



OPEN A retrospective study on the association of ambient air pollutants and temperature co-exposure with female infertility risk in Chengdu, China

Kaili Zhang¹, Wei Chen², Prasanna Divigalpitiya³, Shasha Xing² & Erdan Luo²✉

Few studies explored air pollution's role in female infertility, especially with temperature factors. Investigating these effects is essential given global climate change and declining fertility rates. This retrospective study, conducted in Chengdu, China, included 1158 patients with primary infertility, 804 patients with secondary infertility, and 1809 fertile women who visited outpatient clinics between 2018 and 2023. Individual exposure levels to six air pollutants and temperatures were determined based on residential addresses. Multinomial logistic regression assessed the associations between air pollutants, temperature, and female infertility across five exposure windows (3–36 months before diagnosis). A stratified analysis by age was performed, and the interactions and combined exposure effects were further evaluated. Exposure to NO₂ during 6 and 24 months before diagnosis was associated with a higher risk of primary infertility [OR (95% CI) = 1.17 (1.06–1.28); 1.08 (1.03–1.14)], exposure to PM₁₀ during 24 months before diagnosis was associated with a higher likelihood of primary infertility (OR = 1.32 [1.04–1.57]). Exposure to PM_{2.5} during the 3 months before diagnosis had a higher risk of secondary infertility (OR = 1.32 [1.08–1.56]), as well as during the 36 months before diagnosis (OR = 1.08 [1.01–1.13]). PM₁₀ exposure during the 3 months, 12, and 36 months before diagnosis (OR = 1.09 [1.01–1.17]; 1.21 [1.05–1.38]; 1.14 [1.03–1.23]), was associated with a higher risk of secondary infertility. Higher temperature exposure in the 3 months before diagnosis was associated with a lower risk of both primary and secondary infertility [OR = 0.92 (0.85–0.96); 0.91 (0.83–0.95)]. Women under 32 years of age exhibited increased sensitivity to NO₂, CO, and temperature exposure. Additionally, co-exposure to low temperatures and high concentrations of SO₂ or NO₂ heightened the risk of primary infertility during the 3 months before diagnosis [OR = 1.86 (1.12–3.04); 1.62 (1.13–2.33)]. Co-exposure to low temperatures and high concentrations of PM₁₀ increased the risk of secondary infertility during 3, 12, and 36 months before diagnosis [OR = 1.51 (1.13–2.03); 1.48 (1.07–2.21); 1.71 (1.13–2.52)]. This study emphasizes the potential for mitigating female infertility risk through reduced exposure to NO₂, PM₁₀, and PM_{2.5}, and by appropriately adjusting environmental temperatures.

Keywords Female infertility, Ambient exposure, Air pollution, Temperature, Interaction

Infertility is defined as the inability to achieve pregnancy after one year or more of regular, unprotected intercourse, with this period shortened to 6 months for women aged 35 years and above¹. Based on pregnancy history, infertility is categorized into two major types: primary and secondary. Primary infertility was defined as infertility in women who had not previously been pregnant, while secondary infertility referred to women with a prior pregnancy who subsequently experienced infertility². The global lifetime prevalence of infertility is approximately 17.5%³. In China, around 25% of women attempting to conceive have experienced infertility⁴. Given the high prevalence of female infertility and the unique challenges it poses to reproductive health interventions, this issue has garnered significant research attention.

¹Graduate School of Human-Environment Studies, Kyushu University, Fukuoka 819-0395, Japan. ²School of Medicine, Chengdu Women's and Children's Central Hospital, University of Electronic Science and Technology of China, Chengdu 611731, China. ³Faculty of Human-Environment Studies, Kyushu University, Fukuoka 819-0395, Japan. ✉email: luoerdan@sina.cn

Most cases of infertility in women can be attributed to organic diseases or functional reproductive disorders, such as endometriosis, diminished ovarian reserve, and tubal or pelvic diseases⁵. However, many cases remain unexplained, even in the absence of any diagnosed physiological or pathological basis⁶. Epidemiological and animal studies suggest that environmental factors, particularly air pollution, may contribute significantly to unexplained infertility cases⁷.

Previous studies have reported the adverse effects of air pollution on various aspects of female reproductive health, including pregnancy outcomes⁸, birth outcomes⁹, miscarriage rates¹⁰, and ovarian function¹¹. A negative correlation exists between human fertility and increased air pollution exposure¹². To date, only two studies have directly examined the association between air pollutants and human infertility. These studies indicate that exposure to particulate matter across all size fractions and traffic-related air pollution are associated with a higher incidence of infertility¹³, with exposure to PM_{2.5} linked to a 20% higher likelihood of infertility¹⁴. Three additional studies on the same topic have examined the effects of air pollution on fertility^{15–17}. These studies provide further evidence of the impact of air pollution on reproductive health, indicating that both long-term and short-term exposures to air pollutants may reduce fecundability. Collectively, they support the crucial premise that when investigating the effects of pollutants on infertility risk, it is essential to consider the temporal characteristics of pollution exposure. Additionally, air pollution appears to accelerate reproductive aging, being associated with both earlier menarche and earlier menopause, potentially shortening the reproductive lifespan in women^{18,19}.

In addition to air pollution, temperature is a crucial environmental factor that has garnered increasing attention in epidemiology, public health, and environmental sciences. Several studies have revealed that ambient temperature profoundly impacts human fertility, with these effects potentially extending into subsequent generations²⁰. Prolonged exposure to extreme heat may impair the human reproductive system, affecting ovarian function and ovulation cycles and consequently leading to adverse outcomes for female reproductive health²¹. Pregnant women are particularly susceptible to the effects of temperature changes²². Exposure to extreme heat has been linked to declining fertility rates after nine months²³. However, to the best of our knowledge, few studies have specifically examined the association between ambient temperature and human infertility²⁴. Recent research has begun to explore related aspects, such as the influence of temperature on ovarian reserve and outcomes following ovarian stimulation and IVF²⁵.

Temperature variations not only impact an individual's physical health but may also exacerbate the adverse effects of air pollutants by altering the body's sensitivity. Limited evidence on the interaction between temperature changes and air pollutants has primarily focused on respiratory diseases²⁶, overall population mortality^{27,28}, infectious diseases²⁹, and cardiovascular health³⁰. For example, co-exposure to high temperatures and air pollution during the prenatal and postnatal periods increases the risk of asthma in early childhood²⁶. A study conducted in Germany and Portugal demonstrated that the interaction between air pollutants such as O₃ and PM₁₀ and high temperatures led to increased population mortality^{26,31}. Most studies on environmental exposure and infertility have primarily focused on the isolated effects of air pollution. Given that fluctuations in air pollution and temperature often occur simultaneously and may have complex interactions, it is crucial to investigate their potential joint effects on female infertility.

In addition, a large number of studies have highlighted the important impact of age on female fertility³². Given that female fertility naturally declines with age, particularly after the age of 32³³, stratifying by age allows for a better understanding of how environmental exposures interact with age-related changes in reproductive health. Comparing the effects of air pollution and temperature across two distinct age groups, provides a clearer insight into how these factors may influence infertility risk at different stages of life. Based on medical records from a gynecology hospital, this retrospective study was conducted in Chengdu, a megacity in China (population: 21.4 million), to assess the independent and joint associations between air pollutants, temperature, and female infertility.

Materials and methods

Study sample

This study collected personal information, pregnancy history, and gynecological diagnostic data from women of reproductive age who visited Chengdu Women's and Children's Central Hospital between May 2018 and December 2023. Personal information included detailed residential addresses (down to street and community levels), age, height, weight, and date of diagnosis. Gynecological diagnoses included infertility, polycystic ovary syndrome (PCOS), tubal and pelvic diseases, endometriosis, and uterine fibroids, while pregnancy information included pregnancy, delivery, and miscarriage histories. The study was approved by the Ethics Committee of the Chengdu Women's and Children's Central Hospital [Ethics Approval No. 2023(129)]. All data used in this study were fully anonymized, and participants provided informed consent. The data collection, analysis, and methodological execution of this study adhered to the ethical principles of the Declaration of Helsinki and the Ethical Review Measures for Biomedical Research Involving Humans, issued by the former National Health and Family Planning Commission of the People's Republic of China in 2016. Additionally, the study complied with the relevant laws and regulations of China.

To refine the sample, we first excluded 809 women residing outside Chengdu's administrative boundaries and 413 women with missing personal information, diagnostic data, or pregnancy history from the initial pooled sample (5314 cases). The inclusion criteria for infertility cases were as follows: (1) infertility clinically diagnosed as female-factor infertility, and (2) age between 20 and 42 years. A total of 3505 eligible women with infertility were included. Subsequently, we excluded 370 cases of infertility following in vitro fertilization (IVF) and two cases of tubal ligation. Women diagnosed with any of the following gynecological conditions were also excluded to control organic or functional infertility: (1) PCOS (235 cases); (2) tubal or pelvic diseases, including

blockages, adhesions, hydrosalpinx, and ovulation disorders (204 cases); (3) ovarian dysfunction (114 cases); (4) endometriosis (384 cases); and (5) uterine fibroids (234 cases).

Fertile patients included women who visited outpatient clinics during the same period. The inclusion criteria were as follows: (1) normal sexual activity and a history of spontaneous pregnancy or childbirth, (2) no history of infertility or related chief complaints, and (3) age between 20 and 42 years. Ultimately, 3771 valid female samples were included in the study, consisting of 1158 cases of primary infertility, 804 cases of secondary infertility, and 1809 fertile women. The distribution of samples across different areas of Chengdu is shown in Fig. 1, with most participants residing in central Chengdu (3418 women, 90.64%).

Air pollutants and temperature exposure

This study first collected data from the National Urban Air Quality Real-time Publishing Platform of the China National Environmental Monitoring Centre (<https://air.cnemc.cn:18007/>) on the 24-hour average concentrations of SO_2 , PM_{10} , NO_2 , CO , $\text{PM}_{2.5}$, and the 8-hour rolling average of O_3 across monitoring stations in Chengdu from January 2017 to December 2023. The monthly average concentrations of each pollutant were aggregated and calculated. We used the inverse distance weighting (IDW) method of spatial interpolation to project data from the monitoring stations (locations shown in Fig. 1) onto the entire study area with a spatial resolution of $100 \text{ m} \times 100 \text{ m}$ to estimate the monthly pollutant exposure levels at each participant's residence^{10,34}. In this process, we utilized the Baidu Maps application interface (<https://lbsyun.baidu.com/products/search>) to match the geographic coordinates and convert each participant's specific residential address into spatial coordinates.

In this study, monthly temperature data for each sample were extracted from the 1-km monthly mean temperature dataset for China (1901–2023) published by³⁵ and available from the National Tibetan Plateau/Third Pole Environment Data Center (<https://data.tpdc.ac.cn/home>). This dataset, based on the 30' Climatic Research Unit time-series dataset and the high-resolution climatology dataset released by WorldClim, was created using the delta spatial downscaling approach to produce monthly temperature data for China. Its reliability has been validated using data from 496 meteorological observation stations nationwide.

Since the specific effects of air pollutants and temperature during different exposure periods on infertility remain unclear^{13,14}, this study calculated the monthly moving average levels of pollutants and temperature for each participant during five different exposure windows based on the date of diagnosis to comprehensively assess the effects of individual exposure in both the short and long term. The five exposure windows were 3 months prior to diagnosis (period 1), 6 months prior (period 2), 12 months prior (period 3), 24 months prior (period 4), and 36 months prior (period 5).

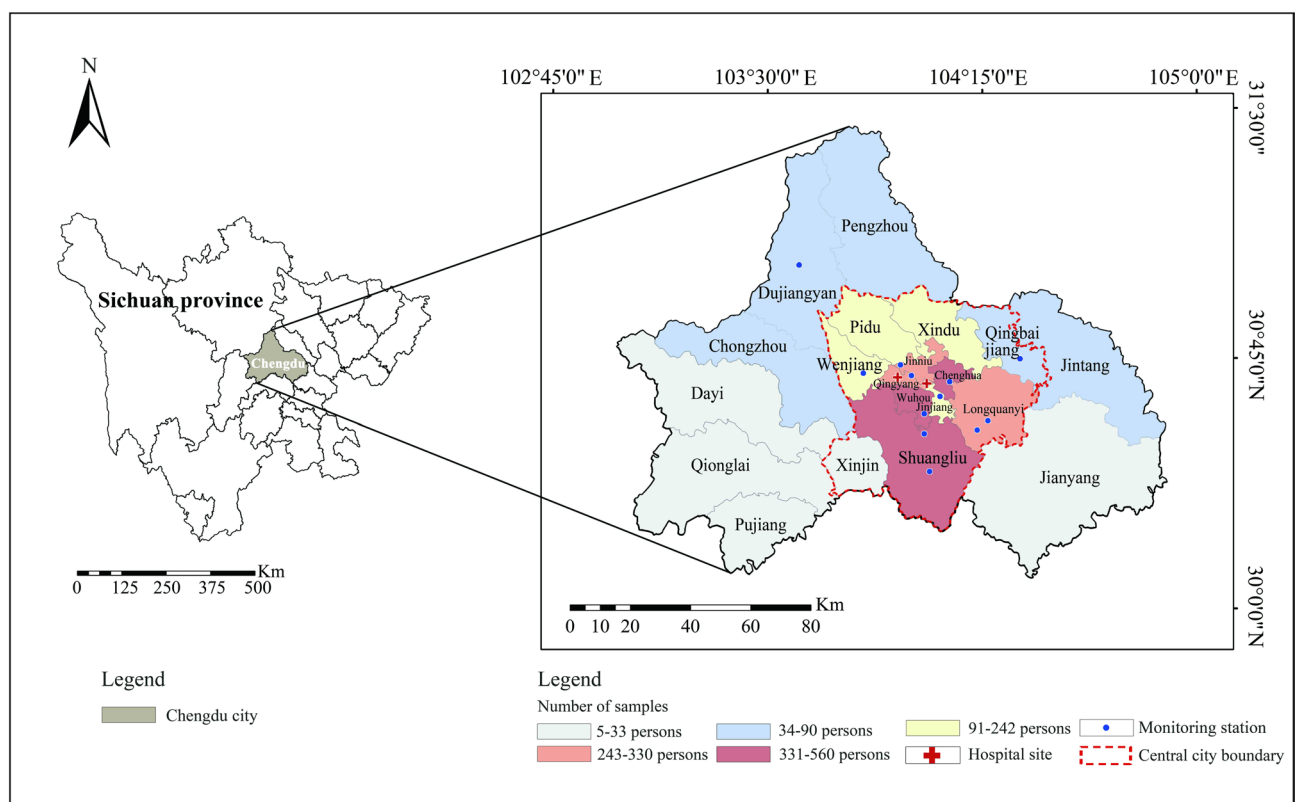


Fig. 1. Location of Chengdu, the spatial distribution of samples, and sites of monitoring stations and hospitals.

Covariates

Referring to previous studies⁴, we included covariates, such as body mass index (BMI), age, employment status, ethnicity, residential region, and history of miscarriages. In addition, we considered surrounding greenness (measured by the monthly normalized difference vegetation index, [NDVI]), traffic conditions (distance from the main road), and meteorological conditions (monthly rainfall) as covariates, as these factors may be closely related to an individual's exposure to pollutants or temperature^{13,36}. Moreover, socioeconomic conditions related to place of residence, including community housing prices, building age, surrounding population density, and gross domestic product (GDP) per square kilometer, were also included as background covariates.

Specifically, we obtained 250 m high-resolution NDVI data from the MOD13A3 dataset regularly released by the US National Aeronautics and Space Administration (NASA) (<https://lpdaac.usgs.gov/products/mod13q1v006/>)³⁷. After processing, NDVI values ranged from −1 to 1, with values closer to 1 indicating higher vegetation coverage. Traffic conditions were assessed using ArcGIS 10.8 to calculate each participant's distance to the nearest main roads, including major, secondary, elevated, expressways, and branch roads. Road network data were sourced from OpenStreetMap (<https://www.openstreetmap.org>). Monthly rainfall data were obtained from the same source as the temperature data, with NDVI and rainfall exposure levels calculated for each exposure window in alignment with air pollutant data. Community housing prices and building age data for residential areas were sourced from the Anjuke platform (<https://chengdu.anjuke.com/>), where the average values of community housing prices and building ages were calculated within a 100 × 100 m grid. Population density data were derived from the 100 m gridded spatial dataset from China's seventh national census published by³⁸ (<https://doi.org/10.6084/m9.figshare.24916140.v1>). GDP data were sourced from 2020 raster data at a 1-km resolution, representing the spatial distribution of GDP within the study area³⁹, downloaded from the Geographic Data Sharing Infrastructure, Global Resources Data Cloud (<http://www.gis5g.com>). Based on existing studies, we created a 500 m radius buffer around each participant's residence to extract the average values of NDVI, community housing prices, building age, population density, and GDP⁴⁰.

Statistical analysis

The independent-sample t-tests (for continuous variables) and chi-square tests (for categorical variables) were first used to analyze differences in characteristics between the groups. Pearson's correlation analysis evaluated the correlation between air pollutants and temperature exposure among the samples. Subsequently, multinomial logistic regression models were employed to investigate the associations between ambient air pollutants, temperature exposure, and female infertility (fertility = 0, primary infertility = 1, secondary infertility = 2). The models were used to calculate odds ratios (ORs), 95% confidence intervals (CIs), and p values. The model for each category of infertility (Y_k) can be expressed as:

$$\text{logit}(P(Y = k)) = \beta_0 + \sum_{i=1}^n \beta_i X_i + \sum_{i=1}^n \gamma_i X_i \cdot Z + \varepsilon \quad (1)$$

In the model, $P(Y = k)$ represents the probability of the outcome Y being in category k , where k corresponds to different infertility types. β_0 is the constant term, β_i are the coefficients for the predictors (pollutants and temperature), and X_i denotes the air pollutants and temperature exposure variables. The interaction term $X_i \cdot Z$ captures the combined effect of air pollutants and temperature, and ε is the error term.

To further explore the differences across subgroups, we conducted stratified analyses based on age (< 32 years and ≥ 32 years). The interaction effects of air pollutants and temperature exposure were assessed by adding interaction terms (product terms) for each air pollutant and temperature to the models and testing for statistical significance⁴¹. Further analyses categorized exposure levels into low and high groups based on the 50 th percentiles of pollutant concentration and temperature within each exposure window, creating new variables. Samples with low exposure levels for both air pollutants and temperature served as the reference group, and detailed analyses were conducted on the joint effects of different exposure combinations⁴². In the final models, the following covariates were adjusted: age (< 32 and ≥ 32), BMI, employment status (employed and unemployed), ethnicity (Han and others), residential region (Central area and Non-central area), history of miscarriage (with and without a history of miscarriage), NDVI, distance from the main road (< 100 m and ≥ 100 m), rainfall, community housing price, building age, surrounding population density, and GDP per km².

All statistical analyses were conducted using Stata 18.0, and spatial calculations were performed using ArcGIS 10.8. R version 4.4.1 was utilized to (1) convert all residential address information into spatial coordinates; and (2) calculate the monthly moving averages of pollutant concentrations, temperatures, NDVI, and rainfall for each exposure window. Statistical significance was set at $P < 0.05$.

The following sensitivity analyses were conducted to assess the robustness of the model results: (1) running two multinomial logistic regression models, with the second model excluding patients who had experienced miscarriages (both induced and spontaneous) to evaluate the stability of the main effects; (2) performing the stratified analysis was conducted according to age (< 32 years and ≥ 32 years).

Results

Characteristics of the study population

The characteristics of the samples are listed in Table 1. The average age of the overall sample was 31.45 years. Compared to the primary infertility group, the secondary infertility group had a higher average age [32.82 (3.95) vs. 30.75 (3.58)] and BMI [21.32 (2.93) vs. 20.93 (2.73)]. As expected, the number of pregnancies [0.00 (0.00) vs. 1.82 (1.11)] and live births [0.00 (0.00) vs. 0.32 (0.50)] in the primary infertility group were zero, differing from the secondary group. The proportion of employed individuals was greater in the primary infertility group, and a

Variables	Overall (n = 3771)	Fertility (n = 1809)	Primary infertility (n = 1158)	Secondary infertility (n = 804)
Age, mean (years)	31.45 (3.85)	31.28 (3.83)	30.75 (3.58)	32.82 (3.95)
<32, n (%)	2075 (55.03%)	1131 (62.52%)	598 (51.64%)	346 (43.03%)
≥ 32, n (%)	1696 (44.97%)	678 (37.48%)	560 (48.36%)	458 (56.97%)
BMI, mean (kg/m ²)	21.14 (2.84)	21.19 (2.86)	20.93 (2.73)	21.32 (2.93)
Employment status				
Employed, n (%)	3188 (84.54%)	1556 (86.01%)	981 (84.72%)	651 (80.97%)
Unemployed, n (%)	583 (15.46%)	253 (13.99%)	177 (15.28%)	153 (19.03%)
Ethnicity				
Han, n (%)	3280 (86.98%)	1611 (89.05%)	978 (84.46%)	691 (85.95%)
Others, n (%)	491 (13.02%)	198 (10.95%)	180 (15.54%)	113 (14.05%)
Residential region				
Central area, n (%)	3418 (90.64%)	1618 (89.44%)	1056 (91.19%)	744 (92.54%)
Non-central area, n (%)	353 (9.36%)	191 (10.56%)	102 (8.81%)	60 (7.46%)
Number of pregnancies, mean	1.20 (1.24)	1.69 (1.16)	0.00 (0.00)	1.82 (1.11)
Number of live births, mean	0.13 (0.36)	0.14 (0.37)	0.00 (0.00)	0.32 (0.50)
History of miscarriage				
Without a history of miscarriage, n (%)	3058 (81.09%)	1624 (89.77%)	939 (81.09%)	495 (61.57%)
With a history of miscarriage(s), n (%)	713 (18.91%)	185 (10.23%)	219 (18.91%)	309 (38.43%)
Distance from the main road, mean (m)	80.03 (102.53)	77.10 (89.23)	81.72 (104.47)	84.19 (128.81)
<100 m, n (%)	2774 (73.56%)	1363 (75.35%)	827 (71.42%)	584 (72.64%)
≥ 100 m, n (%)	997 (26.44%)	446 (24.66%)	331 (28.58%)	220 (27.36%)
Community housing price, mean (CNY)	14469.63 (7610.65)	14674.02 (7386.97)	14111.57 (7144.94)	14525.46 (8674.00)
Building age, mean (years)	15.45 (6.51)	15.43 (6.69)	15.61 (6.35)	15.28 (6.32)
Surrounding population density, mean (persons/km ²)	15122.16 (22235.26)	16248.38 (22825.69)	14696.19 (21875.33)	13201.68 (21255.54)
GDP per km ² , mean (10000 CNY)	1692.36 (2356.07)	1756.62 (2417.06)	1627.64 (2319.82)	1641.01 (2266.19)
NDVI, monthly mean	0.36 (0.08)	0.36 (0.08)	0.36 (0.08)	0.36 (0.08)
Rainfall, monthly mean (mm)	88.62 (6.82)	88.66 (6.66)	88.42 (7.02)	88.81 (6.86)

Table 1. Descriptive statistical characteristics of the study population.

larger proportion of women in this group reported a history of miscarriage [219 (18.91%) vs. 309 (38.43%)]. No marked differences were observed between groups in terms of ethnicity, residential region, distance to the main road, housing price, building age, GDP per km², NDVI, population density, or rainfall.

The exposure levels to each type of pollutant and temperature for the total sample across different exposure windows are presented in Table 2. Correlation tests indicated that exposure to temperature and the six types of air pollutants in the sample were significantly correlated from 2018 to 2023 (Table S1).

Associations of ambient air pollution and temperature exposure with infertility

The results of the multinomial logistic regression, adjusted for all confounding factors, are presented in Table 3. The study found that women exposed to SO₂ during the 3 months prior to diagnosis had a significantly higher risk of primary infertility [OR (95% CI) = 1.31 (1.13–1.64)]. Similarly, women exposed to NO₂ during the 6 and 24 months prior to diagnosis showed an increased risk of primary infertility [OR (95% CI) = 1.17 (1.06–1.28); 1.08 (1.03–1.14)]. Exposure to PM₁₀ in the 24 months prior to diagnosis was associated with a higher likelihood of primary infertility [OR (95% CI) = 1.32 (1.04–1.57)]. For secondary infertility, women exposed to PM_{2.5} during the 3 months prior to diagnosis had a significantly higher risk [OR (95% CI) = 1.32 (1.08–1.56)], as well as during the 36 months prior to diagnosis [OR (95% CI) = 1.08 (1.01–1.13)]. Additionally, PM₁₀ exposure during the 3 months [OR (95% CI) = 1.09 (1.01–1.17)], as well as during the 12 [OR (95% CI) = 1.21 (1.05–1.38)] and 36 months [OR (95% CI) = 1.14 (1.03–1.23)] prior to diagnosis, were all associated with an increased risk of secondary infertility. Regarding ambient temperature, exposure during the 3 months prior to diagnosis was associated with a lower risk of both primary [OR (95% CI) = 0.92 (0.85–0.96)] and secondary infertility [OR (95% CI) = 0.91 (0.83–0.95)].

After excluding samples from women who had experienced miscarriages, the overall trends remained largely consistent (Table S2). Increased exposure to PM₁₀ [OR (95% CI) = 1.04 (1.01–1.11); 1.22 (1.07–1.44)] and NO₂ [OR (95% CI) = 1.04 (1.02–1.08); 1.18 (1.04–1.33)] during the 6 and 24 months prior to diagnosis was still significantly associated with an elevated risk of primary infertility. However, the association between SO₂ exposure and risk of primary infertility was no longer significant. For secondary infertility, increased exposure to PM_{2.5} (during the 3, 24, and 36 months prior to diagnosis) and PM₁₀ (during the 3, 12, and 36 months prior

Category	Exposure window	Mean	SD	Min	25 th	Median	75 th	Max
SO ₂ (µg/m ³)	Period 1	4.96	1.73	1.95	3.32	5.03	6.28	13.08
	Period 2	5.10	1.70	2.02	3.37	5.30	6.28	11.93
	Period 3	5.37	1.72	2.54	3.74	5.60	6.30	12.47
	Period 4	5.93	1.75	2.74	4.57	5.81	6.76	14.02
	Period 5	6.46	1.78	3.55	5.04	6.04	7.61	14.02
NO ₂ (µg/m ³)	Period 1	35.81	9.59	5.78	28.67	35.94	43.33	58.56
	Period 2	35.91	8.42	6.76	29.38	36.09	42.50	55.73
	Period 3	36.81	6.83	11.57	31.56	36.66	42.05	63.04
	Period 4	38.73	6.98	14.47	33.36	38.93	42.71	61.60
	Period 5	40.49	6.93	15.68	35.74	40.02	45.07	61.60
PM _{2.5} (µg/m ³)	Period 1	41.57	9.52	14.93	28.58	38.06	55.00	86.32
	Period 2	40.59	10.37	16.45	30.95	41.32	49.52	61.63
	Period 3	40.82	3.63	25.29	38.92	40.64	42.63	57.22
	Period 4	41.80	4.09	27.22	39.64	41.11	43.10	57.46
	Period 5	42.91	4.66	28.77	40.24	41.71	45.14	57.46
PM ₁₀ (µg/m ³)	Period 1	63.62	9.03	23.06	46.95	62.13	79.35	112.75
	Period 2	62.57	13.48	24.83	51.40	63.09	73.50	95.50
	Period 3	63.44	6.87	38.76	59.76	62.88	66.14	98.87
	Period 4	65.23	8.03	40.53	60.95	63.24	67.87	95.72
	Period 5	67.37	8.98	41.23	61.73	64.48	73.38	95.72
CO (µg/m ³)	Period 1	0.75	0.46	0.29	0.63	0.73	0.86	1.38
	Period 2	0.76	0.74	0.31	0.61	0.66	0.79	1.21
	Period 3	0.82	0.18	0.44	0.74	0.84	0.92	1.32
	Period 4	0.84	0.14	0.41	0.78	0.87	0.94	1.45
	Period 5	0.85	0.11	0.44	0.80	0.87	0.95	1.36
O ₃ (µg/m ³)	Period 1	51.27	9.36	15.79	35.19	49.45	67.26	99.03
	Period 2	51.84	14.65	23.71	39.79	50.36	64.13	93.70
	Period 3	52.21	6.32	36.51	47.10	51.35	56.70	91.14
	Period 4	51.47	5.46	40.03	47.71	50.02	54.88	87.93
	Period 5	50.69	4.77	39.66	47.75	49.83	52.80	87.93
Temperature (°C)	Period 1	16.78	6.60	8.97	9.99	17.78	22.57	27.94
	Period 2	17.25	4.62	9.49	12.55	16.27	22.03	25.28
	Period 3	17.48	0.41	14.83	17.23	17.36	17.49	19.54
	Period 4	17.38	0.32	15.38	17.24	17.37	17.52	18.60
	Period 5	17.35	0.34	15.17	17.22	17.36	17.53	18.39

Table 2. Monthly exposure levels of six ambient air pollutants and temperature among participants in each study period. SD, standard deviation; Min, minimum; Max, maximum; 25 th, 25% quantile; 75 th, 75% quantile.

was significantly associated with elevated risk. Similarly, significant associations between temperature exposure and both primary and secondary infertility were observed during the 3 months prior to diagnosis.

The results of the age-stratified analysis (stratified by the age of 32 years) are shown in Fig. 2. Overall, the regression results for both age groups were similar to those of the main-effects model (Table 3). However, we observed that women under 32 years demonstrated greater sensitivity to NO₂, CO, and temperature exposure concerning infertility risk. Specifically, women younger than 32 had a significantly higher risk of primary infertility when exposed to CO during the 24 and 36 months prior to diagnosis [OR (95% CI) = 1.29 (1.11–1.49); 1.04 (1.01–1.11)]. Exposure to NO₂ during the 6 and 24 months prior to diagnosis was also significantly associated with a higher risk of primary infertility [OR (95% CI) = 1.08 (1.02–1.15); 1.08 (1.01–1.17)]. Additionally, among women under 32, exposure to temperature during the 3 and 24 months prior to diagnosis was significantly associated with an increased risk of primary infertility [OR (95% CI) = 1.04 (1.01–1.09); 1.20 (1.08–1.34)]. Similarly, exposure to temperature during the 3 months prior to diagnosis was significantly associated with an elevated risk of secondary infertility [OR (95% CI) = 1.05 (1.02–1.10)]. In contrast, among women over 32, no significant associations were observed between CO, NO₂, or temperature exposure and the risk of infertility in any exposure window. Furthermore, significant associations between PM_{2.5}, PM₁₀, and SO₂ exposure and infertility risk were observed in both age groups across the relevant exposure windows.

Category	Exposure window	Primary infertility cases			Secondary infertility cases		
		Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
SO ₂	Period 1	1.31	1.13, 1.64	0.004**	1.28	0.88, 1.77	0.558
	Period 2	1.04	0.85, 1.14	0.603	1.17	0.78, 1.56	0.678
	Period 3	1.22	0.75, 1.83	0.619	1.14	0.75, 1.49	0.201
	Period 4	1.11	0.77, 1.82	0.281	1.08	0.88, 1.32	0.754
	Period 5	0.89	0.81, 1.08	0.194	1.07	0.83, 1.39	0.402
NO ₂	Period 1	1.11	0.92, 1.23	0.392	1.08	0.93, 1.22	0.674
	Period 2	1.17	1.06, 1.28	< 0.001***	1.12	0.82, 1.47	0.493
	Period 3	1.09	0.91, 1.48	0.076	1.03	0.91, 1.16	0.349
	Period 4	1.08	1.03, 1.14	0.003**	0.87	0.74, 1.08	0.529
	Period 5	1.03	0.89, 1.31	0.539	1.09	0.89, 1.28	0.095
PM _{2.5}	Period 1	1.21	0.76, 1.92	0.256	1.32	1.08, 1.56	< 0.001***
	Period 2	1.09	0.87, 1.61	0.459	1.18	0.87, 1.58	0.631
	Period 3	1.18	0.79, 1.76	0.072	1.05	0.92, 1.18	0.933
	Period 4	1.08	0.85, 1.56	0.139	1.10	0.81, 1.45	0.385
	Period 5	1.18	0.86, 1.61	0.421	1.08	1.01, 1.13	0.007**
PM ₁₀	Period 1	0.92	0.83, 1.08	0.301	1.09	1.01, 1.17	0.022*
	Period 2	1.04	0.88, 1.14	0.865	1.08	0.93, 1.22	0.244
	Period 3	1.11	0.98, 1.35	0.672	1.21	1.05, 1.38	0.005**
	Period 4	1.32	1.04, 1.57	0.008**	1.16	0.87, 1.54	0.295
	Period 5	1.08	0.82, 1.45	0.823	1.14	1.03, 1.23	0.003**
CO	Period 1	1.06	0.93, 1.15	0.624	1.06	0.94, 1.19	0.272
	Period 2	0.94	0.86, 1.09	0.634	1.14	0.91, 1.47	0.321
	Period 3	1.08	0.91, 1.23	0.402	1.01	0.88, 1.13	0.090
	Period 4	0.92	0.82, 1.08	0.433	1.16	0.85, 1.58	0.772
	Period 5	0.95	0.83, 1.09	0.267	1.02	0.84, 1.21	0.824
O ₃	Period 1	0.91	0.79, 1.07	0.535	0.94	0.87, 1.03	0.376
	Period 2	1.05	0.98, 1.12	0.286	1.05	0.85, 1.29	0.126
	Period 3	0.97	0.83, 1.03	0.211	1.09	0.92, 1.26	0.443
	Period 4	0.98	0.91, 1.06	0.951	0.94	0.85, 1.04	0.399
	Period 5	1.15	0.97, 1.45	0.335	0.95	0.85, 1.06	0.825
Temperature	Period 1	0.92	0.85, 0.96	0.007**	0.91	0.83, 0.95	0.006**
	Period 2	1.03	0.92, 1.15	0.898	0.87	0.75, 1.11	0.259
	Period 3	1.08	0.91, 1.18	0.532	0.95	0.81, 1.11	0.814
	Period 4	0.95	0.72, 1.23	0.747	0.92	0.78, 1.09	0.537
	Period 5	0.94	0.82, 1.11	0.318	1.05	0.89, 1.23	0.313

Table 3. Associations of ambient air pollution and temperature exposure with primary and secondary infertility among participants during different periods. CI, confidence interval; OR, odds ratio. Per 10 µg/m³ increase in air pollutants level or 1 °C increase in temperature. Bold text values indicate significance: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. The model adjusted for all covariates, including age, BMI, ethnicity, employment status, residential region, history of miscarriage, normalized difference vegetation index, distance from the main road, rainfall, community housing prices, building age, surrounding population density, and gross domestic product per square kilometer.

The interaction effects of air pollutants and temperature on infertility

The overall interaction effects across these windows are shown in Table S3. During the 3 months prior to diagnosis, the interaction between NO₂ and temperature was significantly associated with a slight reduction in the risk of primary infertility [OR (95% CI) = 0.98 (0.93–0.99)]. Additionally, interactions between PM₁₀ and temperature during the 3- and 12-month periods before diagnosis were significantly associated with a slight reduction in the risk of secondary infertility [OR (95% CI) = 0.97 (0.91–0.99); 0.93 (0.80–0.98)].

Further analyses assessed the joint effects of six air pollutants and temperature on infertility risk based on combined exposure levels; the results are presented in Fig. 3. Compared to other combinations, women co-exposed to high concentrations of SO₂ or NO₂ along with low temperatures during the 3 months prior to diagnosis had the highest risk of primary infertility [OR (95% CI) = 1.86 (1.12–3.04); 1.62 (1.13–2.33)]. Regarding secondary infertility, women co-exposed to high concentrations of PM₁₀ and low temperatures during the 3-month, 12-month, and 36-month periods prior to diagnosis had the highest risk [OR (95% CI) = 1.51 (1.13–2.03); 1.48 (1.07–2.11); 1.71 (1.13–2.52)]. After excluding women with a history of miscarriage,

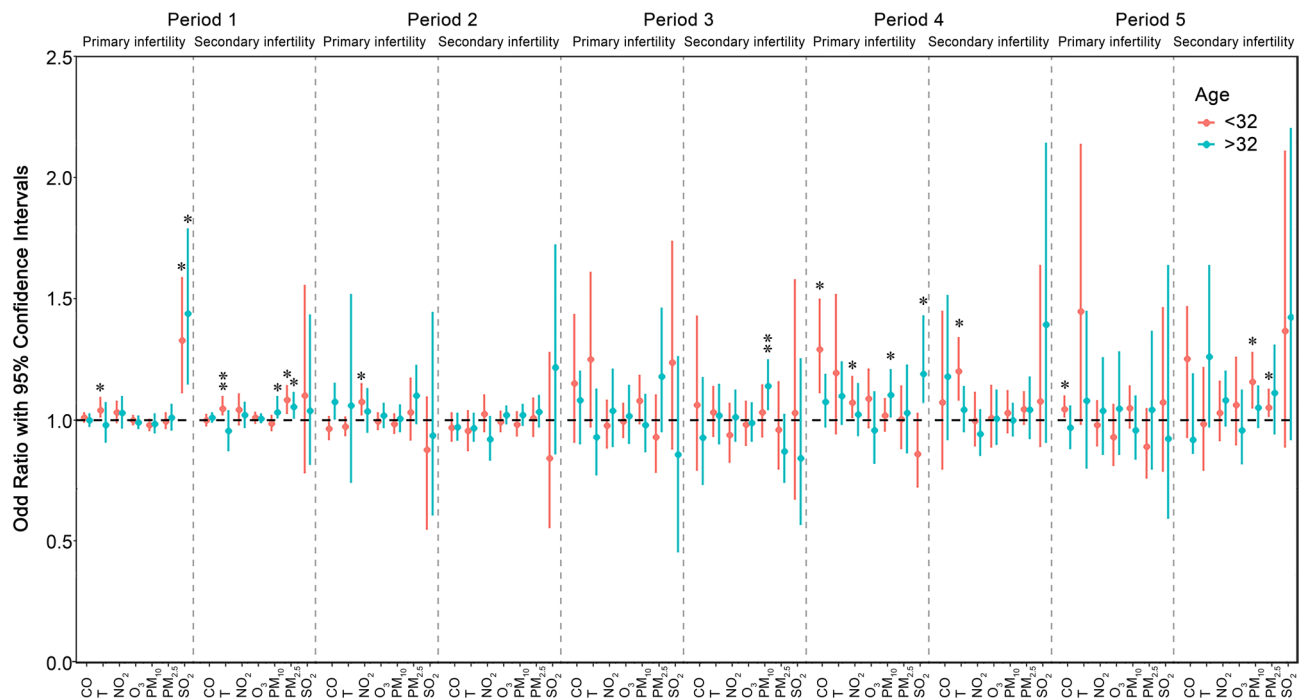


Fig. 2. Association between exposure to air pollutants and temperature and infertility in female subgroups aged above 32 (blue) and below 32 (orange). The dots indicate odds ratios, and the lines are the corresponding 95% confidence intervals. Asterisks indicate significant results: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. T refers to temperature. The model adjusted for covariates, including BMI, ethnicity, employment status, residential region, history of miscarriage, normalized difference vegetation index, distance from the main road, rainfall, community housing prices, building age, surrounding population density, and gross domestic product per square kilometer.

the results remained relatively robust (Table S4 and Table S5). In the 3 months prior to diagnosis, women who were simultaneously exposed to high concentrations of SO_2 or NO_2 and low temperatures still had the highest risk of primary infertility [OR (95% CI) = 2.39 (1.37, 4.59); 2.34 (1.41, 3.77)]. In the 12 and 36 months prior to diagnosis, women simultaneously exposed to high concentrations of PM_{10} and low temperatures still had the highest risk of secondary infertility [OR (95% CI) = 1.62 (1.10, 2.68); 1.72 (1.31, 2.92)].

Discussion

With the ongoing challenges of global climate change and declining fertility rates, understanding the relationship between environmental exposures and infertility among women has become critical in epidemiology, environmental science, and public health. This retrospective cohort study aimed to examine the associations between exposure to ambient air pollutants and temperature and the risks of primary and secondary infertility in women considering both short- and long-term periods (ranging from 3 months to 3 years before diagnosis). This study explored associations between multiple ambient air pollutants exposures and female infertility across different exposure periods. The findings reveal some pollutant- and time-specific patterns, as well as possible interactions with temperature.

The study found that both short-term (within 1 year prior to diagnosis) and long-term (2 years or more prior to diagnosis) exposure to PM_{10} and NO_2 were significantly associated with a higher risk of primary infertility, while exposure to $\text{PM}_{2.5}$ and PM_{10} was significantly associated with an increased risk of secondary infertility. These findings align with existing research on the relationship between air pollution and infertility^{13,14} or fertility outcomes^{15–17}. In a cohort study of pregnancy planners, Wesselink et al. (2022) observed that exposure to $\text{PM}_{2.5}$ and PM_{10} was linked to reduced fertility¹⁷. Similarly, Li et al. (2021) reported that with every $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure, the likelihood of infertility increased by 20%¹⁴. Mahalingaiah et al. (2016) also identified associations between exposure to $\text{PM}_{2.5}$, $\text{PM}_{2.5-10}$, PM_{10} , and traffic-related air pollution with infertility risk¹³. Their study reported significant associations between these pollutants and infertility across the overall sample, while no heterogeneity was found in the association between air pollutants and infertility in the subdivided primary and secondary infertility groups¹³. In contrast, our study found differing results in these subgroups, which may be attributed to differences in study design, such as the inclusion of additional pollutants (NO_2 , CO , O_3 , and SO_2) in our analysis, and differences in exposure levels. For example, the 2-year mean $\text{PM}_{2.5}$ exposure value for the sample in Mahalingaiah et al.'s study was $14.5 \mu\text{g}/\text{m}^3$, compared to $41.80 \mu\text{g}/\text{m}^3$ in our study (Table 2).

Although the biological mechanisms by which air pollutants impact female infertility are not fully understood, compelling evidence suggests that $\text{PM}_{2.5}$, PM_{10} , and NO_2 are strongly associated with reproductive health issues^{12,43}. $\text{PM}_{2.5}$ and PM_{10} are inhalable particles suspended in the air, while NO_2 primarily originates

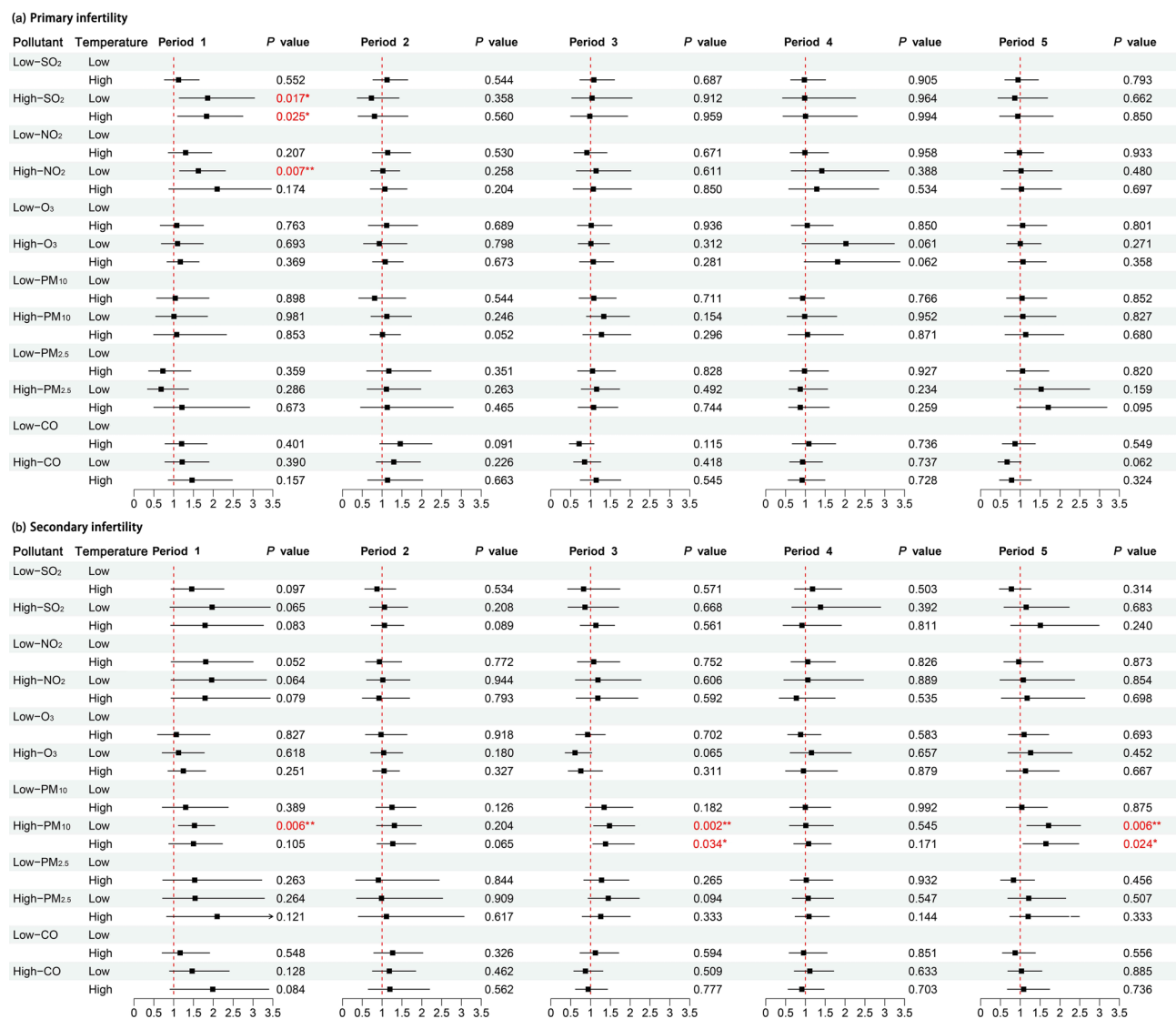


Fig. 3. Joint effect of air pollutants and temperature on primary infertility (a) and secondary infertility (b). The black squares represent odds ratios, and the lines are the corresponding 95% confidence intervals. Red text with asterisks indicates significant results: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$. Odds ratios, confidence intervals, and P-values were estimated by continuous increments in pollutant and temperature levels. The model adjusted for all covariates, including age, BMI, ethnicity, employment status, residential region, history of miscarriage, normalized difference vegetation index, distance from the main road, rainfall, community housing prices, building age, surrounding population density, and gross domestic product per square kilometer.

from vehicle exhaust and industrial emissions. These pollutants can trigger chronic inflammation, endocrine disruption, and oxidative stress⁴⁴, which may impair follicular development and ovulation, consequently affecting female fertility⁴⁵. It is important to note that our study excluded women with diagnosed gynecological conditions such as PCOS, endometriosis, or uterine fibroids to minimize the impact of organic or functional infertility and better isolate associations with environmental exposures. Nonetheless, subclinical inflammation, oxidative stress, or hormonal dysregulation could still contribute to infertility in women without overt diagnoses. For instance, ambient pollutants may impair endometrial receptivity or interfere with oocyte quality even in women without diagnosed reproductive disorders⁴⁶. In addition, women who had never been pregnant appeared more susceptible to ambient exposure of PM₁₀ and NO₂ (Table 3). We hypothesize that, due to its smaller particle size, PM_{2.5} can penetrate deeper into the microcirculation of the reproductive system, potentially making it more challenging for previously pregnant women to conceive again⁸.

Contrary to our hypothesis and previous studies suggesting that higher temperatures increase infertility risk^{21,47}, we observed that higher temperature exposure was significantly associated with a reduced risk of both primary and secondary infertility, particularly during short-term exposure (within 3 months prior to diagnosis) (Table 3). This finding indicates that short-term exposure to higher temperatures may have a protective effect against infertility. One possible explanation is that, in regions like Chengdu—which is characterized by a mild,

humid climate with an average annual temperature of around 16 °C, high relative humidity (~ 80%), and limited sunshine⁴⁸—moderate warming may help alleviate cold-related physiological stress, improve peripheral circulation, and enhance reproductive function. A moderate rise in temperature may improve circulation and metabolic function, potentially benefiting reproductive health and fertility. Based on our findings, we propose that there may be a threshold effect of temperature on infertility, suggesting that local climate conditions should be considered when interpreting these results. The study by Jensen et al. (2021) offers valuable reference, demonstrating that elevated temperatures negatively impact fertility when monthly maximum temperatures exceed 15–20 °C, while moderate temperature increases in colder climates may improve fertility outcomes²⁰.

In addition, our findings suggest that the associations between ambient air pollutants and infertility vary by exposure window, indicating that both timing and duration of exposure may modify environmental effects on reproductive health. This temporal heterogeneity could reflect distinct biological processes. Short-term exposures (e.g., within 3 months) may predominantly affect functional aspects such as ovulation or implantation through transient inflammatory responses¹⁵. Long-term exposures (e.g., 2–3 years) might influence structural or cumulative outcomes like ovarian reserve depletion¹¹. These patterns align with existing evidence that acute and chronic pollution exposures operate through different pathways⁴⁹, though our study design cannot confirm specific mechanisms. Future research should prioritize defining exposure windows based on reproductive biology (e.g., folliculogenesis periods). Additionally, unmeasured early-life or in utero exposures may affect long-term associations, as air pollution has been shown to impair the development of fetal germ cells—an issue not addressable in our study⁵⁰.

In this study, we observed that women under the age of 32 exhibited heightened sensitivity to the risk of infertility due to exposure to NO₂, CO, and temperature. This finding is consistent with the results of previous studies^{51,52}, which may be related to physiological differences and reproductive health status. The reproductive system of younger women tends to be more active and sensitive⁵³, making them more susceptible to the effects of environmental factors such as air pollution and temperature compared to older women. Younger women also experience greater fluctuations in hormone levels, and their immune systems may respond more intensely to environmental pollutants, thereby increasing the risk to their reproductive health⁵⁴. Moreover, as young women are typically in the early stages of their reproductive years and are less likely to have experienced fertility-related health issues, environmental factors may have a more pronounced impact on their fertility when no other health problems are present⁵⁵.

Notably, our study revealed the interaction of combined exposure to air pollution and low temperatures on the risk of female infertility. Although substantial evidence suggests that interactions between temperature fluctuations, including low temperatures, and air pollutants may pose health risks or increase the likelihood of disease^{27,28}, to the best of our knowledge, no epidemiological studies have specifically explored the interaction effects of air pollution and temperature on infertility. Our findings are supported by another study conducted in Chengdu, which showed that the interaction between PM_{2.5}, PM₁₀, and SO₂ at low temperatures increased the risk of chronic obstructive pulmonary disease, with the highest attributable fraction occurring under low-temperature conditions⁵⁶. The temperature and air pollutant levels in their study were similar to those in the present study. Furthermore, a study conducted in the cold climate of Lanzhou, China, found that the impact of PM₁₀, SO₂, and NO₂ on hospital admissions for respiratory diseases was more pronounced on cold days than on warmer days⁵⁷.

From environmental and biological perspectives, the synergistic effect between low temperatures and high concentrations of air pollutants can be explained by several mechanisms, all of which may help mitigate the negative effects of air pollution on fertility and lower the risk of infertility. First, higher temperatures can reduce cold stress responses in the body, helping to maintain hormonal balance and reproductive function²⁰. In contrast, air pollution may exacerbate cold stress by impairing respiratory and cardiovascular function, particularly in colder environments where pollutants tend to accumulate⁵⁸. Thus, the combination of low temperatures and high pollution levels may amplify stress responses, whereas higher temperatures may mitigate these effects. Second, while warmer climates may encourage outdoor activities, which can enhance metabolism and immunity⁵⁹, increased outdoor exposure in polluted environments may also elevate inhalation of harmful pollutants⁶⁰. Therefore, the interaction between temperature and air pollution is crucial: higher temperatures may improve air quality through better pollutant dispersion⁶¹, reducing the risk of exposure during outdoor activities, particularly in urban areas where cold weather often traps pollutants near the ground⁶².

Our study has several limitations. First, estimating individual exposure levels based on the spatial matching of patients' home addresses may introduce bias because we lacked information on the home-living environment, time spent at home, and occupational exposure. Similar to many other studies^{51,63}, the IDW method was used to estimate the pollutant concentrations in the study area, which may have led to spatial inaccuracies in the exposure estimates. Second, this study used the diagnosis date as the starting point for each exposure period; however, there may be a time lag between the actual onset of infertility and the patient's hospital diagnosis, which may affect the accuracy of the exposure window classification. Third, although our study assessed exposure windows of up to 36 months prior to diagnosis to capture relatively short- and medium-term effects, it did not account for early-life or in utero exposures. Given the potential links between such exposures and reproductive health, this represents a limitation of our analysis. Notably, the study period included the COVID-19 pandemic, during which increased stress levels may have negatively affected female fertility. However, psychosocial stress was not directly measured, and this unmeasured confounder may have influenced the observed associations. Fourth, the data were derived from medical records, limiting access to detailed individual-level information, such as smoking habits and personal income. Finally, this study did not distinguish seasonal temperature variations, which may have limited the interpretation of the temperature effects. Our model treated temperature as a continuous linear variable, which may have limited its ability to capture the nonlinear effects of extreme

cold and heat. Future studies should consider nonlinear or threshold-based temperature modeling to better understand its impact on fertility.

Conclusion

This retrospective study conducted in the Chinese megacity of Chengdu contributes to the limited understanding of the association between air pollution, temperature factors, and female infertility. This exploration is crucial, given the growing challenges of global climate change and declining fertility rates. The findings revealed that exposure to PM_{10} and NO_2 was associated with an increased risk of primary infertility, while exposure to PM_{10} and $PM_{2.5}$ was linked to secondary infertility. In contrast, exposure to high temperatures was associated with a reduced risk of infertility. Furthermore, women under the age of 32 were found to be more sensitive to air pollutants and temperature changes. This study also highlighted a synergistic effect between air pollution and low-temperature exposure, which increased the risk of female infertility. These findings emphasize the importance of women avoiding exposure to harmful air pollutants (mainly $PM_{2.5}$, PM_{10} , and NO_2) and adjusting ambient temperatures under appropriate conditions to reduce infertility risk. These results provide a foundation for the development of effective preventive measures. We recommend that the government, along with meteorological and environmental protection agencies, strengthen air pollution monitoring under varying temperature conditions and promptly issue relevant forecasts or warnings, particularly for vulnerable populations, to mitigate infertility risk. Future research using prospective cohort studies is essential to confirm the causal relationship between ambient exposure and infertility. In addition, it is crucial to explore the biological mechanisms by which ambient exposure contributes to infertility. Targeted investigations into specific toxicants such as black carbon particles and volatile compounds from paint may provide deeper insights into biologically relevant exposures.

Data availability

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

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Author contributions

Kaili Zhang conceived and designed the study, and Kaili Zhang, Wei Chen, and Shasha Xing prepared software and performed the statistical analysis. Kaili Zhang prepared the manuscript. Prasanna Divigalpitiya assisted with editing of the paper and provided critical comments. Kaili Zhang and Shasha Xing revised it for important intellectual content. Erdan Luo supervised the research and verified its validity. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Chengdu Women's and Children's Central Hospital [Ethics Approval No. 2023(129)]. All data used in this study were fully anonymized, and participants provided informed consent.

Additional information

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Correspondence and requests for materials should be addressed to E.L.

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