Increased risk of cognitive impairment in patients with components of metabolic syndrome

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Abstract
The number of old adults with cognitive impairment or dementia is anticipated to increase rapidly due to the aging population, especially the number of patients with multiple chronic conditions or metabolic perturbation. Metabolic syndrome (Mets) is among the most hazardous risk factors for cardiovascular disease and is linked to a chronic inflammatory disease. We investigated the National Health and Nutrition Examination Survey (NHANES) database for the years 1999 to 2002 to explore the connection between Mets and cognitive decline.

A total of 2252 NHANES (1999–2002)-registered individuals who were stroke-free and aged ≥60 years were enrolled in this study. This study surveyed the effects of the existence of diverse characteristics of Mets on the individuals’ cognitive performances as measured with the digit symbol substitution test (DSST).

The individuals with more features of Mets achieved lower DSST scores than those with fewer constituents of Mets ($P < 0.001$ for the trend) after adjustments for covariates. The $\beta$ coefficients for the DSST scores of the participants with 1, 2, 3, and ≥4 features of Mets were $-1.545$, $-3.866$, $-4.763$, and $-5.263$, respectively. Cognitive decline was correlated with each of the constituents of Mets, which included high plasma glucose, elevated blood pressure, abdominal obesity, and decreased high-density lipoprotein cholesterol ($P < 0.05$ for the above factors), with the exception of high triglyceride levels ($P > 0.05$).

Mets was positively associated with cognitive decline in individuals aged ≥60 years. The characteristics of Mets that were most strongly associated with cognitive decline were high plasma glucose and elevated blood pressure.

Abbreviations: DSST = digit symbol substitution test, Mets = metabolic syndrome, NHANES = National Health and Nutrition Examination Survey.

Keywords: cognitive impairment, digit symbol substitution test, metabolic syndrome

1. Introduction
The number of old adults with mild cognition impairment or dementia is anticipated to increase rapidly and become a world health problem due to the aging population.\cite{1} The incidence of mild cognition impairment or dementia has been estimated to be 5% to 20% among people older than 65 years.\cite{2} However, dementia is not an avoidable aspect of aging. The progressive loss of cognitive performance contributes to intellectual, behavioral, and functional declines and an inability to learn. Many types of chronic illness contribute to cognitive impairment, including depression, stroke, cardiovascular disease, and hyperglycemia, via mechanisms such as chronic inflammation, microvascular disease, and abnormal glycation end products.\cite{3–6}

Metabolic syndrome (Mets) includes the most hazardous risk factors for cardiovascular disease and is associated with elevated mortality.\cite{7} Additionally, previous studies have linked Mets to chronic inflammation disease.\cite{8} Although each component of Mets, including impaired glucose metabolism,\cite{9} obesity,\cite{9,10} high blood pressure,\cite{11} and dyslipidemia,\cite{12} has been found to adversely influence cognitive function, few studies have surveyed the comparative significances of these features by means of structural equation modeling. This study aimed to explore the connection between cognition impairment and Mets by investigating the National Health and Nutrition Examination Survey (NHANES) database for the years 1999 to 2002. We theorized that individuals with greater numbers of Mets components would exhibit more severe cognitive decline.

2. Subjects and methods
2.1. Ethics statement
This study was exempt from Institutional Review Board review because we investigated deidentified information from the
NHANES database that had been approved by the National Center for Health Statistics Institutional Review Board.

2.2. Study population
To evaluate the US population demographics, health, and nutrition information, the well-designed cross-sectional NHANES investigation was executed by the Centers for Disease Control and Prevention and the National Center for Health Statistics. The participants’ relevant information, which included demographic information, educational level, medical examination results, and questionnaires regarding medical history, was collected from an initial extensive household interview conducted by a trained examiner. Subsequently, the participants underwent a medical examination at a specifically equipped Mobile Examination Center. The NHANES examinations have been conducted annually since 1999, and the data are released every 2 years. In this study, we used 2 NHANES datasets (1999–2000 and 2001–2002), and all of the thorough study operation guides, consent certificates, relevant information, and brochures were accessible on the NHANES website.\(^\text{[13,14]}\) The population surveyed in the current study included adults aged greater than 60 years. The exclusion criteria included individuals without complete information about laboratory results, clinical examinations, the household interview, or the constituents of Mets and those with a history of stroke.

2.3. Definition of metabolic syndrome
According to the revised National Cholesterol Education Program Adult Treatment Panel III, the diagnosis of Mets was based on the existence of 3 of the following constituents: central obesity, a waist circumference ≥40 inches (≥102 cm) in males or ≥35 inches (≥88 cm) in females; an increased plasma triglyceride level ≥1.69 mmol/L (≥150 mg/dL); a low high-density lipoprotein cholesterol level ≤1.03 mmol/L (≤40 mg/dL) in males or ≤1.29 mmol/L (≤50 mg/dL) in females; elevated blood pressure, systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85 mm Hg, and high fasting plasma glucose, ≥100 mg/dL (≥5.6 mmol/L).\(^\text{[13]}\)

2.4. Cognitive function
The individual’s cognitive performances were evaluated with the digit symbol substitution test (DSST), which is also called the Digit Symbol–Coding module of the Wechsler Adult Intelligence Scale, Third Edition (WAIS III). The DSST is commonly utilized to evaluate frontal lobe-related functions, including visuospatial skills, sustained attention, and motor speed-of-processing.\(^\text{[16,17]}\) Adults 60 years and older underwent the DSST between 1999 and 2002 in the NHANES survey.\(^\text{[13]}\) The participants were asked to accurately code a series of symbols within 2 minutes after a preliminary exercise. The points were calculated according to the numbers of accurately drawn symbols, and the maximum score was 133. The individuals did not finish the whole test if they matched none of the example items in the preliminary practice.

2.5. Covariates
Part of the participants’ relevant information was collected by a computer-assisted personal interviewing method. Demographic information, including age, sex, race, educational level, and medical history, was assembled. Smoking status was determined using a detailed questionnaire. Diabetes was clarified on a self-report of a physician-diagnosis questionnaire as the use of diabetic medications (including insulin injections and oral hypoglycemic agents), a fasting plasma glucose level ≥126 mg/dL, or a random plasma glucose level ≥200 mg/dL. Hypertension was clarified on a self-report of the doctor’s diagnosis as the use of blood pressure-lowering medications or an average BP > 140/90 mm Hg. Gait was evaluated with the 20-foot timed walk test, and the use of a walker or cane was acceptable when necessary.\(^\text{[18]}\) Peripheral insensate neuropathy was defined as one or more impaired sensation at 3 sites on both feet (range: 0–6) as in a previous report.\(^\text{[19]}\) The average peak force was obtained by quantifying the isokinetic strength of the knee extensors (quadriceps) in Newtons according to the NHANES examination protocol.\(^\text{[13,14]}\) Self-reported comorbidities, including stroke and heart disease, were recorded. The existence of heart disease was clarified based on whether the participant had ever been informed of disease or had experienced congestive heart failure, angina, or myocardial infarction. All of the protocols, including the waist circumference measurements, biochemical analyses, and blood pressure recordings, utilized standardized procedures based on the Centers for Disease Control and Prevention guidelines.

2.6. Statistical analyses
SPSS (Version 18.0 for Windows, SPSS, Inc., Chicago, IL) was utilized for all of the statistical analyses. Significant differences were indicated when the 2-sided \(P\) values were less than 0.05. Initially, we used a linear regression model to evaluate the effect of each constituent of Mets on the DSST scores. Furthermore, 3 extended model methods with covariate adjustments were utilized. First, we adjusted for age, gender, educational level, and race/ethnicity in model 1. Second, the factors in model 1 plus the white blood cell count, C-reactive protein, total cholesterol, serum folate, and vitamin B12 were adjusted for in model 2. Third, the factors in model 2 plus the histories of angina/angina pectoris, coronary heart disease, and malignancy were further adjusted for in model 3. Fourth, the factors in model 3 plus peripheral insensate neuropathy, the 20-foot timed walk test, and the average peak force were adjusted for in model 4. To evaluate the effects of the existence of increasing numbers of Mets constituents on the declines in the DSST scores, continuous variables representing the Mets constituents and ranging from 1 to 4 were created to allow for the calculation of the \(P\)-values for the trends.

3. Results

3.1. Demographics of the study population
The study population was composed of 2252 stroke-free participants including 952 with Mets and 1300 without Mets. The study population clinical features were categorized according to the presence of Mets as presented in Table 1.

3.2. Correlations between metabolic syndrome constituents and cognition decline
The outcomes of the applications of the models that tested the effects of the increasing numbers of Mets constituents on DSST are illustrated in Table 2. There was a significant linear decrease in the DSST score with increasing numbers of Mets constituents. After further covariate adjustment in Model 4, the \(\beta\) coefficients
of the DSST scores of the participants with 1, 2, 3, and ≥4 features of Mets were 1.545, 3.866, 4.763, and 5.263, respectively (P values for the trends <0.001). An elevated plasma glucose level, high blood pressure, and abdominal obesity but not low high-density lipoprotein cholesterol or hypertriglyceridemia were significantly and negatively correlated with the DSST scores in the fully adjusted models (P <0.05). Moreover, a high glucose level had the strongest effect on the severity of the cognitive decline, and high blood pressure was the 2nd-most significant feature that was associated with cognitive impairment.

4. Discussion

By investigating a symbolic sample of the US population record, this study examined the effects of the presence of different numbers of Mets components on cognitive performance as measured with the DSST. We noted an adverse relationship between the DSST scores and increasing numbers of Mets constituents. Remarkably, a high glucose level and high blood pressure elicited stronger effects on the severity of cognitive decline than the other Mets constituents.

A high glucose level or insulin resistance is connected with an elevated risk of cognitive impairment through various mechanisms. Insulin plays a crucial role in glucose homeostasis by governing the equilibrium between glucose production by the liver and glucose uptake by the target tissues, which include neurons, muscles, and adipocytes. Insulin resistance is commonly defined by target tissues are unable to successfully and satisfactorily react to biological insulin levels. The brain is a high-energy consumption organ; thus, insulin receptors are extensively expressed in the brain, particularly in memory registration-related areas, such as the cerebral cortex, hippocampus, hypothalamus, and amygdala. Furthermore, neurons exhibit denser insulin receptor expression than glial cells, and this expression is particularly high in postsynaptic densities. Defective insulin signaling in the brain caused by reduced insulin receptor substrate expression and the glycation of vital functional and structural proteins promotes the dysfunction of neurons because neurons are highly susceptible to metabolic stress. Moreover, a recent human study that included 186 late middle-aged adults demonstrated that increased insulin resistance severity is correlated with elevated amyloid accumulation in

Table 1

Characteristics of the participants with and without metabolic syndrome.

| Continuous variables, mean (SD) | Nonmetabolic syndrome N = 1300 | Metabolic syndrome N = 952 | P       |
|--------------------------------|--------------------------------|---------------------------|---------|
| Age, years                     | 70.88 (7.687)                  | 70.66 (7.622)             | 0.48    |
| BMI, kg/m²                     | 26.50 (4.77)                   | 30.40 (6.08)              | <0.001  |
| SBP, mmHg                      | 138.96 (23.46)                 | 147.76 (22.12)            | <0.001  |
| DBP, mmHg                      | 69.91 (15.89)                  | 70.53 (16.57)             | 0.396   |
| Waist circumference, cm        | 95.35 (12.55)                  | 105.64 (12.08)            | <0.001  |
| Serum triglycerides, mg/dL     | 58.10 (16.51)                  | 45.35 (13.37)             | <0.001  |
| Serum glucose, mg/dL           | 95.40 (24.74)                  | 119.64 (48.83)            | <0.001  |
| C-reactive protein, mg/dL      | 0.51 (1.05)                    | 0.56 (0.9)                | 0.33    |
| Cholesterol, total, mmol/L     | 5.31 (0.96)                    | 5.44 (1.12)               | 0.002   |
| White blood cell count, SI     | 6.79 (2.01)                    | 7.36 (1.87)               | <0.001  |
| Folate, serum, ng/mL           | 18.55 (10.94)                  | 18.34 (12.83)             | 0.687   |
| Vitamin B12, serum, pg/mL      | 555.00 (341.11)                | 534.35 (602.22)           | 0.273   |
| Time to complete the 20-foot walk, seconds | 6.92 (3.15) | 7.26 (2.78) | 0.009 |
| Average quadriceps peak force, Newtons | 257.05 (89.58) | 252.99 (89.33) | 0.350 |

| Categorical variables, n, %    | Nonmetabolic syndrome N = 1300 | Metabolic syndrome N = 952 | P       |
|--------------------------------|--------------------------------|---------------------------|---------|
| Male                           | 702 (54)                       | 405 (42.5)                | <0.001  |
| Education higher than high school | 518 (39.9) | 308 (32.4) | <0.001 |
| Race                           |                                |                           |         |
| Mexican American               | 218 (9.7)                      | 229 (10.2)                | <0.001  |
| Non-Hispanic White             | 817 (36.3)                     | 558 (24.8)                |         |
| Non-Hispanic Black             | 190 (8.4)                      | 106 (4.7)                 |         |
| Other Hispanic                 | 45 (2.0)                       | 45 (2.0)                  |         |
| Other Race                     | 30 (1.3)                       | 14 (0.6)                  |         |
| Past history                   |                                |                           |         |
| Angina/angina pectoris         | 95 (4.2)                       | 105 (4.7)                 | 0.235   |
| Heart attack                   | 63 (3.7)                       | 106 (4.7)                 | 0.451   |
| Malignancy                     | 148 (6.6)                      | 248 (11)                  | 0.092   |
| Peripheral insensate neuropathy | 269 (22)   | 186 (21.1)                | 0.629   |
| Congestive heart failure       | 8 (0.6)                        | 8 (0.8)                   | 0.312   |
| Type 2 diabetes mellitus       | 52 (4)                         | 229 (24.1)                | <0.001  |
| Dyslipidemia                   | 94 (15.7)                      | 71 (16.4)                 | 0.796   |
| Hypertension                   | 457 (38.9)                     | 502 (69.5)                | <0.001  |
| Prescription medicine taken    |                                |                           |         |
| Antihypertensive agents        | 414 (31.8)                     | 375 (39.4)                | <0.001  |
| Antihyperlipidemic agents      | 80 (6.2)                       | 62 (6.5)                  | 0.727   |
| Antidiabetic agents            | 22 (1.7)                       | 44 (4.6)                  | <0.001  |

BMI = body mass index, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, SBP = systolic blood pressure, SD = standard deviation, WBC = white blood cell.
| Variables         | Model 1 | Model 2 | Model 3 | Model 4 |
|------------------|---------|---------|---------|---------|
| Presence of metabolic syndrome | 1.286 (1.893, 0.829) | 0.001 | 1.345 (1.953, 0.737) | 0.001 |
| P < | 0.001 | 0.001 | 0.001 | 0.001 |
| Presence of metabolic syndrome | 5.763 (8.574, 2.348) | 0.001 | 5.461 (8.390, 1.712) | 0.001 |
| P < | 0.001 | 0.001 | 0.001 | 0.001 |
| High blood pressure | 1.469 (1.712, 1.452) | 0.881 | 1.493 (1.977, 1.294) | 0.682 |
| P < | 0.001 | 0.001 | 0.001 | 0.001 |
| Low HDL-C | 1.545 (4.442, 1.452) | 0.312 | 1.523 (3.170, 1.294) | 0.071 |
| P < | 0.001 | 0.001 | 0.001 | 0.001 |
| Adjusted covariates: Model 1 = age, gender, educational level, and non-Hispanic white race. Model 2 = Model 1 + (peripheral insensate neuropathy, 20-foot timed walk test, average quadriceps peak force). Model 3 = Model 2 + (digit symbol substitution test, HDL-C). Model 4 = Model 3 + (blood cultures, an SPSA model) | 0.025 | 0.024 | 0.025 | 0.024 |
| P < | 0.001 | 0.001 | 0.001 | 0.001 |

5. Conclusion

Our findings revealed that the presence of greater numbers of Mets components is prominently correlated with cognitive decline in the US adult population. Further studies are needed to determine whether the early detection of and interventions for Mets can decrease the risk of developing cognitive impairment.
Moreover, the results of this study highlight the importance and urgency of comprehensive management strategies for Mets. Recognizing and reducing the components of Mets may be helpful to preventing or delaying cognitive decline.

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