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Reduced human fecundity attributable to ambient fine particles in low- and middle-income countries

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ABSTRACT

Background: Exposure to ambient fine particulate matter ($PM_{2.5}$) has been associated with reduced human fecundity. However, the attributable burden has not been estimated for low- and middle-income countries (LMICs), where the exposure–response function between $PM_{2.5}$ and the infertility rate has been insufficiently studied.

Objective: This study examined the associations between long-term exposure to $PM_{2.5}$ and human fecundity indicators, namely the expected time to pregnancy (TTP) and 12-month infertility rate (IR), and then estimated $PM_{2.5}$-attributable burden of infertility in LMICs.

Methods: We analyzed 164,593 eligible women from 100 Demographic and Health Surveys conducted in 49 LMICs between 1999 and 2021. We assessed $PM_{2.5}$ exposures during the 12 months before a pregnancy attempt using the global satellite-derived $PM_{2.5}$ estimates produced by Atmospheric Composition Analysis Group (ACAG). First, we created a series of pseudo-populations with balanced covariates, given different levels of $PM_{2.5}$ exposure, using a matching approach based on the generalized propensity score. For each pseudo-population, we used 2-stage generalized Gamma models to derive TTP or IR from the probability distribution of the questionnaire-based duration time for the pregnancy attempt before the interview. Second, we used spline regressions to generate nonlinear $PM_{2.5}$ exposure–response functions for each of the two fecundity indicators. Finally, we applied the exposure–response functions to estimate number of infertile couples attributable to $PM_{2.5}$ exposure in 118 LMICs.

Results: Based on the Gamma models, each 10 $\mu g/m^3$ increment in $PM_{2.5}$ exposure was associated with a TTP increase by 1.7 % (95 % confidence interval [CI]: -2.3 %–6.0 %) and an IR increase by 2.3 % (95 %CI: 0.6 %–3.9 %). The nonlinear exposure–response function suggested a robust effect of an increased IR for high-concentration $PM_{2.5}$ exposure (>75 $\mu g/m^3$). Based on the $PM_{2.5}$-IR function, across the 118 LMICs, the number of infertile couples attributable to $PM_{2.5}$ exposure exceeding 35 $\mu g/m^3$ (the first-stage interim target recommended by the World Health Organization global air quality guidelines) was 0.66 million (95 %CI: 0.061–1.43), accounting for 2.25 % (95 %CI: 0.20 %–4.84 %) of all couples affected by infertility. Among the 0.66 million, 66.5 % were within the top 10 % high-exposure infertile couples, mainly from South Asia, East Asia, and West Africa.

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Conclusion: $PM_{2.5}$ contributes significantly to human infertility in places with high levels of air pollution. $PM_{2.5}$-pollution control is imperative to protect human fecundity in LMICs.

1. Introduction

Human fertility rates are declining worldwide, with the total fertility rate (the average number of children per woman) falling from 3.3 in 1990 to 2.3 in 2021. (Skakkebæk et al., 2006) Reduced human fecundity is an important, but neglected, public health issue that not only has profound psychological and financial costs for individual couples but also influences the demographic structure and economic development in an aging world. (Martins et al., 2011; Hanna and Gough, 2020; Dyer and Patel, 2012; Cousineau and Domar, 2007; Ledger, 2009) There were 45.0–52.6 million infertile couples worldwide in 2010, and the infertility prevalence was highest in South Asia, followed by Sub-Saharan Africa. (Mascarenhas et al., 2012) It is critical to identify modifiable or preventable risk factors for infecundity to mitigate this public health and societal problem. (Smarr et al., 2017) Due to the complexities embedded in biological and behavioral factors affecting human reproduction, fecundity is difficult to measure directly at individual level. A few clinical indicators measuring reproductive function, including biomarkers of follicular reserve, such as the antral follicle count and anti-Müllerian hormone in women or semen quality in men are commonly used as proxy measures. (Guan et al., 2020; Feng et al., 2021; Kim et al., 2021; Zhang et al., 2023) However, these indicators are often from one partner alone, and cannot represent the fecundity of the couple as a whole. The time to pregnancy (TTP) and infertility rate (IR) can be efficiently applied to comprehensively measure couple's fecundability at the population level. TTP represents the number of calendar months or menstrual cycles required to become pregnant, so a longer TTP indicates reduced fecundity. (Eisenberg et al., 2021) It can be used to quantify the probability of infertility, which is defined by World Health Organization (WHO) as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. These two indicators could be estimated through population-based reproductive survey.

Air pollution, particularly its component of fine particulate matter ($PM_{2.5}$), is thought to play a role in infertility but the results are mixed. For example, a study conducted in the Czech Republic reported that $PM_{2.5}$ exposure was associated with a short-term decrease in couple's ability to conceive. (Slama et al., 2013) A recent study in China also found that $PM_{2.5}$ exposure was associated with reduced human fecundity, as evidenced by both a longer TTP and greater odds of infertility. (Li et al., 2021) By contrast, two studies conducted in the United States reported nonsignificant associations between $PM_{2.5}$ exposure and infertility. (Mahalingaiah et al., 2016; Nobles et al.,2018) The different study populations, study designs, and exposure levels might account for these inconsistent results, which suggest that the association should be investigated in a multicenter study, particularly in the populous low- and middle-income countries (LMICs).

The burden of $PM_{2.5}$-related infecundity has not been estimated for LMICs, where both IR and the baseline number of childbearing couples are much higher than in high-income countries. The main barrier to estimating the adverse impact of $PM_{2.5}$ on infecundity is the scarcity of population-based longitudinal surveys of infertility. Epidemiologic designs commonly used to estimate infertility include incident and prevalent perspective cohorts or pregnancy-based retrospective studies, but are not feasible at a national level, particularly in resource-poor LMICs. The current duration (CD) approach has been applied in cross-sectional studies to estimate TTP and infertility prevalence. (Polis et al., 2017) This approach identifies couples attempting to become pregnant at the time of an interview, and measures their fecundity using the current length of time trying to become pregnant (i.e., the CD value). A distribution of TTP can be estimated from the observed CDs using classical survival analysis methods. IR estimated based on the CD approach is consistent with those from prospective cohort studies. (Louis et al., 2013; Thoma et al., 2013) Therefore, CD is a feasible approach for monitoring human fecundity and its association with $PM_{2.5}$ exposure in LMICs.

To fill the knowledge gap regarding the burden of infertility attributable to air pollution, we performed a multi-country epidemiological study based on the Demographic and Health Surveys (DHS) dataset, and applied the CD approach to evaluate the association between $PM_{2.5}$ exposure and infecundity. We derived exposure–response functions based on the estimated effect of $PM_{2.5}$ on TTP and IR in 49 LMICs, and extrapolated those functions to estimate the burden of $PM_{2.5}$-related infertility in 118 LMICs.

2. Method

2.1. Study population

The study population was extracted from the DHS Program, which is described in detail online (https://dhsprogram.com/). Briefly, a full birth history and reproductive calendar recording the status of births, pregnancies, and contraceptive use before the interview date were collected from women aged 15–49 years old. Information was also collected on sociodemographic characteristics, health history, sexual behaviors and attitudes, fatherhood, birth expectations, and the characteristics of current and former cohabiting partners.

Our target study population was women attempting to get pregnant when interviewed, so the inclusion criteria were 18–44 years old, married or cohabitating, sexually active within the past 4 weeks, and not currently using contraception. We excluded women who were currently pregnant, had given birth in the past 3 months, had postpartum amenorrhea, had never menstruated, were menopausal, or had a hysterectomy or declared infecundity, had inconsistent reporting times, and had missing CD values (described below). Because of the limited availability of data on $PM_{2.5}$ concentrations, we analyzed geocoded survey data for the period 1999–2021. However, 29 surveys with surprisingly high IR values were excluded (Supplementary Fig. 1). We did this based on a previous study that indicated that a serious departure from the assumption of a constant rate over calendar time (see Methods section) would lead to unrealistically high IR values. (Keiding et al., 2021) Ultimately, the analysis included 164,593 eligible women from 100 surveys conducted in 49 LMICs. Supplementary Tables 1 and 2 present the survey-specific stepwise selection of the eligible population and survey-specific estimated TTP and infertility prevalence.

2.2. Health outcomes

Referring to previous studies, including those that have used DHS data, (Keiding et al., 2021; Polis et al., 2017) we calculated the CD in months based on the following self-reported events and their corresponding times. Based on replies to questions about birth history, reproductive calendar, and the contraception of each woman, a CD value was assigned based on the following variables: date of first cohabitation or intercourse with current partner, date of last contraceptive usage, date of last terminated birth, date of last livebirth, duration of postpartum abstinence and amenorrhea after the delivery of last livebirth, and date of interview. For women who had never conceived, CD was calculated as the interview date minus the date of first cohabitation or intercourse with the current partner; for women whose latest event was birth termination, CD was calculated as the date of the interview minus the date of termination; for women whose latest event was a livebirth, CD was calculated as the date of the interview minus the date of the last livebirth, and then minus the maximum duration of postpartum abstinence and postpartum amenorrhea. Finally, if women had ever used any contraception method, their CD was replaced by a new value defined as the interview date minus the date of last contraceptive usage when this new value was smaller than the original one.

If being pregnant is a stochastically repeated event (like residential mobility or hospital visit), its probability can be modeled using a hazard and survival function. According to Keiding et al. (2002), CD is a type of *backward recurrence time* (i.e., an interval starting from the interview date and going back to the timestamp of last pregnancy), given the stationarity assumption that a pregnancy attempt occurs at a constant rate over time. In comparison, the TTP, collected by prospective studies, is a type of *forward recurrence time*. Either backward or forward recurrence time can be utilized to estimate the probability of being pregnant, using the survival model. Next, we derived interpretable statistics, such as expected TTP and IR, from the estimated survival curve, and regressed them against different exposure levels. Furthermore, based on bootstrapped survival curves, we also obtained the confidence intervals (CIs) for those statistics. In this study, we calculated the expected TTP or IR as the month when 50 % of women became pregnant, or the proportion of women who were not yet pregnant after attempting for 12 months (i.e., TTP > 12 months), respectively.

2.3. Exposure assessment

We obtained monthly ground-level $PM_{2.5}$ concentrations from a global dataset during 1998–2021 across a regular $0.01^\circ \times 0.01^\circ$ grid produced by the Atmospheric Composition Analysis Group (ACAG, https://sites.wustl.edu/acag/datasets/surface-pm2-5-archive/#V5.GL.03). These global estimates combine satellite retrievals of aerosol optical depth, chemical transport modeling, and ground-based measurements. Compared with ground-monitored $PM_{2.5}$, the overall accuracy was high ($R^2 = 0.84$ [0.81–0.86]), and the deviance was low (root mean square error = 8.4 [8.3–8.5] $\mu g/m^3$). (van Donkelaar et al., 2021) The gridded $PM_{2.5}$ concentrations were matched to each woman using their geocoded longitude and latitude. We defined three types of $PM_{2.5}$ exposure. First, we calculated the average $PM_{2.5}$ concentration for 12 months before the pregnancy attempt, and the start time of pregnancy preparation was calculated as the date of the interview minus the CD period. Second, we calculated the average $PM_{2.5}$ concentration for the 24 months before the pregnancy attempt. Finally, we also evaluated the effect of $PM_{2.5}$ during pregnancy attempt, which was calculated from the starting time of pregnancy preparation to the time of the interview (truncated at 36 months), i.e., the "exposure during pregnancy attempt." The average $PM_{2.5}$ of 1-year before pregnancy attempt was our primary exposure, because exposure during pregnancy attempt might be influenced by the length of attempt duration, potentially introducing bias when considering temporal trend in $PM_{2.5}$ concentration. (Sheridan et al., 2023) Finally, to control for environmental confounders, we obtained monthly temperatures (Muñoz Sabater, 2019) and levels of light at night (Li et al., 2020) from global products. The two variables were prepared in the same way as $PM_{2.5}$.

2.4. Statistical analyses

We investigated the association between $PM_{2.5}$ exposure and two important indicators of fecundity: TTP and IR. We implemented a generalized propensity score (GPS) matching approach to estimate the adverse effects of $PM_{2.5}$. The GPS-matching approach is an innovative causal inference method described by Wu *et al.* to address continuous exposure to an external factor. (Wu et al., 2022) Briefly, it creates a series of pseudo-populations, for which the distributions of the pre-exposure covariates are exchangeable across different exposure levels (i.e., predetermined small bins of continuous exposure concentrations). In the main analysis, we specified 30 equal disjoint bins ($j = 1, 2, \dots 30$), each of which was assigned a level of exposure (x_j) calculated as the centroid concentration of that bin (i.e., [max–min]/2). For each sample (i), a series of GPSs ($\boldsymbol{s}_i = [s_{i,1} \dots s_{i,30}] = [s_{i,j}]$) could be derived, according to the probabilities of exposure assignment, which were estimated using a 'gradient boosting machine' regression that linked pre-exposure covariates to the categorical exposure level (j). Then, for a specific exposure level (j), each individual ($i = 1, \dots, n$) with its GPS ($s_{i,j}$) predicted based on the exposure level was used in turn as the matching template, to select a original sample (i^*) with the observed exposure level of j and a similar estimated GPS (s_{i^*j}) based on Manhattan $L1$ distance. Replacement was allowed for the selection. Finally, a covariate-balanced pseudo-population of size n was created for each predetermined exposure level (j) for further analysis.

The covariates were categorized as pre- and post-exposure. Pre-exposure covariates were those before the pregnancy attempt, including the year when pregnancy preparation started, baseline maternal age, parity, number of previous births, sex of household head, wealth index, fertility preference, ideal number of children, insurance coverage, and temperature. Satellite-based data on the level of light at night was also considered as indicators of community-level socioeconomic status. (Mellander et al., 2015; Pérez-Sindín et al., 2021) Post-exposure covariates were variables that might change over time and included years of education, maternal body mass index, maternal smoking, maternal employment, household income, and type of energy used for cooking. Because involving post-exposure covariates can violate the requirement of temporal order in causal inference, the GPSs were estimated using the pre-exposure covariates only.

We used two parametric models to estimate the distribution of duration time (T_i) for the pregnancy attempt; first, equation (1):

$$T_{i,j} \sim \mathrm{Dist}(\theta_j),\ \mathrm{Dist} = \textit{Weibull} \text{ or } \textit{generalized Gamma},\ \text{for the } j^{\text{th}} \text{pseudo-population} \quad (1)$$

where T_i was measured using the backward recurrence time (i.e., CD), and Dist() denotes its probability distribution characterized by the parameters $\boldsymbol{\theta}$. We utilized the flexible generalized Gamma distribution ($\boldsymbol{\theta} = [\lambda, \gamma_1, \gamma_2]$) for the main model, and the Weibull distribution ($\boldsymbol{\theta} = [\lambda, \gamma]$) as an alternative for the sensitivity analysis.

To estimate the effect of $PM_{2.5}$ on the time (T_i), let's first considered a simple linear model, assuming that exposure affects only the distribution via the scale parameter (λ):

$$T_{i,j} \sim \mathrm{Dist}(\lambda_j, \gamma), \exp(x_j\beta) \propto \lambda_j \quad (2)$$

With this assumption, the log-transformed expected time (E_j), which is also the expected TTP in this study, is proportional to the exposure. When the outcome is modelled using the Weibull distribution, the regression is also known as the accelerated failure time (AFT) model. The relationship between $PM_{2.5}$ and IR is nonlinear and can be obtained from the cumulative probability function.

Generally, we can introduce a complex model by letting the exposure affect both scale and shape parameters in nonlinear ways. The GPS-matching method provides a flexible way to explore the effects of a two-stage model:

$$\text{Stage 1}: T_{i,j} \sim \mathrm{Dist}(\boldsymbol{\theta}_j),$$

$$\begin{aligned}\text{Stage 2}: &\ \mathrm{Log}[M_j(T)] \sim f_1(x_j),\\ &\ \mathrm{Log}(IR_j) = \mathrm{Log}[1 - \mathrm{CDF}_j(T < 12)] \sim f_2(x_j)\end{aligned} \quad (3)$$

where $M_j()$ and $\mathrm{CDF}_j()$ denote the conditional median and cumulative probability functions estimated from the first stage, respectively, and $f_1()$ and $f_2()$ denote two separate spline smoothing functions to characterize the nonlinear effects of $PM_{2.5}$ on TTP and IR, respectively. To incorporate the uncertainties in the stage 1 estimates, we used meta-regression models in stage 2. We selected the two-stage Gamma model as our primary model, considering that it was complex enough to account for more uncertainties. We evaluated the linear effects as the time ratio (TR) or IR ratio (IRR), which can be interpreted as the fold increase in TTP or IR, respectively, for each 10 μg/m^3 increment in $PM_{2.5}$. Therefore, TR > 1 indicates delayed pregnancy or reduced human fecundity.

We performed multiple sensitivity analyses to test the robustness of the estimated associations. First, we reanalyzed the effects with different numbers of bins (i.e., 20 and 40 bins) using the GPS-matching approach. Then, in addition to $PM_{2.5}$ exposure before the pregnancy attempt, we analyzed the effects of $PM_{2.5}$ exposure during the pregnancy attempt on TTP. Next, we excluded CD values greater than 48 or 72 months in the one-stage AFT model, and then reanalyzed the association. Finally, to examine potential modifiers of the association, we conducted interaction analyses using both pre- and post-exposure covariates in the one-stage AFT model. The statistical significance of the interaction between each modifier and $PM_{2.5}$ was determined using the Wald test.

2.5. Risk assessment

Based on the estimated nonlinear exposure–response functions (ERFs; equation (3), to assess spatial variation in the $PM_{2.5}$-associated increases in IR, we conducted a risk assessment across a study domain of 118 LMICs (there are 140 LMICs in total; 22 countries were excluded from the analysis, as described in the supplementary material), where the baseline numbers on pregnancies are available by pixels. Due to the lack of country-specific baseline TTPs and country-specific 12-month infertility rates, we calculated only the attributable number (AN) of infertile couples in 2015 using the following set of equations:

$$\mathrm{AN}_s = \mathrm{AF}_s \times \mathrm{N}_s,$$

$$\mathrm{AF}_s = 1 - 1/\exp[f(x_s)]$$

$$\mathrm{N}_s = \mathrm{IR}_{s\in r}/(1 - \mathrm{IR}_{s\in r}) \times \mathrm{P}_s \quad (4)$$

where s and r represent spatial pixels and regions defined by the WHO (https://www.who.int/about/who-we-are/regional-offices), respectively; AF_s is the attributable fraction of the increased IR calculated using the nonlinear ERF (f); x_s is the average $PM_{2.5}$ concentration in 2014; N_s is the baseline number of infertile couples; and IR is the region-specific 12-month infertility rate reported by Cox *et al.* (Cox et al., 2022) The unavailable infertility rate of Southeast Asia was interpolated using that rates of neighboring regions. P_s is the gridded number of pregnancies during 2015, generated by the WorldPop dataset. Uncertainties associated with the ERFs and prevalence of infertility were considered in the estimations using a Monte Carlo approach. We first ranked the cities by the level of risk (i.e., AF), from low to high. Next, we generated a plot of the cumulative probability of $PM_{2.5}$-related infertile couples against that of all infertile couples. The plot is also known as the Lorenz curve, which has been utilized to illustrate the inequality in disease burden. (Xue et al., 2023)

All analyses were performed using R software (4.2.0; R Core Team, Vienna, Austria). Statistical inference was performed using the R packages *survival* and *CausalGPS*.

3. Results

3.1. Description

The majority of the 164,593 women attempting to become pregnant were from Sub-Saharan Africa (66.4 %) or South Asia (14.2 %). Nigeria accounted for 13.3 % (21,874), Senegal for 9.4 % (15,484), and India for 7.7 % (12,610) of the total, with the remaining 46 countries contributing for 69.6 % (Figure S1). Their average current age was 30.4 (standard deviation 7.3) years; 36.7 % of these women were unemployed; 63.5 % did not have insurance; 14.0 % were nulliparous; 17.8 % were overweight or obese; and 70.7 % wanted to have another child (Supplementary Table 3). Supplementary Table 3 gives more details on the study participants and compares the included and excluded women. Supplementary Table 4 gives the $PM_{2.5}$ exposure levels of the participants. The median $PM_{2.5}$ exposure during the previous 12 months before pregnancy attempt was 38.3 μg/m^3, with a wide range ($P_{2.5}$–$P_{97.5}$ = 12.2–95.0 μg/m^3). The $PM_{2.5}$ exposure hotspots included South Asia, the Sahara region, and Northwest China (Supplementary Fig. 2).

For the eligible women in each survey, the median TTP and IR were estimated from the distribution of CD (Supplementary Table 2). Overall, the median TTP was 7.5 (interquartile range [IQR] 4.9–9.7) months and the median IR was 38.9 % (IQR: 31.9–43.9 %). Women who lived in Sub-Saharan Africa had a longer median TTP and higher IR, with large ranges of the median TTP (2.4–17.5 months) and infertility (20.1–56.1 %).

After the GPS-matching process, we assessed whether covariates were balanced among different exposure levels and found that all covariates met the criteria (absolute correlation < 0.1, Figure S3). In other words, these covariates in the pseudo population were independent of $PM_{2.5}$ exposure and did not require further adjustment in subsequent analysis.

3.2. Association between $PM_{2.5}$ and TTP

Fig. 1a shows the association between $PM_{2.5}$ exposure and TTP. The two-stage Gamma model was our main model, and a non-significant effect was found. Each 10 μg/m^3 increment in the 1-year $PM_{2.5}$ exposure before the pregnancy attempt was associated with a 1.7 % (95 %CI: -2.3 %–6.0 %) longer TTP. However, in the Weibull distribution model, $PM_{2.5}$ exposure was significantly associated with a longer TTP, suggesting reduced fecundity. With each 10 μg/m^3 increment in the 1-year $PM_{2.5}$ exposure before the pregnancy attempt, the TRs of the one- and two-stage Weibull models were 1.08 (95 %CI: 1.07–1.10) and 1.10 (95 %CI: 1.09–1.11), respectively. The estimated effects were consistent and robust with different exposure assessments, different bins in the GPS-matching process, or different CD values censored in the one-stage AFT model (Supplementary Figure 4). Generally, the effect of $PM_{2.5}$ exposure during pregnancy attempt was smaller. With each 10 μg/m^3 increment in the $PM_{2.5}$ exposure during pregnancy attempt, the TRs of the one-stage and two-stage Weibull models were 1.03 (95 %CI: 1.02–1.04) and 1.04 (95 %CI: 1.01–1.07), respectively, which were not significantly different from that of our main model (i.e., the two-stage Gamma model, TR = 1.00 [95 %CI: 0.94–1.06]), given the uncertainty. Supplementary Figure 5 shows the subpopulation effects. The estimated effect was robust among subpopulations stratified by most of the characteristics. We found that the adverse effect of $PM_{2.5}$ on TTP was stronger in women who attempted to become pregnant at an advanced age. In addition, women who were richer, overweight or obese, smoked, and reported a smaller ideal number of children might be sensitive to the $PM_{2.5}$-related longer TTP.

Setting the theoretical minimum risk exposure level to the average $PM_{2.5}$ exposure after GPS-matching, the nonlinear ERF of the three models showed different patterns. The ERF of the Weibull model had an increasing TR with no threshold, while that of the two-stage Gamma model suggested a J-shaped curve with the lowest TR occurring at the exposure level of ∼ 70 μg/m^3. The inconsistent results among the three models suggested reduced robustness of the $PM_{2.5}$-related effect on TTP; therefore, we did not estimate the disease burden of TTP further.

3.3. Association between $PM_{2.5}$ and infertility rate

Fig. 1b also shows the association between the 1-year $PM_{2.5}$ exposure before pregnancy attempt and IR. All three models gave robust results.

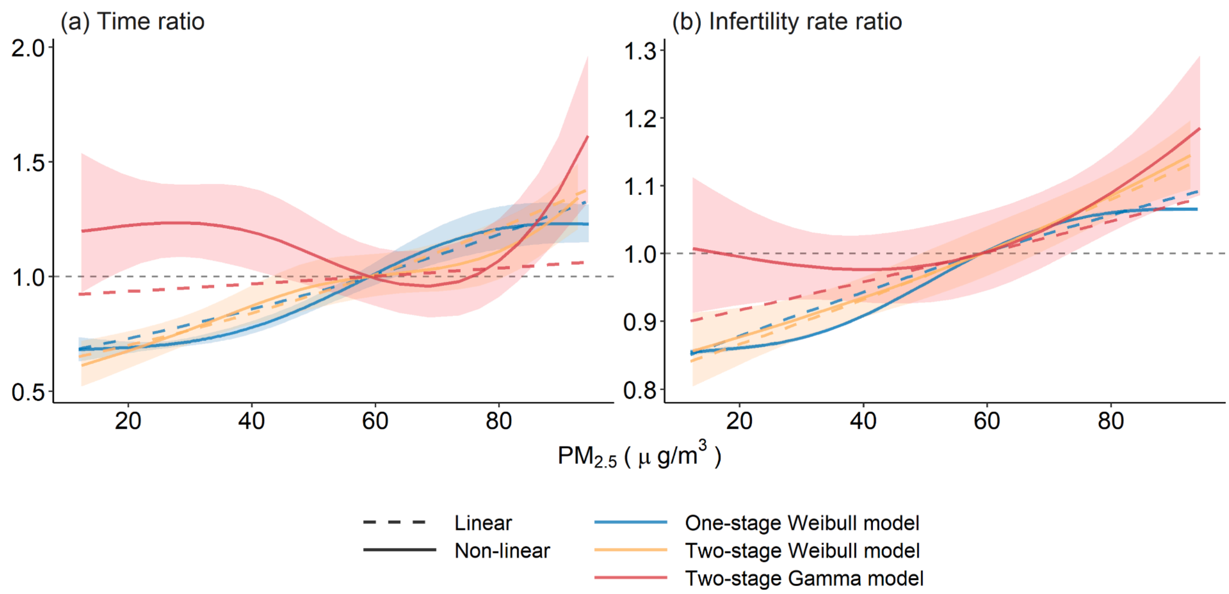

Fig. 1. The linear and nonlinear exposure–response function of $PM_{2.5}$ exposure and time to pregnancy (a) and infertility rate (b). We set the average $PM_{2.5}$ exposure (59 μg/m^3) after GPS-matching process as the reference level.

In the primary two-stage Gamma model, each 10 μg/m^3 increment in $PM_{2.5}$ was associated with a 2.3 % (95 %CI: 0.6–3.9 %) increase in IR. The IR estimated by the two-stage Weibull model was 3.7 % (95 %CI: 3.4–4.1 %). In sensitivity analysis (Supplementary Figure 6), the point-estimated effects of the Gamma model were robust but became slightly smaller when the number of matching bins was 20 (1.3 % [95 %CI: -0.4 %–3.1 %]) or 40 (0.6 % [95 %CI: -0.7 %–2.0 %]), or when estimating 2-year $PM_{2.5}$ exposure before the pregnancy attempt (1.8 % [95 %CI: 0.6 %–3.0 %]) or exposure during the pregnancy attempt (0.7 % [95 %CI: -2.3 %–3.7 %]). The nonlinear ERF of the three models had a similar pattern. The ERFs of the Weibull models suggested increasing adverse effects of $PM_{2.5}$ on IR with no threshold. Although the ERF of the two-stage Gamma model was stable, particularly, for the obvious increasing trend in the IRR corresponding to exposures above 35–40 μg/m^3. Because the two-stage Gamma model considers the larger uncertainty derived from the study design, we used its result to generate the ERF in the risk assessment by resetting the theoretical minimum risk exposure level at IT1 (35 μg/m^3) according to the WHO.

3.4. *Attributable burden of the infertility rate*

The 49 countries analyzed in this study had 16.7 million (95 %CI: 14.8–18.8) infertile couples in 2015. Of these, 0.49 (95 %CI: 0.15–0.99) million or 2.95 % (95 %CI: 0.87 %–5.63 %) were attributable to $PM_{2.5}$ exposure exceeding IT1. Extrapolating this to 118 LMICs, where 29.4 million couples would be affected by infertility, 0.66 million (95 %CI: 0.061–1.43) or 2.25 % (95 %CI: 0.20 %–4.84 %) attributable to $PM_{2.5}$ exposure exceeding IT1. Fig. 2 shows the spatial distribution of infertile couples in the 118 LMICs in 2015. Hotspots included countries in South Asia (India, Pakistan, and Bangladesh), Western Africa (Niger and Nigeria), and East Asia (Nepal and China) (Fig. 2).

Because the estimated nonlinear exposure–response function has a threshold, the spatial distribution of the attributable burden clustered strongly. To explore this, we calculated city-level numbers attributable infertile couples based on a map of level-2 administrative regions (city-level geographic units). We generated a Lorenz curve to visualize the degree of inequality among cities across the 118 LMICs (Fig. 3), and found that nearly 66.5 % of the attributable burden was borne by the top 10 % of high-exposure infertile couples. These infertile couples came from 278 cities in nine countries, which were India, China, Nigeria, Chad, Niger, Bangladesh, Afghanistan, Cameroon, and Pakistan, in order of the attributable number (Fig. 3).

4. Discussion

To the best of our knowledge, this is the first study to provide insight into the effects of $PM_{2.5}$ on human infertility in LMICs. By analyzing DHS data from 1999 to 2021, we found a robust negative association between $PM_{2.5}$ exposure and human fecundity. With each 10 μg/m^3 increment in $PM_{2.5}$ exposure during the year before a pregnancy attempt, the TTP increased 1.7 % and IR increased 2.3 %. In 2015, nearly 0.66 million infertile couples might be attributed to $PM_{2.5}$ exposure in the 118 LMICs. The burden was spatially clustered, and heaviest in South Asia, East Asia, and West Africa.

The negative association between $PM_{2.5}$ exposure and human fertility found here accords with the literature. For outcomes directly related to pregnancy, Slama *et al.* found a 22 % decrease in fecundity with a 10 μg/m^3 increment in short-term $PM_{2.5}$ exposure during the 2 months before unprotected intercourse in the Czech Republic. (Slama et al., 2013) Li *et al.* reported that an 11 % decrease in fecundity was associated with each 10 μg/m^3 increment in the 1-year $PM_{2.5}$ exposure preceding conception. (Li et al., 2021) For outcomes representing fertility factors, $PM_{2.5}$ exposure is negatively associated with sperm concentration, forward motility concentration, and antral follicle count. (Gaskins et al., 2019; Guan et al., 2020; Qiu et al., 2020) $PM_{2.5}$ exposure before oocyte retrieval also decreases the rate of livebirths among women using assisted reproductive technology. (Zhang et al., 2022) An ecological study reported an association between reduced fertility rates and higher traffic-related air pollution levels in Barcelona, Spain. (Nieuwenhuijsen et al., 2014) Two ecological studies conducted in the USA and China also suggested that higher $PM_{2.5}$ pollution levels are associated with lower fertility rates. (Xue and Zhang, 2018; Xue and Zhu, 2018) $PM_{2.5}$ might cause oxidative damage during follicle growth, ovum maturation, and fertilization via excessive reactive oxygen species. (Devine et al., 2012) It might also cause mitochondrial dysfunction and activate apoptotic pathways, further inducing apoptosis in oocytes. (Wang et al., 2021) For males, it could affect sperm production and sperm quality by disrupting the integrity of the blood–testosterone barrier. (Yan et al., 2016).

We used the CD approach to ascertain infertility, which differs from previous studies, which have used retrospective TTP designs, self-reported designs, or prospective TTP designs. Each method has its

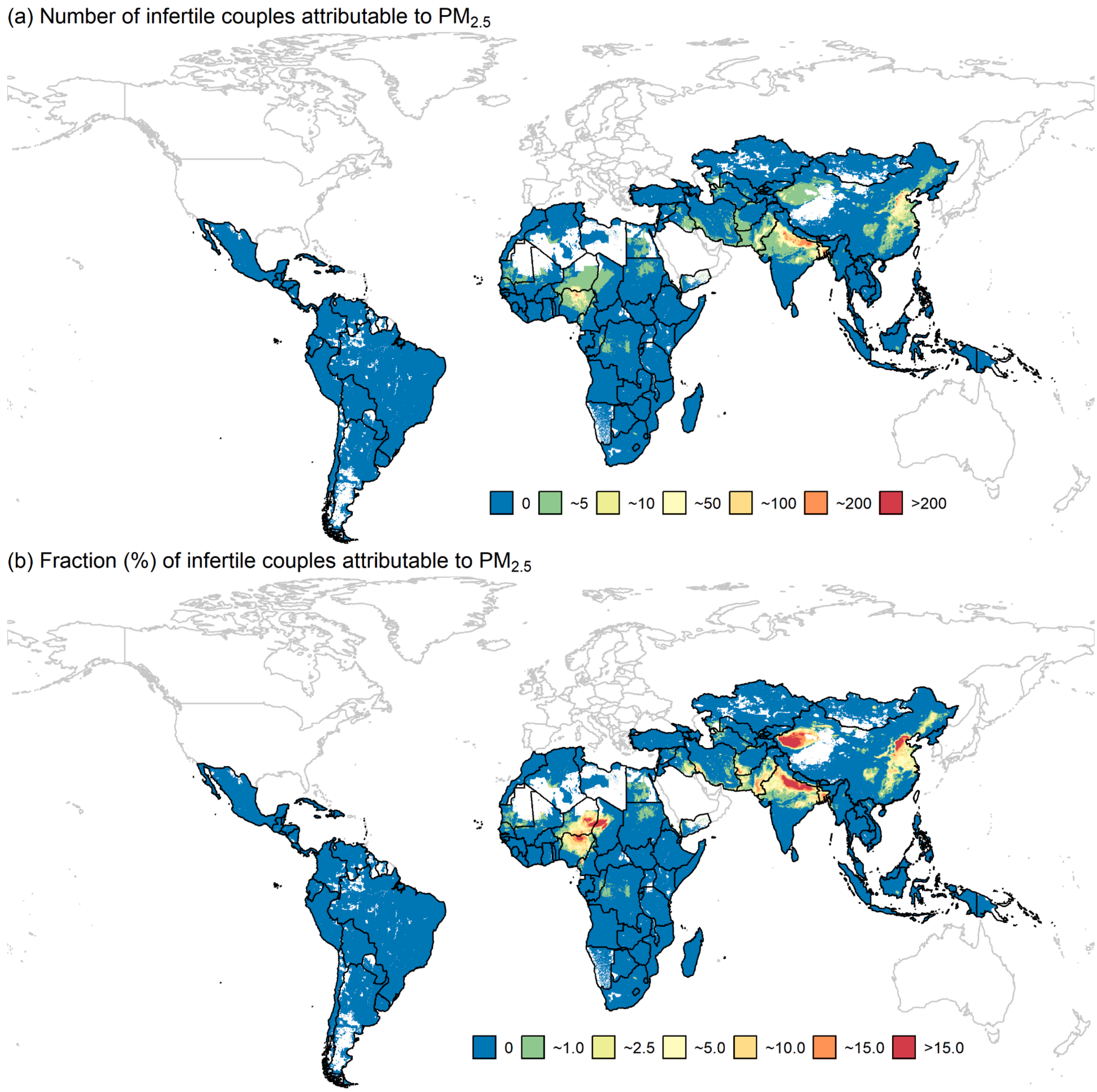

Fig. 2. Infertile couples attributable to $PM_{2.5}$ (>IT1: 35 μg/m^3) of 118 low- and middle-income countries (black boundary) in 2015.

advantages and weaknesses. For example, the most common approach, the retrospective TTP design investigates pregnant women and is more convenient to conduct in medical institutions compared to the prospective TTP design, but it is associated with selection bias as most infertile couples are excluded. The CD approach does not require follow-up, which makes it possible to perform infertility-related studies in LMICs based on a cross-sectional DHS dataset. Under the framework of the CD approach, women who spent a longer period of time attempting to get pregnant were more likely to be over-represented. (Louis et al., 2013) In addition, attenuation bias should not be neglected when addressing risk factors such as $PM_{2.5}$. For example, compared to less-fecund couples, the most-fecund couples were more likely to become pregnant and then dropped from the population attempting to become pregnant. When studying the risk factors for decreased fertility, the less $PM_{2.5}$-exposed couples are depleted more quickly, so the TR between the exposed and unexposed groups would attenuate over time. A previous study suggested that CD has the low attenuation bias but the large variance. (Eijkemans et al., 2019)

Human infertility is a complex multifactorial public health issue that can lead to social stigma, intimate partner violence, and financial distress. (Thoma et al., 2021) Approximately one in six people have been infertile at one point in their lives worldwide. (Cox et al., 2022) Although both male and female causes lead to infertility, women often bear its associated societal burden. (Thoma et al., 2021) Addressing infertility is an important component of sexual and reproductive health and rights, promoting well-being for all people at all ages and achieving sex equality and empowerment of all women and girls. (United Nations, 2015) The present study focused mainly on the biological effects of $PM_{2.5}$ on infertility; however, research has also reported social effects of $PM_{2.5}$ on infertility, such that increased pollution drives up the parental expenditure per child, which increases the marginal costs associated with the number of children and reduces fertility. (Gao et al., 2022) Therefore, understanding the magnitude of $PM_{2.5}$-related infertility is important to be able to develop efficient interventions to protect the ability of reproductive women to decide the number, timing, and spacing of their children. (Cox et al., 2022) Our results suggest that $PM_{2.5}$-related infertile couples concentrate in 9 countries from South Asia, Western Africa, and East Asia, where were coincidence of poor air

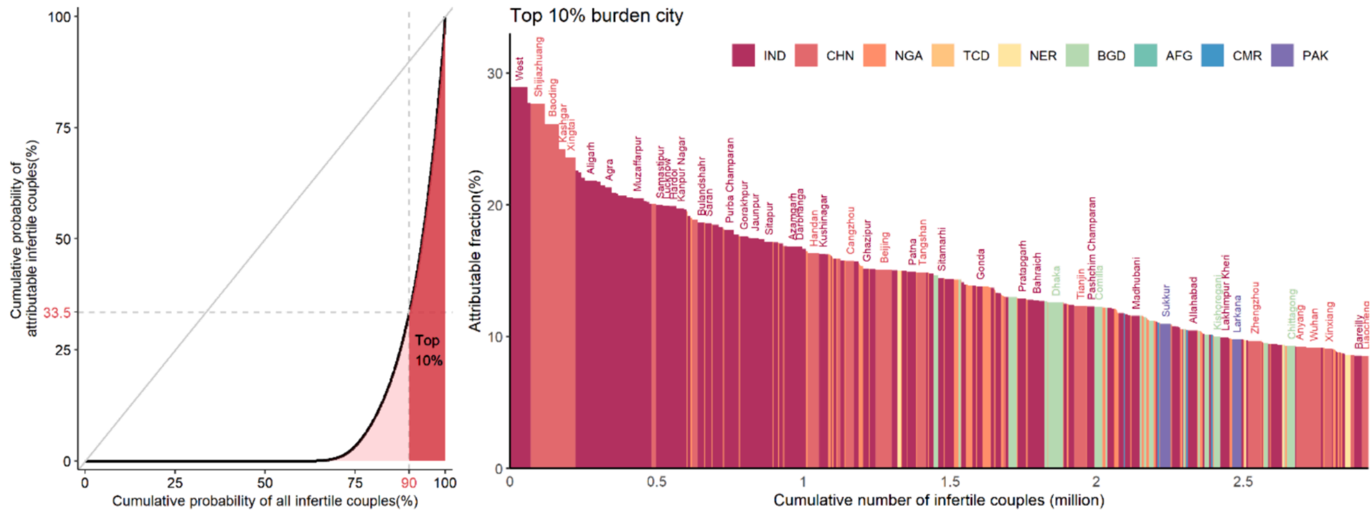

Fig. 3. The Lorenz curves for infertility attributable to $PM_{2.5}$ exposure (left) and the attributable burden of top 10% infertile couples from 278 level-2 administrative regions (city-level) in 2015 (right). 48 cities with more than 20,000 infertile couples was labeled. IND, India; CHN, China; NGA, Nigeria; TCD, Chad; NER, Niger; BGD, Bangladesh; AFG, Afghanistan; CMR, Cameroon; PAK, Pakistan.

quality, dense population and high infertility rate. $PM_{2.5}$ pollutants are from anthropogenic or natural sources (e.g., desert dust). If anthropogenic emissions are effectively controlled and people are well prepared for pollution episodes due to extreme weathers (e.g., by accurately and early warnings), the infertility affected by $PM_{2.5}$ in these areas can be significantly improved.

This study had several limitations. The weakness of the CD approach is mentioned above. In addition, exposure misclassification was unavoidable. The global $PM_{2.5}$ product we utilized to assess $PM_{2.5}$ exposure levels reported larger estimate uncertainty over the relatively under-monitored regions of Africa, Latin America, and Asia. (van Donkelaar et al., 2021) Furthermore, we assessed exposure concentrations before and during pregnancy attempts according to the GPS location at the interview, which neglected the possible migration of women, indoor air pollution, and individual activity patterns that affect the actual exposure level. However, our two-stage models utilized bin-level $PM_{2.5}$ concentrations from the GPS-matching process to estimate the association. The use of a categorical exposure variable could mitigate the impact of misclassification. Second, misclassification of TTP and other covariates due to reporting bias and recall bias was possible. The standard DHS questionnaires do not include a direct question about initiating a pregnancy attempt, so we used the dates of several key events to estimate the start time of such attempts (i.e., time of marriage or cohabitation, last terminated pregnancy, and livebirth delivery described in the Methods). Although such estimations have been used for data in the DHS dataset, (Polis et al., 2017) it is a crude approximation based on maternal recall of reproductive history. However, if the misclassification was random (i.e., nor correlated with the $PM_{2.5}$ exposure status), and it would not introduce bias into the estimated effect. Furthermore, covariates derived from questionnaire may also be influenced by recall bias and reporting bias, such as year of birth, parity. We converted covariates into categorical variables to mitigate the consequences of misclassification. Third, information about women treated for infertility was unavailable from the DHS, so we could not evaluate the relevant impact on our results. Following the CD approach, we also excluded women who were currently pregnant and reported contraceptive use, which means we excluded a fertile population that became pregnant due to contraceptive failure. Because there is no evidence suggesting a relationship between $PM_{2.5}$ exposure and such women, we assumed the influence was small. Forth, we used GPS-matching methods to minimize the impact of confounding factors as much as possible, but the issue of unmeasured confounders may still exist, such as noise exposure (Min and Min, 2017), the environmental factor that might affect male reproductive function but was be adjusted due to data unavailability. Fifth, our study only estimated an overall effect, but different regions may have different effects due to differences in the chemical components of $PM_{2.5}$ pollution. Although evaluating the impact of different components on human fertility is not the focus of the current study, future research should investigate this important issue, that will help in proposing more targeted pollution control measures to protect fertility health. Finally, the reported prevalence of infertility varies greatly among studies due to variation in its definition, different methods used to measure it, and a lack of sufficient studies from different regions. (Cox et al., 2022) Therefore, in our study, the only available region-level 12-month IR and gridded data for pregnant women were used to calculate the $PM_{2.5}$-related disease burden and its spatial variation. However, an accurate spatiotemporal assessment for the systematic estimations of infertility prevalence at global, regional, and national levels should be conducted to fill the gap.

In conclusion, exposure to $PM_{2.5}$ has a detrimental effect on human fecundity by prolonging the time to pregnancy and increasing the IR. Nearly 0.66 million couples are affected by infertility related to $PM_{2.5}$, with the greatest burden observed in South Asia, East Asia, and West Africa. As a modifiable risk factor, it is crucial to implement effective $PM_{2.5}$ pollution-control measures and policies in LMICs.

5. Contributors

MT and TX conceived the study, designed the methodology, performed the analysis and draft the manuscript. HL, HX, and XF contributed to the methodology. RW, JL collected the original data. JZ, FJK, JG, YH, PL, and TZ contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Ethical approval

Procedures and questionnaires for DHS surveys have been reviewed and approved by ICF Institutional Review Board. This study was based on the publicly available DHS data and adhered to its data usage guidelines. No further ethic approval was required.

CRediT authorship contribution statement

Mingkun Tong: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Hong Lu:** Writing – review & editing, Methodology, Data curation. **Huiyu Xu:** Writing – review & editing, Visualization. **Xinguang Fan:** Writing – review & editing, Supervision. **Junfeng (Jim) Zhang:** Writing – review & editing, Supervision. **Frank J. Kelly:** Writing – review & editing, Supervision. **Jicheng Gong:** Writing – review & editing, Supervision. **Yiqun Han:** Writing – review & editing, Supervision. **Pengfei Li:** Writing – review & editing, Supervision. **Ruohan Wang:** Writing – review & editing, Supervision. **Jiajianghui Li:** Writing – review & editing, Supervision. **Tong Zhu:** Writing – review & editing, Supervision. **Tao Xue:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization.

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.

Data availability

The data underlying this article are based on publicly available datasets, and data sources have been provided in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108784.

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