Exposome, 2025, **5(1)**, osaf001
https://doi.org/10.1093/exposome/osaf001
Advance Access Publication Date: 10 January 2025
Research Article

Exposome-wide association study of cognitive function in US older adults using the NHANES data

Hyuna Jang, MS [1], Jiyun Lee, PhD [1,*], Vy Kim Nguyen, PhD [2], Hyeong-Moo Shin, PhD [1]

[1]Department of Environmental Science, Baylor University, Waco, TX, 76798, United States
[2]Department of Biomedical Informatics, Medical School, Harvard University, Boston, MA, 02115, United States

*Corresponding author: Jiyun Lee, PhD, Department of Environmental Science, Baylor University, Waco, TX, 76798, United States (Jiyun_Lee@baylor.edu)

Abstract

Neurodegenerative diseases pose increasing challenges to global aging populations. Cognitive decline in older adults is an initial indicator of neurodegenerative diseases, yet comprehensive research on environmental chemical exposures related to cognitive decline is limited. This study uses Exposome-Wide Association Study (ExWAS) framework to investigate associations of environmental chemicals with cognitive function in individuals aged ≥60 years. We used the Digit Symbol Substitution Test (DSST) scores and chemical biomarker data of the US National Health and Nutrition Examination Survey (NHANES) spanning four cycles (1999-2000, 2001-2002, 2011-2012, 2013-2014). We conducted multiple survey-weighted regression to identify biomarkers associated with DSST scores, Bayesian weighted quantile sum regression to estimate odds ratio (OR) of cognitive decline from multiple exposures to the identified biomarkers, and correlation network analyses to examine relationships among possible important biomarkers and cognitive decline. After correction for multiple comparisons, among 229 biomarkers having a ≥10% detection rate, 40 were associated with DSST scores (q-value <0.05). When assessing the effects of chemical mixtures on cognitive decline, no association between mixtures of chemicals and DSST scores was observed. Correlation network showed that cognitive decline is directly related with age and education level and identified that thiocyanate, m-/p-xylene, triclosan, benzophenone-3 and diphenyl phosphate were weakly related to cognitive function. In conclusion, leveraging the ExWAS framework enables us to identify chemical biomarkers that were not previously discovered from traditional approaches of examining a small number of chemicals at a time. While our findings provide foundation for further research, longitudinal studies are warranted to elucidate causal relationships.

Key words: chemical exposure; cognitive function; Exposome-Wide Association Study (ExWAS); National Health and Nutrition Examination Survey (NHANES); older adults.

Introduction

Increasing incidence of neurodegenerative diseases poses a prominent challenge in societies experiencing global population aging.[1] In the United States alone, more than 6.2 million people were affected by neurodegenerative diseases in 2022, including Alzheimer's disease.[2] These diseases accounted for approximately 300,000 deaths and 3 million disability-adjusted life years (DALYs) during 1990-2016.[3-5] The prevalence of clinical Alzheimer's disease among adults aged 65 years and older is projected to increase from 7.2 million in 2025 to 13.9 million in 2060.[6] In 2021, the United States incurred an annual cost of over $355 billion due to Alzheimer's disease and related dementias, and this societal burden is expected to increase due to the increased health care cost.[7] Consequently, there is growing attention towards the identification of risk factors and treatment development for neurodegenerative diseases.[8]

Neurodegenerative diseases are characterized by the progressive loss of neurons, leading to deterioration in both the structure and function of neural networks.[9] This deterioration ultimately leads to impaired cognitive function.[1,10] Gradual cognitive decline in old age is typically limited to subtle declines that evolve slowly over the years, attributed to normative developmental processes.[11,12] Conversely, mild or precipitous declines in cognitive function can lead to pathological processes underlying Alzheimer's disease and related dementias.[11,13] Thus, early detection of changes in cognitive function, such as mild cognitive impairment, enables timely diagnosis and treatment of neurodegenerative diseases, potentially delaying disease progression.[13,14]

The risk of cognitive decline generally increases due to a combination of genetic and non-genetic factors. Age and genetic factors, including family history and susceptibility genes such as the apolipoprotein E ε4 allele, are the most significant contributors to cognitive decline.[15,16] Other well-known non-genetic risk factors include comorbidities (hypertension, diabetes, and stroke), unhealthy diet, physical inactivity, smoking, and alcohol consumption.[17,18] These risk factors could influence the susceptibility of individual's cognitive function (eg, disease onset, timing, and severity) by interacting with genetic factors.[16,19,20] Therefore, identifying and understanding modifiable risk factors of cognitive decline could be a proactive approach to promoting cognitive health.[17,21]

Several studies have assessed associations between exposures to environmental chemicals and cognitive decline in specific populations. For example, exposures to metals, typically manganese

Received: July 24, 2024; **Revised:** January 03, 2025; **Accepted:** January 07, 2025

(Mn),[22-24] cadmium (Cd),[24-27] lead (Pb),[25-27] barium (Ba),[24] cobalt (Co),[24] cesium (Cs),[24] and thallium (Tl)[24] were reported to increase the risk of low cognitive performance. In addition, higher urinary 3-phenoxybenzoic acid concentrations in adults were associated with cognitive dysfunction[28] and it was observed that butyl benzyl phthalate is a potential cognitive-disrupting compound.[29] However, previous studies examined exposure to a small number of chemicals or compounds individually in association with cognitive function. In addition, they are neither systematic nor comprehensive.

Exposome-Wide Association Studies (ExWAS), derived from Genome-Wide Association Studies (GWAS), are a useful approach for systematically and comprehensively evaluating associations between hundreds of environmental factors and health outcomes.[30] While GWAS aim to identify genetic factors associated with diseases of interest, ExWAS can focus on assessing environmental factors. The ExWAS approach consists of two steps: (1) screening chemical biomarkers by computing an individual association between each biomarker and the health outcome while controlling for type I error; and (2) examining the screened biomarkers using advanced techniques that account for multiple exposures and incorporate dimension reduction methods.[30] Over the past decade, several ExWAS studies have been conducted to elucidate the relationship between environmental chemical exposures and health outcomes.[31] Frequently studied health outcomes were type 2 diabetes,[30,32,33] obesity,[34] and blood pressure.[35,36] Other outcomes included liver enzymes,[37] mental and social well-being,[38] testosterone deficiency,[39] and multiple sclerosis.[40] However, no studies have simultaneously and comprehensively examined environmental chemical exposures associated with cognitive decline in older adults (Table S1).

This study aims to identify environmental chemical biomarkers associated with cognitive decline in US older adults by using the ExWAS approach and the National Health and Nutrition Examination Survey (NHANES) data. First, to screen chemicals or their biomarkers, we examined a single association for each biomarker and identified those that were statistically significant after controlling for multiple comparisons. Second, we evaluated the effects of multiple exposures to those identified biomarkers on cognitive decline. Finally, we extracted a correlation network structure to explore potential pathways between chemical exposures and cognitive decline and further assessed the potential mediating effect of other modifiable factors.

Methods

Study population

NHANES is conducted every two years in the United States by the Centers for Disease Control and Prevention (CDC) and the National Centers for Health Statistics (NCHS). This is a cross-sectional survey designed to assess the health and nutritional status of both adults and children. To obtain a representative sample of the US population, complex, multi-stage, and probability sampling techniques are used. NHANES data are publicly available (https://www.cdc.gov/nchs/nhanes) and include individual questionnaires, physical examinations, and laboratory tests. More details on the design and methods of the NHANES data are available elsewhere.[41] The Institutional Review Board (IRB) of Baylor University has approved this study protocol (IRB No. 2242267).

Our study combined data from four cross-sectional surveys conducted in 1999-2000, 2000-2001, 2011-2012, and 2013-2014, because only these cycles included assessments for cognitive function. Targeting older adults (age $\geq$60 years), our analysis consisted of 4,970 individuals after excluding those with missing cognitive function data (n = 34 946) and those with abnormal urinary creatinine levels (<30 or >300 mg/dL), recommended by the World Health Organization (WHO) for urinary dilution adjustment[42] (n = 1019) (Figure 1).

Cognitive function assessment

In NHANES, the Digit Symbol Substitution Test (DSST), a subscale of the Wechsler Adult Intelligence Scale, was utilized to evaluate primary cognitive processing speed, attention, and working memory.[43] Its application aids in determining the presence of cognitive dysfunction across various stages, including preclinical, prodromal, and dementia phases.[44,45] Administered in a paper-and-pencil format, this cognitive test requires individuals to match symbols to corresponding numbers based on a provided key.[46] The score is the total number of correct matches within 90 to 120s, with lower scores indicating diminished cognitive function.[46] Since 1999, NHANES has administered this test in participants aged 60 years and older. This test occurs during face-to-face interviews at the Mobile Examination Center (MEC) by trained interviewers. Participants have the option to select from English, Spanish, Korean, Vietnamese, or Chinese. In this study, we used DSST z-scores when screening chemical biomarkers related to cognitive function and DSST raw scores below the 25th percentile when defining as cognitive decline, as used by NCHS reports[47] and other previous studies.[48,49]

Measurement of environmental chemical biomarkers

In NHANES, environmental chemical biomarker data were collected from the blood and urine samples of randomly selected participants within specific age groups in a one-third sample. Biospecimen collection at the MEC included collecting, processing, storing, and shipping of blood, urine, and other specimen types. Each MEC was equipped with a laboratory that included a bio-hood, complete blood count, differential analyzer, two centrifuges, refrigerators, and freezers. Quality assurance and quality control (QA/QC) measures were enforced through both internal and external surveillance. QA/QC procedures were performed at the MEC, as well as in contracted and CDC laboratories. The NHANES website offers detailed laboratory measurement methods and QC procedures. We have briefly summarized the chemical assay methods in Table S2. More detailed information is in the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/). Because detailed biological sample collection methods from NHANES participants vary by cycle,[50-53] we used a harmonized and unified version of the NHANES chemical biomonitoring data.[54] A total of 392 environmental chemical biomarkers were examined across the four cycles. These chemicals could be grouped as follows: acrylamide (n = 2), aldehydes (n = 12), aromatic amines (n = 18), bisphenols (n = 3), formaldehyde (n = 1), polychlorinated dibenzo-p-dioxins (PCDD) (n = 14), polychlorinated dibenzofurans (PCDF) (n = 20), metals (n = 33), per- and polyfluoroalkyl substances (PFAS) (n = 16), personal care & consumer product compounds (PCCPCs) (n = 5), pesticides (n = 54), phosphate flame retardants (n = 10), phthalates & plasticizers (n = 18), polycyclic aromatic hydrocarbons (PAHs) (n = 10), polychlorinated biphenyls (PCBs) (n = 69), phytoestrogens (n = 6), parabens (n = 4), smoking-related compounds (SRCs) (n = 15), and volatile organic compounds (VOCs) (n = 82). Detailed information, including the number of observations, detection rate, and lower limit of detection (LLOD) value, is given in Table S3 of

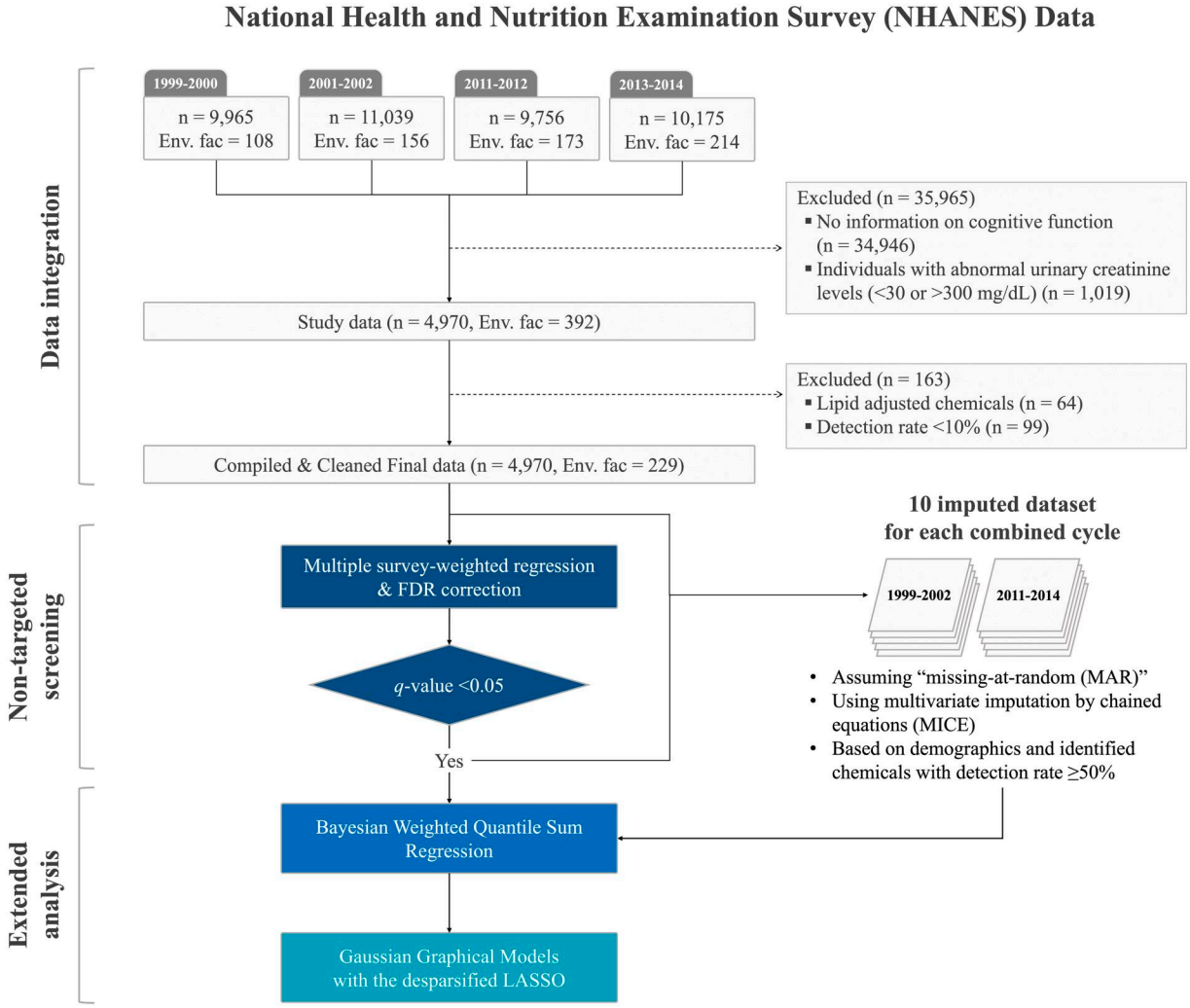

Figure 1. The process of data integration, non-targeted screening, and extended analysis. Data from four cycles of the National Health and Nutrition Examination Survey (NHANES) were used in this study. Final study subjects and environmental factors included in this study were selected based on specified inclusion and exclusion criteria. Abbreviation: Env. fac = environmental factor.

Supplementary Information. In NHANES, all chemical biomarker concentrations below the LLOD were replaced with the LLOD/$\sqrt{2}$. The distribution of each biomarker concentration is provided in Table S4.

Covariates

We selected 13 covariates which are potential confounding or risk factors for cognitive decline identified in previous studies: cycle (1999-2000, 2001-2002, 2011-2012 and 2013-2014), sex (male and female), age group (60-64, 65-69, 70-74, 75-79, and ≥80 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American/Hispanic, and others), family income relative to poverty (a ratio <1 indicates income is below the poverty level, and ratio ≥1 indicates income exceeds the poverty level), marital status (married or living with partner, never married, divorced or separated, and widowed), education level (<high school, high school, and >high school), body mass index (<25, 25-<30, 30-<40, and ≥40 kg/m^2),[55] cotinine level as a proxy of smoking status (<3 and ≥3 ng/mL),[56] alcohol consumption (non-drinker and drinker), and three different health conditions (hypertension, diabetes, and stroke). Alcohol consumption and health conditions were ascertained by self-reported questionnaires (variable name in NHANES): "Had at least 12 alcohol drinks/lifetime? (ALQ110)", "Ever told you had high blood pressure? (BPQ020)", "Ever told you have diabetes? (DIQ010)" and "Ever told you had a stroke? (MCQ160f)".

Statistical analysis

Descriptive statistics of participant characteristics were summarized using mean ± standard deviation (SD), number of cases (n), and percentage (%). The differences in demographic were compared using the chi-squared test. The differences in DSST scores among each covariate were compared using t-tests and ANOVA. A cognitive decline group (ie, participants with the lowest 25th percentile DSST scores) and a normal group (ie, the rest as a reference) were compared using the chi-squared test. All analyses were performed using R version 4.3.1 (R Core Team, https://www.R-project.org/). The critical level of significance was set at $\alpha = 0.05$.

Screening environmental chemical biomarkers related to cognitive function scores

To screen hundreds of chemical biomarkers associated with lower DSST z-scores, we performed an ExWAS non-targeted screening approach to identify biomarkers significantly associated with cognitive function. This approach addresses a

limitation of NHANES data, where the sparsity of the data makes it impossible to form a complete data with measurements for all chemical biomarkers for every participant. In this step, we used complete-cases data (ie, data without missing values) for each chemical with a detection rate of ≥10%. All concentrations were log10-transformed to control a right-skewed distribution and z-standardized. Our study participant characteristics differ across cycles (Table S5) because the NHANES data are collected biennially from different subjects in each cycle. The biospecimen assays were conducted based on the characteristics of the subjects in each cycle. To account for the variations in sample size across cycles, we explored the association between each biomarker and DSST z-scores using multiple survey-weighted regression adjusted for all covariates. To account for the complex survey design, we calculated combining weights using WTMEC2YR, following the NHANES guidelines.[57] *P*-values were corrected using the false discovery rate (FDR, *q*-value) (Figure 1). We used an R package *survey*" to apply survey regression.

Associations between mixtures of identified biomarkers and cognitive decline

After identifying chemical biomarkers associated with DSST z-scores from the first step (*q*-value <0.05), we examined associations of chemical mixtures by including the identified chemical biomarkers with a detection rate of ≥50% with cognitive decline. We defined participants with cognitive decline as those with DSST scores of less than or equal to 26.75 in 1999-2000, 31.00 in 2001-2002, and 33.00 in 2011-2014. We imputed the significant chemical biomarkers identified in our ExWAS analysis because no participants had measurements for all of these biomarkers, making it not feasible to form a complete dataset. To impute the missing value of chemical biomarkers, we employed a multivariate imputation by chained equations (MICE) technique assuming 'missing-at-random (MAR)' to create 10 imputed datasets.[58] We did not impute values below the LLOD because we consider them as undetectable measurements rather than truly missing. To reduce imputation bias due to temporal trends in chemical biomarker concentrations, we generated imputed data separately for each of the 1999-2002 and 2011-2014 cycles. Then, we applied Bayesian weighted quantile sum (BWQS) regression, adjusted for covariates, to estimate the overall effect (β) of an exposure mixture and the relative importance of its individual components (weights).[59,60] BWQS regression employs a Bayesian approach that ensures flexible convergence and allows identifying both positive and negative summed effects without prior restrictions.[59,60] To identify possible important biomarkers in a mixture, we set a cutoff based on the inverse of the number of components in the mixture.[61] We pooled the results from the 10 imputed datasets to estimate the pooled odds ratio (OR), 95% credible intervals (CI), and pooled weights of cognitive decline associated with the biomarker mixture. Pooled estimates from the ten imputed datasets were calculated using Rubin's formulas.[62,63] We used R packages "*BWQS*" for BWQS regression and "*mi*WQS" for pooling.

Interactive impact of chemical biomarkers and selected covariates on cognitive decline

To uncover the interactive impact of identified chemical biomarkers and the selected covariates on cognitive decline, we utilized Gaussian Graphical Models (GGMs) with the desparsified Lasso to derive a partial correlation network structure encompassing the possible important chemical biomarkers, cognitive decline, and all covariates for each of the two combined cycles (1999-2002 and 2011-2014).[64] We applied the survey weights when fitting Lasso regression.[65] Significant *p*-values were adjusted using the Holm-Bonferroni method. Pooled correlations from the ten imputed datasets were calculated using Rubin's formulas.[62,63] We selected non-chemical factors exhibiting statistically significant correlation coefficients with cognitive decline. Finally, we conducted stratified analyses on each category of the non-chemical factors using BWQS regression adjusted for other covariates. We used R packages "*inet*" and "*glmnet*" to extract the correlation network.

Results

Characteristics of study participants

Overall, 4970 participants were included in this study, with 1305 participants classified as the cognitive decline group. Significant differences in DSST z-scores were observed across all covariates (Table 1). Men had lower DSST z-scores than women, and Mexican Americans/Hispanics or widowed individuals had the lowest z-scores. DSST z-scores tended to decrease with increasing age or lower education levels, while they tended to increase as cycles progressed. Smokers scored lower than non-smokers, whereas participants who consumed alcohol scored higher than those who never drank alcohol. No trend was observed with changes in BMI. The differences in participant characteristics across the four selected cycles are provided in Table S5.

Identified chemical biomarkers related to cognitive function test scores

Out of 392 environmental chemical biomarkers examined across all four NHANES cycles, we only evaluated 229 biomarkers with a detection rate of ≥10% (Figure 1). These 229 chemical biomarkers were measured in participants with different sample size across the four cycles, ranging from 297 to 4701 (Table S6). Based on the power calculation results of the general linear model which considered all covariates ($k=13$) and alpha of 0.05,[66,67] we achieved at 80% power to detect effect size of greater than 0.01, which is an average effect size of all biomarkers from power calculations, using the aforementioned sample size (Table S6). We are well-powered to include these chemical biomarkers in our study. Therefore, we included all 229 biomarkers in our study. Among the 229 chemicals, 40 were associated with DSST z-scores (*q*-value <0.05). These included VOCs ($n=8$), PCBs ($n=8$), pesticides ($n=6$), metals ($n=5$), PCCPCs ($n=2$), aldehydes ($n=2$), phthalates ($n=2$), and one each of PAHs, PCDD, PFAS, parabens, phytoestrogen, flame retardants, and SRCs (Figure 2). Metals, except for one biomarker, PAHs, PCBs, phthalates, PCDD, pesticides, and PFAS decreased DSST z-scores. In contrast, aldehydes, flame retardants, parabens, PCCPCs, phytoestrogen, VOCs, except for two biomarkers, and SRCs increased the scores (Table S6). For example, per 1 standard deviation increase in log10-transformed blood Pb level, DSST z-scores decreased by 0.07.

Associations between mixtures of identified biomarkers and cognitive decline

Among 40 biomarkers that were associated with DSST z-scores (*q*-value <0.05), we restricted our analysis to biomarkers that had a detection rate of ≥50% in both cycles within the two combined cycles (1999-2002 and 2011-2014), resulting in 13 and 14 biomarkers in 1999-2002 and 2011-2014 data, respectively. Based on the inverse of the number of components in the mixture, cutoff values for screening potential important biomarkers were 0.077 for 1999-2002 and 0.071 for 2011-2014, respectively. From 1999-

Table 1. Characteristics of the National Health and Nutrition Examination Survey (NHANES) study participants (1999-2000, 2001-2002, 2011-2012, and 2013-2014) included in this study (total = 4970).

	Digit symbol substitution test (DSST) scores			Cognitive decline[a]		*P*-value[c]
				Cognitive normality (*n* = 3665)	Cognitive decline (*n* = 1305)	
	n (%)	Mean ± SD	*P*-value[b]	*n* (%)	*n* (%)	
Sex			<.001			<.001
Male	2545 (51.2)	41.6 ± 17.2		1805 (49.2)	740 (56.7)	
Female	2425 (48.8)	45.6 ± 18.7		1860 (50.8)	565 (43.3)	
Age (years)			<.001			<.001
60-64	1441 (29.0)	49.5 ± 18.7		1177 (32.1)	264 (20.2)	
65-69	1070 (21.5)	45.0 ± 18.0		814 (22.2)	256 (19.6)	
70-74	946 (19.0)	42.9 ± 17.1		705 (19.2)	241 (18.5)	
75-79	605 (12.2)	38.9 ± 16.3		409 (11.2)	196 (15.0)	
Over 80	908 (18.3)	36.2 ± 15.4		560 (15.3)	348 (26.7)	
Cycle			<.001			.619
1999–2000	1104 (22.2)	39.7 ± 19.1		828 (22.6)	276 (21.1)	
2001–2002	1230 (24.7)	43.2 ± 17.9		901 (24.6)	329 (25.2)	
2011–2012	1251 (25.2)	45.1 ± 17.7		910 (24.8)	341 (26.1)	
2013–2014	1385 (27.9)	45.6 ± 17.1		1026 (28.0)	359 (27.5)	
Body mass index (BMI, kg/m^2)			<.001			<.001
Underweight or normal (BMI <25)	1293 (26.0)	43.5 ± 18.4		946 (25.8)	347 (26.6)	
Overweight (25≤BMI < 30)	1847 (37.2)	43.6 ± 17.9		1377 (37.6)	470 (36.0)	
Obesity (30≤BMI < 40)	1456 (29.3)	44.3 ± 17.9		1093 (29.8)	363 (27.8)	
Severe obesity (BMI ≥ 40)	233 (4.7)	44.7 ± 17.4		179 (4.9)	54 (4.1)	
Unknown	141 (2.8)	33.5 ± 16.1		70 (1.9)	71 (5.4)	
Race/ethnicity			<.001			<.001
Non-Hispanic white	2626 (52.8)	48.5 ± 16.8		2212 (60.4)	414 (31.7)	
Non-Hispanic black	986 (19.8)	37.3 ± 16.8		599 (16.3)	387 (29.7)	
Mexican American/Hispanic	1062 (21.4)	35.7 ± 17.7		609 (16.6)	453 (34.7)	
Others	296 (6.0)	48.8 ± 17.8		245 (6.7)	51 (3.9)	
Family income to poverty (%)			<.001			<.001
Ratio <1	725 (14.6)	32.5 ± 17.0		353 (9.6)	372 (28.5)	
Ratio ≥1	3737 (75.2)	45.8 ± 17.3		2952 (80.5)	785 (60.2)	
Unknown	508 (10.2)	42.7 ± 19.0		360 (9.8)	148 (11.3)	
Marital status			<.001			<.001
Married or living with partner	2951 (59.4)	45.8 ± 17.9		2294 (62.6)	657 (50.3)	
Never married	203 (4.1)	43.2 ± 18.7		142 (3.9)	61 (4.7)	
Divorced or separated	681 (13.7)	43.1 ± 18.1		487 (13.3)	194 (14.9)	
Widowed	1026 (20.6)	38.3 ± 17.1		664 (18.1)	362 (27.7)	
Unknown	109 (2.2)	37.0 ± 18.2		78 (2.1)	31 (2.4)	
Education level			<.001			<.001
<High school	1607 (32.3)	30.9 ± 15.3		766 (20.9)	841 (64.4)	
High school	1173 (23.6)	44.8 ± 15.9		921 (25.1)	252 (19.3)	
>High school	2182 (43.9)	52.3 ± 15.4		1975 (53.9)	207 (15.9)	
Unknown	8 (0.2)	29.4 ± 18.6		3 (0.1)	5 (0.4)	
Cotinine level as a proxy of smoking status (ng/mL)			<.001			<.001
Low (<3)	3912 (78.7)	44.5 ± 18.1		2964 (80.9)	948 (72.6)	
High (≥3)	789 (15.9)	40.3 ± 17.5		526 (14.4)	263 (20.2)	
Unknown	269 (5.4)	38.9 ± 17.6		175 (4.8)	94 (7.2)	
Alcohol consumption			<.001			<.001
Non-drinker	797 (16.0)	39.5 ± 17.7		526 (14.4)	271 (20.8)	
Drinker	877 (17.6)	42.3 ± 17.8		645 (17.6)	232 (17.8)	
Unknown	3296 (66.3)	44.9 ± 18.0		2494 (68.0)	802 (61.5)	
Health conditions						
Ever told you had high blood pressure			<.001			.009
No	2129 (42.8)	45.2 ± 18.4		1637 (44.7)	492 (37.7)	
Yes	2833 (57.0)	42.3 ± 17.6		2022 (55.2)	811 (62.1)	
Unknown	8 (0.2)	43.6 ± 25.2		6 (0.2)	2 (0.2)	
Ever told you have diabetes			<.001			<.001
No	3779 (76.0)	44.7 ± 18.3		2875 (78.4)	904 (69.3)	
Yes	1007 (20.3)	38.9 ± 17.0		654 (17.8)	353 (27.0)	
Unknown	184 (3.7)	44.9 ± 15.6		136 (3.7)	48 (3.7)	
Ever told you had a stroke			<.001			<.001
No	4630 (93.2)	44.2 ± 18.0		3476 (94.8)	1154 (88.4)	
Yes	330 (6.6)	34.2 ± 16.4		181(4.9)	149 (11.4)	
Unknown	10 (0.2)	44.6 ± 13.9		8 (0.2)	2 (0.2)	

[a]Cognitive decline was defined as less than the 25th percentile of Digit Symbol Substitution Test (DSST) raw scores.
[b]P-value was estimated using *t*-test or ANOVA.
[c]P-value was estimated using the Chi-square test.

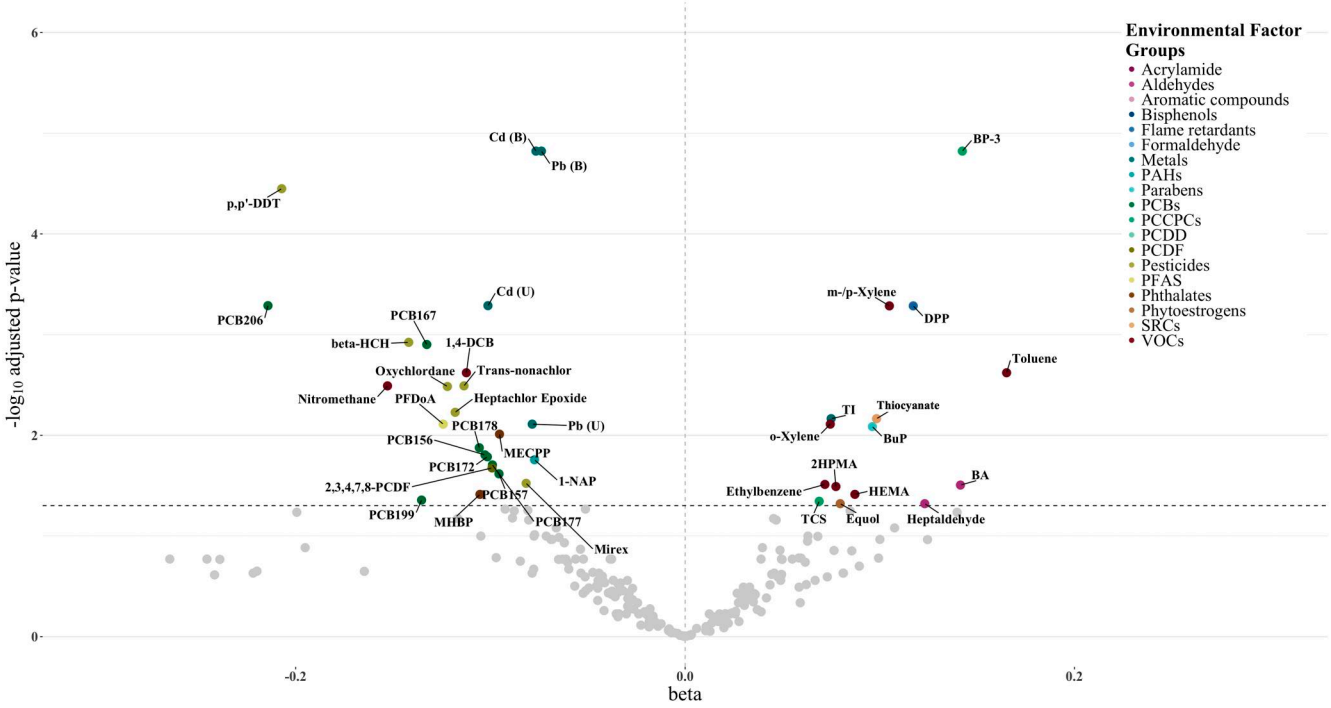

Figure 2. Volcano plot of environmental factors (chemical biomarkers) associated with the Digit Symbol Substitution Test (DSST) z-scores. Significant chemical biomarkers were dotted above the grey dashed line (q-value <0.05). Abbreviations: B = blood, U = urine, Cd = cadmium, Pb = lead, PB-3 = benzophenone-3, BuP = butyl paraben, DDT = dichlorodiphenyltrichloroethane, DPP = diphenyl phosphate, PCB = polychlorinated biphenyl, PFDoA = perfluorododecanoic acid, HCH = hexachlorocyclohexane, TI = thallium, DCB = dichlorobenzene, MECPP = mono-2-ethyl-5-carboxyentyl phthalate, MHBP = mono-3-hydroxy-n-butyl phthalate, 1-NAP = 1-phthol, BA = butyraldehyde, 2,3,4,5,8-PCDF = 2,3,4,7,8-pentachlorodibenzofuran, TCS = triclosan, HEMA = N-acetyl-S-(2-Hydroxyethyl)-L-cysteine, 2HPMA = N-acetyl-S-(2-hydroxypropyl)-L-cysteine, PAHs = polycyclic aromatic hydrocarbon, PCCPCs = personal care and cosmetic products, PCDD = polychlorinated-p-dioxins, PCDF = polychlorinated-p-furans, PFAS = per- and polyfluoroalkyl substances, SRCs = smoking-related compounds, VOCs = volatile organic compounds.

2002, we did not observe the overall effects of chemical exposures on cognitive decline (OR = 1.73, 95% CI, 0.40-7.45). Among the included biomarkers, urinary Pb (weight = 0.15), beta-hexachlorocyclohexane (beta-HCH, weight = 0.09), heptachlor epoxide (weight = 0.08), and p, p'-dichlorodiphenyltrichloroethane (p, p'-DDT, weight = 0.23) had weights greater than a cutoff value. As possible important biomarkers, these are major drivers of cognitive decline in the mixtures. In contrast, we observed significant overall effects of chemical exposures on cognitive decline in the 2011-2014 data, and the effect was opposite to the 1999-2002 data (OR = 0.31, 95% CI, 0.12-0.81). We observed that m/p-xylene (weight = 0.11), thiocyanate (weight = 0.16), triclosan (TCS, weight = 0.10), benzophenone-3 (BP-3, weight = 0.19), and diphenyl phosphate (DPP, weight = 0.19) had weights greater than a cutoff value, identifying them as potentially important biomarkers (Figure 3).

Interactive impact of chemical exposures and health conditions on cognitive decline

Based on the partial correlation network structure newly created in the current study, cognitive decline was associated with non-modifiable risk factors and modifiable factors (refer to legend in Figure 4). In 1999-2002, cognitive decline (defined as DSST raw scores below the 25th percentile) had a positive correlation with older participants (ρ = 0.87 for aged ≥80 years old) and a negative correlation with higher education level (ρ = −0.43 for at least high school degree and −0.32 for more than high school degree), though none was statistically significant. Chemical exposures seemed to have indirect relationships with cognitive decline. When conducting a stratified analysis by age group, higher exposure to a mixture was associated with higher odds of cognitive decline in the group aged over 80 years (OR = 2.16, 95% CI, 1.38-3.39) (Table 2). Similarly, in 2011-2014, cognitive decline had a positive correlation with older participants (ρ = 0.88) and a negative correlation with higher education level (ρ = −0.60 for at least high school degree and −0.32 for more than high school degree). However, cognitive decline had also negative correlations with DPP (ρ = −0.17) and thiocyanate (ρ = −0.11), though none was statistically significant. When conducting a stratified analysis by age group, exposure to a mixture was not associated with cognitive decline in any age group.

Discussion

To the best of our knowledge, this study is the first to comprehensively and systematically investigate the association between environmental chemical exposures and cognitive decline, and to assess their mixture impact. By using the ExWAS approach and the NHANES data, we screened 229 environmental chemical biomarkers and identified those potentially related to cognitive decline. Additionally, we estimated the odds of having cognitive decline from the identified biomarkers to examine mixture effects and investigated previously undiscovered pathways linking chemical biomarkers to cognitive decline by extracting a correlation network structure. This allowed us to understand that cognitive decline can be worsened with increased chemical exposures among those with known risk factors of cognitive decline.

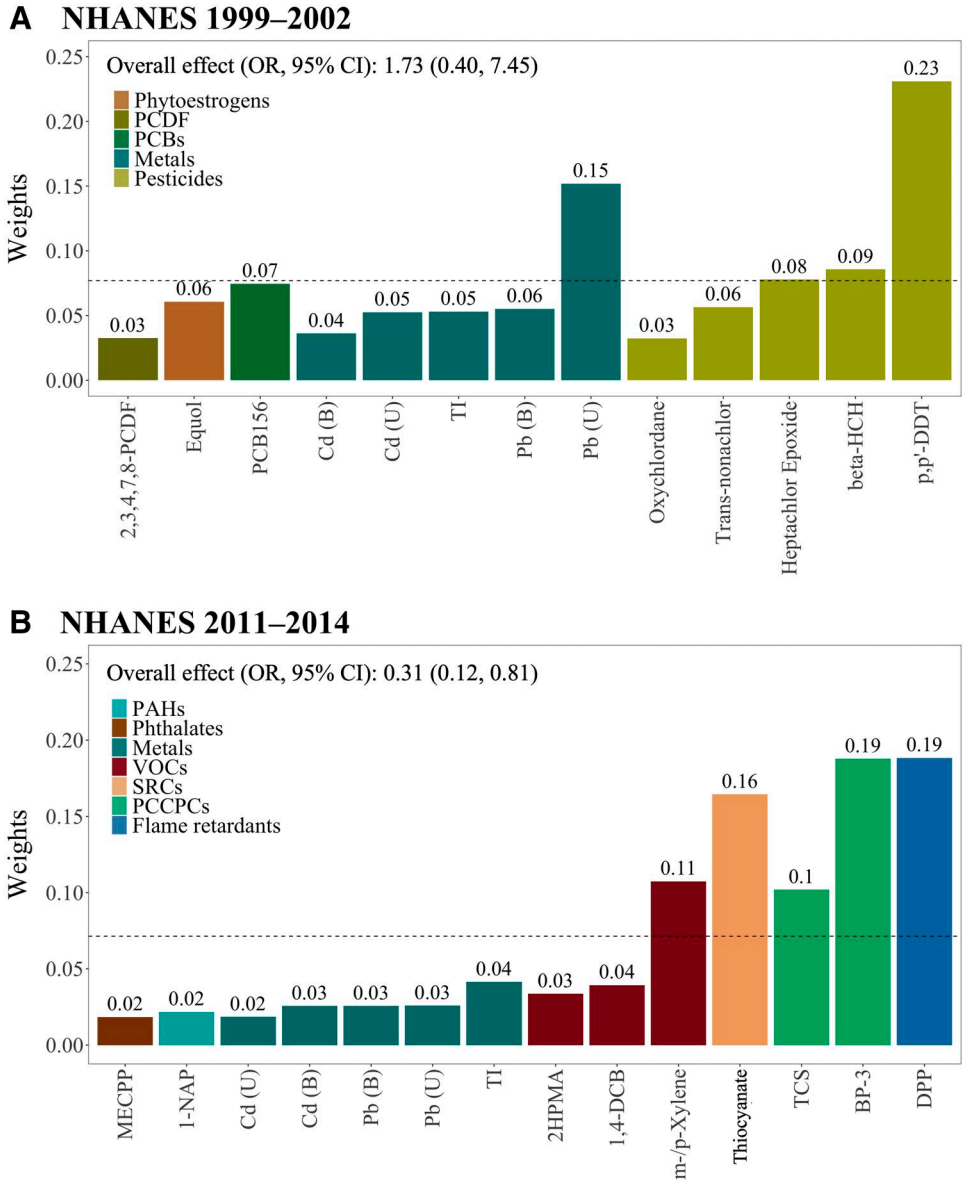

Figure 3. Pooled overall effects of exposure mixtures and relative importance of individual biomarkers associated with cognitive decline by two combined cycles (NHANES 1999-2002 $n = 2334$; case = 605, and 2011-2014 $n = 2636$; case = 700). Cognitive decline is less than or equal to the 25th percentile DSST scores. Estimates were estimated using Bayesian weighted quantile sum regression. All biomarker concentrations were log10-transformed and scaled. The OR and 95% CI were estimated using the logistic regression model adjusted for sex, age group, cycles, body mass index, race/ethnicity, family income to poverty, marital status, education level, smoking status based on the cotinine level, alcohol consumption, and health conditions (diabetes, hypertension, and stroke). Abbreviations: NHANES = the National Health and Nutrition Examination Survey, OR = odds ratio, CI = credible interval, PCDF = polychlorinated dibenzofurans, PCB = polychlorinated biphenyl, 2,3,4,7,8-PCDF = 2,3,4,7,8-pentachlorodibenzofuran, TI = thallium, B = blood, U = urine, Cd = cadmium, Pb = lead, beta-HCH = beta-hexachlorocyclohexane, DDT = dichlorodiphenyltrichloroethane, PAH = polycyclic aromatic hydrocarbon, VOCs = volatile organic compounds, SRCs = smoking-related compounds, PCCPCs = personal care and consumer product chemicals, 1-NAP = 1-naphtol, MECPP = mono-2-ethyl-5-carboxypentyl phthalate, 2HPMA = N-acetyl-S-(2 -hydroxypropyl)-L-cysteine, DCB = dichlorobenzene, TCS = triclosan, BP-3 = benzophenone-3, DPP = diphenyl phosphate.

Among 229 chemical biomarkers investigated in this study, we observed that 40 biomarkers were associated with DSST z-scores. Most of them were metals, pesticides, PCBs, and VOCs. Metals, PCBs, and pesticides, which are known to have neurotoxicity[68-70] and are characterized by persistence and bioaccumulation[71,72] were associated with lower scores, whereas VOCs were associated with higher scores. When assessing mixture effects of exposure to the identified biomarkers with a detection rate of 50% or above, higher exposure to mixtures included in 2011-2014 was associated with low odds of cognitive decline and we identified Pb, p, p'-DDT, beta-HCH, heptachlor epoxide, m-/p-xylene, TCS, BP-3, DDP, and thiocyanate as biomarkers with larger weights than cutoff values, which can be considered major drivers of cognitive decline in the mixtures. From the network analysis, we observed that cognitive decline was relatively strongly correlated with age and education but were weakly correlated with levels of DPP and thiocyanate. After stratification, for the aged ≥80 years old group, we found higher odds of cognitive decline related to higher exposure to the mixture in the 1999-2002 data.

In our extended analyses, we divided the data into two combined cycles (1999-2002 and 2011-2014) and conducted

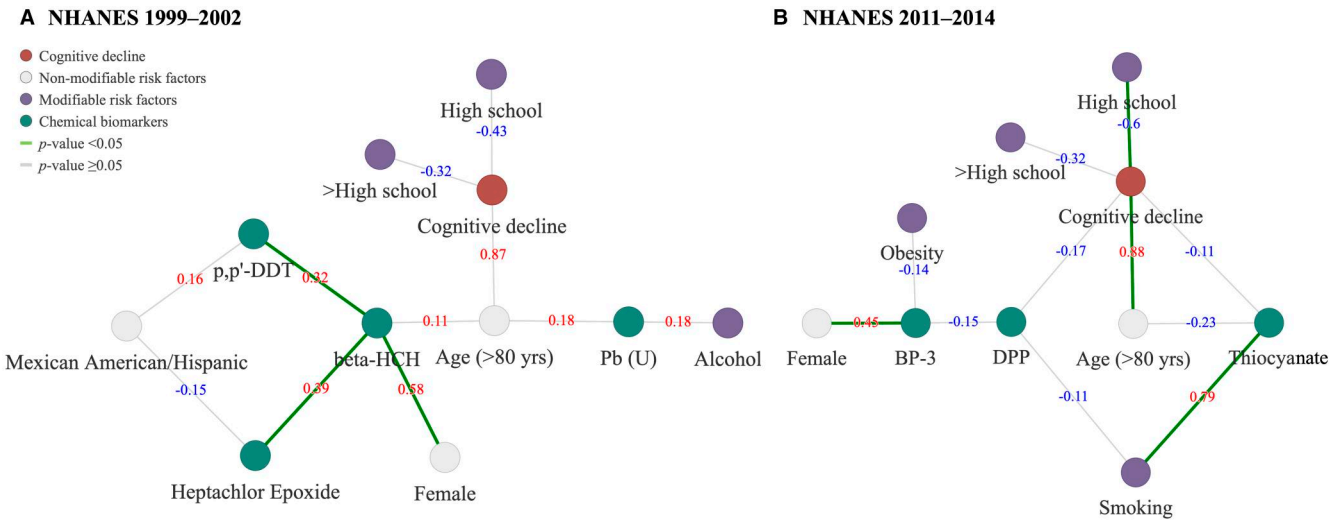

Figure 4. Partial correlation (ρ) network plot depicting the magnitude and direction of correlation coefficients among possible important biomarkers, cognitive decline, and selected covariates. Green lines indicate significance of correlation coefficients (*P*-value < .05). Red numbers indicate positive correlations, and blue numbers indicate negative correlations. Abbreviations: NHANES = National Health and Nutrition Examination Survey, U = urine, yrs = years old, Pb = lead, beta-HCH = beta-hexachlorocyclohexane, DDT = dichlorodiphenyltrichloroethane, BP-3 = benzophenone-3, DPP = diphenyl phosphate.

Table 2. Odds ratio (OR) and 95% credible interval (CI) of cognitive decline associated with chemical mixtures by age, sex, and race/ethnicity (total = 4970) for each of the two combined NHANES cycles (1999-2002, 2011-2014).

	1999–2002		2011–2014	
	n (case)	OR (95% CI)	n (case)	OR (95% CI)
All	2334 (605)	1.69 (0.74, 3.88)	2636 (700)	0.36 (0.15, 0.85)
Age (years)				
60-64	621 (115)	0.94 (0.36, 2.46)	820 (149)	0.46 (0.20, 1.06)
65-69	473 (113)	1.03 (0.33, 3.19)	597 (143)	0.52 (0.20, 1.39)
70-74	449 (107)	1.93 (0.95, 3.91)	497 (134)	0.58 (0.21, 1.63)
75-79	318 (96)	1.38 (0.25, 7.64)	287 (100)	0.41 (0.13, 1.27)
Over 80	473 (174)	**2.16 (1.38, 3.39)**	435 (174)	0.41 (0.14, 1.23)

All chemical biomarker concentrations were log 10-transformed and scaled. Bold values denote statistical significance at the $p<0.05$ level.

independent evaluations. Interestingly, we observed opposing trends in the effects of chemical mixture exposure on cognitive function across these cycles. The composition of measured biomarkers varied significantly between the two periods, with only five biomarkers present in both cycles. During the 1999-2002 cycle, the overall effect of the chemical mixture was greater than 1, indicating a detrimental impact on cognitive function. The biomarkers identified in the mixture demonstrated consistent relationships with cognitive function in the same direction. Metals and pesticides were the major components of this mixture, with key contributors including Pb, p, p'-DDT, beta-HCH, and heptachlor epoxide. These biomarkers were associated with lower cognitive function, as evidenced by negative beta values for DSST z-scores in individual analyses. Stratification by age groups yielded mixed results, leading to non-significant findings. Conversely, in the 2011-2014 cycle, the overall effect of the mixture was less than 1, suggesting a protective influence on cognitive function. This shift could be attributed to major biomarkers with protective properties, primarily VOCs and PCCPCs. The key biomarkers in this mixture included m-/p-xylene, TCS, BP-3, DDP, and thiocyanate. These biomarkers consistently exhibited protective effects on cognitive function, with positive beta values (greater than 1) in single analyses. Moreover, their association with cognitive decline was inverse, with all stratified odds ratios being below 1, contributing to the significance of the overall protective effect. To clarify the distinct differences between the two time periods, more detailed observational studies are required, focusing on the mixture effect of pesticides, VOCs, and PCCPCs.

Our correlation network analysis revealed that p, p'-DDT, beta-HCH, and heptachlor epoxide indirectly influence cognitive decline in individuals aged 80 years and older. In the stratified analysis by age group during the 1999-2002 cycle, we observed that exposure to the chemical mixture in this age group was associated with higher odds of cognitive decline. These findings align with previous studies, which have shown that the risk of low DSST scores increases with age, particularly in individuals with p, p'-DDT levels in the 75th percentile and heptachlor epoxide levels in the 75th percentile.[73]

The impact of chemical exposures on cognitive decline and their mechanisms is relatively well-established for the key biomarkers of the mixture in the 1999-2002 cycle.[26,74-80] However, research on these biomarkers during the 2011-2014 cycle remains limited. For instance, one study reported positive associations between BP-3 levels and DSST scores.[81] BP-3 exposure primarily occurs through sunscreen use as UV filters,[82] but it is also found in other cosmetics such as hair products, shampoos, and food packaging.[83] However, this positive association with cognitive function could be influenced by unmeasured confounders because most studies focused on young populations, leaving a significant research gap for older adults.[84] DDP, an organophosphorus flame retardant and plasticizer, is commonly found in products such as furniture, textiles, building materials, and plastics.[85] Although many studies have explored DDP exposure in children,[86-90] no association was found between DDP exposure and cognitive impairment in the elderly populations, such as those of southern China.[91] Similarly, there is a lack of epidemiological studies investigating the effects of exposure to m-/p-xylene, TCS, and thiocyanate on cognitive function in older adults. Given the limited evidence, additional epidemiological studies are needed to confirm the protective effects observed

from these five biomarkers and to better understand their role in cognitive health in older populations.

Our study has several limitations. Firstly, the cross-sectional nature of the NHANES data precludes establishing causation from our findings. Secondly, chemical biomarker concentration data were from a spot sample of each participant, so they may not represent individual's average exposure over the lifetime of our participants. Thirdly, despite adjusting for confounders associated with cognitive decline based on previous studies, there may still be unmeasured confounding variables influencing our effect estimates. Fourthly, there could be imputation bias on the biomarker data because each NHANES cycle had a different list of chemical biomarkers and only one third of samples from each cycle were used to assess chemical biomarker concentrations. In addition, if the missing data mechanism of NHANES is non-random (ie, missing not at random, MNAR), performing multiple imputation under the assumption of missing at random (MAR) may produce biased estimates.[92] Finally, the ExWAS approach used in this study cannot assess the effects of chemical mixtures, such as additive effects, synergism, potentiation, and antagonism.

Conclusions

In this study, we employed an ExWAS approach to explore 229 environmental chemical biomarkers in association with cognitive decline among US older adults. From the mixture analysis including all identified biomarkers significantly associated with cognitive decline, we observed that p, p'-DDT, beta-HCH, and heptachlor epoxide may exacerbate cognitive decline. The correlation network structure shows that their impact on cognitive decline may be promoted in older adults aged ≥80 years. These findings suggest that combined and prolonged exposure to these chemicals may worsen cognitive impairment in aging populations. Our study underscores the complex interplay between exposure to environmental chemicals and cognitive function in older adults, emphasizing the need for further research to elucidate causal mechanisms and effectively guide public health interventions.

Author contributions

HyunA Jang (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [equal], Software [equal], Visualization [equal], Writing—original draft [equal]), Jiyun Lee (Conceptualization [equal], Data curation [equal], Methodology [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), Vy Kim Nguyen (Data curation [equal], Resources [equal], Writing—review & editing [equal]), and Hyeong Moo Shin (Conceptualization [equal], Supervision [equal], Validation [equal], Writing—review & editing [equal])

Supplementary material

Supplementary material is available at *Exposome* online.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Data availability

The data underlying this article are available in the National Health and Nutrition Examination Survey at https://wwwn.cdc.gov/nchs/nhanes/.

References

1. Hou YJ, Dan XL, Babbar M, *et al.* Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol.* 2019;15:565-581. https://doi.org/10.1038/s41582-9–0244-7
2. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement.* 2024. Accessed June 13, 2024;20. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf
3. Collaborators GBDD. Global, regional, and national burden of Alzheimer's disease and other dementias, 0–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:88-106. https://doi.org/10.1016/S1474-4422(18)30403-4
4. Logroscino G, Piccininni M, Marin B, *et al.* Global, regional, and national burden of motor neuron diseases 0–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17:1083-1097. https://doi.org/10.1016/S1474-4422(18)30404-6
5. Dorsey ER, Elbaz A, Nichols E, *et al.* Global, regional, and national burden of Parkinson's disease, 0–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17:939-953. https://doi.org/10.1016/S1474-4422(18)30295-3
6. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (0–2060). *Alzheimers Dement.* 2021;17:1966-1975. https://doi.org/10.1002/alz.12362
7. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* 2021;17:327-406. https://doi.org/10.1002/alz.12328
8. National Institute of Health. *Looking Forward: Opportunities to Accelerate Alzheimer's and Related Dementias Research.* 2024. Accessed June 13, 2024. https://www.nia.nih.gov/sites/default/files/2022-07/fy24_alzheimers_bypassbudget.pdf
9. Wilson DM, 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. *Cell* 2023;186:693-714. https://doi.org/10.1016/j.cell.2022.12.032
10. Ullah MF, Ahmad A, Bhat SH, Abu-Duhier FM, Barreto GE, Ashraf GM. Impact of sex differences and gender specificity on behavioral characteristics and pathophysiology of neurodegenerative disorders. *Neurosci Biobehav Rev.* 2019;102:95-105. https://doi.org/10.1016/j.neubiorev.2019.04.003
11. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. *Neurology* 2010;75:1070-1078. https://doi.org/10.1212/WNL.0b013e3181f39adc
12. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med.* 2013;29:737-752. https://doi.org/10.1016/j.cger.2013.07.002

13. Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. *Neurol Clin*. 2007;25:577-609. https://doi.org/10.1016/j.ncl.2007.03.008
14. Andrade C, Radhakrishnan R. The prevention and treatment of cognitive decline and dementia: an overview of recent research on experimental treatments. *Ind J Psych*. 2009;51:12-25. https://doi.org/10.4103/9–5545.44900
15. Baumgart M, Snyder HM, Carrillo MC, 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. https://doi.org/10.1016/j.jalz.2015.05.016
16. Fan J, Tao W, Li X, *et al*. The contribution of genetic factors to cognitive impairment and dementia: apolipoprotein E gene, gene interactions, and polygenic risk. *Int J Mol Sci*. 2019;20:1177. https://doi.org/10.3390/ijms20051177
17. Manuello J, Min JS, Mccarthy P, *et al*. The effects of genetic and modifiable risk factors on brain regions vulnerable to ageing and disease. *Nat Commun*. 2024;15:2576.https://doi.org/ARTN10.1038/s41467-4–46344-2
18. Edwards Iii GA, Gamez N, Escobedo G, Jr., Calderon O, Moreno-Gonzalez I. Modifiable Risk Factors for Alzheimer's Disease. *Front Aging Neurosci*. 2019;11:146.https://doi.org/10.3389/fnagi.2019.00146
19. Sepulveda-Falla D, Velez JI, Acosta-Baena N, *et al*. Genetic modifiers of cognitive decline in PSEN1 E280A Alzheimer's disease. *Alzheimers Dement*. 2024;20:2873-2885. https://doi.org/10.1002/alz.13754
20. Faouzi J, Tan M, Casse F, *et al*. Proxy-analysis of the genetics of cognitive decline in Parkinson's disease through polygenic scores. *NPJ Parkinsons Dis*. 2024;10:8.https://doi.org/10.1038/s41531-3–00619-5
21. WD Council. *WDC Dementia Risk Reduction Statement*. Accessed June 14, 2024. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://s3-eu-west-1.amazonaws.com/media.dh.gov.uk/network/353/files/2015/01/WDC-supportive-statement-on-risk-reduction-FINAL-FOR-PUBLICATION-BRANDED-150128-LM.pdf
22. Barahona AJ, Bursac Z, Veledar E, Lucchini R, Tieu K, Richardson JR. Relationship of blood and urinary manganese levels with cognitive function in elderly individuals in the United States by race/ethnicity, NHANES 1–2014. *Toxics* 2022;10:191. https://doi.org/10.3390/toxics10040191
23. Larvie DY, Erikson KM, Armah SM. Elevated whole blood manganese is associated with impaired cognition in older adults, NHANES 3–2014 cycle. *Neurotoxicology* 2022;91:94-99. https://doi.org/10.1016/j.neuro.2022.04.016
24. Wang X, Xiao P, Wang R, *et al*. Relationships between urinary metals concentrations and cognitive performance among U.S. older people in NHANES 1–2014. *Front Public Health*. 2022;10:985127. https://doi.org/10.3389/fpubh.2022.985127
25. Lu K, Liu T, Wu X, Zhong J, Ou Z, Wu W. Association between serum iron, blood lead, cadmium, mercury, selenium, manganese and low cognitive performance in old adults from National Health and Nutrition Examination Survey (NHANES): a cross-sectional study. *Br J Nutr*. 2023;130:1743-1753. https://doi.org/10.1017/S0007114523000740
26. Sasaki N, Carpenter DO. Associations between metal exposures and cognitive function in american older adults. *Int J Environ Res Public Health*. 2022;19:2327. https://doi.org/10.3390/ijerph19042327
27. Song S, Liu N, Wang G, *et al*. Sex Specificity in the mixed effects of blood heavy metals and cognitive function on elderly: evidence from NHANES. *Nutrients* 2023;15:2874. https://doi.org/10.3390/nu15132874
28. Kim UJ, Hong M, Choi YH. Environmental pyrethroid exposure and cognitive dysfunction in U.S. older adults: the NHANES 1–2002. *Int J Environ Res Public Health*. 2021;18:12005. https://doi.org/10.3390/ijerph182212005
29. Yu Y, Wang Y, Dong Y, *et al*. Butyl benzyl phthalate as a key component of phthalate ester in relation to cognitive impairment in NHANES elderly individuals and experimental mice. *Environ Sci Pollut Res Int*. 2023;30:47544-47560. https://doi.org/10.1007/s11356-3–25729-8
30. Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus. *PLoS One*. 2010;5:e10746. https://doi.org/10.1371/journal.pone.0010746
31. Chung MK, House JS, Akhtari FS, Members of the Exposomics Consortium, *et al*. Decoding the exposome: data science methodologies and implications in exposome-wide association studies (ExWASs). *Exposome*. 2024;4:osae001. https://doi.org/10.1093/exposome/osae001
32. Hall MA, Dudek SM, Goodloe R, *et al*. Environment-wide association study (EWAS) for type 2 diabetes in the Marshfield Personalized Medicine Research Project Biobank. *Pac Symp Biocomput*. 2014;:200–211.
33. Patel CJ, Chen R, Kodama K, Ioannidis JP, Butte AJ. Systematic identification of interaction effects between genome- and environment-wide associations in type 2 diabetes mellitus. *Hum Genet*. 2013;132:495-508. https://doi.org/10.1007/s00439-2–1258-z
34. Uche UI, Suzuki S, Fulda KG, Zhou Z. Environment-wide association study on childhood obesity in the U.S. *Environ Res*. 2020;191:110109. https://doi.org/10.1016/j.envres.2020.110109
35. New A, Bennett KP. A precision environment-wide association study of hypertension via supervised cadre models. *IEEE J Biomed Health Inform*. 2020;24:916-925. https://doi.org/10.1109/JBHI.2019.2918070
36. McGinnis DP, Brownstein JS, Patel CJ. Environment-wide association study of blood pressure in the national health and nutrition examination survey (9–2012). *Sci Rep*. 2016;6:30373.https://doi.org/10.1038/srep30373
37. Chi Y, Park JT, Na S, Kwak K. Environment-wide association study of elevated liver enzymes: results from the Korean National Environmental Health Survey 8–2022. *Ann Occup Environ Med*. 2023;35:e27. https://doi.org/10.35371/aoem.2023.35.e27
38. Ni MY, Yao XI, Cheung F, *et al*. Determinants of physical, mental and social well-being: a longitudinal environment-wide association study. *Int J Epidemiol*. 2020;49:380-389. https://doi.org/10.1093/ije/dyz238
39. Lopez DS, Wulaningsih W, Tsilidis KK, *et al*. Environment-wide association study to comprehensively test and validate associations between nutrition and lifestyle factors and testosterone deficiency: NHANES 8–1994 and 9–2004. *Hormones (Athens)*.2020;19:205-214. https://doi.org/10.1007/s42000-0–00179-w
40. Belbasis L, Bellou V, Tzoulaki I, Evangelou E. Early-life factors and risk of multiple sclerosis: an MR-EWAS. *Neuroepidemiology*. 2020;54:433-445. https://doi.org/10.1159/000508229
41. *Health and Nutrition Examination Survey Plan and Operations, 9–2010*. National Center for Health Statistics (U.S.). 2013. Accessed June 13, 2024. https://stacks.cdc.gov/view/cdc/21304
42. WH Organization. *Biological Monitoring of Chemical Exposure in the Workplace Guidelines*. Vol 1. World Health Organization; 1996.
43. Tulsky DS, Saklofske DH, Wilkins C, Weiss LG. Development of a general ability index for the Wechsler Adult Intelligence

Scale—third edition. *Psychol Assess*. 2001;13:566-571. https://doi.org/10.1037//0–3590.13.4.566
44. Donohue MC, Sperling RA, Salmon DP, Alzheimer's Disease Cooperative Study, *et al.* The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71:961-970. https://doi.org/10.1001/jamaneurol.2014.803
45. Amieva H, Meillon C, Proust-Lima C, Dartigues JF. Is low psychomotor speed a marker of brain vulnerability in late life? Digit symbol substitution test in the prediction of Alzheimer, Parkinson, stroke, disability, and depression. *Dement Geriatr Cogn Disord*. 2019;47:297-305. https://doi.org/10.1159/000500597
46. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018;38:513-519. https://doi.org/10.1097/JCP.0000000000000941
47. Brody DJ, Kramarow EA, Taylor CA, McGuire LC. Cognitive Performance in *Adults Aged 60 and Over: National Health and Nutrition Examination Survey, 2011–2014*. Accessed September 17, 2019. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.cdc.gov/nchs/data/nhsr/nhsr126-508.pdf
48. 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. https://doi.org/10.3233/jad-190263
49. Chen SP, Bhattacharya J, Pershing S. Association of vision loss with cognition in older adults. *JAMA Ophthalmol*. 2017;135:963-970. https://doi.org/10.1001/jamaophthalmol.2017.2838
50. CDC/National Center for Health Statistics. *NHANES 9–2000 Laboratory Methods*. Accessed June 13, 2024. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?Cycle=9–2000
51. CDC/National Center for Health Statistics. *NHANES 1–2002 Laboratory Methods*. Accessed June 13, 2024. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2001
52. Centers for Disease Control and Prevention. *National Health Nutrition Examination Survey (NHANES) Laboratory Procedures Manual*. 2011. Accessed June 13, 2024. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2011
53. Centers for Disease Control and Prevention. *National Health Nutrition Examination Survey (NHANES) Laboratory Procedures Manual*. 2013. Accessed June 13, 2024. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2013
54. Nguyen VK, Middleton LYM, Huang L, *et al.* Harmonized US National Health and Nutrition Examination Survey 1988–2018 for high throughput exposome-health discovery. *medRxiv* 2023. https://doi.org/10.1101/2023.02.06.23284573
55. Hales CM, Carroll MD, Fryar CD, Ogden CL. *Prevalence of Obesity and Severe Obesity among Adults: United States, 2017–2018*. NCHS Data Brief, no 360. National Center for Health Statistics; 2020.
56. Kim S. Overview of cotinine cutoff values for smoking status classification. *Int J Environ Res Public Health*. 2016;13:1236. https://doi.org/10.3390/ijerph13121236
57. National Center for Health Statistics, Centers for Disease Control and Prevention. *Analytic and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES)*. National Center for Health Statistics Centers for Disease Control and Prevention. 2006.
58. Chung MK, Buck Louis GM, Kannan K, Patel CJ. Exposome-wide association study of semen quality: Systematic discovery of endocrine disrupting chemical biomarkers in fertility require large sample sizes. *Environ Int*. 2019;125:505-514. https://doi.org/10.1016/j.envint.2018.11.037
59. Hamra GB, Maclehose RF, Croen L, Kauffman EM, Newschaffer C. Bayesian weighted sums: a flexible approach to estimate summed mixture effects. *Int J Environ Res Public Health*. 2021;18:1373. https://doi.org/10.3390/ijerph18041373
60. Colicino E, Pedretti NF, Busgang SA, Gennings C. Per- and polyfluoroalkyl substances and bone mineral density: results from the Bayesian weighted quantile sum regression. *Environ Epidemiol*. 2020;4:e092. https://doi.org/10.1097/EE9.0000000000000092
61. Zang X, Qin W, Xiong Y, *et al.* Using three statistical methods to analyze the association between aldehyde exposure and markers of inflammation and oxidative stress. *Environ Sci Pollut Res Int*. 2023;30:79437-79450. https://doi.org/10.1007/s11356-3–27717-4
62. Barnard J, Rubin D. Miscellanea. Small-sample degrees of freedom with multiple imputation. *Biometrika*. 1999;86:948-955. https://doi.org/10.1093/biomet/86.4.948
63. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91:473-489. https://doi.org/10.1080/01621459.1996.10476908
64. Waldorp L, Haslbeck J. Network inference with the lasso. *Multivariate Behav Res*. 2024;59:738-757. https://doi.org/10.1080/00273171.2024.2317928
65. Friedman JH, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw*. 2010;33:1-22. https://doi.org/10.18637/jss.v033.i01
66. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175-191. https://doi.org/10.3758/bf03193146
67. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Method*. 2009;41:1149-1160. https://doi.org/10.3758/BRM.41.4.1149
68. Chen P, Miah MR, Aschner M. Metals and neurodegeneration. *F1000Res*. 2016; 5:5.https://doi.org/10.12688/f1000research.7431.1
69. Pessah IN, Lein PJ, Seegal RF, Sagiv SK. Neurotoxicity of polychlorinated biphenyls and related organohalogens. *Acta Neuropathol*. 2019;138:363-387. https://doi.org/10.1007/s00401-9–01978-1
70. Richardson JR, Fitsanakis V, Westerink RHS, Kanthasamy AG. Neurotoxicity of pesticides. *Acta Neuropathol*. 2019;138:343-362. https://doi.org/10.1007/s00401-9–02033-9
71. Ali H, Khan E, Ilahi I. Environmental chemistry and ecotoxicology of hazardous heavy metals: environmental persistence, toxicity, and bioaccumulation. *J Chem-Ny*. 2019;2019:1-6730305. https://doi.org/Artn10.1155/2019/6730305
72. Crinnion WJ. Polychlorinated biphenyls: persistent pollutants with immunological, neurological, and endocrinological consequences. *Altern Med Rev*. 2011;16:5-13.
73. Kim SA, Lee YM, Lee HW, Jacobs DR, Jr., Lee DH. Greater cognitive decline with aging among elders with high serum concentrations of organochlorine pesticides. *PLoS One*. 2015;10:e0130623. https://doi.org/10.1371/journal.pone.0130623
74. Lasley SM, Gilbert ME. Glutamatergic components underlying lead-induced impairments in hippocampal synaptic plasticity. *Neurotoxicology*. 2000;21:1057-1068.
75. Ahamed M, Siddiqui MK. Low level lead exposure and oxidative stress: current opinions. *Clin Chim Acta*. 2007;383:57-64. https://doi.org/10.1016/j.cca.2007.04.024
76. Adonaylo VN, Oteiza PI. Pb2+ promotes lipid oxidation and alterations in membrane physical properties. *Toxicology*. 1999;132:19-32. https://doi.org/10.1016/s0300-483x(98)00134-6

77. Kim KS, Lee YM, Lee HW, Jacobs DR, Jr., Lee DH. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 9–2002. *Environ Int*. 2015;75:87-92. https://doi.org/10.1016/j.envint.2014.11.003
78. Aktar MW, Sengupta D, Chowdhury A. Impact of pesticides use in agriculture: their benefits and hazards. *Interdiscip Toxicol*. 2009;2:1-12. https://doi.org/10.2478/v10102-009-0001-7
79. Subramaniam K, Solomon J. Organochlorine pesticides BHC and DDE in human blood in and around Madurai, India. *Indian J Clin Biochem*. 2006;21:169-172. https://doi.org/10.1007/BF02912936
80. Jayaraj R, Megha P, Sreedev P. Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. *Interdiscip Toxicol*. 2016;9:90-100. https://doi.org/10.1515/intox-2016-0012
81. Shi Y, Wang H, Zhu Z, Ye Q, Lin F, Cai G. Association between exposure to phenols and parabens and cognitive function in older adults in the United States: A cross-sectional study. *Sci Total Environ*. 2023;858:160129. https://doi.org/10.1016/j.scitotenv.2022.160129
82. Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. In vitro and in vivo estrogenicity of UV screens. *Environ Health Perspect*. 2001;109:239-244. https://doi.org/10.1289/ehp.01109239
83. Zamoiski RD, Cahoon EK, Michal Freedman D, Linet MS. Self-reported sunscreen use and urinary benzophenone-3 concentrations in the United States: NHANES 3–2006 and 9–2012. *Environ Res*. 2015;142:563-567. https://doi.org/10.1016/j.envres.2015.08.006
84. Mao JF, Li W, Ong CN, He Y, Jong MC, Gin KY. Assessment of human exposure to benzophenone-type UV filters: a review. *Environ Int*. 2022;167:107405.https://doi.org/10.1016/j.envint.2022.107405
85. Wei GL, Li DQ, Zhuo MN, *et al*. Organophosphorus flame retardants and plasticizers: sources, occurrence, toxicity and human exposure. *Environ Pollut*. 2015;196:29-46. https://doi.org/10.1016/j.envpol.2014.09.012
86. Rosolen V, Giordani E, Mariuz M, *et al*. Cognitive performance and exposure to organophosphate flame retardants in children: evidence from a cross-sectional analysis of two european mother-child cohorts. *Toxics*. 2023;11:878. https://doi.org/10.3390/toxics11110878
87. Percy Z, Chen A, Yang W, *et al*. Childhood urinary organophosphate esters and cognitive abilities in a longitudinal cohort study. *Environ Res*. 2022;215:114265.https://doi.org/10.1016/j.envres.2022.114265
88. Doherty BT, Hoffman K, Keil AP, *et al*. Prenatal exposure to organophosphate esters and cognitive development in young children in the Pregnancy, Infection, and Nutrition Study. *Environ Res*. 2019;169:33-40. https://doi.org/10.1016/j.envres.2018.10.033
89. Vuong AM, Percy Z, Yang W, *et al*. Gestational organophosphate esters (OPEs) and executive function in adolescence: the HOME Study. *Environ Res*. 2024;263:120239.https://doi.org/10.1016/j.envres.2024.120239
90. Percy Z, Vuong AM, Xu Y, *et al*. Prenatal exposure to a mixture of organophosphate esters and intelligence among 8-year-old children of the HOME Study. *Neurotoxicology*. 2021;87:149-155. https://doi.org/10.1016/j.neuro.2021.09.005
91. Zhao Y, Liu W, Zhang D, *et al*. Association between organophosphorus flame retardants exposure and cognitive impairment among elderly population in southern China. *Sci Total Environ*. 2022;848:157763. https://doi.org/10.1016/j.scitotenv.2022.157763
92. Carreras G, Miccinesi G, Wilcock A, ACTION consortium, *et al*. Missing not at random in end of life care studies: multiple imputation and sensitivity analysis on data from the ACTION study. *BMC Med Res Methodol*. 2021;21:13. https://doi.org/10.1186/s12874-0–01180-y

Exposome, 2025, 5, 1–12
https://doi.org/10.1093/exposome/osaf001
Research Article