Ecotoxicology and Environmental Safety 284 (2024) 116915

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Long-term effect of fine particulate matter constituents on reproductive hormones homeostasis in women attending assisted reproductive technologies: A population-based longitudinal study

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ARTICLE INFO

Edited by Dr. Renjie Chen

Keywords:
Women's reproductive health
Particulate matter constituents
Reproductive hormones
Assisted reproductive cohort

ABSTRACT

Fine particulate matter ($PM_{2.5}$) may disrupt women's reproductive hormones, posing potential reproductive risks. However, the exact compositions of $PM_{2.5}$ responsible for these effects remain unclear. Our investigation explored the long-term impacts of $PM_{2.5}$ constituents on reproductive hormones, based on a large longitudinal assisted reproductive cohort study in Anhui, China. We included 24,396 reproductive hormone samples from 19,845 women attending assisted reproductive technologies (ART) between 2014 and 2020. Using high-resolution gridded data (1-km resolution), we calculated the residence-specified $PM_{2.5}$ constituents during the year before the month of hormone testing. Relationships between $PM_{2.5}$ constituents [organic matter (OM), chloride (Cl^-), sulfate (SO_4^{2-}), ammonium (NH_4^+), black carbon, and nitrate] and reproductive hormones were investigated using the linear mixed model with subject-specific intercepts. The constituent-proportion model and the constituent-residual model were also constructed. Additionally, cubic spline analysis was used to examine the potential non-linear exposure-response relationship. We found that per interquartile range (IQR) increment in OM was associated with a 5.31 % (3.74 %, 6.89 %) increase in estradiol, and per IQR increment in Cl^- and NH_4^+ were associated with 13.56 % (7.63 %, 19.82 %) and 9.07 % (4.35 %, 14.01 %) increases in luteinizing hormone. Conversely, per IQR increment in OM and Cl^- were associated with −7.27 % (-9.34 %, −5.16 %) and −8.52 % (-10.99 %, −5.98 %) decreases in progesterone, and per IQR increment in SO_4^{2-} was associated with a −9.15 % (-10.31 %, −7.98 %) decrease in testosterone. These associations were held in both proportional and residual models. Moreover, exposure-response curves for estradiol and progesterone with $PM_{2.5}$ constituents exhibited approximately U-shaped. These results suggested that specific $PM_{2.5}$ constituents might disrupt reproductive hormone homeostasis in women attending ART, providing new evidence for formulating $PM_{2.5}$ pollution reduction strategies that could benefit women's reproductive health.

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https://doi.org/10.1016/j.ecoenv.2024.116915
Received 7 May 2024; Received in revised form 9 August 2024; Accepted 20 August 2024

1. Introduction

The homeostasis of reproductive hormones is essential for the maintenance of reproductive health in women of childbearing age. For example, estradiol (E2) plays a pivotal role in ovarian development, ovulation, and endometrial proliferation, and progesterone (P) is crucial for maintaining pregnancy and preventing preterm birth (Li et al., 2023b). Dysregulation of reproductive hormones can lead to decreased fertility and adverse pregnancy outcomes. Therefore, a comprehensive understanding of the factors driving hormonal changes, including environmental factors, is essential for formulating strategies to support female reproductive health.

Accumulated evidence suggests that airborne fine particulate matter ($PM_{2.5}$) may pose risks to reproductive health. Prior studies have linked $PM_{2.5}$ exposure to female reproductive health concerns, such as declining ovarian reserve (Abareshi et al., 2020), reduced clinical pregnancy rates (Fang et al., 2024), and hormonal imbalances. Experimental evidence has shown that $PM_{2.5}$ could disrupt reproductive endocrine functions, yet epidemiological evidence remains inconsistent (Liu et al., 2022a). For instance, in a cohort study among midlife American women, $PM_{2.5}$ was inversely associated with E2 (Wang et al., 2024). However, our previous research among reproductive-age women yielded a suggestive positive association of $PM_{2.5}$ with E2, along with an inverse association with P and testosterone (T) (Fang et al., 2023). Another study focusing on adult women demonstrated that $PM_{2.5}$ was inversely associated with P, but positively associated with T (Wei et al., 2021). These discrepancies could arise from variations in population characteristics, potential nonlinear association, and notably, differences in $PM_{2.5}$ constituents.

$PM_{2.5}$'s toxicity depends largely on its composition, including carbonaceous elements [organic matter (OM), black carbon (BC)], water-soluble minerals [nitrate (NO_3^-), sulfate (SO_4^{2-}), chloride (Cl^-), and ammonium (NH_4^+)], and others. These constituents vary greatly by source, region, and season, each with distinct adverse impacts on human health. Consequently, it is imperative to identify the toxic $PM_{2.5}$ components for developing targeted environmental policies and enhancing our knowledge of how $PM_{2.5}$ affects female reproductive health.

Several epidemiological studies have examined the influence of $PM_{2.5}$ constituents on multiple endocrine hormones, including anti-Müllerian hormone (AMH) (Pang et al., 2024), stress hormones (Niu et al., 2018), and thyroid hormones (Zhou et al., 2022), as well as poor birth outcomes like preterm birth, particularly in women attending assisted reproductive technologies (ART) (Cai et al., 2020). For instance, Pang et al. reported that an interquartile range (IQR) increment in SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC over the 6 months before testing was associated with a decrease in AMH ranging from −7.7 % to −8.3 % (Pang et al., 2024). Additionally, Niu et al. found that an IQR increment in NO_3^- on the prior day was linked to a 12.13 % increase in corticotropin-releasing hormone (Niu et al., 2018). Recently, a study has examined short-term impacts of $PM_{2.5}$ components on reproductive hormones (Tian et al., 2024), nevertheless, people usually experience chronic exposure, and direct evidence on the association of long-term exposure to $PM_{2.5}$ constituents with reproductive hormones remains limited.

To fill this gap, utilizing the fine spatial resolution $PM_{2.5}$ constituents dataset, we assessed the relationships of long-term $PM_{2.5}$ components exposure with reproductive hormones based on female participants in an assisted reproduction cohort in Anhui, China.

2. Methods

2.1. Study area

Anhui Province consists of 16 prefecture-level cities with 63.66 million permanent residents and 14,100 square kilometers. In 2019, Anhui's annual average $PM_{2.5}$ concentration exceeded the national average by 1.28 times (46 μg/m^3 V.S. 36 μg/m^3), significantly surpassing the updated World Health Organization guideline (5 μg/m^3).

2.2. Study subjects

Participants were drawn from the Anhui-assisted reproduction cohort, with detailed information outlined in our prior publication (Fang et al., 2023). Shortly, the cohort enrolled infertile couples attending ART at the Reproductive Medicine Center of the First Affiliated Hospital of Anhui Medical University. Infertility was defined as a couple having normal sex without contraception but not conceiving within a year. In our study, demographic information was gathered using a standardized questionnaire, including age, residence, body mass index (BMI), education, occupation, smoking, parity, infertility duration, and infertility causes, covering the period from 2014 to 2020 based on the time of hormone testing ($n = 25114$). Ethical approval (No. 20160270) was awarded by the Ethics Committee of Anhui Medical University.

Inclusion criteria were participants having detailed residence information, living in Anhui province, and undergoing reproductive hormone testing ($n = 23767$). Exclusion criteria were participants with polycystic ovary syndrome, recurrent pregnancy loss, hypothyroidism, chromosomal anomalies, and hyperprolactinemia ($n = 3654$), those with missing covariate data of age, BMI, education, occupation, and sampling month ($n = 252$), as well as individuals with unassigned $PM_{2.5}$ constituents ($n = 16$). Ultimately, this study included 19,845 females with 24,396 reproductive hormone tests from 16 prefecture-level cities in Anhui, China (Fig. S1).

2.3. Serum reproductive hormones measurement

To accurately evaluate the basal state of the ovaries, blood samples were drawn during the morning of the second or third day of menstruation at the hospital's clinical laboratory (Gao et al., 2022). To optimize the ART treatment program and to maximize the chances of conception, some participants had multiple sample collections at follow-up. After centrifugation to obtain serum, quantification of serum E2, P, T, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) was performed by electrochemiluminescence immunoassay on the autoanalyzer (UniCel Dxl800 Access; Beckman Coulter, Inc., USA). All procedures were conducted under hospital supervision.

2.4. Exposure assessment

We derived the monthly mean $PM_{2.5}$ and its constituents at a fine spatial resolution (0.01° × 0.01°) from the ChinaHighAirPollutants (CHAP) dataset (Wei, 2023b,a) (https://weijing-rs.github.io/product.html). The data was extensively applied for evaluating the unfavorable impacts of air pollutants (Li et al., 2023a; Zhang et al., 2023). Specifically, $PM_{2.5}$ constituent concentration (i.e. BC, Cl^-, SO_4^{2-}, NH_4^+, and NO_3^-) was calculated by the four-dimensional spatiotemporal deep forest model, which integrated ground, satellite, and model data. The cross-validated R^2 values and root mean square error for BC, Cl^-, SO_4^{2-}, NH_4^+, and NO_3^- were 0.82 (1.64 μg/m^3), 0.66 (2.30 μg/m^3), 0.74 (5.99 μg/m^3), 0.71 (4.29 μg/m^3), and 0.75 (6.61 μg/m^3), respectively. Because OM was not directly calculated in the CHAP dataset, OM was approximately expressed as the total $PM_{2.5}$ minus the five existing $PM_{2.5}$ constituents (Zhang et al., 2023).

To estimate individual exposure, we extracted the monthly average $PM_{2.5}$ constituents from 2013 to 2020 according to participants' residential addresses. Meanwhile, to reflect long-term exposure, based on the month of examination, we calculated the average exposure level over the previous year (i.e., the previous 12 months) for each participant. Exposures in the current month of hormone measurements were excluded to minimize potential reverse causal effects (Liu et al., 2023).

For weather parameters, we collected monthly gridded estimates (0.01°×0.01°) on the average temperature and relative humidity (RH) produced by Jing Wenlong, download from https://www.geodata.cn/data/datadetails.html?dataguid = 3034046 and https://www.geodata.cn/data/datadetails.html?dataguid = 5361255&docId = 7037. We then calculated the average temperature and RH values during the year preceding the month of hormone measurements, based on each participant's residence. Additionally, greenness during the same periods was calculated to allow for the adjustment of the model. Greenness was expressed by the normalized difference vegetation index (NDVI) for 500 m buffer surrounding participants' residences (Details information was seen in Supplementary materials).

In addition, we calculated the average values of the above exposures over the six months, two years, and three years before the month of hormone measurement.

2.5. Covariates

Drawing on previous studies on air pollutants and hormones (Liu et al., 2023; Pang et al., 2024), we included several groups of covariates: (1) demographic characteristics: age, educational attainment (≤middle school, high school/vocational school, ≥college), BMI (≤24, >24 kg/m^2), smoking (yes/no), employment status (jobless, workers in manufacturing and agriculture, technical professionals, businessman/service staff, government employees), parity (0, >0), infertility causes (female/non-female factor), hormones testing season (spring, summer, autumn, or winter); (2) Socio-economic factors: annual per capita gross domestic product (GDP) of prefecture-level cities (classified by quartiles), residence (city/village); (3) environmental factors: greenness, temperature, and RH.

2.6. Statistical analysis

Descriptive characteristics were donated as number (percentage) and mean ± standard deviation (SD)/median (P_{25}, P_{75}). Pearson's correlation coefficient was employed to evaluate the correlation across environmental factors. E2, P, and T concentrations were log-transformed to improve the normality of their distribution.

To estimate the impacts of $PM_{2.5}$ and six constituents on reproductive hormones, we employed the multivariable linear mixed model (LMM) with subject-specific random intercepts, considering replicate measurements of the same subject. The percent change with the corresponding 95 % confidence interval (CI) in reproductive hormones per IQR increment of pollutants was calculated by using $100\ \% \times [\exp(\beta) - 1]$. Model 1 adjusted for demographic characteristics; Model 2 incorporated demographic characteristics and socio-economic factors; Model 3 included demographic characteristics, socio-economic factors, and environmental variables. All subsequent analyses were conducted on the basis of Model 3, the fully adjusted model. Given the possible nonlinear associations between weather factors and outcomes, temperature and RH with natural spline functions (degree of freedom (df) = 3) were incorporated into Model 3.

To further validate the reliability of the results of $PM_{2.5}$ constituents, we developed two distinct models: a constituent-proportion model and a constituent-residual model (Kang et al., 2023), which could control the confounding impact of $PM_{2.5}$ and reduce multicollinearity. Since there was a strong correlation between each constituent and $PM_{2.5}$ ($r > 0.8$) (Fig. S2), the constituent-proportion model treated the proportion of each constituent relative to the total $PM_{2.5}$ mass as the independent variable, while adjusting for $PM_{2.5}$. The constituent-residual model took the residuals derived from a linear regression model constructed for $PM_{2.5}$ and each component as the independent variable (Details of the two models were seen in Supplementary materials). Besides, to detect multicollinearity, we computed the variance inflation factor (VIF). Notably, the consistent association between these two models and Model 3 was widely recognized as reliable (Wang et al., 2023).

Since the assumption of linearity between $PM_{2.5}$ constituent and hormones might not stand, the linear term for pollutants in Model 3 was replaced by a natural cubic spline term with two knots equally spaced of pollutants distribution. The likelihood-ratio test was utilized to compare the goodness-of-fit of the two models before and after the replacement to detect potential nonlinear relationships (Shen et al., 2024).

We examined the modified effects by age (under and above 30 years), season (warm/cold) at hormone measurement (warm: May–October), and residence (village/city). The Wald test was employed to assess the significance of the variation in effect sizes across these inter-subgroups.

Sensitivity analyses were conducted to evaluate the stability of the findings. First, in Model 3, we additionally adjusted for infertility duration, with missing data (8.0 %, n = 1946) filled in at a median of 3 years. Second, the df of the natural cubic splines of temperature and RH were replaced with 4 and 5, respectively. Third, to exclude the effect of repeated measurements, our analysis was restricted to the first reproductive hormone sample from each participant (Pang et al., 2024; Wang et al., 2023). Fourth, given potential spatial variations across prefecture-level cities, we employed a multivariable LMM with prefecture-level as the random intercept. Fifth, considering the differences between women attending ART and those in the general population, our analysis was limited to women receiving ART due to non-female factors, i.e., women without fertility problems. Sixth, because the calculation of OM might introduce measurement errors, we downloaded OM (0.1° × 0.1°) from the Tracking Air Pollution (TAP) dataset (http://tapdata.org.cn/); and reanalyzed the relationship between OM and reproductive hormones. Seventh, we used different exposure periods (six months, two years, and three years) to test the long-term impacts of $PM_{2.5}$ constituents on reproductive hormones. Lastly, we applied the Weighted Quantile Sum (WQS) model to handle the health impacts of highly correlated mixed pollutant exposures. This method can estimate the overall impact of the mixture and determine the relative contribution of each component (Pan et al., 2023). More details of WQS are presented **in the** Supplemental material.

All analyses were run in R software 4.2.0. The $P_{\text{two-sided}} < 0.05$ indicated statistically significant.

3. Results

3.1. Descriptive characteristics

In total, 19,845 women who underwent ART submitted 24,396 sample tests. Of the 19,845 women, 16,459 (82.94 %) women conducted one hormone test, and 3386 (17.06 %) women submitted more than one serum hormone sample. More specifically, 2615 (13.18 %) females conducted two hormone tests, 735 (3.70 %) females conducted 3–5 hormone tests, and 36 (0.18 %) females conducted more than 6 hormone tests. The average interval between repeat hormone tests was 87.95 days. Among the 24,396 observations (Table 1), the average age was 31.5 ± 5.4 years. 26.2 % of observations were overweight or obese, 37.0 % received ART owing to non-female factors, and 41.6 % resided in village areas. Median E2, P, and T levels were 40.6 pg/mL, 0.6 ng/mL, and 1.3 nmol/L, respectively. The mean of FSH and LH levels were 7.6 mIU/mL, and 4.7 mIU/mL. There were 445 missing values for E2, 6360 for P, 2459 for T, 671 for FSH, and 557 for LH.

The averages of $PM_{2.5}$, OM, BC, Cl^-, SO_4^{2-}, NH_4^+, and NO_3^- during 1 year before the month of hormone measurements were 54.7 μg/m^3, 20.0 μg/m^3, 3.3 μg/m^3, 1.7 μg/m^3, 10.4 μg/m^3, 7.3 μg/m^3, and 12.0 μg/m^3, respectively. The average values of greenness, temperature, and RH were 0.4, 18.1°C, and 66.6 %, respectively (Table 2).

$PM_{2.5}$ was strongly correlated with each constituent ($r > 0.8$). Moderate to high correlations between the constituents were observed, with r ranging from 0.62 to 0.95. Additionally, $PM_{2.5}$ and its constituents exhibited low to moderate correlations with greenness, temperature, and RH, with $|r|$ ranging from 0.17 to 0.53 (Fig. S2).

Table 1

Characteristics of the study population.

Characteristic	All observations
Total subjects	19,845 (100.0)
Total reproductive hormone samples	24,396 (100.0)
Age; year	
Mean ± SD	31.5 ± 5.4
age ≤ 30	11,994 (49.2)
age > 30	12,402 (50.8)
BMI; kg/m^2	
Mean ± SD	22.3 ± 3.1
≤24	18,004 (73.8)
>24	6392 (26.2)
Education; N (%)	
≤Junior high school	9447 (38.7)
High school/vocational school	9333 (38.3)
≥ College	5616 (23.0)
Employment status; N (%)	
Jobless	8216 (33.7)
Workers in manufacturing and agriculture	5976 (24.5)
Technical professionals	4672 (19.2)
Businessman/service staff	3274 (13.4)
Government staff	2258 (9.3)
Smoking; N (%)	
No	24,191 (99.2)
Yes	205 (0.8)
Infertility causes; N (%)	
Non-female factor	9019 (37.0)
Female factor	15,377 (63.0)
Parity; N (%)	
No	18,656 (76.5)
Yes	5740 (23.5)
Duration of infertility; year; Median (P_{25}, P_{75})	3.0 (2.0, 5.0)
missing	1946
Season of hormones measurement; N (%)	
Spring (March-May)	8975 (36.8)
Summer (June-August)	6491 (26.6)
Autumn (September-November)	5292 (21.7)
Winter (December-February)	3638 (14.9)
Residence; N (%)	
Village	10,146 (41.6)
City	14,250 (58.4)
Prefecture-level annual GDP; ¥ per capita, N (%)	
15,303–33,314	5837 (23.9)
33,314–52,249	6295 (25.8)
52,249–97,470	5266 (21.6)
97,470–122,673	6998 (28.7)
Greenness	0.4 ± 0.1
Temperature; °C	18.1 ± 1.1
Relative humidity; %	66.6 ± 4.1
Reproductive hormones	
E2 (pg/mL); Median (P_{25}, P_{75})	40.6 (25.6, 58.3)
missing	445
P (ng/mL); Median (P_{25}, P_{75})	0.6 (0.3, 0.9)
missing	6360
T (nmol/L); Median (P_{25}, P_{75})	1.3 (0.8, 1.8)
missing	2459
FSH (mIU/mL); mean ± SD	7.6 ± 2.5
Missing	671
LH (mIU/mL); mean ± SD	4.7 ± 2.3
missing	557

Notes: Data are presented as N (%) and mean ± SD or median (P_{25}, P_{75}). N (%): number (percentage); SD: standard deviation; BMI: body mass index; GDP: gross domestic product; P: percentage.

3.2. $PM_{2.5}$ constituents and reproductive hormones

Associations between $PM_{2.5}$ and its constituents and reproductive hormones among multiple LMM with sequential adjustments were estimated (Table 3). We found that the changes in hormones in the three models were largely consistent, i.e., increases in E2 and LH levels were associated with all constituents except BC, whereas decreases in P, T, and FSH levels were associated with each constituent. Specifically, in Model 3, for each IQR increment in $PM_{2.5}$, OM, Cl^-, SO_4^{2-}, NH_4^+, and NO_3^-, E2 levels increased by 4.23 % (2.65 %, 5.84 %), 5.31 % (3.74 %, 6.89 %), 5.56 % (3.57 %, 7.59 %), 3.42 % (1.94 %, 4.91 %), 3.60 % (1.98 %, 5.25 %), and 1.69 % (0.39 %, 3.02 %), respectively, and LH levels increased by 7.69 % (3.18 %, 12.40 %), 7.73 % (3.32 %, 12.33 %), 13.56 % (7.63 %, 19.82 %), 7.67 % (3.41 %, 12.10 %), 9.07 % (4.35 %, 14.01 %), and 4.61 % (0.87 %, 8.49 %), respectively. Conversely, for each IQR increment in $PM_{2.5}$, OM, BC, Cl^-, SO_4^{2-}, NH_4^+, and NO_3^-, P levels decreased by −6.03 % (-8.12 %, −3.89 %), −7.27 % (-9.34 %, −5.16 %), −6.52 % (-8.80 %, −4.20 %), −8.52 % (-10.99 %, −5.98 %), −3.86 % (-5.90 %, −1.77 %), −4.03 % (-6.17 %, −1.83 %), and −2.64 % (-4.33 %, −0.93 %), respectively, T levels decreased by −9.41 % (-10.63 %, −8.17 %), −8.80 % (-9.99 %, −7.58 %), −9.68 % (-11.15 %, −8.18 %), −10.43 % (-11.93 %, −8.90 %), −9.15 % (-10.31 %, −7.98 %), −9.40 % (-10.66 %, −8.11 %), and −7.22 % (-8.28 %, −6.14 %), respectively, and FSH levels decreased by −21.89 % (-25.16 %, −18.48 %), −21.17 % (-24.40 %, −17.81 %), −21.34 % (-25.37 %, −17.09 %), −22.31 % (-26.39 %, −18.00 %), −20.64 % (-23.78 %, −17.37 %), −21.54 % (-24.95 %, −17.98 %), and −17.04 % (-20.02 %, −13.95 %), respectively. Besides, the results for OM from the TAP dataset were consistent with those for OM calculated via the CHAP dataset.

Table 2

Distribution of $PM_{2.5}$ and its constituents, weather conditions, and greenness during 1 year before the month of hormone measurements.

Variables	Mean ± SD	P_0	P_{25}	P_{50}	P_{75}	P_{100}
Air pollutants, μg/m^3						
$PM_{2.5}$	54.7 ± 11.9	21.18	47.28	53.80	61.22	93.23
OM	20.0 ± 6.0	6.29	16.31	19.30	23.15	41.05
BC	3.3 ± 0.8	1.04	2.81	3.30	3.83	6.13
Cl^-	1.7 ± 0.4	0.64	1.37	1.61	1.95	3.66
SO_4^{2-}	10.4 ± 1.7	4.92	9.32	10.25	11.22	16.58
NH_4^+	7.3 ± 1.2	2.91	6.49	7.28	8.01	11.03
NO_3^-	12.0 ± 2.6	3.04	10.65	12.05	13.17	20.88
Weather factors						
Temperature (°C)	18.1 ± 1.1	12.87	17.29	18.05	18.92	22.23
RH (%)	66.6 ± 4.1	55.58	63.40	66.33	69.70	81.09
Greenness						
$NDVI_{500\ m}$	0.4 ± 0.1	0.08	0.30	0.36	0.49	0.79

Notes: SD, standard deviation; P, percentage, $PM_{2.5}$, fine particulate matter; OM, organic matter; BC, black carbon; Cl^-, chloride; SO_4^{2-}, sulfate; NH_4^+, ammonium; NO_3^-, nitrate; RH, relative humidity; $NDVI_{500\ m}$, normalized difference vegetation index for the 500 m buffer around the participant's residential address.

In both the constituent-proportion model and the constituent-residual model (Fig. 1), associations of elevated E2 levels with OM, and elevated LH levels with Cl^- and NH_4^+, remained statistically significant. Similarly, the associations of reduced P levels with OM and Cl^-, and reduced T levels with SO_4^{2-}, remained statistically significant. However, there was no statistically significant relationship between reduced FSH levels and any of the constituents. This means that the negative associations of constituents with FSH in Model 3 might be due to its strong correlation with $PM_{2.5}$ rather than the inherent toxicity of constituents. Therefore, in subsequent analyses, we no longer focused on FSH.

Besides, we observed some statistically significant associations opposite to Model 3, which may be due to potential non-linear associations between reproductive hormones and components. Table S1 showed that the maximum value of VIF was 2.31 in the constituent-proportion models and 1.59 in the constituent-residual models, suggesting no multicollinearity among the variables.

3.3. Exposure-response curves

Exposure-response curves depicting the relationship between $PM_{2.5}$ constituents and reproductive hormones were illustrated (Fig. 2). $PM_{2.5}$ and six constituents exhibited an approximate U-shaped nonlinear relationship with E2 and P ($P_{nonlinear}<0.001$). When constituents were

Table 3
Percentage change and 95 % CI in reproductive hormones for each IQR increment in $PM_{2.5}$ and its constituent concentrations in multiple LMM with sequential adjustments.

Variables	Model 1	Model 2	Model 3
E2 [% change (95 %CI)]			
$PM_{2.5}$	0.95 (−0.28, 2.19)	**3.39 (1.96, 4.83)**	**4.23 (2.65, 5.84)**
OM	**1.46 (0.26, 2.68)**	**4.46 (3.02, 5.92)**	**5.31 (3.74, 6.89)**
OM (TAP)	0.65 (−0.67, 1.99)	**2.53 (1.04, 4.03)**	**2.92 (1.21, 4.66)**
BC	−0.74 (−2.18, 0.72)	0.55 (−1.03, 2.15)	0.83 (−1.02, 2.72)
Cl^-	1.27 (−0.20, 2.77)	**4.91 (3.13, 6.71)**	**5.56 (3.57, 7.59)**
SO_4^{2-}	0.48(−0.69, 1.66)	**2.90 (1.52, 4.30)**	**3.42 (1.94, 4.91)**
NH_4^+	0.65 (−0.65, 1.97)	**2.82 (1.33, 4.32)**	**3.60 (1.98, 5.25)**
NO_3^-	0.28 (−0.76, 1.33)	**1.22 (0.08, 2.37)**	**1.69 (0.39, 3.02)**
P [% change (95 %CI)]			
$PM_{2.5}$	−4.35 (−6.08, −2.60)	−5.51 (−7.42, −3.56)	−6.03 (−8.12, −3.89)
OM	−5.17 (−6.87, −3.45)	−6.91 (−8.84, −4.94)	−7.27 (−9.34, −5.16)
OM (TAP)	−3.5(−5.33, −1.63)	−4.28(−6.27, −2.24)	−6.26 (−8.48, −4.00)
BC	−5.05 (−6.92, −3.14)	−5.40 (−7.40, −3.35)	−6.52 (−8.80, −4.20)
Cl^-	−4.84 (−6.80, −2.83)	−6.65 (−8.92, −4.33)	−8.52 (−10.99, −5.98)
SO_4^{2-}	−2.98 (−4.66, −1.26)	−4.04 (−5.95, −2.09)	−3.86 (−5.90, −1.77)
NH_4^+	−3.13 (−4.93, −1.30)	−4.04 (−6.00, −2.05)	−4.03 (−6.17, −1.83)
NO_3^-	−1.92 (−3.32, −0.49)	−2.23 (−3.70, −0.73)	−2.64 (−4.33, −0.93)
T [% change (95 %CI)]			
$PM_{2.5}$	−10.36 (−11.33, −9.38)	−8.81 (−9.93, −7.68)	−9.41 (−10.63, −8.17)
OM	−9.96 (−10.91, −8.99)	−8.50 (−9.62, −7.37)	−8.80 (−9.99, −7.58)
OM (TAP)	−9.80(−10.85, −8.73)	−7.87(−9.05, −6.67)	−8.78 (−10.13, −7.42)
BC	−9.88 (−11.05, −8.70)	−8.17(−9.46, −6.87)	−9.68 (−11.15, −8.18)
Cl^-	−11.20 (−12.36, −10.02)	−9.77 (−11.14, −8.38)	−10.43 (−11.93, −8.90)
SO_4^{2-}	−10.22 (−11.15, −9.28)	−8.95 (−10.04, −7.85)	−9.15 (−10.31, −7.98)
NH_4^+	−10.80 (−11.83, −9.75)	−9.07 (−10.24, −7.88)	−9.40 (−10.66, −8.11)
NO_3^-	−7.71 (−8.57, −6.84)	−6.37 (−7.31, −5.42)	−7.22 (−8.28, −6.14)
FSH [% change (95 %CI)]			
$PM_{2.5}$	−22.39 (−25.03, −19.67)	−19.70 (−22.80, −16.48)	−21.89 (−25.16, −18.48)
OM	−21.74 (−24.33, −19.06)	−19.45 (−22.53, −16.24)	−21.17 (−24.40, −17.81)
OM (TAP)	−21.59 (−24.48, −18.6)	−17.74 (−21.09, −14.26)	−21.38 (−25.01, −17.59)
BC	−21.78 (−25.00, −18.43)	−18.24 (−21.88, −14.43)	−21.34 (−25.37, −17.09)
Cl^-	−21.98 (−25.20, −18.62)	−19.44 (−23.30, −15.39)	−22.31 (−26.39, −18.00)
SO_4^{2-}	−21.23 (−23.79, −18.59)	−19.15 (−22.17, −16.01)	−20.64 (−23.78, −17.37)
NH_4^+	−22.69 (−25.50, −19.78)	−19.54 (−22.79, −16.14)	−21.54 (−24.95, −17.98)
NO_3^-	−17.86 (−20.28, −15.36)	−14.89 (−17.60, −12.08)	−17.04 (−20.02, −13.95)
LH [% change (95 %CI)]			
$PM_{2.5}$	2.55 (−0.93, 6.14)	**6.55 (2.47, 10.81)**	**7.69 (3.18, 12.40)**
OM	2.64 (−0.75, 6.15)	**6.81 (2.73, 11.06)**	**7.73 (3.32, 12.33)**
OM (TAP)	1.78 (−1.94, 5.65)	**5.58 (1.33, 10.02)**	**7.26 (2.34, 12.42)**
BC	−1.56 (−5.56, 2.61)	1.44 (−3.02, 6.10)	2.06 (−3.13, 7.54)
Cl^-	**6.68 (2.32, 11.22)**	**11.69 (6.4, 17.25)**	**13.56 (7.63, 19.82)**
SO_4^{2-}	3.03 (−0.30, 6.48)	**6.85 (2.87, 10.98)**	**7.67 (3.41, 12.10)**
NH_4^+	**4.11 (0.35, 8.01)**	**8.07 (3.73, 12.59)**	**9.07 (4.35, 14.01)**
NO_3^-	0.97 (−1.97, 4.01)	**3.72 (0.45, 7.09)**	**4.61 (0.87, 8.49)**

Notes: Model 1 was adjusted for age, BMI, education, employment status, smoking, parity, causes of infertility, and season of hormone measurement. Model 2 was further adjusted for residence and GDP. Model 3 was further adjusted for greenness, and nonlinear association of temperature and RH (df = 3).
OM (TAP) was the OM from the Tracking Air Pollution (TAP) dataset.
Bold indicated $P<0.05$.

below the reference value, E2 and P levels decreased with increasing exposure levels, whereas constituents exceeded the reference value, E2 and P levels increased with increasing exposure levels. Additionally, the exposure-response curves for $PM_{2.5}$ constituents and T showed an obvious downward trend, while LH showed a significant upward trend only at higher concentrations of $PM_{2.5}$ constituents.

3.4. *Subgroup analyses*

As shown in Fig. 3, significant variations in effect sizes of specific $PM_{2.5}$ constituents on hormones were observed across age, season, and residence subgroups ($P_{\text{Wald test}}<0.05$). Specifically, first, when exposed to $PM_{2.5}$ constituents, women aged≤30 exhibited a more pronounced increase in E2 levels and a decrease in T levels, whereas women aged>30 had a greater decrease in P levels. Second, E2 and P were more closely linked to certain components in the cool season, while T and LH were more strongly linked to $PM_{2.5}$ constituents in the warm season. Third, E2 and T exhibited higher sensitivity to $PM_{2.5}$ constituents in village areas, whereas P showed greater sensitivity in city areas.

3.5. *Sensitivity analyses*

First, relationships between $PM_{2.5}$ and its constituents and reproductive hormones remained robust after additionally adjusting for infertility duration, varying the df of temperature and RH, keeping only the first hormone test, and taking the prefecture-level as the random intercept. Second, among women without fertility problems, the results of P and T remained unchanged, except for E2 and LH (Table S2). Third, the results of E2, P, and LH for the 6-month and 2-year exposure periods were consistent with those for the 1-year exposure period, whereas the results for the 3-year exposure period were not statistically significant. The results of T were consistent across different exposure periods (Fig. S3). Fourth, the WQS model showed that the mixture of $PM_{2.5}$ and its constituent was significantly linked to increases in E2 and LH, while decreases in P and T. Particularly, OM exhibited the most substantial impact on E2, Cl^- on LH and P, and SO_4^{2-} on T (Fig. S4).

4. Discussion

This large-scale population study is the first to quantitatively assess the impacts of long-term exposure to $PM_{2.5}$ components on reproductive hormones among women attending ART. Our study provided robust evidence of linear associations of increased E2 levels with OM, elevated LH levels with Cl^- and NH_4^+, reduced P levels with OM and Cl^-, and decreased T levels with SO_4^{2-}. Additionally, E2 and P showed U-shaped non-linear exposure-response curves with $PM_{2.5}$ constituents. The results of this study on $PM_{2.5}$ were broadly in line with our previous findings that $PM_{2.5}$ was suggestively positively associated with E2, and significantly inversely associated with P and T (Fang et al., 2023). In comparison, our current study stood out in quantifying the specific constituents of $PM_{2.5}$ on female reproductive hormones.

Using high-resolution $PM_{2.5}$ constituent data, we found that prolonged exposure to OM was linearly linked to elevated E2 levels. Research suggested that high concentrations of E2 were linked to elevated risks of adverse pregnancy outcomes, such as premature rupture of membranes and small for gestational age (Hewitt et al., 2022; Imudia et al., 2012). Our findings demonstrated, in part, that prolonged $PM_{2.5}$ component exposure was linked to adverse pregnancy outcomes (Jiao et al., 2023), which was explainable. We speculated that the positive relationship of $PM_{2.5}$ constituents with E2 might be because of the

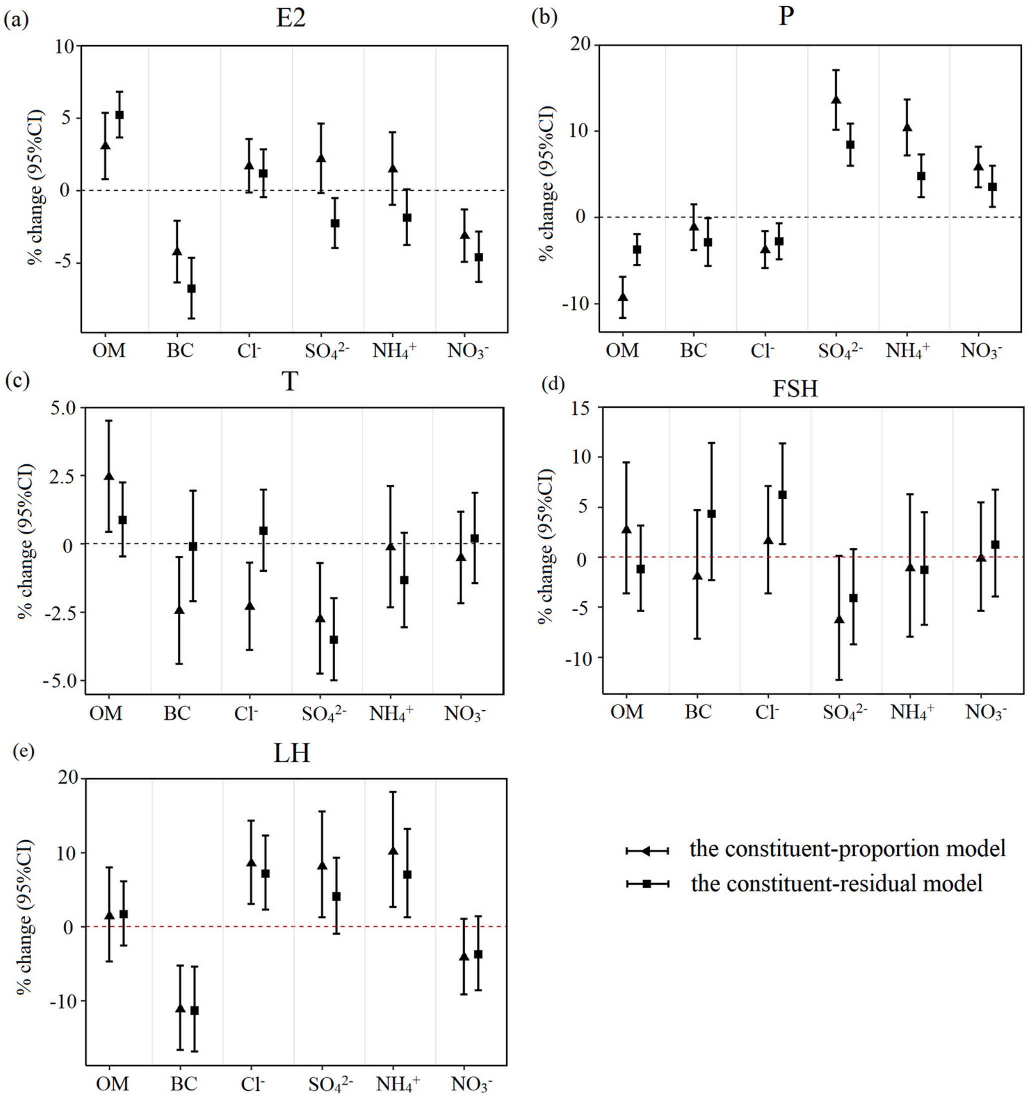

Fig. 1. Percentage change and 95 % CI in reproductive hormones for each IQR increment in $PM_{2.5}$ constituent concentrations in the constituent-proportion model and the constituent-residual model. Notes: covariates included age, BMI, educational level, employment status, smoking, parity, causes of infertility, the season of hormones measurement, residence, GDP, greenness, and nonlinear association of temperature and RH.

interaction of polycyclic aromatic hydrocarbons in OM with the aryl hydrocarbon receptor. This interaction could disrupt the normal regulation of enzymes (such as the cytochrome P450 family) involved in E2 metabolism (Payne and Hales, 2004; Son et al., 2002), leading to a slower metabolic rate of E2 and subsequently higher E2 concentrations in the body. Similarly, another hormone, LH, was linearly and positively associated with Cl^- and NH_4^+ in this study. Our findings were supported by a survey of adult men that showed a 0.6 % increase in LH for each 10 μg/m^3 increment of $PM_{2.5}$. Future studies are warranted to probe the potential biological mechanisms of these associations.

Besides, the decrease in P level was found to be linearly associated with OM and Cl^-. P is known to help stabilize the lining of the uterus and prevent premature contractions, thereby preventing preterm labor (Conde-Agudelo et al., 2023). Many studies have demonstrated that $PM_{2.5}$ constituents may elevate preterm labor risks (He et al., 2022; Li et al., 2019). Therefore, understanding the relationship of $PM_{2.5}$ constituents with P may offer insights into the detrimental consequences of $PM_{2.5}$ constituents on preterm birth. A possible pathway is that smaller-sized constituents can translocate from the lungs to the brain, and then act upon the hypothalamic-pituitary-ovarian (HPO) axis, affecting P synthesis (Hopkins et al., 2018). Additionally, $PM_{2.5}$ constituents might also disrupt DNA methylation, causing ovarian inflammation and oxidative stress, leading to lower P levels (Lei et al., 2019; Niranjan and Thakur, 2017).

Interestingly, our cubic spline analysis revealed an approximate U-shaped nonlinear relationship of $PM_{2.5}$ constituents with E2 and P, consistent with our previous findings on $PM_{2.5}$ (Fang et al., 2023). According to exposure-response curve results, E2 and P showed a decreasing trend when the constituents were below reference values. One possible explanation is that $PM_{2.5}$ constituents could activate the hypothalamus–pituitary–adrenal axis (Niu et al., 2018), thereby inhibiting E2 and P secretion (Acevedo-Rodriguez et al., 2018). Conversely, we noticed that $PM_{2.5}$ constituents above the reference value might increase E2 and P levels. This aligns with an in vitro study that found that $PM_{2.5}$ significantly increased P secretion (Nääv et al., 2020). Nevertheless, further evidence is still needed to elucidate the link between $PM_{2.5}$ constituents and E2 and P levels.

Our study revealed that the decrease in T level was associated with SO_4^{2-}, which was further supported by the exposure-response curves. Similarly, several studies have suggested a link between $PM_{2.5}$ constituents and decreased AMH levels among women (Liu et al., 2023; Pang et al., 2024), as well as decreased sperm quality among men (Liu et al., 2022b; Wang et al., 2023). Although the specific mechanism for the $PM_{2.5}$ constituents-T relationship remains unclarified, two potential

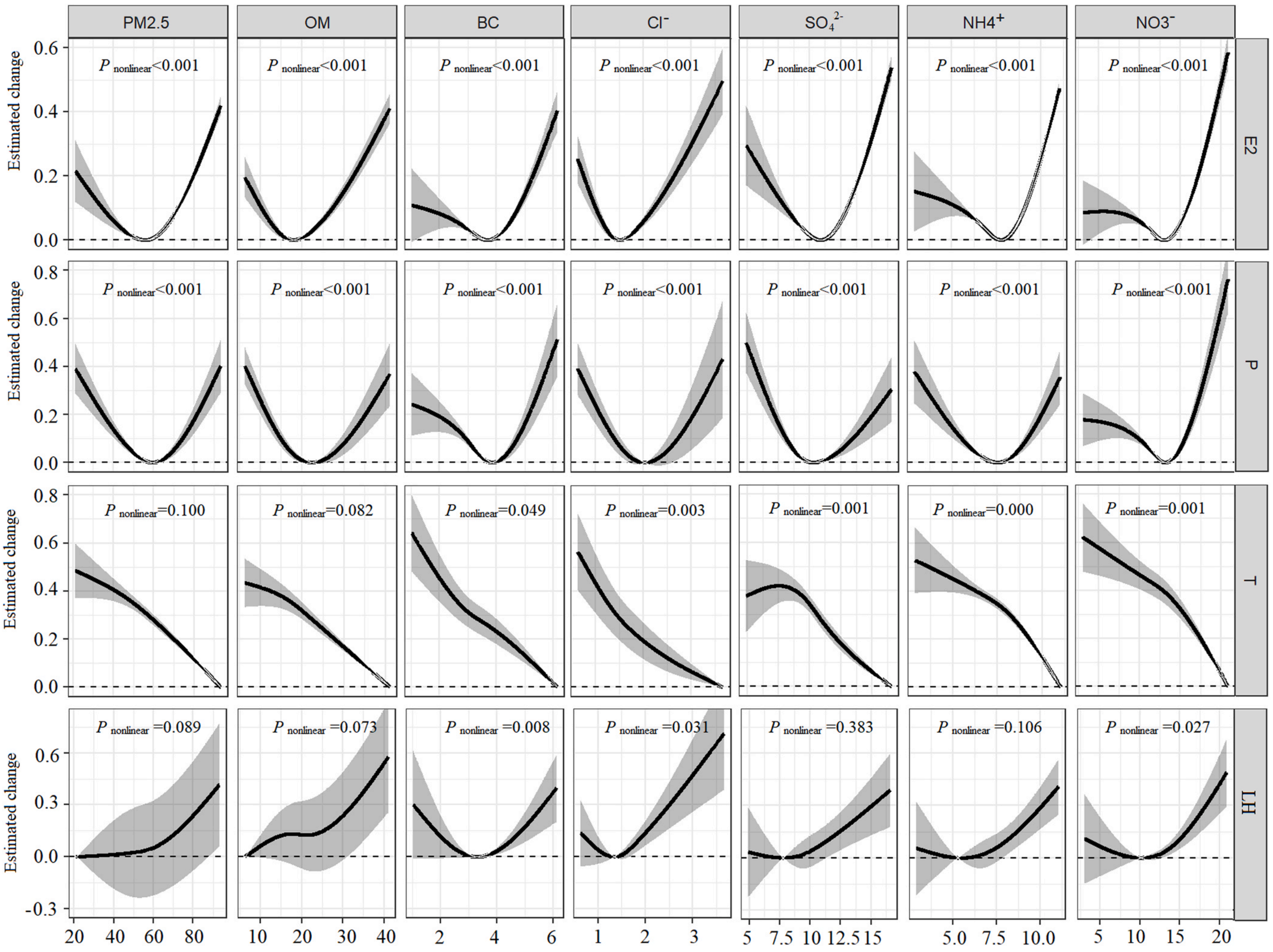

Fig. 2. Exposure-response curves for $PM_{2.5}$ and its constituents with reproductive hormones. Notes: the model was adjusted for age, BMI, educational level, employment status, smoking, parity, causes of infertility, the season of hormones measurement, residence, GDP, greenness, and nonlinear association of temperature and RH. The nonlinear is examined by the likelihood-ratio test. The x-axis represented the average concentrations of each constituent over the 1 year before the month of hormone measurement. The y-axis represented the change with 95 % CI in hormone at a specific constituent concentration compared to the referent concentration (i.e., the concentration corresponding to the lowest point of the exposure-response curve).

pathways have been proposed. First, water-soluble minerals (e.g., SO_4^{2-}) contribute to the uptake of metallic elements in $PM_{2.5}$ by generating an acidic environment in the microcirculation, thus aggravating ovarian tissue damage and lowering T levels (Tao et al., 2021). Second, $PM_{2.5}$ constituents may provoke inflammatory responses and promote the reactive oxygen species production in the hypothalamus, inhibiting the HPO axis, and thus leading to reduced T levels (Ying et al., 2014).

Subgroup analyses suggested that age, season, and residence might modify the effect of specific $PM_{2.5}$ components on reproductive hormones. First, when exposed to $PM_{2.5}$ constituents, women aged$\leq$30 exhibited a greater increase in E2 levels and a decrease in T levels, whereas women aged>30 showed a larger decrease in P levels, consistent with our previous study (Fang et al., 2023). Second, the effects of $PM_{2.5}$ constituents on E2 and P were more evident during the cold season. This could be due to coal and biomass burning and specific meteorological conditions that cause severe $PM_{2.5}$ pollution in colder months (Wang et al., 2014). Conversely, the effects of $PM_{2.5}$ constituents on T and LH levels were more largely during the warm season, likely due to increased outdoor activities leading to higher $PM_{2.5}$ inhalation. Third, in village areas, E2 and T were more sensitive to the $PM_{2.5}$ constituents. Possible reasons lie in that women living in village areas often use wood-burning stoves, increasing exposure to $PM_{2.5}$ constituents from biomass burning. In contrast, in city areas, P was more vulnerable to $PM_{2.5}$ constituents, probably due to dense population and heavy traffic pollution.

Our study possesses several advantages. Firstly, this study is the first to quantitatively assess the relationship between $PM_{2.5}$ constituents and female reproductive hormones based on a large-scale longitudinal study. The large sample size and broad geographic coverage endow this study with robust statistical power to discern these associations. Secondly, we controlled for socio-economic factors (e.g., GDP and residence) and environmental factors (e.g., greenness, temperature, and RH), ensuring the accuracy of our results. Thirdly, both the constituent-proportion model and constituent-residual model consistently identified the most critical constituents while effectively addressing the confounding of $PM_{2.5}$ and potential collinearity issues.

Inevitably, limitations must be acknowledged. Firstly, despite utilizing $PM_{2.5}$ constituents gridded data with a fine spatial resolution ($0.01^\circ \times 0.01^\circ$), there may be exposure misclassification compared to personal wearable measurement techniques. Secondly, due to limitations in exposure assessment methods, we could not evaluate the impact of other $PM_{2.5}$ constituents such as metals. Thirdly, participant relocation during the exposure period was overlooked when calculating exposure levels, potentially introducing measurement errors. Fourthly, despite adjusting for some key confounding factors, residual confounders (e.g., dietary habits) may still exist due to data unavailability.

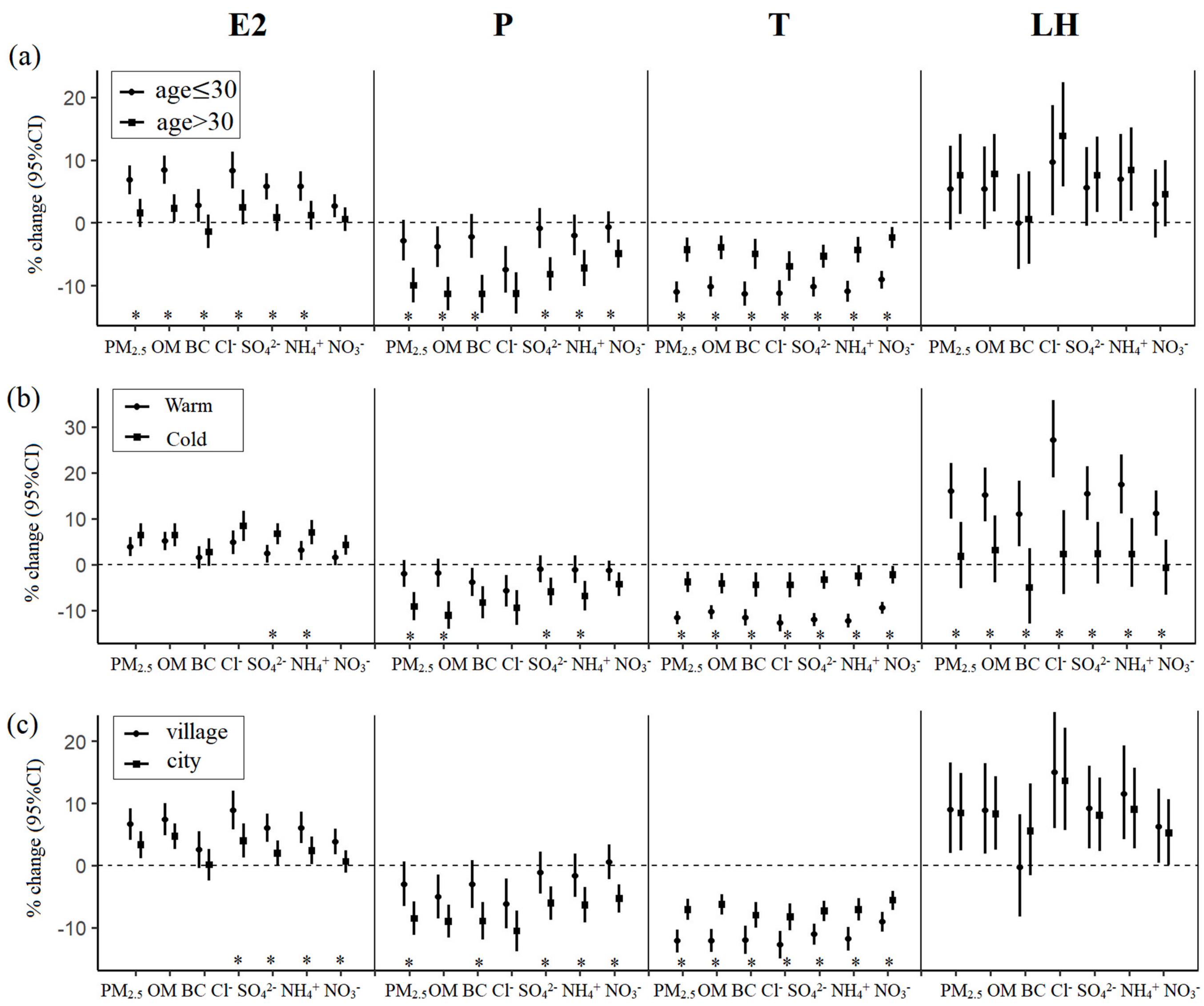

Fig. 3. Percentage change and 95 % CI in reproductive hormones for each IQR increment in $PM_{2.5}$ and its constituents stratified by age (≤30/>30 years), season at hormone measurement (warm/cold), and residence (city/village). Notes: * denotes $P_{\text{Wald test}} < 0.05$, that is, the significant difference across subgroups by Wald test. The model was adjusted for age, BMI, education, employment status, smoking, parity, causes of infertility, the season of hormones measurement, residence, GDP, greenness, and nonlinear association of temperature and RH. The corresponding grouping factors were removed from the model.

Fifthly, on the second or third day of menstruation, E2 levels rise as the follicle develops. This physiologic increase may confuse the association between $PM_{2.5}$ constituents and E2 levels. Lastly, given that participants were women receiving ART, we excluded women with fertility problems in sensitivity analyses, but caution is still warranted in generalizing our findings to a broader group of women.

5. Conclusions

This large-scale population study suggested positive associations of E2 levels with OM, and LH levels with Cl^- and NH_4^+, whereas negative associations of P levels with OM and Cl^-, and T levels with SO_4^{2-} among women attending ART. Our study provides epidemiological evidence for developing the $PM_{2.5}$ controlling strategy to maximize the benefit to female reproductive health. Considering the persistent $PM_{2.5}$ pollution and the increasing concerns about female reproductive issues, further research is urgently needed to validate our results.

CRediT authorship contribution statement

Guoqi Cai: Validation. **Jing Wei:** Resources, Data curation. **Yuting Chen:** Methodology, Investigation. **Tao Zhang:** Investigation. **Yongzhen Peng:** Visualization, Validation, Data curation. **Jianping Ni:** Methodology, Data curation. **Lanlan Fang:** Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Huifen Xiang:** Supervision, Resources, Funding acquisition. **Yubo Ma:** Visualization, Methodology, Formal analysis, Conceptualization. **Faming Pan:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Hui Zhao:** Visualization, Validation, Conceptualization. **Cong Ma:** Validation, Resources, Investigation. **Guosheng Wang:** Methodology, Data curation.

Ethics approval

The study was approved by the local ethics committee of Anhui Medical University.

Source of funding

This study was supported by grants from the funds for National Natural Science Foundation of China, China (No. 82071614) and Scientific Research of Anhui Medical University, China No. 2021lcxk004).

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.

Data availability

The data that has been used is confidential.

Acknowledgments

The authors thank the participants who made this study possible and gratefully acknowledge the role of the staff and volunteers in collecting the data. Acknowledgement for the data support from "National Earth System Science Data Center, National Science & Technology Infrastructure of China. (http://www.geodata.cn)".

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.116915.

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