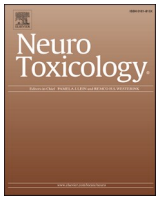
Neurotoxicology 113 (2026) 103404

Contents lists available at ScienceDirect

Neurotoxicology

journal homepage: www.elsevier.com/locate/neuro



Schoolchildren's exposure to potentially toxic metals/metalloids and cognitive impairments in communities of the Brazilian Amazon new agricultural frontiers

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ARTICLE INFO

Edited by Pam Factor-Litvak

Keywords:
Children
Lead
Cognition
Amazon
Agriculture frontier
Mercury

ABSTRACT

Brazilian Amazon communities near new agricultural frontiers are affected by the extensive use of pesticides and dust exposure due to soil erosion. This study investigated the exposure to potentially toxic metals/metalloids and associations with cognitive impairments in Amazonian children living near new agricultural frontiers (soybean crops). This cross-sectional study was conducted in six communities in the Santarém plateau, State of Pará, Brazil. During the 2024 rainy season soy plantation, we collected cubital blood samples of 69 children aged 6–12 years. Metals/metalloids were analyzed by inductively coupled plasma mass spectrometry (ICP-MS). Cognitive evaluation was performed in 53 children using Raven Colorful Matrix, NEPSY II, and FDT tests. Blood lead (PbB) median (range) was 1.9 μg/dL (0.6–40.1), 14.3 % above 3.5 μg/dL. Total blood mercury (THgB) concentrations were 2.11 μg/L (0.45–17.07), of which 17.4 % were above the reference level of 5 μg/L. Non-linear and linear associations were evaluated between metal levels and cognitive outcomes, adjusting for children's age, sex, and maternal education. OLS regressions detected a significant inverse association between Log_2PbB levels and the verbal domain scores (β= −2.71, 95 %-CI: −4.46 to −0.95), which was also non-linearly negatively associated with Raven raw scores. Log_2Hg levels were negatively associated with Raven percentile scores (β= −5.05, 95 %-CI= −10.20–0.11), with Se levels significantly affecting the association. Amazonian children are vulnerable to cognitive impairments associated with lead exposure, likely originating from foods cultivated in naturally Pb-rich soils, and to mercury exposure resulting from a diet rich in contaminated fish.

1. Introduction

The Amazon rainforest has long been under substantial national and international pressure from a variety of human activities—including logging, mining, hydropower development, and agriculture—each carrying important environmental, economic, social, and health risks (Soumis et al., 2000). Over the past decades, scientific research has increasingly documented early neurotoxic effects associated with environmental exposures to mercury (Hg) and lead (Pb) in this region (Fillion et al., 2011; Santos-Lima et al., 2020; Hernandez-Bonilla et al., 2016). In the Amazon, such exposures generally occur under two main scenarios: (i) Hg exposure through consumption of contaminated fish resulting from artisanal and small-scale gold mining (ASGM) activities, In the Amazon, such exposures generally occur under two main scenarios: (i) Hg exposure through consumption of contaminated fish resulting from artisanal and small-scale gold mining (ASGM) activities,

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https://doi.org/10.1016/j.neuro.2026.103404
Received 1 October 2025; Received in revised form 7 January 2026; Accepted 10 February 2026
Available online 11 February 2026
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and Pb exposure reportedly through the consumption of cassava flour in riverine communities (Barbosa et al., 2009), and possibly from other cultivated vegetables. Also, from dust generated during the land preparation, and (ii) pesticide exposure in small agricultural communities located near large-scale soybean monocultures (Passos et al., 2018; Caldas et al., 2015).

The early years of a child's life are marked by significant development. This period is of high sensitivity to environmental influences such as poverty, housing, quality, and family structure (Pantoja et al., 2018). These authors suggest that identifying environmental risk factors and delayed neurodevelopment would be essential for a healthy development. Regarding chemical exposures, other authors argue that in some Amazonian river basins hair Hg concentrations are above the international recommended levels, which are also influenced by the geographical locations of prenatal and/or post-natal development (Freitas et al., 2019). Indeed, methyl mercury neurotoxicity in Amazonian children downstream from gold mining sites has long been reported (Grandjean et al., 1999). At that time, these authors claimed that Hg pollution seemed sufficiently severe to cause adverse effects on brain development. However, prenatal exposure levels were unknown, even if average exposure levels probably had not changed during the recent years before the study. Since then, several other investigations have been conducted, such as Santos et al. (2000), Dutra et al. (2012), de Oliveira et al. (2018), Santos-Lima et al. (2020), among others, all of them putting into evidence the varied health risks posed by Hg environmental exposures during childhood and adolescence.

On the other hand, and concomitantly, Pb exposures among children from local communities of the same Amazon basin have also been occurring over at least the past ten years (Anticona et al., 2012). In their study, these authors concluded that older age, male gender, and mothers' blood lead (PbB) levels $\geq$ 10 μg/dL were the main risk factors for elevated PbB levels in the examined children. The higher risk in boys 7–17 years suggested that exposure could be related to specific activities in their study group, such as fishing and hunting. Continuous monitoring of PbB levels in the Corrientes River population in the Peruvian Amazon was strongly recommended. In addition to these native exposures, other authors have more recently revealed human PbB levels as the first evidence of environmental exposure to industrial pollutants in the Amazonian context (Queiroz et al., 2019).

It is important to underscore that these Hg and Pb exposures do not occur independently or separately. However, they compose a scenario of multiple environmental co-exposures in the vast Amazon basin (Lucchini et al., 2025). Indeed, these authors point out that cross-sectional studies among indigenous and traditional communities consistently demonstrate associations between Hg biomarkers and neurocognitive and neuromotor impairments. In addition, and importantly, they also indicate that co-exposures to microplastics and agrochemicals have increasingly been reported in the region, raising concerns over synergistic toxic effects. Nevertheless, the scientific evidence on these combined exposures remains fragmented and insufficient.

In the context of new agricultural frontiers in a country of continental dimensions such as Brazil, pesticide exposure should be taken into account. Among these, some authors have reported the use of dithiocarbamate-based fungicides in crops from the Santarém Plateau, such as mancozeb (Schwamborn, 2019). This compound contains manganese (Mn) as a coordination element. Several studies have assessed human exposure, particularly in children, to this fungicide in different agricultural settings, including the ISA birth cohort in Costa Rica (Mora et al., 2018). Although Mn is an essential micronutrient, elevated levels in the body have been consistently associated with adverse neuropsychological outcomes in both children and adults, especially when hair manganese is used as a biomarker (Menezes-Filho et al., 2011; Conejo-Bolaños et al., 2024; Viana et al., 2014). Building on this evidence, the present study aims to evaluate children's exposure to potentially toxic metals and metalloids in rural Amazonian communities located near expanding soybean monocultures and to investigate whether such exposures, primarily to lead and mercury, are associated with impairments in cognitive performance.

2. Methods

2.1. Study design and Population

This is a cross-sectional study during the plantation season (rainy period) in March thru May 2024. This study took place in the altiplans of Santarém, western State of Pará in the legal Amazon region where intense transgenic soy crops are in course in the last decade.

Fig. 1 shows the six the communities included, after meetings with local leaderships and assessment of logistic accessibility, including support of school principals. The participating communities are Bom Jardim, Vitalina Mota, Tipizal, Guaraná, Boa Sorte, and Ponta de Pedras. About 300 volunteers were enrolled, which 74 were children aged 6–12 years. We were able to obtain blood sample of 69 of them and 53 children completed the cognitive assessments.

2.2. Ethical considerations

This study has been approved by the Research Ethics Committee on Human Subjects of the Federal University of Western Pará, Approval Number: 6.631.576. The research has been conducted in accordance with the principles of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Parents or legal guardians were informed about the objectives and methods of the study during a meeting with the study participants, when they were informed that they could withdraw from the study at any time. Those who felt comfortable participating signed the Informed Consent Form (ICF) and received a copy containing our contact information for any further questions.

3. Data collection

3.1. Questionnaire and blood sample collection

Trained interviewers applied questionnaires to mothers or caregivers. Data were collected on general daily habits, education level, occupational history, parity, history of active or passive smoking, and proximity to plantation area and potable water source or other source of exposure to potentially toxic metals.

Blood samples were collected by cubital venipuncture in vacuum tubes. Metal-free EDTA tube (Neovaccum®, BD) for metal/metalloids determination was used, and regular EDTA tube for hemogram was also collected. The samples were packed into isothermal boxes containing recyclable ice and transported to the Laboratory of the Federal University of Western Pará.

3.2. Metal determination by ICP-MS

The determination of metals and metalloids in children's blood samples was performed using inductively coupled plasma mass spectrometry (ICP-MS) at the Analytical Center of the School of Pharmaceutical Sciences, University of São Paulo, in Ribeirão Preto, Brazil. Briefly, after appropriate dilution, the samples were transferred to the ICP-MS PE ELAN DRC II (PerkinElmer) autosampler and introduced via the Pt sampler and skimmer cones. A multi-element stock solution containing 1 g/L of Pb and other elements, obtained from PerkinElmer (Norwalk, CT), was used for instrument calibration. Rhodium was used as an internal standard at a concentration of 10 μg/L. A rinse solution consisting of 0.005 % (v/v) Triton X-100 in 2 % (v/v) nitric acid was prepared prior to each run. Final results for metals/metalloids were expressed in μg/L, and lead (Pb) will be expressed in μg/dL.

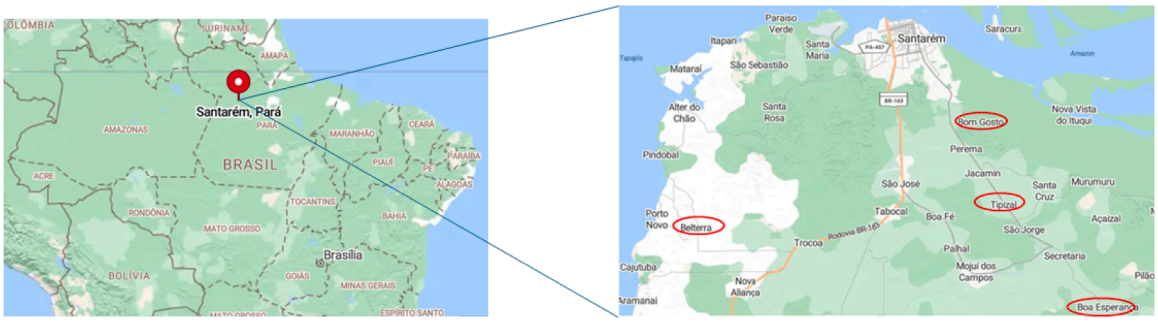

Fig. 1. Schematic map showing the study region in the Santarém Plateau and included communities.

3.3. Cognitive assessments

Intellectual performance assessments of children aged 6–12 years were conducted at their respective elementary schools within the communities. An experienced neuropsychologist (CSL) trained two psychologists from Santarém, Pará, Brazil, who administered the following tests in appropriate rooms provided by the school principals, with minimal external interference whenever possible: Raven's Colored Progressive Matrices, which assesses non-verbal intelligence, is easy to administer and has low cognitive demand for children, providing raw scores and percentile rankings; Five Digits Test (FDT), which evaluates attention and processing speed, expressed as cognitive flexibility and inhibitory control in seconds; and NEPSY-II Language subtests, which measures verbal semantic and phonological fluency (Word Generating - WG).

3.4. Data analysis

The data were described using frequency measures, central tendency, and dispersion. Exposure biomarkers are presented as mean, median, standard deviation (SD), minimum, and maximum. Non parametric correlation test (Spearman correlation) was used to evaluate the correlations among main sociodemographic characteristics of the study population, biomarker levels and children's cognitive scores.

Nonlinear associations were explored by first evaluating single metal models of log-2 transformed blood Pb and Hg concentrations and the six cognitive outcomes using the *gam()* function with "bs" basis from the *mgcv* package. Potential confounders were modeled as linear terms and the smoothing parameter was estimated using the "REML" method. We evaluated smooth terms for the metals with *k* was set at 10 and checked the *k'*, estimated degrees of freedom *(edf), k-index,* and p-value iteratively with the *gam.check()* function. Models that were properly specified had *k'* sufficiently larger than *edf*, *k-index* was greater than 1, and p-value was > 0.05. Of these models, if *edf* was close to 1, then the plots were visually inspected for linearity, and if linearity was met, then these associations were modeled with multivariate linear regression. For properly specified linear and non-linear models, we evaluated all other OLS assumptions before interpreting main effect estimates. Covariates with $r > 0.10$ and $p < 0.05$ were included in all the models. Namely, dichotomized maternal education, reference group was Elementary school, children's age (continuous), and children's sex, reference group was girls. We conducted sex stratified analyses, and tested the robustness of the effect estimates for Pb by removing influential outliers and adding hemoglobin concentration as a covariate. The differences between those with and without cognitive outcomes are described in the supplementary material.

For the models that were properly specified and had significant main effect estimates, interaction terms were introduced between exposure biomarkers to assess potential interactions. Mixture analyses were not considered for this cross-sectional analysis considering the initial scope of this paper and the limited sample size of the study. In the multivariate linear regression models, the cross product was used between the primary metal and the secondary metal as $\log_2$metal, above and below the median, and tertiles. However, for non-linear regressions, we evaluated factor smooth interactions with the basis function "fs." The main metal was kept continuous as $\log_2$metal, and the secondary metal was tested as above and below the median and tertiles. This basis function allows for the calculation of a fully penalized smooth function that includes the group means for each level of the factor. Once significant "fs" basis interactions were identified, stratified models were done with "bs" basis, to numerate effect estimates, plot fitted values, and ease interpretation. The specifications for the nonlinear interaction models were tested the same as previously said. Overall, the models with the lowest AIC were interpreted.

The accepted level of statistical significance for all tests was $p < 0.05$ and $p < 0.10$ for interaction terms. To address potential multiple comparison issues, we also discuss the associations for the main models testing the relationships between six outcomes and two main predictors, Bonferroni-corrected $p < 0.004$. Descriptive and comparative statistical analyses were performed using SPSS® version 26.0 for Windows (IBM Inc., Massachusetts, USA) and R version 4.4.2 (R Core Team, 2024).

4. Results

Table 1 shows that mothers of 74 school-aged children agreed to participate in the study, providing sociodemographic information. Children were predominantly girls (64.8 %), with a mean age of 9.3 years. Most were of mixed race, including indigenous, black, and White people. About half of their mothers had only primary school or less. About 12 % of them were exposed to second-hand cigarette smoke. The great majority was of very low income class; about 82 % had a family income of only one Brazilian minimum salary, corresponding to $250 a month. About one-third of the mothers reported drinking socially. The prevalence of anemic children was considered low, 11 % among boys

Table 1
Sociodemographic characteristics of the study population.

Characteristics	% (n)	% (n)	p-value
Sex	**Boys**	**Girls**	
	39.2 (29)	60.8 (45)	$< 0.01^b$
Age (years) (mean±SD)	9.2 (±1.6)	9.4 (±1.8)	0.471^a
Maternal education			
Primary school or less	46.4 (13)	43.9 (18)	0.836^b
High school or more	53.6 (15)	56.1 (23)	
ETS	13.8 (4)	11.1 (5)	0.730^b
Family income			
≤ One minimal salary	85.7 (24)	84.2 (32)	0.866^b
Maternal drinking			
	32.1 (9)	35.9 (14)	0.954^b
Hemoglobin (g/dL)			
(mean±SD)	13.3 (±0.76)	13.0 (±0.92)	0.336^a
Anemia	11.1 (5)	3.1 (1)	0.461^b

Note: p-values for (a) Student-t test and (b) Chi-square test.

and 3 % among girls, whose mean hemoglobin level was 13 g/dL.

The data in Table 2 describe the metal/metalloid blood levels of 69 children who provided blood samples. The median levels of As, Cd, Mn, Hg, and Se were 5.16, 0.08, 7.71, 2.11, and 189.9 μg/L, respectively. Blood Pb (PbB) median was 1.90 μg/dL, ranging from 0.64 to 40.14 μg/dL; 14.3 % of the children were above the CDC's reference value of 3.5 μg/dL (CDC, 2021). No statistically significant differences in blood biomarker levels according to children's sex were observed.

Mercury blood (HgB) levels ranged from 0.45 to 17.07 μg/L, and 17.4 % of the children were above the reference value of 5 μg/L, according to WHO (2005). Almost 9 % of the children had HgB levels twice as high as this threshold. The micronutrient elements Mn and Se ranged from 3.75 to 27.81 and 78.22–933.25 μg/L, respectively. MnB concentrations were entirely in the physiological range; however, some SeB levels (~9 %) were above the recommended blood levels of 100–300 μg/L (Ryan and Terry, 1996). None of the children had AsB levels above the Brazilian population reference level of 9.87 μg/L (Freire et al., 2015).

None of the metal/metalloid levels correlated with children's age, family income, or maternal education. However, some positive and significant intercorrelations were observed among blood metal levels. Blood Pb and Cd levels (ρ (Spearman rho) = 0.342), Pb and Hg levels (ρ = 0.441), and Pb and Se levels (ρ = 0.245). Selenium levels were also moderately positively correlated with As (ρ = 0.422) and Hg levels (ρ = 0.345). On the other hand, MnB levels were not correlated with any of the metal/metalloid levels. Spearman correlations among the cognitive test scores were moderate, as expected. Specifically, the verbal semantic fluency tests (WG) (ρ = 0.416) and cognitive flexibility and inhibitory control (ρ = 0.749) were the most highly correlated.

The data in Table 4 presents a summary of the neurocognitive evaluations. The descriptive statistics are mean, SD, minimum, and maximum according to children's sex. No statistical differences were observed in the cognitive test scores according to children's sex. In the bivariate correlation analysis (Table 3), it was observed that children's age was positively correlated with the scores in the verbal semantic fluency test (WG) (ρ = 0.301) and with non-verbal Raven raw scores (ρ = 0.464); and negatively correlated with time in seconds in the cognitive flexibility test (ρ = −341), and with seconds in the inhibitory control test (ρ = −306). Similarly, maternal education was positively significantly correlated with the scores in the verbal semantic fluency test (WG) (ρ = 0.314), with Raven's raw score (ρ = 0.450), and with Raven's percentile scores (ρ = 0.507). Concerning metal/metalloid blood levels, only PbB levels were significantly inversely correlated with the cognitive test scores: verbal semantic fluency test (WG) (ρ = −0.373), phonologic fluency (WG) (ρ = −0.351), Raven's raw score (ρ = −0.313), and Raven's percentile scores (ρ = −0.346).Table 4

4.1. Multivariate linear regression analyses

Multivariate linear regression analyses adjusting for children's age, sex, and maternal education indicated a significantly linear association between blood lead and mercury levels with Verbal Semantic (WG) and Raven Percentile, respectively (Table 5). After Log_2 transformation, blood lead levels were inversely associated with the verbal semantic (WG) scores even at the FDR-corrected p-value threshold (β = −2.71, p = 0.004), Fig. 2. After removing three observations with blood lead levels above 20 μg/dL, this inverse association was even higher in magnitude (β = −3.22, p = 0.006). The interaction model with dichotomized blood mercury increased the magnitude of the main effect, although it no longer met the significance threshold (β = −3.83, p = 0.11, Supplementary Table 1) and the interaction term itself was null (p = 0.7). The opposite interaction was not tested since log_2HgB levels were not found to be independently associated with verbal semantic (WG) in the single metal models. Similarly, the interaction model with dichotomized SeB increased the magnitude of the main effect (β = −4.03, p = 0.048), but the interaction term was null (p = 0.5, Supplementary Table 1).

Log two transformed blood mercury (Log_2HgB) levels were inversely associated with Raven's percentile scores (β = −5.05, p = 0.06, Table 5). However, once we introduced SeB in tertiles as an interaction term, the main effect was completely attenuated and no longer significant (β = 1.67, p = 0.78). Table 5 also shows that among children with SeB in the lowest tertile, a doubling of HgB levels did not meaningfully affect the average change of Raven percentile scores. Among those with SeB levels in the highest tertile, a doubling of HgB levels has an average decrease of 14.6 points (95 %CI = −21.5 to −7.7) in their Raven percentile scores, given covariates. However, the interaction for SeB in the third tertile compared to the first was inversely associated with Raven percentile scores and highly significant (β = −16.27, p = 0.023). This term indicates that the difference in average change of Raven percentile scores per each doubling of blood mercury levels is meaningfully different between the third and first SeB tertiles (Supplementary Figure 1). Notably, there was an average increase in Raven percentile scores for SeB in the third tertile compared to the first, given the same levels of blood mercury and other covariates, but this was not significant (β = 12.02, 95 %CI = −4.17–28.21). These associations suggest synergistic effects between mercury, elevated selenium co-exposure on children's cognitive function, while lower levels of selenium may attenuate the negative association of mercury.

4.2. Non-linear restricted cubic spline analyses

Significant nonlinear relationships were estimated for doubling of PbB levels, Raven raw, and Raven percentile scores after adjusting for maternal education level, children's age, and sex. Seventy five percent of the children had PbB concentrations below 1.25 μg/dL, at this range, the association between log_2PbB and Raven raw scores is negative and appears linear before becoming flat for the highest quartile (edf = 2.319, p < 0.008, Fig. 3). To better evaluate this, we removed three observations with blood lead concentrations above 20 μg/dL, and overall, the

Table 2
Blood metal/metalloid levels according to children's sex.

Blood Levels		N	Mean	Median	SD	Min-max	p-value*
Arsenic	**Boys**	26	5.27	5.18	0.69	4.15–7.54	0.401
(μg/L)	**Girls**	43	5.09	5.11	0.66	3.88–6.84	
Cadmium	**Boys**	26	0.09	0.08	0.04	0.02–0.21	0.732
(μg/L)	**Girls**	43	0.08	0.08	0.04	0.02–0.020	
Lead	**Boys**	26	4.95	2.00	9.30	0.90–40.14	0.401
(μg/dL)	**Girls**	43	2.60	1.81	2.81	0.64–14.65	
Manganese	**Boys**	26	8.02	7.16	4.37	4.93–27.81	0.515
(μg/L)	**Girls**	43	7.52	7.59	2.43	3.75–12.12	
Mercury	**Boys**	26	2.63	1.94	2.63	0.45–12.98	0.877
(μg/L)	**Girls**	43	3.96	2.11	3.90	0.61–17.07	
Selenium	**Boys**	26	182.04	143.68	126.20	92.39–709.12	0.877
(μg/L)	**Girls**	43	194.66	153.22	153.35	78.22–933.25	

*Note: Kruskal-Wallis test for median difference between children's sex.

Table 3
Spearman correlation coefficients (ρ) among sociodemographic data, blood metal/metalloid levels and cognitive test scores in school aged children.

		Age (Years)	Matern School.	Family income	AsB	CdB	PbB	MnB	HgB	SeB	Sema. W.G	Phon.WG score	Inhib. Con. Sc.	Cog. Flex. Sc.	Raven raw sc.	Raven Per sc.
Age (Years)	rho						.101	-.070	-.205	**.301**	.180	**-.341**	**-.306**	**.464**	.179	
	p-value		.425	.137	.717	.347	.608	.410	.570	.091	.029	.198	.013	.026	< .001	.199	
	N	74	69	66	69	69	69	69	69	69	53	53	53	53	53	53	
Maternal education	rho		1.000	**.385**	.100	-.032	-.062	.273*	.176	-.157	**.314**	.221	.159	.140	**.450**	**.507**	
	p-value			.001	.430	.803	.625	.029	.165	.217	.028	.127	.274	.339	.001	< .001	
	N		69	66	64	64	64	64	64	64	49	49	49	49	49	49	
Family income	rho			1.000	.116	.035	-.096	-.045	.123	-.106	.141	-.014	.092	.066	.019	.112	
	p-value				.375	.788	.464	.729	.344	.418	.344	.925	.540	.660	.900	.454	
	N			66	61	61	61	61	61	61	47	47	47	47	47	47	
AsB	rho				1.000	-.001	.076	.134	.132	**.422**	-.222	-.237	.248	.207	-.131	-.059	
	p-value					.991	.535	.273	.279	< .001	.117	.094	.080	.146	.360	.681	
	N				69	69	69	69	69	69	51	51	51	51	51	51	
CdB	rho					1.000	**.340**	.085	.101	.060	**-.355**	-.157	-.003	.147	-.105	-.131	
	p-value						.004	.488	.411	.622	.011	.272	.983	.303	.464	.360	
	N					69	69	69	69	69	51	51	51	51	51	51	
PbB	rho						1.000	.114	**.441**	**.245**	**-.373**	**-.351**	-.004	.114	**-.315**	**-.346**	
	p-value							.352	< .001	.042	.007	.012	.980	.427	.024	.013	
	N						69	69	69	69	51	51	51	51	51	51	
MnB	rho							1.000	.296*	.228	-.027	-.022	.190	.196	.245	.166	
	p-value								.014	.059	.849	.876	.181	.169	.083	.243	
	N							69	69	69	51	51	51	51	51	51	
HgB	rho								1.000	**.326**	-.160	-.088	.029	.093	-.170	-.106	
	p-value									.006	.261	.540	.841	.514	.232	.460	
	N								69	69	51	51	51	51	51	51	
SeB	rho									1.000	-.234	-.142	**.283**	.223	-.250	-.142	
	p-value										.098	.319	.044	.115	.076	.320	

(*continued on next page*)

Table 3 (*continued*)

		Age (Years)	Matern School.	Family income	AsB	CdB	PbB	MnB	HgB	SeB	Sema. W.G	Phon.WG score	Inhib. Con. Sc.	Cog. Flex. Sc.	Raven raw sc.	Raven Per sc.
	N								69				51	51	51	
Semantic WG scores	rho										51	51	-.162	.365	.342	
	p-value										1.000	.417	.246	.007	.012	
	N											.002	53	53	53	
Phonological WG scores	rho										53	53	-.254	.378	.245	
	p-value											1.000	.066	.005	.078	
	N											.148	53	53	53	
Inhibitory control scores	rho										53	53	.749	-.223	-.167	
	p-value											1.000	< .001	.109	.232	
	N												53	53	53	
Cognitive flexibility scores	rho											53	1.000	-.315	-.175	
	p-value													.022	.209	
	N												53	53	53	
RAVEN Raw scores	rho													1.000	.869	
	p-value														< .001	
	N													53	53	
Raven Percentile scores	rho														1.000	
	p-value															
	N														53	

Note: bold values to highlight significant Spearman correlation coefficients.

Table 4
Descriptive statistics of the cognitive test scores according to children's sex.

Cognitive tests		N	Mean	SD	Min-max	p-value*
Verbal Semantic WG	Boys	19	19.0	7.5	(5−32)	0.270
	Girls	34	21.6	8.3	(8−37)	
Verbal Phonologic WG	Boys	19	9.0	6.2	(1−27)	0.689
	Girls	34	9.6	4.7	(2−21)	
Cognitive flexibility (sec.)	Boys	19	43.0	26.5	(0−103)	0.142
	Girls	34	46.4	29.2	(5−127)	
Inhibitory control (sec.)	Boys	19	44.5	17.4	(0−71)	0.673
	Girls	34	57.9	39.8	(18−223)	
Raven raw scores	Boys	19	24.4	8.6	(10−45)	0.154
	Girls	34	20.9	5.5	(10−32)	
Raven percentile	Boys	19	33.6	30.5	(1–97.7)	0.075
	Girls	34	26.5	23.0	(2.3–75.0)	

* p-value for Student-t Test.

Table 5
Summary of the multivariate linear regression models of the cognitive outcomes and log_2 transformed Pb and Hg blood levels after adjusting for maternal education, child age, child sex and applying interaction terms to fully adjusted models.

	Non-standardized Beta coefficients	p-value	95 %-CI
Raven Percentile scores			
Intercept	16.03	0.40	(-1.896 24.516)
Log_2HgB	-5.05	0.06	(-10.20 0.11)
Age	0.33	0.87	(-3.48 4.14)
Maternal education secondary education or more	26.12	< .001	(12.97 39.27)
Boys	4.07	0.56	(-9.58 17.73)
Semantic WG NEPSY II			
Intercept	9.97	0.075	(-0.73 20.85)
Log_2PbB	-2.71	0.004	(-4.46 -0.95)
Age	1.29	0.031	(0.16 2.42)
Maternal education secondary education or more	5.8	0.005	(1.96 9.71)
Boys	-3.96	0.059	(-7.96 0.04)
Interaction Model			
Raven Percentile scores			
Log_2HgB	1.67	0.78	(-10.01 13.36)
Tertile 2 - SeB	-1.81	0.87	(-22.69 19.07)
Tertile 3 - SeB	28.29	0.023	(4.90 51.69)
Log_2HgB*Tertile 2 - SeB	3.99	0.59	(-10.49 18.47)
Log_2HgB*Tertile 3 - SeB	-16.27	0.023	(-29.76 -2.79)

WG - Word generation

curve retained its shape, the degree of non-linearity remained about the same, and significance decreased (edf = 2.339, p-value = 0.0118, Supplementary Figure 3).

The inverse association between log_2PbB and Raven percentile scores were slightly non-linear (*edf* = 1.186, $p < 0.01$, Fig. 4). The non-linear negative association between log_2PbB and Raven percentile scores became more pronounced, with a sharper decline for each doubling of PbB level before flattening out, after removing the observations above 20 μg/dL (edf = 1.805, $p < 0.0545$, Supplementary Figure 4).

Non-linear interactions were evaluated between log_2PbB and HgB levels above and below the median for both Raven raw and percentile scores. Both interactions were significant above the median, *edf* = 1.68, p = 0.005 and *edf* = 1.625, p = 0.011, respectively. For those with HgB below the median, a doubling of PbB was linearly associated with an average decrease of Raven raw scores (β = −4.697, 95 %-CI = −8.48 to −0.92, p = 0.026). For HgB above the median, a doubling of PbB was associated non-linearly with an average decrease in Raven raw scores, but the curve and the 95 %-CI appear mostly linear (edf = 1.206, $p < 0.09$, Supplementary Figure 5). For HgB below the median, a doubling of PbB levels was linearly associated with an average decrease in Raven percentile scores (β = −14.25, 95 %CI = −30.29–1.79, p = 0.099). A negative linear relationship was also seen for HgB above the median, although this association no longer met the significance threshold (β = −5.03, 95 %CI = −10.95–0.89, p = 0.112).

4.3. Sensitivity analyses

After adjusting for hemoglobin, the original inverse association remained such that the predicted Raven percentile scores decreased as log_2HgB increased, but the relationship became mildly non-linear (edf = 1.165, p = 0.068, Supplementary Figure 2). After adjusting for hemoglobin, the non-linear association between log_2PbB and Raven raw score remained unchanged (*edf* = 2.252 $p < 0.010$). Interestingly, after the same adjustment, the association between log_2PbB and Raven percentiles became linear and even marginally significant at the FDR-corrected p-value threshold (β = −8.368, 95 %CI = −13.9 to – 2.7, p = 0.005).

We also tested for statistical differences using Pearson's chi-squared test, Fisher's exact test, and the Wilcoxon rank-sum test. These potential confounders and blood metal levels had statistically similar distributions between those included and excluded in our analysis. However, those who completed the neurocognitive test had higher blood Se levels than those who did not ($p < 0.008$).

4.4. Sex-stratified analyses

Sex stratified results show a significant average decrease in verbal semantic fluency (WG) scores for each doubling of PbB levels among girls (β = −3.69, p = 0.004) but not boys (β = −1.61, p = 0.28). In contrast, when doubling PbB levels, there were no statistical differences in the average change in Raven percentile between girls and boys. After adjusting for hemoglobin, the average change in verbal semantic fluency (WG) scores per doubling of PbB levels was not meaningfully different from the original model (β = −2.69, p = 0.005).

Sex-stratified nonlinear analyses between log_2PbB and Raven raw scores showed that both boys and girls had significant negative associations. Among boys with all other covariates constant, the relationship was linear and doubling PbB level was associated with an average decrease of 3.09 Raven raw scores (95 %CI = −5.74 to −0.43). Among girls, the relationship remained non-linear with a mild U-shape (*edf* = 2.67, $p < 0.008$, Supplementary Figure 6). Similarly, the association between log_2PbB and Raven percentile was linear among boys (β = −8.66, p = 0.13), but non-linear among girls (*edf* = 2.633, $p < 0.008$, Supplementary Figure 7).

5. Discussion

This study highlights that school-age children living in communities near soybean and other crop plantations in the Santarém Plateau of the State of Pará, Brazil, have relatively high concentrations of mercury, lead, and selenium in their blood. Significant inverse non-linear associations were observed between blood lead levels and raw scores on the Raven's Colored Progressive Matrices, independent of the child's sex and age, as well as maternal education. Furthermore, we also found that these levels were linearly inversely associated with verbal cognitive test scores, independent of the child's age and maternal education. In its turn, blood mercury levels were inversely associated with percentile scores on the non-verbal Raven scores, after adjusting for maternal education. Moreover, an interaction with blood selenium levels was observed, suggesting that children with low to average blood selenium levels may have an attenuated Hg neurotoxic effect. However, among those with elevated blood selenium levels, the impact of Hg on cognitive function appears exacerbated.

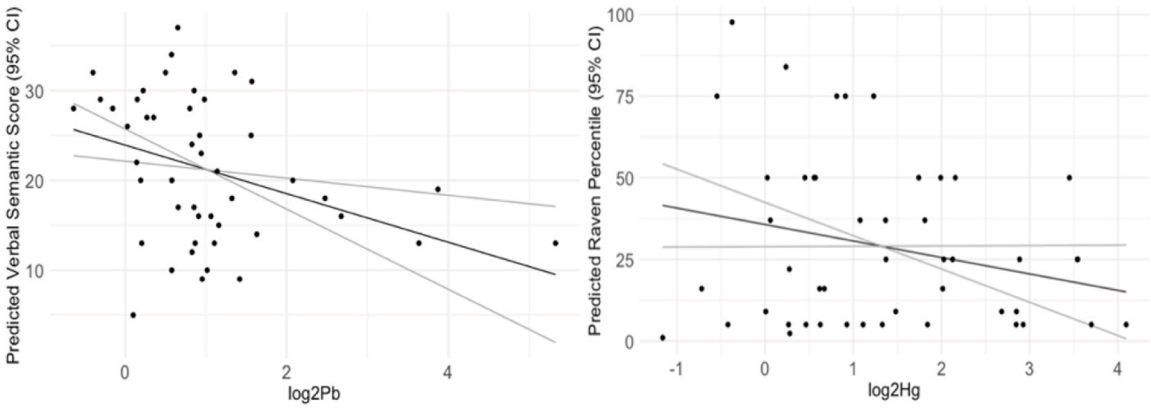

Fig. 2. Partial plots of the cognitive test scores and blood metal levels. a) Verbal semantic (word generating) scores versus log2 transformed PbB levels (p = 0.004); and b) Raven's percentile scores versus $\log_2$ transformed HgB levels (p = 0.06).

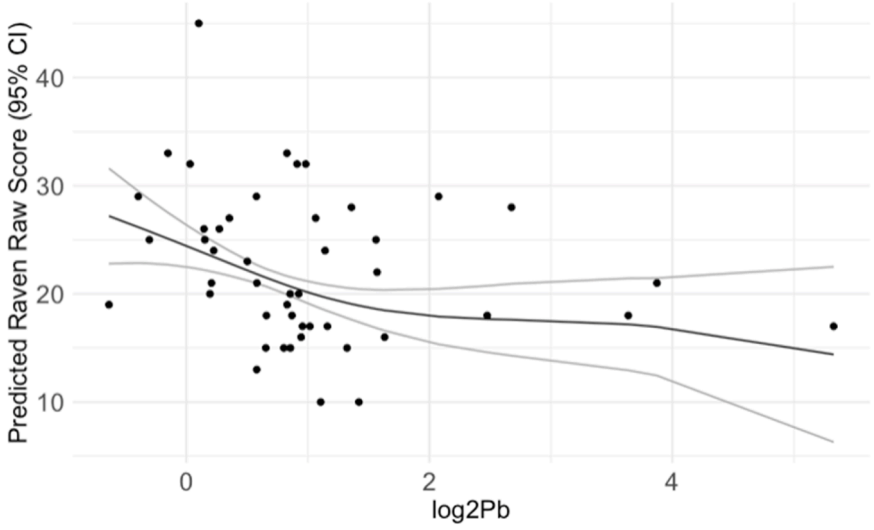

Fig. 3. Non-linear Association between $\log_2$PbB and Predicted Raven Raw scores adjusted by Maternal Education, Child Age, and Sex, *edf = 2.319, p = 0.008*.

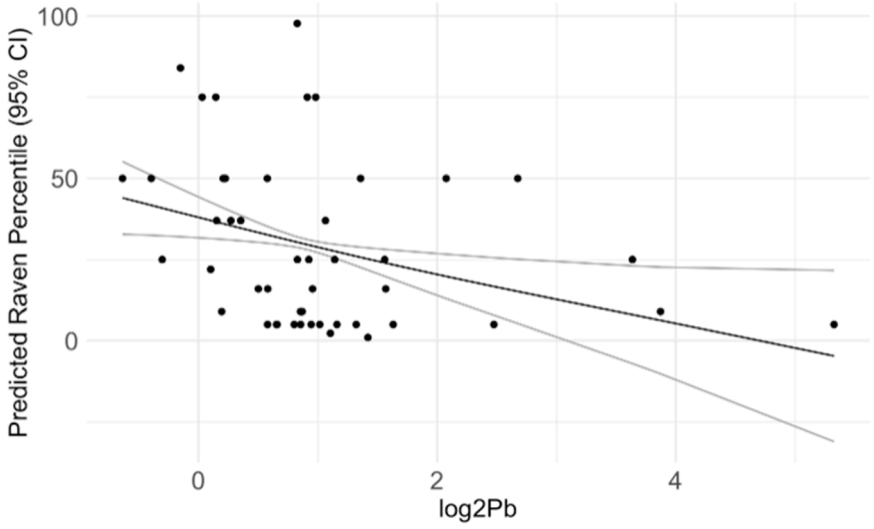

Fig. 4. Non-linear association between $\log_2$PbB and predicted raven percentile scores adjusted by maternal education, Child Age, and Sex, *edf = 1.186, p = 0.0122*.

Since the early 2000s, this region of the Amazon rainforest has been undergoing deforestation to make way for large-scale agricultural projects, particularly monoculture farming—primarily the cultivation of genetically modified soybeans and corn in crop rotation systems. In

addition to the intensive use of pesticides, including herbicides such as glyphosate and Tordon (Morgado et al., 2023), soil disturbance during land preparation promotes erosion and the leaching of soil materials into adjacent water bodies (Silva et al., 2017). A study analyzed sediment samples from tributaries of the Tapajós River, as well as soil samples from manioc cultivation areas. The results revealed significant concentrations of Pb in sediments and soils, ranging from 8.9 to 26.1 mg/kg, and Zn concentrations ranging from 12.7 to 59.1 mg/kg, indicating the influence of polymetallic geological deposits. The Pb content found in the clay samples is likely of natural origin, as the Tapajós River Basin is known to be rich in gold deposits, which are commonly associated with sulfide minerals, including a lead sulfide known as galena (Lima et al., 2021). This leaching process is also observed in cases of mercury contamination in aquatic systems without the influence of ASGM activity. Deforestation via slash-and-burn destabilizes clay- and organic-bound mercury in soils. Formerly stable mercury becomes prone to erosion and is carried into rivers during rainfall events without forest cover (Roulet et al., 2000).

Blood levels of metal/metalloids observed in Amazonian children were moderately elevated. In this current study, PbB levels ranged from 0.64 to 40.14 μg/dL with median level around 2 μg/dL; 14.3 % of the children were above the CDC's blood reference value of 3.5 μg/dL (CDC, 2021). In contrast to our results, children in the Peruvian Amazon had PbB levels ranging 3.0–26.8 μg/dL, with significant differences in age range and sex (Anticona et al., 2012). A recent study of the indigenous population in the Peruvian Amazon found median PbB level in children of 9.49 μg/dL, with 95.8 % exceeding 5 μg/dL. Using Pb isotopic signatures, the authors concluded that the primary exposure sources were river waters and diet rich in hunted wild animals with lead-based ammunition (Mayor et al. 2025). Blood Hg levels were also elevated in 19 % of the children according to WHO reference value of 5 μg/L (WHO, 2008), which ranged from 0.45 to 17.07 μg/L. To the best of our knowledge, no study has assessed the blood mercury levels of Amazonian children. According to a recent scoping review by Santos-Sacramento et al. (2021), all studies evaluated children's exposure by measuring total Hg levels in scalp hair samples.

Concerning selenium levels, it ranged between 78.2 and 933.3 μg/L, with median around 150 μg/L. Very few children (<9 %) had SeB levels above 340 μg/L, considered as the upper normal threshold (Ryan and Terry, 1996). These Se levels were very similar to those in children and adolescents from two riparian communities at the Madeira River, where significantly higher levels were observed during May (Cuniã RESEX 149 μg/L; Belmont 85 μg/L) compared to September (Cuniã RESEX 79 μg/L; Belmont 53 μg/L) (Vega et al., 2017).

Toxic metal exposures have compromised Amazonian children's intellectual performance. This current study observed suggestive cognitive deficits in school-aged children associated with exposure to lead and mercury. Even though only 14 % of those children had PbB levels above the CDC's reference value, we found significant non-linear inverse associations of PbB levels and non-verbal Raven raw scores and a linear association with verbal fluency test scores, after adjusting for maternal school, childreńs sex and age. Additionally, we found that PbB level association with verbal domain was more pronounced in girls. We found no study reporting the cognitive evaluation of Amazonian children exposed to lead. However, Brazilian children of similar socioeconomic status have been evaluated in Bahia, Brazil. Menezes-Filho et al. (2018) found that children aged 6–12 years had median and range PbB values of 1.2 (0.3–15.6) μg/dL. After adjusting for maternal IQ, age, and Mn exposure, child IQ dropped by 8.6 points for a 10-fold increase in PbB levels in Verbal and nonverbal cognitive tests. This is similar to the findings of the current study. The intellectual impairments associated with childhood lead (Pb) exposure have been extensively investigated over the years. Consequently, the reference value for blood lead in children has steadily declined over recent decades—from 10 μg/dL to 5 μg/dL, and more recently to 3.5 μg/dL (CDC 2001, 2012, 2021). Nevertheless, numerous studies have documented cognitive effects at blood lead levels well below these thresholds. For instance, Desrochers-Couture et al. (2018) in a birth cohort study, found that median blood Pb level 0.64 μg/dL was associated with decline in cognitive function in pre-school children, while Wheby (2025) has shown that a one-unit increase in lead levels below 3.5 μg/dL was associated with lower scores in math and in reading in a cohort study of children born in Iowa, USA, from 1989 to 2010 and their test scores for grades 2 through 11.

The scientific literature has consistently demonstrated an association between lead exposure and cognitive impairments in the verbal domains of children. As observed in the present study, deficits in verbal performance are detectable even at relatively low blood lead levels, reinforcing the absence of a safe threshold for neurodevelopmental effects. These findings are corroborated by Agudelo et al. (2024), who reported that blood lead levels are associated with reduced reading acquisition and language performance, indicating that lead disrupts the neural processes that support language learning. Similarly, in a prospective study conducted with Brazilian children, infants exposed to lead through breast milk exhibited lower language development trajectories compared with non-exposed infants, even after adjustment for infant age, maternal education, socioeconomic status, infant sex, and sampling weights (Naspolini et al., 2024). Collectively, these results highlight the particular vulnerability of verbal and language functions to lead neurotoxicity and underscore the potential long-term consequences for academic achievement and learning during the school years.

Mercury exposure and neuropsychological deficits have been very well documented worldwide, and in Amazonian children. In this study, blood Hg levels were linearly inversely associated with non-verbal Raven Percentile scores, after adjusting for maternal education, child age, and sex ($\beta = -5.04$, 95 %-CI −10.2–0.11). Even though no study measured children's blood Hg levels, those investigating children's exposure to mercury, evaluated Hg hair levels. Santos-Lima et al. (2020) assessed 225 children in riverside communities near the Madeira River, Rondônia, Brazil. Total Hg hair levels (median and range) were 2.05 (0.05–21.75) μg/g, significantly inversely associated with verbal and nonverbal cognitive test scores. They found a 10-fold increase in HgH levels was associated with a decrease of around half a standard deviation in Verbal IQ, estimated IQ scores, semantic knowledge, phonological verbal fluency, and visuospatial working memory. Several other studies found associations of hair Hg levels with neuropsychological decrements. Riverine children in Tapajós River presented motor function, attention, and visuospatial performance deficits associated with mercury exposure (Grandjean et al., 1999); about 400 Amazonian children aged 7–12 years (from Brazil and French Guiana), who had HgH levels ranging 0.5–63.8 μg/g, was negatively associated with drawing task scores (Chevrier et al., 2009); neurodevelopmental effects were examined in 1139 children of communities along Madeira River, Rondônia, born form mothers who presented median Hg hair level of 6.64 μg/g at birth, a statistically significant increase in neurodevelopmental (BSID) delays related to Hg exposure was observed (Marques et al., 2016). Finally, in the Peruvian Amazon, children living near ASGM had Hg hair levels 2.06 (±2.43) μg/g, with 32.6 % above 2.0 the WHO reference value, presenting lower general cognitive abilities when compared with those with Hg hair level below this cutoff value (Reuben et al., 2020).

Regarding the interaction of mercury and selenium exposure, we initially hypothesized that the elevated blood selenium levels observed in this population may partially underlie this supposed neuroprotection. Indeed, several studies in Amazonian and broader human populations have documented protective effects of selenium. Selenium forms stable complexes with circulating mercury, thereby enhancing its systemic clearance and reducing bioavailability. Additionally, Se sustains the activity of selenoenzymes, enabling antioxidant defenses that mitigate mercury-induced oxidative stress. For example, Lemire et al. (2011) found that higher Se–Hg molar ratios in blood were associated with reduced neurobehavioral deficits in Amazonian riverine populations. Broader reviews confirm that selenium's binding affinity to mercury and its role in maintaining antioxidant enzyme function are key factors in

preventing or reducing mercury's neurotoxicity (Bjørketlund et al., 2017, Jorge et al., 2024). However, in this study, we found a dual interaction pattern. For those children with low and average blood Se levels, the mercury cognitive effect appears to be null. On the other hand, among children with SeB levels in the third tertile (elevated), there is a sharp and significant drop in the Raven percentile scores (Supplementary Figure 1), suggesting an exacerbation of mercury neurocognitive effect.

This study has several limitations, though they do not undermine its generalizability to children living under comparable conditions of environmental and social inequity, particularly in regions undergoing agricultural expansion. The cross-sectional design precludes causal inferences, and the very limited sample size, which reflects the low population density of Amazonian communities, where small populations are dispersed over large areas, prevented the use a more robust data analysis approach, especially those intended to evaluate combined effects. Consequently, randomization was not feasible, and convenience sampling was employed. The lack of anthropometric data also limited adjustment for height-for-age Z-scores, an indicator of chronic undernutrition, and the geographic dispersion of households impeded the application of the HOME inventory. Unfortunately, due to budgetary limitation, urine samples could not be analyzed for pesticide metabolites, which are known to affect children's neurocognition as well. Despite these constraints, the study has important strengths. It assessed children's intellectual performance using three complementary instruments—measuring nonverbal intelligence, phonological fluency, and executive functions. To our knowledge, this is the first study in rural Amazonian communities to examine blood concentrations of potentially toxic metals and metalloids in relation to cognitive outcomes.

6. Conclusions

This study demonstrates that Amazonian children living in communities adjacent to crop plantations—particularly transgenic soybean fields—are exposed not only to pesticides but also to potentially toxic metals and metalloids. We observed relatively elevated blood lead levels, although most values remained below the current CDC reference threshold. We hypothesize that this exposure is likely attributable to dust from soil erosion and to vegetables, especially manioc, cultivated in Pb-rich soils. Importantly, blood lead levels were inversely non-linearly associated with performance on non-verbal cognitive test and linearly with a verbal cognitive test, which appears to be more pronounced in girls. In addition, children's blood mercury concentrations were comparable to those reported in riverine populations of the Amazon, where exposure occurs primarily through fish consumption; in the present study, Hg levels were linearly and negatively associated with performance non-verbal cognitive test. Evidence of metal co-exposure effects was also observed, particularly the apparent modulation of Hg-related cognitive toxicity by selenium levels. Given the cross-sectional design and limited sample size of this study, larger and longitudinal investigations are warranted to confirm these findings and to better characterize the combined effects of multiple metal exposures on child intellectual function.

Funding

This study was financially supported by the CONFAP Amazon + 10 Initiative (Iniciativa Amazônia +10 do Conselho Nacional das Fundações Estaduais de Amparo à Pesquisa - CONFAP [grant number 00193.00002282/2022–47 by the Federal District Research Support Foundation - FAPDF]; JAMF holds a CNPq productivity researcher scholarship.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Carlos Jose de Souza Passos reports financial support was provided by Brazilian National Council for the State Funding Agencies. 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.

Acknowledgments

First and foremost, the authors would like to thank all the parents and children who voluntarily participated in this study. We are also grateful to the principals of the primary schools in the municipalities of Belterra and Santarém for their full support in carrying out this work. We further acknowledge the assistance of Prof. Adjany Estela de Souza, as well as the undergraduate students from the State University of Pará, who contributed to the administration of the questionnaires.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2026.103404.

Data availability

Data will be made available on request.

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