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Regional specific groundwater arsenic levels and neuropsychological functioning: a cross-sectional study

Melissa Edwards^a, Leigh Johnson^{b,c}, Courtney Mauer^d, Robert Barber^e, James Hall^f, and Sid O'Bryant^{b,c,*}

^aDepartment of Psychology, University of North Texas, Fort Worth, TX, USA

^bDepartment of Internal Medicine, University of North Texas Health Sciences Center, Fort Worth, TX, USA

^cDepartment of Institute for Aging & Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, TX, USA

^dDepartment of Psychology, Texas Tech University, Lubbock, TX, USA

^eDepartment of Pharmacology and Neuroscience, University of North Texas Health Sciences Center, Fort Worth, TX, USA

^fDepartment of Psychiatry, University of North Texas Health Sciences Center, Fort Worth, TX, USA

Abstract

Background—The purpose of the study was to examine the link between GIS-estimated regional specific groundwater levels and neuropsychological functioning in a sample of individuals with and without cognitive impairment.

Methods—This cross-sectional study design analyzed data from 1390 participants (733 Alzheimer's disease, 127 Mild Cognitive Impairment, and 530 with normal cognition) enrolled in the Texas Alzheimer's Research and Care Consortium. Geographic information systems analyses were used to estimate regional specific groundwater arsenic concentrations using the Environmental Systems Research Institute and arsenic concentrations from the Texas Water Development Board.

Results—In the full cohort, regional specific arsenic concentrations were positively associated with language abilities ($p=0.008$), but associated with poorer verbal memory, immediate ($p=0.008$) and delayed ($p<0.001$) as well as poorer visual memory, immediate ($p=0.02$) and delayed ($p<0.001$). The findings varied by diagnostic category with arsenic being related with cognition most prominently among MCI cases.

Conclusions—Overall, estimated regional specific groundwater arsenic levels were negatively associated with neuropsychological performance.

*Corresponding author. sid.o'bryant@unthsc.edu.

Conflict of Interest None to disclose

Keywords

Arsenic; Neuropsychology; Alzheimer's disease; Mild Cognitive Impairment; Groundwater

Background

Alzheimer's disease (AD) is a devastating illness impacting millions of elders, and their loved ones, world-wide (Thies and Bleiler, 2013). Despite the billions of dollars expended, current treatments only slow progression and do not fundamentally alter the neuropathological correlates of the disease. While it has been suggested that the best approach to combating this devastating disease would be through preventative means, the recent NIH Report states there is insufficient evidence to support any current preventative measures, although the report emphasizes diet and nutritional aspects as potentially useful approaches. Additional work is needed to understand the impact of environmental and dietary factors on the risk for developing AD.

Arsenic, a known neurotoxin, is one of the most toxic environmental pollutants (Dho et al., 2010). Inorganic arsenic compounds are released from rocks or industrial and agricultural sources into groundwater (Garelick et al., 2008), which is the most common means of exposure. The current EPA standard for groundwater levels is 10 µg/L though the long-term health impacts of exposure at low concentrations have received less attention (Subcommittee, 1999). While the detrimental impact of acute exposure to high concentrations of arsenic on health is well established, prior work has also documented negative consequences of exposure to groundwater arsenic at levels below the current U.S. standard of 10 µg/L (particularly chronic exposure) (Fatmi et al., 2009; Focazio et al., 2000; Kapaj et al., 2006; Liao et al., 2009; Navas-Acien et al., 2008; Subcommittee, 1999; Subcommittee to Update, 2001). The impact of arsenic exposure at low concentrations on neurocognitive functioning has received less attention. However, it has been proposed that exposure to environmental toxins, including arsenic, has caused a “silent pandemic” in modern society that has gone undetected (Grandjean and Landrigan, 2006). This circumstance has likely remained unnoticed because the neurodevelopmental and neurotoxic consequences of in utero exposure (along with chronic lifetime exposure) may not become evident until neuronal attrition associated with aging occurs (Grandjean and Landrigan, 2006).

Arsenic exposure has been linked to a number of neuropathological correlates of AD including production of β amyloid (Dewji et al., 1995), hyperphosphorylation of tau protein (Vahidnia et al., 2007), oxidative stress (Engstrom et al., 2010), inflammation (Fry et al., 2007; Vega et al., 2001), endothelial cell dysfunction (Luo et al., 2009) and angiogenesis (Meng et al., 2010), all of which have been linked to cognitive dysfunction and AD (Darvesh et al., 2010; Gong and O'Bryant, 2010; Tan et al., 2003; Yin et al., 2010). In animal models, arsenic exposure has been shown to cause morphologic and neurochemical alterations in the hippocampus and other memory-related neuronal structures and expected learning and memory deficits have been noted (Luo et al., 2009; Martinez-Finley et al., 2009; Wang et al., 2009). Based on these data, we have proposed an arsenic exposure hypothesis for AD (Gong et al., 2011).

In a series of studies using geographic information system (GIS) methods for estimating current and chronic arsenic exposures, we have found arsenic to be negatively associated with cognitive status among rural-dwelling adults. In a pilot project of 311 adults age 40 and above, we found arsenic exposure at low concentrations (at or near the current U.S. standard) to be associated with significantly poorer global cognitive functioning (Mini-Mental State Examination [MMSE] scores) (Gong et al., 2011). In a follow-up study of 434 rural-dwelling adults and elders, current and long-term groundwater arsenic concentrations were associated with poorer functioning on tests of executive functioning, language and memory (O'Bryant et al., 2011). In this study, GIS-based estimated arsenic and directly observed arsenic groundwater concentrations were highly correlated.

The purpose of the current study was to examine the link between GIS-estimated regional groundwater arsenic levels and neuropsychological functioning among participants of the Texas Alzheimer's Research and Care Consortium (TARCC) cohort. We hypothesized that regional arsenic concentrations below or near the current U.S. standard would be significantly associated with poorer neuropsychological functioning.

Methods

Participants

This cross-sectional study analyzed data from 1390 participants (733 AD cases, 127 MCI cases, and 530 with normal cognition) enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC) longitudinal study. The methodology of the TARCC protocol has been described elsewhere (O'Bryant et al., 2009; Waring et al., 2008). The TARCC is a state wide Alzheimer's initiative designed to study a wide range of factors, primarily biomarker and genetic factors related to AD. Recruitment occurs through dementia specialty clinics at each site, which have broad catchment areas covering the majority of the state. All patients are age 50 or older and enter the cohort with diagnoses of Alzheimer's disease, mild cognitive impairment (MCI) or with normal cognition. In order to increase enrollment of Mexican American participants into the cohort, additional targeted recruitment efforts have included community-based strategies. Each participant undergoes an annual standardized examination at one of the six participating sites that includes a medical evaluation, neuropsychological testing, an interview and a blood draw. All information is reviewed by consensus committee, consisting of physicians (e.g. geriatrician, psychiatrist, neurologist), neuropsychologists and other research team members and health care providers. This consensus review assigns diagnostic categorizations according to published guidelines for Probable AD (NINCDS-ADRDA criteria; McKhann et al., 1984), MCI (Mayo criteria; Petersen, 2003), and normal cognition. Participants determined to have normal cognition were those considered to perform within normal limits on psychometric testing. Institutional Review Board approval was obtained at each site and written informed consent is obtained for all participants (or informants for AD patients). The demographic characteristics of the sample can be found in Table 1.

TARCC comprises of six sites across the state of Texas including: Texas Tech University Health Sciences Center (Lubbock, TX), University of North Texas Health Science Center (Fort Worth, TX), University of Texas Health Science Center San Antonio (San Antonio,

TX), University of Texas Southwestern Medical Center (Dallas, TX), Texas A&M Health Science Center (Round Rock, TX), and Baylor College of Medicine (Houston, TX). The regions selected to be evaluated within this study were therefore done so based on the location of the six TARCC sites. The mean arsenic concentration level for the TARCC cohort was 4 parts per billion (see Table 1 and Figure), which was below the current U.S. acceptable level of arsenic exposure of 10 parts per billion.

Determination of GIS-Arsenic

GIS is a way of displaying and analyzing geographically reference information. GIS-based methods are commonly used to estimate environmental exposures (AvRuskin et al., 2004; Gong et al., 2011; Khan et al., 2009; O'Bryant et al., 2011; Samadder and Subbarao, 2007; Su et al., 2010). Specifically, GIS allows for the creation of digital maps, which provide geographical representation of elements found in groundwater, such as arsenic. Utilizing the Environmental Systems Research Institute (ESRI, <http://www.esri.com/>) ArcGIS (release 9.2) program, 12,591 arsenic groundwater measurements from the Texas Water Development Board (TWDB, <http://www.twdb.state.tx.us/home/index.asp>) were analyzed. Measurements included 7208 wells from 1995 to 2009. Figure 1 shows the GIS-map based on geographical coordinates with the well measurements as well as the average of all measurements for that well. The types of wells were: 6,697 (36.6%) public supply, 5,223 (28.5%) domestic, 2,451 (13.4%) stock, and 2,131 (11.6%) irrigation (TWDB, <http://www.twdb.state.tx.us>).

In this study, we utilized inverse distance weighted interpolation through ArcGIS software to build a surface map, which divided the whole state of Texas into small cells of 0.8 square miles giving each block an estimated arsenic value based on the 12 radially nearest wells (see Figure 1). The participant data provided had only the first 3 digits of the zip code to associate to a geographical region, so we created a map by dissolving existing 5-digit zip code map into larger 3-digit regions. Each of these larger 3-digit zip code regions were given an arsenic estimate by taking the average of all block values that fell into that region.

The comparability of GIS-based methods and directly observed groundwater toxicants has been demonstrated by others (Babiker et al., 2007; Fytianos and Christophoridis, 2004; Khan et al., 2009; Samadder and Subbarao, 2007; Usali and Ismail, 2010). We recently demonstrated the comparability of GIS-based methods versus actual water assays for deriving estimates of arsenic exposure. In an initial pilot study, we evaluated the agreement between 7 rural well water arsenic measurements and the GIS-based findings, which were comparable (O'Bryant et al., 2011). In a more recent study, we found directly measured concentration of total arsenic 77 rural wells to be highly correlated with the GIS-based estimated concentrations ($r^2=0.85$, $p<0.001$) (unpublished data). Therefore, our work, and that of others, suggests that GIS-based methods can reliably estimate region-specific arsenic water levels.

Neuropsychological Testing

The TARCC neuropsychology core battery consists of commonly utilized instruments in AD clinical/research settings and it overlaps largely with the NACC Uniform Dataset including

digit span (WAIS-R DS, WAIS-III DS, WMS-R DS) (Wechsler, 1997), Trail Making Test (TMT A and TMT B) (Lezak et al., 2004), WMS-III Logical Memory (LM) and Visual Reproduction (VR) (Wechsler, 1997), Boston Naming Test (BNT) (30- and 60-item versions) (Strauss et al., 2006), verbal fluency (FAS) (Strauss et al., 2006), Clock Drawing Test (CLOX1 and 2) (Strauss et al., 2006), the American National Adult Reading Test (AMNART) (Strauss et al., 2006), the Geriatric Depression Scale (GDS-30) (Yesavage et al., 1983), Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and the Clinical Dementia Rating scale (CDR) (Morris, 1993). In order to equate scores and be consistent across tests, all raw scores were converted to scale scores based on previously published normative data (Ivnik et al., 1992; Ivnik et al., 1996; The Psychological Corporation, 1997). For the BNT, we published an independent study demonstrating the psychometric utility of an estimated 60-item BNT score that can be calculated from 30-item versions (Hobson et al., 2011); this estimated 60-item score was used for all 30-item administrations. Age-adjusted scale scores were utilized as dependent variables in analyses.

Statistical Analyses

Linear regression models were created with neuropsychological scale scores as the outcome variables and regional specific arsenic levels as the predictor variable. Covariates (entered as a single step along with arsenic concentrations) included variables previously shown to be significantly related to neuropsychological test scores (age, gender, education) as well as factors previously shown to be related to arsenic exposure (presence/absence of hypertension, hyperlipidemia, obesity (BMI>30), and diabetes. Since selenium levels are known to impact arsenic toxicity (Andersen & Nielsen, 1994; Biswas et al., 1999), current groundwater selenium estimates were included as a covariate within the model. Of note, regional water selenium levels were estimated using GIS-based methods, which were similar to methods used to estimate arsenic exposure levels. Age continued to be significantly related to neuropsychological test scores ($p<0.05$) for a majority of tests when age-adjusted scale scores were examined and therefore remained as a covariate. Scaled scores were utilized with the neuropsychological measures because it allowed for the measures to be compared based on a standardized scale. Unstandardized beta (B), along with the associated standard error (SE), t-score and p-value were calculated for each of the analyses.

Results and Discussion

See Table 1 for descriptive statistics of the sample, neuropsychological test scale scores, as well as mean estimated regional specific arsenic levels. The mean regional specific arsenic levels for the cohort was 3.97 μ g/L (sd=3.3, range = 1.77–15.98) with the breakdown by cognitive group presented in Table 1. An ANOVA comparing regional specific arsenic levels between the three cognitive groups was significant ($F[2, 1334]=4.55, p=0.01$). Post hoc comparisons showed that the AD and normal cognition groups had significantly higher regional specific arsenic levels than the MCI group, but AD and those with normal cognition group were not significantly different from one another. These exposure levels were, on average, below the EPA current standard of 10 parts per billion.

Among the full sample, regional arsenic concentrations were associated with significantly better confrontation naming (BNT [$B=0.21, SE=0.08, t=2.68, p=0.008$]) but significantly

poorer scores on immediate verbal memory (WMS-III LM I [B=-0.23, SE=0.09, t=-2.68, p=0.008]), delayed verbal memory (WMS-III LM II [B=-0.34, SE=0.10, t=-3.58, p<0.001]), immediate visual memory (WMS-III VR I [B=-0.23, SE=0.10, t=-2.36, p=0.02]), and delayed visual memory (WMS-III VR II [B=-0.58, SE=0.11, t=-5.33, p<0.001]).

Next analyses were run by diagnostic group. Among those with normal cognition, higher regional specific arsenic concentrations were associated with better scores on global cognition (MMSE [B=0.08, SE=0.03, t=2.9, p=0.004]) and confrontational naming (BNT [B=0.29, SE=0.10, t=2.83, p=0.005]) (see Table 2). Among those with MCI, regional groundwater arsenic concentration was associated with significantly poorer scores on global cognition (MMSE [B=-0.34, SE=0.13, t=-2.7, p=0.009]), attention (TMT A [B=-0.43, SE=0.18, t=-2.5, p=0.015]), executive functioning (TMT B [B=-0.44, SE=0.18, t=-2.4, p=0.017]), delayed verbal memory (WMS-III LM II [B=-0.43, SE=0.19, t=-2.2, p=0.028]), and delayed visual memory (WMS-III VR II [B=-0.36, SE=0.17, t=-2.2, p=0.034]) (see Table 2). Among AD cases, regional specific arsenic groundwater concentrations were associated with significantly poorer delayed visual memory (WMS-III VR II [B=-0.37, SE=0.10; t=-3.6, p<0.001]) (see Table 2).

Conclusions

In the current study, estimated regional groundwater arsenic concentrations were found to be negatively associated with neuropsychological performance, providing further support for the potential link between arsenic exposure at low concentrations and neurocognitive functioning. In the entire sample, regional arsenic concentrations were negatively associated with all memory scores (visual and verbal, immediate and delayed memory [WMS-III LM 1 and 2; WMS-III VR I and 2]). This work extends on our prior findings that exposure to low concentrations of arsenic may have negative consequences.

This study also yielded results linking higher arsenic concentration levels with better performance on tasks related to global cognition (MMSE). Baum and colleagues (Baum et al., 2010) found similar results in their study, which examined metal concentrations in a sample of individuals with either normal cognition or with a diagnosis of AD. The authors hypothesized that the positive correlation between arsenic and MMSE scores may have been the result of the amyloid plaques, located in the brain, which may be able to envelope significant concentrations of arsenic, thereby depleting the detectable amount of arsenic within the blood stream (Baum et al., 2010). In our prior work using GIS-based arsenic estimates at current residential location, we did not find arsenic concentrations to be positively related to global cognition (MMSE). It remains possible that some unidentified third variable was related to this finding and should be studied further. It is also noteworthy that our prior work was conducted with a rural-dwelling cohort that had a much broader range of age, education, and test scores compared to the cognitively normal participants within the TARCC. These cohort differences may help explain the discrepant findings. The neuropsychological tests utilized in the TARCC and our prior work in Project FRONTIER overlap somewhat, but are also different in many respects. In the current study, arsenic was most consistently related to measures of memory whereas in our prior work, the link was

spread across measures of language, attention, memory and executive functioning. Again, cohort differences may explain this discrepancy given that the TARCC was designed to study the development and progression of AD, a memory-impairment predominant disease.

Prior work has linked arsenic exposure to neurocognitive dysfunction; however, the majority of that work has been with higher-level exposures at toxic sites. Wasserman and colleagues (Wasserman et al., 2004; Wasserman et al., 2007) examined the association between arsenic and cognition in a sample of children in Bangladesh and found arsenic concentrations to be linked with lower intellectual functioning. Bolla-Wilson and Bleeker (Bolla-Wilson and Bleeker, 1987) evaluated a 50-year-old following acute exposure to arsenic and documented deficits in learning and memory, which improved over time with no subsequent exposures. Wright and colleagues (Wright et al., 2006) examined the neuropsychological profile of 31 school-aged children who were residents of Ottawa County, Oklahoma, which contains the Tar Creek Superfund site and found higher hair arsenic concentrations to be significantly associated with poorer scores on tests of intelligence and memory. In a sample of 602 school children age 6–8 years, Rosado and colleagues (Rosado et al., 2007) found that higher urinary arsenic concentrations were significantly associated with poorer visuospatial skills, intelligence, attention and executive functioning.

There were several limitations to the study. One limitation was our inability to estimate long-term low concentration exposure. Tsai and colleagues (Tsai et al., 2003) evaluated 49 junior school students and found that higher chronic groundwater arsenic exposure was significantly related to poorer memory and executive functioning (i.e. switching attention). In our prior study (O'Bryant et al., 2011) we estimated long-term exposure by multiplying current concentrations with the number of years residing in current location. In that study, *long-term* exposure at *low-concentration* was associated with more negative neuropsychological outcomes than current levels and was significantly related to poorer scores in global cognition, visuospatial skills, language, and information processing speed, memory and executive functioning. However, we did not have residential history available for analysis in the TARCC cohort and, therefore, potential longer term exposures could not be evaluated.

There were other limitations to the current study. First is the inability to control for recruitment location. Some of the observed effects among the cognitive groups could have been due to where the participants were recruited from, thereby resulting in a potential selection bias. Specific differences such as quality or access to care or socioeconomic status could have confounded the observed effects. An additional limitation included the use of estimated groundwater as the proxy for actual levels. Our study examined regional exposure rather than individual exposure given that the actual residential address for each participant was not available. The use of 3-digit zip code regions rather than the current residential address was required due to the archival nature of the study. The use of 3-digit zip code (or even 5-digit zip code) regions can obscure regional variability. In fact, Texas has several “hot spots” of high arsenic levels, which could not be fully studied within the scope of this project. Also, due to these “hot spots”, it was likely that the regional specific estimates of arsenic concentrations utilized in this study artificially underestimated actual arsenic exposure levels. There was also a limitation of utilizing GIS-based methods for determining

arsenic exposure as the data was averaged to obtain information concerning the wells, which thereby masked any specific elevations in arsenic concentrations, which could differentially impact individuals in specific locales. Direct water, hair, nail, or even blood levels would have been preferable. The lack of information on water consumption patterns, source of water (i.e. groundwater, bottled water, surface water), as well as food consumption patterns was another limitation of the current study. Arsenic specific genotypes also were not available for study, although we recently completed a genome-wide allelic association study (GWAS) that analyzed a large portion of the AD and normal cognition participants, which will be reviewed in the near future. Finally, this study demonstrated a potential link between current regional arsenic levels from a cross-sectional perspective. Future studies should evaluate this research question longitudinally.

Overall, the current findings demonstrated a significant negative link between regional specific arsenic concentrations (low-level) and neuropsychological performance among those with and without cognitive impairment. Given that over 15-years of groundwater data was available through the TWDB, Texas provided a naturalistic setting to study the health consequences of long-term arsenic exposure across a range of concentrations through the incorporation of direct measurement and GIS-means. The current research team previously created a method that modeled such exposure (O'Bryant et al., 2011) and will continue to study the importance of such exposure on the development and progression of AD. Identification of groundwater arsenic, or other toxic elements, as risk factors for AD would point to a potential population-wide prevention strategy via re-visitation of the Safe Drinking Water Act.

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Figure 1.
GIS-based arsenic concentrations across Texas

Table 1

Descriptive Statistics by Clinical Group

	Normal Cognition N=530		AD cases N=733		MCI cases N=127	
	Mean(SD)	Range	Mean(SD)	Range	Mean(SD)	Range
Sociodemographic						
Age	69.7(8.5)	50–93	76.3(8.1)	54–102	74.2(7.9)	56–91
Education	15.2(2.6)	6–23	14.5(3.0)	3–26	13.6(2.7)	5–20
Gender (%F)	63		57		58	
Medical History						
Hyperlipidemia (% present)	55		60		65	
Hypertension (%present)	57		64		69	
Diabetes (% present)	17		11		25	
Obese (% present)	31		13		42	
Neuropsychological Assessment						
Global Cognition (MMSE)	29.3(1.0)	24–30	20.8(5.3)	2–30	27.5(2.1)	5–20
Disease Severity (CDR SB)	0.2(0.1)	0–1.0	6.3(3.6)	0.5–18.0	1.2(0.8)	0.5–4.5
Semantic Fluency (FAS/COWAT)	11.0(2.9)	2–18	7.4(3.4)	2–17	8.5(2.9)	2–15
Confrontational Naming (BNT)	11.1(3.8)	2–18	6.5(3.6)	2–17	7.8(3.7)	2–17
Verbal Intelligence (AMNART)	11.3(3.7)	2–18	9.1(3.8)	2–18	9.1(3.7)	2–17
Attention (TMT A)	10.5(2.9)	2–18	6.6(3.4)	2–16	9.1(2.8)	2–18
Executive Functioning (TMT B)	10.7(2.6)	2–18	5.3(3.3)	2–16	8.1(3.1)	2–15
Working Memory (WAIS Digit Span)	10.9(2.9)	2–19	8.4(3.1)	1–19	9.2(2.6)	4–19
Verbal Memory Immediate (WMS-III LMI)	12.1(3.2)	2–18	4.0(2.4)	1–12	8.1(2.9)	2–14
Verbal Memory Delayed (WMS-III LMII)	12.8(3.0)	1–19	3.5(2.1)	1–12	8.2(3.3)	2–16
Visual Memory Immediate (WMS-III VRI)	11.5(3.4)	3–18	5.2(2.9)	1–17	8.2(2.9)	2–17
Visual Memory Delayed (WMS-III VRII)	12.9(3.2)	4–19	4.3(2.5)	2–19	8.7(2.8)	2–16
Environmental Exposure						
Arsenic (µg/L)	4.0(3.6)	1.8–12.0	3.9(3.1)	1.8–16.0	3.2(2.6)	1.8–12.0
Selenium (µg/L)	7.4(6.2)	3.4–26.7	6.4(5.4)	2.6–26.7	6.3(5.6)	3.4–26.7

NOTE: MMSE range = 0–30; Trails, COWAT, Boston, AMNART, WAIS Digit Span, WMS-III LMI, LMII, VRI, and VRII = scale scores with a mean of 10 and SD=3. CDR SB range = 0–18.

Table 2

Impact of Arsenic Concentrations on Neuropsychological Functioning by Cognitive Status

	Normal Cognition N=530		MCI N=127		AD N=733	
	B(SE)	p-value	B(SE)	p-value	B(SE)	p-value
Global Cognition (MMSE)	0.08(0.03)	0.004	−0.34(0.13)	0.009	0.13(0.13)	0.339
Disease Severity (CDR Sum of Boxes)	−0.002(0.003)	0.396	0.04(0.04)	0.331	−0.24(0.09)	0.008
Executive Functioning (CLOX 1)	0.35(0.16)	0.034	−0.10(0.18)	0.552	0.22(0.28)	0.422
Visuospatial Functioning (CLOX 2)	0.07(0.11)	0.522	0.01(0.10)	0.882	0.15(0.15)	0.296
Attention (TMT A)	0.005(0.09)	0.958	−0.43(0.18)	0.015	0.03(0.09)	0.732
Executive Functioning (TMT B)	0.13(0.07)	0.074	−0.44(0.18)	0.017	−0.04(0.09)	0.619
Confrontational Naming (BNT)	0.29(0.10)	0.005	0.27(0.19)	0.164	0.12(0.09)	0.165
Semantic Fluency (FAS)	−0.03(0.08)	0.709	−0.13(0.17)	0.434	0.01(0.08)	0.840
Working Memory (WAIS-III Digit Span)	0.05(0.09)	0.547	0.07(0.15)	0.637	0.02(0.08)	0.752
Visual Memory Immediate (WMS-III LM I)	0.05(0.09)	0.553	−0.17(0.17)	0.329	−0.01(0.06)	0.787
Verbal Memory Delayed (WMS-III LM II)	0.01(0.09)	0.895	−0.43(0.19)	0.028	−0.08(0.05)	0.111
Visual Memory Immediate (WMS-III VR I)	0.02(0.11)	0.843	0.09(0.17)	0.586	0.01(0.12)	0.872
Visual Memory Delayed (WMS-III VR II)	−0.10(0.10)	0.314	−0.36(0.16)	0.034	−0.36(0.10)	0.000
Depression (GDS-30)	0.02(0.11)	0.820	0.04(0.35)	0.910	0.06(0.16)	0.679

Note: Covariates included age, gender, education, obesity, hyperlipidemia, hypertension, diabetes and selenium level; B = unstandardized regression coefficient; SE = standard error. MMSE range = 0–30; TMT, FAS/COWAT, Boston, AMNART, WAIS Digit Span, WMS-III LMI, LMII, VRI, and VR II = scale scores with a mean of 10 and SD=3. CDR SB range = 0–18. CLOX range = 0–15.