Asia Pacific Science Press

Asia Pacific Journal of Clinical Medical Research
ISSN(O):3079-8345
ISSN(P):3079-8337
Vol. 2 No.2 (2026)

Urinary Arsenic, Lead, and Their Joint Effects on Hypotension in Children and Adolescents Aged 8–17 Years: A Cross-Sectional Analysis of NHANES 2007–2018

Wen Duan [1]†, Jie Liu [1]†, Xinpei Luo [2]‡, Caixia Liu [3]‡, Zhui Ke [2]*

1. Department of Nuclear Medicine, The First College of Clinical Medical Science, China Three Gorges University & Yichang Central People's Hospital, Yichang, 443003, China

2. Department of Oncology, The Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, 200072, China

3. Department of Urology, Affiliated MinDa Hospital, Hubei Minzu University, Enshi, 445000, China

†These authors contributed equally as first authors.

‡These authors contributed equally as second authors.

Corresponding author: kezhui, kezhui1314@163.com

Abstract: Background: Evidence on the joint effects of arsenic and lead exposure on pediatric hypotension is limited. The modifying roles of age, sex, and body weight in this association remain unclear. Methods: Using NHANES 2007-2018 data (2,043 adolescents aged 8-17y), we employed survey-weighted logistic regression (hypotension risk), weighted linear regression (blood pressure percentiles), and Weighted Quantile Sum regression (joint effects). Results: In weighted logistic regression, Model 1 (adjusted for age, sex, race) showed arsenic fourth quartile increased hypotension risk (OR=1.73, 95%CI:1.13 2.64, P=0.01). After full adjustment (Model 2: Model 1+ BMI, income, sodium, calories, household size), this risk remained significant (OR=1.63, 95%CI:1.03-2.5, P=0.04) with a significant trend (P-trend =0.04). For lead, Model I fourth quartile risk (OR=1.66, 95%CI:1.05-2.64, P=0.03) shifted to third quartile significance in Model 2 (OR=1.54, 95%CI:1.04-2.28, P=0.03). Linear regression revealed arsenic third quartile significantly reduced diastolic blood pressure percentile in both Model 1 (β=6.20, 95%CI:-10.92-1.47, P=0.01) and Model 2 (β=5.75, 95%CI:-10.41-1.09, P=0.02). The Weighted Quantile Sum (WQS) index showed consistent risk in the main model (OR=1.21, 95%CI:1.03-1.42, P=0.02). Stratified analyses (Model 2 based) showed males had higher lead sensitivity Q2 (OR = 2.01, P = 0.005), normal weight individuals had strongest associations lead Q4 (OR = 2.14, P = 0.02): arsenic Q4 (OR = 2.04, P = 0.02) and early puberty (11–13 years) exhibited peak lead risk Q3 (OR = 2.45, P = 0.005). Conclusion: Arsenic and lead additively increase pediatric hypotension risk, with effects modified by sex, BMI, and pubertal stage. Normal-weight males in early puberty are the most vulnerable subgroup.

Keywords: NHANES; Hypotension; Heavy Metals; Lead; Arsenic

Published: Apr 20, 2026

DOI: https://doi.org/10.62177/apjcmr.v2i2.1288

1. Introduction

Abnormal blood pressure (including hypertension and hypotension) during childhood and adolescence is closely associated with the risk of cardiovascular diseases in adulthood, making it a critical focus in public health [1,2]. While research on

hypertension is relatively advanced, systematic exploration of the etiologies and environmental influencing factors of hypotension remains insufficient. In recent years, the potential hazards of environmental heavy metal exposure to the cardiovascular system have gained increasing attention. Among these, arsenic (As) and lead (Pb) have become research hotspots due to their widespread presence in air, water, and food, as well as their neurotoxic and cardiovascular toxic properties [3,4].

Arsenic and lead can enter the body through various exposure routes. Children and adolescents may ingest them via diet (e.g., contaminated water and food), air, and hand-to-mouth contact [5]. Existing studies have shown that arsenic exposure can affect vascular tone through oxidative stress and endothelial dysfunction [6], while lead exposure may interfere with the sympathetic nervous system and the renin-angiotensin system, leading to abnormal blood pressure regulation [7]. However, most current studies focus on the association between heavy metals and hypertension [8,9], and there is no consensus on their relationship with hypotension. For example, Yao et. found no significant association between low-level lead exposure and blood pressure in children, but studies on adults suggest that mixed heavy metal exposure may affect blood pressure distribution [10,11].

Furthermore, children and adolescents are in a critical period of growth and development, with immature blood pressure regulation mechanisms, which may increase their sensitivity to environmental pollutants [5]. Factors such as hormonal changes during puberty and body weight status may further modify the association between heavy metals and blood pressure [12]. Meanwhile, environmental pollutants usually exist in the form of "mixed exposure," and analyzing single pollutants may underestimate their combined effects. Statistical methods such as Weighted Quantile Sum (WQS) regression provide effective tools for interpreting the health effects of mixed exposures [13,14].

Based on this, this study uses large-scale NHANES data to systematically explore the association between urinary arsenic and lead exposure and hypotension in children and adolescents, analyze the dose-response relationship and the combined effects of mixed exposures, and investigate the modifying roles of age, gender, and BMI in these associations. It aims to provide a scientific basis for the prevention of hypotension in children and adolescents and environmental risk management.

2. Methods

2.1 Study population

This study utilized cross-sectional data from six consecutive cycles (2007-2008 to 2017-2018) of the NHANES(https://www.cdc.gov/nchs/nhanes).Employing a stratified multistage probability sampling design, NHANES represents non-institutionalized U.S. children and adolescents aged 8-17 years. The study protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, with written informed consent obtained from all participants/parents/guardians. Through integration of multi-cycle data using NHANES' official weight-combining methodology, the initial screened cohort comprised 9,847 eligible individuals. After excluding 7,804 participants with incomplete data, the final weighted analytical sample represented 2,043 participants.

2.2 Blood pressure (BP)

All blood pressure measurements were conducted at the Mobile Examination Center (MEC). Participants were seated with feet flat on the floor and rested for 5 minutes before measurements. Trained examiners performed three consecutive right-arm blood pressure measurements using a mercury sphygmomanometer with an appropriately sized cuff. The average of ≥2 valid readings was recorded as the final systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. The diagnostic criteria for hypotension strictly adhered to the 2017 American Academy of Pediatrics (AAP) clinical guidelines. Age-, sex-, and height-specific Z-score formulas recommended by the guidelines were employed to calculate blood pressure percentiles, with hypotension defined as either systolic or diastolic blood pressure below the 5th percentile. Specifically: (1) simplified age-based formulas were used to compute Z-scores for children aged 8–12 years, while (2) composite formulas incorporating both age and sex parameters were applied for adolescents aged 13–17 years, with final blood pressure percentiles derived through standard normal distribution conversion for clinical determination [15].

2.3 Urinary arsenic (UAs) and lead (UPb) concentrations

All metal detection data in this study was based on urine samples. During participant appointments at the NHANES Mobile Examination Center (MEC), spot urine samples were collected and analyzed for total arsenic concentrations using dynamic

reaction cell inductively coupled plasma mass spectrometry (DRC-ICP-MS) and for lead concentrations using inductively coupled plasma mass spectrometry (ICP-MS). Comprehensive instructions for laboratory methods utilized to measure the urinary metal concentrations can be found on the NHANES website. The limits of detection (LOD) ranged from 0.26 to 0.74 μg/L for arsenic and 0.05 to 0.28 μg/L for lead (cycle-specific values available in NHANES Laboratory Manuals). Values below LOD were imputed as LOD/√2. Following creatinine correction (μg/g creatinine) to account for urine dilution effects, creatinine-adjusted values underwent natural logarithmic transformation rounded to two decimal places (yielding variables ln_UAs and ln_UPb), with these transformed values directly utilized in subsequent regression analyses.

2.4 Covariates

Based on previous literature, several covariates were included in this study as potential confounding factors. The selected covariates included age, sex, race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other races), household size, family poverty income ratio (PIR), and urinary creatinine (measured by enzymatic method using Roche Cobas 6000 analyzer). Urinary creatinine was used to adjust heavy metal concentrations (μg/g creatinine) to eliminate the effect of urine dilution. Considering that fluctuations in sex hormones may lead to changes in vascular tone, age was grouped according to key stages of sexual development: 8–10 years (pre-puberty), 11–13 years (early puberty), and 14–17 years (mid-puberty) [16]. The family poverty income ratio (PIR) was categorized into a categorical variable based on clinical economic thresholds: <1 (poverty), 1–1.99 (low income), and ≥2 (middle-high income). Additionally, total energy intake (kcal/d) and sodium intake (mg/d) assessed via the first 24-hour dietary recall were also included as covariates in the model. Body mass index (BMI) was calculated using the formula weight (in kilograms) divided by the square of height (in meters). Underweight was an age-and gender-specific BMI below the 5th percentile on the 2000 Centers for Disease Control and Prevention (CDC) age-and gender-specific growth charts, normal weight was a BMI below the 85th percentile but at or above the 5th percentile, overweight was a BMI falling between the 85th and 95th percentiles, and obesity was a BMI at or above the 95th percentile [17].

2.5 Statistical analysis

Data from six NHANES cycles (2007–2018) were merged under a stratified, multi-stage probability design. Sample weights (WTMEC2YR), strata (SDMVSTRA) and primary sampling units (SDMVPSU) were incorporated; original 2-year weights were retained without rescaling. After restricting the sample to participants aged 8–17 years, complete-case analyses were performed.

Descriptive statistics Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). Group differences were assessed with Student's t-tests for continuous measures and χ^2 tests for categorical variables. UAs and Pb concentrations, creatinine-adjusted, were log-transformed and then were categorized based on quartiles (quartile 1. <25th percentile; quartile 2, ≥ 25th to 50th percentile; quartile 3, ≥ 50th to 75th percentile; quartile 4, ≥ 75th percentile). Survey-weighted logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between metal quartiles and hypotension, with Q1 serving as the reference. Model 1 adjusted for age (continuous) and sex. Model 2 additionally adjusted for race/ethnicity, BMI, family income-to-poverty ratio (<1, 1–1.99, ≥2), household size, total daily energy intake and dietary sodium intake. To determine whether the associations between urinary arsenic/lead and hypotension vary by age, sex, or BMI, we applied survey-weighted logistic regression models—mirroring the Model 2—within each stratum (age: 8–10, 11–13, 14–17 years; sex: male/female; BMI: underweight, normal, overweight, obese) and tested for heterogeneity by including interaction terms between metal quartiles and the stratification variables.

The Weighted Quantile Sum (WQS) method has been widely used to investigate the cumulative effects of environmental mixtures on health outcomes and assess the contribution of individual metals[14]. In this study, the WQS regression model was employed to evaluate the cumulative effect of mixed exposure to UAs and Pb on hypotension in adolescents, as well as their respective independent contributions. This data-driven approach assigns weight coefficients to each component in the mixture, with weights ranging from 0 to 1 and summing to 1, where the weight value reflects the relative importance of each component in explaining the variation in health outcomes [18] . The specific steps are as follows:(1) The handling of exposure variables strictly followed the description in Section 2.3. The concentrations of ln_UAs and ln_UPb, after creatinine

adjustment and natural logarithm transformation, were divided into four quartiles (Q1-Q4) respectively, with the lowest quartile group (Q1) serving as the reference.(2) Regarding the inclusion of covariates, unlike "Model 2" in Section 3.1, in the WQS model, BMI was used as a categorical variable to assess the effect modification of different weight categories on the association between mixed UAs and Pb exposure and hypotension. Meanwhile, we also conducted WQS analyses in age subgroups. A bootstrap sampling method (with 1000 repetitions) was adopted, randomly selecting 60% of the samples as the training set and 40% as the validation set. In the training set, the weight coefficients of each metal were estimated through iterative optimization, and a WQS index was constructed, which represents the cumulative effect of all urinary toxicants on blood pressure. A metal was identified as a major contributing factor in the mixture when its average weight exceeded 0.5 (i.e., 1 divided by the total number of variables)[13].(3) We evaluated the predictive performance of the WQS index for hypotension in the validation set and calculated odds ratios (ORs) and 95% confidence intervals (CIs) using weighted logistic regression to quantify the strength of the association between mixed exposure and hypotension. Additionally, we performed subgroup WQS analyses stratified by age to examine the effect modification on the mixed exposure-hypotension association.

In our sensitivity analysis, we initially considered the potential non-linear and non-additive relationships among urine metals. All statistical analyses were performed with R statistical software(V.4.5.1),3 and a two-sided p value <0.05 was considered statistically significant. The R packages gWQS and nhanesR were applied to construct the WQS model and weighted logistic regression.

3. Results

3.1 Baseline characteristics of the participants

This study included a total of 2,043 participants, comprising 1,484 (72.6%) without hypotension and 559 (27.4%) with hypotension. The baseline characteristics of both groups are presented in Table 1. Regarding demographic characteristics, no statistically significant differences were observed in gender distribution (P=0.20), racial composition (P=0.47), or income-to-poverty ratio (P=0.72). However, significant differences existed in age distribution (P<0.001): the hypotension group had a significantly lower proportion of pre-puberty children (8-10 years) compared to the non-hypotension group (23.26% vs 39.96%), while demonstrating a higher proportion of mid-puberty adolescents (14-18 years) (41.14% vs 29.78%). In anthropometric measures, BMI categories showed significant between-group differences (P=0.02), with the hypotension group exhibiting a lower prevalence of obesity (7.87% vs 12.06%). For clinical indicators, the hypotension group demonstrated significantly lower systolic blood pressure (102.7±9.8 vs 107.3±9.3 mmHg, P<0.001) and diastolic blood pressure (44.4±16.1 vs 60.6±8.5 mmHg, P<0.001), consistent with the group definitions. Laboratory analyses revealed no significant differences in urinary creatinine (P=0.32), urinary arsenic (P=0.22), or urinary lead (P=0.82) levels between groups. Dietary intake measures, including sodium intake (P=0.45) and total calorie consumption (P=0.49), also showed no statistically significant differences.

Table 1. Descriptive characteristics of children and adolescents aged 8–17 years with and without hypotension in the 2007–2018 National Health and Nutrition Examination Study (NHANES)

	No hypotension (n=1484)	**Hypotension (n=559)**	**P. value**
Gender n (%)			0.20
Male	729 (49.12%)	293 (52.42%)	
Female	755 (50.88%)	266 (47.58%)	
Race n (%)			0.47
Non-Hispanic White	443 (29.85%)	171 (30.59%)	
Mexican American	337 (22.71%)	129 (23.08%)	
Other Hispanic	147 (9.91%)	65 (11.63%)	
Non-Hispanic Black	366 (24.66%)	118 (21.11%)	
Other Race n (%)	191 (12.87%)	76 (13.6%)	

	No hypotension (n=1484)	Hypotension (n=559)	P. value
Age Group			<0.001
Pre-Puberty (8–10 years)	593 (39.96%)	130 (23.26%)	
Early-Puberty (11–13 years)	449 (30.26%)	199 (35.6%)	
Mid-Puberty (14–17 years)	442 (29.78%)	230 (41.14%)	
Income-to-Poverty Ratio n (%)			0.72
<1.0	448 (30.19%)	179 (32.02%)	
1.0-1.99	411 (27.7%)	152 (27.19%)	
≥2.0	625 (42.12%)	228 (40.79%)	
BMI Category n (%)			0.02
Under weight	417 (28.10%)	153 (27.37%)	
Normal weight	697 (46.97%)	274 (49.02%)	
Over weight	191(12.87%)	88 (15.74%)	
Obesity	179 (12.06%)	44 (7.87%)	
Household size	4.7 ± 1.4	4.8 ± 1.4	0.30
Systolic blood pressure (mmHg)	107.3 ± 9.3	102.7 ± 9.8	<0.001
Diastolic blood pressure (mmHg)	60.6 ± 8.5	44.4 ± 16.1	<0.001
Urinary creatinine (mg/dL)	124.2 ± 64.3	127.4 ± 65.4	0.32
Urinary As (μg/g creatinine)	9.5 ± 21.0	10.9 ± 22.9	0.22
Urinary Pb (μg/g creatinine)	0.4 ± 0.5	0.4 ± 0.4	0.82
Sodium intake (mg)	3278.5± 1714.3	3341.0 ± 1645.7	0.450
Total calorie intake (kcal)	2038.9 ± 944.8	2069.7 ± 891.3	0.493

3.2 Association of single metal exposure with hypotension

Comprehensive analysis reveals significant associations between arsenic/lead exposure and blood pressure dysregulation in children and adolescents. As shown in Table 2, the highest arsenic quartile (Q4) increased hypotension risk by 63% (OR=1.63, 95%CI:1.03-2.58) with significant dose-response trend (p-trend=0.04), while lead exposure Q3 increased risk by 54% (OR=1.54, P=0.03). These findings align with the blood pressure percentile analysis in Table 3: arsenic exposure significantly reduced diastolic pressure (-5.75 percentiles in Q3, P=0.02) with marked linear trend (P-trend=0.049); lead exposure Q4 reduced diastolic pressure by 3.40 percentiles and systolic pressure by 1.82 percentiles, showing borderline significant systolic trend (P-trend=0.05). Crucially, the highest exposure groups (Q4) consistently demonstrated the most pronounced effects across both analyses, with directional consistency between diastolic pressure reduction and increased hypotension risk, suggesting metal exposure may increase hypotension susceptibility by altering blood pressure distribution patterns, particularly diastolic regulation.

Table 2. Associations Between Arsenic and Lead Exposure and Hypotension Risk in Children and Adolescents Aged 8–17 Years

Metal	Model	Exposure Category	Odds Ratio (95% CI)	P-value	P-trend
Log Urinary As (μg/g creatinine)	Model 1	Q2 vs Q1	1.44 (0.93–2.24)	0.11	0.01*
		Q3 vs Q1	1.44 (0.91–2.29)	0.12	
		Q4 vs Q1	1.73 (1.13–2.64)	0.01*	
	Model 2	Q2 vs Q1	1.44 (0.92–2.25)	0.12	0.04*
		Q3 vs Q1	1.42 (0.88–2.29)	0.16	
		Q4 vs Q1	1.63 (1.03–2.58)	0.04*	

Metal	Model	Exposure Category	Odds Ratio (95% CI)	P-value	P-trend
Log Urinary Pb (μg/g creatinine)	Model 1	Q2 vs Q1	1.41 (0.98–2.03)	0.07	0.02*
		Q3 vs Q1	1.66 (1.13–2.45)	0.01*	
		Q4 vs Q1	1.66 (1.05–2.64)	0.03*	
	Model 2	Q2 vs Q1	1.38 (0.96–1.98)	0.09	0.06
		Q3 vs Q1	1.54 (1.04–2.28)	0.03*	
		Q4 vs Q1	1.48 (0.93–2.34)	0.10	

Reference group: Q1 (lowest quartile); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram; Model 1: Adjusted for age, sex and race. Model 2: Model 1 + BMI, income-to-poverty ratio, sodium intake, total calorie intake and household size

Table 3. Analysis of the Impact of Urinary Arsenic (As) and Lead (Pb) Exposure on Systolic and Diastolic Blood Pressure Percentiles in Children and Adolescents Based on Weighted Multivariable Linear Regression

Metal	Exposure Category	Model 1		Model 2	
		β (95% CI)	P. value	β (95% CI)	P. value
Systolic blood pressure percentile (mm Hg)					
Log Urinary As (μg/g creatinine)	Q2 vs Q1	0.68 (-3.81-5.18)	0.76	0.79 (-3.43-5.01)	0.71
	Q3 vs Q1	-0.21 (-4.58-4.17)	0.93	0.30 (-3.89-4.48)	0.89
	Q4 vs Q1	-1.38 (-5.50-2.74)	0.51	0.38 (-3.52-4.28)	0.85
P-trend		0.66		0.90	
Log Urinary Pb (μg/g creatinine)	Q2 vs Q1	-1.98 (-5.80-1.85)	0.31	-1.09 (-4.61-2.44)	0.55
	Q3 vs Q1	-3.92 (-8.11-0.26)	0.07	-2.66 (-6.76-1.44)	0.21
	Q4 vs Q1	-3.82 (-8.22-0.58)	0.09	-1.82 (-5.72-2.09)	0.36
P-trend		0.05*		0.24	
Diastolic blood pressure percentile (mm Hg)					
Log Urinary As (μg/g creatinine)	Q2 vs Q1	-2.31 (-7.44-2.82)	0.37	-2.02 (-7.16-3.11)	0.43
	Q3 vs Q1	-6.20 (-10.92--1.47)	0.01*	-5.75 (-10.41--1.09)	0.02*
	Q4 vs Q1	-4.31 (-9.32-0.70)	0.09	-3.87 (-8.89-1.16)	0.13
P-trend		0.03*		0.05*	
Log Urinary Pb (μg/g creatinine)	Q2 vs Q1	0.50 (-3.77-4.78)	0.82	0.74 (-3.33-4.81)	0.72
	Q3 vs Q1	0.33 (-3.62-4.27)	0.87	0.93 (-3.01-4.87)	0.65
	Q4 vs Q1	-4.01 (-8.41-0.39)	0.08	-3.40 (-7.69-0.90)	0.13
P-trend		0.13		0.22	

Reference group: Q1 (lowest quartile); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram; mmHg: Millimeters of mercury; Model 1: Adjusted for age, sex and race.; Model 2: Model 1 + BMI, income-to-poverty ratio, sodium intake, total calorie intake and household size.

3.3 Effect modification analysis of urinary metal exposure and hypotension association

Effect modification analyses (Table 7) confirmed that pubertal stage significantly modified lead exposure effects, with a significant interaction in mid-puberty (p-interaction = 0.03). This complements subgroup findings showing peak lead effects in mid-puberty (Q3: OR = 2.45, P = 0.005; Table 4), suggesting developmentally specific susceptibility windows. Although arsenic expose demonstrated strong mid-pubertal associations (Q4: OR = 2.62, P = 0.001), no significant age interaction was

detected (p-interaction for mid-puberty = 0.48; Table 7). Gender-stratified analyses (Table 5) indicated male-predominant lead risk (Q2: OR = 2.01, P = 0.005) and female-specific arsenic vulnerability (Q4: OR = 1.82, P = 0.04), but gender interactions were non-significant (P-interaction = 0.89). BMI stratification (Table 6) revealed heightened sensitivity in normal-weight individuals to both metals (lead Q4: OR = 2.14, P = 0.02; arsenic Q4: OR = 2.04, P = 0.02), with borderline arsenic risk in obese individuals (Q4: OR = 2.99, P = 0.07), yet BMI interactions were non-significant (P-interaction > 0.24).

Table 4. Age Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	Age Group	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (μg/g creatinine)	Pre-puberty (8–10y)	Q2 vs Q1	0.66 (0.25-1.72)	0.40
		Q3 vs Q1	0.53 (0.20-1.40)	0.21
		Q4 vs Q1	0.53 (0.22-1.32)	0.18
	Early-puberty (11–13y)	Q2 vs Q1	1.74 (0.95-3.19)	0.08
		Q3 vs Q1	2.45 (1.35-4.46)	0.005**
		Q4 vs Q1	2.02 (1.01-4.02)	0.05
	Mid-puberty (14–17y)	Q2 vs Q1	1.24 (0.72-2.15)	0.44
		Q3 vs Q1	1.29 (0.73-2.31)	0.39
		Q4 vs Q1	1.75 (0.81-3.81)	0.16
Log Urinary As (μg/g creatinine)	Pre-puberty (8–10y)	Q2 vs Q1	0.78 (0.28-2.13)	0.62
		Q3 vs Q1	0.99 (0.38-2.57)	0.98
		Q4 vs Q1	1.34 (0.45-4.00)	0.60
	Early-puberty (11–13y)	Q2 vs Q1	2.01 (1.08-3.74)	0.03*
		Q3 vs Q1	1.18 (0.60-2.31)	0.64
		Q4 vs Q1	1.08 (0.59-1.98)	0.81
	Mid-puberty (14–17y)	Q2 vs Q1	1.61 (0.93-2.78)	0.10
		Q3 vs Q1	2.07 (1.03-4.15)	0.04*
		Q4 vs Q1	2.62 (1.47-4.67)	0.001**

Reference group: Q1 (lowest exposure quartile); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram.

Table 5. Gender Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	Gender	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (μg/g creatinine)	Male	Q2 vs Q1	2.01 (1.26-3.21)	0.005**
		Q3 vs Q1	1.84 (1.04-3.26)	0.04*
		Q4 vs Q1	1.27 (0.71-2.29)	0.43
	Female	Q2 vs Q1	0.80 (0.46-1.39)	0.43
		Q3 vs Q1	1.22 (0.71-2.08)	0.48
		Q4 vs Q1	1.51 (0.82-2.80)	0.19
Log Urinary As (μg/g creatinine)	Male	Q2 vs Q1	1.28 (0.71-2.30)	0.41
		Q3 vs Q1	1.28 (0.70-2.34)	0.42
		Q4 vs Q1	1.51 (0.86-2.64)	0.16
	Female	Q2 vs Q1	1.68 (0.93-3.05)	0.09
		Q3 vs Q1	1.59 (0.92-2.73)	0.10
		Q4 vs Q1	1.82 (1.04-3.20)	0.04*

Reference group: Q1 (lowest exposure quartile); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram.

Table 6. BMI Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	BMI Category	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (μg/g creatinine)	Normal	Q2 vs Q1	1.30 (0.78-2.16)	0.31
		Q3 vs Q1	1.76 (0.98-3.16)	0.06
		Q4 vs Q1	2.14 (1.15-3.97)	0.02*
	Underweight	Q2 vs Q1	2.06 (0.94-4.49)	0.07
		Q3 vs Q1	1.51 (0.62-3.68)	0.37
		Q4 vs Q1	1.37 (0.56-3.35)	0.49
	Overweight	Q2 vs Q1	1.10 (0.46-2.63)	0.83
		Q3 vs Q1	0.78 (0.36-1.66)	0.52
		Q4 vs Q1	0.67 (0.27-1.69)	0.41
	Obese	Q2 vs Q1	0.75 (0.26-2.22)	0.62
		Q3 vs Q1	1.93 (0.70-5.31)	0.21
		Q4 vs Q1	0.62 (0.19-2.03)	0.44
Log Urinary As (μg/g creatinine)	Normal	Q2 vs Q1	1.65 (0.96-2.84)	0.07
		Q3 vs Q1	1.87 (1.04-3.37)	0.04*
		Q4 vs Q1	2.04 (1.14-3.67)	0.02*
	Underweight	Q2 vs Q1	1.20 (0.44-3.23)	0.73
		Q3 vs Q1	0.90 (0.38-2.17)	0.82
		Q4 vs Q1	1.10 (0.45-2.65)	0.84
	Overweight	Q2 vs Q1	1.28 (0.49-3.34)	0.62
		Q3 vs Q1	1.03 (0.38-2.79)	0.96
		Q4 vs Q1	1.17 (0.44-3.07)	0.76
	Obese	Q2 vs Q1	0.71 (0.28-1.79)	0.48
		Q3 vs Q1	1.67 (0.64-4.33)	0.30
		Q4 vs Q1	2.99 (0.94-9.49)	0.07

Reference group: Q1 (lowest exposure quartile); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram;

Table 7. Interaction Analysis for Effect Modification

Metal	Effect Modifier	Interaction P-value
Log Urinary Pb (μg/g creatinine)	Age (Early-puberty)	0.06
	Age (Mid-puberty)	0.03*
	Gender	0.91
	BMI	0.94
Log Urinary As (μg/g creatinine)	Age (Early-puberty)	0.16
	Age (Mid-puberty)	0.48
	Gender	0.89
	BMI	0.24

P-interaction for age groups (vs. pre-puberty reference); * p < 0.05, ** p < 0.01, *** p < 0.001; Units: μg/g – Micrograms per gram

3.4 Association of urinary metal co-exposure with hypotension

The WQS regression model was used to study the effect of mixed metals on hypotension. After adjusting for all selected confounders, the WQS index of mixed metal exposure was significantly associated with the risk of hypotension (master model OR = 1.21, 95% CI: 1.03-1.42, P=0.02), with UAs and Pb weights of 50.03% and 49.97%, respectively, as shown in (Figure 1). Stratified analysis showed that the association was strongest among normal weight adolescents (OR=1.45, 95%CI: 1.16-1.81, P=0.001), and the obese group had the largest effect value but no statistically significant (OR=1.67, 95%CI: 0.92-3.16, P=0.10). The most obvious risk trend was shown in early adolescence (OR=1.27, 95%CI: 0.97-1.69, P=0.09).

Figure 1: Association of metal mixture exposure with hypotension risk in adolescents using weighted quantile sum regression

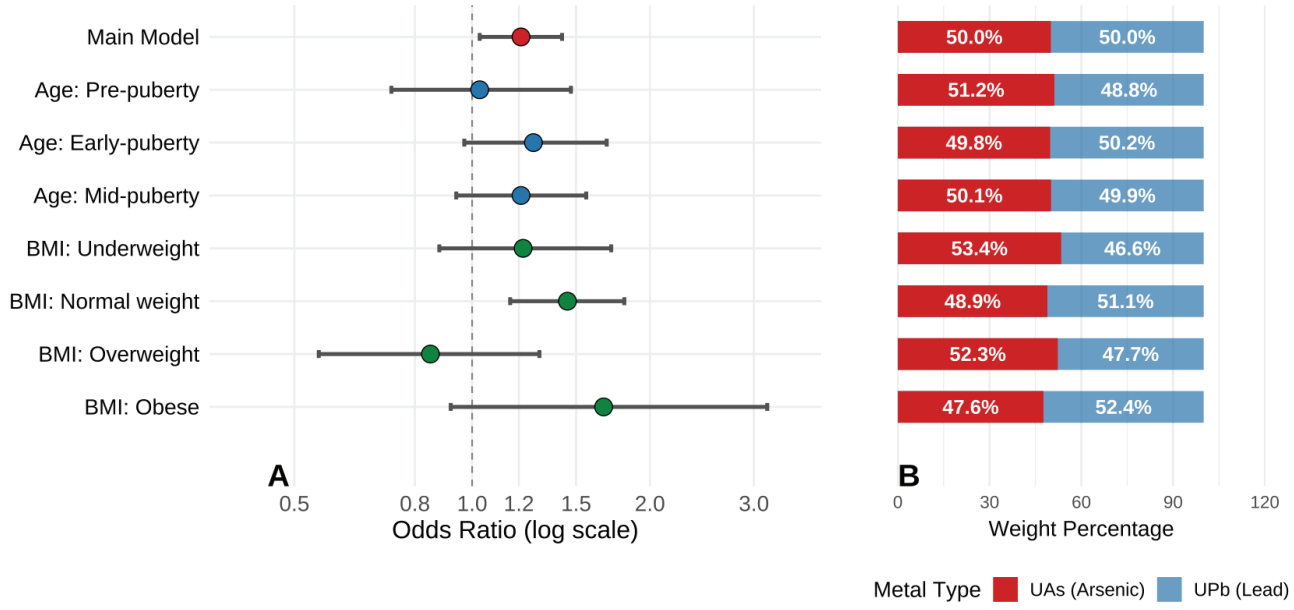

FIGURE 1:

(A) Forest plot showing odds ratios (OR) and 95% confidence intervals for the association between the metal mixture index and hypotension risk.

(B) Bar plot showing weight distribution of arsenic and lead in the weighted quantile sum (WQS) index.

The main model (n=2043) was adjusted for age, sex, race/ethnicity, BMI category, household income, family size, energy intake and sodium intake.

3.5 Sensitivity Analysis

To verify the robustness of the model, sensitivity analyses were performed to assess potential non-linear and non-additive relationships between UAs, UPb, and hypotension. For non-linear relationships, natural spline models (df=3) were compared with linear models using Rao-Scott likelihood ratio tests (LRT). Results showed no significant non-linear trends: LRT=3.36 (P=0.190) for ln_UAs and LRT=1.40 (P=0.489) for ln_UPb, supporting the use of linear models in primary analyses. For non-additive relationships, an interaction term (ln_UAs: ln_UPb) was included in the Weighted Quantile Sum (WQS) model. The interaction term (coefficient=-0.06, SE=0.04, z=-1.60, P=0.11) was not statistically significant, indicating no evidence of synergistic or antagonistic effects between the two metals. In summary, the sensitivity analysis confirmed the robustness of the model, with linear associations and no significant non-additive effects.

4. Discussion

This study investigated the associations of UAs and Pb exposure—both individually and in mixture—with hypotension among 2,043 children and adolescents, while exploring effect modification by pubertal stage, gender, and BMI. Our key findings reveal that both single and co-exposure to arsenic and lead are associated with an increased risk of hypotension, with distinct susceptibility patterns across developmental stages and anthropometric subgroups.

Our primary results highlight three critical observations: (1) individual arsenic and lead exposure are independently associated

with elevated hypotension risk, with more pronounced effects on diastolic blood pressure; (2) arsenic and lead co-exposure demonstrated additive effects on hypotension risk, with nearly equal contributions from each metal; (3) these associations are modified by pubertal stage and BMI, with normal-weight and pubescent adolescents appearing most vulnerable. First, the positive associations between arsenic (Q4: OR=1.63) and lead (Q3: OR=1.54) exposure and hypotension risk, coupled with their dose-dependent reductions in diastolic blood pressure percentiles, align with emerging evidence that environmental metals may disrupt blood pressure regulation beyond hypertension. While most prior studies focus on metal-induced hypertension in adults [19,20], our findings in children and adolescents suggest a contrasting or context-dependent effect—potentially driven by the unique physiological dynamics of pediatric blood pressure regulation, which is still maturing during puberty [21]. The stronger impact on diastolic pressure (e.g., arsenic Q3 reducing diastolic percentiles by -5.75) is noteworthy, as diastolic pressure in youth is more closely linked to vascular resistance and autonomic nervous system (ANS) function [22], hinting at metal-induced disruption of these pathways. Second, the WQS model revealed that co-exposure to arsenic and lead jointly increases hypotension risk (master model OR=1.21), with nearly equal weights (50.03% vs. 49.97%). This finding echoes the combined toxicity mechanism of cadmium-lead mixtures on renal function in a cohort of Mexican children, suggesting that heavy metal mixtures may affect cardiovascular homeostasis through multiple pathway superposition or toxicity amplification effects [23]; our results suggest that arsenic and lead may exert additive effects on hypotension, consistent with their overlapping mechanisms of vascular and neural toxicity. The comparable weights imply neither metal dominates the association, underscoring the need to consider co-exposure in pediatric populations, where cumulative toxicant burdens may disproportionately affect developing systems.

Our effect modification analyses identified key subgroups with heightened vulnerability. Lead's association with hypotension was strongest in early puberty (Q3: OR=2.45), while arsenic showed pronounced effects in mid-puberty (Q4: OR=2.62). Puberty is a critical period for cardiovascular maturation, and early puberty specifically represents a key window for vascular development and sympathetic nervous system maturation. During this stage, the vascular smooth muscle and autonomic regulatory pathways are still plastic, making them highly susceptible to environmental toxicants. Lead, which disrupts calcium signaling, could exacerbate vascular smooth muscle dysfunction during this critical growth phase—potentially amplifying hypotensive effects by impairing vasoconstrictive responses that maintain normal blood pressure. This developmental vulnerability may explain why lead's risk peaks in early puberty, while arsenic—known to alter endothelial nitric oxide (NO) production—might exacerbate diastolic dysfunction as blood pressure stabilizes in mid-puberty [24,25]. Normal-weight adolescents exhibited the strongest association between mixed metal exposure and hypotension (OR=1.45), while obese individuals showed a large but imprecise effect (OR=1.67, 95% CI:0.92–3.16). This contrasts with adult studies linking obesity to hypertension but aligns with the baseline finding that hypotension is less common in obese youth. Normal-weight individuals may lack the adipokine-mediated or volume-expanded buffering mechanisms present in obesity, making their blood pressure regulation more susceptible to metal-induced disruption [26,27]. The wide CI in obese groups likely reflects smaller sample size (hypotension group obesity=7.87%), limiting statistical power. Male-predominant lead risk and female-specific arsenic vulnerability, though non-significant in interaction tests, mirror reports of gender-dependent metal toxicity. Testosterone may enhance lead's vascular effects , while estrogen's modulation of endothelial function could amplify arsenic's impact on diastolic pressure in females—warranting further investigation [28,29].

The observed associations may stem from shared and distinct mechanisms of arsenic and lead toxicity. Arsenic inhibits endothelial NO synthase, reducing NO-mediated vasodilation and lowering diastolic pressure [30]. Lead disrupts calcium homeostasis in vascular smooth muscle, impairing vasoconstriction—critical for maintaining systolic pressure [31]. Together, these effects could shift blood pressure distribution toward hypotension, particularly in developing vasculature. Both metals target the ANS; lead alters sympathetic tone via central nervous system toxicity, while arsenic impairs parasympathetic modulation. In adolescents, wh ere ANS balance is still maturing, such disruption could exaggerate hypotensive tendencies. Though urinary creatinine (a proxy for renal function) showed no group differences, metals may subtly impair renal sodium handling, affecting blood volume and pressure—consistent with our finding that dietary sodium (a key regulator) did not confound associations [32].

Limitations should be noted: (1) Cross-sectional design precludes causal inference; longitudinal studies are needed to establish temporality. (2) Urinary metals reflect recent (not cumulative) exposure; hair or bone biomarkers could better capture long-term burden. (3) Unmeasured confounders (e.g., genetic polymorphisms in metal transporters, physical activity) may influence results. (4) The obese subgroup's wide CI limits interpretation of its large effect size.

5. Conclusion

This study confirmed that environmental arsenic and lead exposure were independent risk factors for hypotension in children and adolescents, and there was a significant additive effect. Normal-weight, early adolescent males are at high risk, and their blood pressure regulation mechanisms may be more susceptible to metal toxicity during the critical period of development.

Funding

No

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Reference

[1] Yang, L., Magnussen, C. G., Yang, L., Bovet, P., & Xi, B. (2020). Elevated blood pressure in childhood or adolescence and cardiovascular outcomes in adulthood: A systematic review. Hypertension, 75(4), 948–955. https://doi.org/10.1161/HYPERTENSIONAHA.119.14168

[2] Benjamin, E. J., Muntner, P., Alonso, A., et al. (2019). Heart disease and stroke statistics—2019 update: A report from the American Heart Association. Circulation, 139(10). https://doi.org/10.1161/CIR.0000000000000659

[3] Cosselman, K. E., Navas-Acien, A., & Kaufman, J. D. (2015). Environmental factors in cardiovascular disease. Nature Reviews Cardiology, 12(11), 627–642. https://doi.org/10.1038/nrcardio.2015.152

[4] Wu, X., Cobbina, S. J., Mao, G., Xu, H., Zhang, Z., & Yang, L. (2016). A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environmental Science and Pollution Research, 23(9), 8244–8259. https://doi.org/10.1007/s11356-016-6333-x

[5] Al Osman, M., Yang, F., & Massey, I. Y. (2019). Exposure routes and health effects of heavy metals on children. Biometals, 32(4), 563–573. https://doi.org/10.1007/s10534-019-00193-5

[6] Zhao, J., Li, A., Mei, Y., et al. (2021). The association of arsenic exposure with hypertension and blood pressure: A systematic review and dose–response meta-analysis. Environmental Pollution, 289, 117914. https://doi.org/10.1016/j.envpol.2021.117914

[7] Zachariah, J. P., Wang, Y., Penny, D. J., & Baranowski, T. (2018). Relation between lead exposure and trends in blood pressure in children. The American Journal of Cardiology, 122(11), 1890–1895. https://doi.org/10.1016/j.amjcard.2018.08.033

[8] Qu, Y., Lv, Y., Ji, S., et al. (2022). Effect of exposures to mixtures of lead and various metals on hypertension, pre-hypertension, and blood pressure: A cross-sectional study from the China National Human Biomonitoring. Environmental Pollution, 299, 118864. https://doi.org/10.1016/j.envpol.2022.118864

[9] Zeng, H., Wang, Q., Wang, H., et al. (2022). Exposure to barium and blood pressure in children and adolescents: results from the 2003–2018 National Health and Nutrition Examination Survey. Environmental Science and Pollution Research, 29(45), 68476–68487. https://doi.org/10.1007/s11356-022-20507-4

[10] Yao, B., Lu, X., Xu, L., Wang, Y., Qu, H., & Zhou, H. (2020). Relationship between low-level lead, cadmium and mercury exposures and blood pressure in children and adolescents aged 8–17 years: An exposure-response analysis of NHANES 2007–2016. Science of The Total Environment, 726, 138446. https://doi.org/10.1016/j.scitotenv.2020.138446

[11] Desai, G., Niu, Z., Luo, W., Frndak, S., Shaver, A. L., & Kordas, K. (2021). Low-level exposure to lead, mercury, arsenic, and cadmium, and blood pressure among 8-17-year-old participants of the 2009–2016 National Health and Nutrition Examination Survey. Environmental Research, 197, 111086. https://doi.org/10.1016/j.envres.2021.111086

[12] Shan, Q. (2022). Trend analysis of the association of urinary metals and obesity in children and adolescents. Chemosphere, 307, 135617. https://doi.org/10.1016/j.chemosphere.2022.135617

[13] Carrico, C., Gennings, C., Wheeler, D. C., & Factor-Litvak, P. (2015). Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. JABES, 20(1), 100–120. https://doi.org/10.1007/s13253-014-0180-3

[14] Guo, X., Li, N., Wang, H., et al. (2022). Combined exposure to multiple metals on cardiovascular disease in NHANES under five statistical models. Environmental Research, 215, 114435. https://doi.org/10.1016/j.envres.2022.114435

[15] Haque, I. U., & Zaritsky, A. L. (2007). Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatric Critical Care Medicine, 8(2), 138–144. https://doi.org/10.1097/01.PCC.0000257039.32593.DC

[16] Herman-Giddens, M. E., Slora, E. J., Wasserman, R. C., et al. (1997). Secondary sexual characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office Settings Network. Pediatrics, 99(4), 505–512. https://doi.org/10.1542/peds.99.4.505

[17] Ogden, C. L., Kuczmarski, R. J., Flegal, K. M., et al. (2002). Centers for Disease Control and Prevention 2000 Growth Charts for the United States: Improvements to the 1977 National Center for Health Statistics Version. Pediatrics, 109(1), 45–60. https://doi.org/10.1542/peds.109.1.45

[18] Duan, W., Xu, C., Liu, Q., et al. (2020). Levels of a mixture of heavy metals in blood and urine and all-cause, cardiovascular disease and cancer mortality: A population-based cohort study. Environmental Pollution, 263, 114630. https://doi.org/10.1016/j.envpol.2020.114630

[19] Abhyankar, L. N., Jones, M. R., Guallar, E., & Navas-Acien, A. (2012). Arsenic exposure and hypertension: A systematic review. Environmental Health Perspectives, 120(4), 494–500. https://doi.org/10.1289/ehp.1103988

[20] Obeng-Gyasi, E. (2019). Lead exposure and cardiovascular disease among young and middle-aged adults. Medical Sciences, 7(11), 103. https://doi.org/10.3390/medsci7110103

[21] Wojcik, M., Starzyk, J. B., Drodz, M., & Drodz, D. (2023). Effects of puberty on blood pressure trajectories — Underlying processes. Current Hypertension Reports, 25(7), 117–125. https://doi.org/10.1007/s11906-023-01241-9

[22] Tanaka, H., Borres, M., Thulesius, O., Tamai, H., Ericson, M. O., & Lindblad, L. E. (2000). Blood pressure and cardiovascular autonomic function in healthy children and adolescents. The Journal of Pediatrics, 137(1), 63–67. https://doi.org/10.1067/mpd.2000.108098

[23] Levin-Schwartz, Y., Politis, M., Gennings, C., et al. (2021). Nephrotoxic metal mixtures and preadolescent kidney function. Children, 8(8), 673. https://doi.org/10.3390/children8080673

[24] Wroblewski, M., Milek, J., Godlewski, A., & Wroblewska, J. (2025). The impact of arsenic, cadmium, lead, mercury, and thallium exposure on the cardiovascular system and oxidative mechanisms in children. CIMB, 47(7), 483. https://doi.org/10.3390/cimb47070483

[25] Perrelli, M., Wu, R., Liu, D. J., et al. (2022). Heavy metals as risk factors for human diseases – a Bayesian network approach. European Review for Medical and Pharmacological Sciences, 26(24), 9275–9310. https://doi.org/10.26355/eurrev_202212_30681

[26] Gomez-Ambrosi, J., Silva, C., Galofre, J. C., et al. (2012). Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. International Journal of Obesity, 36(2), 286–294. https://doi.org/10.1038/ijo.2011.100

[27] Ouchi, N., Parker, J. L., Lugus, J. J., & Walsh, K. (2011). Adipokines in inflammation and metabolic disease. Nature Reviews Immunology, 11(2), 85–97. https://doi.org/10.1038/nri2921

[28] Vaziri, N. D., & Sica, D. A. (2004). Lead-induced hypertension: Role of oxidative stress. Current Science Inc., 6(4), 314–320. https://doi.org/10.1007/s11906-004-0027-3

[29] Vahter, M., Akesson, A., Liden, C., Ceccatelli, S., & Berglund, M. (2007). Gender differences in the disposition and toxicity of metals. Environmental Research, 104(1), 85–95. https://doi.org/10.1016/j.envres.2006.08.003

[30] Barchowsky, A., Dudek, E. J., Treadwell, M. D., & Wetterhahn, K. E. (1996). Arsenic induces oxidant stress and NF-

KB activation in cultured aortic endothelial cells. Free Radical Biology and Medicine, 21(6), 783–790. https://doi.org/10.1016/0891-5849(96)00174-8

[31] Simons, T. J. B., & Pocock, G. (1987). Lead enters bovine adrenal medullary cells through calcium channels. Journal of Neurochemistry, 48(2), 383–389. https://doi.org/10.1111/j.1471-4159.1987.tb04105.x

[32] Mumford, J. L., Wu, K., Xia, Y., et al. (2007). Chronic arsenic exposure and cardiac repolarization abnormalities with QT interval prolongation in a population-based study. Environmental Health Perspectives, 115(5), 690–694. https://doi.org/10.1289/ehp.9686