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Association between blood heavy metals exposure with uterine fibroids among American women: a cross-sectional analysis from NHANES data

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Abstract

Background Excessive exposure to heavy metals has been linked to various health problems, including organ damage, neurological disorders, and reproductive and developmental abnormalities. However, the relationship between heavy metals exposure and uterine fibroids remains uncertain. To explore this association, we conducted a cross-sectional study among American women.

Methods We utilized data from three cycles of the National Health and Nutrition Examination Survey (NHANES, 1999–2006) to evaluate the association between uterine fibroids and blood heavy metal levels, including lead (Pb), cadmium (Cd), and mercury (Hg). Weighted logistic regression, restricted cubic spline (RCS), Bayesian kernel machine regression (BKMR), and subgroup analyse were used to examine the potential relationships between blood heavy metals and uterine fibroids.

Results Of the 4502 American women studied, 542 (12.04%) had uterine fibroids. Elevated levels of all heavy metals were significantly more common in women with uterine fibroids ($P < 0.001$). Blood Hg levels were notably associated with uterine fibroid prevalence in the adjusted model (OR = 1.41, 95% CI: 1.06–1.89, $p = 0.03$). Similar patterns were partly observed for blood Pb and Cd. Age and marital status were significant interaction factors concerning Hg exposure (P for interaction < 0.05). A dose-response relationship with an inflection point at 7μmol/L was identified for Hg, and BKMR models indicated a positive association between mixed heavy metal exposure and uterine fibroid risk.

Conclusions Exposure to blood heavy metals, particularly Hg, is significantly associated with an elevated risk of uterine fibroids. Further prospective studies are necessary to confirm these findings.

Keywords Heavy metal, Exposure, Blood, Uterine fibroids, NHANES

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Introduction

Uterine fibroids, the most prevalent benign tumors in the reproductive system of women in their childbearing years. A cross-sectional analysis utilizing a large, nationally representative sample derived from online surveys indicates that uterine fibroids occur at a prevalence of 5.8% among women aged 18 to 54 in the United States [1]. While many cases of uterine fibroids are asymptomatic and fortuitously discovered, approximately 30% of patients endure severe symptoms that significantly impact their overall well-being [2, 3]. These symptoms encompass abnormal uterine bleeding, pelvic pressure, urinary complications, and infertility [2, 3]. Moreover, the symptomatic manifestation of uterine fibroids often precipitates emotional distress, depression, and anxiety, further exacerbating the quality of life for affected women [4]. Beyond its implications for individual health, the existence of uterine fibroids poses a substantial burden on healthcare systems. These fibroids account for 29% of gynecologic hospitalizations among women aged 15–54 years in the United States and contribute significantly to the prevalence of hysterectomies, particularly among young women [5]. The treatment costs, both direct and indirect, associated with uterine fibroids are substantial, presenting challenges for both healthcare providers and patients alike [6]. Notably, the prevalence of uterine fibroids is disproportionately higher among non-Hispanic Black, who also tend to experience more severe forms of the condition [7]. Additional risk factors for uterine fibroids include age, family history, time since the last birth, premenopausal state, hypertension, and dietary factor [8].

While hormone regulation, genetic factors, and lifestyle choices have established roles in the development of uterine fibroids, emerging evidence suggests that exposure to heavy metals, including occupational exposure, air pollution and dental work, may also be among a comparatively significant contributors to female reproductive health issues [9]. Heavy metals, due to their non-biodegradability and long biological half-life, can enter our bodies through contaminated food. They can accumulate and significantly impact health, particularly causing damage to the female reproductive system, such as organ damage, hormonal imbalances, and developmental issues [10]. Mercury (Hg) is a toxic heavy metal that can accumulate in the body. Lead (Pb), the second most toxic metal after arsenic (As), is a pervasive environmental contaminant that is challenging to decompose. Cadmium (Cd), akin to Pb and Hg, is a non-threshold toxin, threatening health even at negligible concentrations [11]. Heavy metals such as Pb, Cd, and Hg, possess non-essential properties and exhibit high toxicity to humans. These substances are classified as metalloestrogens, capable of independently activating the estrogen receptor, irrespective of estradiol [12, 13]. Furthermore, they have been demonstrated to exert negative influences on the hypothalamic-pituitary-gonadal (HPG) axis, thereby causing deleterious alterations in sexual maturity and functions [14].

Numerous studies have suggested that increased exposure to heavy metals may contribute to the growth and development of fibroid [9]. For example, blood concentrations of Cd have been found to correlate with Cd concentrations in uterine tissues, encompassing both leiomyomas and the surrounding myometrium [15]. Furthermore, investigations have demonstrated associations between elevated blood levels of Cd and Pb and the likelihood of a uterine fibroids diagnosis [16]. However, the existing research examining the link between heavy metals and uterine fibroids has yielded inconsistent results. For instance, some studies have found a significant correlation between blood cadmium levels and fibroid volume, no such correlation has been observed with blood mercury and lead levels [9]. In this study, we hypothesize that exposure to certain levels of these heavy metals may influence the development of uterine fibroids. To address this gap in knowledge, our study aims to investigate whether there is a significant correlation between blood levels of heavy metals (specifically Pb, Cd, and Hg) and the presence of uterine fibroids in American women. The findings may contribute to our understanding of the environmental determinants of uterine fibroids, offering insights for clinical practice and preventive strategy development aim to reduce the burden of this common reproductive health issue.

Methods

Study design

The National Health and Nutrition Examination Survey (NHANES), an ongoing nationwide biennial initiative since 1999, evaluates the health and nutritional metrics of the US populace through a complex, multistage, probabilistic sampling strategy [17]. The present investigation harnesses data from four NHANES cycles spanning 1999 to 2006.

Data collection

Of the 14,543 respondents, 5,552 participants who have responded to the uterine fibroids query were included. After eliminating entries with incomplete heavy metal concentration, demographic information, physical measurements, and smoking and drinking habits data, a final sample size of 4,502 females was examined. The detailed flow diagram was illustrated in Fig. 1.

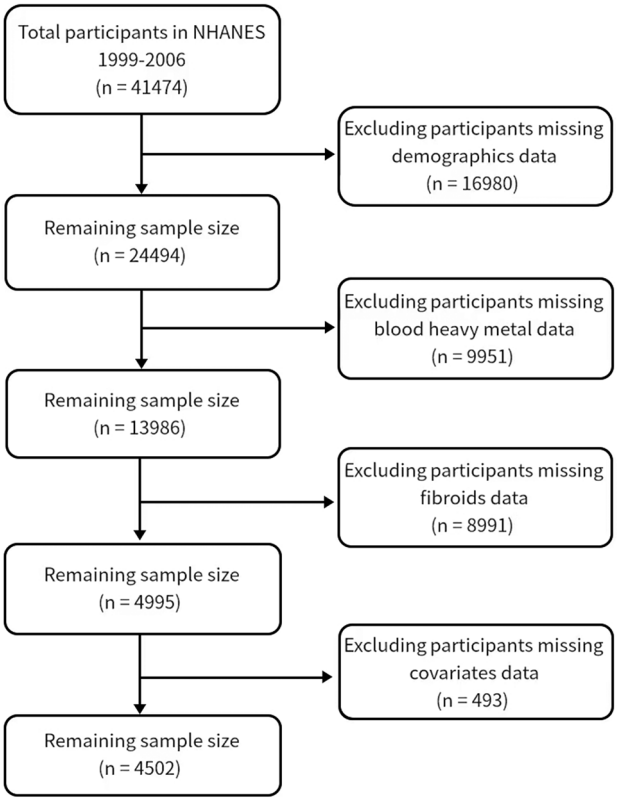

Fig. 1 Flow diagram detailing the enrollment process of study participants

Ethical considerations

The NHANES data, being anonymized, complies with ethical standards, and all participants provided informed consent for the data collection procedures during the survey. The NHANES program has been ethically approved, ensuring participants' rights and safety.

Variable definitions

Dependent variable

Uterine fibroids were determined by a woman's response to the question, "Has a doctor or other health professional ever told you that you had uterine fibroids? (Uterine fibroids are benign (not cancerous) tumors growing in various locations on or within the uterus/womb.)?" in the health questionnaire section of rhq380. Women answering "yes" were considered to have uterine fibroids, whereas women answering "no" were considered without uterine fibroids.

Independent variable

Heavy metal concentration data were derived from the laboratory section of the NHANES database. Whole blood samples were collected by physicians at the NHANES mobile examination center, stored under appropriate frozen (-20℃) conditions, and then shipped for testing and analysis to the National Center for Environmental Health. The lower limits of detection for Pb and Hg in blood reached 0.01 and 0.5 μmoL/L, and 0.89 nmol/L for Cd, respectively. All analytical results achieved using NHANES data processing methods were equal to or exceeded the detection limits.

Covariates

This investigation incorporated an array of variables for each participant, subdivided into demographics and lifestyle habits which were collected in interviews, and body metrics measured by examination. Demographic parameters encompassed age, race, household income, educational attainment, and marital status, whereas body metrics were defined by body mass index (BMI). Lifestyle habits analyzed included smoking and drinking behaviors. These variables were selected based on prior evidence suggesting their potential influence. For instance, race and socioeconomic factors may be associated with environmental exposures and dietary habits [18–20], while smoking and alcohol consumption could increase specific heavy metal exposures [21]. While BMI, as an indicator of obesity, is associated with both uterine fibroids and heavy metal metabolism [22, 23]. Including these covariates ensures a more accurate assessment for confounding factors. The following measures were undertaken to mitigate potential confounding bias. Age was categorized into three groups: less than 30 years, 30 to 40 years, and greater than 40 years. Racial identifiers included White, Black, Mexican American, and other races. Marital status was distinguished between those in a committed relationship, inclusive of married or cohabiting, and single individuals, comprising the never married, widowed, divorced, or separated. Educational background was divided into three categories: below 9 years, 9 to 12 years, and above 12 years of formal education. Household income was interpreted through the Poverty Income Ratio (PIR) [24], the official poverty measure defined by the U.S. Census Bureau, which reflects an individual's socioeconomic status relative to the poverty threshold while accounting for household size. PIR was classified into low income ($PIR \leq 1$), middle income ($1 < PIR \leq 4$), and high income ($PIR > 4$). BMI was calculated by dividing weight by the square of height and was further categorized into < 25 kg/m2 (underweight or healthy weight) and ≥ 25 (overweight or obese). Smoking status was distinguished into never smokers (those who have smoked fewer than 100 cigarettes in their lifetime), past smokers (those who have smoked more than 100 cigarettes but no longer smoke), and current smokers (those who have smoked more than 100 cigarettes and continue to do so). Alcohol consumption was stratified into light drinkers (those with a history of alcohol use in the past year), moderate drinkers (≤ 2 drinks per day for females and ≤ 3 drinks per

day for males), and heavy drinkers (≥ 3 drinks per day for females and ≥ 4 drinks per day for males).

Statistical analysis

Our analysis incorporated appropriate sampling weights, specifically 1/2 wtmec4 year for the period 1999–2002, and 1/4 wtmec2 year for the years 2003–2006, to account for the intricate survey design employed in the NHANES study. Participants were stratified into two groups based on the presence or absence of uterine fibroids. In the descriptive analysis, normally distributed continuous variables were presented as mean ± standard deviation (x ± s), whereas non-normally distributed data were represented as median (M [P25 ~ P75]). Categorical variables were depicted in terms of percentages.

Following this, we evaluated the variability of outcomes in relation to the levels of blood heavy metal among participants, aiming to investigate the association between blood heavy metal exposure and uterine fibroids. In this section of our methodology, utilizing weighted multivariable logistic regression models, we computed the odds ratio (OR) along with the corresponding 95% confidence interval (CI) to gauge the prevalence of uterine fibroids associated with elevated blood heavy metal exposure. We categorized the content of blood heavy metals into three tertiles. The crude model remained unadjusted for any covariates, while model 1 was additionally adjusted for demographic factors, including BMI, pregnancy status, history of smoking, and drinking. Moreover, model 2 extended the adjustment to demographic variables, including age, race, household income, education level, and marital status, building upon model 1. The Variance Inflation Factor (VIF) was calculated to assess the correlation and potential collinearity among covariates. No data imputation methods were necessary, as there were no missing data in the variables of interest.

We performed the sensitivity and subgroup analyses to check the robustness of the main findings. Likelihood ratio tests were employed in weighted regression analysis to explore interactions between various subgroups and levels of blood Hg exposure. The median value of blood Hg levels was used to categorize participants into two groups, as the median is a stable measure of central tendency that minimizes the influence of extreme data points. Subgroups were stratified by factors including age (> 34 years or ≤ 34 years), race/ethnicity (white, black, or other), household income (low, moderate, or high), education level (below 9 years, 9 to 12 years, and above 12 years), marital status (single or attached), smoking status (never, former, or current), and drinking status (few, moderate, or heavy). Logistic regression analyses were then conducted to determine whether significant interactions existed between these subgroups.

To account for the potential non-linear relationship between blood Hg metal exposure and uterine fibroids, we employed restricted cubic spline (RCS) regression models in the adjusted Model 2. To ensure the robustness and representativeness of the results, blood heavy metal concentrations were restricted to the 2.5th to 97.5th percentile range. The optimal number of knots was selected to balance model fit and avoid overfitting, with 3 to 7 knots evaluated based on the lowest Akaike's Information Criterion (AIC). After testing various configurations, five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles were identified as providing the best fit. The model was adjusted for age, race/ethnicity, household income, education level, marital status, smoking status, and drinking status.

We used Bayesian Kernel Machine Regression (BKMR) model to assess the associations between heavy metals and uterine fibroids. BKMR is an advanced statistical method that leverages kernel functions to effectively capture both the individual and joint impacts of mixture exposures on health outcomes, allowing for the estimation of non-linear and non-additive relationships [25]. The impact of heavy metal mixtures on uterine fibroids was evaluated for every 5% change from the median concentration [26, 27]. Initially, the joint effects of the metal mixtures were estimated by comparing the risk of uterine fibroids when all metals were set at specific percentiles (e.g., 1st to 99th) to the baseline risk when all metals were fixed at their 50th percentile. Next, the individual effects of each metal were examined by holding the concentrations of the other metals constant at their 25th, 50th, or 75th percentiles. The exposure-response relationships and potential interaction effects among heavy metals were also explored to better understand the nonlinear and combined influences of the metal mixture on uterine fibroid risk. All BKMR models were adjusted for potential confounding factors, including age, race/ethnicity, household income, education level, marital status, smoking status, and drinking status. was implemented using the Markov Chain Monte Carlo method, with 10,000 iterations to ensure convergence.

Our statistical analyses were conducted using R version 4.2.1, with statistical significance defined by two-tailed p-values less than 0.05.

Results

Our study revealed significant associations between elevated blood heavy metal levels, particularly Hg, and the prevalence of uterine fibroids among U.S. females. Subgroup and dose-response analyses further elucidated the complex relationships, highlighting demographic and behavioral modifiers of these associations. BKMR analysis further reinforced these findings by revealing

Table 1 Characteristics of the study population

Variables	Total($n=4502$)	With Uterine Fibroids ($n=542$)	Without Uterine Fibroids ($n=3960$)
Age			
< 30	1583(35.2)	31(4.1)	1552(31.6)
30–40	1352(30.0)	123(22.7)	1229(31.9)
>=40	1567(34.8)	388(73.2)	1179(36.4)
Race			
White	2127(47.2)	227(41.9)	1900(48.0)
Black	930(20.7)	214(39.5)	716(18.1)
Mexican American	1042(23.1)	67(12.4)	975(24.6)
Other	403(9.0)	34(6.3)	369(9.3)
Marital Status			
Single	1565(34.8)	175(27.9)	1390(35.69)
Attached	2937(65.28)	367(72.19)	2570(64.4)
Income			
Low	914(20.3)	65(9.2)	849(16.0)
Middle	2332(51.8)	278(47.5)	2054(50.2)
High	1256(27.9)	199(43.3)	1057(33.8)
Education			
< 9	337(7.5)	20(2.2)	317(3.7)
9 ~ 12	1638(36.4)	178(31.1)	1460(33.4)
> 12	2527(56.1)	344(66.7)	2183(62.9)
BMI			
<=25	1565(34.8)	147(34.0)	1418(42.2)
25–30	1269(28.2)	395(66.0)	1129(25.6)
>=30	1668(37.1)	255(42.2)	1413(32.2)
Smoke			
Never	2804(62.3)	322(54.8)	2482(58.5)
Former	728(16.2)	102(20.0)	626(16.5)
Now	970(21.5)	118(25.2)	852(25.0)
Alcohol			
Few	1506(33.5)	188(27.3)	1318(27.0)
Moderate	2023(44.9)	274(55.8)	1749(49.2)
Heavy	973(21.6)	80(16.8)	893(23.8)

Percentages in parentheses are weighted, and the frequencies are unweighted. Race: 'Other' refers to Multi-Racial, and other races. Marital status: 'Attached' indicates married or living with a partner, 'Single' includes never married, widowed, divorced, or separated. Income: low (PIR ≤ 1), middle (1 < PIR ≤ 4), high (PIR > 4). Smoking: 'Never' indicates fewer than 100 lifetime cigarettes, 'Former' means over 100 cigarettes but currently non-smoking, 'Now' refers to ongoing smokers with more than 100 cigarettes smoked. Alcohol: 'Few' for past year drinkers, 'Moderate' for ≤ 2 drinks/day, 'Heavy' for ≥ 3 drinks/day

the interactive effects of heavy metal mixtures on uterine fibroids risk.

Demographic characteristics of participants

In this study, a total of 4,502 female participants were included, comprising 542 women with uterine fibroids and 3,960 women without. The median age was 34 years old, while participants with uterine fibroids were generally older, with most being over 40 years of age, and had a BMI typically ranging from 25 to 30, compared to those without uterine fibroids. Significant differences were observed in social characteristics between the two groups, such as household income, race, and marital status. Specifically, the uterine fibroids group had a higher proportion of Black individuals and those with higher income, and married or partnered individuals were more likely to have uterine fibroids. However, no significant differences were found in education levels or smoking history between the groups. The detailed baseline characteristics of the study population are provided in Table 1. Additionally, as shown in Table 2, blood levels of Pb, Cd, and Hg were significantly elevated in women with uterine fibroids compared to those without.

Table 2 Blood cd, pb, and hg differences between group with or without uterine fibroids

Heavy metals	Total($n=4502$)	With Uterine Fibroids ($n=542$)	Without Uterine Fibroids ($n=3960$)
Blood Pb, (μmol/l)	0.048(0.034,0.072)	0.053(0.041,0.082)	0.048(0.034,0.071)
Blood Cd, (nmol/l)	3.560(1.780,5.340)	3.560(2.580,5.870)	3.560(1.780,5.340)
Blood Hg, (μmol/l)	4.740(2.500,8.980)	5.990(3.490,10.980)	4.490(2.500, 8.880)

This table presents the median and interquartile range (25th and 75th percentiles) of blood heavy metal concentrations (Pb, Cd, and Hg) among all participants. The statistical comparisons were performed using the Wilcoxon rank-sum test, which is appropriate for non-normally distributed data

Association of blood heavy metals with uterine fibroids by weighted logistic regression

Logistic regression results of blood Pb, Cd, Hg and uterine fibroids of females are shown in Table 3. All VIF values were below 1.5 across the logistic regression models, indicating no significant multicollinearity among the covariates. In this analysis, the participants were categorized based on the heavy metal concentrations in tertiles 3 range, with the Q1 group serving as the reference group. The crude model demonstrated that the three blood heavy metals exhibited a positive association with uterine fibroids in both the Q2 and Q3 groups (P for trend < 0.001).

Model 1 adjusted for BMI, pregnancy status, history of smoking, and drinking, but the association between blood Pb, Cd, Hg, and uterine fibroids remained strong (P for trend < 0.001). Blood Pb exhibited a positive association with uterine fibroids in the Q2 (OR = 1.79, 95% CI 1.33, 2.41) and Q3 (OR = 1.87, 95% CI 1.46, 2.38) groups, as did blood Cd (OR = 1.61, 95% CI 1.15, 2.26 and OR = 1.75, 95% CI 1.25, 2.46) and blood Hg (OR = 1.61, 95% CI 1.15, 2.26 and OR = 1.75, 95% CI 1.25, 2.46) in the Q2 and Q3 groups, respectively.

Table 3 Odds ratios (95% CI) of uterine fibroids across tertiles of pb, cd, and hg, NHANES 1999–2006

Heavy metals	Crude model[a]	Model 1[b]	Model 2[c]
Blood Pb, (μmol/l)			
Q1	ref	ref	ref
Q2	1.91(1.44,2.53) *	1.96(1.46,2.62) *	1.33(0.97,1.82)
Q3	1.97(1.56,2.48) *	2.09(1.64,2.67) *	1.13(0.86,1.47)
P for trend	< 0.0001	< 0.0001	0.71
Blood Cd, (nmol/l)			
Q1	ref	ref	ref
Q2	1.64(1.19,2.28) *	1.67(1.20,2.31) *	1.33(0.94,1.88)
Q3	1.71(1.28,2.28) *	1.99(1.43,2.77) *	1.26(0.86,1.84)
P for trend	< 0.001	< 0.001	0.32
Blood Hg, (μmol/l)			
Q1	ref	ref	ref
Q2	1.66(1.13,2.46) *	1.68(1.13,2.51) *	1.27(0.86,1.87) *
Q3	1.98(1.49,2.64) *	2.15(1.62,2.85) *	1.41(1.06,1.89) *
P for trend	< 0.0001	< 0.0001	0.03

Crude model[a] without adjustments; Model 1[b] adjusted for BMI, history of smoking, and drinking; Model 2[c] additionally adjusted for age, race, marital status, household income, and education levels. Values marked by "*" showed statistically significance ($P < 0.05$)

Model 2 further adjusted for age, race, marital status, household income, and education levels, in addition to the variables in model 1. Blood Hg remained positively associated with uterine fibroids (*P* for trend = 0.01), with increased odds in both the Q2 (OR = 1.26, 95% CI 0.87, 1.85) and Q3 (OR = 1.46, 95% CI 1.10, 1.94) tertiles. In the Q3 group, blood Pb was correlated with uterine fibroids (OR = 1.19, 95% CI 0.91, 1.55), while *P* for trend was not statistically significant. However, blood Cd showed a weak positive association with uterine fibroids after adjustment in model 2.

Association of blood Hg levels with uterine fibroids by subgroup analysis

To further explore our findings, we conducted a subgroup analysis by dividing blood Hg levels into two groups based on the median value. We then compared the risk of uterine fibroids between groups with higher and lower Hg concentrations to better understand variations across subgroups.

Figure 2 illustrates the relationship between blood Hg levels and uterine fibroids across subgroups. Elevated blood Hg levels were associated with a higher risk of uterine fibroids, particularly in women over 40, nearly all racial groups, those in committed relationships, middle-income individuals, overweight or obese women, former or never smokers, and those with low to moderate alcohol intake. Significant interactions were found for age ($P < 0.001$) and marital status ($P = 0.003$), indicating a stronger effect of elevated Hg levels in older and partnered women.

Association of blood Hg levels with uterine fibroids in the RCS analysis

A dose-response analysis was conducted utilizing a weighted restricted cubic spline regression model to assess the effects of blood Hg levels on the development of uterine fibroids. As illustrated in Fig. 3, the probability of developing uterine fibroids initially declined as blood Hg levels increased, reaching its lowest point at approximately 7μmol/L, after which the likelihood of uterine fibroids began to increase.

Association of blood heavy metals with uterine fibroids by BKMR model

The BKMR analysis revealed potential associations between blood heavy metal levels and the risk of uterine fibroids. Among the three heavy metals studied, Hg exhibited the highest PIP (0.98), followed by Pb (0.63) and Cd (0.19). A noticeable increase in uterine fibroid risk was observed when the combined concentrations of the heavy metal mixture exceeded the 55th percentile (Fig. 4A). When concentrations of the other metals were fixed at the 25th, 50th, and 75th percentiles, both Cd and Hg consistently showed a positive association with fibroid risk. This trend was evident for Pb at the 75th percentile (Fig. 4B). The univariate exposure-response relationship is presented in Fig. 4C. When other heavy metals were held at their median values, Pb and Cd exhibited positive associations with uterine fibroids, while Hg showed an L-shaped relationship with fibroid risk. Additionally, we explored the interactions between these heavy metals, which suggested potential underlying interactions among Pb, Cd, and Hg (Fig. 4D).

Discussion

This study extracted 4502 samples from NHANES 1999–2006 cycles to evaluate the association between blood heavy metals exposure and uterine fibroids in U.S. females. The results demonstrated that blood Hg was significantly associated with uterine fibroids, which persisted significant after adjusting for social characteristics, physical examination and life habits, especially among women older than 40 years and those in a committed relationship. Moreover, a dose-response relationship was observed with an inflection point of 7 umol/L of blood Hg and uterine fibroids. To some extent, blood Pb and blood Cd were correlated with uterine fibroids. BMKR models further indicated that combined exposure to these three heavy metals was positively associated with an increased risk of uterine fibroids.

Extensive literature highlights the influence of persistent and broad-spectrum metal exposure in precipitating oxidative stress, immune responses, and genetic transcription alterations, subsequently contributing to disease progression [28, 29]. Quantifying

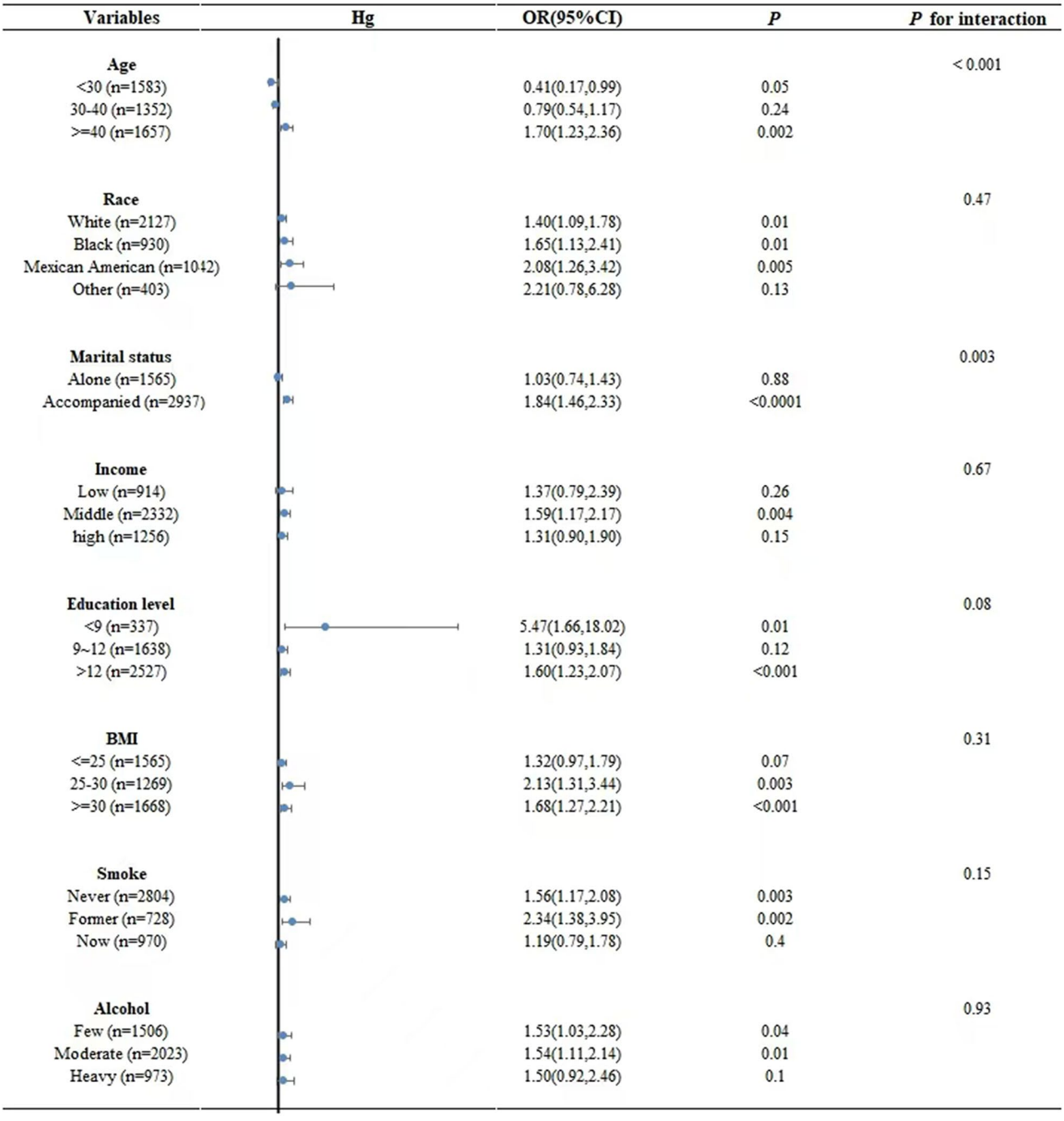

Fig. 2 Stratified forest plot of the association between blood Hg and uterine fibroids

levels of heavy metals in the serum, such as lead, cadmium, and mercury, furnishes crucial perspectives into the physiological consequences of environmental contamination [29–32]. Consequently, delving into the ramifications of heavy metal exposure on disease initiation and progression becomes paramount, especially for disorders with obscure etiology and influences, such as uterine fibroids, primarily associated with genetic factors and sex hormone concentrations [33]. Scholars have further postulated that heavy metals may exhibit hormonal activity and augment exogenous estrogen levels [34]. In our work, we studied blood heavy metals exposure that may contribute to the development of uterine fibroids, which may help to promote the management of patients with uterine fibroids as well as raise awareness of heavy metal exposure.

Pb exists in both organic and inorganic forms, with the former primarily found in leaded gasoline and the latter in dust, soil, and paint [35]. Given its widespread presence, human exposure through soil, water, and dietary sources

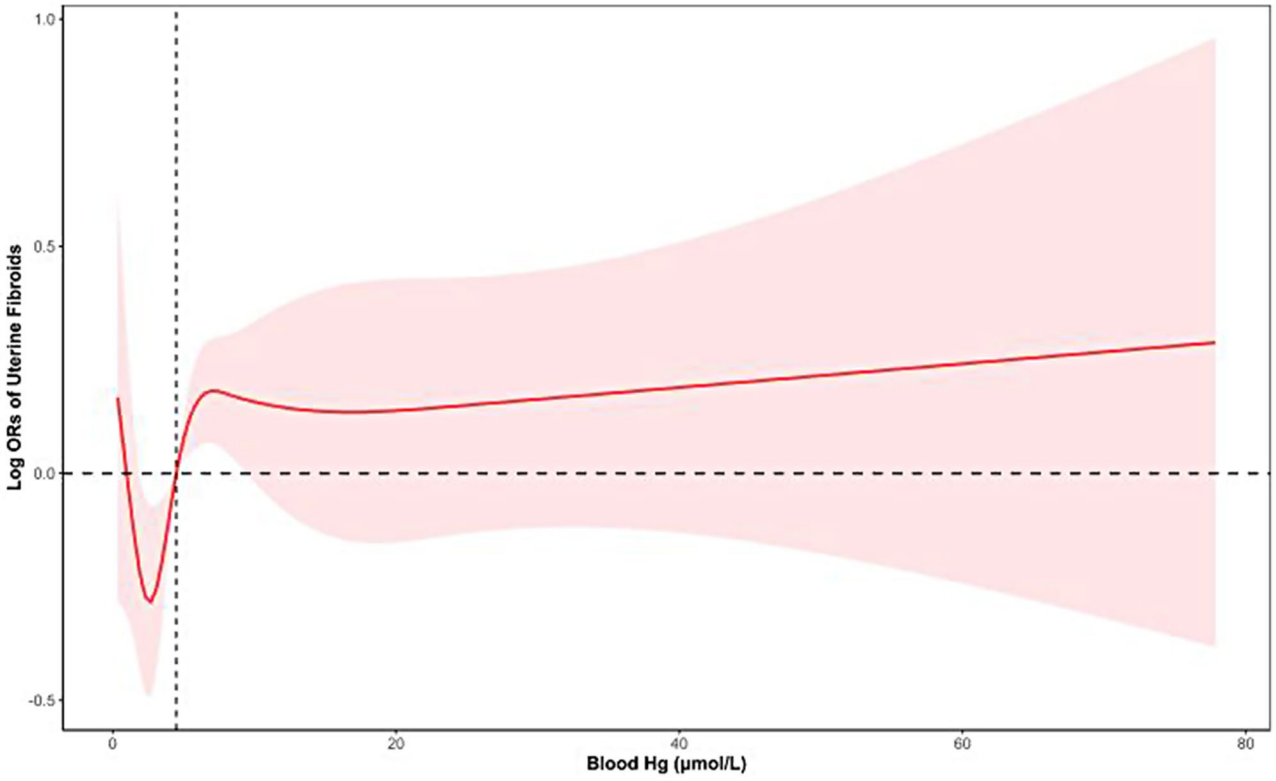

Fig. 3 The dose-response relationship between blood Pb, Cd, Hg and uterine fibroids. The red line and its extended range represent the estimated log ORs and their 95% confidence intervals, respectively. ORs: odds ratios

is almost inevitable, raising significant health concerns [36–38]. Pb residue can disrupt enzymatic activity and cell development, particularly impacting hematopoietic, nervous, and reproductive systems [10, 35, 39]. Notably, Pb exhibits estrogenic activity and functions as an endocrine-disrupting chemical (EDC) both in vivo and vitro [40]. Blood Pb levels have been associated with numerous gynecological conditions, including endometriosis and ovarian dysfunction, attributed to its endocrine-disrupting activities [41, 42]. Pb may also disrupt pubertal timing through the suppression of serum luteinizing hormone (LH) and estradiol (E2) levels. Beyond hormonal disruption, Pb has been found to alter placental microRNA expression, resulting in adverse offspring health outcomes [43]. In our study, association was found between Pb exposure and the prevalence of uterine fibroids.

Cd has gained global attention owing to its considerable environmental pollution and subsequent public health risks [11]. Emerging studies suggest an association between Cd exposure and the prevalence, as well as progression, of uterine fibroids. While the underlying mechanism is still under study, it is postulated that Cd may act beyond classical estrogen receptor pathways, potentially involving cross-talk with hormone and growth factor receptors [44, 45]. Moreover, Cd is implicated in human leiomyoma cell proliferation, bolstering its candidacy as a risk factor for uterine fibroids [45]. Additionally, long-term Cd exposure has been found to modify the phenotype and gene expression of fibroid cells, which increased proliferation, decreased fibrosis, and alteration of benign characteristics of fibroblast-like cells in vitro [46]. Notably, prolonged Cd exposure alters cell migration, increases nuclear size heterogeneity, and promotes fibroma cells to acquire malignant traits, such as progression, invasion, and metastasis [47]. An association was found between blood Cd levels and the prevalence of uterine fibroids in our study.

Hg, a toxic heavy metal with potential antiestrogenic properties, poses significant risks to human health through various exposure routes, including contaminated food, dental amalgam fillings, and polluted air [48]. Of these, methylmercury in fish and marine mammals represents a dominant source of Hg exposure to humans. Dental amalgams, susceptible to wear and tear, pose further health risks [49, 50]. The storage of Hg in human tissues such as the pituitary gland and ovaries can disrupt hormonal balance, affecting the secretion of gonadotropins, prolactin, and thyroid hormones, and impairing the production of estradiol and progesterone [51]. Studies investigating the relationship between heavy metal exposure and uterine fibroids have shown mixed

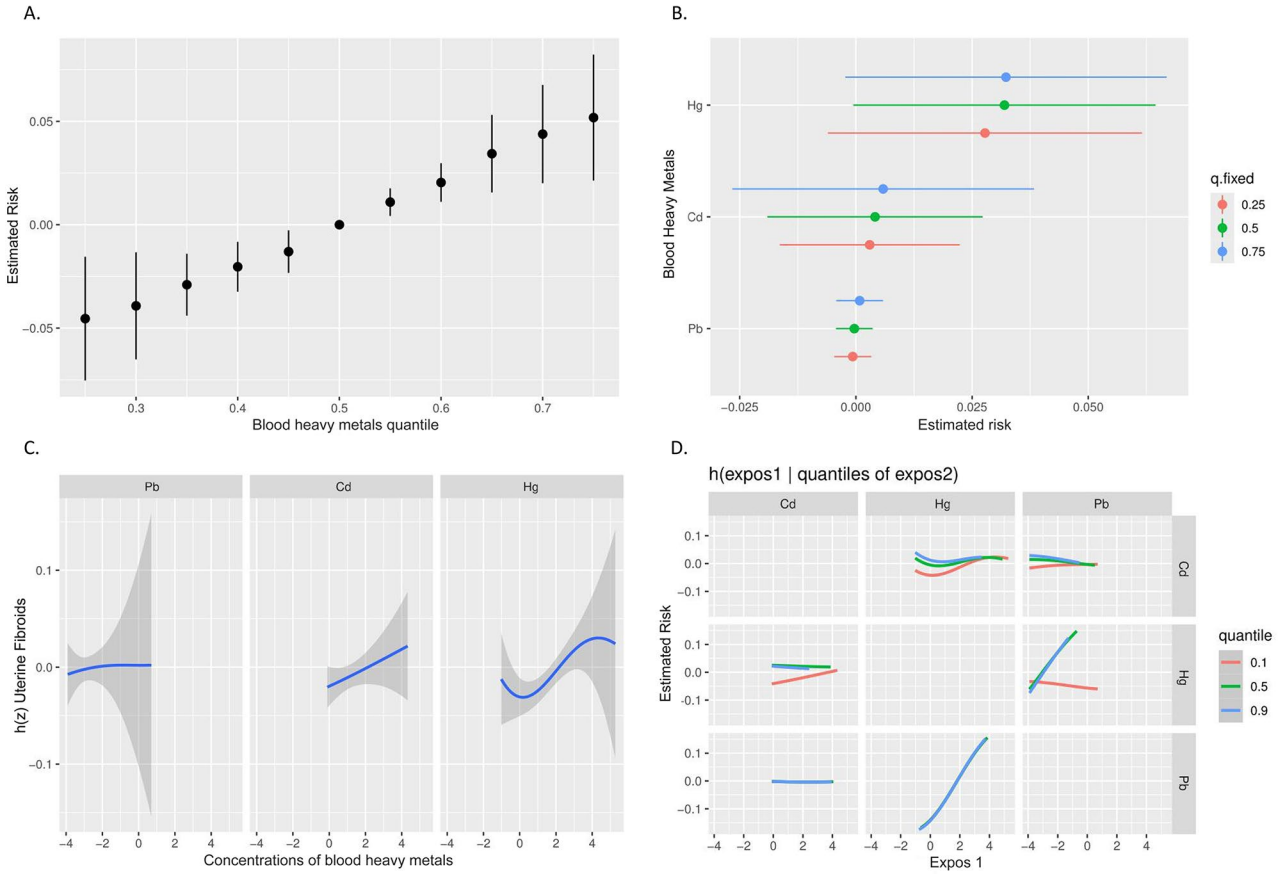

Fig. 4 The associations of blood heavy metal mixtures and uterine fibroids risk evaluated by BKMR model. (**A**). The joint effects of heavy metal mixtures on uterine fibroid risk were estimated using BKMR models for the total population. The analysis compared the risk associated with all metals at specified percentiles to the baseline risk when all metals were fixed at their 50th percentile. (**B**). The associations between individual heavy metals and the risk of uterine fibroids were estimated using BKMR. In these analyses, the concentrations of the other metals were fixed at their respective 25th (red), 50th (green), or 75th (blue) percentiles. (**C**). Exposure-response relationship between heavy metals and uterine fibroids based on BKMR. (**D**). Interaction effects of heavy metals on uterine fibroid risk based on Bayesian Kernel Machine Regression (BKMR) models. The model adjusts for age, race/ethnicity, household income, education level, marital status, smoking status, and drinking status

results. For instance, a study of premenopausal Korean women aged 30–49 found no correlation between serum Hg levels and fibroid volume [9], whereas other research on premenopausal women aged 20–49 showed higher Hg levels in women with fibroids [34]. Furthermore, studies have suggested that women with elevated serum Hg levels face a higher likelihood of being diagnosed with uterine fibroids [51]. Interestingly, some studies propose that uterine fibroids themselves may act as repositories for heavy metals [16]. The variability in results across these studies could potentially be attributed to differences in the participants' ages, the sample sizes or the methods used to measure Hg exposure employed in the research. Our findings add to these research, highlighting a significant interaction between Hg exposure and age. Specifically, our stratified analysis demonstrated women over 40 particularly vulnerable to the harmful effects of Hg. This may be due to the estrogen-like properties of mercury, which have a greater impact on menopausal women [52, 53]. Alternatively, it could be associated with age-related declines in metabolic and immune function. As these functions deteriorate with age, older women may accumulate toxins more easily when exposed to the same levels of mercury, thereby increasing their risk of developing uterine fibroids [54, 55]. Furthermore, our study found that the effect of elevated mercury levels was more pronounced among women with partners. This could be related to shared environmental exposures, as individuals living together are often exposed to similar conditions, potentially leading to higher mercury exposure and exacerbating its impact on uterine fibroids [56]. Another possible explanation is that partnered women may face greater family and societal responsibilities, and the associated psychological and social stressors could amplify the effect of mercury exposure on the risk of developing uterine fibroids [5, 57]. However, the mechanisms underlying this relationship remain unclear, and further research is needed to clarify

whether shared exposures and stress factors contribute significantly to the increased risk of uterine fibroids due to Hg exposure. Our analysis underscores the significant impact of Hg exposure on uterine fibroids, necessitating vigilant monitoring.

The present investigation elucidates a dose-dependent association between blood Hg levels and the prevalence of uterine fibroids among the cohort. Our application of RCS model identifies a critical threshold of 7 umol/L for blood Hg, a concentration that should be circumvented. Our study also employed the BKMR model for analysis. BKMR is a robust analytical method for assessing the joint effects of chemical mixtures, single exposure impacts, non-linear relationships, and potential interactions. In addition to confirming the findings of the weighted logistic model, BKMR analysis identified Hg as the primary contributor to uterine fibroid risk, with Pb and Cd also showing notable associations. Among the three heavy metals studied, Hg exhibited the highest PIP (0.98), followed by Pb (0.63) and Cd (0.19). Through this approach, we observed non-linear relationships between blood Hg and uterine fibroids, along with potential interactions between them. These models provided different perspectives on the effects of blood heavy metals on uterine fibroid risk, reinforcing the comprehensiveness and reliability of our study findings. However, strategic interventions are needed to reduce Hg exposure, starting with stronger regulation of contaminated fish products, cosmetics, and dental fillings. Specific recommendations, such as improving dietary guidelines to limit mercury intake and implementing stricter environmental regulations, could further mitigate risks. High-risk populations, including women diagnosed with uterine fibroids, should undergo routine screening for heavy metals to enable early detection and intervention. Moving forward, research efforts should prioritize the establishment of efficacious treatments for clinical toxicity and the consistent monitoring of serum Hg levels. Future research should include more longitudinal studies and focus on exploring interventions to reduce heavy metal exposure. Understanding regional disparities in exposure risks is also crucial for developing targeted prevention strategies.

Strengths and limitations

The principal strengths of this investigation lie in the application of various statistical methods, such as weighted logistic regression, RCS, BKMR, and subgroup analyses to probe the associations between blood heavy metal exposure and the prevalence of uterine fibroids. Our findings, backed by comprehensive data of NHANES from 1999 to 2006 and a diverse sample of 4502 American women, possess robust credibility and generalizability. This comprehensive data allowed for an intricate examination of potential interaction factors such as age and marital status. Crucially, our study shed light on the adverse role of heavy metal exposure, especially that of Hg, in the prevalence of uterine fibroids, and defined a critical blood mercury level of 7 umol/L that warrants vigilant avoidance. Moreover, our findings presented modest associations of blood Pb and Cd levels with uterine fibroids, and also underlined the potential interactions of these heavy metals. However, despite the strength of the evidence produced, our study highlights an inadequacy in current practices regarding heavy metal monitoring and management within women's health contexts, emphasizing the need for greater attention in this critical area.

However, the present study still has many drawbacks. First, this was a cross-sectional design that precluded the identification of temporal trends in blood heavy metals exposure and uterine fibroids in females. Additionally, the study sample was based on U.S. population survey data and excluded participants with incomplete data. As a result, whether the findings are applicable in other countries and regions requires further research and investigation. Second, the reported prevalence of uterine fibroids in the database may not fully reflect the actual prevalence, as asymptomatic cases are often underdiagnosed. And the stability of Hg estimates at higher concentrations may be influenced by the limited number of observations. Third, the absence of comparable large-scale datasets for external validation raises the potential risk of overfitting in statistical models, and the PIP values derived from the BKMR model cannot be interpreted as evidence of causation. Finally, we lacked data on key lifestyle factors such as sleep, dietary intake, occupational exposure, and environmental pollution, as well as on participants' histories of menstrual or pelvic infections, which may have influenced the findings.

Conclusions

In conclusion, our study highlighted a potential detrimental role of heavy metals exposure in the development of uterine fibroids among American women, and a blood Hg level of 7 μmol/L emerges as vigilantly circumvented. While blood concentrations of Pb and Cd also demonstrated weak associations with uterine fibroids. Nonetheless, despite the persuasive evidence, heavy metal monitoring and management in the context of women's health is still insufficient. Stricter environmental regulations, improved dietary guidelines, and routine screening for high-risk populations are essential. Future research should focus on interventions to reduce heavy metal exposure and explore regional differences in exposure risks.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03596-4 .

Supplementary Material 1

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Author contributions

Yaqin Yang: conceptualization, investigation, methodology, formal analysis, and writing original draft. Meijun Pan: resources, data curation, validation, visualization, writing review, and editing. Wenyuan Zhu: data analysis, literature review, manuscript editing, writing review. Xukai Luo: validation, visualization, writing review, and editing. Xuefang Liang: project administration, funding acquisition, supervision. All authors contributed to the article and approved the submitted version.

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Data availability

The data that support the findings of this study are available from the National Health and Nutrition Examination Survey (NHANES), which is publicly accessible and can be retrieved from their official website at https://www.cdc.gov/nchs/nhanes/. The specific data used for this study spans three cycles from 1999 to 2006.

Declarations

Ethical approval

The NHANES program obtained ethical approval and informed consent from participants in accordance with the guidelines of the NCHS Ethics Review Board (ERB). The protocol numbers referenced are #98 – 12 for NHANES 1999–2004 and #2005-06 for NHANES 2005–2006. Consequently, no additional ethical approval or informed consent was necessitated for this study. Specific information may be accessed at https://www.cdc.gov/nchs/nhanes/irba98.htm.

Competing interests

The authors declare no competing interests.

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