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Air pollution and fecundability: Results from a Danish preconception cohort study

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Abstract

Background: Animal and epidemiologic studies indicate that air pollution may adversely affect fertility. Epidemiologic studies have been restricted largely to couples undergoing fertility treatment or have retrospectively ascertained time-to-pregnancy among pregnant women.

Objectives: We examined the association between residential ambient air pollution and fecundability, the per-cycle probability of conception, in a large preconception cohort of Danish pregnancy planners.

Methods: During 2007–2018, we used the Internet to recruit and follow women who were trying to conceive without the use of fertility treatment. Participants completed an online baseline questionnaire eliciting socio-demographic characteristics, lifestyle factors, and medical and reproductive histories and follow-up questionnaires every 8 weeks to ascertain pregnancy

status. We determined concentrations of ambient nitrogen oxides (NO_x), nitrogen dioxide (NO₂), carbon monoxide (CO), ozone (O₃), particulate matter <2.5 µm (PM_{2.5}) and <10 µm (PM₁₀), and sulfur dioxide (SO₂) at each participant's residential address. We calculated average exposure during the year before baseline, during each menstrual cycle over follow-up, and during the entire pregnancy attempt time. We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs), adjusting for potential confounders and co-pollutants. The analysis was restricted to the 10,183 women who were trying to conceive for <12 cycles at study entry whose addresses could be geocoded.

Results: During 12 months of follow-up, 73% of participants conceived. Higher concentrations of PM_{2.5} and PM₁₀ were associated with small reductions in fecundability. For example, the FRs for a one interquartile range (IQR) increase in PM_{2.5} (IQR=3.2 µg/m³) and PM₁₀ (IQR=5.3 µg/m³) during each menstrual cycle were 0.93 (95% CI: 0.87, 0.99) and 0.91 (95% CI: 0.84, 0.99), respectively. Other air pollutants were not appreciably associated with fecundability.

Conclusions: In this preconception cohort study of Danish women, residential exposures to PM_{2.5} and PM₁₀ were associated with reduced fecundability.

Keywords

Air pollution; fecundability; particulate matter; preconception cohort; time-to-pregnancy; traffic

BACKGROUND

Ambient air pollution is an important environmental threat. The Global Burden of Disease Study estimates that over 4 million deaths are attributable to ambient air pollution every year,¹ and epidemiologic studies demonstrate that air pollution exposure is associated with premature mortality^{2–5} and increased risks of cardiovascular disease,⁶ respiratory disease,^{7–9} cancer,¹⁰ and adverse birth outcomes.^{11, 12} These risks are present even at low exposure levels, indicating that current air quality regulations may be insufficient to protect human health.^{2, 13, 14}

Although infertility, defined as the inability to conceive during 12 months of unprotected intercourse, affects 10–15% of couples,^{15–17} few risk factors have been identified. Some mechanisms through which air pollution is hypothesized to affect other health outcomes may also play a role in the etiology of infertility.^{18–20} Laboratory studies demonstrate that diesel exhaust, particulate matter, and other combustion-related pollutants have hormone-like activity.^{21–23} In mice, chronic exposure to urban pollution in Sao Paulo, Brazil reduced the number of antral follicles and caused longer estrus cycles, higher risk of implantation failure, longer time to pregnancy, and fewer live births.^{24, 25}

The epidemiologic literature also indicates a potential role for air pollution in human fertility. Three ecological studies in Spain,²⁶ China,²⁷ and the United States²⁸ found correlations between fertility rates and concentrations of fine particulate matter (PM_{2.5}) and nitrogen oxides (NO_x) at the census tract or county levels. Studies of couples from the United States^{29–31} and Korea³² who were undergoing fertility treatment consistently reported associations between increasing concentrations of air pollutants at patients' home

address and poorer treatment outcomes. Four epidemiologic studies have evaluated the association of air pollution with fertility among couples trying to conceive spontaneously. Although results varied in magnitude and by pollutant, all four studies found that higher levels of air pollution were associated with reduced fecundability or higher infertility risk.^{33–36} Some of these studies were limited by retrospective assessment of time-to-pregnancy, restriction to couples who had a live birth, or measurement of binary infertility rather than continuous time-to-pregnancy. Here, we examine residential concentrations of ambient air pollution in relation to fecundability, the per cycle probability of conception, in a large cohort of pregnancy planners in Denmark.

METHODS

Cohort selection

Snart-Gravid.dk (SG; translates to ‘soon pregnant’) is an Internet-based preconception cohort of female pregnancy planners, designed to study risk factors for subfertility.^{37, 38} Enrollment began in 2007 and continued until 2011, at which point the study began enrolling male partners and was renamed Snart-Forældre.dk (SF; translates to ‘soon parents’). Enrollment in SF is ongoing. Recruitment originally took place through advertisements on netdokter.dk, min-mave.dk, Facebook, and blogs. Beginning in 2018, we primarily recruit participants through a governmental e-mail box (e-Boks). Eligible female participants are aged 18–49 years, residents of Denmark, and attempting to conceive without the use of fertility treatment. Female participation involves the completion of a baseline questionnaire on socio-demographic characteristics, behavioral factors, and reproductive and medical histories. Participants subsequently complete bi-monthly follow-up questionnaires to ascertain pregnancy status. All participants are required to provide a valid e-mail address and their Civil Personal Registration (CPR) number.

Between June 2007 and November 2018, 12,063 eligible women completed the baseline questionnaire. In the current study, we excluded 385 women with an implausible date of last menstrual period (LMP) data, 1,274 women who had been trying to conceive for > 12 cycles at study entry, and 221 women whose reported residential addresses could not be geocoded. The analytic sample included 10,183 women. For analysis of air pollution during follow-up (see exposure assessment below), we excluded 125 women with air pollution data available during the year before baseline but not during follow-up, for an analytic sample of 10,058 women.

Outcome assessment

At baseline, we collected information on attempt time at study entry, date of the first day of the LMP, cycle regularity, and typical cycle length (for women with regular cycles) or number of periods per year (for women with irregular cycles). On follow-up questionnaires, we asked women for the date of their LMP, whether their cycles had been regular since their previous questionnaire, and the length of their most recent cycle (for women with regular cycles). We also asked women if they were currently pregnant, if they had experienced a pregnancy loss since their previous questionnaire, and if they had initiated fertility treatment. Women who were pregnant reported the LMP date for their pregnancy and how their

pregnancy was confirmed (*e.g.*, urine test, blood test, ultrasound). We asked women who were not pregnant if they were still trying to conceive.

We followed women from their baseline LMP date until pregnancy or one of the following censoring events: 12 cycles of follow-up, initiation of fertility treatment, cessation of pregnancy attempt, or loss to follow-up. We estimated the dates of each cycle that occurred during follow-up using information on self-reported LMP dates and cycle length. We defined the first day of each cycle as the first day of menses. Since follow-up questionnaires were completed bi-monthly, we estimated LMP dates between questionnaires by subtracting cycle length from the later reported LMP date, making sure that the time difference between the earlier reported and the estimated LMP dates was not smaller than half of the cycle length.

Exposure assessment

By linking participants' CPR numbers to the Danish Central Registration System,³⁹ we collected geographical coordinates of all residential addresses from one year before enrollment through the end of follow-up. We obtained daily estimates of individual air pollutant concentrations at each participants' address(es) using the Danish Eulerian Hemispheric Model (DEHM)/Urban Background Model (UBM)/AirGIS modeling system.⁴⁰ This validated system comprises three air pollution models,⁴¹ including the DEHM, which accounts for long-range transport of air pollution down to a resolution of 5.6 km x 5.6 km;^{42, 43} the UBM, which determines the local background level of pollutants on a 1-km² grid resolution for all of Denmark;^{44–46} and the Operational Street Pollution Model (OSPM), which estimates air pollutant concentrations at the residential level.^{42, 43, 47} When comparing annual averages from the 2018 DEHM/UBM/AirGIS models with air pollutant measurements from the 17 stations included in the Danish routine modeling program, correlation coefficients ranged from 0.7–0.9, depending on the pollutant, site, and time period.^{40, 48} For three permanent monitoring stations at street/urban/rural locations, and using 14–18 years of measured data, the correlation with modelled data for the pollutants NO_x, PM_{2.5} were in the range 0.61–0.94 (NO_x) 0.72–0.89 (PM_{2.5}) depending on the applied time resolutions (annual, month, hour).⁴⁹

We linked participant data with daily estimates between 2006 through 2018 of nitrogen dioxide (NO₂), nitrogen oxides (NO_x), carbon monoxide (CO), ozone (O₃), particulate matter <2.5 µm (PM_{2.5}), particulate matter <10 µm (PM₁₀) and sulfur dioxide (SO₂). We averaged daily estimates across three different time periods relative to the pregnancy attempt to identify the most relevant window of exposure. First, we calculated average daily exposure during the year before enrollment as a measure of long-term exposure. Second, we calculated average daily concentrations during each menstrual cycle, which is more temporally granular, reflecting variability across the year. Third, we calculated a “cumulative average” preconception exposure variable, which we defined as the average daily concentrations from baseline LMP date through the last day of a given menstrual cycle. This measure reflects exposure throughout the preconception period.

Covariate assessment

We collected covariate data on the baseline questionnaire, including socio-demographic information (age, educational attainment, annual household income), anthropometrics (height, weight), lifestyle factors (cigarette smoking, alcohol intake, physical activity, sugar-sweetened soda intake, daily multivitamin or folic acid use), reproductive history (gravidity, parity), and intensity of trying to conceive (intercourse frequency, timing of intercourse).

Statistical analysis

We examined associations between individual air pollutants and fecundability by fitting proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs). The FR estimates the per-cycle probability of conception in exposed compared with unexposed women. We calculated FRs for an increase in air pollutant concentrations equivalent to the interquartile range (IQR). We used the Anderson-Gill data structure, with one observation per observed menstrual cycle at risk, to account for left truncation due to delayed entry into the risk set.^{50, 51} We included indicator variables for cycle at risk to account for the decline in baseline fecundability with increasing attempt time. We fitted restricted cubic splines to examine non-linear continuous associations between exposure and outcome.

We selected covariates for adjustment using a directed acyclic graph. Final models adjusted for age (<25, 25–29, 30–34, 35 years), educational attainment (12, 13–15, 16, 17 years), monthly household income (<25,000, 25,000–39,999, 40,000–64,999, 65,000 DKK), parity conditional on gravidity (nulligravid, gravid but not parous, parous), month and year of each cycle, and monthly average ambient temperature (<0, 0–4, 5–9, 10–14, and 15°C). We also adjusted for co-pollutants, including SO₂, NO₂ (to represent NO_x, NO₂, CO, and O₃) and PM_{2.5} (to represent the two sizes of PM (PM_{2.5} and PM₁₀)). We stratified final models by gravidity and parity (nulligravid, gravid but nulliparous, parous), age (<30 vs. 30 years) and BMI (<25 vs. 25 kg/m²). Several studies,^{52, 53} including one of fertility treatment outcomes,⁵⁴ have shown that associations between air pollution and adverse health outcomes may be stronger among individuals with low folate intake. Therefore, we stratified final models by daily multivitamin or folic acid intake. Finally, we conducted a sensitivity analysis restricted to women with <3 cycles of attempt time at study entry, among whom attempt time at study entry is less likely to be misclassified.

Missing data

We used multiple imputation to deal with missing values for covariates and outcome. We used fully conditional specification methods with 400 iterations to generate 5 imputed data sets. Covariate missingness was generally low, ranging from 0% (age) to 9% (income). For women who did not complete any follow-up questionnaires (14%), we assigned them one cycle of follow-up and imputed their pregnancy status at the end of that cycle.

Ethics approval

The study was registered at Aarhus University to comply with Danish law on data protection and approved by the institutional review board at the Boston University Medical Campus. All participants provided online informed consent.

RESULTS

We followed 10,183 women for 35,004 menstrual cycles. During the 12-month study period, 57% of participants conceived (73% after accounting for censoring using life-table methods). Eight percent of women attempted pregnancy for 12 cycles without conception, 10% initiated fertility treatment, 3% stopped trying to conceive, and 22% were lost to follow-up. Loss to follow-up was inversely associated with air pollution exposure, educational attainment and household income.

eTable 1 shows the distribution of pollutants during the year before baseline among SG/SF participants as well as the European Union Air Quality Standard limits. Most participants were exposed to air pollution at levels well below the limit values set by the European Union. Pollutants were highly correlated; for instance, Spearman correlation coefficients for NO_x , NO_2 , and CO ranged from 0.91 to 0.96, and O_3 was strongly inversely correlated with these pollutants (Spearman correlation coefficients ranged from -0.83 to -0.90). The correlation coefficient between $\text{PM}_{2.5}$ and PM_{10} was 0.85. Other correlations between pollutants were moderate. Figure 1a–g shows the spatial distribution of each pollutant across Denmark, and Figure 1h shows the locations of SG/SF participant residences.

Table 1 presents baseline characteristics of participants across categories of NO_x and $\text{PM}_{2.5}$ concentrations. Air pollution concentrations declined over time and exhibited strong seasonal variation, with highest concentrations in the summer. Participants with higher exposure to NO_x were less likely to have low educational attainment compared with lower exposed participants, whereas the opposite was true for $\text{PM}_{2.5}$. For both pollutants, participants with higher exposures were more likely to have lower household income, BMI, and physical activity. They were also less likely to have a previous live birth. Finally, higher exposed participants were less likely to be timing intercourse to the fertile window, but were also less likely to report intercourse <1 time/week.

We found no appreciable association between average air pollution exposure during the year before baseline and fecundability (Figure 2). Results were similar when restricted to participants with <3 cycles of attempt time at study entry. Restricted cubic spline analyses confirmed that there were no strong associations between air pollution during the year before baseline and fecundability (Figure 2a; Figure 3a; eFigures 1a, 2a, 3a, 4a, and 5a).

Assessment of average daily exposures during each menstrual cycle showed that NO_x , NO_2 , CO, O_3 , and SO_2 were not strongly related to fecundability (Figure 2). $\text{PM}_{2.5}$ and PM_{10} concentrations were associated with small reductions in fecundability, particularly when restricting to participants with <3 cycles of attempt time at study entry (FRs for a one IQR increase in $\text{PM}_{2.5}$ (IQR=3.2 $\mu\text{g}/\text{m}^3$) and PM_{10} (IQR=5.3 $\mu\text{g}/\text{m}^3$) were 0.93 [95% CI: 0.87, 0.99] and 0.91 [95% CI: 0.84, 0.99], respectively). In other words, for every one IQR increase in $\text{PM}_{2.5}$ and PM_{10} , participants have 7% and 9% lower probabilities of conceiving in a given menstrual cycle, respectively. In restricted cubic splines analyses, average daily concentrations of $\text{PM}_{2.5}$ during each menstrual cycle (Figure 3b) were associated with reduced fecundability. Reductions in fecundability were also observed for O_3 (eFigure 4b) and PM_{10} (eFigure 5b). Average daily concentrations of other pollutants during each

menstrual cycle were not meaningfully associated with fecundability (Figure 4b; eFigures 2b, 3b, 6b).

Associations for cumulative average concentrations during the entire preconception period were similar to those during each menstrual cycle (Figure 2). For example, among participants with <3 cycles of attempt time at study entry, FRs for a one IQR increase in PM_{2.5} (IQR=2.4 µg/m³) and PM₁₀ (IQR=4.2 µg/m³) concentrations were 0.94 [95% CI: 0.88, 1.00] and 0.93 [95% CI: 0.86, 1.01], respectively. Ozone (IQR=19.8 µg/m³) was also associated with slightly reduced fecundability (FR for a one IQR increase=0.91 [95% CI: 0.81, 1.02]). In restricted cubic spline analyses, preconception concentrations of both PM_{2.5} (Figure 3c) and PM₁₀ (eFigure 5c) were associated with reduced fecundability. Cumulative average concentrations of other pollutants were not associated with fecundability (Figure 4c; eFigures 2c, 3c, 4c, 6c).

Associations were slightly stronger among nulliparous women (eTable 3), but did not differ appreciably across strata of age (eTable 4), BMI (eTable 5), or multivitamin or folic acid supplementation (eTable 6), with the exception of ozone, which was associated with reduced fecundability only among women with no multivitamin or folic acid intake.

COMMENT

Principal findings

In this prospective preconception cohort study of female pregnancy planners residing in Denmark, we found that increasing estimated residential ambient concentrations of PM_{2.5} and PM₁₀ were associated with slightly reduced fecundability. Associations were stronger when examining exposures more proximal to the pregnancy attempt (*i.e.*, cycle-specific exposures that varied over follow-up) than for longer-term exposure windows (*i.e.*, the year before study enrollment). Notably, these associations were observed at relatively low concentrations. NO_x, NO₂, CO, O₃, and SO₂ concentrations were largely unrelated to fecundability. Our results add to the growing literature demonstrating that air pollution, and especially particulate matter, may be related to lower fertility.

Strengths of the study

Our study has several strengths. First, we estimated time-to-pregnancy prospectively in a large cohort of women actively trying to conceive. This is a key advantage over previous studies that have measured time-to-pregnancy retrospectively in early pregnancy,³⁶ restricted to women with a live birth,³³ or ascertained dichotomous measures of infertility.³⁴ Second, we used a validated air pollution modeling approach that has shown a strong correlation with measurements taken at monitoring stations.^{41–43} Linkage to Danish registries allowed us to precisely account for residential mobility during the study period, as residents are required to report address changes within five days of the move. Finally, we collected data on a wide range of confounders. As in any epidemiologic study, unmeasured confounding is possible. We do not suspect strong unmeasured confounding by neighborhood-level socioeconomic status, given the spatial patterns of exposure across Denmark. However, confounding by

other environmental exposures such as noise, green space, or other hazardous pollutants is possible.

Limitations of the study

As we based our exposure assessment solely on participants' residential addresses, we were not able to account for air pollution exposure indoors or in non-residential locations. We also did not consider time-activity patterns. In addition, air pollution concentrations at each residential address were modeled, rather than directly measured. Due to the prospective nature of the study, we expect that exposure misclassification was non-differential with respect to the outcome, which would tend to bias results toward the null in the extreme exposure categories.

We assessed both long- and short-term exposures to try to identify the etiologically relevant window of exposure. Because we did not have sufficiently granular data on the numerous biologic processes that occur leading up to pregnancy (*i.e.*, folliculogenesis, ovulation, implantation), we were unable to measure exposure in finer windows that may be more biologically relevant, as studies of couples undergoing IVF have done.²⁹⁻³² In addition, because the vast majority of couples reside at the same address and exposure was residence-based, we were not able to separate out effects of air pollution on female vs. male partners.

We measured time-to-pregnancy using self-reported information on LMP dates, menstrual cycle length, attempt time at study entry, and pregnancy status during follow-up. These variables were measured retrospectively on bi-monthly follow-up questionnaires, rather than prospectively using daily diaries. To the extent that any of these variables were measured with error, outcome misclassification could result. Given the high use of home pregnancy tests in SG/SF (95%), and the high specificity and sensitivity of home pregnancy tests, we expect pregnancy status was measured with little error. Participants did not receive pregnancy tests as part of their participation in the study, nor did we have a systematic protocol for pregnancy testing; however, over 95% of participants reported using home pregnancy tests, and the median gestational weeks at first pregnancy test was 4 weeks. We were unable to identify losses that occurred before the pregnancy could be identified with home pregnancy tests, which could introduce misclassification of TTP. Because air pollution has been associated with early pregnancy loss in some studies,⁵⁵ in the present work, unidentified early losses could be manifesting as longer TTP. In addition, infertility is a multi-factorial condition with multiple etiologies and we were unable to examine separately the association between air pollution and cause-specific infertility.

Our study population includes volunteer pregnancy planners who were enrolled through the internet. Internet-based recruitment, which has been used in many observational studies and randomized trials, should not bias etiologic associations based on internal comparisons, as we have previously shown in this cohort.⁵⁶ Pregnancy planning is related to higher socioeconomic status. Therefore, air pollution could have a weaker effect among pregnancy planners, who may be more likely to have advantageous housing characteristics (*e.g.*, better filtration⁵⁷) or other built environment features that reduce personal exposure to ambient pollution. Thus, our results may not be generalizable to populations with lower socioeconomic status. In addition, air pollution levels in this cohort and in Denmark

generally are low relative to other parts of the world. Our results thus may not be generalizable to regions with higher exposures. Finally, air pollution exposures were lower among participants who were lost to follow-up, indicating that differential loss to follow-up may have biased our results. If participants lost to follow-up also had lower probability of conception, this would result in upward bias; therefore, we suspect that our results are conservative.

Interpretation

Our findings are largely consistent with the literature on this topic. Specifically, four existing epidemiologic studies have estimated the association between air pollution and fertility in couples trying to conceive spontaneously. In a birth cohort of 1,916 couples from the Czech Republic, FRs for a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ and NO_2 at a nearby air monitoring station were 0.78 (95% CI: 0.65, 0.94) and 0.72 (95% CI: 0.53, 0.97), respectively.³³ In the Nurses' Health Study II, a U.S.-based prospective study of nurses, a 10 $\mu\text{g}/\text{m}^3$ increase in annual $\text{PM}_{2.5-10}$ concentrations was associated with 1.10 times the risk of self-reported infertility (95% CI: 0.96, 1.27).³⁴ Among 501 couples from Michigan and Texas, the FRs for daily ozone concentration the day before ovulation and NO_x concentrations 8 days post-ovulation were 0.83 (95% CI: 0.72, 0.96) and 0.84 (95% CI: 0.71, 0.99), respectively.³⁵ Cycle-specific averages of other pollutants (including CO, $\text{PM}_{2.5}$, PM_{10} , and SO_2) were not related to fecundability. Finally, in a retrospective study of 10,211 couples living in China, average exposure to $\text{PM}_{2.5}$ during 1-, 3-, and 5-year intervals before the attempt was associated with 11% lower fecundability (95% CI: 14%, 8%) and 1.20 times the risk of infertility (95% CI: 1.13, 1.27).³⁶

Several biologic mechanisms exist through which air pollution, and PM specifically, could influence fertility. Animal and *in vitro* studies demonstrate that PM can increase systemic inflammation and oxidative stress,⁵⁸ both of which are relevant for fertility.^{18, 20} Epidemiologic studies have shown that air pollution exposure may diminish ovarian reserve.⁵⁹⁻⁶¹ In addition, epidemiologic studies of couples undergoing *in vitro* fertilization can inform underlying mechanisms, as each step in the reproductive process is observed and measured. For instance, in a cohort of 357 women undergoing fertility treatment at a Massachusetts hospital, associations between traffic-related air pollutants were strongest early in the IVF cycle, specifically before embryo transfer.²⁹ This indicates that air pollution may have adverse effects on folliculogenesis or early embryonic development.

CONCLUSIONS

Our finding of an association between ambient exposure to $\text{PM}_{2.5}$ and PM_{10} and fecundability among Danish pregnancy planners adds to the growing body of literature suggesting an adverse effect of air pollution on human fecundity. Of note, these findings were observed at levels generally lower than the European Union Air Quality Standards, indicating that current air quality standards may be insufficient to protect against adverse reproductive health effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SYNOPSIS

Study question:

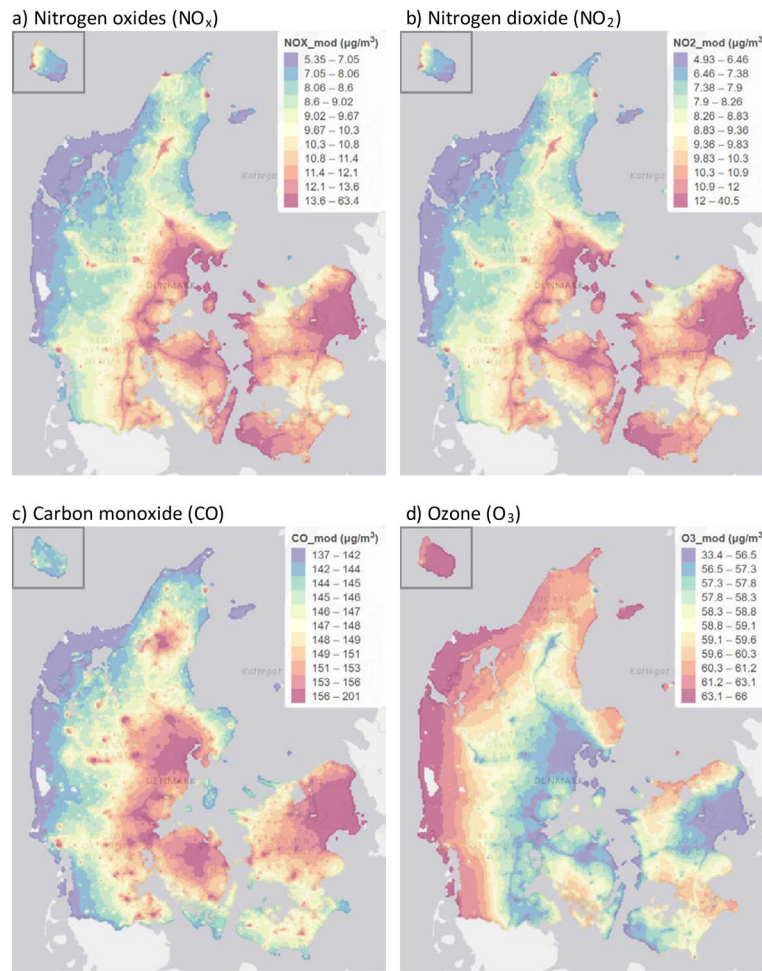
To what extent is ambient air pollution associated with fecundability among couples trying to conceive spontaneously?

What's already known:

Animal and epidemiologic studies support a potential role for air pollution in the etiology of infertility.

What this study adds:

In this preconception cohort of 10,183 female pregnancy planners in Denmark, we found that residential exposure to ambient particulate matter $<2.5 \mu\text{m}$ and $<10 \mu\text{m}$ during the preconception period was related to slightly reduced fecundability. Notably, air pollution in this cohort was low, and almost entirely at levels deemed safe by the European Union air quality standards.



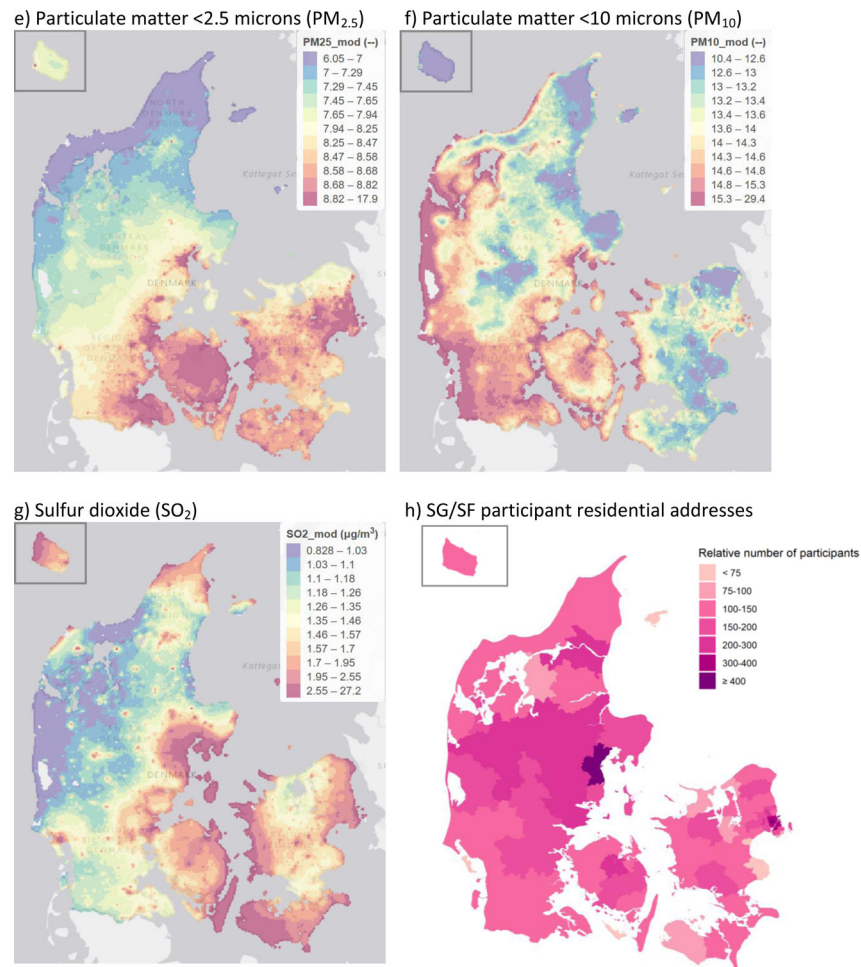


Figure 1. Maps showing spatial distributions across Denmark of a) NO_x, b) NO₂, c) CO, d) O₃, e) PM_{2.5}, f) PM₁₀, g) SO₂ and h) SG/SF participants (number of participants per 100,000 inhabitants). Pollutant maps are annual averages of each pollutant during 2012, modelled with DEHM/UBM at 1km x 1km spatial resolution. Only areas with Danish residential addresses are displayed. Empty cells are unpopulated (*i.e.*, water or forest). The data is displayed in quantile scale, with variable ranges in the color classes, arranged so that each color covers a similar total area in the map. Units for all pollutants are $\mu\text{g}/\text{m}^3$.

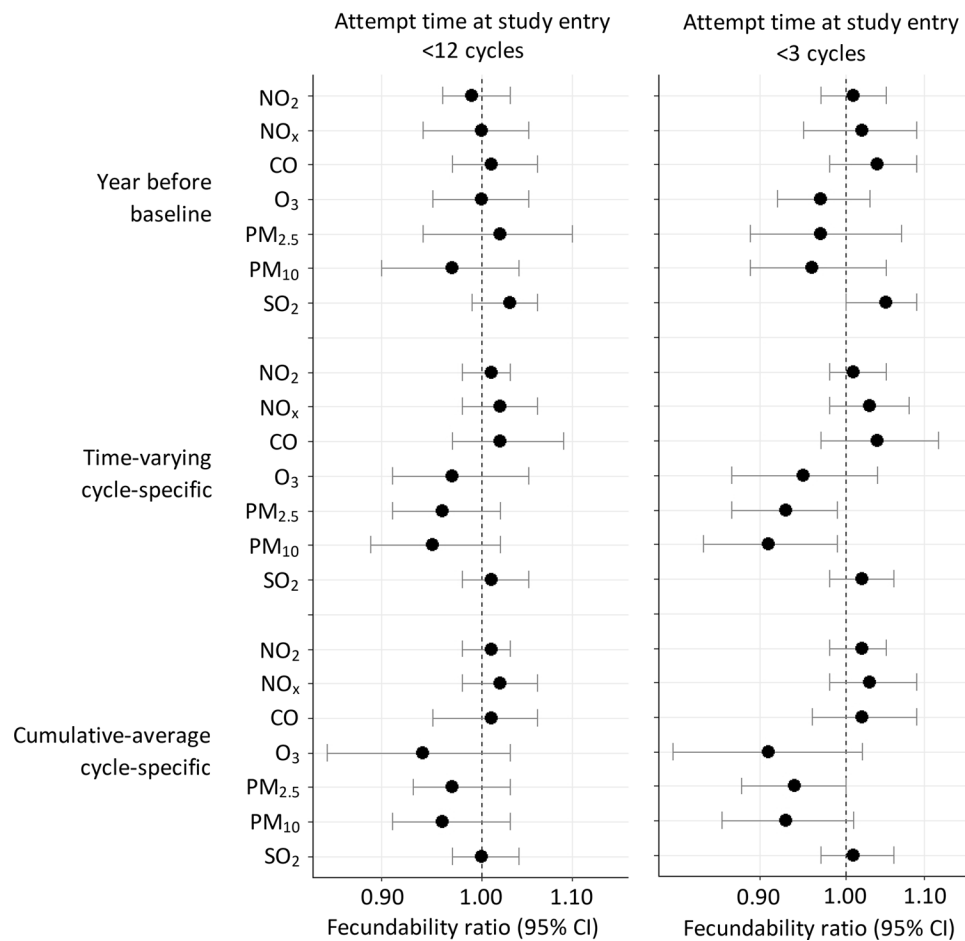


Figure 2.

Association between residential ambient concentrations of air pollutants and fecundability, Snart Gravid and Snart Forældre, 2007–2019. Fecundability ratios are for a one-interquartile range increase in exposure, and are adjusted for age, education, income, parity conditional on gravidity, month of enrollment, year of enrollment, and average monthly ambient temperature. Models for NO_x, NO₂, CO and O₃ are adjusted for PM_{2.5} and SO₂. Models for PM_{2.5} and PM₁₀ are adjusted for NO_x and SO₂. Models for SO₂ are adjusted for NO_x and PM_{2.5}.

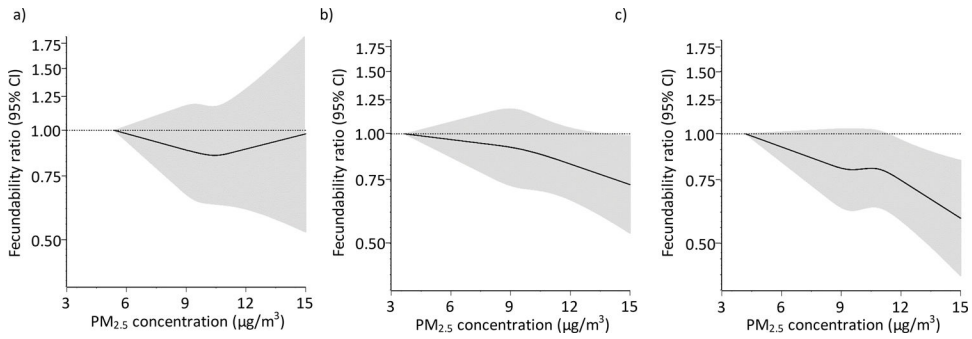


Figure 3.

Association between residential concentrations of particulate matter $<2.5 \mu\text{m}$ ($PM_{2.5}$) and fecundability, fit using restricted cubic splines. $PM_{2.5}$ is modeled as a) the average during the year before baseline, b) average concentration over each menstrual cycle, and c) cumulative-average exposures. The reference value is the lowest observed value in the cohort, and there are three knots located at the 10th, 50th, and 90th percentiles. The x-axis ranges from the minimum value to the 95th percentile. Spline curves are adjusted for age, education, income, parity conditional on gravidity, month of enrollment, year of enrollment, average monthly ambient temperature, and concentrations of NO_x and SO_2 .

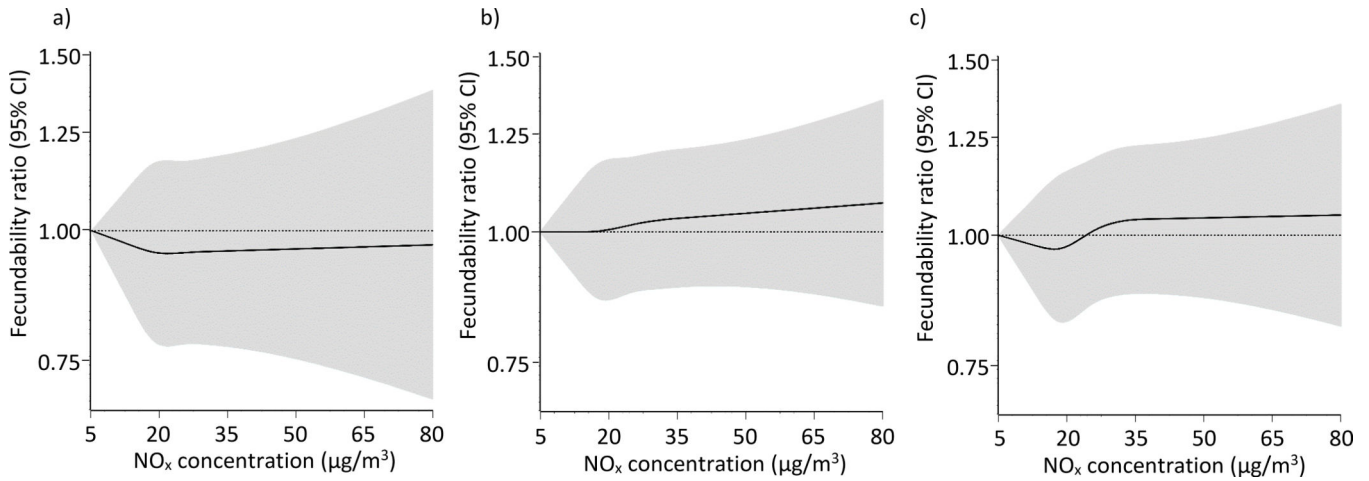


Figure 4.

Association between residential concentrations of nitrogen oxides (NO_x) and fecundability, fit using restricted cubic splines. NO_x is modeled as a) the average during the year before baseline, b) average concentration over each menstrual cycle, and c) cumulative-average exposures. The reference value is the lowest observed value in the cohort, and there are three knots located at the 10th, 50th, and 90th percentiles. The x-axis ranges from the minimum value to the 95th percentile. Spline curves are adjusted for age, education, income, parity conditional on gravidity, month of enrollment, year of enrollment, average monthly ambient temperature, and concentrations of $\text{PM}_{2.5}$ and SO_2 .

Table 1.

Distribution of baseline characteristics by NO_x and PM_{2.5} levels in the year before baseline, Smart Gravid and Smart Forældre

Characteristics ^a	NO _x (µg/m ³)					PM _{2.5} (µg/m ³)				
	Q1: <12.8	Q2: 12.8–16.5	Q3: 16.6–21.0	Q4: 21.1–28.6	Q5: ≥28.7	Q1: <8.5	Q2: 8.5–9.1	Q3: 9.2–9.9	Q4: 10.0–10.7	Q5: ≥10.8
Number	2012	2077	2003	2053	2038	2115	1843	2247	1932	2046
Age (years), mean	28.7	28.6	28.8	28.5	28.7	29.2	28.5	28.4	28.5	28.7
Month of enrollment, %										
December – February	25.9	27.9	24.4	23.4	25.8	32.7	24.1	23.4	24.0	20.5
March – May	26.9	25.5	27.3	23.2	22.4	36.8	28.6	24.5	21.3	14.2
June – August	25.6	24.8	26.2	26.2	31.7	13.0	22.0	25.0	28.6	52.4
September – November	21.7	21.8	22.1	21.6	20.1	17.4	25.3	27.1	26.2	12.9
Year of enrollment, %										
2007 – 2009	30.5	41.3	38.2	54.1	60.9	8.4	20.8	38.1	70.5	88.8
2010 – 2012	16.2	13.6	15.3	13.9	10.9	8.6	15.3	20.2	18.6	7.7
2013 – 2015	23.6	19.5	19.0	16.9	12.5	19.8	28.6	32.7	7.9	3.0
2016 – 2018	29.8	25.6	27.5	15.1	15.8	63.2	35.3	9.0	3.1	0.5
12 years education, %	11.3	12.3	10.3	10.8	9.8	8.6	8.5	10.7	13.6	12.6
Income <25,000/month DKK, %	11.6	14.0	13.0	15.8	16.6	11.5	13.7	16.0	14.8	14.9
BMI (kg/m ²), mean	25.7	24.9	24.0	23.8	23.2	25.2	24.4	24.2	24.4	23.4
Physical activity (MET-hr/wk), mean	56.5	46.7	47.5	41.5	40.0	62.8	54.1	46.6	36.0	32.0
Current regular smoker, %	13.0	12.9	10.0	9.4	8.8	10.7	9.0	10.9	13.2	10.6
Alcohol (drinks/week), mean	2.0	2.1	2.4	2.6	3.0	2.2	2.3	2.3	2.4	2.9
Sugar-sweetened soda (dr/wk), mean	1.3	1.1	1.0	0.9	0.8	1.1	0.9	1.1	1.1	0.9
Daily multivitamins/folic acid use, %	61.5	61.5	66.0	65.2	65.5	64.5	65.9	65.1	60.7	62.9
Nulligravid, %	40.9	43.3	51.4	56.7	63.3	47.2	49.3	48.5	51.3	59.7
Gravid, but nulliparous, %	12.5	14.5	14.1	16.2	17.4	14.1	15.5	14.4	15.7	15.1
Parous, %	46.6	42.2	34.5	27.1	19.4	38.8	35.2	37.1	33.0	25.2
Intercourse <1 time/week, %	20.1	19.4	17.8	15.5	15.4	21.6	17.4	18.5	14.9	15.1
Hormonal last contraception, %	63.8	62.0	59.3	62.2	61.6	59.1	62.2	62.8	62.9	61.6
History of infertility, %	17.3	13.4	9.7	9.6	7.2	12.2	12.3	11.9	11.7	9.3
Doing something to improve chances, %	67.4	62.4	63.9	59.4	57.3	71.7	68.9	65.8	53.6	49.9

Characteristics are standardized to the age distribution of the cohort at baseline.

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