Association between exposure to airborne particulate matter less than 2.5 μm and human fecundity in China

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ABSTRACT

Background: Whether exposure to airborne particulate matter less than 2.5 μm (PM_{2.5}) could impact human fecundity is unclear. We aimed to evaluate the potential impact of PM_{2.5} exposure on time to pregnancy (TTP) and the prevalence of infertility in the general Chinese population.

Method: We collected reproductive information, sociodemographic characteristics, and lifestyle data of 10,211 couples at risk of pregnancy from a large-scale community-based fertility survey in China. Then, we estimated each participant’s 1-year, 3-year, and 5-year average PM_{2.5} exposure levels based on remote sensing information. After adjusting for demographic, lifestyle, and environmental co-variables, discrete-time Cox regression models were used to estimate the fecundability odds ratio (FOR) per 10 μg/m^3 change of PM_{2.5}. We also estimated the odds ratio (OR) of infertility per 10 μg/m^3 change of PM_{2.5}, using logistic regression models.

Findings: Among the 10,211 couples, 6,875 (67%) had conceived spontaneously, with a median TTP of 5 months (interquartile range: 2–10 months). The median PM_{2.5} exposure was 56.8 μg/m^3, with a wide range of 9.2–93.5 μg/m^3. In Cox regression models, each increase of 10 μg/m^3 in the 1-year average PM_{2.5} exposure was associated with a significant decrease in fecundity by 11% (FOR: 0.89; 95% confidence interval [CI]: 0.86–0.92). In logistic regression models, it was also associated with an 20% increased likelihood of infertility (OR: 1.20; 95% CI: 1.13–1.27).

Conclusion: PM_{2.5} exposure was associated with reduced human fecundity, presented by a longer TTP and higher odds of infertility, which might explain the increased infertility rates in areas with heavy PM_{2.5} pollution.

1. Introduction

A recent review in 2012 analyzed 277 health surveys from 190 countries and reported that nearly 50 million couples aged 20–44 years were unable to conceive spontaneously (Mascarenhas et al. 2012). The prevalence of infertility, defined as the inability to achieve pregnancy after 1 year of regular unprotected sexual intercourse, ranges from 3.5 to 16.7% in developed countries and 6.9–9.3% in developing countries (Boivin et al., 2007; Ombelet et al., 2008). Over the last two decades, approximately 10% of couples worldwide have been affected by...
Among various air pollutants, airborne particulate matter less than 2.5 \( \mu \text{m} \) (PM\(_{2.5}\)), a solid and liquid mixture that is suspended in air, has drawn the greatest concern in recent decades due to its wide exposure and serious consequences on human health (Lelieveld et al., 2015). It is well documented that PM\(_{2.5}\) exposure is responsible for many adverse health effects such as hypertension, stroke, chronic obstructive pulmonary disease, asthma, and cancer (Kim et al., 2015), which is associated with nearly 3 million premature deaths per year worldwide (Stanaway et al., 2018). Additionally, emerging evidence has indicated that inhaled PM\(_{2.5}\) could induce inflammation, oxidative stress, or endocrine disruption, which are associated with reproductive health (Carre et al., 2017; Frutos et al., 2015); however, limited studies have estimated its impact on human fecundity (Checa Vizcaíno et al., 2016).

Most of the prior work on PM-related fecundity reduction was conducted among men and focused on sperm quality (Carre et al., 2017; Conforti et al., 2018), while evidence from women is sparse. We only found a pilot study from Czech, which highlighted a short-term decrease in fecundity in association with PM\(_{2.5}\) levels (Slama et al., 2013), while two other studies in the U.S. reported that there is no positive association between PM\(_{2.5}\) exposure and infertility (Mahalingaiah et al., 2016; Nobles et al., 2018). However, three ecological studies appreciably observed associations between higher PM\(_{2.5}\) pollution levels and lower fertility rates in the U.S., Spain and China (Nieuwenhuijsen et al., 2014; Xue and Zhang, 2018; Xue and Zhu, 2018). Studies conducted in couples undergoing in vitro fertilization (IVF) cycles also reported that exposure to PM\(_{2.5}\) pollution is inversely associated with peak serum estradiol levels, the number of oocytes retrieved, oocyte maturation and overall fertilization rates (Choe et al., 2018; Fathi Najafi et al., 2015; Legro et al., 2010; Wang et al., 2019). Why these studies reported disharmonious results on the association between PM\(_{2.5}\) and fecundity remain unclear. The absence of individual-based studies was noted as a significant limitation in the extant evidence for the impact of PM\(_{2.5}\) on fecundity.

In summary, whether long-term exposure to PM\(_{2.5}\) could reduce fecundity in the general population is unclear. More importantly, information from individual-based studies is, unfortunately, lacking. In the present study, to address the limitations of the available knowledge, we evaluated the association between PM\(_{2.5}\) and fecundity based on a large-scale individual-based fertility survey in China. We hypothesized that exposure to PM\(_{2.5}\) during the previous year would be associated with decreased fecundity, presented as a longer time to pregnancy (TTP) and higher odds of infertility.

2. Method

2.1. Study population

The China Fertility Survey of Married Women (CFSMW) is a large-scale individual-based survey that aimed at assessing the prevalence of infertility and corresponding risk factors among general Chinese couples. Detailed information about the survey has been published elsewhere (Zhou et al., 2018); however, in 2010, a strict multistage stratified cluster sampling procedure with a sample unit of a village/street was used to recruit couples of reproductive age (the female spouse was 20–49 years old) from 8 provinces (Inner Mongolia, Heliangong, Beijing, Hebei, Shandong, Anhui, Zhejiang and Fujian) in China. All couples of reproductive ages and long life span in the sampled units were included in the survey. According to the requirements of the family planning policy, women need to register in the local National Health and Family Planning Commission of the People’s Republic of China (NHFPC) before attempting pregnancy, which allowed us to approach all women who were aiming to conceive. After informed consent, couples who had been married for more than a year and did not use birth control were interviewed face-to-face by health professionals comprising local community leaders. A total of 25,270 couples were approached in the survey, of whom 18,571 (response rate 74%) were interviewed from February 2010 to November 2011. During the interview, information on demography, lifestyle, reproductive health, marriage, and childbearing status were formally collected using a standardized questionnaire (Zhou et al., 2018).

In this retrospective TTP cohort study, reproductive information, as well as sociodemographic and lifestyle data of 18,571 couples of the CFSMW, were analyzed. Among them, to minimize the long-term trend as well as recall bias, we identified 10,211 couples had become pregnant spontaneously (N = 6875) or were at risk of pregnancy (N = 3336) during the previous year based on the information regarding childbearing status (Fig. 1). Female characteristics of the total population and analytic population were comparable (Table S1 in the appendix). The survey was approved by the Ethics Committee of Peking University Third Hospital, Beijing, China (No. 2006FC001). All participants signed informed consent forms.

2.2. Outcome assessment

As mentioned in our previous study (Zhou et al., 2018) for childbearing status, female participants were asked to answer the following questions: “Did you have spontaneous pregnancy in the previous year?” If the answer was yes, then the question asked was “How long did it take for you to get pregnant?” (number of months). If the answer was no, then the question asked was “Do you want to become pregnant?” and “How long is it since you are trying to become pregnant?” (number of months). Then, TTP was determined as a discrete variable (Velez et al., 2015). For couples who wanted to become pregnant but did not have a spontaneous pregnancy, TTP was censored upon interviewing (Hu et al., 2018). For couples requiring infertility treatment for this pregnancy, TTP was censored upon treatment initiation. Infertility is defined as the inability to achieve pregnancy after 1 year of regular unprotected sexual intercourse or requiring infertility treatment for this pregnancy (Velez et al., 2015).

2.3. PM\(_{2.5}\) exposure

The remote sensing-derived ground-level PM\(_{2.5}\) concentration of study areas was predicted at a resolution of 0.01° × 0.01° using hybrid geophysical-statistical models with a combination of aerosol optical depth retrievals and ground measurements. The results of cross-validation showed that R\(^2\) for PM\(_{2.5}\) prediction was 85%. The methods have been validated and documented elsewhere and the original dataset is freely available as a public good from the Dalhousie University Atmospheric Composition Analysis Group (van Donkelaar et al., 2016, 2018). Detailed residential addresses were collected for each participant as part of the questionnaire and geocoded into latitude and longitude at a resolution of 0.01° × 0.01° through AMAP and Google Earth. We then calculated PM\(_{2.5}\) exposures for each participant. As the etiologic window during which air pollution may affect fecundity is unclear, we calculated three different time-independent exposure measures: the average PM\(_{2.5}\) concentrations in the 1 prior calendar year, in the 3 prior calendar years, and in the 5 prior calendar years preceding the date of end point (conception or censor).
2.4. Statistical analysis

Given that the natural time scale of TTP is the number of menstrual cycles (Scheike and Jensen 1997), which has a large number of ties, we used discrete-time Cox regression models to estimate the possible associations between PM$_{2.5}$ exposure and fecundity (Allison, 2010; Velez et al., 2015; Xie et al., 2003). Specifically, TTP was treated as time scale in the Cox models, and the odds of achieving pregnancy for each cycle, given the exposure to PM$_{2.5}$, conditional on not being pregnant in the previous cycle were estimated (Velez et al. 2015). This was presented as the fecundity odds ratio (FOR) associated with per 10 μg/m$^3$ increased PM$_{2.5}$ (Allison 2010). FORs $<1$ denote reduced fecundity, or equivalently, longer TTP. We first built a basic Cox model that only included maternal age (continuous), natural cubic spline of ambient temperature, and PM$_{2.5}$ exposure (continuous). Based on the basic Cox model, we predicted the proportion of women who were not yet pregnant by the months of trying on different PM$_{2.5}$ exposure level (less than the lower quartile versus higher than the upper quartile).

We extended the basic Cox models by including additional adjustments that were identified based on previous pieces of literature (Hu et al., 2018; Mahalingaiah et al., 2016; Velez et al., 2015). These covariables included the following: geographic region (random effect), males’ age (continuous), female current body mass index (BMI, continuous), ethnicity (Han, minority), education (primary school or below, middle school, college or above), occupation (clerk, worker, farmer, housewife, others), household income ($<10,000, 10,000–20,000, >20,000$ Yuan per year), cigarette smoking (yes, never), drinking (yes, never), and physical activity ($\geq$once/week, 2–3 times/month, once/month or less). We did not include parity in the model, as parity is influenced by a woman’s fecundity, which would cause over adjustment (Velez et al. 2015). In addition, we used logistic regression models to estimate the odds ratios (ORs) for infertility (Velez et al. 2015). Women who did not become pregnant in the previous year, but had a TTP shorter than 12 months were excluded from the analyses of infertility.

Several sensitivity analyses were conducted to verify the robustness of the previous analyses. We used general Cox proportional hazard models to estimate the impact of PM exposure on TTP after adjusting ties with Efron’s approximation (Allison 2010). Among participants at risk of pregnancy during the previous year, we further identified women who had intercourse with their partner more than once per month as actively trying to become pregnant, and performed an analysis in the
subpopulation. We also rebuilt the main models by adjusting for intercourse frequency. We did not include parity in the main analyses, so we conducted sensitivity analyses restricted to nulliparas. We also conducted sensitivity analyses for TTP restricted to participants who had spontaneous pregnancy in the previous year only.

All the above statistical analyses were performed using R 3.4.2 (R Core Team). All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

3. Results

In total, 10,211 couples who had been pregnant or were at risk of pregnancy during the previous year were included in the analyses (Fig. 2). The general characteristics of the female partners are described in Table 1. The mean (±standard deviation) age was 27.3 (±5.2) years. Almost all the participants were of Han Chinese ethnicity, more than three-quarters had secondary education, 40% were housewives, and more than half reported an household income less than RMB 10,000 Yuan/year. Almost all of the participants were non-smokers or non-drinkers, and more than 80% were physically inactive. Of the 10,211 couples, 6875 (67.3%) had conceived spontaneously during the previous year, with a median TTP of 5 months (interquartile range: 2–10 months). Maternal age, BMI, education, and occupation were significant predictors of TTP (p < 0.05). Maternal ethnicity, annual household income, cigarette smoking, drinking, and physical activity, we found that a 10 μg/m³ increase in the 1-year average PM2.5 exposure was associated with a 11% reduction in fecundity (FOR: 0.89; 95% CI: 0.86–0.94). For a 10 μg/m³ increase in the 3-year and 5-year exposures, the corresponding FOR were 0.89 (95% CI: 0.86–0.92) and 0.89 (95% CI: 0.86–0.93) (Table 3, coefficients of other adjustments were shown in Table S2).

Table 4 presents the associations between PM2.5 exposure and infertility. We found that the OR of infertility increased by 5% (OR: 1.05; 95% CI: 1.02–1.09) per 10 μg/m³ increase in the 1-year average PM2.5 exposure in basic model and by 20% (OR: 1.20; 95% CI: 1.13–1.27) per 10 μg/m³ increase in the 1-year average PM2.5 exposure in the full model. Similar impacts were found in the 3-year or 5-year average PM2.5 exposures (coefficients of other adjustments were shown in Table S3).

When we used the Cox proportional hazard models to estimate the impact of PM exposure on fecundity with Efron’s approximation, we also found that the fecundity decreased by 8% (FOR: 0.92; 95% CI: 0.90–0.94) per 10 μg/m³ increase in the 1-year average exposure to PM2.5 in the basic model and by 11% (FOR: 0.89; 95% CI: 0.86–0.92) in the full model. Similar impacts on fecundity were found in the 3-year or 5-year average PM2.5 exposures (Table S4). Results restricted to women who were actively trying to become pregnant were similar to those...
found among all participants (Table S5). When we rebuilt the models by adjusting for intercourse frequency, the results did not change (Table S6). Results restricted to women who had pregnancy during the previous year were similar to those found among all participants (Table S7). Additionally, when analyses were restricted to nulliparas, we found similar associations between PM$_{2.5}$ exposure and fecundity (Table S8).

### 4. Discussion

Air pollution has been listed as the top 10 threats to global health in 2019, as nine out of 10 people breathe polluted air daily (World Health Organization 2019). However, its impact on reproductive health, the key impetus for sustainable development, has received less attention. In the present study, by analyzing the individual data of 10,211 couples, we observed a reduction in fecundability by 11% as well as increased infertility odds by 20% associated with an increase in PM$_{2.5}$ concentration of 10 µg/m$^3$ over the previous year. To the best of our knowledge, this study is the first to report an appreciable association between personal PM$_{2.5}$ exposure with reduced fecundity among the general population, which could serve as novel evidence for improving fertility protection policy.

To our knowledge, only three studies have investigated the association of PM$_{2.5}$ with TTP and infertility (Slama et al., 2013; Nobles et al., 2018; Mahalingaiah et al., 2016). Slama and colleagues recruited 1,916 couples between 1994 and 1999 in the town of Teplice, and estimated the changes in the odds of achieving pregnancy during the first month of unprotected intercourse by their average PM$_{2.5}$ exposure levels over the 60 days preceding the end of the first month of unprotected intercourse. They found that each increase of 10 µg/m$^3$ in PM$_{2.5}$ exposure was associated with a 22% decrease in fecundity (FOR: 0.88; 95% CI: 0.75–0.94). Conversely, Nobles et al. reported that acute exposure to PM post ovulation was associated with greater fecundity among 500 American couplers (Nobles et al. 2018). Mahalingaiah and colleagues collected the childbearing status of 36,294 female nurses from the Nurses’ Health Study II cohort and then linked them with the predicted individual PM$_{2.5}$ exposure levels. They found that the hazard ratio (HR) of infertility for every 10 µg/m$^3$ increase in PM$_{2.5}$ exposure among women with primary infertility was 1.05 (95% CI: 0.88–1.25). The authors did, however, observe a significant higher risk of infertility for nurses living closer to a major road compared to those living farther from one (Mahalingaiah et al. 2016). In addition to the differences in study populations, as our median levels of PM$_{2.5}$ exposure (56.8 µg/m$^3$) were considerably higher than those in Nobles et al. (10.9 µg/m$^3$) and Mahalingaiah et al. (14.6 µg/m$^3$), it is possible that there is a threshold for the chronic effects of PM$_{2.5}$ exposure on fecundity that studies with limited sample size were unable to detect. Differences in composition of PM$_{2.5}$ could also explain the inconsistent findings; however, more source apportionment studies to confirm the associations and justify source-specific effect are warranted.

Although evidence from an individual-based study is insufficient, the literature evaluating the fertile rate at the city or community level may serve as ample information for the deteriorating fecundity related to PM$_{2.5}$ exposure. Xue et al. conducted a group of time-series studies that analyzed the numbers of births in certain areas with corresponding PM$_{2.5}$ concentrations and found that the fertility rate reduced by 0.7% (95% CI: 0.0–1.4%) with each 5 µg/m$^3$ increase in PM$_{2.5}$ exposure among Americans (Xue and Zhu 2018), and by 2.0% (95% CI: 1.8–2.1%) with each 10 µg/m$^3$ increase in PM$_{2.5}$ exposure among the Chinese (Xue and Zhang 2018). Another study from Spain also reported consistent

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**Table 1**

Characteristics of the female participants in analytic samples.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Analytic population (mean [SD or percent]</th>
<th>TTP (months)</th>
<th>p-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.3 (5.2)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.4 (2.7)</td>
<td>--</td>
<td>0.002</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic Han</td>
<td>97.0 (972.5)</td>
<td>5 (2–10)</td>
<td>0.298</td>
</tr>
<tr>
<td>Minority</td>
<td>2.5 (2.5)</td>
<td>6 (3–9)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school or below</td>
<td>6.8 (6.8)</td>
<td>6 (3–11)</td>
<td>0.014</td>
</tr>
<tr>
<td>Middle school</td>
<td>78.4 (78.4)</td>
<td>5 (2–9)</td>
<td></td>
</tr>
<tr>
<td>College or above</td>
<td>14.6 (14.6)</td>
<td>6 (3–11)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clerk</td>
<td>11.6 (11.6)</td>
<td>6 (3–11)</td>
<td>0.027</td>
</tr>
<tr>
<td>Worker</td>
<td>14.6 (14.6)</td>
<td>5 (3–10)</td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>26.5 (26.5)</td>
<td>5 (2–10)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>40.4 (40.4)</td>
<td>5 (2–9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6.6 (6.6)</td>
<td>5 (3–10)</td>
<td></td>
</tr>
<tr>
<td>Annual household income (Chinese yuan)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10,000</td>
<td>57.7 (57.7)</td>
<td>5 (2–10)</td>
<td>0.506</td>
</tr>
<tr>
<td>10,000–20,000</td>
<td>23.4 (23.4)</td>
<td>5 (2–9)</td>
<td></td>
</tr>
<tr>
<td>&gt;20,000</td>
<td>17.7 (17.7)</td>
<td>5 (3–9)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>99.4 (99.4)</td>
<td>5 (2–10)</td>
<td>0.347</td>
</tr>
<tr>
<td>Yes</td>
<td>0.4 (0.4)</td>
<td>7 (4–14)</td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td>98.0 (98.0)</td>
<td>5 (2–10)</td>
<td>0.772</td>
</tr>
<tr>
<td>Yes</td>
<td>1.7 (1.7)</td>
<td>5 (2–9)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Once/week</td>
<td>3.8 (3.8)</td>
<td>6 (3–8)</td>
<td>0.074</td>
</tr>
<tr>
<td>2–3 times/month</td>
<td>12.0 (12.0)</td>
<td>5 (3–10)</td>
<td></td>
</tr>
<tr>
<td>Once/month or less</td>
<td>83.3 (83.3)</td>
<td>5 (2–9)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; TTP, time to pregnancy; IQR, interquartile range.

$^a$ TTP statistics performed only among women who had been pregnant.

$^b$ Spearman correlations with TTP for continuous characteristics, Wilcoxon rank sum test with TTP for categorical characteristics.

$^c$ Others included individual business, soldier and other unspecific occupations.

### 5. Table 2

Distributions of the PM$_{2.5}$ pollution exposure level.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year average (µg/m$^3$)</td>
<td>50.4 ± 19.7</td>
<td>56.8 (34.0)</td>
<td>9.2</td>
<td>93.5</td>
</tr>
<tr>
<td>3-year average (µg/m$^3$)</td>
<td>52.2 ± 20.3</td>
<td>57.3 (38.8)</td>
<td>8.3</td>
<td>95.8</td>
</tr>
<tr>
<td>5-year average (µg/m$^3$)</td>
<td>54.1 ± 22.2</td>
<td>55.5 (43.8)</td>
<td>8.3</td>
<td>101.3</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range.

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### 6. Table 3

FOR and 95% CI by increased PM$_{2.5}$ exposure level in the basic and full Cox models.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Basic Model$^b$</th>
<th>Full Model$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case of pregnancy</td>
<td>FOR (95% CI)</td>
</tr>
<tr>
<td>1-year average (µg/m$^3$)</td>
<td>6875</td>
<td>0.92 (0.90, 0.94)</td>
</tr>
<tr>
<td>3-year average (µg/m$^3$)</td>
<td>6875</td>
<td>0.91 (0.89, 0.93)</td>
</tr>
<tr>
<td>5-year average (µg/m$^3$)</td>
<td>6875</td>
<td>0.93 (0.91, 0.94)</td>
</tr>
</tbody>
</table>

$^a$ Cox regression models, presented as ratio of the “risk” of being pregnant by each 10 µg/m$^3$ increased exposure level.

$^b$ Only adjusted for maternal age (continuous) and ambient temperature (nature cubic spline).

$^c$ Additionally adjusted for geographic region (random effect), males’ age (continuous), maternal body mass index (nature cubic spline), ethnicity (Han, minority), education level (primary school or below, middle school, college or above), occupation (clerk, worker, farmer, housewife, others), household income (<10,000, 10,000–20,000, >20,000 Yuan/year), cigarette smoking (yes, never), drinking (yes, never) and physical activity (once/week, 2–3 times/month, once/month or less). A total of 475 observations were deleted because the above adjustments were missing; FOR, Fecundability odds ratio; 95% CI, 95% confidence intervals.
Results using similar methods (Nieuwenhuijsen et al. 2014). Taken together with our findings, these data suggest that exposure to PM$_{2.5}$ may impact the fecundity of couples at reproductive ages, presented as a longer TTP, increased odds of infertility, and decreased fertility rate.

There are numerous causes of infertility, ranging from hormonal imbalance, to defects of the ovary and uterus, and low sperm quality. Although most infertility cases are related to specific disorders, approximately 30% of infertile couples have unexplained infertility (Smith et al. 2003). It is well documented that the woman’s age is the most important determinant of fertility. Lifestyle habits such as obesity, smoking, alcohol, and recreational drugs have also been shown to affect the chances of conception (Balen and Rutherford 2007). However, in the present study, we observed a reduction in fecundity by 11% associated with an increase in PM$_{2.5}$ concentration of 10 μg/m$^3$, indicating that PM$_{2.5}$ pollution could be an unignorable risk factor for infertility. Given the higher PM$_{2.5}$ exposure level and the increasing epidemic of infertility in some areas such as northern China (Chen et al., 2018; Zhou et al., 2018), we suggest that the impact of air pollution on reproductive health should be given greater prominence.

Potential biological mechanisms that might explain associations between PM$_{2.5}$ exposure and reduced fecundity are yet to be elucidated. In the present study, we can hardly identify biological mechanisms whereby PM$_{2.5}$ could alter fecundity due to the event-based endpoint design. However, taken together with the pieces of literature evaluating early reproductive outcomes, we can provide an assumption here. First, previous studies suggested that behavioral factors such as libido and frequency of sexual intercourse could be an important mediator of the association between air pollution and fecundity (Slama et al. 2013). However, in the sensitivity analyses, we found similar associations when we performed analyses among women who were actively trying to become pregnant (intercourse more than once a month) or further adjusted intercourse frequency in the models, which suggested that PM$_{2.5}$ could impact human fecundity independently.

Recently, a study of 632 women from an infertility clinic in the U.S. reported that every 2 μg/m$^3$ increase in PM$_{2.5}$ exposure during the 3 months before the measurement was associated with a 7.2% (95% CI: 3.8–10.4) lower antral follicle count. They also noted that the difference in the antral follicle count was approximately equivalent to a 2-year increase in age (Gaskins et al. 2019). Some animal studies have also observed reduced numbers of antral follicles (Veras et al., 2009), reduction in the proportional area occupied by primordial follicles (Ogliari et al. 2013), decreased serum anti-Müllerian hormone levels, increased IL-6 and TNF-α concentrations, and the number of apoptotic cells in mice exposed to PM$_{2.5}$ (Gai et al. 2017). Therefore, we suggest that exposure to PM$_{2.5}$ may enhance follicular atresia through effects on ovarian inflammation, oxidative stress, and apoptosis, which could be a step in the pathway for the impact of PM$_{2.5}$ on fecundity.

Several studies have also suggested a male-mediated pathway (Lafluente et al. 2016). Exposure to higher PM$_{2.5}$ pollution has been linked with increased DNA fragmentation (Rubes et al. 2005), lower sperm motility (Santi et al., 2018), abnormal morphology (Santi et al., 2018; Zhou et al., 2014), and decreased sperm concentrations (Wu et al. 2017). Although the exact mechanism by which PM$_{2.5}$ exposure affects spermatogenesis is still unknown, researchers have suggested that PM-related systemic inflammation, endothelial dysfunction, and damaged blood-testis barrier integrity may play a role. However, these changes in sperm could also be a key step of the pathway for the impact of PM$_{2.5}$ on fecundity.

Some methodological aspects of our study need to be considered.
Most studies estimated associations between environmental risks and fecundity with pregnancy-based TTP, in which infertile couples were excluded in the analysis, which resulted in the systematic under-representation of infertile couples and the selection of a healthier population (Velez et al. 2015). In contrast, another type of study was conducted in infertility clinics and enrolled subfertility populations, even though characteristics of sub-fertile couples may differ from fertile couples, which may also lead to selection bias. In our study, when subgroup analysis was performed among pregnant women, we found a relatively stronger effect of PM$_{2.5}$ on fecundity, which could serve as evidence for the mentioned bias. Given that the study samples were recruited from the general population with a qualified sampling procedure and the geographic distribution represented by the study participants, which can provide information on the most populated areas of China, our findings may be more generalizable than those of the previous studies.

Several limitations to our study need to be acknowledged. We did not assess the impact of PM$_{2.5}$ on specific intermediate processes of fecundity, such as semen quality, menstrual cycle characteristics, endocrine hormone levels, and markers of ovulation, which may weaken the strength of the evidence, further studies are warranted to unravel the effect of these factors. In addition, retrospectively measured TTP in the present study can lead to the problems associated with recall bias, particularly when the follow-up time is long (Cooney et al. 2009). Additionally, miscarriage of a chemical pregnancy may have been missed in some cases before they were realized, which also results in a potential misclassification of TTP. Thus, we must admit that the misclassification of TTP in the present study is likely. However, the reporting accuracy of TTP has been assumed to not be associated with the exposure status, and it can only inflate the standard errors for the FOR. The standard errors may also inflate due to lack of some adjustments such as detailed individual nutritional and behavioral data. Furthermore, misclassification in exposure assessment is a potential concern. Even though we estimated personal exposure based on predicted PM$_{2.5}$ exposures at a resolution of 0.01$^\circ$ × 0.01$^\circ$ and each participant’s detailed home address, exposures on work place and characteristics of the microenvironment, such as indoor air pollution, air purification appliance, and time-activity patterns that may affect the actual personal exposure levels. However, studies have suggested that the use of ambient measurements-based exposure is an acceptable and useful surrogate because regulation typically focuses on these levels (Meng et al. 2005). The reported associations between PM$_{2.5}$ exposure and fecundity may also be limited by the no-consideration of PM-bound chemical species (e.g., toxic metals, pesticides, and polycyclic aromatic hydrocarbons) and other environmental factors, such as noise.

5. Conclusion

In conclusion, our study provides novel evidence that exposure to PM$_{2.5}$ is associated with a longer TTP and increased odds of infertility. Further studies are required to evaluate potential mechanisms and confirm the association between air pollution and fecundity decrements, which might be responsible for increased infertility rates in areas with heavy PM$_{2.5}$ pollution.

Ethical approval

The Ethics Committee of Peking University Third Hospital, Beijing, China approved this study (No. 2006FC001). All participants provided written informed consent.

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CRediT authorship contribution statement

Q. Li: Conceptualization, Methodology, Software, Writing - original draft. Danni Zheng: Data curation, Writing - review & editing. Yuanyuan Wang: Data curation, Writing - review & editing. Rong Li: Data curation, Writing - review & editing. Hongping Wu: Data curation, Writing - review & editing. Suxin Xu: Data curation, Writing - review & editing. Yuelan Kang: Data curation, Writing - review & editing. Yunxia Cao: Data curation, Writing - review & editing. Xiujuan Chen: Data curation, Writing - review & editing. Yinmin Zhu: Data curation, Writing - review & editing. Shuguang Xu: Data curation, Writing - review & editing. Ping Liu: Supervision, Writing - review & editing. Jie Qiao: Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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References