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Adult air pollution exposure and risk of infertility in the Nurses' Health Study II

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STUDY QUESTION: Is there an association between air pollution exposures and incident infertility?

SUMMARY ANSWER: Increased exposure to air pollution is associated with an increased incidence of infertility.

WHAT IS KNOWN ALREADY: Exposures to air pollution have been associated with lower conception and fertility rates. However, the impact of pollution on infertility incidence is unknown.

STUDY DESIGN, SIZE, DURATION: Prospective cohort study using data collected from 116 430 female nurses from September 1989 to December 2003 as part of the Nurses' Health Study II cohort.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Infertility was defined by report of attempted conception for ≥12 months without success. Participants were able to report if evaluation was sought and if so, offer multiple clinical indications for infertility. After exclusion, 36 294 members were included in the analysis. Proximity to major roadways and ambient exposures to particulate matter less than 10 microns (PM_{10}), between 2.5 and 10 microns ($PM_{2.5-10}$), and less than 2.5 microns ($PM_{2.5}$) were determined for residential addresses for the 36 294 members between the years of 1993 and 2003. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using multivariable adjusted Cox proportional hazard models with time-varying covariates.

MAIN RESULTS AND THE ROLE OF CHANCE: Over 213 416 person-years, there were 2508 incident reports of infertility. Results for overall infertility were inconsistent across exposure types. We observed a small increased risk for those living closer to compared to farther from a major road, multivariable adjusted HR = 1.11 (CI: 1.02–1.20). This was consistent for those reporting primary or secondary infertility. For women living closer to compared to farther from a major road, for primary infertility HR = 1.05 (CI: 0.94–1.17), while for secondary infertility HR = 1.21 (CI: 1.07–1.36). In addition, the HR for every 10 $\mu g/m^3$ increase in cumulative $PM_{2.5-10}$ among women with primary infertility was 1.10 (CI: 0.96–1.27), and similarly was 1.10 (CI: 0.94–1.28) for those with secondary infertility.

LIMITATIONS, REASONS FOR CAUTION: Within the 2 year window of infertility diagnosis, we do not have the exact date of diagnosis or the exact timing of the start of attempting conception. As infertility status and subtypes of infertility were prospectively collected biennially, we were unable to tightly examine the timing of exposures on incidence of infertility. In terms of exposure quantification, we used ambient air pollution exposures as a proxy for personal exposures, potentially leading to exposure misclassification. However, several studies suggest that ambient measurements are an acceptable surrogate for individual level exposures in most populations.

WIDER IMPLICATIONS OF THE FINDINGS: We observed an association between all size fractions of PM exposure, as well as traffic-related air pollution, and incidence of infertility. Of note, the strongest association was observed between cumulative average exposures over the course of follow-up and the risk of infertility, suggesting that chronic exposures may be of greater importance than short-term exposures.

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Key words: infertility / air pollution / particulate matter / environment / nurses' health study 2

Introduction

Infertility is a complex disorder that is comprised of female factors (tubal, cervical, uterine, endometriosis, ovarian, hormonal), male factors (based on semen parameters), and unexplained causes. Infertility is defined as attempting conception for 1 year without success, or if age is 35 or greater, attempting for 6 months or more without success (SART, 2008). Over the last two decades, the prevalence of infertility has been approximately 10% worldwide, with some geographic variation - most notably increased prevalence in Sub-Saharan Africa and South Asia (Bachu, 1997; Mascarenhas *et al.*, 2012).

There are known exposures that increase the risk of certain types of infertility, such as sexually transmitted disease causing tubal factor infertility (Miettinen *et al.*, 1990; Grodstein *et al.*, 1993; Mårdh, 2004); gonadotoxic radiation or chemotherapy exposure causing premature ovarian/testicular failure (Green *et al.*, 2009; Barton *et al.*, 2013); greater body mass index (BMI) associated with ovulatory infertility (Grodstein *et al.*, 1994; Bolúmar *et al.*, 2000; Rich-Edwards *et al.*, 2002); and prenatal exposure to endocrine disruptors such as diethylstilbestrol (DES) associated with uterine factor infertility (Palmer *et al.*, 2001; Hoover *et al.*, 2011).

Furthermore, exposure to tobacco smoke has also been associated with poor reproductive outcomes. A number of studies demonstrate a longer time to conception in female smokers (Baird and Wilcox, 1985; Bolúmar *et al.*, 1996; Hull *et al.*, 2000) and a near doubling of number of *in vitro* fertilization (IVF) cycles needed to achieve conception in female smokers undergoing IVF (Augood *et al.*, 1998) as well as a notable decline in success rates in women exposed to secondhand smoke (Meeker *et al.*, 2007; Benedict *et al.*, 2011).

Exposure to air pollution has also been associated with a variety of similar adverse health effects in several human body systems, including human reproduction. Air pollution exposures have been found to have hormonal activity and to be negatively associated with early reproductive outcomes such as fertilization and implantation as observed in human IVF (Legro *et al.*, 2010; Perin *et al.*, 2010) and with birth outcomes, such as low birthweight and prematurity (Bobak, 2000; Morello-Frosch *et al.*, 2000; Shah and Balkhair, 2011; Stieb *et al.*, 2012; Dadvand *et al.*, 2013). One birth-based cohort design with retrospectively assessed time to pregnancy found that each increase of 10 $\mu g/m^3$ in $PM_{2.5}$ levels was associated with reduction in fecundability (month-specific chance of conception) of 22% (95% confidence interval (CI): 6–35%) (Slama *et al.*, 2013). However there has only been a single epidemiologic study on the impact of air pollution on human fertility. This recent cross-sectional study evaluated air pollution and human fertility rates over a 1-year period in Barcelona, Spain (Nieuwenhuijsen *et al.*, 2014). They found a reduction in census tract level fertility rates with increasing census tract levels of traffic-related air pollution (particulate matter (PM) and oxides of nitrogen (NO_x)). The relationship was strongest for particulate matter with an aerodynamic diameter between 2.5 and 10 microns ($PM_{2.5-10}$), with a 13% reduction in fertility, (CI: 6–18% reduction) per inter-quartile range (IQR) increase in $PM_{2.5-10}$.

The objective of this study was to assess the relation between incident infertility and air pollution exposures as measured by exposure to PM less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$), $PM_{2.5-10}$, and PM less than 10 microns in aerodynamic diameter (PM_{10}), as well as traffic-related exposure measured by distance to road in a prospective cohort of women enrolled in the Nurses' Health Study II (NHSII).

Materials and Methods

Study population and case ascertainment

All study participants were members of the NHS II, a prospective cohort started in 1989 when 116 430 female nurses aged 25–42 years completed a baseline questionnaire. At enrollment, the women resided in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas). However, as of the mid-1990s, members of the cohort reside in all 50 states and the District of Columbia. Biennial follow-up questionnaires were mailed with response rates over 90%, and each collects information on incidence of disease and on a variety of dynamic lifestyle characteristics. Women were excluded from the current study if by 1993 they were over 45 years of age ($n = 2765$), no longer responded to questionnaires ($n = 1804$), had undergone a hysterectomy ($n = 4381$) or tubal ligation ($n = 21\,915$), had previously been diagnosed with cancer (other than skin cancer) ($n = 1321$), were under 45 years of age and menopausal ($n = 2914$), had a partner who had undergone a vasectomy ($n = 20\,456$), or had previously reported infertility ($n = 18\,409$). In order to assess exposure, women were also excluded if they did not have at least one home address within the continental United States that would be geocoded to the street segment level ($n = 5541$). After these exclusions, there were a total of 36 294 women available for analysis.

On the baseline questionnaire and each follow-up questionnaire, women were asked to report if they had attempted to become pregnant for at least 1 year without success, the age at which this occurred and, if known, the reason or reasons for the infertility. Women could select one or more of

the following reasons for infertility: (i) tubal factor, (ii) ovulatory factor, (iii) endometriosis, (iv) cervical mucous factor, (v) male factor, (vi) unexplained, or (vii) other reason. Primary infertility was defined as the first report of infertility among nulliparous women. Secondary infertility was defined as first report of infertility among parous women. For all cases, date of diagnosis was assigned at the mid-point between receipt of the questionnaire before and the questionnaire during which infertility was reported.

Exposure assessment

Residential address information was updated for each participant every 2 years as part of the questionnaire mailing process and was geocoded to obtain latitude and longitude for all questionnaire mailing addresses. We calculated distance to road at each residential address as a proxy for all exposures related to traffic. Distance to road (in meters) for all available nurses' addresses was determined using geographic information system (GIS) software (ArcGIS, version 9.2; ESRI, Redlands, CA) and the ESRI StreetPro 2007 data layer. We selected U.S. Census feature class codes to include: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), or A3 (smaller, secondary roads, usually with more than two lanes) road segments. The shortest distance between each address and the closest road segment was calculated. Analyses were conducted using the distance to the closest of all three road types and distance to the two largest road types (A1, A2). Based on the distribution of distance in the cohort and on exposure studies showing exponential decay in exposures with increasing distance from a road (Karner *et al.*, 2010), for our primary analyses we divided distance to road into the following categories: 0–199 m and ≥200 m. We also considered additional cut-points out to 500 m in sensitivity analyses.

Predicted ambient exposure to PM_{10} and $PM_{2.5}$ were generated from nationwide spatiotemporal models (Yanosky *et al.*, 2014). Data were available for each month starting in January 1988 at all of the geocoded addresses of each cohort member. The models used monthly average PM_{10} and/or $PM_{2.5}$ data from the United States Environmental Protection Agency's (USEPA) Air Quality System, a nationwide network of continuous and filter-based monitors, as well as monitoring data from various other sources. The models also used GIS to incorporate information on several geospatial predictors. All PM data and GIS data were used in generalized additive statistical models with smooth terms of space and time to create separate PM prediction surfaces for each month (Yanosky *et al.*, 2014). Since monitoring data on $PM_{2.5}$ is limited prior to 1999, $PM_{2.5}$ in the period before 1999 was modeled using data on PM_{10} and airport visibility (Yanosky *et al.*, 2014). By subtraction of the monthly values, information was also available on $PM_{2.5-10}$. As the etiologic window during which air pollution may affect infertility is not known, we calculated three different time-varying exposure measures: the average air pollution in the 2 prior calendar years, the average air pollution in the 4 prior calendar years, and the cumulative average exposure from 1989 to the current time period.

Additional covariates

We examined possible confounding by numerous *a priori* selected risk factors for infertility or predictors of exposure including: age (in months), race (white/black/other), age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, 17, missing), smoking status (current/former/never), body mass index (BMI-continuous), parity (parous/nulliparous), oral contraception use (never/past/current/missing), history of ever performing rotating shift work (ever/never) (Schernhammer *et al.*, 2011), overall diet quality as measured by the 2010 Alternative Healthy Eating Index (McCullough and Willett, 2006; Chiuve *et al.*, 2012), region (Northeast/Midwest/West /South), and census tract level median income (continuous) and median home value (continuous). Information for all covariates (except age at menarche and race) was updated every 2 years. To identify confounders, each variable (or set of indicator variables) was added separately to a basic model that included age and race. We defined confounders as variables that changed the main effect of traffic exposure or PM by at least 10% when added to this basic model (Greenland, 1989).

Statistical analysis

Person-time accrued from 1 September 1993 until first diagnosis of infertility, loss to follow-up, date of death, or the end of follow-up (31 December 2003), whichever occurred first. Person-time was calculated starting in 1993 to allow for the estimation of up to 4 years of previous PM exposure from baseline enrollment in September, 1989. Person-time was excluded from follow-up for any period in which the home address was outside of the continental United States or was unable to be geocoded to the street segment level. Time-varying Cox proportional hazards models were used to assess the association of incidence of overall infertility or specific reasons for infertility with exposure to roadway proximity or each size fraction of PM. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for categories of roadway proximity or for each 10 microgram per cubic meter ($\mu g/m^3$) increase in PM. Cubic regression splines were used to check for departures of the dose–response function from linearity. The dataset was converted to an Anderson-Gill data structure with a record for each 2-year time period, including person-time, the appropriate exposure calculated for that time period, whether the person was censored during the interval, and covariate information. All Cox models were stratified by age in months and calendar year. An alpha level of 0.05 was used to determine statistical significance.

To assess effect modification, stratified analyses were performed for BMI ($\leq$25 kg/m^2 versus >25 kg/m^2), age in Society for Assisted Reproductive Technologies (SART) categories (0–30, 31–34, 35–37, 38–40, ≥41 years), region of residence (Northeast, Midwest, South, West), and history of rotating shift work (ever versus. never). Separate models stratified by parity (nulliparous and parous) were performed. The statistical significance of any observed effect modification was determined by the Wald test from the multiplicative interaction terms. All statistical analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

Ethical approval

The study was approved by the Institutional Review Boards (IRB) of Boston University School of Medicine/Boston Medical Center and Brigham and Women's Hospital.

Results

A total of 36 294 women comprised this study population for analyses of incident infertility and residential proximity to roadway over the full period of follow-up. The demographic characteristics of the full study population and the analytic cohort overall and by category of roadway proximity are presented in Table I as a full cohort. The average age of the participants in the analytic cohort was slightly less than in the full cohort (36.8 (standard deviation (SD) = 4.2) years versus 38.7 (SD = 4.7) years), the average BMI in both samples was 25, the population was mostly Caucasian with an age at menarche of 12 years or more, and most were former or never smokers. There was little difference between the analytic and full cohorts, with the exception of parity as women in the analytic cohort were less likely to be parous due to restricting the analyses to women under 45 years of age. . Several of the characteristics varied across the distance to road categories in the analytic

Table I Age-standardized baseline characteristics of Nurses' Health Study II participants in the full (N = 116 430) and analytic (N = 36 294) cohorts.

			By distance (m) to nearest A1–A3 roadway	
Characteristics (mean (SD) or percent)	**Full cohort**	**Analytic cohort**	**200+ m**	**0–199 m**
Age (years)[a]	38.7 (4.7)	36.8(4.2)	36.8 (4.2)	36.9 (4.2)
SART age categories[b]				
<30.9	6	9	9	9
31–34.9	18	26	26	26
35–37.9	20	23	24	23
38–40.9	22	21	21	21
≥41	34	20	19	20
Body mass index (kg/m^2)	25.4 (5.7)	25.1 (5.8)	24.9 (5.6)	25.2 (5.9)
0–18.9	4	5	5	5
19.0–20.4	10	12	12	12
20.5–21.9	15	17	18	17
22.0–24.9	25	27	27	26
25.0–29.9	21	21	21	21
≥30	15	15	15	16
Caucasian	92	93	94	92
Currently married	90	84	87	80
Nulliparous	22	33	29	37
Age at menarche (years)				
<12	25	23	23	24
12	30	30	30	30
>12	45	46	46	46
Oral contraception use				
Never	13	18	17	19
Past	72	65	65	64
Current	8	17	17	17
Cigarette smoking				
Never	65	67	68	66
Past	23	23	22	23
Current	11	10	10	11
Ever perform rotating shift work	32	31	32	31
Alternative Healthy Eating Index	39.7 (21.2)	42.4 (19.6)	42.1 (19.4)	42.9 (19.8)
Census tract median income ($10 000)	6.2 (2.3)	6.5 (2.4)	6.6 (2.2)	6.4 (2.5)
Census tract median home value ($100 000)	1.6 (1.2)	1.7 (1.3)	1.7(1.1)	1.9 (1.6)
Residence region				
Northeast	34	36	33	40
Midwest	33	32	34	29
West	15	16	14	19
South	18	15	18	12

Values are standardized to the age distribution of the study population.
[a]Value is not age adjusted.
[b]The 41–42.9 and ≥ 43 Society for Assisted Reproductive Technologies (SART) age categories have been combined due to small sample size.

cohort. For example, more nulliparous women and women in the Northeast lived closer to roadways, and more married women lived further from roadways.

Distributions of the PM metrics are presented in Table II and the correlations between exposure measures are presented in Supplementary Table SI. There was little difference in the distributions of the 2-year

Table II Distributions of the time-varying particulate matter (PM) pollution metrics (September 1993–December 2003) among 36 294 women in the Nurses' Health Study II (NHSII).

Metric	Mean ± SD	Median (IQR)	Min	Max
2-year average ($\mu g/m^3$)				
PM_{10}	24.4 ± 6.2	23.7 (6.9)	4.5	69.9
$PM_{2.5-10}$	9.9 ± 4.5	9.0 (5.2)	−0.2	48.0
$PM_{2.5}$	14.5 ± 3.0	14.6 (4.1)	2.4	28.2
4-year average ($\mu g/m^3$)				
PM_{10}	22.6 ± 5.4	22.0 (6.1)	4.9	56.6
$PM_{2.5-10}$	8.9 ± 4.1	8.0 (4.8)	0.1	43.4
$PM_{2.5}$	13.8 ± 2.7	13.8 (3.8)	2.6	23.9
Cumulative average ($\mu g/m^3$)				
PM_{10}	27.3 ± 6.6	26.3 (7.0)	8.3	74.7
$PM_{2.5-10}$	11.4 ± 4.9	10.3 (5.4)	1.8	53.6
$PM_{2.5}$	15.9 ± 3.1	16.1 (4.2)	4.0	29.3

Note: Negative values for $PM_{2.5-10}$ are possible, as this measure is created by subtraction of the predicted values for PM_{10} and $PM_{2.5}$ at each location.

and 4-year PM measures; however, the cumulative average measures were higher than the other two measures. The mean and standard deviations were similar to the median and IQRs for most measures, reflecting relatively unskewed distributions. For each of the size fractions, different time measures were highly correlated (correlation coefficients >0.88); however, within a time period, $PM_{2.5-10}$ and $PM_{2.5}$ were not well correlated (correlation coefficients ~0.2), but PM_{10} was highly correlated with $PM_{2.5}$ and $PM_{2.5-10}$.

A total of 2508 incident cases of infertility were observed over 213 416 person-years of follow-up. The associations of overall incident infertility with distance to road and the PM metrics are presented in Table III. In basic models (adjusted only for age, race, calendar time, and geographic region), living closer to a roadway, regardless of specific road type or cut-point categorization used, was statistically significantly associated with small increased risk of infertility, compared to living farther from a roadway, basic HR = 1.21 (CI: 1.11–1.30) (Table III). A small elevation in risk was also observed in basic models quantifying the association with each 10 $\mu g/m^3$ increase in all of the $PM_{2.5-10}$ and PM_{10} metrics. No statistically significant deviations from linearity were observed; therefore we present the linear models. This observation was least consistent for $PM_{2.5}$. The unadjusted HRs for each 10 $\mu g/m^3$ increase in cumulative average exposure were PM_{10} = 1.10 (CI: 1.03–1.18), $PM_{2.5-10}$ = 1.14 (CI: 1.03–1.26), and $PM_{2.5}$ = 1.15 (CI: 1.01–1.30).

Parity and area-level socio-economic status (SES) were characteristics observed to confound the relation between distance to road or particulate matter exposure and incidence of infertility, based on a 10% change from the crude effect estimate (Table III). However, we included all *a priori* covariates in the final multivariable models. After the additional multivariable adjustment, the hazard ratio for women living within 199 meters of a major road compared to women living 200 meters or more away remained statistically significant HR = 1.11 (CI: 1.02–1.20) for overall infertility. However, after multivariable adjustment, only the association with $PM_{2.5-10}$ remained consistently elevated, and none of the PM associations remained statistically significant.

The results of the stratified Cox models comparing the effects of each exposure on primary and secondary infertility are presented in Table III. Though the point estimates for the HRs were slightly higher for secondary infertility compared to primary infertility, we did not observe evidence of heterogeneity comparing primary and secondary infertility. Furthermore, only the roadway proximity models for secondary infertility researched statistical significance. For example, comparing those living closer to a major road to women living farther from a major road, the observed association with primary infertility was HR = 1.05 (CI: 0.94–1.17) and for secondary infertility the HR = 1.21 (CI: 1.07–1.36). The multivariable adjusted HR of primary infertility for every 10 $\mu g/m^3$ increase in cumulative $PM_{2.5-10}$ was 1.10 (CI: 0.96–1.27), and for secondary infertility was 1.10 (CI: 0.94–1.28). There was no evidence of effect modification by age, BMI, history of rotating shift work, or region of the country (data not shown).

As noted previously, a participant could report more than one cause of infertility. Although the majority of women reported that the reason for infertility was unknown (n = 558) or not explored (n = 959), among the 834 women reporting the reasons for infertility, ovulatory disorder was implicated in 382 instances, male factor in 295 instances, endometriosis in 170 instances, tubal factor in 126 instances and cervical mucous in 65 instances. The patterns of multiple reports are shown in Supplementary Table SII. No significant or elevated associations were observed for infertility attributed to tubal or cervical factor or endometriosis (data not shown). The patterns of association for ovulatory disorder and for male factor were similar to those for overall infertility (Table IV). For the cumulative average exposure, the multivariable adjusted HR (95% CI) for every 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5-10}$, and $PM_{2.5}$ were: 1.13 (0.94–1.35), 1.14 (0.87–1.49), and 1.22 (0.88–1.70) for ovulatory infertility, and were 1.11 (0.92–1.35), 1.07 (0.80–1.43), and 1.34 (0.92–1.94) for male factor, respectively. There was an increased risk in male factor infertility for every 10 $\mu g/m^3$ increase in the 2-year average of $PM_{2.5}$, basic HR (95% CI) = 1.59 (1.09–2.33) but this was not statistically significant after multivariable adjustment HR (95% CI) = 1.39 (0.94–2.04). In exploratory sub-analyses evaluating ovulatory disorder infertility in nulliparous versus parous women (Supplementary Table SIII), there was a suggestion that the roadway proximity effects were stronger among nulliparous women. PM effects were stronger among parous women, but for nulliparous women some HRs were below one, most with wide confidence intervals. The opposite pattern appeared to be true for male factor infertility (Supplementary Table SIV).

Discussion

This analysis represents, to the best of our knowledge, the first assessment of the association of individual level exposures to air pollution and roadway proximity with the incidence of infertility. We observed small positive statistically significant associations between distance to road and PM size fractions and overall incident infertility. In exploratory analyses of women who reported the reason for infertility, ovulatory disorder and male factor infertility were associated with air pollution exposures in a similar magnitude and pattern as overall infertility.

Previous research investigating the association between air pollution exposures and primary infertility is limited. In the only published epidemiologic study to date, census tract level exposures to oxides of nitrogen

Table III Hazard ratios (HR) and 95% confidence intervals (CI) of overall, primary, and secondary infertility risk by distance to road and particulate matter (PM) exposure from September 1993 to December 2003, among 36 294 women in the Nurses' Health Study II.

Exposure	Person-years	Cases of infertility	Basic HR 95% CI[a]	Multivariable HR 95% CI[b]	Primary infertility (nulliparous) cases	Multivariable HR 95% CI[c]	Secondary infertility (parous) cases	Multivariable HR 95% CI[c]
Distance to A1–A3 roadway (m)								
0–199	89 837	1176	1.21 (1.11–1.30)	1.11 (1.02–1.20)	700	1.05 (0.94–1.17)	476	1.21 (1.07–1.36)
200+	123 580	1332	1.00 (referent)	1.00 (referent)	690	1.00 (referent)	642	1.00 (referent)
2-year average exposure ($\mu g/m^3$)[d]								
PM_{10}	213 416	2508	1.09 (1.01–1.17)	1.04 (0.96–1.11)	1390	1.01 (0.91–1.11)	1118	1.08 (0.97–1.21)
$PM_{2.5-10}$	213 416	2508	1.17 (1.05–1.30)	1.10 (0.98–1.23)	1390	1.06 (0.91–1.23)	1118	1.16 (0.98–1.38)
$PM_{2.5}$	213 416	2508	1.07 (0.93–1.22)	0.98 (0.86–1.12)	1390	0.94 (0.79–1.13)	1118	1.05 (0.85–1.28)
4-year average exposure ($\mu g/m^3$)[d]								
PM_{10}	213 416	2508	1.05 (0.97–1.14)	0.99 (0.91–1.08)	1390	0.93 (0.84–1.04)	1118	1.08 (0.95–1.22)
$PM_{2.5-10}$	213 416	2508	1.13 (1.00–1.28)	1.05 (0.93–1.19)	1390	0.97 (0.82–1.15)	1118	1.14 (0.95–1.38)
$PM_{2.5}$	213 416	2508	1.00 (0.86–1.15)	0.91 (0.78–1.05)	1390	0.82 (0.68–1.01)	1118	1.05 (0.84–1.32)
Cumulative average exposure ($\mu g/m^3$)[d]								
PM_{10}	213 416	2508	1.10 (1.03–1.18)	1.06 (0.99–1.13)	1390	1.06 (0.96–1.16)	1118	1.06 (0.95–1.18)
$PM_{2.5-10}$	213 416	2508	1.14 (1.03–1.26)	1.10 (0.99–1.22)	1390	1.10 (0.96–1.27)	1118	1.10 (0.94–1.28)
$PM_{2.5}$	213 416	2508	1.15 (1.01–1.30)	1.05 (0.93–1.20)	1390	1.05 (0.88–1.25)	1118	1.06 (0.88–1.29)

[a]Adjusted for age (in months), race (white, black, other race), calendar year, and region (Northeast, Midwest, West, South).
[b]Additionally adjusted for current body mass index (continuous), smoking status (current, former, never, missing), parity (parous/nulliparous), oral contraceptive use (never, past, current, missing), age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, 17, missing), overall diet quality (alternate healthy eating index, continuous), history of rotating shift work (ever, never), and Census tract level median income (continuous) and median home value (continuous).
[c]Adjusted for age (in months), race (white, black, other race), calendar year, and region (Northeast, Midwest, West, South), current body mass index (continuous), smoking status (current, former, never, missing), oral contraceptive use (never, past, current, missing), age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, 17, missing), overall diet quality (alternate healthy eating index, continuous), history of rotating shift work (ever, never), and Census tract level median income (continuous) and median home value (continuous).
[d]Per 10 $\mu g/m^3$ increase.

Table IV Basic and fully adjusted hazard ratios and 95% confidence intervals (CIs) of ovulatory disorder related and spousal factor related infertility risk September 1993–December 2003, among 36 294 women in the Nurses' Health Study II.

	Ovulatory disorder related infertility				Male factor infertility		
Exposure	**Person-years**	**Cases**	**Basic HR 95% CI[a]**	**Multivariable HR 95% CI[b]**	**Cases**	**Basic HR 95% CI[a]**	**Multivariable HR 95% CI[b]**
Distance to A1–A3 roads (m)							
0–199	89 837	175	1.20 (0.98–1.48)	1.11 (0.90–1.36)	134	1.14 (0.90–1.44)	1.00 (0.79–1.26)
200+	123 580	207	1.00 (referent)	1.00 (referent)	161	1.00 (referent)	1.00 (referent)
2-year average (10 μg/m^3)							
PM_{10}	213 416	382	1.19 (0.98–1.44)	1.10 (0.90–1.33)	295	1.26 (1.03–1.53)	1.17 (0.95–1.42)
$PM_{2.5-10}$	213 416	382	1.29 (0.98–1.71)	1.16 (0.87–1.54)	295	1.28 (0.95–1.73)	1.16 (0.85–1.59)
$PM_{2.5}$	213 416	382	1.22 (0.86–1.73)	1.09 (0.77–1.55)	295	1.59 (1.09–2.33)	1.39 (0.94–2.04)
4-year average (10 μg/m^3)							
PM_{10}	213 416	382	1.16 (0.93–1.43)	1.04 (0.84–1.30)	295	1.16 (0.93–1.44)	1.05 (0.84–1.32)
$PM_{2.5-10}$	213 416	382	1.24 (0.90–1.71)	1.08 (0.78–1.49)	295	1.18 (0.84–1.65)	1.04 (0.73–1.47)
$PM_{2.5}$	213 416	382	1.16 (0.78–1.70)	1.02 (0.69–1.50)	295	1.30 (0.86–1.98)	1.11 (0.73–1.70)
Cumulative average exposure (10 μg/m^3)							
PM_{10}	213 416	382	1.21 (1.02–1.45)	1.13 (0.94–1.35)	295	1.20 (1.00–1.44)	1.11 (0.92–1.35)
$PM_{2.5-10}$	213 416	382	1.26 (0.97–1.63)	1.14 (0.87–1.49)	295	1.15 (0.87–1.53)	1.07 (0.80–1.43)
$PM_{2.5}$	213 416	382	1.35 (0.97–1.87)	1.22 (0.88–1.70)	295	1.57 (1.09–2.27)	1.34 (0.92–1.94)

[a]Adjusted for age (in months), race (white, black, other race), calendar year, and region (Northeast, Midwest, West, South).
[b]Additionally adjusted for current body mass index (continuous), smoking status (current, former, never, missing), parity (parous/nulliparous), oral contraceptive use (never, past, current, missing), age at menarche (<10, 10, 11, 12, 13, 14, 15, 16, 17, missing), overall diet quality (alternate healthy eating index, continuous), history of rotating shift work (ever, never), and Census tract level median income (continuous) and median home value (continuous).

(NO_x), nitrogen dioxide (NO_2), $PM_{2.5}$ absorbance, and three size fractions of PM (PM_{10}, $PM_{2.5-10}$, and $PM_{2.5}$) were associated with decreases in census tract level fertility rates. Although reductions in fertility were observed with all exposures, only $PM_{2.5-10}$ was statistically significant with an incidence rate ratio of 0.87 (95% confidence interval (CI): 0.82–0.94) per inter-quartile range (IQR) increase (Nieuwenhuijsen *et al.*, 2014). This is complimentary to and consistent with our findings of greater incidence of infertility observed for all exposures, with the greatest hazards observed for exposures to $PM_{2.5-10}$.

Although there are sparse data on air pollution exposures and infertility, the literature evaluating early reproductive outcomes may provide insight into biological mechanisms. A study evaluated the effect of air quality on 7403 IVF cycles from 2000–2007 in northeastern USA. NO_2 concentrations at both the patient's address and at the address of the IVF laboratory, and $PM_{2.5}$ concentrations at the IVF laboratory were negatively associated with odds of pregnancy at time points during the IVF cycle (defined as medication start to pregnancy test), but most statistically significantly after embryo transfer (Legro *et al.*, 2010). Another IVF cohort study with male factor infertility in São Paulo, Brazil used a city-wide average for PM_{10} and reported an increased risk of miscarriage with high preconception air pollution exposures, but no difference in pregnancy rates or clinical pregnancy outcomes (Perin *et al.*, 2010).

The literature is mixed with regard to male factor infertility. Several studies reported a deleterious association between high exposures to air pollution and sperm morphology (Selevan *et al.*, 2000; Gaspari *et al.*, 2003), motility (Guven *et al.*, 2008; Hammoud *et al.*, 2010), and concentration (Sokol *et al.*, 2005; Guven *et al.*, 2008). However, three prospective studies reported null associations between certain air pollutants and sperm concentration: (i) NO_X (Selevan *et al.*, 2000; Rubes *et al.*, 2005), (ii) SO_2 (Selevan *et al.*, 2000; Rubes *et al.*, 2005), (iii) CO (Selevan *et al.*, 2000), (iv) polycyclic aromatic hydrocarbons (Rubes *et al.*, 2005) and (v) PM_{10} (Selevan *et al.*, 2000; Rubes *et al.*, 2005).

Lastly, the relationship between ambient levels of air pollution and ovarian function was characterized in a mouse study, which described increases in estrus cycle length thereby resulting in a decreased number of estrus cycles and decreased fertility (Veras *et al.*, 2009).

The results of the present study should be evaluated in light of several limitations. Infertility is clinically defined as attempted conception for 1 year without success, or 6 months or more if the woman's age is 35 or greater. Infertility status and subtypes of infertility were collected prospectively biennially, and only inquired about attempting pregnancy unsuccessfully for more than 1 year since the last questionnaire return. Within that 2 year window, we do not have the exact date of diagnosis or the exact timing of the start of attempting conception. Therefore, we were unable to tightly examine timing of exposures on incidence of infertility. Furthermore, report of infertility may include those with unrecognized early pregnancy loss. Though participants were able to report cause of infertility if known, there were too few reported cases of tubal factor to quantify the association of air pollution and this common infertility subtype. In order to have a diagnosis of tubal factor infertility, a full evaluation must be completed, including evaluation of fallopian tube patency. In terms of exposure quantification, we used ambient air pollution exposures as a proxy for personal exposures, potentially leading to exposure misclassification. For example, we have no information on the proportion each day the woman spent at home or on the characteristics of the home (e.g. age, ventilation rate, air purification systems, etc.) that may affect their personal levels of ambient PM or traffic pollution. However, several studies suggest that ambient measurements are an acceptable surrogate (Janssen *et al.*, 1998, 2000; Sarnat *et al.*, 2001) for individual level exposures in most populations. In addition, the use of ambient exposures is useful because regulation typically focuses on these levels (Pope and Dockery, 1999). Women who moved addresses would also have an additional source of measurement error, as the exact date of the address change is not known (and we assumed it to be the date of the questionnaire receipt). Selection bias is a potential concern, though demographic information was similar for the small group of women who were excluded based on reported addresses outside the continental United States or lack of street-segment geocode. The exposure distribution of these women is assumed to be similar to the rest of the cohort. As with any study, although we adjusted for a large number of well-characterized time-varying potential confounders, there is the possibility that residual or unmeasured confounding may explain our small elevations in risk. Lastly, our results may not be generalizable to the full population of US women. Although our analytic sample was generally similar to the full cohort, NHSII is comprised of mostly Caucasian women of middle to upper socioeconomic status. Therefore, it is unclear if these results are applicable to other, more diverse populations, or to groups with different exposure characteristics.

This large study has several notable strengths. For this analysis, we had 10 years of detailed residential address history and only included residential addresses with a street segment level geocoding match. The use of only street segment level matches likely reduced exposure misclassification compared to matches to a zip-code centroid or other administrative boundaries (census tract, county, etc.). In addition, prospective information on important covariates was collected biennially allowing for time-varying control of confounding variables. The use of individual residential specific monthly pollution exposures allowed us to examine various time windows of exposure and provided a unique evaluation of long-term exposures and incident infertility. The geographic distribution represented by the study participants provides information on most environments throughout the continental United States.

In summary, within this large prospective cohort, we observed an association between incidence of infertility with roadway proximity and exposures to particulate matter. Effect estimates for chronic exposures were slightly elevated compared to that of 2- and 4-year estimates. This may suggest that chronic exposures may be of greater importance than short-term exposures, or that cumulative exposures may be more closely related to the time of infertility onset, as opposed to diagnosis. Further studies designed specifically to assess the association between incident infertility and specific air pollution exposures are needed to confirm these associations. Furthermore, prospective studies evaluating time to pregnancy in vulnerable populations such as those living close to sources of air pollution is warranted.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors' roles

All authors have made substantial contributions at all levels, from conception and design to data analysis and interpretation, revisions and final edits. S.M. drafted the article and all authors critically revised it for intellectual content. The final version of this article was approved by all authors for publication.

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Conflict of interest

The authors have no actual or potential competing financial interests to disclose.

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