scientific reports

OPEN

Cross-sectional associations between multiple plasma heavy metals and lung function among elderly Chinese

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Environmental exposure to heavy metals may adversely affect lung function particularly in the elderly. However, limited data are available directly evaluating the relationship of heavy metal exposures with lung function in Chinese elderly. We aimed to investigate the associations between plasma metals and lung function among Chinese elderly residents. We conducted a cross-sectional study of 308 elderly residents in an industrial area and a non-industrial area in northwest China and estimated the single and combined effects of plasma metals and their interactions with lung functions (forced vital capacity [FVC], forced expiratory volume in 1 s [FEV1], and FEV1/FVC). We analyzed 12 plasma metals and identified 4 metals by lasso regression and BKMR model for further analysis. Bayesian kernel machine regression (BKMR) and quantile-g computation (QG-comp) models estimated four metals that had greater importance in lung function indicators, namely strontium (Sr), chromium (Cr), cobalt (Co) and nickel (Ni). Subgroup analyses were performed based on the resident areas. Both BKMR and QG-comp models showed metal mixtures was positively associated with FEV1/FVC (0.046 [0.017,0.075]) among all participants but of negative association with FVC, and similar results were found among participants in non-industrial area. The subgroup analysis by region showed higher heavy metal levels in industrial areas than non-industrial area. Sr concentrations were lower in non-industrial area, but they had a negative effect on FVC. In conclusion, plasma Sr, Cr, Co, and Ni levels are significant associated with lung function particularly with restrictive ventilatory dysfunction among the Chinese elderly population.

Keywords Heavy metals, Mixed effect, Lung function, Cross-sectional study, Elderly population

Heavy metals are ubiquitous environmental contaminants found in soil, atmosphere, and water bodies, with their concentrations varying significantly across regions due to diverse human activities[1]. Industries, agriculture, medicine, and technological applications are all inseparable from the use of various metallic elements[2]. While some metallic elements like cobalt (Co), copper (Cu), and zinc (Zn) are essential for human health in trace amounts, excessive exposure can pose significant health risks[3,4]. Humans primarily exposed to heavy metals through inhalation, ingestion, and dermal contact, with potential bioaccumulation occurring through the food chain[5].

Many studies have reported the potential linkage of heavy metals on various physiological systems, including respiratory, digestive, and cardiovascular[5–8]. Recent research has increasingly focused on the impacts of heavy metals on lung function and respiratory diseases[9]. Lung function, typically assessed using indicators such as forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and their ratio (FEV1/FVC)[10–12], serves as a primary indicator of respiratory health and can effectively evaluate environmental pollution levels and ventilatory dysfunction including chronic obstructive pulmonary disease (COPD)[13]. A study on COPD patients among coal miners suggests that mixed heavy metal exposures may impair maintaining cellular redox

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balance and protecting against oxidative stress in monocytes, reducing plasma glutathione-s-transferase activity and glutathione levels, weakening lung function, and indicating a possible pathophysiological process leading to COPD[14]. Elevated blood Cu concentrations have been associated with decreased FVC and FEV1, as well as an increased risk of COPD[15,16]. Moreover, exposure to lead (Pb) and cadmium (Cd) has been identified as a crucial factor in reduced lung function among both adults and children[17,18]. The elderly and residents living near chemical plants are at a higher risk of developing various environmental lung diseases[19], and one of the important factors is heavy metal exposure[20]. However, there are currently few studies on the mixed exposure of heavy metals and lung function among the elderly in industrial communities. Since 1969, the industrial area has been home to numerous metal mining and smelting enterprises. Previous investigations have revealed significant heavy metals contamination of the soil and atmosphere in this area, with concentrations of heavy metals such as nickel (Ni), Cu, cadmium (Cd), chromium (Cr), and cobalt (Co) ranging from 107 to 3045, 116–2580, 7.1–22.7, 115–897, and 23.2-144.3 mg/kg in soil[21]. the concentrations of Ni and Cd far exceed the national standards for soil contamination. Furthermore, comparative analyses have shown that the concentrations of metals and in industrial area are much higher, such as 82 times for Ni, 26 times for Cu, 12 times for arsenic (As), and 6 times for selenium (Se) greater than those in non-industrial area[22]. Recognizing the gravity of the situation, we established the Jinchang cohort in 2011, focusing on employees of the enterprises to assess the multifaceted impacts of heavy metal exposure on human health[23].

Given the complex nature of heavy metal exposure and its potential impact on respiratory health, particularly in vulnerable populations, this study aims to investigate the linear associations, dose-response relationships and mixed effects of 12 heavy metals with lung function among elderly residents in an industrial area and a non-industrial area in northwest China.

Methods

Study setting and participants

This study was conducted in two distinct regions of China's northwest (industrial area and non-industrial area). To broaden our understanding of the health implications on the community population beyond occupational exposure, we designed this study, selecting the industrial area and a neighboring city located 300 km upstream as a non-industrial area. We employed a multi-stage sampling method to select two communities each from industrial and non-industrial zones. Eligible participants were permanent residents (≥ 10 years, with ≥ 8 months annual residency) aged 50 or above, capable of independently answering survey questions, and volunteering for the study. All eligible participants undergoing health checkups in the selected communities were invited to participate. Data collection included epidemiological questionnaire, physical examination, bio-sample collection (morning fasting urine and blood samples), and health checkup data. A total of 308 participants were included in the final analysis (Figure S1).

This study was approved by the Ethics Committee of the School of Public Health, Lanzhou University. This study was reported according to the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines. All participants provided written informed consent.

Outcome definition

The outcomes of this study include indexes of lung function: FVC, FEV1, and FEV1/FVC. The lung function tests were performed using an electronic spirometer (spirometer FGC-A^+, Anhui, China). FEV1/FVC less than 70% can diagnose COPD. COPD can also be graded based on the percentage of FEV1 relative to the predicted value, which can be divided into four severity levels[24].

Heavy metal measurements

We collected fasting blood samples and centrifuged them, then stored them at -80 °C for further analysis. Plasma heavy metals were detected using an inductively coupled plasma mass spectrometer (PlasmaQuant MS ICP-MS, German) equipped with a collision reaction cell. The procedure involved mixing 0.25 ml of plasma with 4.75 mL of nitric acid-Triton X-100 solution. Quality control measures included parallel sample testing (every 10 samples), mixed plasma sample testing (every 96 samples), and spiked recovery experiments (1–2 per 96 samples). Instrument settings were: plasma power 1.35 kW, peristaltic pump speed 15 r/min, cooling gas 10.5 L/min, auxiliary gas 1.35 L/min, and nebulizer gas 0.94 L/min. 12 heavy metals (aluminium [Al], titanium [Ti], strontium [Sr], Pb, vanadium [V], Cr, Co, Ni, Cu, Zn, As, and Se) were measured, with the limit of detection (LOD) ranged from 0.030 to 1.200 ug/L (Table S1). For metals with concentrations below the LOD, LOD/2 was used as a substitution[25].

Covariates

Trained investigators conducted face-to-face questionnaire surveys to collect demographic information, such as age, sex (male/female), marital status (married/living with partner, widowed/divorced/separated), family annual income (< 50000 yuan, ≥ 50000 yuan), lifestyle such as smoking (categorized into three types: current smoker, former smoker, and never smoking, defined as current smoker more than one cigarette per day for the past six months, defined as former smoker not smoking in the past six months but smoking more than one cigarette per day half a year ago[26]), drinking (defined as drinking alcohol once or more per week in the past year, yes/no), physical exercise (yes/no), and medical history, such as cardiovascular diseases (yes/no).

Community doctors performed physical examinations, including height (cm), weight (kg), SBP (systolic blood pressure, mmHg), DBP (diastolic blood pressure, mmHg) measurement. BMI (body mass index, kg/m^2) was calculated using height and weight measurement data. In subsequent analyses, age and BMI were included as continuous variables. The eGFR (estimated glomerular filtration rate) was calculated using the CKD-epidemiology (CKD-EPI) formula, which applies different coefficients for different genders and ethnicities[27].

Additionally, kidney function can be classified into six stages based on the value of eGFR: G1 (normal or high), G2 (mildly decreased), G3a (mildly to moderately decreased), G3b (moderately to severely decreased), G4 (severely decreased), and G5 (kidney failure)[28].

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation or median with interquartile range. Group comparisons were conducted using t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. Due to non-normal distribution, natural logarithmic transformation was applied to FVC, FEV1, FEV1/FVC, and heavy metal concentrations.

Linear regression models were employed to assess relationships between individual heavy metals and lung function indicators. Lasso regression was used to screen metals influencing FEV1/FVC. The Bayesian Kernel Machine Regression (BKMR) model, with 10,000 Markov Chain Monte Carlo iterations, was utilized to study combined exposure effects, considering variable interactions. Posterior inclusion probabilities (PIPs) determined the contribution of heavy metals to the model[29].

Based on PIP rankings, Sr, Cr, Co, and Ni were further analyzed using BKMR regression and quantile-based g computation (QG-comp) to explore their combined effects. QG-comp provided estimation of overall mixture effects, accounting for non-linear and non-additive effects of single and mixed exposures. Restricted cubic spline analysis examined dose-response relationships between the four metals (Sr, Cr, Co, and Ni) and lung function indicators. Furthermore, we incorporated the interaction terms of metals that the BKMR model suggested might have interactions into the linear regression model. We calculated the potential interactions among heavy metals divided into two levels (high and low) based on their medians. Finally, we conducted subgroup analysis by region and explored the univariate effects of exposure to four metals and the overall effect coefficient of QG-comp in different regions. Three models were used: Model 1 without controlling covariates, Model 2 controlling for age and gender, and Model 3 controlling for multiple covariates including age, gender, BMI, physical exercise, smoking, drinking and cardiovascular disease.

All analyses were implemented using R software (Version 4.2.1). A two-sided P value of < 0.05 was considered statistically significant.

Results

Characteristics of participants

There were 34 participants with COPD and 274 without COPD in this study. The median (interquartile range, IQR) age was 70 (66–75) years, with a median BMI of 24.55 (IQR 22.50-27.11) kg/m^2. No significant differences were observed between the COPD and non-COPD groups in terms of age, BMI, eGFR, marital status, family annual income, smoking status, alcohol consumption, physical exercise, kidney function and history of cardiovascular disease. The COPD group had a higher proportion of male participants. This group tended to have lower plasma levels of Pb, V, Cr, Cu, As, Se, FEV1 and FEV1/FVC, while higher levels of FVC (Tables 1 and 2). Participants residing in industrial area were generally older but had lower BMI, FVC, FEV1 levels. Moreover, concentrations of plasma Al, Sr, Pb, V, Co, and Se were significantly higher in the industrial area, except for Ti (Table 2). Comparing to previously reported blood metal levels, we found higher concentrations of Ti, V, Cr, Co, and Ni in our study (Table S3).

Association between plasma metal concentrations and lung function

Figure 1 illustrates the linear relationships between plasma metals and FEV1/FVC, with all three models demonstrating positive linear associations for Sr, Cr, Co, and Ni. Specifically, plasma Sr (0.030 [0.005, 0.055), Cr (0.046 [0.006, 0.086]), Co (0.022 [0.002, 0.042]), Ni (0.02 [0.004, 0.036]) were positively associated with FEV1/FVC. In the BKMR model, these metals ranked among the top five in terms of PIP values: Sr (0.430), Cr (0.329), Co (0.412), and Ni (0.297). A lasso regression model further confirmed the consistent the associations between these metals and FEV1/FVC ratio (Figure S2). Additional analyses of FVC and FEV1 in relation to plasma metals (Figures S3 and Figure S4) revealed a significant negative association between Sr and FVC in Model 3, with a β and 95% CI of -0.057 (-0.110, -0.005), suggesting a complex interplay between these metals and various lung function parameters.

Dose-response relationships between four metals and lung function indicators

The restricted cubic spline analysis with 3-knot indicated positive linear dose-response relationships between FEV1/FVC and Sr ($P_{\text{total}} = 0.010$, $P_{\text{nonlinear}} = 0.260$), Cr ($P_{\text{total}} = 0.020$, $P_{\text{nonlinear}} = 0.245$), and Ni ($P_{\text{total}} = 0.014$, $P_{\text{nonlinear}} = 0.688$). In contrast, Co ($P_{\text{total}} = 0.003$, $P_{\text{nonlinear}} = 0.012$) showed a nonlinear dose-response relationships with FEV1/FVC. Sr displayed a negative linear dose-response relationship with FVC and FEV1, while Co and Ni showed positive linear dose-response relationships. Cr demonstrated a nonlinear trend, initially decreasing and then increasing (Fig. 2, Figs. S7, S8). The BKMR model yielded similar results (Figure S5).

Interactions of four metals with lung function indicators

The BKMR model suggested potential interactions between Cr and Co, Cr and Ni, and Sr and Co regarding FEV1/FVC (Figure S6). Therefore, we incorporated these interaction terms in the linear regression model, revealing significant interactive effects between Sr and Co, and Cr and Co on FEV1/FVC. Specifically, using low concentrations of Cr and Co (below the median) as a reference, the positive associations were observed between the group of low Co and high Cr, the group of high Co and high Cr, the group of low Co and high Cr with the levels of FEV1/FVC (Table 3).

Characteristic	Total	Non-COPD	COPD	*P* value
Number	308	274	34	
Age	70.00 (66.00–75.00)	70.00 (66.00–75.00)	70.00 (68.00–78.00)	0.415
Height, cm	161.14 ± 8.69	160.62 ± 8.57	165.29 ± 8.71	0.003
Weight, Kg	64.53 ± 11.41	64.24 ± 11.35	66.85 ± 11.80	0.208
BMI, Kg/m^2	24.55 (22.50-27.11)	24.54 (22.51–27.12)	24.75 (22.31–27.03)	0.992
SBP, mmHg	132.00 (121.00-138.00)	132.00 (122.00-138.00)	130.00 (120.00-134.50)	0.197
DBP, mmHg	78.00 (73.00–84.00)	78.00 (74.00–84.00)	77.00 (72.25-83.00)	0.273
eGFR, ml/min/1.73m^2	89.10 (81.62–94.54)	89.10 (81.64–94.75)	89.35 (80.02–93.76)	0.729
Gender				
Male	154 (50.00%)	130 (47.45%)	24 (70.59%)	0.011
Female	154 (50.00%)	144 (52.55%)	10 (29.41%)	
Marital status				
Married/living with partner	246 (79.87%)	217 (79.20%)	29 (85.29%)	0.403
Widowed/divorced/separated	62 (20.13%)	57 (20.80%)	5 (14.71%)	
Annual income, yuan				
< 50,000	179 (58.12%)	161 (58.76%)	18 (52.94%)	0.517
≥ 50,000	129 (41.88%)	113 (41.24%)	16 (47.06%)	
Location				
Industrial area	198 (64.29%)	178 (64.96%)	20 (58.82%)	0.481
Non-industrial area	110 (35.71%)	96 (35.04%)	14 (41.18%)	
Physical exercise				
No	76 (24.68%)	63 (22.99%)	13 (38.24%)	0.052
Yes	232 (75.32%)	211 (77.01%)	21 (61.76%)	
Smoking				
Never	225 (73.05%)	201 (73.36%)	24 (70.59%)	0.472
Former smoker	30 (9.74%)	28 (10.22%)	2 (5.88%)	
Current smoker	53 (17.21%)	45 (16.42%)	8 (23.53%)	
Drinking				
No	258 (83.77%)	230 (83.94%)	28 (82.35%)	0.813
Yes	50 (16.23%)	44 (16.06%)	6 (17.65%)	
Cardiovascular disease				
No	97 (31.49%)	86 (31.39%)	11 (32.35%)	0.909
Yes	211 (68.51%)	188 (68.61%)	23 (67.65%)	
Kidney function				
G1	167 (54.22%)	148 (54.01%)	19 (55.88%)	0.859
G2	122 (39.61%)	110 (40.15%)	12 (35.29%)	
G3a	14 (4.55%)	12 (4.38%)	2 (5.88%)	
G3b	5 (1.62%)	4 (1.46%)	1 (2.94%)	
FVC, ml	1882.50 (1343.50-2508.75)	1812.00 (1296.50-2465.50)	2134.50 (1752.00-2917.25)	0.005
FEV1, ml	1586.00 (1105.75-2170.75)	1674.00 (1127.50-2204.25)	1171.50 (941.00-1620.25)	0.003
FEV1/FVC	90.70 (82.72–95.30)	92.05 (86.56–95.80)	57.95 (50.25–64.25)	< 0.001

Table 1. Basic characteristics and lung function of participants by COPD status. *COPD* chronic obstructive pulmonary disease.

Overall effects of four plasma metals

Figure 3 shows the association between mixed exposure to the four plasma metals and FEV1/FVC in the BKMR model. Using the 50th percentile level of all four metals as a reference, an increasing trend in FEV1/FVC was observed with the levels of plasma metal mixture increasing. Concurrently, the mixed effect of the four metals on FVC decreased with plasma metal concentrations increasing, while the effect on FEV1 exhibited an opposite trend. According to the QG-comp analysis, the mixed effect of the four metals on FEV1/FVC was positive, with a coefficient of 0.046(0.017,0.075) (Table 4).

Subgroup analysis of four metals and lung function in different regions

We analyzed the relationship between four metals and lung function by region using linear regression (Table 5). In the non-industrial area, Sr showed a negatively correlated with FVC, with a β coefficient and 95% CI of -0.135 (-0.249, -0.021). Additionally, Sr and Co were positively correlated with FEV1/FVC, with β coefficients and 95% CIs of 0.086 (0.024, 0.161) and 0.061 (0.021, 0.101), respectively. Conversely, in the industrial area, Sr did not

Metals, ug/l	Total (*n* = 308)	Non-COPD (*n* = 274)	COPD (*n* = 34)	*P*	Industrial area (*n* = 198)	Non-industrial area (*n* = 110)	*P*
Aluminum (Al)	483.61 (291.59–663.88)	477.24 (273.63–661.94)	505.31 (328.31–761.01)	0.403	540.97 (340.55–724.20)	365.12 (193.26–549.10)	< 0.001
Titanium (Ti)	106.36 (87.60–118.55)	106.41 (84.87–118.62)	104.53 (97.21–116.77)	0.713	102.50 (70.40–113.38)	114.88 (100.65–125.84)	< 0.001
Strontium (Sr)	100.19 (63.35–165.92)	100.37 (64.00–169.45)	92.45 (56.40–134.35)	0.200	138.01 (97.22–275.88)	58.04 (45.01–72.36)	< 0.001
Lead (Pb)	6.88 (2.06–17.80)	7.47 (2.21–18.49)	3.98 (1.99–8.15)	0.038	8.27 (2.20–18.27)	4.65 (1.53–15.15)	0.022
Vanadium (V)	3.11 (2.06–3.85)	3.12 (2.19–3.91)	2.06 (1.70–3.48)	0.005	3.12 (2.20–4.03)	2.96 (1.82–3.57)	0.011
Chromium (Cr)	21.28 (15.29–29.87)	21.38 (15.82–30.44)	17.12 (12.83–22.91)	0.003	21.34 (16.12–30.58)	20.96 (12.17–28.66)	0.054
Cobalt (Co)	0.22 (0.13–0.42)	0.23 (0.14–0.43)	0.19 (0.08–0.29)	0.115	0.25 (0.16–0.54)	0.17 (0.08–0.28)	< 0.001
Nickel (Ni)	8.90 (3.97–16.31)	9.10 (4.30–16.49)	5.71 (2.63–14.99)	0.069	9.55 (4.05–18.77)	7.41 (3.83–13.55)	0.157
Copper (Cu)	915.13 (802.33–1121.73)	922.08 (822.80–1126.62)	795.84 (755.94–1000.62)	0.007	919.90 (807.73–1164.70)	904.11 (799.90–1071.32)	0.239
Zinc (Zn)	1197.23 (850.24–1945.55)	1226.06 (884.38–1952.91)	1054.90 (805.24–1862.47)	0.176	1126.83 (802.18–2253.86)	1316.46 (981.82–1751.34)	0.882
Arsenic (As)	2.63 (1.79–3.67)	2.73 (1.89–3.70)	2.09 (1.09–3.12)	0.013	2.62 (1.89–3.55)	2.77 (1.61–4.27)	0.498
Selenium (Se)	134.40 (111.65–154.22)	135.53 (111.85–155.51)	123.27 (102.29–140.02)	0.025	143.24 (122.01–156.75)	125.27 (101.65–141.53)	< 0.001

Table 2. Plasma metal concentrations of participants by COPD status and location. *COPD* chronic obstructive pulmonary disease.

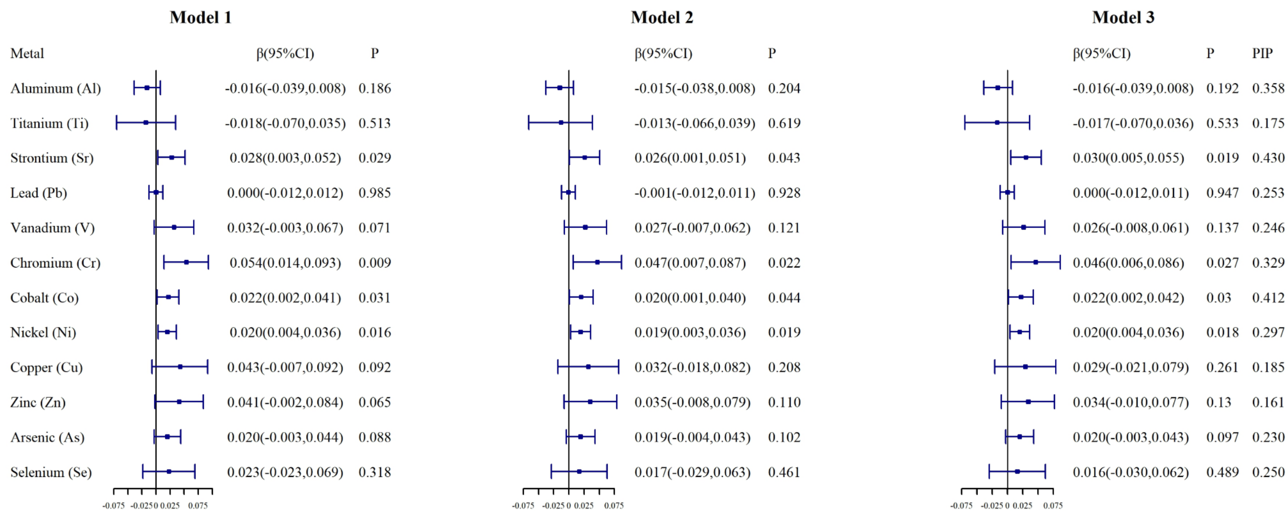

Fig. 1. Associations between plasma metals and FEV1/FVC, and their importance in BKMR models. Model 1 did not adjust for any factors, Model 2 adjusted for age and gender, and Model 3 further adjusted for smoking, drinking, physical exercise, BMI, and history of cardiovascular diseases based on Model2. Posterior inclusion probabilities (PIPs) determined the contribution of heavy metals to BKMR model.

show a significant effect on FVC. However, Cr exhibited a positive effect on FEV1, with a β coefficient and 95% CI of 0.117 (0.002, 0.232). Region-specific QG-comp analysis revealed a positive effect of the four metals on FEV1/FVC in the non-industrial area, with a coefficient and 95% CI of 0.077 (0.024, 0.131) (Table 4).

Discussion

This study investigated the associations between plasma metal concentrations and lung function indices (FVC, FEV1, and FEV1/FVC) in community-dwelling elderly individuals aged over 50 in northwest China. Our findings reveal complex associations between specific metals and lung function parameters, with notable interactions and dose-response relationships. The combined effect of Sr, Cr, Co, and Ni indicated that FEV1 and FEV1/FVC positively associated with metal concentrations, while FVC showed negative association with metal concentrations. Specifically, Sr was significant negatively associated with FVC but showed positive associations with FEV1/FVC. Furthermore, an interaction was observed between Cr and Co on FEV1/FVC. Heavy metal levels were lower in the non-industrial area compared to the industrial area, and the combined effect of the four metals showed a significant positive effect with FEV1/FVC in the non-industrial area.

In this study, 16 heavy metals were measured, including Li (lithium), Al, Ti, Sr, Cd (cadmium), Hg (mercury), Tl (thallium), Pb, V, Cr, Co, Ni, Cu, Zn, As, and Se. However, data for Li, Cd, Hg, and Tl were below the detection limit for over 20% of the samples. Therefore, the remaining 12 heavy metals were included in the subsequent analysis. Metals such as Ti, Pb, and As have been widely studied, and they are known to have certain detrimental effects on lung function[11,30,31]. Additionally, Ni, Cu, Zn, As, Cr, Co and Se are commonly found in industrial area[21] of our study. As a result, these metals were selected as the primary variables for our research design.

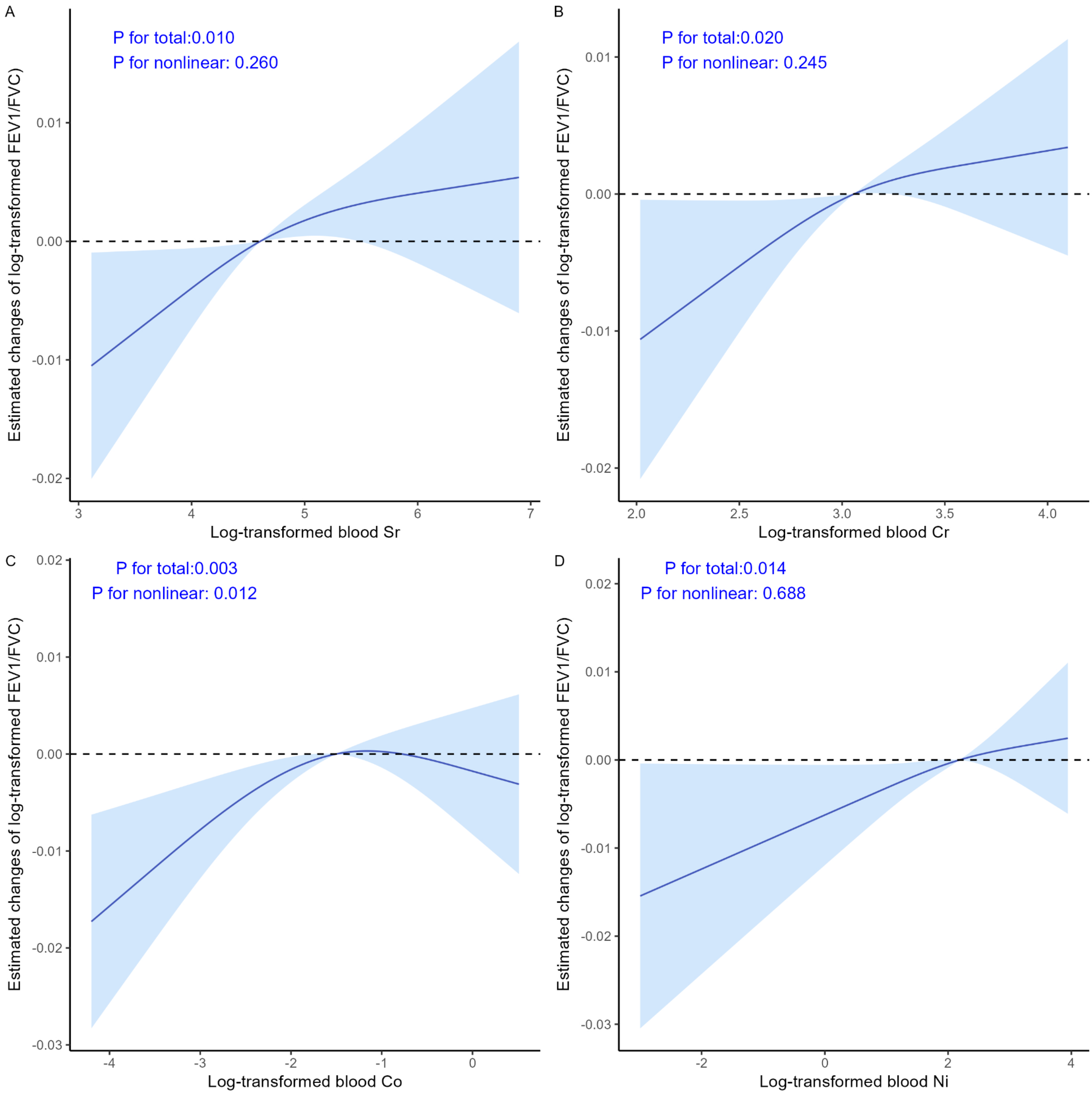

Fig. 2. Dose–response relationships of plasma metals and FEV1/FVC in the restricted cubic spline analysis (**A** Strontium, **B** Chromium, **C** Cobalt, **D** Nickel).

Sr, Cr, Co, and Ni had a greater impact on lung function in this study. A negative effect of strontium (Sr) on forced vital capacity (FVC) was observed, particularly pronounced in non-industrial areas with even lower concentration of Sr. The mechanism of the association between Sr and lung function is still unclear. Sr deficiency may cause metabolic disorders, limb weakness, excessive sweating, delayed bone development, and osteoporosis[32]. Sr, functionally analogous to calcium, can bind to calcium-sensing receptors, induce activation of various signaling pathways[33], and play a role in the contraction of diaphragm and intercostal muscles, thereby indirectly affecting lung ventilation function. Since Sr primarily accumulates in bones, its blood concentration may not accurately reflect its overall distribution in the body. To strengthen the argument, the correlation between urinary Sr concentration after metabolism and lung function can be further investigated. Certain studies have indicated that urinary Sr levels may negatively correlate with FEV1 and FEV1/FVC, suggesting potential harm to lung health[34]. Another study found a positive association between urinary Sr and both FVC and FEV1 after adjusting for multiple urinary heavy metals[17]. These studies reported median urinary Sr concentrations of 138.82 ug/L and 157.86 ug/L, respectively, highlighting variations in urinary Sr levels as potential contributors to differences in lung function outcomes. Furthermore, studies have shown that high concentrations of Sr are detrimental to human health[35], suggesting a nonlinear relationship between heavy metal Sr and human lung function. Both Sr

	β (95%CI)	*P* for interaction
Sr + Co		
Low Sr + low Co	0 (reference)	0.007
Low Sr + high Co	0.054 (-0.018,0.126)	
High Sr + low Co	0.049 (-0.023,0.121)	
High Sr + high Co	0.043 (-0.017,0.102)	
Co + Cr		
Low Co + low Cr	0 (reference)	0.038
Low Co + high Cr	0.073 (0.005,0.141)	
High Co + low Cr	0.049 (-0.018,0.116)	
High Co + high Cr	0.067 (0.004,0.130)	
Ni + Cr		
Low Ni + low Cr	0 (reference)	0.082
Low Ni + high Cr	0.064 (-0.014,0.141)	
High Ni + low Cr	0.050 (-0.023,0.124)	
High Ni + high Cr	0.062 (0.006,0.118)	

Table 3. The interaction effects among metals on FEV1/FVC. The plasma metals were divided into two levels (high and low) based on their median concentration. *Sr* strontium, *Cr* chromium, *Co* cobalt.

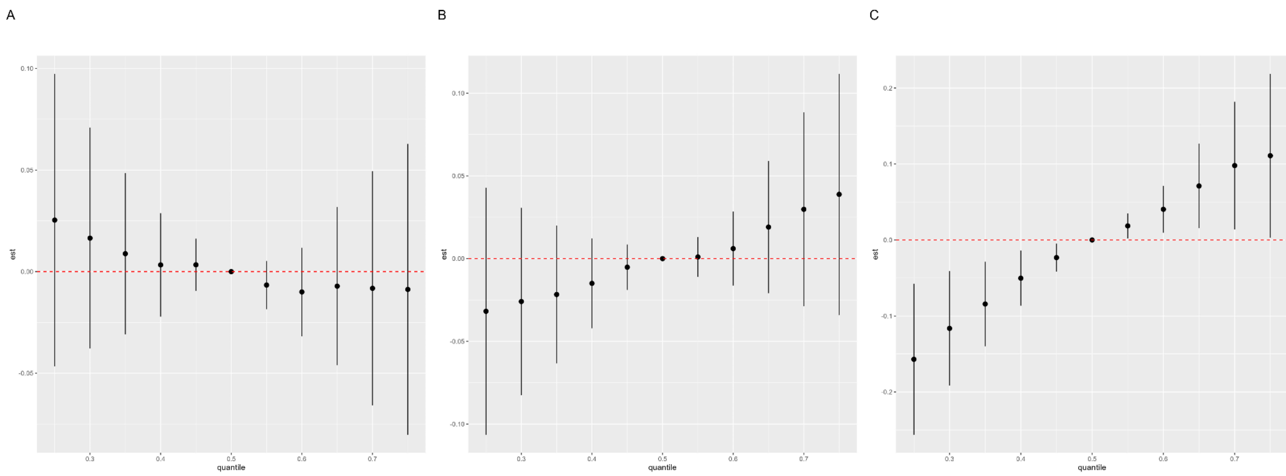

Fig. 3. The results of the BKMR model for the mixed effects of four metals on FVC, FEV1 and FEV1/FVC (**A** FVC: Forced vital capacity; **B** FEV1: Forced expiratory volume in 1 s; **C** FEV1/FVC).

deficiency and excess have adverse effects on the human body. Additionally, multiple environmental pollutants also impact lung function. For instance, harmful gases generated from indoor decoration, such as formaldehyde, volatile Organic Compounds[36,37] and radon[38], severely impair lung function, while the use of certain solid fuels indoors similarly increases indoor concentrations of fine particulate matter, leading to lung damage[39]. These factors may amplify the detrimental effects of Sr. Finally, as this study is cross-sectional, it cannot establish the temporal sequence between low-concentration Sr exposure and the decline in lung function, thus failing to robustly demonstrate a causal link between Sr exposure and reduced lung function.

Exhibited higher concentrations were found in this study compared to levels reported in other literature, especially for Ti, Cr, Co and Ni[15,40,41]. Cr and Co are essential trace elements for human health. Cr typically exists in the trivalent state, influencing insulin activity, blood sugar maintenance, and participating in fat metabolism and protein synthesis[3]. A study on heavy metals and lung function in Shandong, China, pointed out that Cr has a significant negative effect on FVC and FEV1[15], whereas in our study, the effect of Cr on these lung function indicators followed a nonlinear pattern, transitioning from negative to positive. Comparing median Cr concentrations, we found levels much higher than those reported in Shandong (21.28 ug/L versus 1.95 ug/L), suggesting that Cr deficiency might adversely affect lung health. Despite its essential role in the body, hexavalent Cr is highly toxic. Used extensively in manufacturing, hexavalent Cr can cause lung inflammation by upregulating pathways such as leukotriene B4, mitogen-activated protein kinases, nuclear factor-κB (NF-κB), and NF-E2-related factor 2[42] Furthermore, hexavalent Cr is implicated in lung tumorigenesis by transforming stem-like tumor-initiating cells with increased ALDH1A1 expression and activating the NF-κB pathway[43]. Welders exposed to welding dust containing hexavalent Cr show a direct correlation between blood Cr concentration

	β (95%CI)	*P* value
FVC		
Total	− 0.008 (− 0.069,0.054)	0.806
Industrial area	0.041 (− 0.047,0.129)	0.362
Non-industrial area	− 0.074 (− 0.159,0.010)	0.089
FEV1		
Total	0.038 (− 0.024,0.100)	0.226
Industrial area	0.068 (− 0.018,0.154)	0.123
Non-industrial area	− 0.001 (− 0.093,0.091)	0.981
FEV1/FVC		
Total	0.046 (0.017,0.075)	0.002
Industrial area	0.025 (− 0.010,0.060)	0.158
Non-industrial area	0.078 (0.023,0.133)	0.006

Table 4. QG-comp regression analysis by region of four types of metals. *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s.

	Industrial area		Non-industrial area	
	β (95% CI)	*P* value	β (95% CI)	*P* value
FVC				
Sr	− 0.031 (− 0.110,0.048)	0.444	− 0.135 (− 0.249, − 0.021)	0.021
Cr	0.087 (− 0.031,0.205)	0.146	− 0.107 (− 0.233,0.018)	0.092
Co	0.041 (− 0.018,0.100)	0.172	− 0.020 (− 0.084,0.043)	0.528
Ni	0.025 (− 0.016,0.066)	0.223	− 0.060 (− 0.133,0.014)	0.112
FEV1				
Sr	− 0.009 (− 0.087,0.069)	0.814	− 0.048 (− 0.173,0.077)	0.449
Cr	0.117 (0.002,0.232)	0.046	− 0.044 (− 0.18,0.092)	0.524
Co	0.041 (− 0.018,0.099)	0.172	0.036 (− 0.032,0.104)	0.297
Ni	0.039 (− 0.001,0.079)	0.054	− 0.022 (− 0.101,0.058)	0.591
FEV1/FVC				
Sr	0.019 (− 0.012,0.051)	0.227	0.086 (0.012,0.161)	0.024
Cr	0.030 (− 0.016,0.077)	0.202	0.066 (− 0.016,0.149)	0.111
Co	− 0.002 (− 0.026,0.022)	0.872	0.061 (0.021,0.101)	0.003
Ni	0.014 (− 0.002,0.030)	0.090	0.044 (− 0.004,0.092)	0.072

Table 5. Associations between plasma metals and lung function by location. *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s.

and pneumoconiosis incidence[44]. Moreover, Cr (VI) induces oxidative stress and cellular senescence, indirectly impacting lung function[45]. Co, another essential trace element, is vital for human health. A study on rural populations in northwestern China showed that Co has a potential protective effect against restrictive ventilation dysfunction[13], aligning with our findings of Co's positive effect of Co on lung function indicators in this study. However, Co has also been identified as a potential human carcinogen, particularly targeting lung epithelial cells[46], Additionally, Co has been linked independently to COPD progression[24], emphasizing the importance of Co concentration in its impact on lung function.

Ni demonstrated a positive association with FEV1/FVC in our study, although no significant effects of Ni on various lung function indicators were observed across different regions. However, consistently highlighted the negative effect of Ni on lung function. Specifically, Ni is negatively correlated with FEV1[12,40]. Ni exposure is associated with various chronic lung diseases[47] such as asthma and COPD, and Ni has been proven to be a potential carcinogen, which can induce nasal cancer and lung cancer[48] through epithelial-mesenchymal transformation[49].

The mixed-effect analysis of metals in this study showed that the four metals including Sr, Cr, Co, Ni had a negative effect on FVC but a positive effect on FEV1 and FEV1/FVC among community-dwelling elderly individuals aged over 50 in northwest China. Numerous studies have been conducted to investigate the effects of combined exposure to heavy metals on lung function and pulmonary diseases, revealing that mixed exposure to heavy metals exerts varying degrees of influence on lung function across diverse populations, including children, students, the elderly, and occupational workers[15,17,18]. However, the combined effects of multiple heavy metals are multifaceted. In this study, an interaction between Cr and Co on FEV1/FVC was observed. These findings underscore the complexity of heavy metal impacts on lung function, while positive effects on FEV1 and FEV1/

FVC are evident, the decrease in FVC suggests that the combined effect of the four metals may contribute to restrictive ventilation dysfunction. The influence of heavy metals on human health is not only contingent upon their individual concentrations but also varies across different levels. Furthermore, potential interactions among heavy metals can further complicate their overall effects. For instance, while Pb and Cd are commonly regarded as primary culprits for lung function impairment, their detrimental effects on lung function are mitigated or even become insignificant when Se is present[11]. Additionally, studies have shown that exposure to individual heavy metals such as Mo can increase the risk of lung cancer, yet when examining the combined effects of heavy metals, the association with lung cancer becomes less pronounced, highlighting the intricacies of heavy metal exposure[50].

This study primarily evaluates the impact of heavy metals on lung function health among elderly individuals in community settings. Heavy metals are widely present in the environment on which humans depend for survival, and both occupational and non-occupational populations are at risk of exposure. The harmful effects of heavy metals on the human body are not limited to lung damage; numerous studies have demonstrated that heavy metals significantly impair liver and kidney function, induce inflammation, and cause oxidative damage to the body[51,52]. Additionally, heavy metals can synergize with other environmental pollutants, further exacerbating their adverse effects on human health. It is also important to consider the heightened vulnerability of certain populations, such as children, the elderly, and pregnant women, to heavy metal exposure. Therefore, investigating the impact of heavy metal exposure on lung function and other health outcomes and establishing permissible environmental concentration limits for heavy metals is of great significance for protecting public health.

This study utilized various mixed-effects models and interaction analyses to explore the relationship between heavy metal exposure and lung function among elderly community residents in northwest China. However, there are still several limitations. Firstly, due to its cross-sectional study, establishing a causal relationship between heavy metals and lung function levels is challenging. Secondly, the concentrations and types of heavy metals, as well as their patterns of exposure, can vary significantly across different regions, making direct comparisons or extrapolations challenging. Thirdly, the study focused solely on exploring the potential dose-response relationship and combined effects of a limited metals with lung function. The specific mechanisms through which heavy metals may affect lung function, such as inducing oxidative stress damage or altering DNA methylation levels, remain to be fully elucidated. Lastly, the study population, consisting primarily of elderly community residents in northwest China, may not be fully representative of the broader population, particularly in terms of age, lifestyle habits and occupational histories.

Conclusion

In summary, plasma Sr levels show a negative association with lung function, particularly at lower concentrations. Conversely, plasma Cr and Co exhibit positive effects on lung function indicators. The combined effects of heavy metals associated with reduced FVC and elevated FEV1 and FEV1/FVC, suggesting that mixed metal exposure could potentially be associated with restrictive ventilation dysfunction in the elderly population in northwest China. Our findings demonstrate that the concentration of heavy metals is closely related to lung function, underscoring the importance of controlling heavy metal exposure to safeguard respiratory health in older adults.

Data availability

The data presented in this study are available on request from the corresponding author due to ethical reasons.

Received: 6 August 2024; Accepted: 7 March 2025
Published online: 13 March 2025

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Author contributions

Conceptualization, L.M. and A.Y.; Investigation, J.Y., Y.Z., R.W., F.L. and L.M.; Data curation, J.Y., Y.Z and L.M.; Formal analysis, J.Y., A.Y., J.Y. and L.M.; Funding acquisition, R.Z. and L.M.; Methodology, J.Y., R.Z., A.Y. and J.Y.; Writing—original draft preparation, J.Y. and R.Z.; Writing—review and editing J.Y., R.Z., A.Y., J.Y., H.L., R.C., B.L. and L.M.; Supervision, L.M. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by the Scientific Research Project of Health Industry in Gansu Province (GSWSKY2023-15) and the Science and Technology Development Project of Health Industry in Lanzhou City (2021011).

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All the participants consented to take part in the study by signing written informed consent. The study protocol was reviewed, and all methods were approved by the Ethics Committee of the School of Public Health, Lanzhou University on 16 October 2022 with approval number IRB22101601. All methods were carried out in accordance with relevant guidelines and regulations.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-93525-0.

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