Original Research Article

Fine particulate matter and risk of preterm birth and pre-labour rupture of membranes in Perth, Western Australia 1997-2007: A longitudinal study

Gavin Pereira¹,², Michelle L. Bell²,³, Kathleen Belanger², Nicholas de Klerk¹,

¹ Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, 100 Roberts Road, Subiaco WA 6008 Australia

² Center for Perinatal Pediatric and Environmental Epidemiology, School of Medicine, Yale University, New Haven CT

³ School of Forestry and Environmental Studies, Yale University, New Haven, CT

Corresponding author: Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, 100 Roberts Road, Subiaco WA 6008 Australia Email: gpereira@ichr.uwa.edu.au. Phone: +1 203-764-9767

Running title: A longitudinal study of preterm birth and PM₂.₅ in WA

Conflicts of interest and source of funding: none declared. This project was funded by the National Health and Medical Research Council (NHMRC) Program Grant 572742. GP received funding from a NHMRC Early Career Fellowship grant 1052236. MLB and KB received funding from the National Institute of Environmental Health Sciences grants R0101ES016317 and R01ES019587. No competing financial interests.

Acknowledgements: The authors thank the Western Australian Department of Health and Department of Environment and Conservation for providing the data used in this study.
ABSTRACT

OBJECTIVE. A recent longitudinal study reported an association between fine particulate (PM$_{2.5}$) exposure and preterm birth (PTB) in a US cohort. We applied the same design to an Australian cohort to investigate associations with PTB and pre-labour rupture of membranes (PROM).

METHODS. From 287,680 births, we selected 39,189 women who had singleton births at least twice in Western Australia in 1997–2007 (n = 86,844 births). Analyses matched pregnancies to the same women with conditional logistic regression.

RESULTS. For PROM adjusted odds ratios (OR) for 1 μg/m$^3$ increase in PM$_{2.5}$ in the first trimester, second trimester, third trimester, and whole pregnancy were 1.00 (95% confidence interval (CI): 0.97, 1.03), 1.03 (95% CI: 1.00, 1.06), 1.02 (95% CI: 1.00, 1.05), and 1.02 (95% CI: 0.99, 1.05) respectively. For PTB, corresponding ORs were 1.00 (95% CI: 0.96, 1.04), 1.00 (95% CI: 0.96, 1.04), 0.98 (95% CI: 0.94, 1.02), and 0.99 (95% CI: 0.95, 1.04) respectively.

CONCLUSION. Risk of PROM was greater for pregnancies with elevated PM$_{2.5}$ exposure in second trimester than were other pregnancies to the same Australian women at lower exposure. There was insufficient evidence for an association with PTB, indicating that a longer time period might be needed to observe an association if a causal effect exists.
BACKGROUND

Preterm birth is the single most important cause of perinatal mortality in the western world\(^1\). It occurs among 8% of live born infants and 82% of stillborn infants\(^2\). Infants that survive remain at much greater risk of subsequent morbidity, such as respiratory dysfunction and neurodevelopmental impairment than their term counterparts\(^3\,\^4\). The array of sequelae might also extend into the life course beyond the neonatal period\(^5\).

The adverse health effects of exposures to elevated levels of fine particulate matter (PM\(_{2.5}\)) in the ambient air are now well-established\(^6\) with the principal source being combustion emissions\(^7\). We previously observed associations in Western Australia between combustion emissions and fetal growth restriction\(^8\,\^9\) and pre-eclampsia\(^10\), which are both on the causal pathway to PTB. Adverse associations with PTB were also observed for a study in Brisbane, where levels of particulate matter are low by worldwide comparisons\(^11\).

Internationally, although some studies have reported associations between PM\(_{2.5}\) exposure and PTB\(^{12-16}\), evidence for a consistent association remains elusive. It is uncertain whether the results of past studies were affected by individual predisposition\(^{17\,\,18}\) that might vary considerably between women. In Australia, the preterm rate can be as high as 19%-36% in Aboriginal communities\(^19\). The challenge of highly variable predisposition can be addressed by comparing pregnancies of the same women, thereby accounting for individual predisposition to PTB. Using this longitudinal design, we recently observed a 7% increase in risk of PTB per interquartile range increase in PM\(_{2.5}\) exposure for women in Connecticut, USA\(^14\). It remains to be established whether such associations are present in an Australian population.

A recent study on a Spanish cohort reported associations with pre-labour rupture of membranes (PROM)\(^20\), which occurs when the chorioamniotic membranes rupture prior to
labour. If such associations are substantiated, particulate matter effects on PROM might explain associations with PTB as PROM is its leading identifiable cause\textsuperscript{21}. The possible neonatal consequences of PROM include fetal distress, infection and pulmonary hypoplasia\textsuperscript{22}. No study has yet reported associations between PM\textsubscript{2.5} and PROM, comparing pregnancies to the same women.

The aim of this study was to test the hypothesis that PTB and PROM are associated with exposure to ambient PM\textsubscript{2.5} during pregnancy among women in Perth, Western Australia.

**METHODS**

**Study design and population**

This was a longitudinal study of women's exposure to ambient airborne PM\textsubscript{2.5} and PTB across successive pregnancies in Perth, Western Australia from 1997 to 2007. There were 287,680 births during the study period. Participant selection is described in Figure 1. Briefly, we sequentially excluded all births with missing gestational age, parity or mother identifier; multiple gestations; records for which there was a discordance between the year of birth and the parity variable; birth records for which maternal address could not be geocoded by the Department of Health; women who resided further than 40km from the PM\textsubscript{2.5} monitoring station; and births that had less than 75\% of the weekly means of 24-hour averaged PM\textsubscript{2.5} measurements available in each trimester and whole pregnancy. For the preterm analysis, we excluded births with non-spontaneous onset of labour. The remaining reference populations for the PROM and PTB studies were used to calculate prevalence of these events. The reference populations for PTB and PROM were 78,992 births (61,922 women) and 154,684 births (107,029 women), respectively.
For the longitudinal analyses, these reference populations were restricted to records in which at least 75% of the weekly means of 24-hour averaged PM$_{2.5}$ measurements were available in each trimester or for the whole pregnancy, and further restricted to women who gave birth at least twice during the study period. The remaining longitudinal study populations were used to conduct the analyses matched by mother. The longitudinal study populations for PTB and PROM were 31,567 births (14,497 women) and 86,844 births (39,189 women), respectively.

The selection of participants followed the same protocol as the Connecticut study$^{14}$. However we were not able to include stillbirths and births with congenital anomaly in the Connecticut study despite the possibility that these endpoints lie on the causal pathway to PTB$^{10,23-26}$. As we could not identify births with spontaneous onset of labour in Connecticut, we excluded all deliveries by caesarean section in that study. Midwives notifications in Western Australia allowed us to identify births with spontaneous onset of labour. Although it is possible that exposure might promote the risk factors that lead to medically indicated PTB, exposure would be misclassified due to lack of adequate information to pinpoint the time of onset of the indication. Finally, the 40km distance from residence to monitoring station cut-off was selected to reduce exposure misclassification and the same cut-off was applied in the Connecticut study. Distance in this study was calculated from the centroid of the census district of maternal residence.

**Data sources and variables**

Midwives notification records were obtained from the Western Australian Department of Health for all births in Western Australia from January 1, 1997 to December 31, 2007. Each observation contained variables for the residential location at birth, pregnancy-related and socio-demographic risk factors. Pregnancy risk factors were smoking during pregnancy and birth order. Socio-demographic risk factors were maternal age and an index for
socioeconomic disadvantage. The index for socioeconomic disadvantage was derived by the Australian Bureau of Statistics for each census district of maternal residence. Census districts contain on average 240 dwellings. The index of relative socioeconomic disadvantage was derived by the Australian Bureau of Statistics for each census district. The index represents a socioeconomic disadvantage score derived from 2011 national census variables, including income, education and employment. Lower scores indicate relative socioeconomic disadvantage. Census collection districts contain on average 225 dwellings. The index has a national mean of 1000 and a standard deviation of 100.

Daily (24-hour average) PM$_{2.5}$ measurements (taken every day) were obtained from the Western Australian Department of Environment and Conservation PM$_{2.5}$ monitor (Duncraig site). This was the only monitor operational for PM$_{2.5}$ measurements throughout the study period. Similarly, this monitor was used to obtain daily (24-hour average) measurements of carbon monoxide and nitrogen dioxide. Ozone was obtained from the site nearest to the Duncraig site (Swanbourne). Ambient temperature maxima were obtained from the Perth metropolitan site (site number 9225). Co-pollutant and temperature exposures were generated by using the same procedure described below for PM$_{2.5}$ exposure.

**Outcome assessment**

Preterm birth was defined as birth before 37 weeks’ completed gestation. Period of gestation was 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 week’s 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 PROM outcome was defined as
rupture of the membranes at any time before the onset of labour, irrespective of gestation at the time of membrane rupture, and obtained from midwives notification completed by the midwife at birth.

**Exposure assessment**

Daily PM$_{2.5}$ measurements from the closest monitor within 40 km of a subject's residence were assigned to each woman. This distance is the same as that used in our Connecticut study$^{14}$ and comparable with that of 50 km used in a study evaluating exposure assessment among pregnant women$^{28}$. Weekly mean PM$_{2.5}$ levels were calculated as 7-day averages for each monitor of the 1996–2007 period. Mean exposures were computed for each week of gestation and were then used to compute average exposure for each trimester and for the whole pregnancy. This avoided bias due to changes in the frequency of PM$_{2.5}$ measurements$^{29}$. Only measurements to the earlier of birth or gestational week 36 were included in third-trimester and whole-pregnancy analyses.

**Statistical methods and analyses**

To examine the potential for confounding by secular trends caused by factors unrelated to PM$_{2.5}$, the rate of PTB was calculated for the reference population by year of conception and was compared with the temporal trend in mean PM$_{2.5}$.

Pregnancies were matched by mother, and statistical associations were investigated with conditional logistic regression by using odds ratios, 95% confidence intervals, and 2-sided $P$ values. Separate models were fitted for each trimester and for whole-pregnancy exposure. Adjustment was made for smoking during pregnancy, maternal age in years (<20, 20–24, 25–29, 30–34, 35–39, or ≥40), parity (0, 1, 2, or ≥3 children), and the index of relative socioeconomic disadvantage score. These factors have potential to change considerably
between pregnancies and are strong independent risk factors for PTB\textsuperscript{17,30}. All adjustment variables were included in the model as propensity scores derived with logistic regression from the reference population. Unmatched logistic regression was used to derive propensity scores because the matched approach (i) has more limited information due to the small number births per mother (typically two births per woman) and (ii) introduces a greater degree of multicollinearity as the adjustment variables each tend to increase or decrease over time. Results were presented separately for unadjusted analyses, analyses adjusted for risk factors plus unmeasured temporal patterns in the event (PTB/PROM). To account for unmeasured temporal factors, we included a GAM spline function of the date of conception to account for long-term and within-year seasonal variation. The smoothing parameter (degrees of freedom) was selected using generalized cross-validation. We also conducted sensitivity analyses using fixed degrees of freedom. Analyses were conducted in R version 3.0.

Sensitivity analysis to co-pollutant and temperature adjustment was conducted by including these variables separately in the model adjusted for risk factors and unmeasured temporal variation. We also investigated sensitivity to choice of buffer distance from the monitor.

Ethical approval was obtained from the Department of Health Human Research Ethics Committee RA/4/1/5884.

**RESULTS**

*Prevalence of PTB and PROM in the reference populations.* In the study period, 5.0% of births were complicated by PROM and 7.3% were PTB. The PROM rate increased from 1997 to 2002, after which PROM declined to 2007 (Figure 2). Overall, PROM decreased at a rate
of 0.08% of births per year PTB increased at a rate of 0.09% per year in the study period. The levels of PM$_{2.5}$ exhibited a degree of seasonal variation and decreased by 0.28µg/m$^3$ per year over the study period (eFigure 1).

**Characteristics of the longitudinal study populations at study entry.** Majority of women were married nulliparous Caucasian women of age 25-29 years who did not smoke during pregnancy (Table 1). The preterm study population excluded births with non-spontaneous onset of labour, whereas the PROM longitudinal study population included planned caesarean section births which tend to be to women of relatively higher socioeconomic status. Consequently, this population was also relatively older, more likely to be married, Caucasian and nulliparous, and less likely to smoke during pregnancy.

**PTB and PROM outcomes during the study period.** There were 1,542 women (10.6%) that had both a PTB and a term birth during the study period. As PROM has no gestational age restriction, there were more women who had both a PROM birth and a non-PROM birth (N=3,718 women). However, as the incidence of PROM is less than the incidence of PTB, the proportion of women with both PROM and non-PROM births (7.8%) was lower than the proportion of women with both preterm and term births.

**Exposure to PM$_{2.5}$, co-pollutants and ambient maximum temperature.** The median exposure to whole-pregnancy levels of PM$_{2.5}$ was 8.51 µg/m$^3$ with similar levels for trimester exposures (Table 2). Median exposure to whole-pregnancy levels of CO, NO$_2$, O$_3$ and maximum temperature were 269.84 ppb, 7.87 ppb, 19.82 ppb, and 18.08 °C.

**Change in sociodemographic characteristics between pregnancies for the longitudinal PROM study population.** More than a third of the women remained within the same 5-year age category between their first and last births in the study period (36.9%, n = 12,313). The majority of women remained in the same socioeconomic quartile (70.1%, n=27,247), with
4,642 women (11.9%) who moved to an area of lower socioeconomic quartile between their first and last births in the study period. There were 3,479 women (10.0%) who changed level of smoking between their first and last births in the study period. Relatively few non-smoking women became smokers (4.4%, n=1,511). There were 3,741 women (9.5%) who changed their marital status, 2,572 of whom (6.6%) changed from unmarried to married. Almost half of the women changed residential location to a different census district between their first and last births in the study period (48.6%, n=19,046). Of these women that moved, the median distance moved was 5.5 km (25th percentile = 2.4 km, 75th percentile = 11.3 km) and 55.4% moved farther away from the monitor. The median distance-to-monitor increase among the women that moved farther away from the monitor was 3.4 km (25th percentile = 1.2 km, 75th percentile = 7.9 km).

**Amount of variation in gestational age explained by individual factors.** Gestational age differed more between women than between pregnancies to the same woman, indicating the importance of less understood factors such as genetics, social environmental factors, and recurrent health-related behaviours. For gestational age (in weeks), 58.9% of the variation occurred between women, with the remaining 41.1% due to variation between pregnancies to the same woman.

**Within-women association between PTB/PROM and PM$_{2.5}$.** There was insufficient evidence to suggest an adverse association between PM$_{2.5}$ exposure and PTB (Table 3). For PROM, unadjusted associations were observed with all trimester and whole-pregnancy exposure to PM$_{2.5}$. However, adjustment for risk factors and unmeasured temporal factors resulted in attenuation of the effect estimates. The adjusted odds ratio for PROM per 1 µg/m$^3$ increase in second trimester exposure to PM$_{2.5}$ was 1.03 (95% CI: 1.00, 1.06, p-value: 0.026). This
estimate is equivalent to an adjusted odds ratio of 1.08 (95% CI: 1.00, 1.16) per interquartile range increase in second trimester PM$_{2.5}$.

*Sensitivity of PROM associations to co-pollutant and temperature exposures, and choice of buffer distance.* Co-pollutants were separately included in adjusted models to assess sensitivity of the observed odds ratios (eFigures 2-5). The variance of the estimates did not change considerably after adjustment for any co-pollutant but the interval estimates did shift marginally, indicating a degree of collinearity and co-pollutant adjustment did not improve precision of the estimate. This was especially the case for carbon monoxide, for which the PROM odds ratio for third trimester PM$_{2.5}$ exposure became statistically significant. In general, the PROM odds ratios for PM$_{2.5}$ exposure changed only slightly after adjustment for co-pollutant and maximum temperature exposures.

We investigated sensitivity of results to choice of buffer size by decreasing the buffer distance to reduce exposure misclassification by restricting analyses to women who lived closer to the monitoring station. Analyses were restricted to women who lived within 5 km, 10 km, 15 km, 20 km and 30 km of the PM$_{2.5}$ monitoring station (eFigures 6-9). The 95% confidence intervals increased markedly with decreasing distance due to reduction in sample sizes. This led to highly variable odds ratio estimates at the 5 km and 10 km distances. Accordingly, decreasing buffer distance resulted in a trade-off in statistical power, as both sample size and expected exposure misclassification decreased. Interval estimates produced with 20 km, 30 km and 40 km buffers were highly compatible. Applying a 20 km buffer resulted in previous statistically non-significant associations becoming statistically significant for whole pregnancy and third trimester exposure to PM$_{2.5}$.

**DISCUSSION**
**Summary of results.** This was the first longitudinal study to investigate the association between ambient PM$_{2.5}$ and PROM. A 1 µg/m$^3$ increase in second trimester PM$_{2.5}$ was associated with a 3% increase in risk of PROM, while an interquartile range (2.6 µg/m$^3$) increase in exposure was associated with an 8% increase in risk.

**Comparison with past studies.** One other study has investigated the association between PM$_{2.5}$ and rupture of the chorioamniotic membranes$^{20}$. That study reported null associations for rupture of membranes and preterm PROM with PM$_{2.5}$ mass concentration. However, the study reported PM$_{2.5}$ absorbance (a marker for traffic-related particulates) in whole pregnancy and last 3 months prior to rupture were associated with a 0.7-day and 1.3-day reductions in gestational age at membrane rupture in a between-women comparison of 5,555 women in Barcelona, Spain. The study also reported that an interquartile range increase in PM$_{2.5}$ absorbance was associated with a 50% increase in risk of preterm PROM, although did not investigate the association with PROM that could have occurred at any time point in gestation. The Barcelona results imply that PM$_{2.5}$ shortens the time to membrane rupture and that associations can be partially explained by traffic-related PM$_{2.5}$. Our results support those of the Barcelona study, and imply that associations with membrane rupture (at any time in pregnancy) are potentially independent of the onset of labour, and that such associations are observable in a within-women context that is less influenced by individual-level confounding. Further studies are required to establish consistency of results and might benefit from PM$_{2.5}$ source apportionment, assessment of PROM with membrane rupture at any time in pregnancy, and a longitudinal (within-women) design.

We recently observed that elevated PM$_{2.5}$ was associated with increased risk of PTB among women in Connecticut$^{14}$. A 1 µg/m$^3$ increase in whole pregnancy PM$_{2.5}$ was associated with a 5% increase in risk of PTB in the Connecticut study. We did not observe sufficient evidence for such an association among Western Australian women. The mean whole
pregnancy level of PM$_{2.5}$ among Connecticut women was 12.38 µg/m$^3$ compared to 8.55 µg/m$^3$ for women in this study, indicating that better air quality might contribute to non-detection of an association. However, we observed an adverse association with PROM at the same levels of air pollution. The number of women in the longitudinal study population of PTB was approximately half of that in the Connecticut study despite the 11-year study period, which we expected to allow sufficient time for more than one pregnancy. As this was a study of a whole population, statistical power can increase if the PTB rate increases, if family size increases, or if the study period increases. A longer study period would result in additional births to new strata (women) not already included as well as new (higher parity) births to women already included in the sample. Dependence on ground-based monitors also limited the size of the study population. Future studies might benefit from exposure estimates less reliant on ground monitors, such as land-use or satellite-derived PM$_{2.5}$. In this cohort, 41% of variation in gestational length was attributable to variation between pregnancies to the same woman, compared to 34% in the Connecticut study$^{14}$, which might be explained by differences in health inequality. Studies with greater total variation in gestational length plus higher proportions of within-women variation in gestational length are better positioned for studies that adopt our longitudinal design.

Limitations. By the nature of our study design and necessary exclusions, the target population for inference were women who deliver more than one child. Our putative expectation was that the 11-year study period was sufficient for women who would deliver more than one child, did so within this time frame, and therefore our results are externally generalizable to the target population. For the preterm study, the target population for inference was further restricted to those with spontaneous onset of labour. This included births by caesarean section as long as labour had initiated spontaneously and excluded, by definition, births by caesarean section with no onset of labour i.e., planned caesarean sections. If PM$_{2.5}$ exposure explains a
fraction of the antecedents of planned caesarean sections, our results are not necessarily
generalizable to that population. Unfortunately, we had insufficient information on the timing
of these antecedents to calculate exposure estimates and exclusion of births without
spontaneous onset of labour was the most conservative approach.

A limitation of this study was that we had residential locations geocoded to census district
centroids rather than exact street address. Half of the women moved between pregnancies.
However, the median distance moved among those that moved farther from the PM$_{2.5}$
monitor was 3km, which is small relative to buffer distance of 40km used in this study. A
single ground-based PM$_{2.5}$ monitor was used in this study, which resulted in exposure
estimates that lacked spatial variation in PM$_{2.5}$. Exposure models of PM$_{10}$ with high spatial
resolution agree with estimates derived from the closest monitoring station$^{31}$, and it is
plausible that such agreement would be better still for PM$_{2.5}$ which can travel greater
distances.

We addressed the issue of temporal confounding by adjustment for unmeasured temporal
factors (using a GAM spline) as well as adjustment for parity (which has an established
association with the outcome). Adjustment for unmeasured temporal confounding using our
approach to the selection of the smoothing parameter produced results that are comparable
with those from a conservative approach (using 3 degrees of freedom per year) (eTable 1).
However, we note less conservative adjustment, using a quadratic long-term trend, resulted in
a statistically significant association between PROM and third trimester exposure. We were
unable to assess residual temporal confounding by more acute temperature or co-pollutant
exposures under our study design. For the PROM outcome this was because we did not have
the timing of the membrane rupture. For the PTB outcome this was because under our design
excludes exposures after the outcome (preterm birth: <37 weeks completed gestation) would
have been observed.
A further limitation of exposure assessment was that use of a large population database resulted in lack of information on residential moves during pregnancy and time-activity information, which would have attenuated the observed odds ratios if the misclassification was non-differential.

Although the National Environment Protection Council set an Australian standard for coarse particulate matter a standard for PM$_{2.5}$ is only now in the process of being introduced. A mandatory reporting standard for PM$_{2.5}$ has already been instituted by the European Union, Canada, the United States, and guidelines on the setting of such a standard were published by the World Health Organisation more than seven years ago. Australia lags behind developed countries in the introduction of a mandatory reporting standard. Local epidemiologic studies are necessary to inform the setting of such a standard.

**CONCLUSION**

This was the first longitudinal study of PROM, matching pregnancies to the same women. Risk of PROM was greater for pregnancies with elevated PM$_{2.5}$ exposure in second trimester than were other pregnancies to the same Western Australian woman at lower exposure. There was insufficient evidence for an association with PTB, indicating that a longer time period might be needed to observe an association if a causal effect exists.
REFERENCES


**Figure 1.** Selection of the reference populations and longitudinal study populations for the preterm birth (PTB) and pre-labour rupture of membranes (PROM) studies. The starting population was 287,680 births in Western Australia, 1997-2007.

**Figure 2.** Annual mean percentage of spontaneous preterm birth (PTB) and pre-labour rupture of membranes for the reference populations (PROM), with linear trend line for PROM (beta=-0.08% per year, p=0.119) and PTB (beta=+0.09% per year, 0.060)
West. Australia, 1997-2007
287,680 births

Excluded 116 births, missing gestational age, parity or mother identifier

287,564 births

Excluded 17,114 births, multiple gestations

270,450 births

Excluded 1,210 births, discordance between parity and birth year

269,240 births

Excluded 23,882 births, non-geocodable address

245,358 births

Excluded 83,338 births, lived >40km from monitor

162,020 births

Excluded 7,336 births, <75% exposures available

PROM reference population
154,684 births

Excluded 75,692 births, non-spontaneous labour

PTB reference population
78,992 births

Excluded 67,840 births, <2 births per mother

PROM longitudinal study population
86,844 births

Excluded 47,425 births, <2 births per mother

PTB longitudinal study population
31,567 births
Table 1. Maternal characteristics and Birth Outcomes at Study Entry for the Longitudinal Study Populations

<table>
<thead>
<tr>
<th></th>
<th>Preterm Longitudinal Study Population (N=14,497 women)</th>
<th>PROM Longitudinal Study Population (N=39,189 women)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N women</td>
<td>%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>1,266</td>
<td>9.1</td>
</tr>
<tr>
<td>20-24 years</td>
<td>3,101</td>
<td>22.3</td>
</tr>
<tr>
<td>25-29 years</td>
<td>5,096</td>
<td>36.7</td>
</tr>
<tr>
<td>30-34 years</td>
<td>3,457</td>
<td>24.9</td>
</tr>
<tr>
<td>35-39 years</td>
<td>903</td>
<td>6.5</td>
</tr>
<tr>
<td>40+ years</td>
<td>66</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>1,640</td>
<td>11.3</td>
</tr>
<tr>
<td>Married</td>
<td>12,857</td>
<td>88.7</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11,452</td>
<td>79.0</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>635</td>
<td>4.4</td>
</tr>
<tr>
<td>Other</td>
<td>2,410</td>
<td>16.6</td>
</tr>
<tr>
<td><strong>Relative socioeconomic disadvantage index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (low)</td>
<td>4,295</td>
<td>29.7</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>3,869</td>
<td>26.8</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>3,418</td>
<td>23.7</td>
</tr>
<tr>
<td>Quartile 4 (high)</td>
<td>2,863</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No children</td>
<td>10,447</td>
<td>72.1</td>
</tr>
<tr>
<td>1 child</td>
<td>2,633</td>
<td>18.2</td>
</tr>
<tr>
<td>2 children</td>
<td>836</td>
<td>5.8</td>
</tr>
<tr>
<td>≥3 children</td>
<td>581</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Smoked during pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10,561</td>
<td>83.5</td>
</tr>
<tr>
<td>Yes</td>
<td>2,089</td>
<td>16.5</td>
</tr>
<tr>
<td><strong>Events(^a) during the study period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No event pregnancies (^b)</td>
<td>12,657</td>
<td>87.3</td>
</tr>
<tr>
<td>Events for all pregnancies (^c)</td>
<td>298</td>
<td>2.1</td>
</tr>
<tr>
<td>Both event and non-event pregnancies (^d)</td>
<td>1,542</td>
<td>10.6</td>
</tr>
</tbody>
</table>

**PROM:** pre-labour rupture of membranes

\(^a\) Event: either preterm birth (first two columns) or PROM (last two columns)

\(^b\) No event pregnancies: women who did not experience the event in any of her pregnancies during the study period (concordant, uninformative strata)

\(^c\) Events for all pregnancies: women who only experienced pregnancies with the event during the study period (concordant, uninformative strata)

\(^d\) Both event and non-event pregnancies: women who experienced some pregnancies with the event and did not experience the event in other pregnancies during the study period were event (discordant informative strata)
Table 2. Exposure to PM$_{2.5}$, Co-pollutants and Ambient Temperature Maxima for the PROM Longitudinal Study Population

<table>
<thead>
<tr>
<th></th>
<th>1$^{\text{st}}$ trimester</th>
<th>2$^{\text{nd}}$ trimester</th>
<th>3$^{\text{rd}}$ trimester</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM$_{2.5}$ (µg/m$^3$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.56</td>
<td>8.56</td>
<td>8.51</td>
<td>8.55</td>
</tr>
<tr>
<td>IQR</td>
<td>2.59</td>
<td>2.57</td>
<td>2.63</td>
<td>2.15</td>
</tr>
<tr>
<td>25$^{\text{th}}$ – 75$^{\text{th}}$ percentile</td>
<td>7.46 - 10.05</td>
<td>7.46 - 10.04</td>
<td>7.41 - 10.05</td>
<td>7.73 - 9.88</td>
</tr>
<tr>
<td><strong>CO (µg/m$^3$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>300.83</td>
<td>299.56</td>
<td>293.32</td>
<td>313.01</td>
</tr>
<tr>
<td>IQR</td>
<td>353.10</td>
<td>348.00</td>
<td>332.62</td>
<td>379.18</td>
</tr>
<tr>
<td>25$^{\text{th}}$ – 75$^{\text{th}}$ percentile</td>
<td>196.31 – 549.41</td>
<td>196.31 – 544.31</td>
<td>194.72 – 527.34</td>
<td>204.23 – 583.41</td>
</tr>
<tr>
<td><strong>NO$\textsubscript{2}$ (µg/m$^3$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.88</td>
<td>14.82</td>
<td>14.69</td>
<td>15.03</td>
</tr>
<tr>
<td>IQR</td>
<td>7.85</td>
<td>7.74</td>
<td>7.72</td>
<td>7.35</td>
</tr>
<tr>
<td><strong>O$\textsubscript{3}$ (µg/m$^3$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>39.70</td>
<td>39.72</td>
<td>39.86</td>
<td>39.64</td>
</tr>
<tr>
<td>IQR</td>
<td>9.38</td>
<td>9.38</td>
<td>9.72</td>
<td>8.28</td>
</tr>
<tr>
<td>25$^{\text{th}}$ – 75$^{\text{th}}$ percentile</td>
<td>35.38 – 44.76</td>
<td>35.48 – 44.86</td>
<td>35.34 – 45.06</td>
<td>35.74 – 44.02</td>
</tr>
<tr>
<td><strong>Temperature (maximum °C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24.16</td>
<td>24.17</td>
<td>24.13</td>
<td>18.08</td>
</tr>
<tr>
<td>IQR</td>
<td>8.9</td>
<td>8.98</td>
<td>8.85</td>
<td>6.93</td>
</tr>
</tbody>
</table>
Table 3. **Odds Ratios for Preterm Birth (PTB) and Pre-labour Rupture of Membranes (PROM) per 1 µg/m³ Increase in PM$_{2.5}$ Comparing Each Woman’s Preterm/PROM Pregnancy to her Term/non-PROM Pregnancy; Effects by Exposure Period. Women Were Resident in the Western Australia and Delivered a Singleton Neonate at Least Twice During the Period 1997-2007.**

Comparing Each Woman’s Preterm/PROM Pregnancy to her Term/non-PROM Pregnancy; Effects by Exposure Period and Race. Women Were Resident in the Western Australia and Delivered a Singleton Neonate at Least Twice During the Period 1997-2007.

<table>
<thead>
<tr>
<th>Births</th>
<th>Women</th>
<th>Strata</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>OR</td>
</tr>
<tr>
<td>PTB Pregnancy</td>
<td>31,567</td>
<td>14,497</td>
<td>10.6</td>
<td>1.00</td>
</tr>
<tr>
<td>1st trimester</td>
<td>31,567</td>
<td>14,497</td>
<td>10.6</td>
<td>1.00</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>31,567</td>
<td>14,497</td>
<td>10.6</td>
<td>1.00</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>31,567</td>
<td>14,497</td>
<td>10.6</td>
<td>0.99</td>
</tr>
<tr>
<td>PROM Pregnancy</td>
<td>86,844</td>
<td>39,189</td>
<td>9.1</td>
<td>1.07</td>
</tr>
<tr>
<td>1st trimester</td>
<td>86,844</td>
<td>39,189</td>
<td>9.1</td>
<td>1.04</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>86,844</td>
<td>39,189</td>
<td>9.1</td>
<td>1.06</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>86,844</td>
<td>39,189</td>
<td>9.1</td>
<td>1.06</td>
</tr>
</tbody>
</table>

CI: Confidence Interval, PROM: pre-labour rupture of membranes

a. Strata: The informative strata are the women with both event and non-event births during the study period, where the event is PTB, PROM, or PTB and PROM

b. Adjusted for parity, maternal age, smoking tobacco during pregnancy, relative socio-economic disadvantage and unmeasured temporal patterns in the event.

c. P-values are 2-sided and from Wald Chi-square test statistics
Online Supplemental Material

Fine particulate matter and risk of preterm birth and pre-labour rupture of membranes in Perth, Western Australia 1997-2007: A longitudinal study

Gavin Pereira$^{1,2}$, Michelle L. Bell$^{2,3}$, Kathleen Belanger$^2$, Nicholas de Klerk$^1$

1 Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, 100 Roberts Road, Subiaco WA 6008 Australia

2 Center for Perinatal Pediatric and Environmental Epidemiology, School of Medicine, Yale University, New Haven CT

3 School of Forestry and Environmental Studies, Yale University, New Haven, CT
**eTable 1. Sensitivity of the adjusted odds ratios for PROM per 1 µg/m³ Increase in PM$_{2.5}$ to degrees of freedom used for the unmeasured temporal confounding**

<table>
<thead>
<tr>
<th></th>
<th>Original Analyses$^a$</th>
<th>Conservative$^b$</th>
<th>Non-Conservative$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>P</td>
<td>OR  95% CI</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1.02       0.99 , 1.05</td>
<td>0.144</td>
<td>1.02       0.99 , 1.06</td>
</tr>
<tr>
<td>1$^{st}$ trimester</td>
<td>1.00       0.97 , 1.03</td>
<td>0.968</td>
<td>1.00       0.97 , 1.02</td>
</tr>
<tr>
<td>2$^{nd}$ trimester</td>
<td>1.03       1.00 , 1.06</td>
<td>0.026</td>
<td>1.03       1.01 , 1.06</td>
</tr>
<tr>
<td>3$^{rd}$ trimester</td>
<td>1.02       1.00 , 1.05</td>
<td>0.108</td>
<td>1.02       1.00 , 1.05</td>
</tr>
</tbody>
</table>

*a. Original analyses: Used a cubic spline term for temporal confounding with degrees of freedom determined by a data-driven approach (generalized cross-validation)*

*b. Conservative: Used a cubic spline term for temporal confounding with degrees of freedom to produce conservative estimates (3 degrees of freedom per year)*

*c. Non-conservative: Used a quadratic trend term for temporal confounding to account for long-term trend, ignoring seasonal variation*
eFigure 1. Daily (24-hour average) PM$_{2.5}$ measurements at the Duncraig monitoring site 1996-2007, and loess smoothed line for seasonal and secular trend, using a seasonal smoothing span of 90 days.
eFigure 2. Sensitivity of the association between PROM and whole-pregnancy exposure to PM$_{2.5}$ to whole pregnancy co-pollutants and temperature exposure.
eFigure 3. Sensitivity of the association between PROM and first trimester exposure to PM$_{2.5}$ to first trimester co-pollutants and temperature exposure.
eFigure 4. Sensitivity of the association between PROM and second trimester exposure to PM$_{2.5}$ to second trimester co-pollutants and temperature exposure.
**eFigure 5.** Sensitivity of the association between PROM and third trimester exposure to PM$_{2.5}$ to third trimester co-pollutants and temperature exposure.
eFigure 6. Sensitivity of the association between PROM and pregnancy exposure to \( \text{PM}_{2.5} \) to buffer distances that included women residing 5km, 10km, 15km, 20km, 30km and 40km from the \( \text{PM}_{2.5} \) monitoring station.
eFigure 7. Sensitivity of the association between PROM and first trimester exposure to PM$_{2.5}$ to buffer distances that included women residing 5km, 10km, 15km, 20km, 30km and 40km from the PM$_{2.5}$ monitoring station.
eFigure 8. Sensitivity of the association between PROM and second trimester exposure to PM$_{2.5}$ to buffer distances that included women residing 5km, 10km, 15km, 20km, 30km and 40km from the PM$_{2.5}$ monitoring station.
**eFigure 9.** Sensitivity of the association between PROM and third trimester exposure to PM$_{2.5}$ to buffer distances that included women residing 5km, 10km, 15km, 20km, 30km and 40km from the PM$_{2.5}$ monitoring station.