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Association between serum iron, blood lead, cadmium, mercury, selenium, manganese and low cognitive performance in old adults from National Health and Nutrition Examination Survey (NHANES): a cross-sectional study

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Abstract

Cognitive decline is a public health problem for the world's ageing population. This study was to evaluate the relationships between serum Fe, blood Pb, Cd, Hg, Se and Mn and cognitive decline in elderly Americans. Data of this cross-sectional study were extracted from the National Health and Nutritional Examination Survey (NHANES 2011–2014). Cognitive performance was measured by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Animal Fluency and Digit Symbol Substitution Test (DSST) tests. Weighted univariable and multivariate logistic regression analyses were used to assess the associations between six trace elements and low cognitive performance. Subgroup analyses based on diabetes and hypertension history were further assessed the associations. A total of 2002 adults over 60 years old were included. After adjusting covariates, elevated serum Fe levels were associated with the decreased risk of low cognitive performance, especially in the elderly without diabetes history and with hypertension history. High blood Cd levels were associated with the high odds of low cognitive performance in old adults with diabetes and hypertension history. Elevated blood Mn levels were connected with low cognitive performance in old hypertensive people. High blood Pb levels were related to the high odds of low cognitive performance, especially in the elderly without diabetes and hypertension history. High blood Se levels were linked to the decreased risk of low cognitive performance in all the elderly. Appropriate Fe, Se supplementation and Fe-, Se-rich foods intake, while reducing exposure to Pb, Cd and Mn may be beneficial for cognitive function in the elderly.

Key words: **Low cognitive performance: Trace elements: NHANES database**

Ageing, a physiological state of natural development, is featured by physical and cognitive decline[1,2]. Once cognitive impairment occurs, dementia and mortality rates increase in the elderly[3], the typical symptoms are difficulties with memory, language, problem-solving and other thinking skills, which affect a person's ability to perform daily activities[4]. In the USA, more than 16 million family members and other unpaid caregivers provided approximately 18·6 billion hours of care for patients with low cognitive performance in 2019, and the total cost was estimated to be $305 billion in 2020[5]. Before breakthroughs are made in prevention or treatment, low cognitive performance will pose an increasing challenge to the health care system around the world[6]. Therefore, it is necessary and important to detect the preclinical manifestations of low cognition as early as possible and to conduct the intervention.

Trace elements are combined with biological macromolecules such as proteins and nucleic acids to participate in regulating the function of the nervous system[7–9]. Homoeostasis imbalance of trace elements in the brain may cause cognitive impairment[9]. Previous studies have suggested that Fe, Mg and Zn may help to maintain normal cognitive function and enhanced happiness by reducing mental and physical fatigue and positive emotions[7,8,10]. Several studies showed that the level of Fe and Se in the elderly decreased with age, and Se

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, Digit Symbol Substitution Test; NHANES, National Health and Nutritional Examination Survey.

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deficiency may cause cognitive decline in the elderly[11–13]. Moreover, Pb, Cd and Hg exposure were risks for cognitive dysfunction because they had long-term effects on the brain[14,15].

This study was to assess the association between six trace elements (Fe, Pb, Cd, Hg, Se and Mn) in blood and low cognitive performance in the elderly over 60 years old, using the data from the National Health and Nutrition Examination Survey (NHANES) database. Subgroup analyses were conducted based on hypertension and diabetes to evaluate the association in different subpopulations.

Methods

Study population

Data were extracted from 2011–2012 and 2013–2014 NHANES, a representative cross-sectional survey of all non-institutionalised civilian population in the USA. NHANES is a major project of the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention (CDC) and is responsible for compiling life and health statistics. Participants completed surveys about demographics, health history, and diet, and they submitted blood and urine samples during physical examinations. Cognitive assessment was conducted in a household interview or at a Mobile Examination Center (MEC) using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test, the CERAD Word List Recall Test, the Animal Fluency test and the Digit Symbol Substitution Test (DSST)[17,18]. The NHANES protocols were approved by the NCHS Ethics Review Board of the US CDC. All individuals provided written informed consent during the survey. More information about the NHANES database can be obtained at: http://www.cdc.gov/nhanes.

Cognitive performance

The CERAD Word Learning subtest (CERAD W-L) assessed immediate and delayed learning of new language information (memory subdomain) [19]. The CERAD test consisted of three consecutive learning trials and one delayed recall. In each learning tests, participants read ten unrelated words aloud at a time. Then the words from the learning trial were shown on a computer monitor in a random order, and the participants were asked to recall as many of them as possible. Each test was scored between 0 and 10 points, with one point for each correct word. The total score of the three tests and one delayed recall was the CERAD total score.

The Animal Fluency test assessed categorical verbal fluency. Participants were asked to name as many animals as possible in 1 min, and one point was scored for each animal correctly named.

DSST was a performance module in the Wechsler Adult Intelligence Scale (WAIS III), which was used to test sustained attention and working memory[20]. Before the participants started the main test, they performed an exercise using a paper with a key at the top pairing numbers with nine symbols. Participants were asked to copy the corresponding symbols from the 133 boxes with numbers within 120 s. In NHANES, participants who were unable to correctly copy the symbols and numbers in the pretest practice did not continue. In the specified time, the score is the total number of correct matches, and the highest score is 133 points.

The low cognitive performance was assessed by the cut-off points of the 25th percentile of the CERAD, Animal Fluency and DSST tests, which was consistent with methods used in the published studies[21,22]. Participants scoring below the lowest quartile were defined as having low cognitive performance in each cognitive test. The threshold scores of the CERAD, Animal Fluency and DSST tests were 5, 14 and 41 points, respectively.

Serum iron, blood lead, cadmium, mercury, selenium and manganese exposure assessment

A phlebotomist at the MEC collected blood from participants, and the blood was processed and divided into vials. They were then refrigerated or frozen for storage and transported to laboratories across the USA, where most of the tests were completed by remote laboratories. The determination method of serum Fe concentration was a timed-endpoint method, which was determined by DcX800 method. The change in absorbance of the reaction system was monitored at 560 nm at a fixed-time interval, and the change in absorbance was directly proportional to the concentration of Fe in the sample. The concentrations of blood Pb, Cd, Hg, Se and Mn were determined by quadrupole inductively coupled plasma-MS (ICP-MS) technology. For details on the specific methods of blood metal detection and measurement, see NHANES laboratory manual (http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/PbCd_G_met_blood%20metals.pdf).

Potential covariates

Demographic information and history of diseases of participants were extracted from the database. Sex, age and race were self-reported demographic information. Education was assessed by the question 'What is the highest grade or level of school you have completed or the highest degree you have received?' (less than 9th grade/9–11th grade (includes 12th grade with no diploma)/high school graduate or general educational development (GED) or equivalent/some college or AA degree (associate of arts)/college graduate or above). Diabetes and hypertension history were examined by self-reported questionnaire. The BMI was calculated by dividing the weight of the participant by the square of the height (kg/m^2). Smoking history was assessed by the question 'Have you smoked at least 100 cigarettes in your entire life?' (yes/no). The income-poverty ratio (IPR) was a measure of household income divided by the poverty guidelines to calculate the ratio of family income to poverty based on family size, year and state. Alcohol information (yes/no) and marital status (yes/no) were collected through personal interviews.

Statistical analysis

All statistical analyses were performed by SAS software (version 9.4, SAS Institute). Using the proc surveyfreq in SAS software, the final sample size was weighted with WTMEC2YR, SDMVPSU and SDMVSTRA. WTMEC2YR is the MEC exam weight (wtmec2yr) used for weighting. SDMVPSU means that the masked variance

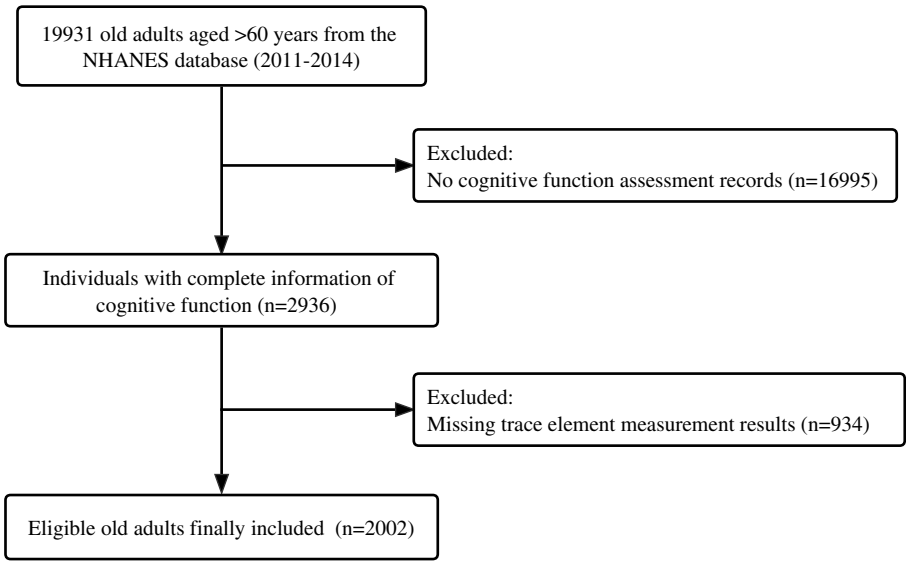


Fig. 1. The flow chart of population screening. NHANES, National Health and Nutritional Examination Survey.

unit pseudo-substrate is sdmvstra, and the masked variance unit pseudo-primary sampling unit (PSU) is sdmvpsu. SDMVSTRA refers to the CI being applied to assess the reliability of an estimate. Quantitative data were tested for normality using Kolmogorov–Smirnov. Abnormal distribution data were presented by median and quartile (M (Q1, Q3)), and comparisons between the two groups were performed using Mann–Whitney *U* test. Qualitative data were expressed as the number and proportion (*n* (%)), and the χ^2 test was used for comparison between the two groups.

All participants were divided into the low cognitive performance and normal cognitive performance groups according to the cut-off points of the 25th percentile of the CERAD, Animal Fluency and DSST tests. Covariates were screened by the difference analysis between the two groups. Weighted univariable and multivariate logistic regression analyses were conducted to evaluate the associations between six trace elements and the risk of low cognitive performance. Model 1 was a crude model without adjusting covariates. Model 2 was first adjusted for demographic information (sex, age, race and marital status) and BMI. Model 3 was the fully adjusted model accounted for these variables as well as IPR, alcohol drinking, diabetes and hypertension history, and smoking status. Weighted random interpolation was performed for missing data. Sensitivity analysis was used to assess the results before and after interpolation. The associations were further explored in individuals with history of diabetes and hypertension. Two-sided $P < 0{\cdot}05$ was considered as statistically significant.

Results

Description of the study population

A total of 19 931 participants were included from NHANES 2011–2012 and 2013–2014. Participants without cognitive function score (*n* 16 995) and laboratory values of trace elements (*n* 934) were excluded. The final inclusion of 2002 individuals was weighted to represent 37,242,171 individuals over the age of 60 years. The flow chart of population screening was shown in Fig. 1.

Characteristics of old adults with low and normal cognitive performance

The characteristics of participants with low and normal cognitive performance according to the CERAD, Animal Fluency and DSST assessments were shown in Tables 1–3. For the CERAD test in Table 1, compared with old adults with normal cognitive performance, the median levels of blood Pb (1·45 ug/dl *v.* 1·38 ug/dl), Cd (0·38 ug/dl *v.* 0·35 ug/dl) and Se (193·03 ug/dl *v.* 192·50 ug/dl) were high, while the median levels of serum Fe (81·00 ug/dl *v.* 86·00 ug/dl), blood Hg (0·86 ug/dl *v.* 1·00 ug/dl) and Mn (8·64 ug/dl *v.* 8·80 ug/dl) were low in participants with low cognitive performance. Differences were found in age, sex, education level, BMI, IPR, diabetes history and hypertension history between the two groups ($P < 0{\cdot}05$). For the Animal Fluency test in Table 2, there were statistical differences in age, race, education level, marital status, BMI, IPR, diabetes history and hypertension history ($P < 0{\cdot}05$). The median levels of blood Pb (1·52 ug/dl *v.* 1·37 ug/dl) and Cd (0·42 ug/dl *v.* 0·34 ug/dl) were higher, while the median levels of serum Fe (76·00 ug/dl *v.* 86·00 ug/dl), blood Hg (0·73 ug/dl *v.* 1·03 ug/dl), Se (186·19 ug/dl *v.* 195·84 ug/dl) and Mn (8·73 ug/dl *v.* 8·79 ug/dl) were lower in the elderly with low cognitive performance than these in the elderly with normal cognitive performance. For the DSST test (Table 3), the results showed the differences in age, race, education level, BMI, IPR, alcohol drinking, diabetes history and hypertension history ($P < 0{\cdot}05$). The median blood Cd (0·40 ug/dl *v.* 0·35 ug/dl) and Mn (8·80 ug/dl *v.* 8·78 ug/dl) levels were high, while the median blood Pb (1·40 ug/dl *v.* 1·41 ug/dl), serum Fe (78·00 ug/dl *v.* 87·00 ug/dl), blood Hg (0·76 ug/dl *v.* 0·99 ug/dl) and Se (190·33 ug/dl *v.* 193·94 ug/dl) levels were low in the elderly with low cognitive performance in comparison with these in the elderly with normal cognitive performance.

British Journal of Nutrition

Table 1. Characteristics of elderly over 60 years of age by cognitive performance status according to CERAD test

	Total (*n* 2002)		CERAD					
			Low cognitive performance (*n* 852)		Normal cognitive performance (*n* 1150)			
Variables	*n*	%	*n*	%	*n*	%	Statistics	*P*
Sex							$\chi2 = 25{\cdot}892$	< 0·001
Male	986	46·34	489	55·17	497	40·96		
Female	1016	53·66	363	44·83	653	59·04		
Age								
M		68·00		71·00		66·00	$Z = 1518{\cdot}169$	< 0·001
Q_1, Q_3		63·00, 74·00		65·00, 79·00		63·00, 72·00		
Race							$\chi2 = 7{\cdot}875$	0·067
Hispanic	372	6·76	183	8·88	189	5·47		
Non-Hispanic White	957	80·63	401	78·29	556	82·05		
Non-Hispanic Black	474	7·74	204	8·42	270	7·33		
Non-Hispanic others	199	4·87	64	4·41	135	5·15		
Education							$\chi2 = 22{\cdot}101$	0·002
Less than 9th grade	248	6·18	160	9·59	88	4·10		
9–11 grade (includes 12 grade with no diploma)	261	9·57	130	12·09	131	8·04		
High school graduate/GED or equivalent	474	22·65	204	24·91	270	21·27		
Some college or AA degree	561	30·63	194	25·11	367	33·98		
College graduate or above	458	30·98	164	28·31	294	32·60		
Marital status							$\chi2 = 1{\cdot}931$	0·174
Married	1107	63·03	457	61·20	650	64·15		
Not married	895	36·97	395	38·80	500	35·85		
BMI kg/m^2								
M		28·00		27·78		28·10	$Z = -238{\cdot}772$	< 0·001
Q_1, Q_3		24·70, 31·90		24·60, 31·30		24·80, 32·60		
IPR								
M		3·04		2·52		3·39	$Z = -916{\cdot}647$	< 0·001
Q_1, Q_3		1·71, 5·00		1·56, 4·30		1·91, 5·00		
Alcohol drinking, M (Q_1, Q_3)							$\chi2 = 1{\cdot}046$	0·314
Yes	1383	73·70	590	72·35	793	74·53		
No	619	26·30	262	27·65	357	25·47		
Diabetes history							$\chi2 = 5{\cdot}951$	0·020
Yes	458	18·86	211	22·56	247	16·60		
No	1544	81·14	641	77·44	903	83·40		
Hypertension history							$\chi2 = 4{\cdot}658$	0·039
Yes	1218	56·68	530	60·96	688	54·08		
No	784	43·32	322	39·04	462	45·92		
Smoking status							$\chi2 = 0{\cdot}195$	0·662
Yes	1008	50·62	455	51·62	553	50·02		
No	994	49·38	397	48·38	597	49·98		
	M	Q_1, Q_3	M	Q_1, Q_3	M	Q_1, Q_3		
Serum Fe (ug/dl)	84·00	64·00, 106·00	81·00	63·00, 103·00	86·00	66·00, 108·00	$Z = -421{\cdot}681$	< 0·001
Blood Pb (ug/dl)	1·40	0·98, 2·11	1·45	0·98, 2·24	1·38	0·99, 1·99	$Z = 233{\cdot}249$	< 0·001
Blood Cd (ug/l)	0·36	0·24, 0·57	0·38	0·24, 0·57	0·35	0·24, 0·56	$Z = 162{\cdot}306$	< 0·001
Blood Hg (ug/l)	0·94	0·50, 1·95	0·86	0·46, 1·67	1·00	0·53, 2·05	$Z = -410{\cdot}162$	< 0·001
Blood Se (ug/l)	192·89	178·71, 207·45	193·03	177·73, 208·75	192·50	179·73, 206·81	$Z = -74{\cdot}700$	< 0·001
Blood Mn (ug/l)	8·79	7·10, 10·93	8·64	6·90, 10·55	8·80	7·20, 11·06	$Z = -351{\cdot}032$	< 0·001

CERAD, consortium to establish a registry for Alzheimer's disease; GED, general educational development; IPR: income-poverty ratio.

Association between six trace elements and low cognitive performance

The associations between six trace elements and cognitive performance were shown in Fig. 2. After adjusting age, sex, race, BMI, IPR, alcohol drinking, diabetes and hypertension history, elevated serum Fe levels were associated with the decreased risk of low cognitive performance (OR = 0·995, 95 % CI 0·990, 0·999) in the Animal Fluency test. High blood Pb levels were related to the high odds of low cognitive performance (OR = 1·102, 95 % CI 1·019, 1·192), while high blood Se levels were linked to the decreased risk of low cognitive performance (OR = 0·987, 95 % CI 0·981, 0·993) in the DSST test among old adults. In addition, the results before interpolation showed that elevated blood Se levels were associated with the decreased risk of low cognitive performance in the DSST test (OR = 0·987, 95 % CI 0·981, 0·991), which was consistent with the results after filling (Supplementary Fig. 1).

Associations between six trace elements and low cognitive performance in old adults with or without diabetes and hypertension history

Figures 3 shows the associations between six trace elements (Fe, Pb, Cd, Hg, Se and Mn) and low cognitive performance in the elderly with or without diabetes and hypertension history. In

Table 2. Characteristics of elderly over 60 years of age by cognitive performance status according to Animal Fluency test

	Animal Fluency test					
	Low cognitive performance (*n* 746)		Normal cognitive performance (*n* 1256)			
Variables	*n*	%	*n*	%	Statistics	*P*
Sex					$\chi^2 = 2{\cdot}326$	0·137
Male	465	49·97	521	45·07		
Female	361	50·03	655	54·93		
Age						
M		73·00		67·00	Z = 1727·700	< 0·001
Q_1, Q_3		66·00, 80·00		63·00, 72·00		
Race					$\chi^2 = 63{\cdot}498$	< 0·001
Hispanic	225	16·04	147	3·53		
Non-Hispanic White	278	62·82	679	86·82		
Non-Hispanic Black	261	16·46	213	4·71		
Non-Hispanic others	62	4·67	137	4·94		
Education					$\chi^2 = 164{\cdot}140$	< 0·001
Less than 9th grade	220	19·44	28	1·56		
9–11 grade (includes 12 grade with no diploma)	169	19·08	92	6·27		
High school graduate/GED or equivalent	205	28·43	269	20·63		
Some college or AA degree	148	19·16	413	34·62		
College graduate or above	84	13·89	374	36·92		
Marital status					$\chi^2 = 19{\cdot}394$	< 0·001
Married	409	51·03	698	67·21		
Not married	417	48·97	478	32·79		
BMI kg/m^2						
M		27·70		28·00	Z = −202·684	< 0·001
Q_1, Q_3		24·20, 32·20		24·90, 31·80		
IPR						
M		1·78		3·61	Z = −2168·61	< 0·001
Q_1, Q_3		1·12, 2·81		2·14, 5·00		
Alcohol drinking, M (Q_1, Q_3)					$\chi^2 = 32{\cdot}878$	< 0·001
Yes	527	63·47	856	77·27		
No	299	36·53	320	22·73		
Diabetes history					$\chi^2 = 13{\cdot}639$	< 0·001
Yes	232	26·98	226	16·03		
No	594	73·02	950	83·97		
Hypertension history					$\chi^2 = 27{\cdot}474$	< 0·001
Yes	552	68·32	666	52·63		
No	274	31·68	510	47·37		
Smoking status					$\chi^2 = 4{\cdot}527$	0·041
Yes	444	55·77	564	48·83		
No	382	44·23	612	51·17		
	M	Q_1, Q_3	M	Q_1, Q_3		
Serum Fe (ug/dl)	76·00	59·00, 102·00	86·00	68·00, 107·00	Z = −701·651	< 0·001
Blood Pb (ug/dl)	1·52	0·99, 2·51	1·37	0·98, 1·98	Z = 406·765	< 0·001
Blood Cd (ug/l)	0·42	0·27, 0·70	0·34	0·23, 0·53	Z = 788·343	< 0·001
Blood Hg (ug/l)	0·73	0·35, 1·50	1·03	0·56, 2·07	Z = −964·029	< 0·001
Blood Se (ug/l)	186·19	170·21, 202·97	195·84	181·62, 209·05	Z = −1026·72	< 0·001
Blood Mn (ug/l)	8·73	6·92, 10·79	8·79	7·17, 10·96	Z = −195·455	< 0·001

GED, general educational development; IPR: income-poverty ratio.

the Animal Fluency test, after adjusting all covariates, high serum Fe levels were related to the decreased risk of low cognitive performance in old people without diabetes history (OR = 0·992, 95 % CI 0·988, 0·997) and with hypertension history (OR = 0·993, 95 % CI 0·988, 0·997). High blood Cd (OR = 2·900, 95 % CI 1·311, 6·417) and blood Mn (OR = 1·037, 95 % CI 1·009, 1·066) levels were associated with the high odds of low cognitive performance in old diabetic and hypertensive adults, respectively. In the DSST test, high blood Pb levels were associated with the increased risk of low cognitive performance in the elderly without diabetes (OR = 1·126, 95 % CI 1·026, 1·235) and hypertension (OR = 1·121, 95 % CI 1·002, 1·255) history. Elevated blood Cd levels were connected with low cognitive performance in old diabetic (OR = 3·177, 95 % CI 1·323, 7·27) and hypertensive (OR = 1·896, 95 % CI 1·056, 3·403) people. High blood Se levels were related to the decreased risk of low cognitive performance in old adults with (OR = 0·989, 95 % CI 0·981, 0·998) and without (OR = 0·986, 95 % CI 0·978, 0·993) diabetes history, with (OR = 0·992, 95 % CI 0·986, 0·997) and without (OR = 0·976, 95 % CI 0·962, 0·990) hypertension history.

Discussion

In the present study, we investigated the associations between six trace elements and the risk of low cognitive performance

British Journal of Nutrition

Table 3. Characteristics of elderly over 60 years of age by cognitive performance status according to DSST

	DSST					
	Low cognitive performance (*n* 826)		Normal cognitive performance (*n* 1176)			
Variables	*n*	%	*n*	%	Statistics	*P*
Sex, n (%)					$\chi^2 = 0{\cdot}349$	0·559
Male	363	45·15	623	46·79		
Female	383	54·85	633	53·21		
Age						
M		72·00		66·00	Z = 1490·746	< 0·001
Q_1, Q_3		66·00, 79·00		63·00, 73·00		
Race					$\chi^2 = 27{\cdot}678$	< 0·001
Hispanic	141	9·47	231	5·71		
Non-Hispanic White	285	70·68	672	84·49		
Non-Hispanic Black	224	13·25	250	5·61		
Non-Hispanic others	96	6·60	103	4·20		
Education					$\chi^2 = 54{\cdot}669$	< 0·001
Less than 9th grade	129	11·54	119	4·10		
9–11 grade (includes 12 grade with no diploma)	135	14·86	126	7·52		
High school graduate/GED or equivalent	194	30·05	280	19·77		
Some college or AA degree	184	26·27	377	32·32		
College graduate or above	104	17·27	354	36·30		
Marital status					$\chi^2 = 3{\cdot}620$	0·066
Married	400	58·98	707	64·61		
Not married	346	41·02	549	35·39		
BMI kg/m^2						
M		27·60		28·00	Z = −147·332	< 0·001
Q_1, Q_3		24·60, 31·80		24·80, 32·00		
IPR						
M		2·28		3·40	Z = −1316·41	< 0·001
Q_1, Q_3		1·29, 3·80		1·92, 5·00		
Alcohol drinking, M (Q_1, Q_3)					$\chi^2 = 26{\cdot}833$	< 0·001
Yes	478	64·52	905	77·27		
No	268	35·48	351	22·73		
Diabetes history					$\chi^2 = 12{\cdot}678$	0·001
Yes	204	25·45	254	16·29		
No	542	74·55	1002	83·71		
Hypertension history					$\chi^2 = 9{\cdot}958$	0·004
Yes	490	63·17	728	54·16		
No	256	36·83	528	45·84		
Smoking status					$\chi^2 = 0{\cdot}343$	0·562
Yes	375	49·61	633	51·01		
No	371	50·39	623	48·99		
	M	Q_1, Q_3	M	Q_1, Q_3		
Serum Fe (ug/dl), M (Q_1, Q_3)	78·00	58·00, 101·00	87·00	68·00, 108·00	Z = −776·870	< 0·001
Blood Pb (ug/dl), M (Q_1, Q_3)	1·40	1·00, 2·13	1·41	0·98, 2·10	Z = 3·563	< 0·001
Blood Cd (ug/l)	0·40	0·26, 0·65	0·35	0·24, 0·53	Z = 506·650	< 0·001
Blood Hg (ug/l)	0·76	0·42, 1·67	0·99	0·53, 2·02	Z = −518·635	< 0·001
Blood Se (ug/l)	190·33	175·00, 204·92	193·94	180·84, 209·06	Z = −578·457	< 0·001
Blood Mn (ug/l)	8·80	7·03, 11·29	8·78	7·13, 10·77	Z = 96·233	< 0·001

DSST, Digit Symbol Substitution Test; GED, general educational development; IPR: income-poverty ratio.

among old adults. Our findings showed that elevated serum Fe levels were related to the decreased risk of low cognitive performance, especially in the elderly without diabetes history and with hypertension history in the Animal Fluency test. High blood Cd and blood Mn levels were associated with the high odds of low cognitive performance in old adults with diabetes and hypertension history, respectively. In the DSST test, high blood Pb levels were associated with the increased risk of low cognitive performance, especially in the elderly without diabetes and hypertension history. Elevated blood Cd levels were connected with low cognitive performance in old diabetic and hypertensive people. High blood Se levels were related to the decreased risk of low cognitive performance in all old adults. No relationships between trace elements and low cognitive performance were discovered in the CERAD test.

Fe plays an important role in brain development, myelination and cognitive function [13,23]. Elevated serum Fe levels were related to the decreased risk of low cognitive performance in the elderly, which was consistent with findings proposed by Kweon et al. [24]. Hare et al. reported that the transferrin-related Fe content in Alzheimer's disease (AD) patients significantly decreased, which may be due to the decreased serum Fe content [25]. Fe is a cofactor of ribonucleotide reductase, which is responsible for the rate-limiting step of DNA synthesis, making Fe essential for cell division and neural tube formation[26,27]. Beyond cell division, neurons need timely and adequate Fe

Variables	Model 1 OR (95%CI)	P	Model 2 OR (95%CI)	P	Model 3 OR (95%CI)	P
CERAD						
Serum Iron	0·996(0·992–0·999)	0·024	0·996(0·991–1·001)	0·089	0·997(0·992–1·001)	0·159
Blood Lead	1·061(0·997–1·130)	0·063	1·020(0·940–1·108)	0·626	1·016(0·947–1·091)	0·643
Blood Cadmium	1·028(0·781–1·353)	0·839	1·062(0·794–1·420)	0·676	1·028(0·771–1·369)	0·848
Blood Mercury	0·967(0·925–1·011)	0·138	0·973(0·934–1·015)	0·193	0·998(0·957–1·040)	0·911
Blood Selenium	0·999(0·997–1·002)	0·591	1·000(0·997–1·003)	0·881	1·001(0·998–1·004)	0·629
Blood Manganese	0·981(0·941–1·022)	0·345	1·000(0·963–1·039)	0·985	1·003(0·966–1·040)	0·890
Animal Fluency						
Serum Iron	0·991(0·986–0·995)	<0·001	0·994(0·989–0·998)	0·005	0·995(0·990–0·999)	0·020
Blood Lead	1·004(0·918–1·097)	0·929	0·986(0·908–1·071)	0·737	0·978(0·901–1·061)	0·576
Blood Cadmium	1·364(1·025–1·814)	0·034	1·364(0·967–1·925)	0·076	1·293(0·880–1·900)	0·183
Blood Mercury	0·937(0·852–1·031)	0·175	0·943(0·861–1·032)	0·195	0·989(0·907–1·079)	0·797
Blood Selenium	0·994(0·989–1·000)	0·058	0·996(0·990–1·002)	0·192	0·997(0·992–1·002)	0·261
Blood Manganese	1·009(0·980–1·039)	0·539	1·020(0·990–1·051)	0·194	1·026(0·998–1·054)	0·068
DSST						
Serum Iron	0·992(0·987–0·997)	0·002	0·996(0·991–1·000)	0·056	0·997(0·991–1·002)	0·251
Blood Lead	1·138(1·045–1·238)	0·004	1·134(1·051–1·223)	0·002	1·102(1·019–1·192)	0·017
Blood Cadmium	1·792(1·218–2·638)	0·004	2·166(1·379–3·404)	0·001	1·637(0·985–2·720)	0·057
Blood Mercury	0·908(0·844–0·977)	0·012	0·918(0·844–0·998)	0·045	1·011(0·956–1·069)	0·696
Blood Selenium	0·985(0·980–0·989)	<0·001	0·984(0·978–0·990)	<0·001	0·987(0·981–0·993)	<0·001
Blood Manganese	1·004(0·967–1·041)	0·843	1·031(0·989–1·075)	0·147	1·038(0·996–1·083)	0·078

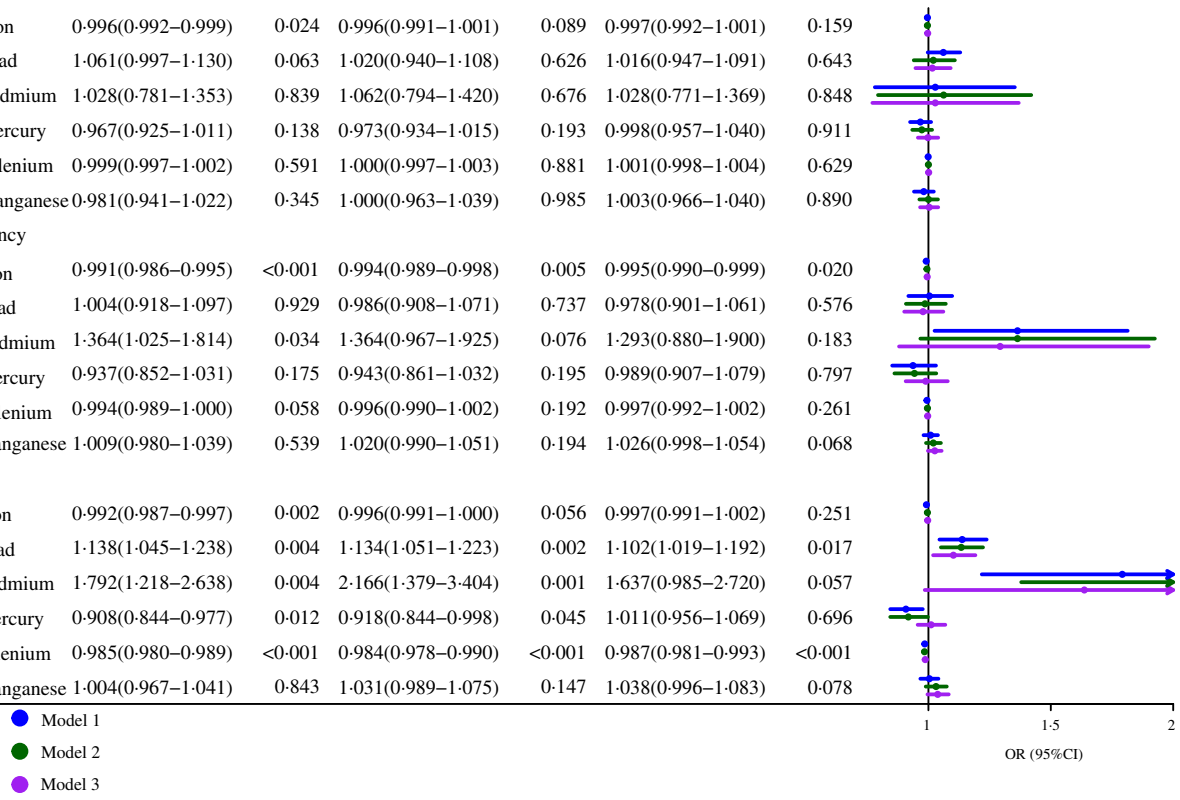


Fig. 2. Association between six trace elements and low cognitive performance in the CERAD, Animal Fluency and DSST tests. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, Digit Symbol Substitution Test.

supply for neurotransmitter synthesis, synapse formation and dendritic arborisation [26]. Excess redox-active Fe can also lead to oxidative damage and cell death [26]. Appropriate Fe supplementation and Fe-rich foods intake may be beneficial for cognitive function in the elderly.

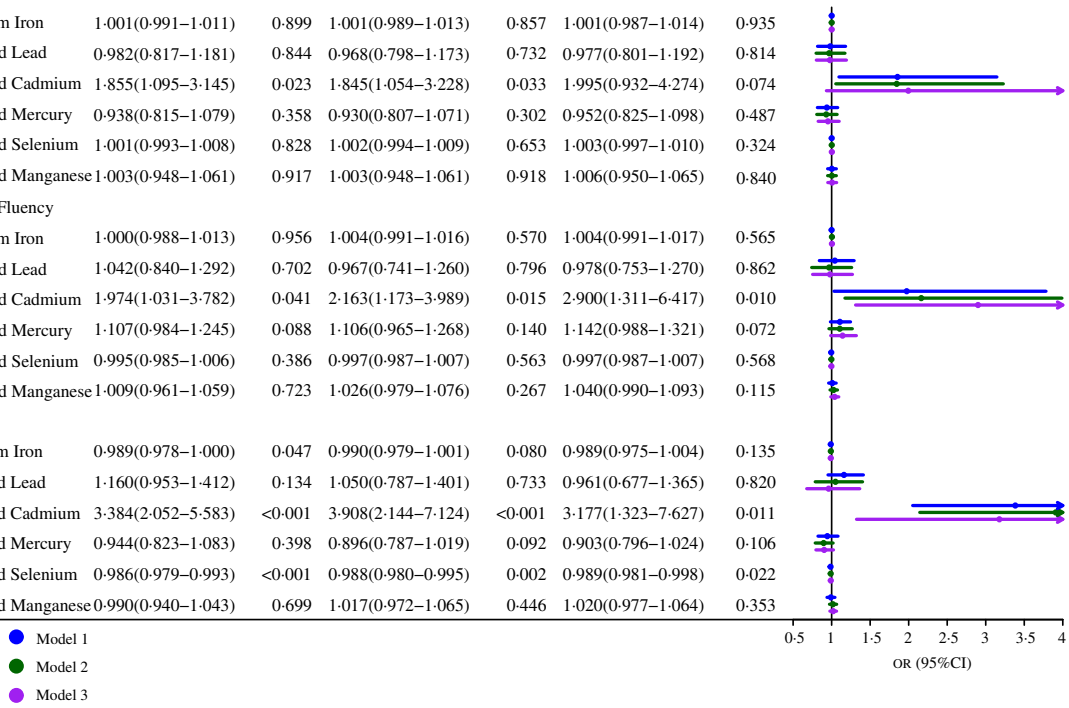
We also found high blood Se levels was associated with the decreased risk of low cognitive performance in all old adults. Se deficiency causes irreversible brain injury[28]. Lower plasma Se levels were associated with a high risk of cognitive impairment[11,29]. A previous study reported the Se concentrations in the erythrocytes, plasma and nails were low in AD patients[30]. A similar association was found in people with diabetes. Serum and urine Se were indicators of body status in diabetes patients[31]. In addition, studies have confirmed that there were some common pathophysiological mechanisms between diabetes and cognitive impairment[32,33]. Appropriate Se supplementation and Se-rich foods intake may be beneficial for cognitive health in the elderly, especially in diabetic and hypertensive individuals.

High Pb exposure was associated with cognitive impairment in older Americans. The existing reports suggested that the presence of Pb in the brain has a potential pro-inflammatory effect on the central nervous system, and neuronal death may be connected with the production of various cytokines and chemokine[34,35]. Early or long-term accumulation of Pb exposure may be related to accelerated cognitive decline in old age[36]. Results of a previous meta-analysis showed that high blood Pb concentrations were associated with poor cognitive performance regarding in verbal and visuospatial abilities, memory, attention and psychomotor function[37]. These were consistent with our findings. Shalan et al. found that vitamin C might reduce intestinal absorption of Pb by reducing ferric iron in the duodenum to ferrous iron to make ferrous iron compete with Pb for intestinal absorption[38]. Appropriate vitamin C supplementation helps reduce Pb levels in the blood, liver and kidneys[39], which may be beneficial for cognitive health in older adults.

Furthermore, blood Cd exposure was in correlation with cognitive function in diabetic and hypertensive elder people. Previous studies showed that Cd homoeostasis is abnormal in individuals who had hypertension or diabetes history[40,41]. Cognitive dysfunction was one of the diabetes and hypertension complications[42,43]. Blood Cd concentration was associated with slower gait speed, which is an early predictor of cognitive decline and dementia[44–46]. A cross-sectional study suggested that increased blood Cd was associated with worse cognitive function in adults aged 60 years or older in the USA[47]. Exposure to Cd could elevate the activity of acetylcholinesterase, leading to hydrolysis and concentration reduction of acetylcholine[48]. Reduced release of acetylcholine was associated with decreased cognitive abilities[49]. Besides, evidence

(a)

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR (95%CI)	*P*	Model 3 OR (95%CI)	*P*
CERAD						
Serum Iron	1·001(0·991–1·011)	0·899	1·001(0·989–1·013)	0·857	1·001(0·987–1·014)	0·935
Blood Lead	0·982(0·817–1·181)	0·844	0·968(0·798–1·173)	0·732	0·977(0·801–1·192)	0·814
Blood Cadmium	1·855(1·095–3·145)	0·023	1·845(1·054–3·228)	0·033	1·995(0·932–4·274)	0·074
Blood Mercury	0·938(0·815–1·079)	0·358	0·930(0·807–1·071)	0·302	0·952(0·825–1·098)	0·487
Blood Selenium	1·001(0·993–1·008)	0·828	1·002(0·994–1·009)	0·653	1·003(0·997–1·010)	0·324
Blood Manganese	1·003(0·948–1·061)	0·917	1·003(0·948–1·061)	0·918	1·006(0·950–1·065)	0·840
Animal Fluency						
Serum Iron	1·000(0·988–1·013)	0·956	1·004(0·991–1·016)	0·570	1·004(0·991–1·017)	0·565
Blood Lead	1·042(0·840–1·292)	0·702	0·967(0·741–1·260)	0·796	0·978(0·753–1·270)	0·862
Blood Cadmium	1·974(1·031–3·782)	0·041	2·163(1·173–3·989)	0·015	2·900(1·311–6·417)	0·010
Blood Mercury	1·107(0·984–1·245)	0·088	1·106(0·965–1·268)	0·140	1·142(0·988–1·321)	0·072
Blood Selenium	0·995(0·985–1·006)	0·386	0·997(0·987–1·007)	0·563	0·997(0·987–1·007)	0·568
Blood Manganese	1·009(0·961–1·059)	0·723	1·026(0·979–1·076)	0·267	1·040(0·990–1·093)	0·115
DSST						
Serum Iron	0·989(0·978–1·000)	0·047	0·990(0·979–1·001)	0·080	0·989(0·975–1·004)	0·135
Blood Lead	1·160(0·953–1·412)	0·134	1·050(0·787–1·401)	0·733	0·961(0·677–1·365)	0·820
Blood Cadmium	3·384(2·052–5·583)	<0·001	3·908(2·144–7·124)	<0·001	3·177(1·323–7·627)	0·011
Blood Mercury	0·944(0·823–1·083)	0·398	0·896(0·787–1·019)	0·092	0·903(0·796–1·024)	0·106
Blood Selenium	0·986(0·979–0·993)	<0·001	0·988(0·980–0·995)	0·002	0·989(0·981–0·998)	0·022
Blood Manganese	0·990(0·940–1·043)	0·699	1·017(0·972–1·065)	0·446	1·020(0·977–1·064)	0·353



(b)

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR (95%CI)	*P*	Model 3 OR (95%CI)	*P*
CERAD						
Serum Iron	0·995(0·991–0·999)	0·022	0·996(0·991–1·001)	0·117	0·997(0·992–1·001)	0·147
Blood Lead	1·082(1·007–1·163)	0·033	1·033(0·950–1·124)	0·434	1·024(0·949–1·106)	0·523
Blood Cadmium	0·916(0·670–1·253)	0·573	0·921(0·656–1·292)	0·624	0·867(0·601–1·249)	0·431
Blood Mercury	0·976(0·926–1·029)	0·363	0·989(0·939–1·041)	0·660	1·014(0·959–1·072)	0·613
Blood Selenium	0·999(0·996–1·002)	0·630	1·000(0·995–1·005)	0·998	1·000(0·996–1·005)	0·823
Blood Manganese	0·973(0·922–1·028)	0·317	0·997(0·950–1·046)	0·896	0·997(0·954–1·043)	0·907
Animal Fluency						
Serum Iron	0·989(0·985–0·994)	<0·001	0·992(0·988–0·996)	<0·001	0·992(0·988–0·997)	0·001
Blood Lead	1·014(0·921–1·117)	0·766	1·001(0·919–1·091)	0·978	0·977(0·898–1·064)	0·586
Blood Cadmium	1·295(0·982–1·708)	0·066	1·224(0·904–1·656)	0·183	1·048(0·768–1·430)	0·761
Blood Mercury	0·921(0·830–1·021)	0·113	0·924(0·837–1·020)	0·112	0·969(0·885–1·061)	0·478
Blood Selenium	0·994(0·988–1·001)	0·073	0·996(0·988–1·003)	0·212	0·997(0·991–1·003)	0·263
Blood Manganese	1·010(0·977–1·045)	0·542	1·018(0·983–1·053)	0·311	1·023(0·991–1·055)	0·156
DSST						
Serum Iron	0·994(0·990–0·998)	0·008	0·998(0·993–1·003)	0·393	0·999(0·994–1·004)	0·641
Blood Lead	1·162(1·049–1·288)	0·005	1·164(1·065–1·271)	0·001	1·126(1·026–1·235)	0·014
Blood Cadmium	1·663(1·112–2·489)	0·015	1·917(1·266–2·901)	0·003	1·411(0·850–2·342)	0·176
Blood Mercury	0·913(0·845–0·988)	0·025	0·930(0·847–1·023)	0·129	1·028(0·969–1·089)	0·349
Blood Selenium	0·984(0·978–0·990)	<0·001	0·983(0·975–0·991)	<0·001	0·986(0·978–0·993)	<0·001
Blood Manganese	1·010(0·964–1·059)	0·667	1·035(0·979–1·094)	0·212	1·046(0·992–1·102)	0·096

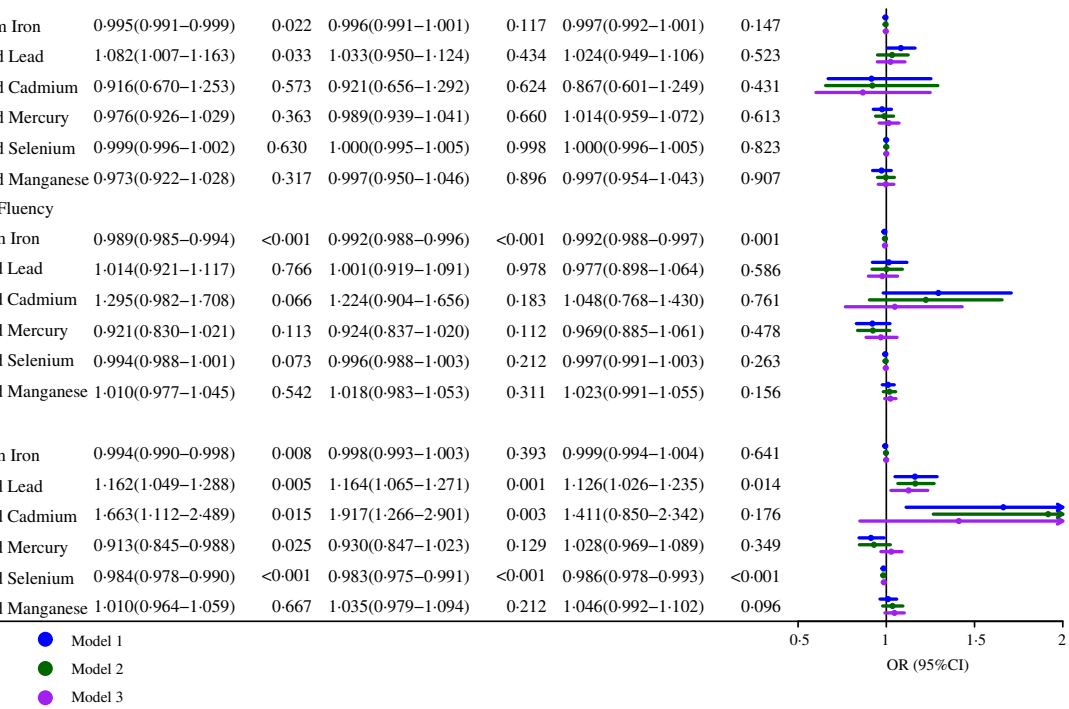
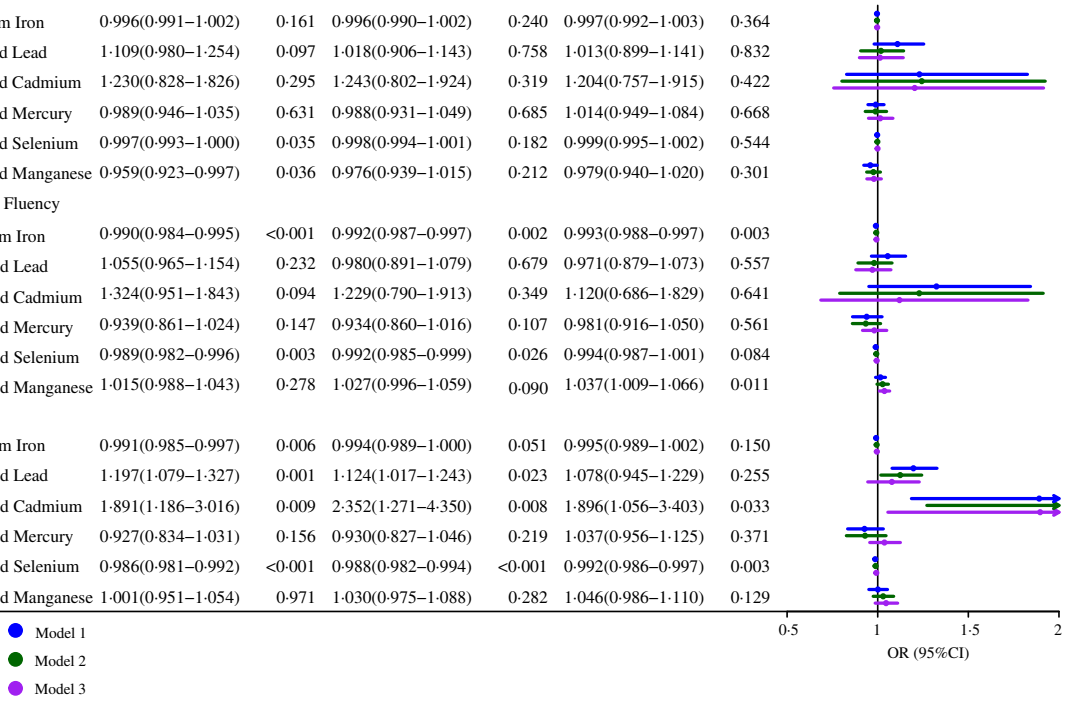


Fig. 3. Association between six trace elements and low cognitive performance of the elderly in different subgroups. (a) With diabetes history; (b) without diabetes history; (c) with hypertension history; (D) without hypertension history. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, Digit Symbol Substitution Test.

(c)

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR (95%CI)	*P*	Model 3 OR (95%CI)	*P*
CERAD						
Serum Iron	0·996(0·991–1·002)	0·161	0·996(0·990–1·002)	0·240	0·997(0·992–1·003)	0·364
Blood Lead	1·109(0·980–1·254)	0·097	1·018(0·906–1·143)	0·758	1·013(0·899–1·141)	0·832
Blood Cadmium	1·230(0·828–1·826)	0·295	1·243(0·802–1·924)	0·319	1·204(0·757–1·915)	0·422
Blood Mercury	0·989(0·946–1·035)	0·631	0·988(0·931–1·049)	0·685	1·014(0·949–1·084)	0·668
Blood Selenium	0·997(0·993–1·000)	0·035	0·998(0·994–1·001)	0·182	0·999(0·995–1·002)	0·544
Blood Manganese	0·959(0·923–0·997)	0·036	0·976(0·939–1·015)	0·212	0·979(0·940–1·020)	0·301
Animal Fluency						
Serum Iron	0·990(0·984–0·995)	<0·001	0·992(0·987–0·997)	0·002	0·993(0·988–0·997)	0·003
Blood Lead	1·055(0·965–1·154)	0·232	0·980(0·891–1·079)	0·679	0·971(0·879–1·073)	0·557
Blood Cadmium	1·324(0·951–1·843)	0·094	1·229(0·790–1·913)	0·349	1·120(0·686–1·829)	0·641
Blood Mercury	0·939(0·861–1·024)	0·147	0·934(0·860–1·016)	0·107	0·981(0·916–1·050)	0·561
Blood Selenium	0·989(0·982–0·996)	0·003	0·992(0·985–0·999)	0·026	0·994(0·987–1·001)	0·084
Blood Manganese	1·015(0·988–1·043)	0·278	1·027(0·996–1·059)	0·090	1·037(1·009–1·066)	0·011
DSST						
Serum Iron	0·991(0·985–0·997)	0·006	0·994(0·989–1·000)	0·051	0·995(0·989–1·002)	0·150
Blood Lead	1·197(1·079–1·327)	0·001	1·124(1·017–1·243)	0·023	1·078(0·945–1·229)	0·255
Blood Cadmium	1·891(1·186–3·016)	0·009	2·352(1·271–4·350)	0·008	1·896(1·056–3·403)	0·033
Blood Mercury	0·927(0·834–1·031)	0·156	0·930(0·827–1·046)	0·219	1·037(0·956–1·125)	0·371
Blood Selenium	0·986(0·981–0·992)	<0·001	0·988(0·982–0·994)	<0·001	0·992(0·986–0·997)	0·003
Blood Manganese	1·001(0·951–1·054)	0·971	1·030(0·975–1·088)	0·282	1·046(0·986–1·110)	0·129



(d)

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR	*P*	Model 3 OR	*P*
CERAD						
Serum Iron	0·995(0·990–1·001)	0·111	0·995(0·988–1·002)	0·181	0·996(0·989–1·003)	0·230
Blood Lead	1·051(0·958–1·154)	0·283	1·028(0·909–1·163)	0·646	1·029(0·923–1·148)	0·594
Blood Cadmium	0·741(0·434–1·266)	0·263	0·740(0·439–1·247)	0·248	0·713(0·417–1·219)	0·208
Blood Mercury	0·957(0·883–1·037)	0·271	0·969(0·896–1·047)	0·414	0·998(0·916–1·088)	0·963
Blood Selenium	1·002(0·997–1·007)	0·369	1·002(0·996–1·009)	0·507	1·002(0·996–1·008)	0·484
Blood Manganese	1·002(0·956–1·052)	0·916	1·020(0·977–1·065)	0·323	1·021(0·979–1·066)	0·319
Animal Fluency						
Serum Iron	0·993(0·986–1·001)	0·081	0·996(0·988–1·004)	0·279	0·997(0·988–1·006)	0·491
Blood Lead	0·991(0·883–1·112)	0·872	0·998(0·898–1·110)	0·972	0·993(0·890–1·107)	0·893
Blood Cadmium	1·424(0·862–2·354)	0·161	1·498(0·886–2·535)	0·127	1·526(0·861–2·704)	0·143
Blood Mercury	0·947(0·838–1·070)	0·370	0·957(0·851–1·076)	0·462	1·007(0·892–1·137)	0·907
Blood Selenium	1·000(0·996–1·004)	0·963	1·000(0·994–1·005)	0·969	0·999(0·995–1·004)	0·730
Blood Manganese	1·006(0·960–1·054)	0·796	1·011(0·961–1·064)	0·653	1·015(0·968–1·064)	0·526
DSST						
Serum Iron	0·996(0·989–1·003)	0·235	0·999(0·990–1·007)	0·731	1·000(0·989–1·010)	0·968
Blood Lead	1·135(1·030–1·251)	0·012	1·151(1·042–1·272)	0·007	1·121(1·002–1·255)	0·046
Blood Cadmium	1·660(1·015–2·714)	0·044	1·799(1·041–3·107)	0·036	1·211(0·543–2·698)	0·630
Blood Mercury	0·907(0·825–0·997)	0·044	0·919(0·805–1·049)	0·201	0·987(0·909–1·071)	0·741
Blood Selenium	0·980(0·971–0·989)	<0·001	0·976(0·965–0·988)	<0·001	0·976(0·962–0·990)	0·002
Blood Manganese	1·011(0·954–1·072)	0·694	1·038(0·971–1·110)	0·263	1·029(0·968–1·094)	0·342

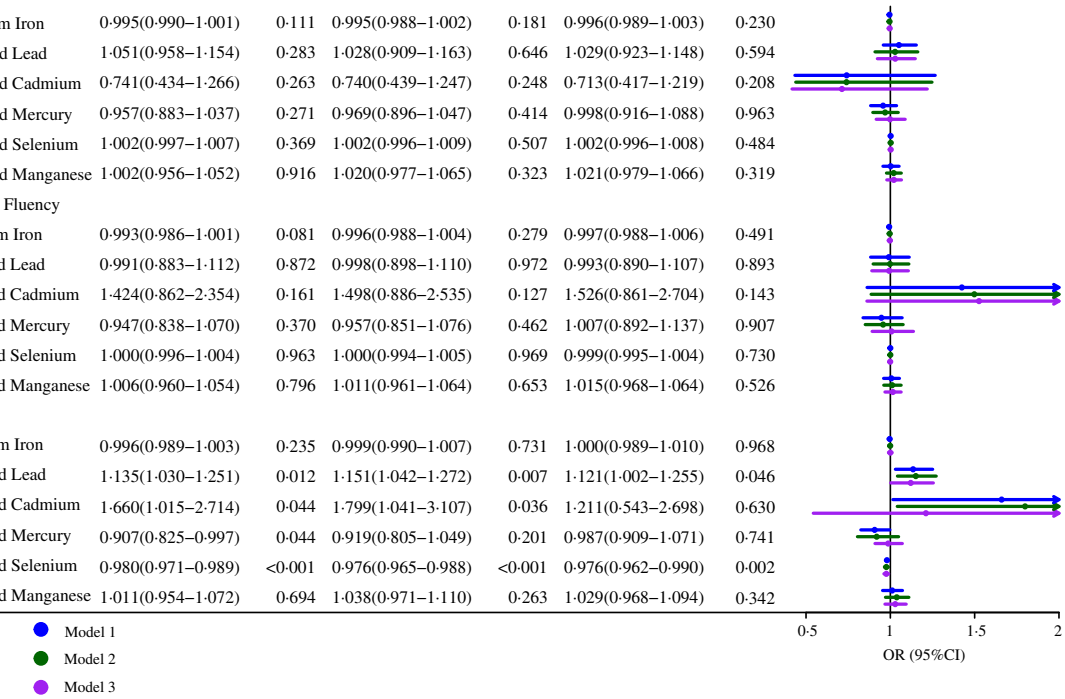


Fig. 3. (Continued)

has indicated that the generation of reactive oxygen species was induced by Cd[50]. An excess of reactive oxygen species may result in inflammation, eventually causing neuron injury and death[50,51].

Damage to Mn homoeostasis may alter the activities of Mn-dependent enzymes and Mn sensitivity pathways, leading to neurotoxicity and the pathophysiology of neurodegenerative diseases[8]. Mn is transported across the blood–brain barrier by the divalent metal transporter 1 and the transferrin receptor system and accumulates in Fe-rich regions of the basal ganglia[52,53]. Mn efflux and inflow transporter genes (SLC30A10 and SLC30A8) mutations can change Mn levels in the Golgi apparatus and induce neurotoxicity through abnormal vesicular trafficking[53,54]. We found that elevated blood Mn was associated with the odds of low cognitive performance among the elderly with hypertension. High blood pressure was associated with cognitive impairment caused by vascular factors [43]. Although Hg exposure may impair nervous system function[55,56], no association with low cognitive performance was discovered in our research. Future studies need to further explore these associations.

Relationships between several trace elements and low cognitive performance were discovered in the Animal Fluency and DSST tests, but not in the CERAD test. The CERAD test is used to assess episodic memory. The Animal Fluency test is utilised to assess verbal fluency and semantic-based memory function, and the sensitive measurement of frontal lobe executive function is evaluated using the DSST test. Thus, the differences in test results may be due to differences in the cognitive areas emphasised by each test.

Herein, we provided reference for the early prevention of cognitive health in the elderly on the relationship between six trace elements in blood and cognitive dysfunction. A representative and high-quality NHANES database was used, and the regression models were adjusted considering the covariates. Moreover, we further explored the association between blood micronutrients and cognitive impairment in old adults with diabetes and hypertension. Several limitations need caution in interpreting our findings. The levels of trace elements in serum or blood measured reflect daily and recent exposure and are considered an indication of current exposure, rather than long-term and lifetime exposure. And heavy metals in urine are considered to be indicators of long-term exposure before kidney damage [57]. It is also necessary to study the effect of exposure to trace elements in urine on cognitive decline in the elderly. In this paper, we focus on trace elements in blood, and future studies in this area will be carried out. In addition, the cognitive tests selected for ease of management and usability did not cover all areas of cognitive function.

Conclusion

Elevated serum Fe and blood Se levels were associated with the decreased risk of low cognitive performance, while high blood Pb, Cd and Mn exposure were related to the high odds of low cognitive performance in old adults, especially in diabetic and hypertensive individuals. Appropriate Fe, Se supplementation and Fe-, Se-rich foods intake, while reducing exposure to Pb, Cd and Mn may be beneficial for cognitive function in the elderly.

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K. L. and W. W. designed the study. K. L. wrote the manuscript. K. L.,T. L., X. W., J. Z. and Z. O. collected, analysed and interpreted the data. W. W. critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

There are no conflicts of interest.

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