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Association between $PM_{2.5}$ and its components and antral follicle count: A multicity study in Chinese adults

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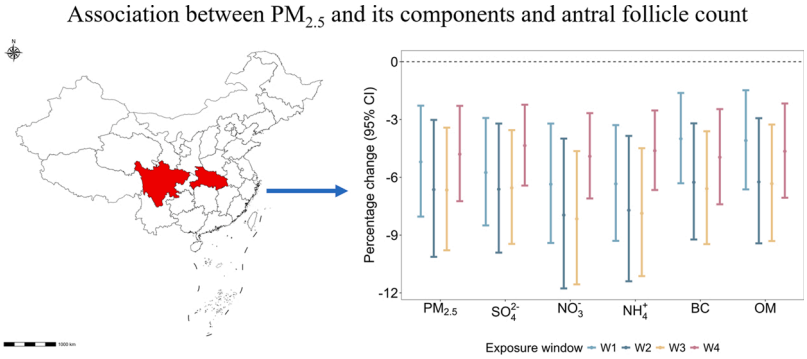
HIGHLIGHT

- The adverse impact of $PM_{2.5}$ and its components on decreased AFC was observed in our multi-city study.
- Modification effect of BMI and season of AFC test was observed.
- An approximately linear relationship between $PM_{2.5}$ and its components and AFC was observed.
- NO_3^- andNH_4^+ contributed most to the joint effect of PM components on AFC.

GRAPHICAL ABSTRACT



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ABSTRACT

Antral follicle count (AFC) is a key biomarker of ovarian reserve, however, its association with fine particulate matter ($PM_{2.5}$) and its chemical components remains inadequately understood. In this study, we estimated the effects of $PM_{2.5}$ mass and its components including sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), organic matter (OM), and black carbon (BC) on AFC among women of reproductive age. We included 4053 women seeking infertility treatment in Sichuan and Hubei provinces, China. A multivariable negative binomial mixed-effect model with city as a random effect was employed to estimate the associations between $PM_{2.5}$ and its components and AFC. Weighted quantile sum regression analysis was performed to evaluate the joint effect of

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$PM_{2.5}$ components on AFC. Our findings showed that exposure to $PM_{2.5}$ mass, SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC was associated with lower AFC. These results suggest that exposure to ambient $PM_{2.5}$ and its chemical components may impair ovarian reserve. Targeted reduction of specific air pollutants represents a potential strategy to protect female reproductive health.

1. Introduction

Ovarian reserve is a principal determinant of fertility and fecundity potential in reproductive-aged women, referring to the quantity and quality of remaining oocytes in the primordial follicle pool of both ovaries [1,2] . Quantitative assessment of ovarian reserve has therefore become a paramount clinical indicator of female fertility, particularly given the modern trend toward delayed childbearing [3]. Antral follicle count (AFC), defined as the total number of small antral follicles (2–10 mm in diameter) in both ovaries as assessed by imaging, serves as a practical surrogate marker for the primordial follicle pool and visually reflects ovarian reserve [4].

The susceptibility of antral follicle development to environmental factors has been increasingly recognized [5]. Among these, ambient air pollution has emerged as a major environmental risk factor for impaired ovarian reserve [6]. Emerging studies have suggested that exposure to fine particulate matter ($PM_{2.5}$) was associated with ovarian damage and impaired ovarian function [7–10]. The toxicity of $PM_{2.5}$ is largely modulated by its heterogeneous chemical components including sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), organic matter (OM), and black carbon (BC) [11,12]. It is, therefore, crucial to estimate the effects of specific $PM_{2.5}$ components on AFC during different stages of follicular development.

Although animal studies have shown that inhalation of $PM_{2.5}$ reduces the proportions of primordial, primary, and small antral follicles, thereby indicating depleted ovarian reserve [8,9,13,14], epidemiological studies specifically estimating the association between $PM_{2.5}$ exposure and AFC in humans remain limited and inconsistent. For example, the Environment and Reproductive Health study reported that exposure to $PM_{2.5}$ during the three months prior to AFC measurement was associated with lower AFC values [15,16]. Conversely, a study of 600 women in Shanxi, China, found no association between $PM_{2.5}$ exposure during follicular development and AFC [17].

To our best knowledge, only one study has assessed the impact of $PM_{2.5}$ and its components on ovarian reserve [18]. Additionally, the joint effect of these components as a mixture has been less well studied. Assessing both the individual and combined effects of $PM_{2.5}$ components and identifying the primary contributors to toxicity is a public health imperative, informing component-specific environmental policies.

Accordingly, we aimed to comprehensively evaluate the associations between exposure to ambient $PM_{2.5}$ mass and its components and AFC among women seeking infertility treatment in Hubei and Sichuan provinces, China. In addition, we investigated the joint effects of $PM_{2.5}$ components as a mixture in relation to AFC.

2. Methods

2.1. Study population

This study consecutively recruited women seeking infertility treatment at the Reproductive Medicine Center of Tongji Hospital in Wuhan, as well as at hospitals and healthcare centers across Sichuan Province. From October 2014 to February 2024, a total of 6669 participants were initially recruited. We excluded 747 participants who either had resided at their reported address for less than one year or lacked a documented residential address.

Further exclusions were applied for individuals with primary ovarian insufficiency, congenital adrenal hyperplasia, chromosomal abnormalities, or congenital genitourinary malformations (n = 69). Additionally, participants with current or previous diseases, surgeries, or treatments known to affect ovarian reserve were excluded (n = 1638), including polycystic ovary syndrome, endometriosis, hyperprolactinemia, hypothyroidism, systemic lupus erythematosus, tumors, or a history of ovarian surgery or pelvic radiotherapy. Participants younger than 20 or older than 45 years (n = 29), or those with missing data on pollutant concentrations, covariates, or AFC measurements (n = 133), were also excluded.

After applying these criteria, a total of 4053 participants were included in the final analysis. The geographic distribution of the included individuals is shown in Fig. 1. All participants provided written informed consent before being recruited into the study.

2.2. Exposure assessment

Daily concentrations of ambient $PM_{2.5}$ and its components (SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC) were obtained from the Tracking Air Pollution (TAP) database (http://tapdata.org.cn/). The detailed methodology for data generation has been described previously [19,20]. Briefly, a two-stage machine learning model was used to estimate daily $PM_{2.5}$ concentrations, integrating satellite remote sensing data, Community Multiscale Air Quality (CMAQ) model outputs, meteorological reanalysis data, land use information, elevation, and population density data. To reduce systematic bias in the CMAQ-simulated $PM_{2.5}$ components, the model incorporated an improved dust emission module and applied the XGBoost algorithm for calibration, based on decision tree-based learning. Daily ambient gaseous pollutants (sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3) and carbon monoxide (CO)) were obtained from the ChinaHighAirPollutants (CHAP) dataset.

Individual exposure to air pollution was matched according to the latitude and longitude of each participant's residential address. Four exposure windows (W) were calculated to capture specific follicular developmental stages (Supplementary Figure S1) [21]: W1: from the secondary to small antral follicle stage (two months prior to AFC measurement); W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle); W3: the entire follicular development stages from the primary to small antral follicle (six months prior to AFC measurement); W4: 1-year prior to AFC measurement, indicating long-term air pollutant exposure. Average pollutant concentrations were calculated for each window.

Additionally, ambient temperature and relative humidity were obtained from the European Centre for Medium Range Weather Forecasts. Individual exposure to these meteorological factors were estimated using data from the nearest monitoring station to each residential address. A 7-day moving average concentration of ambient temperature and relative humidity was calculated.

2.3. Assessment of AFC measurement

AFC was examined to assess ovarian reserve on days 2–5 of an unstimulated menstrual cycle by trained reproductive gynecologists in accordance with standardized clinical guidelines [4,22]. Follicles measuring 2–10 mm in diameter in both ovaries were identified and counted [3].

2.4. Covariates

We used structured questionnaires to collect information on sociodemographic characteristics, lifestyle factors, infertility history,

menstrual cycle traits, health conditions, and disease history. Anthropometric and clinical assessments were performed by trained nurses and physicians. The following variables were included as covariates: age, education (lower than or equal to primary school, junior high school, senior high school or college, postsecondary or university, and equal to or higher than postgraduate), smoking status (yes versus no), infertility type (primary, secondary and unknown), season of AFC measurement, regularity of menstrual cycle (yes versus no), body mass index (BMI) and meteorological factors (ambient temperature and relative humidity). Menstrual cycles lasting 21–35 days were considered regular [23]. Season of AFC measurement was defined based on measurement date of AFC: Spring (March-May), Summer (June-August), Autumn (September-November), and Winter (December-February). The warm season was defined as May 1 to October 31, and the cold season as November 1 to April 30 of the following year. BMI (kg/m^2) was calculated as weight (kg) divided by the square of height (m^2).

2.5. Statistical analysis

Descriptive statistics were used to summarize demographic, clinical, and exposure data. Continuous variables are expressed as medians and interquartile ranges (IQRs), and categorical variables are expressed as frequencies and percentages.

We used multivariable negative binomial regression analysis accounting for overdispersion with city included as a random effect to estimate the associations between $PM_{2.5}$ and its components and AFC [24,25]. In the crude model, we only adjusted for age. In the fully adjusted models, we additionally adjusted for education level, smoking status, infertility type, season of AFC measurement, BMI, menstrual cycle regularity, ambient temperature, and relative humidity. No multicollinearity was detected among covariates, as assessed by variance inflation factors less than 5. We expressed results as the percentage change in AFC, calculated as $100 \times [\exp(\beta) - 1]$, with 95 % confidence intervals (CIs) for each IQR increase in pollutant concentration, where β is the regression coefficient derived from the negative binomial regression.

Exposure-response relationship between $PM_{2.5}$ and its components and AFC was modeled introducing a restricted cubic spline of pollutant concentration within the negative binomial model, adjusting for all covariates in the fully adjusted models. Likelihood ratio test was applied to evaluate the potential nonlinearity.

We conducted subgroup analysis to assess whether the association varied by age, BMI, infertility type and season of AFC measurement. Interaction terms between subgroup factors and pollution concentrations were added to the models to test for heterogeneity between groups.

To assess the combined effects of $PM_{2.5}$ components, we performed weighted quantile sum (WQS) regression analysis. The dataset was randomly split into a training set (40 % of observations) and a validation set (60 %). A WQS index was calculated with 1000 bootstrap iterations in both positive and negative directions, assigning a specific weight to each component.

To evaluate the robustness of our findings, we conducted several sensitivity analyses. First, to minimize the influence of individual behavioral factors, the analyses were restricted to nonsmokers. Second, to control for the potential impact of reproductive health conditions, we limited the analyses to participants with regular menstrual cycles. Third, to assess the effect of $PM_{2.5}$ components independent of total $PM_{2.5}$ mass, we used a component–residual model. In this model, original concentration of PM component was replaced by the residual of each component to total $PM_{2.5}$. Residuals are independent to $PM_{2.5}$, and would reflect the variation in component levels [26]. Fourth, to account for potential covariate imbalance across individuals, we used inverse probability weighting (IPW) method. Detailed information was provided in Supplementary Material: Supplementary method 1. Fifth, to examine whether our estimates were robust to confounding by co-pollutants, we further adjusted for ambient gaseous pollutants (SO_2, NO_2, CO, and O_3) that showed low correlation with $PM_{2.5}$ and its components (Spearman correlation coefficient<0.8) (Table S1). Additionally, to account for center-level variations, analyses were further stratified by province. Finally, we assessed the stability of our results using a two-stage analytical approach. Specifically, in the first stage, we assessed the association between $PM_{2.5}$ and its components and AFC separately within each city. In the second stage, we pooled the city-specific effect estimates using meta-analytic techniques to obtain an overall estimate of the association between $PM_{2.5}$ and its components and AFC. For details on the two-stage analytical approach, see the Supplementary Material: Supplementary method 2.

All statistical analyses were performed using R (version 4.4.2) and SAS (version 9.4). *P*-values were adjusted for multiple comparisons using the Benjamini-Hochberg method. The R package "*glmmTMB*" was used for negative binomial regression, "*metafor*" for meta-analysis, "*WeightIt*" and "*cobalt*" for IPW, and "*gWQS*" for WQS analysis. A two-tailed *P* value < 0.05 was considered statistical significance.

3. Results

3.1. Descriptive characteristics

The characteristics of study participants and their pollutant exposure levels were summarized in Table 1. The median (IQR) age and BMI were 30.00 (28.00, 34.00) years and 21.48 (19.80, 23.52) kg/m^2, respectively. The majority of participants were under 35 years of age

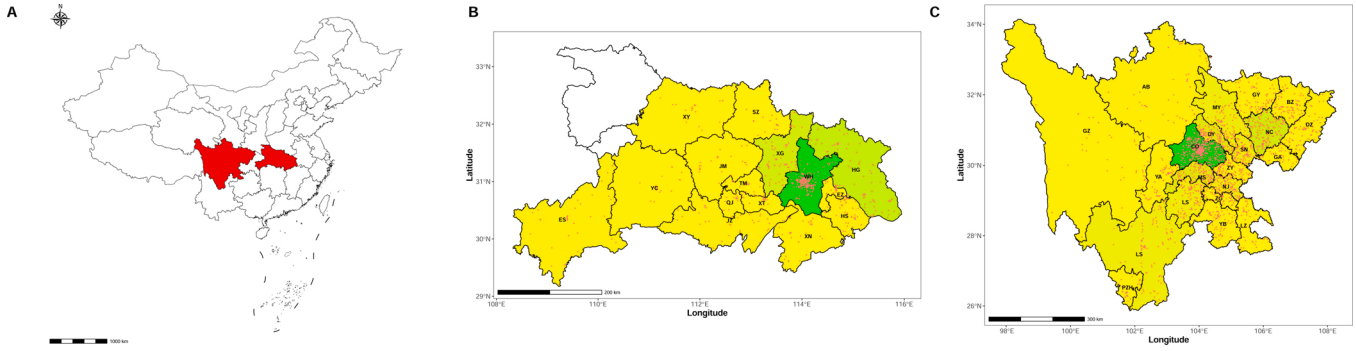

Fig. 1. Locations of the study participants in cities across Hubei and Sichuan provinces, China. **Abbreviation**: AB = Aba Tibetan and Qiang Autonomous Prefecture; BZ = Bazhong; XT = Xiantao; QJ = Qianjiang; TM = Tianmen; CD = Chengdu; DZ= Dazhou; DY= Deyang; EZ = Ezhou; ES = Enshi Tujia and Miao Autonomous Prefecture; GZ = Ganzi Tibetan Autonomous Prefecture; GA = Guangan; GY= Guangyuan; HG = Huanggang; HS = Huangshi; JM = Jingmen; JZ = Jingzhou; LS = Leshan; LS = Liangshan Yi Autonomous Prefecture; MS = Meishan; MY = Mianyang; NC = Nanchong; NJ = Neijiang; PZH = Panzhihua; SY = Shiyan; SZ = Suizhou; SN = Suining; WH = Wuhan; XN = Xianning; XY = Xiangyang; XG = Xiaogan; YA = Yaan; YB = Yibin; YC = Yichang; ZY = Ziyang; ZG = Zigong; LZ = Luzhou.

Table 1
Characteristics of study participants.

Variables	Study population (n = 4053)	Individuals in Hubei (n = 985)	Individuals in Sichuan (n = 3068)
Age (Median [IQR]) (years)	31.00 [28.00, 34.00]	30.00 [27.00, 33.00]	31.00 [28.00, 35.00]
Age, n (%)			
< 35 years	3092 (76.29)	803 (81.52)	2289 (74.61)
≥ 35 years	961 (23.71)	182 (18.48)	779 (25.39)
Education, n (%)			
Lower than or equal to primary school	246 (6.07)	57 (5.79)	189 (6.16)
Junior high school	1022 (25.22)	334 (33.91)	688 (22.43)
Senior high school or college	841 (20.75)	227 (23.05)	614 (20.01)
Postsecondary or university	1814 (44.76)	341 (34.62)	1473 (48.01)
Equal to or higher than postgraduate	130 (3.21)	26 (2.64)	104 (3.39)
Smoking status, n (%)			
No	3870 (95.48)	925 (93.91)	2945 (95.99)
Yes	183 (4.52)	60 (6.09)	123 (4.01)
Season of AFC measurement, n (%)			
Spring (March-May)	1262 (31.14)	403 (40.91)	859 (28.00)
Summer (June-August)	1264 (31.19)	339 (34.42)	925 (30.15)
Autumn (September-November)	808 (19.94)	131 (13.30)	677 (22.07)
Winter (December-February)	719 (17.74)	112 (11.37)	607 (19.78)
Warm season of AFC measurement, n (%)			
No (November - the following April)	1791 (44.19)	429 (43.55)	1362 (44.39)
Yes (May-October)	2262 (55.81)	556 (56.45)	1706 (55.61)
BMI (Median [IQR]) (kg/m^2)			
BMI, n (%)	21.48 [19.80, 23.52]	21.48 [19.82, 23.88]	21.48 [19.80, 23.44]
< 24.0 kg/m^2	3181 (78.49)	747 (75.84)	2434 (79.34)
≥ 24.0 kg/m^2	872 (21.51)	238 (24.16)	634 (20.66)
Infertility type, n (%)			
Primary	2023 (49.91)	651 (66.09)	1372 (44.72)
Secondary	1950 (48.11)	334 (33.91)	1616 (52.67)
Other	80 (1.97)	0 (0.00)	80 (2.61)
Regular menstrual cycle, n (%)			
Yes	3485 (85.99)	842 (85.48)	2643 (86.15)
No	568 (14.01)	143 (14.52)	425 (13.85)
AFC (Median [IQR]) (n)	12.00 [8.00, 17.00]	11.00 [7.00, 16.00]	13.00 [8.00, 18.00]
Pollutant (Median [IQR])			
$PM_{2.5}$ (μg/m^3)			
W1	34.63 [25.85, 50.22]	42.29 [31.61, 59.78]	32.48 [24.09, 46.29]
W2	42.92 [28.95, 60.67]	60.61 [41.91, 74.76]	37.87 [26.24, 54.57]
W3	42.28 [30.68, 55.41]	56.56 [41.77, 67.93]	38.13 [27.97, 50.86]
W4	43.01 [35.15, 50.50]	51.12 [48.36, 54.05]	40.44 [32.60, 45.92]
SO_4^{2-} (μg/m^3)			
W1	6.13 [4.40, 8.98]	7.66 [5.94, 10.30]	5.56 [4.01, 8.45]
W2	7.62 [5.03, 10.64]	10.50 [7.57, 12.73]	6.78 [4.54, 9.68]
W3	7.38 [5.32, 9.78]	9.89 [7.41, 11.74]	6.63 [4.77, 8.94]
W4	7.38 [6.17, 8.89]	8.89 [8.27, 9.66]	6.94 [5.64, 7.93]
NO_3^- (μg/m^3)			
W1	7.36 [4.79, 12.22]	9.71 [6.68, 15.45]	6.57 [4.41, 10.96]
W2	9.90 [5.72, 15.50]	15.21 [9.93, 19.07]	8.26 [5.08, 13.83]
W3	9.67 [6.27, 13.72]	14.21 [9.64, 17.22]	8.60 [5.61, 12.42]
W4	10.01 [8.26, 11.67]	11.82 [10.92, 13.30]	9.47 [7.58, 10.75]
NH_4^+ (μg/m^3)			
W1	4.88 [3.29, 7.83]	6.02 [4.24, 9.41]	4.48 [3.08, 7.26]
W2	6.48 [3.83, 9.78]	9.36 [6.22, 11.77]	5.54 [3.51, 8.91]
W3	6.35 [4.18, 8.71]	8.74 [5.94, 10.65]	5.72 [3.80, 8.03]
W4	6.45 [5.42, 7.51]	7.30 [6.59, 8.31]	6.08 [5.06, 7.10]
OM (μg/m^3)			
W1	9.07 [6.97, 12.54]	10.60 [8.16, 14.85]	8.60 [6.54, 11.80]
W2	10.97 [7.87, 15.17]	15.10 [10.83, 18.24]	9.88 [7.19, 13.68]
W3	10.74 [8.18, 14.02]	14.08 [10.51, 16.83]	9.92 [7.48, 12.82]
W4	11.12 [9.07, 12.85]	12.98 [12.14, 13.71]	10.44 [8.46, 12.02]
BC (μg/m^3)			
W1	1.69 [1.31, 2.28]	2.00 [1.58, 2.72]	1.60 [1.21, 2.15]
W2	2.02 [1.46, 2.75]	2.80 [2.04, 3.40]	1.82 [1.35, 2.46]
W3	1.97 [1.50, 2.59]	2.64 [1.98, 3.14]	1.82 [1.38, 2.32]
W4	2.04 [1.64, 2.41]	2.43 [2.29, 2.58]	1.88 [1.51, 2.22]

Abbreviation: IQR = interquartile range; BMI = body mass index; AFC = antral follicle count; W = window; $PM_{2.5}$ = fine particulate matter; SO_4^{2-} = sulfate; NO_3^- = nitrate; NH_4^+ = ammonium; BC = black carbon; OM = organic matter. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle development); (3) W3: from the primary to small antral follicle stage (six months before measurement); (4) W4: 1-year before measurement representing long-term air pollution exposure.

(76.29 %) and nonsmokers (95.48 %). Most female participants were diagnosed with primary infertility (49.91 %). The median (IQR) AFC was 12.00 (8.00, 17.00).

The median concentrations of $PM_{2.5}$ during W1 to W4 stages were 34.63, 42.92, 42.28 and 43.01 μg/m^3, respectively. Among the $PM_{2.5}$ components, OM exhibited the highest median concentrations across all exposure windows (W1-W4: 9.07, 10.97, 10.74 and 11.12 μg/m^3), followed by NO_3^-, SO_4^{2-}, NH_4^+, and BC**.** Detailed descriptive statistics of individual exposure to $PM_{2.5}$ and its components among participants were shown in Table S2.

3.2. Associations of $PM_{2.5}$ and its components with AFC

Exposure to $PM_{2.5}$ mass and its components (SO_4^{2-}, NO_3^-, NH_4^+, BC and OM) was all associated with decreased AFC (Fig. 2). For example, during the whole follicular development stage of small antral follicle (W3), exposure to $PM_{2.5}$ mass was linked to a 7.01% (95% CI: 3.77%, 10.15%) reduction in AFC. Additionally, among $PM_{2.5}$ components, the effect estimate was larger for NO_3^- and NH_4^+ exposure in W3 stage, with reduction in AFC of 8.51% (95% CI: 5.00%, 11.89%) and 8.17% (95% CI: 4.79%, 11.43%).

The association between $PM_{2.5}$ and its components and decrease of AFC was observed across all exposure windows. The strongest associations for $PM_{2.5}$ mass, SO_4^{2-}, NO_3^-, NH_4^+, and OM exposure with AFC were identified during the transition from primary to secondary follicle stage (W2 stage), with percentage changes (95 % CIs) in AFC of −7.43 %

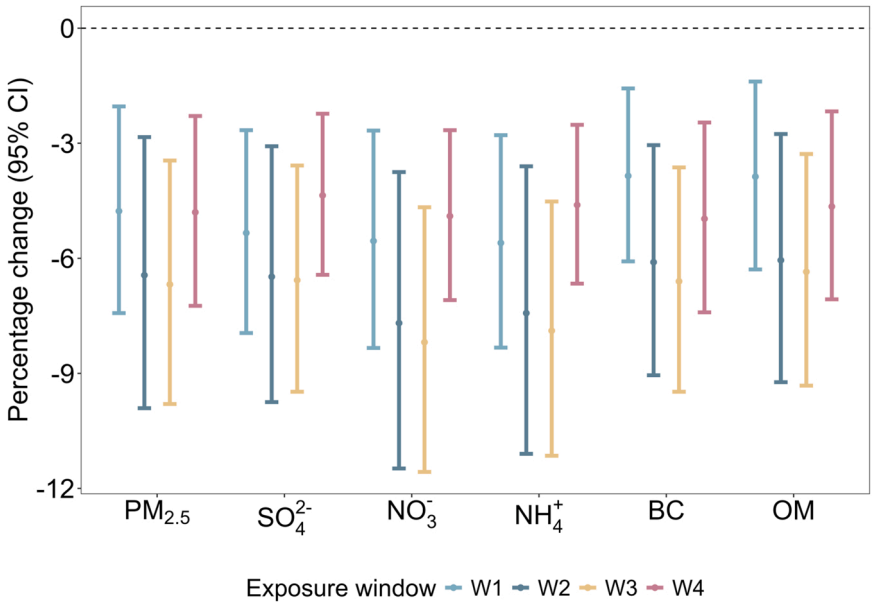

Fig. 2. Association between exposure to $PM_{2.5}$ and its components during different exposure windows and AFC. Models were adjusted for age (continuous), education level (categorical), smoking status (dichotomous), infertility type (dichotomous), season of AFC measurement (categorical), BMI (continuous), menstrual cycle regularity (dichotomous), and 7-day average exposure of ambient temperature (continuous) and relative humidity (continuous) with city treated as a random effect. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle development); (3) W3: from the primary to small antral follicle stage (six months before measurement); (4) W4: 1-year before measurement representing long-term air pollution exposure. **Abbreviation**: W = window; CI = confidence interval; AFC = antral follicle count; $PM_{2.5}$ = fine particulate matter; SO_4^{2-} = sulfate; NO_3^- = nitrate; NH_4^+ = ammonium; BC = black carbon; OM = organic matter.

(95 % CI: −11.01 %, −3.71 %), −7.32 % (95 % CI: −10.68 %, −3.83 %), −8.83 % (95 % CI: −12.73 %, −4.77 %), −8.43 % (95 % CI: −12.20 %, −4.50 %), and −6.93 % (95 % CI: −10.21 %, −3.54 %), respectively (Supplementary Table S3). Exposure to BC during the development stage from primary to small antral follicle (W3 stage) showed the largest reduction in AFC.

The exposure-response relationships between $PM_{2.5}$ mass, its components and AFC were approximately linear across all exposure windows, particularly at higher exposure concentrations (*P* for nonlinear test > 0.05, Fig. 3).

3.3. Subgroup analysis

We conducted subgroup analyses to identify susceptible populations. The association between $PM_{2.5}$ and its components and AFC appeared more pronounced among women with BMI ≥ 24.0 kg/m^2, those diagnosed with other infertility type, and participants who underwent AFC measurement during cold season, compared to their counterparts (Supplementary Table S4). For example, exposure to $PM_{2.5}$ mass during the W3 stage was associated with a 9.24% (95% CI: 2.08%, 15.87%) decrease in AFC among women with BMI ≥ 24.0 kg/m^2, compared to a 6.13% (95% CI: 2.26%, 9.84%) decrease among women with BMI < 24.0 kg/m^2.

3.4. WQS regression analysis

Based on the WQS analysis, NO_3^- was assigned the highest weight for decreased AFC in the W1 and W2 exposure stages (0.71 and 0.86, respectively), followed by SO_4^{2-}, BC, OM and NH_4^+ (Fig. 4). In contrast, during the W3 and W4 stages, NH_4^+ was identified as the most influential PM component on decreased AFC, with weights of 0.61 and 0.79, respectively. However, the joint effect of PM components on AFC was not identified (*P* for WQS index > 0.05).

3.5. Sensitivity analyses

To assess the robustness of the findings, sensitivity analyses were performed. The associations remained consistent when analyses were restricted to nonsmokers and participants with regular menstrual cycles (Supplementary Table S5). Our findings were not materially different when analyses were further adjusted for SO_2, NO_2 and O_3, or we used a complete different statistical analysis, a two-stage analysis to examine the association between $PM_{2.5}$ and its components and AFC (Figure S2, Supplementary Table S6).

4. Discussion

In this multicenter study of women undergoing fertility treatment in Hubei and Sichuan provinces, China, we found that exposure to $PM_{2.5}$ and its components was associated with reduced AFC. Restricted cubic spline analyses indicated an approximately linear relationship between increasing concentrations of $PM_{2.5}$ and its components and decreased AFC. Our analysis further revealed potential heterogeneity, with stronger associations observed among women with higher BMI and those undergoing AFC measurement during the cold season.

While both anti-Müllerian hormone and AFC are established markers of ovarian reserve with comparable accuracy [3,27], the majority of previous studies have focused on the association between $PM_{2.5}$ and anti-Müllerian hormone. Given that AFC measurement could enhance patient comfort and streamline service delivery due to its operational flexibility [28,29], future environmental studies may also prioritize the broader adoption of AFC as a crucial indicator of ovarian reserve.

Our findings are generally consistent with prior studies, though some discrepancies exist. For example, our findings align with a study conducted in Poland involving 511 women reported that $PM_{2.5}$ exposure during the transition from primary to small antral follicle stages was associated with reduced AFC [30]. However, null association was observed in studies from the United States [31] and Shanxi, China [17]. These discrepancies may be attributable to differences in population

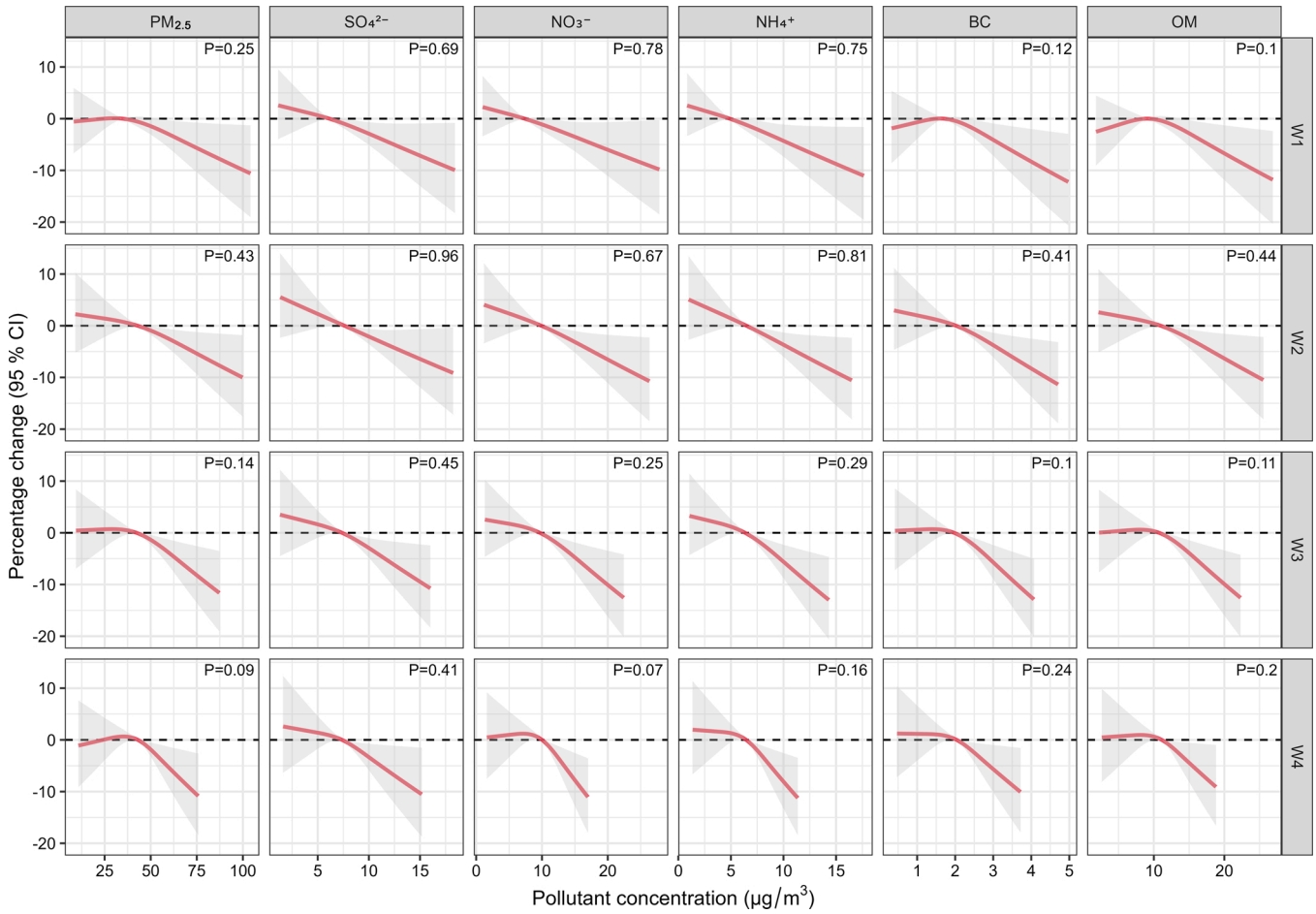

Fig. 3. Exposure-response relationship between $PM_{2.5}$ and its components and AFC. Models were adjusted for age (continuous), education level (categorical), smoking status (dichotomous), infertility type (dichotomous), season of AFC measurement (categorical), BMI (continuous), menstrual cycle regularity (dichotomous), and 7-day average exposure of ambient temperature (continuous) and relative humidity (continuous) with city treated as a random effect. *P* for nonlinearity test was shown in the upper right corner of each panel. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle development); (3) W3: from the primary to small antral follicle stage (six months before measurement); (4) W4: 1-year before measurement representing long-term air pollution exposure. **Abbreviation**: W = window; CI = confidence interval; AFC = antral follicle count; $PM_{2.5}$ = fine particulate matter; SO_4^{2-} = sulfate; NO_3^- = nitrate; NH_4^+ = ammonium; BC = black carbon; OM = organic matter.

characteristics, exposure levels, pollutant sources, and covariate adjustments [32].

We found that exposure to $PM_{2.5}$ components was associated with reduced AFC. A prior study among women in Hubei reported that exposure to $PM_{2.5}$ mass, SO_4^{2-}, NO_3^- and NH_4^+ was associated with decreased ovarian reserve, as measured by anti-Müllerian hormone levels [18]. These components are known to be dominant components to ambient $PM_{2.5}$ mass [33]. Current evidence suggests a harmful impact of $PM_{2.5}$ mass on ovarian reserve; however, the association between $PM_{2.5}$ components and AFC has been less thoroughly examined.

$PM_{2.5}$ may impair ovarian function through multiple pathways, including receptor-mediated pro-apoptotic processes, alterations in signal transduction, endocrine disruption, oxidative stress, and epigenetic modification [34]. Experimental data suggest that $PM_{2.5}$ triggers oxidative stress and inflammation in ovarian tissues, resulting in structural and functional damage [8,35]. Additionally, SO_4^{2-}, NO_3^- and NH_4^+ can enhance the absorption of metallic elements in $PM_{2.5}$ by creating an acidic environment, further aggravating ovarian damage and hormonal abnormalities [36]. BC, a marker of incomplete combustion, is also known to elicit immune responses and systemic inflammation [37]. OM, a mixture of primary and secondary organic particles, contains various compounds polycyclic aromatic hydrocarbons, esters, polychlorinated biphenyls, which has great adverse effect on human health [38]. Thus, our findings are strongly supported by biologically plausible.

Our findings of the associations between $PM_{2.5}$ and its components and AFC were stronger among women with a BMI $\geq$ 24 kg/m^2 compared to those with a BMI $<$ 24 kg/m^2. This may be explained by the heightened baseline systemic inflammation and reduced antioxidant capacity already present in overweight individuals, making their reproductive system more vulnerable to environmental pollutants [39]. Additionally, the more pronounced effects of $PM_{2.5}$ and its components during the cold season could be related to seasonal variations in PM components (e.g., increased emissions from residential heating), changes in atmospheric stability, or altered indoor exposure patterns. This aligns with prior research that found temperature and season to modify the association between air pollution and AFC [40].

Results of WQS regression analysis indicated that NO_3^- and NH_4^+ contributed most to the joint effect of PM components on AFC. This finding was further elaborated in our main analysis, which identified that among $PM_{2.5}$ components, exposure to NO_3^- and NH_4^+ had larger reduction in AFC compared with SO_4^{2-}, BC, and OM. NO_3^- and NH_4^+ are typical secondary inorganic aerosols originating from common precursor substances (such as nitrogen dioxide and ammonia), and they exhibit high correlations, suggesting potential synergistic toxicity [41].

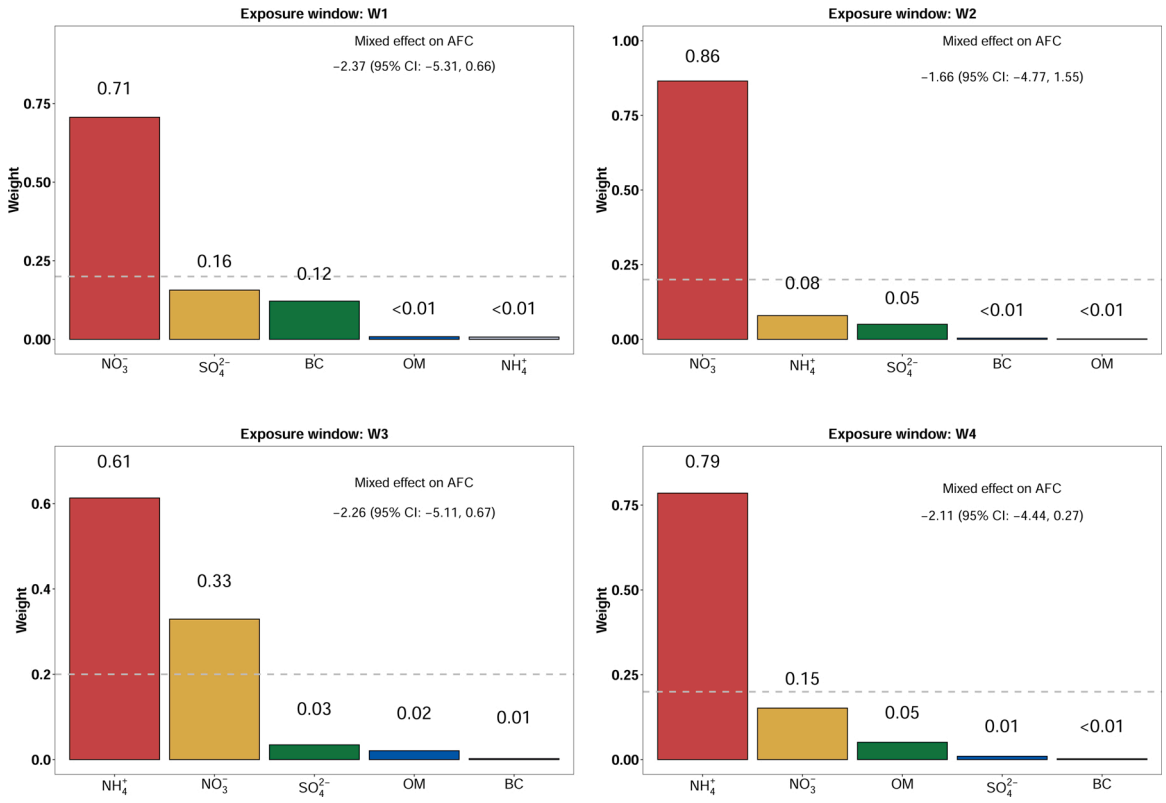

Fig. 4. Estimated weights of $PM_{2.5}$ components contributing to the positive association with AFC, as estimated by weighted quantile sum regression. Models were adjusted for age (continuous), education level (categorical), smoking status (dichotomous), infertility type (dichotomous), season of AFC measurement (categorical), BMI (continuous), menstrual cycle regularity (dichotomous), and 7-day average exposure of ambient temperature (continuous) and relative humidity (continuous) with city treated as a random effect. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle development); (3) W3: from the primary to small antral follicle stage (six months before measurement); (4) W4: 1-year before measurement representing long-term air pollution exposure. **Abbreviation**: W = window; CI = confidence interval; AFC = antral follicle count; $PM_{2.5}$ = fine particulate matter; SO_4^{2-} = sulfate; NO_3^- = nitrate; NH_4^+ = ammonium; BC = black carbon; OM = organic matter.

Abundant evidence has revealed greater toxicity and public health hazards of NO_3^- and NH_4^+ compared to other components [42,43]. These components are mainly generated from agricultural activities (animal feeding operation and fertilizer use), vehicle exhaust, fossil fuel combustion, and biomass burning [44]. Our findings provide a clear evidence base to support implementing targeted regulatory strategies to control the emissions and sources of NO_3^- and NH_4^+, which are highly likely to be effective in improving female reproductive health. The overall joint effect of PM component on AFC was not statistically significant. The interpretation of this finding was difficult, particularly because evidence of the joint effect of PM components on AFC is limited. This result may be due to the complex, non-linear interactions among components or insufficient statistical power for the joint effect. Further investigation is needed to estimate and understand the joint effect of PM components on AFC.

We applied a component-residual model that avoids over-adjustment by separating the residual variation of each component from the total $PM_{2.5}$ mass [26]. Our study found that SO_4^{2-}, NO_3^-, NH_4^+, and BC remained associated with lower AFC, indicating their independent effects beyond $PM_{2.5}$ mass. Additionally, the robustness of our primary findings was reinforced by sensitivity analyses using IPW method, which minimized potential confounding from covariate imbalance [45]. Furthermore, the two-stage analytical method designed to address inter-city heterogeneity confirmed the associations between $PM_{2.5}$ and its components and AFC, thereby enhancing the plausibility of our findings.

Our study not only quantified the association between long-term exposure to $PM_{2.5}$ and its components with AFC, but also identified the most toxic PM component in the joint effect, providing an important scientific basis for the development of targeted air pollution control strategies. Our findings contribute to informing the development of emission reduction policies—such as prioritizing the control of specific industrial or traffic-related PM components—to improve female reproductive health. Adopting targeted strategies to reduce exposure to the most harmful PM components can contribute to more effective prevention of reproductive health risks associated with air pollution.

Our study has several limitations. First, the study population only consisted of women seeking infertility treatment in Hubei and Sichuan provinces, which may limit the generalizability of our findings to all women of reproductive age or to those in other provinces or countries. Additionally, center-level variation (e.g., in ultrasonography equipment or operator skill) may introduce potential bias, despite our use of city-level random effects. Second, individual exposure assessments were estimated solely based on residential addresses without accounting for factors such as personal movement, activity patterns, and workplace environments. This approach may lead to non-differential exposure misclassification and potentially bias the results toward the null. Third, while we examined 5 $PM_{2.5}$ components, data on other potentially harmful components, such as transition metals, were unavailable. Furthermore, the concentrations of PM components were estimated using predictive models (TAP database) rather than being measured directly by analytical instruments, which could also introduce exposure misclassification. Fourth, causal inference is limited by the cross-sectional nature of this study, making it difficult to establish direct cause-and-effect relationships. Fifth, limited sample sizes, particularly for subgroup analyses, lack sufficient power to draw definitive conclusions. Finally, although we adjusted for a range of confounders, residual

confounding from unmeasured factors, such as physical activity, occupational exposures, and dietary habits cannot be entirely excluded. Nevertheless, to the best of our knowledge, this is the first study to estimate the associations between $PM_{2.5}$ and its key components (SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC) and AFC across multiple exposure windows in Chinese adults, providing a strong scientific basis for targeted public health action.

5. Conclusion

In this multicenter study conducted in Hubei and Sichuan, China, we examined the associations between $PM_{2.5}$ mass and its components (SO_4^{2-}, NO_3^-, NH_4^+, BC and OM) and AFC across multiple exposure windows. We found that exposure to $PM_{2.5}$ mass and its components was associated with decreased AFC. These findings provide important epidemiological evidence regarding the risk of depleted ovarian reserve posed by exposure to specific air pollutant components. Our study underscores the need for targeted air quality control strategies aimed at reducing emissions from specific pollutant sources, which may ultimately contribute to the improvement of female reproductive health at the population level.

Environmental implication

This study provides novel evidence that exposure to $PM_{2.5}$ and its major chemical components may impair female ovarian reserve, as indicated by decreased antral follicle count. These findings highlight a potential reproductive health consequence of air pollution and underscore the need for targeted air quality control strategies focusing on specific $PM_{2.5}$ constituents, such as sulfate, nitrate, and black carbon, to protect reproductive health in polluted urban environments.

CRediT authorship contribution statement

Ze Han: Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Jie Yin:** Writing – review & editing. **Wangnan Cao:** Writing – review & editing. **Qiang Zeng:** Writing – review & editing, Data curation. **Shengzhi Sun:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.140428.

Data availability

The authors do not have permission to share data.

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