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Association of plastic-associated chemicals with Alzheimer's disease amyloid-β and cognitive status

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Abstract

Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) for ~20 years prior to dementia onset. Phthalates, routinely added to plastics to increase flexibility, and bisphenol monomers, have been shown to interfere with neural activity/brain function. Phthalate and bisphenol exposure did not show association of individual urinary biomarkers with Aβ or clinical phenotype (mild cognitive impairment (MCI)/AD). Assessing biomarkers in quartiles, low mono(2-ethylhexyl) phthalate (MEHP), but not other biomarkers of di(2-ethylhexyl) phthalate (DEHP), was associated with Aβ+ and with having MCI/AD ($q < 0.05$), while high Bisphenol S (BPS) was associated with Aβ+ ($q < 0.05$). Mixture analysis shows significant association with MCI/AD but not Aβ.

Keywords

Alzheimer's disease, AIBL, biomarkers, bisphenol, cognition, phthalates

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Introduction

Late onset Alzheimer's disease (AD) has no known specific genetic cause, and only a few genetic risk factors are associated with significantly increased risk of disease. The disease has a long lead time between beginnings of amyloid-β (Aβ) accumulation, and the onset of clinical symptoms, and it is anticipated that many lifestyle factors may contribute towards the disease process. One specific lifestyle factor which is not controlled through typical interventions is the ingestion of plastic-associated chemicals such as phthalates and bisphenols.

Phthalates (ortho-phthalate diesters) are a group of high-volume industrial chemicals used mainly as plasticizers added to increase the flexibility of plastics, especially polyvinyl chloride. Bisphenols are a group of chemicals including bisphenol-A (BPA), with primary application as monomers in the production of polycarbonates and certain epoxy resins. Phthalates and bisphenols are however endocrine disrupting chemicals, and human epidemiological research has linked urinary metabolites to multiple adverse health effects, with strong evidence emerging in recent reviews.[1,2] Phthalate exposure is linked to miscarriage, low birthweight, genital structure in boys, childhood

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neurodevelopment, asthma, type-2 diabetes and insulin resistance, early puberty and endometriosis in women, and semen quality.[2] Bisphenol-A is linked to changed genital structure in girls, type-2 diabetes and insulin resistance, obesity, polycystic ovary syndrome, hypertension and cardiovascular disease,[1] with limited research data available on safety of other bisphenols.[3] There is near ubiquitous exposure to common phthalates and bisphenols across all demographics (CDCP, 2015[4]), but epidemiological research on human health effects of phthalates and bisphenols, as with other plastic-associated chemicals, has mostly focused on younger age groups and not specifically investigated older adults.[3]

Phthalates and bisphenols have been shown previously in animal, and in vitro models to affect cognition, neurobiology, and neurological disease models, via several pathological[5–8] processes. Here we aim specifically to test whether the concentration of phthalate metabolites and bisphenols in the urine, either as individuals or mixtures, is associated with the Aβ protein which accumulates in the brains of those with AD, and whether this association is translated through into the clinical stages of mild cognitive impairment (MCI) and AD.

Methods

Study design and approval

The Australian Imaging, Biomarker & Lifestyle (AIBL) study of aging is a population-based cohort of >3000 individuals aged >60 to assist with prospective research into AD.[9] This study was approved by the institutional ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University, and all volunteers gave written informed consent before participating in the study.

In this research, 191 participants (120 cognitively unimpaired [CU], 40 MCI, and 31 AD) with urine samples and PET-Aβ imaging were randomly selected from the AIBL study for phthalate and bisphenol exposure assessed by measuring urinary metabolite concentrations. The study sample was selected such that the age and gender distribution on the PET-Aβ+ and PET-Aβ- groups were similar. The PET-Aβ status was computed using a Centiloid threshold of ≥25CL to define PET-Aβ positivity. Note that using this threshold, 33.3% of the CU group presented abnormal PET-Aβ levels (≥25CL, Table 1). Specific details regarding PET imaging and derivation of the Centiloid values can be found in[10–12] and for phthalates and bisphenols in the Supplemental Material.

After eliminating biomarkers that were below the quantitative limits of detection for more than 75% of the samples (biomarkers MnOP, BP-AF and BPZ), 17/20 urine biomarkers were kept for analyses: twelve phthalate metabolites, including monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), monobenzyl phthalate (MBzP), mono-iso-butyl phthalate (MiBP), monomethyl phthalate (MMP), mono-iso-nonyl phthalate (MiNP), and monocyclohexyl phthalate (MCHP), and five bisphenols including bisphenol-A (BPA), BP-AP, BPB, BPF, and BPS.

Quality assurance and quality control (QA/QC)

Limits of detection (LoD) were defined as the mean of blank levels plus three times the standard deviation. When a chemical was not detected in the blank samples, instrumental detection limit (IDL) was used to calculate the LoD. LoD for each chemical ranged from 0.015–2.4 ng/mL urine in this study.

Analytical precision. Duplicates were analyzed for 18 urine sample pairs, with all results showing good analytical precision (CV < ≅ 20%).

Analytical accuracy. The analytical accuracy was assessed by the deviation of the measured concentration from the expected concentration. Native-fortified (at 0.5, 2, 5, and 20 ng/mL respectively) synthetic urine samples (n = 4 each), as well as Standard Reference Material #3673, were analyzed. Generally, good analytical accuracy (deviation ≤ ± 20%) was observed, and occasionally fair analytical accuracy (deviation ≤ ± 50%) was observed which mostly occurred with native-fortified synthetic urine samples at 0.5 ng/mL.

A total of 12 field blank samples were analyzed to assess for potential contamination during sample processing. A range of consumables used in the sample collection procedures (V-shaped vials, flat vials, plastic pipette tips, other tips, sterile containers and falcon tubes) were tested for background contamination. One mL of synthetic urine was added in the containers and kept overnight at 4C, then analyzed following the same protocol as participant samples.

Statistical analysis

Demographic and clinical characteristics were compared between PET-Aβ groups using Chi-square (gender, *APOE* ϵ4 allele status and diagnosis) and independent samples t-test (age and Centiloid level). Three main cross-sectional exploratory tests were conducted. First, we sought to determine whether levels of phthalate/bisphenol biomarker differed between PET-Aβ groups (Chi-square: unadjusted, Table 1; generalized linear models (GLMs)[13]: adjusted for age, gender and *APOE* ϵ4, Figure 1). Second, we sought to investigate whether any phthalate/bisphenol biomarker

Table 1. Samples clinical and demographic characteristics separated between Aβ-PET + ve and Aβ-PET−ve groups. The p-values are from testing between Aβ− and Aβ+ groups using Chi-square (gender, APOE ϵ4 allele status, diagnosis and the categorical representation of each of the markers studied) and independent samples t-test (age and Centiloid level).

	Total	Aβ−ve	Aβ+ve	p
Samples (n, %)	191	98 (51.3)	93 (48.7)	-
Gender Male (n, %)	97 (50.8)	48 (49.0)	49 (52.7)	0.6084
Age in years (mean, sd)	71.5 (5.8)	70.9 (4.7)	72.0 (6.8)	0.2016
Centiloid abundance (mean, sd)	50.7 (53.9)	6.8 (14.0)	97.0 (39.7)	<0.0001
***APOE* ϵ4 Carriage (n, %)**	101 (52.9)	35 (35.7)	66 (71.0)	<0.0001
Diagnosis (n, %)				<0.0001
CU	120 (62.8)	80 (81.6)	40 (43.0)	-
MCI	40 (20.9)	15 (15.3)	25 (26.9)	-
AD	31 (16.2)	3 (3.1)	28 (30.1)	-
Biomarkers measurement (n, %)				
MCHP				0.4533
>0.13	81 (42.4)	39 (39.8)	42 (45.2)	-
≤0.13	110 (57.6)	59 (60.2)	51 (54.8)	-
MiNP				0.2578
>0.49	63 (33.0)	36 (36.7)	27 (29.0)	-
≤0.49	128 (67.0)	62 (63.3)	66 (71.0)	-
BPB				0.5235
>0.01	68 (35.6)	37 (37.8)	31 (33.3)	-
≤0.01	123 (64.4)	61 (62.2)	62 (66.7)	-
MMP				0.1156
≤1.25	48 (25.1)	21 (21.4)	27 (29.0)	-
(1.25,2]	54 (28.3)	35 (35.7)	19 (20.4)	-
(2,3.6]	45 (23.6)	20 (20.4)	25 (26.9)	-
>3.6	44 (23.0)	22 (22.4)	22 (23.7)	-
MEP				0.2878
≤13.45	48 (25.1)	20 (20.4)	28 (30.1)	-
(13.45,32.7]	57 (29.8)	34 (34.7)	23 (24.7)	-
(32.7,53.7]	38 (19.9)	18 (18.4)	20 (21.5)	-
>53.7	48 (25.1)	26 (26.5)	22 (23.7)	-
MiBP				0.0177
≤5.55	48 (25.1)	22 (22.4)	26 (28.0)	-
(5.55,8.2]	48 (25.1)	31 (31.6)	17 (18.3)	-
(8.2,12.65]	47 (24.6)	28 (28.6)	19 (20.4)	-
>12.65	48 (25.1)	17 (17.3)	31 (33.3)	-
MnBP				0.0443
≤ 9.35	48 (25.1)	27 (27.6)	21 (22.6)	-
(9.35,13.6]	49 (25.7)	32 (32.7)	17 (18.3)	-
(13.6,19.45]	46 (24.1)	20 (20.4)	26 (28.0)	-
> 19.45	48 (25.1)	19 (19.4)	29 (31.2)	-
MCPP				0.8232
≤ 0.6	52 (27.2)	28 (28.6)	24 (25.8)	-
(0.6,1]	49 (25.7)	25 (25.5)	24 (25.8)	-
(1,1.9]	44 (23.0)	20 (20.4)	24 (25.8)	-
> 1.9	46 (24.1)	25 (25.5)	21 (22.6)	-
MbzP				0.5825
≤ 0.9	51 (26.7)	23 (23.5)	28 (30.1)	-
(0.9,1.7]	48 (25.1)	27 (27.6)	21 (22.6)	-
(1.7,3.55]	44 (23.0)	21 (21.4)	23 (24.7)	-
> 3.55	48 (25.1)	27 (27.6)	21 (22.6)	-
MEHP				0.0891
≤ 0.8	49 (25.7)	19 (19.4)	30 (32.3)	-
(0.8,1.5]	48 (25.1)	24 (24.5)	24 (25.8)	-
(1.5,2.65]	46 (24.1)	24 (24.5)	22 (23.7)	-
> 2.65	48 (25.1)	31 (31.6)	17 (18.3)	-
MEOHP				0.9587

(continued)

Table 1. Continued.

	Total	Aβ−ve	Aβ+ve	p
≤ 3.05	48 (25.1)	24 (24.5)	24 (25.8)	-
(3.05,4.1]	48 (25.1)	26 (26.5)	22 (23.7)	-
(4.1,5.85]	47 (24.6)	23 (23.5)	24 (25.8)	-
> 5.85	48 (25.1)	25 (25.5)	23 (24.7)	-
MEHHP				0.5729
≤ 4.5	51 (26.7)	22 (22.4)	29 (31.2)	-
(4.5,6.6]	49 (25.7)	26 (26.5)	23 (24.7)	-
(6.6,9.6]	45 (23.6)	24 (24.5)	21 (22.6)	-
> 9.6	46 (24.1)	26 (26.5)	20 (21.5)	-
MECPP				0.4759
≤ 4.15	48 (25.1)	24 (24.5)	24 (25.8)	-
(4.15,6.6]	51 (26.7)	25 (25.5)	26 (28.0)	-
(6.6,9.9]	44 (23.0)	27 (27.6)	17 (18.3)	-
> 9.9	48 (25.1)	22 (22.4)	26 (28.0)	-
BPA				0.6367
≤ 0.8	60 (31.4)	33 (33.7)	27 (29.0)	-
(0.8,1.1]	38 (19.9)	16 (16.3)	22 (23.7)	-
(1.1,1.85]	45 (23.6)	24 (24.5)	21 (22.6)	-
> 1.85	48 (25.1)	25 (25.5)	23 (24.7)	-
BPF				0.0724
≤ 0.07	62 (32.5)	24 (24.5)	38 (40.9)	-
(0.07,0.1]	39 (20.4)	25 (25.5)	14 (15.1)	-
(0.1,0.3]	53 (27.7)	28 (28.6)	25 (26.9)	-
> 0.3	37 (19.4)	21 (21.4)	16 (17.2)	-
BPS				0.0101
≤ 0.1	49 (25.7)	33 (33.7)	16 (17.2)	-
(0.1,0.3]	60 (31.4)	24 (24.5)	36 (38.7)	-
(0.3,0.5]	38 (19.9)	23 (23.5)	15 (16.1)	-
> 0.5	44 (23.0)	18 (18.4)	26 (28.0)	-
BP.AP				0.0822
≤ 0.04	65 (34.0)	28 (28.6)	37 (39.8)	-
(0.04,0.2]	32 (16.8)	13 (13.3)	19 (20.4)	-
(0.2,0.6]	51 (26.7)	32 (32.7)	19 (20.4)	-
> 0.6	43 (22.5)	25 (25.5)	18 (19.4)	-

Aβ: amyloid-β; CU: cognitive unimpaired; MCI: mild cognitive impairment; AD: Alzheimer's disease; n: number of samples; sd: standard deviation.

could be used to differentiate between CU and MCI/AD groups (GLM: adjusted for age, gender and *APOE* ϵ4, Figure 1).

For these two sets of tests, each biomarker was assessed as either: binary (MCHP, MiNP, BPB), where ≥35% of the data in each biomarker were < LoD (0 represents participant values < LoD, 1 represents participant values > LoD); or categorical, where <35% of the data in each biomarker were < LoD, the data was divided into quartiles. If the number of values below LoD was between 35–75% (markers that had >75% missing data were removed) then the values < LoD were used as the reference, WHILE if the number of values < LoD was lower than 35% then the marker was divided in its quartiles, using the first quartile as reference (see Table 2).

Lastly, to assess the mixture effects of bisphenols and phthalates on PET-Aβ and clinical status (CU versus MCI/AD), accounting for age, gender and *APOE* ϵ4, we used *gcomp* package in R,[14] employing 200 bootstraps within a Bayesian framework that accounts for biomarker correlations. Due to sample size constraints, our modelling is limited to metabolites with a detection rate exceeding 90%, resulting in a total of 10 metabolites (MMP, MEP, MnBP, MiBP, MCPP, BPS, BPA, MEHHP, MECPP, MEOHP). To facilitate the detection of mixture effects, the sample was divided into five quintiles.

Adjusted odds ratios with 95% confidence intervals (CI) and respective p-values were computed for each urine biomarker separately using GLMs. Further assessment of log transformed continuous values using Censored regression[15] (adjusted for age, gender and *APOE* ϵ4) was used on all biomarkers for comparison to standard GLM models given the large proportion of values less than the LoD. Results obtained from each method were assessed, with p-values adjusted for multiple comparisons using false discovery rate (FDR, q-values). All statistical analyses were performed with the R Statistical Environment version 4.2.0.[16]

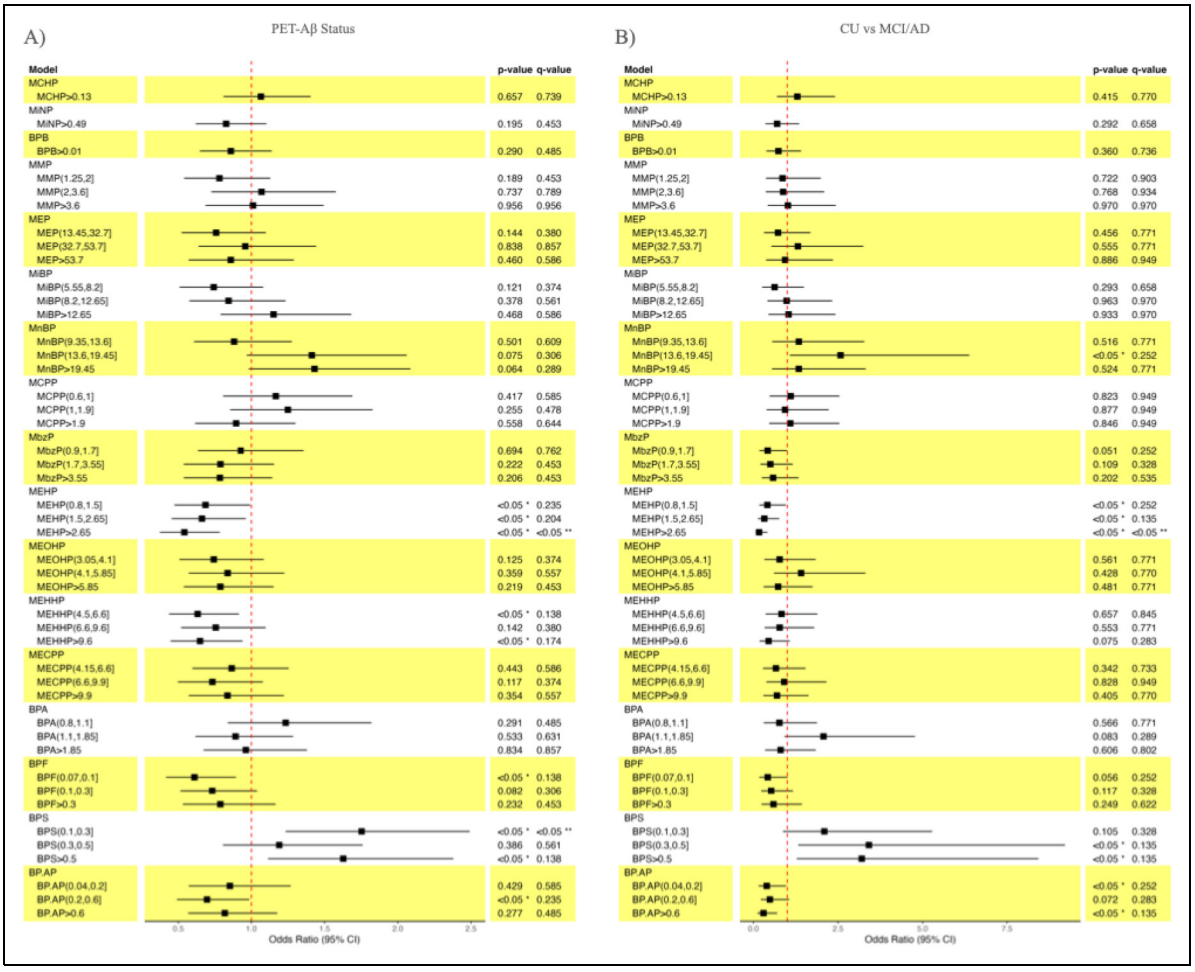

Figure 1. Odd ratios (95% CI) and p/q-values for each categorical biomarker: A) Cross-sectional generalized linear model to investigate association with PET-Aβ status of each categorical biomarker individually and B) Cross-sectional generalized logistic model to check association of each categorical biomarker individually with cognitive status (CU versus MCI/AD). Note that all models were adjusted by gender, age and APOE ϵ4 allele carrier status, the reference was always the first group for each case (0 for the binary markers and the first quartile otherwise), and that the results obtained from each method were assessed, with p-values adjusted for multiple comparisons using false discovery rate (FDR, q-values). CI: confidence interval; CU: cognitively unimpaired; MCI: mild cognitive impairment; AD: Alzheimer's disease.

Results

After excluding those with missing demographic, clinical or urine biomarkers information, 191 participants were included. Table 1 presents demographic and clinical characteristics, categorical distributions of each biomarker for the overall sample and separately for the Aβ-PET groups, and results from cross-sectional exploratory chi-squared tests of biomarker by PET-Aβ status. Three (MiBP, MnBP, and BPS) appeared to be materially different between PET-Aβ groups; however, p-values were only nominally significant ($p < 0.05$).

Among statistical comparisons for PET-Aβ and clinical status, high levels of MEHP (>2.65, compared with low levels [below LoD]) were associated with lower levels of PET-Aβ after adjustment for multiple comparisons (q-value < 0.05), while quartile 2 of BPS (0–0.3, compared with baseline [below LoD]) were significantly associated with PET-Aβ+ (q-value < 0.05). High levels of MEHP were also associated with a decrease in risk of MCI/AD as compared with the CU group (Figure 1). Several other potential associations were observed, but no other significant associations persisted after adjustment for multiple comparisons.

Assessment of the same data using censored regression (Table 2B), did not reveal any further associations with either PET-Aβ groups or between clinical classification.

Lastly, mixture analysis showed that, for PET-Aβ status, quantile-based exposure model estimates an overall mixture effect of 1.19 [95% CI: 0.98–1.43; $p = 0.075$], representing the expected change in PET status associated with a one-

Table 2. A) Limits of detection (LoD) for each of the markers analysed, number and proportion of the total samples that were LoD, and median marker values with their respective interquartile range (IQR) of 25 and 75%. B) Results from censored regression analyses. SE: standard error.

A) Limits of detection				B) Censored regression on quantitative data			
				PET-Aβ status		CU versus MCI/AD	
	LoD Value	Number of LoDs	Median (IQR)	Betas (SE)	p	Betas (SE)	p
MCHP	0.13	110 (58%)	0.13 (0.13–0.30)	0.525 (0.478)	0.272	0.447 (1.071)	0.676
MiNP	0.49	128 (67%)	0.49 (0.49–0.60)	−0.023 (0.021)	0.269	0.015 (0.046)	0.740
BPB	0.01	123 (64%)	0.01 (0.01–0.20)	0.069 (0.175)	0.693	0.420 (0.386)	0.277
MMP	0.16	4 (2%)	2.00 (1.25–3.60)	0.003 (0.012)	0.778	−0.040 (0.032)	0.210
MEP	0.56	0 (0%)	32.70 (13.45–53.70)	0.000 (0.001)	0.936	−0.001 (0.001)	0.502
MiBP	2.41	12 (6%)	8.20 (5.55–12.65)	0.009 (0.007)	0.219	0.000 (0.016)	0.992
MnBP	0.73	0 (0%)	13.60 (9.35–19.45)	0.014 (0.006)	0.011	0.020 (0.014)	0.151
MCPP	0.04	0 (0%)	1.00 (0.60–1.90)	−0.005 (0.008)	0.551	0.008 (0.018)	0.665
MbzP	0.32	22 (12%)	1.70 (0.90–3.55)	−0.009 (0.009)	0.325	0.013 (0.020)	0.516
MEHP	0.65	39 (20%)	1.50 (0.80–2.65)	−0.038 (0.018)	0.033	−0.219 (0.104)	0.035
MEOHP	0.04	0 (0%)	4.10 (3.05–5.85)	−0.016 (0.010)	0.118	−0.042 (0.038)	0.258
MEHHP	0.22	0 (0%)	6.60 (4.50–9.60)	−0.012 (0.006)	0.039	−0.046 (0.026)	0.079
MECPP	0.04	0 (0%)	6.60 (4.15–9.90)	−0.008 (0.007)	0.253	−0.015 (0.018)	0.416
BPA	0.12	2 (1%)	1.10 (0.80–1.85)	0.016 (0.036)	0.651	0.012 (0.078)	0.875
BPF	0.07	62 (32%)	0.10 (0.07–0.30)	0.029 (0.091)	0.751	0.063 (0.199)	0.751
BPS	0.03	7 (4%)	0.30 (0.10–0.50)	0.057 (0.102)	0.580	0.170 (0.223)	0.445
BP.AP	0.04	65 (34%)	0.20 (0.04–0.60)	−0.139 (0.114)	0.221	−1.034 (0.424)	0.015

quintile increase in all exposures simultaneously. For clinical classification, the quantile-based exposure model yields a statistically significant overall mixture effect of 1.30 [95% CI: 1.03–1.64; $p = 0.032$] (Supplemental Table 1).

Discussion

In the current project we tested whether the presence of phthalates or bisphenols in the urine of participants from the AIBL study of aging was associated with either PET-Aβ+, or the presence of MCI/AD. Defining biomarkers into quartile groups identified two markers (MEHP & BPS) statistically associated with PET-Aβ status and clinical group ($q < 0.05$) for at least one quartile of exposure. For MEHP, the nature of the relationship was counter to what was expected, with higher levels being associated with less PET-Aβ protein in the brain and being CU. This should be interpreted with caution. While similar trends were seen for other, more reliable, biomarkers of DEHP exposure, none of these other metabolites (MEHHP, MEOHP, or MECPP) met conventional thresholds for statistical significance. For BPS, higher levels were statistically associated with clinical status, however the 95% CIs for both marker associations were large, and these did not withstand correction for multiple comparisons (Figure 1). No statistically significant associations were observed in censored regression analyses in relation to either the PET-Aβ status or clinical group.

In a previous study assessing phthalates against neurofilament light (NfL), a marker of neurodegeneration[17] found the opposite relationship, with an increase in NfL levels with MEHP levels above 0.618. Regarding BPS, this is the first study that has found a significant association with AD in humans. Many studies have demonstrated the potential neurotoxic effects of BPS, and to a greater extent BPA, however none of these were in human participants.[18] Thus, further work needs to be performed to validate these findings, especially since BPS has replaced BPA in the manufacturing of plastic packaging given BPS is considered a safer alternative.

Evidence for associations between current exposure to phthalates in the elderly as well as those with neurodegenerative disease is limited and inconsistent. Modelling of mixed phthalate metabolites in US elderly ($n = 35, > 60$ years old) suggested both positive and negative associations with cognitive function.[19,20] A study examining phthalates in CSF in a small number of patients with dementia with Lewy bodies (DLB) showed that bis(2-ethylhexyl) phthalate was more abundant in DLB patients than those without.[21] Current evidence on bisphenols is largely limited to mechanistic experimental, rather than human, studies.[22] In addition, studies on early exposure and later onset are not yet available. Moreover, a limitation of these types of studies is that it is challenging to feasibly account for all possible earlier external type of neurotoxicant exposures as this information is self-reported and difficult to measure and obtain.

In the present study, sample size was limited to detect moderate and above associations, so a key limitation is that smaller associations with disease burden may not be identified. The proportion of analytes where the measurement was below the LoD further reduced the power of the study. The analyses also utilized a method designed for data with many values below the LoD,[14] and no further associations were found.

In summary, a set of 17 phthalates and bisphenols were tested in a widely characterized study of aging in Australia, where two (MEHP and BPS) were found to be associated with either PET-Aβ status or with clinical classification, although the relationship for MEHP was counter to what was expected. We also find evidence suggesting that chemical mixture exposure to ten metabolites has an association with clinical classification. Further work needs to be conducted to examine associations in a larger population study.

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Ethical considerations

This study was approved by the institutional ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University.

Consent to participate

All volunteers gave written informed consent before participating in the study.

Author contributions

Rodrigo Canovas: Formal analysis; Methodology; Project administration; Validation; Writing – original draft; Writing – review & editing.
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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

Data can be made available on request.

Supplemental material

Supplemental material for this article is available online.

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