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$PM_{2.5}$ constituent exposures and maternal circulatory homocysteine in early pregnancy

Xuesong Li[1†], Mingyue Ran[1†], Mengyuan Wang[1], Ao Liu[1], Bin Qiao[2], Bin Han[3], Jianmei Wang[1], Zhipeng Bai[3,4] and Yujuan Zhang[1,3*]

Abstract

Background Elevated homocysteine (Hcy) is a pathogenic mechanism of adverse pregnancy outcomes and $PM_{2.5}$–induced cardiovascular diseases. We investigated the associations of fine particulate matter ($PM_{2.5}$) and chemical constituent exposures with maternal circulatory Hcy in early pregnancy.

Methods Serum Hcy and 5-methyltetrahydrofolate in 324 women with pregnancy (162 normal early pregnancy [NEP] and 162 early pregnancy loss [EPL]) were measured by ultra-performance liquid chromatography-tandem triple quadrupole mass spectrometry. Daily exposures to $PM_{2.5}$ and constituents (black carbon [BC], organic matter, nitrate, ammonium, and sulfate) were accessed using data of Tracking Air Pollution in China platform. Nonlinear and linear associations of average pollutant exposures during the post-conception period with serum Hcy were estimated using generalized additive models and multivariable linear regression models, respectively. Weekly cumulative and distributed lag associations between pollutant exposures within three months before serum collection and Hcy were analyzed by distributed lag nonlinear models combined with multivariable linear regression models. Sensitivity analyses were conducted using constituent residuals instead of constituent concentrations.

Results Three–month $PM_{2.5}$ and the five constituent exposures were associated with elevated serum Hcy in all participants, EPL group, and NEP group, with 3–12 weeks before serum collection being the susceptible exposure time windows. Pollutants–related Hcy were generally higher in EPL group than in NEP group. Higher post-conception $PM_{2.5}$, BC, and sulfate exposures increased serum Hcy in lower but not in higher 5-methyltetrahydrofolate subgroup. Sulfate was the highest risk constituent with residual–related increased Hcy. BC residuals of both post-conception and three–month periods increased Hcy in EPL group but not in NEP group.

Conclusions Maternal circulatory Hcy in early pregnancy increased with $PM_{2.5}$ and constituent exposures, with sulfate being the highest risk constituent. BC–related increased Hcy may induce EPL.

Trial registration The study protocol was registered for clinical trials (ChiCTR1900028619) on December 29, 2019.

Keywords Air pollution, Chemical component, Folic acid, Miscarriage, Particulate matter, Pregnancy complication

†Xuesong Li and Mingyue Ran contributed equally to this work.

*Correspondence:
Yujuan Zhang
zhangyj@tmu.edu.cn
[1]Department of Family Planning, The Second Hospital of Tianjin Medical University, Tianjin 300211, China
[2]School of Chemical Engineering, Tianjin University, Tianjin 300072, China
[3]State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, Beijing 100012, China
[4]Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, WA 98195, USA

Background

Air pollution has become one of the significant global concern due to the adverse impacts on human health. Significantly, the leading risk factor for the global burden of disease in 2021 was particulate matter pollution [1]. Ambient fine particulate matter ($PM_{2.5}$) increases the risks of not only respiratory diseases but also cardiovascular diseases and congenital heart defects [2, 3]. Homocysteine (Hcy) is an important metabolite in methionine metabolism, and the remethylation of Hcy depends on 5-methyltetrahydrofolate (5-MeTHF) which is generated by folate cycle [4]. Elevated Hcy plays an independent risk role on cardiovascular diseases [5]. Furthermore, elevated Hcy is also regarded as a potential pathogenic mechanism of cardiovascular diseases induced by $PM_{2.5}$ [6–9].

Numerous studies have found that $PM_{2.5}$ increases the risks of adverse pregnancy outcomes such as preterm birth, low birth weight, hypertensive disorders of pregnancy (HDP), and gestational diabetes mellitus [10, 11]. In addition, our previous studies suggested that ambient $PM_{2.5}$ exposure could induce maternal circulatory oxidative stress and inflammation during the first trimester, and increase the risk of human early pregnancy loss (EPL) [12–15]. EPL is a nonviable intrauterine pregnancy in the first trimester, and accounts for approximately 80% of pregnancy loss [16]. Early pregnancy, i.e., the first trimester, is a crucial period for placentation and embryogenesis, and is also important for long-term health of offspring [17, 18]. In addition, recent studies discovered that black carbon (BC), a main constituent of $PM_{2.5}$, was detected in maternal blood, cord blood, fetal side of human placenta, and fetal organs [19, 20]. More and more researches explored and revealed the adverse constituent effects on pregnancy outcomes and offspring health [21–23]. Consequently, exploring the influences and mechanisms of $PM_{2.5}$ and constituent exposures in special population of early pregnant women is very necessary to provide evidence and guidance for preventing adverse health outcomes.

Epidemiological studies regarding to the effects of $PM_{2.5}$ on Hcy during pregnancy remained limited. Hu et al. (2023) found that prenatal exposure to ambient $PM_{2.5}$ increased the levels of Hcy in maternal blood collected in the third trimester [24]. Hogervorst et al. (2019) reported that maternal $PM_{2.5}$ exposure increased the cord blood Hcy levels probably by inducing oxidative stress [25]. It is worth noting that high levels of maternal blood Hcy in early pregnancy can increase the risk of miscarriage, and decrease placental volume and utero–placental vascular volume [26]. However, the effects of $PM_{2.5}$ on maternal circulatory Hcy measured in early pregnancy is unknown. Additionally, whether there is a difference in the association of $PM_{2.5}$ exposure with serum Hcy between woman with normal early pregnancy (NEP) and woman with EPL remains to be studied.

Therefore, we estimated the associations of $PM_{2.5}$ and constituent exposures with maternal serum Hcy in NEP group and EPL group to fill the gaps. We hypothesized that $PM_{2.5}$ and specific chemical constituents are associated with increased serum Hcy in early pregnant women, and the associations in the EPL group are stronger than that in the NEP group. To our knowledge, this is the first study to explore the associations of $PM_{2.5}$ and constituent exposures with maternal circulatory Hcy in early pregnancy.

Methods

Study participants

This study was conducted between January 2020 and January 2024. We recruited 324 women with early pregnancy (162 EPL and 162 NEP) at the Second Hospital of Tianjin Medical University in Tianjin, China. The matching, diagnosis, inclusion, and exclusion criteria for the participants were consistent with our previous study and were described in detail in Supplementary Material of this study [14]. In particular, to avoid exposure misclassification, women who changed their residential address within one year before serum collection were excluded. Each participant signed an informed consent and answered a pre-designed questionnaire. Demographic characteristics, pregnancy–related information, and residential address of the participant were collected based on the questionnaire. The ovulation date of each participant was estimated using the method previously described [14]. The study protocol was approved by the Medical Ethics Committee of the hospital recruiting participants (No.KY2019K044) and registered for clinical trials (ChiCTR1900028619).

Serum Hcy and 5-MeTHF determinations

Each participant's fasting peripheral blood was collected using an anticoagulant–free vacuum blood collection tube and centrifuged. Then the serum was extracted and stored at − 80 ℃. The serum Hcy and 5-MeTHF were quantified using ultra-performance liquid chromatography-tandem triple quadrupole mass spectrometry (UPLC–MS/MS) [27, 28]. Briefly, appropriate amounts of Hcy (Sigma-Aldrich, Germany) and 5-MeTHF (Toronto Research Chemicals, Canada) standards were added to ultra-pure water and methanol, respectively, to obtain the standard stock solutions at concentrations of 2 mg/mL for Hcy and 1.3 mg/mL for 5-MeTHF. The standard working solutions were prepared by diluting the standard stock solutions with ultra-pure water in concentration ranges from 0.05 to 2 μg/mL for Hcy and from 2.6 to 260 ng/mL for 5-MeTHF.

Then 400 μL ice-cold methanol, 50 μL working standard mix solutions, 50 μL phosphate buffer solution, and 20 μL internal standard mix solutions were sequentially added to a 96-well protein precipitation plate (Cleanert® Protein Precipitation Plate). All the solutions were mixed by shaking for 5 min using a 96-well plate shaker. The protein precipitation and matching collection plate were transferred to the positive pressure device, and the solutions after protein precipitation were collected under positive pressure of nitrogen. The positive pressure range was controlled at 3–6 psi. Subsequently, the supernatants in the collection plate were dried under a gentle nitrogen flow at 50 ℃. The residues were dissolved (in 30 μL of ultra-pure water), vortexed, and centrifuged. After that, 10 μL of each supernatant was transferred into a 250 μL micro-insert with mandrel which was put into an autosampler vial for UPLC–MS/MS.

Electrospray ionization source was used in positive mode with multiple reaction monitoring scan. Sample solution was injected into a ACQUITY BEH C18 column, mobile phase A was water containing 0.1% (v/v) formic acid and mobile phase B was methanol containing 0.1% (v/v) formic acid. Elution gradient was used and the injection volume was 5 μL. The preprocessing methods of serum samples were consistent with that of the above-mentioned working standard mix solutions, except that 50 μL phosphate buffer solution was replaced by 50 μL ultra-pure water. Based on the calibration curves generated with six concentrations of the two standards, the serum Hcy and 5-MeTHF concentrations of each participant were obtained.

Exposure Estimation

The spatiotemporal daily exposures to $PM_{2.5}$ and constituent were predicted using the data set of Tracking Air Pollution in China (TAP) platform (http://tapdata.org.cn) , and matching with each participant's residential address geocoded as longitude and latitude [29, 30]. In brief, 1 km resolution of $PM_{2.5}$ was estimated under the TAP framework by integrating high-resolution satellite retrievals, TAP $PM_{2.5}$ products with 10 km resolution, vegetation index, and land use data [31]. Furthermore, chemical constituents (BC, organic matter [OM], nitrate [NO_3^-], ammonium [NH_4^+], and sulfate [SO_4^{2-}]) with 10 km resolution were derived based on $PM_{2.5}$ data and conversion factors [32].

To explore post-conception and weekly exposure–effect associations, we set up two types of exposure time windows in this study. Average $PM_{2.5}$ and constituent exposures from ovulation to serum collection, i.e., during the post-conception period, and weekly pollutant exposures during lag 1–13 weeks (i.e., the 1st to 13th week before serum collection, nearly three months) were estimated. In addition, during the corresponding exposure time windows, data from Tianjin Meteorological Service were used to calculate average temperature and relative humidity.

Statistical analysis

The demographic characteristics, levels of serum Hcy and 5-MeTHF, and average $PM_{2.5}$, constituents, temperature, and relative humidity were compared between EPL and NEP groups using the paired *t*-, marginal homogeneity, McNemar, or Wilcoxon signed rank test according to the data types. Serum Hcy and 5-MeTHF were natural logarithm transformed to approximate the normal distribution. Spearman correlation coefficients were calculated among pollutant exposures separately during the post-conception period and 13 weeks before serum collection.

Nonlinear associations between average pollutant exposures during the post-conception period and the natural logarithm of serum Hcy (LnHcy) were described using generalized additive models [33, 34]. The confounders adjusted in all statistical models in this study included all demographic characteristics in Table 1, the natural logarithm of serum 5-MeTHF (Ln5-MeTHF), temperature, relative humidity, and group (EPL or NEP). Then, based on the nonlinear associations separately described in EPL and NEP groups, the estimated LnHcy and its 95% confidence intervals (*CI*s) associated with representative percentiles of pollutant concentrations were compared between the two groups using student's *t*-test with unequal variances [15].

Subsequently, we estimated the linear associations of an interquartile range (IQR) increase in post-conception $PM_{2.5}$ and constituent exposures with LnHcy in all participants and the two groups using multivariable linear regression models. Therefore, the regression coefficients (βs) and 95% *CI*s of the models were interpreted as percentage changes in serum Hcy, calculated as $(e^{\beta} - 1) \times 100$ [35, 36]. The IQRs of $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 29, 1.1, 5.8, 6.7, 3.6, and 2.5 $\mu g/m^3$, respectively. In addition, to investigate the independent effect of each constituent holding $PM_{2.5}$ constant, sensitivity analyses were conducted using constituent residuals instead of constituent concentrations [35–37]. The constituent residuals were calculated by constructing linear regression models which used $PM_{2.5}$ as the independent variable and concentration of each constituent as the dependent variable.

Moreover, binary concentrations of $PM_{2.5}$ and constituents were entered into the multivariable linear regression models to compare the difference between LnHcy associated with higher and lower pollutant exposures during the post-conception period. And then, forest plots of subgroup analyses were used to present the specific associations between LnHcy and binary pollutant exposures in different subgroups based on group (EPL or NEP), serum

Table 1 Demographic characteristics and serum determinations

Parameter	EPL ($n=162$)	NEP ($n=162$)	*p*-value
Maternal age (years) (mean ± SD)	32.2 ± 4.5	31.9 ± 4.5	0.226
Gestational age (days after ovulation) (mean ± SD)	48.6 ± 10.5	35.1 ± 5.9	< 0.001
Body mass index (mean ± SD)	22.5 ± 3.0	22.2 ± 3.2	0.487
Gravidity (times) [*n* (%)]			0.537
≤ 2	71 (43.8)	62 (38.3)	
3–4	73 (45.1)	87 (53.7)	
≥ 5	18 (11.1)	13 (8.0)	
Parity (times) [*n* (%)]			< 0.001
0	55 (34.0)	29 (17.9)	
1	88 (54.3)	92 (56.8)	
≥ 2	19 (11.7)	41 (25.3)	
Maternal education [*n* (%)]			0.168
High school or lower	43 (26.5)	48 (29.6)	
College	104 (64.2)	107 (66.0)	
Higher than college	15 (9.3)	7 (4.3)	
Family monthly income per capita (¥) [*n* (%)]			0.237
< 5000	30 (18.5)	39 (24.1)	
5000–7500	59 (36.4)	58 (35.8)	
> 7500	73 (45.1)	65 (40.1)	
Interior renovation either at home or work [*n* (%)]			< 0.001
≥ 1 year ago	147 (90.7)	121 (74.7)	
< 1 year ago	15 (9.3)	41 (25.3)	
Occupational exposure [*n* (%)]			0.523
No	149 (92.0)	153 (94.4)	
Yes	13 (8.0)	9 (5.6)	
Alcohol consumption [*n* (%)]			0.066
No	141 (87.0)	127 (78.4)	
Yes	21 (13.0)	35 (21.6)	
Active smoking [*n* (%)]			< 0.001
No	148 (91.4)	119 (73.5)	
Yes	14 (8.6)	43 (26.5)	
Passive smoking [*n* (%)]			0.073
No	78 (48.1)	94 (58.0)	
Yes	84 (51.9)	68 (42.0)	
Serum Hcy (ng/mL) (Median [IQR])	455.7 (253.8)	416.2 (197.6)	0.002
Serum 5-MeTHF (ng/mL) (Median [IQR])	62.3 (18.1)	54.0 (9.8)	< 0.001
LnHcy (mean ± SD)	6.2 ± 0.4	6.1 ± 0.3	< 0.001
Ln5-MeTHF (mean ± SD)	4.2 ± 0.2	4.0 ± 0.1	< 0.001

Note: 5-MeTHF, 5-methyltetrahydrofolate; EPL, early pregnancy loss; Hcy, homocysteine; IQR, interquartile range; Ln5-MeTHF, the natural logarithm of serum 5-MeTHF; LnHcy, the natural logarithm of serum Hcy; NEP, normal early pregnancy; SD, standard deviation

5-MeTHF (higher or lower), and nine categorical variables in Table 1. The cumulative and distributed lag associations of $PM_{2.5}$ and constituent exposures during lag 1–13 weeks with serum Hcy were analyzed by distributed lag nonlinear models (DLNMs) combined with multivariable linear regression models separately in all participants, EPL group, and NEP group [38]. The constituent residuals were also used to estimate the independent cumulative associations of 13–week constituent exposures with serum Hcy. All statistical analyses were based on SPSS 25.0 and R 4.2.2.

Results

Supplementary Material, Fig. S1 shows the residential distribution of 324 participants. Demographic characteristics and serum determinations are provided in Table 1. Compared to NEP group, EPL group showed a lower parity, longer gestational age, and lower proportion of recent interior renovation and active smoking, because most of the participants in EPL group originally intended to become pregnant, while the participants in NEP group all had unintended pregnancies. The levels of serum Hcy and 5-MeTHF, as well as LnHcy and Ln5-MeTHF, were higher in EPL group than in NEP group. The high 5-MeTHF level in EPL group was probably due to the fact that some participants supplemented folic acid while preparing for pregnancy or after discovering pregnancy. Therefore, Ln5-MeTHF was adjusted as an important covariate in all statistical models. The detailed sample size and levels of serum Hcy during different gestational weeks are shown in the Supplementary Material, Table S1. There was no significant difference in serum Hcy among different gestational weeks in this study. Nevertheless, gestational age was adjusted as a covariate in all statistical models due to the uncertain potential impact on association estimations.

During the post-conception period, the statistical description of the average estimated $PM_{2.5}$ and constituent exposures reflecting large spatiotemporal variations among all participants is illustrated in Table 2. The 10th, 25th, 50th, 75th, and 90th percentiles of pollutant concentrations in EPL and NEP groups were performed in the Supplementary Material, Table S2. There was no difference in air pollutant exposures, temperature, and relative humidity between the two groups were not, indicating that the exposure baselines were comparable (Supplementary Material, Table S3). Spearman correlation coefficients between $PM_{2.5}$ and constituents were high, with the ranges of 0.84–0.95 during the post-conception period and 0.80–0.93 during 13 weeks before serum collection, respectively (Supplementary Material, Fig. S2). Average estimated constituent residuals during the post-conception period were described in Supplementary Material, Table S4.

Increased $PM_{2.5}$, OM, and SO_4^{2-} exposures during the post-conception period were linearly associated with increased LnHcy in all participants (Fig. 1). However, the associations of BC, NO_3^-, and NH_4^+ with LnHcy were nonlinear, presenting a rapidly increased LnHcy when the three constituent concentrations were lower than their respective medians, and a slowly increased or even slightly decreased LnHcy when they were higher than the

Table 2 Average estimated $PM_{2.5}$ and constituent exposures, temperature, and relative humidity during the post-conception period in all participants ($n = 324$)

Parameter	Minimum	10th percentiles	25th percentiles	Median	75th percentiles	90th percentiles	Maximum	IQR	Mean ± SD
$PM_{2.5}$ (μg/m^3)	15.3	23.7	26.2	35.0	55.3	62.9	75.7	29.1	40.3 ± 15.7
BC (μg/m^3)	0.9	1.1	1.3	1.6	2.4	2.7	3.6	1.1	1.8 ± 0.6
OM (μg/m^3)	4.5	6.0	6.4	8.4	12.2	13.7	17.3	5.8	9.2 ± 3.1
NO_3^- (μg/m^3)	2.5	3.4	4.1	6.4	10.9	13.5	18.0	6.7	7.6 ± 3.9
NH_4^+ (μg/m^3)	2.0	2.6	3.0	4.2	6.6	8.4	11.4	3.6	4.8 ± 2.2
SO_4^{2-} (μg/m^3)	3.5	4.2	4.8	5.7	7.4	8.6	12.8	2.5	6.2 ± 1.8
Temperature (℃)	−4.3	2.8	11.2	20.8	26.5	27.8	28.9	15.2	17.9 ± 9.5
Relative humidity (%)	33.3	42.8	48.0	58.0	67.1	72.8	78.0	19.1	57.5 ± 11.2

medians (Fig. 1). When assessed separately in the two groups, the pollutants and LnHcy in EPL group were all linearly and positively correlated; while in NEP group, only $PM_{2.5}$ and SO_4^{2-} exposures linearly increased LnHcy (Fig. 2).

Furthermore, it seemed that the pollutants–related LnHcy were generally higher in EPL group than in NEP group (Fig. 2). Comparisons of the estimated LnHcy associated with the representative percentiles of pollutant concentrations between the two groups were presented in the Supplementary Material, Table S5. The estimated values of LnHcy associated with the 50th percentiles of $PM_{2.5}$ and OM, 25th and 90th percentiles of BC, 10th and 90th percentiles of NO_3^- and NH_4^+, and 50th, 75th, and 90th percentiles of SO_4^{2-} concentrations were higher in EPL group than in NEP group.

With an IQR increase in post-conception BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} exposures, serum Hcy increased by 22.7%, 19.4%, 13.4%, 13.3%, and 11.7% in all participants and 37.3%, 31.5%, 24.8%, 24.2%, and 18.5% in EPL group, respectively, but did not increase in NEP group (Table 3; Fig. 3A). Sensitivity analyses conducted with constituent residuals revealed that BC, OM, NH_4^+, and SO_4^{2-} exposures were still associated with increased Hcy in all participants (Fig. 3B). The associations of BC, NH_4^+, and SO_4^{2-} exposures with increased Hcy were robust in EPL group. SO_4^{2-} exposure was associated with increased Hcy in NEP group. Additionally, SO_4^{2-} was the constituent with the highest residual–related increased Hcy among the five constituents in all participants and the two groups (Table 3; Fig. 3B).

Analyses with binary pollutant exposures showed that compared to lower exposures, higher BC and SO_4^{2-} exposures were associated with 16% and 12% increase in serum Hcy in all participants, respectively (Figs. 4 and 5). These associations were more obvious in the subgroups with EPL, lower serum 5-MeTHF, and lower proportion of other exposures (i.e., occupational exposure, recent interior renovation, smoking, and alcohol consumption), although the differences between each pair of subgroups were not statistically significant (Figs. 4 and 5). Higher $PM_{2.5}$ exposure also increased Hcy in the subgroups with lower serum 5-MeTHF and no passive smoking (Supplementary Material, Fig. S3). There were no significant associations of binary OM, NO_3^-, and NH_4^+ exposures with serum Hcy in any subgroups of EPL or NEP, lower or higher serum 5-MeTHF, parity, or other exposures (Supplementary Material, Fig. S4–S6).

Distributed lag associations of weekly pollutant exposures within 13–week before serum collection with serum Hcy in all participants, EPL group, and NEP group are presented in the Supplementary Material, Fig. S7–S8. Serum Hcy increased with $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} exposures at lag 4–12, 4–12, 3–12, 3–12, 3–12, and 3–12 weeks in all participants; lag 5–11, 4–11, 4–11, 3–11, 3–11, and 3–12 weeks in EPL group; and lag 4–12, 9–12, 10–13, 4–12, 4–12, and 4–12 weeks in NEP group, respectively. Thirteen–week cumulative $PM_{2.5}$ and the five constituent exposures all increased Hcy in all participants and the two groups (Table 4; Fig. 6A).

Sensitivity analyses conducted with constituent residuals revealed that 13–week cumulative BC, OM, and SO_4^{2-} exposures still increased Hcy in all participants and EPL group, while only SO_4^{2-} exposure was associated with increased Hcy in NEP group (Fig. 6B). Similarly to the post-conception exposure, 13–week cumulative SO_4^{2-} exposure was also associated with the highest residual–related increased Hcy among the five constituent exposures (Table 4; Fig. 6B).

Discussion

We investigated the associations of $PM_{2.5}$ and constituent (BC, OM, NO_3^-, NH_4^+, and SO_4^{2-}) exposures with maternal circulatory Hcy in early pregnancy. Thirteen–week (i.e., three–month) $PM_{2.5}$ and the five constituent exposures increased serum Hcy in all participants, EPL group, and NEP group, with 3–12 weeks before serum collection being the susceptible exposure time windows. Pollutants–related Hcy were generally higher in EPL group than in NEP group. Higher post-conception $PM_{2.5}$, BC, and SO_4^{2-} exposures increased serum Hcy in lower 5-MeTHF subgroup, but not in higher 5-MeTHF

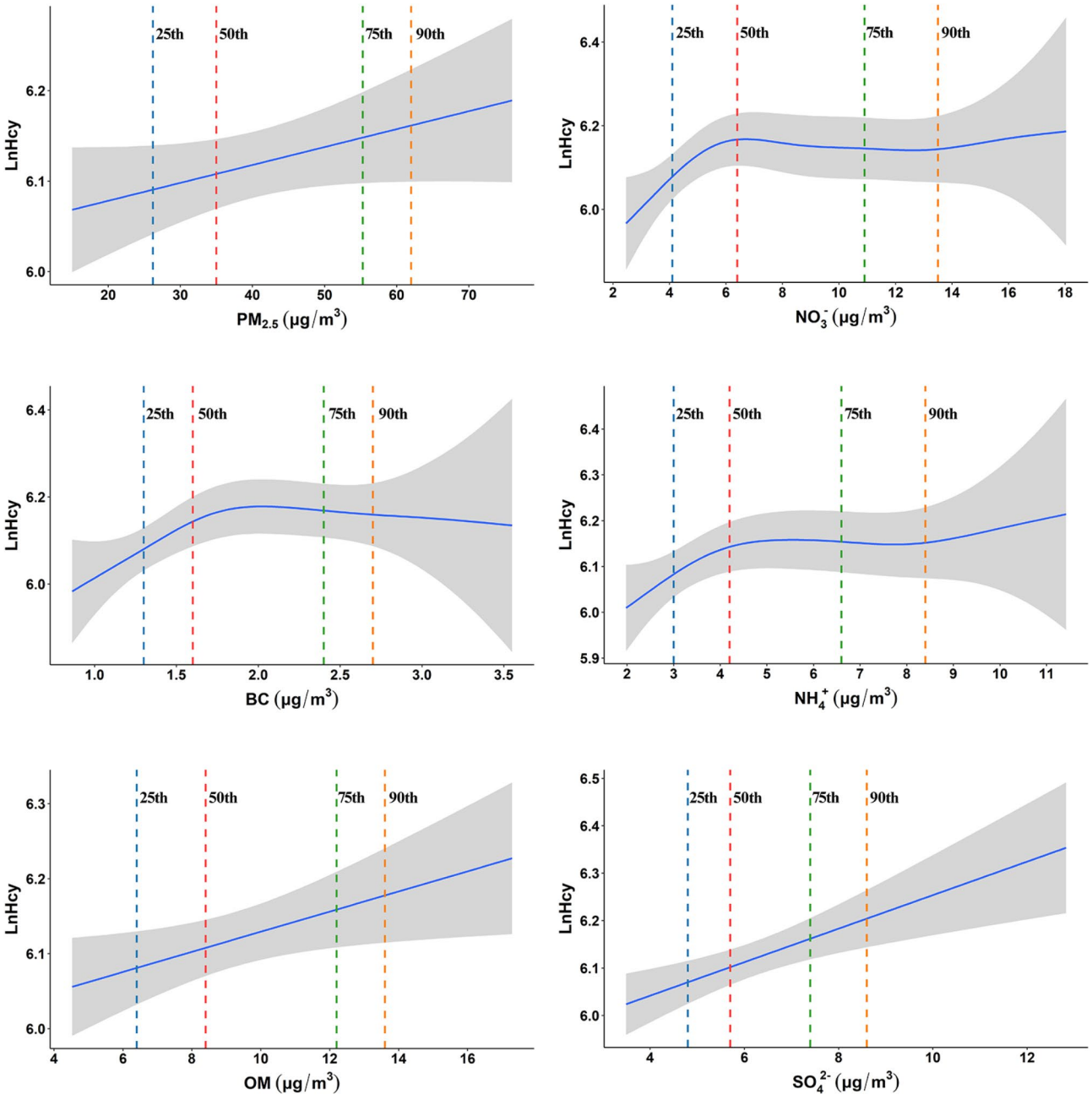

Fig. 1 Associations of average $PM_{2.5}$ and constituent exposures during the post-conception period with the LnHcy in all participants in generalized additive models ($n = 324$). Note: The independent variables included average concentration of $PM_{2.5}$ or each constituent, Ln5-MeTHF, all demographic characteristics presented in Table 1, temperature, relative humidity, and group (EPL or NEP). The intersections of blue, red, green, and orange dashed lines with the X axis represented the 25th, 50th, 75th, and 90th percentiles of pollutant concentrations, respectively

subgroup. SO_4^{2-} was the constituent with the highest and universally significant effects on residual–related increased Hcy among the five constituents in all participants and the two groups. BC was the unique constituent with residual–related increased Hcy in EPL group but not in NEP group, both during the post-conception period and within 13–week before serum collection.

Elevated Hcy was a risk factor for endothelial dysfunction and vascular diseases, which could induce various pregnancy complications such as early pregnancy loss, placental abruption, and HDP [39, 40]. Compared to women with normal pregnancy, women with HDP had higher serum Hcy during early pregnancy [41]. Defective chorionic villous vascularization was associated with

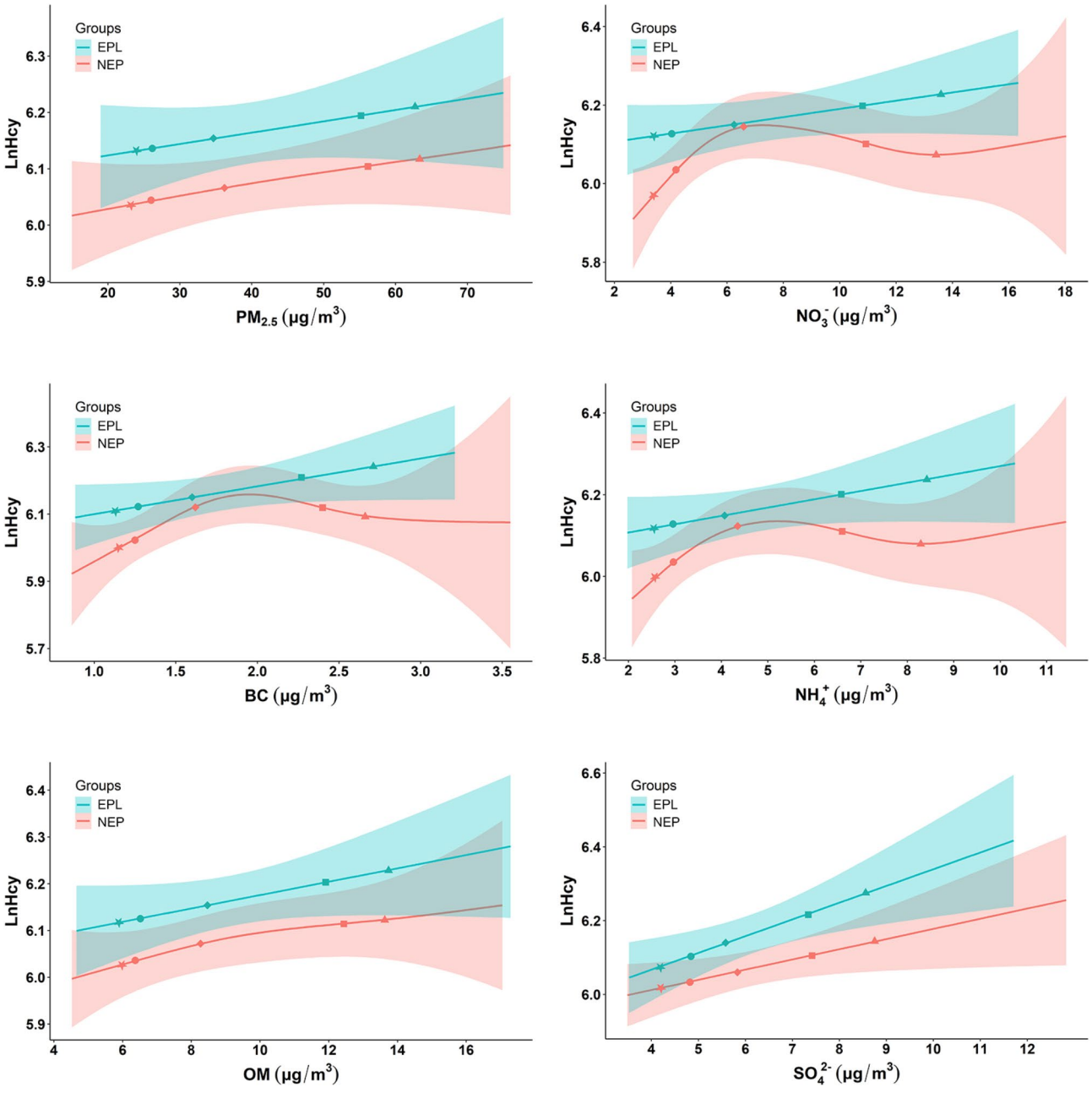

Fig. 2 Associations of average $PM_{2.5}$ and constituent exposures during the post-conception period with the LnHcy in generalized additive models in EPL ($n = 162$) and NEP ($n = 162$) groups. Note: The independent variables included average concentration of $PM_{2.5}$ or each constituent, Ln5-MeTHF, all demographic characteristics presented in Table 1, temperature, and relative humidity. The pentagrams, dots, rhombuses, squares, and triangles represented the estimated LnHcy associated with the 10th, 25th, 50th, 75th, and 90th percentiles of pollutant concentrations, respectively

elevated maternal plasma Hcy [42]. It explained the possible pathogenic mechanism of elevated Hcy on EPL. A matched case-control study found that high plasma Hcy independently increased the risk of EPL occurring at 8–9 weeks of gestation [43]. Consistent with these researches, our study verified the positive association between maternal circulatory Hcy and EPL.

Numerous epidemiological studies demonstrated the positive associations between $PM_{2.5}$ exposure and serum Hcy, but there was large heterogeneity in vulnerable exposure period [6, 7, 9, 44, 45]. Heterogeneity may arise from different study design, sample size, participant characteristics, confounders, exposure assessments, and concentrations, sources, and constituents of $PM_{2.5}$ [46,

Table 3 Associations of an IQR increase in average $PM_{2.5}$ and constituent exposures during the post-conception period with percentage changes in serum Hcy in all participants, EPL group, and NEP group

Parameter	All participants ($n=324$)		EPL ($n=162$)		NEP ($n=162$)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Pollutant concentration						
$PM_{2.5}$	11.5 (-3.9, 29.5)	0.151	20.2 (-6.7, 54.9)	0.153	5.6 (-12.4, 27.2)	0.567
BC	22.7 (7.3, 40.3)	0.003	37.3 (10.6, 70.3)	0.004	9.7 (-8.3, 31.3)	0.310
OM	19.4 (3.9, 37.1)	0.012	31.5 (4.6, 65.5)	0.019	9.2 (-8.7, 30.7)	0.334
NO_3^-	13.4 (1.2, 27.1)	0.031	24.8 (2.6, 51.8)	0.027	6.3 (-7.8, 22.5)	0.397
NH_4^+	13.3 (2.5, 25.2)	0.015	24.2 (4.7, 47.3)	0.013	6.2 (-6.4, 20.4)	0.351
SO_4^{2-}	11.7 (4.9, 19.0)	< 0.001	18.5 (6.8, 31.6)	0.002	6.7 (-1.7, 15.7)	0.118
Constituent residual						
BC	6.8 (2.4, 11.4)	0.002	10.5 (3.3, 18.1)	0.004	2.7 (-3.1, 8.8)	0.369
OM	4.3 (0.4, 8.3)	0.030	5.7 (-0.4, 12.3)	0.067	2.2 (-2.9, 7.6)	0.404
NO_3^-	4.4 (-0.2, 9.3)	0.063	7.3 (-0.5, 15.6)	0.065	2.4 (-3.6, 8.8)	0.440
NH_4^+	5.8 (1.2, 10.5)	0.012	9.2 (1.8, 17.3)	0.015	3.0 (-2.9, 9.3)	0.319
SO_4^{2-}	9.0 (4.6, 13.4)	< 0.001	13.0 (5.9, 20.5)	< 0.001	5.6 (0.1, 11.4)	0.047

Note: The independent variables in the multivariable linear regression models included average concentration of $PM_{2.5}$ or each constituent, or average residual of each constituent, the natural logarithm of serum 5-methyltetrahydrofolate (Ln5-MeTHF), all demographic characteristics presented in Table 1, temperature, relative humidity, and group (EPL or NEP). The IQRs of concentration of $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 29, 1.1, 5.8, 6.7, 3.6, and 2.5 μg/m^3, respectively. The IQRs of residual of BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 0.2, 0.9, 1.5, 0.9, and 1.1, respectively

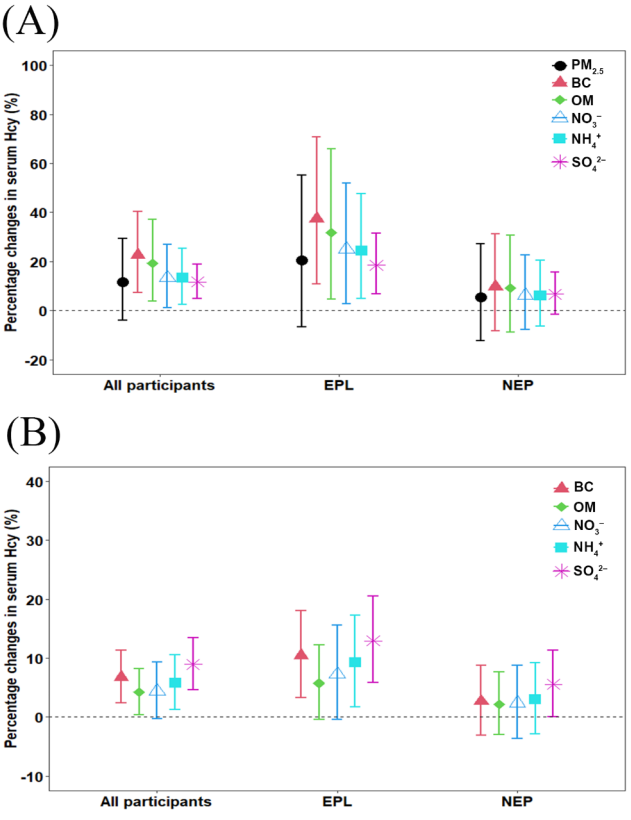

Fig. 3 Associations of an IQR increase in average $PM_{2.5}$ and constituent exposures during the post-conception period with percentage changes in serum Hcy in all participants ($n=324$), EPL group ($n=162$), and NEP group ($n=162$). Note: The independent variables included average concentration of $PM_{2.5}$ or each constituent in (**A**), replaced by residual of each constituent in (**B**), and also included Ln5-MeTHF, all demographic characteristics presented in Table 1, temperature, relative humidity, and group (EPL or NEP). The IQRs of concentration of $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 29, 1.1, 5.8, 6.7, 3.6, and 2.5 μg/m^3, respectively. The IQRs of residual of BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 0.2, 0.9, 1.5, 0.9, and 1.1, respectively

47]. Yang et al. (2021) observed that moving average and daily $PM_{2.5}$ exposures during lag 0–5 days were positively associated with serum Hcy in healthy college students [9]. In village inhabitants around Lake Urmia, six–month exposure to hypersaline $PM_{2.5}$ in polluted region increased plasma Hcy [48]. In women with pregnancy, we found that serum Hcy in early pregnant women including participants in both EPL and NEP groups increased with $PM_{2.5}$ and constituent exposures during three–month especially 3–12 weeks before serum collection. For participants with different gestational weeks, the stages of pregnancy corresponding to the 3–12 weeks before serum collection were different. For instance, for a woman with 12^{+6} gestational weeks, the 3–12 weeks before serum collection meant from the 1st week before ovulation to 10^{+6} gestational weeks. However, for a woman with 5 gestational weeks, it meant from the 9th week before to the 1st week after ovulation. This suggests that women preparing to become pregnant should take precautions against air pollutant exposures as early as possible, rather than after confirmation of pregnancy.

Recent studies have paid close attention to the associations between $PM_{2.5}$ constituents and pregnancy complications. Cai et al. (2020) demonstrated that the constituents, such as BC, NO_3^-, NH_4^+, and SO_4^{2-}, had larger estimated effects than $PM_{2.5}$ mass on preterm birth [49]. Shen et al. (2022) observed that maternal $PM_{2.5}$ exposure increased the risk of HDP, and BC and SO_4^{2-} might play crucial roles [22]. In our study, SO_4^{2-} was the highest risk constituent among the five constituents associated with increased Hcy in all participants and both EPL and NEP groups. Whether SO_4^{2-}–related maternal Hcy increases in early pregnancy induce subsequent

Variables	*n*(%)	Lower BC	Higher BC	*β* (95%*CI*)	*p*-value	*p* for interaction
		LnHcy (Mean ± SD)				
All participants	324 (100.00)	6.05 ± 0.32	6.18 ± 0.34	0.16 (0.05 ~ 0.27)	0.005	
Groups						0.779
NEP	162 (50.00)	6.00 ± 0.28	6.14 ± 0.33	0.12 (-0.04 ~ 0.28)	0.142	
EPL	162 (50.00)	6.10 ± 0.35	6.23 ± 0.35	0.19 (0.02 ~ 0.36)	0.027	
Serum 5-MeTHF						0.666
Lower	162 (50.00)	6.03 ± 0.29	6.17 ± 0.36	0.28 (0.12 ~ 0.44)	<.001	
Higher	162 (50.00)	6.09 ± 0.36	6.19 ± 0.33	0.06 (-0.10 ~ 0.22)	0.442	
Gravidity						0.187
≤ 2	133 (41.05)	6.04 ± 0.34	6.13 ± 0.34	0.17 (-0.01 ~ 0.35)	0.065	
3–4	160 (49.38)	6.04 ± 0.30	6.24 ± 0.34	0.19 (0.04 ~ 0.35)	0.014	
≥ 5	31 (9.57)	6.16 ± 0.32	6.08 ± 0.29	-0.26 (-0.96 ~ 0.44)	0.484	
Parity						0.470
0	84 (25.93)	6.03 ± 0.31	6.24 ± 0.35	0.34 (0.10 ~ 0.57)	0.006	
1	180 (55.56)	6.08 ± 0.31	6.16 ± 0.34	0.07 (-0.07 ~ 0.22)	0.328	
≥ 2	60 (18.52)	6.04 ± 0.34	6.18 ± 0.33	-0.05 (-0.47 ~ 0.36)	0.805	
Maternal education						0.267
High school or lower	91 (28.09)	6.06 ± 0.29	6.28 ± 0.36	0.15 (-0.10 ~ 0.39)	0.243	
College	211 (65.12)	6.05 ± 0.33	6.15 ± 0.33	0.19 (0.05 ~ 0.33)	0.007	
Higher than college	22 (6.79)	6.06 ± 0.34	6.03 ± 0.29	0.33 (-4.28 ~ 4.94)	0.896	
Family monthly income						0.659
≤ 5000	69 (21.30)	6.00 ± 0.27	6.13 ± 0.35	0.14 (-0.15 ~ 0.42)	0.356	
5000–7500	117 (36.11)	6.10 ± 0.33	6.18 ± 0.32	0.21 (0.02 ~ 0.41)	0.037	
≥ 7500	138 (42.59)	6.04 ± 0.33	6.21 ± 0.35	0.13 (-0.05 ~ 0.30)	0.160	
Interior renovation						0.624
≥ 1 year ago	268 (82.72)	6.08 ± 0.33	6.19 ± 0.35	0.17 (0.04 ~ 0.30)	0.009	
<1 year ago	56 (17.28)	5.95 ± 0.24	6.15 ± 0.25	0.21 (-0.04 ~ 0.47)	0.115	
Occupational exposure						0.423
No	302 (93.21)	6.05 ± 0.32	6.17 ± 0.33	0.14 (0.02 ~ 0.25)	0.020	
Yes	22 (6.79)	6.09 ± 0.28	6.33 ± 0.48	-0.21 (-7.53 ~ 7.11)	0.965	
Alcohol consumption						0.966
No	268 (82.72)	6.08 ± 0.33	6.20 ± 0.35	0.16 (0.04 ~ 0.29)	0.012	
Yes	56 (17.28)	5.96 ± 0.27	6.08 ± 0.29	0.10 (-0.18 ~ 0.39)	0.489	
Active smoking						0.410
No	267 (82.41)	6.09 ± 0.33	6.18 ± 0.34	0.17 (0.05 ~ 0.29)	0.008	
Yes	57 (17.59)	5.95 ± 0.26	6.17 ± 0.34	0.02 (-0.31 ~ 0.36)	0.905	
Passive smoking						0.492
No	172 (53.09)	6.04 ± 0.33	6.13 ± 0.33	0.22 (0.05 ~ 0.38)	0.010	
Yes	152 (46.91)	6.08 ± 0.30	6.22 ± 0.34	0.11 (-0.05 ~ 0.27)	0.196	

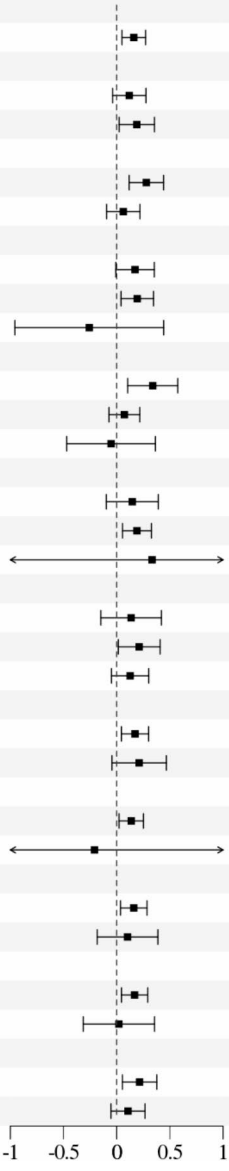

Fig. 4 Forest plot of subgroup analyses on the associations between average BC exposures during the post-conception period (as a binary variable: > or ≤ 1.6 μg/m^3) and percentage changes in serum Hcy. Note: All the associations were adjusted for group (EPL or NEP), Ln5-MeTHF, all demographic characteristics presented in Table 1, temperature, and relative humidity

pregnancy complications, such as HDP, is an issue worthy of future research.

As Bové et al. (2019) confirmed that BC particles could pass human placental barrier, there was an urgent need to explore whether BC exposure increases the risks of pregnancy–related diseases [20]. BC exposure was positively associated with hair cortisol concentration, an important effector of biological stress, in late pregnancy [50]. In addition, BC exposure was also associated with gestational diabetes mellitus [51]. Additionally, BC had relatively higher contribution to $PM_{2.5}$–induced preterm birth [23]. He et al. (2022) reported that the carbonaceous constituents had the largest effect estimates in the associations between preterm birth and $PM_{2.5}$ constituents

Variables	*n*(%)	Lower SO_4^{2-}	Higher SO_4^{2-}	*β* (95%*CI*)	*p*-value	*p* for interaction
		LnHcy (Mean ± SD)				
All participants	324 (100.00)	6.06 ± 0.32	6.18 ± 0.34	0.12 (0.03 ~ 0.21)	0.009	
Groups						0.125
NEP	162 (50.00)	6.02 ± 0.29	6.12 ± 0.33	0.03 (-0.09 ~ 0.15)	0.648	
EPL	162 (50.00)	6.09 ± 0.34	6.25 ± 0.35	0.22 (0.08 ~ 0.36)	0.002	
Serum 5-MeTHF						0.195
Lower	162 (50.00)	6.01 ± 0.27	6.18 ± 0.36	0.24 (0.11 ~ 0.37)	<.001	
Higher	162 (50.00)	6.12 ± 0.36	6.18 ± 0.33	0.04 (-0.08 ~ 0.17)	0.505	
Gravidity						0.088
≤ 2	133 (41.05)	6.06 ± 0.35	6.12 ± 0.34	0.06 (-0.10 ~ 0.21)	0.486	
3–4	160 (49.38)	6.03 ± 0.28	6.25 ± 0.35	0.21 (0.08 ~ 0.34)	0.001	
≥ 5	31 (9.57)	6.18 ± 0.33	6.09 ± 0.28	-0.17 (-0.57 ~ 0.23)	0.411	
Parity						0.336
0	84 (25.93)	6.02 ± 0.29	6.25 ± 0.37	0.23 (0.03 ~ 0.43)	0.026	
1	180 (55.56)	6.09 ± 0.32	6.15 ± 0.33	0.05 (-0.07 ~ 0.18)	0.392	
≥ 2	60 (18.52)	6.01 ± 0.32	6.19 ± 0.34	0.01 (-0.28 ~ 0.30)	0.950	
Maternal education						0.537
High school or lower	91 (28.09)	6.08 ± 0.29	6.27 ± 0.37	0.08 (-0.12 ~ 0.27)	0.439	
College	211 (65.12)	6.05 ± 0.33	6.15 ± 0.33	0.13 (0.02 ~ 0.24)	0.019	
Higher than college	22 (6.79)	6.05 ± 0.33	6.06 ± 0.32	0.39 (-0.61 ~ 1.38)	0.502	
Family monthly income						0.655
≤ 5000	69 (21.30)	5.98 ± 0.24	6.16 ± 0.35	0.17 (-0.06 ~ 0.39)	0.149	
5000–7500	117 (36.11)	6.10 ± 0.32	6.18 ± 0.33	0.15 (-0.01 ~ 0.32)	0.074	
≥ 7500	138 (42.59)	6.06 ± 0.34	6.19 ± 0.35	0.10 (-0.04 ~ 0.24)	0.163	
Interior renovation						0.677
≥ 1 year ago	268 (82.72)	6.09 ± 0.33	6.18 ± 0.36	0.13 (0.03 ~ 0.23)	0.013	
<1 year ago	56 (17.28)	5.95 ± 0.23	6.16 ± 0.25	0.17 (-0.06 ~ 0.40)	0.160	
Occupational exposure						0.268
No	302 (93.21)	6.06 ± 0.32	6.17 ± 0.33	0.10 (0.01 ~ 0.20)	0.037	
Yes	22 (6.79)	6.05 ± 0.23	6.33 ± 0.47	-1.27 (-5.54 ~ 3.00)	0.663	
Alcohol consumption						0.210
No	268 (82.72)	6.07 ± 0.33	6.20 ± 0.34	0.16 (0.06 ~ 0.26)	0.003	
Yes	56 (17.28)	5.99 ± 0.26	6.03 ± 0.31	-0.01 (-0.26 ~ 0.24)	0.931	
Active smoking						0.754
No	267 (82.41)	6.08 ± 0.33	6.19 ± 0.34	0.15 (0.05 ~ 0.26)	0.004	
Yes	57 (17.59)	5.98 ± 0.26	6.12 ± 0.38	-0.00 (-0.24 ~ 0.24)	0.993	
Passive smoking						0.788
No	172 (53.09)	6.02 ± 0.32	6.15 ± 0.34	0.19 (0.07 ~ 0.32)	0.004	
Yes	152 (46.91)	6.11 ± 0.31	6.21 ± 0.35	0.04 (-0.09 ~ 0.18)	0.527	

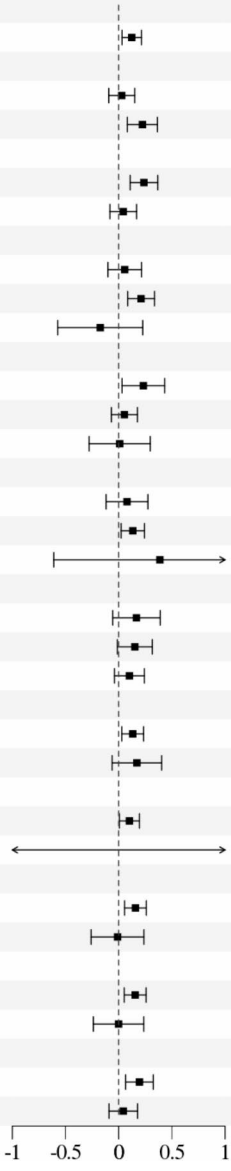

Fig. 5 Forest plot of subgroup analyses on the associations between average SO_4^{2-} exposures during the post-conception period (as a binary variable: > or ≤ 5.7 μg/m^3) and percentage changes in serum Hcy. Note: All the associations were adjusted for group (EPL or NEP), Ln5-MeTHF, all demographic characteristics presented in Table 1, temperature, and relative humidity

[21]. They also observed that susceptible exposure time window for most constituents was early pregnancy. This finding supported the importance of our study on $PM_{2.5}$ constituent exposures during early pregnancy. We found that BC was the unique constituent with residual–related increased Hcy in EPL group but not in NEP group. This suggested that elevated maternal Hcy mediated the pathogenic mechanism of EPL induced by BC.

This study has some limitations. First, personal monitoring of air pollution in women with early pregnancy is difficult because pregnancy is usually detected when menstruation is not on time, which is already the fifth

Table 4 Thirteen – week (3 – month) cumulative associations of an IQR increase in $PM_{2.5}$ and constituent exposures with percentage changes in serum Hcy in all participants, EPL group, and NEP group

Parameter	All participants ($n=324$)		EPL ($n=162$)		NEP ($n=162$)	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Pollutant concentration						
$PM_{2.5}$	66.0 (34.6, 104.8)	< 0.001	62.9 (16.9, 126.9)	0.005	70.9 (28.7, 127.0)	< 0.001
BC	65.4 (38.7, 97.1)	< 0.001	79.9 (37.8, 134.8)	< 0.001	52.7 (19.8, 94.7)	< 0.001
OM	67.5 (38.4, 102.6)	< 0.001	78.1 (33.2, 138.1)	< 0.001	60.3 (22.7, 109.5)	< 0.001
NO_3^-	73.7 (44.6, 108.5)	< 0.001	80.9 (35.2, 142.1)	< 0.001	71.9 (35.0, 118.7)	< 0.001
NH_4^+	64.9 (40.1, 94.1)	< 0.001	71.8 (32.7, 122.4)	< 0.001	62.9 (31.3, 102.2)	< 0.001
SO_4^{2-}	34.5 (22.7, 47.5)	< 0.001	40.4 (21.5, 62.1)	< 0.001	29.9 (14.2, 47.7)	< 0.001
Constituent residual						
BC	7.5 (1.8, 13.5)	0.011	12.0 (2.9, 21.9)	0.010	1.2 (-6.2, 9.3)	0.754
OM	5.5 (0.04, 11.3)	0.051	9.5 (0.8, 18.9)	0.033	1.0 (-6.3, 8.8)	0.801
NO_3^-	4.4 (-1.8, 11.0)	0.167	5.5 (-4.2, 16.1)	0.277	2.9 (-5.1, 11.5)	0.494
NH_4^+	4.6 (-1.7, 11.3)	0.157	5.9 (-4.0, 16.7)	0.255	2.7 (-5.4, 11.6)	0.525
SO_4^{2-}	15.1 (8.1, 22.5)	< 0.001	21.1 (9.7, 33.8)	< 0.001	9.6 (0.5, 19.6)	0.040

Note: The independent variables simultaneously included three cross–basis functions generated by lag 1–13 weeks before serum collection and weekly exposure to pollutant (concentration of $PM_{2.5}$ or each constituent, or residual of each constituent), temperature, and relative humidity, respectively, Ln5-MeTHF, all demographic characteristics presented in Table 1, and group (EPL or NEP). The IQRs of concentration of $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 29, 1.1, 5.8, 6.7, 3.6, and 2.5 μg/m^3, respectively. The IQRs of residual of BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 0.2, 0.9, 1.5, 0.9, and 1.1, respectively

week of pregnancy. In other words, the first month of the first trimester has passed. Thus, to estimate three–month $PM_{2.5}$ and constituent exposures before serum collection, we used TAP data, an efficient and feasible exposure assessment method that has been validated by an increasing number of environmental epidemiological studies [52–54]. However, the estimated exposures could not fully reflect actual individual exposures, especially indoor $PM_{2.5}$ exposures, a risk factor with considerable health hazards [55]. This may lead to bias in association estimations, usually toward the null [22, 51]. In our study, the spatial resolution of chemical constituents was relatively low, which could induce measurement error. Datasets of constituents with higher spatial resolution need to be developed. Second, we conducted this study in Tianjin, a city with relatively serious air pollution. The associations found in our study need to be verified by a national or global multicenter study [56]. Third, EPL is a gradual process, and symptoms do not always appear immediately after embryonic or fetal death. It is therefore difficult to determine the specific time that EPL occurred. In addition, EPL was diagnosed prior to serum samples collection and Hcy measurement. Therefore, the data obtained in this study were not suitable for mediation analysis. Although we found that the EPL group was more vulnerable to $PM_{2.5}$–related increased serum Hcy than the NEP group, it was uncertain whether the increased serum Hcy in EPL was due to individual susceptibility to $PM_{2.5}$ and chemical constituents, or the disease state, or both. The specific mechanism needs to be further verified through animal or cell experiments in the future.

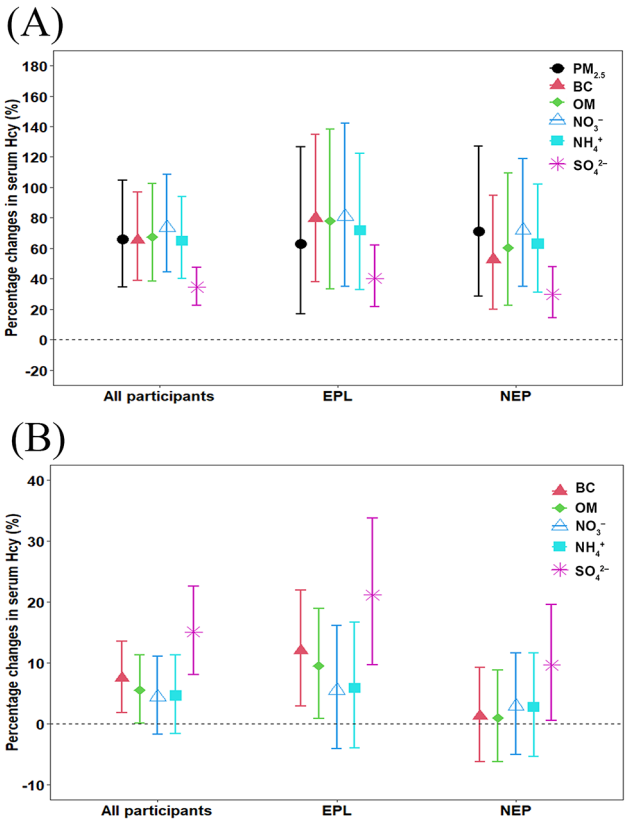

Fig. 6 Thirteen – week (3 – month) cumulative associations of an IQR increase in $PM_{2.5}$ and constituent exposures with percentage changes in serum Hcy in all participants ($n = 324$), EPL group ($n = 162$), and NEP group ($n = 162$). Note: The independent variables simultaneously included three cross–basis functions generated by lag 1–13 weeks before serum collection and weekly exposure to pollutant (concentration of $PM_{2.5}$ or each constituent in [A], replaced by residual of each constituent in [B]), temperature, and relative humidity, respectively, Ln5-MeTHF, all demographic characteristics presented in Table 1, and group (EPL or NEP). The IQRs of concentration of $PM_{2.5}$, BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 29, 1.1, 5.8, 6.7, 3.6, and 2.5 μg/m^3, respectively. The IQRs of residual of BC, OM, NO_3^-, NH_4^+, and SO_4^{2-} in the analyses were 0.2, 0.9, 1.5, 0.9, and 1.1, respectively

Conclusion

This study provided new insights into the impacts and mechanisms of $PM_{2.5}$ exposure during pregnancy. Maternal circulatory Hcy in early pregnancy increased with $PM_{2.5}$ and constituent exposures, with SO_4^{2-} being the highest risk constituent. Three to twelve weeks before serum collection were the susceptible exposure time windows. Early pregnant women with lower serum 5-MeTHF were more vulnerable to post-conception $PM_{2.5}$, BC, and SO_4^{2-} exposures than women with higher serum 5-MeTHF. Pollutants–related Hcy were generally higher in EPL group than in NEP group. BC–related increased Hcy may involve in pathogenic mechanism of EPL induced by $PM_{2.5}$. Whether the increased maternal Hcy in the first trimester associated with $PM_{2.5}$ and constituent exposures will induce subsequent pregnancy complications and affect the health of offspring needs further study.

Abbreviations

5-MeTHF	5-methyltetrahydrofolate
95% CI	95% confidence interval
BC	Black carbon
DLNM	Distributed lag non-linear model
EPL	Early pregnancy loss
Hcy	Homocysteine
HDP	Hypertensive disorders of pregnancy
IQR	Interquartile range
NEP	Normal early pregnancy
NH_4^+	Ammonium
NO_3^-	Nitrate
OM	Organic matter
$PM_{2.5}$	Fine particulate matter
SO_4^{2-}	Sulfate
TAP	Tracking Air Pollution in China
UPLC–MS/MS	Ultra-performance liquid chromatography-tandem triple quadrupole mass spectrometry

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01160-z .

Supplementary Material 1

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Author contributions

Xuesong Li: Formal analysis, Investigation, Writing– original draft. Mingyue Ran: Formal analysis, Investigation, Writing– original draft. Mengyuan Wang: Investigation. Ao Liu: Investigation. Bin Qiao: Investigation. Bin Han: Formal analysis. Jianmei Wang: Resources. Zhipeng Bai: Conceptualization, Funding acquisition, Supervision. Yujuan Zhang: Conceptualization, Funding acquisition, Project administration, Writing– review & editing. All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

Our research was approved by the Medical Ethics Committee of the Second Hospital of Tianjin Medical University, China (No. KY2019K044). Each participant signed a written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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