepancies observed across studies in the literature on the relationship between cognitive functioning and MetS.

Limitations

Several limitations exist with regard to the current study. The presence of MetS at DHS - 1 and 2 was used as a proxy for duration, and whether or not these individuals met MetS criteria

for the duration of the study in unknown. Also, the severity of the syndrome (number of components present) was not assessed, and it is possible that an additive effect exists and having more components results in poorer cognitive performance, though such a relationship has not always been observed (Falkowski et. al., 2014). The analyses that found significant effects occurred in subgroups that had substantially less participants than the sample at large and, in effect, reduced power, limiting the ability to identify small cognitive effects related to MetS. The MoCA, though able to capture small effects of MetS in some homogenous subgroups, may not be a sensitive enough measure to quantify the types of changes that are brought about by prolonged exposure to MetS among the sample at large. Although performance on other screening tests used in past research have reported significant findings, the very characteristics that make the MoCA well suited for use in the DHS (its brevity of administration while assessing multiple cognitive domains), may have contributed to the negative findings among the DHS sample as well as in various subgroups in the current study. This is further supported by the exploratory investigation of additional neuropsychological subtests in the DHBAS subsample, as significant differences were found on demographically corrected FAS and CVLT scores despite the smaller sample size.

The MoCA was also used to investigate the extent to which cognitive domains are differentially affected by prolonged exposure to MetS, and it was divided into subsections based on face validity following factor analyses procedures that found a one dimensional factor structure. Such an approach to dividing the MoCA has some important limitations. The finding of a single factor best characterizes the variance of the measure indicates that, although the MoCA was constructed to measure distinct cognitive domains, it may not actually do so, and

dividing the MoCA by the face validity of specific items did not address this issue. Research has found subsections of the MoCA to correlate with factors that had similar content and were derived from a larger neuropsychological battery through factor analysis but, with the exception of the executive/visuouspatial section, which showed a fair ability to predict impairment on other tests of executive and visuouspatial abilities, the remaining sections had poorer utility in predicting impairment in specific domains (Moafmashhadi & Koski, 2013). Thus, the MoCA may not be suitable to detect subtle effects that MetS has on distinct cognitive domains.

Many of the subsample analyses were performed with homogenous groups that had much fewer participants, resulting in less power, which may have contributed to negative findings since the effect sizes between MetS and cognition were small, and even among subgroups other variables continued to account for a much larger amount of variance in MoCA performance (such as the impact of education among individuals over the age of 55).

This project set out to examine the effects of duration of MetS on cognition and how this might vary due to demographic characteristics of the sample. To accomplish this aim, the sample was divided in a number of different ways in order to investigate MetS exposure among various groups, which resulted in numerous analyses. Though conducting these analyses allowed for great depth of investigation into the association between MetS and cognition, it also resulted in an inflation of alpha and increased the likelihood of Type I error. Conversely, the inclusion of multiple variables as covariates reduced the degrees of freedom in the analyses, adversely affecting the power. Though doing so was important for the aims of the current investigation, as research suggests the relationship between MetS and cognitive functioning is likely moderated by the variables included in various models, the large number of covariates coupled with small

effect sizes may have contributed to the negative findings in the current study by increasing the chance of a Type II error. Limitations regarding the use of the DHBAS subsample for further investigation of the correlation between MetS status and cognitive impairment include the smaller sample size and the self selection of this subgroup. Also, though some significant differences were observed on MoCA scores in certain subgroups, differences were too small for clinical significance.

Conclusion

In conclusion, the presence of MetS was associated with small decrements in cognitive functioning, primarily among older African American women and older men, and duration of MetS appears to have less of an impact than concurrent presence of the syndrome. The syndrome also appears to be dynamic, rather than stable, across time. The dynamic nature of the syndrome combined with the finding that concurrent MetS is related to cognitive deficits, supports the potential of reversing adverse cognitive effects related to the syndrome. The impact of demographic factors is important to examine from multiple perspectives when investigating the relationship between MetS and cognitive functioning, as MetS prevalence can differ based on demographic variables and distinct methods for accounting for demographic and lifestyle factors (such as running analyses in cohesive subgroups rather than covarying for relevant variables) can uncover relationships through some techniques that can be hidden in others. Also, several demographic factors were accounted for in the present study that are not always controlled for in investigations into MetS and cognition, and these factors had substantial impact among certain

groups in the current study. These include income, consumption of alcohol, smoking, cardio-respiratory fitness in addition to age, education, gender, and race and future studies should take the contribution of such factors into account when investigating MetS and cognitive performance. The MetS is a common reversible disorder with a small effect on cognition that is independent of duration, and certain groups are more susceptible to such effects, particularly middle aged men and older African American women.

TABLE 1
Dallas Heart Study Sample Characteristics by Duration of MetS Status

Measures	**Absent n=707**	**Improved n=125**	**Incident n=209**	**Prolonged n=273**	**Total n=1314**	*p* value
Female	55.0%	60.8%	53.6%	57.1%	55.9%	.561
Race/Ethnicity						
Black	42.4%	52.0%	45.9%	48.7%	45.2%	.085
White	39.7%	28.8%	34.9%	31.5%	36.3%	
Hispanic	15.3%	16.0%	18.2%	18.7%	16.5%	
Other	2.5%	3.2%	1.0%	1.1%	2.0%	
Drinking Status						
Current Drinker	77.1%*	64.0%	73.2%	67.4%	73.3%	.008
Recent Abstainer	15.4%	24.8%	15.8%	22.3%	17.8%	
Life Abstainer	7.5%	11.2%	11.0%	10.3%	9.0%	
Smoking Status						
Current Smoker	23.1%	16.8%	19.6%	17.6%	20.8%	.325
Past Smoker	20.1%	24.0%	23.4%	24.9%	22.0%	
Never Smoker	56.9%	59.2%	56.9%	57.5%	57.2%	
Education (years)	13.0*	12.4	12.5	12.5	12.7	<.001
Age DHS-2 (years)	48.5*	52.2	50.4[a]	52.9[a]	50.1	<.001
Median Income	$40,000 - $49,999	$35,000 - $39,999	$40,000 - $49,999	$35,000 - $39,999	$40,000 - $49,999	-
MoCA Score	24.1[a,b]	23.2	23.2[a]	23.1[b]	23.7	<.001

* statistically significant from all other groups

[a,b] statistically significant difference between groups

TABLE 2
Exercise and Fitness Data by Duration of Metabolic Syndrome Status

Measures	**Absent n=710**	**Improved n=126**	**Incident n=209**	**Prolonged n=273**	**Total n=1318**	*p* value
Tread Mill Peak Speed (km/hr)	12.9[a,b]	12.5	12.0[b]	11.9[a]	12.5	<.001
Metabolic Equivalent Task Per week[1]	2494.4	2404.6	2356.0	2038.7	2368.4	.464
Intentional[2]	1789.9	1744.4	1878.5	1578.7	1755.5	.660
Moderate[3]	704.4	660.2	477.5	459.9	612.9	.245
Vigorous[4]						
Treadmill VO_{2Max}[e]	29.7*	27.0[a]	24.9	23.2[a]	27.4	<.001

[1]((Hours/Day * 60) = Minutes/Day) * Days/Week * Metabolic Equivalent Task Value = Metabolic Equivalent Task * min/week

Absent n = 692, Improved n =121, Incident n = 205, Prolonged n = 270

[2]Total Intentional Metabolic Equivalent Task *min/week = SUM of Metabolic Equivalent Task *min/ for Questions 9-15 of the MESA Activity Scale

[3]Total Intentional Moderate Metabolic Equivalent Task *min/week = Questions 9, 10, 13, and 14 of the MESA Activity Scale

[4]Total Intentional Vigorous Metabolic Equivalent Task *min/week =Questions 11, 12, and 15 of the MESA Activity Scale

* statistically significant from all other groups

[a,b] statistically significant difference between groups

TABLE 3
Dallas Heart Brain and Aging Study Sample Characteristics by Duration of Metabolic Syndrome Status

Measures	**Absent n=75**	**Improved n=14**	**Incident n=16**	**Prolonged n=32**	**Total n=137**	*p* value
%Female	58.7%	78.6%	31.3%	59.4%	57.7%	.067
Race/Ethnicity						
Black	42.7%	42.9%	43.8%	46.9%	43.8%	.784
White	50.7%	35.7%	50.0%	43.8%	47.4%	
Hispanic	5.3%	21.4%	6.3%	9.4%	8.0%	
Other	1.3%	-	-	-	0.7%	
Drinking Status						
Current Drinker	79.5%*	85.7%	66.7%	56.3%	73.1%	.041
Recent Abstainer	16.4%	-	33.3%	34.4%	20.9%	
Life Abstainer	4.1%	14.3%	-	9.4%	6.0%	
Smoking Status						
Current Smoker	16.4%	14.3%	37.5%	12.5%	17.8%	.374
Past Smoker	30.1%	21.4%	18.8%	37.5%	29.6%	
Never Smoker	53.4%	64.3%	43.8%	50.0%	52.6%	
DHS MoCA Score	24.6	25.9[a,b]	22.9[a]	23.1[b]	24.2	.023
Education	13.6[a]	13.0	13.4	12.5[a]	13.3	.040
Age at DHBAS	65.9	68.1	68.2	66.7	66.7	.241
Time to Follow-up	4.6[a]	5.3[a]	4.6	4.8	4.7	.037

* statistically significant from all other groups

[a,b] statistically significant difference between groups

TABLE 4
Dallas Heart Brain and Aging Study Subsample by Consensus Diagnosis, Impaired Testing, and MetS status

Categories	No MetS	MetS at Both	Total	*p* value*
Consensus Diagnosis				
Normal Controls (%)	31 (73.8%)	11 (26.2%)	42	.675
Cognitively Imp. (%)	42 (70%)	18 (30%)	60	
[Alzheimer's Dis. (%)]	[2 (33.3%)]	[4 (66.7%)]	[6]	
Impairment on Testing				
Normal (%)	33 (80.5%)	8 (19.5%)	41	.064
Impaired (%)	42 (63.6%)	24 (36.4%)	66	

*Chi-Square Analyses

TABLE 5

Demographically Corrected Means and Standard Deviations and ANCOVA Results for MoCA Total Score by MetS Group and Race and Gender and Age Groups

Sample	Significant Covariates (< .15)	Absent M (SD)	Improved M (SD)	Incident M (SD)	Prolonged M (SD)	Total M (SD)	*p* value
Men	Education, race, income, age, alcohol,	23.7 (3.3) n=318	23.3 (3.3) n=49	23.4 (3.3) n=97	23.3 (3.6) n=142	23.4 (4.1) n=581	.615
Women	Age, education, race, income, alcohol	23.8 (3.3) N=389	24.1 (.3) n=76	23.5 (3.3) n=112	23.7 (3.3) n=156	23.8 (3.9) n=733	.640
African Am.	Age, education gender, income	22.4 (3.4) n=300	23.1 (3.4) n=65	21.9 (3.4) n=96	22.1 (3.4) n=133	22.4 (3.9) n=594	.098
White	Age, education	25.9 (2.6) n=281	25.5 (2.5) n=36	25.6 (2.5) n=73	26.2 (2.6) n=86	25.8 (3.3) n=476	.329
Hispanic	Education, age, gender	22.6 (3.3) n=108	21.4 (3.3) n=20	22.6 (3.3) n=38	22.0 (3.3) n=51	22.2 (4.0) n=217	.373

TABLE 6
Demographically Corrected Means and Standard Deviations for MoCA Total Scores by Age and MetS

Sample	Covariates	Absent M (SD)	Improved M (SD)	Incident M (SD)	Prolonged M (SD)	Total M (SD)	*p* value
≥ Age 55	Education, gender, race, alcohol, income	23.4 (3.2) n=193	23.1 (3.8) n= 52	22.7 (3.2) n= 69	22.6 (3.2) n=115	23.0 (3.6) n=429	.256
< 55 years old	Education, gender, race, alcohol, income, age	23.9 (3.3) n=514	24.0 (3.3) n=73	23.7 (3.3) n=140	24.0 (3.3) n=158	23.9 (4.2) n=885	.883
Woman ≥ Age 55	Education, race, alcohol, income, fitness	23.1 (3.3) n=106	23.8 (3.2) n= 33	22.5 (3.3) n=34	22.9 (3.3) n=68	23.1 (3.6) n=241	.387
Men ≥ Age 55	Education, race, income	23.8[a,b] (3.0) n=87	21.6[a] (3.1) n=19	23.1 (3.0) n=35	22.6[b] (3.1) n=47	22.8 (3.5) n=188	.027
African Am. ≥ Age 55	Education, income	21.5 (3.4) n=74	21.8 (3.4) n=24	20.1 (3.4) n=30	20.5 (3.4) n=56	21.0 (3.7) n=184	.090
African Am. Men ≥ Age 55	Education	21.5 (3.4) n=33	20.6 (3.4) n=9	20.7 (3.4) n=14	20.0 (3.4) n=20	20.7 (3.8) n=76	.457
African Am. Women ≥ Age 55	Education, income	21.5 (3.4) n=41	22.9[a,b] (3.3) n=15	19.5[a] (3.3) n=16	20.8[b] (3.3) n=36	21.2 (3.6) n=108	.037
White ≥ Age 55	Education	25.8 (2.5) n=100	25.2 (2.4) n=16	25.1 (2.4) n=30	25.4 (2.5) n=44	25.4 (3.0) n=190	.517
White Men ≥ Age 55	Education	25.9 (2.3) n=43	24.2 (2.3) n=7	25.2 (2.3) n=18	25.0 (2.3) n=19	25.1 (2.8) n=87	.261
White Women ≥ Age 55	Education	25.6 (2.7) n=57	26.0 (2.6) n=9	25.1 (2.7) n=12	25.6 (4.3) n=25	25.6 (3.3) n=103	.904

[a,b] statistically significant difference between groups

TABLE 7
Demographically Corrected Means and Standard Deviations and ANCOVA Results for MoCA Total Scores by MetS Group in Education Subgroups

Sample	Significant Covariates ($p < .15$)	Absent M (SD)	Improved M (SD)	Incident M (SD)	Prolonged M (SD)	Total M (SD)	*p* value
≥ 12 Years of Educ.	Education, age, gender, race, alcohol, income	24.2 (3.2) n= 629	24.4 (3.2) n=106	23.8 (3.2) n=180	24.1 (3.2) n=228	24.1 (3.9) n=1143	.429
<12 Years of Educ.	Age, education, race, smoking	20.5 (3.7) n=78	19.7 (3.6) n=19	20.3 (3.6) n=29	20.6 (3.7) n=45	20.3 (4.1) n=171	.807
Men ≥ 12 Years Educ.	Age, education, race, alcohol, income	24.0 (3.2) n=285	23.9 (3.2) n=41	23.8 (3.2) n=87	23.9 (3.2) n=101	23.9 (4.0) n=514	.932
Women ≥ 12 Years Educ.	Education, age, race, alcohol, income	24.4 (3.2) n=344	24.7 (3.2) n=65	23.9 (3.2) n=93	24.2 (3.2) n=127	24.3 (3.8) n=629	.436
African Am. ≥ 12 Educ.	Education, age, alcohol, income, gender	22.7 (3.4) n=273	23.7* (3.3) n=58	22.1 (3.3) n=87	22.3 (3.3) n=115	22.7 (3.9) n=533	.020
White with ≥ 12 Educ.	Education, age	26.0 (2.5) n=273	25.5 (2.5) n=32	25.8 (2.5) n=72	26.5 (2.5) n=80	26.0 (3.3) n=457	.178

* statistically significant from all other groups

TABLE 8
Demographically Corrected Means and Standard Deviations and ANCOVA Results for MoCA Total Scores by MetS Status and Exercise and Fitness Groups

Sample	**Significant Covariates ($p < .15$)**	**Absent M (SD)**	**Improved M (SD)**	**Incident M (SD)**	**Prolonged M (SD)**	**Total M (SD)**	*p* value
No weekly intentional MetS	Education, fitness, gender, race, alcohol, smoking, income	22.9 (3.4) n=155	22.9 (3.3) n=26	23.1 (3.3) n=51	23.0 (3.4) n=76	23.0 (4.1) n=308	.972
Any weekly intentional MetS	Education, gender, race, alcohol, income, age	24.0 (3.3) n= 535	24.0 (3.2) n=94	23.6 (3.2) n=154	23.8 (3.3) n=194	23.8 (3.9) n=977	.536
High Fit Group	Education, gender, race, alcohol, income, age, smoking	24.2 (3.1) n=425	23.8 (3.2) n=63	24.1 (3.1) n=84	24.0 (3.1) n=85	24.0 (4.1) n=657	.750
Low Fit Group	Education, gender, race, alcohol, income, age	23.2 (3.4) n=282	23.5 (.3.4) n=62	22.8 (3.4) n=125	23.2 (3.4) n=188	23.2 (3.9) n=657	.596

TABLE 9
Duration of MetS Components Controlling for Age and Education

Measure	Absent	Improved	Incident	Prolonged	η^2	*p* value
Blood Pressure	n=431	n=64	n=329	n=489		
MoCA	24.5[a,b]	23.9	23.6[a,c]	22.9[b,c]	.016	< .001
Triglyceride	n=843	n=121	n=175	n=169		
MoCA	23.4[a]	24.1	23.9	24.2[a]	.008	.015
HDL	n=648	n=225	n=129	n=310		
MoCA	23.6	23.8	23.8	23.5	.002	.433
Waist Circ.	n=513	n=110	n=104	n=581		
MoCA	23.9	23.7	24.0	23.4	.002	.412
Blood Glucose	n=745	n=113	n=222	n=219		
MoCA	24.0[a]	23.5	23.5	22.7[a]	.006	.046

[a,b,c] statistically significant difference between groups

TABLE 10
Demographically Corrected Scores for Select Neuropsychological Tests by Metabolic Syndrome Status at Dallas Heart Brain and Aging Study

Measure	Covariates	Absent	Prolonged	η^2	*p* value
FAS	Income	49.1 (9.2) n= 70	41.6 (9.2) n= 30	.126	<.001
Animals	None	50.8 (10.9) n= 75	47.3 (9.2) n= 32	.023	.119
CVLT Total Learning	None	45.9 (11.0) n= 71	40.2 (13.6) n= 31	.048	.027
CVLT Delay	None	50.2 (10.7) n=72	46.0 (8.0) n=31	.038	.050
TMT-A	Age	54.1 (11.5) n= 75	49.5 (11.6) n= 32	.033	.062
TMT-B	Income	49.9 (10.8) n= 70	45.6 (10.8) n= 27	.032	.082

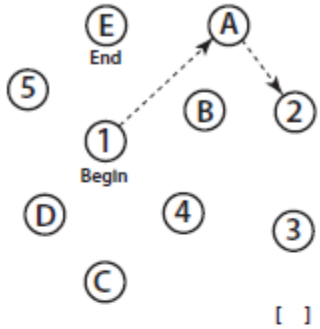
FAS; phonemic verbal fluency, Animals; category verbal fluency, CVLT; California Verbal Learning Test, TMT-A; Trail Making test A, TMT-B: Trail Making Test B

APPENDIX A
Copy of MoCA Protocol

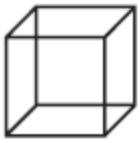
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

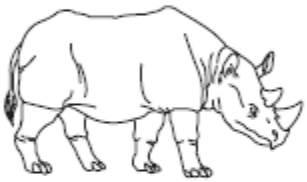
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ]



[ ]

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD Version 7.1 **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX B
MoCA Subcomponent Divisions for Hypothesis 2

Method 1 for dividing the MoCA

[1A] **Visuospatial:** Cube (1 point) Clock (3 points)

Executive: Alternating Trail Making (1 point)

Attention: Forward Digit Span (1 point), Backward Digit Span (1 point), Vigilance (1 point), and Serial 7's (3 points)

Memory: Delayed Recall (5 points)

[1B] Naming: (3 points)

Language: Sentence Repetition (2 points) and Verbal Fluency (1 point)

Abstraction: (2 points)

Orientation: (6 Points)

Method 2 for Dividing the MoCA

[2A] **Executive:** Alternating Trail Making (1 point)

Attention: Forward Digit Span (1 point), Backward Digit Span (1 point), Vigilance (1 point), Serial 7's (3 points)

Memory: Delayed Recall (5 points)

Abstraction: (2 points)

[2B] **Visuospatial:** Cube (1 point) Clock (3 points)

Naming: (3 points)

Language: Sentence Repetition (2 points) and Verbal Fluency (1 point)

Orientation: (6 Points).

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