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Exposure to ambient particulate matter and ovarian reserve impairment among reproductive age women in China

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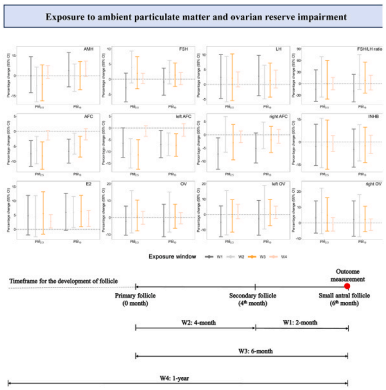
HIGHLIGHTS

- We assessed the impact of ambient particulate matter on various ovarian reserve indicators.
- $PM_{2.5}$ and PM_{10} was associated with decreased AFC and increased E2 level.
- Modification effects of age and BMI was observed.

GRAPHICAL ABSTRACT



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ABSTRACT

Ovarian aging, characterized by a decline in ovarian reserve, is a critical concern in female reproductive health. However, the evidence linking ambient air pollution exposure with ovarian reserve impairment remains limited. We aimed to estimate the association between exposure to fine particulate matter ($PM_{2.5}$) and respirable particulate matter (PM_{10}) and key indicators of ovarian reserve, including antral follicle count (AFC), ovarian volume (OV), anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), FSH/LH ratio, and inhibin B (INHB). The cohort consisted of women attending an infertility clinic at the Tongji Reproductive and Environmental (TREE) study between 2018 and 2020. We used multivariate linear and Poisson regression models to estimate the association between $PM_{2.5}$ and PM_{10} exposure and these

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ovarian reserve indicators. Our results showed that $PM_{2.5}$ and PM_{10} exposure were associated with a reduction in AFC and an increase in E2 levels, highlighting the adverse effects of ambient air pollution on ovarian reserve. Our findings have important public health implications, emphasizing the urgent need for interventions to safeguard female reproductive health and reduce exposure to ambient air pollution.

1. Introduction

Infertility, affecting approximately 17.5 % of couples globally, has emerged as a significant concern in recent years [1–3]. According to the Seventh Population Census in China, the total fertility rate in 2020 was reported to be 1.3 [4]. An important contributing factor to declining fertility is decreased ovarian reserve, characterized by a reduction in quantity and/or quality of oocytes in the ovaries, which is typically assessed through markers such as antral follicle count (AFC), anti--Müllerian hormone (AMH), and follicle-stimulating hormone (FSH). Decreased ovarian reserve can lead to reduced ovarian responsiveness and may adversely affect the success of assisted reproductive technologies [5–7]. Additionally, decreased ovarian reserve has been linked to menstrual irregularities and may increase the risk of premature ovarian failure [8]. Therefore, identifying modifiable risk factors for ovarian reserve impairment is crucial for enhancing fertility and improving female reproductive health.

Numerous factors, including demographic, genetics, and environmental factors, have been identified as risk factors for ovarian reserve impairment [9]. Alarmingly, over 99 % of the global population is exposed to air pollution levels exceeding the limits set by the World Health Organization [10]. The adverse effects of fine particulate matter ($PM_{2.5}$) and respirable particulate matter (PM_{10}) on health are well documented [11]. Previous studies have suggested that exposure to $PM_{2.5}$ is associated with a reduction in ovarian reserve, as measured by AMH and AFC [12–16]. However, the evidence remains limited and heterogeneous [17,18]. For example, a study conducted in Tehran, Iran, found no evidence of an association between exposure to PM_{10} and $PM_{2.5}$ and AMH levels [17]. Additionally, few studies have examined the association between ambient air pollution and ovarian reserve as measured by ovarian volume (OV) and other serum sex hormones, such as estradiol (E2), FSH/LH ratio, luteinizing hormone (LH) and inhibin B (INHB) [19].

Accordingly, we aimed to comprehensively estimate the association between exposure to ambient $PM_{2.5}$ and PM_{10} and key indicators of ovarian reserve in women attending an infertility clinic in China. The ovarian reserve indicators included AFC (total, left, and right), OV (total, left, and right), AMH, FSH, LH, E2, FSH/LH ratio, and INHB.

2. Methods

2.1. Study population

Study participants were derived from the ongoing Tongji Reproductive and Environmental (TREE) study, a longitudinal cohort study initiated in December 2018 and continuing through 2020. Detailed information about the TREE study has been published elsewhere [20]. A total of 1374 individuals residing in Hubei province for at least one year with detailed residential addresses were enrolled in our study. We excluded: (1) 1 participant diagnosed with primary ovarian insufficiency; (2) 43 participants diagnosed with chromosomal abnormalities or congenital genitourinary malformations; (3) 296 participants with a history of ovarian surgery, polycystic ovary syndrome, or endometriosis; (4) 22 participants with endocrine or immune system disorders, such as hyperprolactinemia, hypothyroidism, or systemic lupus erythematosus; (5) 10 participants with a history of tumors or pelvic radiotherapy treatment; and (6) 14 participants younger than 20 or older than 45 years. The final analysis included 988 participants (Fig. 1). Ethical approval for the study was obtained from the Tongji Medical College Ethics Committee, and all participants provided informed consent prior to enrollment.

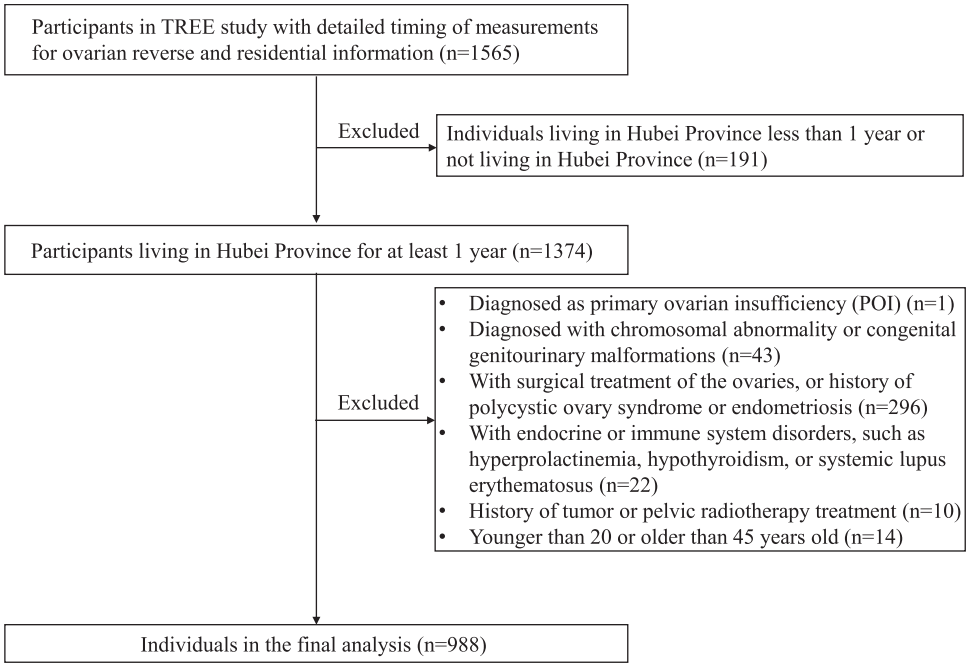

Fig. 1. Flowchart of the study participants.

2.2. Assessment of ovarian reserve

Ovarian reserve in this study was evaluated using several indicators, including OV, AFC, AMH, FSH, LH, E2, INHB, and FSH/LH ratio. The assessments were performed by reproductive gynecology specialists and other trained professionals. Further details can be found in previous publications [20,21].

Blood samples were collected during the early follicular phase of the menstrual cycle (days 2–5), and serum was separated for hormone analysis. Serum AMH levels were measured using commercial enzyme-linked immunosorbent assays (ELISA) from Ansh Labs. Serum FSH levels were determined using a direct chemiluminescence immunoassay on the ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Additional hormones, including LH, E2, and INHB, were assessed using chemiluminescence immunoassays on the same system. The FSH/LH ratio was calculated as the ratio of FSH to LH levels.

OV and AFC were assessed for both the right and left ovaries by transvaginal ultrasound during days 2–5 of an unstimulated menstrual cycle. OV for each ovary (in mm^3) was calculated using the formula for the volumes of a prolate ellipsoid: [length (mm) × width (mm) × width (mm)] × (π/6). Total OV was estimated by summing the volumes of the right and left ovaries. Follicles measuring 2–10 mm in diameter were counted, and total AFC was calculated as the sum of follicles in both ovaries [19].

2.3. Exposure assessment

We obtained daily ambient concentrations of $PM_{2.5}$ ($\mu g/m^3$), PM_{10} ($\mu g/m^3$) and ambient gaseous pollutants (sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3) and carbon monoxide (CO)) from the ChinaHighAirPollutants (CHAP) dataset. This dataset, widely used to study the association between ambient air pollution and human health [22–24], provides long-term, full-coverage, and high-resolution data. It incorporates various data sources, methodologies, including ground station measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations, and artificial intelligence techniques to capture the spatiotemporal variability of air pollution. With a tenfold cross-validation R^2 of 0.92 for $PM_{2.5}$ and 0.90 for PM_{10}, this dataset demonstrates high accuracy and reliability [25–27].

We used participants' residential addresses to estimate their average exposure to ambient air pollutants across different exposure windows (Fig. 2) [28]. Evaluating exposure to air pollutants before and during key stages of early follicle development (i.e., primary follicle, secondary follicle and small antral follicle) is crucial for estimating the impact of air pollution on ovarian reserve impairment. In our study, we selected four 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 prior to measurement); (4) W4: 1-year prior to measurement, representing long-term air pollution exposure.

2.4. Covariates

We used standardized questionnaires to collect information on individual demographic, behavioral, and health characteristics, and disease and treatment history. Clinical examinations were performed by registered nurses and doctors. We included the following variables as potential confounders: maternal age, education, smoking status, alcohol consumption, current employment status, passive smoking, causes of infertility, type of infertility, duration of infertility, season of indicator measurement, warm season of indicator measurement, regular menstrual cycle, and body mass index (BMI). Maternal age was categorized as < 30 or ≥ 30 years [28]. Passive smokers were defined as individuals exposed to secondhand smoke for at least 15 min daily, either at home or work [29]. We defined the warm season as May 1st to October 30th. A regular menstrual cycle was defined as having a duration between 21 to 35 days [13]. BMI (kg/m^2) was calculated by dividing weight (kg) by the square of height (m), and categorized as < 24.0 kg/m^2 or ≥ 24 kg/m^2 [28]. Daily ambient temperature and relative humidity data were obtained from the National Climate Data Center and assigned to each participant based on the nearest monitoring station.

2.5. Statistical analysis

Demographic and clinical characteristics were presented using descriptive statistics. Continuous variables were expressed as means ± standard deviations (SD), and categorical variables as frequencies and percentages.

Poisson regression with a log-link function was used to estimate the association between $PM_{2.5}$ and PM_{10} exposure and AFC, which is more suitable for count data than linear regression. The association with other ovarian reserve indicators was estimated using multivariate linear regression. In the crude models, we only adjusted for age (< 30 versus ≥ 30 years). In the fully adjusted models, we additionally adjusted for education (primary school or less, junior high school, senior high school or college, postsecondary or university, postgraduate or higher), smoking status (yes versus no), alcohol consumption (yes versus no), employment status (yes versus no), passive smoking (yes versus no), season of indicator measurement (spring [March-May], summer [June-August], autumn [September-November], and winter [December-February]), warm season of indicator measurement (yes versus no), causes of infertility (female, male, both, and unexplained), infertility type (primary versus secondary infertility), infertility duration (continuous, years), BMI (<24 kg/m^2 versus ≥ 24 kg/m^2), and regular menstrual cycle (yes versus no). We imputed missing values using the *chained equations* method. To reduce the influence of potential outliers,

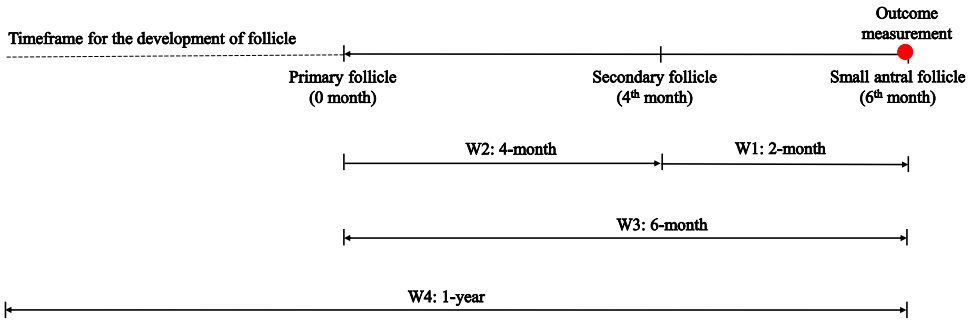

Fig. 2. Exposure windows before and during the development of antral follicles. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the primary to secondary antral follicle stage (four months prior to secondary follicle development); (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.

OVs and serum hormone levels were natural log-transformed. We assessed multicollinearity using the variance inflation factor (VIF), with values greater than 5 indicating multicollinearity. In our analysis, no significant multicollinearity was detected (data not shown).

We presented the results as percentage change, calculated as $100 \times [\exp(\beta) - 1]$, with corresponding 95 % confidence interval (95 % CI) per interquartile range (IQR) increase in air pollutant concentrations. In the formula, β denotes the regression coefficient estimated from the regression analysis.

To examine the exposure-response relationship between air pollutant exposure and ovarian reserve, we introduced a restricted cubic spline of $PM_{2.5}$ or PM_{10} concentration into the fully adjusted models.

We conducted several sensitivity analyses to assess the robustness of our results. First, to minimize the influence of individual behavioral characteristics or reproductive health conditions, we restricted the analysis to nonsmokers, non-alcohol drinkers, women with regular menstrual cycles, or those without diminished ovarian reserve, respectively. Diminished ovarian reserve was defined as AFC ≤ 7, FSH ≥ 10 mIU/ml, or AMH ≤ 1.1 ng/ml [29]. Second, we repeated our main analyses exclusively among women diagnosed with infertility attributed to female factors. Third, to address the potential impact of meteorological factors, we additionally adjusted for the 7-day moving average exposure to ambient air temperature and relative humidity in the fully adjusted models. Fourth, we constructed two-pollutant models to examine the independent effects of ambient particulate matter on ovarian reserve indicators, adjusting for gaseous air pollutants one at a time. This adjustment was made when the Spearman correlation between ambient PM and the co-pollutant < 0.8 (Table S1) [30].

We performed subgroup analyses to evaluate whether the association between $PM_{2.5}$ or PM_{10} exposure and ovarian reserve varied by age ($<$ 30 versus $\geq$ 30 years) and BMI ($<$ 24 versus $\geq$24 kg/m^2). We tested the potential effect modification by including a multiplicative interaction term in the models.

All results were presented as percentage change with 95 % confidence intervals (CIs). A two-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.3.1 and SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Characteristics of study participants and exposure

The characteristics of the study population were presented in Table 1. The analytical sample included 988 participants, with a mean (SD) age of 30.86 (4.57) years and a mean BMI of 22.00 (3.02) kg/m^2. Most participants were over 30 years old (58.51 %) and non-obese (75.71 %). Additionally, participants were predominantly nonsmokers (94.03 %), non-drinkers of alcohol (77.02 %), and currently unemployed (53.64 %). Most participants reported having a regular menstrual cycle (85.32 %), while 47.67 % were exposed to passive smoking. Concentrations of $PM_{2.5}$ and PM_{10} during the four exposure windows were shown in Table S2. The mean concentrations of $PM_{2.5}$ and PM_{10} exposure from the primary to small antral follicle stage (W3) were 48.80 μg/m^3 and 77.65 μg/m^3, respectively.

3.2. Association between exposure to air pollutants and ovarian reserve

Exposure to $PM_{2.5}$ and PM_{10} was linked to reduced ovarian reserve, as indicated by lower AFC and higher E2 levels (Fig. 3). Specifically, exposure to $PM_{2.5}$ and PM_{10} was consistently associated with reduced total and left AFC across the W1, W2, and W3 stages. Additionally, an IQR increment in PM_{10} was associated with increased E2 levels, with percentage changes of 5.96 % (95 % CI: 0.64 %, 11.56 %), 6.30 % (95 % CI: 0.92 %, 11.96 %), and 3.76 % (95 % CI: 0.99 %, 6.61 %) during W2, W3, and W4, respectively. We found no evidence of any association between $PM_{2.5}$ and PM_{10} exposure and other ovarian reserve indicators, including AMH, FSH, LH, INHB, FSH/LH ratio, and OV. Detailed results were shown in Table S3-S4.

Table 1
Characteristics of study participants (n = 988).

Variables	Study population (n = 988)
Age (years ± SD)	30.86 ± 4.57
Age, n (%)	
< 30 years	410 (41.49)
≥ 30 years	578 (58.51)
Education, n (%)	
Lower than or equal to primary school	55 (5.57)
Junior high school	342 (34.62)
Senior high school or college	223 (22.57)
Postsecondary or university	341 (34.51)
Equal to or higher than postgraduate	27 (2.73)
Smoking, n (%)	
No	929 (94.03)
Yes	59 (5.97)
Alcohol drinking, n (%)	
No	761 (77.02)
Yes	227 (22.98)
Season of indicator measurement, n (%)	
Spring [March-May]	114 (11.54)
Summer [June-August]	365 (36.94)
Autumn [September-November]	401 (40.59)
Winter [December-February]	108 (10.93)
Warm season of indicator measurement, n (%)	
No (November - the following April)	271 (27.43)
Yes (May-October)	717 (72.57)
Reasons of infertility, n (%)	
Female	504 (51.01)
Male	146 (14.78)
Both	223 (22.57)
Unexplained	115 (11.64)
Current employment status, n (%)	
No	530 (53.64)
Yes	458 (46.36)
Passive smoking, n (%)	
No	517 (52.33)
Yes	471 (47.67)
BMI (kg/m^2 ± SD)	22.00 ± 3.02
BMI, n (%)	
< 24.0 kg/m^2	748 (75.71)
≥ 24.0 kg/m^2	240 (24.29)
Duration of infertility (years ± SD)	3.42 ± 2.64
Infertility type, n (%)	
Primary	648 (65.59)
Secondary	340 (34.41)
Regular menstrual cycle, n (%)	
No	145 (14.68)
Yes	843 (85.32)
Ovarian reserve indicators	
AMH (ng/ml)	3.36 (2.62)
FSH (mIU/ml)	8.08 (3.06)
LH (mIU/ml)	4.26 (2.07)
FSH/LH ratio	2.28 (2.93)
INHB (pg/ml)	112.83 (61.38)
E2 (pg/ml)	43.90 (29.44)
AFC (n)	12.04 (6.25)
Right AFC (n)	6.19 (3.40)
Left AFC (n)	5.90 (3.39)
OV (mm^3)	5061.51 (3710.29)
Right OV (mm^3)	2670.74 (2392.74)
Left OV (mm^3)	2376.25 (2383.73)

Abbreviation: BMI = body mass index; AMH = anti-müllerian hormone; FSH = follicle-stimulating hormone; AFC = antral follicle count; E2 = estradiol; INHB = inhibin B; LH = luteinizing hormone; OV = ovarian volume; SD = standard deviation.

3.3. Exposure-response relationship between air pollutants and ovarian reserve

A restricted cubic spline regression analysis was conducted to evaluate the exposure-response relationship between particulate matter

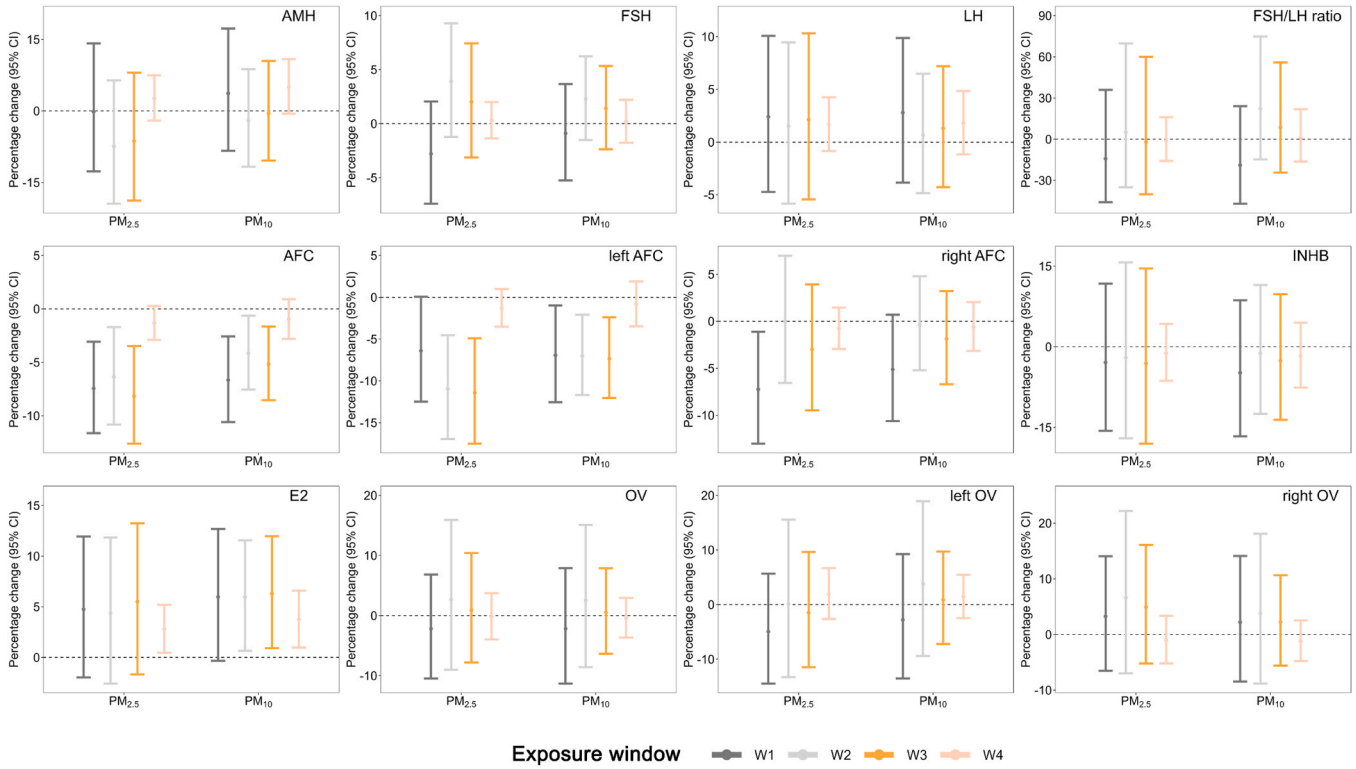

Fig. 3. Percentage changes of ovarian reserve indicators associated with an interquartile range increase in ambient particulate matter across different exposure windows. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from the 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: $PM_{2.5}$ = particulate matter with aerodynamic diameter < 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter < 10 μm; CI = confidence interval; AFC = antral follicle count; E2 = estradiol; AMH = anti-müllerian hormone; FSH = follicle-stimulating hormone; INHB = inhibin B; LH = luteinizing hormone; OV = ovarian volume.

exposure and ovarian reserve indicators. An increasing concentration of $PM_{2.5}$ and PM_{10} was consistently associated with a decreasing trend in AFC and an increasing trend in E2 levels, except during the W4 stage (Fig. 4).

3.4. Sensitivity analysis

The sensitivity analyses conducted among women with regular menstrual cycles, women diagnosed with infertility due to female factors, and nonsmokers or nondrinkers showed no material differences from the main analyses. The results remained consistent after further adjusting for ambient temperature and relative humidity. However, when the analysis was restricted to women without diminished ovarian reserve, the results were not statistically significant (Table S5-S6). Additionally, the results remained robust after further adjustment for NO_2, O_3 and CO.

3.5. Subgroup analysis

We performed a subgroup analysis to identify subpopulations more susceptible to the effects of $PM_{2.5}$ and PM_{10} exposure. The association between particulate matter exposure and a decrease in AFC was more pronounced among women with a BMI ≥ 24.0 kg/m^2 and those younger than 30 years (Fig. 5) (Table S7-S8). For example, exposure to PM_{10} during the W1 stage was associated with a −6.73 % (95 % CI: −12.47 %, −0.62 %) decrease in AFC among women younger than 30 years, compared to a −5.86 % (95 % CI: −11.33 %, −0.06 %) decrease in women older than 30 years (Table S8). Similarly, in subgroups with a BMI < 24.0 kg/m^2 and younger than < 30 years, exposure to $PM_{2.5}$ and PM_{10} was associated with higher E2 levels compared to their counterparts (Table S8). For example, PM_{10} exposure during the W1 stage was associated with a reduction of −8.26 % (95 % CI: −15.11 %, −0.88 %) in AFC among women with a BMI ≥ 24 kg/m^2, compared to a −6.48 % (95 % CI: −11.19 %, −1.53 %) decrease among women with a BMI < 24 kg/m^2.

4. Discussion

Among 988 women attending an infertility clinic in Hubei, China, our findings provide evidence that exposure to $PM_{2.5}$ and PM_{10} is associated with reduced AFC and increased E2 levels during the small antral follicle development stages. The associations were more pronounced among women with a BMI ≥ 24.0 kg/m^2 or those younger than 30 years old. To our best knowledge, this is the first comprehensive investigation exploring the association between exposure to particulate matter and multiple indicators of ovarian reserve.

The typically used clinical markers of ovarian reserve include basal FSH, AMH and AFC [31]. However, other serum hormones, such as LH, E2 and INHB, and OV also reflect biological changes in aging ovaries and are considered potential indicators of ovarian reserve [32]. To provide a comprehensive assessment of ovarian reserve, our study utilized a combination of biochemical measures and ultrasound imaging, including AMH, AFC, FSH, LH, E2, INHB, the FSH/LH ratio, and OV. A decline in ovarian reserve is typically characterized by lower levels of AMH, INHB, AFC, or reduced OV, or higher levels of FSH, LH or E2 [33].

We found that exposure to $PM_{2.5}$ and PM_{10} was associated with a decline in AFC, a key marker of ovarian reserve. This result was confirmed by a study of US women, which found a −7.2 % (95 % CI: −10.4 %, −3.8 %) decrease in AFC associated with per 10 μg/m^3 increment in $PM_{2.5}$ [16]. Similarly, our findings were also consistent with a European study of 511 women [33,34]. Additionally, we found that exposure to $PM_{2.5}$ and PM_{10} was associated with increased E2

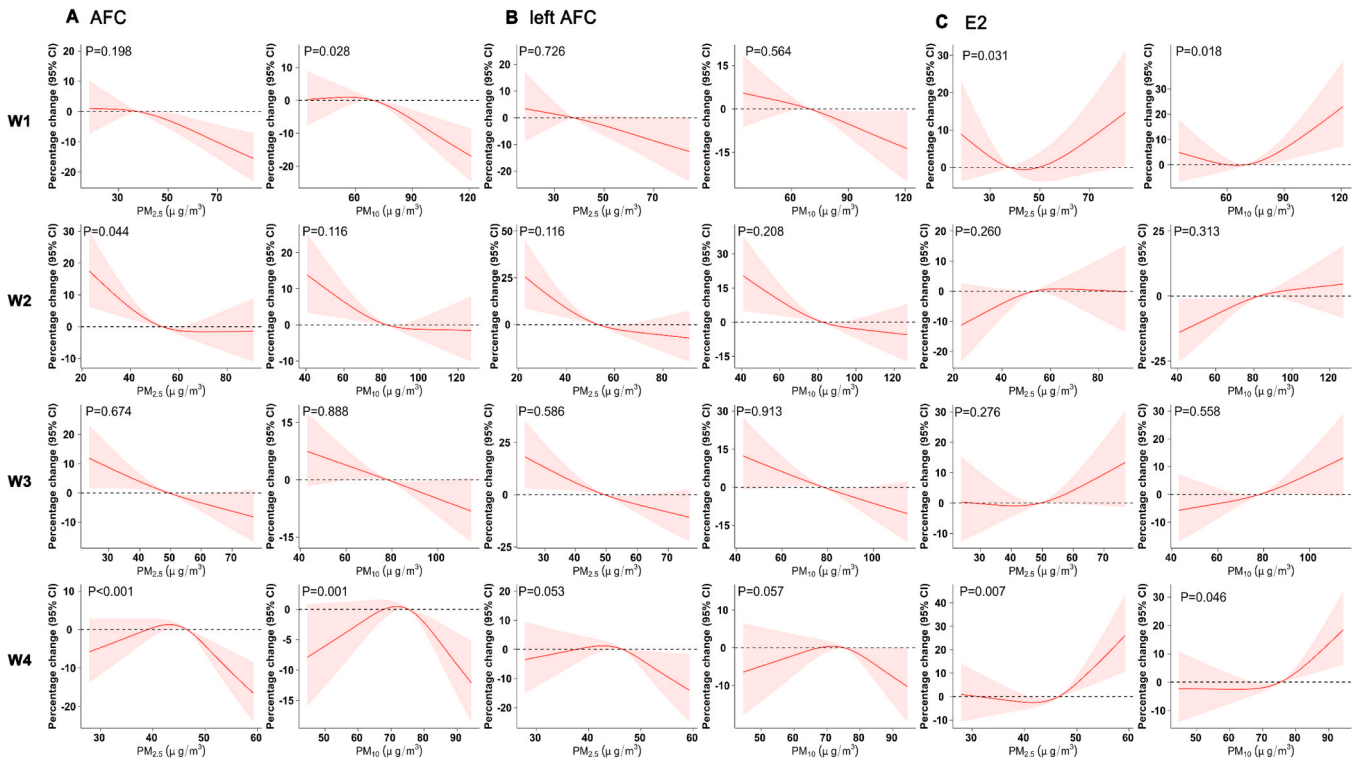

Fig. 4. Exposure-response curves for the association between exposure to ambient particulate matter and (A) AFC, (B) left AFC, and (C) E2 during different exposure windows. Exposure windows (W): (1) W1: from the secondary to small antral follicle stage (two months prior to measurement); (2) W2: from 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: $PM_{2.5}$ = particulate matter with aerodynamic diameter < 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter < 10 μm; AFC = antral follicle count; E2 = Estradiol; CI = confidence interval.

levels. In Poland, women exposed to higher PM_{10} levels during the early luteal phase had higher E2 levels compared to those in lower exposure areas [35]. Ambient particulate matter has an adverse effect on sex hormone production and secretion, potentially through direct stimulation, the upregulation of glucocorticoid-sensitive genes, and chemokine receptor-dependent pathways [36,37]. Additionally, ambient air pollutants are complex mixtures of hazardous components, including metals and endocrine disrupting compounds, which may further disrupt E2 biosynthesis and metabolism [37].

We found no evidence of an association between exposure to $PM_{2.5}$ and PM_{10} and levels of AMH and FSH, which is consistent with previous studies [14,18]. A study by Namvar et al. in Tehran, Iran, similarly found no significant association between PM_{10} and $PM_{2.5}$ exposure and serum AMH levels [18]. However, our results contrast with several other studies [12,13,15,38,39]. For example, a study conducted in Shandong, China, found that $PM_{2.5}$ and PM_{10} exposure during the primary to small antral follicle stage were associated with declined AMH levels, with percentage changes of −2.1 % (95 % CI: −3.5 %, −0.6 %) and −4.5 % (95 % CI: −7.1 %, −1.9 %), respectively [39]. These discrepancies may be attributed to differences in study populations, exposure assessments, unmeasured or unknown confounders, and PM chemical components. The PM is a complex mixture, including organic carbon, elemental carbon, soluble ions (such as sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), and metals [40]. The chemical components of PM are critical in determining its toxicity [41], and they vary substantially across different locations. Certain PM chemical components have been associated with ovarian reserve impairment, such as SO_4^{2-}, NO_3^-, organic matter and NH_4^+ [12,15].

Several mechanisms have been proposed to explain the impact of ambient air pollution on ovarian reserve impairment [42]. Exposure to PM_{10} can cause intracellular toxic effects and trigger apoptosis through elevated levels of reactive oxygen species, DNA damage, and hydroxyl radicals [43]. In female mice, exposure to $PM_{2.5}$ has been shown to inhibit embryo development and impair fertility by inducing apoptosis in ovarian granulosa cells and oocytes [44]. $PM_{2.5}$-induced follicle atresia has been linked to mitochondria-dependent granulosa cell apoptosis and changes in the expression of genes related to oxidative stress and oxidative phosphorylation [42]. Additionally, exposure to $PM_{2.5}$ can suppress the expression of various hormones, thereby affecting ovarian function [45].

We found that the association between $PM_{2.5}$ and PM_{10} exposure and a decline in AFC was more pronounced among younger women and those with a higher BMI, which was consistent with a study conducted among US women [17]. Ambient PM and its harmful constituents can enter the bloodstream after being inhaled into the respiratory system. Reproductive activities are particularly active in younger women, characterized by accelerated follicular development and increased synthesis of reproductive hormones, which demand a higher blood flow. These heightened reproductive activities likely increase exposure to PM in younger women [46]. Additionally, women with higher BMI values were in chronic inflammation and higher levels of oxidative stress, and cellular antioxidant defense mechanisms would be weakened [47]. Ambient air pollution might exacerbate this adverse response and cause the impair of follicle development.

This study has several limitations. First, we relied on validated gridded estimates from spatial-temporal models to represent air pollution exposure at participants' residential addresses, without considering their movement patterns. This may lead to exposure misclassifications and bias our results towards a null association [48]. Second, we recruited participants from couples attending a reproductive center in Hubei, China, which may limit the generalizability of our findings to the general population or other countries. Third, although we adjusted for a wide range of confounders, there may be additional factors that potentially confound the association between particulate matter and ovarian

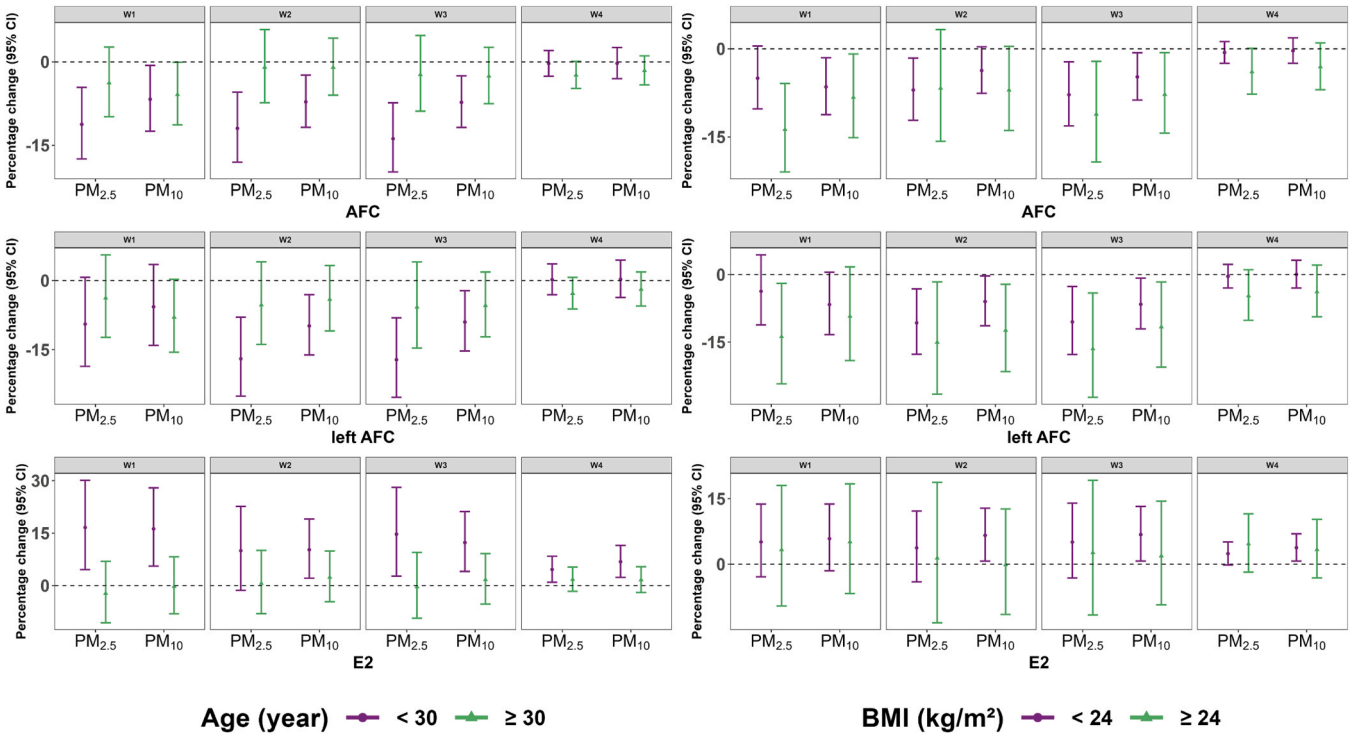

Fig. 5. Percentage changes in ovarian reserve indicators associated with an interquartile range increase in ambient particulate matter, stratified by age and BMI, during different exposure windows.Participants were stratified by age (< 30 or ≥ 30 years) and BMI (< 24 or ≥ 24 kg/m^2). Exposure windows (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: $PM_{2.5}$ = particulate matter with aerodynamic diameter < 2.5 μm; PM_{10} = particulate matter with aerodynamic diameter < 10 μm; AFC = antral follicle count; E2 = estradiol; CI = confidence interval; BMI = body mass index.

reserve that we did not account for.

5. Conclusions

Among 988 women attending an infertility clinic in China, exposure to $PM_{2.5}$ and PM_{10} was associated with decreased AFC and increased E2 levels. These associations were more pronounced in younger women and those with higher BMI values. Our findings suggest that particulate matter might be a novel risk factor for women's reproductive health.

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CRediT authorship contribution statement

Changjiang Liu: Writing – review & editing, Conceptualization. **Wangnan Cao:** Writing – review & editing. **Qiang Zeng:** Writing – review & editing, Data curation. **Jing Wei:** Writing – review & editing, Data curation. **Jie Yin:** Writing – review & editing. **Tian Liang:** Writing – review & editing. **Jiayi Liu:** Writing – review & editing, Data curation. **Ze Han:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Shengzhi Sun:** Writing – review & editing, Supervision, 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.2024.136212.

Data availability

Data will be made available on request.

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