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Article

Independent and Combined Associations between Metals Exposure and Inflammatory Markers among the General U.S. Adults

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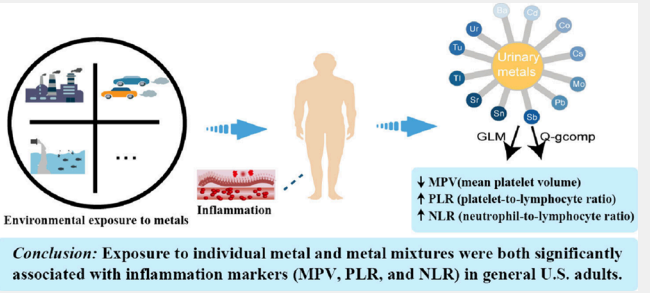
ABSTRACT: Exposure to metals can trigger a series of diseases by dysregulating the human immune system, but there is still a lack of systematic studies assessing the independent and combined effects of exposure to metals on immune function in the general population, particularly concerning inflammation markers. This cross-sectional study was designed to mainly examine the associations between urinary metal mixtures and inflammatory markers, including white blood cell (WBC), platelet count (PLT), mean platelet volume (MPV), MPV/PLT ratio (MPR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR). A total of 3451 participants aged ≥20 years were selected from the 2013−2016 National Health and Nutrition Examination Survey. Generalized linear models were used to investigate the relationships of exposure to single metals on inflammatory markers. Associations between coexposure to multiple metals and inflammatory markers were determined using weighted quantile sum regression and quantile g-computation. Barium, cadmium, lead, thallium, and cobalt showed significant associations with MPV, PLR, and NLR. Metal mixtures showed a negative association with MPV, while they had positive associations with PLR and NLR. Overall, our study highlights the significant effects of multiple metals exposure on inflammation markers, including MPV, PLR, and NLR, among U.S. adults. Thereinto, uranium, cadmium, and cobalt were identified as major contributors. Further prospective studies representative of other countries are warranted to either validate or refute our findings.



KEYWORDS: *Cross-sectional study, Metals exposure, Inflammatory markers, NHANES, Weighted quantile sum regression, Quantile g-computation*

1. INTRODUCTION

Metal exposure has been one of the main environmental problems.[1] Humans are exposed to multiple metals mainly through the air, water, soil media, or food chain.[2,3] Accumulating studies have found that exposure to heavy metals and metalloids could impact the levels of immunoglobulin produced by immune cells[4−6] and then can trigger a range of diseases by causing inflammation and damaging the immune system.[7−9] Although inflammation is a protective response that protects the host from harmful stimuli by activating immune and nonimmune cells to eliminate necrotic cells and promote tissue repair,[10,11] chronic low-grade inflammation can lead to a breakdown of immune tolerance and impair normal immune function, which increases the risk of developing noncommunicable diseases.[12−14] Therefore, it is extremely important for deeply understanding the health risks of metals to study the associations between multiple metals and inflammation.

Generally, white blood cell (WBC) counts, mean platelet volume (MPV), platelets (PLT), lymphocytes, and neutrophils are employed to indicate the degree of inflammation as particular blood cell clusters.[15,16] Studies have shown that a decrease in MPV is associated with low-grade inflammation as well as inflammatory disease inflammation, such as periodontitis as well as rheumatoid joints.[17,18] Also, some WBC-derived parameters, such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), have been recognized as highly sensitive markers of occult inflammation as well.[19] The MPV/PLT ratio (MPR) is equally essential in predicting cardiovascular disease and inflammation.[20] Nowadays, these readily available hematological parameters not only have been widely used to determine the severity of inflammation but also have a potential prognostic significance for malignancies,[21,22] autoimmune diseases,[19,23] and cardiovascular diseases.[24,25] However, few population studies have systematically reported the independent and combined effects of multiple metals on such inflammatory markers.

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Table 1. Basic Characteristics of Study Participants from NHANES (2013−2016)[a]

	Overall	WBC ($\times 10^9$/L)	PLT ($\times 10^{10}$/L)	MPV (fL)	MPR ($\times 10^{-2}$)	PLR	NLR
	N (%)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Total	3451 (100.0)	7.0 (5.9, 8.6)	23.0 (19.8, 27.0)	8.3 (7.7, 9.0)	3.6 (3.0, 4.4)	113.5 (90.0, 138.8)	2.0 (1.5, 2.6)
Age, year							
20−39	1196 (35.9)	7.4 (6.1, 9.1)	23.9 (20.6, 27.9)	8.3 (7.8, 9.0)	3.5 (2.9, 4.3)	107.9 (86.8, 130.9)	1.9 (1.5, 2.5)
40−59	1167 (37.1)	6.8 (5.7, 8.5)	23.5 (20.3, 27.1)	8.1 (7.6, 8.9)	3.5 (2.9, 4.2)	115.6 (91.9, 142.0)	2.0 (1.5, 2.5)
≥60	1088 (27.0)	6.7 (5.7, 8.1)	21.8 (18.1, 25.4)	8.3 (7.8, 9.1)	3.9 (3.2, 4.8)	119.2 (93.1, 150.0)	2.1 (1.6, 2.9)
p-value		<0.001	<0.001	0.008	<0.001	<0.001	<0.001
Sex							
Male	1693 (48.3)	6.9 (5.8, 8.4)	21.9 (18.7, 25.4)	8.2 (7.7, 8.9)	3.8 (3.1, 4.6)	111.1 (87.1, 137.3)	2.0 (1.5, 2.6)
Female	1758 (51.7)	7.1 (5.9, 8.8)	24.1 (20.8, 28.5)	8.3 (7.8, 9.1)	3.4 (2.8, 4.2)	116.8 (92.4, 140.0)	2.0 (1.5, 2.6)
p-value		0.049	<0.001	<0.001	<0.001	<0.001	0.362
Race/ethnicity							
Mexican American	551 (16.0)	7.4 (6.2, 9.0)	24.2 (20.6, 28.2)	8.5 (7.8, 9.2)	3.5 (2.9, 4.3)	107.9 (88.2, 137.1)	1.9 (1.5, 2.6)
Other Hispanic	392 (11.4)	7.5 (6.2, 8.9)	24.3 (20.9, 28.5)	8.4 (7.8, 9.0)	3.4 (2.9, 4.3)	111.8 (89.6, 135.8)	1.9 (1.5, 2.5)
Non-Hispanic White	1333 (38.6)	7.0 (5.9, 8.7)	22.8 (19.6, 26.6)	8.2 (7.7, 9.0)	3.7 (3.0, 4.5)	115.5 (90.6, 139.4)	2.1 (1.6, 2.7)
Non-Hispanic Black	668 (19.4)	6.4 (5.2, 7.9)	23.9 (19.9, 28.0)	8.3 (7.8, 9.0)	3.5 (2.9, 4.4)	110.0 (85.2, 138.2)	1.5 (1.1, 2.1)
Non-Hispanic Asian	402 (11.6)	6.7 (5.5, 8.3)	23.6 (20.2, 27.3)	8.1 (7.6, 8.7)	3.5 (2.9, 4.2)	108.6 (88.8, 135.6)	1.8 (1.4, 2.3)
Other Race	105 (3.0)	6.6 (5.7, 8.6)	24.6 (20.8, 28.4)	8.2 (7.6, 9.0)	3.4 (2.7, 4.1)	116.4 (95.7, 148.8)	1.9 (1.5, 2.4)
p-value		<0.001	<0.001	<0.001	0.015	0.010	<0.001
BMI, kg/m^2							
<25 (normal)	977 (27.9)	6.4 (5.5, 7.8)	22.8 (19.7, 26.6)	8.2 (7.6, 8.9)	3.6 (3.0, 4.4)	118.2 (94.5, 143.9)	1.9 (1.5, 2.6)
25−30 (overweight)	1132 (33.6)	6.8 (5.8, 8.4)	22.5 (19.4, 26.2)	8.2 (7.8, 8.9)	3.7 (3.0, 4.5)	112.2 (88.9, 140.0)	2.0 (1.5, 2.6)
≥30 (obese)	1342 (38.5)	7.6 (6.3, 9.1)	23.7 (20.4, 28.1)	8.4 (7.8, 9.1)	3.5 (2.9, 4.3)	110.9 (87.2, 134.3)	2.0 (1.6, 2.6)
p-value		<0.001	<0.001	0.002	0.039	0.005	0.026
Education							
Less than ninth grade	365 (5.8)	7.2 (6.0, 8.8)	23.4 (20.1, 27.4)	8,4 (7.8, 8.9)	3.6 (2.9, 4.4)	110.8 (83.1, 130.7)	1.9 (1.4, 2.4)
9−11th grade	402 (8.8)	7.2 (6.2, 9.2)	23.7 (20.3, 27.5)	8.4 (7.8, 9.0)	3.6 (2.9, 4.4)	110.0 (87.3, 137.5)	2.1 (1.5, 2.8)
High school education or higher	2683 (85.4)	6.9 (5.8, 8.6)	23.1 (19.8, 27.0)	8.2 (7.7, 9.0)	3.6 (3.0, 4.4)	114.3 (90.6, 139.3)	2.0 (1.5, 2.6)
p-value		0.026	0.375	0.265	0.902	0.077	0.107
Smoking							
Never	1959 (56.1)	6.8 (5.7, 8.3)	23.4 (20.1, 27.1)	8.2 (7.7, 9.0)	3.5 (2.9, 4.3)	116.8 (93.3, 139.3)	1.9 (1.5, 2.5)
Former	817 (25.3)	6.8 (5.7, 8.4)	22.3 (18.6, 25.9)	8.3 (7.7, 9.1)	3.8 (3.1, 4.6)	116.3 (90.6, 147.7)	2.1 (1.6, 2.8)
Current	675 (18.6)	8.2 (6.6, 9.7)	23.9 (20.1, 27.6)	8.2 (7.8, 9.0)	3.5 (2.9, 4.3)	101.4 (80.4, 128.5)	2.0 (1.5, 2.8)
p-value		<0.001	0.001	0.364	0.001	<0.001	<0.001
Drinking							
No	901 (20.5)	6.9 (5.9, 8.6)	23.4 (19.8, 27.7)	8.3 (7.8, 9.0)	3.5 (2.9, 4.4)	111.2 (89.1, 136.7)	1.9 (1.5, 2.5)
Yes	2550 (79.5)	7.0 (5.8, 8.6)	23.0 (19.8, 26.9)	8.2 (7.7, 9.0)	3.6 (3.0, 4.4)	114.5 (90.0, 140.0)	2.0 (1.6, 2.6)
p-value		0.971	0.196	0.314	0.335	0.127	0.045
FIPR							
<1.3	1015 (20.3)	7.4 (6.1, 8.9)	23.7 (20.1, 27.8)	8.3 (7.8, 8.9)	3.6 (2.9, 4.3)	109.3 (87.9, 135.3)	1.9 (1.5, 2.6)
1.3−3.5	1476 (40.7)	7.1 (5.9, 8.8)	22.8 (19.5, 26.7)	8.3 (7.8, 9.0)	3.6 (3.0, 4.5)	112.6 (87.5, 138.5)	2.0 (1.5, 2.6)
>3.5	960 (39.0)	6.7 (5.7, 8.3)	23.0 (19.9, 26.9)	8.2 (7.7, 9.0)	3.6 (3.0, 4.3)	116.9 (94.8, 140.6)	2.0 (1.5, 2.6)
p-value		<0.001	0.042	0.351	0.194	0.008	0.489
Survey year							
2013−2014	1749 (49.9)	7.0 (5.9, 8.6)	22.9 (19.8, 27.1)	8.3 (7.8, 9.0)	3.7 (3.0, 4.4)	113.6 (91.3, 140.0)	2.0 (1.5, 2.7)
2015−2016	1702 (50.1)	7.0 (5.8, 8.7)	23.2 (19.8, 26.9)	8.2 (7.7, 9.0)	3.5 (3.0, 4.4)	113.1 (89.0, 138.1)	2.0 (1.6, 2.5)
p-value		0.743	0.784	0.279	0.453	0.311	0.617

[a]PLT platelet count, MPV mean platelet volume, PLR platelet count to lymphocyte count ratio, MPR mean platelet volume to platelet count ratio, WBC white blood cell, NLR neutrophil to lymphocyte ratio, BMI body mass index, FIPR the family income-to-poverty ratio.

Recently, some investigations indicated the impact of exposure to a single metal or two metals on inflammatory markers.[26−28] For example, blood lead (Pb) levels were found to be positively correlated with NLR in the occupational population.[27] Positive effects of exposure to both Pb and cadmium (Cd) on NLR and PLR were observed in residents living near the mining and smelting area.[28] Additionally, to more accurately estimate synergistic or antagonistic interactions of metals on inflammation markers, many researchers have focused on studying the association between multimetal exposure and specific inflammatory markers.[15,28,29] Occupational populations or highly exposed populations in some specific areas, in general, were mainly selected in these studies. While the relationship of metal coexposure with MPV was investigated in Chinese urban areas, their conclusions were contradictory.[30,31] Therefore, it is urgent to determine the association between metals coexposure and inflammatory markers in the general population.

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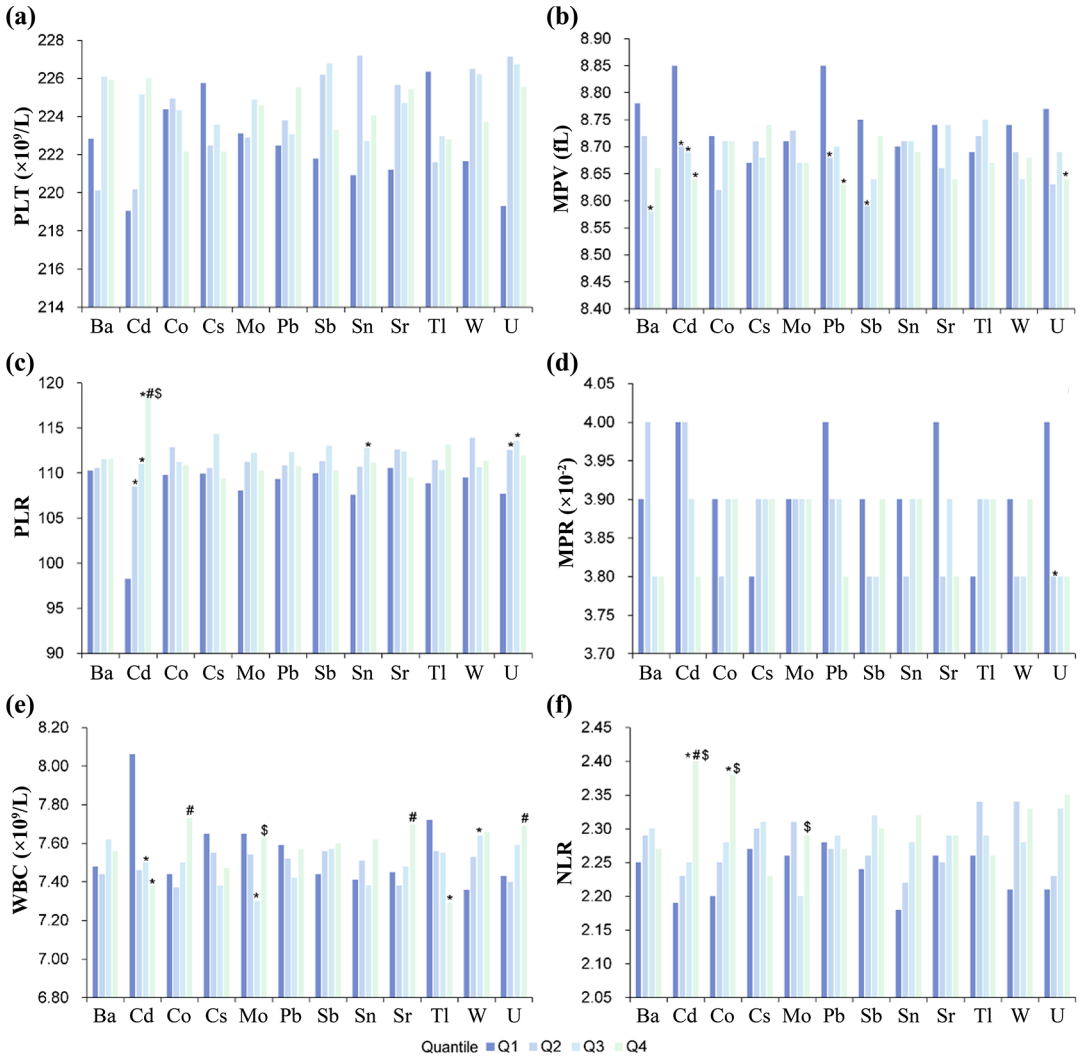

Figure 1. Geometric mean levels of inflammatory markers in urinary metals under quartiles (adjusted for age, sex, race, education level, FIPR, BMI, smoking, drinking, urine creatinine, survey period) *: Indicates a significant difference from Q1. #: Indicates a significant difference from Q2. $: Indicates a significant difference from Q3.

Hence, general adults with complete information on metal exposure and inflammatory markers from the 2013−2016 National Health and Nutrition Examination Survey (NHANES) were selected to investigate effects of metals on inflammatory markers using generalized linear models (GLMs), weighted quantile sum (WQS) regression, and quantile g-computation. This study aims to systematically provide epidemiological evidence on the independent and combined relationships of metal exposure with the inflammatory response in general populations.

2. METHODS

2.1. Study Population

NHANES is a series of surveys designed to assess the health and nutritional status of adults and children in the United States, and details of the study design, method, or data are available online (https://www.cdc.gov/nchs/nhanes/index.htm). In this study, we collected NHANES data from two consecutive cycles (2013−2014 and 2015−2016). Initially, 3922 individuals with available data on inflammatory markers and urinary measurements were included. We further excluded individuals: 1) aged <20 years (n = 203); 2) those who missed data in urinary metals, urinary creatinine and blood counts (n = 268). Finally, the analysis identified 3451 participants in the present study (see Figure S1 in the Supporting Information). All participants provided their informed consent.

2.2. Measurement of Exposures and Outcomes

For the 2013−2016 survey cycle, 13 urinary metals were determined. We initially included barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), lead (Pb), antimony (Sb), tin (Sn), strontium (Sr), thallium (Tl), tungsten (W), uranium (U), and manganese (Mn). These metals were determined by inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS) to acquire accurate quantification. The limit of detection (LOD) was shown in Table S1 in the Supporting Information. Mn was excluded from the subsequent analysis because of the low detection rate (28.63%) in urine. In addition, the LOD divided by the square root of 2 was used to replace metal concentrations below the LOD. Urine creatinine was detected by an Enzymatic Roche Cobas 6000 Analyzer and considered as an adjustment for further analysis.

Inflammatory markers were obtained mainly on a Coulter DxH 800 hematology analyzer. We acquired complete blood counts (CBC) from the data of serum samples detected during the 2013−2016 cycles. From CBC, we derived the inflammatory markers, including WBC (10^9/L), PLT (10^9/L), MPV (fL), MPR, NLR, and PLR. Additionally detailed information about the above-mentioned measurement is available at the NHANES Web site (http://www.cdc.gov/nchs/nhanes.htm).

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2.3. Covariate

We included age, sex, race (Mexican American, Other Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and other), education level (less than ninth grade, 9−11th grade, high school education or higher), the family income-to-poverty ratio (FIPR) (low-income <1.3, moderate-income 1.3−3.5, high-income >3.5), body mass index (BMI, kg/m^2), smoking status, drinking status, survey period, and urinary creatinine as covariates in our analysis. Smoking status was classified as never smoked (smoking less than 100 cigarettes in a lifetime), formerly smoked (smoking at least 100 cigarettes in a lifetime but had quit smoking at the time of the survey), and now smoking (smoking at least 100 cigarettes in their lifetime and currently smoke every day or some days). Drinking status was defined as participants who drank at least 12 alcohol drinks during a year.

2.4. Statistical Analysis

The concentrations of urinary metals and inflammatory markers were natural logarithmically transformed due to skewed distributions. The basic characteristics of participants were described by median (interquartile range, IQR), frequency, and percentage. Kruskal−Wallis tests were used to assess if the levels of inflammatory markers and urinary metals differ by the covariate category level. Pairwise Spearman's correlations among 12 metals were calculated and presented by a correlation-matrix heat map.

GLMs were used to estimate the independent effects of metals with inflammatory markers. Log-transformed urinary metals were included in the model according to quartile groups, and the lowest concentration group was utilized as the reference group in the analysis. The GLM was adjusted for age (continuous), sex, race, education level, FIPR, BMI (continuous), smoking, drinking, survey period, and urine creatinine. Strata, sampling units, and subsample weights were considered in the model, since NHANES uses a complex sampling design. Imputation of missing covariate data was employed.

To assess the combined effect of multiple metals on inflammatory markers, WQS regression (implemented with R package "gWQS") and quantile g-computation (from the R package "qgcomp") was used in this study.[32,33] Briefly, we used 40% of the data set for training in the WQS regression, then the remaining 60% of the data set was employed for validation. And we discussed the positive and negative relationship between multiple metals and inflammatory markers separately, due to the effect of exposure was limited the same direction in the WQS model. To further investigate the effect of each increasing quartile of all metals on inflammatory markers, in addition, the quantile g-computation was used, which removes the limitation of orientational homogeneity and considers the nonlinearity and nonadditivity.[34,35]

All analyses were performed in R software (version 4.1). Statistical significance was considered at two-tailed p-values <0.05.

3. RESULTS

3.1. Basic Information Description

Overall, the average age of 3451 participants involved in this study was 47.7 years, with 48.3% males (Table 1). More than two-thirds of the population was overweight or obese, with a BMI of ≥25 kg/m^2. And nearly half of participants had a history of smoking. Moreover, the median concentrations of six inflammatory markers except NLR differed by sex, with higher levels in females than in males. Meanwhile, most inflammatory markers had significant differences in age, race, and BMI subgroups. The PLT and WBC significantly decreased with increased age, which might be related to immune senescence.[36] The quantity and function of lymphocytes, antigen presentation, and some components of innate immunity decline with age, leading to a reduction in the ability to create an efficient immune response and an increase in the level of inflammation.[37] Obesity could impair immunity and induce chronic low-grade inflammation.[38] Thus, the subsequent analyses were adjusted for age and BMI in priority.

Table S2 shows the median concentrations of 12 urinary metals in the total population as well as in each covariate stratum. Results of comparative analysis for most metals, similarly, showed statistically significant differences in sex, race, BMI, and FIPR. Spearman pairwise correlation coefficients (r) of metals ranged from 0.21 to 0.77 (see Figure S2 in the Supporting Information), which indicated a strong correlation between Tl and Cs (r = 0.77) as well as between Ba and Sr (r = 0.75).

3.2. Independent Association between Metals and Inflammatory Markers

To reveal changes in the levels of inflammatory markers at different concentrations of exposure to individual metals, metal concentrations were categorized into quartiles (Figure 1). With each quartile increase of Cd, notably, there were some significant changes in the levels of WBC, MPV, PLR, and NLR. However, for all metals, there was little variation in PLT and MPR levels. Furthermore, the single effect of metals in inflammatory markers was explored deeply via using GLMs (Figure 2 and Table S3 in the Supporting Information). The

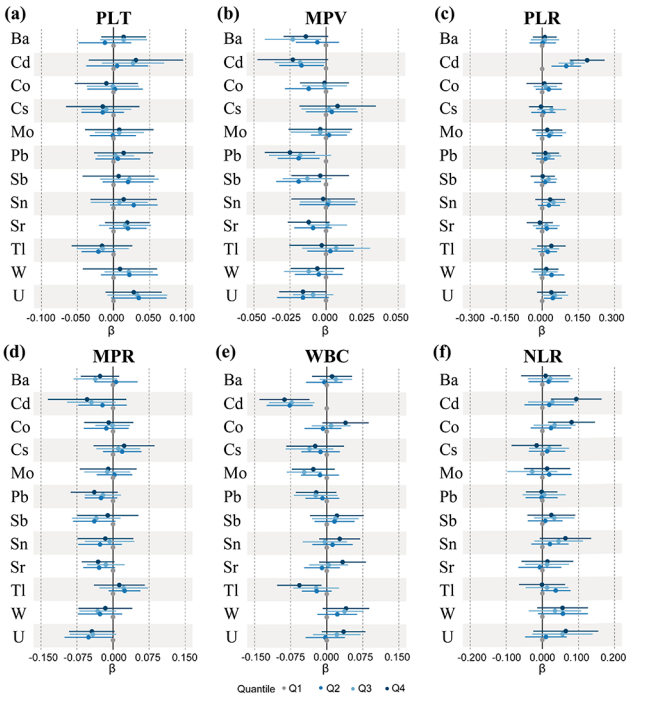

Figure 2. Associations between urinary metals and inflammatory markers in NHANES 2013−2016. The model was adjusted for age, sex, race, education level, FIPR, BMI, smoking, drinking, urine creatinine, and survey period.

covariate-adjusted results suggested that most metals were negatively correlated with WBC, MPV, and MPR levels while positively correlated with PLR and NLR levels. We identified a negative association with MPV in the second quantile (β = −0.019, 95% CI = −0.034, −0.005) and the highest quantile (β = −0.025, 95% CI = −0.043, −0.008) compared to the lowest quantile of Pb. Similarly, the negative relationship between Ba and MPV was observed as well, with 0.026 of the p-trend value. However, even though no significant trend was observed between Cd and MPV, a significant negative

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correlation with MPV was observed in both the second quartiles (β = −0.017, 95% CI = −0.033, −0.002) and the third quartiles (β = −0.018, 95% CI = −0.036, −0.001) of Cd. And as the Cd level gradually increased from the lowest to the highest quantile, each quartile level of WBC significantly decreased by 0.077, 0.073, and 0.088, respectively. Besides, a significant positive association between Cd and PLR was observed, with p-trend <0.001. Both Cd (β = 0.094, 95% CI = 0.023, 0.164) and Co (β = 0.081, 95% CI = 0.016, 0.146) were positively associated with NLR levels. Consistent with the information presented above, in particular, there was not a significant association between PLT and any metal.

3.3. Relationship of Inflammatory Markers with Coexposure to Multiple Metals

To analyze the changes in inflammatory markers elicited by coexposure to multiple metals, we first fitted a WQS regression model. As showed in Figure 3a, in the positive WQS model,

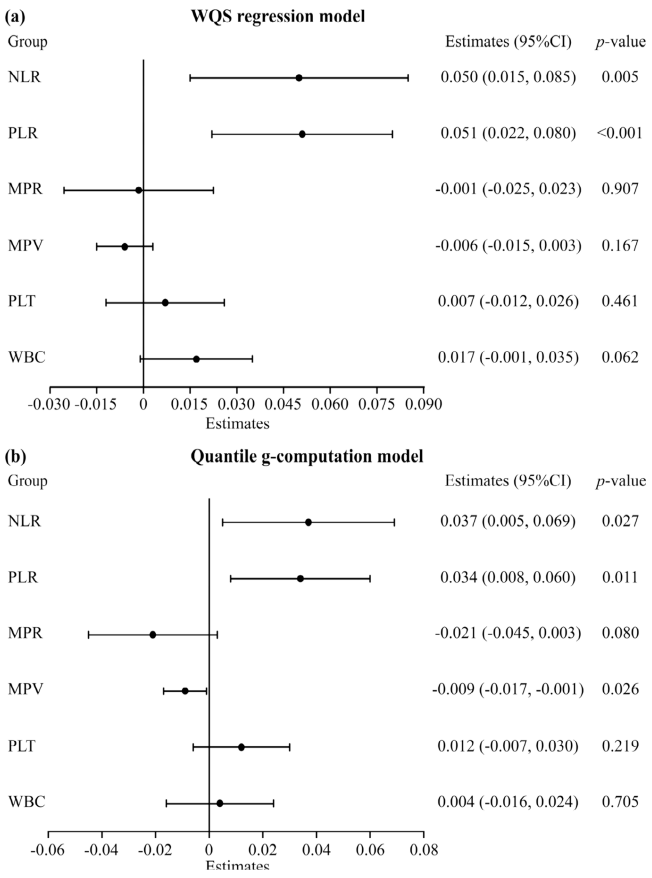

Figure 3. (a) Association of total 12 urinary metals coexposure with 6 inflammatory markers levels by the positive WQS regression model. (b) Association of total 12 urinary metals coexposure with 6 inflammatory markers levels by the quantile g-computation model. These models were adjusted for age, sex, race, education level, FIPR, BMI, smoking, drinking, urine creatinine, and survey period.

multiple metals coexposure significantly increased NLR (β = 0.050, 95% CI = 0.015, 0.085) and PLR (β = 0.051, 95% CI = 0.022, 0.080). It was worth noting that three metals (Sn, Cd, and U) contributed to higher WQS index of NLR and PLR simultaneously (Figure 4a and Figure S3 in the Supporting Information). Except for the NLR, both Co and W showed significant contributions as well. No statistically significant effects on the other markers were found in their positive WQS model, but higher weighted values of Pb, Cd, Sr, and Co in these markers were still observed (see Figure S3 in the Supporting Information). Additionally, although there were no statistical significances for all WQS indexes in the negative model (see Figure S4 in the Supporting Information), we were able to observe both Ba and Pb as the potentially main drivers of the model for NLR and PLR on the weighting plots (see Figure S5 in the Supporting Information).

In the quantile g-computation model, the substantial mixed effect of multiple metals on MPV, PLR, and NLR was observed as well (Figure 3b). There was a significant negative joint effect of 12 urinary metals with MPV (β = −0.009, 95% CI = −0.017, −0.001). As shown in Figure 4b, U contributed the largest negative weight (0.325) on MPV, while the more significant metals producing positive effects were Cs (0.608) and Co (0.391). Otherwise, a mixture of 12 metals produced a positive directional association on PLR (β = 0.034, 95% CI = 0.008, 0.060) and NLR (β = 0.037, 95% CI = 0.008, 0.060). And for PLR, the key metal producing a positive effect was Cd (0.521), while Sr (0.351) and Cs (0.337) contributed negative weights (Figure 4c). Similarly, Cd (0.213) and Co (0.374) had influential positive contributions to NLR (Figure 4d). The main metals produced negative directional association on NLR were Cs (0.234), Ba (0.215), Tl (0.175), etc. However, there was no evidence of statistically significant associations between metal mixtures and WBC, PLT, and MPR (see Figure S6 in the Supporting Information), which was consistent with results of the WQS regression model.

4. DISCUSSION

In this study, a large nationally representative general population in the U.S. was used to explore the independent and combined relationships between metal exposure and inflammatory markers with GLMs, the WQS regression model, and the quantile g-computation model. In the adjusted GLMs, we discovered that independent exposure to Ba and Pb had negative effects on MPV. The positive association between Cd and PLR as well as the negative effect of Cd and Tl on WBC was also observed. High levels of Cd and Co were associated with increased NLR. Moreover, the positively combined effect of multiple metals on NLR was revealed by using both the WQS regression model and the quantile g-computation model, in which Cd and Co showed influential contributions once again. The coexposure to metal mixtures was positively associated with PLR and negatively associated with MPV.

In the analysis of single metal exposure, the level of MPV would be increased with reducing the Pb concentration in urine, which was consistent with previous studies.[30,39] But it was worth noting that the relationship was the opposite for blood lead and MPV, which may be induced by the strong accumulation and slow metabolism of metal lead in the body.[29,40] Besides, U and Tl contributed the largest to the negative association of multiple metals coexposure with MPV in this study, instead of Pb, which was also observed in a rat investigation.[41] However, some conflicting conclusions were reported in published population studies. Association between urine concentrations of 23 metals and MPV was examined in a community population in China, which indicated that U was positively linked with the risk of increased MPV.[30] The significant association between Tl with MPV was not observed in Chinese urban adults,[31] but a positive correlation of Tl with MPV was determined among residents living in a metal-contaminated area of China.[39] MPV in these analyses was

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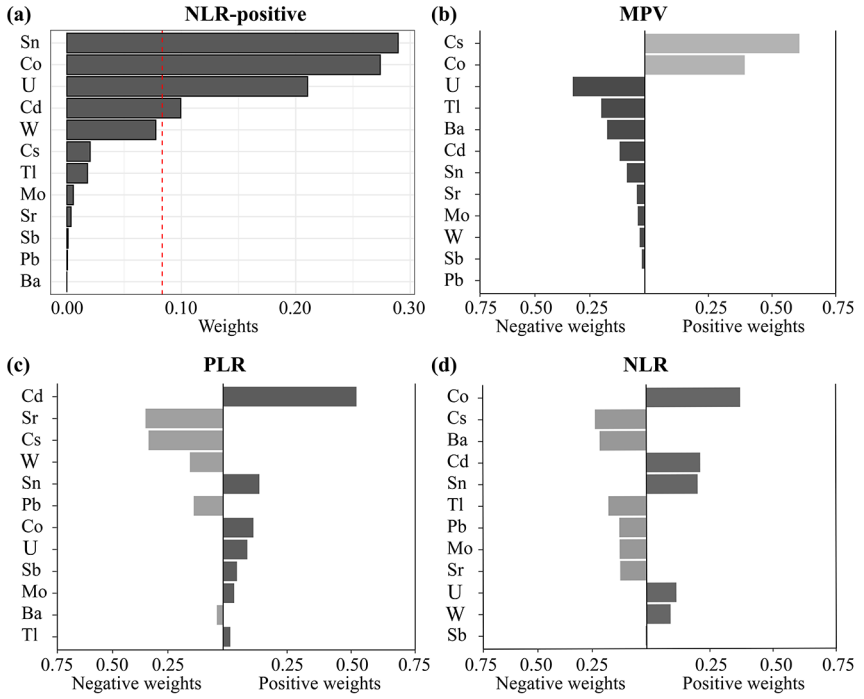

Figure 4. (a) Weights in the positive WQS regression model between NLR and WQS index of a total 12 urinary metals. (b–d) Weights corresponding to the proportion of the effect per metal mixtures on MPV, PLR, and NLR in the quantile g-computation model, respectively. All models were adjusted for age, sex, race, education level, FIPR, BMI, smoking, drinking, urine creatinine, and survey period.

categorized according to the range of MPV reference values in the Chinese population, which might explain this contradiction.

What is more, results from two models, usually using to evaluate the mixed effect of pollutants, simultaneously indicated a significantly positive association of multiple metals coexposure with NLR and PLR levels among U.S. adults. It suggested that NLR and PLR calculated by two leukocyte subtypes was able to sensitively reflect changes of inflammatory response under multiple metals exposure, which was similar to a compound inflammatory reactor.[42,43] Thereinto, the high-level NLR (or PLR) was correlated with the increase of Cd, Co, and Sn concentrations in this study. An elevated NLR of residents in mining areas in northwest China who were exposed to metals Cd and Pb in blood was found.[28] For the blood cobalt, on the contrary, a lower level of NLR was observed in Swedish workers who were exposed to Co.[15] The reason for the discrepancies between these studies and our study may be that the selected populations had a high occupational exposure risk and the type of sample was different, which resulted in a varied concentration of metals. In addition, there is a lack of studies on the association of Sn with inflammatory markers at present. Organotin compound can activate NF-κB, which could regulate the production of inflammatory mediators.[44,45] This may indicate that Sn could cause changes in inflammatory markers through inflammatory signaling pathways, which is recommended for more studies to confirm.

Oxidative stress is one of the key mechanisms of immune inflammation.[46] Cd has been reported to activate oxidative stress-related genes that damage mitochondria by inducing oxidative stress, thereby triggering apoptosis of lymphocytes.[47,48] Similarly, there have been similar reports that Co also has an inhibitory effect on lymphocytes.[49,50] $CoCl_2$ was able to induce a time-dependent reduction of T lymphocytes.[51] Based on the above findings, metals Cd and Co may trigger lymphocyte apoptosis by inducing oxidative stress, resulting in an increase in NLR and PLR, and stimulating the immune response. In a chronically inflammatory organism, the proinflammatory cytokine Interleukin-6 (IL-6) activates receptors on the megakaryocyte by binding to circulating soluble isoforms of the IL-6 receptor, which subsequently binds to gp130 to begin a trans-signaling process that leads to enhanced platelet formation.[52,53] Simultaneously, these immature cells, even platelets, travel swiftly to areas of inflammation, where they are activated and endure wear and tear.[54] This might explain the decrease in MPV in our study.

To the best of our knowledge, this work is the first to systematically explore the independent and combined associations between multiple metal exposure and inflammatory markers in a large-size general population, which data are from a nationally representative study in the U.S. Most importantly, two models based on different assumed principles were used to determine the mixed effects, which were fully adjusted for available covariates to reduce the potential bias caused by several confounding factors. It is important to acknowledge some limitations of our study. First, the NHANES data are cross-sectional, and we only used a single collected urine sample for biomonitoring of metal in-exposure levels. It is difficult to achieve a breakthrough in causality. Second, because the measured metals have different half-lives in vivo, there may be measurement errors that do not accurately represent the true exposure to metals. Third, markers included in our analysis reflecting inflammatory status are still incomplete, and the mixed effects of multiple metal exposure on other biomarkers including IL-6 and C-reaction protein need to be further discussed. Although many works suggested that MPV and PLR could be as a prognostic marker

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for thrombosis or diseases,[55−57] such as ischemic stroke, periodontitis, and rheumatoid joints,[17,18,58] finally, it must be said it is far away for using the metals concentration in urine to obtain the level of MPV/PLR/NLR and predict the inflammation response.

5. CONCLUSIONS

In conclusion, our findings suggested that exposure to metals, especially Co, Cd, Sn, Ba, U, and Tl, could cause changes in inflammatory marker levels. PLR, NLR, and MPV may serve as potential biomarkers of immune inflammation resulting from coexposure to metals. While our study provides systematic epidemiological evidence for the effect of metals coexposure on inflammatory markers, further exploration is needed to understand the mechanisms underlying its impact on inflammation.

■ ASSOCIATED CONTENT

Data Availability Statement

Data will be made available on request.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00097.

Details on participants selection and metals levels (Figure S1, Tables S1 and S2), correlations between urinary metals (Figure S2), supplemented results of WQS regression and the quantile g-computation model (Figures S3−S6) (PDF)

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Xinrui Feng: conceptualization, data curation, writing - original draft; **Yaoyu Luo:** methodology, investigation, validation, writing - review and editing; **Min Zheng:** data curation, software, writing - original draft; **Xiaojie Sun & Xiantao Shen:** conceptualization, writing - review, supervision, project administration.

Author Contributions

#X.F., Y.L., and M.Z. contributed equally.

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Notes

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