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Insulin resistance and cognitive test performance in elderly adults: National health and nutrition examination survey (NHANES)

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ABSTRACT

Objectives: To examine the relationship between homeostatic model of insulin resistance (HOMA-IR) and cognitive test performance among population ≥ 60 years in a national database.
Hypothesis: Higher insulin resistance is associated with lower cognitive test performance score in the population ≥ 60 years.
Participants: We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 and 2001–2002.
Measurements: Cognitive test performance was measured by the Digit Symbol Substitution (DSS) exercise score. The main independent variable was the homeostasis model assessment of insulin resistance (HOMA-IR). We used bivariate analysis and generalized linear model adjusting for age, gender, race, education, body mass index, and systolic and diastolic blood pressures; total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride levels; and physical activity, diabetes mellitus, stroke, and congestive heart failure. STATA 14 was used to analyze the data taking into consideration the design, strata and weight.
Results: Of the 1028 participants, 44% were male and 85% were white. The mean age was 70.0 ± 0.28 (SE) years. Their average HOMA-IR was 3.6 ± 0.14 and they had a mean of 49.2 ± 0.8 correct DSS score in the cognitive test. Adjusting for the confounding variables, HOMA-IR was associated with decline in DSS score (B = −0.30, 95% confidence interval = −0.54 and −0.05, p = 0.01). The model explained 44% of the variability of the DSS score (R^2 = 0.44). Significant predictors of decline in DSS score were age, gender, race, and education (p = 0.01).
Conclusion: Insulin resistance as measured by HOMA-IR was independently associated with lower cognitive test performance score among elderly participants aged ≥ 60 years. Longitudinal studies are needed to test the mechanism and the causal relationship.

1. Introduction

Accelerated age-related cognitive decline leading to dementia poses a major problem to our health care system. The number of dementia cases is rising alarmingly worldwide [1–3], especially Alzheimer's disease dementia (ADd) and vascular dementia (VaD), which account for about 70% and 17% of U.S. dementia cases, respectively [4]. In the continuing absence of clinically effective treatments, the number of ADd cases alone is expected to rise in the U.S. from 1.5 million today to 13.8 million by 2050 [5]. The annual healthcare costs for dementia cases by 2050 are expected to reach an unsustainable $1.1 trillion without inflation [6].

Seeking a modifiable risk factor behind this health care crisis, much attention has been given to the metabolic syndrome. This syndrome, which can be alleviated by diet and exercise [7–9], is a cluster of cardiovascular and type 2 diabetes (T2D) risk factors diagnosed by the presence of 3 out of 5 conditions (abdominal obesity, elevated triglycerides, reduced high-density lipoprotein [HDL] cholesterol, elevated blood pressure, and elevated fasting glucose) [10,11]. It has been argued that the metabolic syndrome can promote cognitive decline and ADd risk [12,13]. This hypothesis is nevertheless controversial given conflicting evidence on the association of the metabolic syndrome with cognitive decline [13–15] and AD risk [16,17]. Indeed, a meta-analysis of cognitive studies through 2013 found that the metabolic syndrome

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has only a marginally negative effect (p = 0.05) on cognition in those less than ≤70 years old and no effect on those > 70 years old [17]. Moreover, while the metabolic syndrome is consistently associated with VaD [14,15], that is not the case for ADd [18,19]. For those ≥75 years old, the metabolic syndrome may actually lower risk of cognitive decline [16,17] and ADd [20,21].

The degree to which the metabolic syndrome promotes cognitive decline and AD risk is thus unclear. Yet one of the metabolic syndrome's most common (albeit non-obligatory) features, peripheral (systemic) insulin resistance, does appear to accelerate cognitive decline and increase AD risk [22,23]. As assessed by glucose tolerance tests or the homeostasis model assessment of insulin resistance (HOMA-IR), peripheral insulin resistance is often associated with cognitive decline in healthy middle aged and elderly individuals [24–29] and in mild cognitive impairment (MCI) cases [30], accelerated conversion of MCI to ADd [31], ADd pathology [32], and elevated risk for ADd [33,34] and probably VaD [35].

Peripheral insulin resistance is of special interest in understanding and treating cognitive decline since it can induce brain insulin resistance [36,37] and can be reduced with diet [38–45] and exercise [46,47]. Consequently, elevated peripheral insulin resistance occurring with advanced aging may explain development of brain insulin resistance seen with advanced aging [48–51] and ADd [52]. Cognitive decline in the elderly may thus be due in part to peripherally induced brain insulin resistance [53]. This hypothesis is consistent with studies reporting that HOMA-IR is negatively associated with cognitive function in middle aged and elderly humans even in the absence of diabetes [24-28]. Yet the most recent study on middle-aged people without diabetes found no more than a marginal association of HOMA-IR with cognition [54,55]. We consequently reassessed this association in late middle-aged and elderly non-diabetics in the database of the National Health and Nutrition Examination Survey (NHANES: http://www.cdc.gov/nchs/nhanes.htm). Such a reassessment benefits not only from the scale of the database, but from the fact that it is compiled from a nationally representative sampling of non-institutionalized residents of the U.S. [56].

Table 1
NHANES 1999–2002 Population Characteristics (N = 1028).

Variable	Number (weighted %)	Weighted Mean (SE)
Age (years)		70.0 (0.28)
Sex		
Male	508 (44.4)	
Female	520 (55.6)	
Race/ethnicity		
Caucasian/non-Hispanic	629 (84.7)	
African-American	130 (5.6)	
Hispanic-American	250 (7.4)	
Other	19 (2.4)	
Highest level of education		
Grade school	377 (25.3)	
High school	235 (28.9)	
College	416 (45.8)	
Physical activity level		
Low	495 (43.2)	
Moderate or high	533 (56.9)	
Body mass index		
$< 30\ kg/m^2$	733 (70.7)	
$\geq 30\ kg/m^2$	295 (29.3)	
Blood pressure		
Systolic (mm Hg)		137.8 (0.9)
Diastolic (mm Hg)		68.7 (0.7)
Lipid levels		
Total cholesterol (mg/dl)		212.4 (1.6)
Low density lipoprotein (LDL, mg/dl)		128.2 (1.5)
High density lipoprotein (HDL, mg/dl)		54.8 (0.7)
Triglycerides (mg/dl)		147.1 (2.0)
HOMA-IR		3.6 (0.14)
DSS score		49.2 (0.78)
Comorbid conditions		
Congestive heart failure	47 (4.5)	
No congestive heart failure	981 (95.5)	
Diabetes	198 (16.5)	
No diabetes	830 (83.5)	
Stroke	52 (5.1)	
No stroke	976 (94.9)	

2. Methods

2.1. Study population

Since 1999, NHANES has been conducted every two years on a random and representative sample of U.S. households. People are selected to participate based on gender, race/ethnicity, age, and place of residence. We combined data from the 1999–2000 and 2001–2002 study cycles, because these cycles collected data on both HOMA-IR and cognition. Judging from the measure of cognition used by NHANES, the Digit Symbol Substitution (DDS) subtest of the Wechsler Adult Intelligence Scale, 3rd edition, the subjects were cognitively normal for their age as explained in the Results. In these two study cycles, HOMA-IR and cognition were both tested in 508 males and 520 females ≥ 60 years old (mean ± SE = 70 ± 0.28 years). Subjects with diabetes were not excluded. It is unknown if any of the subjects suffered from depression, because such data were not collected on individuals 60 years or older by NHANES before 2005. It is also unknown if any of the subjects suffered from mild cognitive impairment (MCI) or ADd, but the latter are probably few given that NHANES subjects are not institutionalized and the mean DDS scores were normal as noted above. Table 1 characterizes the 1028 individuals in our study population, which is summarized in the Results.

2.2. Insulin resistance testing

As indicated above, HOMA-IR was used as a measure of peripheral insulin resistance. This is calculated from fasting plasma levels of glucose (FPG) and fasting serum levels of insulin (FSI) [57]. FPG was measured in the morning after an 8–24 h fast using the hexokinase enzymatic reference method (Roche Diagnostics, Indianapolis, IN). FIS was measured in the same blood samples by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). All measurements were performed at the University of Missouri-Columbia School of Medicine Department of Child Health, Diabetes Reference Laboratory, Columbia, MO, David Goldstein, M.D., Director. HOMA-IR was calculated as follows: ([FPG (mmol/L) × FIS (μU/ml)]/22.5) [57].

While the validity of HOMA-IR as a surrogate measure of peripheral insulin sensitivity has been questioned recently given its failure to correlate with diet-induced insulin sensitivity in dogs [58] and its erroneous prediction of differences in insulin sensitivity between non-diabetic African and European Americans [59], virtually all clinical studies report a significant correlation of HOMA-IR (or the similarly derived QUICKI index) with insulin sensitivity directly measured with the euglycemic - hyperinsulinemic clamp technique in normal, pre-diabetic, and diabetic cases of various ethnicities [60–63].

2.3. Cognitive function testing

As noted above, the DSS subtest of the Wechsler Adult Intelligence Scale, 3rd edition was used to measure cognitive test performance [64]. As detailed online (https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/CFQ.htm and www.nber.org/nhanes/2001_2002/downloads/cfq_b_doc.pdf), this test presents subjects with a page at the top of which are a series of digits in two rows; each digit is paired with a simple graphic symbol below it. The bottom of the page also has two rows of the same digits ordered randomly, but with no symbols below them.

Using the digit-symbol code shown in the two rows at the top of the page, subjects are asked to draw the correct symbol below each unpaired digit in the bottom two rows. After a practice test to ensure that each subject understands the instructions, a test is run to determine how many correct symbols are drawn under each digit within 120 s.

3. Demographic and health-related variables

Potential confounding factors include age; gender; race (Caucasian, African-American, Hispanics, and others); education (less than high school, high school, and college); body mass index; systolic and diastolic blood pressures (mm Hg); total cholesterol, serum low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride levels; and diabetes, stroke, and congestive heart failure (yes/no). Descriptions of the survey, sampling procedures, and details of the laboratory tests evaluated can be found on the CDC website (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman).

3.1. Statistical analysis

Descriptive statistics was used to characterize the subjects (weighted mean ± SE for continuous variables, and number and percent for categorical variables). To test the statistical differences in the DSS score among the population characteristics subgroups, *t*-test and analysis of variance (ANOVA) were used and $p < 0.05$ was considered statistically significant. To test the correlation between cognitive test performance score and HOMA-IR, we used Pearson correlation and p value < 0.05 was considered statistically significant.

A generalized linear model (GLM) [65,66] was used to examined independent association between the DSS score and HOMA-IR adjusting for the potential confounding effects of age, gender, race/ethnicity, education, physical activity, body mass index (BMI), blood pressure (systolic and diastolic), triglycerides, cholesterol, diabetes, stroke, and congestive heart failure. We estimated the adjusted regression coefficient (β) and 95% confidence intervals (CI) of the DSS score and $p < 0.05$ was considered statistically significant.

All analyses were performed using STATA software version 14 (StataCorp, College Station, TX) and adjusted for the survey design using the SVY procedure. Sample weights were included in all the analyses as recommended by NCHS guidelines. Sample weights provided by the National Center for Health Statistics (NCHS), were used to correct for differential selection probabilities and to adjust for noncoverage and nonresponse. All coefficients and variance estimates are from weighted analyses.

4. Results

The characteristics of our study population are listed in Table 1. The 1028 individuals in the population had a mean age of 70 ± 0.28 [SE] years with 44.4% males and 55.6% females. They were predominantly Caucasians of non-Hispanic origin (84.7%) without a history of diabetes (83.5%), stroke (94.9%), or congestive heart failure (95.5%). Most (70.7%) were not obese (body mass index [BMI] < 30 kg/m^2). As the low frequency of diabetes and obesity predict, the mean HOMA-IR score was low (3.6 ± 0.14 [SE]). About half the study population had some college education (45.8%) and were physically active (56.9%). Mean systolic blood pressure (137.8 mm Hg) was pre-hypertensive, but mean diastolic blood pressure was normal. Mean levels of triglycerides and of both low and high-density lipoprotein (LDL and HDL) cholesterol were also normal. Mean total cholesterol (212.4 mg/dl) was borderline high.

On average, the study participants had a DSS score of 49.2 ± 0.78 (SE), which is close to the mean DSS score of all NHANES 1999–2002 subjects 60–63 years old [67] and to normal subjects 60–79 in other studies (Salthouse, 1992; Hoyer et al., 2004). The DDS scores were negatively correlated with age ($r = -0.25$, $p = 0.001$) and systolic blood pressure ($r = -0.15$, $p = 0.001$), but positively correlated with diastolic blood pressure ($r = 0.10$, $p = 0.01$), total cholesterol ($r = 0.07$, $p = 0.02$), and HDL ($r = 0.10$, $p = 0.0003$) (Table 2).

Table 2
Correlation of DSS Score with HOMA-IR, Age, Blood Pressure, and Lipid Levels (N = 1028).

Variable	Correlation coefficient (r)	p-Value
Age (years)	−0.25	0.001
HOMA-IR	−0.03	0.300
Systolic blood pressure	−0.15	0.001
Diastolic blood pressure	0.10	0.011
Total cholesterol (mg/dl)	0.07	0.020
Low density lipoprotein (LDL, mg/dl)	0.02	0.554
High density lipoprotein (HDL, mg/dl)	0.10	0.003
Triglycerides (mg/dl)	0.03	0.252

Table 3
NHANES 1999–2002 DSS Score by Population Characteristics and Comorbidity (N = 1028).

Variable	Weighted mean of DSS score	Linearized SE	p-Value
Sex			
Male	48.0	0.9	0.08
Female	50.2	1.1	N
Race/ethnicity			
Caucasian/non-Hispanic	51.7	0.8	0.001
African-American	34.5	1.8	
Hispanic-American	33.7	1.6	
Other	43.5	7.6	
Highest level of education			
Grade school	35.9	1.4	0.001
High school	50.3	1.1	
College	55.9	0.8	
Physical activity level			
Low	44.9	1.2	
Moderate or high	52.8	1.0	0.0002
Body mass index			
< 30 kg/m^2	48.2	1.1	
≥ 30 kg/m^2	51.8	1.1	0.04
Comorbid conditions			
Congestive heart failure	38.2	1.8	0.001
No congestive heart failure	49.7	0.8	
Diabetes	45.1	1.7	0.02
No diabetes	50.0	0.9	
Stroke	38.8	2.3	0.001
No stroke	49.8	0.7	

Results of bivariate analyses (Table 3) showed statistically significant associations of DSS scores with race/ethnicity, education level, physical activity level, obesity, and several co-morbidities (diabetes, stroke, and congestive heart failure). Caucasian/non-Hispanic participants had a higher mean DSS scores than other racial/ethnic groups ($p = 0.001$). Participants with higher levels of education had a higher mean DSS score than those with less education ($p = 0.001$). Physically active participants had a higher mean DSS score than those who were not physically active ($p = 0.0002$). Non-obese participants had lower DSS score compared to obese participants ($p = 0.04$). Participants with one of the studied comorbid conditions had lower mean DSS scores than those who did not have these comorbidities, specifically diabetes ($p = 0.02$), stroke ($p = 0.001$), or congestive heart failure ($p = 0.001$).

The multivariate analyses shown in Table 4 demonstrated that HOMA-IR was associated with a reduction in DSS score after controlling for all the confounding variables studied (age, gender, race/ethnicity, education, physical activity, body mass index (BMI), blood pressure, triglycerides, cholesterol, diabetes, stroke, and congestive heart failure) (adjusted $\beta = -0.30$, 95% confidence interval [CI]: -0.54 to -0.05, $p = 0.02$). This generalized linear model explains 44% of the variability in the DSS scores ($R^2 = 0.44$).

Table 4
Multivariate analysis of NHANES 1999–2002 DSS scores and HOMA-IR adjusting for the demographics, lipid levels, blood pressure, and comorbid conditions (N = 1028).

Dependent variable = DSS score	Adjusted β	Linearized SE	*t*-Value	p-Value	95% Confidence Interval	
Homa-IR	− 0.30	0.12	− 2.49	0.019	− 0.54	− 0.05
Age	− 0.86	0.07	13.17	0.001	− 0.99	− 0.72
Sex						
Male	(Reference)					
Female	5.27	1.33	3.959533	0.001	2.55	8.00.00
Race/ethnicity						
Caucasian/non-Hispanic	(Reference)					
African-American	− 16.03	1.42	11.27	0.001	− 18.94	− 13.12
Hispanic-American	− 11.89	1.64	− 7.24	0.001	− 15.24	− 8.53
Other	− 9.83	5.35	− 1.84	0.077	− 20.78	1.12
Highest level of education						
Grade school	(Reference)					
High school	9.57	1.44	6.64	0.001	6.62	12.51
College	15.74	1.20	13.15	0.001	13.29	18.19
Physical activity level						
Low	− 2.11	1.31	− 1.61	0.118	− 4.77	0.56
Moderate or high	(Reference)					
Body mass index						
$< 30\ kg/m^2$	− 0.80	1.29	− 0.62	0.541	− 3.44	1.84
$\geq 30\ kg/m^2$	(Reference)					
Blood pressure						
Systolic	− 0.04	0.02	− 1.73	0.094	− 0.08	0.01
Diastolic	0.06	0.03	1.88	0.070	0.00	0.12
Lipid levels						
Total cholesterol	− 0.27	1.80	− 0.15	0.881	− 3.96	3.41
LDL	0.28	1.80	0.16	0.875	− 3.39	3.96
HDL	0.26	1.80	0.14	0.886	− 3.42	3.94
Triglycerides	0.06	0.36	0.17	0.868	− 0.67	0.79
Comorbid conditions						
Congestive heart failure	(Reference)					
No congestive heart failure	3.03	1.83	1.65	0.109	− 0.72	6.77
Diabetes	(Reference)					
No diabetes	1.84	1.34	1.37	0.180	− 0.90	4.58
Stroke	(Reference)					
No stroke	4.19	2.35	1.79	0.084	− 0.60	8.99

Additional factors that were significantly associated with lower DSS score were male gender (relative to female); African-American, or Hispanic-American (relative to whites); and lower educational levels (relative to high education level) (p = 0.01) (Table 4).

5. Discussion

Our study of the NHANES 1999–2000 and 2001–2012 data base supports previous reports that insulin resistance, as measured by HOMA-IR, is inversely associated with cognitive function in the elderly [24,25,30,38,39] While NHANES 1999–2000 and 2001–2002 employed the DSS test as the only measure of cognitive function, this is an especially sensitive measure of cognitive decline in those not showing clinical levels of such decline [68,69] and is thought to assess multiple cognitive domains, including perceptual speed [70], memory [71], and attention [72,73] irrespective of age. Moreover, in the elderly, declining DSS scores have been found to predict progression to dementia [74].

Since the vast majority of the study population (83.5%) lacked a history of diabetes, the observed association of peripheral insulin resistance and cognitive impairment is not due to hyperglycemia and not partially masked by antidiabetic medication. It also does not appear to be the result of the temporal lobe atrophy with which peripheral insulin resistance is associated in late middle age and elderly non-diabetics, because such atrophy is not directly related to the cognitive decline seen in such individuals [24,25]. That may be a product of the previously noted ability of peripheral insulin resistance to induce brain insulin resistance, which necessarily interferes with insulin's roles in neuronal function [75].

The ability of peripheral insulin resistance to induce brain insulin resistance has been shown repeatedly in rodents made insulin resistant by high fat and/or high sugar diets[53–59,76]. This phenomenon has been studied most extensively with high fat diets, which produce peripheral insulin resistance via an early rise in fatty acids and later by more widespread elevations in proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha (TNFα) [77]. Crossing the blood-brain barrier [78], such cytokines can stimulate neuronal cytokine receptors, which activate enzymes that serine phosphorylate insulin receptor substrate-1 (IRS-1) and thereby impair insulin signaling [79]. Peripheral insulin resistance could also impair insulin's brain functions in at least two other ways. One is by decreasing brain uptake of plasma insulin as observed in a study of CSF insulin in high fat diet-induced obesity [80]. The other is by decreasing clearance of brain Aβ. This is suggested by the finding that insulin facilitates hepatic clearance of plasma Aβ [81], interference with which impairs brain clearance of that peptide [82]. Indeed, high fat diets are often found to raise levels of Aβ in animal models of AD [83,84].

The association of peripheral insulin resistance with cognitive decline in diabetes could be due not only to the mechanisms just described for non-diabetics, but also to the deleterious effects of hyperglycemia on brain function. These include cellular toxicity [85], microglial activation [86], and disrupted metabolic homeostasis and plasticity [87,88] in the brain. Their contribution to cognitive decline is difficult to study in the NHANES database, however, because the antidiabetics taken by most diabetics could mask the effect of residual hyperglycemia on cognition [89].

5.1. Limitations of the study

While we have established an association between insulin resistance and cognitive decline in the elderly adult, we are unable to establish a causal relationship between the two due to the cross-sectional nature of the study. It is conceivable that cognitive decline may lead to changes in diabetes management and other modifiable preventive mechanisms, such as dietary decision-making. This study is further limited by reliance on one measure of cognition (DSS) utilized in NHANES and by constraints inherent in that measure. For instance, it is possible that differences in test understanding or testing conditions, rather than true differences in global cognition may be responsible for differences in test scores. We did not adjust for apolipoprotein (APOE) genotyping, as these data was not recorded in the database. AD patients carrying a copy of the e4 allele do not appear to benefit cognitively from intranasal insulin, whereas those without a copy do [90,91]. Despite the limitations of this study, our findings from a nationally representative database further strengthen the association between insulin resistance and cognitive test performance.

In conclusion, our results demonstrate an independent association between insulin resistance and lower cognitive state in a nationwide population. Given that poor late-life cognitive state has been associated with progression to dementia, it is imperative to further investigate the exact mechanisms, and possible intervention of such comorbidities.

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