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Fine particulate matter and its chemical constituents on oocyte quality in controlled ovarian hyperstimulation cycles: A prospective cohort study in China

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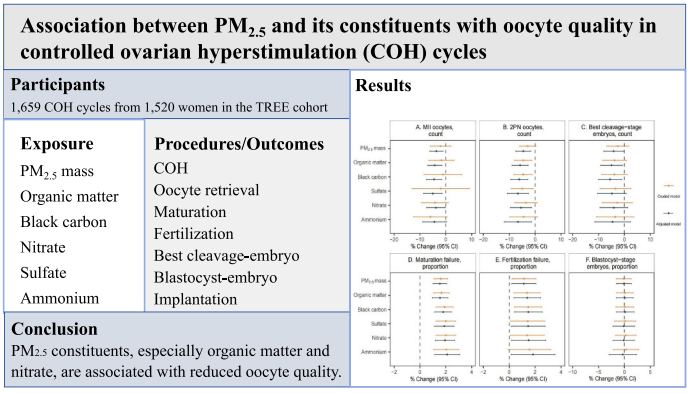
HIGHLIGHTS

- We estimated the associations between $PM_{2.5}$ constituents and oocyte quality outcomes.
- Exposure to major constituents of $PM_{2.5}$ is associated with reduced oocyte quality.
- Nitrate and organic matter showed stronger associations than other constituents.
- Associations were stronger in women with a BMI $\geq$ 24.0 kg/m^2 or under 35 years old.

GRAPHICAL ABSTRACT



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ABSTRACT

Previous studies have examined the association between fine particulate matter ($PM_{2.5}$) and female oocyte quality; however, the specific chemical constituents influencing this association remain unclear. In this study, we examined the association between $PM_{2.5}$ constituents and oocyte quality in Hubei Province, China, using a generalized estimating equations model. We used a weighted quantile sum model to identify which $PM_{2.5}$ constituents most strongly impact oocyte quality. Our results showed that exposure to $PM_{2.5}$ constituents,

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including organic matter, black carbon, nitrate, sulfate, and ammonium, was associated with a decreased count of MII oocytes, 2PN oocytes, best cleavage-stage embryos, and increased rates of maturation failure and fertilization failure. Nitrate and organic matter demonstrated the strongest associations compared to the other constituents analysed. The most susceptible exposure windows differed depending on the reproductive outcomes measured, suggesting that different stages of follicular development exhibit differing sensitivities to $PM_{2.5}$ exposures. These findings highlight the importance of reducing secondary aerosol precursor emissions, particularly those from fossil fuel combustion and biomass burning.

1. Introduction

There is growing recognition that fine particulate matter ($PM_{2.5}$), a prevalent ambient air pollutant, may adversely affect reproductive health, with accumulating evidence supporting its potential role in impairing fertility. Previous studies have indicated that exposure to $PM_{2.5}$ is associated with reduced male sperm quality [1–4]; however, directly assessing the impact of $PM_{2.5}$ on oocyte quality in natural cycles remains challenging, due to the lack of routine monitoring and difficulty in accessing oocytes among healthy women of reproductive age. This limitation positions the *in vitro* fertilization (IVF) process as a valuable model for investigating the potential effects of $PM_{2.5}$ on female reproductive outcomes under closely monitored clinical conditions.

Several epidemiological studies have examined the association between $PM_{2.5}$ exposure and oocyte quality, but the findings remain inconsistent. Some have reported a significant association between $PM_{2.5}$ exposure and a reduced number of MII oocytes [5–7], whereas others have found no such association [8,9]. One potential explanation for these inconsistencies is that $PM_{2.5}$ is a complex mixture of different chemical constituents, some of which may confer greater reproductive toxicity than others. Variations in $PM_{2.5}$ sources and chemical compositions across regions may therefore contribute to disparate results.

Biologically, it is plausible that exposure to $PM_{2.5}$ could impair oocyte quality by inducing oxidative stress through systemic pathways, activating the NF-κB/IL-6 inflammatory pathway, and initiating mitochondria-dependent apoptotic pathways [10,11]. These processes ultimately contribute to granulosa cell apoptosis, follicular atresia, and accelerated activation of primordial follicles [10,11].

Accordingly, we aimed to estimate the association between exposure to specific $PM_{2.5}$ chemical constituents and oocyte quality during 1659 controlled ovarian hyperstimulation (COH) cycles among 1520 women in a prospective cohort conducted in Wuhan, China, between 2018 and 2020. We focused on women undergoing COH because this protocol enables the systematic collection and laboratory assessment of oocyte quality, providing unique, detailed data on early reproductive outcomes that are not readily available in the general population. We also sought to identify which $PM_{2.5}$ constituents the most significant contributors among the $PM_{2.5}$ chemical constituents affecting oocyte quality and to determine potential susceptible exposure windows.

2. Materials and methods

2.1. Study participants

During IVF treatment, controlled ovarian hyperstimulation (COH) plays a crucial role in stimulating the ovaries using medication to promote the maturation of multiple follicles, facilitating subsequent oocyte retrieval. Physicians prescribe individualized COH regimens—such as long, short, or antagonist protocols—based on each participant's clinical condition. After 8–13 days of stimulation, recombinant human chorionic gonadotropin (hCG) is administered to trigger final oocyte maturation, followed by oocyte retrieval occurring 34–36 h later under ultrasound guidance. Retrieved oocytes are then cultured and assessed for maturity, while partner semen samples are analysed and prepared for fertilization. Clinicians subsequently select and transfer the best-quality cleavage-stage embryos or blastocysts into the woman's uterus.

The study population was drawn from 2006 assisted reproductive technology (ART) cycles of the Tongji Reproductive and Environmental (TREE) study, which involved IVF conducted at the Tongji Reproductive Centre between December 2018 and February 2020. We excluded cycles involving artificial insemination (n = 305), missing sample collection (n = 29), use of donor sperm (n = 2), or unknown residential addresses (n = 11), a total of 1659 ovarian stimulation cycles from 1520 couples were included in the analysis (Fig. S1). The study protocol was approved by the Institutional Review Board of Tongji Medical College, and written informed consent was obtained from all participants.

2.2. Outcome assessment

This study included six parameters to evaluate oocyte quality, defined according to the criteria established by the Vienna consensus [12]. These parameters included MII oocyte count, 2PN oocyte count, best cleavage-stage embryo count, maturation failure proportion, fertilization failure proportion, and blastocyst-stage embryo proportion.

The MII oocyte count reflects the number of oocytes that reached the Metaphase II stage with the first polar body, indicating maturity and competence for fertilization. The maturation failure proportion was defined as the ratio of oocytes that failed to mature, including those arrested at the germinal vesicle, metaphase I, or degenerated stages, to the total number of oocytes retrieved [13]. The 2PN count refers to the number of retrieved oocytes that successfully fertilized and exhibited two pronuclei in the zygote. Fertilization failure included both total fertilization failure (0PN without cleavage) and abnormal fertilization (1PN or ≥3PN), with the fertilization failure proportion calculated as the ratio of failed fertilized oocytes to the number of MII oocytes [13,14]. The best cleavage-stage embryo was defined as an embryo with < 20 % fragmentation, containing 7–9 cells on day 3, and showing no multinucleation. The blastocyst-stage embryo proportion was calculated as the ratio of blastocyst formed to the number of oocytes selected for continued culture after day 3.

2.3. Exposure assessment

Residential addresses were collected using a standardized and structured questionnaire. We obtained daily concentrations of fine particulate matter ($PM_{2.5}$) and its chemical constituents (including organic matter, black carbon, nitrate, sulfate, and ammonium) from the Tracking Air Pollution in China (TAP) dataset (http://tapdata.org.cn) [15,16], This dataset has a spatial resolution of 10 km and is a high-quality resource for $PM_{2.5}$, integrating artificial intelligence and multi-source data to address air pollution heterogeneity. The accuracy of estimated $PM_{2.5}$ and its constituents from the TAP dataset has been validated, with R^2 values ranging from 0.67 to 0.80. We obtained daily ambient temperature and relative humidity from the CHAP and HiMIC-Monthly datasets at a 1-km spatial resolution, both of which demonstrated high quality with cross-validation coefficients of determination of 0.99 and 0.96, respectively [17,18].

We used the annual average concentrations of $PM_{2.5}$ and its chemical constituents prior to oocyte retrieval to represent long-term exposure during the primordial, preantral, and antral follicle stages (Fig. S2). Additionally, we calculated average concentrations during three specific critical periods of oocyte development to identify potential critical

exposure windows. These periods included (1) the follicle initiation stage: this stage spans from the primordial to the preantral follicle stage, which covers approximately 9 months, from one year prior to 85 days before oocyte retrieval; (2) the follicle growth and selection stage: this stage extends from the preantral to the antral follicle stage, approximately 75 days from 85 days before to 10 days before oocyte retrieval; and (3) the follicle maturation stage: this stage goes from the antral to preovulatory follicle stage, lasting 11 days, from 10 days before oocyte retrieval to the retrieval day [19,20].

2.4. Covariates

Demographic, lifestyle, and clinical data were collected at enrolment or extracted from electronic medical records. Causes of infertility were assessed by clinical physicians and categorized as female factors (e.g., tubal or pelvic abnormalities, ovulation disorders, or diminished ovarian reserve), male factors (e.g., weak or abnormal spermatozoa), mixed, or unexplained. Alcohol consumption was defined as drinking alcoholic beverages at least once a week. Passive smoking was defined as daily exposure to second-hand smoke for more than 15 min, while active smoking (n = 74) was excluded from the analysis due to its limited sample size.

We selected potential covariates based on prior studies [21,22], which included maternal age (<30, 30–34, ≥35 years), body mass index (BMI) (<18.5, 18.5–23.9, 24–27.9, ≥28 kg/m^2), passive smoke exposure (yes or no), drinking status (yes or no), maternal education level (below high school, high school and above), cause of infertility (female, male, mixed, and unexplained), daily ambient temperature (continuous) and relative humidity (continuous). We assessed multicollinearity among covariates using generalized variance inflation factors.

2.5. Statistical analysis

Given that some women underwent multiple cycles, we used generalized estimating equations with an exchangeable correlation structure to account for intra-individual correlations when assessing associations between $PM_{2.5}$ mass or its specific chemical constituents and oocyte quality outcomes. The outcomes included MII oocyte count, 2PN oocyte count, best cleavage-stage embryo count, maturation failure proportion, fertilization failure proportion, and blastocyst-stage embryo proportion. Poisson regression was used for count outcomes, while linear regression was used for continuous outcomes. We constructed both crude and fully adjusted models. For the crude models, we only included $PM_{2.5}$ mass or its chemical constituents. For the fully adjusted models, we additionally adjusted for maternal age, BMI, passive smoke exposure, drinking status, maternal education level, cause of infertility, a natural spline of daily ambient temperature (3 degrees of freedom), and a natural cubic spline of relative humidity (3 degrees of freedom). Results are reported as percentage change per interquartile range (IQR) increase in exposure concentrations.

To examine dose-response relationships between $PM_{2.5}$ constituents and oocyte quality, we used penalized regression splines for $PM_{2.5}$ mass or its constituents, with the degree of smoothness for each spline selected via restricted maximum likelihood estimation [23].

To identify potential vulnerable exposure windows, we fitted models that simultaneously included average concentrations of $PM_{2.5}$ mass or its constituents during the three defined stages of follicle development: follicle initiation, follicle growth and selection, and follicle maturation [24].

To examine whether the association varied by personal characteristics, we conducted subgroup analyses by age (<30, 30–34, ≥35 years) and BMI (<24, ≥24 kg/m^2), given advanced maternal age and obesity are known adverse factors for female fertility [20,25].

To evaluate the impact of joint exposure to multiple $PM_{2.5}$ chemical constituents, weighted quantile sum (WQS) regression was used [26]. WQS regression is widely used to assess the combined effects of complex pollutant mixtures, such as $PM_{2.5}$ constituents [27–29]. Specifically, the concentrations of each constituent were divided into quartiles and assigned ordinal scores. The dataset was randomly split into a 40 % training set and a 60 % validation set. In the training set, constituent weights were estimated using 1000 bootstrap samples, and the average weight across iterations was calculated for each constituent. Those with average weights exceeding 1 divided by the number of constituents were considered key contributors. A weighted index was subsequently constructed by summing the weighted quartile scores, and this index was entered into the regression model in the validation set to evaluate its association with the outcomes.

Covariates included in the model were consistent with those used in the main analysis to adjust for potential confounders. Based on existing evidence [30], a positive direction of the weighted index was assumed for constituents hypothesized to increase the risk of oocyte maturation and fertilization failure, while a negative direction was assumed for those expected to reduce the number of MII oocytes, 2PN oocytes, best-quality embryos, and the proportion of blastocyst-stage embryos.

We conducted several sensitivity analyses to evaluate the robustness of our findings. First, we refitted the models using an alternative $PM_{2.5}$ dataset with 1-km resolution for $PM_{2.5}$ mass and overlapping constituents (sulfate, nitrate, and ammonium) [31]. Second, given the high correlation between $PM_{2.5}$ mass and its chemical constituents ($r > 0.8$), a two-pollutant model that additionally adjusted for $PM_{2.5}$ mass was not appropriate [32,33]. Instead, we performed a residual-based analysis. Specifically, $PM_{2.5}$ mass was regressed on each constituent to obtain residuals, representing the portion of $PM_{2.5}$ mass not explained by that constituent. Both the residuals and corresponding constituent concentrations were then included in the regression models for oocyte-related outcomes to assess the independent effects of the constituents [34]. Third, to minimize the potential influence of artificial interventions on fertilization outcomes, we excluded duplicate cycles and ICSI cycles, restricting analyses to each participant's first COH cycle and conventional IVF cycles only. Fourth, to control for the potential impact of male factors, we excluded all cycles involving male-related infertility diagnoses (e.g., oligozoospermia and spermatid malformations). Fifth, to address the right-skewed distribution of oocyte-related outcomes, we applied a log (x + 1) transformation for normalization and refitted the models, thereby enhancing estimate stability and reducing the influence of extreme values. Sixth, we used a quantile-based g-computation (QGC) method to further assess the joint effects of $PM_{2.5}$ constituents [35].

All analyses were conducted using R software (version 4.3.1), with a two-sided significance level set at 0.05.

3. Results

A total of 1520 women undergoing 1659 COH cycles were included in the study (Table 1). The majority of participants were younger than 30 years (42.6 %) and of normal weight (64.8 %). Additionally, 62.9 % had less than a high school education, 94.6 % did not use tobacco, and 77.5 % did not consume alcohol. Nearly half of the women were exposed to second-hand smoke (47.9 %).

Among the 1659 COH cycles, the median values for various outcomes were as follows: MII oocyte count was 9.0, 2PN oocyte count was 6.0, best cleavage-stage embryo count was 3.0, maturation failure proportion was 12.5 %, fertilization failure proportion was 26.8 %, and blastocyst-stage embryo proportion was 66.7 %. During the year preceding oocyte retrieval, participants were exposed to median (IQR) levels of 49.1 (7.9) μg/m^3 for $PM_{2.5}$, 12.7 (1.8) μg/m^3 for organic matter, 2.4 (0.3) μg/m^3 for black carbon, 8.8 (1.3) μg/m^3 for sulfate, 12.0 (2.3) μg/m^3 for nitrate, and 7.4 (1.4) μg/m^3 for ammonium (Table S1). No significant multicollinearity among covariates was observed (Table S2).

Both $PM_{2.5}$ and its constituents were significantly associated with oocyte maturation failure proportion, 2PN oocyte count, fertilization failure proportion, and best cleavage-stage embryos count (Fig. 1). The magnitude of these associations varied among constituents, with the

Table 1
Basic characteristics from 1659 *in vitro* fertilization (IVF) cycles among 1520 women enrolled in study.

Characteristic	*n* (%) or Median (IQR)
Maternal age, year	
< 30	707 (42.6)
30 – 35	512 (30.9)
≥ 35	440 (26.5)
Maternal BMI, kg/m^2	
< 18.5	152 (9.2)
18.5 – 23.9	1075 (64.8)
24.0 – 27.9	348 (20.9)
≥ 28	84 (5.1)
Education level	
Less than high school	1043 (62.9)
High school and above	616 (37.1)
Passive smoke	
No	865 (52.1)
Yes	794 (47.9)
Active smoke	
No	1569 (94.6)
Yes	74 (5.4)
Alcohol use	
No	1285 (77.5)
Yes	364 (22.5)
Cause of infertility	
Female factor	947 (57.1)
Male factor	405 (24.4)
Mix factor	176 (10.6)
Unexplained	131 (7.9)
Fertilization protocol	
IVF	1023 (61.7)
ICSI	636 (38.3)
Oocyte-related IVF outcomes	
MII oocytes, count	9.0 (9.0)
2PN oocytes, count	6.0 (7.0)
Best cleavage-stage embryos, count	3.0 (5.0)
Maturation failure, proportion, %	12.5 (25.0)
Fertilization failure, proportion, %	26.8 (27.4)
Blastocyst-stage embryos, proportion, %	66.7 (45.7)

Abbreviations: BMI, body mass index; ICSI, intracytoplasmic sperm injection; MII, metaphase II; PN, distinct pronuclei.

strongest associations observed for nitrate. Specifically, an IQR increase in nitrate was associated with a 5.03 % reduction (95 % confidence interval [CI]: −8.61 %, −1.46 %) in MII oocyte count, a 6.66 % reduction (95 % CI: −10.73 %, −2.58 %) in 2PN oocyte count, a 1.94 % increase (95 % CI: 1.20 %, 2.68 %) in maturation proportion, and a 1.50 % increase (95 % CI: 0.16 %, 2.83 %) in fertilization failure proportion in the fully adjusted models.

To identify critical exposure windows, we assessed the effects of $PM_{2.5}$ and its constituents across different stages of follicle development. The most pronounced associations were observed during the follicle growth and selection stage for MII oocyte count and 2PN oocyte count, during the initiation stage for maturation failure proportion, and during the follicle maturation stage for best cleavage-stage embryo count (Table 2). For example, during the follicle maturation stage (from 10 days before oocyte retrieval to the day of retrieval), an IQR increase in exposure to organic matter, black carbon, nitrate, sulfate, and ammonium was associated with decreases in best cleavage-stage embryo count of 7.92 % (95 % CI: −12.73 %, −3.11 %), 7.51 % (95 % CI: −12.61 %, −2.40 %), 6.49 % (95 % CI: −11.38 %, −1.60 %), 6.76 % (95 % CI: −11.79 %, −1.73 %), and 6.05 % (95 % CI: −11.00 %, −1.09 %), respectively.

To examine the exposure-response relationships between $PM_{2.5}$ constituents and oocyte quality, we employed generalized additive mixed models with penalized regression splines for each $PM_{2.5}$ constituent. These associations observed between $PM_{2.5}$ constituents and markers of oocyte quality were generally linear (Figs. S3–S5).

When fertilization failure was categorized into two subtypes: total fertilization failure and abnormal fertilization, no statistically significant associations were observed with $PM_{2.5}$ exposure (Table 3). The odds ratio for total fertilization failure was 1.08 (95 % CI: 0.99, 1.18; $P = 0.067$), and for abnormal fertilization, it was 1.00 (95 % CI: 0.92, 1.09; $P = 0.99$).

To assess the joint effects of exposure to the chemical mixture, we conducted WQS regression analyses. Overall, each 1-unit increase in the mixture of the five constituents was associated with a 3.00 % decrease (95 % CI: −5.00 %, −1.00 %) in MII oocyte count, a 3.00 % decrease (95 % CI: −5.00 %, −1.00 %) in 2PN oocyte count, and a 1.62 % increase (95 % CI: 0.12 %, 3.11 %) in the fertilization failure proportion (Table S4). Within the chemical mixture, organic matter contributed most to the reduction in 2PN oocyte count (weight = 0.53) and to the increase in fertilization failure rate (weight = 0.52). For MII oocyte count, nitrate was the primary contributor (weight = 0.32), followed by sulfate (weight = 0.23) and organic matter (weight = 0.22) (Fig. 2).

Stratified analyses demonstrated that the observed associations were more pronounced among women younger than 30 years and those aged 30–34 years, as well as among individuals with a BMI ≥ 24 kg/m^2, particularly in terms of MII oocyte count, 2PN oocyte count, and best cleavage-stage embryo count (Tables S6–S7).

We conducted a wide range of sensitivity analyses to confirm the robustness of our findings. Results obtained using the 1-km resolution dataset were consistent with those of the main analysis (Table S8). Residual analysis suggested that $PM_{2.5}$ constituents influenced oocyte-related outcomes independently of $PM_{2.5}$ mass (Table S9). Excluding cycles involving ICSI and repeated COH attempts, as well as applying data transformations, did not substantially alter the results (Tables S10–S12). However, exclusion of cycles with male infertility attenuated the observed effect sizes (Table S13).

In the Qgcomp analysis, an increase in the constituent mixture was associated with changes in MII oocyte and 2PN oocyte counts, and with maturation failure and fertilization failure rates (Table S14). Organic matter contributed the most to both 2PN oocyte count and fertilization failure rate, consistent with the WQS results. For MII oocyte count, sulfate had the greatest weight, followed by organic matter (Fig. S6).

4. Discussion

In this prospective cohort study of 1659 controlled ovarian hyperstimulation (COH) cycles, we examined the associations between $PM_{2.5}$ constituents and declines in oocyte quality. We found that exposure to $PM_{2.5}$ constituents, particularly organic matter and nitrate, was associated with reduced number of MII oocytes, 2PN oocytes, and best cleavage-stage embryos, as well as increased rates of maturation and fertilization failure. The most susceptible exposure windows differed by outcomes, suggesting that different stages of follicular development may have varying sensitivities to $PM_{2.5}$ exposures.

While the adverse reproductive effects of $PM_{2.5}$ mass have been documented, such as decreased yields of total and mature oocytes [36, 37], our study provides novel insight into the specific chemical components driving these associations. To date, only a few studies have investigated the association between $PM_{2.5}$ constituents on oocyte-related outcomes [38,39]. Our findings align with previous work by Zhang et al., who reported that exposure to sulfate, organic matter, and black carbon during the year preceding oocyte retrieval was associated with reductions in both 2PN oocyte count and the number of available cleavage-stage embryos [38]. Likewise, another study conducted in the southeastern United States (US) examined the association between exposure to organic carbon, a subtype of organic matter, during the three months before oocyte retrieval and ovarian stimulation, which led to poorer oocyte survival, lower fertilization rates, and compromised embryo outcomes [39]. However, these prior studies focused on individual constituents without considering the weighted contributions of multiple constituents under mixed exposure conditions. To our knowledge, the present study is the first to systematically examine the association between $PM_{2.5}$ constituents and oocyte quality across different

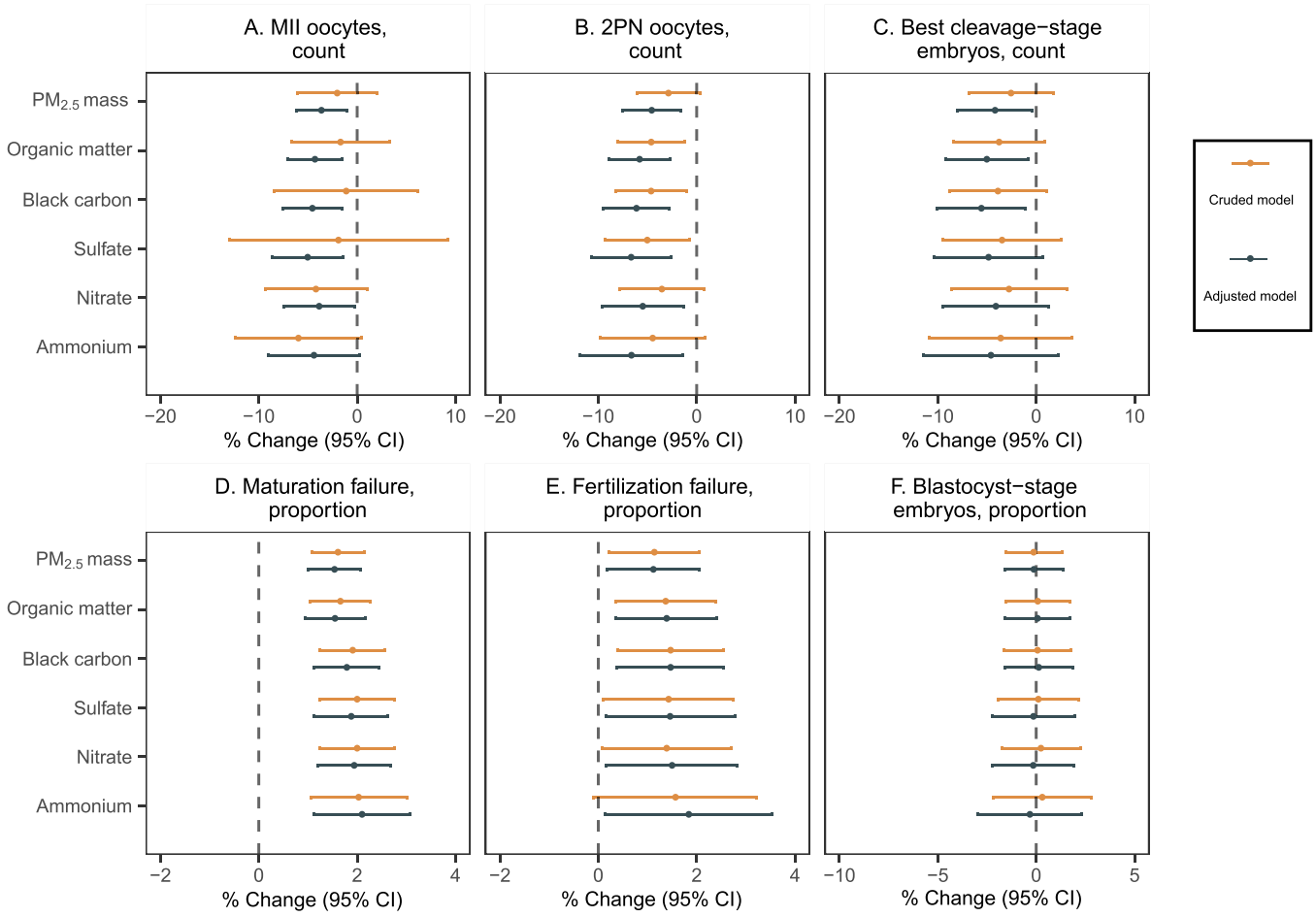

Fig. 1. Percent changes in oocyte quality associated with an interquartile range (IQR) increase in $PM_{2.5}$ and its chemical constituent concentrations throughout oocyte development. The crude model included only $PM_{2.5}$ mass or its constituents. The fully adjusted model was additionally adjusted for age, body mass index, alcohol use, education level, passive smoking status, infertility reason, and average temperature and humidity. (A) MII oocyte count (1520 women; 1659 cycles), (B) 2PN oocyte count (1514 women; 1646 cycles), and (C) Best cleavage-stage embryo count (1473 women; 1578 cycles) were analysed using generalized estimating equation models with an exchangeable correlation structure, Poisson distribution. (D) Maturation failure proportion (1520 women; 1659 cycles), (E) Fertilization failure proportion (1514 women; 1646 cycles), and (F) Blastocyst-stage embryo proportion (1242 women; 1291 cycles) were analysed using generalized estimating equation models with an exchangeable correlation structure, Gaussian distribution. Corresponding numeric data are reported in Table S3.

critical stages of follicle development.

Furthermore, existing research has primarily focused on later reproductive endpoints, such as live births [40], leaving a knowledge gap regarding the impact of air pollution on earlier stages of reproduction. In our study, the maturation failure rate and MII oocyte count reflect oocyte maturity, while the fertilization failure rate and 2PN count reflect fertilization ability. Positive associations between $PM_{2.5}$ constituents and higher failure rates, along with reduced counts of MII oocytes, 2PN oocytes, and best-embryos, suggest that impaired oocyte and embryo quality may serve as key intermediaries linking $PM_{2.5}$ exposure and poor reproductive outcomes.

We found that the association was strongest during follicle initiation stage for oocyte maturation failure, during the follicle growth and selection stage for MII and 2PN oocyte counts, and during the follicle maturation stage for the best cleavage-stage embryo count. From a folliculogenesis perspective, the 85-day cycle is typically regarded as the gamete refreshing period, during which follicles progress from preantral to antral stages (2–10 mm in diameter) and undergo exponential growth in the final 11 days. Our findings were consistent with prior studies, which have primarily focused on reduced oocyte yields within these windows [37,41]. For example, Deng et al. reported that $PM_{2.5}$ exposure during the follicle growth and selection stage was linked to lower MII oocyte yields [41].

Mechanistically, $PM_{2.5}$ and its chemical constituents can accumulate in ovarian tissue [42], triggering oxidative stress and inflammation that promote granulosa cell apoptosis and follicular atresia. Disruption of autophagy pathways and hormonal signalling associated with exposure to $PM_{2.5}$ and its chemical constituents may further accelerate primordial follicle depletion and impair oocyte maturation [35,43].

Among the constituents examined, organic matter emerged as the predominant contributor to the decline in oocyte quality, particularly for outcomes related to fertilization. Organic matter in $PM_{2.5}$, largely derived from fossil fuel combustion, secondary organic aerosols, and biomass burning [44,45], is known to induce oxidative stress, inflammation, and hormonal disruption through multiple biological pathways, including aryl hydrocarbon receptor (AHR) activation and DNA damage [46–50]. These mechanisms may directly compromise oocyte and cumulus-oocyte complex integrity, similar to those observed in sperm damage [46,51,52].

We found that nitrate was the leading contributor to reductions in MII oocyte count. Formed predominantly from atmospheric reactions of nitrogen oxides emitted from vehicles and industry, nitrate has been associated with reproductive dysfunction via disruption of the hypothalamic-pituitary-gonadal axis [53,54]. Although direct evidence linking nitrate to oocyte quality remains limited, epidemiological studies suggest that nitrate may impair reproductive function by contributing to diminished ovarian reserve [55], menstrual irregularities [56], and low birth weight [57].

Table 2
Association between an interquartile range (IQR) increase in $PM_{2.5}$ and its chemical constituent concentrations during three different oocyte development stages and oocyte quality.

Outcome	$PM_{2.5}$ constituents	Initiation stage		Growth and selection stage		Maturation stage	
		% Change (95 % CI)	*P*-value	% Change (95 % CI)	*P*-value	% Change (95 % CI)	*P*-value
MII oocytes, count	$PM_{2.5}$ mass	−1.98 (−5.37, 1.40)	0.251	−6.77 (−10.72, −2.82)	0.001	1.78 (−1.65, 5.20)	0.309
	Organic matter	−2.68 (−6.33, 0.97)	0.150	−5.59 (−9.33, −1.86)	0.003	0.62 (−2.84, 4.08)	0.727
	Black carbon	−2.22 (−5.92, 1.48)	0.240	−6.00 (−9.95, −2.06)	0.003	0.63 (−2.84, 4.09)	0.723
	Nitrate	−1.54 (−5.11, 2.02)	0.396	−6.69 (−10.49, −2.88)	0.001	2.00 (−1.12, 5.13)	0.209
	Sulfate	−2.23 (−5.80, 1.34)	0.221	−6.36 (−9.89, −2.83)	< 0.001	1.57 (−1.65, 4.79)	0.339
	Ammonium	−1.67 (−5.59, 2.26)	0.406	−7.28 (−11.22, −3.33)	< 0.001	2.56 (−0.63, 5.74)	0.115
Maturation failure, proportion	$PM_{2.5}$ mass	1.54 (0.79, 2.28)	< 0.001	1.62 (0.51, 2.74)	0.004	−0.28 (−1.36, 0.80)	0.608
	Organic matter	1.52 (0.69, 2.36)	< 0.001	1.26 (0.24, 2.29)	0.016	0.04 (−1.04, 1.12)	0.939
	Black carbon	1.57 (0.72, 2.43)	< 0.001	1.26 (0.21, 2.31)	0.019	0.19 (−0.92, 1.31)	0.731
	Nitrate	1.38 (0.60, 2.17)	0.001	1.54 (0.45, 2.63)	0.006	−0.15 (−1.24, 0.94)	0.787
	Sulfate	1.40 (0.59, 2.21)	0.001	1.29 (0.32, 2.26)	0.009	−0.18 (−1.28, 0.91)	0.741
	Ammonium	1.36 (0.48, 2.23)	0.002	1.50 (0.41, 2.60)	0.007	−0.34 (−1.45, 0.77)	0.548
2PN oocytes, count	$PM_{2.5}$ mass	−2.58 (−6.36, 1.20)	0.180	−9.80 (−14.14, −5.46)	< 0.001	3.47 (−0.37, 7.31)	0.077
	Organic matter	−4.02 (−8.08, 0.03)	0.052	−8.10 (−12.15, −4.06)	< 0.001	1.68 (−2.24, 5.60)	0.401
	Black carbon	−3.49 (−7.57, 0.59)	0.094	−8.43 (−12.59, −4.26)	< 0.001	1.59 (−2.36, 5.54)	0.429
	Nitrate	−2.42 (−6.41, 1.58)	0.236	−9.59 (−13.83, −5.36)	< 0.001	3.79 (0.28, 7.30)	0.034
	Sulfate	−3.09 (−7.11, 0.93)	0.132	−8.99 (−12.83, −5.15)	< 0.001	3.29 (−0.34, 6.92)	0.075
	Ammonium	1.09 (−0.38, 2.55)	0.146	0.47 (−1.05, 1.98)	0.545	1.04 (−0.34, 2.42)	0.140
Fertilization failure, proportion	$PM_{2.5}$ mass	0.97 (−0.28, 2.22)	0.127	0.54 (−1.01, 2.10)	0.496	1.18 (−0.26, 2.62)	0.107
	Organic matter	1.18 (−0.19, 2.54)	0.091	0.74 (−0.68, 2.16)	0.305	1.20 (−0.16, 2.56)	0.082
	Black carbon	1.13 (−0.22, 2.48)	0.100	0.66 (−0.77, 2.08)	0.366	1.22 (−0.14, 2.59)	0.079
	Nitrate	1.00 (−0.33, 2.32)	0.140	0.33 (−1.18, 1.84)	0.670	1.15 (−0.22, 2.51)	0.099
	Sulfate	1.01 (−0.33, 2.35)	0.141	0.50 (−0.80, 1.81)	0.450	1.09 (−0.25, 2.43)	0.111
	Ammonium	1.89 (0.25, 3.53)	0.024	1.56 (−0.47, 3.59)	0.131	1.05 (−0.55, 2.65)	0.198
Best cleavage-stage embryos, count	$PM_{2.5}$ mass	−0.80 (−5.69, 4.08)	0.747	−5.09 (−10.43, 0.25)	0.062	−7.25 (−12.28, −2.23)	0.005
	Organic matter	−1.63 (−6.89, 3.63)	0.543	−4.92 (−9.77, −0.08)	0.046	−7.92 (−12.73, −3.11)	0.001
	Black carbon	−1.74 (−7.01, 3.53)	0.518	−5.18 (−10.12, −0.24)	0.040	−7.51 (−12.61, −2.40)	0.004
	Nitrate	0.24 (−4.99, 5.47)	0.929	−3.77 (−9.07, 1.53)	0.163	−6.49 (−11.38, −1.60)	0.009
	Sulfate	−0.67 (−5.97, 4.63)	0.804	−4.62 (−9.41, 0.17)	0.059	−6.76 (−11.79, −1.73)	0.008
	Ammonium	0.22 (−5.57, 6.01)	0.941	−4.25 (−9.66, 1.17)	0.125	−6.05 (−11.00, −1.09)	0.017
Blastocyst-stage embryos, proportion	$PM_{2.5}$ mass	0.66 (−1.25, 2.58)	0.498	1.83 (−0.61, 4.27)	0.141	−5.54 (−7.66, −3.42)	< 0.001
	Organic matter	1.15 (−0.98, 3.29)	0.291	0.98 (−1.20, 3.16)	0.379	−5.11 (−7.24, −2.97)	< 0.001
	Black carbon	1.19 (−0.92, 3.31)	0.269	0.63 (−1.51, 2.77)	0.566	−4.43 (−6.50, −2.35)	< 0.001
	Nitrate	0.76 (−1.26, 2.77)	0.462	1.62 (−0.75, 4.00)	0.180	−4.71 (−6.74, −2.68)	< 0.001
	Sulfate	0.43 (−1.66, 2.52)	0.687	0.99 (−1.10, 3.08)	0.352	−4.46 (−6.53, −2.39)	< 0.001
	Ammonium	0.70 (−1.53, 2.92)	0.539	1.36 (−1.01, 3.74)	0.261	−4.76 (−6.84, −2.68)	< 0.001

Abbreviations: $PM_{2.5}$, fine particulate matter; MII, Metaphase II; PN, distinct pronuclei.
Note: The oocyte development periods included the follicle initiation stage (from one year to 85 days before oocyte retrieval, approximately 9 months), the growth and selection stage (from 85 days to 10 days prior to oocyte retrieval, approximately 75 days), and the follicle maturation stage (from 10 days before oocyte retrieval to the day of oocyte retrieval, 11 days). The average exposures during each of these periods were simultaneously incorporated into stage-specific linear models.

Table 3
Odds ratios for total fertilization failure and abnormal fertilization per interquartile range (IQR) increase in $PM_{2.5}$ and its chemical constituents throughout oocyte development (1520 women, 1659 cycles).

$PM_{2.5}$ constituents	Total fertilization failure		Abnormal fertilization	
	OR	*P*-value	OR	*P*-value
$PM_{2.5}$ mass	1.08 (0.99, 1.18)	0.067	1.00 (0.92, 1.09)	0.990
Organic matter	1.09 (0.99, 1.19)	0.073	1.01 (0.91, 1.11)	0.897
Black carbon	1.10 (0.99, 1.21)	0.068	0.99 (0.89, 1.10)	0.853
Nitrate	1.11 (0.98, 1.25)	0.093	1.01 (0.90, 1.14)	0.830
Sulfate	1.08 (0.97, 1.22)	0.170	1.00 (0.88, 1.13)	0.989
Ammonium	1.11 (0.96, 1.29)	0.156	1.02 (0.88, 1.19)	0.767

Abbreviations: OR, Odds Ratio; $PM_{2.5}$, fine particulate matter.

The association between $PM_{2.5}$ and its constituents with oocyte counts was more pronounced among younger and obese women. In individuals with obesity, a state of chronic low-grade inflammation, marked by increased macrophage infiltration, can amplify the inflammatory response triggered by $PM_{2.5}$ exposure [58,59]. In contrast, women with lower BMI typically have less baseline inflammation and a weaker immune response, resulting in comparatively lower reproductive risk at equivalent exposure levels [60]. Age also appears to play a pivotal role in vulnerability to $PM_{2.5}$-related reproductive harm. Younger women may be more sensitive to PM exposure, possibly because their ovarian reserve and hormone levels are higher, and thus more responsive to air pollution exposure [20,61].

Several limitations of this study should be acknowledged. First, while oocyte fertilization failure is complex and driven by multiple biological pathways, our analysis could not dissect specific failure mechanisms, such as arrest during the second meiotic division. Future studies incorporating detailed embryo kinetics and advanced statistical modelling are needed to elucidate these associations. Second, although $PM_{2.5}$ constituent concentrations were estimated at a 10 km spatial resolution, we lacked data on participants' daily mobility and activity patterns, potentially leading to exposure misclassification. Such non-differential misclassification would likely bias our findings toward the null. Third, due to data constraints, we did not analyse individual metal constituents or specific organic matter compositions within the $PM_{2.5}$ mass, which may limit our understanding of their respective contributions to the observed effects. Future studies using finer spatial and temporal exposure assessments are also warranted to improve exposure accuracy. Fourth, as this is an observational cohort study, we cannot establish causality, and our findings should be interpreted as associative rather than causal.

5. Conclusions

In summary, exposure to major chemical constituents of $PM_{2.5}$ is

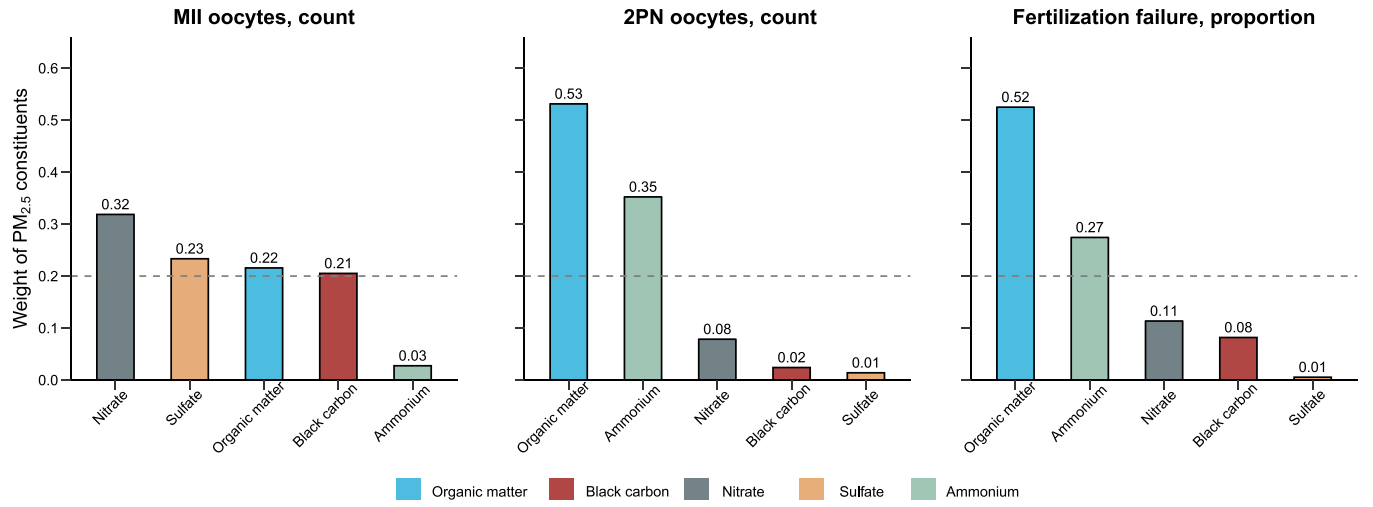

Fig. 2. The importance of $PM_{2.5}$ chemical constituents in associations with oocyte quality. Each bar corresponds to a particular component, with the length of the bar reflecting its relative weight obtained from the WQS regression; the x-axis represents the relative weight share, while the y-axis displays the different $PM_{2.5}$ components. Corresponding numeric data are reported in Table S5.

associated with reduced oocyte quality, with organic matter and nitrate showing the strongest associations. Our findings highlight the potential reproductive significance of secondary aerosol precursors.

Environmental implications

Evidence regarding the association between exposure to $PM_{2.5}$ constituents and oocyte quality remains limited. In this prospective study of 1659 ovarian stimulation cycles from 1520 women, we found that exposure to $PM_{2.5}$ and its constituents was associated with decreased numbers of MII oocytes, 2PN oocytes, and best cleavage-stage embryos, and increased rates of oocyte maturation and fertilization failure. Nitrate and organic matter showed more pronounced associations compared to other constituents. These findings highlight the importance of reducing emissions of secondary aerosol precursors.

CRediT authorship contribution statement

Jiayi Liu: Conceptualization, Methodology, Software, Writing – original draft. **Jie Yin:** Conceptualization. **Wangnan Cao:** Supervision, Project administration. **Qiang Zeng:** Supervision, Project administration. **Shengzhi Sun:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Rui Chen:** Supervision, Project administration.

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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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.139098.

Data availability

Data will be made available on request.

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