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Association of Zinc, Iron, Copper, and Selenium Intakes with Low Cognitive Performance in Older Adults: A Cross-Sectional Study from National Health and Nutrition Examination Survey (NHANES)

Suyun Li, Wenjun Sun and Dongfeng Zhang*
Department of Epidemiology and Health Statistics, School of Public Health, Qingdao University, Qingdao, Shandong Province, China

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Abstract.
Background: The association of zinc, iron, copper, and selenium intakes with cognitive function is poorly understood so far.
Objective: To examine the associations of dietary and total zinc, iron, copper, and selenium intakes with low cognitive performance.
Methods: Cross-sectional study data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014 was used. Zinc, iron, copper, and selenium intakes from foods and supplements were estimated from two non-consecutive 24-hour diet recalls. Cognitive function was measured by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) Word Learning sub-test, Animal Fluency test, and Digit Symbol Substitution test (DSST). For each cognitive measurement, people whose score were lower than the age group stratified lowest quartile were defined as low cognitive performance. Logistic regression and restricted cubic spline models were applied to examine the associations of dietary and total zinc, iron, copper, and selenium intakes with different measures of low cognitive performance.
Results: A total of 2,332 adults aged 60 years or older were included. The association between zinc, iron, copper, and selenium intake and low cognitive performance was significant in different test. Compared with the lowest quartile of total copper intake, the weighted multivariate adjusted ORs (95% CI) of the highest quartile were 0.34 (0.16–0.75) for low cognitive performance in DSST. L-shaped associations between total copper or selenium and low cognitive performance in DSST and animal fluency were found.
Conclusion: Dietary and total zinc, copper, and selenium intakes might be inversely associated with the prevalence of low cognitive performance.

Keywords: Cognition, copper intake, eating, selenium intake, zinc intake

INTRODUCTION

With the increase of life expectancy, the number of the elderly population is increasing worldwide, which will inevitably lead to a series of health problems. For instance, the elderly often suffer from memory and

*Correspondence to: Dongfeng Zhang, MD, Department of Epidemiology and Health Statistics, School of Public Health, Qingdao University, 38 Dengzhou Road, Qingdao, Shandong 266021, China. Tel.: (+86) (0532) 82991712; E-mail: zhangdf1961@126.com.

cognitive decline; however, both normal aging and neurological diseases were associated with changes in cognition [1]. If the cognitive decline continuously deteriorates without any prevention and intervention, then it will gradually develop into pathological mild cognitive impairment (MCI) and dementia. Alzheimer's disease (AD) is the main type of dementia [2]. According to statistics released by National Center for Health Statistics, Centers for Disease Control and Prevention in 2016, AD ranked sixth among the top ten causes of death in the United States (US) in 2015 [3]. Among elderly women over 80 years old, AD ranks third in the order of all causes of death, after heart disease and malignant tumors [3, 4]. The process from cognitive decline to AD is a continuous and irreversible process; additionally, there is no effective treatment for AD so far, and the effects of the existing drugs are limited. Thus, preventing AD and its pre-clinical manifestations (low cognitive performance) as early as possible, and exploring the modifiable lifestyle and other risk factors for low cognitive performance is necessary and important.

Extensive research efforts have been done in past decades; however, the etiology of cognitive impairment has not been fully explained. Previous studies have shown that many personal and environmental factors may be related to low cognitive performance, such as age [5], education [6], smoking [7], alcohol [8], physical exercise [9], vitamin or fruit intake [10], depression [5], obesity [11], etc.

Trace elements, such as zinc, iron, copper, and selenium, are essential microelements to our body functions because they are necessary components of many enzymes and part of the structure of thousands of proteins which are involved in DNA repair process, prevention of oxidative damage to DNA, and maintenance of DNA methylation [12]. Thus trace elements are important in regulating of cellular function and neuromodulation and might have crucial roles in antioxidant protection [13]. Their antioxidant effect may limit damage caused by free radicals, and thus prevent or slow down the process of cognitive decline due to the damaging effects of free radicals on neurons [14].

Even though meta-analyses have been published on trace metals in brain, serum, and cerebrospinal fluid (CSF) depicting a composite scenario of metals distribution among different body districts [15–19], data about epidemiological study on the association between dietary trace element intake and low cognitive performance are still limited [20–22]. Therefore, we analyzed a large dataset of non-institutionalized civilians aged 60 years or over in the US from the continuous National Health and Nutrition Examination Survey (NHANES) to investigate the association between dietary and total (dietary plus supplementary) intake of zinc, iron, copper, and selenium and low cognitive performance.

METHODS

Study design and participants

The NHANES is an ongoing 2-year-cycle cross-sectional survey administered by the Centers for Disease Control and Prevention (CDC) of US, designed to evaluate the nutrition and health status of the US non-institutionalized civilian population. Participants were selected by a complex, stratified, multistage sample design to represent the US general population. Participants first took part in a household interview and then completed a further survey in a mobile examination center (MEC). The NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board of the US CDC, and written informed consent from all the participants were provided during the survey. Two cycles (2011–2012, 2013–2014) with information on dietary and total zinc, iron, copper, and selenium intake as well as cognitive performance measures were combined and used in the analysis. A total of 19,931 individuals participated in the NHANES during 2011–2014, and our analyses were limited to the adult participants aged 60 years or older who participated in the MEC cognitive function survey. Participants with extreme values (>Q3 + 3IQR) of 24 h recall data for trace elements dietary intake ($n = 670$) were excluded. Those who did not complete the cognitive function surveys or with missing or unreliable values for the three cognitive function measures ($n = 16{,}536$) were also excluded. Furthermore, those with missing values for the dietary intake of the four trace elements ($n = 222$) were also excluded. Finally, 2,503 participants aged 60 years or older (1,215 men and 1,288 women) were included in the analyses. The flow chart of participants was shown in Supplementary Figure 1.

Dietary and supplemental intakes

In each cycle, dietary intake data were assessed by using two 24-hour recall interviews. The first 24-hour recall interview was conducted face-to-face during the MEC interview, and the second one was taken

through telephone interview several days later. For the analysis, total dietary intake of the trace elements was calculated by averaging data of the two dietary recalls if available; otherwise, the single dietary recall data was used. In addition, supplements intake of the trace elements during the past 30 days were also collected from the survey, and averaged to represent the daily supplementary intake amount. The total daily trace element intake was calculated by summing the daily dietary and supplemental intake. Details of the methodology of the calculation of the nutrients intake could be found at the website [23].

Low cognitive performance outcomes

For the cycles of 2011–2012 and 2013–2014, cognitive function was tested at the MEC among participants aged 60 years and older [24, 25]. The assessments include three tests: Consortium to Establish a Registry for Alzheimer's disease (CERAD) Word Learning subset, the Animal Fluency test, and the Digit Symbol Substitution Test (DSST). The CERAD test was used to evaluate immediate and delayed recall of new verbal information (memory sub-domain). It consisted of three consecutive learning trials as well as a delayed recall, and for each test, the participants were asked to recall as many of the newly learned words as possible immediately after 10 words were read or after a few minutes. The scores for each trial was presented as the number of right answers, which ranges from 0 to 10, and the sum of the scores for the three immediate trials and a delayed trial added up to the total score of the CERAD. The Animal Fluency test was commonly used in previous studies, to assess categorical verbal fluency that was a vital component of executive function. Participants were required to answer with as many animal names as possible in one minute, and could obtain one point for each correct answer. The total score was summarized as the number of correct answers. The DSST test is a module of the Wechsler Adult Intelligence Test, which has been frequently used to assess participants' processing speed, sustained attention, and working memory. Each participant taking part in the DSST test was provided a piece of paper and a key that showed the pair relationship of 9 numbers and symbols, and was asked to match the right symbols for 133 boxes with numbers in two minutes. The total score was summarized as the number of the correct match, ranging from 0 to 133. Because so far there is no gold standard on the cutoff scores for the DSST, CERAD, and Animal Fluency test to indicate low cognitive performance or cognitive decline, we selected the lowest quartile in the study group as the cutoff values to indicate different types of low cognitive performance, which was consistent with the methods used in the previously published literature [26]. Besides, age was the major risk factor for cognitive decline, thus we firstly divided the elderly into three age groups (60–69, 70–79, $\geq$80) and calculated the lowest quartile for each group, then applied lowest quartile stratified by age groups as the cut-offs to define the cognitive performance status. Regarding the DSST test, the cut-off values of low cognitive performance were 37, 32, and 28 for the three age groups, respectively. For the animal fluency test, the cut-off values were 13, 12, and 11, and for the CERAD test, the cut-off values were 21, 19, and 16, respectively. For each measure, participants were divided into two groups: those with scores lower than the corresponding cutoff values were classified into the low cognitive performance group, and the others was assigned to normal cognitive performance group. In addition, to reflect the information of overall cognitive function, a standardized z-score was computed for each participant based on the mean and standard deviation of each cognitive test, and the average score was computed as the composite score of cognitive performance.

Covariates

Age, gender, race, marital status, and educational level were obtained from in-person household interviews. Educational level was classified into three categories (less than high school, high school, higher than high school). Total energy intake was obtained from the 24-hour dietary recall. Smoking status was divided into three group (everyday smoking, sometimes smoking, and not at all) based on the self-report of the participants to the question "Do you now smoke cigarettes". Participants were defined as alcohol drinkers if they had ever had at least 12 alcohol drinks per year. History of hypertension, diabetes, stroke, or heart attack was defined as self-reported physician diagnosis of hypertension, diabetes, stroke, or heart attack [27].

Statistical analysis

All statistical analyses were adjusted for survey design and weighting variables to account for the complex sampling design, and ensure nationally representative estimates. Because we combine two cycles of the NHANES data, new sample weights

(the original 2-year sample weight divided by 2) was constructed according to the analytical guidelines of the NHANES.

Mean and SD was used for describing the characteristics of continuous variables between the different groups if they follow normal distribution, otherwise, median and interquartile range (IQR) was used. Student's *t*-test or Wilcoxon rank-sum test was used to compare the mean levels of continuous variables between low cognitive performance group and normal cognitive performance group based on their distribution. Pearson chi-squared test or Fisher's exact test was performed to compare the distribution of the categorical variables between low cognitive performance group and normal cognitive performance group. Dietary and total zinc, iron, copper, and selenium intakes were categorized into quartiles and higher quartile indicate higher level of intake. Additionally, based on the recommended daily allowance (RDA) and the total intake of each micro nutrients, we also divided the participants into two groups (meeting the RDA or below the RDA). Logistic regression analyses were conducted to examine the associations between dietary and total zinc, iron, copper, and selenium intakes and the prevalence of low cognitive performance, with the lowest quartile of intake as the referent category. The crude model did not adjust any confounders, and multivariate-adjusted model adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (ever, or never), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d). Trend tests for dietary and total nutrients intakes and each measures of low cognitive performance were carried out using continuous measures of these variables by assigning the mid-value to each quartile. Stratified analyses by three age groups were also conducted to further address the concern on the confounding by age. Linear regression was conducted to test the association between meeting the RDA of the micro nutrients and low cognitive performance. In addition, we included all the micro nutrients in the same logistic regression model simultaneously. We used restricted cubic spline models with 3 knots to further investigate the dose-response relationship between the total zinc, iron, copper, and selenium intake and different measures of low cognitive performance after adjusting for the confounders [28]. We also conducted analyses by constructing multivariate linear regression model, with the composite score as the dependent variable, and the dietary and total intake of iron, zinc, copper, and selenium and the other confounders as the independent variables. All statistical analyses were performed with Stata 15.0 (Stata Corporation, College Station, TX). $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the sample by different measures of low cognitive performance were summarized in Table 1. For all the three different measures of cognitive function, there were significant differences between people with low cognitive performance and normal cognitive performance in the distribution of race, marital status, education, diabetes, stroke, and total energy intake ($p < 0.001$). People with low cognitive performance tended to have lower education level, less total energy intake, higher prevalence of diabetes and stroke, and less dietary and total zinc, iron, copper, and selenium intake than people with normal cognitive performance. For the DSST and CERAD, people with low cognitive performance were more likely to be male, while the normal cognitive performance people tended to be female ($p < 0.001$). The prevalence of hypertension and heart attack in people identified with low cognitive performance with DSST was significantly higher than that of people with normal cognitive performance. Alcohol drinking rate was significantly lower in people with low cognitive performance with DSST and animal fluency than the participants with normal cognitive performance ($p < 0.001$). Participants in low cognitive performance group with DSST had higher probability to be everyday smokers ($p < 0.001$).

Table 2 presented the associations between dietary and total zinc intake and different measures of low cognitive performance. The crude odds ratios (ORs) with 95% confidence intervals (CIs) of low cognitive performance indicated that dietary and total zinc intake had significant inverse associations with the three measures of low cognitive performance. After adjustment for the potential confounding, the weighted multivariate adjusted ORs (95% CI) of low cognitive performance in DSST cognitive decline were 0.42 (0.18–0.97) for the highest quartile versus the lowest quartile of total zinc intake.

Table 1
Characteristics of the population by cognitive performance status

	DSST test			CERAD test			Animal fluency test		
	Low cognitive performance	Normal cognitive performance	*p*	Low cognitive performance	Normal cognitive performance	*p*	Low cognitive performance	Normal cognitive performance	*p*
N	537	1795		512	1820		439	1893	
Age in years at screening, median (IQR)[a]	69 (64, 76)	68 (63, 74)	0.05	69 (64, 76)	68 (63, 75)	0.05	69 (64, 76)	68 (63, 75)	0.021
Gender, *n* (%)[b]									
Male	290 (54.0%)	816 (45.5%)	<0.001	309 (60.4%)	797 (43.8%)	<0.001	209 (47.6%)	897 (47.4%)	0.96
Female	247 (46.0%)	979 (54.5%)		203 (39.6%)	1023 (56.2%)		230 (52.4%)	996 (52.6%)	
Race, *n* (%)[b]									
Mexican American	76 (14.15)	123 (6.85)	<0.001	63 (12.3)	136 (7.47)	<0.001	35 (7.97)	164 (8.66)	<0.001
Other Hispanic	114 (21.23)	126 (7.02)		77 (15.04)	163 (8.96)		59 (13.44)	181 (9.56)	
Non-Hispanic White	124 (23.09)	1019 (56.77)		185 (36.13)	958 (52.64)		125 (28.47)	1018 (53.78)	
Non-Hispanic Black	203 (37.8)	361 (20.11)		152 (29.69)	412 (22.64)		172 (39.18)	392 (20.71)	
Other Race	20 (3.72)	166 (9.25)		35 (6.84)	151 (8.3)		48 (10.93)	138 (7.29)	
Marital status, *n* (%)[b]									
Married	252 (47.01)	1047 (58.39)	<0.001	275 (53.71)	1024 (56.36)	<0.001	229 (52.28)	1070 (56.58)	<0.001
Widowed	134 (25)	307 (17.12)		99 (19.34)	342 (18.82)		103 (23.52)	338 (17.87)	
Divorced	66 (12.31)	269 (15)		66 (12.89)	269 (14.8)		54 (12.33)	281 (14.86)	
Separated	34 (6.34)	27 (1.51)		21 (4.1)	40 (2.2)		19 (4.34)	42 (2.22)	
Never married	37 (6.9)	93 (5.19)		32 (6.25)	98 (5.39)		27 (6.16)	103 (5.45)	
Living with partner	13 (2.43)	50 (2.79)		19 (3.71)	44 (2.42)		6 (1.37)	57 (3.01)	
Education, *n* (%)[b]									
<High school	313 (58.5%)	266 (14.8%)	<0.001	213 (41.7%)	366 (20.1%)	<0.001	179 (40.9%)	400 (21.1%)	<0.001
High school	123 (23.0%)	428 (23.8%)		124 (24.3%)	427 (23.5%)		118 (26.9%)	433 (22.9%)	
>High school	99 (18.5%)	1101 (61.3%)		174 (34.1%)	1026 (56.4%)		141 (32.2%)	1059 (56.0%)	
Smoking status, *n* (%)[b]									
Everyday	74 (27.5%)	155 (17.1%)	<0.001	63 (23.8%)	166 (18.3%)	0.05	48 (23.3%)	181 (18.7%)	0.21
Sometimes	16 (5.9%)	31 (3.4%)		14 (5.3%)	33 (3.6%)		10 (4.9%)	37 (3.8%)	
Not at all	179 (66.5%)	719 (79.4%)		188 (70.9%)	710 (78.1%)		148 (71.8%)	750 (77.5%)	
Alcohol drinking, *n* (%)[b]	327 (61.8%)	1261 (70.6%)	<0.001	349 (69.2%)	1239 (68.4%)	0.74	264 (61.0%)	1324 (70.3%)	<0.001
Diabetes, *n* (%)[b]	181 (35.3%)	373 (21.8%)	<0.001	140 (28.9%)	414 (23.8%)	0.02	138 (32.9%)	416 (23.0%)	<0.001
Hypertension, *n* (%)[b]	364 (67.8%)	1094 (61.0%)	0.004	324 (63.3%)	1134 (62.4%)	0.72	301 (68.6%)	1157 (61.2%)	0.004
Heart attack, *n* (%)[b]	65 (12.1%)	138 (7.7%)	0.002	53 (10.4%)	150 (8.3%)	0.16	44 (10.0%)	159 (8.4%)	0.3
Stroke, *n* (%)[b]	64 (11.9%)	86 (4.8%)	<0.001	47 (9.2%)	103 (5.7%)	0.01	44 (10.0%)	106 (5.6%)	0.001
Total energy, mean (SD)[c]	1633.67 (690.86)	1837.53 (634.89)	<0.001	1722.06 (666.76)	1809.86 (648.88)	0.01	1608.96 (623.17)	1832.71 (653.58)	<0.001
Dietary zinc(mg/d), median (IQR)[a]	8.05 (5.51, 10.72)	9.36 (7.07, 12.07)	<0.001	8.75 (6.32, 11.53)	9.20 (6.79, 11.92)	0.04	7.99 (5.56, 10.68)	9.35 (6.95, 12.09)	<0.001
Dietary iron (mg/d), median (IQR)[a]	11.44 (8.20, 15.59)	12.82 (9.65, 16.99)	<0.001	11.84 (8.72, 16.24)	12.73 (9.48, 16.81)	<0.001	11.63 (8.44, 16.15)	12.74 (9.59, 16.76)	<0.001
Dietary copper (mg/d), median (IQR)[a]	0.91 (0.70, 1.22)	1.09 (0.85, 1.41)	<0.001	1.00 (0.74, 1.30)	1.07 (0.83, 1.39)	<0.001	0.94 (0.71, 1.23)	1.08 (0.83, 1.40)	<0.001
Dietary selenium (mcg/d), median (IQR)[a]	84.80 (63.60, 116.20)	97.05 (73.25, 124.70)	<0.001	90.35 (67.80, 20.08)	95.35 (71.68, 123.30)	0.06	84.60(62.90, 113.80)	96.50 (73.15, 25.45)	<0.001
Total iron, median (IQR)[a]	12.15 (8.57, 17.40)	13.75 (10.07, 19.53)	<0.001	12.63 (8.95, 17.73)	13.56 (9.94, 19.29)	<0.001	12.60 (8.76, 18.40)	13.57 (9.95, 19.15)	0.001
Total zinc, median (IQR)[a]	9.64 (6.21, 14.59)	12.10 (8.13, 19.57)	<0.001	10.64 (7.20, 17.25)	11.72 (7.77, 18.87)	<0.001	9.69 (6.26, 16.85)	11.80 (7.97, 18.97)	<0.001
Total copper, median (IQR)[a]	1.03 (0.76, 1.43)	1.31 (0.95, 1.82)	<0.001	1.15 (0.81, 1.58)	1.27 (0.91, 1.78)	<0.001	1.05 (0.77, 1.53)	1.28 (0.91, 1.77)	<0.001
Total selenium, median (IQR)[a]	92.65 (69.50, 31.35)	111.55 (82.35, 151.15)	<0.001	105.03 (72.30, 141.50)	107.75 (79.63, 148.00)	0.01	96.65 (67.85, 135.20)	109.75 (81.15, 150.15)	<0.001

[a]*p* value was tested by Wilcoxon rank-sum test; [b]*p* value was tested by Chi-square test or Fisher's exact; [c]*p* value was tested by two sample *t* test.

Table 2
Weighted odds ratios (95% confidence intervals) of low cognitive performance by quartiles of zinc intakes, NHANES 2011–2014

	DSST test				CERAD test				Animal fluency test			
	Low	Normal	Crude[a]	Multivariate-adjusted[b]	Low	Normal	Crude[a]	Multivariate-adjusted[b]	Low	Normal	Crude[a]	Multivariate-adjusted[b]
Dietary zinc intake, mg/d												
Q1 (0.75–6.65)	197	384	1 (reference)	1 (reference)	144	437	1 (reference)	1 (reference)	159	422	1 (reference)	1 (reference)
Q2 (6.66–9.19)	127	483	0.42 (0.26, 0.66)	0.96 (0.42, 2.19)	138	472	0.92 (0.65, 1.31)	1.37 (0.71, 2.66)	115	495	0.56 (0.41, 0.79)	0.99 (0.58, 1.67)
Q3 (9.20–12.57)	130	529	0.43 (0.26, 0.72)	1.12 (0.51, 2.44)	137	522	0.79 (0.57, 1.09)	2.14 (1.24, 3.71)	100	559	0.54 (0.37, 0.79)	0.77 (0.38, 1.59)
Q4 (12.58–27.79)	83	399	0.31 (0.20, 0.50)	0.94 (0.41, 2.16)	93	389	0.62 (0.40, 0.98)	1.82 (0.75, 4.40)	65	417	0.36 (0.23, 0.56)	0.71 (0.31, 1.61)
p_{trend}			<0.001	0.066			0.02	0.980			<0.001	0.043
Total zinc intake, mg/d												
Q1 (0.75–5.64)	116	160	1 (reference)	1 (reference)	82	194	1 (reference)	1 (reference)	94	182	1 (reference)	1 (reference)
Q2 (5.65–9.16)	137	413	0.44 (0.22, 0.89)	1.1 (0.53, 2.25)	128	422	0.65 (0.40, 1.07)	2.34 (1.37, 3.98)	108	442	0.38 (0.24, 0.61)	0.85 (0.49, 1.46)
Q3 (9.17–13.96)	141	474	0.37 (0.20, 0.70)	0.82 (0.36, 1.84)	129	486	0.58 (0.37, 0.91)	1.64 (0.88, 3.04)	99	516	0.39 (0.25, 0.63)	0.74 (0.40, 1.36)
Q4 (13.97–53.80)	143	748	0.22 (0.14, 0.35)	0.42 (0.18, 0.97)	173	718	0.55 (0.35, 0.88)	1.88 (0.82, 4.32)	138	753	0.31 (0.19, 0.51)	0.68 (0.30, 1.54)
p_{trend}			<0.001	0.035			0.098	0.777			0.008	0.272

[a]Crude model did not adjust any confounders. [b]Adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d).

The associations between dietary and total iron intake and different measures of low cognitive performance were presented in Table 3. The crude OR and 95% CIs of low cognitive performance indicated that dietary and total iron intake had significant inverse associations with low cognitive performance in DSST. After adjustment for the potential confounding, the weighted multivariate adjusted ORs (95% CI) of low cognitive performance in DSST were 0.44 (0.21–0.95) for the highest quartile versus the lowest quartile of total iron intake.

Table 4 presented the associations between dietary and total copper intake and different measures of low cognitive performance. The crude OR and 95% CIs of low cognitive performance indicated that dietary copper intake had significant inverse associations with all the three measures of low cognitive performance, and total copper intake had significant inverse associations with low cognitive performance in DSST and animal fluency. After adjustment for the potential confounding, compared to the lowest quartile, the weighted multivariate adjusted ORs (95% CI) of low cognitive performance in DSST were 0.37 (0.21–0.63) and 0.34 (0.16–0.75) for the highest quartile of dietary and total copper intake, respectively.

For associations between dietary and total selenium intake and different measures of low cognitive performance, the results were shown in Table 5. In the crude model, the crude OR and 95% CIs of low cognitive performance indicated that total selenium intake had significant inverse associations with low cognitive performance in DSST and animal fluency. Compared with the lowest quartile of total selenium intake, the weighted multivariate adjusted ORs (95% CI) of the highest quartile were 0.48 (0.25–0.92) for low cognitive performance in DSST. Sensitivity analysis additionally adjusted for stroke status in the multivariate-adjusted model for the three different measures of low cognitive performance also yielded similar results to the primary analyses (data not shown). We also performed stratified analyses which showed that the associations between dietary, total trace element intake, and poor cognitive performance in each age group appeared similar with that in the overall study subjects.

The association between meeting the RDA of the micro nutrients and low cognitive performance was described in Table 6. In the crude model, meeting the RDA of the zinc, iron, copper, and selenium were negatively associated with low cognitive performance. However, after adjusting for the potential confounders, only total copper intake was

Table 3
Weighted odds ratios (95% confidence intervals) of low cognitive performance by quartiles of iron intakes, NHANES 2011–2014

	DSST test				CERAD test				Animal fluency test			
	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted
Dietary iron intake, mg/d												
Q1 (1.265–9.35)	191	406	1 (reference)	1 (reference)	163	434	1 (reference)	1 (reference)	152	445	1 (reference)	1 (reference)
Q2 (9.36–12.87)	128	503	0.54 (0.34, 0.83)	1.24 (0.55, 2.78)	132	499	0.59 (0.40, 0.88)	1.43 (0.66, 3.10)	108	523	0.5 (0.33, 0.75)	0.63 (0.31, 1.28)
Q3 (12.88–17.44)	122	483	0.5 (0.30, 0.83)	0.61 (0.27, 1.41)	116	489	0.53 (0.38, 0.76)	1.11 (0.52, 2.36)	93	512	0.5 (0.32, 0.80)	0.77 (0.43, 1.39)
Q4 (17.45–38.65)	96	403	0.4 (0.28, 0.58)	0.75 (0.39, 1.44)	101	398	0.58 (0.38, 0.88)	0.88 (0.45, 1.71)	86	413	0.59 (0.41, 0.85)	0.53 (0.24, 1.14)
p_{trend}			<0.001	0.002			0.04	0.205			0.041	0.048
Total iron intake, mg/d												
Q1 (1.265–7.60)	99	187	1 (reference)	1 (reference)	85	201	1 (reference)	1 (reference)	79	207	1 (reference)	1 (reference)
Q2(7.61–12.24)	172	528	0.62 (0.37, 1.05)	1.21 (0.56, 2.64)	162	538	0.75 (0.54, 1.04)	1.50 (0.68, 3.35)	134	566	0.52 (0.31, 0.87)	0.62 (0.28, 1.41)
Q3 (12.25–17.94)	146	537	0.47 (0.27, 0.81)	0.79 (0.37, 1.67)	140	543	0.57 (0.39, 0.82)	0.84 (0.45, 1.57)	111	572	0.47 (0.31, 0.70)	0.67 (0.38, 1.19)
Q4 (17.95–47.75)	120	543	0.32 (0.22, 0.49)	0.44 (0.21, 0.95)	125	538	0.61 (0.38, 1.00)	1.00 (0.47, 2.12)	115	548	0.56 (0.37, 0.85)	0.62 (0.31, 1.25)
p_{trend}			<0.001	0.002			0.177	0.445			0.333	0.206

[a]Crude model did not adjust any confounders. [b]Adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d).

Table 4
Weighted odds ratios (95% confidence intervals) of low cognitive performance by quartiles of copper intakes, NHANES 2011–2014

	DSST test				CERAD test				Animal fluency test			
	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted
Dietary copper intake, mg/d												
Q1 (0.19–0.70)	139	254	1 (reference)	1 (reference)	122	271	1 (reference)	1 (reference)	109	284	1 (reference)	1 (reference)
Q2 (0.71–0.96)	160	418	0.56 (0.39, 0.81)	0.43 (0.27, 0.66)	118	460	0.48 (0.33, 0.70)	0.79 (0.53, 1.17)	130	448	0.77 (0.50, 1.20)	0.89 (0.51, 1.55)
Q3 (0.97–1.30)	137	537	0.37 (0.26, 0.54)	0.55 (0.31, 0.98)	147	527	0.52 (0.33, 0.83)	0.83 (0.43, 1.61)	115	559	0.56 (0.39, 0.81)	0.54 (0.29, 1.00)
Q4 (1.31–3.14)	101	586	0.21 (0.14, 0.31)	0.37 (0.21, 0.63)	125	562	0.38 (0.24, 0.59)	0.60 (0.31, 1.17)	85	602	0.33 (0.25, 0.45)	0.42 (0.17, 1.01)
p_{trend}			<0.001	<0.001			<0.001	0.225			<0.001	0.005
Total copper intake, mg/d												
Q1 (0.21–0.57)	60	95	1 (reference)	1 (reference)	58	97	1 (reference)	1 (reference)	54	101	1 (reference)	1 (reference)
Q2 (0.58–0.91)	162	327	0.89 (0.59, 1.34)	0.69 (0.41, 1.15)	120	369	0.45 (0.25, 0.84)	1.01 (0.65, 1.56)	114	375	0.4 (0.20, 0.82)	0.74 (0.42, 1.33)
Q3 (0.92–1.37)	163	565	0.43 (0.28, 0.66)	0.49 (0.25, 0.98)	152	576	0.35 (0.20, 0.61)	0.99 (0.61, 1.63)	132	596	0.35 (0.17, 0.71)	0.50 (0.23, 1.07)
Q4 (1.38–4.41)	152	808	0.23 (0.15, 0.36)	0.34 (0.16, 0.75)	182	778	0.35 (0.20, 0.63)	0.90 (0.50, 1.62)	139	821	0.24 (0.12, 0.45)	0.65 (0.31, 1.36)
p_{trend}			<0.001	0.006			0.076	0.657			<0.001	0.031

[a]Crude model did not adjust any confounders. [b]Adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d).

Table 5
Weighted odds ratios (95% confidence intervals) of low cognitive performance by quartiles of selenium intakes, NHANES 2011–2014

	DSST test				CERAD test				Animal fluency test			
	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted
Dietary selenium intake, mcg/d												
Q1 (11.2–68.5)	163	371	1 (reference)	1 (reference)	134	400	1 (reference)	1 (reference)	146	388	1 (reference)	1 (reference)
Q2 (68.6–95.0)	154	483	0.75 (0.54, 1.04)	1.34 (0.76, 2.35)	138	499	0.8 (0.51, 1.23)	1.32 (0.68, 2.57)	117	520	0.62 (0.41, 0.93)	1.82 (1.00, 3.34)
Q3 (95.1–129.0)	124	537	0.48 (0.35, 0.65)	1.06 (0.58, 1.92)	139	522	0.8 (0.57, 1.11)	1.02 (0.56, 1.84)	112	549	0.55 (0.37, 0.80)	1.44 (0.67, 3.07)
Q4 (129.1–281.1)	96	404	0.44 (0.25, 0.78)	0.99 (0.44, 2.21)	101	399	0.61 (0.43, 0.87)	1.25 (0.67, 2.33)	64	436	0.32 (0.21, 0.49)	0.78 (0.33, 1.85)
p_{trend}			0.018	0.121			0.026	0.316			<0.001	0.010
Total selenium intake, mcg/d												
Q1 (13.4–53.2)	65	107	1 (reference)	1 (reference)	53	119	1 (reference)	1 (reference)	53	119	1 (reference)	1 (reference)
Q2 (53.3–88.5)	185	430	0.74 (0.43, 1.26)	0.76 (0.38, 1.55)	142	473	0.62 (0.31, 1.21)	0.53 (0.31, 0.89)	148	467	0.5 (0.31, 0.81)	1.08 (0.52, 2.25)
Q3 (88.6–127.7)	140	572	0.36 (0.23, 0.56)	0.87 (0.47, 1.63)	149	563	0.54 (0.29, 1.00)	0.89 (0.46, 1.75)	114	598	0.31 (0.19, 0.50)	0.99 (0.41, 2.38)
Q4 (127.8–347.1)	147	686	0.27 (0.17, 0.44)	0.48 (0.25, 0.92)	168	665	0.53 (0.30, 0.92)	1.09 (0.58, 2.05)	124	709	0.26 (0.15, 0.46)	0.49 (0.22, 1.05)
p_{trend}			<0.001	0.002			0.112	0.767			0.001	0.081

[a]Crude model did not adjust any confounders. [b]Adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d).

Table 6
Weighted odds ratios (95% confidence intervals) of low cognitive performance for being below the RDA or meeting or being above the RDA of zinc, iron, copper, and selenium intakes, NHANES 2011–2014

	DSST test				CERAD test				Animal fluency test			
	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted	Low	Normal	Crude	Multivariate-adjusted
Total zinc intake, mcg/d												
< RDA	274	587	1 (reference)	1 (reference)	226	635	1 (reference)	1 (reference)	208	653	1 (reference)	1 (reference)
≥ RDA	263	1,208	0.42 (0.31, 0.56)	0.71 (0.42, 1.19)	286	1,185	0.65 (0.50, 0.84)	1.49 (0.87, 2.57)	231	1,240	0.54 (0.37, 0.80)	0.75 (0.41, 1.38)
Dietary iron intake, mg/d												
<RDA	113	209	1 (reference)	1 (reference)	92	230	1 (reference)	1 (reference)	87	235	1 (reference)	1 (reference)
≥RDA	424	1,586	0.45 (0.29, 0.70)	0.61 (0.27, 1.35)	420	1,590	0.68 (0.48, 0.97)	0.72 (0.34, 1.55)	352	1,658	0.52 (0.34, 0.79)	0.47 (0.19, 1.17)
Total copper intake, mcg/d												
<RDA	212	395	1 (reference)	1 (reference)	171	436	1 (reference)	1 (reference)	159	448	1 (reference)	1 (reference)
≥RDA	325	1,400	0.33 (0.26, 0.42)	0.54 (0.31, 0.92)	341	1,384	0.63 (0.45, 0.88)	1.46 (0.88, 2.40)	280	1,445	0.54 (0.39, 0.74)	0.79 (0.43, 1.42)
Total selenium intake, mcg/d												
<RDA	80	124	1 (reference)	1 (reference)	64	140	1 (reference)	1 (reference)	64	140	1 (reference)	1 (reference)
≥RDA	457	1,671	0.37 (0.24, 0.57)	0.77 (0.28, 2.13)	448	1,680	0.49 (0.29, 0.83)	1.06 (0.42, 2.66)	375	1,753	0.35 (0.24, 0.51)	0.42 (0.15, 1.13)

[a]Crude model did not adjust any confounders. [b]Adjusted for age (years), gender, race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d).

significantly associated with low cognitive performance in DSST, with a multivariate ORs (95% CI) of 0.54 (0.31, 0.92). In addition, when we included all the micro nutrients in the same model simultaneously, only copper intake was significantly associated with low cognitive performance, which verifies that the association between copper intake and low cognitive performance was robust. Results for the multivariate linear regression model with the composite score as the dependent variable was listed in Supplementary Table 1. The composite score of cognitive performance increases 31.43 unit averagely for each 100-unit increase of dietary copper intake.

Figure 1 depicted the results of the restricted cubic spline analyses. For low cognitive performance in the DSST and animal fluency, we found a suggestion of L-shaped associations between them and total copper or selenium. The prevalence of low cognitive performance in DSST decreased with increasing intakes of total copper intake, and showed a non-linear dose-relationship ($p_{\text{nonlinearity}} = 0.001$). For total selenium intake, the ORs of low cognitive performance in DSST and animal fluency decreased with increasing intakes of total selenium intake in a linear dose-relationship manner ($p_{\text{nonlinearity}} = 0.946, 0.459$, respectively). The association between low cognitive performance in CERAD and the total iron, zinc, copper, and selenium intake were not significant (figure not shown).

DISCUSSION

In this study, we combined NHANES 2011–2012 and NHANES 2013–2014 data and included 2,332 US participants aged 60 years or older, and evaluated

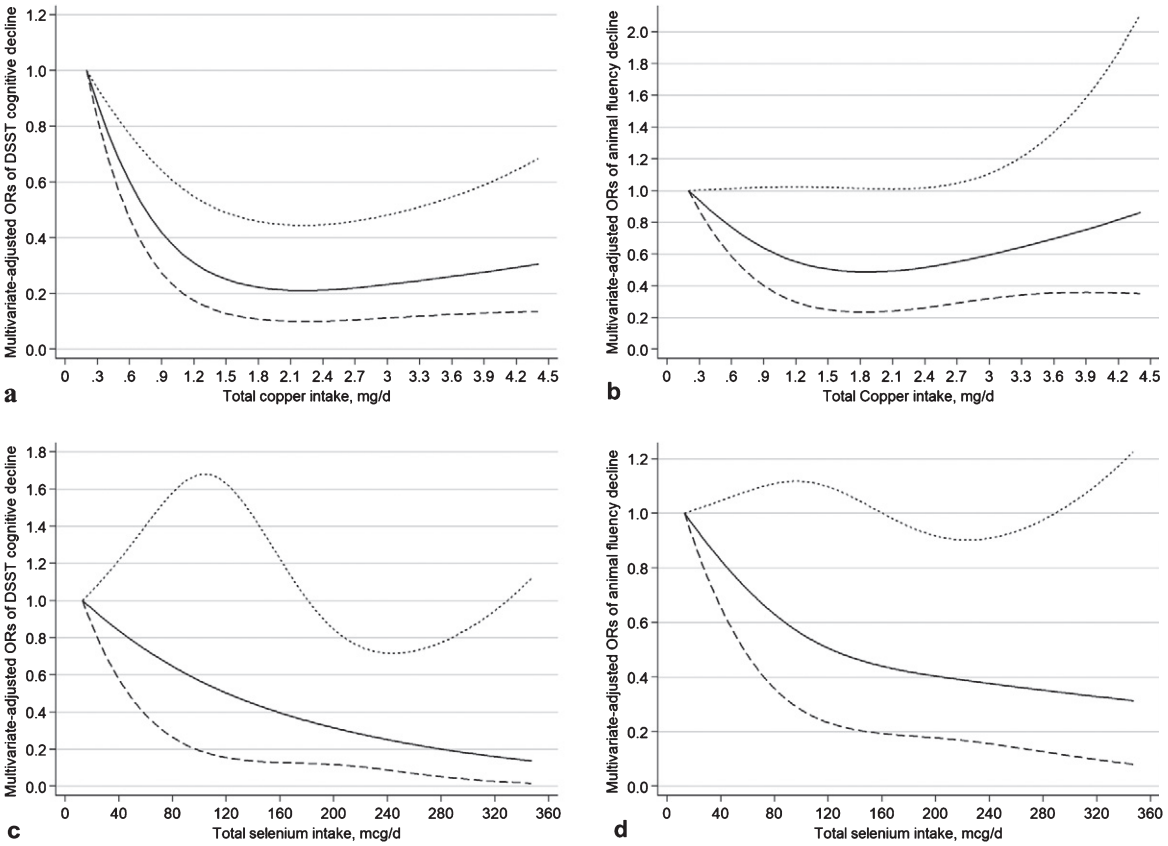

Fig. 1. Restricted cubic spline model of the ORs of low cognitive performance with total copper and selenium intakes[1]. [1]Adjusted for age (years), gender (male, or female), race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race), educational level (less than high school, high school, higher than high school), marital status (married, widowed, divorced, separated, never married, living with partner), smoking status (everyday smoking, sometimes smoking, not at all), alcohol drinking (ever, or never), hypertension (yes, or no), diabetes (yes, or no), heart disease (yes, or no), and total daily energy intake (kcal/d). The solid lines represent the ORs, and dashed lines represent the 95% CIs. a) $p_{\text{nonlinearity}} = 0.001$; b) $p_{\text{nonlinearity}} = 0.109$; c) $p_{\text{nonlinearity}} = 0.946$; d) $p_{\text{nonlinearity}} = 0.459$.

the relationships of dietary and total zinc, iron, copper, and selenium intakes with three measure of low cognitive performance. After adjusted for the potential cofounders, the association between zinc, copper, and selenium intake and low cognitive performance was significant in different tests and an L-shaped dose–response relationship was detected for total copper and selenium intake.

To date, many original studies and meta-analyses have reported the involvement of zinc in the pathology of AD and cognitive function [15, 18]. However, only few studies focused on the association between dietary intake of zinc and cognitive function or AD so far [20, 21, 29]. For instance, Ortega et al. examined 260 Spaniards aged 65–90 years and found that higher dietary intake of several nutrients including zinc was associated with better cognitive performance [21]. Yaffe et al. administered cognitive tests to 2,166 adults aged 61–87 years, half of whom were given zinc supplements (80 mg/d) for several years, and no significant differences between groups was found [29]. In a multicenter prospective intervention study, a randomized double-blind placebo-controlled trial in 387 healthy adults aged 55–87 years was conducted to investigate the effects of zinc supplementation on cognitive function, which revealed that zinc supplementation was associated with improved scores in two cognitive tests (attention and spatial working memory) [20]. Our study suggested that moderate zinc intake was negatively associated with low cognitive performance. The exact mechanism of the association between zinc intake and low cognitive performance was not clear so far, however, some speculations might be as follows. First, zinc is a part of the antioxidant enzyme superoxide dismutase and metallothioneins, and seems to play significant role in maintaining metabolic homeostasis and antioxidant mechanism [30]. In addition, zinc is a component of more than 1,000 proteins including copper/zinc superoxide dismutase (CuZnSOD), and several proteins involved in DNA-damage repair such as p53 [12, 31].

To our knowledge, many studies have explored the associations between serum, plasma, or CSF copper level and AD [15, 16, 19], and many studies indicated that AD patients have higher levels of copper in plasma but lower levels in the brain [32], which suggested that copper dysregulation might be involved in the process of AD or low cognitive performance. However, as far as we know, studies focused on dietary copper intake/copper exposure and low cognitive performance were relatively limited, with inconsistent results. A cohort study of 3,718 participants by Morris et al. reported among the subjects whose diets were high in saturated and trans fats, higher copper intake was associated with a faster rate of cognitive decline, while no association was found in subjects with low saturated and trans fatty acids dietary intake [22]. Another ecological study by Shen et al. found a positive association between the copper concentration in the soil and AD mortality [33]. In contrast, a randomized control phase II clinical trial evaluated the efficacy of oral copper supplementation of 8 mg/d in 68 patients with mild AD for 12 months, and found no significant differences in cognitive function between the experimental and control groups [34]. In this study, we used dietary and total copper intake as the copper exposure measurement and found a negative association between dietary, total copper intake and low cognitive performance. The mechanism involved in this association is not well established. But it seems that copper deficiency might cause decreased cytochrome oxidase level, and then lead to energy deficiency, which may cause brain cells to die, and influence the cognitive function [13]. Besides, copper deficiency might lead to brain inflammation and oxidative stress, which is supposed to be involved in the progress of cognitive decline and AD [13]. However, having a low dietary intake does not mean there is a copper deficiency, and copper absorption decreases as dietary copper intake increases [35]. In addition, some studies also suggested that excess copper might lead to increases of ceruloplasmin, which could also be involved in inflammation and low cognitive performance [16, 36]. Further studies should be warranted in the future.

As for selenium, it is an important part of some antioxidant selenoproteins such as glutathione peroxidases and thioredoxin reductases, which have been suggested to protect the neurons and astrocytes from lipoperoxidation and oxidative damage by the free radicals [37]. Moreover, free radicals and its oxidative stress effect have been suggested to be involved in the pathogenesis of low cognitive performance [38, 39], thus selenium deficiency and low level of antioxidants has been implicated in the pathophysiology of low cognitive performance and AD. Many previous studies have investigated the association of selenium level and AD; however, the results were inconsistent. Some studies reported that selenium levels were much higher in AD patients than the controls [40, 41]. In addition, Cardoso. et al did not spot any significant change in low cognitive performance people [42], and observed no differences in total selenium

concentration in serum or CSF of AD subjects compared to mildly cognitively impairment patients and healthy controls [43]. However, most of the previous published studies found a reduced level of blood selenium in AD patients [44, 45]. The reason for this inconsistence might be related to their usual exposure to selenium; different selenium exposure reflects in a different response in terms of blood markers. Some previous studies also found lower plasma selenium level was associated with higher risk of low cognitive performance [46, 47], which is in line with our results and suggested that a high selenium level might be negatively associated with the risk of cognitive decline and AD. Our study focused on the dietary and total selenium intake, and found the high selenium intake might be negatively associated with the prevalence of low cognitive performance in a linear dose-relationship manner.

Our study has several strengths. A major strength is the use of a large nationally representative sample of elderly adults in the US, and the NHANES survey has high quality for the survey methods and quality control. In this study, we combined two cycles of the survey, which can provide more samples for robust associations. Besides, the inverse associations between dietary and total copper, selenium intakes, and low cognitive performance remained significant after adjustment for major confounders, and we further investigated the dose-response relationship using restricted cubic spline. In addition, for the measurement of trace element intake, both dietary and total intakes were taken into consideration. For the cognitive function measures, multi-dimensions (including CERAD, DSST, and animal fluency test) were applied.

We acknowledge some limitations of our study. Firstly, this is a cross-sectional study, and the risk of unmeasured confounders from a large number of dietary, environmental, and lifestyle factors is high, so we cannot evaluate the causal relationships of the associations between dietary intake and low cognitive performance. Since the study subjects with the worst cognitive performance could experience deterioration of their metabolic or nutritional status, they might have lower levels of trace elements in consequence [48], thus further prospective cohort studies are needed to confirm the temporal relationships. Secondly, for the measurement of trace elements, dietary and total intakes were used; however, serum levels were not included in the analysis, because serum level data was only available for a minor part of the included participants. Our dietary data was collected through two 24-hour recalls; although it has been suggested to have high validity, there could be recall bias and the self-report dietary intake might be subjective. Besides, because trace element content might be different even in the same foods depending on the soil level of the place from where they were produced, assessing dietary intake through dietary records might not be accuracy. In addition, AD and low cognitive performance might be related with complex metals dysregulation in the brain, and the different chemical form of copper and the other trace elements might play complex role in the etiology of AD and low cognitive performance, which could not be assessed in the diet and become another limitation of our study. Further studies working on the association between different chemical forms and cognition or AD is warranted in the future.

In conclusion, our results indicated that dietary and total zinc, copper, and selenium intakes might be inversely associated with low cognitive performance in US older adults, and an L-shaped dose–response relationship was detected. Further prospective cohort studies are warranted to confirm these findings.

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SUPPLEMENTARY MATERIAL

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