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Associations between blood cadmium levels and cognitive function in a cross-sectional study of US adults aged 60 years or older

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ABSTRACT

Objectives The relationship between cadmium exposure and cognition has been well studied in children. However, the association between environmental cadmium exposure and cognitive function has not been researched extensively in older adults. Our goal was to evaluate the association between cognitive function and blood cadmium levels in US adults aged 60 years or older.

Design A cross-sectional study.

Setting The US National Health and Nutrition Examination Survey (NHANES).

Participants A total of 2068 adults aged 60 years or older who completed four cognitive assessment tests and blood cadmium detection in two waves of NHANES (2011–2014).

Main outcome measures Cognitive assessment was conducted by 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). We created a composite cognitive z-score to represent global cognitive function.

Results The median blood cadmium concentration in the study participants was 0.35 µg/L, and the IQR was 0.24–0.56 µg/L. In linear regression analyses, adjusting for demographics, behaviour and medical history, blood cadmium as a continuous variable was inversely associated with the composite z-score (µg/L, β=−0.11, 95% CI −0.20 to −0.03). Similarly, there was a significant association between quartiles of blood cadmium and composite z-score, with somewhat lower scores in the upper quartile of exposure (blood cadmium ≥0.63 µg/L) compared with those in the lower quartile of exposure (blood cadmium <0.25 µg/L) (µg/L, β=−0.14, 95% CI −0.25 to −0.03), and there was a trend by quartiles of blood cadmium (P<0.0001).

Conclusions Our findings suggest that increased blood cadmium is associated with worse cognitive function in adults aged 60 years or older in the USA.

Strengths and limitations of this study

► We created a composite cognitive z-score representing global cognitive function to minimise the floor or ceiling effect of a single cognitive test and control for a range of factors that are known to affect cognitive function in our models.
► Our sample is very large and representative. Therefore, the association between cognitive function and cadmium exposure is more reliable.
► This study is cross-sectional, which restricts our assessments of the temporal relationships of the associations.

than double by 2050 and to more than triple by 2100, increasing from 962 million globally in 2017 to 2.1 billion in 2050 and 3.1 billion in 2100.[1] Age-related progressive cognitive decline will be a major public health challenge. It is estimated that, in the USA, approximately 36% of those over age 70 years are cognitively impaired,[2] and 5.1 million elderly people have dementia,[3] with an expected doubling by 2050.[4]

Cadmium is a heavy metal in the Earth's crust. Food and tobacco smoke are the main sources of cadmium in the body. Cadmium exerts its toxic effects on the kidneys and bone and on the central nervous system. Animal experiments revealed that cadmium can be transported directly from the olfactory epithelium to the central nervous system, bypassing the blood–brain barrier (BBB).[5] Additionally, a study showed that rats exposed to 10 ppm cadmium ($CdCl_2$ salt) in drinking water for 90 days had enhanced fluorescent dye permeability to the brain. The observed alteration in BBB permeability has been found to be coupled with a widespread depletion in free radical scavenging enzyme activities and other antioxidants in microvessels.[6] In addition to increasing the permeability of

INTRODUCTION

The population is ageing rapidly worldwide, and the number of older persons—those aged 60 years or over—is expected to more

BMJ

the BBB, cadmium has also been shown to accumulate in the choroid plexus, which is an important component of the BBB that can directly damage the general plexus structure, or selectively impair critical regulatory mechanisms.[7] López et al[8] reported that rat brain cortical neurons placed in serum-free medium containing 10 µm cadmium had a large amount of neuronal apoptosis and axon disappearance after 24 hours. An in vitro study also confirmed that the cerebral cortical neurons exposed to 5 µm, 10 µm or 20 µm cadmium are targets of cadmium toxicity.[9] In children, the negative effects of cadmium on cognition have been extensively reported.[10–13] However, the relationship between cadmium exposure and cognitive function in the elderly is unclear so far. In a cross-sectional study of 125 older people (age range 50–82 years) in Brazil, blood cadmium (mean, 0.90 µg/L) was negatively associated with working memory capacity.[14] A Chinese cohort study of 188 elderly individuals also reported a negative relationship between plasma cadmium levels (mean, 1.75 µg/L) and cognitive scores.[15] However, other studies failed to find a significant association between cadmium and neurocognitive test scores in older adults.[16–18] Therefore, we analysed a large dataset of non-institutionalised civilians in the US aged 60 years or over from the continuous National Health and Nutrition Examination Survey (NHANES 2011–2014) to reveal the relationship between cadmium exposure and cognitive function.

METHODS

Data sources and study population

NHANES is a complex, multistage survey of non-institutionalised civilians in the USA that combines interviews and physical examinations. The interview includes demographic, socioeconomic, dietary and health-related questions. The examination component consists of medical, dental and physiological measurements, as well as laboratory tests administered by highly trained medical personnel.[19] Weights are computed to arrive at a sample that is representative of the US population. We merged two cycles, 2011–2012 and 2013–2014, for this analysis. In this study, our research subjects were older adults aged 60 years or above. Respectively, 1687 and 1785 older adults aged ≥60 years participated in the cognitive function test in the 2011–2012 and 2013–2014 cycles. Excluding participants who did not complete cognitive testing or blood cadmium measurement, a total of 2068 older adults were included in our analysis.

Cognitive assessment

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). The CERAD Word List Learning test and the CERAD Word List Recall test were designed to assess immediate and

delayed learning ability for new verbal information.[20] For the learning trials, participants were instructed to read aloud 10 unrelated words, one at a time, as they were presented. Immediately following the presentation of the words, participants recalled as many words as possible. In each of the three learning trials, the order of the 10 words is changed. The delayed word recall occurred after the other two cognitive exercises (Animal Fluency and DSST) were completed (approximately 8–10 min from the start of the word learning trials). The maximum score possible on each trial is 10. The Animal Fluency test examines categorical verbal fluency,[21] a component of executive function in which participants were asked to name as many animals as possible in 1 min. The DSST, a performance module from the Wechsler Adult Intelligence Scale (WAIS III), is used to assess processing speed, sustained attention and working memory.[22] The exercise was conducted using a paper form that has a key at the top containing nine numbers paired with symbols. Participants have 2 min to copy the corresponding symbols in the 133 boxes that adjoin the numbers. The score is the total number of correct matches. Higher scores represent better cognitive function for all tests.

Measurement of blood cadmium levels

Blood samples were collected from participants by venipuncture in prescreened phials or vacuum tubes. After collection, the samples were transported and stored at a temperature of 4°C until receipt by the processing laboratory; the samples were then kept at −20°C until analysis. Whole blood cadmium concentrations were determined using inductively coupled plasma mass spectrometry after a simple dilution sample preparation step. Further methodological details on the laboratory analyses are described elsewhere.[23 24] The limits of detection (LODs) were 0.16 µg/L (NHANES 2011–2012) and 0.10 µg/L (NHANES 2013–2014). In cases where the result was below the limit of detection, the value was the detection limit divided by the square root of 2. A total of 107 (5%) participants had measurements below the LOD.

Covariates

We included a variety of covariates based on previous research[14 15] in this study that are thought to be related to cognitive function and/or cadmium exposure: race-ethnicity (Mexican American/other Hispanic, non-Hispanic white, non-Hispanic black and other race), age (continuous variable), education level (<high school, high school and >high school), poverty–income ratio (ratio of family income to poverty, ≤0.99 and ≥1.00), gender (male and female), marital status (married/living with partner, widowed/divorced/separated and never married), tobacco smoking (smoked at least 100 cigarettes in life and smoke now as current, smoked at least 100 cigarettes in life but does not smoke now as former, and smoked less than 100 cigarettes in life and not smoke now as never), alcohol consumption (<12 drinks/year and ≥12 drinks/year), diabetes (yes and no), hypertension (yes and no),

stroke (yes and no) and coronary heart disease (yes and no).

Statistical analyses

We used SAS V.9.2 for statistical analyses. Following the NHANES Analytical Guidelines,[25] the MEC exam sample weights (WTMEC2YR) were used for analyses. Since we merged the 2011–2012 and 2013–2014 survey cycles, weights (WTMEC4YR) for combined NHANES survey cycles were calculated according to the NHANES file.[25] Survey procedures were used to take the complex, multi-stage sampling design of NHANES into account. Because of the wide range of cognitive function in the elderly population, individual cognitive tests are subject to floor and ceiling effects. To minimise such effects, we created a composite cognitive z-score by using the average of the standardised scores of the four cognitive tests (CERAD Word List Learning Test, CERAD Word List Recall Test, Animal Fluency Test and DSST). The Kolmogorov-Smirnov test was used to test the normality assumption of the composite z-score. Descriptive statistics for our study population including proportions, means and percentiles were calculated. Univariate analyses of the association between the covariates and composite z-score were performed by univariate linear regression. Significant covariates in univariate analyses were included in the multiple linear regression. The multiple linear regression models were used to assess the association between blood cadmium as a continuous variable and composite z-score adjusted for age, gender, ethnicity, education, poverty–income ratio, marital status, alcohol consumption, diabetes, hypertension, stroke and coronary heart disease. In addition, we evaluated the association between quartiles of blood cadmium levels and composite z-scores. Due to the large impact of stroke on cognitive function, we conducted sensitivity analyses with and without individuals who had suffered a stroke. In each model, those who had missing data on covariates were excluded from the multiple linear regression. Statistical tests for linear trends were conducted by modelling quartiles as an ordinal variable using integer values and p value for trend based on the Wald test. P values <0.05 were considered statistically significant.

RESULTS

Data from four cognitive function tests were available for 2934 (84.50%) of the 3472 participants evaluated. Blood cadmium data were available for 2068 (70.48%) of these people. Study participants were on average approximately 69.14 years old. The composite z-score had a normal distribution (P=0.1273) and ranged from −2.53 to 2.50 (mean, 0.24; SE 0.04), with lower scores indicating worse cognitive function. The median blood cadmium concentration in the study participants was 0.35 µg/L, and the IQR was 0.24–0.56 µg/L. The demographic characteristics of those who completed the CERAD Word List Learning test, the CERAD Word List Recall test, the Animal Fluency test

and the Digital Symbol Substitution test and had blood cadmium measures are presented in table 1. All covariates besides tobacco smoking were associated with the composite z-score in the univariate analyses (table 2).

Blood cadmium as a continuous variable was inversely associated with the composite z-score in unadjusted model 1 (µg/L, β=−0.19, 95% CI −0.29 to −0.08) (table 3), and the association was also significant in model 2 adjusted for age, gender, ethnicity, education, poverty–income ratio and marital status (µg/L, β=−0.09, 95% CI −0.18 to −0.01) (table 3). In addition, the association still existed in model 3 adjusted for age, gender, ethnicity, education, poverty–income ratio, marital status and alcohol consumption (µg/L, β=−0.11, 95% CI −0.19 to −0.02) (table 3). Then, we adjusted for diabetes, hypertension, stroke and coronary heart disease in model 4, and the association was significant as before (µg/L, β=−0.11, 95% CI −0.20 to −0.03) (table 3).

Table 5 presents the results of sensitivity analyses. Excluding individuals who suffered a stroke, blood cadmium as a continuous variable was also inversely associated with the composite z-score adjusted for age, gender, ethnicity, education, poverty–income ratio, marital status, alcohol consumption, diabetes, hypertension and coronary heart disease (µg/L, β=−0.12, 95% CI −0.20 to −0.04). Similarly, the highest quartile was inversely associated with the composite z-score (µg/L, β=−0.13, 95% CI −0.23 to −0.03). The trend still existed moving from the lowest quartile to the highest quartile (p trend=0.0107).

DISCUSSION

In this study of US adults aged 60–80 years, we found a significant inverse association between blood cadmium levels and cognitive function scores, and this correlation did not change after controlling for potential confounding factors.

The average concentration of blood cadmium was 0.50 µg/L in our study. A study analysing data from the 1999–2004 US NHANES adults aged over 40 years found that the mean blood cadmium concentration was 0.59 µg/L (0.54–0.63).[26] The median (IQR) concentration of blood cadmium in our study was 0.35 µg/L (0.24–0.56). A cross-sectional study using data from the third US NHANES with adults over 60 years old found that the median (IQR) concentration of blood cadmium was 0.39 µg/L (0.29–0.49).[27] Thus, it can be seen that the level of blood cadmium in this study is consistent with previous studies.

The association between cadmium and children's IQ has been recognised in previous studies.[10 11 28] So far, however, the evidence for the relationship between cadmium and cognitive function in elderly populations has been limited and inconclusive. There are some studies whose results are consistent with the current study. For example, a Chinese study of elderly persons aged 65 years or older found a significant association between increased

Table 1 Characteristics of the study population (n=2068)

Variables	N	Weighted sample	(%)*	Variables	N	Weighted sample	Mean (SE)*	Median (IQR)*
Gender				Age (year)	2068	38452144	69.14 (0.24)	67.66 (62.89–73.83)
Male	1011	17 508 127	45.53	Blood cadmium (µg/L)	2068	38452144	0.50 (0.02)	0.35 (0.24–0.56)
Female	1057	20 944 017	54.47	CERAD learning score	2068	38452144	19.48 (0.27)	19.00 (16.27–22.16)
Race-ethnicity				CERAD recall score	2068	38452144	6.09 (0.10)	5.77 (4.12–7.34)
Mexican American/other Hispanic	385	2 618 094	6.81	Animal Fluency score	2068	38452144	18.14 (0.21)	17.38 (13.51–21.00)
Non-Hispanic white	988	30 935 957	80.45	**DSST score**	2068	38452144	52.20 (0.66)	52.68 (40.09–63.92)
Non-Hispanic black	491	2 980 219	7.75	z-score	2068	38452144	0.24 (0.04)	0.28 (−0.28 to 0.80)
Other race	204	1 917 874	4.99					
Education level								
<High school	531	6 133 440	15.95					
High school	490	8 783 404	22.84					
>High school	1046	23 530 632	61.19					
Missing	1	4669	0.01					
Poverty–income ratio								
≤0.99	333	3 298 332	8.58					
≥1	1550	32 672 780	84.97					
Missing	185	2 481 032	6.45					
Marital status								
Married/living with partner	1201	25 353 317	65.93					
Widowed/divorced/separated	742	11 403 761	29.66					
Never married	124	1 689 836	4.39					
Missing	1	5230	0.01					
Tobacco smoking								
Current	257	3 965 965	10.31					
Former	784	15 571 098	40.49					
Never	1026	18 907 598	49.17					
Missing	1	7483	0.02					
Alcohol consumption								
≥12 drink/year	1397	27 847 784	72.42					
<12 drink/year	640	10 098 855	26.26					
Missing	31	505 505	1.31					
Diabetes								
Yes	472	7 293 920	18.97					
No	1508	29 747 613	77.36					
Missing	88	1 410 611	3.67					
Hypertension								
Yes	1262	21 869 127	56.87					
No	804	16 514 849	42.95					
Missing	2	68 168	0.18					
Stroke								
Yes	138	2 341 705	6.09					
No	1926	36 057 144	93.77					
Missing	4	53 295	0.14					
Coronary heart disease								
Yes	172	3 086 811	8.03					
No	1886	35 263 550	91.71					
Missing	10	101 784	0.26					

*Weighted percentage, mean, SE, median and IQR.
CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, Digit Symbol Substitution Test.

Table 2 Univariate analyses of the association between z-score and covariates (n=2068): NHANES 2011–2014

Variables	Score mean (SE)*	F value	P values
Gender		14.85	0.0005
Male	0.16 (0.05)		
Female	0.32 (0.04)		
Age (year)	–	–20.39†	<0.0001
Race-ethnicity		25.11	<0.0001
Mexican American/other Hispanic	–0.28 (0.05)		
Non-Hispanic white	0.33 (0.05)		
Non-Hispanic black	–0.13 (0.05)		
Other race	0.14 (0.06)		
Education level		79.48	<0.0001
<High school	–0.34 (0.05)		
High school	0.05 (0.05)		
>High school	0.47 (0.04)		
Poverty–income ratio		68.63	<0.0001
≤0.99	–0.30 (0.06)		
≥1	0.31 (0.04)		
Material status		7.46	0.0022
Married/living with partner	0.31 (0.05)		
Widowed/divorced/separated	0.10 (0.04)		
Never married	0.31 (0.12)		
Alcohol consumption		27.46	<0.0001
<12 drinks/year	0.04 (0.03)		
≥12 drinks/year	0.32 (0.05)		
Tobacco smoking		1.95	0.1587
Current	0.15 (0.08)		
Former	0.22 (0.04)		
Never	0.29 (0.05)		
Hypertension		25.79	<0.0001
Yes	0.15 (0.04)		
No	0.38 (0.04)		
Diabetes		26.98	<0.0001
Yes	–0.03 (0.04)		
No	0.31 (0.05)		
Stroke		13.24	0.0010
Yes	–0.16 (0.10)		
No	0.27 (0.04)		
Coronary heart disease		28.41	<0.0001
Yes	–0.11 (0.07)		
No	0.28 (0.04)		

*Weighted mean and SE.
†t value.
NHANES, National Health and Nutrition Examination Survey.

blood cadmium levels and worse cognitive function after adjustment for age, sex, education, body mass index and apolipoprotein E genotype.[15] Its sample size was 188, and six cognitive assessment tests are used comprehensively to evaluate cognitive function. Another study on people aged 50–82 years with 135 individuals in Brazil found that high blood cadmium concentration alone and in combination with elevated blood lead concentration was associated with an important cognitive construct, poor working memory capacity, after adjustment for age, sex, income, haemoglobin and haematocrit.[14] However, a Korean study suggested that serum cadmium levels were significantly higher in the Alzheimer's disease (AD) group without age adjustment but was not significant after adjustment for age.[16] It was a small sample of 207 individuals (89 patients with AD and 118 cognitively normal people), and it only adjusted for age and years of education to evaluate the association between cadmium and cognitive function, which can affect the reliability of the results. The reason for the difference in the above study results may be due to different biological samples in different countries, sample sizes and covariates adjusted in the models. The sample sizes of these studies are small, and only demographic factors are included in their models. In contrast, our sample size was larger with 2068 individuals. In addition to demographics, we adjusted for more factors (alcohol consumption and medical history) that have been reported to be related to cadmium and/or cognitive function.[29–34] Therefore, the results are probably more stable and reliable.

The exact mechanisms with which cadmium exposure affects cognition have yet not to be revealed. The possible mechanisms are as follows. First, studies suggest that cadmium exposure can increase the activity of acetylcholinesterase, which can hydrolyse acetylcholine and reduce its concentration,[35] and there is a positive correlation between acetylcholine deficiency and cognitive impairment.[36] Moreover, studies show that cadmium induces the formation of reactive oxygen species (ROS).[37 38] Excessive ROS can cause superoxide reaction of nucleic acid and protein and make the chromatin concentrate and fragment, also cause inflammation, eventually leading to neuronal damage and death. Other studies suggest that the cytotoxicity of cadmium can be attributable to the interference of cadmium with intracellular cation homoeostasis.[39 40] Cadmium can upregulate the internal concentration of calcium in neurons, thereby affecting the synthesis and release of neurotransmitters, eventually leading to neuronal dysfunction.[40]

There are several strengths and limitations in our study. First, we have a large sample size and good representativeness of the subjects. Second, we created a composite cognitive z-score representing global cognitive function to minimise the floor or ceiling effect of a single cognitive test and adjusted for multiple potential confounders in our models. Third, NHANES did not include an occupation code to screen for cadmium-exposure jobs such as smelting, electroplating, pigment manufacture and application, and alkaline battery manufacturing. Fourth, due to the lack of laboratory indicators such as cotinine, we only used self-reported smoking in analyses, which could cause some bias. Fifth, we created a composite cognitive

Table 3 Blood cadmium levels (continuous) in relation to cognitive function (composite z-score): NHANES 2011–2014

Variables	Model 1 (n=2068)* β (95% CI)¶	P values	Model 2 (n=1882)† β (95% CI)¶	P values	Model 3 (n=1852)‡ β (95% CI)¶	P values	Model 4 (n=1757)§ β (95% CI)¶	P values
Cadmium as continuous (µg/L)	−0.19 (−0.29 to 0.08)	0.0013	−0.09 (−0.18 to 0.01)	0.0263	−0.11 (−0.19 to 0.02)	0.0131	−0.11 (−0.20 to 0.03)	0.0087
Gender								
Female			0.24 (0.16 to 0.32)	<0.0001	0.26 (0.18 to 0.35)	<0.0001	0.26 (0.18 to 0.34)	<0.0001
Male			referent	referent	referent	referent	referent	referent
Age (year)			−0.053 (−0.058 to 0.047)	<0.0001	−0.051 (−0.056 to 0.046)	<0.0001	−0.05 (−0.06 to 0.04)	<0.0001
Race-ethnicity								
Mexican American/other Hispanic			−0.45 (−0.57 to 0.33)	<0.0001	−0.45 (−0.56 to 0.33)	<0.0001	−0.46 (−0.59 to 0.33)	<0.0001
Non-Hispanic black			−0.37 (−0.48 to 0.27)	<0.0001	−0.35 (−0.45 to 0.25)	<0.0001	−0.31 (−0.42 to 0.21)	<0.0001
Other race			−0.19 (−0.32 to 0.06)	0.0045	−0.17 (−0.30 to 0.05)	0.0083	−0.14 (−0.27 to 0.02)	0.0217
Non-Hispanic white			referent	referent	referent	referent	referent	referent
Education level								
<High school			−0.49 (−0.63 to 0.36)	<0.0001	−0.48 (−0.61 to 0.34)	<0.0001	−0.45 (−0.59 to 0.31)	<0.0001
High school			−0.37 (−0.47 to 0.27)	<0.0001	−0.36 (−0.46 to 0.26)	<0.0001	−0.35 (−0.44 to 0.26)	<0.0001
>High school			referent	referent	referent	referent	referent	referent
Poverty-income ratio (PIR)								
≥1			0.27 (0.14 to 0.41)	0.0003	0.28 (0.13 to 0.41)	0.0005	0.27 (0.12 to 0.41)	0.0005
≤0.99			referent	referent	referent	referent	referent	referent
Material status								
Married/living with partner			−0.01 (−0.23 to 0.22)	0.9447	−0.02 (−0.24 to 0.20)	0.8723	−0.03 (−0.23 to 0.17)	0.7420
Widowed/divorced/separated			−0.06 (−0.24 to 0.12)	0.5277	−0.07 (0.24 to 0.11)	0.4419	−0.07 (−0.23 to 0.09)	0.3654
Never married			referent	referent	referent	referent	referent	referent
Alcohol consumption								
≥12 drinks/year					0.12 (0.05 to 0.20)	0.0026	0.11 (0.04 to 0.19)	0.0056
<12 drinks/year					referent	referent	referent	referent
Hypertension								
Yes							−0.06 (−0.14 to 0.02)	0.1240
No							referent	referent

Continued

Table 3 Continued

Variables	Model 1 (n=2068) * β (95% CI)¶	P values	Model 2 (n=1882)† β (95% CI)¶	P values	Model 3 (n=1852)‡ β (95% CI)¶	P values	Model 4 (n=1757)§ β (95% CI)¶	P values
Diabetes								
Yes							−0.19 (−0.26 to 0.11)	<0.0001
No							referent	referent
Stroke								
Yes							−0.17 (−0.36 to 0.01)	0.0653
No							referent	referent
Coronary heart disease								
Yes							−0.04 (−0.20 to 0.12)	0.5924
No							referent	referent

*Unadjusted.
†Adjusted for age, gender, ethnicity, education, PIR and marital status.
‡Adjusted for age, gender, ethnicity, education, PIR, marital status and alcohol consumption.
§Adjusted for age, gender, ethnicity, education, PIR, marital status, alcohol consumption, diabetes, hypertension, stroke and coronary heart disease.
¶Weighted β and 95% CI.
Similarly, there was a significant inverse association between quartiles of blood cadmium and composite z-score in model 1, with somewhat lower scores in the upper quartile of exposure (μg/L, blood cadmium ≥0.63 μg/L) compared with the lower quartile of exposure (blood cadmium <0.25 μg/L) (μg/L, β=−0.27, 95% CI −0.38 to −0.16) (table 4). It was also significant in model 2 (μg/L, β=−0.11, 95% CI −0.21 to −0.02) (table 4), model 3 (μg/L, β=−0.14, 95% CI −0.24 to −0.04) (table 4) and model 4 (μg/L, β=−0.14, 95% CI −0.25 to −0.03) (table 4). There was a trend by quartiles of blood cadmium in each model (all p trend <0.05) (table 4).
NHANES, National Health and Nutrition Examination Survey.

Table 4 Blood cadmium levels (categorical) in relation to cognitive function (composite z-score): NHANES 2011–2014

Variables	Model 1 (n=2068)* β (95% CI)¶	P values	Model 2 (n=1882)† β (95% CI)¶	P values	Model 3 (n=1852)‡ β (95% CI)¶	P values	Model 4 (n=1757)§ β (95% CI)¶	P values
Cadmium as categorical (µg/L)								
0~	referent	referent	referent	referent	referent	referent	referent	referent
0.25~	0.03 (−0.08 to 0.14)	0.5442	0.04 (−0.04 to 0.13)	0.2955	0.04 (−0.04 to 0.12)	0.3570	0.04 (−0.05 to 0.12)	0.3891
0.38~	−0.18 (−0.28 to 0.08)	0.0010	−0.02 (−0.13 to 0.10)	0.7556	−0.04 (−0.15 to 0.08)	0.5302	−0.04 (−0.15 to 0.07)	0.4890
0.63–3.60	−0.27 (−0.38 to 0.16)	<0.0001	−0.11 (−0.21 to 0.02)	0.0220	−0.14 (−0.24 to 0.04)	0.0056	−0.14 (−0.25 to 0.03)	0.0113
P trend	<0.0001		0.0148		0.0041		<0.0001	
Gender								
Female			0.23 (0.16 to 0.31)	<0.0001	0.26 (0.18 to 0.34)	<0.0001	0.26 (0.18 to 0.33)	<0.0001
Male			referent	referent	referent	referent	referent	referent
Age (year)			−0.053 (−0.057 to 0.048)	<0.0001	−0.051 (−0.056 to 0.046)	<0.0001	−0.049 (−0.055 to 0.043)	<0.0001
Race-ethnicity								
Mexican American/other Hispanic			−0.45 (−0.57 to 0.34)	<0.0001	−0.45 (−0.56 to 0.34)	<0.0001	−0.46 (−0.59 to 0.33)	<0.0001
Non-Hispanic black			−0.37 (−0.48 to 0.27)	<0.0001	−0.35 (−0.45 to 0.24)	<0.0001	−0.31 (−0.42 to 0.21)	<0.0001
Other race			−0.18 (−0.30 to 0.05)	0.0071	−0.15 (−0.28 to 0.03)	0.0157	−0.13 (−0.25 to 0.01)	0.0403
Non-Hispanic white			referent	referent	referent	referent	referent	referent
Education level								
<High school			−0.49 (−0.63 to 0.35)	<0.0001	−0.47 (−0.61 to 0.33)	<0.0001	−0.44 (−0.59 to 0.30)	<0.0001
High school			−0.37 (−0.47 to 0.26)	<0.0001	−0.36 (−0.46 to 0.25)	<0.0001	−0.35 (−0.44 to 0.25)	<0.0001
>High school			referent	referent	referent	referent	referent	referent
Poverty–income ratio (PIR)								
≥1			0.27 (0.14 to 0.41)	0.0002	0.27 (0.13 to 0.40)	0.0004	0.27 (0.13 to 0.40)	0.0004
≤0.99			referent	referent	referent	referent	referent	referent
Material status								
Married/living with partner			−0.01 (−0.24 to 0.22)	0.9515	−0.02 (−0.24 to 0.20)	0.8674	−0.03 (−0.24 to 0.17)	0.7394
Widowed/divorced/separated			−0.05 (−0.23 to 0.13)	0.5706	−0.06 (−0.24 to 0.11)	0.4800	−0.07 (−0.23 to 0.10)	0.4040
Never married			referent	referent	referent	referent	referent	referent
Alcohol consumption								
≥12 drinks/year					0.13 (0.05 to 0.21)	0.0018	0.12 (0.04 to 0.20)	0.0046
<12 drinks/year					referent	referent	referent	referent
Hypertension								
Yes							−0.06 (−0.13 to 0.02)	0.1240
No							referent	referent

Continued

Table 4 Continued

Variables	Model 1 (n=2068)* β (95% CI)¶	P values	Model 2 (n=1882)† β (95% CI)¶	P values	Model 3 (n=1852)‡ β (95% CI)¶	P values	Model 4 (n=1757)§ β (95% CI)¶	P values
Diabetes								
Yes							−0.19 (−0.27 to 0.11)	<0.0001
No							referent	referent
Stroke								
Yes							−0.17 (−0.35 to 0.01)	0.0569
No							referent	referent
Coronary heart disease								
Yes							−0.04 (−0.21 to 0.12)	0.5769
No							referent	referent

*Unadjusted.
†Adjusted for age, gender, ethnicity, education, PIR and marital status.
‡Adjusted for age, gender, ethnicity, education, PIR, marital status and alcohol consumption.
§Adjusted for age, gender, ethnicity, education, PIR, marital status, alcohol consumption, diabetes, hypertension, stroke and coronary heart disease.
¶Weighted β and 95% CI.
NHANES, National Health and Nutrition Examination Survey.

Table 5 Association between blood cadmium levels and cognitive function (composite z-score) excluding individuals who suffered a stroke (n=1636): NHANES 2011–2014*

Blood cadmium (µg/L)	β (95% CI)†	P values	P trend
Cadmium as continuous	−0.12 (−0.20 to 0.04)	0.0060	–
Cadmium as categorical			
0~	referent	referent	0.0107
0.25~	0.04 (−0.05 to 0.13)	0.3579	
0.38~	−0.04 (−0.15 to 0.08)	0.5067	
0.63~3.60	−0.13 (−0.23 to 0.03)	0.0159	

*Adjusted for age, gender, ethnicity, education, PIR, marital status, alcohol consumption, diabetes, hypertension, and coronary heart disease.
†Weighted β and 95% CI.
NHANES, National Health and Nutrition Examination Survey.

z-score by using the average of the standardised scores of the four cognitive tests, which provided a more complete picture of the relationship between blood cadmium and cognitive function but limited us in explaining the practical meaning of the effect size. Nevertheless, this study is a cross-sectional study that restricted us in assessing the temporal relationships of the associations.

It has been found that gender, age, education level, race-ethnicity, poverty–income ratio, alcohol consumption and diabetes can contribute to cognitive function, and their effects should be considered in future research on the association between cadmium exposure and cognitive function. Through the results, we find that the regression coefficients change from positive to negative and decrease with the increase in blood cadmium, regardless of whether the difference is significant. There is a trend, to some extent, that can provide a basis for future studies.

The investigation of the inverse association between blood cadmium and cognitive function is very significant for putting forward some strategies towards delaying of cognitive function descending of older adults. Because cadmium is an accumulative poison, coming primarily from food and tobacco smoke, exposure can be modified through healthy eating and behavioural habits. Such changes will have a vital impact on the improvement of cognitive function in adults aged 60 years or older.

CONCLUSIONS

Our findings suggest that increasing blood cadmium is associated with worse cognitive function in older adults aged 60 years or older in the USA. The results need verification in other populations.

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