

Internal Metal(loid)s Are Potentially Involved in the Association Between Ambient Fine Particulate Matter and Blood Pressure: A Repeated-Measurement Study in North China

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Abstract

Background The effects of ambient fine particulate matter (PM_{2.5}) exposure on blood pressure have been widely reported. However, there remains uncertainty regarding the underlying roles of particulate matter components. We aimed to investigate the association between ambient PM_{2.5} exposure and blood pressure, as well as the potential mediating effects of trace metal(loid)s, in a repeated-measurement study that enrolled women of childbearing age. **Methods** Our study included 35 participants from Hebei Province, China, each of whom was visited five times. During each visit, questionnaire surveys were conducted, blood pressure was measured, and blood was collected. The daily PM_{2.5} exposure for all participants was estimated according to their residential addresses using a spatiotemporal model that combined monitoring data with satellite measurements and chemical-transport model simulations. This model was used to calculate average PM_{2.5} concentrations 1, 3, 7, 15, 30, and 60 days prior to each visit. Serum concentrations of various trace metal(loid)s were measured using an inductively coupled plasma-mass spectrometer. A linear mixed-effects model was used to investigate associations among study variables. **Results** PM_{2.5} concentration was positively associated with both systolic and diastolic blood pressures, with or without adjustments for potential confounders. Likewise, PM_{2.5} concentration was positively associated with serum concentrations of manganese and arsenic, and negatively associated with serum concentrations of nickel, tin, and chromium. Only the serum concentration of molybdenum was negatively associated with systolic blood pressure. **Conclusion** Ambient PM_{2.5} exposure may contribute to elevated blood pressure, potentially by interfering with internal metal(loid) intake in the human body.

Background

Ambient fine particulate matter (PM_{2.5}) was ranked as the fifth global mortality risk factor in 2015 [1] and is an important risk factor for cardiovascular and cardiopulmonary diseases [2, 3]. Many studies have reported that ambient PM_{2.5} exposure can elevate blood pressure [4, 5, 6], thereby increasing the risk of hypertension [7, 8]. PM_{2.5} is mainly composed of various inorganic constituents [9, 10, 11]. Of these, the roles of various trace metal(loid)s in blood vessel injuries or the development of hypertension are of public concern [12, 13, 14] and are the focus of ongoing research.

Results from epidemiological surveys and experimental studies indicate that toxic metal(loid)s such as arsenic (As), cadmium, and lead (Pb) can elevate blood pressure [15, 16, 17]. In addition, the relationship between the intake of essential trace elements and blood pressure has been widely studied at the population level; however, the dose-response relationships are complicated [18, 19, 20], due to challenges in maintaining blood pressure within a certain range. Likewise, the influences of various metal(loid)s on blood vessel injuries depend on individual intake levels, as well as interaction effects among metal(loid)s. Generally, greater exposure to toxic metal(loid)s or disturbance in the balance of essential trace elements in the human body can lead to adverse effects on blood pressure stability. Elevated PM_{2.5} exposure has been shown to induce systemic injuries via oxidative stress and inflammation pathways [21, 22], in which various metal(loid)s are involved [23, 24]. Although population studies have been conducted, there remains a lack of clarity regarding whether PM_{2.5} affects blood pressure by interfering with the internal balance of metal(loid)s in the human body.

To the best of our knowledge, there have been few studies regarding the relationships of population PM_{2.5} exposure with internal metal(loid) levels. A study conducted in Shanxi Province, China, revealed that long-term indoor air pollution was closely related to toxic-element exposure and essential trace elements in hair [12]. However, this study had several limitations, as it used a cross-sectional study design without follow-up validation. Another study showed that the concentration of chromium (Cr) in PM_{2.5} was positively correlated with the concentration in urine [25]. Therefore, our study aimed to investigate the relationship between ambient PM_{2.5} concentration and blood pressure, as well as the potential involvement of various serum toxic metal(loid)s and essential trace elements, in a population of women of childbearing age in northern China.

Methods

Population Recruitment

This study was carried out in the Mancheng District of Baoding City in Hebei Province, China. Women were invited to join the study if they met the following inclusion criteria: 1) they were local residents who had resided in the district for at least 2 years; 2) they were aged 18 to 50 years old; and 3) they had no history of cardiovascular disease, hepatitis, cancer, diabetes, rheumatoid arthritis, chronic renal failure, or chronic lung disease. The first visit took place in January 2015, with four follow-up visits conducted in March 2015, June 2015, January 2016, and April 2016. During each visit, questionnaire surveys were conducted, blood pressure was measured, and blood was collected. Each participant rested for more than 5 min; their blood pressure was measured twice using an electronic manometer (OMRON, Japan), and the value of the second measurement was recorded for analysis. When measurements appeared questionable, a mercury sphygmomanometer was used for confirmation. Questionnaire surveys were used to obtain information regarding each participant's height, weight, age, residence, occupation, educational background, smoking status, passive smoking status, frequency of alcohol consumption (wine or beer), and exercise habits. In total, 35 women (157 person-visits) were included in this study, following exclusion of women who were visited fewer than three times. Our study protocol was approved by the institutional review board of Peking University, and written informed consent was obtained from all participants.

Quantification of Serum Metal(loid)s

Fasting blood samples were collected by healthcare workers. Serum from each sample was then immediately divided into several screw-top vials and stored at -80 °C to reduce the need for repeated freeze-thaw cycles before analysis. Serum concentrations of copper (Cu), zinc (Zn), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), molybdenum (Mo), selenium (Se), tin (Sn), chromium (Cr), lead (Pb), arsenic (As), and cadmium (Cd) were measured using inductively coupled plasma-mass spectrometry (ICP-MS; ELAN DRC II, PerkinElmer, USA). Standard serum samples (ClinChek® Serum Control, Level II; RECIPE GmbH, Germany) were used for quality control. The limits of detection of the metal(loid)s of interest were 0.60 ng/mL (Cu), 1.20 ng/mL (Zn), 0.16 ng/mL (Mn), 18.00 ng/mL (Fe), 0.02 ng/mL (Co), 0.10 ng/mL (Ni), 0.04 ng/mL (Mo), 1.00 ng/mL (Se), 0.14 ng/mL (Sn), 0.04 ng/mL (Cr), 0.05 ng/mL (Pb), 1.00 ng/mL (As), and 0.06 ng/mL (Cd). Quantitative analyses were conducted at the Central Laboratory of Biological Elements in the Peking University Health Science Center, and experiments were conducted in accordance with China Metrology Accreditation protocols.

Ambient PM_{2.5} Concentrations

The daily distributions of PM_{2.5} were estimated using a well-established data fusion model [26] that combines monitoring values with satellite remote-sensing measurements and simulations from a chemical-transport model. These estimates agree well with ground surface monitoring observations and cover a robust spatiotemporal range. Based on the home addresses of the 35 women, ambient PM_{2.5} exposures were estimated for each woman. The average PM_{2.5} concentrations at 1, 3, 7, 15, 30, and 60 days prior to each visit day (i.e., the “lag time”) were denoted as Lag-1, Lag-3, Lag-7, Lag-15, Lag-30, and Lag-60, respectively.

Data Analyses

Means, medians, interquartile ranges (IQRs), standard deviations, and minimum and maximum values were used to describe the data distributions. The associations between dependent variables (Y) and target independent variables (X_T) of concern were analyzed using a linear mixed-effects model, which included a random intercept for each participant to adjust for within-subject correlations due to repeated measurements. Two models (“Model-I” and “Model-II”) were used to examine the relationships between PM_{2.5} and blood pressure, PM_{2.5} and serum metal(loid)s, and serum metal(loid)s and blood pressure. In addition, considering the effects of ambient temperature on blood pressure, Model-III was used to investigate the relationship between PM_{2.5} and blood pressure. The components of each model were as follows:

Model-I:	$Y = \beta_1 \times X_T + \gamma(S)$	(1)
Model-II:	$Y = \beta_1 \times X_T + \beta_{2-11} \times CF_{1-10} + \gamma(S)$	(2)
Model-III:	$Y = \beta_1 \times X_T + \beta_{2-12} \times CF_{1-11} + \gamma(S)$	(3)

The three models incorporated fixed terms with coefficients of β_1 for X_T and β_{2-12} for potential confounders (CF_{1-10} ; i.e., age, body mass index, location, occupation, education, smoking status, passive smoking status, alcohol consumption, and exercise; CF_{11} , ambient temperature), as well as a random intercept for each participant, $\gamma(S)$. The change in blood pressure (mmHg) was calculated for every 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}. Metal(loid) concentrations were log₁₀-transformed to meet normality assumptions in analyses of the associations between PM_{2.5} and serum metal(loid)s. The percentage change (PC) in each metal(loid) per IQR increase in mean PM_{2.5} concentration was calculated as follows:

$$PC = [10^{\text{IQR}(\text{PM}_{2.5}) \times \beta_1} - 1] \times 100\%$$

4

The associations between serum metal(loid)s and blood pressure were expressed as absolute changes in blood pressure (mmHg) per IQR increase in each metal(loid). A value of $P < 0.05$ (two-sided) was considered to indicate statistical significance. All statistical analyses were performed using R software (v. 3.6.2; R Core Team 2019).

Results

Population Characteristics

In total, 35 women were included in our study. Among them, 21 (60%), 10 (29%), and 4 (11%) women were visited five, four, and three times, respectively. The participants all belonged to the Han ethnic group; approximately half of them lived in rural areas. The overall mean (standard deviation) age and body mass index were 35.3 (6.5) years and 24.3 (3.2) kg/m², respectively. Few participants (2%) were active smokers, but a relatively large proportion experienced passive smoking (42%). Most participants did not drink white wine, whereas 30% drank beer (less than once per week). In terms of educational background, approximately 77% completed high school. Most of the participants were technicians (45%) or factory workers (22%). Data regarding population characteristics were captured for all participants, except for 4% of the participants with regard to passive smoking status (Table 1).

Table 1
Population characteristics of the 35 women recruited during the five visits in North China

	Visit time					
	1st	2nd	3rd	4th	5th	Overall
No. of subjects	33	35	32	25	32	157
Age (years)	35.0(6.5) ^a	34.9(6.5)	35.5(6.5)	35.4(7.0)	35.8(6.4)	35.3(6.5)
BMI (kg/m ²)	24.4(3.3)	24.3(3.3)	24.3(3.1)	24.6(3.1)	24.1(3.2)	24.3(3.2)
Location						
Rural	16(48) ^b	17(49)	17(53)	14(56)	15(47)	79(50)
County	17(52)	18(51)	15(47)	11(44)	17(53)	78(50)
Occupation						
Farmer	5(15)	5(14)	5(16)	5(20)	6(19)	26(17)
Worker	8(24)	8(23)	7(22)	6(24)	6(19)	35(22)
Technician	14(42)	16(46)	14(44)	10(40)	17(53)	71(45)
Business and Service	5(15)	5(14)	5(16)	3(12)	3(9)	21(13)
Others	1(3)	1(3)	1(3)	1(4)	0(0)	4(3)
Education						
Primary School or below	1(3)	1(3)	1(3)	1(4)	1(3)	5(3)
Junior middle school	7(21)	7(20)	6(19)	5(20)	6(19)	31(20)
High school	18(55)	18(51)	17(53)	13(52)	16(50)	82(52)
^a Data are presented as the mean (standard deviation).						
^b Data are presented as the number of subjects (percentage).						
^c Missing data.						

Visit time						
College or above	7(21)	9(26)	8(25)	6(24)	9(28)	39(25)
Smoking						
NO	32(97)	35(100)	32(100)	25(100)	30(94)	154(98)
YES	1(3)	0(0)	0(0)	0(0)	2(6)	3(2)
Passive Smoking						
NO	20(61)	19(54)	15(47)	13(52)	17(53)	84(54)
YES	12(36)	15(43)	16(50)	10(40)	13(41)	66(42)
NA ^c	1(3)	1(3)	1(3)	2(8)	2(6)	7(4)
Drinking-white						
NO	33(100)	34(97)	30(94)	25(100)	30(94)	152(97)
YES	0(0)	1(3)	2(6)	0(0)	2(6)	5(3)
Drinking-beer						
Never	28(85)	19(54)	14(44)	21(84)	25(78)	107(68)
< 1/week	5(15)	16(46)	17(53)	4(16)	5(16)	47(30)
1 ~ 3/week	0(0)	0(0)	0(0)	0(0)	2(6)	2(1)
> 3/week	0(0)	0(0)	1(3)	0(0)	0(0)	1(1)
Exercise						
< 1/week	23(70)	23(66)	22(69)	18(72)	20(62)	106(68)
1 ~ 3/week	3(9)	5(14)	5(16)	3(12)	8(25)	24(15)
> 3/week	7(21)	7(20)	5(16)	4(16)	4(12)	27(17)
^a Data are presented as the mean (standard deviation).						
^b Data are presented as the number of subjects (percentage).						
^c Missing data.						

Association Between PM_{2.5} Exposure and Blood Pressure

Across all five visits, the mean (standard deviation) systolic and diastolic blood pressures were 116.3 (14.4) and 75.1 (10.8) mmHg, respectively (Additional file 1: Table S1). For all 35 women, relatively higher mean PM_{2.5} concentrations were observed during the first, second, and fourth visits, followed by the third and fifth visits (Fig. 1). A similar trend was observed for blood pressure. Overall, PM_{2.5} concentrations across all five visits were > 100 µg/m³, which is higher than the national annual standard of 35 µg/m³.

Three models were constructed to investigate the relationship between $PM_{2.5}$ and blood pressure (Fig. 2). The univariate model indicated that higher $PM_{2.5}$ concentrations were associated with elevated systolic and diastolic blood pressures, except for Lag-1 concentrations. After adjustments for potential confounders due to population characteristics and lifestyle habits (i.e., age, body mass index, location, occupation, education, smoking, passive smoking, alcohol consumption, and exercise), similar results were obtained. However, after addition of outdoor temperature into the model, only Lag-7, Lag-30, and Lag-60 $PM_{2.5}$ concentrations were positively associated with blood pressure. Detailed results are provided in Additional file 1: Table S2.

$$\text{Model-I: } BP = \beta_1 \times PM_{2.5} + \gamma(S)$$

$$\text{Model-II: } BP = \beta_1 \times PM_{2.5} + \beta_{2-11} \times CF_{1-10} + \gamma(S)$$

$$\text{Model-III: } BP = \beta_1 \times PM_{2.5} + \beta_{2-12} \times CF_{1-11} + \gamma(S)$$

The model incorporated fixed terms with coefficients of β_1 of $PM_{2.5}$, β_{2-11} of potential confounders (CF_{1-10} , i.e. age, BMI, location, occupation, education, smoking, passive smoking, drinking wine or beer and exercise; CF_{11} : ambient temperature), as well as a random intercept each subject $\gamma(S)$. The data were shown with the estimated value with 95% confidence interval. The $PM_{2.5}$ concentration were assessed according to subject's addresses by a spatiotemporal model, which fused monitoring data with satellite measurements and chemical transport model simulations.

Associations Between $PM_{2.5}$ and Serum Metal(loid)s

In total, 13 trace metal(loid)s were measured with a 100% detection rate, except for Pb, with a detection rate of 96% (Additional file 1: Table S3). The associations with $PM_{2.5}$ exposure varied according to lag day and the type of potential confounders used in the model (Table 2 and Additional file 1: Table S4). Serum Mn concentration was positively associated with Lag-7, Lag-30, and Lag-60 $PM_{2.5}$ concentrations with or without adjustments for population characteristics and lifestyle habits; serum As was positively associated with Lag-1, Lag-3, and Lag-7 concentrations. $PM_{2.5}$ concentrations were consistently negatively associated with serum Ni and Cr concentrations based on the model with adjustments for all confounders; serum Sn was negatively associated with Lag-1, Lag-3, and Lag-60 concentrations. The largest changes in metal(loid) concentration per IQR increase in mean $PM_{2.5}$ concentration were 12.1% for Mn (Lag-30), -30.0% for Ni (Lag-60), -13.8% for Sn (Lag-1), 39.0% for Cr (Lag-30), and 4.42% for As (Lag-3). Cu, Zn, Fe, Mo, Pb, and Cd were not significantly associated with $PM_{2.5}$ exposure; Co and Se were only significantly associated with Lag-1 $PM_{2.5}$ concentrations.

Table 2

Associations between outdoor PM_{2.5} and serum metal(loid)s among the recruited 35 women in North China

	Lag-1 ^a		Lag - 3		Lag - 7		Lag - 15		Lag - 30		Lag - 60	
	PC (%) ^b	P	PC (%)	P	PC (%)	P	PC (%)	P	PC (%)	P	PC (%)	P
Cu ^c	3.50	0.119	2.68	0.268	0.94	0.662	0.54	0.829	0.14	0.959	1.01	0.695
Zn	0.02	0.995	1.04	0.707	0.84	0.732	2.00	0.489	1.28	0.675	0.52	0.858
Mn	2.64	0.553	7.76	0.110	10.1	0.019	9.25	0.068	12.1	0.026	11.9	0.021
Fe	-6.45	0.380	0.41	0.960	2.42	0.742	8.12	0.357	3.93	0.670	2.60	0.767
Co	-5.82	0.011	-3.82	0.132	-1.83	0.423	-0.30	0.910	-1.69	0.554	-2.86	0.293
Ni	-22.8	0.001	-26.4	< 0.001	-22.2	0.001	-25.2	0.001	-28.2	< 0.001	-30.0	< 0.001
Mo	-2.12	0.431	-2.05	0.481	-3.56	0.161	-1.32	0.663	-3.80	0.231	-3.50	0.249
Se	4.12	0.049	3.49	0.123	2.29	0.253	1.02	0.663	1.61	0.521	2.18	0.363
Sn	-13.8	0.002	-13.2	0.006	-8.56	0.055	-9.14	0.079	-9.69	0.079	-13.1	0.011
Cr	-33.5	0.002	-37.6	0.001	-34.9	0.001	-33.7	0.007	-39.0	0.002	-38.5	0.001
Pb	13.1	0.387	2.85	0.855	-4.34	0.745	-14.0	0.342	-12.0	0.450	-6.96	0.656
As	3.58	0.029	4.42	0.012	3.63	0.021	3.22	0.082	3.48	0.077	3.45	0.066
Cd	-4.78	0.239	-6.44	0.136	-6.26	0.102	-5.39	0.234	-7.62	0.107	-9.26	0.037
^a Mean concentration of PM _{2.5} in the <i>N</i> days before the visit time, i.e. 1, 3, 7, 15, 30, and 60 days.												
^b Estimate percentage changes of metal(loid)s per IQR increase of mean PM _{2.5} concentration using the linear mixed-effects model: $\log_{10}M = \beta_1 \times PM_{2.5} + \beta_{2-11} \times CF_{1-10} + \gamma(S)$, then $PC = (10^{IQR(PM_{2.5}) \times \beta_1} - 1) \times 100\%$. The model incorporated fixed terms with coefficients of β_1 to model the effects of PM _{2.5} , β_{2-11} of potential confounders (CF_{1-10} , i.e. age, BMI, location, occupation, education, smoking, passive smoking, drinking wine or beer, and exercise), as well as a random intercept each subject $\gamma(S)$.												
^c The abbreviations of the concerned metal(loid)s were Copper (Cu), zinc (Zn), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), molybdenum (Mo), selenium (Se), stannum (Sn), chromium (Cr), lead (Pb), arsenic (As), and cadmium (Cd)												

Associations between Serum Metal(loid)s and Blood Pressure

We further analyzed the associations between serum metal(loid)s and blood pressure. Only serum Mo was associated with systolic blood pressure, when using a linear mixed-effects model adjusted for population characteristics and lifestyle habits. A reduction in systolic blood pressure by 3.16 mmHg was associated with an IQR increase in Mo. No significant associations were observed between other metal(loid)s and blood pressure (Table 3 and Additional file 1: Table S5).

Table 3

Associations between serum metal(loid)s and blood pressure among the recruited 35 women in North China using Model-II

Metal(loid)s ^a	Systolic blood pressure		Diastolic blood pressure	
	β_1 ^b	<i>P</i>	β_1	<i>P</i>
Cu	-0.67	0.699	0.35	0.790
Zn	0.44	0.722	-0.50	0.592
Mn	0.10	0.675	-0.01	0.956
Fe	0.50	0.411	-0.12	0.791
Co	-0.67	0.730	-0.10	0.948
Ni	-1.00	0.108	-0.19	0.685
Mo	-3.16	0.018	-2.00	0.054
Se	-0.59	0.703	-0.94	0.426
Sn	-0.93	0.386	-0.16	0.848
Cr	-0.08	0.497	-0.05	0.721
Pb	-0.29	0.183	-0.12	0.854
As	1.66	0.173	0.18	0.314
Cd	0.75	0.425	0.12	0.867

^a The abbreviations of the concerned metal(loid)s were Copper (Cu), zinc (Zn), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), molybdenum (Mo), selenium (Se), stannum (Sn), chromium (Cr), lead (Pb), arsenic (As), and cadmium (Cd)

^b Estimate blood pressure changes (mmHg) per IQR increase of metal(loid)s (M) using the linear mixed-effects model: $BP = \beta_1 \times M + \beta_{2-11} \times CF_{1-10} + \gamma(S)$. The model incorporated fixed terms with coefficients of β_1 of M, β_{2-11} of potential confounders (CF_{1-10} , i.e. age, BMI, location, occupation, education, smoking, passive smoking, drinking wine or beer, and exercise), as well as a random intercept each subject $\gamma(S)$.

Discussion

Our study included a group of local women of childbearing age in northern China; multiple follow-ups were conducted to explore the potential involvement of serum metal(loid)s in the relationship between PM_{2.5} and blood pressure. Overall, systolic and diastolic blood pressures were positively associated with ambient PM_{2.5} exposure after adjustments for important confounders. In addition, serum concentrations of the metal(loid)s Mn, Ni, Sn, Cr, and As were associated with PM_{2.5} exposure. However, with the exception of Mo, no significant associations were observed between serum concentrations of the other metal(loid)s and blood pressure. In general, our results indicate that PM_{2.5} pollution may have adverse effects on blood pressure in adult women; these effects may be mediated by the intake of various metal(loid)s.

Our study mainly focused on women of childbearing age and demonstrated the potential adverse effects of PM_{2.5} on blood pressure in this population. The study area experiences relatively high PM_{2.5} pollution. The average outdoor PM_{2.5} concentration over the five visits was > 100 µg/m³, which is significantly higher than the national annual standard of 75 µg/m³ in China. Furthermore, this concentration is higher than concentrations observed in other provinces in China, as well as concentrations observed in the USA, Brazil, and the Netherlands [27, 28, 29, 30, 31, 32]. We found that PM_{2.5} was positively associated with both systolic and diastolic blood pressures after adjustments for the main confounders, with or without including ambient temperature. Similar results were also obtained in a cross-sectional study of 39 million adults of childbearing age in China [33]. To the best of our knowledge, there have been few other studies regarding the effects of PM_{2.5} on blood pressure in women of childbearing age. The associations between PM_{2.5} exposure and systolic and diastolic blood pressures have been widely reported for other populations, but the results of these studies have been inconsistent. Some studies indicated that ambient PM_{2.5} exposure was positively associated with both systolic and diastolic blood pressures [6, 34], whereas others reported that PM_{2.5} exposure was only positively associated with systolic blood pressure [35, 36, 37, 38]. A number of studies have also found that PM_{2.5} exposure was not significantly associated with either systolic or diastolic blood pressures [27, 30, 39]. This inconsistency could have multiple sources, such as study design, PM_{2.5} exposure level, sample size, and participant characteristics. Our study had a repeated-measurement design, which involved five visits. In most other repeated-measurement studies, the participants received two to four visits [36, 40, 41]. Likewise, in previous studies, the intervals between surveys were shorter than 2 weeks [42, 43]; in our study, the intervals between surveys were several months in length. PM_{2.5} concentrations fluctuated greatly between any two consecutive visits. Hence, we were able to investigate the effects of PM_{2.5} exposure on blood pressure in the study population, as well as any lag effects related to PM_{2.5} exposure. For example, the difference in PM_{2.5} concentrations between the first and third surveys was > 100 µg/m³, which is much larger than the changes reported in other repeated-measurement studies [40, 43]. However, our study included only 35 women; thus, the study had fewer participants than other similar studies. This may have affected the reliability of the dose-response analysis.

Both organic and inorganic components of PM_{2.5} may contribute to the adverse effects of PM_{2.5} on blood pressure. Polycyclic aromatic hydrocarbons, organic constituents of PM_{2.5}, are reportedly not significantly associated with the risk of hypertension [44, 45]. Thus, our study focused mainly on inorganic metal(loid) components, because their associations with blood pressure are well-known [19, 20]. In northern China, metal elements comprise a large proportion of PM_{2.5} [9, 10, 11]. Inhalable particulate matter may be an important exposure route by which many metals enter the body [46]. Therefore, it is important to investigate how the inorganic components of PM_{2.5} affect blood pressure stability. Here, we found that PM_{2.5} concentration was significantly correlated with some serum metal(loid)s positively with serum Mn and As, and negatively with serum Ni, Sn, and Cr. Our previous study revealed that indoor air pollution level was associated with hair metal(loid) concentrations (positively with As and Pb, and negatively with Ni, Sn, Cr, and Co) in women in Shanxi Province, China [12]. However, a study conducted in Wuhan did not find any significant associations between urinary metal contents and PM_{2.5} exposure [25]. The relationships between PM_{2.5} exposure and internal metal(loid) concentrations can vary with location, PM_{2.5} concentration, lifestyle, exposure biomarkers, and other factors. Compared with other biomarkers, serum metal(loid)s can indicate recent exposure (days) in a

population and have been used as exposure biomarkers in previous studies [47, 48]. Although diet is the main intake route for various metal(loid)s [46], it was not considered in our study. Hence, additional in-depth studies are needed to confirm our findings.

Toxicity patterns associated with nutrients and toxic metals vary. For essential trace metals, toxic effects usually occur when their exposure levels are above or below their acceptable ranges. For toxic metals, toxic effects on blood pressure usually increase linearly with their exposure concentrations, especially when the exposure levels are above threshold levels [16, 19]. Our study findings indicate that PM_{2.5} may interfere with the balance of trace elements in the body by enhancing the levels of toxic metals and reducing the levels of nutrient elements. However, we did not find a strong relationship between serum metal(loid)s and blood pressure. Possible explanations are that the serum concentrations of various metal(loid)s do not represent long-term exposure levels, or that they are subject to lag effects, which were not investigated in our study. Another explanation is that PM_{2.5} may induce blood vessel injuries via other pathways, such that the effects of internal metal(loid) intake are negligible. To the best of our knowledge, there is little evidence that internal metal(loid) intake contributes to the association between PM_{2.5} and blood pressure. Further research is needed to clarify the results obtained in this study.

Our study had two important limitations. First, the metal(loid) contents in outdoor PM_{2.5} were not measured, and the quantities inhaled by the participants could not be determined. Second, the effects of dietary foods were not considered. However, we were able to reveal the impact of PM_{2.5} on blood pressure and the potential involvement of metal(loid)s. PM_{2.5} concentrations during our study period were relatively high and varied greatly over the five visits; thus, we could investigate the effects of high levels of PM_{2.5} exposure on blood pressure. Because we adopted a repeated-measurement design, we effectively reduced the influences of some confounding factors. Furthermore, by collecting serum samples, we were able to characterize population internal exposure to PM_{2.5}.

Conclusions

To the best of our knowledge, this is the first study to investigate whether internal metal(loid)s are involved in the association between outdoor PM_{2.5} concentration and blood pressure by using multiple follow-ups in northern China. For our study population, we conclude that greater PM_{2.5} exposure was associated with elevated blood pressure, perhaps due to an imbalance of internal metal(loid)s. Our results help to illuminate the adverse health effects of PM_{2.5} on human blood pressure.

Declarations

Ethics approval and consent to participate

Our study protocol was approved by the institutional review board of Peking University, and written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare they have no actual or potential competing financial interests.

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Authors' contributions

B.W., Y.Y. and C.L. conceived the study. T.X. obtained PM2.5 concentration data. C.L. perform the analysis and wrote the first draft of the manuscript. L.Q., B.W., B.J., S.G., X.W., M.G., Y.Y., X.Z. and Z.L. participated the study design, sample collection and analysis. L.Q., B.W., T.X., J.C., B.J., S.G., X.W., M.G., Y.Y., Y.X, X.Z. and Z.L. reviewed and edited the manuscript. B.W. and Y.Y. managed the program. All the authors read and approved the final manuscript.

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Figures

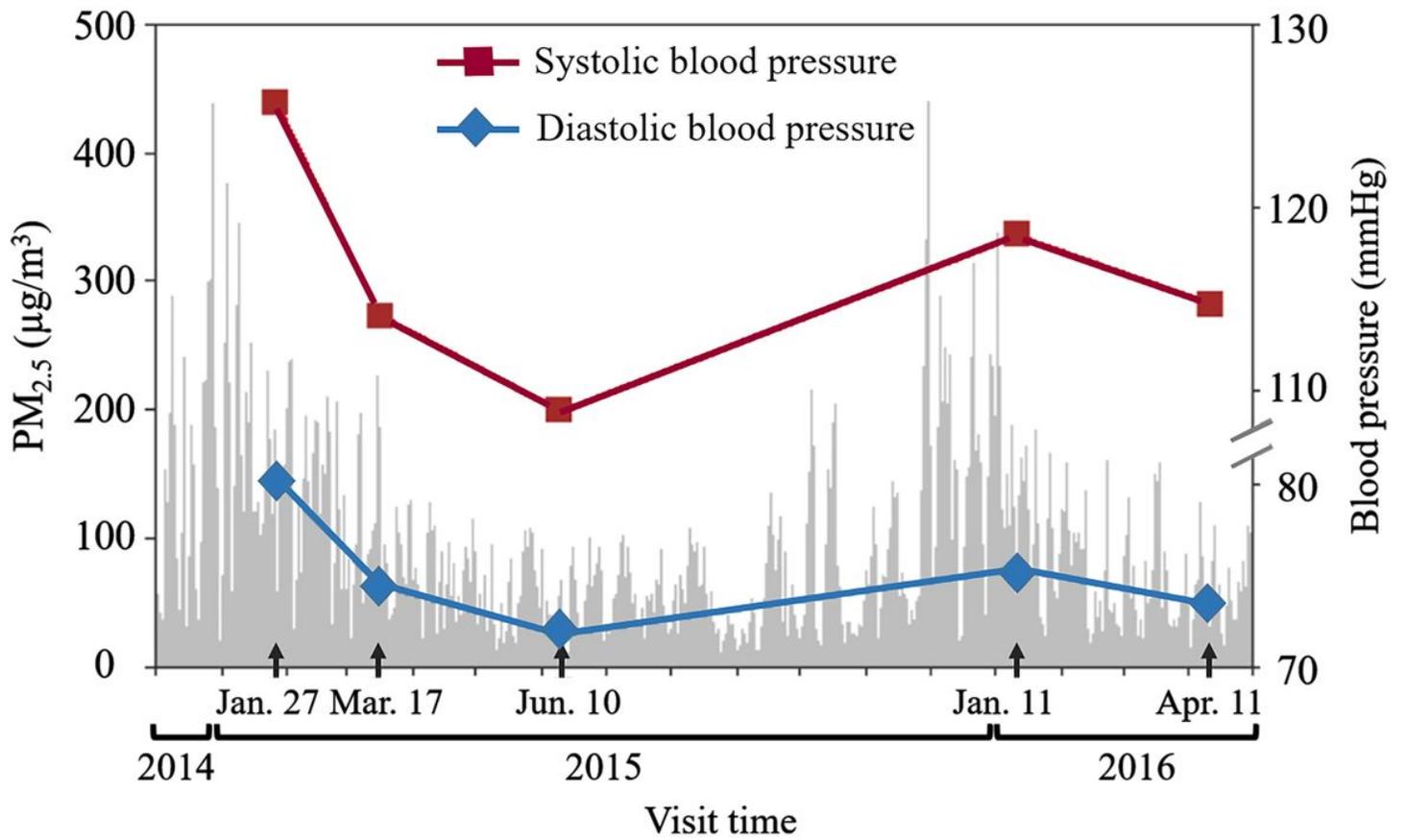


Figure 1

Change trend of the daily average PM2.5 concentration and blood pressure of the 35 women.

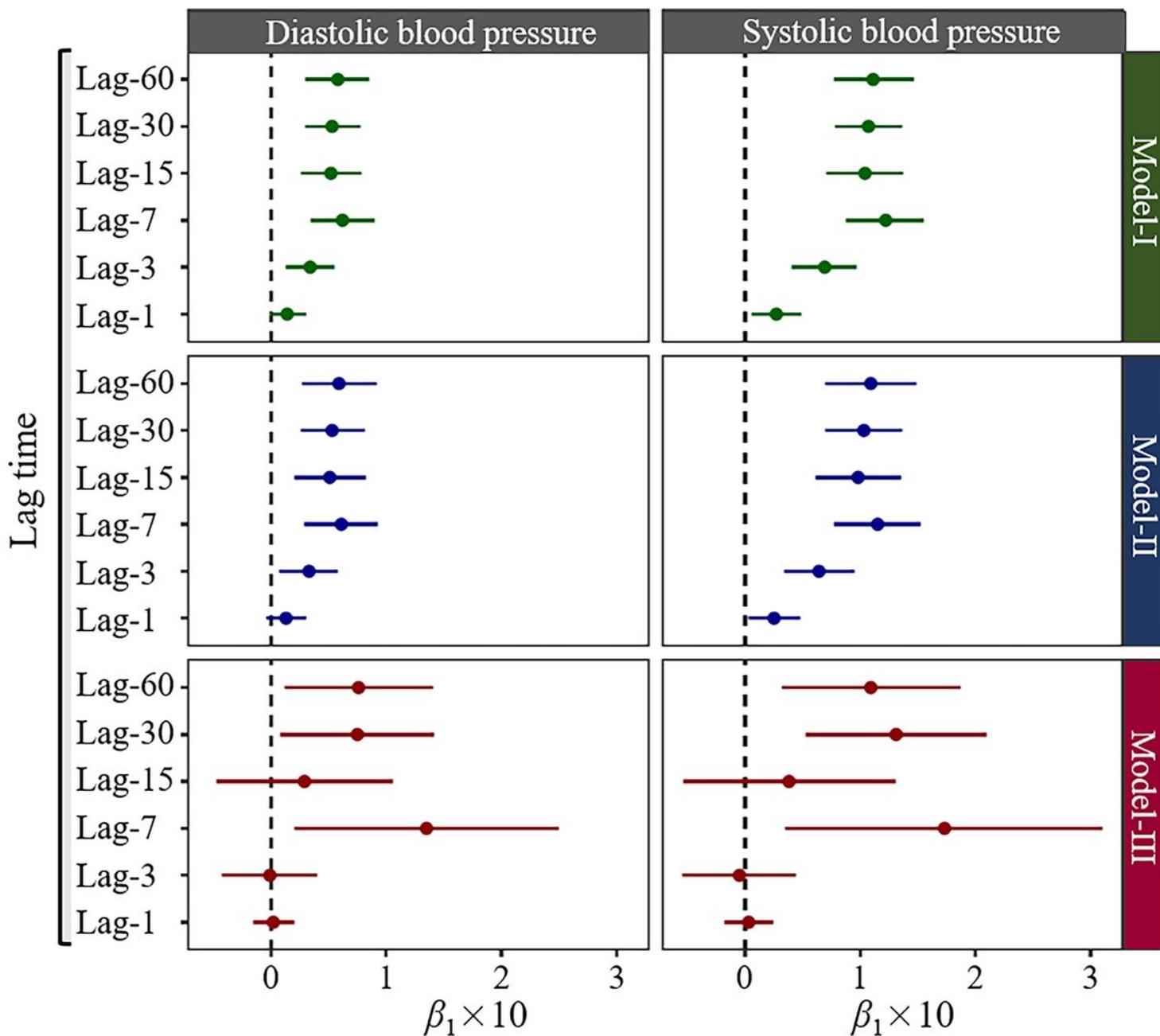


Figure 2

Estimate blood pressure changes (mmHg) per 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ using three linear mixed-effects model as follows: Model-I: $\text{BP} = \beta_1 \times \text{PM}_{2.5} + \gamma(\text{S})$ Model-II: $\text{BP} = \beta_1 \times \text{PM}_{2.5} + \beta_2 \cdot 11 \times \text{CF1-10} + \gamma(\text{S})$ Model-III: $\text{BP} = \beta_1 \times \text{PM}_{2.5} + \beta_2 \cdot 12 \times \text{CF1-11} + \gamma(\text{S})$

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