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Adult Air Pollution Exposure and Risk of Uterine Leiomyoma in the Nurses' Health Study II

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Abstract

Background—Air pollution, particularly from vehicle exhaust, has been shown to influence hormonal activity. However, at present, it is unknown whether air pollution exposure is associated with the occurrence of uterine leiomyomata, a hormonally sensitive tumor of the uterus.

Methods—Proximity to major roadways and outdoor levels of PM less than 10 microns (PM₁₀) or 2.5 microns (PM_{2.5}) or between 10 and 2.5 microns (PM_{10–2.5}) in diameter were determined for all residential addresses from September 1989 to May 2007 for 85,251 women aged 25–42 at enrollment in the Nurses' Health Study II who were alive and responding to questionnaires, premenopausal with intact uteri, without diagnoses of cancer, or prevalent uterine leiomyomata. Incidence of ultrasound- or hysterectomy-confirmed uterine leiomyomata and covariates were reported on biennial questionnaires sent through May 2007. Multivariable time-varying Cox proportional hazard models were used to estimate the relation between distance to road or PM exposures and uterine leiomyomata risk.

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Results—During 837,573 person-years of follow-up, there were 7,760 incident cases. Living close to a major road and exposures to PM₁₀ or PM_{10–2.5} were not associated with an increased risk of uterine leiomyomata. However, each 10 µg/m³ increase in 2-year average, 4-year average, or cumulative average PM_{2.5} was associated with an adjusted hazard ratio (HR) of 1.08 (95% confidence interval (CI):1.00–1.17), 1.09 (95%CI:0.99–1.19) and 1.11 (95%CI:1.03–1.19), respectively.

Conclusions—Chronic exposure to PM_{2.5} may be associated with a modest increased risk of uterine leiomyomata.

Keywords

Air pollution; Distance to road; Uterine Fibroids; Leiomyoma; Prospective cohort

Uterine leiomyomata, known commonly as uterine fibroids, are present in a vast majority of women of reproductive age.¹ Clinically significant disease is characterized by increase in uterine size, heavy menses potentially leading to anemia, pelvic pain, increased urinary frequency, and abdominal distension.^{2,3} Cumulative incidence of uterine leiomyomata is approximately 70% in white women and 80% in African-American women by the age of 50 years.⁴ However incidence of clinically significant disease ranges between 15–30%.¹ Treatment interventions include hormonal regulation of menses and surgical myomectomy in refractory cases.⁵ For women who have completed childbearing, hysterectomy is the gold standard treatment for uterine leiomyomata related symptoms.⁶

Many risk factors for uterine leiomyomata have been evaluated, including lifestyle, diet, anthropometric, genetic, and hormonal factors. Uterine leiomyomata are hormonally responsive clonal tumors of the uterus and are further categorized by their location in the uterus.⁷ A number of studies have evaluated exposure to environmental endocrine disruptors, such as diethylstilbestrol^{8,9} (mixed), phenols¹⁰ (null), dioxin¹¹ (protective), and polychlorinated biphenyls (increased),¹² but no clear patterns have emerged. A more recent study evaluated exposure to polycyclic aromatic hydrocarbons, another environmental estrogen-like compound, and odds of uterine leiomyomata expressing the aryl-hydrocarbon receptor¹³. Living closer to a polycyclic aromatic hydrocarbon producing company was associated with increased odds of uterine leiomyomata with aryl-hydrocarbon receptor over-expression.¹³ As air pollution is a major source of polycyclic aromatic hydrocarbons,¹⁴ and components of air pollution have been shown to have hormonal activity and to bind the aryl-hydrocarbon receptor in *in vitro* studies.^{15–17} At present, it is unknown whether air pollution exposure is associated with the occurrence of uterine leiomyomata as no prior epidemiologic studies have assessed this relationship.

METHODS

Study Population

The Nurses' Health Study II (NHSII) is a prospective cohort study of US female nurses. The cohort was initiated in 1989 when 116,686 female US registered nurses, 25 to 42 years old, completed a mailed questionnaire and provided informed consent. At baseline the nurses resided in fourteen states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts,

Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina and Texas), however, there is now at least one cohort member in all fifty states. Follow-up questionnaires, with response rates above 90%, are mailed every two years to update information on risk factors and the occurrence of major illnesses. These questionnaires also provide biennially updated information on residential addresses. Women were included in the current study if they were alive at the given questionnaire cycle, premenopausal, free of cancer (other than non-melanoma skin cancer), had no history of infertility, had intact uteri, and did not have a diagnosis of uterine leiomyomata prior to 1993. In addition, women were included only if they had at least one home address within the continental United States that could be geocoded to the street segment to allow the assignment of exposure (80–90% of the addresses for each biennial questionnaire cycle were successfully geocoded to the street segment level).

Assessment of Outcome

Initial assessment of uterine leiomyomata was performed in the 1993 NHSII questionnaire. Participants were asked if they had ever had a previous diagnosis of uterine leiomyomata, and if yes, to provide the date of diagnosis and method of confirmation (pelvic exam, ultrasound, or hysterectomy). Subsequent questionnaires asked each woman if she had been diagnosed with uterine leiomyomata before, during, or after the current two year study period. During the follow-up intervals, women were considered a case only if the diagnosis was confirmed via ultrasound or hysterectomy. Cases of uterine leiomyomata reported with only a pelvic exam as the method of confirmation were censored at the time of diagnosis, and were not considered cases. If these women later confirmed a diagnosis of uterine leiomyomata: by either ultrasound or hysterectomy, they were then counted as a case at the time of the original report. For all cases, the mid-point between the receipts of the questionnaire before and after diagnosis was assigned as the date of diagnosis. We used date of diagnosis to mark uterine leiomyomata incidence as opposed to the initiation of uterine leiomyomata development. Marshall et al. performed a validation study of 243 NHSII participants who self-reported a new diagnosis of uterine leiomyomata confirmed by ultrasound or hysterectomy. Self report was compared to medical record review and an average confirmation rate of 93% was found ¹⁸.

Exposure Assessment

We used distance to road at each biennial questionnaire address as a proxy for traffic exposure. Distance to road (in meters) for all available addresses from September 1989 to May 2007 was determined using Geographical Information System (GIS) software (ArcGIS 9.2, ESRI, Redlands, CA). Road segments from the ESRI StreetMap Pro 2007 files were selected by US Census Feature Class Code 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. Based on the distribution of distance to road in this population and exposure studies that have shown an exponential decay in exposures with increasing distance from a road, with levels equal to background concentrations at 150–200m, we categorized the exposure based on distance (0–50m, 51–199m, and 200+m).^{19–23} To determine if larger

roads (with more traffic) had a greater association with uterine leiomyomata risk, we also examined models restricted to distance to A1 and A2 roads only.

Predicted ambient exposure to PM₁₀, PM_{10-2.5}, and PM_{2.5} is available for each month since January 1988. These values are generated at each address in the residential address histories of each cohort member. These predictions are generated at the specific address level from nationwide expansions of previously validated spatiotemporal models.^{24,25} The models use monthly average PM₁₀ and/or PM_{2.5} data from USEPA's Air Quality System, a nationwide network of continuous and filter-based monitors, as well as monitoring data from various other sources. The models also incorporate a number of geographic information system (GIS) based predictors such as population density, land use, elevation, distance to road, PM point sources as well as meteorology. All PM data and GIS data were used in generalized additive statistical models²⁶ with smooth terms of space and time to create separate PM prediction surfaces for each month. By subtracting monthly PM₁₀ and PM_{2.5} values, information was also available on PM_{10-2.5}. As the etiologic window during which air pollution would influence uterine leiomyomata is unknown, we calculated three different chronic exposure measures: the average air pollution in the prior 2 calendar years, the average air pollution in the 4 prior calendar years, and a time-varying cumulative average exposure.

Additional Covariates

Information on potential confounders and effect modifiers is available every two years. Therefore, when appropriate, each woman was assigned updated covariate values from each questionnaire cycle. We examined possible confounding by numerous risk factors for uterine leiomyomata including: age (in months), race (Caucasian vs other), smoking status (current/former/never), body mass index (BMI, kg/m²), age at menarche (9, 10, 11, 12, 13, 14, 15, 16, 17 years), parity (nulliparous/parous), diagnosis of infertility, age at first birth (26, 26–30, 31 years), age at last birth (26, 26–30, 31–35, 36 years), time since last birth (<1, 1–3, 4–5, 6–7, 8–9, 10–12, 13–15, 16 years), total months of exclusive breast feeding (none, 1–3, 4–6, 7–12, 13–18, 19–24, 25–36, 37 months) oral contraception use (never, current, former), antihypertensive medication use and blood pressure (using medication yes/no and diastolic blood pressure (<65, 65–74, 75–84, 85–89, 90 mmHg) overall diet quality as measured by the Alternative Healthy Eating Index,²⁷ physical activity (MET-hrs/week), and individual-level socioeconomic status (marital status, household income, and if the nurse lived alone) and area-level socioeconomic status (Census tract level median home value and median family income). To adjust for potential differences in PM composition or diagnosis patterns by region of the country, we also considered adjustment for region (Northeast, Midwest, South, West). To determine potential confounding, each variable (or set of indicator variables) was added separately to a model including age and race *a priori*. Variables that changed the effect estimates of exposure of interest by 10% or more were considered to be confounders of the relation between traffic or air pollution and uterine leiomyomata risk, and were included in “parsimonious” models.²⁸ To examine the impact of all potential confounders, we also present models adjusted for all considered factors.

Statistical Analysis

As noted above, exposure information was updated every 2 years, therefore prospective time-varying Cox proportional hazards models were used to assess the relationship of uterine leiomyomata with distance to road or PM. We used cubic splines to test for the linearity of all continuous exposures. Person-months of follow-up time were calculated from July 1, 1993 until censoring. Censoring occurred at first onset of: menopause, diagnosis of infertility, hysterectomy, or cancer, date of death, loss to follow-up, or the end of follow-up (June 30, 2009). All models were based on a biennial time scale and were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). To tightly control for age and calendar year, we estimated separate baseline hazards for age in months and calendar year in the Cox models. Statistical analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC). In sensitivity analyses to examine associations with more severe cases of uterine leiomyomata, we ran models restricted to those cases of uterine leiomyomata confirmed by hysterectomy only. To determine if there was effect modification by age, we performed models stratified by age (dichotomized at age 35) and created multiplicative interaction terms to assess statistical significance of differences in age-strata specific HRs and 95% CIs. We used a $p < 0.05$ to assess statistical significance of our effects.

RESULTS

A total of 85,251 women comprised the study population for analyses of residential proximity to road, PM_{10} , $PM_{10-2.5}$, and $PM_{2.5}$ and risk of uterine leiomyomata. Selected characteristics of the population over the full period of follow-up are presented in Table 1 for the full cohort and by distance to road category. The mean (standard deviation) age during follow-up was 42.6 (5.3) years, the cohort was mostly parous, and over two-thirds were never smokers. There was little difference in covariates (age, BMI, income, race, age at menarche) between the distance to road categories, with the exception of a trend toward lower parity among women living closer to a major roadway and women in the Northeast living closer to roadways than women in other regions. The mean and median levels of each of the time windows were similar within each pollutant, and there were wide ranges for all pollutants (Table 2).

Among 837,573 person-years of follow-up, there were a total of 7,760 incident cases of surgically or ultrasonographically confirmed uterine leiomyomata. In models only adjusted for age and calendar time, living closer to a roadway was associated with small, but generally not statistically significant, elevations in the risk of uterine leiomyomata, compared to living further from a roadway (Table 3). BMI, parity, age at first birth, age at last birth, total months of exclusive breastfeeding, and months since last birth individual- and area-level socioeconomic status, antihypertensive drugs and diastolic blood pressure, and region of the country met our definition of confounders and were included in our parsimoniously adjusted models. There was little difference in the results from the parsimoniously and multivariable adjusted models, and in the full cohort no associations were observed between uterine leiomyomata and distance to road. However, although there was no statistically significant evidence of effect modification by age, among younger women (< 35 years of age), women living closest (0–50m) to a roadway did have elevated,

but nonstatistically significant risks of uterine leiomyomata compared to women living 200m or more away. This elevation was not observed among women over age 35.

There was no statistically significant evidence of deviations from linearity for any of our continuous measures of PM, therefore, we present the results in terms of a 10 $\mu\text{g}/\text{m}^3$ increase. And again, there was little difference between the parsimoniously and multivariable adjusted models. There was no association observed between increasing exposure to PM_{10} or $\text{PM}_{10-2.5}$ and risk of uterine leiomyomata in any of the time windows examined in the full cohort (Table 4). However, each 10 $\mu\text{g}/\text{m}^3$ increase in 2-year average, 4-year average, and time-varying cumulative average exposure to $\text{PM}_{2.5}$ was associated with a hazard ratio of 1.08 (95%CI: 1.00, 1.17), 1.09 (95%CI: 0.99, 1.19) and 1.11 (95%CI: 1.03, 1.19), respectively. In models stratified by age, these results were stronger among the younger women, although again there was no statistically significant evidence of effect modification.

In analyses restricted to cases diagnosed by hysterectomy only (2,183 cases), there was little evidence of relationships between uterine leiomyomata risk and distance to road, or any of the measures of PM (results not shown).

DISCUSSION

In this study, we did not observe a relationship between distance to road or larger size fractions (PM_{10} , $\text{PM}_{10-2.5}$) of particulate matter or residential distance to road and the risk of uterine leiomyomata overall. However, a suggestive association was seen between exposure to the smallest sized fraction, $\text{PM}_{2.5}$, and increased uterine leiomyomata risk that was consistent across all of the examined time windows of exposure. There was also a suggestion of higher and more consistent risks among women 35 years of age or younger, although there was no statistically significant evidence of effect modification by age. To the best of our knowledge, this is the first epidemiologic study to assess the association between degree of exposure to air pollution and uterine leiomyomata.

To the best of our knowledge, no other study has examined the impact of air pollution exposures on the risk of uterine leiomyomata. However, a handful of studies have examined the impact of cigarette smoking, a much higher exposure to particles, on uterine leiomyomata incidence. A case-control study performed in Italy demonstrated a protective effect of tobacco smoking on odds of uterine leiomyomata.²⁹ A study of risk factors for surgically removed uterine leiomyomata in the California Teachers Study, a prospective cohort study, demonstrated a protective effect in smokers.³⁰ The Black Women's Health Study and Nurses' Health Study, two large prospective studies evaluating first-hand tobacco smoking and risk of uterine leiomyomata, reported null associations between tobacco smoke exposure and risk of uterine leiomyomata.^{31,32} The Uterine Fibroid Study evaluated risk factors with different sub-types of uterine leiomyomata categorized by tumor location (submucosal, intramural, subserosal, and diffuse disease); this study demonstrated increased risk of diffuse uterine leiomyomatosis in tobacco smokers.³³ However comparisons between air pollution exposures and tobacco exposures must be undertaken cautiously as studies have

suggested that tobacco smoke has an anti-estrogenic effect,^{34,35} where limited *in vitro* studies have suggest estrogenic effects of air pollution.¹⁶

This study has limitations to consider. We used ambient exposures as a proxy for personal exposures, likely 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 the experienced levels of ambient PM or traffic pollution. However, studies suggest that ambient measurements are an acceptable surrogate^{36–38} for personal exposures in most populations. In addition, this approach is useful because regulation typically focuses on ambient levels.³⁹ Another limitation is that the NHSII cohort is not representative of the general US population in terms of socio-economic status (SES) and race. The NHSII cohort is predominantly Caucasian (although the racial distribution is representative of US licensed nurses at baseline) with residence in neighborhoods of medium to high SES. Hence, we were unable to evaluate effect modification by race. Finally, our strict definition of UL allowed us to identify clinically symptomatic uterine leiomyomata. However we were unable to assess the impact of air pollution exposure on the development of non-clinically evident uterine leiomyomata disease. As with any study, although we adjusted for a large number of well-characterized time-varying potential confounders, there is always the possibility that residual or unmeasured confounding may explain our small elevations in risk.

This large study has several notable strengths. For this analysis, we had 14 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). Prospective information on several covariates was collected biennially allowing for time-varying control of confounding variables. Self-report of uterine leiomyomata had been previously validated with excellent concordance between medical record and self-report. The use of individual residential specific monthly pollution exposures is state of the art and allows us to examine various time windows of exposure. The geographic distribution represented by the participants of this study provides information on most environments throughout the continental US.

This study identified a modest association between chronic fine PM exposure and incidence of uterine leiomyomata and distance from road and uterine leiomyomata incidence among women age 35 and under. Repeat studies are needed to confirm these associations. Furthermore, studies looking at the association between air pollution and fibroids may be warranted in countries with much higher levels of air pollution.

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Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
GIS	Geographic Information Systems
HR	Hazard Ratio
PM	Particulate Matter
NHSII	Nurses' Health Study II
PM₁₀	Course Particulate Matter, 10 micron diameter
PM_{2.5}	Fine Particulate Matter, 2.5 micron diameter
SES	Socio-economic Status

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Table 1

Selected Age-standardized Characteristics of the Nurses' Health Study II Participants with Exposure Data (N=85,251) Over the Period of Follow-Up (1993–2007)

	Entire Cohort	By Distance (m) to Nearest A1-A3 Roadway ^b		
		200+ m	51–199 m	0–50 m
Mean (SD)				
Age (in years) ^a	42.6 (5.3)	42.7 (5.3)	42.5 (5.4)	42.5 (5.4)
Body Mass Index (kg/m*m)	26.0 (6.0)	25.8 (5.9)	26.0 (6.1)	26.5 (6.4)
Physical Activity (MET-hrs/week)	18.4 (25.8)	18.2 (25.4)	18.6 (26.0)	18.8 (27.4)
Alternative Healthy Eating Index	52.8 (9.8)	52.6 (9.8)	53.1 (9.8)	52.7 (9.9)
Census tract median income (\$10,000)	6.69 (2.38)	6.76 (2.29)	6.69 (2.47)	6.33 (2.56)
Census tract median home value (\$100,000)	1.72 (1.23)	1.66 (1.07)	1.84 (1.39)	1.75 (1.56)
Percent of Person-Time				
Caucasian race	94	95	93	93
Age at Menarche (years)				
Less than 12	23	22	23	23
12	30	30	30	30
Greater than 12	47	47	47	46
Parity				
Nulliparous	19	15	20	24
Parous	81	84	79	75
Oral Contraception Use				
Never	14	13	15	15
Past	75	75	73	74
Current	10	10	10	10
Cigarette Smoking				
Never	68	69	66	66
Current	9	8	9	10
Former	24	23	24	24
Individual Level SES				
Married	64	66	61	59
Live Alone	7	6	9	11
Household Income (\$)				
>15,000	0	0	0	0
15,000–19,999	1	0	0	0
20,000–29,999	3	1	1	1
30,000–39,999	6	2	3	4
40,000–49,999	18	6	6	7
50,000–74,999	15	18	19	21
75,000–99,999	16	15	15	14
100,000–149,999	9	17	16	14

	Entire Cohort	By Distance (m) to Nearest A1-A3 Roadway ^b		
		200+ m	51–199 m	0–50 m
150,000	0	10	9	8
Region of Residence				
Northeast	34	32	36	41
Midwest	34	36	31	31
West	15	13	20	14
South	17	19	13	13

^aValue is not age adjusted

^bEach cohort member may be in multiple distance categories over follow-up

NOTE: Values are standardized to the age distribution of the study population.

Table 2

Distributions of the Particulate Matter Pollution Metrics ($\mu\text{g}/\text{m}^3$) Among 85,251 Women in the Nurses' Health Study II over the Full Period of Follow-Up (1993–2007).

Metric	Mean (SD)	Median (IQR)	Min	Max
24-month average				
PM ₁₀	22.6 (6.2)	21.8 (7.0)	3.7	72.3
PM ₁₀₋₂₅	9.0 (4.6)	8.0 (5.2)	−0.2	54.0
PM _{2.5}	13.7 (3.0)	13.6 (4.1)	2.0	28.2
48-month average				
PM ₁₀	21.3 (5.5)	20.7 (6.2)	4.0	60.1
PM ₁₀₋₂₅	8.3 (4.2)	7.3 (4.9)	0.1	46.0
PM _{2.5}	13.1 (2.7)	13.0 (3.7)	2.2	23.9
Cumulative average				
PM ₁₀	25.8 (6.4)	25.0 (6.8)	5.1	80.6
PM ₁₀₋₂₅	10.6 (4.8)	9.6 (5.3)	1.5	60.7
PM _{2.5}	15.2 (3.1)	15.3 (4.2)	2.7	29.3

Table 3
Basic and Fully Adjusted Hazard Ratios and 95% Confidence Intervals (CIs) of Uterine Leiomyoma Risk (1993–2007) by Residential Proximity to Roadway, Among 85,251 Women in the Nurses' Health Study II

Exposure	Person-years	Cases	All Women				35 Years old	>35 Years old
			Basic HR 95% CI ^a	Parsimonious Adjusted HR 95% CI ^b	Multivariable Adjusted HR 95% CI ^c	Multivariable Adjusted HR 95% CI ^c	Multivariable Adjusted HR 95% CI ^c	
Distance to A1-A3 Roads (m)								
0-50	97,011	925	1.05 (0.98-1.12)	1.02 (0.95-1.09)	1.01 (0.93-1.09)	1.15 (0.85-1.56)	1.01 (0.94-1.09)	
51-199	213,961	2,043	1.05 (1.00-1.11)	1.05 (1.00-1.11)	1.04 (0.98-1.11)	0.98 (0.76-1.25)	1.06 (1.00-1.12)	
200+	526,601	4,792	reference	reference	reference	reference	reference	
Distance to A1-A2 Roads (m)								
0-50	10,406	103	1.07 (0.88-1.30)	1.01 (0.83-1.23)	1.00 (0.80-1.25)	1.34 (0.65-2.74)	1.00 (0.81-1.22)	
51-199	42,862	404	1.02 (0.92-1.13)	1.02 (0.92-1.12)	1.02 (0.91-1.15)	0.70 (0.62-1.51)	1.02 (0.92-1.13)	
200+	784,305	7,253	reference	reference	reference	reference	reference	

^a Adjusted for age and calendar time

^b Adjusted for age, calendar time, race, and covariates that consistently changed the effect estimates at least 10% in univariate models (current body mass index, parity, age at first and last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use and blood pressure, region of the country, individual level SES (marital status, household income, live with others or alone), and Census tract level median income and median home value)

^c Adjusted for age, calendar time, race, current body mass index, smoking status, overall diet quality, physical activity, infertility, parity, oral contraceptive use, age at menarche, age at first and last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use and blood pressure, region of the country, individual level SES (marital status, household income, live with others or alone), and Census tract level median income and median home value

NOTE: A total of 360 cases were diagnosed in women 35 Years old, and 7,400 were diagnosed in women over 35.

Table 4

Basic and Fully Adjusted Hazard Ratios and 95% Confidence Intervals (CIs) of Uterine Leiomyoma Risk (1993–2007) for Each 10 $\mu\text{g}/\text{m}^3$ Increase in Particulate Matter, Among 85,251 Women in the Nurses' Health Study II

Exposure	All Women			35 Years old		>35 Years old	
	Basic HR 95% CI ^a	Parsonomious Adjusted HR 95% C ^b	Multivariable Adjusted HR 95% CI ^b	Multivariable Adjusted HR 95% CI ^c	Multivariable Adjusted HR 95% CI ^c	Multivariable Adjusted HR 95% CI ^c	
24 month Average Exposure							
PM ₁₀	1.02 (0.98–1.06)	1.04 (0.99–1.09)	1.04 (0.99–1.09)	1.16 (0.95–1.41)		1.03 (0.99–1.08)	
PM _{10-2.5}	0.98 (0.95–1.05)	1.03 (0.96–1.10)	1.03 (0.97–1.10)	1.27 (0.95–1.71)		1.02 (0.96–1.09)	
PM _{2.5}	1.07 (0.99–1.15)	1.08 (1.00–1.17)	1.08 (1.00–1.17)	1.12 (0.79–1.61)		1.08 (0.99–1.17)	
48 month Average Exposure							
PM ₁₀	1.02 (0.98–1.06)	1.04 (0.99–1.09)	1.04 (1.00–1.09)	1.17 (0.93–1.48)		1.03 (0.98–1.07)	
PM _{10-2.5}	1.00 (0.94–1.05)	1.02 (0.95–1.10)	1.02 (0.96–1.10)	1.89 (0.85–1.66)		1.02 (0.95–1.09)	
PM _{2.5}	1.08 (0.99–1.18)	1.09 (1.00–1.19)	1.09 (0.99–1.19)	1.28 (0.86–1.92)		1.08 (0.99–1.18)	
Cumulative Average Exposure							
PM ₁₀	1.01 (0.97–1.04)	1.04 (1.00–1.08)	1.04 (1.00–1.08)	1.21 (1.00–1.45)		1.03 (0.99–1.08)	
PM _{10-2.5}	0.98 (0.93–1.03)	1.01 (0.95–1.08)	1.01 (0.95–1.06)	1.30 (0.99–1.69)		1.00 (0.94–1.07)	
PM _{2.5}	1.08 (1.00–1.17)	1.11 (1.03–1.20)	1.11 (1.03–1.19)	1.23 (0.88–1.73)		1.11 (1.02–1.19)	

^a Adjusted for age and calendar time

^b Adjusted for age, calendar time, race, and covariates that consistently changed the effect estimates at least 10% in univariate models (current body mass index, parity, age at first and last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use and blood pressure, region of the country, individual level SES (marital status, household income, live with others or alone), and Census tract level median income and median home value)

^c Adjusted for age, calendar time, race, current body mass index, smoking status, overall diet quality, physical activity, infertility, parity, oral contraceptive use, age at menarche, age at first and last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use and blood pressure, region of the country, individual level SES (marital status, household income, live with others or alone), and Census tract level median income and median home value

NOTE: A total of 360 cases were diagnosed in women 35 Years old, and 7,400 were diagnosed in women over 35.