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Association between multiple urinary trace metal elements and lumbar bone mineral density in adults

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ABSTRACT

Urinary trace metal elements are key biomarkers for assessing exposure to toxic metals, and are significant contributors to osteoporosis (OP). Epidemiological research examining the connection between adult bone mineral density (BMD) and trace metal elements exposure is still very scarce, nevertheless. The study aims to clarify the association between trace metal elements exposure and BMD. This cross-sectional study included 3,441 adults (aged 20 to 59) from 2011 to 2018 National Health and Nutrition Examination Survey (NHANES). Weighted multivariable logistic regression analysis, subgroup analysis, smoothing curve fitting and threshold effect analysis were conducted to explore the association between four urinary trace metal elements (barium, cesium, antimony, and tin) and BMD. We found that urinary cesium, antimony, and tin were positively associated with lumbar BMD, while urinary barium demonstrated an inverted U-shaped association in US adults. The results of this study are helpful for the development of strategies for bone mineral density management.

Keywords: urinary trace metal elements, BMD, osteoporosis, adults, NHANES

Abbreviations:
OP: osteoporosis
BMD: bone mineral density
NHANES: National Health and Nutrition Examination Survey
UCL: urinary cesium level
UAL: urinary antimony level
UTL: urinary tin level
UBL: urinary barium level

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INTRODUCTION

Bone mineral density (BMD) serves as a widely recognized indicator for assessing skeletal health. This measurement[1] undergoes substantial growth throughout childhood and adolescence, typically reaching its maximum level around the age of 20. Insufficient BMD levels may contribute to osteoporosis (OP), a condition that often develops asymptomatically until bone fractures manifest, profoundly impacting personal health outcomes and daily functioning.[2,3] OP is increasingly recognized as a major public health concern, driven by an aging population.[4] Studies[5,6] show that BMD is significantly lower in individuals over 50, and the increasing prevalence of OP is imposing a substantial financial burden on society, and OP treatment costs are projected to exceed $20 billion by 2025. Bone is a crucial component of the human body, facilitating hematopoiesis, mobility, storage, structural support, and immune defense. Bone mass is maintained through a balance between bone resorption and formation.[5,7] Identifying risk factors for declining bone density is crucial to prevent the progression of OP.

Trace metal elements pollution has become a pervasive environmental issue, with these persistent contaminants infiltrating ecosystems through multiple exposure routes, creating serious threats to ecological balance and public health.[8,9] The proliferation of metallic pollutants has escalated dramatically following the advent of industrial modernization.[10] These non-essential metals are typically resistant to degradation, and some can undergo redox reactions, forming bioactive substances that remain toxic even at low doses. Consequently, these substances are recognized contributors to various health issues, such as diabetes, cancer, heart disease, neurodegenerative conditions like Parkinson's and Alzheimer's, and persistent inflammatory disorders.[11,12]

Trace metal elements exposure has also been associated with long-term bone disorders, such as OP.[13,14] As the primary route for eliminating most metals from the body, urine production and excretion play a critical role in human metabolism.[15] Total body and lumbar spine are two preferred sites suitable for BMD from adolescents to old age.[16] Therefore, this study explores the impact of four urinary trace metal elements on lumbar BMD in US adults, using the most recent National Health and Nutrition Examination Survey (NHANES) data.

MATERIALS AND METHODS

Study subjects

The NHANES comprises a series of cross-sectional studies performed by the United States Centers for Disease Control and Prevention (CDC). The objective of NHANES is to evaluate the health of the non-institutionalized population nationwide. In this study, data from the 2011 to 2018 cycles were combined to form a nationally representative dataset of 39,156 participants. Initially, individuals with missing urinary metal data were excluded (N = 28,537). Those with missing lumbar BMD data were excluded (N = 4,970) and those under 20 years of age (N = 2,208), resulting in 3,441participants whose data were analyzed (Figure 1). Informed consent was obtained from all participants, and the survey protocol was authorized by the National Center for Health Statistics Research Ethics Review Board.

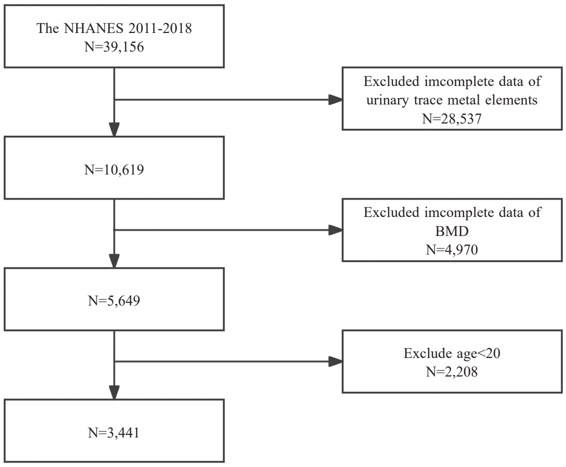

Fig. 1 Flowchart of participants selection
NHANES: National Health and Nutrition Examination Surve
BMD: bone mineral density

Exposure and outcome variable

Lumbar BMD was assessed via dual-energy X-ray absorptiometry. The bone density measurements were conducted by professionally trained and certified radiologists. A lumbar scan can provide bone measurement data for the lumbar BMD. Detailed information was obtained from the NHANES and Nutrition Examination database.

Urine samples were collected at mobile testing facilities, subsequently stored under controlled conditions, processed systematically, and transported to the Laboratory Sciences Division of the National Center for Environmental Health for comprehensive analysis. Metal concentrations in urine were quantified through inductively coupled plasma mass spectrometry (ICP-MS), with detailed protocols outlined in the NHANES laboratory procedures manual. All urinary metal concentrations below the lower limit of detection (LOD) were imputed using LOD divided by $\sqrt{2}$, in accordance with NHANES guidelines. Although the proportion of <LOD values for antimony (23.38%) and tin (17.17%) was relatively high, this approach minimizes potential bias. Additionally, log-transformation was applied to normalize distributions before modeling, and sensitivity analyses confirmed the robustness of the associations.[17] All analyzed metallic elements demonstrated detection percentages above 75%, with comprehensive detection statistics for individual trace metal elements presented in Supplementary Table 1.

Covariates

In this investigation, lumbar bone mineral density served as the primary outcome measure, with urinary concentrations of four trace metal elements functioning as exposure variables. Potential confounding factors influencing BMD were systematically extracted from the NHANES 2011–2018 database, encompassing demographic characteristics, lifestyle indicators, and biochemical parameters for comprehensive adjustment in multivariable models. The analysis accounted for demographic factors (sex, age, race, educational level), health indicators (body mass index (BMI), smoking status, alcohol consumption, diabetic status, hypertension), socioeconomic measures (income-poverty ratio), and biochemical markers including nitrogen content in blood urea nitrogen, serum uric acid, serum phosphorus, serum calcium, 25-hydroxyvitamin D.

Statistical analysis

The statistical procedures in this investigation were performed utilizing R software version 4.2.1 (The R Foundation) alongside EmpowerStats version 4.2.1 (X & Y Solutions Inc). Urinary trace metal element concentrations exhibited non-normal distribution characteristics, requiring natural logarithmic transformation during regression modeling. All analytical processes strictly adhered to CDC-established protocols, with proper application of NHANES survey weights to accommodate the intricate multistage cluster sampling design inherent in the dataset. Categorical data are presented as counts and corresponding percentages, while continuous measurements are reported using mean values accompanied by standard deviations (SD). For nonlinear associations, an iterative algorithm is employed to determine the threshold point, followed by fitting separate regression models on each segment of the identified threshold. Subgroup evaluations were conducted through stratified regression frameworks to examine potential effect modifications. The association between urinary trace metal elements and lumbar BMD employed univariate and multivariate line regression models. Three models were constructed and used in our analyses. In Model I, no covariates were adjusted. Model II was adjusted for gender, age, and race. Model III was adjusted for gender, age, race, education level, BMI, alcohol consumption, smoking status, diabetes, hypertension, income-to-poverty ratio, alkaline phosphatase, serum albumin, aspartate aminotransferase, alanine aminotransferase, 25-hydroxyvitamin D, blood glucose. To further explore the association between urinary trace metal elements with lumbar BMD in different population settings, the subgroup analysis was performed by stratified multivariate regression analysis.

Effect sizes with 95% confidence intervals were reported. To address the non-linearity between urinary trace metal elements concentrations and lumbar BMD, curve model selection and smooth curve fitting were employed, as regression-based methods are often inadequate for handling non-linear associations. In cases of non-linearity, a recursive approach is used to pinpoint the inflection point, which is subsequently followed by the implementation of a two-stage regression model on both sides of the identified inflection point. Subgroup analysis was carried out using hierarchical regression models. To assess potential variations in subgroup association, an interaction variable was incorporated into the analysis. Statistical significance was determined using a threshold of $P < 0.05$.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline demographic characteristics of study participants. Our analysis included 3,441 subjects with balanced gender distribution (50.86% males vs 49.14% females), demonstrating a mean age of 39.05 ± 11.47 years. Educational attainment exceeding high school level was observed in 59.4% (n = 2044) of participants. The cohort comprised 33.91% non-Hispanic White individuals (n = 1167), with 61.61% reporting non-smoking status (n = 2120). Chronic condition prevalence included diabetes in 7.41% (n = 255) and hypertension in 22.73% (n = 782). Socioeconomic indicators revealed 68.76% (n = 2366) maintained income levels above poverty thresholds. The mean lumbar BMD value with SD was recorded as 1.03 ± 0.15 g/cm^2. Significantly elevated levels of barium, cesium, and antimony were observed in male urine samples, whereas tin concentrations were comparatively reduced relative to female participants.

Table 1 Urinary metal characteristics of the study participants in NHANES 2011–2018 (N=3,341)

	Total	**Male (%)**	**Female (%)**	**P-value**
	n = 3,441	n = 1,750	n = 1,691	
Age (year)	39.05 ± 11.47	38.68 ± 11.57	39.43 ± 11.36	0.054
Race, N (%)				0.018
Mexican-American	529 (15.37%)	256 (14.63%)	273 (16.14%)	
Other Hispanic	365 (10.61%)	162 (9.26%)	203 (12.00%)	
Non-Hispanic White	1167 (33.91%)	591 (33.77%)	576 (34.06%)	
Non-Hispanic Black	716 (20.81%)	382 (21.83%)	334 (19.75%)	
Other	664 (19.30%)	359 (20.51%)	305 (18.04%)	
Education, N (%)				<0.001
Under high school	635 (18.45%)	349 (19.94%)	286 (16.91%)	
High school or equivalent	762 (22.14%)	420 (24.00%)	342 (20.22%)	
Above high school	2044 (59.40%)	981 (56.06%)	1063 (62.86%)	
Smoking, N (%)				<0.001
Yes	1321 (38.39%)	795 (45.43%)	526 (31.11%)	
No	2120 (61.61%)	955 (54.57%)	1165 (68.89%)	
Diabetes, N (%)				0.742
Yes	255 (7.41%)	125 (7.14%)	130 (7.69%)	
No	3123 (90.76%)	1591 (90.91%)	1532 (90.60%)	
Borderline	63 (1.83%)	34 (1.94%)	29 (1.71%)	
Hypertension, N (%)				0.317
Yes	782 (22.73%)	410 (23.43%)	372 (22.00%)	
No	2659 (77.27%)	1340 (76.57%)	1319 (78.00%)	
BMI, N (%)				<0.001
Normal (<25)	1100 (31.97%)	533 (30.46%)	567 (33.53%)	
Overweight (25–29.9)	1079 (31.36%)	637 (36.40%)	442 (26.14%)	
Obese (≥30)	1262 (36.68%)	580 (33.14%)	682 (40.33%)	
Income-to-poverty ratio, N (%)				0.104
<1.31	1075 (31.24%)	512 (29.26%)	563 (33.29%)	0.030
1.31–3.50	1299 (37.75%)	688 (39.31%)	611 (36.13%)	
>3.50	1067 (31.01%)	550 (31.43%)	517 (30.57%)	
Blood urea nitrogen (mmol/L)	4.50 ± 1.56	4.79 ± 1.59	4.20 ± 1.47	<0.001
Serum uric acid (mg/dL)	5.36 ± 1.36	6.00 ± 1.26	4.69 ± 1.11	<0.001
Serum phosphorus (mg/dL)	3.73 ± 0.55	3.70 ± 0.56	3.76 ± 0.54	0.001
Serum calcium (mg/dL)	9.37 ± 0.33	9.42 ± 0.32	9.32 ± 0.33	<0.001
25-hydroxyvitamin D (nmol/L)	60.13 ± 24.50	57.84 ± 22.08	62.50 ± 26.57	<0.001
Barium (ug/L)	1.78 ± 2.53	1.93 ± 2.90	1.62 ± 2.05	<0.001
Cesium (ug/L)	4.99 ± 3.84	5.18 ± 4.13	4.79 ± 3.50	<0.001
Antimony (ug/L)	0.08 ± 0.17	0.09 ± 0.21	0.06 ± 0.09	<0.001
Tin (ug/L)	1.07 ± 3.86	1.03 ± 4.08	1.10 ± 3.63	0.018
Lumbar BMD (g/cm²)	1.03 ± 0.15	1.03 ± 0.16	1.04 ± 0.14	0.044

NHANES: National Health and Nutrition Examination Survey
BMI: body mass index
BMD: bone mineral density

The association between urinary trace metal elements and lumbar BMD

Analysis of Model II revealed a significant positive association between urinary cesium level (UCL) and lumbar BMD (β = 0.007; 95% CI, 0.001, 0.014; p = 0.032). In fully adjusted model (Model III), the positive association was still stable (β = 0.007; 95% CI, 0.000, 0.013; p = 0.044), indicating that each unit of increased UCL was associated with 0.007 higher unit of lumbar BMD. We also converted UCL from a continuous variable to a categorical variable (quartiles) to conduct the sensitivity analysis. Compared with the lowest UCL quartile (Quartile 1), the lumbar BMD increased with the higher UCL quartiles group. The mean lumbar BMD of the highest UCL quartile (Quartile 4) was 0.015 unit higher compared with the lowest quartile (β = 0.015; 95% CI, 0.002, 0.029; p = 0.024; Table 2).

A positive association between urinary antimony level (UAL) and lumbar BMD was observed both in Model I (β = 0.020; 95% CI, 0.013, 0.026; p < 0.001) and Model II (β = 0.009; 95% CI, 0.003, 0.015; p = 0.005). The fully adjusted Model III maintained statistical significance (β = 0.006; 95% CI, 0.000, 0.012; p = 0.040), with parameter estimates indicating a 0.006-unit elevation in lumbar BMD per unit increase in UAL. This persistent association suggested that every incremental unit in urinary antimony level corresponded to a 0.006-unit elevation in lumbar BMD. To assess robustness, UAL was transformed from a continuous measure into categorical quartiles for supplementary analysis. Lumbar BMD exhibited an upward trend corresponding with elevated UAL quartile categories. When comparing the highest quartile (Quartile 4) to the baseline group (Quartile 1), a statistically significant difference of 0.019 units in lumbar BMD was observed (β = 0.019; 95% CI, 0.005, 0.033; p = 0.007), as detailed in Table 2.

Statistical analyses revealed a significant positive association between urinary tin level (UTL) and lumbar BMD. Initial evaluations in the crude model (Model I) demonstrated a β coefficient of 0.024 (95% CI, 0.017, 0.031; p < 0.001), with this association persisting in partially adjusted analyses (Model II; β = 0.018; 95% CI, 0.011, 0.025; p < 0.001). The fully adjusted multivariable model (Model III) maintained statistical significance (β = 0.013; 95% CI, 0.006, 0.020; p < 0.001), suggesting each standard unit elevation in UTL corresponds to a 0.013-unit increase in lumbar BMD measurements after accounting for all covariates. For sensitivity assessment, urinary tin element levels were transformed from a continuous scale into categorical quartiles. Progressive increases in lumbar bone mineral density were observed across ascending quartile groups relative to the baseline lowest quartile (Quartile 1). Participants in the top quartile (Quartile 4) exhibited a 0.021-unit elevation in mean lumbar BMD versus Quartile1 (β = 0.021; 95% CI, 0.007, 0.035; p = 0.003), with detailed comparisons presented in Table 2.

Table 2 The association between urinary trace metal elements and lumbar BMD, weighted

	β[a] (95% CI[b])		
	Model I[c]	Model II[d]	Model III[e]
Barium			
Continuous	0.007 (0.001, 0.014) 0.028	0.008 (0.002, 0.015) 0.01187	0.008 (0.001, 0.014) 0.017
Quartile 1	Reference	Reference	Reference
Quartile 2	0.009 (–0.005, 0.023) 0.223	0.010 (–0.004, 0.024) 0.153	0.011 (–0.002, 0.025) 0.102
Quartile 3	–0.001 (–0.015, 0.013) 0.875	–0.001 (–0.014, 0.013) 0.936	0.002 (–0.011, 0.016) 0.737
Quartile 4	–0.011 (–0.024, 0.003) 0.133	–0.010 (–0.023, 0.004) 0.166	–0.006 (–0.020, 0.008) 0.397
P for trend	–0.004 (–0.009, 0.000) 0.054	–0.004 (–0.008, 0.000) 0.063	–0.003 (–0.007, 0.002) 0.204

Cesium			
Continuous	0.022 (0.014, 0.029) <0.001	0.018 (0.011, 0.026) <0.001	0.014 (0.007, 0.021) <0.001
Quartile 1	Reference	Reference	Reference
Quartile 2	–0.002 (–0.015, 0.012) 0.774	–0.001 (–0.015, 0.012) 0.831	0.000 (–0.013, 0.013) 0.980
Quartile 3	0.001 (–0.013, 0.015) 0.867	0.003 (–0.010, 0.017) 0.651	0.005 (–0.009, 0.018) 0.509
Quartile 4	0.015 (0.001, 0.029) 0.031	0.016 (0.003, 0.029) 0.019	0.015 (0.002, 0.029) 0.024
P for trend	0.005 (0.000, 0.009) 0.030	0.005 (0.001, 0.009) 0.015	0.005 (0.001, 0.009) 0.019
Antimony			
Continuous	0.020 (0.013, 0.026) <0.001	0.009 (0.003, 0.015) 0.005	0.006 (0.000, 0.012) 0.040
Quartile 1	Reference	Reference	Reference
Quartile 2	0.008 (–0.006, 0.021) 0.251	0.007 (–0.007, 0.020) 0.322	0.009 (–0.005, 0.022) 0.202
Quartile 3	0.022 (0.009, 0.036) 0.001	0.020 (0.006, 0.033) 0.004	0.022 (0.008, 0.036) 0.001
Quartile 4	0.019 (0.005, 0.033) 0.007	0.012 (–0.002, 0.026) 0.091	0.019 (0.005, 0.033) 0.007
P for trend	0.007 (0.003, 0.012) 0.001	0.005 (0.001, 0.009) 0.026	0.007 (0.003, 0.012) 0.002
Tin			
Continuous	0.024 (0.017, 0.031) <0.001	0.018 (0.011, 0.025) <0.001	0.013 (0.006, 0.020) <0.001
Quartile 1	Reference	Reference	Reference
Quartile 2	–0.002 (–0.016, 0.011) 0.728	–0.001 (–0.014, 0.012) 0.853	0.002 (–0.011, 0.015) 0.723
Quartile 3	0.004 (–0.009, 0.018) 0.533	0.004 (–0.009, 0.018) 0.534	0.006 (–0.007, 0.020) 0.354
Quartile 4	0.023 (0.009, 0.037) 0.001	0.018 (0.004, 0.032) 0.011	0.021 (0.007, 0.035) 0.003
P for trend	0.007 (0.003, 0.012) 0.001	0.006 (0.001, 0.010) 0.010	0.007 (0.002, 0.011) 0.004

In sensitivity analysis, urinary trace metal element level was converted from a continuous variable to a categorical variable (median split, tertiles or quartiles).
[a] Effect size; [b] 95% CI, 95% confidence interval; [c] Model I, no covariates were adjusted;
[d] Model II, adjusted for gender, age, and race; [e] Model III, adjusted for gender, age, race, education level, BMI, alcohol consumption, smoking status, diabetes, hypertension, income-to-poverty ratio, blood urea nitrogen, serum uric acid, serum phosphorus, serum calcium, 25-hydroxyvitamin D.
BMD: bone mineral density

Nonlinear association between urinary trace metal elements and lumbar BMD

Through threshold effect modeling, we identified a critical urinary barium level (UBL) value of −0.357 (K) that demarcated opposing associations. Below this threshold, urinary barium concentrations exhibited a positive association with lumbar bone mineral density ($\beta = 0.014$; 95% CI, 0.002, 0.025; $p = 0.020$). Conversely, when UBL exceeded this critical value, the association reversed to demonstrate a significant inverse association ($\beta = –0.011$; 95% CI, –0.018, –0.003; $p = 0.005$).

Following covariate adjustment, the log-likelihood ratio test yielded a P-value of 0.003 (Table 3). Barium concentrations demonstrated an inverted U-shaped association with lumbar BMD (Figure 2). No significant threshold effects (breakpoint K) emerged in analyses of UCL, UAL, or UTL relative to lumbar BMD.

Table 3 The threshold effect analysis of barium and lumbar BMD

	Lumbar BMD			
	Barium	**Cesium**	**Antimony**	**Tin**
Model I				
A linear effect	–0.002 (–0.007, 0.003) 0.401	0.007 (0.000, 0.013) 0.044	0.008 (0.002, 0.014) 0.0088	0.003 (–0.004, 0.009) 0.4129
Model II				
Inflection point (K)	–0.357	1.383	–2.604	–0.887
< the effect of segment K1	0.014 (0.002, 0.025) 0.020	0.001 (–0.010, 0.013) 0.813	0.017 (0.008, 0.027) 0.001	0.001 (–0.007, 0.008) 0.876
> the effect of segment K2	–0.011 (–0.018, –0.003) 0.005	0.014 (–0.000, 0.028) 0.052	–0.006 (–0.018, 0.007) 0.350	0.044 (–0.009, 0.096) 0.104
The effect difference between 2 and 1	–0.024 (–0.040, –0.008) 0.004	0.013 (–0.009, 0.034) 0.254	–0.023 (–0.042, –0.005) 0.014	0.043 (–0.012, 0.098) 0.124
The predicted value of the equation at the inflection point	1.050 (1.041, 1.058)	1.036 (1.028, 1.044)	1.052 (1.043, 1.061)	1.041 (1.032, 1.049)
Log-likelihood ratio test	0.003	0.253	0.014	0.123

BMD: bone mineral density

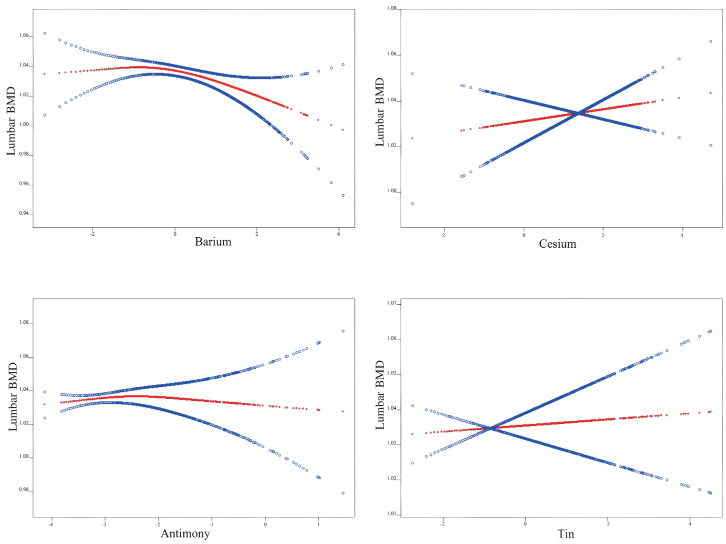

Fig. 2 Smoothed curve fittings for the association between urinary trace metal element concentrations and lumbar bone mineral density (BMD) among US adults

Each panel shows the adjusted relationship between log-transformed urinary concentrations of barium, cesium, antimony, and tin (x-axis) and lumbar BMD (y-axis). Solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Covariates adjusted in the models include age, sex, race/ethnicity, education level, body mass index (BMI), smoking status, alcohol consumption, diabetes, hypertension, income-to-poverty ratio, blood urea nitrogen, serum uric acid, serum phosphorus, serum calcium, 25-hydroxyvitamin D.

Subgroups analysis

In order to evaluate whether the association between urinary trace metal elements and lumbar BMD was consistent in overall population and find the potential different population settings, we conducted subgroup analysis and interaction test stratified by gender, race, education, smoking status, BMI, diabetes and hypertension (Figure 3). Our results demonstrated that the associations were not consistent.

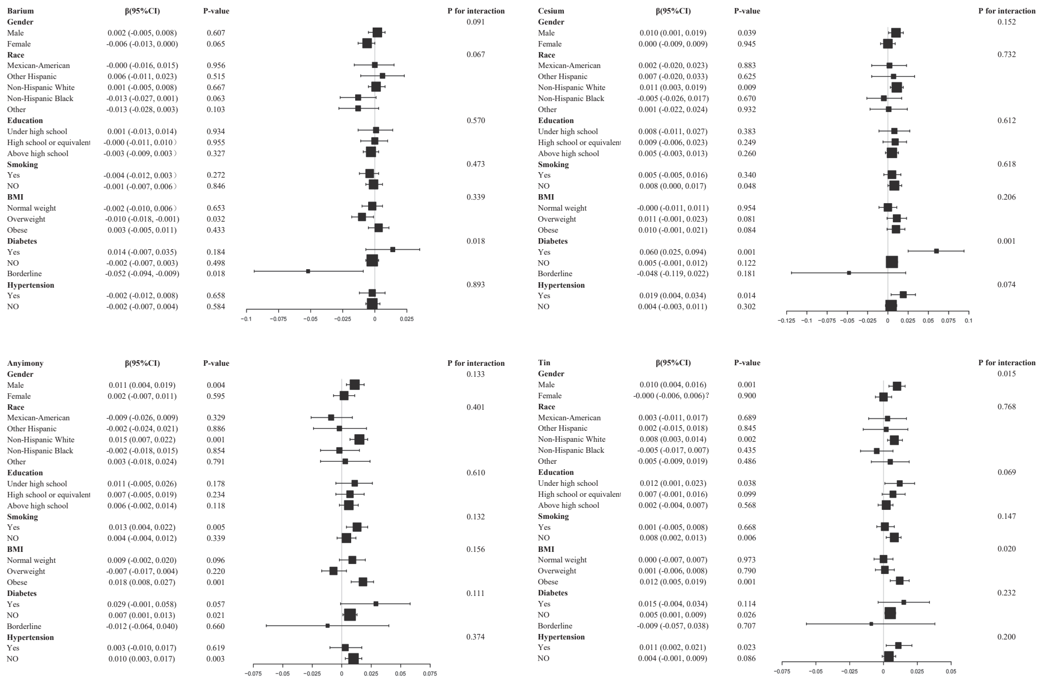

Fig. 3 Stratified analyses of the association between urinary trace metal element concentrations and lumbar bone mineral density (BMD) by demographic and clinical subgroups

Forest plots present β coefficients and 95% confidence intervals for the associations between urinary concentrations of barium, cesium, antimony, and tin and lumbar BMD across subgroups defined by gender, race/ethnicity, education, smoking status, body mass index (BMI), category, diabetes status, and hypertension. Effect modification was assessed by including interaction terms in multivariable regression models adjusted for all covariates listed in Figure 2. P-values for interaction are shown on the right side.

Our analysis revealed a significant interaction effect between UBL and lumbar BMD in diabetic populations (P for interaction = 0.018). Stratified analysis demonstrated nonsignificant associations across diabetes status categories: diabetic participants showed β = 0.014 (95% CI, –0.007, 0.035; p = 0.184), nondiabetic individuals exhibited β = –0.002 (95% CI, –0.007, 0.003; p = 0.498), and those in the prediabetic range displayed β = –0.052 (95% CI, –0.094, –0.009; p = 0.018). Furthermore, analysis revealed no statistically significant associations with effect modifiers, as all interaction terms demonstrated P-values exceeding the 0.05 threshold.

The analysis revealed a significant interaction effect between UCL and lumbar BMD in the context of diabetes status (interaction P-value = 0.001). Among individuals with diabetes, a positive association was observed between UBL and lumbar BMD (β = 0.060; 95% CI, 0.025, 0.094; p = 0.001). However, no significant association was found in non-diabetic individuals (β = 0.005; 95% CI, −0.001, 0.012; p = 0.122) or those with pre-diabetes (β = −0.048; 95% CI, −0.119, 0.022; p = 0.181). Additionally, no statistically significant interactions with effect modifiers were detected (all P for interaction > 0.05).

Subgroup analyses consistently showed no significant association between UAL and lumbar BMD across all categories (all P for interaction > 0.05). Statistical analysis revealed significant interactions between urinary tin level (UTL) and lumbar BMD for gender (P for interaction = 0.015) and BMI (P for interaction = 0.020). A significant positive association was observed between UTL and lumbar BMD in male individuals (β = 0.010; 95% CI, 0.004, 0.016; p = 0.001), while no significant association was found in females (β = 0.000; 95% CI, –0.006, 0.006; p = 0.900). Among obese individuals, elevated UTL was associated with increased lumbar BMD (β = 0.012; 95% CI, 0.005, 0.019; p = 0.001), whereas no significant association was observed in nonobese individuals (β = 0.000; 95% CI, –0.007, 0.007; p = 0.973) or those with prediabetes (β = 0.001; 95% CI, –0.006, 0.008; p = 0.790). Additionally, no statistically significant interactions with effect modifiers were detected (all P-values > 0.05).

DISCUSSION

This study evaluated the association between urinary trace metal element concentrations (barium, cesium, antimony, and tin) and lumbar BMD in adults using a nationally representative dataset. An inverted U-shaped association was identified between urinary barium levels and lumbar BMD, whereas positive associations were observed for urinary cesium, antimony, and tin concentrations with lumbar BMD. These findings contribute valuable insights into the role of urinary trace metal elements in bone health, underscoring the importance of further research.

Barium, an alkaline earth metal, is more abundant than zinc and ranks 14th in crustal abundance.[18] As the industrial uses of barium increases, evaluating the risk of barium toxicity has becomes increasingly important. Barium is primarily inhaled or ingested by humans,[19] and its exposure is associated with kidney and cardiovascular disorders, as well as metabolic, neurological, and behavioral issues.[20] However, there is limited research on the effect of barium on bone health, and the findings are inconsistent. A study conducted in Guangxi, China, investigated the association between various metals and OP in elderly female. The study found no significant association between barium and OP.[13] This study firstly identifies a non-linear association between UBL and lumbar BMD. However, the mechanism by which barium affects BMD remains poorly understood. Some studies have indicated oxidative stress and reactive oxygen species (ROS) induced by excessive barium exposure significantly impact bone metabolism.[21-23] ROS are known to stimulate osteoclast activity and production,[21] and oxidative stress caused by ROS negatively affects bone homeostasis and resorption.[24,25] Because bone tissue and calcium ions share similar radii and chemical environments, bone tissue is the primary site of barium accumulates.[26] In recent years, barium-containing nanocomposites have recently been identified as potential materials for bone tissue and fracture healing.[27] Therefore, the exact mechanism by which barium affects bone density remains to be elucidated.

Cesium, a naturally occurring alkali metal, is typically found in low concentrations in rocks, soils, and dust. Cesium enters the human bloodstream mainly through the digestive, respiratory, or integumentary systems, subsequently accumulating in the kidneys, skeletal muscles, liver, and erythrocytes. Existing literature associates cesium exposure with alterations in neurocognitive function and coronary heart disease, while suggesting it may offer protective effects against hypertension. This study is the first to establish a positive association between UCL and lumbar BMD. However, the mechanisms by which cesium affects bone health remain poorly understood.

Studies have pointed out that cesium may affect potassium dependent signaling pathways in osteoclasts by competitively replacing potassium in cells.[28,29] In addition, cesium may indirectly affect bone metabolism by inducing oxidative stress (similar to metal elements such as cadmium and barium), but the specific mechanism is not mentioned.[30,31] Notably, cesium can form functional composites with graphene quantum dots (QDs) under alkaline conditions, a property that may have potential applications in targeted delivery systems of bone repair materials.[32]

Antimony is a metalloid primarily found in nature as sulfide minerals and exhibits metallic properties.[33] It mainly enters the human body through dermal absorption, respiratory tract,[34] or gastrointestinal intake,[35,36] accumulating chiefly in the liver, and bones.[37] Current research links antimony exposure to altered immune,[38] neurological,[39,40] and reproductive functions.[40,41] This study is the first to establish a positive association between UAL and lumbar BMD. Most of the existing studies are either observational studies or animal experiments, and there is limited evidence directly investigating the causal association between antimony and BMD.[42,43]

Tin is a common metallic element widely distributed across various minerals and natural environments.[44] Human exposure to tin occurs mainly through the following pathways: respiratory tract,[45] digestive tract,[46] skin absorption,[44] and then accumulation in lung,[45] kidney, liver and other tissues.[47] This study is the first to establish a positive association between UTL and lumbar BMD. Bayesian kernel machine regression analyses revealed that co-exposure to urinary tin and molybdenum positively correlates with increased BMD, indicating tin's potential role as a trace element in preserving bone homeostasis.[48] Although it has been shown that tributyltin exposure leads to increased levels of oxidative stress markers in bone tissue of mice and exacerbates osteocyte apoptosis. However, more direct evidence is needed.[49]

Conventionally, BMD management prioritizes established factors such as nutritional supplementation (calcium, 25-hydroxyvitamin D) and physical activity. This study elucidates the association between environmental metal elements exposure and BMD, indicating that preventive strategies should incorporate mitigation measures (eg, reducing specific metal elements exposure among highly exposed individuals). These findings lay the groundwork for expanding the scope of BMD intervention strategies. Furthermore, dose-response relationships were established to refine intervention thresholds: notably, the inverted U-shaped association observed for barium suggests a potential safe exposure window. Future research could leverage this study's identified threshold (–0.357 log-transformed concentration) to define optimal population-level barium exposure ranges, thereby informing targeted exposure limit development. Additionally, the more pronounced association between tin and BMD in males and obese individuals underscores the necessity of incorporating individual characteristics (eg, sex and metabolic status) into strategy formulation to achieve targeted prevention. This approach facilitates personalized management frameworks and advances evidence-based BMD stewardship.

This study has several notable strengths. First, the data were derived from the NHANES, a nationally representative US database. Second, urinary trace metal element concentrations were selected as biomarkers for systemic metal elements exposure, as they more accurately reflect long-term exposure compared to blood concentrations. Third, advanced statistical methods, such as multivariate logistic regression, facilitated a precise assessment of the independent association between urinary trace metal element concentrations and lumbar BMD, effectively reducing bias by adjusting for multiple potential confounding factors. A comprehensive analysis of the intricate dose-response association between urinary trace metal element concentrations and lumbar BMD was performed through multiple stratified analyses (eg, by gender, race, lifestyle, and disease status) and smooth curve fitting to examine nonlinear associations and identify inflection points. This methodological approach minimized potential confounders, enhanced the validity of the findings, and yielded detailed and reliable data to inform future research. In addition to commonly studied trace metal elements, such as cadmium and lead, which are associated with an increased risk of OP, this study identified barium, cobalt, cesium, and molybdenum as influential factors for lumbar BMD, highlighting the necessity of further research into these trace metal elements.

However, this study has several limitations. First, establishing a causal association between trace metal element exposure and lumbar BMD is challenging, as this cross-sectional study could only identify associations between variables. To advance understanding of these associations, future research should prioritize establishing causal links between trace metal elements exposure and bone mineral density. Prospective cohort studies could help clarify temporal relationships and identify long-term risks. Moreover, further mediation analysis may uncover potential biological pathways through which trace metal elements exert their effects on bone health. Complementary experimental studies, including in vivo animal models and in vitro osteoblast/osteoclast culture systems, are also needed to explore metal-specific cellular mechanisms in bone remodeling. These integrated approaches will be instrumental in elucidating the complex interplay between environmental trace metal elements exposure and skeletal health. Second, although numerous potential confounders were controlled for in the analysis, some factors may have been overlooked. These include unmeasured environmental chemicals, individual medication histories, and dietary habits, all of which could have influenced the outcomes. Third, this study was limited to examining a select number of urinary trace metal elements. The human body may be exposed to a wide array of trace metal elements and other hazardous substances through multiple exposure pathways. Future studies should broaden their scope to comprehensively evaluate the impact of diverse environmental factors on bone density.

CONCLUSION

This study identified significant associations between urinary concentrations of barium, cesium, antimony, and tin and lumbar bone mineral density in US adults. Specifically, barium demonstrated an inverted U-shaped relationship with lumbar BMD, while cesium, antimony, and tin showed positive associations. Although these findings suggest a potential link between environmental trace metal elements exposure and bone health, causal interpretations should be made with caution due to the cross-sectional design. Further longitudinal and mechanistic studies are warranted to confirm these associations and explore the underlying biological mechanisms.

DECLARATIONS

Ethics approval and consent to participate

Not applicable, because NHANES belongs to public databases, the patients involved in the database have obtained ethical approval, users can download relevant data for free for research and publish relevant articles, and our study is based on open-source data, and the Affiliated Hospital of Shandong University of Traditional Chinese Medicine do not require research using publicly available data to be submitted for review to their ethics committee, so there are no ethical issues and other conflicts of interest.

Consent for publication

Not applicable, because this paper did not reveal any personal information of patients.

Authors' contributions

(1) Renhao Zhang, Jiusong Wang, Zhengze Zhang and Kai Meng, conceiving and designing the study.

(2) Renhao Zhang, Tianyu Fu, Fengyue Guo, Guoli Zhang and Xingshi Wang, collecting the data.

(3) Renhao Zhang, Tianyu Fu, Fengyue Guo, Guoli Zhang and Xingshi Wang, analyzing and interpreting the data.

(4) Renhao Zhang, writing the manuscript.

(5) Jiusong Wang, Zhengze Zhang and Kai Meng, providing critical revisions that are important for the intellectual content.

(6) All authors approved the final version of the manuscript.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Availability of data and materials

The survey data are publicly available on the internet for data users and researchers throughout the world (www.cdc.gov/nchs/nhanes/).

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SUPPLEMENTARY INFORMATION

Supplementary Table 1 LOD for metals and total population detection rate for each trace metal element

Variable name	LOD	<LOD (%)
Ba	0.084	1.16
Cd	0.055	5.53
Cs	0.13	0.00
Co	0.024	1.07
Mn	0.13	69.84
Mo	0.8	0.00
Pb	0.03	0.19
Sb	0.022	23.38
Tl	0.018	0.68
Sn	0.2	17.17
W	0.018	16.49

Values below the limit of detection (LOD) were replaced with LOD/√2 as recommended by NHANES guidelines. Only metals with sufficient detection rates and biological plausibility were included in the main analysis.
NHANES, National Health and Nutrition Examination Survey; Ba, barium; Cd, cadmium; Cs, cesium; Co, cobalt; Mn, manganese; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; Sn, tin; W, tungsten.