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Association between exposure to organophosphate esters and cognitive function in older adults in the United States: NHANES 2011–2014

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Abstract

Background Organophosphate esters (OPEs) are widely used as an alternative to the brominated flame retardant polybrominated diphenyl ethers. The effects of OPEs on the cognitive abilities of older adults remain unclear.

Methods A cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey 2011–2014. Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word learning test, the CERAD word recall test, the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST). OPE metabolites with detection rates above 50% were included in the study. Weighted multiple linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models were used to examine the effects of individual and mixed exposures to OPE metabolites on cognitive function.

Results A total of 762 older adults were included. The weighted linear regression model revealed a positive association between Ln DPHP, Ln BDCPP, and Ln BCPP and the DSST score, while a negative association was observed between Ln DBUP and the DSST score. In the positive WQS model, the index was correlated with DSST score ($\beta = 2.65$, 95% CI: 0.40 ~ 4.90, $P = 0.02$), with DPHP having the highest weight. The results of BKMR analysis indicated a borderline statistical significance in the increase of DSST score when the mixture of OPEs is set to a specific 90th percentile compared to all mixture concentrations set to the median.

Conclusions Overall exposure to OPE metabolites are associated with improved cognitive function in older adults in the United States. Further prospective studies with large sample sizes are needed to confirm these results.

Keywords Organophosphate esters, Cognitive function, WQS, BKMR, Older adults

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Introduction

Global aging is a serious social issue. In the United States, the number of people aged over 65 is expected to reach 83.7 million in 2050, which is almost double the 43.1 million in 2012 and accounts for about a quarter of the total population [1]. The health and quality of life of older individuals have become critical challenges. As individuals age, their brains undergo structural and functional changes, leading to cognitive decline, such as reduced thinking, memory, reasoning, and behavioral skills [2, 3]. If cognitive decline is left unchecked, it can progress to pathological mild cognitive impairment and dementia [4]. According to the National Center for Health Statistics, more than six million Americans may have dementia caused by Alzheimer's disease, with the majority being over the age of 65 [5]. The progression from cognitive decline to Alzheimer's disease is a continuous process, and there is currently no cure. So, it is important to prevent cognitive decline as early as possible [6]. Modifiable factors such as diet and chronic disease can contribute to low cognitive performance, while recent studies have also reported the association between environmental analogs and cognitive function [7–10].

Organophosphate esters (OPEs) are a class of alkyl or aryl chemicals containing phosphoric acid. With the previous generation of brominated flame retardants, polybrominated diphenyl ethers, being restricted in several countries due to their neurotoxicity, reproductive toxicity, and other health hazards, OPEs were widely added as a substitute in building materials, furniture, textiles, electronic products. It is also commonly used as a plasticizer in personal care products and food packaging [11, 12]. OPEs have been consistently produced for over a decade [13], resulting in the widespread detection of OPEs and their metabolites in human urine and blood samples [14, 15]. Although it was once thought to have a faster metabolic rate than brominated flame retardants and less environmental persistence, recent studies have clearly shown that it also has remote migration and can accumulate in the human body and cause health hazards, such as neurotoxicity [14]. One animal study has reported that exposure to tris(2-chloroethyl) phosphate at doses of 50–250 mg/kg for 60 days led to decreased spatial learning and memory ability, as well as apoptosis of hippocampal cells in female rats [16]. In addition, other studies have also demonstrated that exposure to OPEs can induce changes in neuronal differentiation, migration, and neurotransmitter levels in zebrafish [17, 18].

Most OPEs are easily metabolized into dialkyl or diaryl groups and various hydroxylated products upon entering the body. Therefore, urinary OPE metabolites are often used as non-invasive biomarkers to identify and quantify exposure to OPEs in humans [19, 20]. The number of epidemiological studies on OPE metabolites and cognitive performance is limited, with a focus on the developmental neurotoxicity of OPEs. As a result, these studies have been conducted on pregnant women or children, rather than the older adults [21–23]. It is still unknown whether the neurotoxicity of OPEs reported in experimental studies can be validated in the older adult population.

In this study, we utilized data from the National Health and Nutrition Examination Study (NHANES) 2011–2014 to investigate the urinary OPE metabolites in an older adult population and their association with cognitive performance. To obtain a more comprehensive understanding of the health effects of OPEs, we employed multiple statistical methods to assess the effects of individual and combined exposures to OPE metabolites on cognitive function.

Methods

Study population

NHANES is a nationally representative cross-sectional survey designed to assess the health and nutritional status of Americans. It collects demographic characteristics, anthropometric data, dietary supplements, laboratory tests, and questionnaire information. The survey employs a multi-stage sampling design and includes approximately 5,000 individuals per cycle. Participation is voluntary, and all procedures are approved by the NCHS Research Ethics Committee with written informed consent from participants.

The data used in this study were obtained from the NHANES 2011–2014 cycle because both cognitive function assessments and OPE metabolites measurements were conducted during this period. Specific inclusion criteria were as follows: (1) adults aged 60 years and above; (2) subjects provided urine samples and had their OPE metabolites measured; (3) cognitive function was assessed; (4) no missing data for covariates of demographic characteristics, body mass index (BMI), and lifestyle behaviors. A total of 3131 older adults aged 60 years and over had complete cognitive function test data. Of these, 2188 and 181 older adults were excluded due to missing data on urine OPE metabolites or covariates, respectively. Eventually, 762 subjects were included in this study (Fig. S1).

Cognitive function assessment

The cognitive assessment was conducted through a home interview or at the Mobile Examination Center using four tests: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word learning test, the CERAD word recall test, the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST).

The CERAD word learning test and CERAD word recall test are designed to assess the immediate and delayed learning of new verbal information. The CERAD word learning test was administered three times, with the order of words changing each time. Participants were asked to read aloud ten unrelated words and then recall as many words as possible. The score was the total number of words recalled over the three tests (0–30 points). The CERAD recall test was administered after the other two cognitive tests (AFT and DSST) were completed (approximately 8–10 min from the start of the CERAD word learning trials), and the score was the total number of words recalled (0–10 points). AFT is an integral part of the executive function that evaluates language fluency. Participants were asked to name as many animals as possible within one minute, and the total number of accurate names was counted as points. The DSST is a test module of the Wexler Adult Intelligence Scale that assesses sustained attention, processing speed, and working memory. It was conducted using a paper form with nine numbers paired with symbols at the top of the form. Participants had two minutes to copy the corresponding symbols in 133 boxes adjacent to the numbers. The total number of correct matches was the score. Higher scores in all four tests indicate better cognitive function.

Laboratory test of OPEs

Urine specimens were collected and cryopreserved until subsequent laboratory analysis. The OPE metabolites tested included: diphenyl phosphate (DPHP), bis(1,3-dichloro-2-propyl) phosphate) (BDCPP), bis(1-chloro-2-propyl) phosphate (BCPP), bis(2-chloroethyl) phosphate (BCEP), dibutyl phosphate (DBUP), dibenzyl phosphate (DBZP), and 2,3,4. 5-tetrabromobenzoic acid (TBBA). Laboratory assays were performed using enzymatic hydrolysis of urine conjugates, automated off-line solid phase extraction, reversed-phase high performance liquid chromatography separation, and isotope dilution-electrospray ionization tandem mass spectrometry. Simultaneous runs of high and low concentration quality control materials and reagent blanks were performed to ensure the accuracy and reliability of the data. Standard statistical probability rules were used to assess the levels of OPE metabolites in urine samples. Metabolites with a detection rate of over 50% were selected for subsequent statistical analysis. Urine values of OPE metabolites below the limit of detection (LOD) were replaced by the detection limit/$\sqrt{2}$. The experimental procedures are described in the NHANES laboratory data [24, 25].

Covariates

To account for potential confounders, we included several covariates in our analysis based on previous studies [26, 27]. These factors included gender(male, and female), age group(60–69, 70–79, and ≥ 80 years), race (Mexican–American, other Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and other race), education level (less than high school, high school graduate or GED or equivalent, and some college or above), marital status (married or living with partner, widowed or divorced or separated, and never married), BMI group (< 18.5, 18.5-, 25-, and ≥ 30 kg/m^2), household income poverty ratio (PIR) group (< 1, 1-, and ≥ 3), alcohol drinker (yes, and no), physical activity level(sedentary, low, moderate and high), Mediterranean diet (MeDi) score(< 3.5, 3.5-, and ≥ 4.5), history of cardiovascular disease(yes, and no), history of diabetes (yes, no, and borderline), depression status(yes, and no), cotinine level (< LOD, and > LOD), and urine creatinine. Alcohol consumption status was assessed using the survey question, "Had at least 12 alcohol drinks/1 yr?" Participants who responded "yes" were classified as alcohol drinkers. Moderate to vigorous leisure time physical activity is coded as metabolic equivalent of task (MET) minutes per week by multiplying the duration of the activities by the intensity-specific MET scores. It was then classified into four levels according to the 2018 national physical activity guidelines: sedentary (no regular physical activity), low (insufficient regular activity, < 500 MET minutes/week), moderate (500–1000 MET minutes/week), and high (> 1000 MET minutes/week) [28, 29]. The MeDi score reflected adherence to the traditional Mediterranean diet and was calculated based on 9 food components, using sex-specific energy-adjusted intake medians as cut-off values. The total MeDi score ranges from 0 to 9, with higher scores indicating greater adherence [29]. The MeDi score was analyzed as a categorical variable according to tertiles. Cardiovascular disease history was determined if participants self-reported having been informed by a physician with conditions such as congestive heart failure, coronary heart disease, angina pectoris, heart attack, stroke, hypertension, or high cholesterol levels [26]. Depression was identified using the Patient Health Questionnaire, a nine-item screening tool that assesses the frequency of depressive symptoms over the past two weeks, with a total score range of 0 to 27. Depression was defined as a score of ≥ 10 [26].

Statistical analyses

The R survey package was used for weight analyses of the complex, multistage sampling design of NHANES. The missing values for depression status and MEDi scores accounted for 0.26% and 9.18% respectively, and multiple imputation was used to handle these missing values. An analysis of variance (ANOVA) or t-tests was used to examine differences in cognitive function

scores between groups. Since the concentration of each OPE metabolite was skewed, the natural logarithm transformation was applied to the concentration of each metabolite for subsequent analyses. Weighted linear regression models were employed to assess the association between urinary OPE metabolite concentrations and scores on the four cognitive function tests. Model 1 was a univariate linear regression model without correction for any covariates. Model 2 was adjusted for gender and age group. Model 3 further adjusted for other covariates, including race, marital status, education level, PIR group, alcohol drinker, physical activity level, MeDi score, history of cardiovascular disease, history of diabetes, depression status, cotinine level, and creatinine. Additionally, this study utilized restrictive cubic curves (RCS) to fit the association between OPE metabolite concentrations and the four cognitive function scores.

To gain a deeper understanding of the relationship between cognitive function and combined exposure to OPE metabolites, both weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR) models were used in this study.

WQS regression is a common statistical method that offers a high degree of flexibility in assessing the overall impact of environmental mixtures. It allows for the presence of collinearity and combines the advantages of dimensionality reduction and variable selection techniques to identify the main chemical substances contributing to the association by calculating a predictive index weighted by the correlation with the outcome. The following are the functions of the WQS regression model:

$$g(\mu) = \beta_0 + \beta_1 WQS + z'\varphi$$

$$WQS = \sum_{i=0}^{c} \overline{w}_i q_i$$

β_0 and β_1 are the intercept, and regression coefficients of the WQS index, respectively. z' represents the covariate vector, and ϕ represents the covariate regression coefficient vector. wi is the weight of the ith component, which takes values in the range 0–1. q_i is the different quantiles, representing the changes in the respective variables. g(μ) is the link function. A linear link is assumed for the OPE metabolite concentrations and cognitive function. 40% and 60% of the data were randomly assigned to the training and validation sets, respectively. The WQS regression contains both positive and negative models. The positive model assumes that the components of the WQS index are all positively correlated with cognitive functioning. While the negative model assumes that the components of the WQS index are all negatively related to cognitive function.

The BKMR model is also a common statistical approach that combines Bayesian and machine learning methods to perform iterative regression on the exposure–response function. The following are its basic functions:

$$Yi = h(zi1, \ldots, zim) + xi'\beta + \in i$$

Yi is the health response of individual i (i = 1,..., n). h() is the constructed exposure response function, including nonlinear/component interactions. Z is the vector of multiple exposure variables, and Zim is the m^{th} environmental exposure. €i is an independent residual that is assumed to follow $a \sim N(0, \sigma^2)$ normal distribution. xi and β refer to potential confounders and the corresponding coefficients. The BKMR model for this study was fitted by running a Markov chain Monte Carlo sampler for 20,000 iterations. The overall effect of mixed OPE metabolite exposures on the four cognitive function scores was analyzed by fixing all OPE metabolite concentrations at a specific percentile compared to when all OPE metabolite concentrations were fixed at the 50th percentile. The effect of each single OPE metabolite on cognitive function was analyzed when fixing the other OPE metabolite concentrations at the 50th percentile. In addition, the interaction effect of each pair of OPE metabolites was recorded when the other metals were fixed at a specific quartile.

All analyses were performed using R software (version 4.1.0). The significance level for the two-sided statistic was set at 0.05.

Results

Participant characteristics

The study included 762 older participants, of whom 371 (48.7%) were male and 391 (51.3%) were female. The highest percentage of participants were in the 60–69 age group (53.4%), and the largest racial group was non-Hispanic White (49.6%). The majority of participants were married or living with a partner (58.7%), and over 70% had a high school education or higher. A total of 617 participants (81.0%) had a history of cardiovascular disease, 174 (22.8%) had a history of diabetes, and 79 (10.4%) were in a state of depression. The study subjects had an average MeDi score of 3.74 ± 1.02 points. A total of 150 participants (40.4%) had a high level of physical activity. The basic characteristics of the study participants are detailed presented in Table S1.

The average scores for the CERAD word learning test, CERAD word recall test, AFT, and DSST were 19.02 ± 4.55, 6.0 ± 2.25, 16.78 ± 5.51, and 46.43 ± 17.45,

respectively. Statistically significant differences were found between groups for the four cognitive function test scores across age group, race, education level, PIR group, history of cardiovascular disease, history of diabetes, and depression status ($P < 0.05$). The male participants had significantly higher scores in CERAD word learning, CERAD word recall, and DSST than the female participants ($P < 0.05$). Differences in DSST score were also statistically significant across marital status and MeDi score groups ($P < 0.05$). Additionally, there were statistically significant differences in AFT and DSST scores among participants with varying alcohol consumption statuses and levels of physical activity ($P < 0.05$). Further details are provided in Table 1.

Urinary OPE metabolite concentrations

Table 2 displays the urinary levels of seven metabolites of OPEs. Among these, DPHP, BDCPP, BCPP, BCEP, and DBUP had a detection rate of over 50% and were therefore included in subsequent analyses. DPHP had the highest detection rate and median concentration (86.4% and 0.64 μg/L), followed by BDCPP (86% and 0.52 μg/L). Fig. S2 presents the correlations between the five OPE metabolites and cognitive function scores. The strongest correlation was observed between Ln BDCPP and Ln BCEP ($r = 0.48$), followed by the correlation between Ln BDCPP and Ln DPHP ($r = 0.45$). Among these metabolites, Ln DPUP exhibited the strongest correlation with cognitive function scores ($r = 0.09$).

Association of OPE metabolites with cognitive function revealed by linear regression model

The results of the weighted linear regression model for the relationship between the five OPE metabolites in urine and cognitive function are shown in Table 3. In the univariate linear regression model (Model 1), Ln DPHP were marginally positively associated with CERAD word learning score (β = 0.23, 95% CI: −0.01 ~ 0.48) and DSST score (β = 0.91, 95% CI: 0.00 ~ 1.82), respectively. After adjusting for age group and gender (Model 2), these associations were weakened. After further adjusting for race, education level, marital status, PIR group, alcohol drinker, physical activity level, MeDi score, history of cardiovascular disease, history of diabetes, depression status, cotinine level, and urine creatinine (Model 3), the results indicated that the DSST score increased as the concentrations of Ln DPHP, Ln BDCPP, and Ln BCPP increased (β = 0.86, 95% CI: 0.07 ~ 1.64; β = 0.87, 95% CI: 0.14 ~ 1.61; β = 1.40, 95% CI: 0.49 ~ 2.32, respectively). However, there was a negative association between Ln DBUP and the DSST score, with each unit increase in Ln DBUP corresponding to an average decrease of 1.40 points in the DSST score (β = −1.40, 95% CI: −2.41 ~ −0.39). The RCS analysis indicated that Ln DPHP ($P_{non\text{-}linearity} = 0.05$), Ln BDCPP ($P_{non\text{-}linearity} = 0.09$), Ln DBUP ($P_{non\text{-}linearity} = 0.05$) and Ln BCPP ($P_{non\text{-}linearity} = 0.10$) exhibited linear associations with DSST score (Fig. 1).

Association of OPE metabolites with cognitive function revealed by WQS regression model

Table 4 presents the relationship between mixed exposure to OPE metabolites and the four cognitive function test scores using the WQS regression model. After adjusting for all covariates, there was no significant association between OPE metabolites and cognitive function in the negative model ($P > 0.05$). However, assuming that all beta coefficients were positive, a significant association was observed between the WQS index and DSST score (β = 2.65, 95% CI: 0.40 ~ 4.90, $P = 0.02$). Among the OPE metabolites, DPHP had the greatest weight on the DSST score (weight index = 0.41), followed by BDCPP (weight index = 0.29). None of the other metabolites exceeded the cut-off indicating significant weight (1/number of metabolites). The estimated weights for OPE metabolites in the positive WQS regression model are depicted in Fig. 2.

Association of OPE metabolites with cognitive function revealed by BKMR model

Figure 3 illustrates the overall effect of mixed exposure to OPE metabolites on the four cognitive function test scores. Setting mixture levels at a specific 90th percentile indicated a marginal statistical difference in the change in DSST score compared to when all mixture concentrations were set at the median, suggesting an increase in DSST score as the mixture was exposed at high concentrations (Fig. 3D). Although the overall effect on the other three cognitive function test scores was not statistically significant when all five OPE metabolites were above their 50th percentile, there was still a significant increasing trend (Fig. 3 A-C). Figure 4 displays the univariate exposure–response functions and 95% confidence intervals for each metabolite in relation to cognitive function scores, with the other four OPE metabolites fixed at the median. When DBUP was at a low concentration, the CERAD word learning score and CERAD word recall score showed a decreasing and then increasing trend as its concentration increased, while the AFT score and DSST score showed different trends of increasing and decreasing, respectively. Ln-DPHP, Ln-BDCPP, and Ln-BCPP all exhibited a positive association with DSST score at low exposure concentrations. When the other OPE metabolite concentrations were fixed at the 25th percentile, 50th percentile, or 75th percentile, no significant change in the cognitive function score was observed for single metabolite exposure levels at the 75th percentile compared with

Table 1 Association of cognitive functioning scores with basic demographic characteristics

Characters	CERAD word learning score		CERAD word recall score		AFT score		DSST score	
	$\overline{x} \pm s$	*P*	$\overline{x} \pm s$	*P*	$\overline{x} \pm s$	*P*	$\overline{x} \pm s$	*P*
Gender		**< 0.001**		**< 0.001**		0.71		**< 0.001**
Male	18.21 ± 4.55		5.59 ± 2.23		16.86 ± 5.64		43.98 ± 16.39	
Female	19.79 ± 4.43		6.40 ± 2.21		16.71 ± 5.39		48.75 ± 18.11	
Age group (years)		**< 0.001**		**< 0.001**		**< 0.001**		**< 0.001**
60–69	20.09 ± 4.31		6.58 ± 2.06		17.72 ± 5.81		50.81 ± 17.50	
70–79	18.23 ± 4.42		5.66 ± 2.24		16.17 ± 5.30		42.91 ± 16.69	
≥ 80	17.09 ± 4.62		4.93 ± 2.26		14.93 ± 4.20		38.97 ± 14.52	
Race		**< 0.001**		**< 0.001**		**< 0.001**		**< 0.001**
Mexican American	19.30 ± 4.47		6.24 ± 2.06		18.18 ± 5.88		44.01 ± 17.16	
Other Hispanic	16.68 ± 4.39		4.95 ± 1.99		14.43 ± 4.54		34.07 ± 16.49	
Non-Hispanic White	19.47 ± 4.47		6.10 ± 2.28		18.10 ± 5.35		51.06 ± 16.55	
Non-Hispanic Black	18.65 ± 4.44		5.76 ± 2.29		14.91 ± 5.28		39.84 ± 15.21	
Non-Hispanic Asian	19.92 ± 5.08		7.08 ± 2.03		14.75 ± 4.99		52.05 ± 17.85	
Other Race	18.43 ± 2.59		5.79 ± 1.72		18.43 ± 5.24		50.14 ± 10.82	
Marital status		0.17		**0.01**		0.05		**0.02**
Married/ living with partner	19.25 ± 4.51		6.15 ± 2.23		17.16 ± 5.67		47.81 ± 16.81	
Widowed/divorced/separated	18.61 ± 4.64		5.77 ± 2.34		16.14 ± 5.21		44.11 ± 18.37	
Never married	19.29 ± 4.37		5.95 ± 1.88		16.93 ± 5.51		46.83 ± 16.73	
Education level		**< 0.001**		**< 0.001**		**< 0.001**		**< 0.001**
Less than high school	16.73 ± 4.58		5.19 ± 2.16		13.98 ± 4.62		31.01 ± 14.76	
High school graduate/GED/equivalent	19.01 ± 4.53		5.91 ± 2.34		15.93 ± 4.86		44.47 ± 15.05	
Some college or above	19.95 ± 4.23		6.37 ± 2.17		18.28 ± 5.56		53.42 ± 14.99	
BMI group (kg/m^2)		0.49		0.22		0.31		0.18
< 18.5	17.47 ± 5.68		5.33 ± 2.50		14.80 ± 5.96		37.20 ± 16.23	
18.5-	19.27 ± 4.59		6.16 ± 2.28		16.47 ± 5.74		45.79 ± 18.57	
25-	18.92 ± 4.61		5.83 ± 2.23		16.76 ± 5.39		47.11 ± 17.34	
≥ 30.0	19.03 ± 4.42		6.10 ± 2.23		17.12 ± 5.44		46.70 ± 16.75	
PIR group		**< 0.001**		**< 0.001**		**< 0.001**		**< 0.001**
<1	17.74 ± 4.79		5.71 ± 2.25		15.13 ± 6.15		36.71 ± 17.28	
1-	18.59 ± 4.57		5.74 ± 2.26		16.08 ± 4.89		43.32 ± 16.47	
≥ 3	20.04 ± 4.23		6.42 ± 2.19		18.25 ± 5.60		53.90 ± 15.56	
Alcohol drinker		0.85		0.88		**0.009**		**0.03**
Yes	19.04 ± 4.39		5.99 ± 2.21		17.12 ± 5.70		47.30 ± 17.34	
No	18.97 ± 4.91		6.02 ± 2.36		15.98 ± 4.96		44.36 ± 17.55	
Physical activity level		0.13		0.08		**< 0.001**		**< 0.001**
Sedentary	18.71 ± 4.90		5.79 ± 2.41		15.53 ± 5.28		41.18 ± 17.13	
Low	18.96 ± 4.51		5.95 ± 2.39		16.86 ± 5.12		48.74 ± 15.72	
Moderate	19.98 ± 4.11		6.47 ± 1.98		17.56 ± 4.97		48.41 ± 16.64	
High	18.99 ± 4.36		6.06 ± 2.10		17.67 ± 5.92		49.58 ± 17.84	
MeDi score		**0.04**		0.12		0.21		**< 0.001**
< 3	18.89 ± 4.65		5.85 ± 2.29		16.43 ± 5.10		44.82 ± 17.02	
3-	18.65 ± 4.48		5.94 ± 2.36		16.69 ± 5.92		44.69 ± 17.33	
≥ 4.5	19.67 ± 4.48		6.26 ± 2.05		17.31 ± 5.40		50.60 ± 17.47	
History of cardiovascular disease		**0.004**		**0.003**		**0.001**		**< 0.001**
Yes	18.79 ± 4.64		5.88 ± 2.28		16.43 ± 5.26		44.91 ± 17.35	
No	20.00 ± 4.07		6.51 ± 2.06		18.29 ± 6.27		52.87 ± 16.42	
History of diabetes		**0.001**		**0.001**		**0.002**		**< 0.001**

Table 1 (continued)

Characters	CERAD word learning score		CERAD word recall score		AFT score		DSST score	
	$\bar{x} \pm s$	*P*	$\bar{x} \pm s$	*P*	$\bar{x} \pm s$	*P*	$\bar{x} \pm s$	*P*
Yes	17.95 ± 4.50		5.47 ± 2.26		15.48 ± 5.38		39.32 ± 16.80	
No	19.40 ± 4.54		6.19 ± 2.21		17.20 ± 5.51		48.63 ± 17.13	
Borderline	18.24 ± 4.22		5.70 ± 2.57		16.58 ± 5.20		46.76 ± 16.57	
Depression status		**0.002**		0.423		**0.001**		**< 0.001**
Yes	17.51 ± 4.67		5.81 ± 2.22		14.85 ± 5.65		37.39 ± 17.48	
No	19.20 ± 4.51		6.02 ± 2.26		17.00 ± 5.46		47.47 ± 17.15	
Cotinine level		0.10		0.09		**0.001**		**<0.001**
<LOD	19.37 ± 4.60		6.18 ± 2.23		17.63 ± 5.42		49.48 ± 16.90	
>LOD	18.81 ± 4.52		5.89 ± 2.27		16.25 ± 5.51		44.51 ± 17.52	

PIR household income poverty ratio, *LOD* limit of detection

Table 2 Concentration of urinary OPEs metabolites among study participants

OPEs metabolites (ug/L)	Detection rate	GM	Percentiles				
			P_5	P_{25}	P_{50}	P_{75}	P_{95}
DPHP	86.4%	0.60	ND	0.26	0.64	1.26	5.04
BDCPP	86.0%	0.51	ND	0.19	0.52	1.18	4.66
BCPP	50.8%	0.15	ND	ND	0.10	0.28	0.99
BCEP	82.8%	0.37	ND	0.13	0.36	0.87	3.11
DBUP	63.5%	0.16	ND	ND	0.16	0.32	0.64
DBZP	0.03%	0.04	ND	ND	ND	ND	ND
TBBA	0.05%	0.04	ND	ND	ND	ND	ND

GM geometric mean, *ND* below detection limit

the 25th percentile (not shown in the figure). This study further examined bivariate exposure–response relationships. Each OPE metabolite exhibited similar slopes at different levels of the other metabolites, suggesting no interactions between the metabolites (not shown in the figure).

Discussion

As a novel environmental pollutant, the potential health effects of OPEs on humans have received significant attention. However, whether exposure levels in the real environment impact the cognitive abilities of populations remains unknown. Population-based epidemiological studies in this field are scarce, particularly in the older adults, which are burdened with increasing social demands. To our knowledge, this is the first study to investigate the effects of OPE exposures on cognitive function in older adults. Interestingly, this study found that certain OPE metabolites were associated with increased cognitive function scores in older adults.

Only one study [30] conducted in northern China has investigated the concentrations of OPE metabolites in the older adults, which reported detection rates of 79% for DPHP, 76% for BDCPP, 20% for BCEP, and 28% for BCPP in the urine of 76 healthy residents aged 60–69 years. In contrast, our study had higher detection rates for OPE metabolites (> 80% for DPHP, BDCPP, and BCEP and > 50% for BCPP). OPEs can be categorized into three structural types: chlorinated, alkyl, and aryl OPEs, with BCEP and BCPP being metabolites of chlorinated OPEs. Research has indicated that chlorinated OPEs are predominant in the environmental media of the Great Lakes region in the United States, while aryl OPEs are more common in northern China [31, 32]. These differences in primary OPE exposure types may explain the variations in detection rates. Another recent study [33] reported median urinary concentrations of DPHP, BDCPP, and DCEP in Chinese adolescent population of 0.22 μg/L, 0.19 μg/L, and 0.27 μg/L, respectively, all of which were lower than the median concentrations in our study (0.64 μg/L, 0.52 μg/L, and 0.36 μg/L, respectively). It is worth noting that the samples from these two studies were collected approximately three years later than our study but with lower levels of OPE exposures.

Table 3 Associations between OPE metabolites and cognitive function in NHANES,2011–2014

OPE metabolites (ug/L)		CERAD word learning score		CERAD word recall score		AFT score		DSST score	
		β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*
Ln DPHP	Model1	0.23(−0.01 ~ 0.48)	0.06	0.03(−0.10 ~ 0.15)	0.66	0.18(−0.14 ~ 0.50)	0.27	0.91 (0.00 ~ 1.82)	0.05
	Model2	0.18 (−0.05 ~ 0.41)	0.12	0.00 (−0.12 ~ 0.11)	0.98	0.12(−0.19 ~ 0.42)	0.45	0.18 (−0.05 ~ 0.41)	0.12
	Model3	0.24(−0.03 ~ 0.50)	0.08	−0.02 (−0.15 ~ 0.13)	0.81	0.14 (−0.19 ~ 0.47)	0.41	**0.86 (0.07 ~ 1.64)**	**0.032***
Ln BDCPP	Model1	−0.09(−0.32 ~ 0.14)	0.44	0.00 (−0.12 ~ 0.11)	0.99	−0.19(−0.48 ~ 0.11)	0.21	0.27(−0.58 ~ 1.11)	0.54
	Model2	−0.06 (−0.28 ~ 0.15)	0.57	0.02 (−0.09 ~ 0.12)	0.76	−0.25 (−0.53 ~ 0.03)	0.09	−0.06 (−0.28 ~ 0.15)	0.57
	Model3	−0.14 (−0.39 ~ 0.11)	0.27	0.01 (−0.12 ~ 0.13)	0.93	−0.27 (−0.58 ~ 0.04)	0.09	**0.87 (0.14 ~ 1.61)**	**0.021***
Ln BCEP	Model1	−0.19(−0.45 ~ 0.07)	0.16	−0.10(−0.23 ~ 0.04)	0.16	−0.11(−0.45 ~ 0.22)	0.51	−0.89(−1.86 ~ 0.08)	0.07
	Model2	−0.09 (−0.34 ~ 0.15)	0.46	−0.04 (−0.16 ~ 0.08)	0.53	−0.09 (−0.41 ~ 0.24)	0.61	−0.09 (−0.34 ~ 0.15)	0.46
	Model3	−0.06(−0.33 ~ 0.20)	0.65	−0.01 (−0.15 ~ 0.12)	0.87	0.08(−0.26 ~ 0.41)	0.65	−0.03 (−0.82 ~ 0.75)	0.93
Ln DBUP	Model1	0.04(−0.29 ~ 0.37)	0.79	0.01(−0.15 ~ 0.18)	0.88	0.27(−0.16 ~ 0.70)	0.22	−1.18(−2.40 ~ 0.05)	0.06
	Model2	0.16 (−0.15 ~ 0.47)	0.31	0.08 (−0.07 ~ 0.24)	0.30	0.29 (−0.12 ~ 0.70)	0.17	0.16 (−0.15 ~ 0.47)	0.31
	Model3	0.14(−0.21 ~ 0.48)	0.43	0.08 (−0.10 ~ 0.25)	0.38	0.31(−0.12 ~ 0.74)	0.16	**−1.40 (−2.41 ~ −0.39)**	**0.007***
Ln BCPP	Model1	0.08(−0.23 ~ 0.39)	0.62	−0.05(−0.21 ~ 0.11)	0.53	−0.10(−0.51 ~ 0.31)	0.63	0.72(−0.45 ~ 1.88)	0.23
	Model2	0.28 (−0.02 ~ 0.58)	0.07	0.06 (−0.09 ~ 0.21)	0.42	−0.05 (−0.44 ~ 0.34)	0.81	0.28 (−0.02 ~ 0.58)	0.07
	Model3	0.24 (−0.07 ~ 0.55)	0.13	0.05(−0.11 ~ 0.21)	0.56	−0.14 (−0.53 ~ 0.25)	0.49	**1.40 (0.49 ~ 2.32)**	**0.003***

Model 1: unadjusted for any confounding factors. Model2: adjusted for age group and gender. Mode3: adjusted for age group, gender, race, marital status, education level, PIR group, alcohol drinker, physical activity level, MeDi score, history of cardiovascular disease, history of diabetes, depression status, cotinine level, and creatinine; *:*P* < 0.05

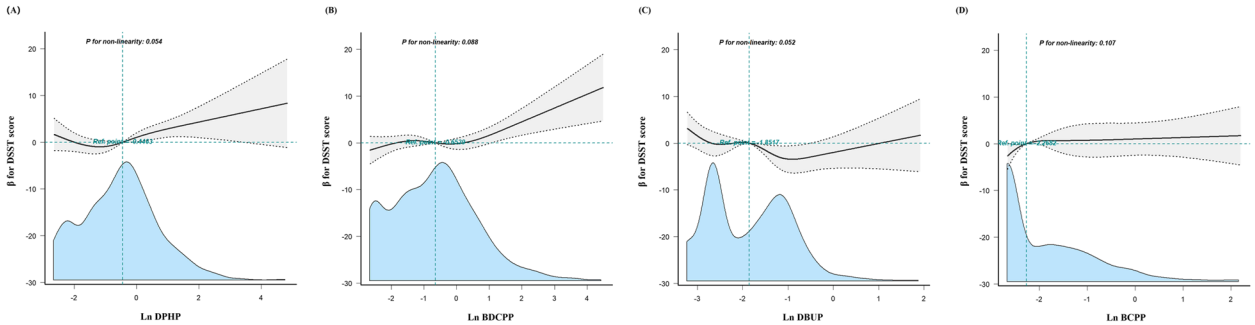

Fig. 1 The association between OPE metabolite concentrations and DSST scores by utilized restrictive cubic curves. **A** for DPHP; **B** for BDCPP; **C** for DBUP; **D** for BCPP

A study assessing temporal trends in exposure levels of OPE metabolites in the US population found a significant increase in BDCPP in urine samples between 2002 and 2015, with concentrations in 2015 being as much as 16 times higher than in 2002, reflecting increasing exposure to OPEs in the Americans [34]. This may be attributed to the large volume of OPEs placed on the United States market during that period. Production of TCPP, TDCPP, and TCEP (parent compounds of BCPP, BDCPP, and BCEP) in the US has been reported to have increased from < 14,000 metric tons per year in the mid-1980s to approximately 38,000 metric tons per year in 2012 [35]. Current research on the effects of OPEs on cognitive function is limited to pediatric populations, and the findings are inconsistent. A cohort study conducted in the United States found that for each log unit increase in BDCPP, BCEP, and DPHP in urine, there was a 1 to 2 point decrease in full-scale IQ among socioeconomically disadvantaged children [22]. Another study observed that for every tenfold increase in maternal urine DPHP, children's working memory function decreased by a mean of 3.9 points (95% CI: −7.3 ~ −0.5) at age 7 years [21]. However, other studies did not observe a negative effect of these five metabolites on children's cognitive performance [23, 36]. Even one of these studies found a positive association between maternal urine BCEP concentrations

Table 4 Association between WQS index and cognitive function

Cognitive function		β	95% CI	*P*
CERAD word learning score	**Positive model**	**0.45**	**−0.11 ~ 1.01**	**0.12**
	Negative model	0.53	−0.17 ~ 1.23	0.14
CERAD word recall score	Positive model	0.24	−0.07 ~ 0.81	0.13
	Negative model	0.14	−0.19 ~ 0.81	0.43
AFT score	Positive model	0.74	−0.25 ~ 1.74	0.14
	Negative model	0.71	−0.19 ~ 1.61	0.12
DSST score	Positive model	**2.65**	**0.40 ~ 4.90**	**0.02***
	Negative model	1.58	−0.34 ~ 3.48	0.10

Model adjusted for age group, gender, race, marital status, education level, PIR group, alcohol drinker, physical activity level, MeDi score, history of cardiovascular disease, history of diabetes, depression status, cotinine level, and creatinine; *:*P* < 0.05

and children's cognitive abilities at age 8 years, with each log unit increase in BCEP being associated with an average increase of 0.81 points in children's cognitive scores. All of these studies are limited by their small sample sizes, whereas our study has the largest sample size. In this study, both the BKMR and WQS results suggest that the overall effect of mixed exposure to OPE metabolites has no negative impact on human cognitive function.

Organophosphates used as insecticides are potent inhibitors of acetylcholinesterase (AChE) and can cause the excessive accumulation of acetylcholine in the body, leading to neurological disorders. OPEs, which have a similar structure to organophosphorus pesticides, have been found to significantly inhibit AChE when organisms are exposed to them [37, 38]. However, most studies have used OPE exposure doses that are much higher than environmental exposure concentrations. In 2019, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment concluded in its review that organophosphate flame retardants are weak inhibitors of AChE at most and are also unlikely to cause neurotoxicity at human exposure levels through other mechanisms of action, such as the inhibition of gamma-aminobutyric acid [39].

In this study, DPHP and BDCPP were found to be the metabolites that had the greatest influence on the DSST score. TPHP, which is often added to electronic devices and nail polish, is the parent chemical of DPHP and can activate PPARγ [40]. PPARγ agonists have the potential to modulate various signalling molecules/pathways, including matrix metalloproteinase-9, mitochondrial uncoupling protein 2, mitoNEET expression, and Wnt signalling. They can also reduce oxidative stress, inflammation, and apoptosis in the central nervous system, with neuroprotective potential in the treatment of Alzheimer's disease, Parkinson's disease, and cerebral ischemia [41]. The above may be the potential reason for the positive association of DPHP on cognitive function. The positive effect of BDCPP on cognitive function may involve modulation by sex hormones. Both estrogens and androgens can affect cognitive function in the brain either directly through amyloid toxicity and oxidative stress or indirectly through other endocrine systems [42]. An animal experiment found that dihydrotestosterone (DHT), 17β-estradiol, and Pueraria mirifica herb extract (PME) exerted neuroprotective effects on cognitive impairment in androgen-deficient male rats, with the strength of recovery from synaptic degeneration in the rat hippocampus being E2 ≥ PME > DHT [43]. One study, also based on NHANES data, found a positive association between urinary BDCPP exposure levels and estradiol in adult males [44].

The results of the weighted linear regression model found a negative association between Ln DBUP and DSST scores. At the same time, the results of the BKMR model showed a complex relationship between DBUP and cognitive function. As the concentration of Ln DBUP increased, scores on the CERAD word learning test and CERAD word recall test initially decreased and then increased. When Ln DBUP reached a certain threshold, its association with cognitive function was no longer statistically significant. DBUP has both beneficial and detrimental effects on population health. On the one hand, DBUP exposure is negatively associated with the prevalence of central obesity [45]. On the other hand, it is positively associated with sleep disorders [46]. Obesity can lead to diabetes, hypertension, dyslipidemia, and further cardiovascular disease, increasing the risk of cognitive impairment [47]. Sleep disorders are a risk factor for poor physical and mental health, which can also impair cognitive performance [48]. At present, research on the effects of DBUP on the nervous system is very limited, especially in population-based epidemiological studies. The results of this study suggest the complexity of the relationship between low-dose environmental DBUP exposure and cognitive function, which requires further investigation in the future.

A recent study, based on an exogenous exposure assessment method, concluded that dietary intake was the predominant route of OPE intake in the elderly population [49]. OPEs primarily enter the human diet through two pathways. First, crops, livestock, and aquatic products can absorb OPEs from contaminated soil and water. Second, food may become contaminated with OPEs during production, industrial processing, and storage [50]. In Belgium, fats and oils, as well as grains, have been reported as the most severely contaminated food categories, while in Sweden, processed foods are the primary sources of OPE contamination [51, 52]. A review

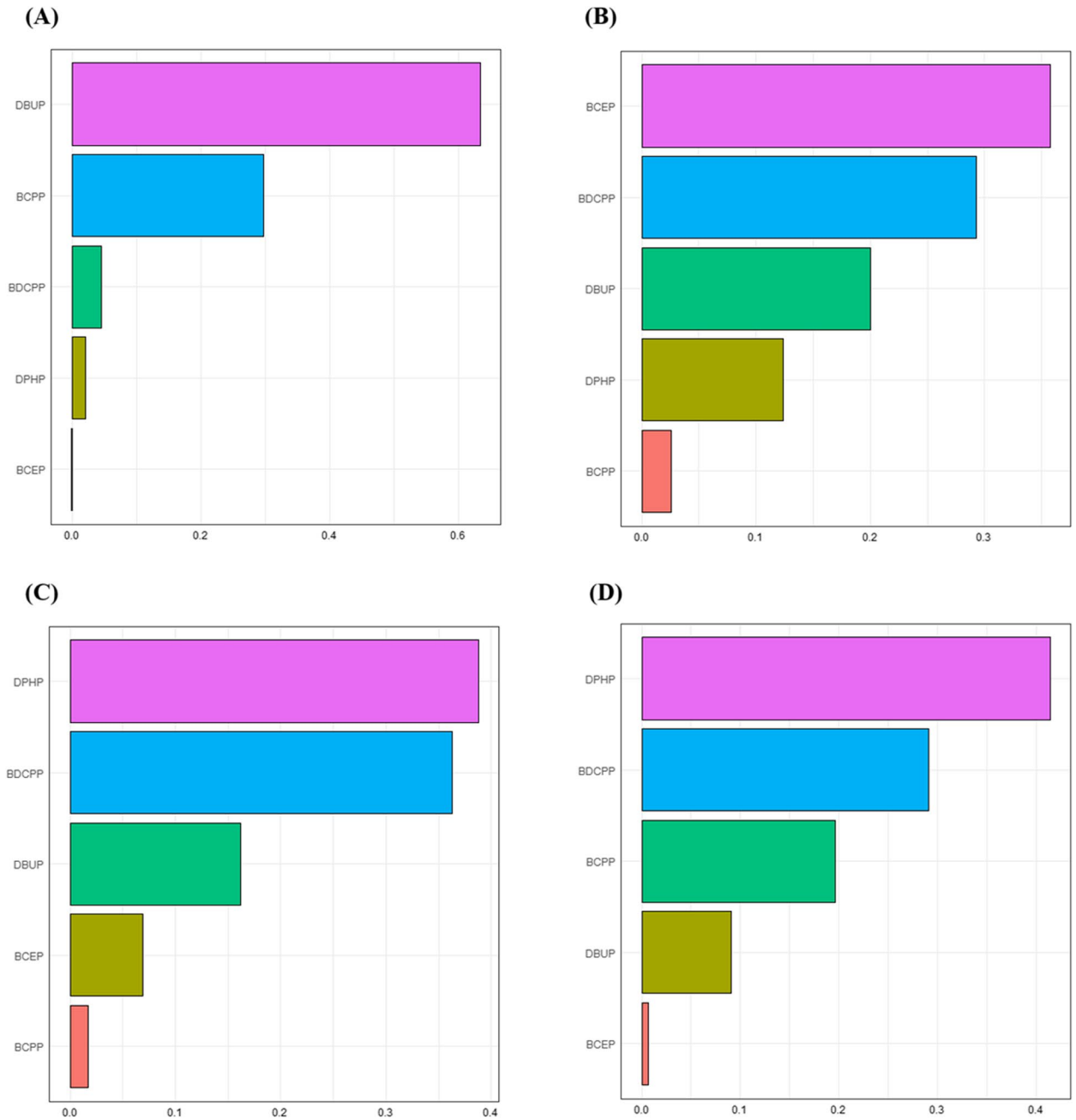

Fig. 2 Index weights of each OPE metabolite in the positive WQS regression model. **A** CERAD word learning score; **B** CERAD word recall score; **C** AFT score; **D** DSST score. Model adjusted for age group, gender, race, marital status, education level, PIR group, alcohol consumption status, history of hypertension, history of diabetes, history of stroke, cotinine level, and creatinine

summarized the concentrations and distribution of 30 OPEs in various food samples globally, finding that the concentrations of OPEs in meat and fish products in the United States were higher than those in other countries [50]. In food collected from local markets in Albany, New York, the median concentrations of∑OPEs (the sum of 15 OPEs) were higher in meat (6.76 ng/g wet weight) and fish/seafood (7.11 ng/g wet weight), exceeding the exposure levels observed in other types of food [53]. Individuals who consumed meat once a week or more had a reduced risk of developing cognitive impairment [54]. Fish, which contains long-chain n-3 polyunsaturated fatty acids, may also have a protective effect on cognitive function in the older adults. For example, a Japanese

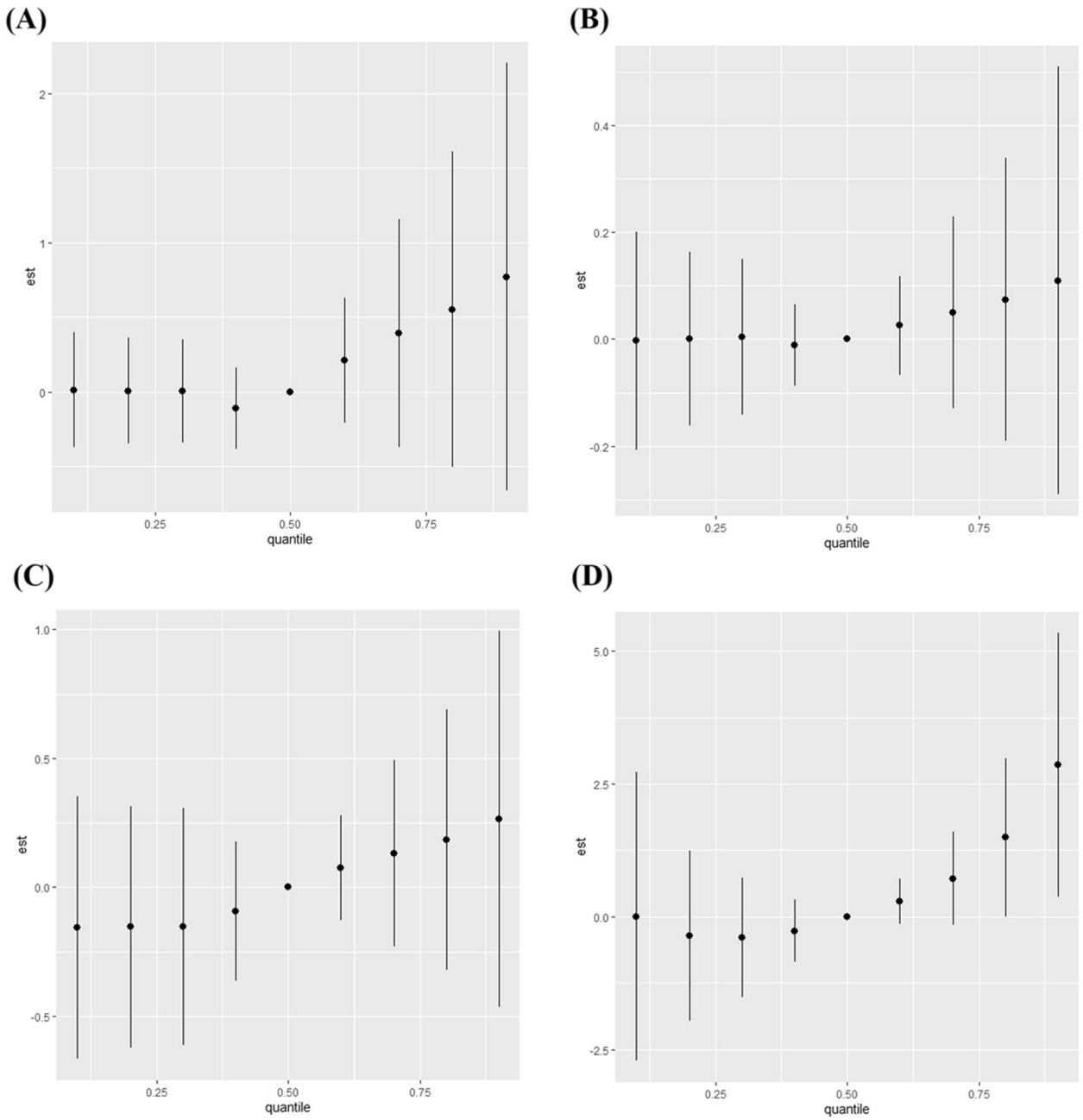

Fig. 3 The overall effect of OPE metabolites on the cognitive function. **A** CERAD word learning score; **B** CERAD word recall score; **C** AFT score; **D** DSST score. Model adjusted for age group, gender, race, marital status, education level, PIR group, alcohol consumption status, history of hypertension, history of diabetes, history of stroke, cotinine level, and creatinine

cohort study showed a negative association between fish intake and dementia [55]. This suggests that dietary patterns may partially explain the beneficial effects of OPEs on cognitive function. This study calculated the MeDi score and found that participants in the highest MeDi score group had higher levels of cognitive function. After adjusting for MeDi score as a covariate, some OPE metabolites still showed a positive association with cognitive function. However, conducting a comprehensive and detailed assessment of dietary patterns involves certain complexities, and the MeDi score is not the only indicator for evaluating these patterns. Therefore, future research should further investigate the dietary sources of OPE exposure among older adults in the United States, as

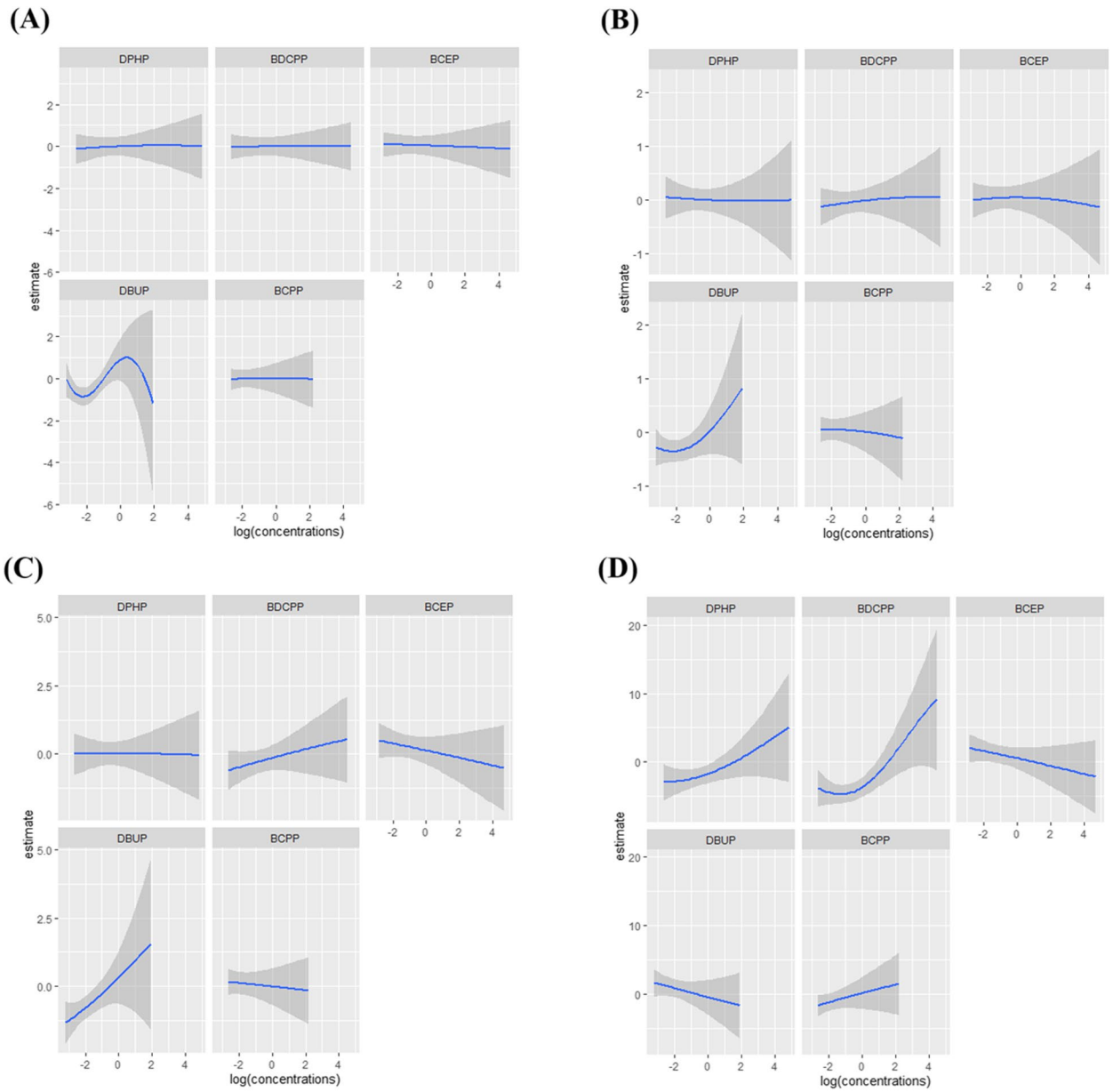

Fig. 4 Univariate exposure–response functions and 95% credible bands for each OPE metabolite with the other metabolites fixed at their medians. **A** The relationship between OPE metabolites and CERAD word learning score; **B** The relationship between OPE metabolites and CERAD word recall score; **C** The relationship between OPE metabolites and AFT score; **D** The relationship between OPE metabolites and DSST score. Model adjusted for age group, gender, race, marital status, education level, PIR group, alcohol consumption status, history of hypertension, history of diabetes, history of stroke, cotinine level, and creatinine

well as the specific impacts of dietary habits on the relationship between OPEs and cognitive function.

The primary strength of this study is the utilization of three statistical methods to explore the potential effects of individual and mixed exposure to OPE metabolites on cognitive function in older adults. It is the first epidemiological study in older adults with a moderate sample size, and the findings contribute to a better understanding of the health effects of OPEs. However, there are some limitations to this study. The cross-sectional design of this study makes it challenging to establish the causal temporal phase between exposure factors and outcomes. Therefore, our findings need to be confirmed by subsequent prospective studies with large sample sizes. Additionally, the urine collected in this study was spot urine only, not the "gold standard"

24-h urine, and it is challenging to determine how consistent spot urine is with 24-h urine. This study investigated the health effects of OPEs through the urinary metabolites, without data on their parent compounds. Furthermore, this study did not provide a detailed analysis of the specific sources of OPE exposure. OPE exposure may arise from various pathways, including diet and consumer products (such as furniture, electronics, and plastic products containing flame retardants). This study was unable to clearly distinguish the contributions of different sources to the levels of OPE metabolites. Given that diet may be an important route of OPE intake, the evaluation of dietary patterns in this study relied solely on the MeDi score, which may not be comprehensive enough and could limit a thorough understanding of the relationship between OPE exposure and its health effects. Finally, this study may have unknown confounding factors that were not adjusted for, and future research with larger sample sizes and more comprehensive adjustment for confounding factors is needed to validate our findings.

Conclusions

This study explored the association between cognitive function and exposure levels of OPE metabolites among individuals aged over 60 years in the United States. The results indicated that, in the context of mixed exposure, overall exposure to OPEs did not have a significant negative impact on cognitive function, while the exposure levels of certain metabolites, such as DPHP, BDCPP, and BCPP, may be positively associated with cognitive function. Given the widespread exposure to OPEs, prospective studies are needed to confirm our findings and gain a deeper understanding of the effects of low-dose OPE exposures on neurological function.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05841-9.

Supplementary Material 1.

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Authors' contributions
RL and QZ provided the research ideas.BJ and YL analyzed the data. BJ, RL and TW wrote the main manuscript text. MX, WW and QZ prepared the figures. ZH and BJ improved the writing quality. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The NHANES protocol was reviewed and approved by the NCHS Research Ethics Committee. All participants provided written informed consent prior to participation.

Consent to publication
Not applicable.

Competing interests
The authors declare no competing interests.

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