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

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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 (Q_4) of exposure to the lower exposure quartiles (Q_1-Q_3) 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 $PM_{2.5}$, PM_{10} and NO_2 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; Goldenberg 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-

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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/m^3 of PM_{10} and 1.24 (95% CI: 1.08, 1.41) per 10 μg/m^3 of $PM_{2.5}$. In addition, exposure to ozone increased the risk of PTB with a summary EE 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 $PM_{2.5}$ and O_3, 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 (Q_4) of exposure during specific time periods of pregnancy with the risk in the reference exposures, i.e. in the lower exposure quartiles (Q_1-Q_3).

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 ($PM_{2.5}$), respirable particles with aerodynamic diameter less than or equal to 10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3). 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 (Q_4) of exposure to the reference category, comprising the lower exposure quartiles (Q_1-Q_3), 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 ($\geq Q_4$) of the mean exposure distribution, while the reference category comprised the remaining quartiles (Q_1-Q_3). 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 $\geq Q_4$ vs. Q_1-Q_3) 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

Table 1
Characteristics of the study population, The Espoo Cohort Study, 1984–1990.

Characteristic	n (%)
Total	2568 (100.00)
Preterm birth (PTB)	
< 37 weeks of gestation	195 (7.82)
31–36 weeks of gestation	178 (7.19)
Mean gestational age for all PTB (Mean $\pm$ SD)	34.48 $\pm$ 2.34
Gender	
boy	1311 (51.05)
girl	1257 (48.95)
Maternal age at delivery (years)	
< 25	370 (14.41)
25-30	960 (37.38)
> 30	1216 (47.35)
missing	22 (0.86)
Family socioeconomic status	
High	597 (23.25)
Low or medium	1959 (76.29)
missing	12 (0.47)
Single parent or guardian	
yes	183 (7.13)
no	2385 (92.87)
Maternal smoking in pregnancy	
yes	364 (14.17)
no	2199 (85.63)
missing	5 (0.19)
Environmental tobacco smoke exposure of the pregnant mother	
yes	101 (3.93)
no	1874 (72.98)
missing	593 (23.09)

Table 2

Distributions of air pollution parameters in the different seasons in Espoo, Finland over the study period 1983–1990.

	Mean ± SD	Minimum	25th percentile	Median	75th percentile	Range	Maximum
$PM_{2.5}$ (µg/m³)							
Mean average	17.22 ± 16.59	0.68	5.55	12.17	23.3	160.53	161.21
Spring	23.53 ± 20.09	1.08	9.17	17.46	31.60	160.13	161.21
Summer	12.31 ± 10.88	0.77	4.49	8.73	16.63	59.97	60.75
Fall	14.81 ± 16.87	0.68	3.75	9.03	19.41	122.29	122.97
Winter	18.21 ± 14.94	0.73	7.29	13.35	26.06	91.33	92.06
PM_{10} (µg/m³)							
Mean average	18.40 ± 17.24	0	6.20	13.05	24.87	167.93	167.93
Spring	24.79 ± 20.63	1.25	9.67	18.76	33.4	166.69	167.93
Summer	13.54 ± 11.74	0.88	5.20	9.74	18.30	66.34	67.22
Fall	15.91 ± 17.46	0.89	4.21	10.04	21.48	123.79	124.68
Winter	19.37 ± 15.80	0	7.80	14.16	27.67	95.97	95.97
CO (ppb)							
Mean average	259.60 ± 141.82	77.63	169.43	224.33	306.64	2109.94	2187.57
Spring	304.32 ± 167.10	113.58	206.16	263.03	353.60	2073.99	2187.57
Summer	207.23 ± 123.98	77.63	127.89	167.39	243.30	997.85	1075.48
Fall	224.51 ± 107.36	99.23	157.46	192.83	262.92	1173.81	1273.05
Winter	302.77 ± 133.33	141.87	210.47	266.76	348.12	916.39	1058.26
NO_2 (ppb)							
Mean average	3.39 ± 2.88	0.22	1.31	2.43	4.53	25.01	25.23
Spring	3.52 ± 2.93	0.22	1.44	2.75	4.58	25.01	25.23
Summer	2.57 ± 2.57	0.24	0.91	1.66	3.27	16.57	16.81
Fall	3.20 ± 2.69	0.42	1.38	2.28	4.12	17.25	17.67
Winter	4.27 ± 3.06	0.39	1.81	3.42	6.24	15.49	15.87
SO_2 (ppb)							
Mean average	2.47 ± 2.97	0.14	0.63	1.37	3.18	29.20	29.33
Spring	2.44 ± 2.44	0.18	0.75	1.72	3.23	18.34	18.52
Summer	1.60 ± 1.80	0.14	0.42	0.84	2.05	11.96	12.09
Fall	1.91 ± 2.37	0.21	0.52	1.01	2.41	20.82	21.03
Winter	3.94 ± 4.18	0.37	1.03	2.45	4.97	28.97	29.33
O_3 (ppb)							
Mean average	24.71 ± 10.10	0.21	17.60	23.96	32.25	71.61	71.82
Spring	32.85 ± 8.50	5.10	28.69	34.19	38.59	52.99	58.09
Summer	29.44 ± 8.03	10.49	23.71	29.22	34.43	61.33	71.82
Fall	19.68 ± 5.94	1.09	16.38	20.16	23.47	48.95	50.04
Winter	16.68 ± 7.58	0.21	11.61	16.50	21.86	33.55	33.76

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/m³, microgram per cubic meter. All the distribution parameters are mean concentrations of the pollutants.

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/m³, 21.66 µg/m³, 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.
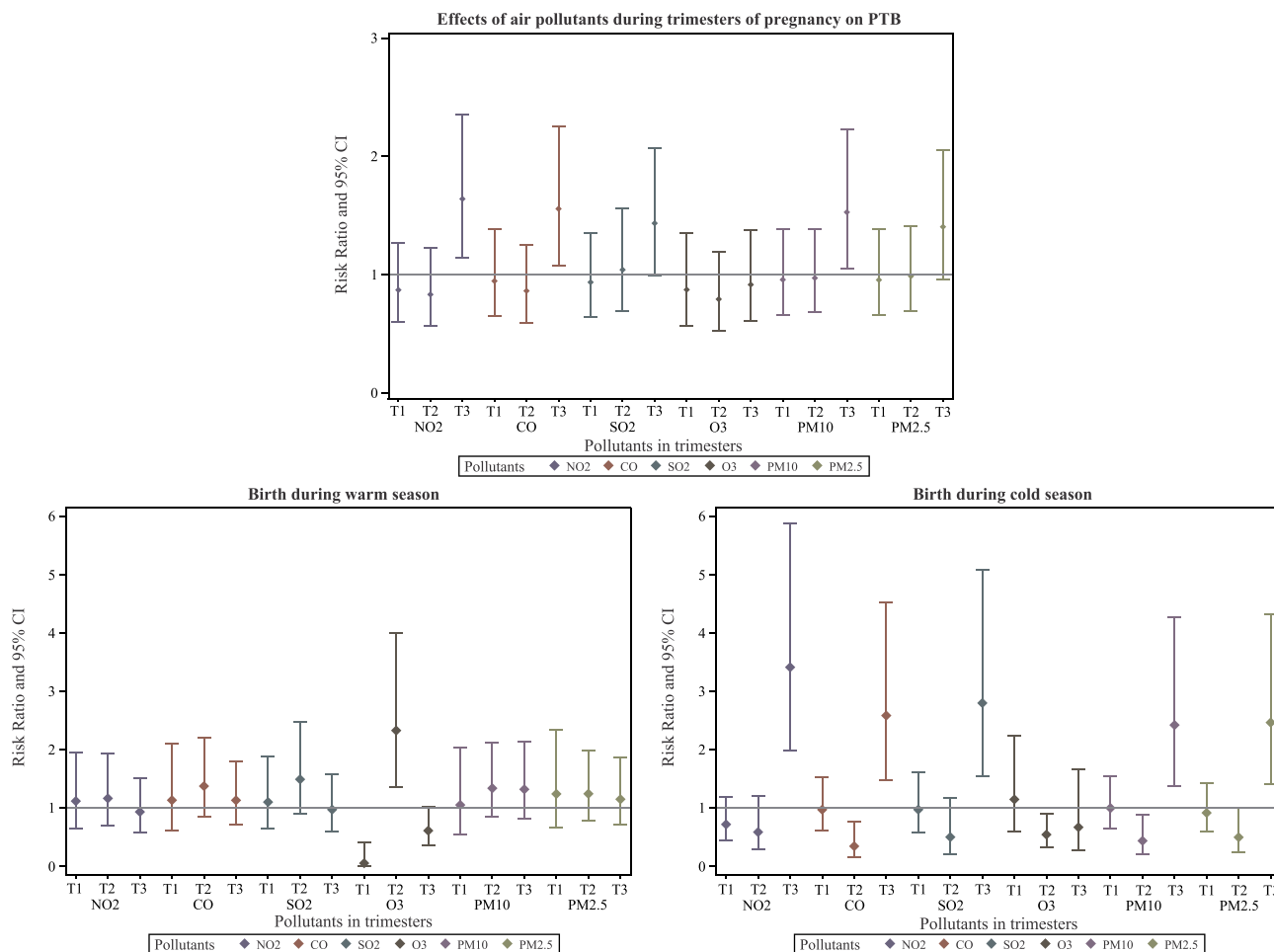
Fig. 1. Adjusted risk ratios (RRs) with 95% confidence intervals (CI) of PTB by comparing highest quartile (Q_4) to lower three quartiles (Q_1-Q_3) of each pollutant exposure during each trimester of pregnancy. All the estimates are from twopollutant models with O_3 and the results for O_3 are from the two-pollutant model with $PM_{2.5}$. CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with a diameter up to 2.5 μm; PM_{10}, particulate matter with a diameter up to 10 μm; ppb, parts per billion; SO_2, sulfur dioxide; μg/m^3, microgram per cubic meter. Cutoffs for highest quartile of exposure: $PM_{2.5}$, ≥ 22.1 μg/m^3; PM_{10}, ≥ 24.1 μg/m^3; NO_2, ≥ 5.1 ppb; CO, ≥ 329.7 ppb; SO_2, ≥ 4.7 ppb; O_3, ≥ 26.0 ppb. Warm season included spring and summer (March to August) and the cold season included autumn and winter (September to February).

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
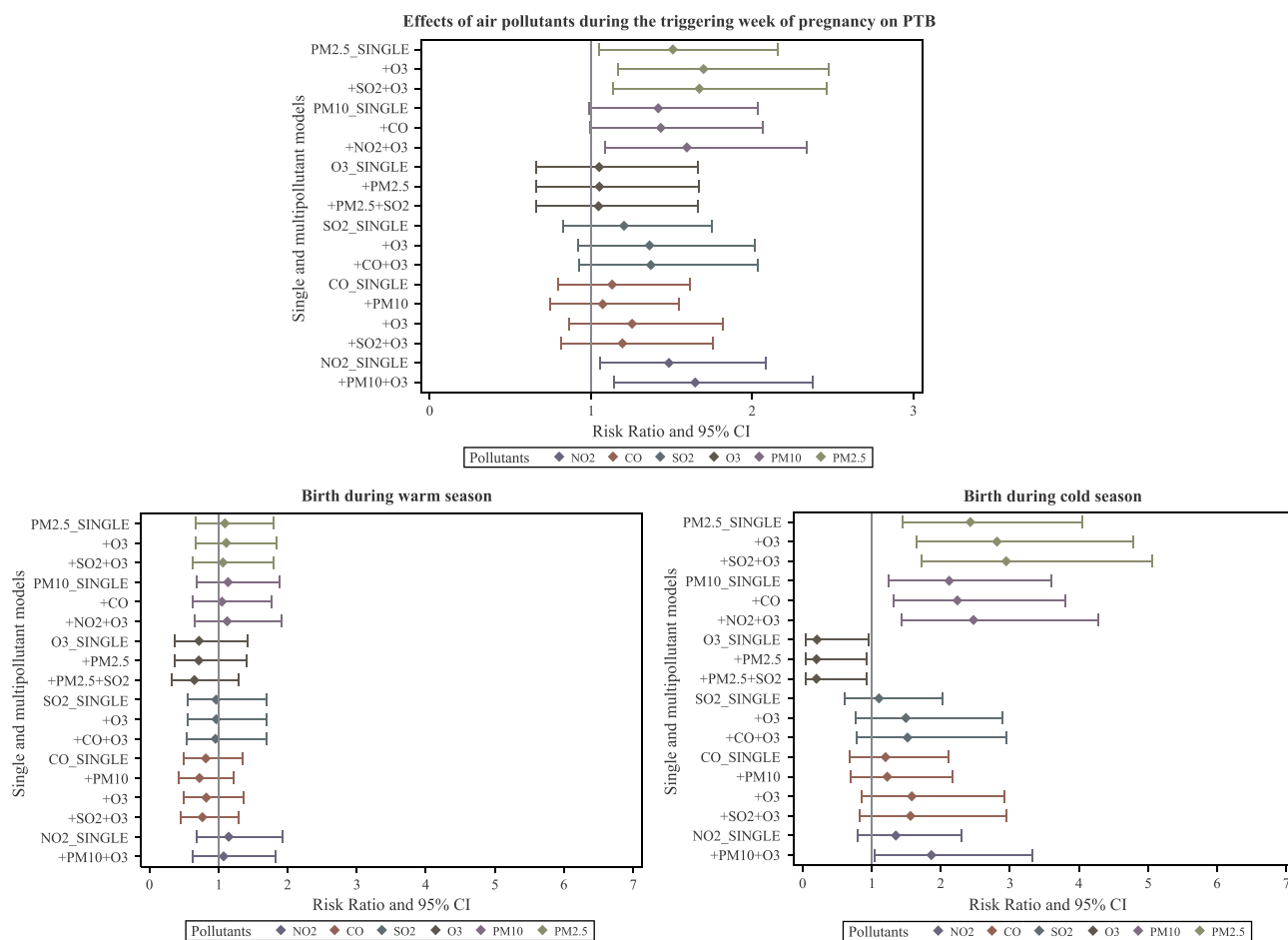
triggering PTB.

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

Fig. 2. Adjusted risk ratios (RRs) with 95% confidence intervals (CI) of PTB by comparing highest quartile (Q_4) to lower three quartiles (Q_1-Q_3) of each pollutant exposure during the triggering week of pregnancy. CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with a diameter up to 2.5 μm; PM_{10}, particulate matter with a diameter up to 10 μm; ppb, parts per billion; SO_2, sulfur dioxide; μg/m^3, microgram per cubic meter. Cutoffs for highest quartile of exposure: $PM_{2.5}$, ≥22.1 μg/m^3; PM_{10}, ≥24.1 μg/m^3; NO_2, ≥5.1 ppb; CO, ≥ 329.7 ppb; SO_2, ≥4.7 ppb; O_3, ≥26.0 ppb. Warm season included spring and summer (March to August) and the cold season included autumn and winter (September to February). Season specific estimates are adjusted for ambient temperature during the exposure period of interest (natural cubic spline with 4df) along with other covariates.

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 fullterm 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

Table 3
Joint effects of air pollutant exposures during the triggering week of pregnancy on preterm birth, The Espoo Cohort Study, 1984–1990.

Pollutants		n/N	% of PTB	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	ERR (95% CI)[a]	RERI (95% CI)[a]
$PM_{2.5}$	O_3						
Low ($< Q_4$)	Low ($< Q_4$)	63/983	6.4	1	1		
High ($> Q_4$)	Low ($< Q_4$)	46/502	9.2	1.43 (0.99, 2.06)	1.62 (1.04, 2.52)	0.62 (0.04, 1.52)	
Low ($< Q_4$)	High ($> Q_4$)	40/617	6.5	1.01 (0.69, 1.48)	1.17 (0.81, 1.68)	0.17 ($-$0.19,0.68)	
High ($> Q_4$)	High ($> Q_4$)	24/330	7.3	1.13 (0.72, 1.79)	1.43 (0.84, 2.45)	0.43 ($-$0.16,1.45)	$-$0.36 ($-$1.39, 0.53)
PM_{10}	O_3						
Low ($< Q_4$)	Low ($< Q_4$)	65/987	6.6	1	1		
High ($> Q_4$)	Low ($< Q_4$)	44/498	8.8	1.34 (0.93, 1.94)	1.51 (0.97, 2.35)	0.51 ($-$0.03,1.35)	
Low ($< Q_4$)	High ($> Q_4$)	40/626	6.4	0.97 (0.66, 1.42)	1.11 (0.77, 1.60)	0.11 ($-$0.23,0.60)	
High ($> Q_4$)	High ($> Q_4$)	24/321	7.5	1.14 (0.72, 1.78)	1.41 (0.83,2.39)	0.41 ($-$0.17, 1.39)	$-$0.21 ($-$1.17, 0.65)
NO_2	O_3						
Low ($< Q_4$)	Low ($< Q_4$)	65/936	6.9	1	1		
High ($> Q_4$)	Low ($< Q_4$)	44/549	8.0	1.15 (0.80, 1.67)	1.27 (0.86, 1.88)	0.27 ($-$0.14,0.88)	
Low ($< Q_4$)	High ($> Q_4$)	44/726	6.1	0.87 (0.60, 1.26)	0.97 (0.68, 1.39)	$-$0.03 ($-$0.32,0.39)	
High ($> Q_4$)	High ($> Q_4$)	20/221	9.1	1.30 (0.81, 2.10)	1.55 (0.93, 2.59)	0.55 ($-$0.07,1.59)	0.31 ($-$0.52, 1.24)
CO	O_3						
Low ($< Q_4$)	Low ($< Q_4$)	70/983	7.12				
High ($> Q_4$)	Low ($< Q_4$)	39/502	7.77	1.09 (0.75, 1.59)	1.15 (0.75, 1.77)	0.15 ($-$0.25,0.77)	
Low ($< Q_4$)	High ($> Q_4$)	45/667	6.75	0.95 (0.66, 1.36)	1.02 (0.72, 1.45)	0.02 ($-$0.28,0.45)	
High ($> Q_4$)	High ($> Q_4$)	19/280	6.79	0.95 (0.58,1.55)	1.08 (0.63, 1.84)	0.08 ($-$0.37,0.84)	$-$0.10 ($-$0.90, 0.63)
SO_2	O_3						
Low ($< Q_4$)	Low ($< Q_4$)	68/963	7.06	1	1		
High ($> Q_4$)	Low ($< Q_4$)	41/522	7.85	1.11 (0.77, 1.61)	1.16 (0.78, 1.74)	0.16 ($-$0.22,0.74)	
Low ($< Q_4$)	High ($> Q_4$)	50/796	6.28	0.89 (0.63, 1.27)	0.97 (0.69, 1.36)	$-$0.03 ($-$0.31,0.36)	
High ($> Q_4$)	High ($> Q_4$)	14/151	9.27	1.31 (0.76, 2.27)	1.46 (0.83, 2.57)	0.46 ($-$0.17,1.57)	0.33 ($-$0.51, 1.38)

Note: All the estimates are from modified Poisson regression models. CO, carbon monoxide; CI, confidence interval; ERR, Excess Relative Risk; 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; RERI, Relative Excess Risk Due to Interaction; RR, Risk Ratio; SO_2, sulfur dioxide.

There was no evidence of synergistic effects between short-term air pollution exposure to '$PM_{2.5}$ and O_3', 'PM_{10} and O_3' or 'CO and O_3' on the risk of PTB.

[a] Adjusted for season of birth, gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure of pregnant mother and single parenthood.

age information was missing in the baseline data, we used that information from the Finnish Medical Birth Registry from January 1, 1987, which provides objective and physician-validated information from the official medical records of mothers in Finland. The possibility of outcome misclassification is also reduced by the systematic use of ultrasound in Finland for estimation of gestational age.

We were able to adjust for several potential confounders, including information on maternal characteristics, other environmental exposures at home, and behavioral factors, such as smoking. Information on these was obtained from the extensive questionnaire that the mothers replied to at the time of the baseline study. A potential limitation of our study is that we did not have information on whether the birth was natural or induced due to some medical condition. However, Savitz et al. (2005) and Guan et al. (2019) provided evidence that spontaneous and induced preterm births have similar risk factors, including smoking. As we adjusted for such factors, information on the type of induction of birth was not considered to be critical for the validity of our effect estimates.

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 $PM_{2.5}$ in 3rd trimester, which is consistent with our estimate. However, they found that PM_{10} was significantly associated with PTB in 1st trimester. In addition, they showed a significant association between O_3 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 PM_{10} on PTB with a lag time of 12–22 days, but found no significant effect in relation to NO_2 or O_3 exposure during the warm season. Moreover, they observed a linear relation with PM_{10} and NO_2 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 impacts of $PM_{2.5}$ and PM_{10} 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 NO_2 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 O_3 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; Cuffe 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; Vadillo-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.

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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. **Maritta S. Jaakkola:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Jouni J.K. Jaakkola:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Supervision, Funding acquisition.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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

References

Aalto, J., Pirinen, P., Jylhä, K., 2016. New gridded daily climatology of Finland: permutation-based uncertainty estimates and temporal trends in climate. J. Geophys. Res. Atmos. 121, 3807–3823. https://doi.org/10.1002/2015JD024651.

Arroyo, V., Díaz, J., Ortiz, C., Carmona, R., Sáez, M., Linares, C., 2016. Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). Environ. Res. 145, 162–168. https://doi.org/10.1016/j.envres.2015.11.034.

Bell, M.L., Belanger, K., 2012. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. J. Expo. Sci. Environ. Epidemiol. 22, 429–438. https://doi.org/10.1038/jes.2012.42.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., et al., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 379, 2162–2172. https://doi.org/10.1016/S0140-6736(12)60820-4.

Blencowe, H., Lee, A.C.C., Cousens, S., Bahalim, A., Narwal, R., Zhong, N., et al., 2013. Preterm birth-associated neurodevelop-mental impairment estimates at regional and global levels for 2010. Pediatr. Res. 74, 17–34. https://doi.org/10.1038/pr.2013.204.

Boyle, A.K., Rinaldi, S.F., Norman, J.E., Stock, S.J., 2017. Preterm birth: inflammation, fetal injury and treatment strategies. J. Reprod. Immunol. 119, 62–66. https://doi.org/10.1016/j.jri.2016.11.008.

Carder, M., McNamee, R., Beverland, I., Elton, R., Van Tongeren, M., Cohen, G.R., et al., 2008. Interacting effects of particulate pollution and cold temperature on cardiorespiratory mortality in Scotland. Occup. Environ. Med. 65, 197–204. https://doi.org/10.1136/oem.2007.032896.

Challis, J.R., Lockwood, C.J., Myatt, L., Norman, J.E., Strauss 3rd, J.F., Petraglia, F., 2009. Inflammation and pregnancy. Reprod. Sci. 16, 206–215. https://doi.org/10.1177/1933719108329095.

Chang, H.H., Reich, B.J., Miranda, M.L., 2012. Time-to-event analysis of fine particle air pollu-tion and preterm birth: results from North Carolina, 2001-2005. Am. J. Epidemiol. 175, 91–98. https://doi.org/10.1093/aje/kwr403.

Cuffe, J.S., Xu, Z.C., Perkins, A.V., 2017. Biomarkers of oxidative stress in pregnancy complications. Biomarkers Med. 11, 295–306. https://doi.org/10.2217/bmm-2016-0250.

Darrow, L.A., Klein, M., Flanders, W.D., Waller, L.A., Correa, A., Marcus, M., et al., 2009. Ambient air pollution and preterm birth: a time-series analysis. Epidemiology 20, 689–698. https://doi.org/10.1097/EDE.0b013e3181a7128f.

Dastoorpoor, M., Idani, E., Goudarzi, G., Khanjani, N., 2018. Acute effects of air pollution on spontaneous abortion, premature delivery, and stillbirth in Ahvaz, Iran: a time-series study. Environ. Sci. Pollut. Res. Int. 25, 5447–5458. https://doi.org/10.1007/s11356-017-0692-9.

Ekman-Ordeberg, G., Dubicke, A., 2012. Preterm cervical ripening in humans. Facts Views Vis. Obgyn. 4, 245–253.

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

Public. Health. 2014 901017. https://doi.org/10.1155/2014/901017.

Fuchs, F., Monet, B., Ducruet, T., Chaillet, N., Audibert, F., 2018. Effect of maternal age on the risk of preterm birth: a large cohort study. PloS One 13 (1), e0191002. https://doi.org/10.1371/journal.pone.0191002.

Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Epidemiology and causes of preterm birth. Lancet 371, 75–84. https://doi.org/10.1016/S0140-6736(08)60074-4.

Guan, T., Xue, T., Gao, S., Hu, M., Liu, X., Qiu, X., et al., 2019. Acute and chronic effects of ambient fine particulate matter on preterm births in Beijing, China: a time-series model. Sci. Total Environ. 650 (Pt 2), 1671–1677. https://doi.org/10.1016/j.scitotenv.2018.09.279.

Huynh, M., Woodruff, T.J., Parker, J.D., Schoendorf, K.C., 2006. Relationships between air pollution and preterm birth in California. Paediatr. Perinat. Epidemiol. 20, 454–461. https://doi.org/10.1111/j.1365-3016.2006.00759.x.

Jaakkola, J.J., Gissler, M., 2004. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am. J. Publ. Health 94, 136–140.

Jaakkola, J.J., Hwang, B.F., Jaakkola, N., 2005. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. Environ. Health Perspect. 113 (3), 357–361. https://doi.org/10.1289/ehp.7242.2005 Mar.

Jaakkola, J.J., Jaakkola, N., Ruotsalainen, R., 1993. Home dampness and molds as determinants of respiratory symptoms and asthma in pre-school children. J. Expo. Anal. Environ. Epidemiol. 3 (Suppl. 1), 129–142.

Joseph, K.S., Fahey, J., Shankardass, K., Allen, V.M., O'Campo, P., Dodds, L., et al., 2014. Effects of socioeconomic position and clinical risk factors on spontaneous and iatrogenic preterm birth. BMC Pregnancy Childbirth 14, 117. https://doi.org/10.1186/1471-2393-14-117.

Kauhaniemi, M., Stojiljkovic, A., Pirjola, L., Karppinen, A., Härkönen, J., Kupiainen, K., et al., 2014. Comparison of the predictions of two road dust emission models with the measurements of a mobile van. Atmos. Chem. Phys. 14, 9155–9169. https://doi.org/10.5194/acp-14-9155-2014.

Klepac, P., Locatelli, I., Korošec, S., Kunzli, N., Kukec, A., 2018. Ambient air pollution and pregnancy outcomes: a comprehensive review and identification of environmental public health challenges. Environ. Res. 167, 144–159. https://doi.org/10.1016/j.envres.2018.07.008.

Kukkonen, J., Kangas, L., Kauhaniemi, M., Sofiev, M., Aarnio, M., Jaakkola, J.J.K., 2018. Modelling of the urban concentrations of PM2.5 on a high resolution for a period of 35 years, for the assessment of lifetime exposure and health effects. Atmos. Chem. Phys. 18, 8041–8064. https://doi.org/10.5194/acp-18-8041-2018.

Lago, F., Dieguez, C., Gómez-Reino, J., Gualillo, O., 2007. Adipokines as emerging mediators of immune response and inflammation. Nat. Clin. Pract. Rheumatol. 3, 716–724.

Lee, S.J., Hajat, S., Steer, P.J., Filippi, V., 2008. A time-series analysis of any short-term effects of meteorological and air pollution factors on preterm births in London, UK. Environ. Res. 106, 185–194. https://doi.org/10.1016/j.envres.2007.10.003.

Leem, J.H., Kaplan, B.M., Shim, Y.K., Pohl, H.R., Gotway, C.A., Bullard, S.M., et al., 2006. Exposures to air pollutants during pregnancy and preterm delivery. Environ. Health Perspect. 114, 905–910. https://doi.org/10.1289/ehp.8733.

Li, S., Guo, Y., Williams, G., 2016. Acute impact of hourly ambient air pollution on preterm birth. Environ. Health Perspect. 124, 1623–1629. https://doi.org/10.1289/EHP200.

Li, Q., Wang, Y.Y., Guo, Y., Zhou, H., Wang, X., Wang, Q., et al., 2018. Effect of airborne particulate matter of 2.5 μm or less on preterm birth: a national birth cohort study in China. Environ. Int. 121, 1128–1136. https://doi.org/10.1016/j.envint.2018.10.025.

Liu, L., Johnson, H.L., Cousens, S., Perin, J., Scott, S., Lawn, J.E., et al., 2012. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 379, 2151–2161. https://doi.org/10.1016/S0140-6736(12)60560-1.

Liu, S., Krewski, D., Shi, Y., Chen, Y., Burnett, R.T., 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ. Health Perspect. 111 (14), 1773–1778 [PubMed: 14594630].

Maroziene, L., Grazuleviciene, R., 2002. Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. Environ. Health 1, 6.

Monn, C., Becker, S., 1999. Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine (PM2.5) and coarse particles (PM10-2.5) in outdoor and indoor air. Toxicol. Appl. Pharmacol. 155, 245–252. https://doi.org/10.1006/taap.1998.8591.

Moosgaard, B., Vestergaard, P., Heickendorff, L., Melsen, F., Christiansen, P., Mosekilde, L., 2005. Vitamin D status, seasonal variations, parathyroid adenoma weight and bone mineral density in primary hyperparathyroidism. Clin. Endocrinol. 63 (5), 506–513. https://doi.org/10.1111/j.1365-2265.2005.02371.x.

Morley, R., Carlin, J.B., Pasco, J.A., Wark, J.D., 2006. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. J. Clin. Endocrinol. Metab. 91, 906–912. https://doi.org/10.1210/jc.2005-1479.

Ngo, D.T., Sverdlov, A.L., McNeil, J.J., Horowitz, J.D., 2010. Does vitamin D modulate asymmetric dimethylarginine and C-reactive protein concentrations? Am. J. Med. 123, 335–341. https://doi.org/10.1016/j.amjmed.2009.09.024.

Nadeau-Vallee, M., Obari, D., Palacios, J., Brien, M.-E., Duval, C., Chemtob, S., et al., 2016. Sterile inflammation and pregnancy complications: a review. Reproduction 152, R277–R292. https://doi.org/10.1530/REP-16-0453.

Olsson, D., Ekstrom, M., Forsberg, B., 2012. Temporal variation in air pollution concentrations and preterm birth-a population based epidemiological study. Int. J.

Environ. Res. Publ. Health 9, 272–285. https://doi.org/10.3390/ijerph9010272.

Peelen, M.J., Kazemier, B.M., Ravelli, A.C., De Groot, C.J., Van Der Post, J.A., Mol, B.W., et al., 2016. Impact of fetal gender on the risk of preterm birth, a national cohort study. Acta Obstet. Gynecol. Scand. 95, 1034–1041. https://doi.org/10.1111/aogs.12929.

Rantala, A.K., Jaakkola, M.S., Makikyro, E.M., Hugg, T.T., Jaakkola, J.J., 2015. Early respiratory infections and the development of asthma in the first 27 years of life. Am. J. Epidemiol. 182, 615–623. https://doi.org/10.1093/aje/kwv093.

Ritz, B., Yu, F., Chapa, G., Fruin, S., 2000. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology 11 (5), 502–511 [PubMed: 10955401].

Rothman, K.J., 1986. Modern Epidemiology, 2nd Printing. United States of America, pp. 313–326 Library of Congress Catalog Card No. 85-82480.

Rothman, K.J., Greenland, S., Lash, T.L., 2008. Modern Epidemiology, third ed. Library of Congress Cataloging-in-Publication Data, United States of America, pp. 71–83.

Sagiv, S.K., Mendola, P., Loomis, D., Herring, A.H., Neas, L.M., Savitz, D.A., et al., 2005. A time-series analysis of air pollution and preterm birth in Pennsylvania. Environ. Health Perspect. 113, 602–606. https://doi.org/10.1289/ehp.7646.1997–2001.

Savitz, D.A., Dole, N., Herring, A.H., Kaczor, D., Murphy, J., Siega-Riz, A.M., et al., 2005. Should spontaneous and medically indicated preterm births be separated for studying aetiology? Paediatr. Perinat. Epidemiol. 19, 97–105. https://doi.org/10.1111/j.1365-3016.2005.00637.x.

Schifano, P., Lallo, A., Asta, F., De Sario, M., Davoli, M., Michelozzi, P., 2013. Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001-2010. Environ. Int. 61, 77–87. https://doi.org/10.1016/j.envint.2013.09.005.

Shah, P.S., Balkhair, T., 2011. Knowledge Synthesis Group on Determinants of Preterm/LBW births. Air pollution and birth outcomes: a systematic review. Environ. Int. 37 (2), 498–516. https://doi.org/10.1016/j.envint.2010.10.009.

Siddika, N., Rantala, A.K., Antikainen, H., Balogun, H., Amegah, A.K., Ryti, N.R.I., et al., 2019. Synergistic effects of prenatal exposure to fine particulate matter (PM2.5) and ozone (O3) on the risk of preterm birth: a population-based cohort study. Environ. Res. 176, 108549. https://doi.org/10.1016/j.envres.2019.108549.

Sofiev, M., Kouznetsov, R., Prank, M., Soares, J., Vira, J., Tarvainen, V., 2016. A longterm reanalysis of atmospheric composition and air quality. ITM 35. https://itm.marvin.vito.be/index.html4pp.

Sofiev, M., Vira, J., Kouznetsov, R., Prank, M., Soares, J., Genikhovich, E., 2015. Construction of the SILAM Eulerian atmospheric dispersion model based on the advection algorithm of Michael Galperin. Geosci. Model Dev. (GMD) 8, 3497–3522. https://doi.org/10.5194/gmd-8-3497-2015.

Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111. https://doi.org/10.1016/j.envres.2012.05.007.

Strand, L.B., Barnett, A.G., Tong, S., 2011. Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. BMC Med. Res. Methodol. 11, 49.

Sultana, Z., Maiti, K., Aitken, J., Morris, J., Dedman, L., Smith, R., 2017. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. Am. J. Reprod. Immunol. 77. https://doi.org/10.1111/aji.12653.

Sun, Q., Yue, P., Deiuliis, J.A., Lumeng, C.N., Kampfrath, T., Mikolaj, M.B., et al., 2009. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 119. https://doi.org/10.1161/CIRCULATIONAHA.108.799015.

Vadillo-Ortega, F., Osornio-Vargas, A., Buxton, M.A., Sánchez, B.N., Rojas-Bracho, L., Viveros-Alcaráz, M., et al., 2014. Air pollution, inflammation and preterm birth: a potential mechanistic link. Med. Hypotheses 82, 219–224.

Vicedo-Cabrera, A.M., Olsson, D., Forsberg, B., 2015. Exposure to seasonal temperatures during the last month of gestation and the risk of preterm birth in Stockholm. Int. J. Environ. Res. Publ. Health 12, 3962–3978. https://doi.org/10.3390/ijerph120403962.

Vuori, E., Gissler, M., 2014. Perinataalitilasto – Synnyttajat, Synnytykset Ja Vastasyntyneet 2013 [Perinatal Statistics: Partu-Rients, Deliveries and Newborns 2013]. Terveyden ja hyvinvoinnin laitos (THL), Helsinki. http://urn.fi/URN:NBN:fife2014101345161.

Wigle, D.T., Arbuckle, T.E., Turner, M.C., Berube, A., Yang, Q., Liu, S., et al., 2008. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J. Toxicol. Environ. Health B Crit. Rev. 11, 373–517. https://doi.org/10.1080/10937400801921320.

Windham, G.C., Hopkins, B., Fenster, L., Swan, S.H., 2000. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 11, 427–433 [PMID:10874550].

Zeitlin, J.A., Saurel-Cubizolles, M.J., Ancel, P.Y., Europop Group, 2002. Marital status, cohabitation, and risk of preterm birth in Europe: where births outside marriage are common and uncommon. Paediatr. Perinat. Epidemiol. 16, 124–130 [PMID:12064266].

Zhao, Q., Liang, Z., Tao, S., Zhu, J., Du, Y., 2011. Effects of air pollution on neonatal prematurity in Guangzhou of China: a time-series study. Environ. Health 10, 2. https://doi.org/10.1186/1476-069X-10-2.

Zou, G.Y., 2008. On the estimation of additive interaction by use of the four-by-two table and beyond. Am. J. Epidemiol. 168, 212–224. https://doi.org/10.1093/aje/kwn104.