

## Preplanned Studies

## Acute Effects of Exposure to Fine Particulate Matter and Its Constituents on Sex Hormone Among Postmenopausal Women — Beijing, Tianjin, and Hebei PLADs, China, 2018–2019

Yanlin Tian<sup>1,2,&</sup>; Jiaonan Wang<sup>3,&</sup>; Jianlong Fang<sup>3</sup>; Chen Chen<sup>3</sup>; Feng Zhao<sup>3</sup>; Yi Zhang<sup>3</sup>; Peng Du<sup>3</sup>; Yawei Li<sup>3</sup>; Wanying Shi<sup>3,4</sup>; Yuanyuan Liu<sup>3</sup>; Enmin Ding<sup>3</sup>; Song Tang<sup>3</sup>; Xu Yue<sup>2</sup>; Xiaoming Shi<sup>3,5,#</sup>

### Summary

#### What is already known on this topic?

Exposure to fine particulate matter (PM<sub>2.5</sub>) was linked to endocrine hormone disruption in the reproductive system. Nonetheless, it was unclear which specific components of PM<sub>2.5</sub> were primarily responsible for these associations.

#### What is added by this report?

The study presented the initial epidemiological evidence that brief exposure to PM<sub>2.5</sub> can elevate estradiol levels in postmenopausal women. Various particle components had unique effects, with water-soluble ions and specific inorganic elements like Ag, As, Cd, Hg, Ni, Sb, Se, Sn, and Tl potentially playing significant roles in increasing estradiol levels.

#### What are the implications for public health practice?

The study established that the prevalence of air pollution, along with its specific components, has been recognized as a novel risk factor affecting the balance of sex hormones.

Recent studies have identified exposure to fine particulate matter (PM<sub>2.5</sub>) as a potential risk factor for a range of adverse health outcomes (1–3). However, investigations into the relationship between PM<sub>2.5</sub> constituents and sex hormone levels have predominantly focused on men or women of reproductive age (4–5), leaving a gap in our understanding concerning postmenopausal women. Given that PM<sub>2.5</sub> can act as a xenobiotic influencing reproductive hormones, it is crucial to investigate its role in disease incidence among this demographic. Thus, our cross-sectional study sought to evaluate the correlations between short-term exposure to PM<sub>2.5</sub> and its components with sex hormone levels in postmenopausal women. This analysis utilized data from the Sub-Clinical Outcomes of Polluted Air in

China. Additionally, we aimed to pinpoint the primary elements within the constituents in the Beijing-Tianjin-Hebei (BTH) region and adjacent areas (6). Our results indicate that PM<sub>2.5</sub> exposure is associated with a delayed increase in sex hormone levels, notably estradiol. Additionally, specific constituents of PM<sub>2.5</sub>, particularly inorganic elements such as Ag, As, Cd, Hg, Ni, Sb, Se, Sn, Tl, and V, appear to be key contributors to elevated estradiol levels. The identification of air pollution and its distinct constituents as a novel risk factor for sex hormone equilibrium highlights the necessity of prioritizing interventions to mitigate its adverse effects on postmenopausal women.

In total, 1,033 women aged 40 years and older were recruited for the study, with participants stratified across age groups (40–49, 50–59, 60–69, 70–79, and 80–89 years) from the BTH region and adjacent areas using a stratified random sampling method between October 2018 and March 2019. This region, comprising nine cities, is known for high levels of air pollution and was selected for its advanced atmospheric monitoring infrastructure. Hourly data on ambient PM<sub>2.5</sub> levels and its components were sourced from the Chinese National Ambient Air Quality Monitoring Network. The exposure of participants to ambient PM<sub>2.5</sub> and its constituents was estimated using data from the monitoring stations within 2 km of their residences. We calculated the cumulative average exposure across different lag periods using these hourly data. After excluding 196 women who had not reached menopause and 95 participants with incomplete information, 742 postmenopausal women were included in the final analysis. The specific inclusion and exclusion criteria for participants are detailed in Supplementary Figure S1 (available at <https://weekly.chinacdc.cn/>). For more comprehensive information about the study design, refer to the published study (7). Pollutant gases such as nitrogen dioxide (NO<sub>2</sub>)

and ozone (O<sub>3</sub>), along with PM<sub>2.5</sub> components like organic carbon (OC), elemental carbon (EC), water-soluble ions, and inorganic elements, were assessed using the closest fixed-site monitoring stations. Components that were detected below the limit of detection (<LOD) more than 25% of the time, including Br, Cs, Cu, Mo, Sc, Si, and Te, were excluded from our analysis. In cases where the components were undetectable (<LOD), we substituted half of the detection limit for the actual value. Serum samples were analyzed for sex hormone levels [T (testosterone) and E<sub>2</sub> (estradiol)] using automated biochemical analyzers after storage at -80 °C for a period of up to six months. Demographic information, physical characteristics, and lifestyle data were gathered through in-person interviews.

Spearman's correlations assessed the correlation matrix between PM<sub>2.5</sub> and its components. Generalized linear models elucidated the influences of PM<sub>2.5</sub> and its components on estradiol and testosterone levels. Time-lag patterns were identified by computing PM<sub>2.5</sub> concentrations at varying lag times (0-day, 1-day, 2-day, 3-day, 7-day, and 14-day). The most significant hormone level changes corresponding to each interquartile range (IQR) increase in PM<sub>2.5</sub> informed the selection of the lag period to investigate the impact of PM<sub>2.5</sub> components on sex hormones. Adjustments were made for multiple covariates, including: 1) demographic factors such as age, monitoring site, income, education, living status, and marital status; 2) lifestyle factors like smoking, alcohol consumption, vegetarianism, dietary supplements, and physical activity; 3) physical health indicators, including body mass index (BMI); 4) other airborne pollutants, namely O<sub>3</sub> and NO<sub>2</sub>; and 5) meteorological conditions like relative humidity and ambient temperature. When examining PM<sub>2.5</sub> component effects on sex hormones, models were additionally controlled for PM<sub>2.5</sub> concentrations to mitigate confounding influences. Data analysis was performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), with *P*-values adjusted for false discovery rate (FDR) in multiple comparisons. Statistical significance was determined at a two-sided *P*-value of less than 0.05.

Among the 742 postmenopausal women studied, the average age was 68.9±11.4 years. Their testosterone levels measured 0.68±1.81 nmol/L, while estradiol levels were 41.7±81.1 pmol/L. The majority had received 9 years or less of formal education, 77.9% were married, and 89.4% lived with others. Smoking

prevalence was 4.4%, and alcohol consumption was reported by 2.2% of participants (Table 1). The average concentrations of PM<sub>2.5</sub>, EC, and OC were 67.3 µg/m<sup>3</sup>, 6.6 µg/m<sup>3</sup>, and 12.0 µg/m<sup>3</sup>. Further statistical details on PM<sub>2.5</sub> components, gaseous pollutants, and meteorological factors can be found in Supplementary Table S1 (available at <https://weekly.chinacdc.cn/>). In Supplementary Figure S2 (available at <https://weekly.chinacdc.cn/>), the Spearman's correlation matrix illustrates the relationships between 3-day average PM<sub>2.5</sub> exposures and its constituents, revealing mostly weak to moderate correlations, except for OC, Se, Pb, and Zn.

Figure 1 shows the lag pattern of associations between PM<sub>2.5</sub> and estradiol. The most significant effects were observed at a 3-day lag of exposure, followed by a gradual decrease over time, and eventually became statistically insignificant at longer lags. Each IQR increase in a 3-day lag period of PM<sub>2.5</sub> (38.6 µg/m<sup>3</sup>) was associated with an elevated estradiol level of 24.7 pmol/L [95% confidence interval (CI): 9.47, 39.98 pmol/L] (Supplementary Table S2, available at <https://weekly.chinacdc.cn/>).

Our investigation revealed that a 3-day exposure to PM<sub>2.5</sub> and its components is worth a closer examination for their potential influence on sex hormone regulation. As demonstrated in Figure 2 and Supplementary Table S2, clear correlations were detected between sex hormone levels over the 3-day lag and specific PM<sub>2.5</sub> components, such as NH<sub>4</sub><sup>+</sup> [-55.22 (-92.21, -18.24) pmol/L], Cl<sup>-</sup> [-21.63 (-40.13, -3.12) pmol/L], and Na<sup>+</sup> [26.27 (13.48, 39.05) pmol/L]. On the other hand, there were no notable relationships with other carbon fractions and water-soluble ions vis-à-vis estradiol levels. When examining inorganic elements, we found significant correlations with elevated sex hormone levels for Ag, As, Cd, Hg, Ni, Pb, Sb, Se, Sn, Tl, V, and Zn. However, after multiple comparison adjustments (FDRs>0.05), the positive links between Pb, and Zn exposures and estradiol were no longer statistically significant. Moreover, a rise in OC, As, Sb, and Sn exposure corresponded with an increase in testosterone levels, although these associations were attenuated following adjustment for FDR.

## DISCUSSION

This research is the first to investigate how PM<sub>2.5</sub> and its particulate components affect reproductive hormone levels in postmenopausal women. A multi-

TABLE 1. Characteristics of the study population (N=742) in Beijing, Tianjin, and Hebei PLADs, China, 2018–2019.

Characteristics	N (or mean±SD)	% (or range)
Age (years)	68.9±11.4	43–91
<65	284	38.3
≥65	458	61.7
Education		
9 years or less	562	75.7
10 years or above	180	24.3
Marriage		
Married	578	77.9
Not married	164	22.1
Habitation		
Live alone	79	10.6
Live with others	663	89.4
Smoking		
No	709	95.6
Yes	33	4.4
Drinking		
No	726	97.8
Yes	16	2.2
Vegetarian diet		
No	678	91.4
Yes	64	8.6
Often use nutrient supplements		
No	660	88.9
Yes	82	11.1
Physical exercise		
No	240	32.3
Yes	502	67.7
BMI (kg/m <sup>2</sup> )		
<28.0	567	76.4
≥28.0	175	23.6
Sex hormone biomarker		
Estradiol (pmol/L)	41.7±81.1	18.4–1,305
Testosterone (nmol/L)	0.68±1.81	0.087–32.1

Abbreviation: PLADs=provincial-level administrative divisions; N=number; SD=standard deviation.

center cross-sectional study revealed a delayed impact of PM<sub>2.5</sub> exposure on elevated sex hormones, particularly estradiol, with the most notable effect occurring 3 days after exposure. Various particulate components, especially water-soluble ions and inorganic elements such as Ag, As, Cd, Hg, Ni, Sb, Se, Sn, and Tl, were significantly associated with higher estradiol levels. These results have implications for

future public health strategies to reduce the health risks related to PM<sub>2.5</sub> exposure in postmenopausal women.

Recent studies (1–5) have indicated an association between short-term PM<sub>2.5</sub> exposure and disruptions in reproductive hormone levels within China, particularly affecting estradiol, progesterone, and the T/E2 ratio (1). Consistent with prior research, our study found a significant positive correlation between PM<sub>2.5</sub> exposure with a 3-day lag and elevated estradiol levels. While some research has reported nonsignificant or negative associations between PM<sub>2.5</sub> exposure and sex hormone levels (3), these discrepancies may be attributable to varying PM<sub>2.5</sub> concentration levels, different chemical compositions, and unique characteristics of the study populations (5). It is important to note that the older adults in our study may exhibit increased sensitivity to PM<sub>2.5</sub>-associated health effects due to their generally poorer health status, which could impair their ability to adapt to PM<sub>2.5</sub> exposure (7). Additionally, there was an observed increase in testosterone levels with higher exposure to As, Sb, and Sn, but the statistical significance of these relationships was lost after applying FDR adjustments. It appears that PM<sub>2.5</sub> may stimulate the secretion of estradiol and potentially modulate other sex hormones, such as testosterone, within the normal physiological range. This modulation is particularly relevant among postmenopausal women, considering their testosterone secretion is substantially lower than estradiol.

Several plausible mechanisms have been proposed to explain the adverse effects of PM<sub>2.5</sub> and its components on sex hormones. First, it is suggested that PM<sub>2.5</sub> exposure can stimulate the hypothalamic-pituitary-gonadal (HPG) axis, a key regulator of sex hormone secretion, thus potentially elucidating the observed associations (5). Second, exposure to PM<sub>2.5</sub> and its components may trigger the hypothalamic-pituitary-adrenal (HPA) axis, leading to reduced levels of testosterone and follicle-stimulating hormone (FSH) (8). Lastly, oxidative stress and inflammation pathways activated by PM<sub>2.5</sub> exposure, through a chemokine receptor-dependent mechanism, could contribute to the damage of sex hormones (9–10).

This study is subject to some limitations. First, the utilization of PM<sub>2.5</sub> measurements from monitoring sites as proxies for personal exposure likely led to exposure misclassification. Second, the assessment of sex hormone homeostasis was based on a single blood sample and only two indicators, which may not account for significant intra-individual variability given

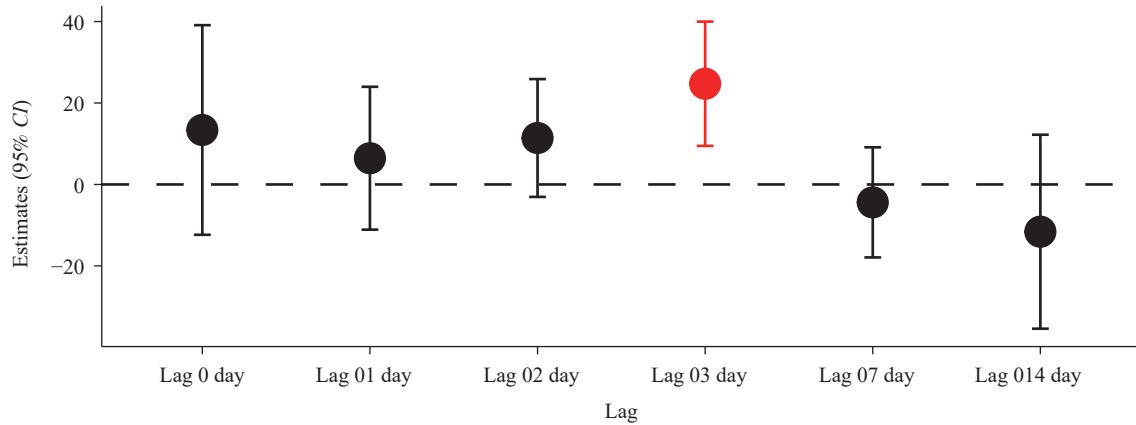


FIGURE 1. Changes (95% CIs) in estradiol associated with an IQR increase in PM<sub>2.5</sub> mass concentrations over various multiple-day lag periods in Beijing, Tianjin, and Hebei PLADs, China, 2018–2019.

Note: A significant association ( $P < 0.05$ ) was indicated by a red dot for confidence intervals (as bars), and black dots indicated statistically insignificant. Adjusted covariates include age, monitoring site, income level, education level, marital status, habitation status, smoking, drinking, vegetarian diet, nutrient supplements, physical exercise, BMI, temperature, relative humidity, ozone, and NO<sub>2</sub>.

Abbreviation: CI=confidence interval; IQR=interquartile range; PLADs=provincial-level administrative divisions; NO<sub>2</sub>=nitrogen dioxide; BMI=body mass index.

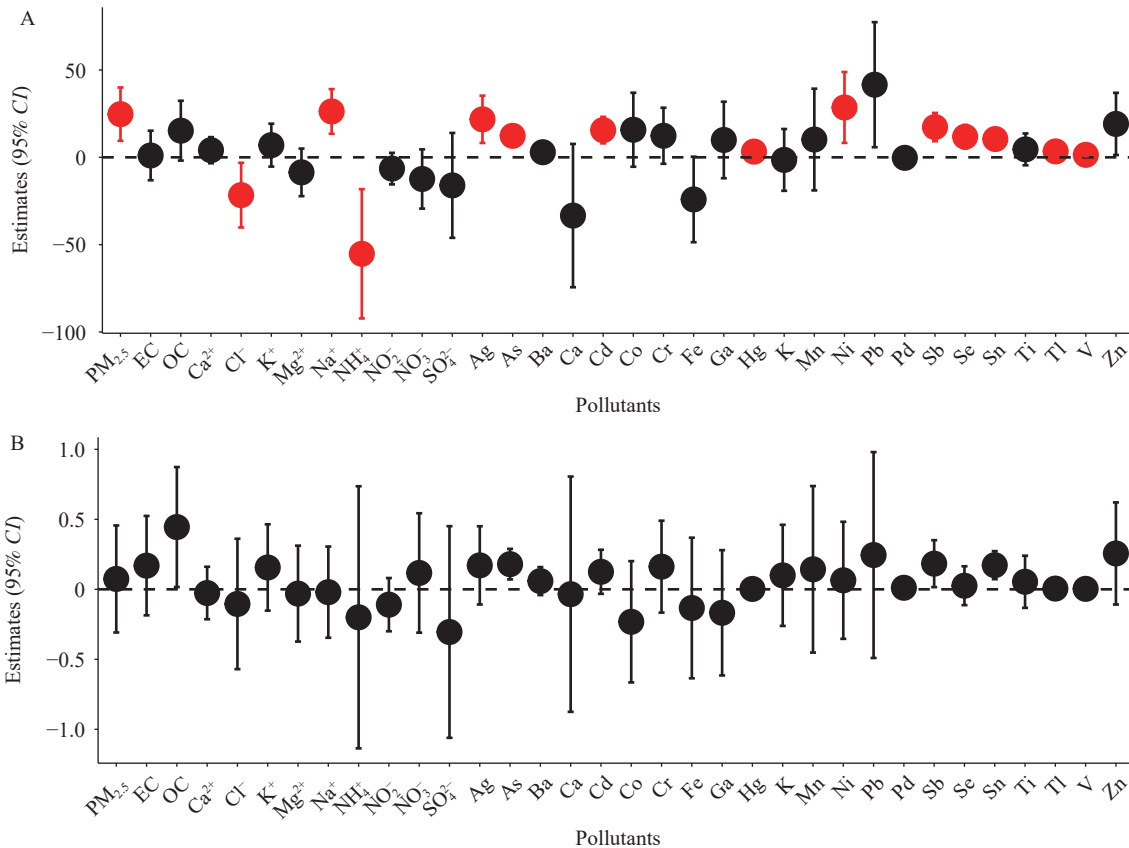


FIGURE 2. Changes (95% CIs) in sex hormones associated with an IQR increase in PM<sub>2.5</sub> and its constituents at a 3-day lag concentration prior to the investigation in Beijing, Tianjin, and Hebei PLADs, China, 2018–2019.

Note: Adjusted covariates in this study encompass various factors such as age, monitoring site, income level, education level, marital status, habitation status, smoking, drinking, vegetarian diet, nutrient supplements, physical exercise, BMI, temperature, relative humidity, ozone, and NO<sub>2</sub>. Any statistically significant associations with adjusted  $P$ -values for FDR  $< 0.05$  were indicated by red dots along with error bars; and black dots indicated statistically insignificant with adjusted  $P$ -values for FDR.

Abbreviation: E<sub>2</sub>=estradiol; T=testosterone; CI=confidence interval; IQR=interquartile range; BMI=body mass index; NO<sub>2</sub>=nitrogen dioxide; FDR=false discovery rate.

the sensitivity of serum sex hormones to environmental exposures. Third, the cross-sectional design precludes causal inferences and raises concerns about reverse causation due to the concurrent measurement of air pollution exposure and health outcomes. Fourth, potential unmeasured confounders, such as the participants' health status and external sources of estrogen-like soybean milk or bird's nest, may have influenced the results. Although the sample size was adequate to detect an association between PM<sub>2.5</sub> exposure and elevated sex hormone levels, it was not sufficiently large to uphold the association in the face of multiple comparisons. Fifth, the specificity of the results is somewhat limited, as other unaccounted variables may impact the findings and restrict the determination of a chronological relationship. Sixth, considering the epidemiological nature of the study, pinpointing a lag time between the impact on the organ system and the production and metabolism of hormones is challenging and may require further inquiry through animal studies underpinned by existing biological and epidemiological knowledge. Finally, the study focused on Chinese postmenopausal women with an average age of 68.9, meaning the findings may not extend to other ethnicities or younger age demographics.

In conclusion, this study presented the initial epidemiological evidence suggesting that even brief exposure to PM<sub>2.5</sub> could lead to a delayed increase in estradiol levels in postmenopausal women. Components of PM<sub>2.5</sub>, particularly heavy metals like Ag, As, Cd, Hg, Ni, Sb, Se, Sn, Tl, and V, may be the primary contributors to elevated estradiol levels. However, no significant link between PM<sub>2.5</sub> and its components with testosterone levels was observed. These results underscore the importance of targeted interventions to minimize PM<sub>2.5</sub> exposure in postmenopausal women. Recommendations include reducing exposure to water-soluble ions and heavy metals, improving health literacy, conducting additional studies, implementing strategies to decrease PM<sub>2.5</sub> levels, and promoting personal protective measures.

**Conflicts of interest:** No conflicts of interest.

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# Corresponding author: Xiaoming Shi, shixm@chinacdc.cn.

<sup>1</sup> Chinese Research Academy of Environmental Sciences, Beijing, China; <sup>2</sup> Collaborative Innovation Center of Atmospheric Environment and Equipment Technology, Jiangsu Key Laboratory of Atmospheric Environment Monitoring and Pollution Control (AEMPC), Nanjing University of Information Science & Technology, Nanjing City, Jiangsu Province, China; <sup>3</sup> China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China; <sup>4</sup> Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, and Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China; <sup>5</sup> National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China.

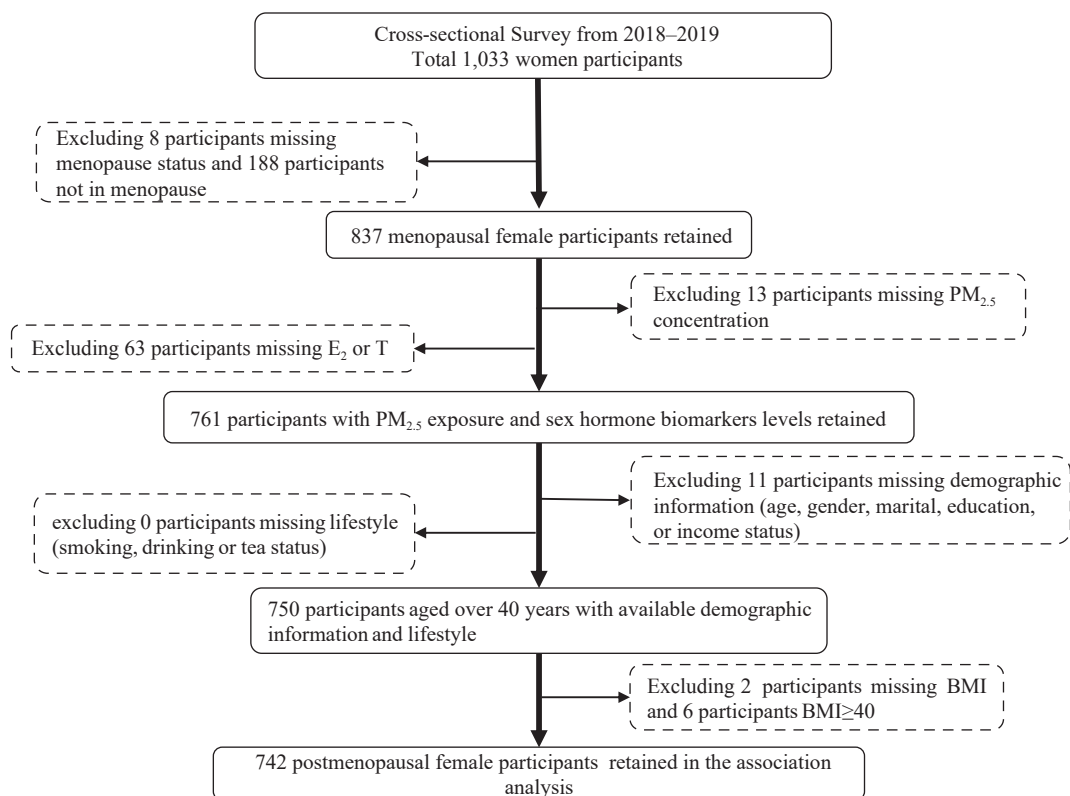
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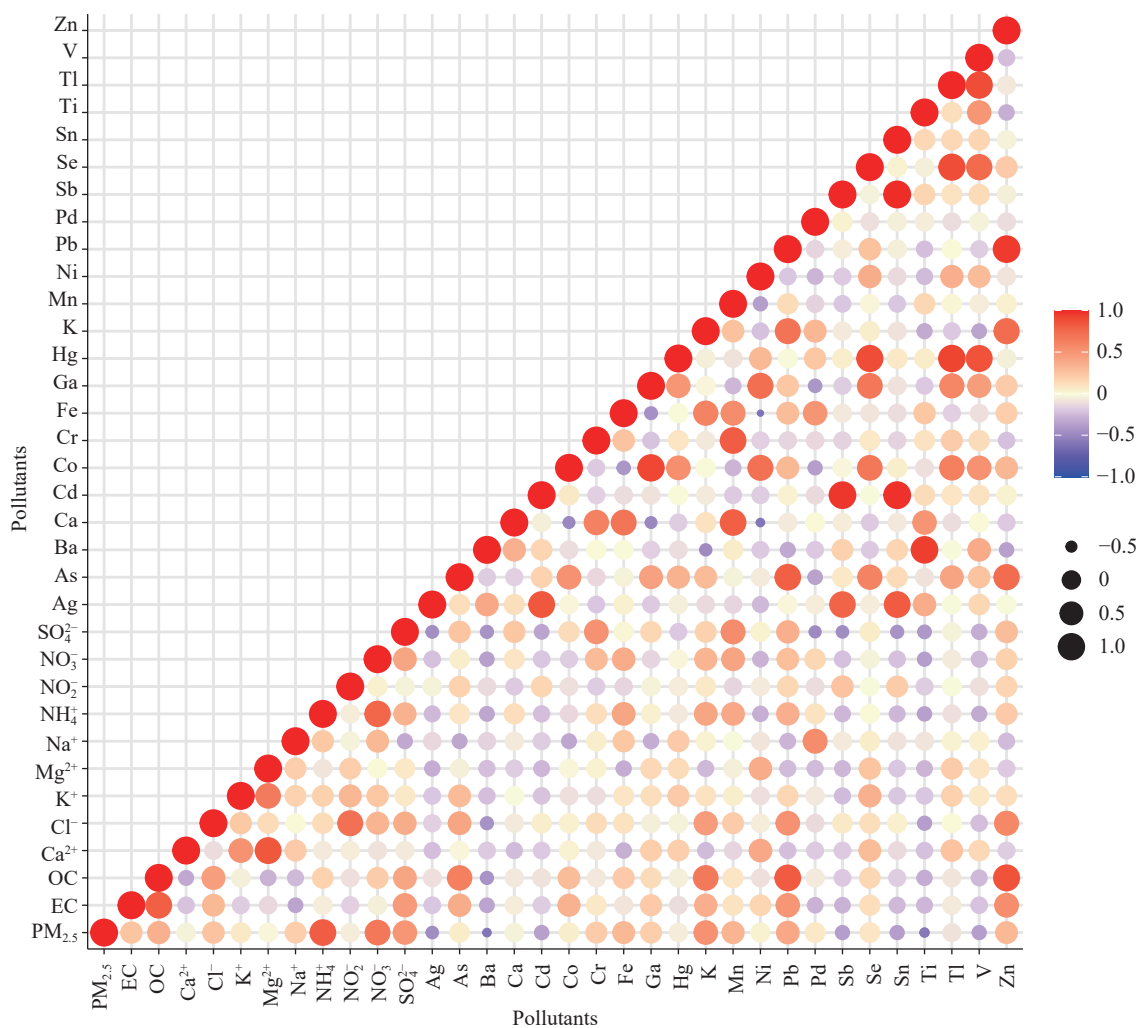
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## SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. Flow chart of study inclusion and exclusion criteria.  
Abbreviation: E<sub>2</sub>=estradiol; T=testosterone; BMI=body mass index.



SUPPLEMENTARY FIGURE S2. Spearman's correlation matrix of 3-day average concentrations of PM<sub>2.5</sub> and its constituents.

Note: The magnitude of the Spearman's correlation coefficient was denoted by the size of dots, and black has no meaning. The color of dots from blue to red represents the change in the correlation from negative to positive.

SUPPLEMENTARY TABLE S1. Statistical description of the concentrations of PM<sub>2.5</sub>, its chemical constituents, gaseous pollutants, and meteorological factors in Beijing, Tianjin, and Hebei PLADs, China, 2018–2019.

Exposures	Min	Max	Median	Mean	SD	IQR
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	14.9	121.3	66.9	67.3	27.3	38.6
Carbon fractions (µg/m <sup>3</sup> )						
EC	0.86	29.40	2.97	6.60	6.84	8.17
OC	1.83	36.30	9.27	12.00	8.33	10.40
Water-soluble ions (µg/m <sup>3</sup> )						
Ca <sup>2+</sup>	0.12	16.10	0.58	1.86	3.39	1.87
Cl <sup>-</sup>	0.33	8.91	2.35	2.41	1.82	2.49
K <sup>+</sup>	0.06	5.60	0.68	0.96	1.04	1.17
Mg <sup>2+</sup>	0.01	1.43	0.08	0.22	0.31	0.22
Na <sup>+</sup>	0.15	5.65	0.71	0.98	0.91	0.49
NH <sub>4</sub> <sup>+</sup>	1.63	23.90	8.35	9.45	5.50	7.00
NO <sub>2</sub> <sup>-</sup>	0.04	7.78	0.17	1.03	1.54	1.57
NO <sub>3</sub> <sup>-</sup>	1.47	41.40	9.07	13.00	9.87	13.30
SO <sub>4</sub> <sup>2-</sup>	0.46	23.20	10.27	9.20	5.36	8.37
Inorganic elements (ng/m <sup>3</sup> )						
Ag	0.50	85.50	4.53	10.70	16.90	13.70
As	0.33	159.00	9.37	17.00	26.00	12.70
Ba	5.36	287.00	23.10	43.70	67.70	17.70
Ca	16.60	999.00	451.70	479.00	251.00	379.00
Cd	0.04	104.00	4.18	11.70	21.00	9.61
Co	0.01	44.60	3.30	4.71	4.83	7.41
Cr	0.28	36.10	5.55	7.59	7.64	4.82
Fe	36.60	1,603.00	495.20	561.00	287.00	374.00
Ga	0.01	40.60	3.49	5.09	4.44	6.75
Hg	0.01	48.60	0.33	0.91	3.63	0.77
K	0.75	1,648.00	838.80	853.00	364.00	419.00
Mn	0.71	146.00	56.70	66.50	30.30	41.00
Ni	0.03	64.60	5.31	9.12	10.70	8.66
Pb	21.40	226.00	66.90	82.70	50.10	66.00
Pd	0.50	1,452.00	2.12	182.00	473.00	6.99
Sb	0.50	290.00	13.80	39.70	67.30	36.20
Se	1.29	84.60	7.37	7.66	6.21	3.87
Sn	0.50	330.00	15.80	35.50	64.90	24.30
Ti	2.86	205.00	35.80	49.50	47.90	23.20
Tl	0.01	109.00	2.01	2.57	7.94	1.61
V	0.06	113.00	0.68	2.60	9.01	0.66
Zn	76.80	744.00	238.70	282.00	169.00	139.00
Meteorological factors						
Temperature (°C)	-11.60	9.03	4.33	3.96	4.60	4.15
Relative humidity (%)	29.00	82.50	61.00	59.70	12.40	18.20
Gaseous pollutants (µg/m <sup>3</sup> )						
NO <sub>2</sub>	26.1	81.0	56.4	55.4	15.4	24.1
O <sub>3</sub>	10.8	61.7	21.5	26.2	13.6	8.8

Abbreviation: PLADs=provincial-level administrative divisions; Min=minimum value; Max=maximum value; SD=standard deviation; IQR=interquartile range; EC=elemental carbon; OC=organic carbon; NO<sub>2</sub>=nitrogen dioxide; O<sub>3</sub>=ozone.



SUPPLEMENTARY TABLE S2. Betas and 95% CIs for E<sub>2</sub> based on each interquartile range (IQR) increase in the concentrations of PM<sub>2.5</sub> and its constituents.

Exposures	Beta (95% CI)	P	FDR
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	24.72 (9.47, 39.98)	<0.01	0.01
Carbon fractions (µg/m <sup>3</sup> )			
EC	1.07 (-13.11, 15.25)	0.88	0.92
OC	15.26 (-1.85, 32.37)	0.08	0.15
Water-soluble ions (µg/m <sup>3</sup> )			
Ca <sup>2+</sup>	4.1 (-3.38, 11.57)	0.28	0.38
Cl <sup>-</sup>	-21.63 (-40.13, -3.12)	0.02	0.05
K <sup>+</sup>	6.97 (-5.3, 19.25)	0.27	0.36
Mg <sup>2+</sup>	-8.61 (-22.23, 5.01)	0.22	0.31
Na <sup>+</sup>	26.27 (13.48, 39.05)	<0.01	<0.01
NH <sub>4</sub> <sup>+</sup>	-55.22 (-92.21, -18.24)	<0.01	0.01
NO <sub>2</sub> <sup>-</sup>	-6.45 (-15.47, 2.57)	0.16	0.24
NO <sub>3</sub> <sup>-</sup>	-12.39 (-29.35, 4.56)	0.15	0.23
SO <sub>4</sub> <sup>2-</sup>	-16.06 (-46.07, 13.96)	0.29	0.39
Inorganic elements (ng/m <sup>3</sup> )			
Ag	21.76 (8.21, 35.3)	<0.01	0.01
As	12.32 (7.04, 17.6)	<0.01	<0.01
Ba	2.93 (-1.97, 7.82)	0.24	0.34
Ca	-33.34 (-74.36, 7.67)	0.11	0.18
Cd	15.59 (8.01, 23.18)	<0.01	<0.01
Co	15.79 (-5.39, 36.97)	0.14	0.22
Cr	12.35 (-3.69, 28.39)	0.13	0.21
Fe	-24.11 (-48.59, 0.37)	0.05	0.10
Ga	9.93 (-11.97, 31.84)	0.37	0.46
Hg	3.27 (1.14, 5.4)	<0.01	0.01
K	-1.48 (-19.17, 16.21)	0.87	0.91
Mn	10.18 (-18.92, 39.29)	0.49	0.58
Ni	28.55 (8.26, 48.83)	0.01	0.02
Pb	41.58 (5.78, 77.38)	0.02	0.05
Pd	-0.29 (-2.22, 1.64)	0.77	0.85
Sb	17.32 (9.24, 25.41)	<0.01	<0.01
Se	11.8 (5.09, 18.5)	<0.01	<0.01
Sn	10.46 (5.6, 15.33)	<0.01	<0.01
Ti	4.55 (-4.55, 13.66)	0.33	0.42
Tl	3.38 (1.39, 5.37)	<0.01	<0.01
V	1.42 (0.61, 2.24)	<0.01	<0.01
Zn	19.13 (1.33, 36.93)	0.04	0.07

Abbreviation: E<sub>2</sub>=estradiol; CI=confidence interval.