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Sex-specific associations between co-exposure to multiple metals and externalizing symptoms in adolescence and young adulthood

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ABSTRACT

Externalizing disorders, such as attention-deficit/hyperactivity disorder (ADHD), account for the majority of the child/adolescent referrals to mental health services and increase risk for later-life psychopathology. Although the expression of externalizing disorders is more common among males, few studies have addressed how sex modifies associations between metal exposure and adolescent externalizing symptoms. This study aimed to examine sex-specific associations between co-exposure to multiple metals and externalizing symptoms in adolescence and young adulthood. Among 150 adolescents and young adults (55% female, ages: 15–25 years) enrolled in the Public Health Impact of Metals Exposure (PHIME) study in Brescia, Italy, we measured five metals (manganese (Mn), lead (Pb), copper (Cu), chromium (Cr), nickel (Ni)) in four biological matrices (blood, urine, hair, and saliva). Externalizing symptoms were assessed using the Achenbach System of Empirically Based Assessment (ASEBA) Youth Self-Report (YSR) or Adult Self Report (ASR). Using generalized weighted quantile sum (WQS) regression, we investigated the moderating effect of sex (i.e., assigned at birth) on associations between the joint effect of exposure to the metal mixture and externalizing symptoms, adjusting for age and socioeconomic status. We observed that metal mixture exposure was differentially associated with aggressive behavior in males compared to females ($\beta = -0.058$, 95% CI [-0.126, −0.009]). In males, exposure was significantly associated with more externalizing problems, and aggressive and intrusive behaviors, driven by Pb, Cu and Cr. In females, exposure was not significantly associated with any externalizing symptoms. These findings suggest that the effect of metal exposure on externalizing symptoms differs in magnitude between the sexes, with males being more vulnerable to increased externalizing symptoms following metal exposure. Furthermore, our findings support the hypothesis that sex-specific vulnerabilities to mixed metal exposure during adolescence/young adulthood may play a role in sex disparities observed in mental health disorders, particularly those characterized by externalizing symptoms.

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1. Introduction

Externalizing disorders such as attention-deficit/hyperactivity disorder (ADHD), are estimated to affect 7–10% of children and adolescents, making them among the most common youth mental health disorders (Merikangas et al., 2009; Samek and Hicks, 2014). Expression of externalizing disorders and related symptoms (e.g., aggression, impulsivity) during adolescence has been associated with mental health problems later in life, including substance abuse and antisocial personality disorder (Babinski et al., 1999; Biederman et al., 2008; Elkins et al., 2007; Fergusson et al., 2008; Samek and Hicks, 2014). Numerous studies have explored potential risk factors contributing to adolescent externalizing symptoms; several of these studies have implicated environmental metal exposure (Bao et al., 2009; Burns et al., 1999; Khan et al., 2011; Menezes-Filho et al., 2014; Rodrigues et al., 2018; Rodríguez-Carrillo et al., 2022; Yousef et al., 2011). Associations between adolescent externalizing symptoms and single metal exposures such as lead and manganese are particularly well-established (Bao et al., 2009; Burns et al., 1999; Khan et al., 2011; Renzetti et al., 2021; Yousef et al., 2011). Despite recent evidence suggesting synergistic effects of metals on child neurobehavior (Renzetti et al., 2021), few studies have assessed the impact of mixed metal exposure on externalizing symptoms during adolescence/young adulthood. Given most individuals are faced with a mixture of exposures in daily life (Levin-Schwartz et al., 2021), examining associations between metal mixture exposure and adolescent neurobehavior is crucial to better understand the real-world impact of metal exposure during key periods of brain development.

Externalizing disorders and related symptoms are more commonly expressed in males compared to females (Samek and Hicks, 2014). Sex differences in externalizing disorders and/or symptoms may emerge from a variety of biological and environmental factors, including environmental toxicant exposures (Cahill, 2006; Rechtman et al., 2020; Torres-Rojas and Jones, 2018). Differential susceptibility to metal exposure has been previously related to sex differences in child and adolescent neurobehavior (Burns et al., 1999; Gade et al., 2021; Joo et al., 2018; Llop et al., 2013; Menezes-Filho et al., 2014; Rechtman et al., 2020; Vahter et al., 2007). However, with the exception of lead, whose neurotoxicity has been largely suggested to impact males more than females (Gade et al., 2021; Llop et al., 2013; Polanska et al., 2018; Ris et al., 2004; Singh et al., 2018; Vahter et al., 2007), the sex-specific neurotoxicity of many metals is still unclear. Studies on other metals such as manganese have found evidence of sex-specific neurotoxicity in both sexes, with varying results based on the neurobehavioral outcome (e.g., IQ, attention) and/or time of exposure (e.g., prenatal, childhood) (Menezes-Filho et al., 2014; Mora et al., 2015). Lead has also shown varying sex-specific effects based on these factors (Joo et al., 2018; Merced-Nieves et al., 2022). Importantly, such studies have mainly focused on metal exposure during the prenatal and/or early childhood periods, leaving adolescence and young adulthood as relatively understudied exposure windows (Rechtman et al., 2020). Given, adolescence and young adulthood are timepoints of emergent sex differences in brain and behavior (Raznahan et al., 2010; Sisk and Zehr, 2005), examining interactions between sex and metal exposure during adolescence/young adulthood may bring novel insight into sex-specific vulnerabilities unique to this critical developmental window.

In this study, we take a data driven approach to investigate how combined exposure to five neuroactive metals lead (Pb), manganese (Mn), chromium (Cr), copper (Cu) and nickel (Ni) measured in four biological matrices (blood, urine, hair, and saliva) during adolescence and young adulthood associate with externalizing symptoms in adolescents and young adults enrolled in Public Health Impact of Metals Exposure (PHIME) study. We hypothesized that these neuroactive metals are jointly acting, yielding a so-called "mixture effect" that is associated with increased externalizing symptoms. In particular, we hypothesized that sex (i.e., assigned at birth) modifies the association between metal mixture exposure and externalizing behaviors during adolescence/young adulthood, with males being more vulnerable to increased externalizing behaviors following metal mixture exposure.

2. Materials and methods

2.1. Participants

The PHIME study investigates associations between metal exposure from anthropogenic emissions and developmental health outcomes in adolescents and young adults (n = 717) living in Lombardy, Italy. Details of the study have been described elsewhere (Lucas et al., 2015; Lucchini et al., 2012a). Inclusion criteria included: birth in the areas of interest; family residence in Brescia for at least two generations; residence in the study areas since birth. The exclusion criteria included: having a neurological, hepatic, metabolic, endocrine, or severe psychiatric disorder; using neuroactive medications; having clinically diagnosed motor deficits or cognitive impairment, and having visual deficits that are not adequately corrected. Between 2016 and 2021, a subset of PHIME participants (n = 207) participated in a voluntary follow-up study, involving biological sample collection, additional self and interviewer-assisted questionnaires, and neuropsychological tests. Metals (Mn, Pb, Cr, Cu, and Ni) were measured in saliva, hair, blood, and urine collected in the same follow-up visit. Out of the 207 PHIME participants, 45 subjects were excluded due to incompletion of the Achenbach System of Empirically Based Assessment (ASEBA) Youth Self Report (YSR) (Achenbach and Rescorla, 2001, 2007) or ASEBA Adult Self Report (ASR) (Achenbach and Rescorla, 2003, 2015). Additionally, 12 subjects were excluded for missing covariate data (n = 3), or missing exposure data in at least one biomarker (n = 9). The present study therefore included 150 adolescents and young adults (55% female, ages 15–25 years). Written informed consent was obtained from participants and the parents of participants below the age of consent (<16 years of age). Study procedures were approved by the Institutional Review Board (IRB) of the University of California, Santa Cruz and the ethical committees of the University of Brescia, and the Icahn School of Medicine at Mount Sinai.

2.2. Biomarkers of exposure

Biological samples including venous whole blood, spot urine, saliva and hair were collected using procedures previously described at the adolescent/young adult study visit (Eastman et al., 2013; Lucas et al., 2015; Smith et al., 2007). Complete overview of biomarkers can be found in Table 2. Biological samples were processed and analyzed for metal concentrations at the Physical Science Building laboratory facility of University of California Santa Cruz, using magnetic sector inductively coupled plasma mass spectroscopy (Thermo Element XR ICP-MS) and standardized testing materials as described elsewhere (Eastman et al., 2013; Lucas et al., 2015; Smith et al., 2007). The majority of measurements were above the sample limits of detection (LODs). Sample LODs were calculated by converting the analytical LOD (analytical LOD in ng/mL of analyzed sample digestate) to an LOD in the original sample based on the average sample amount (e.g., mg or mL, depending on sample type) processed for analyses; measurements below the LOD were assigned a value of one half the sample LOD. Percentage of metals in biological samples above the LODs are reported in Table 2.

Table 1
Sex-Stratified sociodemographic and behavioral characteristics of adolescents and young adults enrolled in the PHIME cohort who were included in the current study (n = 150).

Characteristic	All Participants (n = 150) Mean ± SD or %		Males (*n* = 67) Mean ± SD or %	Females (*n* = 83) Mean ± SD or %	p[a]
Age (years)	19.2 ± 2.50		18.6 ± 2.62	19.6 ± 2.35	**0.04**
SES					
Low	26.0%		22.4%	28.9%	0.26
Medium	49.3%		56.7%	43.4%	
High	24.7%		20.9%	27.7%	
Externalizing Problems	49.6 ± 8.80		49.8 ± 8.96	49.4 ± 8.71	0.92
Clinical (n = 8) (5 females, 3 males)	68.12 ± 2.70	67.7 ± 2.08	68.4 ± 3.21		0.65
Borderline Clinical (n = 9) (5 females, 4 males)	61.1 ± 1.27	60.8 ± 1.5	61.4 ± 1.14		0.36
Aggressive Behavior	54.5 ± 5.65		54.4 ± 5.17	54.5 ± 5.86	0.85
Clinical (n = 3) (3 females, 0 males)	74.7 ± 4.16		NA	74.7 ± 4.16	NA
Borderline Clinical (n = 9) (5 females, 4 males)	61.1 ± 1.27		60.8 ± 1.5	61.4 ± 1.14	0.36
Rule-breaking Behavior	52.6 ± 3.66		52.7 ± 3.60	52.4 ± 3.73	0.85
Clinical (n = 0)	NA		NA	NA	NA
Borderline Clinical (n = 3) (2 females, 1 male)	67.0 ± 1.00		68.0 ± NA	66.5 ± 0.707	0.66
Intrusive[b]	52.9 ± 4.89		53.8 ± 5.69	52.4 ± 4.31	0.12
Clinical (n = 1) (0 females, 1 male)	73.0 ± NA	73.0 ± NA	NA	NA	
Borderline Clinical (n = 5) (3 females, 2 males)	67 ± 1.22	67.0 ± 0	67.0 ± 1.73		0.76

SES socioeconomic status.

[a] Differences in the distribution of age and SES between males and females were tested using Wilcoxon rank-sum or Chi-square tests. Differences in the distribution of T-scores for YSR/ASR scales were tested using logistic regression, adjusted for age and SES. Differences in the distribution for YSR/ASR T-scores within the borderline and/or clinical ranges were tested using Wilcoxon rank-sum tests..

[b] Analysis included participants who completed the ASR intrusive scale (N = 107).

2.3. ASEBA YSR and ASR questionnaires

To assess behavioral outcomes, participants self-administered the Achenbach System of Empirically Based Assessment Youth Self Report (YSR) (Achenbach and Rescorla, 2001, 2007) or Adult Self Report (ASR) (Achenbach and Rescorla, 2003, 2015) in the presence of a trained psychologist. The YSR and ASR are self-report questionnaires that assess behavioral, emotional, and social problems (Ediati et al., 2015; Ivanova et al., 2015). The YSR is designed for ages 11–18, whereas the ASR is designed for ages 18–59. Among the PHIME participants included in this study (n = 150), 43 participants (ages 15–17) completed the Youth Self Report (YSR), and 107 participants (ages 18–25) completed the Adult Self-Report (ASR).

The ASR and YSR consist of 3 summary scales derived from corresponding syndrome scales: internalizing problems, externalizing problems, and total problems. Items on ASR/YSR are rated on a 3-point Likert scale: 0 being "not true", 1 "partly or sometimes true", and 2 "very/often true". Items that correspond to each syndrome scale are combined to compute a raw score for each scale. For summary scales (e.g., externalizing problems), raw scores are computed by combining scores of their corresponding syndrome scales. The ASR externalizing problems score is computed by combining scores on the aggressive behavior, rule-breaking behavior, and intrusive syndrome scales. Similarly, the YSR externalizing problems score is computed by combining scores from the aggressive behavior and rule-breaking behavior syndrome scales. Raw scores on both syndrome and summary scales are used to compute T-scores (mean = 50, standard deviation = 10) with predefined clinical cut-offs based on population norms. T-scores for the YSR/ASR range from 25 to 100 for summary scales and 50–100 for syndrome scales. Additionally, according to the ASEBA multicultural manual, T-scores greater than 63 for summary scales and greater than 69 for syndrome scales are considered clinically significant (>98th percentile) (Tesei et al., 2020). T-scores between 60 and 63 (summary scales), or 65–69 (syndrome scales) are considered borderline clinically significant (93rd to 98th percentile).

The ASR and YSR have corresponding counterparts for several syndrome scales; scores on these counterparts can be directly compared (Achenbach, 2019). Several studies have aggregated ASR and YSR scores to assess behavioral and emotional problems in early to late adolescence (Coelho et al., 2013; Le Fur et al., 2020; Ly et al., 2011; Morosan et al., 2017; Zondervan-Zwijnenburg et al., 2020). Furthermore, both the YSR and ASR have been validated and used across several cultures (Achenbach, 2010, 2019; Bianchi et al., 2022; Ivanova et al., 2007, 2015; Morosan et al., 2017; Rescorla et al., 2007), including Italian populations (Gatta et al. n.d.; Graziano et al., 2016; Tesei et al., 2020). For this study, we used versions that have been validated in the Italian population and used T-scores from the following YSR/ASR scales to assess externalizing symptoms: externalizing problems, aggressive behavior, and rule-breaking behavior. T-scores from the ASR intrusive scale, and the YSR/ASR internalizing problems and total problems summary scales were also assessed. These scores were then used in subsequent statistical analyses.

2.4. Statistical analysis

2.4.1. Covariates

Sociodemographic data (i.e., sex assigned at birth, age, and parental occupation and education) were collected through questionnaires (Butler et al., 2019). An index of family socioeconomic status (SES; low, medium or high) was calculated from parental age, occupation and education (Butler et al., 2019; Cesana et al., 1995; Lucchini et al., 2012b).

2.4.2. Descriptive statistics

Visual inspection and descriptive statistics (geometric mean (GM) and geometric standard deviation (GSD)) were used to characterize the metal concentrations in different biological matrices. Spearman's rank correlations were used to assess differences in metal concentrations between each metal biomarker in males and females, respectively (Fig. S4). Wilcoxon rank-sum tests and Chi-Square tests were used to assess differences in the distribution of covariates (age, SES) between males and females (Table 1). Logistic regression (adjusted for age and SES), was used to assess differences in the distribution of behavioral outcomes between males and females (Table 1). Wilcoxon rank-sum tests were used to compare the distribution of behavioral outcomes within the clinical and/or borderline clinical ranges between males and females (Table 1). Descriptive statistics were performed using R 4.2.2.

2.4.3. Generalized weighted quantile sum regression: sex-stratified interaction model

To examine the moderating effect of sex on associations between the

Table 2
Metal concentrations (Mn, Pb, Cr, Cu and Ni) measured in blood, urine, hair and saliva collected from the 150 PHIME adolescents included in the current study.

Metal Concentration	LOD Range	% > LOD	All Participants GM ± GSD	Males (N = 67)	Females (N = 83)	p[a]
Saliva (ug/L)						
SPb	0.002–0.180	91	0.202 ± 3.05	0.199 ± 2.74	0.205 ± 3.33	0.71
SCr	0.046–0.219	91	0.519 ± 3.71	0.596 ± 3.75	0.465 ± 3.66	0.52
SMn	0.044–0.108	96	3.23 ± 2.97	3.41 ± 2.59	3.10 ± 3.30	0.82
SNi	0.021–0.341	97	11.33 ± 3.14	1.42 ± 3.22	1.26 ± 3.08	0.91
SCu	0.025–1.075	97	9.15 ± 2.40	8.46 ± 2.30	9.74 ± 2.48	0.30
Hair (ug/g)						
HPb	0.00007–0.006	100	0.096 ± 3.14	0.064 ± 3.06	0.132 ± 2.90	**< 0.001**
HCr	0.0005–0.006	100	0.039 ± 2.74	0.029 ± 2.65	0.049 ± 2.67	**< 0.01**
HMn	0.0005–0.017	100	0.061 ± 2.62	0.044 ± 2.22	0.078 ± 2.76	**< 0.001**
HNi	0.0006–0.036	87	0.035 ± 4.88	0.023 ± 4.38	0.050 ± 4.93	**< 0.001**
HCu	0.0008–0.089	100	10.3 ± 1.65	9.01 ± 1.48	11.4 ± 1.74	**< 0.01**
Urine (ug/L)						
UPb	0.012–0.147	98	0.343 ± 2.57	0.391 ± 2.42	0.309 ± 2.66	0.16
UCr	0.018–0.160	96	0.287 ± 3.15	0.360 ± 3.02	0.240 ± 3.18	0.07
UMn	0.068–0.175	80	0.268 ± 3.64	0.286 ± 3.81	0.254 ± 3.52	0.74
UNi	0.095–0.341	97	1.18 ± 2.53	1.15 ± 2.34	1.20 ± 2.70	0.45
UCu	0.141–0.504	100	5.95 ± 1.91	5.91 ± 1.80	5.98 ± 2.00	0.99
Blood (ug/L)						
BPb	0.071–0.230	100	8.49 ± 1.56	9.69 ± 1.55	7.62 ± 1.52	**< 0.001**
BCr	0.040–0.378	63	0.335 ± 4.68	0.355 ± 4.10	0.320 ± 5.21	0.60
BMn	0.175–0.815	100	8.57 ± 1.50	8.01 ± 1.38	9.05 ± 1.57	0.12
BNi	0.095–1.160	73	1.93 ± 7.30	1.61 ± 6.15	2.23 ± 8.30	0.75
BCu	0.352–2.200	100	593 ± 1.30	522 ± 1.19	658 ± 1.32	**< 0.001**

LOD limit of detection (analytical LOD adjusted for sample amount), *GM* geometric mean, *GSD* geometric standard deviation.
[a] Differences in the distribution of variables between males and females were tested using linear regression on log-transformed concentrations, adjusted for age, sex, and SES.

metal mixture (5 metals, 4 biological matrices) and externalizing symptoms measured by the YSR or ASR, we used sex-stratified interaction weighted quantile sum (WQS) regression models (Gennings et al., 2022). Briefly, weighted quantile sum (WQS) regression is a data driven, mixtures-based ensemble modeling strategy that tests for associations between exposure to a mixture containing multiple, potentially correlated variables and an outcome of interest (Carrico et al., 2015). WQS is implemented over two steps: 1) estimation of a weighted index representing the association between the mixture components and the outcome using bootstrap sampling of observations; 2) a significance test for the regression coefficient associated with the WQS index (Carrico et al., 2015; Gennings et al., 2022). The WQS index is calculated as $WQS_j = \sum_{i=1}^{c} w_i q_{i,j}$, where WQS is the mixture index, $q_{i,j}$ is the ranked (quantiled) concentration for an ith predictor and jth subject, and w_i is the empirically estimated weight corresponding to q_i (Eggers et al., 2022). Weights associated with each predictor provide an indication of each predictor's contribution to the overall association between the mixture and the outcome. All weights are constrained to sum to one, enabling sorting by relative importance.

The WQS stratified interaction model (Busgang et al., 2022; Gennings et al., 2022), builds upon the WQS by allowing for estimation of the WQS index in the presence of interaction with a continuous or categorical variable.

The parametrization for the WQS stratified-interaction model is given by: $\beta_0 + \beta_1 WQS + \beta_2 x + \beta_{12} xWQS$, where x is an indicator for a binary variable (e.g., sex). When x = 0, these terms would be: $\beta_0 + \beta_1 WQS$, and when x = 1, they would be $(\beta_0 + \beta_2) + (\beta_1 + \beta_{12})WQS$. Thus, β_2 indicates the change in the intercept due to the binary variable, β_{12} is the change in the slope of WQS due to the variable, and $\beta_1 + \beta_{12}$ is the slope for the category when x = 1. In such a parameterization, the WQS stratified interaction model allows for strata-specific weights and regression coefficients (Gennings et al., 2022). We used a sex-stratified interaction WQS model, which allowed for sex-specific weights and regression coefficients. In our model parameterization, the beta estimate associated with WQS index is the slope for the reference group (males), the sum of the betas associated with the WQS index and the interaction term is the slope for the comparison group (females), and the beta for the interaction between WQS index and sex is the difference in slopes between males and females (Gennings et al., 2022). Our models estimated across 50 bootstrap samples, and 100 repeated holdouts (Tanner et al., 2019). Metal concentrations were ranked in deciles to estimate the weights for each holdout. By using WQS with repeated holdouts, the data are randomly partitioned 100 times to produce a distribution of effect estimates and mixture weights, where the mean or the median can be taken as the final estimate. Given the differences in outcomes, the WQS analysis for the externalizing problems summary scale used linear regression, while the WQS analyses for the aggressive behavior, rule-breaking behavior and intrusive syndrome scales used quasi-Poisson regression. For all analyses, the directionality of the association of the WQS index was constrained in the positive direction to assess the hypothesized harmful effects of the metal mixture on externalizing symptoms.

3. Results

3.1. Demographic characteristics

Table 1 reports the demographic and behavioral characteristics of the 150 adolescents and young adults included in this study, stratified by sex. A comparison of demographic characteristics between adolescents included the current study, the follow-up study (n = 207) and the full PHIME cohort (n = 717) can be found in the Supplementary Material (Table S1). Participants mean age was 19.1 (SD = 2.5) when the YSR or ASR was administered. There was a significant age difference between sexes, with females being significantly older than males (p = 0.04). Socioeconomic status did not significantly differ by sex. Mean T-scores on the externalizing problems, aggressive behavior, and rule-breaking behavior YSR/ASR scales were not clinically significant for either sex, and did not significantly differ by sex. Mean T-scores on the ASR intrusive scale (n = 107) were not clinically significant for either sex, and did not significantly differ by sex. Across the externalizing problems, aggressive behavior and rule-breaking behavior scales, ~7% of T-scores from either sex fell within the clinical range (n = 11: 8 females, 3 males), and ~11% fell within the borderline clinical range (n = 16: 9 females, 7 males). For the ASR intrusive scale, less than 1% of T-scores from either sex fell within the clinical range (n = 1: 0 females, 1 male),

and ~5% fell within the borderline clinical range (n = 5: 3 females, 2 males). Histograms displaying T-Score distributions of YSR/ASR scales for males and females are shown in Supplementary Material (Fig. S1).

3.2. Exposure characteristics

Metal concentrations in the different matrices are reported in Table 2. Blood Cu and Pb concentrations significantly differed by sex, with Cu concentrations higher in females compared to males (males: 522 ± 1.19 μg/L, females: 658 ± 1.32 μg/L; $p < 0.001$) and blood Pb concentrations significantly higher in males compared to females (Males: 9.69 ± 1.55 μg/L, Females: 7.62 ± 1.52 μg/L; $p < 0.001$). Hair metal concentrations were significantly higher in females compared to males for all metals (Table 2). Metal concentrations in saliva and urine did not significantly differ by sex.

3.3. Sex-specific effects of exposure to metal mixtures and externalizing symptoms

Table 3 provides a summary of the distribution of effect estimates from the WQS sex-stratified interaction models for the externalizing problems, aggressive behavior, rule-breaking behavior, and intrusive scales. Results from the WQS sex-stratified interaction models suggest sex-specific vulnerabilities to the combined effect of metal mixture exposure on externalizing symptoms in adolescents/young adults. The interaction between the WQS index and sex was significant for the aggressive behavior syndrome scale (Table 3; (β = −0.058, 95% CI [−0.126, −0.009]) and borderline significant for the externalizing problems summary scale (β = −0.594, 95% CI [−1.090, 0.141], and the intrusive syndrome scale (β = −0.040, 95% CI [−0.115, 0.008]). In males, metal mixture exposure was significantly associated with higher scores on the externalizing problems. aggressive behavior, and intrusive scales (Table 3; β = 0.487, 95% CI [0.065, 0.947]; β = 0.043, 95% CI [0.011, 0.109]; β = 0.041, 95% CI [0.002, 0.100], respectively). In females, metal mixture exposure was not significantly associated with scores on either the externalizing problems (β = −0.044; 95% CI [−0.551, 0.300]), aggressive behavior (β = −0.013; 95% CI [−0.059, 0.026]) or intrusive (β = −0.005; 95% CI [−0.047, 0.028]) scales. Metal mixture exposure was not significantly associated with scores on the rule-breaking behavior syndrome scale for either sex (Table 3; Females: β: = 0.010; 95% CI [−0.011, 0.053]). Fig. 1 displays the distributions of the 100 repeated holdouts for the externalizing problems, aggressive behavior scales. The distribution of the 100 repeated holdouts for the rule-breaking behavior scale can be found in Supplementary Material (Fig. S2). Results from non-interaction models showed a significant association between the metal mixture and the externalizing problems summary scale only (Supplementary Material - Table S2). Results from models for the internalizing and total problem summary scales were not significant (Supplementary Material - Table S3, Table S4).

Table 3
Associations between metal mixture exposure and externalizing symptoms among adolescent and young adult PHIME participants.

Outcome	Parameter	Median	2.5th percentile	97.5th percentile
Externalizing Problems	WQS index	**0.487**[c]	**0.065**	**0.947**
	Female	−0.044	−0.551	0.300
	WQS index X Female	−0.594	−1.090	0.141
Aggressive Behavior[a]	WQS index	**0.043**[c]	**0.011**	**0.109**
	Female	−0.013	−0.059	0.026
	WQS index X Female	**−0.058**[c]	**−0.126**	**−0.009**
Rule-breaking Behavior[a]	WQS index	0.005	−0.021	0.030
	Female	0.010	−0.011	0.053
	WQS index X Female	0.006	−0.032	0.047
Intrusive[a,b]	WQS index	**0.041**[c]	**0.002**	**0.100**
	Female	−0.005	−0.047	0.028
	WQS index X Female	−0.040	−0.115	0.008

Note: Effect estimates (median, 2.5 percentile, 97.5 percentile) from WQS sex-stratified interaction regressions for externalizing symptoms, across 100 holdout datasets. The slope associated with WQS is for males; the interaction between WQS and sex is the difference in slopes between males and females. N = 150; training n ~45, validation n ~105; βs were constrained in the positive direction.

[a] Association with WQS index assessed using quasi-Poisson regression.

[b] Association with WQS index assessed among participants who completed the ASR intrusive scale (N = 107; training n ~32, validation n ~75; βs were constrained in the positive direction).

[c] Association is statistically significant.

Given the significant associations found between the metal mixture and externalizing symptoms in males, we assessed the distribution of estimated weights for males across the repeated holdouts (Fig. S3) to identify potential metals of concern among each of the four biological matrices (blood, hair, saliva, urine). In males, Pb, Cu and Cr were the highest contributing metals across all 3 scales. For the externalizing problems and aggressive behavior scales, Pb and Cr (in all matrices combined) contributed to ~21–22% of the relative weights for males and Cu (in all matrices combined) contributed to ~23–24% (Fig. 2). For the intrusive scale, Pb and Cu (in all matrices combined) contributed to ~18% of the relative weights for males, and Cu (in all matrices combined) contributed to ~25%. Similarly, for each scale in males, all blood metals had mean weights above the threshold of 1/40 = 0.025 (where 40 is the total number of weights, 20 for boys and 20 for girls) (Fig. 1; Fig. S3). For both externalizing problems and aggressive behavior, most saliva metals (except saliva Ni) had mean weights above this threshold. Most saliva metals (except saliva Ni and saliva Mn) were also above this threshold for the intrusive scale. In hair, only Cr and Cu had mean weights above the cut off across all 3 scales. None of the urine metals had mean weights above the threshold for any of the 3 scales. Overall, these results suggest that Pb, Cu, and Cr may be driving the association between metal mixture exposure and increased externalizing symptoms in males. Furthermore, these results suggest that blood and saliva may be important biomarkers for assessing associations between metal mixture exposure associations and externalizing symptoms in adolescence/young adulthood.

4. Discussion

To our knowledge, this is the first study to examine sex-specific associations between metal mixture exposure and adolescent/young adult neurobehavior using multiple biological matrices (blood, saliva, hair, urine). We observed that associations between exposure to a mixture of neuroactive metals and externalizing symptoms differed by sex, suggesting sex-specific vulnerability to metal neurotoxicity during adolescence and young adulthood. In males, exposure to the metal mixture was associated with more externalizing symptoms (i.e., externalizing problems, aggressive behavior, intrusive behavior). These associations were predominantly driven by Pb, Cu and Cr. In females, metal exposure was not associated with externalizing symptoms. Our results suggest that a) the effect of co-exposure to neurotoxic metals differs by sex and b) adolescence and young adulthood are sensitive developmental periods for metal exposure. Additionally, our findings suggest these sex-specific associations are due to combined exposure to multiple metals, emphasizing the importance of examining metal mixtures to better understand the impact of metal exposure on adolescent and young adult neurobehavior.

Previous epidemiological studies have similarly observed sex-specific associations between metal exposure and adolescent externalizing symptoms (Burns et al., 1999; Joo et al., 2018; Menezes-Filho et al., 2014; Mora et al., 2015; Naicker et al., 2012), suggesting that male and female neurobehavior are not equally vulnerable to metal exposure

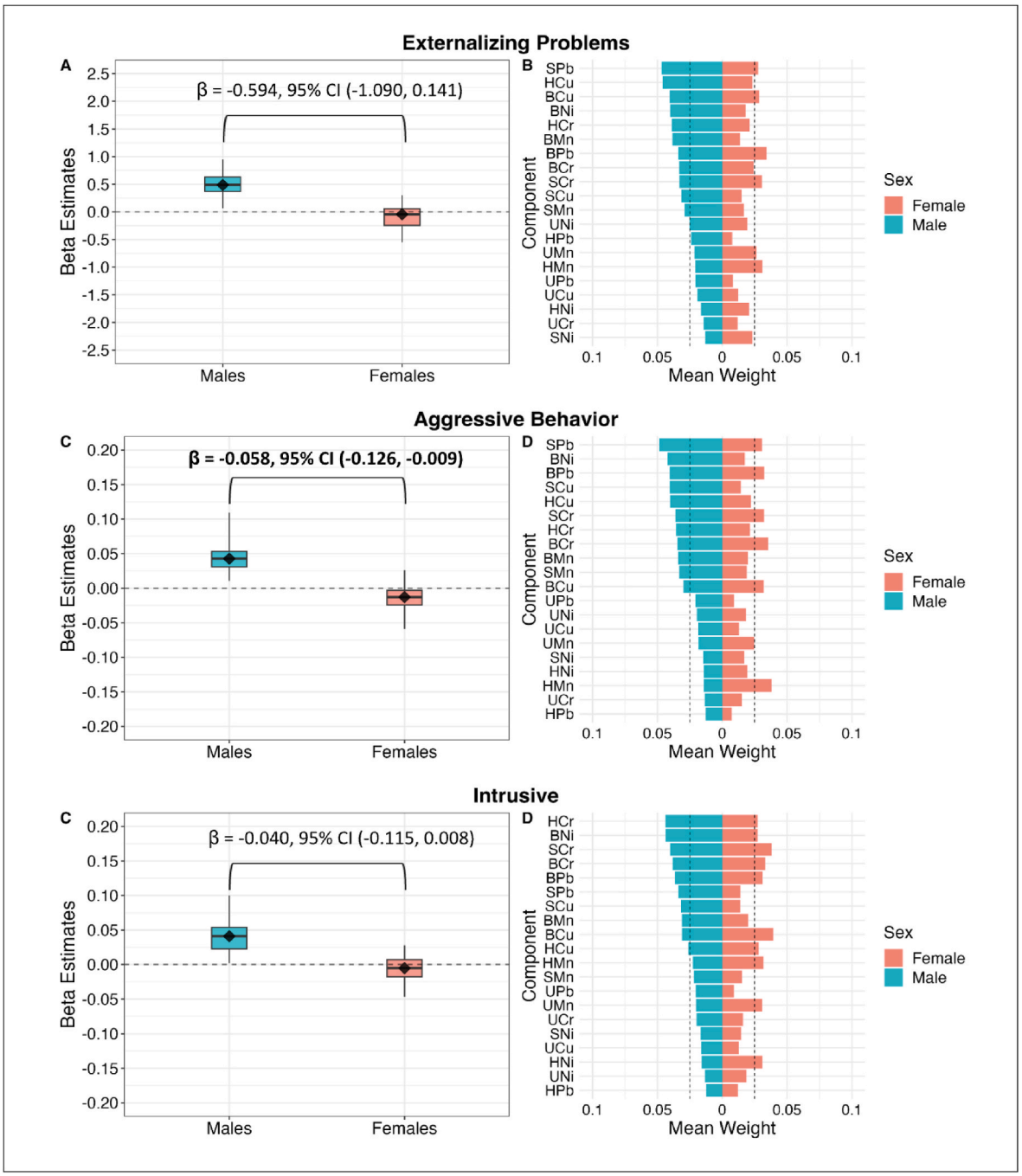

Fig. 1. The moderating effect of sex on associations between the WQS metal mixture index and externalizing symptoms among the 150 PHIME participants included in the current study. (A–D) Results from the WQS sex-stratified interaction regression models for the YSR/ASR externalizing problems and aggressive behavior scales, using 100 repeated holdouts and controlling for sex, age, and SES (N = 150; training n ~ 45, validation n ~ 105). **(E–F)** Results from the WQS sex-stratified interaction regression models for the ASR intrusive scale (N = 107; training n ~ 32, validation n ~ 75). **(A,C,E)** Distribution of WQS estimates for males and females. Diamonds show the median effect estimate for the 100 holdouts, boxplots show the 25th, 50th and 75th percentiles, and whiskers show the 2.5th and 97.5th percentiles. **(B,D,F)** Mean estimated sex-specific weights from the 100 holdouts. The dotted lines represent the threshold from the equi-weighted index (i.e., 1/(2c)), where c is the number of components in the mixture.

in adolescence. Sex differences in brain development may confer sex-specific vulnerabilities to metal neurotoxicity during adolescence and young adulthood. Multiple studies have found that males display a relatively protracted maturation in brain regions associated with externalizing symptoms (e.g., amygdala, prefrontal cortex) compared to females, particularly in early and late adolescence (Fish et al., 2020; Gennatas et al., 2017; Lenroot et al., 2007; Lenroot and Giedd, 2010; Mills et al., 2014; Uematsu et al., 2012). Such findings suggest males may be more vulnerable to metal neurotoxicity in adolescence, and in turn, are at greater risk for metal-associated psychopathology. For example, Pb exposure in males has been consistently linked with externalizing symptoms in adolescence and young adulthood, particularly delinquency (Dietrich et al., 2001; Emer et al., 2020; Needleman et al., 1996, 2002; Wright et al., 2008) and aggression (Burns et al., 1999; Naicker et al., 2012). Results from these studies also support our finding that Pb (in all matrices combined) was a top contributor to the association between the metal mixture and externalizing symptoms in males (Fig. 1; Fig. 2). While comparatively less studies have linked Cu

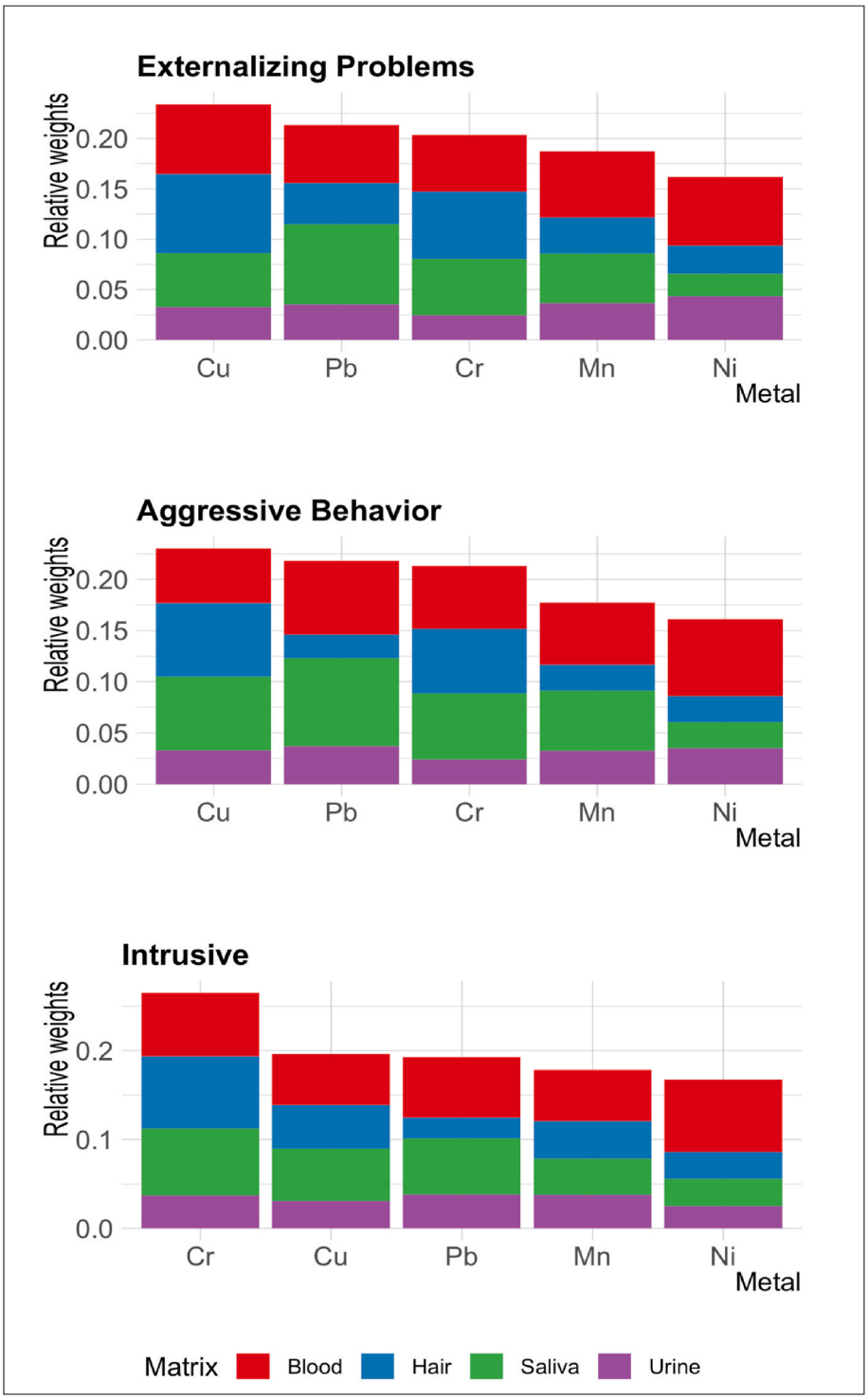

Fig. 2. - Metals contributing to increased externalizing symptoms in males, summed across all biological matrices. Relative mean weights for each metal across the four biological matrices (blood, hair, saliva, urine), using WQS sex-stratified regression with 100 repeated holdouts.

and/or Cr with externalizing symptoms, altered Cu and Cr concentrations have been observed in children/adolescents with ADHD (Li et al., 2020; Russo, 2010; Skalny et al., 2020; Viktorinova et al., 2016) and youth and adults (majority male) with violent behavioral history (Cromwell et al., 1989; Marlowe et al., 1991; TOKDEMIR et al., 2003; Walsh et al., 1997). Current epidemiological data also suggests Cu and Cr may similarly exhibit sex-specific neurotoxicity. Zhou et al. (2015) observed sex-specific associations between Cu exposure and working memory deficits in adolescence, with results suggesting greater susceptibility among males. This Cu-associated deficit in working memory may be attributed to its impact on attention (Alemany et al., 2017; Amorós et al., 2019; Kicinski et al., 2015; Marlowe and Bliss, 1993; Salustri et al., 2010; Zhou et al., 2015). Amorós et al. (2019) observed similar sex-specific associations between Cr exposure and attentional deficits in childhood; results also suggested greater vulnerability among males. Impaired attention (e.g., inattention, distractibility) is a common feature of externalizing disorders (Harrison et al., 2012; Samek and Hicks, 2014) and is predictive of externalizing-related

psychopathology (e.g., substance use disorder) in adolescence (Elkins et al., 2007). Therefore, our finding that Cu and Cr (in all matrices combined) were also top contributors to the observed associations in males is similarly supported, albeit less directly, by previous literature.

Sex differences in metal exposure may also contribute to the associations observed in this study (Vahter et al., 2007). We observed significant sex differences in blood Pb and blood Cu, with males displaying higher blood Pb and lower blood Cu concentrations (Table 2). Previous studies have also observed higher blood Pb concentrations in adolescent and young adult males (Burm et al., 2016), suggesting that males may experience greater Pb exposure during adolescence and young adulthood. Greater exposure in males may potentially contribute to their heightened vulnerability to metal neurotoxicity during adolescence/young adulthood. However, in most biological matrices (excluding hair), males and females exhibited comparable concentrations of metals, indicating that our findings cannot be solely attributed to sex differences in exposure. Moreover, the absence of significant associations in females, despite having higher concentrations of both blood Cu and hair metals, as well as a greater proportion falling within the clinical and borderline clinical ranges (Table 1), reinforces this notion. Future studies should longitudinally assess metal exposure and externalizing symptoms to elucidate whether sex-specific associations are consistently observed throughout adolescence and young adulthood.

Our results build upon previous literature by assessing the combined effect of multiple metals on adolescent/young adult externalizing symptoms. Traditionally, epidemiological studies examining metal exposure have used individual exposure biomarkers (e.g., blood, urine), as proxies of total environmental exposure. However, as metals have different toxicokinetics across various biological media, each biomarker provides unique, yet complementary information on specific biochemical processes. As such, recent epidemiological studies have begun to integrate exposure information from multiple biomarkers to more accurately estimate total body burden (Bauer et al., 2020; Invernizzi et al., 2023; Levin-Schwartz et al., 2020). In line with this, we focused on a mixture of 5 metals (Mn, Pb, Cu, Cr, Ni) using 4 biological matrices (blood, saliva, hair, urine). Several studies have suggested that co-exposure to certain metals leads to enhanced neurotoxicity, attributed to their unique chemical properties and similar neurobiological mechanisms of action (Lopes de Andrade et al., 2021). Metals within our mixture that have demonstrated synergistic neurotoxicity include Pb, Cu, and Mn (Chen et al., 2016; Lu et al., 2018; Tao et al., 1999). Previous observations have shown that metal co-exposure can exacerbate neurodevelopmental deficits in children and adolescents (Claus Henn et al., 2014; Sanders et al., 2015). Findings from preclinical animal studies suggest that when co-exposed, metals may alter accumulation, retention and distribution of other metal components (Chen et al., 2016). In particular, Mn has been shown to increase accumulation of various metals in the brain, notably Pb (Chandra et al., 1983; Chen et al., 2016), and Cu (Mercadante et al., 2016). Cu has also been observed to increase accumulation of Pb (Tao et al., 1999). Therefore, although Pb, Cu and Cr were found to contribute most to the associations between the metal mixture and externalizing symptoms in males, their greater influence may be driven by synergistic interactions with other metals in the mixture (e.g., Mn). To account for these potential synergistic effects, future studies should similarly evaluate multiple metals as a mixture, rather than solely assessing them individually.

Our study has several limitations. First, sex differences in unmeasured covariates and possible unmeasured exposures may bias our results. Our use of self-report questionnaires to assess externalizing symptoms may also bias our results. Furthermore, our WQS stratified interaction modeling approach assumed a linear association between the metal mixture and externalizing symptoms, which may not hold true for all metals within the mixture. Future studies should conduct similar analyses on a larger cohort of participants with longitudinal exposure and outcome data to detect more substantial and clinically meaningful effect sizes. Additionally, future studies should explore non-linear associations to further elucidate the relationship between metal mixture exposure and externalizing symptoms in adolescence and young adulthood.

5. Conclusion

Exposure to metals during adolescence and/or young adulthood may exert a sex-specific impact on externalizing symptoms, suggesting metal exposure may potentially contribute to the sex differences observed in mental health disorders. Our results emphasize the importance of considering sex as an effect modifier in addition to a covariate when investigating associations between environmental exposures and neurobehavior. By utilizing a WQS stratified interaction modeling approach, we can identify potential sex-specific vulnerabilities to environmental mixtures, and thereby provide valuable insights to guide targeted public health interventions.

CRediT authorship contribution statement

Kristie Oluyemi: Conceptualization, Formal Analysis, Visualization, Data Curation, Writing – original draft. **Elza Rechtman:** Writing – review & editing, Visualization, Software, Conceptualization. **Azzurra Invernizzi:** Writing – review & editing, Software, Investigation, Data curation. **Chris Gennings:** Writing – review & editing, Methodology, Conceptualization. **Stefano Renzetti:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation. **Alessandra Patrono:** Project administration, Investigation, Data curation. **Giuseppa Cagna:** Project administration, Investigation, Data curation. **Abraham Reichenberg:** Supervision, Investigation, Conceptualization. **Donald R. Smith:** Resources, Investigation, Funding acquisition, Data curation. **Roberto G. Lucchini:** Writing – review & editing, Funding acquisition. **Robert O. Wright:** Funding acquisition. **Donatella Placidi:** Supervision, Project administration, Funding acquisition. **Megan K. Horton:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used GPT 3.5 in order to review select sentences for grammar and syntax (e.g., wordiness). After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118443.

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