ACS Partner Journal

ENVIRONMENT & HEALTH

pubs.acs.org/EnvHealth

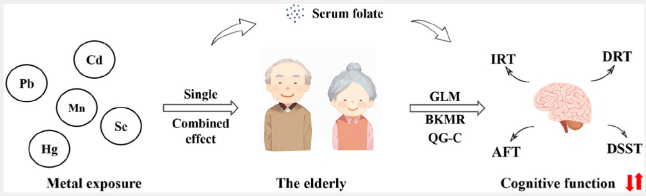
Article

Associations between Metals, Serum Folate, and Cognitive Function in the Elderly: Mixture and Mediation Analyses

Luli Wu, Ye Xin, Junrou Zhang, Xin Yang, Tian Chen, and Piye Niu*

Cite This: *Environ. Health* 2024, 2, 865–874

Read Online



ABSTRACT: Exposure to metals may potentially impact cognitive health in the elderly; however, the evidence remains ambiguous. The specific role of serum folate in this relationship is also unclear. We aimed to evaluate the individual and joint impact of metals on cognition in the elderly from the United States and explore the potential mediating effect of serum folate. Data from the NHANES 2011–2014 were used, with inductively coupled plasma mass spectrometry (ICP-MS) employed to measure blood metal concentrations. Cognitive function was assessed using tests for immediate, delayed, and working memory: Immediate Recall test (IRT), the Delayed Recall test (DRT), the Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST). Generalized linear regression models (GLMs), Bayesian kernel machine regression model (BKMR), and quantile g-computation (QG-C) models were used to assess associations between metals (lead, cadmium, mercury, selenium, manganese) and cognition, with mediation analyses examining serum folate's involvement in metal effects. This study included 2002 participants aged ≥60. GLMs revealed the negative association between cadmium and the z-scores of IRT (β: −0.17,95% CI: −0.30, −0.04) and DSST (β: −0.15,95% CI: −0.27, −0.04), with negative effects also observed in the BKMR and QG-C models. Selenium displayed significantly positive association with cognition across various statistical models, including GLMs, QG-C, and BKMR. Serum folate played a mediating role in the effects of cadmium and selenium exposure on DSST z-scores, with a proportion of mediation of 17% and 10%, respectively. Our study assessed the impact of metal mixtures on cognition in the elderly population, finding that high selenium level was strongly associated with better cognitive performance, while cadmium was associated with lower cognitive function scores. Serum folate might partially mediate the association between cadmium, selenium, and DSST z-scores.

KEYWORDS: *Metals, Cognitive function, Serum folate, Quantile g-computation, Bayesian kernel machine regression, Mediating effect*

1. INTRODUCTION

Cognitive health has become a significant public health concern, particularly for the aging population.[1] Cognitive decline has the potential to progress into a condition known as mild cognitive impairment (MCI). Older adults have a higher risk of cognitive impairment, 16.6% of adults over 65 have MCI.[2] Cognitive decline may serve as a precursor to various neurodegenerative diseases, affecting older adults' quality of life and imposing economic burdens. By 2030, dementia cases are projected to reach 82 million globally due to aging populations.[3] Cognitive impairment is characterized by a decline in one or more cognitive domains, such as memory, executive function, attention, language, or visuospatial skills. This decline is attributed to various factors like age, genetics, environment, lifestyle.[4−6] Identification of modifiable environmental risk factors can substantially impact the prevention and treatment of cognitive decline and related dementias.[7]

Multiple metals may have a significant impact on the neuropathological alterations that occur in older individuals. Neurotoxic effects are commonly associated with metals like cadmium (Cd) and lead (Pb), even when individuals are exposed to low levels of these metals that are typically encountered in the general population.[8,9] A prospective cohort study found that Cd may adversely affect the neurodevelopment of children, while urinary selenium (Se) was positively associated with children's general cognitive score.[10] A cross-sectional study among U.S. adults suggested that dietary exposure to Cd was responsible for reduced cognitive performance in attention and perception on the basis of National Health and Nutrition Examination Survey (NHANES) data.[11] Manganese (Mn) is a vital trace metal indispensable for regular physiological processes, including maintaining neuronal health. The toxicokinetics could be altered by interactions among mixture components, potentially resulting in amplified (synergistic) or reduced (antagonistic) toxicity.[12,13] Nevertheless, there is an insufficiency of research

Received: April 2, 2024
Revised: June 18, 2024
Accepted: June 19, 2024
Published: July 9, 2024

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865–874

examining the impact of mixed metals on cognition in older individuals when considering both toxic and essential metals.

Serum folate has been proposed to be related to human cognitive function, contributing to the maintenance of various cognitive aspects such as memory, learning ability, and attention. Folate plays a crucial role in supporting the health and normal function of nerve cells. A case-control study found that low blood folate levels were associated with MCI and Alzheimer's disease (AD) in older Chinese adults.[14] A randomized controlled trial showed folate supplementation has beneficial effects on cognitive function in later life.[15] There is also evidence suggesting that metals can influence serum folate levels. For instance, serum Pb and Cd levels have been inversely associated with red blood cell folate levels in the U.S. adult population.[16] However, whether serum folate mediates the association between metals and cognitive function remains unclear.

The main objective of this study is to investigate the associations between five metals (Pb, Cd, Hg, Se, Mn), individually and as mixtures, and cognitive function in the U.S. elderly population based on 2cycles of NHANES data (2011–2014). In addition, we explore the mediating role of serum folate in the relationship between metal and cognitive function.

2. METHODS

2.1. Study Population

The NHANES, carried out by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC), is an extensive study that assesses the health and nutritional status of both adults and children in the United States, aiming for nationwide representation. This survey integrates health interviews, physical examinations, and various tests conducted in clinical and laboratory settings. The Mobile Examination Centers (MECs) are where the examinations take place. NHANES obtained approval from the National Center for Health Statistics Ethics Review Board. Prior to collecting any data, all participants provided written informed consent in accordance with the Public Health Service Act.

Data were obtained from the two continuous NHANES cycles from 2011 to 2014, which provided information on four cognitive tests in people aged 60 years and above. We excluded participants who did not partake in cognitive tests and had incomplete information on the blood metals and covariates. Ultimately, a total of 2002 participants were included in the final analysis (Figure S1).

2.2. Measurements of Blood Metals and Serum Folate

The concentrations of the following whole blood metals: Pb, Cd, mercury (Hg), Se, and Mn were primarily assessed using inductively coupled plasma mass spectrometry (ICP-MS, PerkinElmer Norwalk, CT, www.perkinelmer.com) at the Division of Laboratory Sciences, National Center for Environmental Health, and CDC. This analytical method directly measures the metals content in whole blood specimens following a straightforward dilution sample preparation procedure. Serum folate was measured by isotope-dilution high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS, Thermo Fisher Scientific, Waltham, MA, USA, www.thermofisher.com). Initially, the sample is mixed with a buffer and internal standard, followed by automated solid-phase extraction. The separation and measurement are performed using LC-MS/MS, with quantification based on peak area ratios. Serum total folate represents the sum of the biologically active folate forms. Serum total folate was used in our study.

2.3. Cognitive Function Assessment

Cognitive functioning has been periodically assessed in NHANES surveys, either during the household interview or as part of the MECs. Implementing a range of cognitive assessments, including but not limited to 1) the Immediate Recall test (IRT) and Delayed Recall test (DRT) from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which focuses on word learning and recall; 2) the Animal Fluency test (AFT); and 3) the Digit Symbol Substitution test (DSST). In our study, we evaluated the cognitive function of elderly individuals using these four cognitive tests. To assess the subdomain of memory, the IRT and DRT were used to evaluate the capacity to acquire and retain new verbal information in terms of immediate and delayed learning ability.[17] The IRT consists of three consecutive learning trials, where participants are directed to individually articulate 10 unrelated words as they are displayed. The DRT occurs after the other two cognitive exercises (AFT and DSST) were accomplished (approximately 8–10 min after the initiation of the word learning trials). The AFT evaluates the verbal fluency within categories, a component of executive function. In the test, participants are asked to identify as many animals as they can within a duration of 60 s, earning one point for each correctly identified animal. The DSST, derived from the Wechsler Adult Intelligence Scale (WAIS III), is a performance module that assesses processing speed, sustained attention, and working memory. To complete the test, a paper sheet is used, which includes a key at the top consisting of 9 numbers combined with symbols. Participants are given 120 s to replicate the corresponding symbols within the 133 boxes adjacent to the numbers, and the final score is determined by the number of accurate matches achieved. Higher scores indicate superior cognitive functioning.

2.4. Covariates

Based on previous literature, we utilized a direct acyclic graph (DAG; Figure S2) to identify potential confounding factors. To adjust for confounding, all models included the following covariates: gender (male or female), age (continuous variable), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, or Others), Body Mass Index (BMI) (continuous variable), marital status (married or living with partner, separated or divorced or widowed, or never married), education (Less than ninth grade, 9–11th grade, High School grad/GED or equivalent, Some college or AA degree, College graduate or above), smoking (current or former, or never), alcohol drinking (current or never), hypertension and diabetes. A drinker was defined as someone who consumed at least 12 alcohol drinks in one year. A smoker was defined as someone who had smoked at least 100 cigarettes in thei lifetime and is currently smoking.

2.5. Statistical Analysis

The demographic characteristics and cognitive function were summarized using descriptive analysis. Categorical variables were presented as frequency (proportion), while continuous variables were analyzed using means, standard deviation, or medians with interquartile ranges. The Kruskal–Wallis H test and Mann–Whitney U test were used to compare variations in the four cognitive test scores. To enhance comparability across different cognitive tests, standardized z-scores were employed. Continuous blood metal concentrations were log-transformed to normalize the skewed distributions before the statistical analysis. Spearman correlations were used to summarize pairwise associations among log-transformed blood metal concentrations. The complex multistage sampling design has been taken into account in all analyses using svydesign method, and a newly constructed sampling weight (1/2 wtint2yr) for the merged two-cycle data was used, following NHANES analytical guidelines.

The generalized linear regression analyses were conducted to investigate the association between individual metal levels and cognitive function. The blood metals were classified into four quartiles (Q1 to Q4) based on the distribution of concentrations. The linear regression model was also used to investigate the association between metal levels and serum folate. The Bayesian kernel machine regression model (BKMR) model was employed to accurately estimate the joint and individual effects of mixture components as well as potential interactions.[18] Moreover, the possible complex nonlinear and nonadditive relationships between the mixture components and outcome were estimated by BKMR model.[19] The quantile-based g-computation (QG-C) model was utilized to

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865–874

Table 1. Demographic Characteristics and Four Cognitive Function Tests of Study Participants (N = 2002)[a]

Characteristics	Total (n = 2002)[b]	IRT	DRT	AFT	DSST
Total, M (P25, P75)		19(16–22)	6(4–8)	16(13–20)	46(33–58)
Gender					
Male	977(48.80%)	18(15–21)	6(4–7)	16(13–20)	43(32–54)
Female	1025(51.20%)	20(17–23)	7(5–8)	16(13–20)	49(35–61)
p-value		<0.001	<0.001	0.391	<0.001
Age (years)					
60–69	1101(55.00%)	20(17–23)	6(5–8)	17(14–21)	49(36–62)
≥70	901(45.00%)	18(15–21)	5(4–7)	15(12–19)	42(30–53)
p-value		<0.001	<0.001	<0.001	<0.001
BMI (kg/m^2)					
<25	550(27.47%)	19(15–22)	6(4–8)	16(13–20)	45(33–58)
25–29.9	694(34.67%)	19(16–22)	6(4–7)	16(13–20)	45(33–59)
≥30	758(37.86%)	19(16–22)	6(5–8)	16(13–20)	46(33–58)
p-value		0.123	0.004	0.204	0.518
Smoking status					
Current smoker	249(12.40%)	19(16–22)	6(4–8)	16(13–20)	41(30–53)
Former smoker	760(38.00%)	19(16–22)	6(4–7)	16(13–20)	45(34–57)
Nonsmoker	993(49.60%)	19(16–22)	6(4–8)	16(13–20)	47(33–60)
p-value		0.093	0.096	0.500	<0.001
Drinking status					
Current drinker	1374(68.60%)	19(16–22)	6(4–8)	17(13–20)	47(34–60)
Nondrinker	628(31.40%)	19(15–22)	6(4–8)	15(12–19)	43(30–55)
p-value		0.437	0.874	<0.001	<0.001
Race					
Mexican American	164(8.2%)	18(15–21)	6(4–7)	16(13–19)	38(26–52)
Other Hispanic	213(10.6%)	17(15–20)	6(4–7)	15(13–19)	34(23–48)
Non-Hispanic White	955(47.7%)	19(16–22)	6(4–8)	17(14–21)	50(40–63)
Non-Hispanic Black	473(23.6%)	19(16–22)	6(4–8)	15(11–18)	39(29–52)
Non-Hispanic Asian	167(8.3%)	20(16–22)	7(5–8)	14(12–17)	49(38–63)
Other Race	30(1.5%)	19(16–20)	6(5–7)	17(13–22)	44(38–57)
p-value		<0.001	<0.001	<0.001	<0.001
Education					
Less than ninth grade	246(12.20%)	16(14–19)	5(3–6)	14(11–17)	25(19–33)
9–11th grade	266(13.30%)	18(15–21)	5(4–7)	14(11–18)	36(29–46)
High School grad/GED or equivalent	469(23.40%)	19(16–22)	6(4–7)	16(12–19)	44(34–55)
Some college or AA degree	567(28.30%)	20(17–23)	6(5–8)	17(14–21)	52(41–62)
College graduate or above	454(22.70%)	21(17–23)	7(5–8)	18(15–22)	56(45–66)
p-value		<0.001	<0.001	<0.001	<0.001
Marital status					
Married	1110(55.40%)	19(16–22)	6(4–8)	16(13–20)	47(35–60)
Widowed	381(19.00%)	18(15–21)	6(4–7)	15(12–18)	40(29–54)
Divorced	288(14.40%)	19(17–23)	6(5–8)	17(13-21)	47(35–61)
Separated	49(2.40%)	18(15–21)	6(4–7)	15(12–18)	28(22–49)
Never married	119(5.90%)	20(16–23)	7(5–8)	15(13–20)	46(34–59)
Living with partner	55(2.70%)	19(16–22)	6(4–8)	18(15–21)	49(36–58)
p-value		<0.001	<0.001	<0.001	<0.001
Diabetes					
Yes	456(22.80%)	19(15–21)	6(4–7)	15(12–18)	42(28–52)
No	1461(73.00%)	19(16–22)	6(4–8)	16(13–20)	47(35–60)
Borderline	85(4.20%)	19(16–22)	5(4–7)	15(13–20)	47(36–56)
p-value		0.003	0.002	<0.001	<0.001
Hypertension					
Yes	1226(61.20%)	19(16–22)	6(4–7)	16(12–19)	44(32–56)
No	776(38.80%)	20(16–22)	6(5–8)	17(14–21)	49(36–61)
p-value		0.002	0.011	<0.001	<0.001

[a]Note: IRT, Immediate Recall test; DRT, Delayed Recall test; AFT, Animal Fluency test; DSST, Digit Symbol Substitution test; BMI: Body Mass Index. [b]Frequency (proportion).

investigate the synergistic effect of various metal exposures and determine the individual contribution of each exposure to the outcome, achieved by computing weights.[20] Mediation analysis was conducted to investigate whether serum folate mediated the

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865–874

Table 2. Distribution of Blood Metals (N = 2002), NHANES, USA, 2011−2014

Metals (μg/L)	Percentile					Mean ± SD[b]
	5th	25th	50th	75th	95th	
Pb[a]	0.60	1.01	1.47	2.20	4.28	1.87 ± 1.64
Cd	0.11	0.25	0.38	0.63	1.40	0.52 ± 0.45
Hg	0.20	0.50	0.97	1.98	6.04	1.78 ± 2.54
Se	155.16	177.65	193.26	208.41	237.54	195.3 ± 33.8
Mn	5.03	6.96	8.74	11.15	15.30	9.40 ± 4.05

[a]μg/dL. [b]SD: standard deviation.

Table 3. Association between Blood Metals and the z-Score of Four Cognitive Tests by the Generalized Linear Regression Model[a]

Metals		IRT z-score, β (95%CI)	DRT z-score, β (95%CI)	AFT z-score, β (95%CI)	DSST z-score, β (95%CI)
Pb	Q1	ref.	ref.	ref.	ref.
	Q2	0.02(−0.09,0.13)	0.03(−0.09,0.14)	0.04(−0.08,0.15)	0.01(−0.09,0.11)
	Q3	−0.11(−0.23,0.004)	−0.03(−0.15,0.08)	0.06(−0.06,0.17)	0.02(−0.08,0.12)
	Q4	−0.05(−0.17,0.07)	−0.04(−0.16,0.09)	0.06(−0.06,0.18)	−0.07(−0.18,0.03)
P for trend		0.158	0.384	0.312	0.206
Cd	Q1	ref.	ref.	ref.	ref.
	Q2	−0.05(−0.16,0.06)	0.03(−0.09,0.14)	0.002(−0.11,0.12)	−0.05(−0.14,0.05)
	Q3	−0.03(−0.15,0.08)	−0.07(−0.19,0.05)	−0.05(−0.17,0.07)	−0.08(−0.18,0.02)
	Q4	**-0.17(−0.30, −0.04)**	−0.05(−0.18,0.09)	−0.12(−0.25,0.02)	**-0.15(−0.27, −0.04)**
P for trend		**0.027**	0.268	0.074	**0.009**
Hg	Q1	ref.	ref.	ref.	ref.
	Q2	0.02(−0.09,0.14)	0.02(−0.09,0.14)	0.08(−0.04,0.19)	0.05(−0.05,0.15)
	Q3	0.06(−0.06,0.17)	0.02(−0.09,0.14)	0.05(−0.06,0.17)	0.002(−0.10,0.10)
	Q4	0.02(−0.09,0.14)	0.05(−0.07,0.17)	0.03(−0.09,0.15)	0.06(−0.05,0.16)
P for trend		0.568	0.410	0.734	0.480
Se	Q1	ref.	ref.	ref.	ref.
	Q2	**0.19(0.07,0.30)**	**0.14(0.03,0.26)**	0.05(−0.06,0.17)	**0.19(0.09,0.28)**
	Q3	**0.12(0.002,0.23)**	**0.11(0.00,0.23)**	0.04(−0.07,0.16)	**0.18(0.09,0.28)**
	Q4	**0.19(0.07,0.30)**	**0.14(0.03,0.26)**	0.08(−0.03,0.20)	**0.19(0.09,0.28)**
P for trend		**0.008**	**0.033**	0.206	**<0.001**
Mn	Q1	ref.	ref.	ref.	ref.
	Q2	0.03(−0.08,0.15)	0.08(−0.03,0.20)	−0.07(−0.18,0.04)	0.07(−0.03,0.17)
	Q3	0.04(−0.08,0.15)	**0.12(0.01,0.24)**	−0.04(−0.15,0.08)	0.05(−0.05,0.15)
	Q4	−0.02(−0.13,0.10)	0.10(−0.02,0.21)	**-0.12(−0.23,-0.001)**	0.05(−0.04,0.15)
P for trend		0.803	0.075	0.090	0.371

[a]Note: Model adjusted for gender, age, race, BMI, marriage status, education, smoking, alcohol drinking, hypertension, and diabetes. IRT, Immediate Recall test; DRT, Delayed Recall test; AFT, Animal Fluency test; DSST, Digit Symbol Substitution test. Values in bold indicate statistically significant results (p < 0.05).

association between metal levels and cognitive function. All models were adjusted for factors, such as gender, age, race, BMI, marital status, education, smoking, alcohol drinking, hypertension, and diabetes.

Statistical analyses were carried out using the R software (version 4.0.3), the R package "bkmr", "qgcomp" and "mediation" were used for BKMR, QG-C and mediation analysis, respectively. A two-sided p-value of <0.05 was considered statistically significant.

3. RESULTS

3.1. Characteristics of the Study Participants

The demographic information and cognition characteristics of the study population were depicted in Table 1. Of the 2002 participants included in the analysis, 977(48.80%) were male; The median IRT, DRT, AFT, and DSST scores were 19 [interquartile range (IQR): 6], 6(IQR:4), 16(IQR:7) and 46(IQR:25), respectively. Female had higher IRT, DRT, and DSST scores than male (p < 0.001). Those aged 60−69 group had higher cognitive scores than those aged 70 or greater (p < 0.001). Scores on the four cognitive tests differed by race (p < 0.001) and marital status (p < 0.001). Participants with diabetes or hypertension exhibited lower scores in the IRT (p = 0.003, p = 0.002, respectively), DRT (p = 0.002, p = 0.011, respectively), AFT (p < 0.001), and DSST (p < 0.001).

3.2. Distribution of Blood Metals and Correlations

The distributions of five blood metals were shown in Table 2. Median values of blood Pb, Cd, Hg, Se, and Mn across all participants were 1.47 μg/dL, 0.38, 0.97, 193.26, and 8.74 μg/L, respectively. The detection rates of metals were listed in Table S1. Below the detection limit, detection limit divided by the square root of 2 is used instead. The spearman correlations between concentrations of log-transformed blood metals in the study participants are shown in Figure.S3. The correlation coefficients of Cd with Pb and Mn were found to be 0.28 and 0.16, respectively.

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865−874

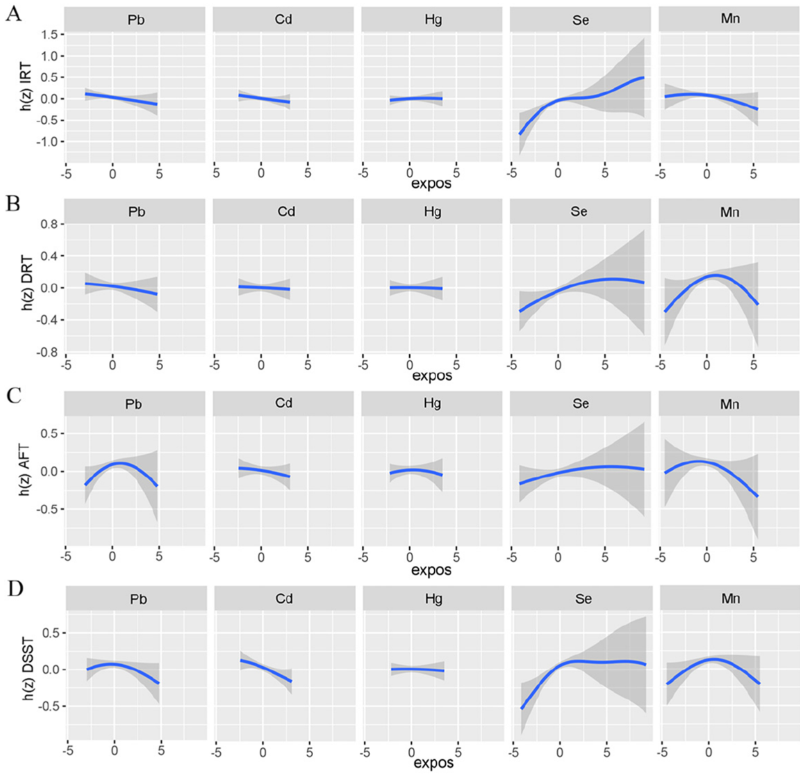


Figure 1. Univariate exposure-response functions and 95% confidence intervals (shaded areas) in IRT (A), DRT (B), AFT (C), and DSST (D) for Pb, Cd, Hg, Se, and Mn, with other elements held at the median, by Bayesian kernel machine regression analyses.

3.3. Association between Blood Metals and Cognitive Function Revealed by GLMs

Table 3 displays the associations between blood metals and four cognitive tests using generalized linear regression adjusted for all covariates. Specifically, compared to those in the lowest quartile of the Cd levels, individuals in the highest quartile exhibited significantly lower z-scores for IRT (β: −0.17,95% CI: −0.30, −0.04) and DSST (β: −0.15,95% CI: −0.27, −0.04). The quartile-specific estimates suggest clear negative trends between Cd and IRT (p = 0.027), DSST (p = 0.009) z-scores. There were significant positive associations between Se levels above the first quartile and IRT, DRT, and DSST z-scores. The P-trend for Se and IRT, DRT, DSST z-scores were all significant (p = 0.008, p = 0.033, p < 0.001, respectively). There was a significant positive association between the third quartile of Mn levels and DRT z-scores (β:0.12, 95% CI:0.01,0.24) compared to the lowest quartile of Mn. The highest quartile of Mn levels was inversely related to AFT z-scores (β: −0.12,95%CI: −0.23, −0.001).

3.4. Bayesian Kernel Machine Regression Analyses

To further explore the potential nonlinearities, additive or interactive effects, we employed the BKMR model, which provides an estimation of the joint effects of the five blood metals. Figure 1 displays the exposure-response relationships for each metal, with other metals held at median concentrations, after adjusting for all covariates. The relationships between metals and cognitive outcome can be denoted as h(z). Similar to findings from GLMs, the BKMR analyses suggested a positive association between Se levels and IRT, DRT, DSST, DSST z-scores (Figure 1); There exists a negative association between Cd levels and DSST z-scores (Figure 1). Interestingly, the results indicated nonlinear, inverted U-shaped relationships between Mn levels and DRT, AFT, DSST z-scores (Figure 1).

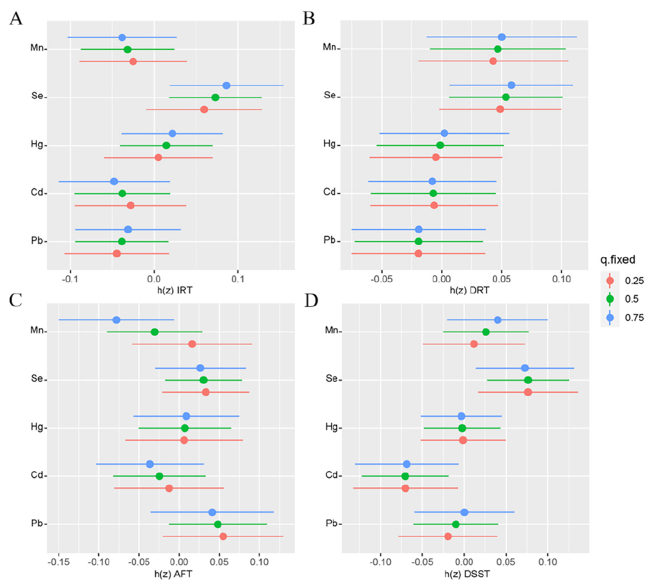


Figure 2. Single-exposure effect of individual metals on the z-scores of IRT (A), DRT (B), AFT (C), and DSST (D) (estimates and 95% confidence intervals) when all the other metals are fixed at their 25th, 50th, or 75th percentile Bayesian kernel machine regression analyses.

In Figure 2, the impact of altering the interquartile range (IQR) for each metal on the z-scores of four cognitive tests is depicted. We found significant positive association between Se levels and DSST, DRT and IRT z-scores (Figure 2A, B, D). There may be an interaction between Se and other metals, as the effect estimates of Se on IRT and DRT z-scores increase

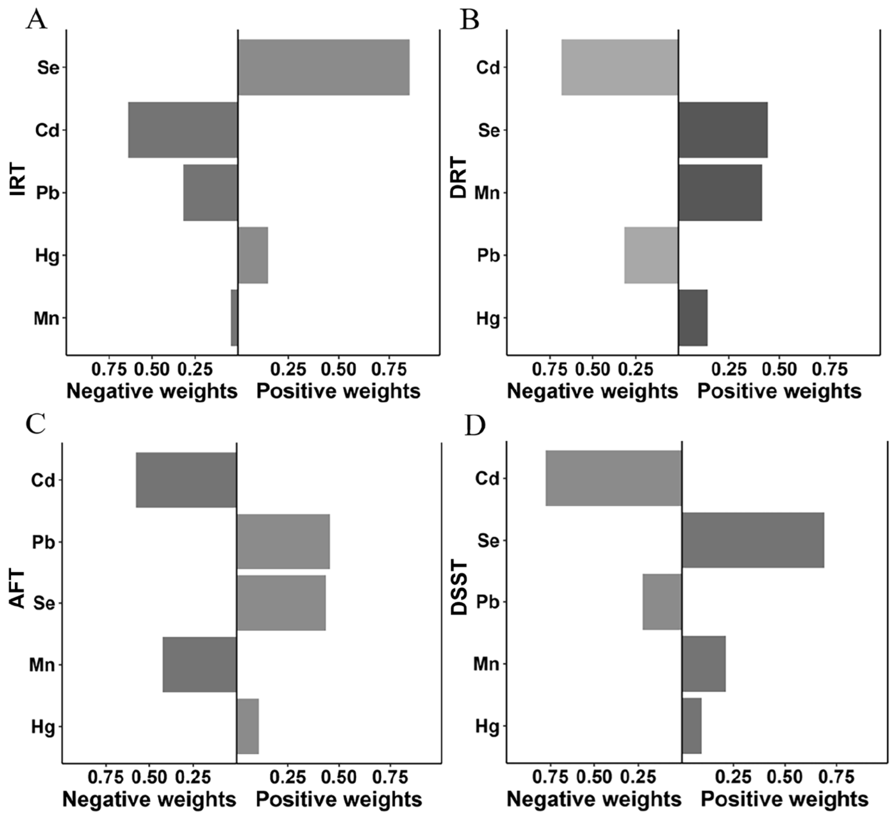


Figure 3. Weights corresponding to the proportion of the positive or negative partial effect per metal mixtures on the z-scores of IRT (A), DRT (B), AFT (C), and DSST (D) in the Quantile g-computation model.

with higher levels of the mixture. There was a significant negative association between Cd levels and DSST z-scores (Figure 2D). Interestingly, as the concentration of the metal mixture increased, the effect estimates of Mn on AFT z-scores become inverse (Figure 2C).

To more fully investigate possible interactions among metals, we depicted the bivariate exposure-response functions curves. Figure S4 showed potential pairwise interactions between Se and Pb, Mn, where the positive slope of Se with AFT z-scores is slightly steeper at lower Pb levels and higher Mn levels. To examine the overall effect of metal mixture, we estimated how changes in all metals within the mixture simultaneously affect cognitive test z-scores relative to their median levels. (Figure S5). We did not observe any significant mixed metal effects, but there is a weak trend of decreased cognitive functions in terms of IRT, AFT, DSST, and an increased trend in DRT (Figure.S5). Among the metals in the mixture, Se, Cd may be the dominant contributors (PIP = 1.0, 0.82, respectively, Table S2).

3.5. Quantile g-Computation Analysis

In the quantile g-computation, Cd contributed the largest negative weights in the association with IRT, DRT, AFT, and DSST z-scores (Figure 3). Consistent with results from the GLMs and BKMR analyses, Se contributed the largest positive weights in the association with IRT, DRT, DSST z-scores (Figure 3). The association between the metal mixture and cognitive function was weak (Figure.S6).

3.6. Association between Blood Metals and Serum Folate

A multivariate linear regression model was adopted to investigate the association between blood metals and serum folate. As presented in Table 4, Pb (β: −5.80, 95% CI: −8.45, −3.15, p < 0.001), Cd (β: −6.37, 95% CI: −8.91, −3.83, p < 0.001) had a significantly negative association with serum folate. Significant positive association between Se (β: 20.49, 95% CI: 10.26, 30.72, p < 0.001) and serum folate was observed.

Table 4. Multivariate Linear Regression of Metal Levels with Serum Folate (N = 1945)[a]

Metal	β	95%CI	p-value
Pb	−5.80	(−8.45, −3.15)	<0.001
Cd	−6.37	(−8.91, −3.83)	<0.001
Hg	−1.18	(−2.71, 0.36)	0.132
Se	20.49	(10.26, 30.72)	<0.001
Mn	1.96	(−2.25,6.16)	0.361

[a]Note: All covariates were adjusted in model.

3.7. Serum Folate Involved in the Effects of Metal on Cognitive Function

We conducted mediation analysis to further explore the mediating effects of serum folate on the association between metal exposure and cognitive function. The significant direct effects of exposure on outcome, as well as exposure and mediated effects, were included in the analysis. Prior to the mediation analysis, we found that folate levels were associated with better AFT and DSST scores (Table S3). We only listed the significant results in Table 5, serum folate significantly mediated the associations between Cd (mediated proportion = 0.17, 95% CI: 0.06,0.57), Se (mediated proportion = 0.10, 95% CI: 0.003,0.27) and the DSST z-scores, respectively.

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865−874

Table 5. Mediating Effects of Serum Folate on the Association between Metal and DSST z-Score[a]

Metal	Indirect effects, β (95%CI)	Direct effects, β (95%CI)	Total effects, β (95%CI)	Proportion of mediation (95%CI)
Pb	**−0.03(−0.05,−0.01)**	−0.06(−0.23,0.08)	−0.10(−0.26,0.04)	0.25(−2.80,5.22)
Cd	**−0.03(−0.06,−0.02)**	**−0.16(−0.29,−0.03)**	**−0.20(−0.33,−0.07)**	**0.17(0.06,0.57)**
Se	**0.10(0.002,0.24)**	**0.88(0.38,1.44)**	**0.98(0.39,1.52)**	**0.10(0.003,0.27)**

[a]Note: All covariates were adjusted in model. Values in bold indicate statistically significant results ($p < 0.05$).

4. DISCUSSION

In this study, we evaluate the individual and overall effects of Pb, Cd, Hg, Se, and Mn on cognitive function (IRT, DRT, AFT, DSST scores) and the potential mediating effects of serum folate in the elderly from the U.S. We observed the positive associations between blood Se and cognitive function, while Cd had the most significant negative association with cognitive function in GLMs, BKMR and QG-C model. Moreover, Se was positively correlated with serum folate, Cd was negatively correlated with serum folate. Serum folate was involved in the effects of Se, Cd on DSST z-scores. Besides, Mn showed an inverted U-shaped nonlinear relationship on cognition. There may be potential interactions between Se and Mn, Pb in association with AFT. We found that the population had relatively low exposure to metals but slightly higher Se levels compared to other studies (Table S4). This discrepancy may be due to regional, dietary, or other differences.

Se plays a crucial role in maintaining normal brain function. Our findings align with previous studies indicating a positive link between Se and cognitive function.[21,22] Research has highlighted that Se deficiency is common among older adults, suggesting that Se supplementation could potentially enhance cognitive abilities.[22] Lower Se levels are associated with a higher cognitive decline risk in older individuals,[23] as exemplified by the French EVA cohort's study.[24] The neuroprotective functions of Se are multifaceted, involving the modulation of neurotransmitter levels, reduction of oxidative stress, mitigation of neuroinflammation, and repair of neural cell damage.[25] Animal studies have further indicated that increased Se levels may promote the proliferation of precursor cells in the hippocampus and stimulate adult neurogenesis.[26] Selenoprotein P (SEPP1) plays a critical neuroprotective role by enhancing neuronal survival and inhibiting apoptosis in response to amyloid β-induced oxidative stress.[27] These findings highlight Se's importance in cognitive function and potential therapeutic benefits through supplementation.

We observed a negative association between Cd exposure and IRT and DSST z-scores, indicative of reduced sustained attention and working memory. Supporting these findings, cross-sectional and longitudinal studies have shown that increased Cd exposure is associated with significant cognitive declines in older adults, as evidenced by results from multiple studies in older populations and a specific longitudinal study in China.[28−30] Recent research suggests that chronic Cd exposure impairs cognitive functions through the activation of the lnc-Gm10532/m6A/FIS1 axis-mediated mitochondrial fission and dysfunction.[31] Additionally, Cd promotes neurotoxicity by activating astrocytes and triggering the secretion of inflammatory mediators, culminating in neuronal apoptosis.[32]

Surprisingly, we observed a curvilinear association between Mn levels and cognition. This implies that an optimum concentration of Mn may serve as a protective element against cognitive impairments, excessive levels may pose risks. Additionally, several cross-sectional studies have reported that elevated Mn levels are associated with poorer cognitive function.[33] The exact molecular mechanism underlying Mn's impact on cognitive function has not been fully established. Excessive Mn exposure is neurotoxic, which may be related to oxidative stress, neuroinflammation, neurotransmission disruption, α-synuclein aggregation and amyloid production.[34]

High plasma folate levels have been positively associated with global cognitive score.[35] Conversely, low folate status has been linked to poor cognitive function and an increased risk of dementia in the elderly.[36] Folate supplementation is effective in reducing plasma homocysteine (Hcy) levels, an independent risk factor for AD and vascular dementia.[37] Animal studies have shown that high folate levels are beneficial for early sensory development - motor function, spatial learning and memory in adolescence and adulthood.[38] Chronic folate deficiency induces glucose and lipid metabolism disorders and subsequent cognitive dysfunction in mice.[39] There is an inverse relationship between Cd and folate, it hypothesized that Cd accumulation may cause impaired gut microbiota through ROS production and increased oxidative stress, thereby affecting folate absorption, and Cd may interfere with the enzymes of the folate cycle.[16] Both Se and folate are nutritional supplements capable of regulating redox and Hcy homeostasis in the body. Se may potentially impact the metabolism or utilization of folate. One study demonstrated that cosupplementation of Se and folate resulted in the recovery of synaptic plasticity and cognitive ability in AD mice, potentially through reversing lipid metabolism disorders.[40] Therefore, it is reasonable to speculate that folate may be involved in the potential mechanism underlying metal-related cognitive effects.

Further, the results of BKMR analysis suggested interaction between Se and Pb, Mn on the association with AFT z-scores. As the brain is a common target organ for Pb and other metals, potential additive or synergistic effects induced by the metal mixtures would be anticipated.[41] Se is a recognized antioxidant and may interact with Pb to counteract its toxic properties through the action of SEPP.[42] Additionally, Se has antioxidant, anti-inflammatory, and antiapoptotic properties, and may mitigate Mn-mediated neurotoxicity by reducing the accumulation of Mn, acting as a neuroprotective agent.[43]

We investigated the impact of the five mixed metals on cognition as a whole. It is possible that the diverse metals have varying effects on cognition, and may interact with each other (e.g., synergism, antagonism). Specifically, Se exhibits a beneficial effect, whereas Cd and Pb may have detrimental effects, and Mn may have a bidirectional effect, potentially leading to a canceling effect. Additionally, other underlying factors might influence the results. Consequently, the mixing curve does not demonstrate a noticeable mixing effect. Nevertheless, this highlights the significance of conducting studies on mixed exposure.

Our study has several strengths. A major strength lies in the use of BKMR and QG-C analysis to estimate the overall effect of the metal mixture and identify the relative contribution of

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865−874

each metal, investigate the possible nonlinear association between metal exposure and cognition and drew robust and stable conclusions. Second, we explored the mediating effect of serum folate on the association between metals and cognition, providing insights into potential mechanisms. Third, we used data of the elderly population in two cycles of NHANES, ensuring a large sample size and an authoritative, nationally representative data set. Further research is necessary to uncover the mechanisms underlying the cognitive effects of metals to gain a comprehensive understanding of their influence.

Several limitations should also be noted. The cross-sectional design of NHANES imposed limitations on inferring causality between metal exposures and cognition. We focused only on the effect of a few blood metals on cognition from an epidemiological perspective, and we did not delve into the specific mechanisms by which metals affect human health. While we may not rule out the potential effects of residual and other confounding factors.

5. CONCLUSION

We present evidence of an association between several metals and cognitive function in older adults in the context of mixtures. High Se levels are linked to better cognitive performance, whereas higher Cd levels are associated with poorer cognitive scores. Serum folate appears to mediate the relationship between metal exposure and cognitive function. Further research is required to confirm these associations and elucidate the underlying mechanisms by which metals affect cognition among older adults to develop interventions to prevent cognitive decline.

■ ASSOCIATED CONTENT

Data Availability Statement

A full list of data sets supporting the results in this research article can be found at: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2011.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00071.

Detailed information for instrumental analysis; LOD and PIPs of metals; association of serum folate with cognitive; participant selection flow; bivariate correlation and interaction between analytes; joint effects of metal mixtures on cognition (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Piye Niu − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*; orcid.org/0000-0002-0155-3438; Email: niupiye@ccmu.edu.cn

Authors

Luli Wu − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*

Ye Xin − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*

Junrou Zhang − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*

Xin Yang − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*

Tian Chen − *Department of Occupational Health and Environmental Health, School of Public Health and Beijing Key Laboratory of Environmental Toxicology, School of Public Health, Capital Medical University, 100069 Beijing, China*; orcid.org/0000-0003-1272-0905

Complete contact information is available at: https://pubs.acs.org/10.1021/envhealth.4c00071

Author Contributions

Luli Wu: Writing - original draft, Formal analysis, Visualization; **Ye Xin**: Data curation, Formal analysis; **Junrou Zhang**: Data curation; **Xin Yang**: Data curation; **Tian Chen**: Writing - review &editing; **Piye Niu**: Conceptualization, Supervision, Writing - review &editing.

Notes

The authors declare no competing financial interest.
Ethical Approval: We declare that this paper is original, has not been published before, and is not currently being considered for publication by another journal. NHANES was approved by the National Center for Health Statistics Ethics Review Board. Consent to Participate: All written informed consent of participants was obtained in agreement with the Public Health Service Act prior to any data collection.

■ ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (No. 81973007).

■ REFERENCES

(1) Anderson, L. A.; Egge, R. Expanding efforts to address Alzheimer's disease: the Healthy Brain Initiative. *Alzheimers. Dement.* **2014**, *10*, S453−S456.

(2) Petersen, R. C.; Lopez, O.; Armstrong, M. J.; Getchius, T. S.D.; Ganguli, M.; Gloss, D.; Gronseth, G. S.; Marson, D.; Pringsheim, T.; Day, G. S.; Sager, M.; Stevens, J.; Rae-Grant, A. Practice guideline update summary: Mild cognitive impairment. *Neurology.* **2018**, *90*, 126−135.

(3) Patterson, C. World Alzheimer Report 2018: The State of the Art of Dementia Research. *New Frontiers Alzheimer's Disease International (Adi).* 2018. https://www.alzint.org/resource/world-alzheimer-report-2018/.

(4) Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers. Dement.* **2022**, *18*, 700−789.

(5) Demurtas, J.; Schoene, D.; Torbahn, G.; Marengoni, A.; Grande, G.; Zou, L.; et al. Physical Activity and Exercise in Mild Cognitive Impairment and Dementia: An Umbrella Review of Intervention and Observational Studies. *J. Am. Med. Dir. Assoc.* **2020**, *21*, 1415−1422.

(6) Weng, X.; Tan, Y.; Fei, Q.; Yao, H.; Fu, Y.; Wu, X.; et al. Association between mixed exposure of phthalates and cognitive function among the U.S. elderly from NHANES 2011−2014: Three statistical models. *Sci. Total Environ.* **2022**, *828*, 154362.

(7) Baumgart, M.; Snyder, H. M.; Carrillo, M. C.; Fazio, S.; Kim, H.; Johns, H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers. Dement.* **2015**, *11*, 718−726.

(8) Bakulski, K. M.; Seo, Y. A.; Hickman, R. C.; Brandt, D.; Vadari, H. S.; Hu, H.; et al. Heavy Metals Exposure and Alzheimer's Disease and Related Dementias. *J. Alzheimers Dis.* **2020**, *76*, 1215−1242.

(9) Vlasak, T.; Jordakieva, G.; Gnambs, T.; Augner, C.; Crevenna, R.; Winker, R.; et al. Blood lead levels and cognitive functioning: A meta-analysis. *Sci. Total Environ.* **2019**, *668*, 678−684.

(10) Kippler, M.; Bottai, M.; Georgiou, V.; Koutra, K.; Chalkiadaki, G.; Kampouri, M.; et al. Impact of prenatal exposure to cadmium on cognitive development at preschool age and the importance of selenium and iodine. *Eur. J. Epidemiol.* **2016**, *31*, 1123−1134.

(11) Ciesielski, T.; Bellinger, D. C.; Schwartz, J.; Hauser, R.; Wright, R. O. Associations between cadmium exposure and neurocognitive test scores in a cross-sectional study of US adults. *Environ. Health.* **2013**, *12*, 13.

(12) Lister, L. J.; Svendsen, C.; Wright, J.; Hooper, H. L.; Spurgeon, D. J. Modelling the joint effects of a metal and a pesticide on reproduction and toxicokinetics in Lumbricid earthworms. *Environ. Int.* **2011**, *37*, 663−670.

(13) Spurgeon, D. J.; Jones, O. A.; Dorne, J. L.; Svendsen, C.; Swain, S.; Sturzenbaum, S. R. Systems toxicology approaches for understanding the joint effects of environmental chemical mixtures. *Sci. Total Environ.* **2010**, *408*, 3725−3734.

(14) Ma, F.; Wu, T.; Zhao, J.; Ji, L.; Song, A.; Zhang, M.; et al. Plasma Homocysteine and Serum Folate and Vitamin B(12) Levels in Mild Cognitive Impairment and Alzheimer's Disease: A Case-Control Study. *Nutrients.* **2017**, *9*, 725.

(15) Ma, F.; Wu, T.; Zhao, J.; Han, F.; Marseglia, A.; Liu, H.; et al. Effects of 6-Month Folic Acid Supplementation on Cognitive Function and Blood Biomarkers in Mild Cognitive Impairment: A Randomized Controlled Trial in China. *J. Gerontol. Ser. A-Biol. Sci. Med. Sci.* **2016**, *71*, 1376−1383.

(16) Wang, B. K.; Chen, W. L. Detrimental health relationship between blood lead and cadmium and the red blood cell folate level. *Sci. Rep.* **2022**, *12*, 6628.

(17) Fillenbaum, G. G.; Belle, G.; Morris, J. C.; Mohs, R. C.; Mirra, S. S.; Davis, P. C.; et al. Consortium to Establish a Registry for Alzheimer's Disease (CERAD): The first twenty years. *Alzheimer's & Dementia.* **2008**, *4*, 96−109.

(18) Bobb, J. F.; Valeri, L.; Claus Henn, B.; Christiani, D. C.; Wright, R. O.; Mazumdar, M.; Godleski, J. J.; Coull, B. A.; et al. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. *Biostatistics.* **2015**, *16*, 493−508.

(19) Bobb, J. F.; Claus Henn, B.; Valeri, L.; Coull, B. A. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. *Environ. Health.* **2018**, *17*, 67.

(20) Keil, A. P.; Buckley, J. P.; O'Brien, K. M.; Ferguson, K. K.; Zhao, S.; White, A. J. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. *Environ. Health. Perspect.* **2020**, *128*, 47004.

(21) Li, S.; Sun, W.; Zhang, D. 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). *J. Alzheimers Dis.* **2019**, *72*, 1145−1157.

(22) Sasaki, N.; Carpenter, D. O. Associations between Metal Exposures and Cognitive Function in American Older Adults. *Int. J. Environ. Res. Public Health.* **2022**, *19*, 2327.

(23) Yan, X.; Liu, K.; Sun, X.; Qin, S.; Wu, M.; Qin, L.; et al. A cross-sectional study of blood selenium concentration and cognitive function in elderly Americans: National Health and Nutrition Examination Survey 2011−2014. *Ann. Hum. Biol.* **2020**, *47*, 610−619.

(24) Berr, C.; Balansard, B.; Arnaud, J.; Roussel, A. M.; Alperovitch, A. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. *J. Am. Geriatr. Soc.* **2000**, *48*, 1285−1291.

(25) Wu, H.; Zhao, G.; Liu, S.; Zhang, Q.; Wang, P.; Cao, Y.; et al. Supplementation with selenium attenuates autism-like behaviors and improves oxidative stress, inflammation and related gene expression in an autism disease model. *Journal of Nutritional Biochemistry.* **2022**, *107*, 109034.

(26) Leiter, O.; Zhuo, Z.; Rust, R.; Wasielewska, J. M.; Gronnert, L.; Kowal, S.; et al. Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging. *Cell Metab.* **2022**, *34*, 408−423.

(27) Rayman, M. P. Selenium and human health. *Lancet.* **2012**, *379*, 1256−1268.

(28) Li, H.; Wang, Z.; Fu, Z.; Yan, M.; Wu, N.; Wu, H.; et al. Associations between blood cadmium levels and cognitive function in a cross-sectional study of US adults aged 60 years or older. *Bmj Open.* **2018**, *8*, No. e020533.

(29) Xiao, L.; Zan, G.; Qin, J.; Wei, X.; Lu, G.; Li, X.; et al. Combined exposure to multiple metals and cognitive function in older adults. *Ecotoxicol. Environ. Saf.* **2021**, *222*, 112465.

(30) Liu, H.; Su, L.; Chen, X.; Wang, S.; Cheng, Y.; Lin, S.; et al. Higher blood cadmium level is associated with greater cognitive decline in rural Chinese adults aged 65 or older. *Sci. Total Environ.* **2021**, *756*, 144072.

(31) Deng, P.; Zhang, H.; Wang, L.; Jie, S.; Zhao, Q.; Chen, F.; et al. Long-term cadmium exposure impairs cognitive function by activating lnc-Gm10532/m6A/FIS1 axis-mediated mitochondrial fission and dysfunction. *Sci. Total Environ.* **2023**, *858*, 159950.

(32) Phuagkhaopong, S.; Ospondpant, D.; Kasemsuk, T.; Sibmooh, N.; Soodvilai, S.; Power, C.; et al. Cadmium-induced IL-6 and IL-8 expression and release from astrocytes are mediated by MAPK and NF-kappaB pathways. *Neurotoxicology.* **2017**, *60*, 82−91.

(33) Ruiz-Azcona, L.; Markiv, B.; Expósito, A.; Pozueta, A.; García-Martínez, M.; Fernández-Olmo, I.; et al. Poorer cognitive function and environmental airborne Mn exposure determined by biomonitoring and personal environmental monitors in a healthy adult population. *Sci. Total Environ.* **2022**, *815*, 152940.

(34) Nyarko-Danquah, I.; Pajarillo, E.; Digman, A.; Soliman, K. F. A.; Aschner, M.; Lee, E. Manganese Accumulation in the Brain via Various Transporters and Its Neurotoxicity Mechanisms. *Molecules.* **2020**, *25*, 5880.

(35) Boumenna, T.; Scott, T. M.; Lee, J. S.; Palacios, N.; Tucker, K. L. Folate, vitamin B-12, and cognitive function in the Boston Puerto Rican Health Study. *Am. J. Clin. Nutr.* **2021**, *113*, 179−186.

(36) Ramos, M. I. A. L.; et al. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. *American Journal of Clinical Nutrition.* **2005**, *82* (6), 1346−1352.

(37) Wald, D. S.; Kasturiratne, A.; Simmonds, M. Serum homocysteine and dementia: meta-analysis of eight cohort studies including 8669 participants. *Alzheimers. Dement.* **2011**, *7*, 412−417.

(38) Zhou, D.; Li, Z.; Sun, Y.; Yan, J.; Huang, G.; Li, W. Early Life Stage Folic Acid Deficiency Delays the Neurobehavioral Development and Cognitive Function of Rat Offspring by Hindering De Novo Telomere Synthesis. *Int. J. Mol. Sci.* **2022**, *23*, 6948.

(39) Zhao, M.; Yuan, M. M.; Yuan, L.; Huang, L. L.; Liao, J. H.; Yu, X. L.; et al. Chronic folate deficiency induces glucose and lipid metabolism disorders and subsequent cognitive dysfunction in mice. *Plos One.* **2018**, *13*, No. e0202910.

(40) Zhang, Z. H.; Cao, X. C.; Peng, J. Y.; Huang, S. L.; Chen, C.; Jia, S. Z.; et al. Reversal of Lipid Metabolism Dysregulation by Selenium and Folic Acid Co-Supplementation to Mitigate Pathology in Alzheimer's Disease. *Antioxidants.* **2022**, *11*, 829.

(41) Mendez-Armenta, M.; Rios, C. Cadmium neurotoxicity. *Environ. Toxicol. Pharmacol.* **2007**, *23*, 350−358.

(42) El-Ansary, A.; Bjørklund, G.; Tinkov, A. A.; Skalny, A. V.; Al Dera, H. Relationship between selenium, lead, and mercury in red blood cells of Saudi autistic children. *Metab. Brain Dis.* **2017**, *32*, 1073−1080.
(43) Nkpaa, K. W.; Nkpaa, B. B.; Amadi, B. A.; Ogbolosingha, A. J.; Wopara, I.; Belonwu, D. C.; et al. Selenium abates manganese-induced striatal and hippocampal toxicity via abrogation of neurobehavioral deficits, biometal accumulation, oxidative stress, inflammation, and caspase-3 activation in rats. *Psychopharmacologia.* **2022**, *239*, 399−412.

https://doi.org/10.1021/envhealth.4c00071
Environ. Health 2024, 2, 865−874