Poor ovarian response is associated with air pollutants: A multicentre study in China

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Summary

Background Human evidence on the association between air pollution and ovarian response is scarce. Poor ovarian response (POR) with an incidence of 5–35% is a tricky problem in IVF treatment.

Methods In this large-scale multicentre study, we included 2186 women with POR (< 4 oocytes retrieved) and 7033 women with a normal ovarian response (10–15 oocytes retrieved), who underwent their first *in vitro* fertilization treatment in five cities in northern China during 2015–2020. Average concentrations of six air pollutants ($PM_{2.5}$, PM_{10}, O_3, NO_2, CO, and SO_2) during different exposure windows (5 days, 1, 3, 6, and 12 months) before oocyte pick up (OPU) were calculated using data from the air monitoring station nearest to the residential site as approximate individual exposure. Logistic regression models were employed to assess the association between exposure to air pollutants and the risk of POR. Stratification analyses were conducted based on female age. Sensitivity analyses were performed in poor responders identified by Bologna criteria and women with unexpected POR.

Findings We detected that increased SO_2 exposure during all exposure windows before OPU was associated with a higher risk of POR, especially for women ≤ 30 years old. In the stratified analysis, the effect sizes were larger for the unexpected poor ovarian response.

Interpretation The findings provide human evidence for adverse effects of exposure to ambient air pollutants on ovarian response and underscore the need to reduce ambient air pollution exposure in women of reproductive age to protect human fertility.

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Research in context

Evidence before this study

Human evidence on the association between air pollution and ovarian response is scarce. In our previous study, we preliminarily observed that ambient air pollution exposure was negatively correlated with the ovarian response. Poor ovarian response (POR, < 4 oocytes retrieved) with an incidence of 5−35% is a tricky problem in IVF treatment. The association of air pollution with POR remains elusive.

Added value of this study

This large-scale multicentre study revealed a positive association between exposure to SO_2 and the risk of POR, especially for women ≤ 30 years and unexpected POR. The findings provide human evidence for adverse effects of ambient air pollutants on ovarian response.

Implications of all the available evidence

The available human evidence highlights the need to reduce ambient air pollution exposure in women of reproductive age to protect human fertility.

Introduction

Air pollution has long been considered a public health threat due to its proven association with cardiovascular, respiratory, endocrine, reproductive disorders, and even all-cause mortality risk.[1−5] The underlying biological mechanisms involving inflammation, oxidative stress, endocrine disruption, and epigenetic modification have been documented.[1,6,7] Accumulating studies provide evidence of the potential correlation between ambient air pollutants exposure and adverse reproductive outcomes.[8−13] In our previous studies, we observed that ambient air pollution exposure was negatively correlated with the outcomes of *in vitro* fertilization (IVF) treatment, including oocyte yield, pregnancy, and live birth.[8,13] However, the correlations between air pollution and oocyte yield observed in our previous are preliminary due to the absence of adjustment of the ovarian reserve markers and starting dose of gonadotropin (Gn).[8]

Ovarian reserve is defined as the quantity and quality of the ovarian follicle pool, which has been widely considered an indicator of a woman's reproductive potential or fertility.[14] A wide variety of biomarkers have been proposed as predictors of ovarian response, including anti-Mullerian hormone (AMH), antral follicle count (AFC), basal follicle-stimulating hormone (FSH), basal estradiol (E_2), and inhibin B, of which, AMH remains the preferred one.[15] Several studies have demonstrated that increased exposure to fine particulate matter was associated with lower ovarian reserve markers.[16−19] A cross-sectional study based on 67 women residing in Sabzevar, Iran revealed a detrimental association of exposure to PM_1 and $PM_{2.5}$ with serum levels of AMH.[19] Another study by Hood *et al.* (2021) included 565 women seeking infertility evaluation and treatment and reported that higher exposure to $PM_{2.5}$ was associated with lower AFC.[17]

Unlike the abovementioned pre-treatment diagnostics, a post-treatment review of ovarian response to stimulation provides valuable diagnostic information with clinical importance, which could indicate the capacity of the ovary to produce a sufficient number of oocytes and withstand the normal attrition in each IVF cycle.[20] Poor ovarian response (POR) to stimulation is a condition in which fewer than four follicles and/or oocytes are developed/obtained following ovarian stimulation with the intention of obtaining more follicles and oocytes.[21] The incidence of POR during assisted reproductive technology treatment is estimated to be approximately 5−35%, and tackling it is a challenge for both patients and clinicians.[22] Therefore, emerging studies have been devoted to uncovering the underlying factors which may contribute to the development of POR.[23−26] Even though previous studies have provided pieces of animal evidence for the adverse impact of air pollution on oocyte quality and development,[27−29] limited epidemiologic studies investigated the association between air pollution and ovarian response.[8,30,31] In this scenario, studies aimed at disentangling the possible effects of air pollution exposure on the risk of POR are warranted.

In this large-scale multicentre retrospective study, we merged data from six reproductive centres in five different provincial capitals (municipalities) in northern China, including Shenyang, Tianjin, Shijiazhuang, Taiyuan, and Hohhot, to investigate the association between exposure to six major pollutants ($PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3) and the risk of POR.

Methods

Study population

This retrospective study was conducted in six reproductive centres in five different provincial capitals (municipalities) of northern China between January 2015 and

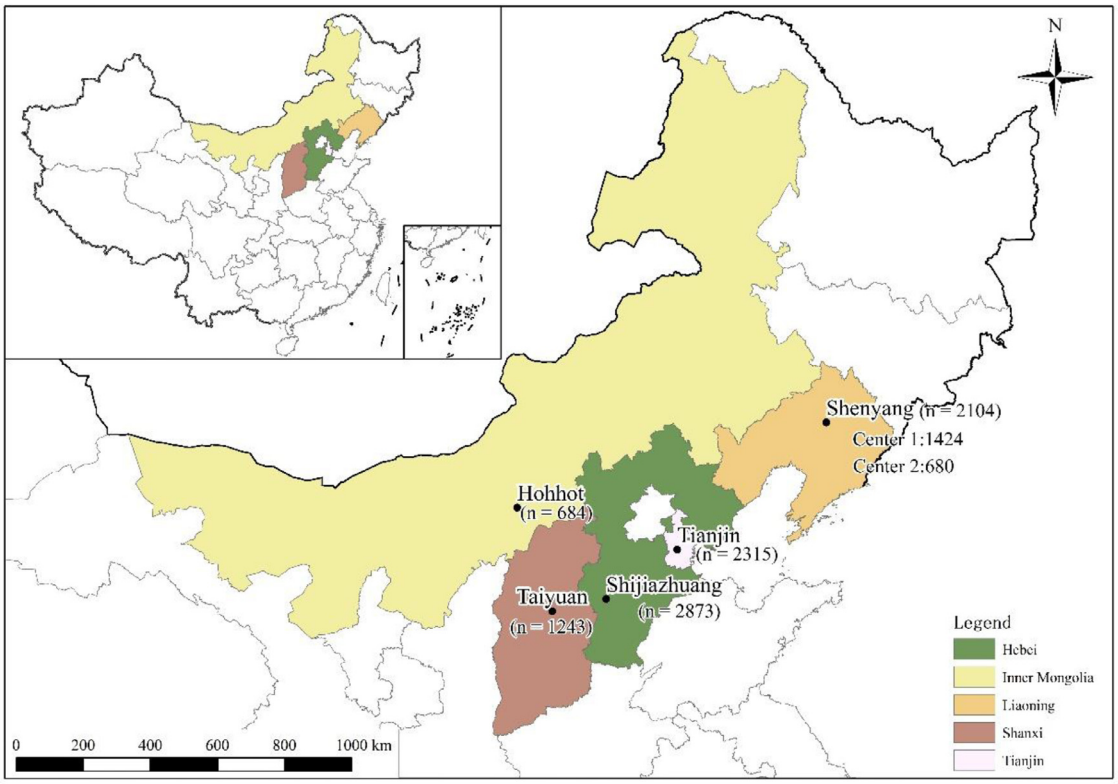

Figure 1. Location distributions and sample sizes (n) of the five cities in this study.

December 2020 (Figure 1). We included infertile women undergoing their first IVF treatment who lived in the city where the reproductive centre was located. The exclusion criteria are: (1) women underwent natural cycle or mild stimulation regimen; (2) > 40 years of age; (3) used preimplantation genetic testing; (4) used donor oocyte or sperm; (5) with missing residential address; (6) had a history of ovarian surgery. Moreover, we used the ovarian response as a key criterium: women with less than four oocytes retrieved were considered as POR; while normal ovarian response (NOR) was defined as 10–15 oocytes retrieved. In total, 2186 women with POR and 7033 women with NOR were included for analysis. Demographical and clinical data were extracted from the database used in the reproductive centres.

IVF procedure and outcome assessment

As described in our previous studies, the overall IVF procedure generally included four stages: controlled ovarian hyperstimulation (COH), oocyte retrieval, embryo transfer, and pregnancy tests.[8,32] Patients underwent one kind of COH regimen: gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist, according to their ovarian function tests and other indications. Ovulation was triggered using human chorionic gonadotropin (hCG) when there were three or more follicles with diameter ≥ 18 mm. Oocyte retrieval was performed under transvaginal ultrasound guidance 34–36 h after the trigger.

The basal circulating follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) levels were measured on menstrual cycle day 2 or day 3. The results of the sex hormone assay were obtained from the database of reproductive centres.

The primary outcome was the ovarian response to ovarian stimulation, which is usually classified as poor (≤ 3 oocytes retrieved), suboptimal (4–9 oocytes), normal (10–15 oocytes), and excessive (> 15 oocytes).[33,34] To investigate the possible effects of air pollution exposure on ovarian response, we included the women with poor or normal ovarian response for the primary analysis. Women with POR were further subdivided into poor responders and unexpected POR for sensitivity analyses. Poor responders were identified according to the Bologna criteria and designated as the POR-B group. In detail, at least two of the following three features must be present: (i) Advanced maternal age (≥ 40 years) or any other risk factor for POR; (ii) A previous POR (≤ 3 oocytes with a conventional stimulation protocol); (iii) An abnormal ovarian reserve test (i.e., AFC ≤ 7 follicles or AMH ≤ 1.1 ng/ml). Moreover, the women <40 years of age, with AMH>1.1 ng/ml, were considered as unexpected POR.

Exposure

Data on the 24-hour average concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and an 8-hour rolling average of O_3 concentrations at monitoring stations in the cities involved between January 2014 and December 2020 were obtained from the China National Environmental Monitoring Centre.[35] The stations with more than 20% data missed were excluded, therefore, the numbers of monitoring stations in Shijiazhuang, Taiyuan, Tianjin, Shenyang, and Hohhot involved in this study were 22, 7, 27, 8, and 6, respectively. The missing data can be considered to occur completely at random. The residential address for each woman was geocoded by Google Map and then the nearest monitoring station was identified for individual exposure assessment. Average concentrations of the six major air pollutants for five periods of 5 days, 1, 3, 6, and 12 months before the day of oocyte pick-up (OPU) were calculated using daily concentrations to estimate individual exposure. These five periods represent the acute (5 days), subacute (1 and 3 months), and long-term exposure (6 and 12 months), allowing us to explore the critical period of exposure, during which immediate and long-term change in ovarian reserve caused by chemical injury to ovarian could be observed, as reported in previous studies.[16,36]

Statistics

Descriptive statistics were calculated and compared between women with POR and NOR. Continuous variates are presented as the median (interquartile range, IQR), while categorical variates are shown as the number (percentage, %). Differences in demographic and clinical characteristics between the two cohorts were evaluated using Mann-Whitney U tests for the continuous variables and Chi-square tests or Fisher's exact test for the categorical variables.

Multivariable logistic regressions were used to assess the association between air pollution exposure and ovarian response. A robust estimator of covariance matrix was used to account for the clustering of individuals within cities.[37] Covariates associating ovarian response and air pollution exposure were adjusted in models based on previous studies,[8,25,38] including age (continuous), BMI (continuous), smoking status (smoker or non-smoker), infertility cause (female factor, male factor, both, or unexplained), COH protocol (antagonist, long agonist, ultra-long agonist, or others), starting dose of Gn (continuous), AMH (continuous), FSH (continuous), LH (continuous), E_2 (continuous), and residential city (Shenyang, Tianjin, Shijiazhuang, Taiyuan, or Hohhot). Specifically, two models were fitted: Model 1 adjusted for covariates other than basal sex hormone level; Model 2 adjusted for all of the abovementioned confounders. Data on air pollutants exposure were categorized into quartiles (Q1−Q4) due to non-linearity, and the lowest quartile was considered the reference group. Overall linear trends were tested across quartiles using the median concentration in each quartile as a continuous variable. Multicollinearity of pollutants was assessed using the variance inflation factor (VIF). A VIF < 4 was considered no multicollinearity, and then we implemented a multi-pollutant model in which exposure to the other air pollutants was adjusted in the form of quartiles.[8]

Stratified analyses were performed based on the categories of age ($\leq$ 30, 31-35, $>$ 35 years), the well-known factor associated with ovarian reserve.[39] In addition, several sensitivity analyses were conducted to test the robustness of the results in our main effect models. First, we assessed the association between air pollution and the risk of unexpected POR and poor responders determined by Bologna criteria, respectively, employing multivariate logistic models. Furthermore, to better adjust for potential confounding factors and selection bias, we conducted propensity score (PS) matching between unexpected POR and NOR and the POR-B and NOR cohorts, respectively. Variables used to construct PS were determined using multivariate logistic regression. Specifically, age, BMI, COH protocol, the starting dose of Gn, AMH, and FSH for unexpected POR and NOR matching; age, BMI, infertility cause, COH protocol, the starting dose of Gn, AMH, FSH, and E_2 for matching between POR-B and NOR (Table S1). Unexpected POR and POR-B were matched at a ratio of 1:2 to NOR using the nearest neighbour matching with a 0.2 calliper width and the largest matching order, respectively. Differences in the air pollutants exposure level between the two PS matched cohorts were evaluated using Mann-Whitney U tests. Finally, considering the potential exposure bias caused by the distance between the residential address and the monitoring station, a sensitivity analysis was conducted on the subpopulation of women who lived within 2 kilometres of monitoring stations.

All statistical analyses were performed using SPSS version 26.0, and a two-sided significance level of $p < 0.05$ was considered as statistically significant.

Ethics

This study was approved by the Ethics Committee of the Shengjing Hospital of China Medical University (ethical approval number: 2018PS24F). All data used in this study were anonymous and did not have any identifiers. Written informed consent for this study was not required in accordance with local legislation and national guidelines.

Role of funders

The funders had no role in study design, data collection, data analyses, interpretation, or writing of the paper.

Results

Characteristics and air pollutant exposure of study population

In total, 2186 women with POR and 7033 women with NOR were included. The characteristics of the study population are summarized in Table 1. Women with POR were older than those with NOR [34.00 (5.64) vs. 31.59 (5.18), $p < 0.001$]. There were also significant differences in terms of the type, cause, and duration of infertility between the two groups ($p < 0.001$). Moreover, starting dose of Gn used in the POR cohort was higher than that in the NOR cohort [300.00 (75.00) vs. 225.00 (100.00), $p < 0.001$]. Regarding basal circulating levels of sex hormones, women with POR had lower levels of AMH and LH ($p < 0.001$). No difference was observed in BMI and ethnicity between the two groups.

Levels of the exposure to six air pollutants during different exposure windows are presented in Table 2. The VIF was < 4, which indicated no multicollinearity, and hence, multipollutant models were performed.

Air pollutant exposure and the risk of POR

In models without the adjustment of sex hormone level, we detected that long-term $PM_{2.5}$ exposure was

	POR (n = 2186)	NOR (n = 7033)	*p*-value
Age, years, median (IQR)	34.00 (5.64)	31.59 (5.18)	< **0.001**** [f]
BMI, kg/m^2, median (IQR)	22.60 (4.90)	22.58 (4.70)	0.109 [f]
Ethnicity, N (%)			0.966 [g]
Han	2076 (95.0%)	6678 (95.0%)	
Mongolian	32 (1.5%)	101 (1.4%)	
Hui	15(0.7%)	49 (0.7%)	
Manchu	45 (2.1%)	156 (2.2%)	
Others	18 (0.8%)	49 (0.7%)	
Smoking status, N (%)			0.474 [g]
Smoker	19 (0.9%)	49 (0.7%)	
Non-smoker	2167 (99.1%)	6984 (34.6%)	
Infertility type, N (%)			< **0.001**** [g]
Primary	1307 (59.8%)	4597 (65.4%)	
Secondary	879 (40.2%)	2436 (34.6%)	
Infertility cause, N (%)			< **0.001**** [g]
Female factor	1166 (53.3%)	3462 (49.2%)	
Male factor	280 (12.8%)	1261 (17.9%)	
Both	654 (29.9%)	1970 (28.0%)	
Unexplained	86 (3.9%)	340 (4.8%)	
Infertility duration, years, median (IQR)	3.00 (4.00)	3.00 (3.00)	< **0.001**** [f]
COH protocol, N (%)			< **0.001**** [g]
Antagonist	967 (44.2%)	1593 (22.7%)	
Long agonist	612 (28.0%)	2009 (57.0%)	
Ultra-long agonist	156 (7.2%)	1046 (14.9%)	
Others [a]	451 (20.6%)	385 (5.5%)	
Starting dose of Gn, IU, median (IQR)	300.00 (75.00)	225.00 (100.00)	< **0.001**** [f]
Number of oocytes retrieved, median (IQR)	2.00 (2.00)	12.00 (3.00)	< **0.001**** [f]
AMH, ng/mL, median (IQR) [b]	0.89 (1.02)	3.13 (2.39)	< **0.001**** [f]
FSH, mIU/mL, median (IQR) [c]	8.54 (4.84)	6.83 (2.41)	0.373 [f]
LH, mIU/mL, median (IQR) [d]	3.71 (2.65)	4.21 (2.88)	< **0.001**** [f]
E2, pg/mL, median (IQR) [e]	47.52 (44.00)	44.00 (32.15)	0.065 [f]

***Table 1*: Demographic and clinical characteristics of the study population.**

[a] Other COH protocols included progestin-primed ovarian stimulation protocol (PPOS), short agonist, ultra-short agonist, and luteal-phase ovarian stimulation.

[b] n = 880 for POR and n = 2935 for NOR.

[c] n =1914 for POR and n = 6186 for NOR.

[d] n =1910 for POR and n = 6187 for NOR.

[e] n =1886 for POR and n = 6136 for NOR.

[f] Differences between the two cohorts were evaluated using Mann-Whitney U tests.

[g] Differences between the two cohorts were evaluated using Chi-square tests.Abbreviations: POR, poor ovarian response; NOR, normal ovarian response; IQR, interquartile range; BMI, body mass index; Gn, gonadotropin; AMH, anti-müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol.

Air pollutant	Exposure window	Min	25%	Median	75%	Max	IQR
$PM_{2.5}$ ($\mu g/m^3$)	5 days before OPU	14.83	52.17	68.50	92.50	502.17	40.33
	1 month before OPU	23.35	56.00	70.74	92.39	324.10	36.39
	3 months before OPU	25.84	58.27	71.62	94.69	257.07	36.42
	6 months before OPU	29.31	61.09	74.63	97.20	237.30	36.11
	12 months before OPU	44.84	63.13	79.14	94.92	208.74	31.79
PM_{10} ($\mu g/m^3$)	5 days before OPU	15.50	86.67	112.00	139.33	547.50	52.66
	1 month before OPU	23.90	93.97	114.23	134.13	395.00	40.16
	3 months before OPU	41.71	97.48	114.99	133.25	306.57	35.77
	6 months before OPU	47.58	102.58	120.16	137.58	242.68	35.00
	12 months before OPU	62.77	107.04	119.89	139.27	216.54	32.23
O_3 ($\mu g/m^3$)	5 days before OPU	1.40	27.00	49.00	84.17	258.67	57.17
	1 month before OPU	5.16	30.62	51.84	82.74	217.10	52.12
	3 months before OPU	7.01	34.00	52.60	79.91	181.68	45.91
	6 months before OPU	11.14	33.82	49.31	74.52	153.77	40.70
	12 months before OPU	16.17	36.06	45.37	81.69	107.99	45.63
NO_2 ($\mu g/m^3$)	5 days before OPU	2.02	14.67	19.83	26.83	123.00	12.16
	1 month before OPU	2.74	15.10	20.03	26.06	97.16	10.96
	3 months before OPU	4.14	15.82	20.03	25.00	80.55	9.18
	6 months before OPU	6.36	16.90	20.68	25.17	69.13	8.27
	12 months before OPU	7.80	18.67	21.40	24.71	57.06	6.04
SO_2 ($\mu g/m^3$)	5 days before OPU	1.05	5.67	9.33	16.83	245.00	11.16
	1 month before OPU	1.32	5.97	9.68	16.97	202.10	11.00
	3 months before OPU	1.68	6.43	10.30	17.95	164.19	11.52
	6 months before OPU	1.63	7.42	12.30	21.28	127.91	13.86
	12 months before OPU	2.51	9.83	14.91	24.55	82.46	14.72
CO (mg/m^3)	5 days before OPU	0.12	0.63	0.83	1.12	6.25	0.49
	1 month before OPU	0.17	0.67	0.83	1.10	4.68	0.43
	3 months before OPU	0.26	0.70	0.86	1.10	4.76	0.40
	6 months before OPU	0.35	0.77	0.96	1.18	2.52	0.41
	12 months before OPU	0.61	0.85	0.99	1.26	1.96	0.41

***Table 2*: The distributions of six air pollutants during different exposure windows.**
Abbreviations: Min: minimum; Max: maximum; IQR, interquartile range.

associated with a higher risk of POR (Table 3). Specifically, women in the highest quartile of $PM_{2.5}$ exposure during 6 months (OR: 1.44, 95%CI: 1.06, 1.96) and 12 months (OR: 1.54, 95%CI: 1.10, 2.14) before OPU had a higher risk of POR compared with those in the lowest quartile. Women in the third quartile of O_3 exposure during 3 months (OR: 1.19, 95%CI: 1.00, 1.42) and 12 months (OR: 1.28, 95%CI: 1.08, 1.53) before OPU were more likely to have a POR compared with the first quartile. In addition, significant positive dose-response correlations between SO_2 exposure and risk of POR were observed in each exposure window (all p-trend $<$ 0.001). After adjusting sex hormone levels, the positive relationships between SO_2 exposure and risk of POR were attenuated (all p-trend $<$ 0.01), while no association between the other five air pollutants and POR was detected (Figure 2).

Moreover, given that age is a well-known factor associated with ovarian reserve, we conducted a stratified analysis based on the categories of female age (Figure 3 and S1). For women $\leq$ 30 years old, the results were in accordance with the main effect models. Nevertheless, for women at age of 31-35 years, higher SO_2 exposure during 6 months to 3 months prior to OPU was associated with a higher risk of POR, and for women older than 35 years old, acute and short-term (1 month) SO_2 exposure was positively correlated with risk of POR (Figure 3). No association was detected with other air pollutants (Figure S1).

Sensitivity analysis

To test the robustness of the findings in the main models, we conducted several sensitivity analyses. For unexpected POR, similar associations with larger effect sizes were detected (Table 4), however, the positive dose-response association between SO_2 exposure and risk of the poor responder determined by Bologna criteria was only observed in acute and short-term windows (Table S2). Due to the large difference in the sample size of unexpected POR, POR-B, and NOR cohorts, PS matching was performed. After PS matching, the unexpected

Air pollutant	Exposure window	Odds ratio (95% Confidence interval) [a]				p-trend
		Q1	Q2	Q3	Q4	
$PM_{2.5}$ ($\mu g/m^3$)	5 days before OPU	Ref	0.96 (0.82, 1.12)	0.97 (0.80, 1.16)	1.03 (0.82, 1.29)	0.560
	1 month before OPU	Ref	**0.84 (0.72, 0.99)***	0.96 (0.78, 1.16)	1.09 (0.85, 1.40)	0.101
	3 months before OPU	Ref	0.93 (0.79, 1.10)	0.83 (0.67, 1.03)	1.12 (0.85, 1.48)	0.090
	6 months before OPU	Ref	0.90 (0.76, 1.08)	1.09 (0.87, 1.36)	**1.44 (1.06, 1.96)***	**0.001****
	12 months before OPU	Ref	0.88 (0.73, 1.07)	1.07 (0.83, 1.40)	**1.54 (1.10, 2.14)***	**< 0.001****
PM_{10} ($\mu g/m^3$)	5 days before OPU	Ref	0.91 (0.79, 1.05)	**0.84 (0.72, 0.98)***	0.83 (0.69, 1.00)	0.151
	1 month before OPU	Ref	0.84 (0.98, 1.13)	0.84 (0.98, 1.15)	0.71 (0.87, 1.05)	0.237
	3 months before OPU	Ref	0.77 (0.89. 1.03)	**0.82 (0.70, 0.97)***	0.97 (0.80, 1.19)	0.326
	6 months before OPU	Ref	0.91 (0.79, 1.06)	**0.78 (0.66, 0.91)***	0.90 (0.73, 1.10)	0.138
	12 months before OPU	Ref	1.14 (0.98, 1.32)	0.97 (0.82, 1.14)	0.83 (0.70, 1.00)	0.082
O_3 ($\mu g/m^3$)	5 days before OPU	Ref	1.05 (0.91, 1.22)	0.99 (0.84, 1.15)	0.85 (0.72, 1.01)	0.112
	1 month before OPU	Ref	1.05 (0.90, 1.22)	1.08 (0.91, 1.28)	**0.81 (0.67, 0.98)***	0.421
	3 months before OPU	Ref	**1.19 (1.02, 1.39)***	**1.19 (1.00, 1.42)***	0.91 (0.75, 1.10)	**0.015***
	6 months before OPU	Ref	1.10 (0.94, 1.28)	1.17 (0.99, 1.39)	0.86 (0.71, 1.04)	0.216
	12 months before OPU	Ref	**1.36 (1.17, 1.57)****	**1.28 (1.08, 1.53)****	0.98 (0.82, 1.18)	**0.020***
NO_2 ($\mu g/m^3$)	5 days before OPU	Ref	1.00 (0.86, 1.16)	0.88 (0.74, 1.03)	0.95 (0.78, 1.17)	0.590
	1 month before OPU	Ref	1.01 (0.87, 1.17)	0.90 (0.76, 1.06)	0.85 (0.69, 1.05)	0.089
	3 months before OPU	Ref	0.99 (0.85, 1.15)	0.94 (0.79, 1.11)	0.99 (0.79, 1.22)	0.858
	6 months before OPU	Ref	0.89 (0.76, 1.03)	0.94 (0.79, 1.12)	0.90 (0.72, 1.13)	0.478
	12 months before OPU	Ref	0.97 (0.84, 1.13)	0.95 (0.80, 1.13)	0.91 (0.73, 1.13)	0.378
SO_2 ($\mu g/m^3$)	5 days before OPU	Ref	**1.26 (1.09, 1.47)****	**1.44 (1.22, 1.70)****	**1.64 (1.35, 2.00)****	**< 0.001****
	1 month before OPU	Ref	**1.33 (1.14, 1.56)****	**1.48 (1.24, 1.76)****	**1.65 (1.33, 2.04)****	**0.001****
	3 months before OPU	Ref	**1.56 (1.33, 1.83)****	**1.62 (1.34, 1.96)****	**1.98 (1.57, 2.48)****	**< 0.001****
	6 months before OPU	Ref	**1.63 (1.38, 1.93)****	**1.82 (1.49, 2.21)****	**2.10 (1.67, 2.64)****	**< 0.001****
	12 months before OPU	Ref	**2.06 (1.71, 2.49)****	**2.38 (1.92, 2.96)****	**2.53 (2.01, 3.19)****	**< 0.001****
CO (mg/m^3)	5 days before OPU	Ref	0.86 (0.74, 1.00)	0.86 (0.73, 1.00)	0.86 (0.71, 1.04)	0.712
	1 month before OPU	Ref	1.02 (0.88, 1.18)	0.94 (0.80, 1.11)	0.86 (0.71, 1.04)	0.287
	3 months before OPU	Ref	**0.81 (0.70, 0.94)***	1.14 (0.96, 1.34)	1.05 (0.86, 1.27)	0.543
	6 months before OPU	Ref	0.94 (1.09, 1.27)	0.93 (1.11, 1.32)	0.99 (1.21, 1.47)	0.150
	12 months before OPU	Ref	0.90 (0.77, 1.05)	0.95 (0.80, 1.13)	1.08 (0.89, 1.31)	0.127

***Table 3*: Association between exposure to air pollutants and the risk of POR (N = 9219).**
Abbreviations: OPU: oocyte pick-up.
[a] Models adjusted for age, BMI, smoking status, infertility cause, COH protocol, starting dose of Gn, and residential city.

POR group consisted of 260 women who matched 506 women in the control group. Except for COH protocol and oocyte yield, no basic or clinical parameter was significantly different (Table S3 and Figure S2). Comparing the air pollutant exposure between the two groups, we detected that the women with unexpected POR had higher exposure to SO_2 during every window while lower long-term exposure to O_3 (Figure 4). Given that the ovarian response was significantly associated with the regimen of stimulation, we conducted PS matching in the subpopulation of women who underwent antagonist and long agonist COH protocol respectively, to further adjust for the bias introduced by the unbalanced covariates (Table S4). Consistent with the findings in the overall population (Figure 4), significant differences in SO_2 and O_3 exposure between unexpected POR and NOR were also detected in the antagonist subgroup, and we observed that the women with unexpected POR had higher long-term exposure to NO_2 (Table S5). However, in the long antagonist subpopulation, exposure differences between the two cohorts were only significant for SO_2 (Table S5). In addition, 62 poor responders and 82 women with NOR were matched, while infertility cause, COH protocol, and oocyte yield were significantly different between the two cohorts after matching (Table S6 and Figure S3). We observed that poor responders had higher SO_2 exposure in the windows except for 5 days before OPU and lower O_3 exposure in short-term to long-term windows (3, 6, and 12 months before OPU) (Figure S4). Furthermore, significant associations between SO_2 exposure and higher risk of POR were observed in all exposure windows, except acute exposure, in the sensitivity analysis of women living within 2 kilometres of the monitoring stations (Table S7).

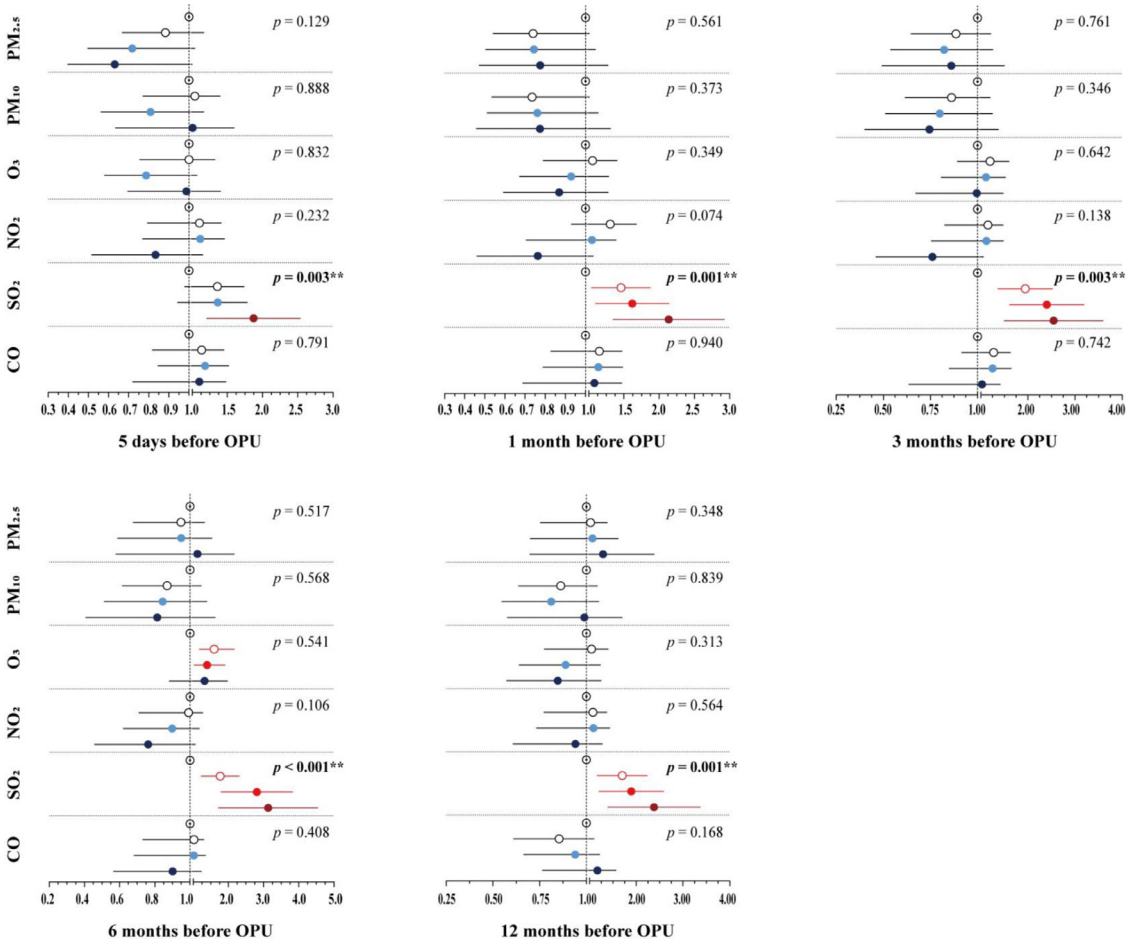

Figure 2. Association between the exposure to air pollutants and the risk of POR. Multivariate logistic models adjusted for age, BMI, smoking status, infertility cause, COH protocol, starting dose of Gn, AMH, FSH, LH, E_2, and residential city. The graph shows the adjusted odds ratio of the risk of POR for pollutant levels in the second (white circles), the third (light blue circles), and the fourth (dark blue circles) quartiles compared with the first quartile (hollow circles) of each pollutant. Line segments represent 95% confidence interval. Significant associations (p-value <0.05) are shown in red. p values represent linear trends across quartiles. Abbreviations: POR, poor ovarian response; BMI, body mass index; COH, controlled ovarian hyperstimulation; Gn, gonadotropin; AMH, anti-müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol.

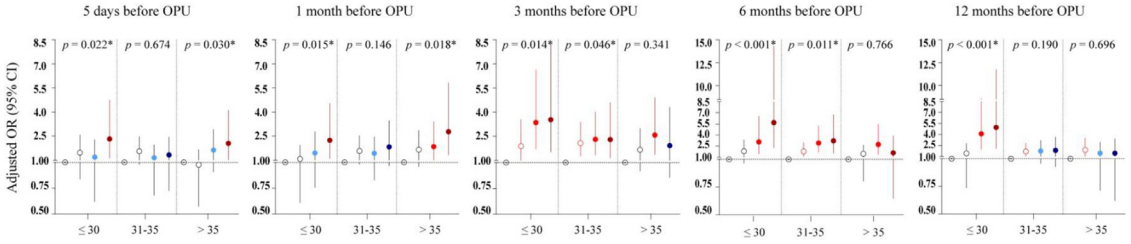

Figure 3. Association between the exposure to SO_2 and the risk of POR in different categories of female age. Multivariate logistic models adjusted for age, BMI, smoking status, infertility cause, COH protocol, starting dose of Gn, AMH, FSH, LH, E_2, and residential city. The graph shows the adjusted odds ratio of the risk of POR for pollutant levels in the second (white circles), the third (light blue circles), and the fourth (dark blue circles) quartiles compared with the first quartile (hollow circles) of each pollutant. Line segments represent 95% confidence interval. Significant associations (p-value <0.05) are shown in red. p values represent linear trends across quartiles. Abbreviations: POR, poor ovarian response; BMI, body mass index; COH, controlled ovarian hyperstimulation; Gn, gonadotropin; AMH, anti-müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol.

Air pollutant	Exposure window	Odds ratio (95% Confidence interval) [a]				p-trend
		Q1	Q2	Q3	Q4	
$PM_{2.5}$ ($\mu g/m^3$)	5 days before OPU	Ref	0.76 (0.50, 1.14)	0.69 (0.42, 1.13)	0.65 (0.35, 1.22)	0.442
	1 month before OPU	Ref	0.79 (0.52, 1.21)	0.99 (0.59, 1.64)	1.04 (0.53, 2.04)	0.708
	3 months before OPU	Ref	1.00 (0.66, 1.52)	0.88 (0.49, 1.57)	1.11 (0.53, 2.34)	0.613
	6 months before OPU	Ref	0.99 (0.63, 1.57)	0.89 (0.46, 1.73)	1.59 (0.65, 3.91)	0.098
	12 months before OPU	Ref	0.87 (0.59, 1.28)	0.87 (0.50, 1.53)	2.17 (0.99, 4.76)	0.141
PM_{10} ($\mu g/m^3$)	5 days before OPU	Ref	0.99 (0.67, 1.46)	0.66 (0.40, 1.10)	1.00 (0.54, 1.86)	0.864
	1 month before OPU	Ref	0.71 (0.46, 1.10)	0.71 (0.40, 1.23)	**0.48 (0.23, 0.99)***	0.141
	3 months before OPU	Ref	0.72 (0.46, 1.12)	0.57 (0.31, 1.06)	0.58 (0.26, 1.32)	0.203
	6 months before OPU	Ref	0.67 (0.42, 1.08)	0.55 (0.27, 1.08)	0.65 (0.25, 1.68)	0.378
	12 months before OPU	Ref	0.72 (0.49, 1.07)	**0.46 (0.26, 0.81)***	0.87 (0.43, 1.76)	0.917
O_3 ($\mu g/m^3$)	5 days before OPU	Ref	1.08 (0.75, 1.55)	0.79 (0.52, 1.18)	0.90 (0.56, 1.45)	0.419
	1 month before OPU	Ref	0.90 (0.62, 1.31)	0.89 (0.59, 1.36)	0.60 (0.35, 1.03)	0.061
	3 months before OPU	Ref	1.28 (0.87, 1.87)	1.17 (0.77, 1.79)	0.72 (0.41, 1.25)	0.125
	6 months before OPU	Ref	1.21 (0.82, 1.78)	1.34 (0.90, 1.99)	0.70 (0.40, 1.22)	0.211
	12 months before OPU	Ref	1.25 (0.87, 1.79)	0.88 (0.57, 1.37)	0.75 (0.44, 1.29)	0.167
NO_2 ($\mu g/m^3$)	5 days before OPU	Ref	1.14 (0.77, 1.69)	1.08 (0.70, 1.66)	0.79 (0.46, 1.36)	0.312
	1 month before OPU	Ref	1.28 (0.86, 1.91)	1.02 (0.65, 1.61)	0.74 (0.42, 1.31)	0.209
	3 months before OPU	Ref	1.48 (0.99, 2.20)	1.19 (0.75, 1.89)	0.83 (0.47, 1.45)	0.357
	6 months before OPU	Ref	0.90 (0.61, 1.35)	0.71 (0.46, 1.11)	0.57 (0.33, 1.01)	0.052
	12 months before OPU	Ref	0.95 (0.64, 1.42)	0.87 (0.55, 1.38)	0.77 (0.47, 1.28)	0.300
SO_2 ($\mu g/m^3$)	5 days before OPU	Ref	**2.15 (1.40, 3.30)****	**2.16 (1.35, 3.44)****	**3.06 (1.82, 5.16)****	**< 0.001****
	1 month before OPU	Ref	**2.32 (1.47, 3.67)****	**2.84 (1.74, 4.65)****	**3.71 (2.12, 6.49)****	**< 0.001****
	3 months before OPU	Ref	**3.57 (2.19, 5.82)****	**4.07 (2.41, 6.87)****	**4.98 (2.66, 9.32)****	**0.001****
	6 months before OPU	Ref	**2.61 (1.56, 4.39)****	**5.34 (3.05, 9.34)****	**5.71 (2.90, 11.23)****	**< 0.001****
	12 months before OPU	Ref	**3.85 (2.20, 6.75)****	**4.91 (2.66, 9.06)****	**6.35 (3.27, 12.31)****	**< 0.001****
CO (mg/m^3)	5 days before OPU	Ref	0.88 (0.61, 1.30)	0.83 (0.55, 1.25)	0.75 (0.46, 1.23)	0.264
	1 month before OPU	Ref	0.93 (0.63, 1.38)	0.91 (0.59, 1.41)	0.68 (0.41, 1.15)	0.142
	3 months before OPU	Ref	1.00 (0.68, 1.48)	0.77 (0.48, 1.22)	0.63 (0.36, 1.09)	0.071
	6 months before OPU	Ref	0.79 (0.53, 1.17)	0.74 (0.47, 1.16)	0.72 (0.43, 1.21)	0.250
	12 months before OPU	Ref	**0.63 (0.43, 0.94)***	0.77 (0.52, 1.12)	0.88 (0.54, 1.43)	0.935

***Table 4*: Association between exposure to air pollutants and the risk of unexpected POR.**
Abbreviations: OPU: oocyte pick-up.
[a] Models adjusted for age, BMI, smoking status, infertility cause, COH protocol, starting dose of Gn, AMH, FSH, LH, E_2, and residential city.

Discussion

In our previous study, a declining trend in oocyte yield was observed with an increase in exposure to $PM_{2.5}$, PM_{10}, and SO_2, among which, the average difference in oocyte yield for SO_2 was the largest.[8] However, due to the data limitation, we did not adjust for the sex hormone in the previous study, and hence, the results were preliminary. In this multicentre retrospective study, we expanded the sample size, 2186 women with POR and 7033 women with NOR were included to investigate the possible effects of air pollution exposure on ovarian response. After adjusting sex hormone levels, significant positive associations between SO_2 exposure in all windows before OPU and the risk of POR were observed, especially for unexpected POR. Moreover, we detected that women with unexpected POR and poor responders had a lower level of long-term exposure to O_3, compared with the matched women with NOR.

There are limited epidemiologic investigations on the association between air pollution and ovarian response.[30,31] A retrospective study conducted on 292 French patients suggested that acute exposures to higher levels of NO_2 or PM_{10} were associated with lower ovarian response, while the O_3 exposure from 60 days to 30 days before OPU was correlated with a higher ovarian response,[30] which was consistent with our findings in part. Notably, the study of Carré *et al.* (2017) is quite different from our study in exposure estimation and statistical analysis. In detail, Carré *et al.* (2017) calculated individual exposure based on the data from a single regional air station while did not include SO_2 in analyses due to the undetectable dose. In addition, Carré *et al.* (2017) evaluated acute exposure by classifying the levels of air pollutants as good and poor groups according to the world health organization recommendation rather than the quartile used in our study. Regarding statistical analysis, no confounding factors

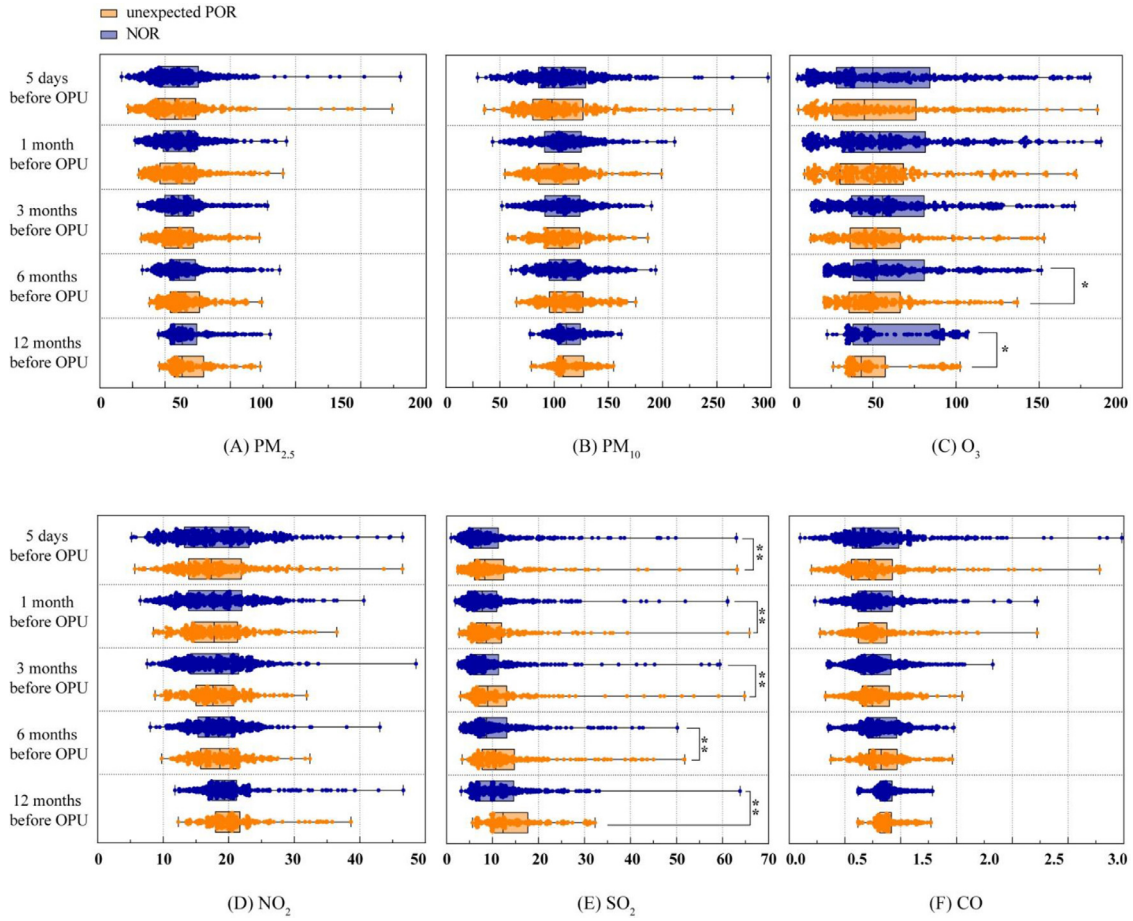

Figure 4. Comparison of air pollution exposure levels in women with unexpected POR (n = 260) and matched women with NOR (n = 506). Each point represents the exposure level of a participant. Line segments represent the minimum to maximum exposure level. *$p < 0.05$, **$p < 0.001$. Abbreviations: POR, poor ovarian response; NOR, normal ovarian response.

were adjusted in the study of Carré *et al.* (2017). Gaskins *et al.*(2019a) conducted a prospective study to examine the association between time-varying exposure to air pollutants and IVF outcomes and reported a significant association of black carbon with higher odds of failure prior to ET, including the cycle cancellation due to POR. However, Gaskins *et al.*(2019a) did not assess effects of SO_2 and O_3 exposure on ovarian response or adjust the basal sex hormone levels. Similar to the results of Gaskins *et al.*'s study, a positive association between exposure to $PM_{2.5}$ and the risk of POR were observed in models without the adjustment of basal sex hormone levels.

Recently, a study enrolled 600 women with a spontaneous menstrual cycle in north China and assessed the association between exposure to air pollutants and AFC change.[40] Feng *et al.* (2021) reported that long-term exposure to air pollutant SO_2 is associated with lower AFC. Combined with our findings, atmospheric SO_2 exposure may have detrimental effects on ovarian reserve, both in terms of pre-treatment diagnostics and post-treatment review of the response to stimulation. SO_2, a major air pollutant, is mainly related to coal-fired heating and automobile exhaust.[41] Previous studies have suggested that exposure to SO_2 was associated with adverse reproductive outcomes in the general population, including lower fecundability, preterm birth, neonatal defects, and so on.[42–44] However, the mechanisms underlying the detrimental effects of SO_2 on female fertility have not been well demonstrated. One potential mechanism involves the reduced production of reactive oxygen species.[45]

In the stratification analysis, we detected inconsistent results across age subgroups of women. Specifically, for younger women (≤ 30 years old), the results were in accordance with the main effect models. However, for women aged 31-35 years, the positive association of SO_2 exposure with risk of POR was only observed in short- and medium-term exposure windows (3 to 6 months), and for older women (> 35 years old), such association was only detected in acute and short-term (1 month) exposure windows. One explanation for

the discordance was that the impact of air pollution was attenuated by age. It is well known that female fertility declines with age. The probability of conception per unit time is relatively stable between the onset of puberty in women and their early thirties.[39] Advanced maternal age is generally considered to begin around age 35, and soon after a dramatic decline in oocyte quantity and quality can be seen.[46] In humans, it takes ~ 6 months for an oocyte to fully mature.[47] Specifically, in the human ovary, greater than 120 days are required for the primary follicles to reach the secondary follicle stage, whereas 71 days are needed to grow from the secondary to the early antral stage, and it takes 14 days for an antral follicle to become a dominant follicle.[48] Therefore, the findings of stratified analyses indicated that SO_2 exposure might affect oocytes mature for women aged 31-35 years, while for women older than 35 years, the SO_2 exposure might primarily have impact on the ovarian response to stimulation.

O_3 is a secondary air pollutant, which generates when hydrocarbons and nitrogen oxides combine in the presence of sunlight and there could be substantial non-linearities in this process.[49] A study by Legro *et al.* (2010) reported a positive association between O_3 concentration at the patient's address and the chance of live birth, however, after modelling for interactions of NO_2 and O_3 at the IVF lab, the association was null.[50] Similarly, Boulet *et al.* (2019) detected that O_3 was weakly positively associated with implantation and live birth.[51] In sensitivity analyses, we detected that women with NOR had higher O_3 exposure than poor responders and women with unexpected POR, nevertheless, no significant correlation was observed in multipollutant models for O_3. Therefore, the results should be interpreted with caution, and further studies are warranted to verify our findings.

In interpreting our findings, several limitations should be taken into consideration. First, the individual estimation of air pollution exposure was calculated using the concentrations of pollutants in their residential address as a proxy. However, due to the privacy protection, we can not obtain the exact time the subjects spent at home or the floor level on which the subjects lived, therefore, the exposure estimation was inaccurate. Second, the data on AFC were not available which may introduce selection bias in identifying poor responders and women with unexpected POR. In addition, we could not assess the association between ovarian reserve markers in this study, due to missing data on the date of the test. Third, PS matching was used in the sensitivity analyses, however, unbalanced covariates remained between the POR-B and NOR cohorts after matching, which might bias the comparisons. Moreover, there might be residual confounders that were not considered, such as socioeconomic status, occupational exposure, and so on. Finally, the retrospective nature of this study might not allow us to identify a causal relationship between air pollution and POR. Limited by the weakness inherent in the study design, the demonstrated observations were only associative, and the underlying mechanism remains unclear. Nevertheless, our study also has several strengths. Given that POR is commonly associated with early IVF failure and tackling it is quite challenging, a deep study may have clinical importance. Furthermore, our study may also benefit from its large-scale population, wide range of air pollution exposure, and large time span. We merged all data from six reproductive centres in five different provincial capitals (municipalities), covering most of north China, thus, this study could partly reflect the status of the infertile population and air pollution in northern China.

In summary, this large-scale multicentre retrospective cohort study in north China detected a significant inverse correlation between SO_2 exposure during all exposure windows before OPU and the risk of POR, especially for unexpected POR. These findings highlight the need and urgency to reduce ambient air pollution exposure in women of reproductive age to protect human fertility. Further studies are warranted to confirm our findings and determine the underlying biological mechanism.

Contributors

Shanshan Wu: conceptualisation, formal analysis, investigation, writing-original draft; Guimin Hao, Yunshan Zhang, Xiujuan Chen, and Haiqin Ren: data collection, data curation; Yanli Fan, Yinfeng Zhang, Xingyu Bi, Chen Du, and Lina Bai: data collection; Xueqing Wu: resources, data collection, data curation; Jichun Tan: conceptualisation, funding acquisition, supervision, writing-review & editing; Shanshan Wu and Jichun Tan: directly accessed and verifiied the underlying data. All authors read and approved the final version of the manuscript.

Declaration of interests

The authors declare that they have no conflict of interest.

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Data sharing statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104084.

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