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Air pollution and fecundability in a North American preconception cohort study

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Abstract

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Lauren A. Wise and Elizabeth E. Hatch reports financial support was provided by National Institutes of Health. Lauren A. Wise reports a relationship with AbbVie Inc that includes: consulting or advisory. Dr. Lauren Wise serves as a consultant for AbbVie, Inc. and the Gates Foundation, She also receives in-kind donations for primary data collection in Pregnancy Study Online (PRESTO) from Swiss Precision Diagnostics (home pregnancy tests) and Kindara.com (fertility apps). All of these relationships are for work unrelated to this manuscript.].

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108249.

Background: Animal and epidemiologic studies indicate that air pollution may adversely affect fertility. However, the level of evidence is limited and specific pollutants driving the association are inconsistent across studies.

Methods: We used data from a web-based preconception cohort study of pregnancy planners enrolled during 2013–2019 (Pregnancy Study Online; PRESTO). Eligible participants self-identified as female, were aged 21–45 years, resided in the United States (U.S.) or Canada, and were trying to conceive without fertility treatments. Participants completed a baseline questionnaire and bi-monthly follow-up questionnaires until conception or 12 months. We analyzed data from 8,747 participants (U.S.: 7,304; Canada: 1,443) who had been trying to conceive for < 12 cycles at enrollment. We estimated residential ambient concentrations of particulate matter < 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) using validated spatiotemporal models specific to each country. We fit country-specific proportional probabilities regression models to estimate the association between annual average, menstrual cycle-specific, and preconception average pollutant concentrations with fecundability, the per-cycle probability of conception. We calculated fecundability ratios (FRs) and 95% confidence intervals (CIs) and adjusted for individual- and neighborhood-level confounders.

Results: In the U.S., the FRs for a 5-μg/m^3 increase in annual average, cycle-specific, and preconception average $PM_{2.5}$ concentrations were 0.94 (95% CI: 0.83, 1.08), 1.00 (95% CI: 0.93, 1.07), and 1.00 (95% CI: 0.93, 1.09), respectively. In Canada, the corresponding FRs were 0.92 (95% CI: 0.74, 1.16), 0.97 (95% CI: 0.87, 1.09), and 0.94 (95% CI: 0.80, 1.09), respectively. Likewise, NO_2 and O_3 concentrations were not strongly associated with fecundability in either country.

Conclusions: Neither annual average, menstrual cycle-specific, nor preconception average exposure to ambient $PM_{2.5}$, NO_2, and O_3 were appreciably associated with reduced fecundability in this cohort of pregnancy planners.

Keywords

Air pollution; Fertility; Time to pregnancy; Preconception cohort

1. Introduction

Infertility, defined as the inability to conceive during 12 months of unprotected intercourse, affects 10–15% of reproductive-aged couples in the United States (U.S.) and Canada (Bushnik et al., 2012; Thoma et al., 2013; Chandra et al., 2013). Infertility can exact a substantial emotional and financial toll on affected couples. Fertility treatments have an annual healthcare cost of over $5 billion in the U.S. (Stephen et al., 2016; Sunderam et al., 2018), and are inaccessible to large portions of the population (Chandra et al., 2014; Chin et al., 2015; Seifer et al., 2008; Sunderam et al., 2018; Liu et al., 2021). As couples delay childbearing, infertility rates and use of fertility treatments are expected to increase (Chandra et al., 2014). Therefore, identification of factors that influence the probability of spontaneous (medically-unassisted) conception is an important public health goal.

Epidemiologic research indicates that air pollution may adversely affect fertility (Carre et al., 2017; Checa Vizcaino et al., 2016). Ecologic studies in the U.S. (Xue and Zhu, 2018b), Spain (Nieuwenhuijsen et al., 2014), and China (Xue and Zhu, 2018a) have found that counties or census tracts with higher levels of air pollution have lower fertility rates. Associations between air pollution and markers of fertility have also been reported in studies of couples undergoing *in vitro* fertilization (IVF) (Boulet et al., 2019; Choe et al., 2018; Dai et al., 2021; Gaskins et al., 2018, 2019; Iodice et al., 2021; Jin et al., 2022; Legro et al., 2010; Li et al., 2020; Liu et al., 2022, 2023; Qiu et al., 2019; Shi et al., 2021; Tartaglia et al., 2022; Wu et al., 2021, 2023; Zeng et al., 2020; Zhang et al., 2022; Quraishi et al., 2019) and among couples trying to conceive spontaneously (Li et al., 2021; Mahalingaiah et al., 2016; Mendola et al., 2017; Nobles et al., 2018; Slama et al., 2013; Wesselink et al., 2020, 2022). However, the pollutants associated with reduced fertility and the window of exposure during which an association was observed were not consistent across studies. For example, long-term $PM_{2.5}$ concentrations have generally not been strongly associated with reduced fertility (Mahalingaiah et al., 2016; Wesselink et al., 2022; Quraishi et al., 2019) (with the exception of a retrospective cohort in China) (Li et al., 2021), whereas $PM_{2.5}$ concentrations across the menstrual cycle and during specific critical windows of IVF (*e.g.*, between oocyte retrieval and embryo transfer) were associated with reduced fertility in some (Gaskins et al., 2019; Slama et al., 2013; Wesselink et al., 2022), but not all (Legro et al., 2010; Nobles et al., 2018) studies (Liu et al., 2023). Similar inconsistencies in the relevant timing of exposure exist for studies examining NO_2 (Choe et al., 2018; Gaskins et al., 2019; Legro et al., 2010; Nobles et al., 2018; Wesselink et al., 2022; Quraishi et al., 2019) and O_3 (Choe et al., 2018; Gaskins et al., 2019; Legro et al., 2010; Nobles et al., 2018; Wesselink et al., 2022).

Air pollution exposure could influence fertility through several hypothesized mechanisms. Animal (Gai et al., 2017; Ogliari et al., 2013; Veras et al., 2009) and human (Gaskins et al., 2019) studies indicate that air pollution exposure could accelerate reproductive aging through depletion of primordial follicles or effects on oocyte quality. Air pollution exposure more proximal to each menstrual cycle has been associated with cycle length (Merklinger-Gruchala et al., 2017) and reproductive hormone concentrations (Ye et al., 2020) in epidemiologic studies. Acute exposures may influence inflammatory and oxidative stress pathways that affect oocyte maturation and endometrial receptivity (Nobles et al., 2018). Therefore, examination of multiple critical windows of exposure can provide insight into relevant etiologic mechanisms.

In the present report, we examined the association between annual average, menstrual cycle-specific, and preconception average residential ambient air pollution concentrations with fecundability, the per-cycle probability of conception, within a large web-based preconception cohort study.

2. Methods

2.1. Study design and population

Pregnancy Study Online (PRESTO) is a web-based prospective cohort study of couples trying to conceive (Wise et al., 2015). Recruitment, primarily through social media, began in June 2013 and is ongoing. Potential participants complete an online screener questionnaire to determine eligibility. Eligible participants self-identify as female, are aged

21–45 years, reside in the U.S. or Canada, and are trying to conceive without use of fertility treatment. Participation involves completion of a baseline questionnaire and brief follow-up questionnaires every eight weeks for up to 12 months. The baseline questionnaire ascertains information on socio-demographics, lifestyle factors, medical history, and reproductive health. Follow-up questionnaires collect data on pregnancy status and update information on exposures and covariates.

In the present analysis, we included 10,490 participants who enrolled in the study between June 2013 and April 2019 (Figure S1). We excluded 200 participants with implausible menstrual cycle data at baseline, 1,153 participants who had been trying to conceive for ≥ 12 cycles at enrollment, 330 participants whose addresses could not be geocoded, and 60 participants who resided in Hawaii, Alaska, or U.S. territories. The final analytic sample (n = 8,747) included 7,304 participants residing in the contiguous U.S. and 1,443 participants residing in Canada.

2.2. Exposure assessment

On baseline and follow-up questionnaires, participants reported their residential addresses. We geocoded addresses using ArcGIS 10.3 (ESRI, Redlands, CA), as previously described. (Wesselink et al., 2020) We predicted residential ambient concentrations of $PM_{2.5}$, NO_2, and O_3 at each residential address using national-level spatiotemporal models, separately for the U.S. and Canada, given differences in data availability and quality.

In the U.S., we predicted two-week average concentrations of $PM_{2.5}$, NO_2, and O_3 at the residential address of each participant from 2012 to 2019. Briefly, we used a regionalized hierarchical spatiotemporal model that was originally developed at University of Washington for the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) and has been expanded to a national scale (Bergen et al., 2013; Keller et al., 2015; Kirwa et al., 2021; Sampson et al., 1994; Szpiro et al., 2009; Wang et al., 2016, 2018; Young et al., 2016; Wang et al., 1994). The model operates at the continuous spatial scale and characterizes the two-week average air pollution surface at precisely-geocoded locations as a linear combination of temporal basis functions with spatially-varying co-efficients and spatiotemporal residuals. It utilizes universal kriging to incorporate dependence on a large suite of geographic, meteorologic, and census covariates. It also uses smoothing through a spatial random effect and incorporates extensive regulatory and research ground-level monitoring data. The ground-level monitoring dataset comprised approximately 1,500 regulatory monitors and 940 investigator-deployed non-regulatory monitors across the U.S. and was supplemented with satellite measures of tropospheric NO_2. We divided the U.S. into climatic/topographic regions (nine for $PM_{2.5}$; three for NO_2 and O_3) to facilitate nationwide estimation that accounts for sub-national region-specific features and pollution processes and applied smoothing at regional boundaries to avoid artificial discontinuities. The model has been validated using a suite of cross-validation techniques, including prediction of spatial and temporal contrasts (Keller et al., 2015; Sampson et al., 1994).

In Canada, we estimated monthly concentrations of $PM_{2.5}$, NO_2, and O_3 at each participant's residential address. For prediction of $PM_{2.5}$, we combined Aerosol Optical Depth retrievals from NASA MODIS, MISR, and SeaWIFS satellites with the GEOS-Chem chemical transport model (van Donkelaar et al., 2019). We then calibrated estimates with measurements of regional ground-based $PM_{2.5}$ using a geographically-weighted regression method (van Donkelaar et al., 2019). For NO_2 estimates, we combined a land-use regression model with geographically-varying monthly scaling factors derived from the Canada Air Pollution Surveillance monitoring data, as has been done in other contexts (Bechle et al., 2015). The land-use regression model is a nationwide model developed using monitoring data from 179 sites during 2014–2016 to capture spatial gradients across Canada. Predictor variables in the final model included satellite based NO_2, Normalized Difference Vegetation Index (NDVI; a measure of green space) within 250 m, population within 20 km, length of railways within 750 m, average temperature within 10 km, area of industrial land use within 10 km, and length of expressways and highways within 250 m. We created a 30 m resolution raster for the final NO_2 predictions. Monthly scaling factors were created based on Bayesian kriging and applied to the land use regression model to calculate monthly estimates of NO_2. For O_3, we used a combination of a hybrid O_3 prediction system with a geographically varying monthly scaling factor derived from monitoring data to predict monthly 8-hour maximum concentrations. We used the monthly O_3 surface for 2015, developed from the hourly ground level O_3 concentration estimates from Global Environmental Multi-scale Modelling Air Quality and Chemistry, which incorporates ground-level observation data to calibrate hourly O_3 predictions at a 10-km^2 resolution (The Canadian Urban Environmental Health Research Consortium, 2021). We based monthly estimates on the monthly average of the highest rolling 8-hour average concentration (The Canadian Urban Environmental Health Research Consortium, 2021). We developed spatiotemporal scaling factors for each month at each monitor from the Canada National Air Pollution Surveillance monitoring data (Government of Canada, 2022). For each month, we created an interpolated surface based on the monitor scaling factors at each monitor using Bayesian kriging and applied the monthly scaling surfaces to the 2015 predicted estimates to generate monthly O_3 estimates from 2012 to 2019.

2.3. Outcome assessment

Fecundability, defined as the per-cycle probability of conception, is a sensitive, couple-based marker of fertility (Weinberg et al., 1989). We operationalized fecundability as time-to-pregnancy by calculating the number of discrete menstrual cycles each participant took to conceive. At baseline, participants reported how many menstrual cycles they had been trying to conceive. On baseline and follow-up questionnaires, participants reported the date of their last menstrual period (LMP) and their menstrual cycle regularity and length. We used these responses to estimate the dates of each menstrual cycle, which we used in calculating exposure measures (see Section 2.5). On follow-up questionnaires, participants reported if they were currently pregnant, had experienced any pregnancy losses since their previous questionnaire, if they had initiated fertility treatment, and (if not currently pregnant) if they were still trying to conceive. Participants who reported a pregnancy were asked how the pregnancy was confirmed (*e.g.*, urine test, blood test, ultrasound); more than 95% of participants reported using home pregnancy tests to confirm their pregnancy. For participants who were lost to follow-up, we identified outcome information by contacting participants directly via phone or email, searching for birth announcements and baby registries online, and linking with birth registries in selected states (CA, FL, MA, MI, OH, PA, and TX). For participants whose outcome information we found using these methods (43% of those lost to follow-up), we calculated their LMP date as due date – 280 days, which we used to estimate time-to-pregnancy.

2.4. Covariate assessment

We collected individual-level covariate data on the baseline questionnaire, including sociodemographic characteristics (age, race/ethnicity [based on self-report using categories and allowing participants to check all that apply], annual household income, educational attainment), lifestyle factors (physical activity, smoking, use of multivitamins or folic acid), reproductive history (history of infertility, parity), and intensity of trying to conceive (intercourse frequency, doing something to improve chances of conception such as timing intercourse to the fertile window). We collected data on neighborhood-level covariates from various sources. We used the U.S. and Canadian Census block population data to estimate the population within 5,000 m around the residence. We obtained data on residential green space exposure using NDVI from the Landsat 8 satellite (U.S. Geological Survey, Reston, VA), which we downloaded from Google Earth Engine (Google, Mountain View, CA), and estimated the annual maximum NDVI within 50 m of each participant's residence (informed by previous work in this cohort) (Willis et al., 2023). We acquired data on ambient temperature from the Global Land Data Assimilation System (GLDAS) version 2.1 (Rodell et al., 2004), which is derived using ground and satellite observations combined with land surface models and data assimilation techniques to predict three hour temporal resolution and a horizontal spatial resolution of 0.25 decimal degrees (Colston et al., 2018; Ji et al., 2015). Finally, we linked participant addresses to 2010 Census tract data on median household income, % of census tract with < high school education, and % of census tract that identifies as non-Hispanic white (or, in Canada, % visible minority, defined as persons other than Aboriginal peoples who are non-Caucasian or non-white).

2.5. Statistical analysis

We conducted all analyses in parallel in the U.S. and Canada, due to the differences in exposure assessment methods and contextual differences (*e.g.*, healthcare access, social context) across the two countries. We used life-table methods to calculate the proportion of participants who conceived during the study period. We used an Anderson-Gill data structure, with one observation per menstrual cycle, to allow for delayed entry into the risk set and to update exposures over time (Howards et al., 2007; Schisterman et al., 2013). Participants contributed follow-up time until the cycle of conception or experience of a censoring event (initiation of fertility treatment, stopped trying to conceive, 12 cycles of attempt time, or lost to follow-up), whichever came first. We fit proportional probabilities regression models (log-binomial regression models with an indicator variable for cycle at risk to account for the decline in baseline fecundability with increasing attempt time) to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs). The FR represents the per-cycle probability of conception for a given exposure contrast; FRs<1 indicate an exposure associated with reduced fecundability. We analyzed each participant's first pregnancy during the study period only.

We estimated exposure concentrations during three different time periods: 1) concentrations during the year before enrollment, 2) time-varying menstrual cycle-specific concentrations [*i.e.*, average concentrations from the first to last day of each menstrual cycle], and 3) preconception average menstrual cycle-specific concentrations [*i.e.*, average from study enrollment through the most recent menstrual cycle]. For the 4% of participants who changed residences during the study period, we updated their address and air pollution concentrations accordingly. We examined exposure linearly (*i.e.*, estimated the FR for a 5-unit increase in exposure) and categorically (with categories derived based on the distribution in the cohort: <6, 6-<8, 8-<10, and ≥ 10 μg/m^3 for $PM_{2.5}$, <4, 4-<8, 8-<12, and ≥ 12 ppb for NO_2, and < 24, 24-<30, 30-<36, 36-<42 and ≥ 42 ppb for O_3, with the top two O_3 categories combined in the U.S. and the bottom two O_3 categories combined in Canada, based on the different distributions across countries).

We selected confounders *a priori* based on a literature review and a directed acyclic graph. In final models, we adjusted for age (<25, 25–29, 30–34, 35–39, ≥40 years), annual household income (<50,000, 50,000–99,999, 100,000–149,999, ≥150,000 U.S. dollars), educational attainment (≤12, 13–15, 16, ≥17 years), parity (nulliparous, parous), race/ethnicity (conceptualized as a social construct manufactured to justify systems of oppression and privilege; Hispanic, non-Hispanic Black, non-Hispanic Asian, non-Hispanic white, non-Hispanic mixed or other race), population within 5,000 m (quintiles), annual maximum NDVI within 50 m (quintiles), cycle-specific average ambient temperature (quintiles), census tract median household income (quintiles), % of census tract with < high school education (quintiles), % of census tract that identifies as non-Hispanic white (quintiles), season and year of each cycle, and geographic region (U.S.: Pacific [CA, OR, WA], Mountain [AZ, CO, ID, MT, NM, NV, UT, WY], West North Central [IA, KS, MN, MO, NE, ND, SD], West South Central [AR, LA, OK, TX], East North Central [IL, IN, MI, OH, WI], East South Central [AL, KY, MS, TN], South Atlantic [DE, DC, FL, GA, MD, NC, SC, VA, WV], Mid-Atlantic [NJ, NY, PA], New England [CT, MA, ME, NH, RI, VT]; Canada: British Columbia, Alberta, Manitoba/Saskatchewan/ Northwest Territories/Yukon, Quebec, Ontario, eastern provinces). Finally, we adjusted each model for copollutants (*i.e.*, for models of $PM_{2.5}$, we adjusted for NO_2 and O_3 concentrations.).

Loss to follow-up differed across categories of air pollution concentrations. For example, in the U.S., 21% of participants with annual average NO_2 concentrations ≥ 12 ppb were lost to follow-up, compared with 12% of participants with concentrations < 4 ppb. We used inverse probability of continuation weights to account for differential loss to follow-up (Hernan et al., 2000; Howe et al., 2016). as has been previously described in this cohort (Wesselink et al., 2018; Wesselink et al., 2018). Briefly, we calculated stabilized weights that were inversely proportional to the probability of remaining in the study at each cycle. By applying these weights to our regression models, we reweighted the population so that it was balanced for factors related to loss to follow-up.

We conducted several sensitivity analyses. First, we restricted models to nulliparous participants to minimize the potential for reverse causation, wherein couples may change residential locations after having their first child. In other words, where participants live when they enroll in the study may be influenced by their demonstrated fertility. Second, we restricted models to participants living in urban areas to reduce residual confounding by urbanicity. Next, we restricted analyses to participants who had been trying to conceive for < 3 cycles at enrollment, a group in whom outcome misclassification is less likely (due to shorter attempt time) and confounder misclassification is minimized (due to behavior change stemming from concerns about fertility) (Wise et al., 2020). Because ambient air pollution may have a stronger effect on populations with low socioeconomic status, we conducted stratified analyses by educational attainment (<college degree vs. college degree or higher) and household income (<\$75,000 vs. ≥\$75,000 USD/year). Finally, we stratified by age (<30 vs. ≥ 30 years) to determine whether older participants were more sensitive to air pollution exposure.

We used multiple imputation with fully conditional specification methods (van Buuren, 2007) to account for missing data. Missingness was generally low for covariates, ranging from 0% (*e.g.*, age) to 3% (household income). We did not have missing exposure data. For the 13% of participants who did not complete any follow-up questionnaires, we assigned them one cycle of follow-up and imputed their outcome status at that cycle. We conducted a sensitivity analysis restricting to participants who completed at least one follow-up questionnaire. For analysis, we statistically combined estimates across the 20 imputed data sets using Rubin's rule (Rubin, 2004).

3. Results

The 8,747 participants included in the analysis resided in all 48 contiguous U.S. states and all 10 Canadian provinces, and most participants resided in urban areas (72%). After accounting for censoring, 78% of participants from the U.S. and 74% of participants from Canada conceived during 12 cycles of pregnancy attempt time. Cycle-specific concentrations of $PM_{2.5}$ were slightly higher in the U.S. compared with Canada (median = 7.3 and 6.1 $\mu g/m^3$ (), respectively; Figure S2), and showed seasonal variation in both countries, with peaks in January and July every year (Figure S5). NO_2 concentrations were similar in the U.S. and Canada (median = 6.2 and 6.5 ppb, respectively; Figure S3), and peaked annually in January in both countries (Figure S5). Conversely, O_3 concentrations were higher in Canada than in the U.S. (median = 34.3 and 26.3 ppb, respectively; Figure S4), and we observed strong seasonal trends in both countries (peak in the summer; Figure S5). Spearman correlations between air pollutant concentrations are presented in Tables S1 and S2.

Ambient air pollution concentrations were moderately correlated with individual-level sociodemographic characteristics (Tables 1, S3, and S4). For example, non-Hispanic white individuals tended to have lower ambient concentrations of $PM_{2.5}$ and NO_2, but higher concentrations of O_3 compared with other racial/ethnic groups. Air pollution concentrations were also related to neighborhood-level characteristics. $PM_{2.5}$ and NO_2 concentrations correlated positively with urbanicity and population density and inversely with NDVI; associations were in the opposite direction for O_3.

In adjusted models, $PM_{2.5}$ concentrations during any of the three measured time windows were not appreciably associated with fecundability in either the U.S. or Canada (Table

2). Adjusted models were generally slightly attenuated relative to unadjusted models, with several individual (*e.g.*, race/ethnicity) and neighborhood level (*e.g.*, NDVI, census tract median household income) covariates contributing to the change in estimate. In the U.S., the FRs for a 5-μg/m^3 increase in annual average, cycle specific, and preconception average $PM_{2.5}$ concentrations were 0.94 (95% CI: 0.83, 1.08), 1.00 (95% CI: 0.93, 1.07), and 1.00 (95% CI: 0.93, 1.09), respectively. In Canada, the corresponding FRs were 0.92 (95% CI: 0.74, 1.16), 0.97 (95% CI: 0.87, 1.09), and 0.94 (95% CI: 0.80, 1.09), respectively. Likewise, restricted cubic spline analyses did not show strong associations between $PM_{2.5}$ concentrations and fecundability (Fig. 1). There was some evidence of an association between preconception average $PM_{2.5}$ concentrations and lower fecundability, but results were non-monotonic in the U.S. and imprecise in Canada.

For NO_2 concentrations, no consistent monotonic associations with fecundability were observed in either country (Table 2). FRs for a 5-ppb increase in annual average, cycle specific, and preconception average NO_2 concentrations were 1.04 (95% CI: 0.98, 1.10), 1.01 (95% CI: 0.96, 1.06), and 1.02 (95% CI: 0.97, 1.08), respectively in the U.S. and 0.94 (95% CI: 0.79, 1.11), 0.95 (95% CI: 0.83, 1.10), and 0.97 (0.82, 1.13), respectively in Canada. Restricted cubic spline analyses showed a slight inverted-U shape in the U.S., particularly for annual average NO_2 concentrations; in Canada, increasing concentrations of all three measures of NO_2 were associated with slightly lower fecundability, but estimates were imprecise (Fig. 2).

O_3 concentrations were also not strongly associated with fecundability in either country, with patterns essentially the inverse of those observed for NO_2 (Table 2; Fig. 3). FRs for a 5-ppb increase in annual average, cycle specific, and preconception average O_3 concentrations were 0.99 (95% CI: 0.94, 1.05), 1.00 (95% CI: 0.97, 1.03), and 0.99 (95% CI: 0.96, 1.02), respectively in the U.S. and 1.08 (95% CI: 0.94, 1.25), 1.02 (95% CI: 0.94, 1.09), and 1.02 (95% CI: 0.95, 1.11), respectively in Canada.

When we restricted to nulliparous participants (Table S5), annual average $PM_{2.5}$ concentrations were inversely associated with fecundability in the U.S. and Canada (FRs for a 5-μg/m^3 increase were 0.88 [95% CI: 0.74, 1.04] and 0.81 [95% CI: 0.57, 1.15], respectively). The results for other exposure metrics were similar to the main analysis. Results were consistent with the main analysis when we restricted to participants with < 3 cycles of attempt time at enrollment (Table S6) or participants residing in urban areas (Table S7). Likewise, there were not meaningful and consistent differences across strata of educational attainment (Table S8), household income (Table S9), or age (Table S10). Finally, results were similar when we restricted to participants who completed at least one follow-up questionnaire (Table S11), with the exception of annual average $PM_{2.5}$ concentrations and fecundability in Canada, which were stronger than the primary analysis.

4. Discussion

In this prospective cohort study of pregnancy planners residing in the U.S. or Canada, we found that residential ambient concentrations of $PM_{2.5}$, NO_2, and O_3 were not strongly or monotonically associated with fecundability. We analyzed exposures during the year before study enrollment, during each pregnancy attempt cycle, and averaged across the preconception period to address different hypothesized etiologic processes. None of the three exposure windows showed a strong deleterious effect of pollutants on fertility.

Studies examining the association of $PM_{2.5}$ exposure with fertility have reported mixed findings. Long-term $PM_{2.5}$ concentrations were associated with lower fertility in a retrospective cohort study conducted in China (Li et al., 2021) but not in a prospective cohort study of U.S. nurses (Mahalingaiah et al., 2016), a Danish preconception cohort study (Wesselink et al., 2022), or a study of couples undergoing IVF at four U. S. fertility clinics (Quraishi et al., 2019). Median annual $PM_{2.5}$ concentrations in the Chinese study were much higher (56.8 μg/m^3) than in other studies (14.6, 9.6, and 8.7 μg/m^3, respectively), which could explain the discrepancy. Our results (median $PM_{2.5}$ concentrations were 7.5 μg/m^3 in the U.S. and 6.5 μg/m^3 in Canada) are consistent with the null results from similar studies in low exposure settings (Mahalingaiah et al., 2016; Wesselink et al., 2022; Quraishi et al., 2019) and indicate that long-term $PM_{2.5}$ exposure may only be harmful for fertility at high levels.

Other studies have assessed short-term $PM_{2.5}$ exposure in relation to fertility. Several have measured cycle-specific concentrations: a birth cohort study in the Czech Republic (Slama et al., 2013) and a Danish preconception cohort study (Wesselink et al., 2022) found inverse associations between cycle-specific $PM_{2.5}$ concentrations and fecundability, whereas a U.S. preconception cohort study did not (Nobles et al., 2018). Our results are consistent with the latter. Finally, studies of populations undergoing IVF have assessed exposure at even finer windows. In the EARTH study, higher $PM_{2.5}$ concentrations during ovarian stimulation and from oocyte retrieval to embryo implantation were associated with higher probability of IVF failure (Gaskins et al., 2019). However, another IVF cohort did not find an association between $PM_{2.5}$ concentrations during critical windows and fertility (Legro et al., 2010). We cannot make direct comparisons between our findings and those from IVF studies owing to differences in the temporal resolution of pollution data (two-week vs. daily resolution) and lack of accurate information on the timing of early pregnancy events (*e.g.*, conception, implantation) in our cohort.

We found little association between NO_2 concentrations and fecundability, which agrees with other studies of long-term NO_2 exposure, including a Danish preconception cohort study (Wesselink et al., 2022) and a study of couples undergoing IVF at four clinics in the U.S. (Quraishi et al., 2019). However, studies that have examined acute NO_2 exposure during narrow developmental windows have observed associations with fertility. Specifically, three studies of couples undergoing IVF, two in the U.S. (Gaskins et al., 2019; Legro et al., 2010) and one in Korea, (Choe et al., 2018) found that NO_2 concentrations during ovarian stimulation were associated with lower probabilities of intrauterine pregnancy and live birth. A preconception cohort study of couples from Michigan and Texas, U.S., found that NO_x concentrations 8 days after ovulation, but not at other time points or averaged across the menstrual cycle, were associated with reduced fecundability (Nobles et al., 2018).

We found no meaningful association between O_3 concentrations and fecundability, in agreement with most of the literature on this topic, including a Danish preconception cohort study (Wesselink et al., 2022) and three IVF cohorts (Choe et al., 2018; Gaskins et al., 2019; Legro et al., 2010). However, the preconception cohort study of couples from Michigan and Texas mentioned above found an association between O_3 concentrations on 5 and 1 days before ovulation, but not on other specific days or averaged across the menstrual cycle (Nobles et al., 2018). The difference in timing of exposure assessment in the latter study could explain the discrepant results, as could chance.

Previous studies, both in couples trying to conceive spontaneously and through IVF, have shown consistently that residential proximity to major roads is associated with reduced fertility (Gaskins et al., 2018, 2019; Mahalingaiah et al., 2016; Mendola et al., 2017; Nieuwenhuijsen et al., 2014; Wesselink et al., 2020; Quraishi et al., 2019). In fact, a previous analysis in PRESTO found that living close to major roads and having a higher density of major roads around the home was associated with reduced fecundability in the U.S. and Canada (Wesselink et al., 2020). There are several potential reasons for the dissimilarity between these results and the relatively null results from the current study. First, road proximity is an imperfect proxy for traffic-related air pollution. This heterogeneous exposure measure includes non-tailpipe emissions, such as road dust and brake wear, and other components of traffic, such as noise (OECD, 2020). A growing body of work also shows that traffic delay (*i.e.*, congestion) may have its own unique influence on health (Levy et al., 2010; Pedde et al., 2017; Willis et al., 2022). Second, features of the built environment such as green space or neighborhood context (Gascon et al., 2016) may modify associations between environmental hazards and fecundability. We have previously published results that demonstrate associations between higher residential green space and improved fecundability (Willis et al., 2023) as well as higher neighborhood disadvantage and impaired fecundability (Willis et al., 2022). Therefore, other structural factors that are highly correlated with road proximity may account for the observed associations.

Our study had several important limitations. First, we relied on interpolated estimates of exposure rather than measured values at the location of interest. While we used state-of-the-art models that have been validated against monitoring data, these models perform better in some locations than others. For example, models in both countries tend to perform better in urban areas; however, restricting to urban areas did not appreciably change our results. In addition, our exposure assessment was residence-based and did not account for indoor air pollution exposure or time-activity patterns (*i.e.*, air pollution exposure at locations other than the residence) (Chaix et al., 2013; Lane et al., 2013; Weisskopf and Webster, 2017). Therefore, exposure misclassification could have biased our results based on how predictors of exposure misclassification relate to the outcome (*e.g.*, occupational factors, socioeconomic status). Finally, although we accounted for residential mobility by updating address information throughout follow-up, we did not have information on the precise date of address change, which may have resulted in some additional misclassification of exposure.

Second, we derived outcome information from self-reported attempt time at enrollment, typical cycle length, LMP dates, and pregnancy status. Outcome misclassification could have occurred to the extent that we measured these variables with error. Pregnancy attempt time at enrollment may be misclassified, particularly for participants with longer periods of time before enrolling. However, a sensitivity analysis restricted to participants with < 3 cycles of attempt time at enrollment yielded similar results to the main analysis, indicating that this is not an important source of bias. In a validation study of self-reported LMP dates in PRESTO, participants reported similar LMP dates prospectively on a menstrual charting app vs. retrospectively on follow-up questionnaires (Wise et al., 2015). Finally, because we did not collect daily measures of urinary human chorionic gonadotropin, we almost certainly missed some conceptions that ended in early losses before they could be reasonably detected via home pregnancy tests. However, most participants were testing for pregnancy at home (95%) and the average gestational weeks at pregnancy detection in the cohort was 4.0 (interquartile range: 3.7–4.4), indicating that participants were testing early for pregnancy, sometimes before a missed period. Gestational weeks at first positive pregnancy test was similar across air pollution exposure categories. Therefore, we expect that outcome misclassification was minimal and non-differential with respect to exposure.

As in any observational study, unmeasured confounding is a possibility. Although we controlled extensively for individual- and neighborhood-level confounders, there are, for example, other environmental exposures, such as ambient noise, which are correlated with the exposure and for which we could not adjust. Given the broad geographic distribution of the cohort and recruitment over a seven-year period, our results may also be biased due to residual confounding from secular trends by space and/or time.

Our study population comprised North American pregnancy planners who were recruited via the internet. Our results may not generalize to geographic regions with higher levels of ambient air pollution. We have previously demonstrated that internet-based recruitment of participants should not bias etiologic measures of association based on internal comparisons (Hatch et al., 2016). However, pregnancy planners tend to have higher socioeconomic status compared with non-planners, and although we did observe some socioeconomic heterogeneity in our cohort, most participants were college educated and had incomes of >$75,000. Ambient exposure to air pollution may have less of an effect in high socioeconomic populations due to housing characteristics, residential location, or other protective built environment features that could reduce personal exposure to pollution of ambient origin. Therefore, our results may not generalize to populations with lower socioeconomic status. Although we found that the association of air pollution and fertility was relatively consistent across strata of educational attainment and income, we had limited power to assess effect modification in the lowest socioeconomic status group.

In summary, our results indicate that relatively low levels of ambient $PM_{2.5}$, NO_2, and O_3 during the year before the pregnancy attempt, averaged across each menstrual cycle, and averaged across the preconception period are not appreciably related to fecundability. It remains possible that exposure to higher levels of air pollution (beyond what we observed in this study population), exposures during specific critical windows during the early reproductive process, and/or other components of air pollution (*e.g.*, components of $PM_{2.5}$, heavy metals) may have an adverse effect on fertility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that has been used is confidential.

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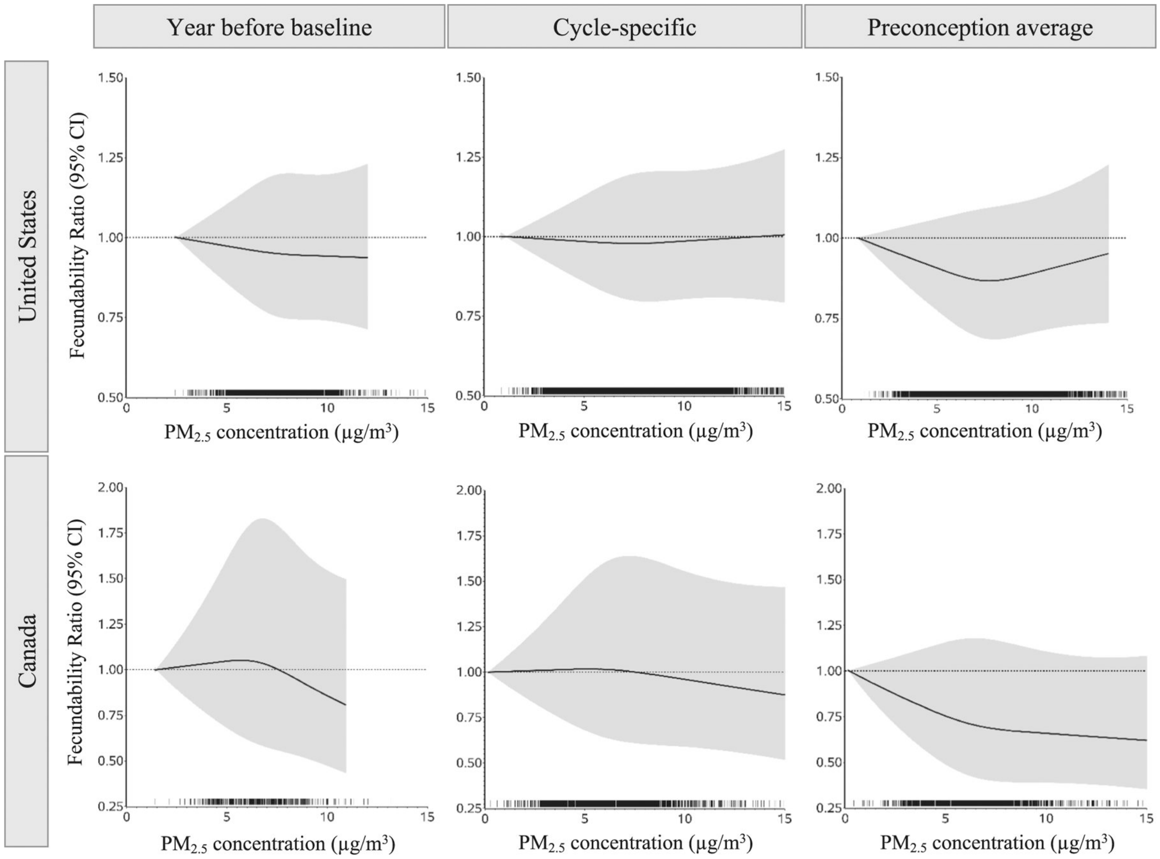

Fig. 1.

Associations of PM2.5 concentrations (annual average during year before baseline [left column], time-varying menstrual cycle-specific [middle column], and time-varying preconception average [right column]) with fecundability, fit using restricted cubic splines, United States (top row) and Canada (bottom row), PRESTO, 2013–2019. Splines are trimmed at the 99th percentile and have three knots each at the 10th, 50th, and 90th percentiles. Models are adjusted for age, household income, education, parity, race/ethnicity, population with 5,000 m, annual maximum NDVI, annual average temperature, census tract median household income, % of census tract with < high school education, % of census tract non-Hispanic white, season, calendar year, geographic region, and co-pollutants.

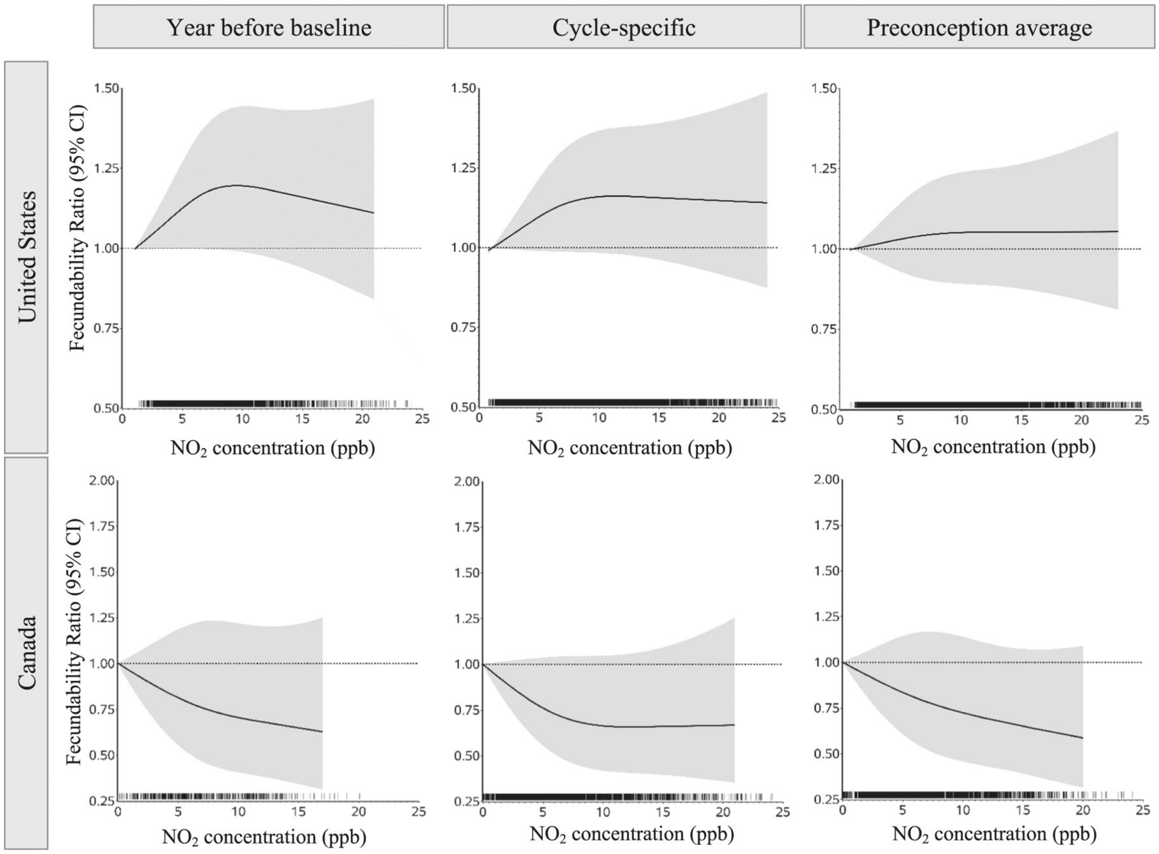

Fig. 2.

Associations of NO_2 concentrations (annual average during year before baseline [left column], time-varying menstrual cycle-specific [middle column], and time-varying preconception average [right column]) with fecundability, fit using restricted cubic splines, United States (top row) and Canada (bottom row), PRESTO, 2013–2019. Splines are trimmed at the 99th percentile and have three knots each at the 10th, 50th, and 90th percentiles. Models are adjusted for age, household income, education, parity, race/ethnicity, population with 5,000 m, annual maximum NDVI, annual average temperature, census tract median household income, % of census tract with < high school education, % of census tract non-Hispanic white, season, calendar year, geographic region, and co-pollutants.

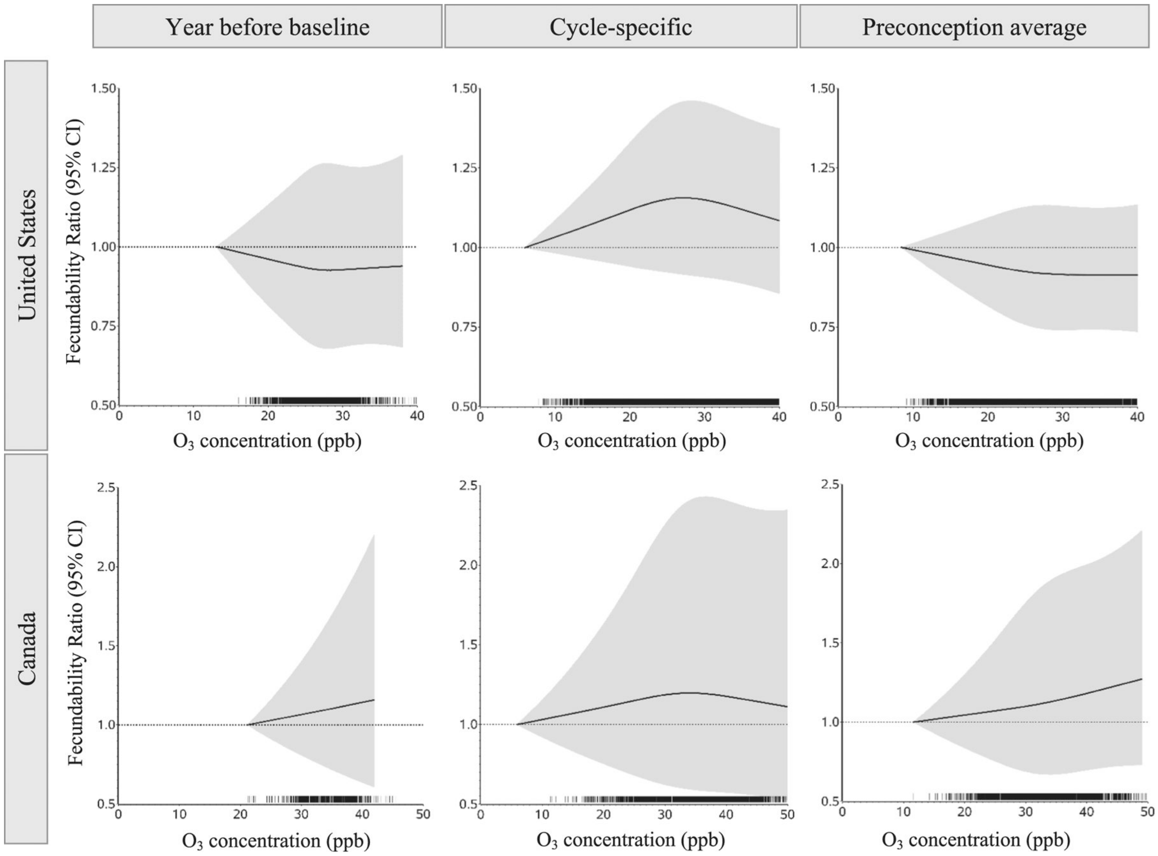

Fig. 3.

Associations of O_3 concentrations (annual average during year before baseline [left column], time-varying menstrual cycle-specific [middle column], and time-varying preconception average [right column]) with fecundability, fit using restricted cubic splines, United States (top row) and Canada (bottom row), PRESTO, 2013–2019. Splines are trimmed at the 99th percentile and have three knots each at the 10th, 50th, and 90th percentiles. Models are adjusted for age, household income, education, parity, race/ethnicity, population with 5,000 m, annual maximum NDVI, annual average temperature, census tract median household income, % of census tract with < high school education, % of census tract non-Hispanic white, season, calendar year, geographic region, and co-pollutants.

Table 1

Baseline characteristics of participants by residential ambient concentrations of particulate matter < 2.5 μm ($PM_{2.5}$) in the year before baseline, Pregnancy Study Online, 2013–2019.

	United States					Canada				
		Annual average $PM_{2.5}$ concentration (μg/m^3)					Annual average $PM_{2.5}$ concentration (μg/m^3)			
	Total	**<6**	**6-<8**	**8-<10**	**≥10**	**Total**	**<6**	**6-<8**	**8-<10**	**≥10**
Number of participants	7,304	1,009	3,707	2,216	372	1,350	514	556	239	41
Age (years), mean	29.9	30.0	29.9	30.0	30.2	29.5	29.1	29.6	29.5	29.7
Race/ethnicity, %										
Non-Hispanic White	82.5	88.7	83.9	79.4	71.6	89.3	92.6	87.3	86.9	90.6
Non-Hispanic Black	4.0	0.6	3.4	6.5	3.2	1.0	0.2	1.3	2.0	0.0
Non-Hispanic Asian	1.8	1.2	1.3	2.1	5.3	2.4	1.2	4.1	1.3	0.0
Hispanic	7.5	5.6	7.2	7.5	14.8	2.4	1.6	2.5	4.2	0.0
Non-Hispanic other/mixed race	4.3	3.9	4.2	4.5	5.1	4.8	4.4	4.8	5.7	8.7
≤High school, %	6.1	6.5	6.2	6.1	4.2	5.1	3.8	6.4	5.4	0.0
Household income < 50,000 USD, %	22.6	19.0	23.2	23.1	22.7	16.2	15.5	17.0	16.1	17.3
Relationship duration (years), mean	5.1	5.4	5.1	5.0	5.3	5.3	5.2	5.2	5.3	5.3
Resides at same address as partner, %	98.7	99.0	98.7	98.8	97.1	98.3	98.1	98.4	99.2	96.7
Body mass index (kg/m^2), mean	28.3	27.7	28.7	28.1	27.7	27.4	27.6	27.6	26.1	28.0
Physical activity (MET hours/week), mean	31.7	32.3	31.0	32.0	34.5	33.2	32.3	32.7	38.1	27.7
Current smoker, %	7.5	7.3	8.1	7.1	4.7	8.4	8.5	7.8	6.8	16.4
Daily use of multivitamins, %	78.9	82.2	78.3	78.6	77.7	77.4	76.8	78.0	76.9	69.7
Parous, %	34.1	33.1	36.7	31.8	24.8	24.5	19.6	23.0	24.3	37.6
History of infertility, %	10.8	8.8	11.4	11.2	8.5	7.1	5.9	7.0	9.0	9.3
Attempt time at study entry (cycles), mean	2.8	2.6	2.8	2.8	3.1	2.6	2.6	2.6	2.6	2.9
Intercourse frequency < 1 time/week, %	21.1	20.9	21.6	20.7	17.4	20.1	19.8	19.2	18.4	17.8
Doing something to improve chances, %	78.0	80.1	77.5	78.1	77.4	76.8	73.7	78.9	78.9	73.6
Population within 5,000 m buffer, mean	87,100	30,300	70,400	122,400	196,100	109,000	50,300	131,600	185,700	119,200
Annual maximum NDVI in 50 m buffer, mean	0.60	0.68	0.62	0.56	0.42	0.55	0.60	0.53	0.50	0.48
Annual mean temperature (○ Celsius)	13.5	10.3	13.5	14.8	16.2	5.9	5.4	6.5	6.1	3.9
Urban census tract, %	71.0	45.8	69.8	80.9	93.7	77.5	62.5	86.7	90.3	77.6

	United States					Canada				
		Annual average $PM_{2.5}$ concentration ($\mu g/m^3$)					Annual average $PM_{2.5}$ concentration ($\mu g/m^3$)			
	Total	**<6**	**6-<8**	**8-<10**	**≥10**	**Total**	**<6**	**6-<8**	**8-<10**	**≥10**
Census tract median household income[b]	60,100	66,900	59,800	57,800	58,800	78,900	79,900	79,900	74,400	77,300
Census tract % ≤high school education	11.6	9.3	11.3	12.5	15.0	16.7	17.3	16.1	16.2	15.7
Census tract % non-Hispanic white	73.1	84.7	75.6	66.6	55.1	81.5	88.4	77.6	75.1	81.4
NO_2 concentration (ppb), mean	7.4	4.9	6.8	8.6	12.1	7.3	5.1	8.1	9.9	9.6
O_3 concentration (ppb), mean	27.0	28.4	27.3	26.3	25.8	34.2	33.5	34.5	34.8	33.8

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

[b]Units = U.S. dollars and Canadian dollars.

MET = metabolic equivalent of task; NDVI = normalized difference vegetation index; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter < 2.5 μm; USD = United States dollars.

Table 2

Association between residential ambient air pollution concentrations and fecundability, Pregnancy Study Online, 2013–2019.

Exposure	United States (n = 7,304)				Canada (n = 1,443)			
	No. of cycles	No. of preg-nancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	No. of cycles	No. of preg-nancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)
$PM_{2.5}$ (μg/m^3)								
Year before baseline								
Continuous[b]	29,246	4,329	0.91 (0.83, 0.99)	0.94 (0.83, 1.08)	5,245	743	0.93 (0.77, 1.13)	0.92 (0.74, 1.16)
Categorical								
<6	3,983	624	Reference	Reference	1,964	283	Reference	Reference
6-<8	14,623	2,177	0.98 (0.91, 1.06)	0.97 (0.90, 1.05)	2,103	308	1.01 (0.87, 1.17)	0.93 (0.77, 1.12)
8-<10	9,125	1,306	0.92 (0.83, 1.01)	0.94 (0.85, 1.05)	1,030	134	0.93 (0.77, 1.13)	0.91 (0.72, 1.16)
≥10	1,515	222	0.99 (0.95, 1.04)	1.00 (0.95, 1.06)	148	18	0.85 (0.54, 1.34)	0.85 (0.56, 1.28)
Cycle-specific								
Continuous[b]	29,227	4,329	0.96 (0.90, 1.01)	1.00 (0.93, 1.07)	4,719	677	0.93 (0.84, 1.04)	0.97 (0.87, 1.09)
Categorical								
<6	7,426	1,127	Reference	Reference	2,299	342	Reference	Reference
6-<8	11,365	1,699	0.96 (0.89, 1.03)	1.00 (0.92, 1.07)	1,343	199	0.97 (0.82, 1.14)	0.98 (0.83, 1.17)
8-<10	7,210	1,034	0.91 (0.84, 0.98)	0.96 (0.88, 1.05)	643	80	0.82 (0.65, 1.03)	0.87 (0.68, 1.12)
≥10	3,226	469	0.93 (0.84, 1.02)	0.97 (0.86, 1.09)	434	56	0.86 (0.66, 1.12)	0.95 (0.72, 1.25)
Preconception average								
Continuous[b]	29,237	4,329	0.97 (0.91, 1.04)	1.00 (0.93, 1.09)	4,749	677	0.93 (0.82, 1.05)	0.94 (0.80, 1.09)
Categorical								
<6	5,629	891	Reference	Reference	2,088	319	Reference	Reference
6-<8	13,026	1,901	0.95 (0.89, 1.03)	0.99 (0.91, 1.07)	1,509	216	0.95 (0.81, 1.12)	0.91 (0.76, 1.10)
8-<10	7,885	1,124	0.92 (0.85, 0.99)	0.97 (0.88, 1.07)	765	94	0.88 (0.71, 1.09)	0.89 (0.70, 1.14)
≥10	2,697	413	0.98 (0.88, 1.09)	1.03 (0.90, 1.17)	387	48	0.82 (0.62, 1.10)	0.83 (0.60, 1.13)
NO_2 (ppb)								
Year before baseline								
Continuous[b]	29,246	4,329	1.00 (0.97, 1.04)	1.04 (0.98, 1.10)	5,546	785	0.96 (0.88, 1.05)	0.94 (0.79, 1.11)
Categorical								

Exposure	United States (n = 7,304)				Canada (n = 1,443)			
	No. of cycles	No. of preg-nancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	No. of cycles	No. of preg-nancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)
<4	5,130	769	Reference	Reference	1,158	171	Reference	Reference
4-<8	13,804	2,027	1.01 (0.95, 1.08)	1.00 (0.91, 1.09)	2,048	300	0.97 (0.81, 1.16)	0.87 (0.66, 1.13)
8-<12	6,620	1,000	1.03 (0.96, 1.12)	1.01 (0.89, 1.14)	1,508	208	0.93 (0.77, 1.12)	0.82 (0.55, 1.22)
≥12	3,692	533	0.99 (0.96, 1.03)	0.97 (0.83, 1.14)	832	106	0.90 (0.71, 1.15)	0.78 (0.49, 1.25)
Cyde-specific								
Continuous[b]	29,227	4,329	1.01 (0.98, 1.04)	1.01 (0.96, 1.06)	5,538	785	0.97 (0.91, 1.05)	0.95 (0.83, 1.10)
Categorical								
<4	6,752	967	Reference	Reference	1,462	212	Reference	Reference
4-<8	12,374	1,832	1.06 (0.99, 1.14)	1.05 (0.97, 1.14)	1,956	280	0.94 (0.79, 1.11)	0.88 (0.69, 1.11)
8-<12	5,980	927	1.09 (1.00, 1.18)	1.09 (0.97, 1.22)	1,164	164	0.97 (0.81, 1.17)	0.89 (0.66, 1.18)
≥12	4,121	603	1.02 (0.93, 1.12)	1.00 (0.86, 1.17)	956	129	0.93 (0.76, 1.15)	0.87 (0.61, 1.26)
Preconception average								
Continuous[b]	29,237	4,329	1.00 (0.97, 1.03)	1.02 (0.97, 1.08)	5,542	785	0.98 (0.91, 1.06)	0.97 (0.82, 1.13)
Categorical								
<4	6,069	908	Reference	Reference	1,399	214	Reference	Reference
4-<8	12,722	1,858	1.03 (0.95, 1.11)	1.03 (0.95, 1.12)	1,986	269	0.90 (0.76, 1.07)	0.84 (0.67, 1.06)
8-<12	6,361	956	1.04 (0.96, 1.13)	1.05 (0.94, 1.17)	1,192	187	1.06 (0.88, 1.27)	0.93 (0.69, 1.25)
≥12	4,085	607	1.01 (0.92, 1.11)	1.03 (0.89, 1.19)	965	115	0.86 (0.69, 1.07)	0.81 (0.54, 1.20)
				O_3 (ppb) [c]				
Year before baseline								
Continuous[b]	29,246	4,329	1.01 (0.97, 1.05)	0.99 (0.94, 1.05)	5,546	785	1.06 (0.98, 1.15)	1.08 (0.94, 1.25)
Categorical								
<24	4,466	669	Reference	Reference	143	19	Reference	Reference
24-<30	20,578	3,050	1.02 (0.95, 1.11)	1.01 (0.92, 1.11)	759	93		
30-<36	3,771	551	1.06 (0.96, 1.18)	1.02 (0.90, 1.16)	2,757	373	1.08 (0.88, 1.32)	1.04 (0.91, 1.19)
36-<42	317	49	0.87 (0.69, 1.10)	0.91 (0.70, 1.20)	1,790	286	1.23 (1.00, 1.52)	1.11 (0.92, 1.35)
≥42	114	10			97	14	1.08 (0.64, 1.83)	1.12 (0.87, 1.45)
Cyde-specific								
Continuous[b]	29,227	4,329	0.98 (0.96, 1.00)	1.00 (0.97, 1.03)	5,538	785	1.03 (0.98, 1.07)	1.02 (0.94, 1.09)

Exposure	United States (n = 7,304) No. of cycles	No. of pregnancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	Canada (n = 1,443) No. of cycles	No. of pregnancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)
Categorical								
<24	11,404	1,772	Reference	Reference	603	91	Reference	Reference
24-<30	8,156	1,222	0.96 (0.90, 1.03)	1.01 (0.93, 1.09)	1,497	204		
30-<36	6,983	959	0.91 (0.85, 0.98)	0.97 (0.88, 1.06)	1,332	189	1.06 (0.90, 1.26)	1.13 (0.92, 1.39)
36-<42	2,230	319	0.90 (0.82, 1.00)	0.95 (0.83, 1.08)	1,233	167	1.01 (0.84, 1.20)	1.05 (0.81, 1.34)
≥42	454	57			873	134	1.20 (0.99, 1.45)	1.11 (0.82, 1.49)
Preconception average								
Continuous[b]	29,237	4,329	0.98 (0.95, 1.00)	0.99 (0.96, 1.02)	5,542	785	1.03 (0.98, 1.07)	1.02 (0.95, 1.11)
Categorical								
<24	10,409	1,648	Reference	Reference	461	67	Reference	Reference
24-<30	11,046	1,532	0.92 (0.86, 0.98)	0.96 (0.89, 1.03)	1,476	199		
30-<36	6,138	902	0.93 (0.86, 1.00)	0.97 (0.88, 1.06)	1,759	246	1.11 (0.94, 1.31)	1.12 (0.91, 1.37)
36-<42	1,325	201	0.92 (0.82, 1.04)	0.95 (0.82, 1.10)	1,237	169	1.03 (0.86, 1.24)	1.06 (0.83, 1.35)
≥42	319	46			609	104	1.21 (0.97, 1.50)	1.23 (0.90, 1.69)

[a] Adjusted for age, household income, education, parity, race/ethnicity, population with 5,000 m, annual maximum NDVI, annual average temperature, census tract median household income, % of census tract with < high school education, % of census tract non-Hispanic white, season, calendar year, geographic region, and co-pollutants.

[b] Continuous estimates are for a 5 μg/m3 (or ppb) increase in exposure.

[c] Due to small numbers and different distributions of O_3 across countries, we combined the top two categories of O_3 concentration in the U.S. the bottom two categories of O_3 concentration in Canada.