Short-term prenatal exposure to ambient air pollution and risk of preterm birth - A population-based cohort study in Finland

Nazeeba Siddikaa,b, Aino K. Rantalaa,b, Harri Antikainenec, Hamudat Balogunab, A. Kofi Amegahd, Niilo R.I. Rytia,b, Jaakko Kukkanene, Mikhail Sofieve, Maritta S. Jaakkolaa,b, Jouni J.K. Jaakkolaa,b,∗

a Center for Environmental and Respiratory Health Research, Faculty of Medicine, P.O. Box 5000, 90014, University of Oulu, Oulu, Finland
b Medical Research Center Oulu, Oulu University Hospital, P.O. Box 8000, 90014, University of Oulu, Oulu, Finland
c Geography Research Unit, P.O. Box 3000, 90014, University of Oulu, Oulu, Finland
d Public Health Research Group, Department of Biomedical Sciences, University Post Office, University of Cape Coast, Cape Coast, Ghana
e Finnish Meteorological Institute, P.O. Box 503, 00101, Helsinki, Finland

ARTICLE INFO

Keywords:
Air pollution
Fine particulates
Nitrogen dioxide
Prenatal exposure
Preterm birth

ABSTRACT

Background: Previous studies have provided evidence that prenatal exposure to low-level air pollution increases the risk of preterm birth (PTB), but the findings of the effects of short-term exposure have been inconclusive. Moreover, there is little knowledge on potential synergistic effects of different combinations of air pollutants.

Objectives: To assess independent and joint effects of prenatal exposure to air pollutants during the week prior to the delivery on the risk of PTB.

Methods: The study population included 2568 members of the Espoo Cohort Study, living in the City of Espoo, Finland, born between 1984 and 1990. We assessed individual-level prenatal exposure to ambient air pollutants of interest based on maternal residential addresses, while taking into account their residential mobility. We used both regional-to-city-scale dispersion modelling and land-use regression–based method to estimates the pollutant concentrations. We contrasted the risk of PTB in the highest quartile (Q4) of exposure to the lower exposure quartiles (Q1-Q3) during the specific periods of pregnancy. We applied Poisson regression analysis to estimate the adjusted risk ratios (RRs) with their 95% confidence intervals (CI), adjusting for season of birth, maternal age, sex of the baby, family’s socioeconomic status, maternal smoking, and exposure to environmental tobacco smoke during pregnancy, single parenthood, and exposure to other air pollutants (this in multi-pollutant models).

Results: The risk of PTB was related to exposures to PM2.5, PM10 and NO2 during the week prior to the delivery with adjusted RRs of 1.67 (95%CI: 1.14, 2.46), 1.60 (95% CI: 1.09, 2.34) and 1.65 (95% CI: 1.14, 2.37), from three-pollutant models respectively. There were no significant joint effects for these different air pollutants (during the week prior to the delivery).

Conclusion: Our results provide evidence that exposure to fairly low-level air pollution may trigger PTB, but synergistic effects of different pollutants are not likely.

1. Introduction

Preterm birth (PTB) is the leading cause of perinatal mortality and morbidity worldwide (Blencowe et al., 2013; Liu et al., 2012). Globally, 14.9 million babies are born preterm each year (Blencowe et al., 2012; Goldberg et al., 2008). The occurrence of premature birth in Finland has been reported to be 5.7% of all births (Vuori and Gissler, 2014).

There is some evidence that environmental exposures play a role in the etiology of PTB (Wigle et al., 2008). Environmental exposures may have their effect in different phases of pregnancy (Darrow et al., 2009; Shah and Balkhair, 2011; Stieb et al., 2012), with associations reported most commonly for exposures taking place in the early pregnancy (the first month or first trimester) (Huynh et al., 2006; Leem et al., 2006; Maroziene and Grazuleviciene, 2002) or in the late pregnancy (third trimester, last 6 weeks, last month, or last week) (Li et al., 2018; Liu et al., 2003; Ritz et al., 2000; Sagiv et al., 2005). The effects of short-
term exposure to air pollution on the risk of PTB have previously been studied mainly in areas with relatively high levels of air pollution (Dastoorpoor et al., 2018; Guan et al., 2019; Zhao et al., 2011), so potential effects related to low-level air pollution remain unknown.

Klepac and colleagues. (2018) conducted recently a comprehensive systematic review and meta-analysis of the effects of ambient air pollution on the risk of preterm birth. Exposure to particulate matter over the entire pregnancy was found to increase the risk of preterm birth with a summary-effect estimate of 1.09 (95% CI: 1.03, 1.16) per 10 μg/m³ of PM10 and 1.24 (95% CI: 1.08, 1.41) per 10 μg/m³ of PM2.5. In addition, exposure to ozone increased the risk of PTB with a summary effect of 1.03 (1.01–1.04) per 10 ppb. The results for exposures during specific time-periods of gestation were inconclusive due to limited number of studies with homogeneous exposure measures. They also identified several common methodological problems in the studies that have been reported so far, including limited control of confounding, compromised assessment of prenatal exposure, and limited assessment of the role of relevant time windows of exposure. They recommended that future studies should address the issues related to complex mixture of exposures, as well as residential mobility of mothers during pregnancy.

Our previous findings from the Espoo Cohort Study suggest that average exposure to both particulate matter and ozone over the entire pregnancy increase the risk of preterm birth at relatively low levels of air pollution. In addition, we found significant joint effects of individual air pollutants, such as PM2.5 and O3, i.e. they act synergistically potentiating each other’s adverse effects (Siddika et al., 2019).

In the present study, we assessed potential effects of exposure to air pollutants during specific time windows of pregnancy (i.e. trimesters) on the risk of preterm birth (PTB). We were especially interested in assessing both independent and joint effects of prenatal short-term exposure to air pollutants on the risk of PTB, our main focus being to investigate whether exposure in the week prior to the delivery triggers PTB. We were able to address several methodological problems identified by Klepac and colleagues. We assessed individual-level prenatal exposure to all the main air pollutants by taking into account all the residential addresses of the mothers during pregnancy. We adjusted for several important individual-level confounders, as well as potential confounding by other pollutants applying multi-pollutant models. We adjusted for exposure during other time periods of exposure when assessing the effects of exposure one week prior to delivery.

2. Methods

2.1. Study design

We conducted a population-based cohort study in Southern Finland. We compared the risk of PTB in the highest quartile (Q4) of exposure during specific time periods of pregnancy with the risk in the reference exposures, i.e. in the lower exposure quartiles (Q1–Q3).

2.2. Study population

The study population comprised the members of the Espoo Cohort Study (Jaakkola et al. 1993, 2005; Rantala et al., 2015). The source population included all the children of the city of Espoo, Finland, born between January 1, 1984 and March 31, 1990. Espoo, located across the western border of Helsinki, is the second largest municipality in Finland with a population of 279,000. A random sample of children living in Espoo in 1991 was taken from the roster of Statistics Finland. The study population included a total of 2568 children (response rate 80.3%) whose parents filled in the baseline questionnaire. In the present analyses, we excluded newborns with gestational age < 31 weeks (n = 17, 0.7%) or ≥ 47 weeks (n = 3, 0.1%) or those with missing information on gestational age (n = 72, 2.8%) or air pollution exposure (n = 49, 1.9%). The actual study population included 2427 individuals (94.5% of the baseline population). The study protocol was approved by the Ethics Committee of Oulu University Hospital (Oulu, Finland).

2.3. Health outcome

The primary outcome of interest was preterm birth (PTB), which was defined as a live birth before the 37th week of pregnancy. Information on gestational age (GA) was from the baseline data collection, and if missing, from the Finland’s Medical Birth Registry for children born on or later than January 1, 1987.

2.4. Exposure assessment

We assessed individual-level prenatal exposure to ambient air pollutants of interest at all residential addresses from conception to birth. This approach took into account potential residential mobility during pregnancy. The exposures of interest included the following air pollutants: particles with aerodynamic diameter less than or equal to 2.5 μm (PM2.5), respirable particles with aerodynamic diameter less than or equal to 10 μm (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3). The pollutant data were based on a cascade of nested simulations of the system for integrated modelling of atmospheric composition (SILAM) (http://silam.fmi.fi, Sofiev et al., 2016), obtained from the Finnish Meteorological Institute (FMI). The model started from the global scale to capture the background levels of long-living pollutants, zoomed to Europe and Northern Europe, finally reaching the spatial resolution of 0.1° × 0.1° (Sofiev et al., 2015). Details of the SILAM setup and the model evaluation can be found in the study conducted by Kukkonen et al. (2018). The FMI also provided the temperature data, which have been produced by interpolating the daily temperature records of about two hundred climate stations in Finland and the neighboring countries onto a 10 km × 10 km grid using kriging interpolation (Aalto et al., 2016). The home coordinates of the mothers were retrieved from the Population Register Centre of Finland. To extract daily levels of air pollutants and temperature at the home coordinates, we used Geographical Information System (GIS). The exposure parameters in the analysis were the mean concentration of trimesters and of the 7-day exposure prior to the preterm birth or corresponding gestational period among term births.

To describe the general air pollution concentrations during the study, we formed a time series of minimum, mean and maximum daily air pollution concentrations at the central coordinate of the province of Espoo, Finland, over the study period 1983–1990 using the same databases, programs and methods as described above.

2.5. Covariates

The statistical models were fitted with covariates that have been reported to be determinants of the preterm birth in previous literature. They included maternal age (Fuchs et al., 2018), sex of the baby (Peelen et al., 2016), family’s socioeconomic status (high vs. low or medium parental education and occupation) (Joseph et al., 2014), single parenthood (Zeitlin et al., 2002), maternal smoking during pregnancy (Jaakkola and Gissler, 2004), maternal exposure to environmental tobacco smoke during pregnancy (Windham et al., 2000), and exposure to other air pollutants (the latter in multipollutant models). We adjusted for these as potential confounders in the multivariable statistical model.
In the multi-pollutant models, we applied a source-based approach by fitting one traffic related pollutant (PM$_{2.5}$, NO$_2$, CO) and one stationary fossil fuel combustion related pollutant (PM$_{10}$, SO$_2$). We also fitted two-pollutant models with O$_3$ and each pollutant. Finally, we considered three-pollutant models with one traffic related, one stationary fossil fuel combustion related pollutant and O$_3$. In our previous article, we provide details of the categorization of the family’s socioeconomic status and present all the above-mentioned confounders in a Directed Acyclic Graph (DAG) (Siddika et al., 2019, Fig. 1).

2.6. Statistical methods

We used risk ratio (RR) as the measure of the effect of prenatal exposure to air pollution on the risk of PTB. We compared the risk of PTB in the highest quartile (Q4) of exposure to the reference category, comprising the lower exposure quartiles (Q1-Q3), during specific time periods of pregnancy. We applied Poisson regression analysis to estimate the adjusted RRs, with their 95% confidence intervals (95% CI). We categorized all air pollution exposure variables into quartiles based on overall data, including the averages during the entire pregnancy. We fitted single-, two-, and three-pollutant models.

First, we studied the associations between trimester-specific exposures and the risk of PTB. In each model, we have mutually adjusted for other trimesters to get an independent effect of air pollution exposure during a specific trimester. Further, we assessed the association with short-term exposure by choosing the exposure period of interest entitled as the “triggering week”- i.e. the last 7 days preceding delivery for the preterm babies and for the term babies the 8th month of pregnancy. The exposure category was defined as the highest quartile (≥Q4) of the mean exposure distribution, while the reference category comprised the remaining quartiles (Q1-Q3). The reason we did not consider the last 7 days preceding birth for the term babies as ‘exposure period’ was that it would not correspond to the same exposure time periods of pregnancy that were used for the preterm babies. In other words, the 8th month of pregnancy for term births corresponds to the pregnancy week 31–36, during which most of the preterm births took place. Thus, this approach allowed comparison of corresponding time periods of pregnancy for both types of births. For the same reason, we excluded births that took place before 31 weeks. In the modelling, we took into account previous exposures during pregnancy by adjusting for the mean exposure (contrasts ≥ Q4 vs. Q1-Q3) in the first trimester (defined as gestational weeks 1–13), second trimester (gestational weeks 14–26), and the 7th gestational month (gestational weeks 27–30).

To examine potential heterogeneity related to season, we further performed analyses stratified by two birth seasons, i.e. warm season and cold season. The warm season included spring and summer (March to August) and the cold season included autumn and winter (September to February). In these season-specific stratified analyses, we further adjusted for ambient temperature as a potential confounder, in addition to the other covariates mentioned. The mean temperature during the exposure period of interest was fitted by applying natural cubic splines with 4 degrees of freedom (df) in each stratified season. We selected the df by judging the model fit according to the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC). The exposure period for temperature was chosen to be identical with the exposure period applied for the air pollution analyses.

We studied both the independent and joint effects of different air pollutant exposures during the triggering week of pregnancy on the risk of PTB. For the analysis of joint effect, we chose the pollutants that were not strongly correlated to each other. The statistical methods of this analysis have been described in detail in our previous article (Siddika et al., 2019). In short, for example, we compared the risk of PTB in three different exposure categories, defined for example as: 1) high PM$_{2.5}$ and low O$_3$ (i.e. A), 2) low PM$_{2.5}$ and high O$_3$ (i.e. B), and 3) high PM$_{2.5}$ and high O$_3$ (i.e. AB), to the reference category of ‘low PM$_{2.5}$ and low O$_3$’ exposure. We quantified the relative risk due to interaction (RERI) on an additive scale. We estimated interactions on the additive scale because their interpretation is more relevant from public health perspective (Rothman, 1986; Rothman et al., 2008). The 95% CI for RERI was estimated using the method of variance estimates recovery (Zou, 2008).

We conducted several sensitivity analyses. First, we elaborated on the role of potential ‘fixed cohort bias’ by excluding study subjects with estimated conception dates 31 weeks (shortest gestation) before the cohort started or 46 weeks (longest gestation week) before it ended, following the method provided by Strand et al. (2011). Second, we also estimated the effects by using the time to event approach in Cox regression model described by Chang et al., (2012). In addition, we conducted analyses in which we included all PTBs that took place before 37 weeks of gestation (i.e. without restricting the gestational weeks), giving a sample size of 2443 and another analysis by applying air pollution data as continuous variables, giving the estimates for a 10-unit increase in each pollutant.

All the analyses were performed using PROC GENMOD procedure in SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

The characteristics of the study population are presented in Table 1. There were altogether 195 cases of preterm birth, corresponding to a prevalence of 7.8%. Among these, 7.2% took place in the gestational weeks 31–36. In our study population, most mothers were older than 30 years, and 23.4% belonged to the highest categories of socioeconomic status.

3.2. Exposure distributions

The distributions of daily air pollution parameters in the province of Espoo over the study period 1983–1990 are shown in Table 2. The air pollution distributions during the triggering week of pregnancy in this...
study are provided in Table S1.

The concentrations of almost all the air pollutants were highest in the spring season during the study period. The high particulate matter concentrations in spring are mainly caused by resuspended dust from the street and road surfaces (Kauhaniemi et al., 2014). The mean daily concentrations of PM$_{2.5}$, PM$_{10}$, CO, NO$_2$, O$_3$ and SO$_2$ during the triggering week were 19.91 μg/m$^3$, 21.66 μg/m$^3$, 298.59 ppb, 4.38 ppb, 23.79 ppb and 3.97 ppb, respectively (Table S1). The correlation matrix for all the studied pollutants during the triggering week of pregnancy showed moderate to high correlation with each other, except that O$_3$ showed a negative correlation with the other pollutants (Table S2).

### 3.3. Air pollution exposure during trimesters and preterm birth

Fig. 1 shows the effects of air pollution exposure during each trimester of pregnancy on the risk of PTB. Each trimester-specific estimate was adjusted for exposures during other trimesters. Exposure to NO$_2$, CO, SO$_2$, PM$_{10}$, and PM$_{2.5}$ during the third trimester increased the risk of PTB substantially, with adjusted RRs of 1.64 (95% CI: 1.14, 2.36), 1.56 (95% CI: 1.08, 2.25), 1.43 (95% CI: 0.99, 2.07), 1.53 (95% CI: 1.05, 2.23) and 1.40 (95% CI: 0.96, 2.05), respectively, from two-pollutant models with ozone. The effect estimates were substantially greater for babies born during the cold season, with adjusted RRs of 3.41 (95% CI: 1.98, 5.88), 2.59 (95% CI: 1.48, 4.53), 2.80 (95% CI: 1.54, 5.08), 2.42 (95% CI: 1.37, 4.28) and 2.47 (95% CI: 1.41, 4.32), respectively. However, exposure to O$_3$ during the second trimester showed a substantially increased risk of PTB for babies born during the warm season only, with an adjusted RR of 2.33 (95% CI: 1.36, 4.00) from a two-pollutant model with PM$_{2.5}$. Other effect estimates for all the pollutants during each trimester are given in Table S3.

### Table S2

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>25th percentile</th>
<th>Median</th>
<th>75th percentile</th>
<th>Range</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$ (μg/m$^3$)</td>
<td>17.22 ± 16.59</td>
<td>0.68</td>
<td>5.55</td>
<td>12.17</td>
<td>23.3</td>
<td>160.53</td>
<td>161.21</td>
</tr>
<tr>
<td>Spring</td>
<td>23.53 ± 20.09</td>
<td>1.08</td>
<td>9.17</td>
<td>17.46</td>
<td>31.60</td>
<td>160.13</td>
<td>161.21</td>
</tr>
<tr>
<td>Summer</td>
<td>12.31 ± 10.88</td>
<td>0.77</td>
<td>4.49</td>
<td>8.73</td>
<td>16.63</td>
<td>59.97</td>
<td>60.75</td>
</tr>
<tr>
<td>Fall</td>
<td>14.81 ± 16.87</td>
<td>0.68</td>
<td>3.75</td>
<td>9.03</td>
<td>19.41</td>
<td>122.29</td>
<td>122.97</td>
</tr>
<tr>
<td>Winter</td>
<td>18.21 ± 14.94</td>
<td>0.73</td>
<td>7.29</td>
<td>13.35</td>
<td>26.06</td>
<td>91.33</td>
<td>92.06</td>
</tr>
<tr>
<td>PM$_{10}$ (μg/m$^3$)</td>
<td>18.40 ± 17.24</td>
<td>0</td>
<td>6.20</td>
<td>13.05</td>
<td>24.87</td>
<td>167.93</td>
<td>167.93</td>
</tr>
<tr>
<td>Spring</td>
<td>24.79 ± 20.63</td>
<td>1.25</td>
<td>9.67</td>
<td>18.76</td>
<td>33.4</td>
<td>166.69</td>
<td>167.93</td>
</tr>
<tr>
<td>Summer</td>
<td>13.54 ± 11.74</td>
<td>0.88</td>
<td>5.20</td>
<td>9.74</td>
<td>18.30</td>
<td>66.34</td>
<td>67.22</td>
</tr>
<tr>
<td>Fall</td>
<td>15.91 ± 17.46</td>
<td>0.89</td>
<td>4.21</td>
<td>10.04</td>
<td>21.48</td>
<td>123.79</td>
<td>124.68</td>
</tr>
<tr>
<td>Winter</td>
<td>19.37 ± 15.80</td>
<td>0</td>
<td>7.80</td>
<td>14.16</td>
<td>27.67</td>
<td>95.97</td>
<td>95.97</td>
</tr>
<tr>
<td>CO (ppb)</td>
<td>259.60 ± 141.82</td>
<td>77.63</td>
<td>169.43</td>
<td>224.33</td>
<td>306.64</td>
<td>2109.04</td>
<td>2187.57</td>
</tr>
<tr>
<td>Spring</td>
<td>304.32 ± 167.10</td>
<td>113.58</td>
<td>206.16</td>
<td>263.03</td>
<td>353.60</td>
<td>2073.99</td>
<td>2187.57</td>
</tr>
<tr>
<td>Summer</td>
<td>207.23 ± 123.98</td>
<td>77.63</td>
<td>127.89</td>
<td>167.39</td>
<td>243.30</td>
<td>997.85</td>
<td>1075.48</td>
</tr>
<tr>
<td>Fall</td>
<td>224.51 ± 107.36</td>
<td>99.23</td>
<td>157.46</td>
<td>192.83</td>
<td>262.92</td>
<td>1173.81</td>
<td>1273.05</td>
</tr>
<tr>
<td>Winter</td>
<td>302.77 ± 133.33</td>
<td>141.87</td>
<td>210.47</td>
<td>266.76</td>
<td>348.12</td>
<td>916.39</td>
<td>1058.26</td>
</tr>
<tr>
<td>NO$_2$ (ppb)</td>
<td>3.39 ± 2.88</td>
<td>0.22</td>
<td>1.31</td>
<td>2.43</td>
<td>4.53</td>
<td>25.01</td>
<td>25.23</td>
</tr>
<tr>
<td>Spring</td>
<td>3.52 ± 2.93</td>
<td>0.22</td>
<td>1.44</td>
<td>2.75</td>
<td>4.58</td>
<td>25.01</td>
<td>25.23</td>
</tr>
<tr>
<td>Summer</td>
<td>2.57 ± 2.57</td>
<td>0.24</td>
<td>0.91</td>
<td>1.66</td>
<td>3.27</td>
<td>16.57</td>
<td>16.81</td>
</tr>
<tr>
<td>Fall</td>
<td>3.20 ± 2.69</td>
<td>0.42</td>
<td>1.38</td>
<td>2.28</td>
<td>4.12</td>
<td>17.25</td>
<td>17.67</td>
</tr>
<tr>
<td>Winter</td>
<td>4.27 ± 3.06</td>
<td>0.39</td>
<td>1.81</td>
<td>3.42</td>
<td>6.24</td>
<td>15.49</td>
<td>15.87</td>
</tr>
<tr>
<td>SO$_2$ (ppb)</td>
<td>2.47 ± 2.97</td>
<td>0.14</td>
<td>0.63</td>
<td>1.37</td>
<td>3.18</td>
<td>29.20</td>
<td>29.33</td>
</tr>
<tr>
<td>Spring</td>
<td>2.44 ± 2.44</td>
<td>0.18</td>
<td>0.75</td>
<td>1.72</td>
<td>3.23</td>
<td>18.34</td>
<td>18.52</td>
</tr>
<tr>
<td>Summer</td>
<td>1.60 ± 1.80</td>
<td>0.14</td>
<td>0.42</td>
<td>0.84</td>
<td>2.05</td>
<td>11.96</td>
<td>12.09</td>
</tr>
<tr>
<td>Fall</td>
<td>1.91 ± 2.37</td>
<td>0.21</td>
<td>0.52</td>
<td>1.01</td>
<td>2.41</td>
<td>20.82</td>
<td>21.03</td>
</tr>
<tr>
<td>Winter</td>
<td>3.94 ± 4.18</td>
<td>0.37</td>
<td>1.03</td>
<td>2.45</td>
<td>4.97</td>
<td>28.97</td>
<td>29.33</td>
</tr>
<tr>
<td>O$_3$ (ppb)</td>
<td>24.71 ± 10.10</td>
<td>0.21</td>
<td>17.60</td>
<td>23.96</td>
<td>32.25</td>
<td>71.61</td>
<td>71.82</td>
</tr>
<tr>
<td>Spring</td>
<td>32.85 ± 8.50</td>
<td>5.10</td>
<td>28.69</td>
<td>34.19</td>
<td>38.59</td>
<td>52.99</td>
<td>58.09</td>
</tr>
<tr>
<td>Summer</td>
<td>29.44 ± 8.03</td>
<td>10.49</td>
<td>23.71</td>
<td>29.22</td>
<td>34.43</td>
<td>61.33</td>
<td>71.82</td>
</tr>
<tr>
<td>Fall</td>
<td>19.68 ± 5.94</td>
<td>1.09</td>
<td>16.38</td>
<td>20.16</td>
<td>23.47</td>
<td>48.95</td>
<td>50.04</td>
</tr>
<tr>
<td>Winter</td>
<td>16.68 ± 7.58</td>
<td>0.21</td>
<td>11.61</td>
<td>16.50</td>
<td>21.86</td>
<td>33.55</td>
<td>33.76</td>
</tr>
</tbody>
</table>

Abbreviations: CO, carbon monoxide; IQR, Interquartile range; NO$_2$, nitrogen dioxide; O$_3$, ozone; PM$_{2.5}$, particulate matter with a diameter of 2.5 μm; PM$_{10}$, particulate matter with a diameter of 10 μm; ppb, parts per billion; SD, standard deviation; SO$_2$, sulfur dioxide; μg/m$^3$, microgram per cubic meter. All the distribution parameters are mean concentrations of the pollutants.
3.4. Short-term air pollution exposure and preterm birth

Fig. 2 shows the effect estimates for the relations between mean short-term air pollution exposures in the week preceding birth and the risk of PTB. The corresponding effect estimates are provided in Table S4. All the effect estimates were adjusted for previous time periods of exposure. Both exposure to PM$_{2.5}$ and PM$_{10}$ increased the risk of PTB significantly, with an adjusted RRs of 1.67 (95% CI: 1.14, 2.46) and 1.60 (95% CI: 1.09, 2.34), respectively, from the three-pollutant models (Fig. 2 and Table S4). Stratifying the analyses by the birth season revealed that these associations were present mainly in the cold season, with adjusted RRs of 4.49 (95% CI: 2.72, 7.42) and 3.99 (95% CI: 2.39, 6.65), respectively (Table S4). These effect estimates were significant also when adjusting for ambient temperature, adjusted RRs of 2.95 (95% CI: 1.72, 5.06) and 2.47 (95% CI: 1.43, 4.28) respectively (Fig. 2 and Table S4).

Exposure to NO$_2$ increased the risk of PTB with an adjusted RR of 1.65 (95% CI: 1.14, 2.37), from the three-pollutant model with PM$_{10}$ and O$_3$. After stratification for season, the association was seen only among babies born in the cold season with an adjusted RR of 1.86 (95% CI: 1.05, 3.33) (Fig. 2 and Table S4). The associations related to CO and SO$_2$ followed a similar pattern, showing stronger associations, i.e. higher RRs, in the cold season (Fig. 2 and Table S4). In contrast, there was no evidence suggesting any impact of O$_3$ exposure on triggering PTB.

The point estimates and confidence intervals were similar after taking in to account for the ‘fixed cohort bias’ by restriction of the study population (see Methods). Cox’s regression analysis with the time-to-event approach produced similar effect estimates for each pollutant (The main findings are given in Supplementary Table S5). We also performed sensitivity analyses, including all PTBs that took place before 37 weeks of gestation and fitting air pollutant exposures as continuous variables in the models. These single-pollutant models showed consistent results (Tables S6 and S7).

3.5. Joint effects of short-term air pollution exposures on preterm birth

Table 3 presents the joint effects of air pollutant exposures during the triggering week of pregnancy on the risk of PTB. There were no significant joint effects of short-term exposures to different air pollutants (in the week prior to the delivery) on the risk of PTB. However, while assessing potential effects of simultaneous exposure to ‘high NO$_2$ and high O$_3$’ and ‘high SO$_2$ and high O$_3$’ during triggering week of pregnancy, we detected slightly synergistic effects on PTB. The effect estimates were slightly higher than expected based on their independent effects on additive scale (for NO$_2$ and O$_3$: RERI = 0.55–(-0.03) - 0.27) = 0.31; 95%CI: 0.52 to 1.24 and for SO$_2$ and O$_3$: RERI = 0.46–(-0.03) - 0.16) = 0.33; 95%CI: 0.51 to 1.38, but they
were not statistically significant, because the confidence intervals included 0.

4. Discussion

4.1. Main findings

In this population-based cohort study of exposure to air pollutants in the metropolitan area close to the capital of Finland, the highest levels of exposure to PM$_{2.5}$, PM$_{10}$ and NO$_2$ during the week prior to the delivery were related to significant 67% (95% CI: 14%, 146%), 60% (95% CI: 9%, 134%) and 65% (95% CI: 14%, 137%) increases in the risk of PTB, respectively. These associations were more pronounced during the cold season of the year. Exposure to O$_3$ did not show any triggering effect on PTB. There were no significant joint effects for these different air pollutants (during the week prior to the delivery).

4.2. Validity of results

This population-based cohort study was based on a random sample of children living in the City of Espoo in Southern Finland, which was identified from the Roster of Statistics Finland. We achieved a high response rate of 80.3%. Thus, potential selection bias is minimized. Sensitivity analyses indicated that the fixed cohort bias is minimal in our study. The likelihood of exposure misclassification was minimized by assessing prenatal exposure to air pollution at individual level, independently from the assessment of the health outcome (PTB). The maternity leave starts in Finland in the gestational week 35–36 in full-term pregnancies, and the mother gets sick leave earlier when needed. Bell and Belanger (2012) estimated that approximately 9%–32% of women in the U.S. move during pregnancy. If such change in exposure conditions could not be identified, it would lead to potential exposure misclassification (Bell and Belanger, 2012). To minimize such exposure misclassification, we assessed exposure taking into account potential changes in residential address. The availability of high-quality exposure information is a strength of our study: temporal resolution of 1 h (averaged to daily mean for the analysis) and spatial resolution of 0.1° × 0.1° by SILAM simulations downscaled to hundreds of meters. We were not able to take into account exposure to indoor air pollution or maternal outdoor activity patterns, for example going to work, shopping or travelling. However, lack of information on these potential confounders is common in similar epidemiologic studies and it is difficult to know whether it would compromise the validity of the effect estimates.

The assessment of the outcome of interest (i.e. preterm birth) was based on information available on the duration of pregnancy collected in the baseline data collection through questionnaire. At the time of the data collection, there was not yet any knowledge about potential effects of prenatal air pollution exposure on the risk of PTB, which is why any systematic error (i.e. bias) is unlikely in our study. When the gestational
showed a significant association between O₃ and PTB in the 1st trimester. In addition, they provided a summary effect estimate (SEE) for PM 2.5 in 3rd trimester, with respect to effects of most air pollutants on PTB. Klepac et al., (2018) trimester of pregnancy is the most susceptible period of pregnancy with regard to acute impact of PM on PTB. We found no significant acute impact of PM on PTB. We found no impact during cold season, when using a lag period up to 30 days preceding birth, so their results can be deemed as consistent with our results. Another time-series study, conducted in Brisbane, Australia (Li et al., 2016), where the ambient temperature is relatively high, did not find any significant acute impact of PM on PTB. We found no impact during the warm season. On the other hand, our results showed substantial term effect of PM on the risk of PTB. This is consistent with the results of another study in Stockholm, where they found no such association during warm or cold season (Vicedo-Cabrera et al., 2015). Our study showed no evidence of an association between short-term exposure to PM₂.₅ and O₃, ‘PM₁₀ and O₃’ or ‘CO and O₃’ on the risk of PTB.

### 4.3. Synthesis with previous knowledge

Our population-based cohort study provided evidence that the 3rd trimester of pregnancy is the most susceptible period of pregnancy with respect to effects of most air pollutants on PTB. Klepac et al., (2018) provided a summary effect estimate (SEE) for PM₂.₅ in 3rd trimester, which is consistent with our estimate. However, they found that PM₁₀ was significantly associated with PTB in 1st trimester. In addition, they showed a significant association between O₃ and PTB in the 1st trimester and 2nd trimesters, while we found a significant association only in the 2nd trimester among those who were born during warm season. Our results are consistent with the hypothesis that exposure to the highest quartile of air pollution levels triggers PTB within 7 days. These results are in line with some studies that have reported effects of short-term exposure to air pollution on the risk of PTB, but those results are not directly comparable due to differences in the exposure windows that they considered, ranging from 0 to 30 days before birth (Sagiv et al., 2005; Dastoorpoor et al., 2018; Arroyo et al., 2016; Darrow et al., 2009; Schifano et al., 2013; Li et al., 2016). A time-series analysis conducted by Schifano et al. (2013) in Rome, Italy, found a significant effect of PM₁₀ on PTB with a lag time of 12–22 days, but found no significant effect in relation to NO₂ or O₃ exposure during the warm season. Moreover, they observed a linear relation with PM₁₀ and NO₂ during cold season, when using a lag period up to 30 days preceding birth, so their results can be deemed as consistent with our results. Another time-series study, conducted in Brisbane, Australia (Li et al., 2016), where the ambient temperature is relatively high, did not find any significant acute impact of PM on PTB. We found no impact during the warm season. On the other hand, our results showed substantial triggering effects of PM₂.₅ and PM₁₀ during cold season. Our estimates were reduced noticeably after adjusting for the corresponding ambient temperatures during the cold season, which suggests that ambient temperature during cold season strengthens the triggering effect of PM. In other words, we found that ambient temperature modified the short-term effect of PM on the risk of PTB. This is consistent with the results by Carder et al. (2008) which indicated that the effects of PM on health are strengthened by low temperature (Carder et al., 2008). We found that the previous week's exposure to NO₂ significantly increased the risk of PTB. This result was consistent with a study conducted in Stockholm in 2012 (Olsson et al., 2012), but in contrast to results from another study in Stockholm, where they found no such association during warm or cold season (Vicedo-Cabrera et al., 2015). Our study showed no evidence of an association between short-term exposure to O₃ and the risk of PTB. This finding was consistent with the results of several other studies (Lee et al., 2008; Li et al., 2016; Olsson et al., 2012; Vicedo-Cabrera et al., 2015).

We applied systematically multi-pollutant models to adjust for...
potential confounding by other pollutants, and to elaborate on potential joint effects between negatively correlated pollutants. We did not find any significant joint effects of short-term exposure to different air pollutants (the week prior to the delivery) on the risk of PTB. However, in our previous study, we found significant joint effects of individual air pollutants, such as PM$_{2.5}$ and O$_3$ exposure during entire pregnancy on the risk of PTB (Siddika et al., 2019). To our knowledge, this is the first study that investigates potential joint effects of short-term prenatal exposure to air pollutants on the risk of PTB.

### 4.4. Biological plausibility

The underlying mechanisms through which air pollutant exposures in the days prior to delivery might trigger preterm birth are still unclear, but few pathways could be involved. For example, pathways related to placental or fetal hypoxia, inflammation, or oxidative stress have been associated with both PTB (Boyle et al., 2017; Cufet et al., 2017; Nadeau-Vallee et al., 2016; Sultana et al., 2017) and air pollution exposure (Erickson and Arbour, 2014). Inhaled gaseous pollutants and particulate matter can deposit deep into the lungs and may enter the circulatory system, through which they may reach the intrauterine compartment or induce systemic inflammation (Monn and Becker, 1999). PM$_{2.5}$ exposure also induces visceral adiposity (Sun et al., 2009) and adipocytes produce several pro-inflammatory signals that elicit inflammatory response (Lago et al., 2007; Vadiilo-Ortega et al., 2014). Changes in the intrauterine inflammatory milieu may initiate cervical ripening, rupture of the amniotic sac, or increased myometrium contractility, and thus, lead to PTB (Challis et al., 2009; Ekman-Ordeberg and Dubicke, 2012). Biological mechanisms for the observed effect modification of air pollution associations by seasons are very complex. Season may affect seasonal pattern of exposure, such as outdoor activities, vitamin D levels which are related to sunlight exposure as well as gestational age (Morley et al., 2006). There is a clear seasonal variation in vitamin D status among Scandinavian women (Moosgaard et al., 2005). Vitamin D deficiency is associated with increased amount of circulating inflammatory proteins which seems to be associated with modulating C-reactive protein levels (Ngo et al., 2010) and PTB.

### 5. Conclusions

Our population-based cohort study conducted in Espoo, Finland, provides evidence that short-term exposure to PM (both PM$_{2.5}$ and PM$_{10}$) and NO$_2$ are associated with triggering premature birth, particularly during the cold season. These results strengthen the evidence that short-term exposure to air pollutants may trigger premature delivery even among people living in an area with relatively low average concentrations of air pollution. Improvements in air quality, for example through implementing laws and regulations and stricter air pollution standards, are needed even in the less polluted regions of the world.

### Funding

This study was supported by the Academy of Finland [grant numbers 266314, 267675, 267995 (APTA Consortium) and 31071 and 31072 (GLORIA Consortium)], The Research Foundation of the Pulmonary Diseases and Nordforsk [grant number 75007 (NordicWelfAir)], N.S. received PhD scholarships from the Health and Biosciences Doctoral Programme (HBS DP) and the Oulu University Scholarship Foundation. The funders had no role in study design, data collection or analysis, decision to publish, or preparation of the manuscript.

### Ethics approval

The study protocol was approved by the Ethics Committee of Oulu University Hospital (Oulu, Finland).

---

**CRediT authorship contribution statement**

Nazeeba Siddika: Conceptualization, Methodology, Formal analysis, Writing - original draft. Aino K. Rantala: Conceptualization, Methodology, Formal analysis, Writing - review & editing. Harri Antikainen: Methodology, Data curation, Software, Writing - review & editing. Hamudat Balogun: Writing - review & editing. A. Kofi Amegah: Writing - review & editing. Niilo R.I. Ryti: Writing - review & editing. Jaakko Kukkonen: Conceptualization, Methodology, Writing - review & editing, Funding acquisition. Mikhail Sofiev: Methodology, Writing - review & editing. Marita S. Jaakkola: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Supervision, Funding acquisition.

### Declaration of competing interest

None.

### Acknowledgement

We gratefully acknowledge the help of Riitta Aittamaa for preparing the figures in appropriate size and resolution.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109290.

### References


Erickson, A.C., Arbour, L., 2014. The shared pathophysiological effects of particulate air pollution and the social environment on fetal-placental development. J. Environ.


