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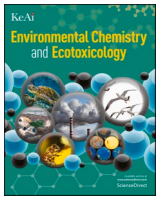

Research Paper

Volatile organic compound and metal/metalloid exposure associated with adverse child growth in electronic waste recycling area: Mediating role of urinary metabolomics

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ABSTRACT

The impact of volatile organic compound (VOC) and metal/metalloid exposure on child growth remains inadequately characterized in electronic waste recycling settings, with underlying toxic mechanisms poorly understood. We aim to investigate the effects of VOC and metal/metalloid exposure on the growth of children in the electronic waste recycling area, exploring underlying potential mechanisms through urinary metabolomics. We measured growth indicators, urinary VOC metabolites, metals/metalloids, and metabolomic profiles in children (n = 409) from an electronic waste recycling area. Using the U.S. Centers for Disease Control and Prevention Child Growth Standards, 117 children (28.6 %) were diagnosed with growth failure. These children exhibited significantly elevated urinary concentrations of 6 VOC metabolites and metals/metalloids, which correlated inversely with weight-for-age and height-for-age z-scores compared to normally developing peers. Metabolomic analyses revealed exposure-associated disturbances in metabolic pathways, identifying riboflavin, trehalose, and xanthosine as key metabolites linked to adverse growth outcomes. Mediation analysis demonstrated that riboflavin and xanthosine significantly mediated associations between VOC metabolites and metals/metalloids and growth indicators (mediation proportions: 11.1–12.9 %), suggesting these exposures impair growth partly through disruption of riboflavin and xanthosine homeostasis. Collectively, our findings established that VOC and metal/metalloid exposures contribute to growth failure in children from electronic waste recycling areas, highlighting the urgent need for enhanced pollution control measures to protect pediatric health.

1. Introduction

Driven by rapid technological obsolescence, global electronic waste generation reached approximately 60 million tons in 2024, with significant volumes exported to developing nations for resource recovery [1–3]. However, reliance on informal recycling practices, such as open burning and acid immersion, has caused severe environmental pollution in these regions [4]. Regulatory interventions in electronic waste recycling areas like Guiyu have significantly decreased exposure to most persistent organic pollutants, with studies showing 4- to 7-fold reductions in polycyclic aromatic hydrocarbons exposure [5] and two orders of magnitude reductions in polychlorinated biphenyls levels [6]. However, these measures had limited impact on some volatile organic compounds (VOCs) and metals/metalloids. Our prior study found that 12 of 18 measured urinary VOC metabolites significantly increased from 2016 to 2021 [7]. Additionally, metals/metalloids emission analysis of

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formal e-waste dismantling workshops showed copper (Cu), nickel (Ni), and manganese (Mn) releases comparable to or exceeding those of informal workshops [8]. This sustained high exposure may stem from the inherent resistance to removal of some VOCs [9], abundant metals/metalloids in electronic waste, and atomization escape during processing [8]. Notably, VOCs and metals/metalloids are co-released during common electronic waste processing activities (e.g., heating, and shredding) and persist simultaneously in environmental matrices at these sites [8]. While VOCs dominate atmospheric emissions and inhalation risks, metals/metalloids accumulate in dust/soil, creating multi-pathway exposure [10,11]. Their co-persistence created technologically intractable mixture exposures distinct from regulated persistent organic pollutants. Additionally, epidemiological evidence linked both VOCs and metals/metalloids to multiorgan toxicity including cardiovascular impairment, hepatotoxicity, carcinogenesis, and neurodevelopmental disruption [12–15]. Critically, their combined exposure may amplify toxic effects synergistically [16]. For example, enzymatic benzene activation yields reactive semiquinones and quinones, which generate oxygen ions via redox cycling, indirectly exacerbating oxidative stress from environmental metal/metalloid exposure [17]. Although exposure to either metals/metalloids or VOCs mixture is linked to increased risk of metabolic syndrome, simultaneous exposure accelerates its development, further elevating the risk [18]. Given these concerns, VOCs and metals/metalloids should be prioritized as key pollutants, with comprehensive assessments of their combined exposure profiles and associated health risks for populations in Guiyu.

Environmental risks contributed to 25 % of the global disease burden in 2017, according to the World Health Organization, and their reduction could prevent a quarter of deaths in children under five annually [19]. Children are more vulnerable to environmental pollutants due to their developing physiology, and early exposure can permanently alter their structure, physiology, and metabolism, significantly affecting long-term health [20]. The U.S. National Toxicology Program data indicated that children with blood lead (Pb) levels below 10 μg/dL may experience delayed puberty, while maternal levels below 5 μg/dL correlated with fetal birth weight loss and subsequent growth stunting [21]. Meta-analyses further corroborated consistent associations between exposure to Pb, cadmium (Cd), arsenic (As), and mercury (Mo) and impaired growth trajectories in children [22]. Potential mechanisms include impaired placental nutrient transport and disruption of bone growth or growth plate morphology [20,23]. Only one study utilizing 2011–2018 National Health and Nutrition Examination Survey data has revealed an association between VOC exposure and reduced growth parameters in children [24]. This growth-impairing effect may be mediated through disruption of the balance between bone formation and resorption during skeletal development [25]. However, the impact of single and combined exposure to VOCs and metals/metalloids on child growth in the context of electronic waste pollution remains understudied. Current research primarily established statistical links between these exposures and growth indicators, with limited investigation into underlying biological mechanisms.

Metabolomics offers a powerful approach to understanding how environmental factors affect child growth by analyzing metabolic changes [23,26]. Although previous research has identified metabolites and pathways connecting environmental exposure to growth impairment [27,28], the extent to which urinary metabolites mediate exposure-outcome relationships is unknown. Urinary biomarkers are valuable for early disease detection because they directly reflect real-time systemic physiology through blood filtration, without homeostatic regulation or storage [29]. This allows for the identification of pathological signatures before clinical symptoms appear, enabling early intervention [29]. In this study, we used metabolomics, a meet-in-the-middle strategy, and mediation analysis to: (1) characterize VOC and metal/metalloid exposure-induced metabolic disruptions and (2) quantify their mediating effects on growth failure. To our knowledge, no studies have employed this approach to clarify the mechanistic pathways linking e-waste pollutants to child growth outcomes via changes in the urinary metabolome.

This study measured and compared urinary concentrations of 18 VOC metabolites and 18 metals/metalloids in children with and without growth failure in Guiyu. We then explored the individual and joint effects of differential VOC metabolite and metal/metalloid exposure on child growth indicators. In addition, urine metabolomics analysis was performed to identify metabolites and pathways linked to VOC and metal/metalloid exposure and child growth. Our aim is to elucidate the effects of co-exposure to VOCs and metals/metalloids on child growth and their underlying biological mechanisms, thereby providing reference for targeted intervention strategy to safeguard the healthy growth of children in electronic waste recycling areas.

2. Materials and methods

2.1. Study population and sample collection

This research received approval from the Research Ethics Committee of South China Institute of Environmental Sciences, Ministry of Ecology and Environment. In October 2021, investigators recruited children from neighborhoods near the electronic waste dismantling sites in Guiyu Town, Shantou City. Children were included for analysis if they: 1) resided in the survey area; 2) had not self-reported genetic history or recent infectious diseases; 3) avoided consumed fried or grilled food in the past week; and 4) had not smoking or drinking behavior. A total of 409 children met the above criteria, comprising 207 boys and 202 girls aged 2 to 16 years. All participants or their guardians were informed about the purpose of this study. Collect fasting morning urine samples from participants in clean 50 mL polypropylene centrifuge tubes and promptly place them in a low-temperature transport box. Upon arrival at the laboratory, store the samples in a − 20 °C freezer until analysis. Furthermore, participants' general information (e.g., age, sex, weight, etc.), lifestyle (i.e., exercise time and sleep time) and additional details (e.g., passive smoking and maternal education level) were surveyed to reflect confounding factors that may affect statistical results.

2.2. Urinary VOC metabolites measurement

The chemicals used in this study are of analytical or reagent grade, detailed information can be available in Text S1. The pretreatment process for urinary thiodiglycolic acid (TGA), 2-aminothiazoline-4-carboxylic acid (ATCA), *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA), Mandelic acid (MA), *N*-acetyl-S-(3,4-dihydroxybutyl)-l-cysteine (DHBMA), *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine (2-HPMA), *N*-acetyl-S-(*N*-methylcarbamoyl)-l-cysteine (AMCC), (*R*)-2-thioxothiazolidine-4-carboxylic acid (TTCA), *N*-acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA), *N*-acetyl-S-(benzyl)-L-cysteine (BMA), *N*-acetyl-S-(n-propyl)-L-cysteine (BPMA), Phenylglyoxylic acid (PGA), *N*-acetyl-S-(3-hydroxypropyl)-L-cysteine (3-HPMA), Trans,trans-muconic acid (MU), 2-methylhippuric acid (2-MHA), 3-methylhippuric acid & 4-methylhippuric acid (3&4-MHA), *N*-acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA), and *N*-acetyl-S-(2-carboxy propyl)-L-cysteine (CPMA) is identical, as outlined in our previous article [30]. Briefly, isotope-labeled internal standards and formic acid buffer were added to each 1 mL of urine supernatant, then incubated with 10 μL of β-glucuronidase/sulfatase at 37 °C overnight. Subsequently, the solid phase extraction procedure was initiated to enrich and purify the target analytes. The eluent was obtained by sequentially adding methanol, water, 0.1 % formic acid in water (v:v), urine sample mixture, and 2 % formic acid in acetonitrile (*v*/v) to the polar-enhanced polymer cartridges. After drying and redissolution, 100 μL of supernatant was utilized for instrumental analysis.

Eighteen VOC metabolites were separated using an ultra-high-performance liquid chromatography system (Vanquish Autosampler, Thermo Fisher Scientific, USA) and were simultaneously measured by

electrospray tandem mass spectrometry (TSQ Quantis Triple Quadrupole system, Thermo Fisher Scientific, USA). The analysis parameters included a mobile phase flow rate of 0.4 mL/min, an injection volume of 2 μL, and a program temperature of 40 °C. The total analysis time was 15.01 min, with mobile phase gradient settings detailed in Table S2. Due to the difficulty in separating the isomers 3-MHA and 4-MHA, they were quantified together as 3&4-MHA, consistent with previous studies [30]. All analytes were determined in negative mode. We ensured the reliability of our analysis results through quality assurance and control. Water, matrix, and reagent blanks were included in each batch. The procedure was identical for blanks and urine samples, with no significant background contamination detected. The linearities of most urinary VOC metabolites were greater than 0.980. Mean recoveries from two spiked sample levels ranged from 95.7 % to 108 %, except for PGA (Table S3). The limit of detection (LOD) was determined from the signal-to-noise ratios of target analytes, ranging from 0.150 to 30.0 μg/L for VOC metabolites (Table S4). Relative standard deviations for all analytes were below 15.0 %, except for PGA (15.7 %) (Table S3). Furthermore, 8.00 % of randomly selected samples from each batch were reanalyzed to calculate the coefficient of variation, which spanned from 4.65 % to 14.5 %, excluding CYMA (21.5 %) and BPMA (32.1 %) (Fig. S1).

2.3. Urinary metals/metalloids measurement

Sample preparation for urinary Cu, tin (Sn), Pb, Cd, cobalt (Co), chromium (Cr), Mn, Mo, vanadium (V), Ni, gallium (Ga), As, selenium (Se), rubidium (Rb), strontium (Sr), antimony (Sb), tellurium (Te), and cesium (Cs) analysis using a straightforward dilution method. Before dilution, the urine samples were centrifuged at 13,000 rpm for 15 min and subsequently filtered using 0.45 μm micropore filters (Welch Technology Company, Zhejiang province, China) to minimize matrix effect interference. Then 600 μL of filtered urine was transferred to a new 15 mL polypropylene tube, followed by the addition of 100 μL of internal standard and 5.3 mL of 2 % diluted nitric acid (v:v) to achieve a tenfold dilution for instrument analysis. Eighteen metals/metalloids were then conducted with an inductively coupled plasma mass spectrometer (Agilent 7800, USA). Quantification was performed using a seven-point calibration curve with mixed multi-element standards and internal standards correction (i.e., scandium, germanium, yttrium, indium, terbium, and bismuth). The instrument operating conditions are as follows: cooling gas flow rate at 15.0 L/min, auxiliary gas flow rate at 1.0 L/min, atomized gas flow rate at 1.0 L/min, atomizer temperature at 3 °C, and the peristaltic pump speed at 0.1 rps. Furthermore, Jaffe's colorimetric method was used to quantify urinary creatinine levels to correct for urine dilution's effect on analyte concentration [30].

Quality assurance and quality control measures were applied to ensure the reliability of metal/metalloid concentrations. Procedural and reagent blanks were prepared to assess background contamination. No significant contamination was observed, with a low LOD ranging from 0.002 to 0.363 μg/g (Table S4). The linear correlation coefficients for the standard curves of all analytes exceeded 0.990. Average relative recoveries for 18 metals/metalloids in spiked samples (3.00 μg/L and 10.0 μg/L) ranged from 92.6 % to 114 %, except for Ni and As in the low spiked samples, which slightly exceeded 130 % (Table S3). Relative standard deviations for all metals/metalloids were below 20 % (Table S3).

2.4. Urine metabolomics analysis

The pre-treatment procedure for urine metabolomics is as follows: Urine was diluted to 200 μL to achieve a creatinine concentration of 4 mmol/L. Proteins were precipitated by adding 600 μL of ice-cold acetonitrile-methanol (1:1, *v*/v), vertexing for 5 min, and incubating at −20 °C for 15 min. After centrifugation at 14,000 rpm for 20 min at 4 °C, the supernatant was analyzed by ultra-high performance liquid chromatography coupled with quadrupole/orbitrap high-resolution mass spectrometry (Vanquish UPLC systems coupled with Q-Exactive Orbitrap-HRMS, Thermo Fisher Scientific Co., Germany).

Chromatographic separation was achieved using an ACQUITY UPLC® HSS T3 column (150 × 2.1 mm, 1.8 μm, Waters, USA) with a flow rate of 0.3 mL/min. The mobile phase consisted of 0.1 % formic acid in water (A) and acetonitrile (B), with a column temperature of 40 °C and a 2 μL injection volume. Gradient elution was performed as follows: 0–3 min, 2 % B; 3–12 min, 2–98 % B; 12–14 min, 98 % B; 14.0–14.1 min, 98–2 % B; 14.1–18 min, 2 % B. MS detection employed electrospray ionization with spray voltages of 3.5 kV and − 2.5 kV in positive and negative modes, respectively, and a capillary temperature of 325 °C. Sheath and auxiliary gas flows were set to 40 and 10 arbitrary units, respectively. Data were acquired using full scan MS (resolution 70,000, *m/z* 70–1050) and dd-MS2 (resolution 17,500, top 5 ions fragmented with stepped normalized collision energy at 20 %, 40 %, and 60 %).

Our previous research established reliable metabolomics references, demonstrating stable instrument performance and inapparent drift in quality control samples derived from pooled urine [23]. Raw data was processed using Compound Discoverer 3.3 SP2 software (Thermo Fisher Scientific Co., Germany) using an untargeted metabolomics workflow including: Align Retention Times, Detect Compounds, Group Compounds, Predict Compositions, Search ChemSpider, Assign Compound Annotations, Fill Gaps, Mark Background Compounds, Search mzVault, and Search Mass Lists. Peak alignment parameters included retention time (0.5 min tolerance) and mass (5 ppm tolerance). Compound detection was based on a signal-to-noise ratio of 10 and a peak intensity threshold of 1×10^6. Features with detection rate $\leq$ 50 % or relative standard deviation $\geq$20 % in QC samples were excluded. Metabolite validation against the mzCloud database resulted in the identification of 180 urinary metabolites.

2.5. Growth indicators calculation

Child growth was assessed using weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ), and body mass index-for-age z-scores (BMIZ), calculated against U.S. Centers for Disease Control and Prevention reference parameters [31]. These parameters, derived from a cohort of healthy children raised under optimal conditions (e.g., breastfeeding, non-smoking mothers, adequate healthcare), represent the standard physiological growth trajectory [31,32]. Quantifying individual deviations from this trajectory via WAZ, HAZ, and BMIZ provides an objective basis for diagnosing growth status among children. WAZ assesses the dynamic changes in weight, with a value < -2 indicating underweight. HAZ recorded linear growth status, where a score < -2 indicates stunting. BMIZ evaluates the proportion of fat to muscle content in bodies, and a value < -2 is defined as wasting. In this study, growth failure in children were defined by the presence of any of the following states: underweight, stunting, or wasting [33]. All indicators are calculated using the LMS method:

$$Z = \left((X/M)^L - 1\right)/(L \times S) \quad (1)$$

where X is the physical measurement (e.g. weight, height, or BMI) of children in Guiyu; L (skew), M (median), and S (generalized coefficient of variation) are the age-specific and sex-specific LMS parameters. This study used LMS parameters from the Centers for Disease Control and Prevention (for children aged 2–20) because World Health Organization LMS parameters only cover children under 10 [34].

2.6. Statistical analysis

Data statistics and modeling were performed using R studio (version 4.1.3). Differences in baseline characteristics and urinary concentrations of VOC metabolites and metals/metalloids between children with and

without growth failure were examined with Chi-square tests and Mann-Whitney *U* tests. VOC metabolites and metals/metalloids measured below the LODs were imputed as LODs/$\sqrt{2}$. Target analyte concentrations underwent logarithmic conversion prior to correlation analysis. Statistical significance for correlation and differential analyses was set at a two-tailed *p*-value of less than 0.05.

Spearman correlation analysis assessed associations among VOC metabolites and metals/metalloids. Multiple linear regression explored linear associations of differential VOC metabolites and metals/metalloids with child growth indicators. Significant exposures identified by multiple linear regression were further analyzed for non-linear relationships with growth indicators using restricted cubic spline regression. Stratified analyses were then employed to assess the sensitivity of primary linear associations in different subgroup. Additionally, quantile g-computation, weighted quantile sum, and Bayesian kernel machine regression examined the impact of mixed exposure to screened VOC metabolites and metals/metalloids on growth indicators. These models mentioned above were adjusted for age, sex, maternal education levels, passive smoking, exercise time, and sleep time. Using the R package "qgcomp" with exposures discretized into 4 quantiles and 500 iterations for variance estimation, we quantified the joint effect of simultaneous one-quantile increases in crucial VOC metabolites and metals/metalloids on child growth indicators. When this joint effect showed statistically significant associations, we examined the bidirectional weights, which are constrained to sum to ±1 within their respective positive and negative effect directions, to determine individual contributions. In weighted quantile sum model, we divided the data into training and testing sets in a 4:6 ratio. Using the "gWQS" package, we generated 1000 bootstrap samples from the training set to derive the weight index and fit the model on the validation set. For the index significantly associated with growth, we examined component weights to determine the relative contributions of individual VOC metabolites and metals/metalloids within the mixture.

However, quantile g-computation and weighted quantile sum regression models fail to evaluate the nonlinearity and interactions within mixtures. Thus, we employed a Bayesian kernel machine regression model to validate the above results of mixture analyses, as this approach accommodates nonlinear exposure-response relationships and interactions without requiring predefined parametric forms [35]. Specifically, the joint effects of VOCs and metals/metalloids on growth indicators were assessed by comparing growth indicator estimates per 10th percentile change from the median VOC and metal/metalloid concentration (reference value). Posterior inclusion probabilities quantified each VOC metabolites and metal/metalloid's relative importance, with a threshold greater than 0.5 indicating significant contribution. Univariate and bivariate exposure-response functions evaluated individual effect and interaction of VOC metabolites and metal/metalloids. Using the "bkmr" package, we implemented the Bayesian kernel machine regression model with 15,000 Markov Chain Monte Carlo iterations for all analyses to ensure accuracy.

Integrating three analytical models provides complementary advantages for mixture analysis: quantile g-computation regression quantifies joint intervention effects, weighted quantile sum regression evaluates unidirectional exposure-response associations, and Bayesian kernel machine regression characterizes complex exposure-response curved surface form, collectively offering multidimensional insights. Triangulating results across methods strengthens causal inference: agreement in key exposure identification validates toxicity drivers, while divergence indicates potential interactions. This integration mitigates individual model limitations, ensuring robust conclusions about mixture health hazards.

To identify molecular perturbations, we employed a metabolomics workflow including a metabolome-wide association study, pathway enrichment analysis, and the meet-in-the-middle approach. The metabolome-wide association study explored associations between urine metabolomics, urinary VOC metabolites and metals/metalloids, and child growth indicators. Due to the right-skewed distribution of metabolite concentrations, data were log2 transformed for normalization. Covariates in the metabolome-wide association study analysis were consistent with previous analyses. Subsequently, the meet-in-the-middle approach identified overlapping metabolites. Pathway enrichment analysis, using the Small Molecule Pathway Database in MetaboAnalyst website (version 6.0), identified pathways associated with these overlapping metabolites. Finally, the quantile g-computation and weighted quantile sum models assessed the contribution of individual metabolites to the association between the mixture, WAZ, and HAZ. Mediation analysis investigated the role of dominated metabolites in mediating the relationship between VOC and metal/metalloid exposure and growth indicators, to elucidate underlying mechanisms.

3. Result

3.1. Basic characteristics

The basic characteristics of participants are presented in Table 1. The geometric mean age was 8.50 ± 2.89 years, with a slightly higher proportion of boys (50.6 %). Most participants had low maternal education levels (middle school or less) and sufficient sleep (over 9 h). More than half exercised for less than one hour daily or were frequently exposed to passive smoking. Among 409 participants, 117 children (28.6 %) were diagnosed with growth failure. Age, sex, passive smoking, maternal education level, exercise time, and sleep time were adjusted in all correlation models referring to previous research, although no significant differences with these confounders between the two groups were

Table 1
Baseline characteristics of children in the electronic waste recycling area.

Characteristic[a]	All children	Growth failure [b]	Normal	*p*-Values [c]
N (%)	409	117 (28.6)	292 (71.4)	
Weight (kg)	25.4 ± 11.1	20.2 ± 7.60	27.9 ± 11.4	
Height (cm)	128 ± 18.4	120 ± 17.1	131 ± 18.1	
WAZ	−0.990 ± 1.31	−2.40 ± 1.20	−0.420 ± 0.850	
HAZ	−0.720 ± 1.24	−1.62 ± 1.43	−0.350 ± 0.930	
BMIZ	−0.875 ± 2.17	−2.30 ± 3.43	−0.306 ± 0.880	
Age (years)	8.50 ± 2.89	8.14 ± 2.91	8.65 ± 2.88	0.058
Sex				0.472
boys	207 (50.6)	63 (53.8)	144 (49.3)	
girls	202 (49.4)	54 (46.2)	148 (50.7)	
Exercise time				0.597
≤ 1 h	241 (58.9)	72 (64.9)	169 (59.5)	
1–2 h	117 (28.6)	29 (24.1)	88 (31.0)	
≥ 2 h	37 (9.00)	10 (9.00)	27 (9.50)	
Passive smoking				0.488
yes	216 (53.6)	58 (50.4)	158 (54.9)	
no	187 (46.4)	57 (49.6)	130 (45.1)	
Maternal education level				0.140
middle school or less	363 (91.9)	97 (88.2)	266 (93.3)	
high school or above	32 (8.10)	13 (11.8)	19 (6.70)	
Sleeping time				0.442
< 9 h	79 (19.7)	27 (23.5)	52 (18.1)	
9–10 h	189 (47.0)	50 (43.5)	139 (48.4)	
≥ 10 h	134 (33.3)	38 (33.0)	96 (33.5)	

Abbreviations: WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; BMIZ, body mass index-for-age z-scores.

[a] Continuous variables are presented as geometric mean (standard deviance) and categorical variables are presented as n (%).

[b] Children with growth failure is defined as WAZ, HAZ, or BMIZ less than −2.

[c] Differences in continuous variables are assessed using the Mann-Whitney U test, while differences in categorical variables are evaluated using the Chi-Square test.

observed ($p > 0.05$).

3.2. Distribution of VOC metabolites and metals/metalloids in urine

The concentration distribution and inter-group comparison of urinary VOC metabolites and metals/metalloids in growth failure cases versus controls are presented in Table 2. Among the VOC metabolites, TGA had the highest concentration in both groups, followed by 3-HPMA and MA. For metals/metalloids, Rb was the highest, followed by Sr and As. Children with growth failure had higher concentrations of DHBMA, AMCC, CYMA, 2-HPMA, TGA, PGA, HPMMA, ATCA, Cr, Co, Ni, Cu, As, Rb, Mo, Sn, and Pb compared to normal children ($p < 0.05$), suggesting that these differential VOC metabolites and metals/metalloids may be associated with child growth. Additionally, strong correlations between VOC metabolites and between metals/metalloids were observed through Spearman correlation analysis, meaning that the impacts of single VOC and metal/metalloid exposure on child growth may be affected by other VOCs and metals/metalloids (Fig. S2).

3.3. Association between individual VOC metabolites and metals/metalloids and child growth indicators

Multiple linear regression models were used to analyze the linear correlations between individual VOC metabolites and metals/metalloids and child growth indicators (Fig. 1 and Table S5). After adjusting for confounding factors, we observed that DHBMA, HPMMA, ATCA, TGA, Cu, Mo, Sn, and Pb were linked to reduced WAZ ($p < 0.05$) (Fig. 1A). Similarly, PGA, HPMMA, AMCC, 2-HPMA, TGA, ATCA, Co, Rb, Cr, Pb, Cu, Ni, and Sn, negatively correlated with HAZ ($p < 0.05$) (Fig. 1B). In examining BMIZ, only Ga demonstrated a positive effect (Fig. S3). Consequently, TGA, HPMMA, ATCA, Cu, Sn, and Pb, associated with WAZ and HAZ, were included in the subsequent mixture analysis to assess their combined effects on child growth. RCS regression models revealed no nonlinear associations (p for overall <0.05, p for non-linear >0.05) (Fig. S4 and S5), indicating that exposure to these VOCs and metals/metalloids adversely affect child growth in a dose-dependent manner.

3.4. Associations between a mixture of VOC metabolites and metals/metalloids and child growth indicators

Mixture analysis models based on linear additivity assumption were employed to explore the joint effect of TGA, HPMMA, ATCA, Cu, Sn, and Pb exposure on child growth indicators. Quantile g-computation regression models showed that a quartile increase in the mixture was associated with reduced WAZ [−0.549 (95 % CI: −0.772, −0.331)] and

Table 2
Concentrations distribution of urinary VOC metabolites and metals/metalloids of children in the electronic waste recycling area (μg/g creatinine).

Parent compounds	Variables	Growth failure				Normal				*p*-values
		5th	50th	90th	GM	5th	50th	90th	GM	
1,3-Butadiene	DHBMA	92.2	198	344	204	88.0	170	293	173	0.002
Benzene	MU	21.3	74.6	224	80.0	19.3	81.2	306	81.5	0.948
Acrylamide	AAMA	22.9	57.9	160	63.5	22.1	51.6	125	55.0	0.096
N, *N*-Dimethyl formamide	AMCC	34.1	67.0	144	73.7	32.2	59.4	113	62.4	0.010
Acrylonitrile	CYMA	0.901	1.83	4.37	1.94	0.693	1.58	3.53	1.70	0.020
1-Bromopropane	BPMA	0.267	3.74	13.0	3.37	0.530	3.67	20.4	3.86	0.488
Propylene oxide	2-HPMA	15.7	38.4	77.6	37.2	16.4	33.8	68.5	34.3	0.019
1,2-dichloroethane	TGA	664	1.27×10^3	1.90×10^3	1.24×10^3	436	960	1.69×10^3	977	<0.001
Ethylbenzene or Styrene	PGA	90.6	276	496	259	70.8	211	450	206	0.001
Toluene	BMA	2.47	10.4	33.6	10.8	3.56	8.83	25.0	9.75	0.152
Acrolein	3-HPMA	296	808	2.68×10^3	888	229	759	2.26×10^3	806	0.306
Crotonaldehyde	HPMMA	127	271	416	278	125	229	403	235	0.001
Xylene	2-MHA	17.1	42.2	105	43.3	13.9	40.8	99.3	42.7	0.359
Xylene	3&4-MHA	73.2	187	455	184	65.4	179	579	209	0.343
Methyl methacrylate	CPMA	146	295	612	313	131	269	625	290	0.129
Carbon disulfide	TTCA	3.22	32.2	170	28.7	2.22	24.7	166	24.6	0.393
Cyanide	ATCA	120	294	723	309	81.5	241	507	228	<0.001
Ethylbenzene or Styrene	MA	108	413	1.29×10^3	422	97.9	339	1.33×10^3	373	0.103
	V	10.1	34.6	77.3	34.3	10.5	32.1	73.5	31.4	0.166
	Cr	13.8	30.8	61.9	31.5	12.2	27.7	51.2	27.6	0.015
	Mn	0.282	2.10	15.0	2.43	0.296	1.69	8.79	1.94	0.070
	Co	0.145	0.614	1.37	0.553	0.129	0.513	1.14	0.486	0.045
	Ni	1.61	6.76	16.2	6.58	1.31	5.85	14.4	5.34	0.048
	Cu	15.3	38.7	99.1	42.6	15.4	30.6	71.5	33.3	0.001
	Ga	18.6	47.7	117	50.4	19.5	58.6	117	56.6	0.013
	As	50.0	116	208	119	41.8	93.2	202	99.6	0.020
	Se	6.40	11.5	22.2	13.4	6.46	11.8	19.2	12.1	0.994
	Rb	672	1.39×10^3	2.99×10^3	1.46×10^3	491	1.07×10^3	2.79×10^3	1.16×10^3	0.001
	Sr	56.1	194	406	179	39.2	188	415	169	0.531
	Mo	38.1	103	185	99.0	32.2	79.7	157	79.2	0.001
	Cd	0.349	0.763	1.51	0.775	0.315	0.661	1.29	0.681	0.090
	Sn	0.587	1.51	5.07	1.86	0.501	1.22	3.36	1.33	0.007
	Sb	0.040	0.127	0.618	0.149	0.038	0.128	0.401	0.127	0.601
	Te	0.048	0.158	0.368	0.154	0.047	0.137	0.328	0.138	0.123
	Cs	5.13	9.15	16.4	9.34	4.50	8.15	15.4	8.48	0.056
	Pb	0.951	2.67	10.5	3.13	0.723	2.42	6.24	2.40	0.035

Abbreviations: VOCs, volatile organic compounds; DHBMA, *N*-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine; MU, Trans,trans-muconic acid; AAMA, *N*-acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, *N*-acetyl-S-(*N*-methylcarbamoyl)-l-cysteine; CYMA, *N*-acetyl-S-(2-cyanoethyl)-L-cysteine; BPMA, *N*-acetyl-S-(n-propyl)-L-cysteine; 2-HPMA, *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine; TGA, Thiodiglycolic acid; PGA, Phenylglyoxylic acid; BMA, *N*-acetyl-S-(benzyl)-L-cysteine; 3-HPMA, *N*-acetyl-S-(3-hydroxypropyl)-L-cysteine; HPMMA, *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; 2-MHA, 2-methyl hippuric acid; 3&4-MHA, 3-methylhippuric acid & 4-methylhippuric acid; CPMA, *N*-acetyl-S-(2-carboxypropyl)-L-cysteine; TTCA, (*R*)-2-thioxothiazolidine-4-carboxylic acid; ATCA, 2-aminothiazoline-4-carboxylic acid; MA, Mandelic acid; 5th, fifth percentile; 50th, fiftieth percentile; 90th, ninetieth percentile; GM, geometric mean; Mann-Whitney U tests are used to assess differences in VOC metabolite and metal/metalloid concentrations between children with and without growth failure.

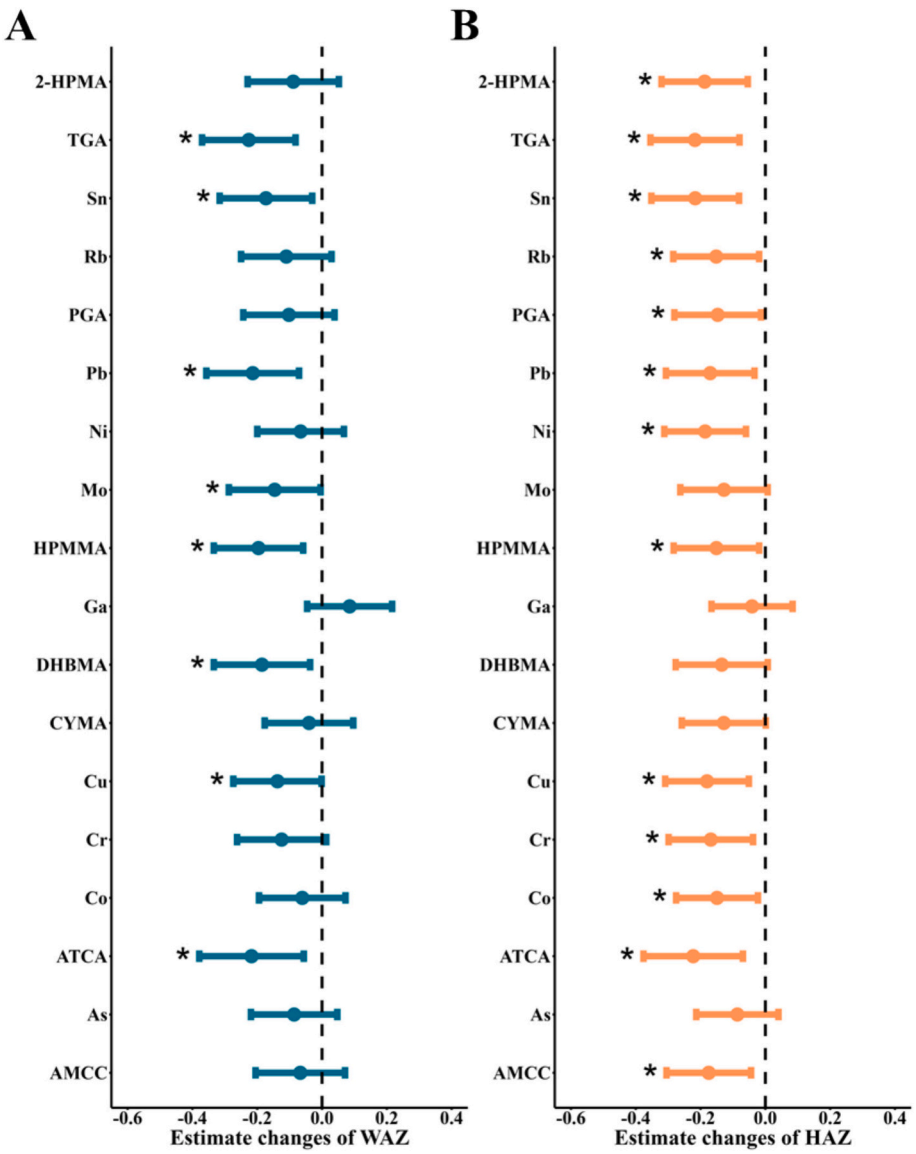

Fig. 1. Associations of individual VOC metabolites and metals/metalloids with WAZ (A) and HAZ (B) based on multiple linear regression models. Age sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all models. Asterisk represent a significant association existing between VOC metabolites and metals/metalloids and child growth indicators. Abbreviations: VOC, volatile organic compound; WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; DHBMA, *N*-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine; AMCC, *N*-acetyl-S-(*N*-methylcarbamoyl)-L-cysteine; CYMA, *N*-acetyl-S-(2-cyanoethyl)-L-cysteine; 2-HPMA, *N*-acetyl-S-(2-hydroxypropyl)-L-cysteine; TGA, Thiodiglycolic acid; PGA, Phenylglyoxylic acid; HPMMA, *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid.

HAZ [−0.552 (95 % CI: −0.776, −0.335)], respectively ($p < 0.05$) (Fig. 2A and *D*). The primary contributors to the joint effect on WAZ were TGA (28.9 %), HPMMA (26.9 %), and Pb (25.8 %) (Fig. 2B). For HAZ, the dominant contributors were TGA (23.5 %), Pb (17.5 %), and ATCA (17.4 %) (Fig. 2E). In weighted quantile sum regression models, the weight index was negatively associated with WAZ [−0.371 (95 % CI: −0.628, −0.114)]) and HAZ [−0.310 (95 % CI: −0.574, −0.045)], respectively ($p < 0.05$) (Fig. 2C and F). For the joint effect on WAZ, TGA occupied the highest weight (39.9 %), followed by HPMMA (23.3 %) and Pb (20.5 %) (Fig. 2C). For HAZ, TGA, Pb, and ATCA contributed 41.5 %, 25.8 %, and 11.2 % to the total effect, respectively (Fig. 2F).

Additionally, the more flexible Bayesian kernel machine regression model was also used to strengthen our results. Mixtures at various percentiles showed a negative association with WAZ and HAZ, respectively, compared to the median mixture ($p < 0.05$) (Fig. 3A and C). TGA (PIP = 0.885) and Pb (PIP = 0.822) were significant contributors to the joint effect on WAZ, while HPMMA (PIP = 0.828) and ATCA (PIP = 0.812) primarily influenced HAZ (Table S6). We also assessed the robustness of associations between single mixture components at different percentiles and child growth indicators. The negative association between TGA and WAZ was strengthened, while the relationship with HAZ weakened as other components shifted from the 25th to the 75th percentile ($p < 0.05$) (Fig. 3B and D). Consequently, exposure to a mixture of some VOCs and metals/metalloids was linked to adverse child growth, with 1,2-dichloroethane, cyanide, crotonaldehyde, and Pb being crucial factors driving the harmful effect.

3.5. *Exploring the potential mechanisms VOCs and metals/metalloids exposure affecting child growth through urinary metabolomics*

Of the 180 urinary metabolites detected, four screened VOC metabolites and metals/metalloids (i.e., TGA, HPMMA, ATCA, and Pb) were significantly associated with changes of 50, 56, 108, and 17 metabolites respectively, after adjusting for covariates ($p < 0.05$) (Fig. 4A).

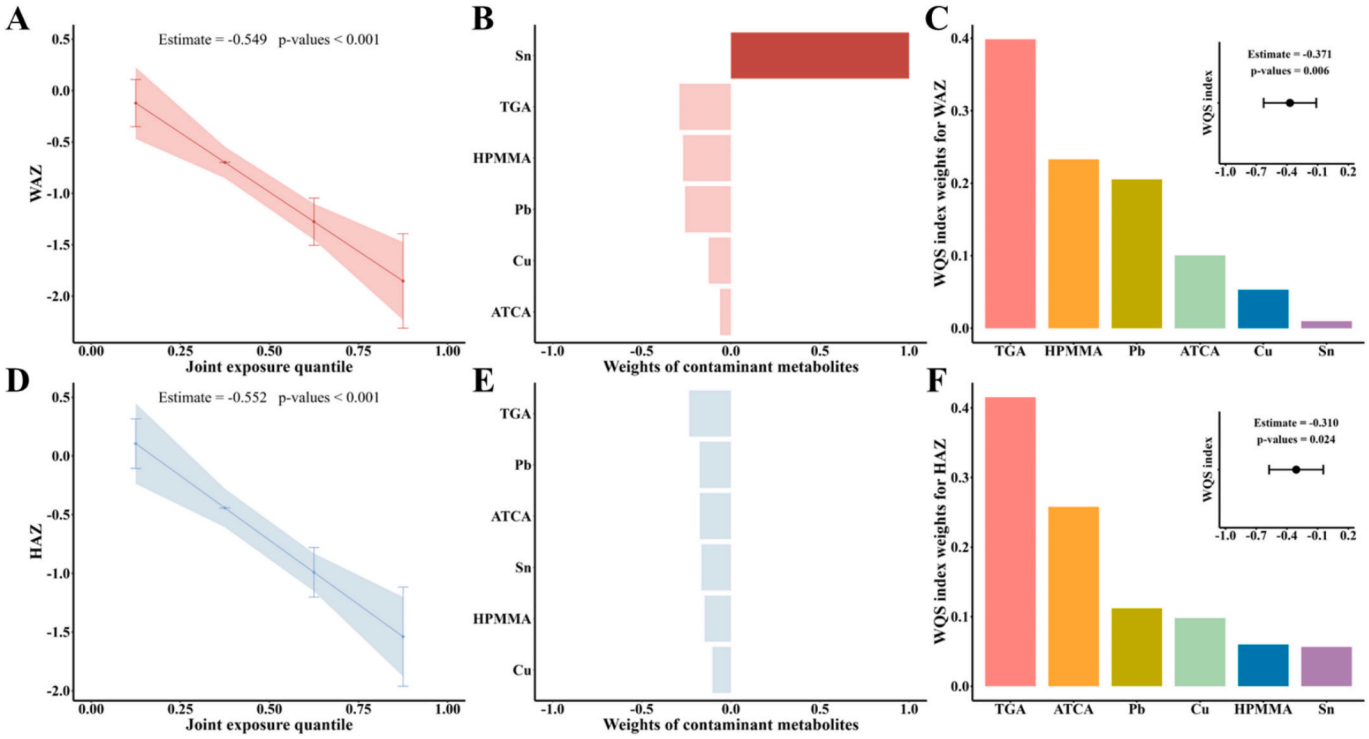

Fig. 2. Associations between a mixture of VOC metabolites and metals/metalloids and child growth indicators based on quantile g-computation regression and weighted quantile sum regression models. (A) Association between a mixture with WAZ based on the quantile g-computation regression model. (B) Weights of individual metabolites in the association between a mixture and WAZ based on the quantile g-computation regression model. (C) Association between a mixture and WAZ, and weights of single metabolites in the overall effect based on the weighted quantile sum regression model. (D) Association between a mixture and HAZ based on the quantile g-computation regression model. (E) Weights of individual metabolites in the association between a mixture and HAZ based on the quantile g-computation regression model. (F) Association between a mixture and HAZ and weights of single metabolites in the overall effect based on the weighted quantile sum regression model. Age, sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all models. Weights directions are restrained in negative directions in the weighted quantile sum regression models. Abbreviations: VOC, volatile organic compounds; WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; TGA, Thiodiglycolic acid; HPMMA, *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid.

Higher exposure levels of TGA, HPMMA, and ATCA were mainly linked to the upregulation of amino acids and their metabolites such as glutamic acid, 4-acetamidobutanoic acid, *N*-acetyl-L-aspartic acid, and phenylacetylglutamine. Elevated level of Pb were linked with the downregulation of N6-acetyl-L-lysine levels and the upregulation of glutamic acid, Alpha-*N*-phenylacetyl-L-glutamine and Cyclo(leucyl-prolyl). In the metabolome-wide association study on child growth indicators, there were 62 and 60 urinary metabolites significantly associated with WAZ and HAZ, respectively ($p < 0.05$) (Fig. 4B). Besides 3-methylpyridine, 3-methylhistidine, indole, androsterone glucuronide, 4-pyridoxic acid, pipecolic acid, L-histidine, L-tyrosine, acetylcarnosine, *L*-acetylcarnitine, and L-carnitine, other 51 urinary metabolites also show a negative correlation with WAZ. *L*-acetylcarnitine and L-carnitine levels showed a significant positive correlation with HAZ, whereas the other 58 metabolites showed a significant negative correlation. Based on the meet-in-the-middle method, 56 overlapping urinary metabolites were identified in both metabolome-wide association study for VOC metabolites and metals/metalloids and metabolome-wide association study for child growth indicators (Fig. 4C).

Pathway enrichment analysis of overlapping urinary metabolites identified 17 potentially involved in the metabolic process related to child growth (Fig. S7). Among them, the levels of *N*-acetyl-L-aspartic acid, phenylacetylglutamine, nudifloramide, trehalose, xanthosine, riboflavin, folic acid, glycocholic acid, and indoleacetic acid were significantly elevated in children with growth failure (Fig. S8). Strong positive correlations between differential metabolites were observed (Fig. S9), and mixture analysis assessed their combined effects on child growth. By using the quantile g-computation regression models, each quartile increase in the mixture was associated with a decrease of 0.599 points in WAZ (95 % CI: −0.795, −0.402), and riboflavin contributed the most to the mixture effect (23.5 %), followed by xanthosine (16.8 %), trehalose (14.6 %), nudifloramide (14.6 %), phenylacetylglutamine (11.3 %), and folic acid (10.5 %) ($p < 0.05$) (Fig. 5A and B). For HAZ, each quartile increase in the mixture was significantly associated with a decrease of 0.520 points (95 % CI: −0.730, −0.309), and xanthosine (26.7 %) made the largest contribution to the association, followed by trehalose (20.3 %), riboflavin (14.3 %), nudifloramide (13.0 %), and indoleacetic acid (10.2 %) ($p < 0.05$) (Fig. 5D and E). In weighted quantile sum regression models, the weight index was negatively associated with WAZ [−0.424 (95 % CI: −0.744, −0.105)]) and HAZ [−0.510 (95 % CI: −0.856, −0.163)], respectively ($p < 0.05$) (Fig. 5C and F). For the joint effect on WAZ, xanthosine occupied the highest weight (35.2 %), followed by folic acid (15.6 %), trehalose (13.4 %), and riboflavin (11.7 %) (Fig. 5C). For HAZ, xanthosine, trehalose, indoleacetic acid, and riboflavin contributed 32.1 %, 17.1 %, 13.2 %, and 11.9 % to the total effect, respectively (Fig. 5F). The four models shared three urinary metabolites: xanthosine (purine metabolism), trehalose (trehalose degradation), and riboflavin (riboflavin metabolism) (Fig. 5G).

3.6. *Mediating role of urinary metabolites*

We evaluated the potential mediation effect of riboflavin, trehalose, and xanthosine on the associations between VOC metabolites and metals/metalloids and child growth indicators. Riboflavin and xanthosine were significantly correlated with elevated levels of VOC metabolites and decreased child growth indicators. Specifically, riboflavin partially mediated the negative impacts of ATCA and TGA on growth indicators, with mediation proportions between 11.1 % and 12.9 % ($p <$

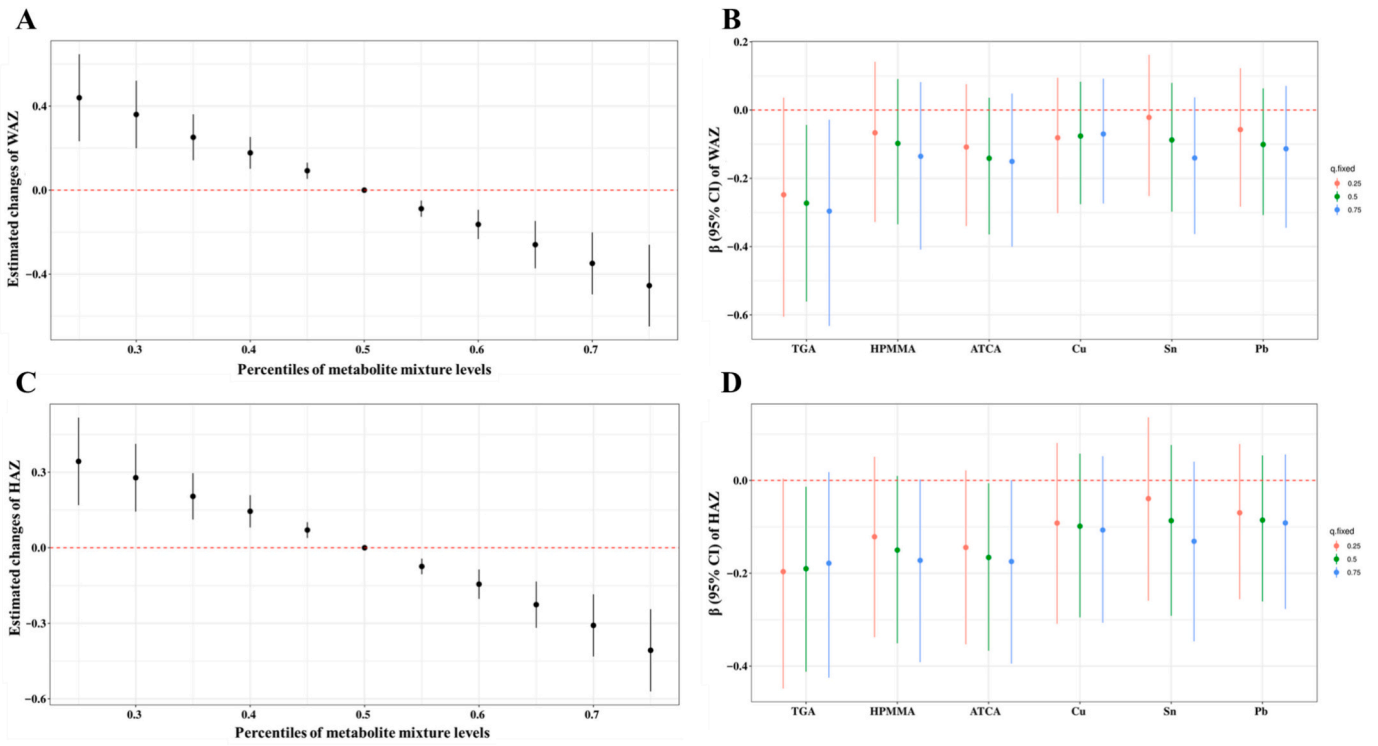

Fig. 3. Associations between a mixture of VOC metabolites and metals/metalloids and child growth indicators based on Bayesian kernel machine regression model. (A) Estimated changes of the association between a mixture and WAZ when the mixture is set at different percentiles compared to the 50th percentile. (B) Estimated changes of the association between single metabolites and WAZ when the other metabolites are fixed at either the 25th (red line), 50th (green line), or 75th percentiles (blue line). (C) Estimated changes of the association between a mixture and HAZ when the mixture is set at different percentiles compared to the 50th percentile. (D) Estimated changes of the association between single metabolites and HAZ when the other metabolites are fixed at either the 25th (red line), 50th (green line), or 75th percentiles (blue line). Age, sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all models. Abbreviations: VOC, volatile organic compounds; WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; TGA, Thiodiglycolic acid; HPMMA, *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.05) (Fig. 6A). Xanthosine partially mediated the association between TGA and WAZ and HAZ, with mediation proportions respectively being 12.7 % and 12.1 % ($p < 0.05$) (Fig. 6B). The highest mediation ratio was 12.9 %, linked to the role of riboflavin in the relationship between ATCA and WAZ (Fig. 6A). No significant mediation effects were found for the above metabolites on the association between Pb and HPMMA with growth indicators (Table S10 and S11). These results imply that 1,2-dichloroethane and cyanide exposure may impair child growth by increasing riboflavin or xanthosine, especially due to crotonaldehyde.

3.7. Stratified analysis

This study employed stratified analysis to investigate how age, sex, passive smoking, maternal education, exercise duration, and sleep duration influenced the relationship between individual VOC metabolites, metals/metalloids, and child growth indicators (Fig. S6). Exposure to VOCs primarily affected girls' growth, while metals/metalloids mainly impacted boys' growth, likely due to differing physiological structures and activity preferences. Older children showed increased sensitivity to metal/metalloid exposure, possibly due to cumulative effects. Children exposed to passive smoking had a greater number of negatively associated VOC metabolites with growth indicators compared to those not exposed, highlighting the detrimental effects of passive smoking on growth. Notably, all VOC metabolites and metals/metalloids, except TGA, were negatively associated with growth indicators in children of mothers with low education levels, while no such associations were found in children of highly educated mothers. This suggests that educated mothers may promote better hygiene awareness, reducing exposure to VOCs and metals/metalloids. However, the effects of exercise and sleep duration were not observed in this study.

4. Discussion

Using targeted exposure assessment and untargeted metabolomics analysis, this study identified and characterized associations between VOC and metal/metalloid exposure, perturbations of the children metabolome, and child growth indicators. We observed that exposure to VOC metabolite and metal/metalloid mixture (i.e., TGA, HPMMA, ATCA, Cu, Sn, and Pb) was associated with reduced child growth indicators. TGA, HPMMA, ATCA, and Pb played crucial roles in driving the exposure effects of mixture. Further metabolomics analysis revealed metabolic disturbances from specific VOCs and metals/metalloids exposure, pinpointing riboflavin, trehalose, and xanthosine as key metabolites in relation to adverse child growth. In addition, mediation analysis displayed that 1,2-dichloroethane and cyanide (the parent compound of TGA and ATCA, respectively) exposure may impair child growth by increasing riboflavin and xanthosine levels. Altogether, our research unveiled the detrimental effects and potential mechanisms of specific VOCs and metals/metalloids on child growth in the electronic waste recycling area, underscoring the urgent need to mitigate these pollutants during electronic waste recycling to safeguard child health.

Most population-based exposome studies have focused on the effects of a single environmental pollutant [36]. However, humans are exposed to multiple chemicals simultaneously, and models concentrating on a single pollutant may mislead exposure-outcome interpretation [37]. This study used mixture analysis models to investigate the joint effects of VOCs and metals/metalloids on child growth, offering a valuable reference for future research. We also observed that a single pollutant

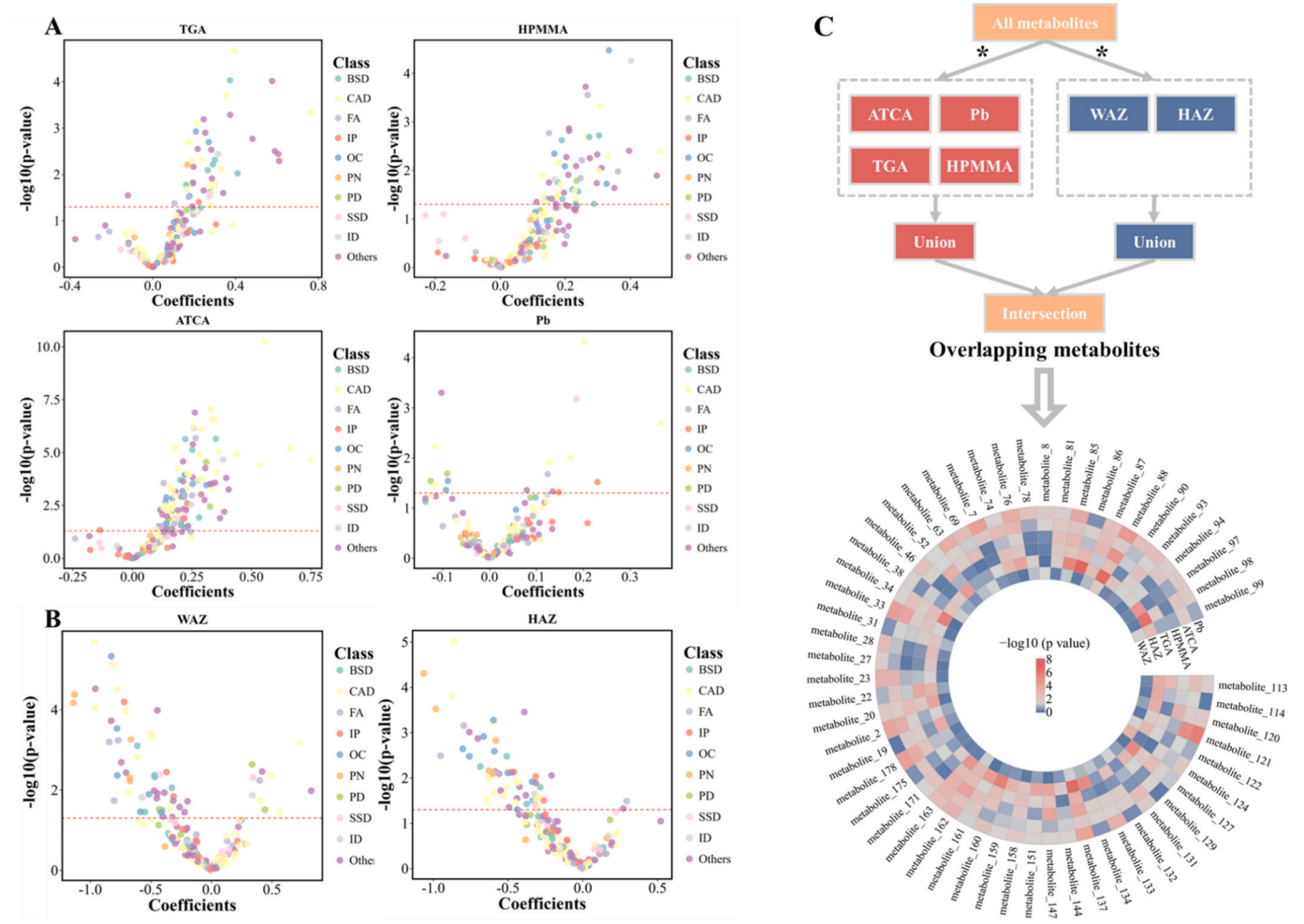

Fig. 4. Metabolome-wide association study on urinary VOC metabolites and metals/metalloids and child growth indicators (WAZ/HAZ). (A) Associations between VOC metabolites and metals/metalloids and urinary metabolites, analyzed by multiple linear regression models. The x-axis shows the estimated changes of the association between VOC metabolites and metals/metalloids and urinary metabolites, and the y-axis shows its value of −log10 (*p*-value). The significance *p*-value threshold of 0.05 is shown as a red dashed line. Exact *p*-values and regression coefficients of overlapping urinary metabolites are provided in Table S8. (B) Associations between urinary metabolites and WAZ/HAZ, analyzed by multiple linear regression models. The x-axis shows the estimated changes of the association between urinary metabolites and WAZ/HAZ, and the y-axis shows its value of −log10 (*p*-value). The significance *p*-value threshold of 0.05 is shown as a red dashed line. Exact *p*-values and regression coefficients of overlapping urinary metabolites are provided in Table S9. Different-colored dots represent different types of metabolites. Age, sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all models. (C) Overlapping urinary metabolites that are significantly associated with VOC metabolites and metals/metalloids and growth indicators. *$p < 0.05$. Red and blue solid rectangles circular heatmap of respectively represent significant and insignificant associations. Full name and case number of urinary metabolites are provided in Table S7. Abbreviations: VOC, volatile organic compounds; WAZ, weight-for-age z-scores; HAZ, height-for-age z-scores; TGA, Thiodiglycolic acid; HPMMA, *N*-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine; ATCA, 2-aminothiazoline-4-carboxylic acid; BSD, Benzene and substituted derivatives; CAD, Carboxylic acids and derivatives; FA, Fatty Acyls; IP, Imidazopyrimidines; OC, Organooxygen compounds; PN, Purine nucleosides; PD, Pyridines and derivatives; SSD, Steroids and steroid derivatives; ID, Indoles and derivatives. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

metabolite, HPMMA, exhibited varying contributions across different mixture models (Bayesian kernel machine regression vs. weighted quantile sum). This highlights the limitations of relying on single mixture analysis for identifying key pollutants, suggesting that combining multiple models may yield a more reliable result [38]. Thus, combining quantile g-computation regression, weighted quantile sum regression, and Bayesian kernel machine regression models, we synthetically identified Pb, 1,2-dichloroethane, cyanide, and crotonaldehyde as the main pollutants affecting child growth in electronic waste recycling areas.

Our findings on the association between Pb exposure and the adverse growth of children in the electronic waste recycling area are in line with several studies. In the INMA-Asturias cohort, exposure to a urinary metals/metalloids mixture was significantly related to reduced childhood height, with Pb being the primary contributor to the joint effect [39]. In rural Bangladesh, boys (n = 800) showed a decrease of approximately 0.085 in growth indicators as urinary Pb levels elevated from 1.90 μg/L to 3.80 μg/L [40]. However, other studies, including the Maternal-Infant Research on Environmental Chemicals Child Development Plus study and the US National Toxicology Program, did not find similar effects [21,41]. Variations in environmental exposure may explain these discrepancies. Previous studies have elucidated several cellular and molecular mechanisms by which Pb exposure affects child growth. Evidence suggests that Pb negatively impacts the function of osteoblasts and osteoclasts, essential for bone growth, by altering circulating hormone levels such as 1,25-dihydroxy vitamin D3 [42]. Additionally, Pb can inhibit the absorption of zinc and iron, contributing to deficiencies during critical growth periods in children [42]. An animal study found decreased expression of insulin-like growth factors 1 and 2 in Pb-exposed mice, although this pathway requires further

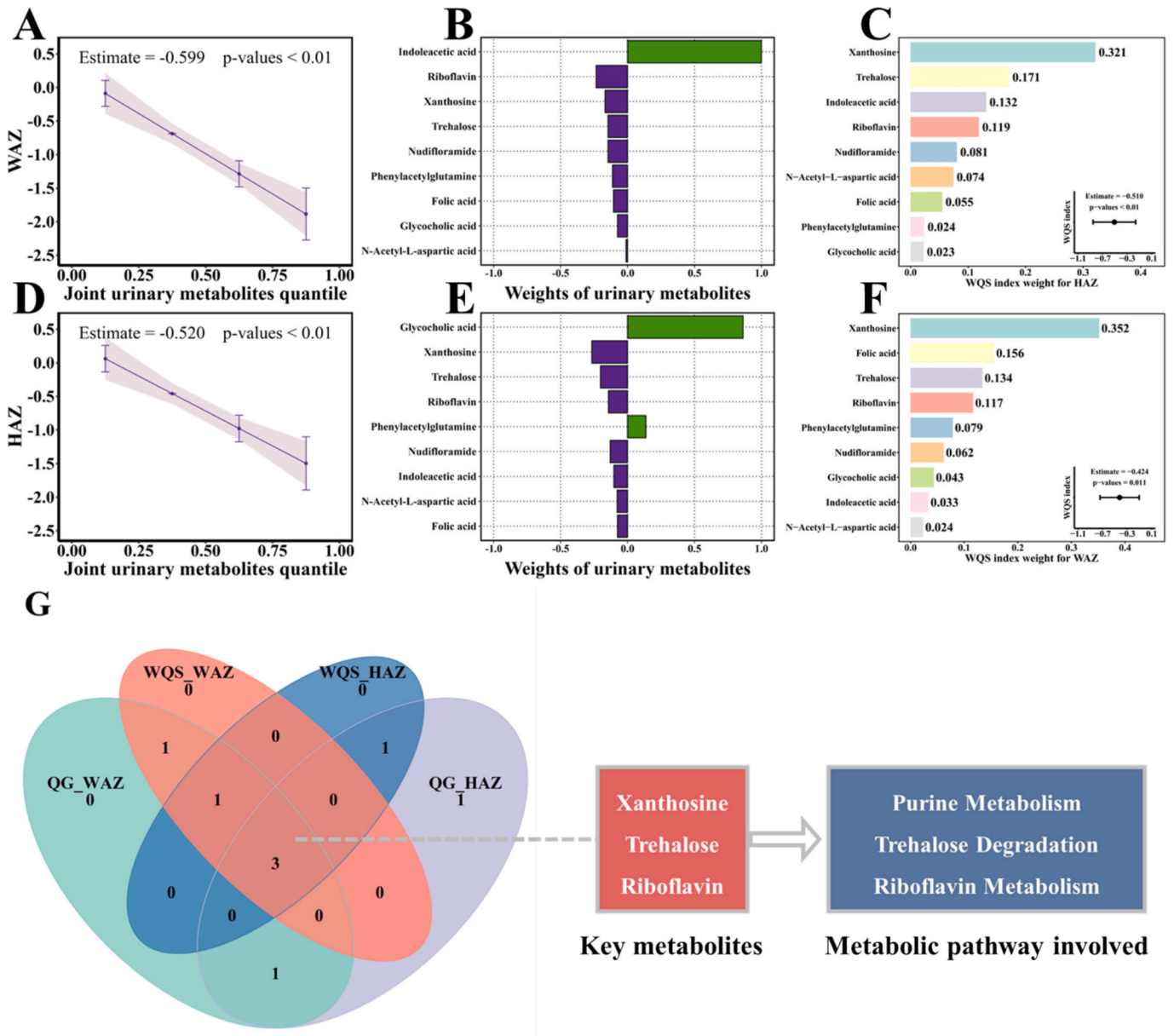

Fig. 5. Joint effects of urinary differential metabolites on child growth indicators and identification of dominate contributors. (A) Association between a mixture with WAZ based on the quantile g-computation regression model. (B) Weights of individual metabolites in the association between a mixture and WAZ based on the quantile g-computation regression model. (C) Association between a mixture and WAZ, and weights of single metabolites in the overall effect based on the weighted quantile sum regression model. (D) Association between a mixture and HAZ based on the quantile g-computation regression model. (E) Weights of individual metabolites in the association between a mixture and HAZ based on the quantile g-computation regression model. (F) Association between a mixture and HAZ and weights of single metabolites in the overall effect based on the weighted quantile sum regression model. (G) Common urinary metabolites with weights greater than 0.1 and their involved metabolic pathways in all mixture analysis models. Age, sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all models. Weights directions are restrained in negative directions in the weighted quantile sum regression models. Abbreviations: WAZ, weight-for-age z-scores; HAZ, height-for-age z-score.

exploration in epidemiological research [43].

Research on the impact of VOC exposure on child growth is limited. Our study revealed negative associations between urinary metabolites of 1,2-dichloroethane, cyanide, and crotonaldehyde and child growth indicators, differing from findings in adults. A study of 17,524 adults using data from six National Health and Nutrition Examination Survey cycles (2005–2006, 2011–2012, 2013–2014, 2015–2016, 2017–2018, and 2017–2020) suggested that exposure to crotonaldehyde and cyanide may be linked to obesity [44]. Similarly, the Korean National Environmental Health Survey program (2015–2017) ($n = 3787$) found that the benzene metabolite t,t-MA was linked to increased adult BMI [45]. Inverse effects may be derived from variations in physiological traits, metabolic processes, and lifestyle factors [46]. Children's higher basal metabolic rate may make their organs, particularly the gut, more susceptible to VOC-induced changes, potentially leading to decreased food intake [47]. In contrast, unhealthy eating patterns may cause weight gain in exposed adults [48]. Although an animal study suggests VOC exposure might increase beneficial gut bacteria that counteract glycolipids [49], potentially influencing weight regulation, the significant variation in gut microbiota driven by individual diet means this potential pathway requires further validation [50].

Following the urine metabolomics analysis, we found that riboflavin metabolism, trehalose degradation, and purine metabolism may be involved in VOCs and metals/metalloids-induced poor child growth

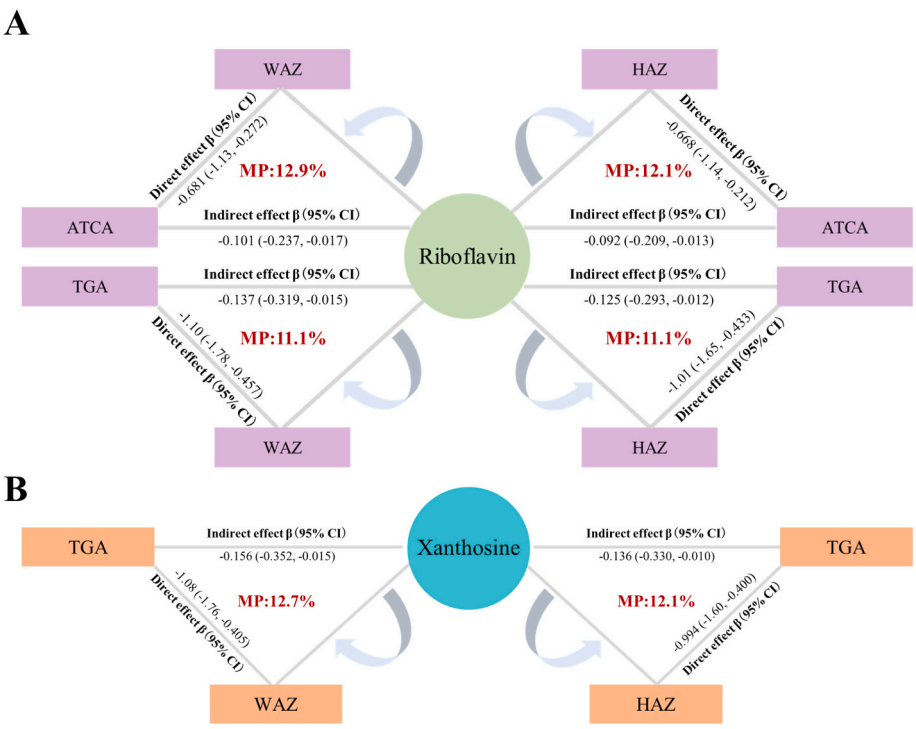

Fig. 6. Mediating effects of key urinary metabolites on the association between VOC metabolites and child growth indicators. Only statistically significant mediation effects are displayed. All results are provided in Table S10 and Table S11. Age, sex, maternal education levels, passive smoking, exercise time, and sleep time are adjusted in all linear regression models. Abbreviations: WAZ, weight-for-age z-scores; HAZ, height-for-age z-score; ATCA, 2-aminothiazoline-4-carboxylic acid; TGA, Thiodiglycolic acid; MP, Mediated proportion.

effect. A recent study based on the South East Asian Nutrition Surveys (n = 1383) observed an increased risk of overweight or abdominal obesity in children with lower daily intake of riboflavin [51]. Similar negative associations also exist between riboflavin intake and BMI and trunk fat mass in 1131 Mexican American children [52]. These associations may stem from riboflavin's role in regulating energy balance, potentially prioritizing energy expenditure towards central nervous system development over growth [53]. While epidemiological studies on trehalose's effects on child growth are limited, existing evidence indicates it can alter gut microbiota homeostasis, which is vital for neonatal metabolic balance and development [54,55]. For instance, trehalose can enhance microbial short-chain fatty acid production, benefiting the regulation of metabolic disorders like obesity and diabetes [54,56]. Furthermore, by fostering beneficial gut bacteria, trehalose can indirectly promote hepatic lipid metabolism [57]. Prior research suggested a link between hair heavy metal, purine metabolism involving xanthosine, and child adverse growth [23]. Another placental multi-omics analysis has also identified xanthosine as a crucial molecular marker in fetal growth and development [58].

In this study, riboflavin and xanthosine partially mediated the inverse association between specific VOC metabolites and child growth indicators. Given that riboflavin and xanthosine levels were elevated in the urine of children with growth failure, we hypothesize that VOC exposure may impair growth by increasing riboflavin and xanthosine. Trehalose did not act as a mediator, suggesting its biological role is complex and potentially regulated by multiple factors [59]. Intricate signaling pathways or feedback loops may obscure its mediatory function [59]. Taken together, riboflavin, xanthosine, and trehalose as the metabolic signatures of VOC and metal/metalloid exposure might play a significant role in the etiology of poor child growth in electronic waste recycling areas.

This study has several strengths. Firstly, the electronic waste dismantling process releases various pollutants, creating a realistic exposure scenario. Secondly, we examined the joint effects of multiple VOCs and metals/metalloids on child growth using mixture analysis models with the identification of key VOCs and metals/metalloids. Lastly, we highlighted the important role of urinary metabolites in the relationship between VOC and metal/metalloid exposure and child growth, enhancing our understanding of these adverse effects. However, some limitations in this study need to be indicated. Firstly, it did not establish a causal association between exposure to a mixture of VOCs and metals/metalloids and child growth, as it is a cross-sectional investigation. Additionally, although numerous confounders were adjusted in our statistical modeling, some potentially important factors, such as individual nutritional information and parental growth status, were not captured in our questionnaire and may impact the reliability of our findings.

5. Conclusions

In summary, our research indicates that individual and combined exposure to VOCs and metals/metalloids, specifically including 1,2-dichloroethane, crotonaldehyde, cyanide, and Pb, may negatively impact child growth. Metabolomics analysis suggests that perturbed riboflavin, trehalose, and xanthosine by the above key VOC and metals/metalloid exposure may play important roles in contributing to impaired child growth. Further research is needed to confirm our findings, elucidate metabolic mechanisms, and evaluate biomarkers for predicting and preventing the negative impact of environmental pollution from electronic waste recycling on child growth.

CRediT authorship contribution statement

Meng-Yang Li: Writing – original draft, Methodology, Investigation, Formal analysis. **Tong Zheng:** Investigation. **Shu-Fei Zhang:** Investigation. **Ye Liu:** Methodology, Formal analysis. **Tian-Hong Chen:** Investigation. **Jia-Rong Wang:** Investigation. **Ying-Xin Yu:** Writing – review & editing, Supervision. **Yang Zhou:** Investigation. **Ming-Deng**

Xiang: Investigation. **Yun-Jiang Yu:** Writing – review & editing, Supervision. **Hong-Xuan Kuang:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.enceco.2025.08.012.

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