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Previous Hepatitis A Virus Infection Is Related to Slower Psychomotor Speed in Elderly Adults

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Background. Patients with chronic viral hepatitis are at a higher risk for cognitive dysfunction. Little is known about the association between hepatitis A virus (HAV) infection and cognitive function.

Methods. From the National Health and Nutrition Examination Survey, 1999–2002, we selected study participants (≥60 years, $n = 1,529$) without hepatitis B, C, or D virus infection; without previous hepatitis A vaccination; and without abnormal liver function. HAV-seropositive participants represented people with previous HAV infection. Psychomotor speed and executive functioning domain of cognitive function were measured by the Digit Symbol Substitution Test (DSST).

Results. HAV-seropositive participants had lower DSST scores than HAV-seronegative participants (weighted mean, 44.4 vs 53.9, $p < .001$). We designated HAV-seronegative participants as the reference group. Univariate analysis demonstrated that the weighted β coefficient of DSST score was −9.55 (95% confidence interval [CI] −9.57 to −9.54, $p < .001$) for the HAV-seropositive participants. In a multivariable model, the weighted adjusted β coefficient of DSST score was −2.48 (95% CI −2.49 to −2.46, $p < .001$) for the HAV-seropositive participants.

Conclusion. HAV seropositivity is associated with slower psychomotor speed among the U.S. community-dwelling elders.

Key Words: Hepatitis A—Neuropsychological tests—Cross-sectional studies—National Health and Nutrition Examination Survey.

HEPATITIS viruses primarily target the liver, but extrahepatic manifestations such as glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, pancreatitis, diabetes mellitus, and thrombocytopenia have also been reported (1–3). Neurological involvements of hepatitis virus infection include mononeuritis, mononeuritis multiplex, Guillain–Barré syndrome, postviral encephalitis, transverse myelitis, or seizure (1,4,5). Owing to a diversity of clinical manifestations, hepatitis virus infection should be considered as a systemic disease (1).

Several lines of evidence indicated that the patients who suffered from liver diseases often demonstrated some form of neuropsychological consequences (6,7). Published experimental results from neuropsychological tests, magnetic resonance spectroscopy, electroencephalogram, and P300 event–related potentials support the presence of cognitive dysfunction in patients infected with hepatitis C virus (HCV) (8–10). Karaivazoglou and colleagues (11) reported that patients infected with hepatitis C and hepatitis B virus were similarly impaired in cognitive function. Nevertheless, as of today, the association between hepatitis A virus (HAV) infection and cognitive function has not been examined.

Although HAV infection is typically self-limited, patients sometimes develop neurological complications, like seizure or encephalitis (4,12,13), or chronic systematic sequelae, such as diabetes or atherosclerosis (2,3,14,15). Given these co-occurred complications were also known as risk factors for cognitive dysfunction (16–18), we hypothesized that HAV infection might play a role in the deterioration of cognitive function. We tested the hypothesis by analyzing data from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2002.

Methods

Study Design and Population

The NHANES is a population-based survey designed to collect information on the health and nutrition of the U.S. household population. The NHANES used a stratified and

cluster sampling design to obtain a representative sample of the noninstitutionalized civilian U.S. population. Detailed survey operations manuals, consent documents, and brochures of the NHANES 1999–2002 are available in the NHANES Web site (19,20).

Psychomotor speed and executive functioning domain of cognitive function were assessed in the NHANES participants aged 60 years and older using the Digit Symbol Substitution Test (DSST). Among the 2,975 participants who completed the DSST, we excluded 223 people with hepatitis B, C, or D virus infection; 175 people with previous HAV vaccination; and 880 people with missing study parameters. We also excluded 168 persons who had abnormal liver function tests so that HAV-seropositive participants represented people with previous HAV infection. Those with nonmissing values tended to perform better in the DSST (43.2 vs 38.3 points), be younger (71.4 vs 72.7 years), be non-Hispanic white (64.3% vs 57.7%), have higher education level, and have higher annual family income. Thus, the analytic sample consisted of 1,529 participants with complete information on the DSST, HAV marker, and covariates required for analyses.

Cognitive Function

The DSST, a component of the Wechsler Adult Intelligence Test (21) and a test of visuospatial and motor speed of processing, has a considerable executive function component and is frequently used as a sensitive measure of frontal lobe executive functions (22,23). Participants were asked to copy symbols that were paired with numbers within 2 minutes. Following the standard scoring method, one point is given for each correctly drawn symbol. The maximum score is 133. Other cognitive domains such as short-term memory, long-term memory, and verbal ability were not assessed in the NHANES 1999–2002.

HAV Marker

Hepatitis A antibody was measured using enzyme immunoassay, and the results were expressed as "positive" or "negative." The assay used in this measurement cannot differentiate between natural infection and vaccination. Therefore, seropositivity for hepatitis A antibody reflects either natural or vaccine-induced immunity.

Covariates

Age, gender, race, educational level, and annual family income were obtained from self-report. Diabetes mellitus was defined by a self-report doctor's diagnosis, the presence of a fasting glucose level of 126 mg/dL or greater, the presence of a random glucose level of 200 mg/dL or greater, or the use of diabetic medications (insulin or oral antidiabetic agents). The presence of hypertension was defined by a self-report of the doctor's diagnosis, the use of antihypertensive medications, or an average blood pressure of 140/90 mmHg or higher. Other comorbidities including stroke, myocardial infarction, coronary heart disease, congestive heart failure, angina, asthma, chronic bronchitis, and emphysema were ascertained by self-report. Cardiovascular disease was defined if participants had stroke, myocardial infarction, angina, coronary heart disease, or congestive heart failure, whereas lung disease was defined if participants had asthma, chronic bronchitis, or emphysema. Kidney disease was defined by a history of kidney problem or hemodialysis, an estimated creatinine clearance of less than 60 mL/min (using the Modification of Diet in Renal Disease formula), or the presence of microalbuminuria (spot urine microalbumin to creatinine ratio $\geq$30 mg/g). Thyroid dysfunction was defined by current use of thyroid medications (thyroid hormone or antithyroid agents) or abnormal thyroxine level (T4 < 5.4 or T4 > 12.8 μg/dL). Body mass index (BMI) was calculated as weight (kg) divided by height square (m^2). Plasma homocysteine was measured by an automated fluorescence polarization immunoassay method with the Abbott IMX system and the Abbott Axsym system (Abbott Diagnostics, Abbott Park, IL). Serum vitamin B_{12} and red blood cell folate levels were measured using the Bio-Rad Laboratories folate/vitamin B_{12} radioassay kit (Bio-Rad Laboratories, Hercules, CA). C-reactive protein (CRP) was quantified by latex-enhanced nephelometry with a Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics, Inc., Somerville, NJ). Plasma fibrinogen concentration was determined by the Clauss clotting method with an STA Compact Analyzer (Diagnostica Stago, Parsippany, NJ). Total cholesterol, serum thyroxine level, alanine aminotransferase, aspartate aminotransferase, and uric acid were measured with Hitachi analyzers (Roche Diagnostics, Indianapolis, IN). The participants were identified to have recent exercise hobby if they did moderate or vigorous activities for at least 10 minutes in leisure time or muscle-strengthening activities over past 30 days. Current smoker was determined by plasma cotinine level of 14 ng/mL or greater. Alcohol intake was determined by asking "In any 1 year, have you had at least 12 drinks of any type of alcohol beverage?" and was dichotomized.

Statistical Analysis

Study participants were classified into two groups based on HAV immunoglobulin G (IgG) status: HAV IgG (+), seropositive HAV indicating past HAV infection, and HAV IgG (−), seronegative HAV indicating no past HAV infection.

Baseline differences between the two groups were determined by Student's *t* test (for continuous variables) and chi-square test (for categorical variables). Right-skewed continuous variables including folate, vitamin B_{12}, CRP, and homocysteine were log transformed before Student's *t* test was performed. With seronegative HAV participants as the reference group, differences of DSST score (β coefficients)

Table 1. Characteristics of the Study Population (weighted samples)

Characteristics	No. (%)*			*p* Value†
	Total	HAV IgG (+)	HAV IgG (−)	
No. (% of total population), million	23.3 (100.0)	14.2 (61.0)	9.1 (39.0)	
Unweighted number (% of total population)	1,529 (100.0)	1,074 (70.2)	455 (29.8)	
DSST score, *M* (*SD*)‡	48.1 (17.4)	44.4 (17.1)	53.9 (16.3)	<.001
Demography				
Age, *M* (*SD*), y	70.8 (7.2)	71.8 (7.5)	69.2 (6.5)	<.001
Female	13.2 (56.9)	8.1 (56.8)	5.2 (57.1)	<.001
Non-Hispanic white	20.3 (87.1)	11.5 (81.4)	8.7 (96.2)	<.001
Less than a high school education	6.4 (27.3)	4.8 (34.0)	1.5 (16.8)	<.001
Annual family income <20,000 USD	7.3 (31.3)	5.6 (39.4)	1.7 (18.8)	<.001
Comorbidities				
Cardiovascular disease§	5.2 (22.2)	3.3 (23.2)	1.9 (20.8)	<.001
Hypertension	15.7 (67.7)	9.8 (68.8)	6.0 (65.9)	<.001
Diabetes mellitus	3.7 (15.7)	2.3 (16.0)	1.4 (15.3)	<.001
Lung disease§	4.3 (18.5)	2.7 (18.7)	1.7 (18.3)	<.001
Kidney disease	7.8 (33.5)	5.0 (35.3)	2.8 (30.8)	<.001
Thyroid dysfunction‖	3.4 (14.5)	2.0 (14.2)	1.4 (14.9)	<.001
BMI and biomarkers				
BMI, *M* (*SD*), kg/m^2	28.2 (5.4)	28.1 (5.3)	28.3 (5.5)	<.001
RBC folate, median (IQR), ng/mL	344 (186)	331 (176)	364 (191)	<.001
Serum vitamin B_{12}, median (IQR), pg/mL	470 (279)	458 (287)	487 (261)	<.001
CRP, median (IQR), mg/dL	0.27 (0.41)	0.28 (0.39)	0.26 (0.46)	<.001
Homocysteine, median (IQR), umol/L	9.27 (3.85)	9.56 (4.10)	9.02 (3.25)	<.001
Fibrinogen, *M* (*SD*), mg/dL	390 (80)	390 (80)	390 (81)	<.001
Uric acid, *M* (*SD*), mg/dL	5.66 (1.50)	5.75 (1.57)	5.52 (1.36)	<.001
Total cholesterol, *M* (*SD*), mg/dL	213 (40)	215 (39)	211 (40)	<.001
Health behavior				
Exercise hobby in recent 1 mo¶	13.3 (57.1)	7.4 (52.5)	5.8 (64.3)	<.001
Current smoker	3.7 (16.0)	2.2 (15.4)	1.5 (16.8)	<.001
Alcohol intake >12 drinks/y	14.4 (61.7)	8.3 (58.4)	6.1 (67.0)	<.001

Notes: BMI = body mass index; CRP = C-reactive protein; DSST = Digit Symbol Substitution Test; HAV IgG (+) = seropositive for antihepatitis A virus immunoglobulin G; HAV IgG (−) = seronegative for antihepatitis A virus immunoglobulin G; IQR = interquartile range; RBC = red blood cell; USD = U.S. dollar.

*Values were expressed as weighted number (percent of the group population) unless otherwise specified and the unit of weighted number is million.

†Baseline differences between HAV IgG (+) and HAV IgG (−) were determined by Student's *t* test for continuous variables and chi-square test for categorical variables.

‡Values in the continuous variables were expressed as *M* (*SD*), whereas values were expressed as median (IQR) in the right-skewed continuous variables.

§Cardiovascular disease includes stroke, myocardial infarction, angina, coronary heart disease, or congestive heart failure, whereas lung disease includes asthma, chronic bronchitis, or emphysema.

‖Thyroid dysfunction includes abnormal thyroid function tests or currently using medication for thyroid dysfunction.

¶Exercise hobby indicates participation in moderate activities, vigorous activities, or muscle-strengthening activities in leisure time.

were obtained using linear regression. We further calculated the differences of DSST score (β coefficients) while stratified on each of the baseline characteristics to investigate whether the association between HAV seropositivity and DSST performance was similar across participant subgroups, as defined by a range of baseline characteristics. Effect modifications of baseline characteristics on the association between DSST performance and HAV seropositivity were examined by creating interaction terms, namely, Baseline Characteristics × HAV Status, in linear regression. A significant interaction effect was defined if significance levels of interaction term were less than .05 in linear regression.

In multivariable analysis, multiple linear regression was used to assess the relation of HAV seropositivity with DSST score. We used an extended-model approach for covariates adjustment: model 1 = demographic variables (age, sex, race, education, and annual family income); model 2 = model 1 + comorbidities (cardiovascular disease, hypertension, diabetes mellitus, lung disease, kidney disease, and thyroid dysfunction); model 3 = model 2 + BMI + biomarkers (total cholesterol, folate, serum vitamin B_{12}, CRP, homocysteine, fibrinogen, and uric acid); and model 4 = model 3 + health behavior (exercise hobby, smoking status, and alcohol consumption).

We used the NHANES population weights (full-sample 4-year mobile examination center exam weight) for statistical analysis to generalize our results to the civilian household population of the United States. We also analyzed our data without the weights. Data analyses were performed using Statistics Package for Social Science 15.0 software (SPSS, Inc., Chicago, IL).

Results

Characteristics of the Study Population

Baseline characteristics of the study population as a whole (*n* = 1,529, weighted mean age = 70.8 years) and by HAV IgG groups were summarized (Table 1). The weighted

mean DSST score was lower in seropositive HAV group (44.4 vs 53.9, $p < .001$). More than half of the weighted study sample was non-Hispanic white (87.1%), and the weighted mean BMI was 28.2 kg/m^2. Sixty-one percent of weighted study participants were HAV seropositive.

Univariate Analysis, Subgroup Analysis, and Effect Modification

Stratified on a variety of baseline characteristics, the differences of DSST score (β coefficients), comparing participants with seropositive HAV to those with seronegative HAV, were summarized (Figure 1). Overall speaking, comparing participants with seropositive HAV to those with seronegative HAV, the unweighted β coefficient was −11.3 (95% confidence interval [CI] −13.2 to −9.3, $p <.001$) and the weighted β coefficient −9.55 (95% CI −9.57 to −9.54, $p <.001$).

The subgroup analysis demonstrated that the association between HAV seropositivity and DSST performance was consistent across the baseline characteristics. We did not find significant effect modifications of baseline characteristics on the association between DSST performance and HAV.

Multivariable Analysis

In the multiple linear regression, participants with seropositive HAV tended to have lower DSST scores compared with those with seronegative HAV (Table 2). The β coefficients for the association between DSST score and HAV IgG status were consistent across models. The adjusted β coefficients of DSST score in the full-adjusted model were −2.01 (95% CI −3.66 to −0.37, $p = 0.016$) and −2.48 (95% CI −2.49 to −2.46, $p <0.001$), unweighted and weighted, respectively.

Discussion

Among the U.S. noninstitutionalized older adults, previous HAV infection was associated with poorer cognitive function. This indicates that HAV infection may play a role in the decline of cognitive function or persons with lower cognitive performance may have increased risk for HAV infection. In our study, we have such strength as using a large national representative sample and comprehensive consideration of covariates. Several reports previously investigated the prevalence of HAV infection among people with intellectual disability. Williamson and colleagues (24) reported that the prevalence of HAV antibody in residents of institutions for intellectual disability was higher than that in the general population. Poovorawan and colleagues (25) demonstrated a high prevalence (92%) of HAV antibody among the young residents in the Institute for the Mentally Handicapped. These reports were in line with the negative association between HAV infection and cognitive function; however, they had weakness in terms of small sample size and external validity. Participants of the previous reports were confined to small groups of intellectual disabled patients. Moreover, no cognitive test was administered in any of the studies. To our knowledge, our study is the first report to describe the association between HAV infection and cognitive function among community-dwelling older adults using a large group of geographically dispersed and ethnically diverse national population-based sample. Potential confounders affecting cognition were comprehensively considered.

Our study shows that HAV is an independent inverse correlate of cognitive function. Possible explainable factors include lifestyle, environment, inflammatory, and immunologic effects of HAV infection on brain damage and cooccurred complications of acute HAV infection. With regard to lifestyle and environmental factors, HAV-seropositive participants in our study tended to live in a poorer environment and pay less attention to health on the account of lower education level, lower annual family income, lower level of folate, and less exercise activity. We did not adjust for other factors associated with poor environment and unhealthy behavior, such as lead poisoning or illicit drug use. In aspects of comorbidities, we observed a higher prevalence of diabetes mellitus in HAV-seropositive participants, whereas no significant differences in cardiovascular diseases and hypertension. Indeed, neither biologic findings in the atheromatous plaque (26) nor longitudinal reports from the Heart Outcomes Prevention Evaluation studies (27) supported the notion that exposure to HAV might be associated with an excess risk for atherosclerosis or cardiovascular events. In contrast, because the majority of the diabetic participants in our study were affected with type 2 diabetes, a high prevalence of HAV seropositivity among the diabetic elders implies a possible interplay between HAV infection and type 2 diabetes. Wang and colleagues (28) recently reported a related finding that HCV infection was an independent predictor of type 2 diabetes. Although the mechanistic relationship between HAV infection and cognitive dysfunction is still unclear, direct demyelination and disruption in tryptophan metabolism were implicated in HCV-infected patients with neurological or psychological manifestations (29–31). Altogether, future research effort to provide a deeper understanding of the association between HAV infection and cognitive dysfunction is needed.

The demonstrated results have several clinical implications. First, HAV infection may serve as a surrogate marker to early identify people at risk for lower cognitive performance. Timely preventive measures or intervention might ameliorate the deterioration process of cognitive decline in susceptible older adults. Second, hepatitis A is a preventable disease. Therefore, the possible neuropsychological influence of HAV vaccination in older adults needs to be further examined. Last, the successful experience of HCV antiviral treatment in the reduction of depressive symptoms

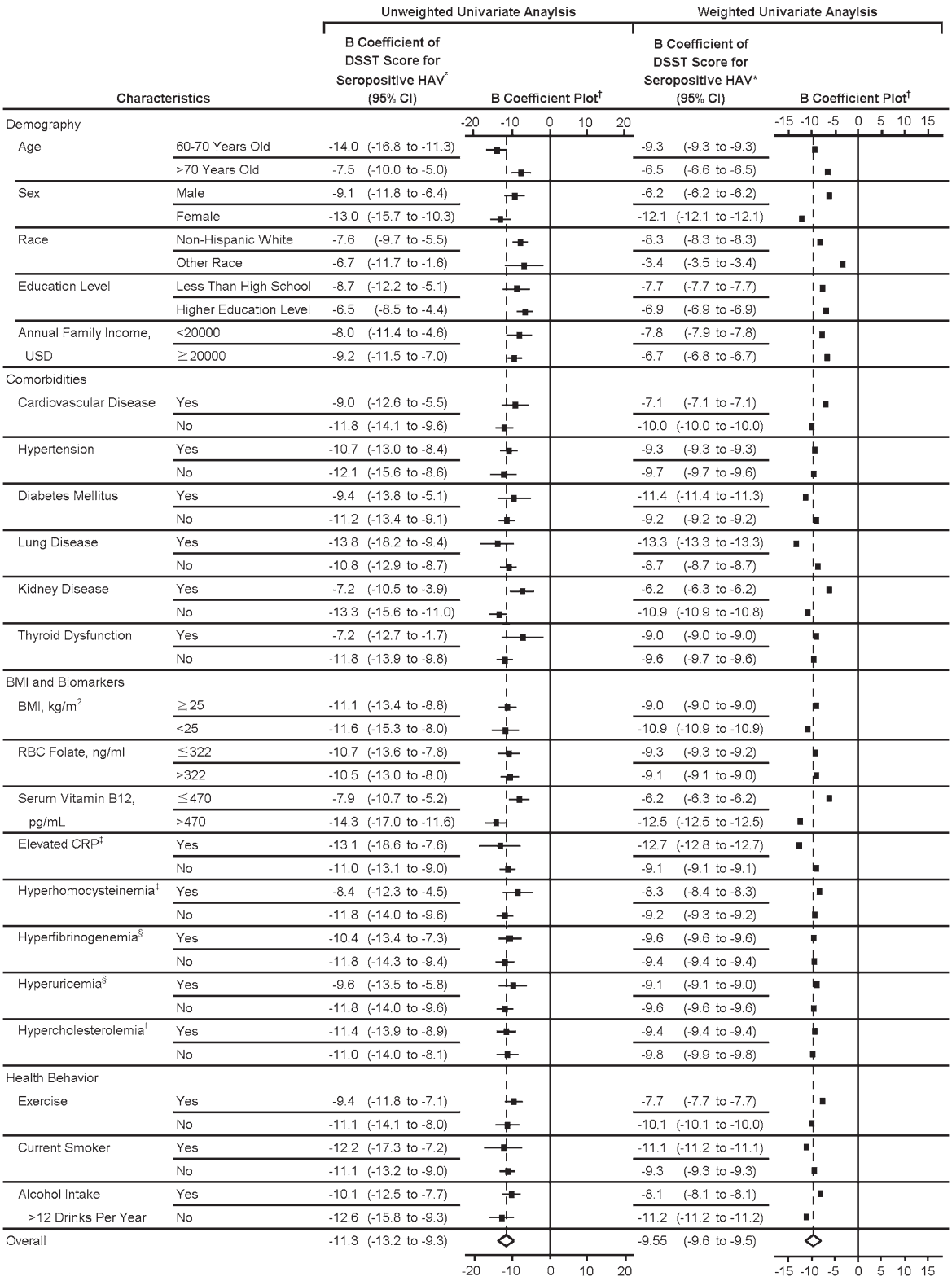

Figure 1. Effect of HAV seropositivity on cognition according to baseline characteristics.

Notes: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DSST, Digit Symbol Substitution Test; HAV = hepatitis A virus; HAV IgG (+), seropositive for antihepatitis A virus immunoglobulin G; HAV IgG (–), seronegative for antihepatitis A virus immunoglobulin G; RBC, red blood cell; USD, U.S. dollar.*Seronegative HAV group was the reference group.†The diamond incorporates the point estimate, represented by the vertical dashed line, and the 95% CI of the overall effect.‡Elevated CRP means serum CRP level of >1 mg/dL, whereas hyperhomocysteinemia means serum homocysteine level of >11.9 μmol/L.§Hyperfibrinogenemia means serum fibrinogen level of >400 mg/dL, whereas hyperuricemia means serum uric acid level of >7 mg/dL in men and >5.7 mg/dL in women.‖Hypercholesterolemia means serum total cholesterol level of ≥200 mg/dL.

Table 2. Effect of Hepatitis A Virus Seropositivity on Cognition in Multivariable Analysis

	Unweighted Linear Regression†		Weighted Linear Regression†	
Models*	Difference of DSST Score, β Coefficient (95% CI)	*p* Value	Difference of DSST Score, β Coefficient (95% CI)	*p* Value
Univariate	−11.3 (−13.2 to −9.3)	<.001	−9.55 (−9.57 to −9.54)	<.001
Multivariable				
Model 1	−2.33 (−4.00 to −0.65)	.007	−2.72 (−2.73 to −2.71)	<.001
Model 2	−2.39 (−4.05 to −0.74)	.005	−2.84 (−2.85 to −2.83)	<.001
Model 3	−2.19 (−3.84 to −0.55)	.009	−2.59 (−2.60 to −2.58)	<.001
Model 4	−2.01 (−3.66 to −0.37)	.016	−2.48 (−2.49 to −2.46)	<.001

Notes: CI = confidence interval; DSST = Digit Symbol Substitution Test.

*Adjusted covariates: model 1 = demographic variables (age, sex, race, education, and annual family income); model 2 = model 1 + comorbidities (cardiovascular disease, hypertension, diabetes mellitus, lung disease, kidney disease, and thyroid dysfunction); model 3 = model 2 + body mass index + biomarkers (total cholesterol, folate, vitamin B_{12}, C-reactive protein, homocysteine, fibrinogen, and uric acid); model 4 = model 3 + health behavior (exercise hobby, smoking status, and alcohol consumption).

†Seronegative hepatitis A virus group was the reference group.

(32) and improvement of cognitive function (33) suggested that search for the candidate treatment target for HAV infection is worth pursuing.

Our study has the following limitations that deserve comments. First, the cross-sectional nature of data does not allow any causal inference. The relationship between cognitive function and HAV infection should be studied prospectively, and more studies are needed to clarify if direct effects of HAV on cognitive function exist. Second, we relied on self-report to ascertain medical comorbidities and health-related behaviors. Such variables were potentially affected by depression, which was not examined in the NHANES participants older than 60 years. Third, some possible confounding factors such as hepatitis E virus (HEV) and human immunodeficiency virus (HIV) infections were unknown in our study population. HEV is transmitted through the fecal–oral route and may have neurological or extrahepatic manifestations as HAV (2,34). Homosexual men and drug users are at increased risk for HAV and HIV infections (35). HIV infection is related to persistent and progressive changes in emotional and cognitive functions (36). However, because data on HIV and HEV infections among the NHANES participants older than 60 years were not available, the possibility of coinfection cannot be excluded. Fourth, the DSST was the only neurocognitive test in the NHANES 1999–2002, so we had no other neurocognitive tests for comparison. Finally, we had no information about the time when participants were infected with HAV, so we could not know when participants with seropositive HAV had lower cognitive function after infection.

In conclusion, HAV seropositivity is associated with slower psychomotor speed among the U.S. community-dwelling elders after adjusting for multiple covariates. Our study is the first report to demonstrate the relationship between HAV seropositivity and cognition in elderly adults. Further studies are needed to elucidate the role of HAV infection in the cognitive decline of the aging brain. Our study also provides a milieu to examine the possible protective effect of HAV vaccination.

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