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Elemental analysis of hair provides biomarkers of maternal hardship linked to adverse behavioural outcomes in 4-year-old children: The QF2011 Queensland Flood Study

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ABSTRACT

Background: Exposure to adverse experiences during pregnancy, such as a natural disaster, can modify development of the child with potential long-term consequences. Elemental hair analysis may provide useful indicators of cellular homeostasis and child health. The present study investigated (1) if flood-induced prenatal maternal stress is associated with altered hair elemental profiles in 4-year-old children, and (2) if hair elemental profiles are associated with behavioural outcomes in children.

Methods: Participants were 75 children (39 boys; 36 girls) whose mothers were exposed to varying levels of stress due to a natural disaster (2011 Queensland Flood, Australia) during pregnancy. At 4 years of age, language development, attention and internalizing and externalizing problems were assessed and scalp hair was collected. Hair was analyzed by inductively coupled plasma mass spectrometry (ICP-MS) for 28 chemical elements.

Results: A significant curvilinear association was found between maternal objective hardship and copper levels in boys, as low and high maternal objective hardship levels were associated with the highest hair copper levels. Mediation analysis revealed that low levels of maternal objective hardship and high levels of copper were associated with lower vocabulary scores. Higher levels of maternal objective hardship were associated with higher magnesium levels, which in turn were associated with attention problems and aggression in boys. In girls, high and low maternal objective hardship levels were associated with high calcium/potassium ratios.

Conclusion: Elemental hair analysis may provide a sensitive biomonitoring tool for early identification of health risks in vulnerable children.

1. Introduction

Natural disasters are becoming more frequent as a result of climate change, and they pose a significant challenge to global health and disease risk. Natural disasters may disrupt water and food supply, cause poverty and social tensions and increase the mental health burden [1,2]. It is estimated that children are particularly vulnerable to those challenges and endure 88% of the health burden caused by natural disasters,

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with poorer children suffering the most [1]. Their risk of serious injuries or dying is immense, and between 5% and 43% of these children may experience mental health problems [1–4]. Research has shown that exposure to adverse experiences, such as natural disasters, during critical growth phases in early childhood affects their developmental trajectories with potentially profound long-term consequences [1–5]. Children exposed to natural disasters such as fires, floods, hurricanes, ice storms or earthquakes, experience altered physical growth [2,6], more severe symptoms of mental health disturbances [1,7] and have higher child mortality rates [1,2]. These deleterious effects are more pronounced if the exposure occurs during sensitive periods of brain and organ development. For example, children exposed to prenatal maternal hardship during the 1998 Quebec ice storm display motor deficits [8], underdeveloped language and cognitive skills [9,10], and metabolic disease phenotypes, including diabetes and obesity [11–13]. The QF2011 Queensland Flood study showed that maternal exposure to a flood can affect the child's development, including neurodevelopment [14–16], temperament [17], theory of mind [18], and anxiety [19]. These findings highlight the urgent need for non-invasive and accessible tools for early screening of health risks in children exposed to adverse experiences.

Elemental analysis of hair provides a robust [20], non-invasive and cost-effective health screening tool [21,22] with predictive and diagnostic value [20] that may facilitate risk assessment and delivery of targeted interventions to vulnerable pregnant mothers and their children. Hair is easy to collect and store, and it represents a unique source for long-term, retrospective biological indicators in the assessment of elemental homeostasis or metabolic changes after adverse environmental exposure [21–23]. Minerals found in hair segments originate from blood and are bound by proteins in the hair follicle [21]. The hair follicle cells incorporate minerals into hair during growth as part of an excretory mechanism for metabolic waste [22]. Because the plasma concentration of minerals and trace elements varies over time, hair elongation is able to capture longitudinal metabolic changes [21] and provides biomarkers of pathology [24], behaviour [25], stress [26] and environmental toxicants [27,28].

Using profiles of chemical elements sampled from hair, behavioural correlates have been identified for various trace elements and toxic metals [29–31]. Excess toxic metals deposited in hair, such as cadmium, and excess/deficient minerals, such as copper, sodium, potassium, calcium, and magnesium are associated with cognitive, behavioural and intellectual impairments [29,30,32]. Moreover, altered hair magnesium levels are associated with attention deficit hyperactivity disorder (ADHD) [33,34], anxiety, motor, memory, and learning impairments [35] in humans and experimental studies. Because neurodevelopmental and psychiatric disorders [36,37] and adverse experiences such as stress [38,39] are accompanied by metabolic changes, elemental profiles in hair provide accessible predictive and diagnostic biomarkers of altered nervous system function [40]. In addition, hair elemental profiles provide sensitive indicators of stress [25] and complex disease risk [24]. Here, we determined if elemental hair analysis generates indicators of environmental exposure and child neurodevelopmental and behavioural outcomes.

Taking advantage of the quasi-random nature of stress distribution associated with natural disasters, this study explored the relationship between prenatal maternal subjective distress (emotional distress experienced as a result of a disaster, such as post-traumatic stress disorder, emotional distress, panic symptoms, dissociative experience) and objective hardship (events experienced as a result of a flood-related disaster, such as physical injury, damage to residence, change in daily routines, financial loss) during the 2011 Queensland Flood in Australia. Data were interpreted in relation to the levels of elements in children's hair, and child behavioural outcomes at 4-years of age. The goals were to (1) determine if the levels of prenatal maternal subjective distress and objective hardship are associated with hair elemental profiles, and (2) determine if hair elemental profiles are associated with neurodevelopmental and behavioural outcomes. The findings suggest that elemental hair analysis provides a biomonitoring approach for early identification of vulnerable individuals at risk to facilitate timely intervention and improve long-term health outcomes.

2. Methods

2.1. Participants

The initial sample consisted of 230 English-speaking women who were pregnant with a singleton and were living in the general vicinity of Brisbane, Australia, when a flood occurred in mid-January 2011. The flood inundated 20,000 homes, causing more than $1 billion in damages [41]. During this disaster, a randomized clinical trial of midwifery care was ongoing [42]. Pregnant women in this study who met inclusion criteria were invited to participate in the current study. Additional pregnant women in the flood area were recruited by various media sources. A detailed description of the study protocol can be found in King et al. [43]. Ethics approval was obtained from the study site's ethical review board (# 1844 M), the affiliated university ethics committee (#2013001236) and the University of Lethbridge ethics committee (##2021–061). All mothers provided written, informed consent at each time point in the study. Scalp hair was obtained from 100 children, although 25 samples had insufficient amounts to conduct analyses on the hair. As such, we report data from 75 children (39 boys; 36 girls). The children were, on average, 48.8 months of age (SD=0.6 months; range=48.0–50.8 months, Table 1).

2.2. Subjective distress

Subjective distress was assessed with the Composite Scale of Maternal Subjective Stress (COSMOSS), which is a composite scale from three traumatic stress measures. These included 1) the Impact of Event Scale-Revised (IES-R) [44]; 2) the Peritraumatic Distress Inventory (PDI) [45]; and 3) the Peritraumatic Dissociative Experiences Questionnaire (PDEQ) [45]. The 22 items of the IES-R examined participants for current post-traumatic symptoms, such as intrusive thoughts, hyperarousal, and avoidance/numbing, using a 0 (not true) to 4 (extremely true) Likert scale. Emotional distress and panic symptoms were assessed from the 13-item PDI test, and dissociative-like experiences were measured using the PDEQ; both the PDI and PDEQ ask participants to recall their experiences at the time of the disaster. Principal component analysis (PCA) was used to derive an algorithm to combine scores from all three tests: $COSMOSS = 0.358 * IESR + 0.397 * PDI + 0.387 * PDEQ$. Moreover, the COSMOSS variable was standardized with a mean of 0, hence positive scores reflect results above the mean. The association analysis between hair trace element levels and maternal subjective distress showed no statistical significance. Thus, we proceeded with analyses between hair trace elements in children and maternal objective hardship scores.

2.3. Objective hardship

Flood-related objective hardship was assessed using the Queensland Flood Objective Stress Scale (QFOSS) [43]. This unique scale consists of items from four previously defined dimensions [46]: Threat (e.g., Were you injured?), Loss (e.g., Did you experience loss of income?), Scope (e.g., What percentage of your neighborhood was flooded?), and Change (e.g., Did you spend time in a shelter?). This scale was based on previous disaster-related prenatal maternal stress research [47,48]. Points assigned to each QFFOSS item were determined by group consensus. Scores on each dimension ranged from 0 (no impact) to 50 (extreme impact). The scores of each dimension were summed, resulting in a total possible score ranging from 0 to 200. Test-retest reliability for the total score was $r = 0.91$ and ranged from $r = 0.66$ to $r = 0.90$ for the four dimensions.

Table 1
Descriptive statistics for the behavioural outcomes and hair element content levels (in ppm) in boys and girls at 4 years of age. Means, SD, ranges and % of values (for each element) below the LOQ (limit of quantification) are displayed.

	Boys			Girls		
Variables	**N**	**Mean (SD)**	**Range (% below LOQ)**	**N**	**Mean (SD)**	**Range (% below LOQ)**
Age						
Child's age at assessment	39	48.79 (0.63)	47.97–50.46	36	48.77 (0.62)	48.03–50.79
Prenatal stress						
Maternal objective hardship	39	22.82 (18.21)	4.00–81.00	36	24.17 (18.47)	2.00–74.00
Behavioural outcomes						
Attention problems	36	52.86 (5.38)	50.00–70.00	31	50.97 (2.49)	50.00–62.00
Internalizing behaviour	36	44.78 (11.28)	29.00–77.00	31	41.84 (10.30)	29.00–68.00
Externalizing behaviour	36	43.97 (11.26)	28.00–73.00	31	40.52 (8.41)	28.00–56.00
Autism spectrum scale	37	13.40 (7.08)	1.00–28.00	31	13.40 (6.54)	4.00–32.00
BMI	37	16.30 (1.31)	13.60–19.00	35	15.80 (0.99)	13.80–18.10
Estimated IQ	39	109.10 (11.40)	88.00–136.00	36	110.30 (11.71)	79.00–133.00
Expressive Vocabulary	39	114.82 (13.07)	86.00 – 139.00	36	115.81 (11.38)	89.00 – 139.00
Nutritional elements						
Boron (B)	39	4.87 (7.06)	0–33.04 (5.0)	36	2.96 (2.67)	0–13.13 (3.1)
Calcium (Ca)	39	319.97 (173.31)	71.98–749.98 (0)	36	415.73 (232.4)	115.23–1001.51 (0)
Chromium (Cr)	39	0.34 (0.22)	0.12–1.59 (0)	36	0.347 (0.11)	0.20–0.67 (0)
Cobalt (Co)	39	0.02 (0.01)	0.006–0.062 (0)	36	0.041 (0.053)	0.0068–0.26 (0)
Copper (Cu)	39	32.20 (29.07)	8.21–136.53 (0)	36	45.29 (40.75)	10.52–197.09 (0)
Iron (Fe)	39	12.64 (10.15)	7.01–71.28 (0)	36	12.05 (4.14)	5.87–24.04 (0)
Magnesium (Mg)	39	42.82 (29.24)	10.85–124.64 (0)	36	68.62 (38.81)	10.30–174.47 (0)
Manganese (Mn)	39	0.45 (1.27)	0.099–8.16 (0)	36	0.32 (0.28)	0.11–1.51 (0)
Molybdenum (Mo)	39	0.044 (0.022)	0.0035–0.10 (0)	36	0.069 (0.048)	0.0184–0.26 (0)
Nickel (Ni)	39	0.45 (0.34)	0.10–1.93 (0)	36	0.58 (0.31)	0.24–1.79 (0)
Phosphorus (P)	39	123.76 (15.50)	100.86–158.53 (0)	36	120.02 (10.60)	96.67–139.07 (0)
Potassium (K)	39	467.27 (506.97)	21.40–2157.77 (0)	36	341.87 (406.90)	8.28–1667.24 (0)
Selenium (Se)	39	0.58 (0.079)	0.41–0.79 (0)	36	0.61 (0.13)	0.39–0.97 (0)
Silicon (Si)	39	47.45 (15.80)	27.97–124.24 (0)	36	71.50 (54.50)	33.91–275.64 (0)
Sodium (Na)	39	405.79 (603.64)	26.01–3643.27 (0)	36	287.54 (319.65)	23.59–1478.81 (0)
Zinc (Zn)	39	134.94 (67.04)	41.82–332.03 (0)	36	157.70 (152.71)	34.52–924.16 (0)
Ratios						
Calcium/ Potassium (Ca/K)	39	13.42 (18.42)	0.16–34.60 (0)	36	7.56 (14.27)	0.18–64.46 (0)
Sodium/ Magnesium (Na/Mg)	39	13.42 (18.24)	0.23–85.05 (0)	36	5.78 (6.32)	0.29–21.67 (0)
Sodium/ Potassium (Na/K)	39	1.84 (1.17)	0.25–6.83 (0)	36	1.55 (1.83)	0.26–9.45 (0)
Zinc/ Copper (Zn/Cu)	39	7.63 (8.34)	0.46–40.91 (0)	36	5.22 (4.42)	0.80–22.21 (0)
Toxic elements						
Aluminium (Al)	39	17.81 (14.97)	6.18–101.73 (0)	36	19.30 (9.57)	6.57–42.80 (0)
Antimony (Sb)	39	0.12 (0.35)	0.018–2.24 (0)	36	0.087 (0.06)	0.025–0.39 (0)
Barium (Ba)	39	0.58 (0.29)	0.17–1.45 (0)	36	0.90 (0.82)	0.23–4.86 (0)
Beryllium (Be)	39	0.005 (0.006)	0–0.024 (23.1)	36	0.0055 (0.0122)	0–0.06 (42.3)
Bismuth (Bi)	39	0.098 (0.15)	0.01–0.67 (0)	36	0.18 (0.37)	0.02–1.97 (0)
Cadmium (Cd)	39	0.058 (0.04)	0.0061–0.16 (0)	36	0.072 (0.057)	0.0091–0.32 (0)
Lead (Pb)	39	1.709 (1.431)	0.21 – 6.21 (0)	36	2.151 (1.458)	0.656 – 7.405 (0)
Lithium (Li)	39	0.0053 (0.0108)	0–0.054 (59.2)	36	0.0094 (0.0303)	0–0.16 (56.0)
Mercury (Hg)	39	0.29 (0.24)	0.015–0.99 (0)	36	0.59 (0.81)	0.036–5.00 (0)
Platinum (Pt)	39	0.001 (0.001)	0–0.0046 (18.2)	36	0.0024 (0.0041)	0–0.020 (2.9)
Thallium (Tl)	39	0.00048 (0.006)	0–0.0025 (13.3)	36	0.0003 (0.0003)	0–0.020 (6.1)
Tin (Sn)	39	0.42 (0.28)	0.085–1.40 (0)	36	0.75 (0.59)	0.066–3.25 (0)

The average maternal objective hardship score was 23.5 (SD=18.5; range=2.0–81.0), which was significantly higher than that of mothers for whose children hair samples were not available (M=18.3; SD=15.1, $p = 0.027$).

2.4. Child assessments

The children's body mass index was calculated by dividing their weight (kg) by their height (m^2). The children's autistic-like symptoms were assessed using the 15-item by maternal report Autism Spectrum Rating Scales – Short Form [49]. The children's symptoms of anxiety, attention deficit hyperactivity disorder, depression, somatic complaints, and internalizing and externalizing problems were assessed by maternal report using the 112-item Child Behavior Checklist [50]. The children's executive functioning abilities were assessed by an examiner using the NEPSY-II: A Developmental Neuropsychological Assessment [51]. The children's language was assessed in the lab using the Peabody Picture Vocabulary – IV [52]. The children's cognitive functioning was assessed by an examiner using the Wechsler Preschool and Primary Scale of Intelligence™ – Fourth Edition Australian and New Zealand Standardised Edition [53]. The children's motor functioning was assessed in person using the Beery-Buktenica Developmental Test of Visual-Motor Integration [54]. See Table 1 for descriptives.

2.5. Hair sampling and elemental hair analysis

About 0.6–0.8 g of scalp hair was collected from each participant at 4 years of age. Hair specimens up to 2.5 cm length were cut using clean stainless-steel scissors and stored in Ziploc bags. Elemental hair analysis was performed by CanAlt Health Laboratories (Ontario, Canada), a laboratory accredited under ISO 15189 for hair element analysis, according to previous reports [24,25]. The unwashed hair samples (300 ± 5 mg) were transferred to centrifuge tubes and the exact weight was noted. 3.0 ml of reagent-grade nitric acid (HNO_3; Fisher Scientific, Ontario, Canada) was added and then samples were incubated for 25 min. Elements of interest were stabilized by adding an acid microwave digest. Each sample was diluted by a factor of 50 with Type 1 distilled water and then analyzed by inductively coupled plasma mass spectrometry (ICP-MS; PerkinElmer Elan DRC II, Connecticut, USA). Standardized calibration solutions of known concentrations were used for comparison to quantify the sample (Inorganic Ventures, Virginia, USA and High Purity Standards, South Carolina, USA).

Quality control occurred at three levels. Two processing controls were used; the first involved a blank sample to control for possible contamination of HNO_3, water, and test tubes. The second served as in-house hair sample control to control for processing variables. In addition, two analytical controls were used; an international standard solution (CCV, continuing calibration verification; CPI International, California, USA) controlled for the optimization and calibration of the ICP-MS, and a certified standard hair reference material (GBW07601; Certified Reference Material, Institute of Geophysical and Geochemical Exploration, Hebei Province, China) with a known concentration of the elements was run with every ten samples to ensure proper readings by the ICP-MS system. Finally, duplicate samples were run to ensure robust processing standards and readings.

This study considered 28 trace elements and 4 ratios (Table 1) for which previous evidence indicated relevance to child development and behaviour (Supplemental Table 1). Selected elements were grouped into nutritional elements and toxic metals for simplicity. Five elements (B, Be, Li, Pt, Tl) had negative values or values below the level of quantification (LOQ; see Table 1 for % of values with LOQ). Negative values were replaced by 0, because 0 is the lowest possible biological value.

2.6. Statistical analysis

SPSS 20 for Windows 11.5.0 (IBM Corporation, Armonk, New York, USA) was used for statistical analysis. Linear and quadratic associations between maternal subjective distress and objective hardship and the concentration of 28 hair trace elements and 4 ratios were obtained for boys and girls separately. The Benjamini-Hochberg procedure of multiple comparisons was applied to the results. Mediation analyses were performed using the PROCESS module for SPSS [55]. In these analyses, the predictor was maternal objective hardship levels, the mediators were the hair trace element levels, and the outcomes were the children's neurodevelopmental and behavioural scores (Table 1). Mediation analyses were conducted if significant linear and/or quadratic associations before or after correction for multiple comparisons were observed between maternal objective hardship levels and hair element levels. The outcome variables for the mediation were chosen based on literature associations between trace element and phenotype (Supplemental Table 1). For significant linear effects, a simple mediation was tested with all behavioral outcome measures (Supplemental Table 1). For significant quadratic associations, curvilinear mediations were tested, such that the mediation effect (noted theta) continuously changes as objective hardship changes. Furthermore, a pick-a-point approach was conducted to determine the objective hardship range for which the

Table 2
Linear and quadratic associations between maternal objective hardship levels and nutritional element content levels in the hair of 4-year-old children. Values in italics indicate $p = 0.051$ to $p = 0.1$. The R^2 is reported as percentage. Values in **bold** indicate $p < 0.05$. 'adj. p' indicates p-value following Benjamimi-Hochberg (B-H) test of multiple comparisons.

	Linear Effect				Linear and Quadratic Effects								
	R^2	p	adj p	Linear β	R^2	p	adj p	Linear β	p	adj p	Quad β	p	adj p
	Males												
Boron (B)	3.09	0.28	0.90	-0.176	3.22	0.55	0.94	-0.292	0.59	0.83	0.122	0.82	0.86
Calcium (Ca)	1.94	0.40	0.90	0.139	3.57	0.52	0.94	-0.260	0.63	0.83	0.419	0.44	0.85
Chromium (Cr)	0.08	0.87	0.91	0.027	0.98	0.84	0.94	0.325	0.55	0.83	-0.313	0.57	0.85
Cobalt (Co)	*7.27*	*0.10*	0.59	0.270	9.38	0.17	0.79	-0.186	0.72	0.83	0.478	0.37	0.85
Copper (Cu)	**20.28**	**0.00**	*0.06*	0.450	**46.53**	**0.00**	**0.00**	**-1.156**	**0.01**	*0.06*	**1.686**	**0.00**	**0.00**
Iron (Fe)	0.19	0.79	0.90	-0.043	1.55	0.75	0.94	-0.410	0.46	0.83	0.385	0.48	0.85
Magnesium (Mg)	**11.30**	**0.04**	0.31	0.336	*11.84*	*0.10*	0.63	0.107	0.84	0.88	0.241	0.64	0.85
Manganese (Mn)	0.79	0.59	0.90	-0.089	1.20	0.80	0.94	-0.290	0.60	0.83	0.212	0.70	0.86
Molybdenum (Mo)	0.00	1.00	1.00	0.000	0.32	0.94	0.94	0.176	0.75	0.83	-0.185	0.74	0.86
Nickel (Ni)	4.20	0.21	0.90	0.205	5.95	0.33	0.94	0.620	0.25	0.83	-0.436	0.42	0.85
Phosphorus (P)	0.16	0.81	0.90	0.040	6.63	0.29	0.94	-0.757	0.16	0.83	0.837	0.12	0.75
Potassium (K)	0.78	0.59	0.90	0.088	3.44	0.53	0.94	0.599	0.27	0.83	-0.536	0.33	0.85
Selenium (Se)	0.29	0.74	0.90	0.054	3.55	0.52	0.94	-0.512	0.35	0.83	0.594	0.28	0.85
Silicon (Si)	2.16	0.37	0.90	0.147	2.82	0.60	0.94	0.401	0.46	0.83	-0.267	0.62	0.85
Sodium (Na)	2.14	0.37	0.90	0.146	3.28	0.55	0.94	0.481	0.38	0.83	-0.351	0.52	0.85
Zinc (Zn)	0.66	0.62	0.90	0.081	0.75	0.87	0.94	0.175	0.75	0.83	-0.098	0.86	0.86
Calcium/ Potassium (Ca/K)	0.77	0.59	0.90	-0.088	2.21	0.67	0.94	-0.464	0.40	0.83	0.395	0.47	0.85
Sodium/ Magnesium (Na/Mg)	0.34	0.72	0.90	-0.059	0.44	0.92	0.94	0.040	0.94	0.94	-0.103	0.85	0.86
Sodium/ Potassium (Na/K)	0.33	0.73	0.90	0.057	1.56	0.75	0.94	-0.290	0.60	0.83	0.365	0.51	0.85
Zinc/Copper (Zn/Cu)	0.87	0.57	0.90	0.093	**19.71**	**0.02**	0.17	**1.454**	**0.01**	*0.06*	**-1.428**	**0.01**	**0.05**
	Females												
Boron (B)	4.51	0.21	0.67	-0.212	4.51	0.47	0.73	-0.216	0.70	0.82	0.004	0.99	0.99
Calcium (Ca)	0.69	0.63	0.79	-0.083	9.43	0.20	0.54	*-1.009*	*0.07*	0.23	*0.972*	*0.08*	0.26
Chromium (Cr)	0.52	0.68	0.79	0.072	1.06	0.84	0.84	0.303	0.60	0.82	-0.242	0.67	0.84
Cobalt (Co)	1.83	0.43	0.78	-0.135	*15.41*	*0.06*	0.24	**-1.289**	**0.02**	0.14	**1.212**	**0.03**	0.13
Copper (Cu)	0.33	0.74	0.79	0.057	3.93	0.52	0.73	-0.538	0.34	0.62	0.625	0.27	0.49
Iron (Fe)	*7.77*	*0.10*	0.46	0.279	**25.57**	**0.01**	**0.05**	**1.600**	**0.00**	**0.04**	**-1.387**	**0.01**	*0.06*
Magnesium (Mg)	2.38	0.37	0.78	-0.154	7.57	0.27	0.59	-0.868	0.12	0.32	0.750	0.18	0.39
Manganese (Mn)	0.07	0.88	0.88	0.026	5.64	0.38	0.73	0.765	0.18	0.39	-0.776	0.17	0.39
Molybdenum (Mo)	1.52	0.47	0.78	-0.123	3.55	0.55	0.73	0.322	0.57	0.97	-0.468	0.41	0.87
Nickel (Ni)	0.87	0.59	0.79	-0.093	1.22	0.82	0.84	0.094	0.87	0.93	-0.196	0.73	0.86
Phosphorus (P)	0.79	0.61	0.79	-0.089	2.82	0.62	0.73	-0.535	0.35	0.62	0.469	0.41	0.63
Potassium (K)	3.83	0.25	0.69	-0.196	3.97	0.51	0.73	-0.080	0.89	0.93	-0.121	0.83	0.87
Selenium (Se)	0.50	0.68	0.78	0.071	10.14	0.17	0.73	*1.043*	*0.06*	0.82	*-1.021*	*0.07*	0.63
Silicon (Si)	4.64	0.21	0.67	0.215	8.64	0.23	0.54	0.841	0.13	0.32	-0.657	0.24	0.47
Sodium (Na)	0.30	0.75	0.79	-0.055	1.36	0.80	0.84	0.267	0.64	0.82	-0.338	0.56	0.74
Zinc (Zn)	**10.78**	**0.05**	0.30	0.328	**16.69**	**0.05**	0.23	-0.433	0.41	0.68	0.799	0.14	0.37
Calcium/ Potassium (Ca/K)	**14.80**	**0.02**	0.22	0.385	**36.67**	**0.00**	**0.01**	**-1.080**	**0.02**	0.14	**1.538**	**0.00**	**0.03**
Sodium/ Magnesium (Na/Mg)	1.55	0.47	0.78	-0.124	2.80	0.63	0.73	0.226	0.69	0.82	-0.368	0.52	0.73
Sodium/ Potassium (Na/K)	**13.57**	**0.03**	0.22	0.368	**29.73**	**0.00**	**0.02**	*-0.891*	*0.07*	0.23	**1.322**	**0.01**	*0.06*
Zinc/Copper (Zn/Cu)	2.85	0.32	0.79	-0.169	3.08	0.60	0.54	-0.020	0.97	0.23	-0.156	0.78	0.26

mediation was significant and then the direction of the mediation within that range.

3. Results

3.1. Maternal objective hardship levels and nutritional hair element content levels reveal linear and quadratic associations

As shown in Table 2, in boys, levels of maternal objective hardship were significantly associated with copper **(linear β = 0.45, p = 0.00001, adj. p = 0.06; quadratic β = 1.69, p = 0.0001, adj. p < 0.0001)** magnesium **(linear β = 0.34, p = 0.04, adj. p = 0.31)**, and zinc/copper ratio **(quadratic β = −1.428, p = 0.01, adj. p = 0.05)**. Specifically, a significant ($p = 0.04$, adj. $p = 0.31$) linear association between the maternal objective hardship and magnesium did not remain significant (adj. $p > 0.05$) after controlling for multiple comparisons, however, a significant ($p < 0.0001$) quadratic (U-shaped) association observed between maternal objective hardship levels and levels of copper ($p < 0.0001$), remained highly significant (adj. $p < 0.0001$) following correction for multiple comparisons. Higher levels of copper were observed when maternal objective hardship levels were both low and high. The association between higher maternal objective hardship and high levels of magnesium were not significant (adj. $p > 0.05$) after controlling for multiple comparisons. Finally, a significant ($p < 0.01$) quadratic (∩-shaped) association was observed between maternal objective hardship levels and the ratio of zinc/copper, which remained significant (adj. $p < 0.05$) following correction for multiple comparisons. The highest zinc/copper ratios were observed at moderate maternal objective hardship levels.

In girls, higher levels of maternal objective hardship were significantly associated with levels of zinc **(linear β = 0.33, p = 0.05, adj. p = 0.3)**, iron **(quadratic β = −1.39, p = 0.01, adj. p = 0.06)**, cobalt **(quadratic β = 1.21, p = 0.03, adj. p = 0.13)** and calcium/potassium ratio **(linear β = 0.39, p = 0.02, adj. p = 0.22; quadratic β = 1.54, p = 00001, adj. p = 0.03)** and sodium/potassium ratio **(linear β = 0.37, p = 0.03, adj. p = 0.22; quadratic β = 1.32, p = 0.01, adj. p = 0.06)**. Specifically, higher levels of maternal objective hardship were associated with higher levels of zinc and higher ratios of calcium/potassium and sodium/potassium ratios. However, none of these associations remained significant (zinc, adj. $p = 0.3$; iron, adj. $p = 0.06$; cobalt, adj. $p = 0.13$; calcium/potassium ratio adj. $p = 0.22$; sodium/potassium adj. $p = 0.22$) following correction for multiple comparisons. For the curvilinear associations, the maternal objective hardship and cobalt (U-shaped) association did not remain significant (adj. $p > 0.05$) following test of multiple comparisons, while iron (∩-shaped; adj. $p = 0.06$) and the maternal objective hardship - sodium/potassium ratio (adj. $p = 0.06$; U-shaped) associations became trends after a test of multiple comparison. Higher iron levels tended to be associated with moderate levels of maternal objective hardship. Higher sodium/potassium ratios tended to be associated with both low and high maternal objective hardship levels. Finally, the maternal objective hardship calcium/potassium ratio (U-shaped) association remained significant (adj. $p = 0.03$) when considering multiple comparisons; higher calcium/potassium ratios were associated with both low and high maternal objective hardship levels.

3.2. Linear and quadratic associations between maternal objective hardship levels and toxic hair element content levels

As shown in Table 3, in boys higher levels of maternal objective hardship were associated with higher levels of cadmium **(linear β = 0.34, p = 0.03)**; however, this association did not remain significant (adj. $p = 0.30$) after test of multiple comparisons. In girls, a significant U-shaped quadratic association between maternal objective hardship and arsenic levels was observed **(quadratic β = −1.24, p = 0.02)**; however, this association did not remain significant (adj. $p = 0.27$) after test of multiple comparisons.

Table 3

Linear and quadratic associations between maternal objective hardship levels and toxic element content levels in the hair of 4-year-old children. Values in italics indicate $p = 0.051$ to $p = 0.1$. The R^2 is reported as percentage. Values in **bold** indicate $p < 0.05$. 'adj. p' indicates p-value following Benjamimi-Hochberg (B-H) test of multiple comparisons.

	Linear Effect				Linear and Quadratic Effects								
	R^2	p	adj p	Linear β	R^2	p	adj p	Linear β	p	adj p	Quad β	p	adj p
	Males												
Aluminium (Al)	0.17	0.81	0.95	-0.041	1.36	0.78	0.93	-0.383	0.49	0.90	0.360	0.51	0.50
Antimony (Sb)	0.65	0.63	0.90	-0.081	0.84	0.86	0.93	0.054	0.92	0.93	-0.142	0.80	0.78
Arsenic (As)	*8.65*	*0.07*	0.31	-0.294	8.68	0.20	0.66	-0.236	0.66	0.93	-0.061	0.91	0.50
Barium (Ba)	*8.50*	*0.07*	0.31	0.292	8.50	0.20	0.66	0.282	0.59	0.93	0.010	0.98	0.50
Beryllium (Be)	0.33	0.73	0.94	0.058	4.10	0.47	0.79	0.666	0.22	0.77	-0.638	0.242	0.50
Bismuth (Bi)	0.01	0.95	0.98	0.011	1.50	0.76	0.93	0.394	0.47	0.90	-0.402	0.47	0.50
Cadmium (Cd)	**11.55**	**0.03**	0.31	0.340	13.15	0.08	0.66	-0.057	0.91	0.93	0.417	0.42	0.50
Lead (Pb)	3.45	0.26	0.84	0.186	*11.88*	*0.10*	0.66	**1.096**	**0.04**	0.52	*-0.955*	*0.07*	0.50
Lithium (Li)	1.05	0.53	0.90	-0.102	5.82	0.34	0.79	-0.787	0.15	0.77	0.719	0.19	0.50
Mercury (Hg)	1.63	0.44	0.90	0.128	4.22	0.46	0.79	-0.377	0.49	0.90	0.529	0.33	0.50
Platinum (Pt)	0.002	0.98	0.98	-0.023	0.66	0.89	0.94	0.221	0.69	0.93	-0.256	0.64	0.50
Thallium (Tl)	0.92	0.56	0.90	-0.096	1.14	0.81	0.93	0.049	0.93	0.93	-0.152	0.78	0.78
Tin (Sn)	0.83	0.58	0.90	0.091	3.96	0.48	0.79	0.646	0.24	0.77	-0.582	0.29	0.50
	Females												
Aluminium (Al)	5.82	0.16	0.73	0.241	8.40	0.24	0.76	0.744	0.18	0.60	-0.527	0.34	0.62
Antimony (Sb)	1.63	0.46	0.94	0.128	9.27	0.20	0.76	*0.994*	*0.08*	0.50	*-0.909*	*0.10*	0.62
Arsenic (As)	2.02	0.41	0.94	0.142	*16.12*	*0.06*	0.72	**1.318**	**0.02**	0.22	**-1.235**	**0.02**	0.32
Barium (Ba)	0.11	0.85	0.94	-0.033	0.18	0.97	0.97	0.050	0.93	0.93	-0.087	0.88	0.88
Beryllium (Be)	7.15	0.11	0.73	0.267	9.27	0.20	0.76	-0.189	0.73	0.79	0.479	0.39	0.62
Bismuth (Bi)	1.14	0.53	0.94	-0.107	2.36	0.67	0.87	0.238	0.68	0.79	-0.362	0.53	0.62
Cadmium (Cd)	0.33	0.74	0.94	-0.057	4.42	0.47	0.84	0.576	0.31	0.67	-0.665	0.24	0.62
Lead (Pb)	0.26	0.77	0.94	0.051	3.90	0.52	0.84	0.649	0.26	0.67	-0.627	0.27	0.62
Lithium (Li)	0.74	0.62	0.94	0.086	6.69	0.32	0.81	0.850	0.13	0.58	-0.802	0.16	0.62
Mercury (Hg)	0.14	0.83	0.94	-0.037	2.88	0.62	0.87	0.482	0.40	0.67	-0.545	0.34	0.62
Platinum (Pt)	0.08	0.87	0.94	-0.029	1.31	0.80	0.87	-0.376	0.51	0.67	0.365	0.53	0.62
Thallium (Tl)	5.48	0.17	0.73	-0.234	5.76	0.38	0.81	-0.402	0.47	0.67	0.177	0.75	0.82
Tin (Sn)	0.00	1.00	1.0	0.001	1.74	0.75	0.87	0.414	0.47	0.67	-0.434	0.45	0.62

3.3. Mediation analyses

Mediation analyses were characterized by sex differences. The analyses were conducted for significant linear and/or quadratic associations before or after correction for multiple comparisons between maternal objective hardship levels and the hair trace element levels. Our data showed, a significant mediation effects of copper ($p = 0.0002$) and magnesium levels ($p = 0.03$) on maternal objective hardship and vocabulary score and attention and externalizing problem in boys, and no significant ($p = 0.13$) mediation in girls.

In boys, curvilinear mediation revealed that trace hair copper levels mediated the relationship between objective hardship and child vocabulary score. Specifically, as objective hardship increased, the mediation effect of objective hardship on vocabulary through copper levels increased, such that the effect was negative when objective hardship was below 25 and positive above that value. However, it was only significant ($p = 0.0002$) between 4 and 12 such that higher levels of copper were associated with lower vocabulary scores in boys (Fig. 1). For all other levels of maternal objective hardship, copper did not mediate the effect of maternal objective hardship on the boy's vocabulary scores. Moreover, copper levels (quadratic effect) did not mediate the relationship between maternal objective hardship and child somatic symptoms (CBCL), attention problems (CBCL), internalizing problems (CBCL), autistic-like symptoms (ASRS), cognitive functioning (WPPSI), gross and fine motor functioning (ASQ-3), and executive functioning (NEPSY).

Furthermore, in boys, magnesium levels (linear effect) mediated the relationship between maternal objective hardship and the Attention subscale and Externalizing Problem scale of the Child Behavior Checklist (Fig. 2). In both cases, higher levels of maternal objective hardship were associated with high magnesium levels, which were associated with higher (poorer) Attention and Externalizing Problem scores. Magnesium levels (linear effect) did not mediate the relationship between maternal objective hardship levels and child somatic symptoms (CBCL), internalizing problems (CBCL), and autistic-like symptoms (ASRS).

No significant ($p > 0.05$) mediation effects were observed in girls. However, the effect of maternal objective hardship on the calcium/potassium ratio was significant ($p = 0.03$) and the effect of calcium/potassium on attention was also significant ($p = 0.04$). There was no mediation effect of maternal objective hardship on attention through calcium/potassium, however.

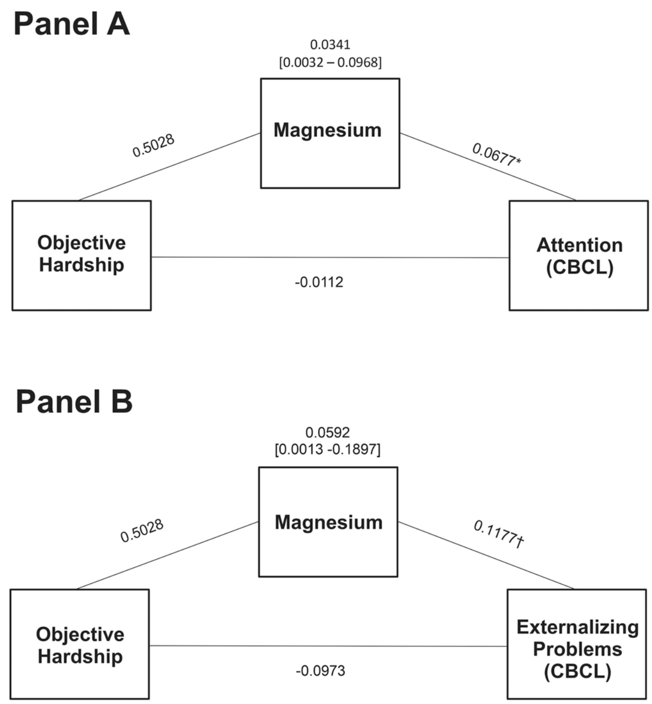

Fig. 2. Hair magnesium levels mediate the relationship between maternal objective hardship levels and CBCL Attention sub-scales levels (Panel A) and between maternal objective hardship levels and CBCL Externalizing Problem levels (Panel B) in boys. In both cases, higher levels of maternal objective hardship levels were associated with higher levels of trace hair magnesium levels, which in turn, were associated with higher CBCL scores.

4. Discussion

Increased occurrence of natural disasters due to climate change is a significant determinant of global health outcomes [56]. Of particular concern are their effects on the most vulnerable populations, pregnant women and their children [57]. Accessible biomarkers that predict adverse health outcomes due to exposure to maternal stress during prenatal sensitive periods of brain and organ development are urgently

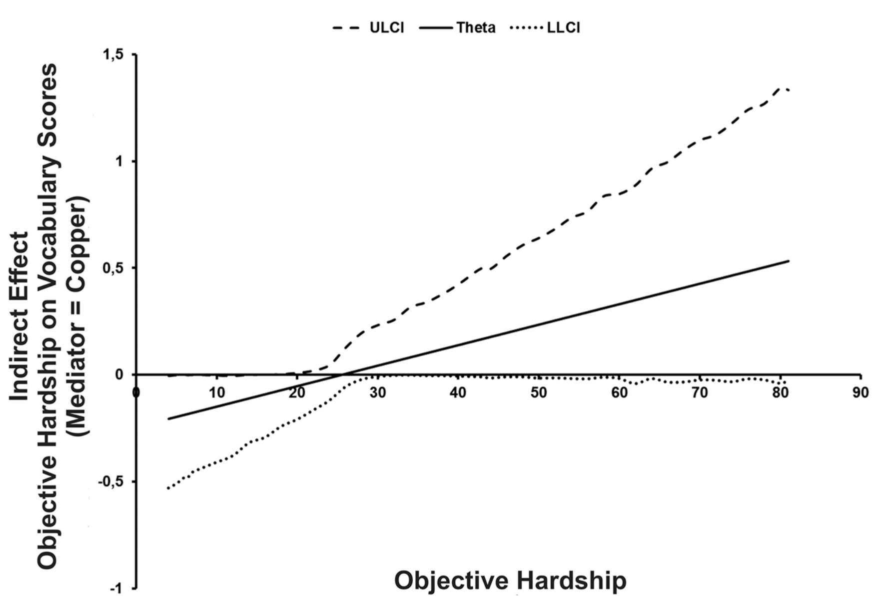

Fig. 1. Hair copper levels mediate relationship between maternal objective hardship and vocabulary scores in boys. At maternal objective hardship levels ranging between 4 and 12 higher levels of copper were associated with lower vocabulary scores in boys. For all other levels of maternal objective hardship, copper did not mediate the effect of maternal objective hardship on the boys' vocabulary scores.

needed. This study is the first to show that maternal objective hardship during pregnancy is linked to sex-specific changes in hair trace element levels and corresponding changes mediate suboptimal behavioural outcomes in children. Specifically, in boys, maternal objective hardship scores ranging between 4 and 12 were associated with higher hair copper deposits and lower vocabulary scores. Moreover, higher scores in maternal objective hardship were associated with higher levels of hair magnesium, which in turn was associated with increased externalizing behaviour and poor attention. In girls, however, high maternal objective hardship was associated with elevated calcium/potassium ratios, and calcium/potassium had an effect on attention. These data suggest that flood-induced maternal objective hardship is associated with altered hair element levels and behavioural outcomes in children and that boys and girls may be affected differently.

Sex differences in the response to prenatal maternal hardship and other early life adverse experiences have been explored in detail [4,58]. For instance, prenatal maternal hardship puts males at higher risk to develop language and motor deficits associated with neurodevelopmental disorders as compared to females [59–62]. Here we report that boys at four years of age are at particular risk of impaired language development, poor attention, and externalizing problems when exposed to maternal objective hardship linked to the 2011 Queensland Flood. The present study expands on previous knowledge by describing a curvilinear association between prenatal maternal hardship and hair trace element changes. These observations support the use of elemental hair analysis for early biomonitoring to predict the risk of behavioural disabilities in children exposed to maternal hardship.

Changes in hair trace element deposition have been observed previously in children with behavioural impairments and neurodevelopmental disorders, where they were mainly linked to adverse experiences, diet or environmental toxins [40]. Specifically, children exposed to environmental factors via diet or air pollution were reported to be at higher risk for attention deficits [62,63], hyperactivity [33] and delayed language development [29]. These children's hair showed an elevated toxic metal (aluminum, lead and cadmium) burden [62] and changes in essential elements (copper, zinc and magnesium).

Copper is an essential trace element for all living cells, and altered copper levels can affect zinc balance, interfere with adrenal hormone production [29,40], modify brain development and function [64], and impair behaviours [29,65]. Animal studies have shown that low copper levels during early development result in smaller brains with collapsed cerebral hemispheres and shallow convolution along with hypomyelination [66]. Behavioural changes associated with abnormal copper levels include irritability, fear, nervousness, learning and memory impairments, and communication problems, including language deficits [29,67,68]. It has been suggested that some of these behavioural impairments result from altered copper regulation of dopamine and norepinephrine neurotransmitter systems [29,40]. The relationship between hair copper levels and language development in children reveals dyslexic [69] and autistic traits [70] associated with significantly higher hair copper content compared to controls. Here, our findings confirm previous observations by showing that boys with the highest copper levels in their hair have lower vocabulary scores. Notably, we expand on this knowledge and demonstrate through curvilinear association that children born to mothers with lower maternal objective hardship scores (4−12) exhibited the lowest vocabulary scores, and this was mediated by high hair copper levels.

In line with the previous observations, children at higher risk for autism are believed to suffer from copper toxicity [71] in addition to low hair zinc levels and altered zinc/copper ratio. Zinc deficiencies can lead to irritability, fear, nervousness and communication problems [29,67]. The hair zinc/copper ratio has been proposed as a potential biomarker of autism spectrum disorder [30,70]. Here we report a curvilinear association between maternal objective hardship and zinc/copper ratio, as high and low maternal hardship results in children showing reduced hair zinc/copper ratios. However, the zinc/copper ratio did not show mediation effects on behavioural outcomes in children, potentially due to a small sample size. Nevertheless, the findings support the notion that an adverse prenatal environment can alter the homeodynamic regulation within the body [72].

In addition to copper and zinc, an association between child development and other trace elements including hair magnesium has been reported [33,73]. Magnesium is an essential element involved in cellular functions such as DNA, RNA and protein synthesis [35]. It is also required for normal brain development and optimal nerve transmission via regulation of excitatory neurotransmitter glutamate and the inhibitory actions of gamma aminobutyric acid (GABA) [35]. Abnormal serum and hair magnesium levels, however, have been associated with behavioural changes such as hyperactivity, nervousness, and aggression in children [33,73–75]. In the present study, higher levels of maternal objective hardship were associated with higher magnesium levels and higher CBCL Attention subscale and Externalizing Problem scores in boys. Specifically, magnesium levels mediated the relationship between maternal objective hardship on CBCL scores so that higher maternal objective hardship was associated with higher hair magnesium levels which in turn were related to higher aggression and poor attention. These findings are similar to those delineated by Marlow and Bliss (1993) reporting that higher magnesium levels are associated with greater parent- and teacher-rated distractibility, aggression and communication in a group of 3.6-year-old preschool-aged children. Thus, the present results support previous findings [33,62,68] that suggest that elevated magnesium levels are linked to inattention and aggression in boys. Our findings demonstrate for the first time that flood-induced maternal objective hardship is associated with changes in hair magnesium levels and that these are related to impaired attention and aggression in preschool boys.

The behavioural consequences of altered essential element levels such as calcium and potassium are particularly striking. Calcium and potassium participate in fundamental intracellular processes and help regulate muscle contraction, blood pressure, insulin secretion, and nervous system function [40,76,77]. Moreover, the ratio of calcium and potassium influences important physiological and metabolic functions, including thyroid gland activity [78]. A high calcium/potassium ratio indicates low thyroid activity [78,79]. In this study we report that low and high maternal objective hardship both lead to high calcium/potassium ratios, hence low thyroid gland activity in girls. A major behavioural outcome associated with high hair calcium/potassium ratio and reduced thyroid gland activity are slow metabolism, fatigue, inattention and mental dysfunction [76,78]. Interestingly, we observed an association with calcium/potassium levels and attention in girls, with increasing hair calcium/potassium ratios linked to declining attention. However, there was no mediation effect of maternal objective hardship on attention through hair calcium/potassium ratio in girls potentially due to a small sample size.

The sex-specific hair elemental signatures and behavioural outcomes reported in this study are not surprising. Prenatal development in boys and girls may involve different metabolic pathways, and maternal nutrients may be differently invested into male and female fetuses [80–82]. For instance, placental growth for a female fetus may utilize more energy and nutrients than for a male fetus [80,81]. Therefore, one may expect that maternal hardship results in sex-specific trace element levels [83], as supported by the present findings.

In spite of striking sex differences in this study, one factor remained consistent between boys and girls: the lack of effect produced by moderate levels of maternal objective hardship on hair element levels. Contrary to the adverse effects of low and high levels of maternal objective hardship on hair trace element levels in boys and girls, moderate amounts of maternal objective hardship showed no impact. Specifically, boys of mothers with moderate levels of hardship showed lower copper levels and higher zinc/copper ratios and girls exhibited a trend toward increased iron levels but normal calcium/potassium ratios. These findings suggest partial tolerance or resilience to moderate amounts of prenatal maternal hardship, which is in support of the stress inoculation hypothesis stating that children exposed to moderate adversity early in life develop stress systems that are protective against later life adversity [84–86]. It remains to be investigated how moderate exposure to maternal objective hardship may be protective against heightened trace element levels and if stress response systems via metabolic regulation may have played a protective role.

Based on tolerance to moderate maternal objective hardship, life adversity including natural disasters may not necessarily result in adverse health outcomes, unless the exposure level is severe [6]. It was proposed that the intensity of the experience might be a better predictor of poor pregnancy outcomes and child long-term health outcomes [6]. Accordingly, only mothers who experienced three or more adverse events during hurricane Katrina were at higher risk of preterm birth and smaller babies [6]. Moreover, a study of the September 11, 2001, World Trade Center attack reported increased risk of fetal intrauterine growth retardation among women exposed to high levels of polycyclic aromatic hydrocarbon (PAH) or particulate matter during pregnancy [87]. These findings suggest that exposure intensity acts according to a U-shape curve, with moderate amounts of exposure being least likely to produce negative effects, and lower and high amounts promoting adverse outcomes in children.

Although negative health outcomes following exposure to high amounts of distress during natural disasters are well documented [1,15,88], adverse effects of low amounts of disaster-related distress are less investigated. The present results show that low levels of maternal hardship is associated with high hair copper levels and language development deficits in boys at four years of age. This suggests a role for secondary stresses, such as poor nutrition and lack of resources [6], or exposure to environmental contamination, such as water, soil and air pollution typically caused by a flood [89,90]. The accumulation and excretion of these environmental pollutants may be influenced by sex-specific physiological responses to stress [83,91], which may in part explain the sexually dimorphic observations. Therefore, it may be beneficial to measure the maternal chemical element concentrations in hair along with the stress levels and correlate these with health outcomes in children in future studies.

Strengths of this study include: (1) comprehensive ICP-MS analysis of 28 toxic and essential trace elements in hair; (2) quantification of maternal objective hardship (into low, moderate and high) linked to a major natural disaster; (3) linear and quadratic association and mediation analysis between hair elements and maternal objective hardship, and mediating role of element levels on behavioural outcomes; and (4) investigation of sex-specific effects of flood-induced maternal objective hardship on hair element levels. The findings provide support for the concept that mental functions have biological underpinnings, and that altered essential trace elements levels are associated with neurochemical processes and ultimately behavioural impairments [76]. The findings support the notion that chemical accumulation in non-regenerating tissues like hair are stable, and provide robust long-term indicators of metabolic processes [65]. Hair collection is non-invasive and practical, and offers potential for early risk assessment in children exposed to natural disasters and other tragedies [33,62,92].

The main limitations of this study include: (1) lack of a control group or children not exposed to flood prenatally; (2) small sample size: (3) lack of information about dietary intake and lifestyle; (4) lack of environmental chemistry data and contamination as a result of flood or mining; and (5) the lack of further biochemical testing of the children. Thus, more comprehensive studies are required to substantiate the present findings within a developmental origins of health and disease (DOHaD) framework. Nevertheless, the present data show a clear association between flood-induced maternal objective hardship with hair chemical element levels and behavioural phenotypes in children. Based on biomonitoring through elemental hair analysis, the present data propose a potential biological mechanism to explain sex-specific behavioural and cellular homodynamic abnormalities during child development. These tools may ultimately support current efforts in identifying the most vulnerable children in need of early intervention to improve long-term health outcomes.

Ethical approval

Ethics approval was obtained from the study site's ethical review board (# 1844 M), the affiliated university ethics committee (#2013001236) and the University of Lethbridge ethics committee (##2021–061).

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CRediT authorship contribution statement

MA, GM, SK, SzK, and DL conceived the study and designed experiments. GS and DL collected the data. GE and DL performed statistical analysis. PB and NA performed hair analysis. TK assisted with literature review and table creation. MA, GM, SzK and DL wrote the manuscript.

Conflict of interest statement

Declaration of Competing Interest: Authors declare there is no conflict of interest regarding the publication of this paper.

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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.jtemb.2022.127036.

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