Particulate matter exposure increases the risk of reduction in human fecundity in South Asia

Huailin Wang  
School of Public Health, Sun Yat-Sen University  https://orcid.org/0000-0002-6334-3575

Zhenghong Zhu  
School of Public Health, Sun Yat-Sen University

Tarik Benmarhnia  
University of California, San Diego

Bin Jalaludin  
UNSW Australia

Xin Chen  
School of Public Health, Sun Yat-sen University

Maimaitiminjiang Wulayin  
School of Public Health, Sun Yat-sen University

Cunrui Huang  
Tsinghua University  https://orcid.org/0000-0002-9139-8354

Tuantuan Zhang  
School of Atmospheric Sciences, Sun Yat-sen University

Lianlian Xu  
School of Atmospheric Sciences, Sun Yat-sen University

Qiong Wang  ( wangqiong@mail.sysu.edu.cn )  
School of Public Health, Sun Yat-sen University

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Abstract

The estimated infertility prevalence in South Asia was among the highest in the world, however, epidemiological study concerning the effects of particulate matter exposure was absent in this region. Utilizing the well-adopted Demographic and Health Survey data, 27,462 eligible women were included to estimate fecundity and its association with particulate matter exposure in South Asia. The couple’s fecundity, including time to pregnancy and infertility prevalence, was estimated to be from 5.53 to 11.57 months, and from 26–49%, respectively. An overall association of reduced fecundity with increased particulate matter exposure was identified, with adjusted fertility time ratios (95% confidence intervals) being 1.05 (1.04, 1.06), 1.04 (1.03, 1.05), and 1.01 (1.01, 1.02) per 10 µg/m$^3$ increment in PM$_1$, PM$_{2.5}$, and PM$_{10}$, respectively. Furthermore, millions of months’ delay in achieving pregnancy might be attributed to particulate matter exposure. Here, our findings suggest that human fecundity is threatened by ambient particulate matter in South Asia.

Introduction

A severe decline in birth rates has been reported in the world over the past half-century $^1$. In most industrialized regions, birth rates have continuously declined to below the replacement level (2.1 children per woman), a rate that guarantees the reproduce and sustain the population for more than 40 years $^2$. Such a decline trend has also been observed in low- and middle-income countries. Total fertility rates (TFRs) decreased in all countries and territories between 1950 and 2017 $^3$. And, 57 countries (including India, Pakistan, and Bangladesh) had a more than 2.0% annual decline in TFR between 2010 and 2019 $^4$, and 151 and 183 countries were projected to have a TFR lower than the replacement level by 2050 and 2100, respectively $^5$. As an essential threat to population sustainable development, and subsequent economic, social, environmental, and geopolitical consequences, it is critical to understand why and how fertility rates are declining.

While some of the declines in birth rate can be attributable to behavioral factors like contraceptive use and changing childbearing preference $^6,7$, declining fecundity has also been suggested as a possible reason. Fecundity is the biological ability to reproduce, which was usually measured in terms of time to pregnancy (TTP) and infertility. In 2010, an estimated 48.5 million (95%CI: 45.0, 52.6) couples worldwide were infertile $^8$, of which 14.4 million (95%CI: 12.2, 16.8) couples were living in South Asia, ranking as the highest in the world. The high infertility prevalence in these regions is partly due to the specific disorders in either male or female reproductive systems. However, the cause of unexplained infertility needs further investigation.

Biologically, fecundity depends on several factors, including ovulation, semen quality, gamete characteristics, implantation, and early zygote development $^1,9$, and these functions can be affected by external environmental factors $^1,10−12$. Given that a decline in TFRs appeared around 1900 in the regions
with early industrialization, Skakkebæk et al.\textsuperscript{1,2} claimed that impaired reproductive capacity may partially be due to increased exposure to deleterious environmental pollutants related to fossil fuels.

In recent years, air pollution has been linked to infertility. Most toxicological and epidemiological studies on air pollution and decreased fecundity focused on sperm quality\textsuperscript{13} and reported that high-level air pollutant exposure, especially fine particulate matter (PM) exposure, was associated with impaired semen quality, including declined sperm concentration, count, and total motility. Other studies focused on treatment outcomes for couples undergoing in vitro fertilization\textsuperscript{14–17} and suggested a link between air pollution, such as PM, and reduction in peak serum estradiol levels, the number of oocytes retrieved, oocyte maturation, and overall fertilization rates. Nevertheless, the evidence regarding particulate matter exposure on the fecundity of the general population is even scarcer\textsuperscript{18–21}, and none from South Asia. Mitigating the modifiable risk of fecundity is of importance for global public health and the achievement of the UN Sustainable Development Goals, especially in low- and middle-income countries (LMICs) where couples have limited resources for infertility treatment.

We hypothesize that high particulate matter exposure during the period of “at risk” of pregnancy would extend the TTP, and conduct the investigation in South Asian countries where both air pollution level and infertility rate are quite high. A feasible method, the current duration (CD) approach, is applied to estimate the couple’s fecundity, i.e., TTP and infertility prevalence, and a significant relationship between PM exposure (PM\textsubscript{1}, PM\textsubscript{2.5}, and PM\textsubscript{10}) and a reduction in fecundity is identified.

**Results**

**Population characteristics.**

This study involved 806,915 women and 27,462 were eligible for the CD calculation. Among the women included in the study, most were from India (56.5%), aged 25–34 years (41.2%), had ever 2–4 children (41.4%), lived in rural areas (65.4%), attended secondary or higher education (50.6%), had no insurance cover (68.2%), had a normal body mass index (48.4%), and were non-smokers (79.1%). In terms of reproductive history and fertility preference, most women had never terminated a pregnancy (78.6%), did not know about the fertile period (76.7%) but knew a modern method of contraception (98.6%), and did not want a baby within next nine months (64.4%). These characteristics were different between eligible and non-eligible women. More detailed information on the participants is summarized in Table 1, and their characteristics by country are also presented in Supplementary Tables S1 to S4.
Table 1
The characteristics of the whole study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total DHS population (N = 806,915)</th>
<th>CD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>55,832</td>
<td>6.9</td>
</tr>
<tr>
<td>India</td>
<td>699,686</td>
<td>86.7</td>
</tr>
<tr>
<td>Nepal</td>
<td>36,329</td>
<td>4.5</td>
</tr>
<tr>
<td>Pakistan 2017–2018</td>
<td>15,068</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Age at interview (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–24</td>
<td>198,920</td>
<td>24.7</td>
</tr>
<tr>
<td>25–34</td>
<td>248,399</td>
<td>30.8</td>
</tr>
<tr>
<td>35–44</td>
<td>193,961</td>
<td>24.0</td>
</tr>
<tr>
<td>Others</td>
<td>165,635</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>594,158</td>
<td>73.6</td>
</tr>
<tr>
<td>Other</td>
<td>212,757</td>
<td>26.4</td>
</tr>
<tr>
<td><strong>Total children ever born</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>241,120</td>
<td>29.9</td>
</tr>
<tr>
<td>1</td>
<td>112,692</td>
<td>14.0</td>
</tr>
<tr>
<td>2–4</td>
<td>378,038</td>
<td>46.8</td>
</tr>
<tr>
<td>5–7</td>
<td>66,379</td>
<td>8.2</td>
</tr>
<tr>
<td>8–20</td>
<td>8,685</td>
<td>1.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>560,260</td>
<td>69.4</td>
</tr>
<tr>
<td>Urban</td>
<td>246,655</td>
<td>30.6</td>
</tr>
</tbody>
</table>

These characteristics of eligible and non-eligible women were different ($P < 0.001$); N: The frequency of each group; %: Proportion of each group.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total DHS population (N = 806,915)</th>
<th>CD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>231,130</td>
<td>28.6</td>
</tr>
<tr>
<td>Primary</td>
<td>113,429</td>
<td>14.1</td>
</tr>
<tr>
<td>Secondary or higher</td>
<td>462,356</td>
<td>57.3</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not covered</td>
<td>609,557</td>
<td>75.5</td>
</tr>
<tr>
<td>Covered</td>
<td>125,322</td>
<td>15.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>72,036</td>
<td>8.9</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (18.5 to &lt; 25.0 kg/m²)</td>
<td>459,903</td>
<td>57.0</td>
</tr>
<tr>
<td>Overweight or obese (≥ 25.0 kg/m²)</td>
<td>145,560</td>
<td>18.0</td>
</tr>
<tr>
<td>Underweight (&lt; 18.5 kg/m²)</td>
<td>165,238</td>
<td>20.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>36,214</td>
<td>4.5</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>737,693</td>
<td>91.4</td>
</tr>
<tr>
<td>Yes</td>
<td>13,384</td>
<td>1.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>55,838</td>
<td>6.9</td>
</tr>
<tr>
<td>Wealth index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorest</td>
<td>153,684</td>
<td>19.0</td>
</tr>
<tr>
<td>Poorer</td>
<td>170,255</td>
<td>21.1</td>
</tr>
<tr>
<td>Middle</td>
<td>167,976</td>
<td>20.8</td>
</tr>
<tr>
<td>Richer</td>
<td>160,334</td>
<td>19.9</td>
</tr>
<tr>
<td>Richest</td>
<td>154,666</td>
<td>19.2</td>
</tr>
</tbody>
</table>

These characteristics of eligible and non-eligible women were different ($P < 0.001$); N: The frequency of each group; %: Proportion of each group
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total DHS population (N = 806,915)</th>
<th>CD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Ever terminated pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>701,498</td>
<td>86.9</td>
</tr>
<tr>
<td>Yes</td>
<td>105,417</td>
<td>13.1</td>
</tr>
<tr>
<td>Knows a modern method of contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16,935</td>
<td>2.3</td>
</tr>
<tr>
<td>Yes</td>
<td>734,148</td>
<td>97.7</td>
</tr>
<tr>
<td>Have current knowledge of fertile period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No, doesn't know correctly</td>
<td>648,017</td>
<td>80.3</td>
</tr>
<tr>
<td>Yes, knows correctly</td>
<td>141,051</td>
<td>17.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>17,847</td>
<td>2.2</td>
</tr>
<tr>
<td>Want a baby soon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>757,919</td>
<td>93.9</td>
</tr>
<tr>
<td>Yes</td>
<td>48,996</td>
<td>6.1</td>
</tr>
</tbody>
</table>

These characteristics of eligible and non-eligible women were different (P < 0.001); N: The frequency of each group; %: Proportion of each group

The TTP and infertility prevalence estimations.

Figure 1 shows the CD estimated TTP distributions for up to 36 months for each Country. Median estimated TTPs (95% confidence intervals; 95% CIs hereafter) were from 5.33 (4.55, 6.26) months for Nepal to 11.57 (9.38, 13.76) months for Pakistan. The corresponding infertility prevalence estimations (95% CIs) defined by the probability of not having conceived within one year were from 26% (23%, 30%) to 49% (42%, 55%). As suggested by Keiding et al, the estimated median TTP and infertility prevalence for Pakistan might not be valid, as the survival curve was irregular, i.e., the CD approach might not apply to the data from Pakistan. Therefore, we didn’t include it in the following analyses.

Table S5 presents the infertility prevalence among the included participants by demographic characteristics. The overall prevalence was 33% (31%, 35%), within which, the prevalence of primary (among nulliparous women) and secondary infertility (among parous women) was 25% (23%, 29%) and
37% (34%, 40%), respectively. The infertility prevalence in women with and without ever-terminated pregnancy was both 33%. A higher infertility prevalence was observed for older women and those with less education, living in urban areas, or with the least wealth. Among women who desired fertility and who had no knowledge of the fertile period, the infertility prevalence was also higher.

**Air pollution exposure.**

The locations of the study sample and spatial distribution of the PM$_{2.5}$ concentrations in the included countries are presented in Fig. 2. The annually average concentrations of PM$_{2.5}$ varied in countries, with the highest concentration observed over Bangladesh (mean ± standard deviation; 53.5 ± 7.7 µg/m$^3$), followed by that over India (42.7 ± 16.8 µg/m$^3$), and Nepal (26.4 ± 15.5 µg/m$^3$). Northwestern Bangladesh, the southwestern and southern edge of Nepal, and northern India are the hardest hits. Similar features were observed for PM$_1$ (Fig. S1) and PM$_{10}$ (Fig. S2). The average concentrations of PM$_1$, PM$_{2.5}$, and PM$_{10}$ exposure for the studied samples were lower than the national-averaged annual levels in Bangladesh, but they were higher for other countries.

**Association between fertility time and particulate matters.**

Overall, reduced fecundity was associated with an increased PM exposure, with adjusted FTRs (95% CIs) being 1.05 (1.04, 1.06), 1.04 (1.03, 1.05), and 1.01 (1.01, 1.02) per 10 µg/m$^3$ increment in PM$_1$, PM$_{2.5}$, and PM$_{10}$, respectively (Fig. 3). The association was strongest for PM$_1$ exposure, then for PM$_{2.5}$, and PM$_{10}$. When estimated by each country separately, we observed heterogeneous associations. For India and Nepal, an increase in PM exposure was associated with decreased fecundity (FTR > 1). However, the association in Bangladesh was not significant. Moreover, our estimations were moderately robust for covariates adjustment.

We found a remarkable heterogeneity in the association between PM exposure and fecundity among different subgroups (Fig. 4). For the three PM indicators, the associations were stronger for non-educated women (vs. educated ones) and rural residents (vs. urban ones) (Cochran Q test $P$ value < 0.05). Although no apparent heterogeneity was observed in subgroups stratified by women’s age, parity, and their family’s wealth, there was a trend that the associations got stronger from the richest families to the poorest families.

**Increased TTP burden attributable to particulate matter.**

Among the women of childbearing age, the increased months of TTP attributable to PM$_{2.5}$ exposure greater than the WHO guideline (5 µg/m$^3$) were 2.34 (95%CI: 0.08, 4.41) million months in Nepal to 571.42 (95% CI: 492.13, 646.29) million months in India (Table 2). The burden attributable to PM$_1$ and PM$_{10}$ exposure was also considerable.
Table 2
Total burden of annual time-to-pregnancy extension attributable to particulate matter exposure in each country

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (thousand)</th>
<th>Time-to-pregnancy extension (million months)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PM$_1$</td>
<td>PM$_{2.5}$</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>43029.141</td>
<td>1.17 (-32.48, 30.72)</td>
<td>4.34 (-32.66, 37.85)</td>
</tr>
<tr>
<td>India</td>
<td>687403.801</td>
<td>489.73 (424.22, 552.07)</td>
<td>571.42 (492.13, 646.29)</td>
</tr>
<tr>
<td>Nepal</td>
<td>7181.089</td>
<td>3.19 (1.41, 4.88)</td>
<td>2.34 (0.08, 4.41)</td>
</tr>
</tbody>
</table>

Population is the average annual number of women of childbearing age of the country. PM: particulate matter

Sensitivity analyses for the estimated associations.

The robustness of our main findings was further confirmed by multiple sensitivity analyses, and an overall negative effect of PM exposure on fecundity (i.e., an increased PM exposure associated with reduced fecundity) was observed. After accounting for possible pregnancy recognition delay, naturally, the estimated TTPs were shorter and the infertility prevalence became lower (Table S6). The overall associations only changed slightly except for Nepal where the relationship was positive (i.e., an increased PM exposure associated with an increased fecundity) but estimated to be negative in the original estimations, and for Bangladesh where the original estimated null association changed to significantly negative (Table S7). In the sensitivity analyses, either adding the season of starting “at risk” of pregnancy in the models to address the possible violation of the stationarity assumption under which CD can be used to estimate the TTP, or restricting the studied CD within 24 and 12 months to address possible recall bias, the associations were unchanged (Table S8 and Table S9). Sensitivity analyses also showed that missing values of covariates did not affect the findings (Table S10).

Discussion

We estimate couple’s fecundity (i.e., the TTP and infertility prevalence) in South Asian countries using a feasible CD approach, and identify the association between higher levels of PM exposure (PM$_1$, PM$_{2.5}$, and PM$_{10}$) and fecundity reduction during the period of “at risk” of pregnancy, especially for non-educated and rural-lived women. The associations are moderately robust to covariate adjustment and delayed pregnancy recognition, and highly robust to recall bias, missing values of covariates, and possible violations of the assumption under which CD can be used to estimate the TTP.

Previous studies$^{22,23}$ have applied the CD approach to estimate the TTP and infertility using the DHS data, suggesting that the method is valid for some countries. Their estimated TTP ranged from 6 to 8
months, and the infertility prevalence (defined as 12 months or more of pregnancy attempts) was 24%-38%, which bears a large resemblance to our estimations. However, our estimations in infertility were higher than a previous DHS report. That report estimated infertility in 2002 for 47 national DHS surveys, among which, Bangladesh, India, and Nepal surveys were included. Primary infertility and secondary infecundity for women aged 25–49 years were estimated as 2.1% and 20.6% for Bangladesh, 3.0% and 26.7% for India, 2.3% and 26.7% for Nepal, respectively. The discrepancies in estimations between the present study and that report could be due to the different definitions of infertility. The latter estimated infertility during the past five years and included women who ever had sexual intercourse and did not use contraception during that period, which implies that women “not at risk” of pregnancy may have also contributed to the denominator and hence biasing the estimation of infertility downwards. Despite this, we observed a similar phenomenon that secondary infertility was higher than primary infertility.

Successfully using the CD approach based on DHS data is a cost-effective manner to estimate infertility in LMICs, as the DHS data are nationally representative and publically available. The main constraint of applying the CD approach to the DHS data in some countries is the nonmonotonicity of histograms for the CD frequency and of “too few” current durations close to zero. The Pakistan 2017 survey in the present study was is a case in point. We tried to partly solve this problem following the suggestion of the previous study, by using the precise date, not just the month of an interview for the CD calculation. To improve the applicability of DHS data in the study on human fecundity, we recommend asking more explicit questions about CD, for example, adding a question “How long have you been trying to become pregnant? (number of months)” for the women not using any contraception because they desire to conceive soon.

Few previous epidemiological studies have examined the association of air pollution with fecundity in the general population compared to the male infertility population or couples undergoing IVF. Nevertheless, the extant findings are inconsistent. A birth cohort study in the Czech Republic observed a decreased fecundity with a short-term PM$_{2.5}$ exposure. Another retrospective study in China reported that long-term exposures to PM$_{2.5}$ (including exposure of 1, 3, and 5 years before the pregnancy attempt) were associated with reduced fecundity and increased risk of infertility. On the contrary, a study in the United States reported that an acute PM$_{10}$ exposure (6 days post ovulation) was associated with enhanced fecundability and another study, also from the United States, observed a null association between PM$_{2.5-10}$ concentrations and infertility among nurses in the United States. The inconsistency may be partly because of the differences in the focus of the exposure windows. It should be noted that during the period of trying to be pregnant, the ambient particulate matter exposure for each menstrual cycle is time-varying, and the achievement of pregnancy in one cycle is conditioned on pregnancy failure in the previous cycle. These features should be considered in the association estimation. A study in Denmark estimated the probability of conception for each cycle and observed higher levels of PM$_{2.5}$ and PM$_{10}$ exposure were associated with slightly decreased fecundability. In agreement with this study, we
also estimated the effects of time-vary particulate matter exposure for each cycle and found similar associations of higher levels of particulate matter exposures (PM$_1$, PM$_{2.5}$, and PM$_{10}$) during the period of “at risk” of pregnancy with reduced fecundity. Moreover, our study was based on a more representative sample compared with the Denmark study, which recruited women using the internet and could have resulted in selection bias. To the best of our knowledge, there was an absence of investigations on particulate matter exposure and human fecundity in South Asia, where the estimated infertility prevalence is among the highest in the world $^8$.

Although the exact biological mechanisms through which the PM could influence fecundity remain unclear, previous studies have provided some evidence. In vitro and in vivo studies suggested that PM exposure could induce inflammatory and oxidative stress, or inhibit functions of local endometrial stem cells, subsequently leading to damage to ovaries $^{27}$ and endometrial tissue $^{28}$ and reducing the pregnancy rate. And, the PM constituents, such as heavy metals and polycyclic aromatic hydrocarbon, are well-known endocrine disruptors, which can lead to impaired female reproductive capacity by interfering with the hypothalamus-pituitary-thyroid axis to disrupt the endocrine system $^{29}$. Epidemiologic studies linking PM exposure and impaired semen quality $^{13,30}$, and also treatment outcomes in couples undergoing IVF $^{14-17}$, also support the association between higher PM exposure and reduced human fecundity.

We found heterogeneous characteristics of the associations among the surveyed countries. The main results showed that PM exposure was associated with reduced fecundity in Nepal and India. However, the association was not observed in Bangladesh. This result was unexpected given that the Bangladeshi women in the study experienced the worst PM exposure. A previous study similarly reported that PM$_{10}$ exposure around implantation was associated with greater fecundability $^{25}$. This study also suggested that the effects of acute ambient air pollution exposure around ovulation and implantation, and cycle-average exposure during the period of pregnancy attempts on fecundity were different. However, we were unable to distinguish the effects of acute and long-term exposure using the DHS data. On the other hand, our sensitivity analyses suggested that the examined association for Bangladesh was only sensitive to pregnancy recognition delay. Given this, the unanticipated associations may be also due to sampling variability or certain information biases, such as a failure to identify a pregnancy at the time of the interview. In this case, the CD approach provides survival function about the time until pregnancy detection but not to the time to pregnancy, which may induce a bias if the pregnancy recognition delay is not uniform across exposure levels $^{31}$. Disentangling the association of acute and long-term exposure with fecundity is an important issue for further research, and reducing the abovementioned bias in quality control should be critical for future DHS surveys.

Among subgroups stratified by characteristics, the associations were significantly stronger for women who were non-educated (vs. educated ones) and rural residents (vs. urban ones). Moreover, we found an increasing trend of associations from the richest families to the poorest families. These findings support that people from disadvantaged socio-economic groups tend to be more vulnerable to air pollution exposure. Non-educated and rural-lived women may be less likely to be aware of the necessity of taking
protective measures against harmful environments such as air pollution exposure when trying to conceive. Furthermore, they usually have limited access to health care, for example, preconception care. It suggests that in addition to general air quality management to reduce PM exposure of the whole population, strengthening health education and necessary preconception care for vulnerable groups are also critical.

According to our estimation, the extended months of TTP attributable to the PM exposure were considerable. Using the global air quality guideline released by WHO in 2021 as the theoretical minimum risk exposure level, the current level of PM in South Asian countries contributed to millions of months’ delay in achieving pregnancy in each country in the survey year. Although we were unable to estimate the exact number of women suffering from infertility attributable to PM exposure, undoubtedly the number would be non-negligible. Maintaining human reproduction at a reasonable level (e.g., the replacement level which is calculated as 2.1 children per woman) is essential for population sustainable development, and subsequent economic, social, environmental, and human health consequences. Therefore, understanding why and how the ongoing fertility declines are taking place and taking corresponding preventive measures, are related to the achievement of almost all UN Sustainable Development Goals. The estimated infertility prevalence in South Asia was among the highest globally. From the perspectives of our findings, improving air quality would be of great benefit to the whole population in this area by preventing infertility attributable to PM exposure. This can also be generalized to other low- and middle-income countries where couples have limited resources for infertility treatment.

Nevertheless, this study has several limitations. First, since the DHS surveys did not directly ask questions about the CD, we used several important assumptions to identify women who were “at risk” of pregnancy and calculated the CD indirectly as we stated in the Methods. Although we used a detailed history of reproductive and contraceptive use and improved our methods by using the exact date of the interview for the CD calculation compared with previous studies, the bias of the calculated CD could not be ruled out. Further, we did not take into account whether the studied women were in multiple relationships, which could also bias the calculation. However, such a phenomenon of multiple relationships is not common for women in South Asia. Second, for the TTP and infertility estimation, all TTP studies applying the CD approach have an inherent limitation in that they don’t include pregnancies because of contraceptive failure. This may induce bias in the estimations of TTP and infertility for a more fertile population or a population with a high rate of contraceptive failure. As we did not have access to information on possible infertility treatment (although it is likely to be uncommon in these countries) or cessation of pregnancy attempts of the couples, we were unable to evaluate the potential impact on our estimation. Third, we assessed exposure based solely on participants’ residential addresses, while the lack of information on air pollution exposure indoors or in non-residential locations, and the temporal activities could have resulted in the misclassification of exposure. However, the misclassification tends to be non-differential, which would attenuate the effect of estimations. Fourth, we performed AFT modeling utilizing an advanced R package “eha”, which enabled us to consider the time-varying features of particulate matter exposure during the period of trying to be pregnant, and therefore estimating the effect
of PM exposure on the time of achieving pregnancy for each cycle conditioned on pregnancy failure in the previous cycle. However, to the best of our knowledge, the modeling is currently unable to estimate the nonlinear relationships. As a trade-off, we assumed the relationship between PM exposure and the time of achieving pregnancy was linear, and also the temperature exposure was adjusted in the models as quintiles.

**Conclusion**

In this subcontinental study in South Asia, we applied a feasible CD approach to estimate couples’ fecundity, i.e., the TTP and infertility prevalence. We also innovatively demonstrated a close association between higher levels of PM exposure (PM$_{1}$, PM$_{2.5}$, and PM$_{10}$) and fecundity reduction, especially for people from disadvantaged socio-economic groups. Such associations were robust to covariate adjustment, recall bias, missing values of covariates, and possible violations of the assumption under which CD can be used to estimate the TTP. Our findings suggest that infertility attributable to PM exposure is substantial but can be mitigated by improving air quality and enabling vulnerable groups through strengthening health education and necessary preconception care.

**Methods**

**Population data.**

The population’s data were obtained from the Demographic and Health Surveys (DHS), which are nationally representative household surveys covering worldwide LMICs. These surveys were conducted approximately at 5-year intervals. From 1984 to now, DHS has completed seven rounds of the survey and all surveys were standardized across countries.

For the surveys, females of reproductive age (15–49 years) were interviewed by well-trained interviewers and their socioeconomic status, fertility, reproductive history, etc. were collected using standard questionnaires. Although the surveys were cross-sectional and did not follow the same women over time, an option for longitudinal analysis has been embedded: the contraceptive calendar. The calendar was developed by collecting each woman’s contraceptive behavior and pregnancy experience over 5 to 7 years before the interview. Thus, it can be used to longitudinally analyze changes in women’s reproductive lives in recent periods.

Further, in recent surveys, the location (longitude and latitude) of survey clusters (surveyed village or residential cluster) were available, so that environmental variables such as air pollutants and meteorological factors could be linked to each surveyed sample. Based on this, we included eight DHS surveys from South Asian countries, including three in Bangladesh (DHS phases 5–7), three in Nepal (DHS phases 5–7), one in Pakistan (phase 7), and one in India (phase 7).

We have been approved to use the data by adhering to the data usage guidelines. The DHS data is publically available and anonymous thus no further ethical approval is required.
The current duration (CD) calculations.

Fecundity is the biological ability to reproduce, which is generally indicated by TTP and infertility. Infertility is defined as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” by the World Health Organization (WHO)\(^{32}\). However, measuring the TTP can be challenging regardless of epidemiological study design\(^{33}\). Pregnancy-based retrospective TTP measurement could miss the women who never get pregnant, while prospective cohorts could miss unplanned pregnancies as the women without pregnancy attempts would not join the cohort. The CD approach was recently developed to estimate the TTP and infertility prevalence among women trying to conceive. The CD refers to a self-reported time of trying to conceive at the time of the interview. It can include couples without pregnancy attempts and couples that will never get pregnant. The efficiency of the CD approach has been validated when compared with the retrospective and prospective designs\(^{33}\). Previous studies\(^{22,23}\) have applied the CD approach in the DHS data to estimate the TTP and reported that it was a cost-effective method for measuring infertility in LMICs.

In this study, by referring to Polis’s work\(^ {23}\), we included women ‘at risk’ of pregnancy and collected their information based on the contraceptive calendar. The inclusion criteria were: (1) at the age of 18–44 years, (2) married or cohabitating, (3) sexually active within the past 4 weeks, and (4) not using any birth control method (and had not been sterilized). Women who (1) were currently pregnant, (2) had given birth in the past 3 months or were postpartum amenorrheic, (3) were menopausal or had a hysterectomy or had never menstruated, and (4) had no reproductive calendar data were excluded (Specific inclusion and exclusion of study population are available in Table S11).

We calculated the CD for each woman included in the study. First, we identified reproductive events including pregnancy, live birth, termination, and also the history of contraceptive use and the date of these events. Then women were divided into four groups according to their reproductive characteristics and the CD was calculated: (1) for women who have never used any birth control method but have never conceived, a CD was calculated as the date of interview minus the date of the first cohabitation with a current partner; (2) for women with the most recent event was live birth and did not use contraception since then, a CD was calculated as the date of interview minus duration of postpartum abstinence or duration of postpartum menorrhea whichever was the maximum; (3) for women where the most recent event was termination and did not use contraception since then, a CD was calculated as the date of interview minus date of termination; (4) for women the most recent event was any method of conception but not currently using contraception, a CD was calculated as the date of interview minus date of last contraception used.

Exposure assessment.

The daily mean 2-m air temperature and daily/annual mean surface concentrations of PM\(_{1}\), PM\(_{2.5}\), and PM\(_{10}\) from 2000 to 2018 were obtained using the Modern-Era Retrospective Analysis for Research and
Application, version 2 (MERRA-2) reanalysis product with a 0.5°×0.625° horizontal resolution. The PM was estimated as:

\[
PM_1 = (1.375 \times SO4 + BCPHOBIC + BCPHILIC + 1.8 \times OCPHOBIC \\
+ 1.8 \times OCPHILIC + 0.7 \times DU001 + SS001 + SS002) \times AIRDENS
\]

\[
PM_{2.5} = 1.375 \times SO4SMASS + BCSMASS + 1.8 \times OCSMASS + DUSMASS_{2.5} \\
+ SSSMASS_{2.5}
\]

\[
PM_{10} = (1.375 \times SO4 + BCPHOBIC + BCPHILIC + 1.8 \times OCPHOBIC \\
+ 1.8 \times OCPHILIC + DU001 + DU002 + DU003 + 0.74 \times DU004 \\
+ SS001 + SS002 + SS003 + SS004) \times AIRDENS
\]

where \(SO4, BCPHOBIC, BCPHILIC, OCPHOBIC, OCPHILIC, DU001, DU002, DU003, DU004, SS001, SS002, SS003, \) and \(SS004\) are the surface mixing ratios (kg kg\(^{-1}\)) of sulfate, hydrophobic black carbon, hydrophilic black carbon, hydrophobic organic carbon, hydrophilic organic carbon, dust (bin 001, 0.1-1.0 µm), dust (bin 002, 1.0-1.8 µm), dust (bin 003, 1.8-3.0 µm), dust (bin 004, 3.0–6.0 µm), sea salt (bin 001, 0.03–0.1 µm), sea salt (bin 002, 0.1–0.5 µm), sea salt (bin 003, 0.5–1.5 µm), and sea salt (bin 004, 1.5-5.0 µm), respectively. \(AIRDENS\) represents surface air density (kg m\(^{-3}\)). \(SO4SMASS, BCSMASS, OCSMASS, DUSMASS_{2.5}, \) and \(SSSSMASS_{2.5}\) are surface mass concentrations (kg m\(^{-3}\)) of sulfate, black carbon, organic carbon, dust (PM\(_{2.5}\)), and sea salt (PM\(_{2.5}\)), respectively. MERRA-2 is the latest and first long-term global atmospheric reanalysis to assimilate aerosol observations and represent aerosol-climate interactions from the National Aeronautics and Space Administration (NASA), which was well evaluated and adopted in studies of premature mortality. The 2-m air temperature and surface concentrations of PM\(_1\), PM\(_{2.5}\), and PM\(_{10}\) were bilinearly interpolated into the DHS geocoded residential address.

We assigned daily PM\(_1\), PM\(_{2.5}\), and PM\(_{10}\) exposure for each woman from the date they were trying to become pregnant to the date of the interview, by spatially matching the DHS geocoded locations (longitude and latitude) with the gridded PM concentration. In this study, the date trying to become pregnant was calculated as the date of the interview minus the CD period. Given that the TTP is the number of menstrual cycles, we further averaged the daily PM concentration as monthly exposure for statistical analysis. To adjust for the potential confounding effect of ambient temperature, we also collected daily mean temperatures and assigned monthly exposure for each woman as we did for PM exposure.

**Estimation of the TTP and infertility prevalence.**

Commonly, the CD is regarded as backward recurrence times. Based on the assumptions that the pregnancy attempts happens at a constant rate (stationarity), and the distribution of TTP is independent
of calendar time, the CD can be used to infer an underlying distribution of TTP by applying survival methods that based on the theory of backward recurrence time 42.

We estimated the survival function of TTP from the CD using parametric survival methods relying on the Yamaguchi distribution 42. The corresponding 95% CIs were calculated using bootstrap methods with 500 samples 23,42. The CD was censored after 36 months as in previous studies 23,41. From the estimated survival function, we extracted the estimations and 95% CIs for the median TTP and prevalence of infertility (i.e., the proportion of women not yet pregnant by 12 months of trying according to the WHO definition 32). We further estimated the prevalence of primary (among nulliparous women) and secondary infertility (among parous women), as well as the infertility prevalence in women with and without ever terminated pregnancy separately, by demographic characteristics, age (18–34 vs. 35–44 years), education (no education, primary, secondary or higher education), residence (urban vs. rural), wealth index (poorest, poorer, middle, richer, richest), fertility preference (“does not want another birth soon” vs. “wants birth soon, now or within next nine months”), and knowledge of any modern contraceptive method (yes vs. no).

**Examination of the effects of air pollution on fecundity.**

The estimation of underlying TTP distribution from CD favors the accelerated-failure-time (AFT) model, therefore we used AFT to estimate the effects of air pollution exposure on fecundity. Since the observed CD follow the same structure as TTP 42, the effects of exposure on CD is also an effective estimation of the exposure on TTP 43. The AFT model has been previously applied to CD data 43,44.

As the PM exposure was time-varying, we treated the data as a counting process format and applied the advanced AFT model for effect estimation by risk sets, which enabled us to estimate the effect of PM exposure on the time of achieving pregnancy for each cycle conditioned on pregnancy failure in the previous cycle. Parametric AFT models were used for effect estimation 45, with the CD censored after 36 months 23,41. The AFT model is constructed as follows:

$$
\log(CD_i) = \alpha + \beta_{PM}x_{PM} + \beta_1x_1 + \cdots + \beta_px_p + \epsilon_i
$$

in which \(i\) represents the individuals and \(\log(CD_i)\) represents their log-transformed survival time. \(x_1\) to \(x_p\) are the covariables with the coefficients \(\beta_1\) to \(\beta_p; \epsilon_i\) is the residual. \(x_{PM}\) is the PM exposure (including PM\(_1\), PM\(_{2.5}\), and PM\(_{10}\), respectively) and \(\beta_{PM}\) is the coefficient of each PM exposure per 10µg/m\(^3\) increments in the PM concentration. To interpret the effect estimations easier, we further transformed \(\beta_{PM}\) to fertility time ratio (FTR, the exponential of \(\beta_{PM}\)). In the model, we set the coefficients as the expected time for achieving pregnancy, thus an FTR > 1 (i.e. \(\beta > 0\)) indicates that females tend to have longer times to conceive, i.e., reduced fecundity.

We ran both unadjusted and adjusted models. In the unadjusted models, we only included the PM exposure and residential cluster (residential cluster defined by the DHS as a sampling unit), which was
included as the random effect. In the adjusted models, we additionally included age, education, residence, body mass index, wealth index, parity, and mean temperature. The mean temperature was also treated as a time-varying covariate and included as a monthly temperature quintile in the adjusted models. We applied the above AFT models for each country and also the whole study sample. When the study population was from multiple survey waves (for Bangladesh, Nepal, and the whole studied sample), we additionally included survey waves (as a category variable) in the models.

We also conducted stratified analyses by age (18–34 vs. 35–44 years), parity (nulliparous vs. parous), education (no education, primary, secondary, or higher education), residence (urban vs. rural), and wealth index (poorest, poorer, middle, richer, richest). Cochran Q tests were performed to examine the heterogeneity among different subgroups.

**Examination of the TTP extension burden attributable to particulate matters.**

We further estimated the extended TTP attributable to particulate matters for the included countries in the survey years. We used a standard method of attributable risk assessment:

$$AF_{i,t} = 1 - \frac{1}{FTR_i (C_i - C_0)/10}$$

in which $i$ is the country, $FTR_i$ is the estimate of the association between PM exposure and TTP, $C_i$ is the annual averaged PM level of each country in the survey years, and $C_0$ is the recommended average annual level of PM based on the global air quality guideline released by WHO in 2021, which is 15 µg/m$^3$ for PM$_{10}$, and 5 µg/m$^3$ for PM$_{2.5}$, respectively. As there is no WHO guideline for PM$_1$, we still used the 5 µg/m$^3$ recommended average annual level. Therefore, $AF_{i,t}$ can be explained as the attributable fraction of TTP extension since the PM exposure is beyond the WHO recommended exposure level.

Then the attributable number of TTP extensions was estimated as:

$$AN_{i,t} = N_{i,t} \times MedianTTP_{i,t} \times AF_{i,t}$$

here, $N_{i,t}$ is the average number of females of reproductive age (15–49 years) of each country in the survey years, which was obtained from World Population Prospects 2022, United Nations. $Median TTP_{i,t}$ is our estimated TTP for each country. Therefore, $AN_{i,t}$ can be explained as the extended months of TTP attributable to PM exposure beyond the WHO recommended exposure level.

**Sensitivity analyses.**

Multiple sensitivity analyses were performed to examine the robustness of TTP estimation and the association between air pollution and fecundity. First, to account for potential delayed pregnancy recognition, we performed a simulation study to account for possible pregnancy recognition bias. We simulated a random month of delay across 0 to 3 months before the inclusion interview with a normal
distribution (mean = 1.5, sd = 0.5). The simulated delay months were subtracted from the originally observed CD. Then, we used newly calculated CD to estimate the TTP and infertility, as well as the association of air pollution with fecundity. Second, couples’ attempts to pregnant in a population may vary with time, e.g., a seasonal pattern of pregnancy planning was observed in previous studies. In this case, the stationarity assumption under which CD can be used to estimate the TTP would be violated, leading to bias. To test and address this issue, we repeated the main analyses examining the effects of air pollution on fecundity by adding the season of initiation in the models. Third, although the questionnaire of the DHS survey has been evaluated and validated, potential recall bias may also exist and bias our estimation. In addition, we estimated TTP relying on the assumptions of stationarity, which tends to hold for shorter intervals. Thus, we restricted our samples to a CD of less than 24 and 12 months to re-estimate the associations. Fourth, we used multiple imputations to deal with missing values of covariates. We used fully conditional specification methods with 400 iterations to generate 5 imputed datasets. Then we repeated the main analysis using each complete dataset and summarized the results based on Rubin’s rules.

We cleaned the DHS data and calculated CD using Stata 15.0 (StataCorp LP, College Station, TX, USA). All statistical analyses were performed with R (version 4.1.1; R Development Core Team), and packages “survival”, and “eha” were used. All tests were two-sided, and a $P$-value of < 0.05 was considered to be statistically significant.

**Declarations**

**Data availability**


**Code availability**

Our computer codes are accessible to researchers upon request to the corresponding author.

**Competing interests**

The authors declare no competing interests.

**References**


**Figures**
Figure 1

Survival function for the time-to-pregnancy and infertility prevalence estimated using a CD approach. Infertility prevalence is defined by the probability of not having conceived within 12 months. Solid blue lines represent the curves for the estimated time-to-pregnancy while dotted lines represent the 95% confidence intervals around those curves.
Figure 2

The spatial patterns of the studied samples and PM$_{2.5}$ concentrations. Shadings are PM$_{2.5}$ concentrations ($\mu g/m^3$) and black dots indicate the location of each survey cluster. The table below shows the average annual particulate exposure of the study countries and the eligible women. PM: particulate matter.
Figure 3

Association between fertility time and particulate matter exposure (per 10 μg/m³): Analysis by country.
FTR: Fertility Time Ratio; In the model without adjusting for covariates, only the survey cluster (residential cluster defined by DHS as a sampling unit) was included as the random effect. In the models that adjusted for covariates, age (15-17, 18-24, 25-34, 35-44, 45-49 years), education (no education, primary, secondary or higher education), residence (urban or rural), body mass index (normal, overweight or obese, or underweight), wealth index (poorest, poorer, middle, richer, richest), parity (nulliparous or parous), and mean temperature were additionally adjusted.
### Figure 4

**Association between fertility time and particulate matters (per 10 μg/m³) in subgroups.** The P-value of Cochran's Q test is shown on the right side of the figure. PM: particulate matters; The models were adjusted for age (15-17, 18-24, 25-34, 35-44, 45-49 years), education (no education, primary, secondary or higher education), residence (urban vs. rural), body mass index (normal, overweight or obese, or underweight), wealth index (poorest, poorer, middle, richer, richest), parity (nulliparous, parous), mean temperature, and survey cluster (included as a random effect).

### Supplementary Files

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- SupplementaryInformation.docx