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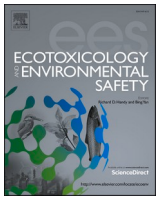

Childhood blood-lead level predicts lower general, non-selective hippocampal subfield volumes in midlife

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ABSTRACT

Millions of adults and children are exposed to high levels of lead, a neurotoxicant, each year. Recent evidence suggests that lead exposure may precipitate neurodegeneration, particularly if the exposure occurs early or late in life, with unique alterations to the structure or function of specific subfields of the hippocampus, a region involved in memory and Alzheimer's disease. It has been proposed that specific hippocampal subfields may thus be useful biomarkers for lead-associated neurological disease. We turned to a population-representative New Zealand birth cohort where the extent of lead exposure was not confounded by social class (the Dunedin Study; born 1972–1973 and followed to age 45) to test the hypothesis that early life lead exposure (blood-lead level at age 11 years) is associated with smaller MRI-assessed gray matter volumes of specific subfields of the hippocampus at age 45 years. Among the 508 Dunedin Study members with childhood lead data and adult MRI data passing quality control (93.9 % of those with lead data who attended the age-45 assessment wave, 240[47.2 %] female), childhood blood-lead levels ranged from 4 to 31 μg/dL (M[SD]=10.9[4.6]). Total hippocampal volumes were lower among adults with higher childhood blood-lead levels (b=-102.6 mm^3 per 5 ug/dL-unit greater blood-lead level, 95 %CI: −175.4 to −29.7, p=.006, β=-.11), as were all volumes of the 24 hemisphere-specific subfields of the hippocampus. Of these 24 subfields, 20 demonstrated negative lead-associations greater than β=-.05 in size, 14 were statistically significant after adjustment for multiple comparisons (p_{FDR}<.05), and 9 remained significant after adjustment for potential confounders *and* multiple comparisons. Children exposed to lead demonstrate smaller volumes across all subfields of the hippocampus in midlife. The hypothesis that lead selectively impairs specific subfields of the hippocampus, or that specific subfields may be markers for lead-associated neurological disease, requires further evaluation.

1. Introduction

Lead is a neurotoxicant in wide industrial and commercial use. Evidence suggests that lead exposure across the lifespan may elevate risk for neurodegenerative disease in old age, particularly if the exposure occurs very early (Reuben, 2018) or very late (Shih et al., 2007) in life. This risk remains under characterized: dose-response associations for clinical outcomes, mechanisms of effect, factors that influence individual differences, and the dynamics of exposure timing and degeneration onset have not been established.

In this regard, the interaction of lead exposure with the structural integrity of the hippocampus has emerged as an important research focus owing to the hippocampus's involvement in memory and Alzheimer's disease and related dementias (ADRDs), as well as emerging evidence that this region may demonstrate specific vulnerability to lead. Specifically, in rodent models, low-level early life lead exposure has

Abbreviations: MRI, Magnetic Resonance Imaging; MSD, MeanStandard Deviaion.

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been linked to later differential metabolism, (Yun et al., 2019) gene expression, (Li et al., 2021) and microstructural integrity (Lindquist et al., 2015) in the hippocampus. Two past observational studies, meanwhile, have identified smaller total hippocampal volumes and altered metabolism among adults occupationally exposed to lead (Jiang et al., 2008; Weisskopf et al., 2007). Finally, our team has previously reported smaller total hippocampal volume among adult members of the population-representative New Zealand birth cohort, the Dunedin Study, who were more exposed to lead as children (Reuben et al., 2020). In that investigation, however, findings suggested that lead-brain-structure differences were not specific to the hippocampus. Among adult members of the Dunedin Study (N=508 analytic sample) who received lead testing in childhood (age 11) and underwent structural MRI in adulthood (age 45), higher childhood blood-lead levels were associated with smaller volumes of all subcortical brain regions examined (12 of 12), not just the hippocampus.

Two studies, one in rodents (Meng et al., 2003) and one new investigation of blood-lead levels among male workers in the smelting industry in Xi'an, China (N=49; mean age=43.1), (Shi et al., 2023) have recently suggested that lead exposure may selectively impair specific subfields of the hippocampus. If this is true, it would suggest that earlier examination of total hippocampal volume in relation to childhood lead exposure in the Dunedin Study may have masked differences at the subfield level – differences that may be relevant to understanding the pathogenicity of lead in the aging brain and specific cellular mechanisms that may be future targets for intervention. Notably, recent studies have suggested that hippocampal subfield volumes display differential associations with ADRD pathology, with specific subfields outperforming total hippocampal volume in clinical tasks such as predicting progression of patients with mild cognitive impairment to full dementia (Khan et al., 2015). As the authors of the Xi'an study noted, their selective subfield findings also suggest they may have found specific "predictive imaging markers for neurological damage associated with high lead exposure." (Shi et al., 2023)

In an attempt to replicate and expand the recent report from Xi'an, China, here we further probe previously reported associations between childhood blood-lead levels and adult total hippocampal volume in the Dunedin Study (Reuben et al., 2020) with an investigation expanded to all 12 hippocampal subfields (Fig. 1) (Shi et al., 2023). Following the methods of Shi et al., (Shi et al., 2023) we report findings separately for left and right hemisphere subfields.

2. Methods

2.1. Study design and population

Participants were members of the Dunedin Study. The full cohort comprises all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible based on residence in the province and who participated in the first assessment at age 3. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island (Poulton et al., 2015). On adult health, the cohort matches the New Zealand National Health and Nutrition Survey on key indicators (e.g. body mass index, smoking, visits to a physician) (Poulton et al., 2015) and the NZ Census of citizens of the same age on educational attainment (Richmond-Rakerd et al., 2020). The cohort is primarily white (as self-described using fixed categories, assessed to determine population-representativeness). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, (Poulton et al., 2015) with the most recent data collection completed in April 2019, at age 45 years. Owing to increasing national and international research interest in the early 1980s into the potential harms of lead exposure, (Wilson and Horrocks, 2008) blood-lead was measured in the cohort at the age 11 assessment (1983–1984) (Silva et al., 1988). For the current study, archived childhood blood-lead data were linked to MRI measures of hippocampal subfield volume at age 45 years.

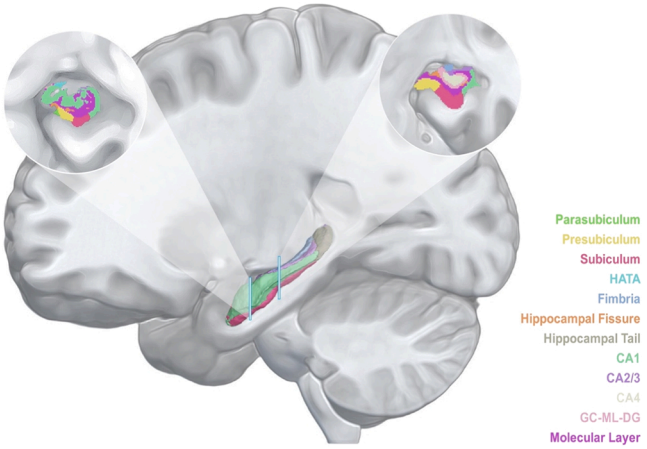

Fig. 1. The 12 subfields of the hippocampus.

2.2. Measures

2.2.1. Childhood blood-lead levels

Approximately 30 ML of venous blood was collected at age 11 years from each Study member who participated in the assessment carried out at the Research Unit and who freely agreed to give blood; 579 of the 803 children (72 %) who attended the Unit agreed to give blood. A further 122 children were assessed in their schools, where blood could not be drawn; these children tended to live outside city limits. Whole blood samples were analyzed through graphite furnace atomic absorption spectrophotometry. Blood-lead is reported in micrograms per deciliter (1 μg/dL=0.0483 μmol/l). Details on the method of blood collection, storage, and analysis have been previously described (Silva et al., 1988). Study members, researchers, and staff at midlife follow-up were blind to archival blood-lead levels (Wilson and Horrocks, 2008).

2.2.2. Hippocampal subfield volumes

At age 45, Study members were scanned using a MAGNETOM Skyra 3 T scanner (Siemens Healthcare GmbH) with a 64-channel head coil at the Pacific Radiology imaging center in Dunedin, New Zealand. High resolution T1-weighted images were obtained with an MP-RAGE sequence with the following parameters: TR = 2400 ms; TE = 1.98 ms; 208 sagittal slices; flip angle, 9°; FOV, 224 mm; matrix =256×256; slice thickness = 0.9 mm with no gap (voxel size 0.9×0.875×0.875 mm); and total scan time = 6 minutes and 52 seconds. Structural MRI data were analyzed using the recon-all pipeline in FreeSurfer 6.0, followed by the segmentHA_T1 function (Iglesias et al., 2015) to derive hemisphere-specific estimates of grey matter volumes for the following hippocampal subfields: hippocampal tail, subiculum, cornu ammonis (CA) 1, CA3, CA4, hippocampal fissure, presubiculum, parasubiculum, molecular layer HP, GC-ML-DG, fimbria, HATA. Total bilateral hippocampal grey matter volume estimates were extracted from the automatic segmentation ("aseg") step of recon-all, and the segmentations were visually inspected for quality control to ensure accurate delineation of the hippocampus (Reuben et al., 2020; Knodt et al., 2022). Only individuals passing quality control for whole-brain analyses were included in the current analytic sample of adults with archived childhood blood-lead data and adult MRI data (N=508). Among the complete sample of cohort members who received MRI scans (N=875), 4 were excluded due to major incidental findings or previous injuries (e.g., large tumors or extensive damage to the brain/skull), 9 due to missing field map scans, and 1 due to poor surface mapping.

2.3. Statistical analysis

Associations between childhood blood-lead levels and adult hippocampal subfield volumes were tested using ordinary least squares (OLS) regression where each subfield volume was regressed independently onto childhood blood-lead levels and the covariate of sex. Additional models to rule out potential confounding factors adjusted for covariates previously published in investigations of childhood blood-lead levels and adult brain volumes, (Reuben et al., 2020) including sex, childhood family socioeconomic status, and maternal IQ. Family socioeconomic status was assessed via the Elley-Irving scale assigning parental occupations into one of six status groups [6=professional; 1=unskilled laborer] based on required education and expected compensation (Elley and Irving, 1976). (A continuous socioeconomic status scale was not available during the Study members' childhoods.) Maternal IQ was assessed via the Science Research Associates verbal test (Thurstone and Thurstone, 1973) administered to Study mothers when participants were 3 years old.

Secondary study analyses additionally adjusted for total bilateral hippocampal volume to test whether lead-hippocampal-subfield associations reflected hippocampal-wide or subfield-specific differences. Senstitivty tests utilized total intracranial volume in place of total hippocampal volume in these analyses to better reflect the analytic approach of Shi et al (Shi et al., 2023).

Lead level was analyzed as a continuous measure. Statistical-effect sizes are presented in clinically meaningful 5 μg/dL units, approximately 1 SD in the cohort and a multiple of the historic international "level of concern" (10 μg/dL) as well as the US-Centers for Disease Control (CDC) reference value for elevated lead levels at the time of adult follow-up and neuroimaging (5 μg/dL). Mean hippocampal subfield volumes for Study members above the historic level of concern were also compared to those at or below (≤10 μg/dL) using Student's t-test. With an analytic sample of 508, analyses were potentially sensitive to statistical-effect sizes as low as Cohen's $f^2 = 0.02$ at power = 0.80. The threshold for statistical significance was 2-tailed, p-value <.05. We additionally applied the Benjamini-Hochberg FDR correction for multiple comparisons (Benjamini and Hochberg, 1995). Analyses were conducted using Stata v16.1.

This study involved analysis of existing data rather than new data collection. The project premise and analysis plan were pre-registered (http://tinyurl.com/9bzetz7x). Findings were checked for reproducibility by an independent data-analyst (ARK), who recreated the code by working from the manuscript and applied it to a fresh dataset. This report follows STROBE reporting guidelines (von Elm et al., 2007).

3. Results

As previously reported, (Reuben et al., 2020) of the 579 original Study members who were tested for blood-lead level at age 11 years, 541 attended the age-45 assessment (representing 96.0 % of the lead-tested cohort members still alive), 508 of whom (93.9 %, 240[47.2 %] female) also had MRI data passing quality control. Participants alive at age 45 with (N=564) and without childhood blood-lead data (N=433) did not differ to a statistically significant extent in terms of their mothers' IQs or their childhood family socioeconomic status (Reuben et al., 2020). As with the full lead-tested cohort, (Reuben et al., 2020) there was no significant childhood socioeconomic gradient in lead exposure within the N=508 analytic sample: participants in the current study with high childhood blood-lead levels belonged to all socioeconomic groups as children (Pearson's r=-.015 between blood-lead level and family socioeconomic status, p=.736). Supplement Table S1 presents Study member characteristics on key study variables.

Within the analytic sample, childhood blood-lead levels ranged from 4 to 31 μg/dL (mean=10.9, SD=4.6) (Fig. 2); 230 participants (45.3 %; 93[40.4 %] female) had blood-lead levels above the historic international "level of concern" (10 μg/dL) and 478 (94.1 %; 223[46.7 %] female) had childhood levels that would be considered above the CDC reference value for elevated lead-levels at the time of brain imaging, in 2018 (5 μg/dL) (US-Centers for Disease Control, 2017). Females had lower lead-levels than males (mean difference −0.95 μg/dL; t=-2.328, p=.020) (Fig. 2).

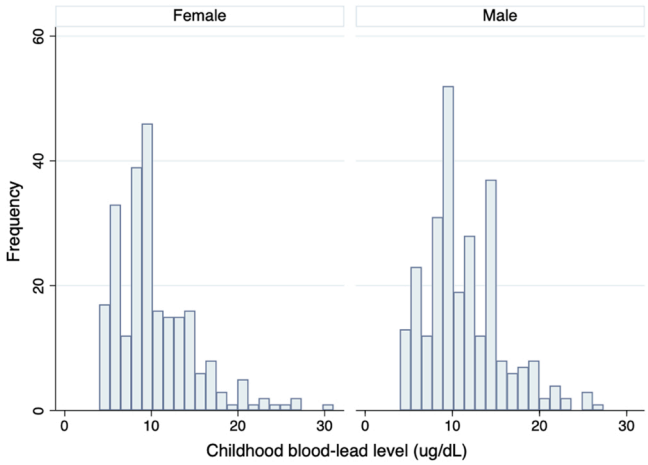

Fig. 2. Childhood blood-lead levels (age 11 years) in the Dunedin Study current analytic sample (N=508).

Mean (SD) total bilateral grey matter volume of the hippocampus was 8670.0 (827.0) mm^3. Total hippocampal volumes were lower among adults with higher childhood blood-lead levels. After adjustment for sex, each 5 μg/dL-unit greater childhood blood-lead level was associated with a 102.6 mm^3 lower total hippocampal volume (95 %CI: −175.4 to −29.7, p=.006, β=-.11), an approximately 1 % deficit per 5 μg/dL-unit greater childhood blood-lead level.

Table 1
Associations of blood-lead levels at age 11 years with hippocampal subfield volumes (mm^3) at age 45 years (N=508).

	Adjusted for sex			
	b	**95 % CI**	***p*-value**	**FDR-corrected *p*-value**
Left				
Hippocampal tail	-6.10	(-12.49, 0.28)	.061	.081
Subiculum	**-4.94**	**(-9.44, −0.44)**	**.032**	**.051**
CA1	***-8.90***	***(-16.08, −1.72)***	***.015***	***.033***
Hippocampal fissure	-0.38	(-2.47, 1.70)	.719	.784
Presubiculum	-3.00	(-7.02, 1.04)	.145	.174
Parasubiculum	-0.63	(-1.73, 0.47)	.260	.297
Molecular layer HP	***-7.78***	***(-13.27, −2.28)***	***.006***	***.018***
GC-ML-DG	***-3.37***	***(-6.15, −0.58)***	***.018***	***.033***
CA3	***-3.27***	***(-5.96, −0.59)***	***.017***	***.033***
CA4	**-2.67**	**(-5.23, −0.12)**	**.040**	**.058**
Fimbria	-0.17	(-1.43, 1.09)	.794	.796
HATA	***-0.98***	***(-1.79, −0.17)***	***.018***	***.033***
Right				
Hippocampal tail	**-6.83**	**(-13.38, −0.28)**	**.041**	**.058**
Subiculum	***-7.35***	***(-11.30, −3.40)***	***<.001***	***.002***
CA1	***-10.43***	***(-17.87, −3.00)***	***.006***	***.018***
Hippocampal fissure	***-2.43***	***(-4.60, −0.26)***	***.028***	***.048***
Presubiculum	***-4.25***	***(-7.37, −1.14)***	***.008***	***.021***
Parasubiculum	-0.85	(-1.90, 0.20)	.112	.141
Molecular layer HP	***-9.05***	***(-14.38, −3.72)***	***.001***	***.008***
GC-ML-DG	***-4.69***	***(-7.55, −1.84)***	***.001***	***.008***
CA3	***-4.04***	***(-6.93, −1.15)***	***.006***	***.018***
CA4	***-4.03***	***(-6.64, −1.42)***	***.003***	***.014***
Fimbria	-0.17	(-1.46, 1.12)	.796	.796
HATA	***-1.50***	***(-2.43, −0.57)***	***.002***	***.012***

Note. Statistical effect-size estimates depict mm^3-unit change in subfield volumes for each 5-μg/dL higher level of blood lead in childhood. Statistically significant associations (p<.05) are highlighted in bold text, with italics added for those surviving FDR correction.

All hippocampal subfield volumes (Fig. 1) were also lower among adults with higher childhood blood-lead levels (Table 1). After adjustment for sex, childhood blood-lead level was associated with smaller volumes of all 24 hemisphere-specific hippocampal subfields, 17 of which demonstrated statistically significant associations at α=.05, with 14 surviving FDR correction. 20 subfields demonstrated negative associations stronger than β=-.05 in size (approximately b=-.80 mm^3). In both hemispheres, lead associations were the largest for CA1 (left CA1 b=-8.90 mm^3, 95 %CI: −16.08 to −1.72, p=.015, p_{FDR}=.033; right CA1 b=-10.43 mm^3, 95 %CI: −17.87 to −3.00, p=.006, p_{FDR}=.018). Additional adjustment for the covarites of sex, childhood family socioeconomic status, and maternal IQ (Supplement Table S2) did not meaningfully alter the pattern of results, although effects sizes were modestly attenuated (by between b=|0.01| to b=|0.77|mm^3) and 2 subfield associations were no longer statistically significant at α=.05. (9 total subfield associations survived FDR correction in the full covariate-adjusted models).

Reflecting the tendency for global deficits across hippocampal subfield volumes, only two subfields remained significantly associated with childhood blood-lead levels after statistical adjustment for sex and total bilateral hippocampal volume: the right subiculum (adjusted b=-2.85, 95 %CI: −5.44 to −0.26, p=.031) and the right HATA (adjusted b=-0.81, 95 %CI: −1.57 to −0.54, p=.036). Neither of these survived FDR correction (p_{FDR} >.05). Sensitivity tests correcting for total intracranial volume rather than bilateral hippocampal volume yielded 9 significant subfields, 4 of which survived FDR correction: the right subiculum, molecular layer HP, GC-ML-DG, and HATA (Supplement Table S3).

Sex-stratified analyses did not identify any notable patterns in lead-subfield-association differences (Supplement Table S4). Lead-associated subfield-volume deficits were greater among females than males in 15 of the 24 hemisphere-specific subfields, and greater among males than females in 9 of the subfields.

4. Discussion

In this study of childhood lead exposure and adult hippocampal subfield volumes among members of a population-representative birth cohort followed to midlife, childhood blood-lead level was associated with lower volumes of all subfields of the hippocampus, two-thirds statistically significantly and more than half surviving FDR correction for 24 tests. Results suggest that recent reports of specific subfield differences among occupationally lead-exposed adult men in Xi'an, China, may be specific to that population, study, or lead-exposure profile. The suggestions that specific atrophy in the left GC-ML-DG and CA4 subfields may be "predictive imaging markers for neurological damage associated with high lead exposure" requires continued evaluation.

In their examination of a highly lead-exposed group (blood-lead level greater than or equal to 30.0 μg/dL) compared to a "control group" (blood-lead level less than 10 μg/dL), Shi et al. (2023) found no significant differences in total hippocampal volume between the two groups but reported significantly smaller volumes of the left GC-ML-DG and CA4 subfields. In our study, the volumes of these two subfields showed negative associations with blood-lead levels that were no greater or lesser than most other hippocampal subfields. Volumes of the left and right CA1 were smallest, and volumes of the right subiculum and right HATA were smaller independently of total hippocampal volume, although these associations did not survive FDR correction. These differences between the current study and the Xi'an study may reflect power differences (and thus the likelihood of type II error rates) or else the influence of differential lead-exposure timing (primarily adulthood in Xi'an versus childhood in Dunedin) on hippocampal structure. In support of the latter, a rodent study that investigated early life lead exposure influence on hippocampal subfield integrity over the lifespan identified lead-hippocampal-subfield integrity differences that varied over time, with early differences giving way to more global deficits as the study rodents aged (Meng et al., 2003). However, the CA1 was identified in that study as showing more severe structural impairments than other regions – which is a finding echoed, moderately, in the current study.

There are important differences between this study and the Xi'an study. First, as noted above, their participants were tested for lead exposure in adulthood, concurrent with MRI, whereas the Dunedin Study members were tested for lead exposure in childhood but underwent MRI in midlife. Second, their sample had higher lead exposures (mean blood-lead level of 21.34 ±17.85 μg/dL in Xi'an compared to 10.9 ±4.6 μg/dL in Dunedin) and were investigated using group comparisons rather than the current study's method of continuous regression. Third, their study was restricted to a small sample of men, whereas the Dunedin Study is population-representative and includes equal numbers of men and women.

There are limitations to the current study. First, it was observational and cannot establish causation. Second, it was conducted in only one cohort from one country and should be replicated in other samples in other countries. Third, adult lead-levels contemporaneous with MRI imaging were not assessed, nor was cumulative lead exposure across adulthood. Fourth, the small size of many hippocampal subfields makes them challenging to resolve at the scanning resolution of our protocol (voxel size 0.9×0.875×0.875 mm^3) as well as that of Shi et al. (1×1×1 mm^3) (Shi et al., 2023). Findings regarding hippocampal subfields segmented at this resolution should be interpreted with caution. Higher spatial-resolution imaging of the hippocampus will be necessary to confirm the current results in future studies.

5. Conclusion

Children exposed to lead demonstrate smaller volumes across all subfields of the hippocampus in midlife. The hypothesis that specific subfields may be useful as predictive imaging markers for lead-associated neurological damage requires further evaluation.

Ethics

The Dunedin Study Phase45 was approved by the NZ-HDEC (Health and Disability Ethics Committee) and the Duke Campus IRB and Duke Medical School IRB. The study protocol was approved by the institutional ethical review boards of the participating universities and was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Study members (or their legal guardian when they were children) gave written informed consent before each assessment.

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CRediT authorship contribution statement

Ahmad Hariri: Writing – review & editing, Supervision, Project

administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Aaron Reuben:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **David Ireland:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Annchen R. Knodt:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aaron Specht:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **Sandhya Ramrakha:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Terrie Moffitt:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Avshalom Caspi:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Ahmad Hariri reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.116658.

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