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ABSTRACT

BACKGROUND. It remains unclear as to whether fine particulate ($PM_{2.5}$) exposure affects risk of preterm birth and pre-labour rupture of membranes. Unmeasured, poorly measured and undiscovered individual-level confounders might have introduced bias into past studies that relied on between-women comparisons.

METHODS. This was a longitudinal study of preterm birth and pre-labour rupture of membranes in Rochester, New York, 2004-2012 (N=3,264 women, N=7,121 singleton births). We used conditional logistic regression to match pregnancies to the same women and estimate the odds of each outcome associated with average $PM_{2.5}$ concentrations during each trimester and whole pregnancy.

RESULTS. For preterm birth, adjusted odds ratios (95% CI) for 1 $\mu g/m^3$ increase in $PM_{2.5}$ in the first trimester, second trimester, third trimester, and whole pregnancy were 1.11 (1.04, 1.18), 1.09 (1.02, 1.16), 1.06 (1.00, 1.13), and 1.17 (1.07, 1.28), respectively. For pre-labour rupture of membranes, corresponding ORs were 1.00 (0.97, 1.04), 0.99 (0.96, 1.02), 0.99 (0.96, 1.03), and 0.99 (0.94, 1.04), respectively.

CONCLUSION. Risk of preterm birth was greater for pregnancies with elevated $PM_{2.5}$ exposure than other pregnancies to the same women at lower exposure. We did not observe an association between $PM_{2.5}$ concentrations and pre-labour rupture of membranes.

Keywords: preterm birth, particulate matter, air pollution, longitudinal study, matched analysis

BACKGROUND

Preterm birth is a significant contributor to perinatal mortality in developed countries[1]. Subsequent morbidities include respiratory dysfunction and neurodevelopmental impairment[2, 3], and it is plausible that the array of sequelae might also extend well beyond the neonatal period[4]. Pre-labor rupture of membranes occurs when the chorioamniotic membranes rupture prior to labour and is the leading identifiable cause of preterm birth.

There is now suggestive evidence that fine particulate matter air pollution < 2.5 μg in aerodynamic diameter ($PM_{2.5}$), which has an established causal effect on cardiovascular endpoints[5], might also explain a fraction of cases of preterm birth[6] and pre-labour rupture of membranes[7, 8]. A recent meta-analysis by Saptopka et al. suggests a consistent link between $PM_{2.5}$ exposure and preterm birth[6]. Unfortunately, it is too early to conclude that there is sufficient evidence for an association because this meta-analysis was based on only six studies and error can be compounded by meta-analyses when there are few studies plus systematic bias. Moreover, as the etiology of preterm birth is not fully understood, residual confounding by unknown or poorly measured factors can have a systematic influence across all of the published studies to date. All studies in the meta-analysis relied on between-women comparisons. The likelihood of residual confounding is greatest for studies that rely on between-women comparisons, as 59%-66% of variation in gestational length can be attributed to factors that vary between women, rather than factors that vary between pregnancies to the same women[8, 9]. Matching pregnancies to the same women accounts for individual predispositions, such as genetic factors [10], social determinants [11], and other non-time varying individual-level confounders that are unmeasured, poorly measured, or remain to be discovered.

This is one of a series of longitudinal studies that compared $PM_{2.5}$ exposure and these outcomes of pregnancies to the same women [8, 9, 12], with the aim of replicating the same design in different study locations worldwide. Replication in other areas is important because observing adverse effects is conditional on a range of factors that can vary geographically, including the composition and toxicity of the air pollution mixture[13], the absolute level of exposure[14], and the underlying susceptibility of the population [15].

The aim of this study was to test the hypothesis that preterm birth and pre-labour rupture of membranes are associated with exposure to ambient $PM_{2.5}$ during pregnancy among women in Rochester, New York.

METHODS

Study design and population

This was a longitudinal study of the effects of women's exposure to ambient airborne $PM_{2.5}$ total mass during pregnancy on the occurrence of preterm birth and pre-labour rupture of membranes across successive pregnancies in the Finger Lakes region of New York State from 2004 to 2012. There were 130,070 live births during the study period. Participant selection is illustrated in Figure 1. Briefly, we sequentially excluded all births with missing gestational age, parity, or mother identifier; multiple gestations; and records for which there was a discordance between the year of birth and the parity variable or duplication of the parity variable. For the preterm birth study we excluded births by caesarean section or where labour was induced in order to include only spontaneous preterm birth. We then excluded births to women who had fewer than 2 births during the study period and births to women who had concordant outcomes. We included only the mothers (strata) who had at least one

preterm birth or pre-labour rupture of membranes outcome due to resource constraints associated with geocoding maternal addresses and because the within-strata effect estimate does not depend on outcome-concordant strata (i.e. women who had all pre-labour rupture of membranes or all preterm births).

Figure 1 here

Data sources and variables

Maternal and infant data were obtained from the Finger Lakes Region Perinatal Data System (FLRPDS), which includes demographic and clinical data for mothers and neonates from 10 birthing hospitals in the nine-county Finger Lakes region of New York State. The FLRPDS contains data for all live births in the region from 1998 to the present. Because changes were made to the variables included in the FLRPDS in 2004, the current analysis includes only birth records from January 1, 2004 to December 31, 2012 in order to ensure uniformity of data across subjects. Each birth record contained variables for the residential location at birth, and pregnancy-related and socio-demographic risk factors, including maternal race/ethnicity, drug use during pregnancy, exercise during pregnancy, maternal age, smoking during pregnancy, pre-pregnancy weight, depression during pregnancy and parity.

We geocoded the maternal residential addresses at the time of birth and determined the Environmental Protection Agency (EPA) $PM_{2.5}$ mass concentration monitor closest to each address, which were used to determine exposure variables as described below. Daily maximum temperature exposures were obtained from the closest National Oceanic and Atmospheric Administration (NOAA) weather monitoring site.

Births were also excluded from the analyses if the relevant $PM_{2.5}$ monitor was not operational during the exposure period of interest. The final study population consisted of 7,121 births to 3,264 women.

Exposure assessment

Daily $PM_{2.5}$ measurements obtained from the closest monitor to a subject's residence were assigned to each pregnancy. Weekly mean $PM_{2.5}$ levels were calculated as 7-day averages for each monitor throughout the 2004–2012 period. Mean exposures were computed for each week of gestation and were then used to compute average $PM_{2.5}$ concentrations for each trimester and for the whole pregnancy. This avoided bias due to changes in the frequency of $PM_{2.5}$ measurements[16]. By definition, pregnancies are not at risk of preterm birth after gestational week 36. For this reason, only measurements prior to either birth or gestational week 36 (whichever was earlier) were included in the calculation of third-trimester and whole-pregnancy exposures for the preterm birth analyses.

Outcome assessment

Preterm birth was defined as birth before 37 weeks completed gestation, as obtained from birth certificate records. This was the best clinical estimate of gestational age, based on ultrasonography data or on last menstrual period if ultrasonography data were not available. First and second trimesters were defined as gestational weeks 1–13 and 14–26, respectively. The third trimester was defined as commencing at week 27 and ending at the end of week 36 or at birth, whichever was earlier. The pre-labour rupture of membranes outcome was defined as rupture of the membranes before the onset of labour, irrespective of gestation at the time of membrane rupture, and obtained from the birth certificate record.

Statistical methods and analyses

Pregnancies were matched by mother, and conditional logistic regression was used to estimate odds ratios and 95% confidence intervals associated with a 1 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Separate models were fitted for each trimester and for whole-pregnancy exposures.

The main results are presented for women who resided no further than 40km from the $PM_{2.5}$ monitoring station (buffer distance criterion); and births that had at least 75% of weekly means of 24-hour averaged $PM_{2.5}$ measurements available in each trimester and whole pregnancy (non-missing criterion). We repeated analyses using 10km, 20km and 30km buffer distances; and 95% and 0% as the non-missing criterion.

All adjustment variables were included in the model as propensity scores derived with unmatched logistic regression. Risk factor adjustment was made for illegal drug use during pregnancy (yes/no), exercise during pregnancy for >30 minutes (<1, 1, 2, 3, 4, 5, 6, ≥7 occasions per week), maternal age in years (<20, 20–24, 25–29, 30–34, 35–39, or ≥40), parity (0, 1, 2, or ≥3 children), pre-pregnancy weight, depression during pregnancy (not depressed at all, a little depressed, moderately depressed, very depressed, received medication for depression and whether the mother had an antenatal visit in the first trimester (yes/no). Adjustment was also made for the number of cigarettes smoked in the three months prior to pregnancy, in the 1st trimester, 2nd trimester, and 3rd trimester. These factors have potential to change between pregnancies.

Results are presented for analyses adjusted for risk factors plus unmeasured temporal patterns in the events. To account for unmeasured temporal factors, we included a GAM spline function [17] of the date of conception to account for long-term and within-year seasonal

variation. Three knots per year were used for the smoothing parameter (degrees of freedom). Analyses were conducted in R version 3.0.

Sensitivity analysis to temperature adjustment was conducted by including this variable separately in the model adjusted for risk factors and unmeasured temporal variation. Analyses were also stratified by race/ethnicity.

Complete-case analyses tend to remove whole strata if there is a single missing value. We addressed this issue by applying multiple imputation using chained equations for missing adjustment variables (eAppendix, eTable 1). So as not to introduce bias, we applied multiple imputation prior to excluding <2 births per woman and prior to excluding births to women with concordant preterm birth/pre-labour rupture of membranes outcomes (N= 122,466 pre-labour rupture of membranes study, N=58,566 preterm birth study included in the multiple imputation).

RESULTS

Prevalence of preterm birth and pre-labour rupture of membranes. In the study period, 12.2% of births were complicated by pre-labour rupture of membranes and 7.3% were preterm birth. Overall, pre-labour rupture of membranes increased at a rate of 0.23% of births per year over the 9 year study period. There appeared to be no obvious secular trend in spontaneous preterm birth.

Characteristics of the study populations at study entry. There were 7,121 pregnancies to 3,264 women in the total study population (mean 2.2 pregnancies per woman) (Figure 1). The majority of women were nulliparous, white, aged 25-29 years, and did not smoke during pregnancy (Table 1). The pre-labour rupture of membranes study included caesarean section

births, which tend to be to women of higher socioeconomic status. Consequently, the women for the pre-labour rupture of membranes study were relatively older, more likely to be white and nulliparous, more likely to exercise and less likely to smoke during pregnancy. The proportion of women who smoked and the proportion of women who smoked more heavily (>10 cigarettes per day) generally decreased during pregnancy with the greatest reduction between the three months prior to pregnancy and 1st trimester.

Table 1 here

Exposure to $PM_{2.5}$ and ambient maximum temperature. Whole pregnancy exposure to $PM_{2.5}$ decreased by 0.45µg/m^3 per year over the study period. The median exposure to whole-pregnancy levels of $PM_{2.5}$ was 9 µg/m^3 (IQR 2 µg/m^3) with similar levels for trimester exposures (Table 2). The median whole pregnancy average of maximum temperature was 16 ^{O}C.

Table 2 here

Change in characteristics between first and last pregnancies of women in the study period in the total study population. More than a third of women remained within the same 5-year age category between their first and last births in the study period (39%, n = 1,129). There were 1,904 women (62%) whose pre-pregnancy weight increased between their first and last births in the study period (mean increase 5.4kg). Approximately the same proportion of women exercised less (34%, n=802), exercised more (36%, n=852) and did not change their level of exercise (31%, n=732) in the subsequent pregnancy. For 10% of women (n=324), pre-pregnancy smoking increased between the first and last pregnancy in the study period. For these women, the level of pre-pregnancy smoking increased by 10 cigarettes per day (median). Relatively few non-smoking women became smokers (5%, n=162). Depression

increased for 18% (n=439) and decreased for 17% (n=420) of women between the first and last pregnancy in the study period.

Half of the women in the study changed residential location between their first and last births in the study period (52%, n=1,682). However, the closest monitor did not change for the majority of the women in the study (95%, n=3,096). Of these women that moved, the median distance moved was 4.9 km (25^{th} percentile = 1.9 km, 75^{th} percentile = 11.6 km) and 52% moved farther away from the monitor. The median distance-to-monitor increase among the women that moved farther away from the monitor was 2.6 km (25^{th} percentile = 0.9 km, 75^{th} percentile = 7.3 km). Of the movers that lived within 40km of a monitor during the first pregnancy, 5% (n=67) moved outside of a 40km buffer during the next pregnancy. Of the movers that lived farther than 40km of a monitor during first pregnancy, 23% (n=82) moved within a 40km buffer during the next pregnancy.

Amount of variation in gestational age explained by individual factors. For gestational age (in weeks), 46% of the variation occurred among women (with the remaining 54% due to variation between pregnancies to the same women) indicating the possible importance of less understood factors such as genetics, social environmental factors, and recurrent health-related behaviours that vary among women. For whole-pregnancy exposure to $PM_{2.5}$, 91% of the variation occurred between pregnancies to the same women, indicating sufficient within-strata variation in the exposure to undertake this matched study.

Within-women association between study outcomes and $PM_{2.5}$. Unadjusted models indicated adverse associations between whole pregnancy and trimester-specific exposure to $PM_{2.5}$ and pre-labour rupture of membranes, but adverse associations were eliminated after adjustment (Table 3).

For preterm birth, unadjusted and adjusted associations were observed with all trimesters and whole-pregnancy exposure to $PM_{2.5}$. The OR estimates for trimester-specific exposures decreased with the progression of pregnancy, indicating a possible early-pregnancy effect. However, overlap of the confidence intervals indicated insufficient evidence that the effects were different from each other. The adjusted odds ratio for preterm birth per 1 $\mu g/m^3$ increase in whole pregnancy exposure to $PM_{2.5}$ was 1.17 (95% CI: 1.07, 1.28). This estimate is equivalent to an adjusted odds ratio of 1.38 (95% CI: 1.15, 1.65) per interquartile range increase in whole pregnancy $PM_{2.5}$.

Table 3 here

The adjusted odds ratio for preterm birth per 1 $\mu g/m^3$ increase in whole pregnancy exposure to $PM_{2.5}$ for white and African American women were 1.15 (95% CI: 1.02, 1.28) and 1.25 (95% CI: 1.02, 1.53), respectively. The point estimates imply that African American women might be a more susceptible population, although the interval estimates overlapped.

Sensitivity of associations to temperature exposures; choice of buffer distance, and missing exposure values. Null associations were observed between $PM_{2.5}$ exposure and pre-labour rupture of membranes and these associations were not sensitive to temperature adjustment, choice of buffer distance and missing exposure values (Table 4). Decreasing buffer distance and applying stricter completion criteria for missing exposure values resulted in a trade-off in statistical power, as both sample size and expected exposure misclassification decreased. Effect estimates for pre-labour rupture of membranes were similar with different buffer sizes (10, 20, 30, and 40km) with lack of evidence of an association at all buffer distances. For preterm birth, results for whole pregnancy exposure were robust to buffer size (OR = 1.11 to 1.23). Results for preterm birth and pre-labour rupture of membranes were similar with different thresholds for completeness of exposure data.

Table 4 here

DISCUSSION

Summary of results. We observed evidence for a within-women association between $PM_{2.5}$ exposure and risk of preterm birth. The estimated effects were not sensitive to the choice of buffer distance or missing $PM_{2.5}$ values.[18]

Study design. We applied a quasi-experimental design[19] whereby outcomes and exposures of pregnancies (observations) to the same women (strata) were compared to produce a "within-women" (within-strata) estimate of the association[20]. The design accounts for all time-invariant factors that tend to vary between women. These include potential confounders such as race, as well as risk factors such as genetic predisposition and recurrent health-related behaviours. The design also accounts for factors that vary over a period longer than the period of observation within-strata. This includes longer-term changes in outcome assessment, antenatal care, maternal education/health-knowledge and family disposable income. The method requires explicit adjustment for factors that do change during the period of observation within-strata, such as parity and age. Explicit adjustment for unmeasured temporal factors endeavours to address remaining temporal confounding. Our study design is similar, but not equivalent, to the case-crossover design commonly used to investigate acute exposure-outcome associations[21]. Unlike the case-crossover design our method enables investigation of longer-term exposures, allows for multiple events per stratum, and ensures that gestational age does not vary within strata during the exposure period. Interference between the exposures and outcomes of observations at different times within strata might influence results, analogous to "carry-over effects" in longitudinal experimental studies. This could occur, for example, if women who deliver a preterm child modify their health

behaviours to avoid recurrence, stop work to care for their child, or move house to better access health services. We expect this interference will minimally affect results because there is insufficient evidence to suggest that the direction of change in exposure is systematic, because women consciously decreasing air pollution exposure to avoid recurrence of preterm birth is unlikely to be prevalent, and because the preterm birth did not always precede the term birth. Nonetheless, the possibility of interference cannot be completely disregarded. If an association is observed, our design provides considerably greater support for the credibility of a causal effect than studies relying on between-strata comparisons. However, if an association is not observed the existence of an underlying causal effect cannot be disregarded as the effect of interest might only be observable between women.

Comparison with past studies. Sapkota *et al* conducted a meta-analysis of six studies relying on between-women comparisons, which indicated a 1% increase in risk of preterm birth for each 1-μg/m^3 increase in $PM_{2.5}$ (OR 1.01, 95 % CI: 1.01, 1.01)[6]. The result of Sapkota's meta-analysis was largely driven by a single study that accounted for 95% of the overall analysis weight. We have applied consistent methodology to investigate such associations with a longitudinally matched (within-women) design using independent study populations in Connecticut USA and Western Australia [8, 9, 12], and now Rochester, New York, USA. A meta-analysis of these three studies using the inverse variance method indicates a 1% (OR 1.01, 95% CI: 0.98, 1.14) increase in risk using a random effects model and a 3% (OR 1.03, 95% CI: 1.00, 1.06) increase in risk using a fixed effects model per 1-μg/m^3 increase in whole pregnancy $PM_{2.5}$ exposure, which are consistent with the pooled estimate relying on between-women comparisons. For our meta-analysis we found evidence for heterogeneity with I^2 =83% (95% CI: 49%, 95%) and Cochran's Q=12. As we applied consistent methodology for our studies the variability is likely due to differences in exposure or differences in the susceptibility of study populations. For each 1-μg/m^3 increase in whole

pregnancy $PM_{2.5}$ we observed adjusted odds ratios for preterm birth of 1.17 (95% CI: 1.07, 1.28) in Rochester, 1.05 (95% CI: 1.00, 1.11) in Connecticut and 0.99 (95% CI: 0.95, 1.04) in Western Australia. The median level of $PM_{2.5}$ exposure in pregnancy in this Rochester study was equivalent to the Australian study (9 $\mu g/m^3$) but lower than the Connecticut study (12.38 $\mu g/m^3$), indicating that a 1 unit increase in exposure could have different meaning across locations in relation to the baseline pollution levels. However, due to their relative proximity, the composition and sources [12] of the particulates might be more similar between Rochester and Connecticut, than Western Australia. The Rochester cohort had a greater proportion of higher-risk populations based on racial backgrounds (African American), teen pregnancies, and higher order parity. It is possible that these groups of women with already greater risk of preterm birth are also more susceptible to the harmful effects of $PM_{2.5}$, which might explain partially the greater effect estimates observed in this study. The present study suggests higher risk than indicated by earlier work but is statistically compatible with some previous estimates. Given the limited number of studies providing evidence of an association, and the limitations in research design, more efforts to replicate such analyses in other populations is warranted.

We did not observe evidence for an adverse association with pre-labour rupture of membranes despite having observed an adverse association with preterm birth, and despite adverse associations with pre-labour rupture of membranes reported in our previous study in Western Australia [8] and with preterm pre-labour rupture of membranes reported in the study by Dadvand *et al* .in Spain [7]. Differences in ascertainment is possible given the large difference in incidence of pre-labour rupture of membranes in this cohort (12%) and that from the Western Australian study (5%) [8]. It is possible that the self-reported incidence of pre-labour rupture of membranes on birth certificates over-estimates the incidence of pre-labour rupture of membranes in medical records. It is also possible that pre-labour rupture of

membranes with longer latency (more detrimental than shorter latency) is more likely to be acknowledged as a problem and therefore more likely to be reported. It is possible that these errors differ by individual, differ according to the level of and approach to antenatal care, and consequently differ by geographic region.

In this study the point estimates (odds ratios) for the association between $PM_{2.5}$ and preterm birth decreased with increasing trimester of exposure, a result that was also observed in the Connecticut study[9]. The mechanism by which elevated early pregnancy exposure leads to preterm birth remains unclear. Systemic inflammation might be an important pathway, as women exposure to $PM_{2.5}$ early in pregnancy have been reported to have higher C-reactive protein concentrations[22]. The stronger association with preterm birth for exposure to $PM_{2.5}$ earlier in pregnancy might indicate the importance of the role of placental implantation/function. Other studies have observed associations between air pollution and pre-eclampsia, and have indicated impaired placental function as a plausible pathway[23, 24]. Although preterm birth is associated with hypertension and exposure to air pollution has been reported to increase the risk of pregnancy-induced hypertensive disorders [25], blood pressure does not increase early in pregnancy. Although we did not observe an association with pre-labour rupture of membranes, it still might explain the association observed with preterm birth if the influence of $PM_{2.5}$ on membrane rupture is stronger earlier in pregnancy. However, we had insufficient information to investigate this hypothesis. Firstly, there were only 156 pregnancies cases with both pre-labour rupture of membranes and preterm birth. Also, pre-labour rupture of membranes very early in gestation tends to be associated with longer latency, which leads to greater exposure misclassification due to insufficient information on gestational week of membrane rupture for those pregnancies.

Limitations. For the preterm study, the target population for inference was further restricted to spontaneous preterm births. If $PM_{2.5}$ exposure explains a fraction of the antecedents of

iatrogenic preterm births our results are not necessarily generalizable to that population. As we had insufficient information on the timing of these antecedents, including iatrogenic preterm births would have introduced systematic exposure misclassification, so excluding iatrogenic cases was the most conservative approach. Our previous studies in Connecticut and Western Australia indicated that results were not sensitive to this exclusion[8, 9]. We did not have sufficient information to accurately distinguish caesarean sections with labour from those without labour. We expect that if a causal effect on preterm birth exists, the exclusion of caesarean sections with labour would inflate the variance of the estimate.

Monitor density limited the ability to adjust for other criteria air pollutants. More specifically, applying the completion criteria of >75% non-missing (during pregnancy and within the study period) and a buffer distance of 40km resulted in no available study population for NO_2 and a reduction in sample size of 28% for CO. The utility of adjustment for SO_2 would have been diminished by collinearity, as a high Spearman correlation (>0.6) was observed with whole pregnancy $PM_{2.5}$.

The estimates for preterm birth were not sensitive to the choice of buffer distance, a result that has also been observed for associations with low birth weight[18]. This result might reflect the overlap in the study population at different buffers. However, the result could also be due to spatial similarity in the toxicity of $PM_{2.5}$ or indicate that larger buffer sizes better serve as a proxy for where women spent their time. A detailed investigation of these issues was beyond the scope of this study.

CONCLUSION

There was insufficient evidence for an association between $PM_{2.5}$ exposure during pregnancy and pre-labour rupture of membranes. Risk of preterm birth was greater for pregnancies with elevated $PM_{2.5}$ exposure than other pregnancies to the same women at lower exposure.

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Figure 1. Selection of the Study Populations for the Preterm Birth (PTB) and Pre-Labour Rupture of Membranes Studies (PROM). The Starting Population was 130,070 Live Births in Rochester, New York, 2004-2012.

Table 1. Maternal Characteristics at the Time of Study Entry (First Birth in the Study Period) for the Women in the Preterm and Pre-labour Rupture of Membranes Studies

	Preterm Study (N=668 women)		Pre-labour Rupture of Membranes Study (N=2,782 women)	
	N women	**%**	**N women**	**%**
Age				
<20 years	125	19	362	14
20-24 years	216	33	720	27
25-29 years	183	28	909	34
30-34 years	94	14	551	21
35-39 years	33	5	132	5
40+ years	1	0	12	0
Race/ethnicity				
African American	118	18	307	11
Hispanic	38	6	114	4
White	494	75	2265	83
Asian	3	1	20	1
Other	5	1	18	1
Parity				
No children	418	63	2146	77
1 child	131	20	387	14
2 children	80	12	166	6
≥3 children	39	6	83	3
Pre-pregnancy weight				
<55 kg	178	27	681	25
55 - 63 kg	147	23	756	28
63 - 74 kg	176	27	605	22
>74 kg	148	23	678	25
Antenatal visit in 1st trimester				
Visited in 1st trimester	513	81	2285	85
Exercise during pregnancy >30 min				
<1 occasion per week	251	46	937	40
1 occasion per week	47	9	219	9
2 occasions per week	86	16	445	19
3 occasions per week	61	11	339	14
4 occasions per week	30	6	163	7
5 occasions per week	32	6	127	5
6 occasions per week	7	1	29	1
≥7 occasions per week	35	6	100	4
Depression during pregnancy				
Not depressed at all	359	64	1654	69
A little depressed	148	26	546	23
Moderately depressed	39	7	132	6
Very depressed	7	1	22	1
Very depressed and had to be helped	8	1	29	1
Illegal drug use during pregnancy				
Used drugs	31	4.7	88	3

Pre-pregnancy smoking [a]				
None	458	69	2121	76
1-4 cigarettes per day	35	5	91	3
5-9 cigarettes per day	33	5	102	4
10-19 cigarettes per day	65	10	229	8
≥20 cigarettes per day	77	12	239	9
1st trimester smoking				
None	504	75	2276	82
1-4 cigarettes per day	36	5	126	5
5-9 cigarettes per day	32	5	92	3
10-19 cigarettes per day	62	9	167	6
≥20 cigarettes per day	34	5	120	4
2nd trimester smoking				
None	522	78	2376	85
1-4 cigarettes per day	34	5	107	4
5-9 cigarettes per day	37	6	88	3
10-19 cigarettes per day	53	8	149	5
≥20 cigarettes per day	22	3	61	2
3rd trimester smoking				
None	531	80	2400	86
1-4 cigarettes per day	37	6	111	4
5-9 cigarettes per day	38	6	85	3
10-19 cigarettes per day	48	7	130	5
≥20 cigarettes per day	14	2	55	2

a. Pre-pregnancy smoking: smoking in the 3 months prior to pregnancy

Table 2. Exposure to $PM_{2.5}$ and Ambient Maximum Temperature for the Study Population

	1st trimester	2nd trimester	3rd trimester	Pregnancy
$PM_{2.5}$ ($\mu g/m^3$)				
Median	9	9	9	9
IQR	3	3	3	2
25^{th} – 75^{th} percentile	7 - 10	7 - 10	7 - 10	8 - 10
Temperature (maximum °C)				
Median	14	15	16	16
IQR	15	15	15	5
25^{th} – 75^{th} percentile	8 - 23	8 - 23	8 - 24	13 - 18

Table 3. Odds Ratios for Preterm Birth and Pre-labour Rupture of Membranes per 1 μg/m^3 Increase in $PM_{2.5}$ Comparing Each Woman's Preterm Pregnancy to her Term Pregnancy; Effects by Exposure Period. Women resided in Rochester, New York and delivered a singleton neonate at least twice during the period 2004-2012. Women lived within 40km of a monitor and had at least 75% of weekly means non-missing in the exposure period.

			Unadjusted		Adjusted		Adjusted		Fully Adjusted	
	Births	Women			Propensity score A		Propensity scores A, B		Propensity scores A, B, C	
	N	N	OR	95% CI	OR [a]	95% CI	OR [b]	95% CI	OR [c]	95% CI
Preterm birth										
Whole pregnancy	1,004	461	1.23	1.13 , 1.34	1.23	1.13, 1.34	1.22	1.12, 1.33	1.17	1.07 , 1.28
1st trimester	1,025	470	1.14	1.07 , 1.22	1.15	1.08, 1.22	1.14	1.07, 1.22	1.11	1.04 , 1.18
2nd trimester	1,030	474	1.12	1.06 , 1.19	1.12	1.06, 1.19	1.12	1.05, 1.19	1.09	1.02 , 1.16
3rd trimester	1,029	472	1.08	1.02 , 1.15	1.09	1.03, 1.15	1.09	1.03, 1.15	1.06	1.00 , 1.13
Pre-labour rupture of membranes										
Whole pregnancy	3,940	1,829	1.15	1.10 , 1.20	1.15	1.10 , 1.21	1.14	1.09 , 1.20	0.99	0.94 , 1.04
1st trimester	4,095	1,902	1.07	1.04 , 1.11	1.07	1.04 , 1.11	1.06	1.03 , 1.10	1.00	0.97 , 1.04
2nd trimester	4,139	1,917	1.09	1.06 , 1.12	1.09	1.06 , 1.13	1.08	1.05 , 1.12	0.99	0.96 , 1.02
3rd trimester	4,167	1,928	1.06	1.03 , 1.09	1.06	1.03 , 1.09	1.06	1.03 , 1.09	0.99	0.96 , 1.03

CI: Confidence Interval

a. Propensity score A: smoking tobacco during each trimester of pregnancy and pre-pregnancy, exercise during pregnancy, depression during pregnancy, illegal drug use during pregnancy, pre-pregnancy weight, and antenatal visit in first trimester.
b. Propensity score B: unmeasured temporal factors
c. Propensity score C: parity, maternal age

Table 4. Adjusted Odds Ratios for Preterm Birth and Pre-labour Rupture of Membranes per 1 μg/m^3 Increase in Whole Pregnancy $PM_{2.5}$ Comparing Each Woman's Preterm Pregnancy to her Term Pregnancy; Effects by Buffer Distance and Exposure Completion Criterion. Women resided in Rochester, New York and delivered a singleton neonate at least twice during the period 2004-2012.

			Preterm birth				Pre-labour rupture of membranes			
Buffer distance[a]	**Completion criteria [b]**	**Co-adjustment[c]**	**Births (N)**	**Women (N)**	**OR [d]**	**95% CI**	**Births (N)**	**Women (N)**	**OR [d]**	**95% CI**
10 km	75%		371	172	1.11	0.96, 1.28	1,318	620	0.97	0.89, 1.05
20 km	75%		607	284	1.23	1.10, 1.37	2,398	1,125	0.96	0.90, 1.02
30 km	75%		727	340	1.21	1.09, 1.34	2,948	1,383	0.98	0.92, 1.04
40 km	75%		1,004	461	1.17	1.07, 1.28	3,940	1,829	0.99	0.94, 1.04
40 km	0%		1,137	519	1.15	1.06, 1.25	4,657	2,145	0.98	0.94, 1.03
40 km	95%		610	282	1.18	1.03, 1.34	2,488	1,170	0.99	0.91, 1.07
40 km	75%	Temp	1,004	461	1.21	1.09, 1.35	3,658	1,829	1.00	0.94, 1.06
None [e]	0%		1,466	668	1.15	1.07, 1.23	6,071	2,782	0.99	0.96, 1.03

CI: Confidence Interval

a. Buffer Distance: Maximum distance between the $PM_{2.5}$ monitoring station and the maternal residence.

b. Completion Criterion: Minimum percentage of $PM_{2.5}$ weekly means non-missing in the exposure period allowed in the analysis.

c. Additional adjustment for ambient temperature as a linear plus quadratic term

d. Adjusted for propensity scores for parity, maternal age, smoking tobacco during each trimester of pregnancy and pre-pregnancy, exercise during pregnancy, depression during pregnancy, illegal drug use during pregnancy, pre-pregnancy weight, antenatal visit in first trimester, and unmeasured temporal patterns in the event

e. No restriction, meaning all births included in analyses.