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Effects of Air Pollution on the Risk of Low Birth Weight in a Cold Climate

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Abstract: There is accumulating evidence that prenatal exposure to air pollution disturbs fetal growth and development, but little is known about these effects in cold climates or their season-specific or joint effects. Our objective was to assess independent and joint effects of prenatal exposure to specific air pollutants on the risk of low birth weight (LBW). We utilized the 2568 children of the Espoo Cohort Study, born between 1984 and 1990 and living in the City of Espoo. We conducted stratified analyses for births during warm and cold seasons separately. We analyzed the effect estimates using multi-pollutant Poisson regression models with risk ratio (RR) as the measure of effect. The risk of LBW was related to exposure to CO (adjusted RR 1.44, 95% confidence interval [CI]: 1.04–2.00) and exposure to O_3 in the spring–summer season (1.82, 1.11–2.96). There was also evidence of synergistic effects between CO and O_3 (relative risk due to interaction (RERI), all year 1.08, 95% CI: 0.27–4.94, spring–summer 3.97, 2.17–25.85) and between $PM_{2.5}$ and O_3 (all year 0.72, −0.07–3.60, spring–summer 2.80, 1.36–19.88). We present new evidence of both independent and joint effects of prenatal exposure to low levels of air pollution in a cold climate on the risk of LBW.

Keywords: air pollution; low birth weight; prenatal exposure

1. Introduction

Birth weight is commonly used as a measure of fetal growth. The World Health Organization (WHO) defines low birth weight (LBW) as any live birth weighing less than 2500 g [1]. LBW has been recognized as an important risk factor for fetal and neonatal mortality and morbidity, delayed growth and cognitive development, and development of several chronic diseases later in life [2]. It has been estimated that 15% to 20% of all births worldwide are LBW, i.e., more than 20 million births a year [3]. In Finland, the prevalence of low birth weight is approximately 4.3% [4,5].

Humans are surrounded by air pollution throughout their life; however, the prenatal period is possibly the most vulnerable period. During this period, children are especially susceptible to adverse effects of environmental exposures [6]. The evidence on the impact of prenatal exposure to air pollutants on fetal growth and development has been summarized in several systematic

reviews and meta-analyses; however, the results and conclusions have been inconsistent and even controversial [6–10]. Maisonet et al. [11] presented already two decades ago associations between outdoor air pollution and the risk of term LBW in Northeastern cities of the United States. Their study found that maternal exposure to SO_2 and CO during the second and third trimesters, respectively, increase the risk of LBW. Pedersen et al. [12] compiled recently data from 14 prospective birth cohorts involving 12 European countries (i.e., European Study of Cohorts for Air Pollution Effects (ESCAPE)). An increase of 5 $\mu g/m^3$ in prenatal exposure to $PM_{2.5}$ and PM_{10} was associated with 18% and 16% increased risk of LBW, respectively. Even exposure to $PM_{2.5}$ concentrations below the limit values recommended by the European Union were associated with an increased risk of LBW. Several meta-analyses have summarized the effects related to exposure to PM on the risk of adverse pregnancy outcomes [6,8,13,14]. Stieb et al. [9] reported summary-effect estimates for reduced birth weight, ranging from 11.4 g per 1 ppm of CO to 28.1 g per 20 ppb of NO_2. In a recent original study from our team on the effect of air pollution on preterm birth (PTB), we found an increased risk of PTB with maternal exposure to relatively low levels of air pollution. We also found synergistic effects of $PM_{2.5}$ and ozone [15].

The study by Pederson et al. [12] on the effect of air pollution included several European countries but did not include Finland. Based on our systematic literature search, the present study is the first to investigate potential effects of air pollution on LBW in a cold subarctic climate (also called subpolar or boreal climate) present in Finland.

In general, concentrations of the most relevant air pollutants in the Helsinki region have been found to be lower than the corresponding values in major Central and Southern European cities [16]. However, pollutant levels in Finland may be substantially higher in unfavorable weather conditions in winter, spring, and summer. Emissions into the air are generated from residential wood combustion, vehicular traffic, resuspended dust, energy production, and industry, especially in urban areas. In addition, long-range transport has a notable contribution to air pollutant concentrations in Finland, including smoke episodes from forest fires [17].

Although there was substantial evidence on the effects of prenatal exposure to air pollution on fetal growth, there were no previous studies conducted in cold climate with relatively low levels of air pollution. None of the previous studies have elaborated potential interactions between different pollutants or potential seasonal differences in their effects on fetal growth.

To fill these gaps in knowledge, we assessed potential effects of maternal exposure to air pollutants during pregnancy on the risk of LBW in a cold climate. The specific objectives were to assess potential joint effects related to specific air pollutants with exposure taking place in different phases of the pregnancy, as well as to elaborate potential season-specific effects.

2. Materials and Methods

2.1. Study Population

The source population included all children of the city of Espoo, Finland, who were born between 1 January 1984 and 31 March 1990. Espoo is an urban–suburban municipality (with a population of 279,000), located across the western border of Helsinki, the capital of Finland. 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 of the Espoo Cohort Study [18–20]. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study protocol was approved by the Ethics Committee of Oulu University Hospital (Oulu, Finland).

2.2. Exposure Assessment

We assessed individual-level prenatal exposure to ambient air pollutants of interest based on exposure conditions at all the residential addresses of the cohort members from conception to birth.

The pollutant data were based on a cascade of nested simulations performed using the system for integrated modelling of atmospheric composition (SILAM) (http://silam.fmi.fi) [21,22]. The model computations were first conducted on a global scale, to capture the global background levels of pollutants and subsequently zoomed both to Europe and Northern Europe, reaching the spatial resolution of 0.1° × 0.1° for the Northern European domain [22]. This dataset was also used as a regional background by Kukkonen et al. [23] for fine resolution modelling of the concentrations of fine particulate matter ($PM_{2.5}$) in the Helsinki Metropolitan Area from 1980 to 2014. For a more detailed description of the emission and dispersion computations used in this study, the reader is referred to the abovementioned study [23]. In the study area, the spatial resolution applied in this study corresponded to around 5.5 km in the east–west direction and 11.1 km in the north–south direction.

We used the ambient air temperature data, which was 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 [24]. The home coordinates of the mothers were retrieved from the Population Register Center of Finland, and Geographical Information System (GIS) was used to extract daily levels of air pollutants and temperature at the home coordinates. The exposures of interest included the following air pollutants: fine particulate matter with a dry diameter up to 2.5 μm ($PM_{2.5}$), respirable particulate matter with a dry diameter up to 10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3).

2.3. Outcome of Interest

The main outcome of interest was LBW. We defined LBW in the present study as birth less than 3000 g (LBW_{3000}). We selected a higher than the traditional cut point (2500 g) for LBW. Our alternative cut point LBW_{3000} is justified because it maintains the conceptual idea that reduction in fetal growth and the resulting low birth weight may indicate adverse effects of environmental exposures and/or other factors. This was also justified because it increased the statistical efficiency of our analyses and enabled testing the hypothesis about the effects of air pollution on fetal growth. We conducted sensitivity analyses using the traditional LBW less than 2500 g (LBW_{2500}). The information on birth weight and gestational age was retrieved from the baseline data collection, and if the information was missing, then we retrieved the information from the Finnish Medical Birth Registry, which started data collection on 1 January 1987.

2.4. Covariates

We identified a set of determinants of LBW based on previous literature and assessed their potential role as confounders in the multivariable statistical models. These covariates included maternal age [25,26], gender [27,28], family socioeconomic status [29,30], maternal smoking during pregnancy [31,32], environmental tobacco smoke exposure [33,34], and marital status [35,36]. In the two-pollutant models, we also adjusted for the other pollutants. In addition, to assess potential effect modification by season, we conducted stratified analyses by two birth seasons, i.e., cold season (autumn–winter) and warm season (spring–summer). We also considered other air pollutants as potential confounders when assessing the effect of one pollutant. We first fitted one-pollutant models and then considered two-pollutant models by fitting one traffic related ($PM_{2.5}$, NO_2, and CO) and one stationary fossil fuel combustion-related pollutant (PM_{10} and SO_2). We also fitted two-pollutant models with O_3 as the main secondary pollutant and another pollutant. Family socioeconomic status was categorized as low (including both parents having no degree and having a vocational degree but being unemployed), high (including both parents having an academic degree and being white-collar workers or entrepreneurs), and middle (including all the other combinations of education and occupation, e.g., other parent low and high category and both parents' students). Environmental tobacco smoke was defined as exposure to tobacco smoke produced by another smoking person. We treated missing information on environmental tobacco smoke (n = 593) by fitting an indicator variable called missing

to prevent reduction in study population. The appropriateness of this approach was evaluated in a sensitivity analysis.

2.5. Statistical Methods

We conducted multivariate Poisson regression analysis to obtain adjusted risk ratios (RR) with their 95% confidence intervals (95% CI) as the measure of effect of exposure to air pollution during the entire pregnancy on the risk of LBW. We compared the risk of LBW among babies with the highest quartile (Q4) of exposure to the reference categories of exposure, i.e., those with exposure in the lower exposure quartiles (Q1–Q3). We fitted both single- and two-pollutant models.

We studied both the independent and joint effects of different air pollutants during the entire pregnancy on the risk of LBW. Potential interaction was estimated on an additive scale because it has the most relevance for public health [37]. The statistical methods for estimating joint effects have been described in detail in our previous article [15]. In short, for example, we compared the risk of LBW in three different exposure categories, defined as (1) high CO and low O_3 (A), (2) low CO and high O_3 (B), and (3) high CO and high O_3 (AB), and these were compared to the reference category of "low CO and low O_3" exposure. Here, high and low refer to the exposure levels that were above or below the Q4 value, respectively. Similar categorization was carried out for the analysis of the joint effect between $PM_{2.5}$ and O_3. Estimates for the independent and joint effects were derived from the modified Poisson regression analysis by fitting both crude and adjusted models [38]. We assessed the excess relative risk (ERR) for the independent and joint effects of the air pollutants of interest. The relative risk due to interaction (RERI) was quantified on an additive scale by calculating the risk that is more than expected based on summing the independent effects related to these exposures. This can be expressed in terms of ERRs as follows:

$$\text{RERI} = \text{ERR (AB)} - \text{ERR (A)} - \text{ERR (B)}$$

We estimated the 95% CI for RERI using the method of variance estimates recovery [38]. For RERI, the null value corresponded to a statistical significance level of $p = 0.05$. Applying a similar procedure, we also studied the indsependent and joint effects of other pollutant exposures and their combinations with O_3 (i.e., between $PM_{2.5}$ and O_3 and between CO and O_3) on the risk of LBW. For the joint-effects analyses, we chose those pollutants that were not strongly correlated with each other but that showed the highest increases in effect estimates in the multipollutant models

To examine the potential modifying effect by season, we 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).

We have conducted several sensitivity analyses (i) by applying the air pollution data as continuous variables, (ii) by providing the effect estimates per a 10-unit increase in each pollutant, and (iii) by comparing the air pollution levels below and above the median values.

Analyses were carried out 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

Table 1 shows the characteristics of the study population. There was a total of 344 (13.4%) infants born with LBW_{3000}, defined as <3000 g, and among these, 218 (8.5%) were full term babies. Approximately 48.0% of our participant mothers were above 30 years and 23.4% belonged to the highest categories of socioeconomic status. The majority of mothers did not smoke (85.8%), and 73.0% were not exposed to environmental tobacco smoke during pregnancy.

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

Characteristic	Low Birth Weight <3000 g *n* (%)	Non-Low Birth Weight *n* (%)	Total *n* (%)
Total	344 (13.40)	2216 (86.56)	2568 (100.00)
Mean birth weight (Mean ± SD)	2742.02 ± 228.59	3675.24 ± 406.62	3523.41 ± 559.77
Gender			
boy	157 (45.64)	1149 (51.85)	1311 (51.05)
girl	187 (54.36)	1067 (48.15)	1257 (48.95)
Maternal age at delivery (years) [1]			
<25	59 (17.25)	308 (14.03)	370 (14.53)
25–30	115 (33.63)	845 (38.48)	960 (37.71)
>30	168 (49.12)	1043 (47.50)	1216 (47.76)
Family socioeconomic status [2,3]			
high	76 (22.22)	520 (23.57)	597 (23.36)
low or medium	266 (77.78)	1686 (76.43)	1959 (76.64)
Single parent or guardian			
yes	35 (10.17)	147 (6.63)	183 (7.13)
no	309 (89.83)	2069 (93.37)	2385 (92.87)
Maternal smoking in pregnancy			
yes	77 (22.38)	287 (12.97)	364 (14.17)
no	267 (77.62)	1925 (87.03)	2204 (85.83)
Environmental tobacco smoke exposure of the pregnant mother [4]			
yes	17 (6.91)	84 (4.88)	101 (5.11)
no	229 (93.09)	1639 (95.12)	1874 (94.89)

[1] The ages of 22 persons were missing. [2] High vs. low or medium parental education and occupation. [3] There were 12 persons with missing information in this category. [4] There were 593 persons with missing information on prenatal environmental tobacco smoke exposure. Birth weight was missing among 8 babies, and exposure information was missing among 43 mothers.

3.2. Exposure Distributions

Table 2 presents the mean values and distributions of air pollutants and ambient temperature for the entire pregnancy. The mean concentrations of $PM_{2.5}$, PM_{10}, CO, NO_2, O_3, and SO_2 during the entire pregnancy were 19.6 μg/m^3, 21.4 μg/m^3, 295.1 ppb, 4.3 ppb, 3.9 ppb, and 23.8 ppb, respectively. The mean temperature was 4.8 °C. Table 2 presents also skewness and kurtosis of the distributions of air pollutants in the footnote. Based on these measures, only the distribution of SO_2 deviated substantially from normal distribution (kurtosis 5.266).

Table 2. Distributions of air pollution and temperature parameters during entire pregnancy, Espoo 1 January 1983–31 March 1990.

Pollutants	Mean ± SD	Minimum	25th Percentile	Median	75th Percentile	IQR	Maximum
$PM_{2.5}$ (μg/m^3)	19.62 ± 4.50	3.01	16.93	19.53	22.10	5.17	38.48
PM_{10} (μg/m^3)	21.35 ± 5.12	3.17	18.47	21.15	24.06	5.59	43.78
CO (ppb)	295.09 ± 51.50	119.89	264.02	295.97	329.74	65.72	482.45
NO_2 (ppb)	4.31 ± 1.23	0.21	3.63	4.41	5.07	1.44	8.73
SO_2 (ppb)	3.94 ± 1.95	0.19	2.76	3.75	4.71	1.95	15.88
O_3 (ppb)	23.79 ± 2.80	11.20	21.64	23.93	26.00	4.36	36.93
Temperature (°C)	4.82 ± 2.84	−6.58	2.59	4.94	7.28	4.69	15.50

Note: Normality tests: $PM_{2.5}$ skewness = 0.104, kurtosis = 1.724; PM_{10} skewness = 0.276, kurtosis = 2.086; CO skewness = −0.228, kurtosis = 0.448; O_3 skewness = −0.093, kurtosis = −0.217; NO_2 skewness = −0.374, kurtosis = 1.029; SO_2 skewness = 1.667, and kurtosis = 5.266.

Table 3 represents the correlations of the average concentration of air pollutants. In most cases, the correlation was positive and the lowest Pearson correlation coefficient was found between CO and SO_2. For O_3, however, we detected negative correlations between O_3 and CO and between SO_2 and O_3, with the coefficient r being −0.26151 and −0.36899, respectively. The Spearman correlations between SO_2 and the other pollutant did not differ substantially from the corresponding Pearson correlation coefficients ($PM_{2.5}$ = 0.90292, PM_{10} = 0.92383, CO = 0.92383, and NO_2 = 0.95573).

Table 3. Pearson correlation coefficients for air pollutant exposures during entire pregnancy.

Pollutants	$PM_{2.5}$	PM_{10}	CO	NO_2	SO_2	O_3
$PM_{2.5}$	1.00000	0.99685	0.89702	0.91916	0.90082	−0.28581
PM_{10}		1.00000	0.90623	0.93464	0.92367	−0.27277
CO			1.00000	0.97227	0.84810	−0.26151
NO_2				1.00000	0.89592	−0.30946
SO_2					1.00000	−0.36899
O_3						1.00000

Note: CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with a diameter up to 2.5 micrometers; PM_{10}, particulate matter with a diameter up to 10 micrometers; and SO_2, sulfur dioxide.

Table 4 shows the effects of average air pollution exposures during the entire pregnancy on the risk of low birth weight. The risk of LBW_{3000} increased in relation to the highest quartile of CO in the two-pollutant model that adjusted for PM_{10} (adjusted RR 1.44; 95% CI 1.04–2.00). The effect estimates for CO showed a similar pattern among babies born during spring and summer (adjusted risk ratio [aRR] 1.61; 1.01–2.55) and during autumn and winter (aRR 1.26; 0.78–2.03) when adjusting for PM_{10}. In addition, among babies born during spring and summer, the two-pollutant model that adjusted for O_3 showed increased risk of LBW_{3000} (crude RR 1.29, 1.17–3.13). Exposure to O_3 was related to an increased risk of LBW_{3000} among babies born during spring and summer in the single-pollutant model (aRR 1.80, 1.10–2.94) and in the two-pollutant model adjusting for the other pollutants (e.g., adjusting for CO: aRR 1.88, 1.15–3.09). The risk of LBW_{3000} was also increased in relation to NO_2 in the full model and among babies born during autumn or winter, although the lower 95% confidence interval (95% CI) was <1.00 (Table 4). The risk of LBW_{3000} was not related to $PM_{2.5}$, PM_{10}, or SO_2 exposure in any of the models. However, when SO_2 was adjusted for CO in the two-pollutant model, we found an increased risk with an aRR of 1.72 (95% CI 1.06–2.81).

We neither found any linear association when fitting air pollutant exposures as continuous variables in the models (Table A1) nor any increased risk when using exposure cutoff values at Q_3 (median value) in our analyses (Table A2).

Table A3 presents the results of the sensitivity analyses using the traditional definition of low birth weight less than 2500 g (LBW_{2500}). The risk of LBW_{2500} increased in relation to $PM_{2.5}$. The adjusted RRs among children born in warm seasons varied from 2.31 to 2.45, being statistically significant in the single-pollutant model and when adjusting for O_3. The adjusted RRs of CO were systematically elevated and mainly statistically significant with higher effect estimates among children born during the warm season. Also, the adjusted RRs for SO_2 were elevated. The effect estimates for O_3 were elevated and statistically significant in all two-pollutant models, and the effect was stronger among children born in the warm season.

Table 4. The effects of air pollution exposure during entire pregnancy on low birth weight less than 3000 g (N = 2517), The Espoo Cohort Study, 1984–1990.

Single and Multipollutant Models	Low Birth Weight <3000 g		Spring–Summer (Warm Season)		Autumn–Winter (Cold Season)	
	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	Crude RR (95% CI)	Adjusted RR (95% CI) [2]	Crude RR (95% CI)	Adjusted RR (95% CI) [2]
$PM_{2.5}$($Q_4 \geq 22.1$ $\mu g/m^3$) [3]	0.90 (0.70–1.15)	0.89 (0.69–1.16)	1.06 (0.77–1.45)	1.09 (0.79–1.50)	0.67 (0.43–1.04)	0.64 (0.40–1.01)
($PM_{2.5}$ + O_3)	0.90 (0.70–1.17)	0.90 (0.69–1.16)	1.11 (0.81–1.54)	1.14 (0.82–1.58)	0.64 (0.40–1.01)	0.60 (0.38–0.96)
($PM_{2.5}$ + SO_2)	0.80 (0.55–1.17)	0.79 (0.54–1.16)	1.21 (0.72–2.04)	1.19 (0.70–2.02)	0.51 (0.29–0.90)	0.50 (0.28–0.89)
PM_{10}($Q_4 \geq 24.1$ $\mu g/m^3$) [3]	0.86 (0.67–1.12)	0.86 (0.66–1.11)	1.01 (0.73–1.39)	1.03 (0.74–1.43)	0.67 (0.43–1.03)	0.64 (0.41–1.00)
(PM_{10} + CO)	0.66 (0.46–0.93)	0.66 (0.47–0.94)	0.70 (0.43–1.14)	0.72 (0.44–1.16)	0.57 (0.33–0.96)	0.55 (0.32–0.95)
(PM_{10} + NO_2)	0.71 (0.48–1.04)	0.70 (0.89–1.89)	0.97 (0.55–1.69)	0.98 (0.56–1.72)	0.51 (0.29–0.89)	0.49 (0.88–2.44)
NO_2 ($Q_4 \geq 5.1$ ppb) [3]	1.00 (0.79–1.29)	1.00 (0.78–1.28)	1.02 (0.74–1.41)	1.05 (0.76–1.45)	0.98 (0.66–1.45)	0.94 (0.63–1.40)
(NO_2 + PM_{10})	1.30 (0.90–1.88)	1.30 (0.89–1.89)	1.05 (0.60–1.83)	1.07 (0.61–1.87)	1.49 (0.90–2.45)	1.46 (0.88–2.44)
(NO_2 + SO_2)	1.05 (0.70–1.59)	1.03 (0.67–1.58)	1.13 (0.64– 2.01)	1.08 (0.59–1.97)	0.97 (0.53–1.77)	0.95 (0.52–1.76)
CO ($Q_4 \geq 329.7$ ppb) [3]	1.11 (0.87–1.41)	1.11 (0.86–1.41)	1.24 (0.90–1.69)	1.27 (0.92–1.73)	0.95 (0.64–1.40)	0.91 (0.61–1.35)
(CO + O_3)	1.12 (0.88–1.43)	1.11 (0.80–1.40)	**1.29 (1.17– 3.13)**	1.31 (0.95–1.80)	0.93 (0.63–1.38)	0.89 (0.60–1.33)
(CO + PM_{10})	**1.47 (1.06– 2.03)**	**1.44 (1.04– 2.00)**	**1.60 (1.01– 2.54)**	**1.61 (1.01–2.55)**	1.30 (0.81–2.08)	1.26 (0.78–2.03)
(CO + SO_2)	1.28 (0.90–1.83)	1.25 (0.88–1.78)	**1.78 (1.09– 2.90)**	**1.72 (1.06– 2.81)**	0.92 (0.55–1.55)	0.89 (0.53–1.49)
SO_2 ($Q_4 \geq 4.7$ ppb) [3]	0.99 (0.77–1.26)	0.99 (0.77–1.27)	0.98 (0.71–1.36)	1.03 (0.74–1.43)	0.99 (0.67–1.46)	0.96 (0.64–1.43)
(SO_2 + O_3)	1.00 (0.77–1.28)	1.00 (0.77–1.29)	1.03 (0.74–1.44)	1.08 (0.78–1.51)	0.95 (0.64–1.43)	0.91 (0.61–1.38)
(SO_2 + $PM_{2.5}$)	1.16 (0.80–1.67)	1.18 (0.81–1.72)	0.84 (0.49–1.43)	0.90 (0.52–1.56)	1.47 (0.90–2.40)	1.46 (0.89–2.41)
(SO_2 + CO)	0.82 (0.57–1.18)	0.85 (0.59–1.22)	0.62 (0.37–1.03)	0.67 (0.40–1.12)	1.04 (0.62–1.75)	1.05 (0.62–1.76)
(SO_2 + NO_2)	0.95 (0.63–1.44)	0.98 (0.64–1.50)	0.89 (0.50–1.58)	0.97 (0.53–1.78)	1.01 (0.56–1.84)	1.00 (0.54–1.84)
O_3 ($Q_4 \geq 26$ ppb) [3]	1.04 (0.82–1.33)	1.05 (0.79–1.38)	**1.82 (1.11– 2.96)**	**1.80 (1.10– 2.94)**	0.89 (0.65–1.22)	0.88 (0.64–1.20)
(O_3 + $PM_{2.5}$)	1.02 (0.80–1.31)	1.03 (0.78–1.36)	**1.86 (1.14– 3.06)**	**1.85 (1.12– 3.04)**	0.84 (0.61–1.15)	0.82 (0.59–1.12)
(O_3 + CO)	1.06 (0.83–1.36)	1.06 (0.80–1.40)	**1.91 (1.17– 3.13)**	**1.88 (1.15– 3.09)**	0.89 (0.65–1.21)	0.87 (0.63–1.19)
(O_3 + SO_2)	1.04 (0.81–1.34)	1.05 (0.79–1.38)	1.83 (1.12–3.00)	1.83 (1.11–3.02)	0.88 (0.64–1.22)	0.86 (0.62–1.19)

Note: All the estimates are from Poisson regression models. In the two-pollutant models, the pollutants were included as dichotomous variables. 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 micrometers; PM_{10}, particulate matter with a diameter up to 10 micrometers; ppb, parts per billion; RR, Risk Ratio; SO_2, sulfur dioxide; and $\mu g/m^3$, microgram per cubic meter. [1] Adjusted for the season of birth and other confounders (including gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure of pregnant mother, and single parenthood); [2] adjusted for gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure, and single parenthood; and [3] single pollutant model.

3.3. The Joint Effects of Air Pollution Exposures on the Risk of Low Birth Weight

Table 5 presents the joint effects of CO and O_3 and of $PM_{2.5}$ and O_3 on the risk of LBW_{3000}. The assessment of potential effects related to simultaneous CO and O_3 exposures showed that there was a synergistic effect on the risk of LBW_{3000}: the joint effect of "high CO and high O_3" exposure on LBW_{3000} was related to an adjusted RR of 1.88 (95% CI: 1.20–2.95). Based on the estimate of RERI, there was a 108% (95% CI: 27%–494%) excess risk associated with the joint effect of CO and O_3 at their highest exposure levels when compared to the risk that would be expected based on summing their

independent effects. There was suggestive evidence of a synergistic effect between high $PM_{2.5}$ and high O_3 (RERI 0.72, 95% CI: −0.07–3.60), although the 95% CI included the null value 0. Table A4 shows that the similar pattern of joint effects was present also on LBW_{2500}, although the estimates of RERI were greater for both effects of CO and O_3 (4.03, 95% CI: 1.61–9.28) and $PM_{2.5}$ and O_3 (3.53, 95% CI: 1.19–8.70).

Table 5. Joint effect of CO and O_3 and of $PM_{2.5}$ and O_3 during entire pregnancy on low birth weight less than 3000 g, The Espoo Cohort Study, 1984–1990.

CO Entire Pregnancy	O_3 Entire Pregnancy	n/N	% of LBW <3000 g	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	ERR (95% CI) [1]	RERI (95% CI) [1]
Low (<Q_4)	Low (<Q_4)	183/1351	13.55	1	1		
High (>Q_4)	Low (<Q_4)	69/545	12.66	0.93 (0.71–1.23)	0.93 (0.70–1.23)	−0.07 (−0.30–0.23)	
Low (<Q_4)	High (>Q_4)	63/532	11.84	0.87 (0.66,1.16)	0.87 (0.64,1.19)	−0.13 (−0.36–0.19)	
High (>Q_4)	High (>Q_4)	23/89	25.84	**1.91 (1.24,2.94)**	**1.88 (1.20,2.95)**	**0.88 (0.20– 1.95)**	**1.08 (0.27– 4.94)**
$PM_{2.5}$ Entire Pregnancy	**O_3 Entire Pregnancy**						
Low (<Q_4)	Low (<Q_4)	187/1320	14.17	1	1		
High (>Q_4)	Low (<Q_4)	65/568	11.44	0.81 (0.61–1.07)	0.81 (0.61–1.08)	−0.19 (−0.39–0.08)	
Low (<Q_4)	High (>Q_4)	73/566	12.90	0.91 (0.69–1.19)	0.91 (0.68–1.22)	−0.09 (−0.32–0.22)	
High (>Q_4)	High (>Q_4)	13/63	20.63	**1.46 (0.83– 2.56)**	1.44 (0.81–2.56)	0.44 (−0.19–1.56)	0.72 (−0.07,3.60)

Note: All estimates are from modified Poisson regression models. CI, confidence interval; ERR, Excess Relative Risk; O_3, ozone; PM_{10}, particulate matter with a diameter up to 10 micrometers; RERI, Relative Excess Risk Due to Interaction; and RR, Risk Ratio. [1] 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.

Table 6 shows joint effects of the pollutants on LBW_{3000} during spring–summer season. The joint effect of high $PM_{2.5}$ and high O_3 was substantially higher during the spring–summer season, with an adjusted RR of 4.30 (95% CI: 0.66–10.16), compared to what would be expected based on their independent effects (1.1 for $PM_{2.5}$ and 1.8 for O_3). The relative risk due to interaction (RERI) was 2.80 (95% CI: 1.36–19.88). These observations should be interpreted with caution; although an increased adjusted RR was observed, the RR was not statistically significant, apart from RERI. However, the risk based on RERI was statistically significant, which suggests that $PM_{2.5}$ and O_3 enhance each other's effects. Interestingly, ozone—either alone or in combination with the other pollutants—increased the risk of LBW_{3000} only when the pregnancy took place close to or during the cold season.

Table 6. Joint effect of CO and O_3, and of $PM_{2.5}$ and O_3 exposures during entire pregnancy on low birth weight less than 3000 g in spring and summer (Stratified by season), The Espoo Cohort Study, 1984–1990.

CO Entire Pregnancy	O_3 Entire Pregnancy	n/N	% of LBW <3000 g	Adjusted RR (95% CI) [1]	ERR (95% CI) [1]	RERI (95% CI) [1]
Low (<Q_4)	Low (<Q_4)	102/822	12.41	1	1	
High (>Q_4)	Low (<Q_4)	53/382	13.87	1.18 (0.84–1.65)	0.18 (0.16–0.65)	
Low (<Q_4)	High (>Q_4)	10/67	14.93	1.23 (0.63–2.36)	0.23 (0.37–1.36)	
High (>Q_4)	High (>Q_4)	8/10	80.00	**5.38 (2.50–11.57)**	**4.38 (1.50–10.57)**	**3.97 (2.17,25.85)**
$PM_{2.5}$ Entire Pregnancy	**O_3 Entire Pregnancy**					
Low (<Q_4)	Low (<Q_4)	104/810	12.84	1	1	
High (>Q_4)	Low (<Q_4)	51/392	13.01	1.06 (0.76–1.49)	0.06 (−0.24–0.49)	
Low (<Q_4)	High (>Q_4)	13/72	18.06	1.44 (0.80–2.58)	0.44 (−0.20–1.58)	
High (>Q_4)	High (>Q_4)	5/7	71.43	**4.30 (0.66–10.16)**	**3.30 (1.50–10.57)**	**2.80 (1.36–19.88)**

All estimates are from modified Poisson regression models. CI, confidence interval; ERR, Excess Relative Risk; O_3, ozone; RERI, Relative Excess Risk Due to Interaction; RR, Risk Ratio; and SO_2, sulfur dioxide. [1] 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.

4. Discussion

4.1. Main Findings

The results of the Espoo Cohort Study on the effects of prenatal air pollution exposure on low birth weight strengthened the evidence that maternal exposure to air pollutants during pregnancy increases the risk of LBW using both 3000 g and the traditional 2500 g as the cut point. These are the first findings in a cold climate with relatively low levels of air pollution. Babies with the highest exposure to CO had an increased risk of LBW_{3000}, with estimates varying between 11–44% depending on adjustment for other pollutants. The effect estimates were even higher among children born during the warm season with a 24% to 78% increase in the risk. Among babies born during the warm season, the highest exposure to O_3 was related to an 80% to 88% risk increase. The effect estimates for LBW_{2500} were systematically higher.

None of the previous studies had elaborated potential interactions between different pollutants or potential seasonal differences in their effects on fetal growth. Thus, we present novel evidence of synergistic effects related to the highest exposure levels of CO and O_3 as well as of $PM_{2.5}$ and O_3. The presence of high average levels of both CO and O_3 increased the risk of LBW_{3000} by 108% (27–394%) more than what would be expected from summing their independent effects. The corresponding risk increase for the joint effect of $PM_{2.5}$ and O_3 was 72% (95% CI: −7–260%). The synergistic effects observed were even stronger among children who were born in the spring–summer season.

4.2. Validity of Results

Selection bias was minimized in this study, as it was a population-based study with a good response rate at 80.3%. Potential for selection bias from excluding mothers who did not receive any prenatal care was also minimal, as practically all pregnant women in Finland receive prenatal care [39].

Ideally, exposure assessment should be based on personal monitoring of pregnant women throughout the pregnancy, but this was not feasible in a large epidemiologic study with current methods. Misclassification of prenatal exposure to air pollution was minimized, as we were able to use maternal residential addresses throughout the pregnancy period to get an excellent coverage for the exposure assessment. In addition, the exposure assessment method used was independent of the outcome assessment, which reduced the likelihood of any major bias. Air pollution constitutes a complex mixture of pollutants, which may have strong correlations between each other especially when emitted from the same types of sources, such as traffic and heating. We present results from single-pollutant and two-pollutant models to quantify the independent effects of the main air pollutants. The potential problem of collinearity was reduced by fitting only one pollutant from each main source in the model, traffic ($PM_{2.5}$, NO_2, or CO), heating (PM_{10} or SO_2), and O_3 as a secondary pollutant.

Both weight and gestational age of the infant, that are relevant for the outcome assessment, were based primarily on self-report. For accuracy, any information missing was retrieved from the baseline data collection at the Birth Clinic and the Finnish Medical Birth Registry. The weight and gestational age of any child was taken and recorded in the hospital immediately after delivery, and this was reported into the database of the Finnish Medical Birth Registry and marked on the card that each mother receives in Finland during their pregnancy. The gestational age was estimated using the last menstrual cycle in combination with the findings in the ultrasound examination.

Low birth weight can be considered an indicator of disturbance in fetal growth and development that is caused by genetic factors and/or environmental exposures during pregnancy. The WHO has used a birth weight of less than 2500 g as an indicator of prematurity since 1948 [4]. This cut point was introduced in Finland by professor of pediatrics Arvo Ylppö already in 1919, because gestational age-based measurements were considered inaccurate. He presented that babies with low birth weight should receive special care. There is evidence that, in populations with good nutritional status, the traditional cut point may not be a sufficiently sensitive indicator for identifying fetal growth disturbance and related health risks at birth or later in life. In a study of 1,372,092 singleton births in

seven western countries including Finland, Sweden, Norway, Denmark, Scotland, the Netherlands, and Flanders in Belgium, the risk of perinatal death increased substantially with birth weights from 2500 g to 3000 g [40]. Our choice of birth weight less than 3000 g as a cut point for low birth weight in these populations is a more sensitive and thus better indicator of health risk than the traditional cut point of 2500 g. Therefore, we have presented the primary results using LBW_{3000}, but for comparison, we also conducted sensitivity analyses using LBW_{2500} as the outcome.

Our study has several strengths. First, we used GIS-based exposure assessment data to estimate the weather conditions and air pollutant concentrations for each participant mother. We were able to geocode all respondents' residential addresses using the home coordinates obtained from the Population Register Center over the study period, and we were able to use this information in the exposure assessment as it was utilized in the modelling. In addition, we were able to get all mothers' residential addresses during the entire pregnancy rather than relying solely on the mothers' address at the time of delivery. The measurement of the outcome of interest (i.e., LBW) was obtained from the birth registry, which is a very reliable source in the studied area.

We were able to adjust in the models for several potential confounders, including maternal age, family socioeconomic status, gender, maternal smoking during pregnancy, environmental tobacco smoke exposure of the pregnant mother, single parenthood, and season of birth. We were unable to adjust for some other potentially important confounders, such as maternal alcohol consumption, income, maternal medical history, ethnicity/race, indoor exposures, and occupational exposures both indoors and outdoors. However, since we adjusted for family socioeconomic status, it is likely to cover a major part of the potential influence of these missing covariates. However, a potential limitation of our study is that we could not adjust for other covariates such as maternal nutrition, parity, caffeine and drug consumption, mother's activity during pregnancy, and mother's BMI.

4.3. Synthesis with Previous Knowledge

Our results provide evidence that maternal exposure to carbon monoxide (CO) is associated with an increased risk of LBW in infants. The effect was stronger among babies who were born during the spring–summer season and in the presence of high exposure to O_3. These findings are consistent with the result from a study conducted by Maisonet et al. [11] in the US. They reported an adjusted OR of 1.31 (95% CI: 1.06–1.62) per 1 ppm increase in average exposure to CO during the 3rd trimester. A population-based retrospective study conducted in Brazil [41] also found an association between the fourth quartile exposure to CO during the entire pregnancy and the risk of LBW (1.33 95% CI: 0.93–1.90). In a systematic review and meta-analysis conducted by Stieb et al. [9], a statistically significant association between maternal exposure to CO and risk of LBW was reported with a summary OR of 1.07 (95% CI: 1.02–1.12) per 1 ppm. In a case-control study conducted in Peru [42], maternal exposure to CO was associated with low birth weight with an adjusted OR of 3.53 (95% CI 0.95–13.23) per ≥3.82 ppm increase in exposure.

Several epidemiological studies have investigated the association between ambient particulate matter and adverse pregnancy outcomes (including LBW); the results of these studies have been summarized in several meta-analyses. In Lamichhane et al. (2015) [43], birth weight measured as a continuous outcome was negatively associated with 10 $\mu g/m^3$ increase in PM_{10} (−10.31 g, 95% CI: −13.57 to −3.13 g) exposure during the whole pregnancy. Pedersen et al. [12] compiled data from 14 prospective birth cohorts involving 12 European countries (European Study of Cohorts for Air Pollution Effects (ESCAPE)). An increase of 5 $\mu g/m^3$ in prenatal exposure to $PM_{2.5}$ and PM_{10} was associated with an 18% (1.18; 95% CI: 1.06–1.33) and 16% (1.16; 95% CI: 1.00–1.35) increased risk of LBW, respectively. Even exposures to $PM_{2.5}$ concentrations below the minimum recommended level by the European Union were associated with an increased risk of LBW [12]. Our study showed a 9% (1.09; 95% CI: 0.79–1.50) and a 3% (1.03; 95% CI: 0.74–1.43) increase in the risk of LBW in the highest quartile of exposure to $PM_{2.5}$ and PM_{10} among babies born during the warm season. Our result is consistent with a meta-analysis including 14 original studies conducted by Sapkota et al. [14]. Their

result suggested a 9% increase in the risk (1.09; 95% CI: 0.90–1.32) related to a 10 μg/m^3 increase in $PM_{2.5}$ exposure and 2% increase in the risk (1.02; 95% CI: 0.99–1.05) related to a 10 μg/m^3 increase in PM_{10}.

We found no evidence of any effect related to exposure to NO_2. Our analyses showed an RR of 1.00 for LBW (95% CI: 0.78–1.28) in relation to NO_2 exposure after adjusting for potential confounders during the whole pregnancy. The Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health [44] reported a significant negative association between NO_2 and LBW. This result is consistent with our results and with the results from Stieb et al. [45].

We provided evidence that high exposure to O_3 increases the risk of LBW_{2500} in all babies and the risk of LBW_{3000} among the babies who were born in the warm season (March–August) but not among the babies who were born in the cold season. Our results are consistent with the findings by Chen et al. [46]. The Brisbane study with a study period of over 10 years found a similar effect in the single-pollutant model for ozone. They assessed the potential effects of air pollution on birth outcomes applying Cox's proportional hazards model that provides hazard ratios (HRs) and 95% confidence intervals (95% CI) associated with an interquartile range (IQR) increase in each pollutant.

We found that high levels of $PM_{2.5}$ and O_3 exposures during entire pregnancy increase the risk of LBW_{3000} synergistically showing an excess risk of 280% above an additive effect among babies born in the spring and summer seasons. This result is consistent with our previous study on air pollution and PTB [15] in which we found a 230% excess risk in PTB. According to our literature search, this study is the first one that estimates the joint effects of air pollutants on the risk of LBW.

4.4. Biological Plausibility

Studies that have accumulated over the recent years have shown that development and maintenance of good uteroplacental circulation in the pregnant mother is a major precondition for a healthy pregnancy outcome, as the latter is highly dependent on a well-working placenta. Healthy placenta can transfer enough oxygen and nutrients that are required for healthy fetal development and energy transfer from the maternal body to the fetus [47,48]. Developing fetuses are especially vulnerable to adverse effects of environmental pollutants because prenatal exposure to toxic and irritant pollutants can cause inflammation in the fetal lungs [49]. However, the mechanisms underlying many of the adverse effects on fetuses related to air pollutants remain so far unclear. NO_2 and SO_2 exposures are considered to have some toxic effects on the functional and developmental growth of exposed fetuses. The mechanisms underlying such an effect include stimulation of the formation of cell-damaging lipid peroxides and reduction of the maternal antioxidant reserves [50,51].

The effects that both particulate matter and carbon monoxide have on birth weight have been reported and explained by transfer of these pollutants from the mother to the lungs of the growing fetus via the placenta [52]. The amount of oxygen available in the placenta for the fetus will be compromised if an increased amount of CO reduces the oxygen-carrying capacity of maternal hemoglobin, which is responsible for delivering oxygen into the fetal circulation [53,54]. Maternal exposure to PM has been reported to cause oxidative stress in the mother, leading to pulmonary and placental inflammation, which alters blood coagulation factors, and this triggers hemodynamic responses. The latter, in turn, reduce birth weight through impaired transplacental oxygen and nutrient exchange [55]. PM can also cause oxidative inflammation in the lungs of the mother and placenta, and such inflammation may lead to reduction in the fetal growth [56].

Concerning inflammatory responses, particulate matter inhaled by the mother can induce a strong adverse reaction in the maternal body. It has been reported that $PM_{2.5}$—fine granulate PM—becomes enriched in the maternal blood stream when inhaled or ingested and moves through the placenta into the embryo, where it can seriously interfere with embryonic development. It can cause apoptosis and interfere with apoptotic pathways that are active during embryonic development [57]. In general, there are three different pathways. One is extrinsic and mediated through "death receptors", i.e., directed through influence outside of the cells and the tissues; the second one is intrinsic and

involves mitochondria; and the third one is intrinsic as well, based on cellular stressors that affect the endoplasmic reticulum (ER). Using primary fetal alveolar cells, Che et al. (2014) [58] demonstrated that exposure of these cells to fine particulate matter, contained in cooking oil fumes, can upregulate proapoptotic signaling mediators and can downregulate antiapoptotic ones. Specifically, the extrinsic death receptor pathway and the intrinsic mitochondrial pathways were activated [58]. In another study, cultured rat embryos experienced growth retardation when exposed to $PM_{2.5}$. The authors found both an activation of apoptotic pathways as well as cell cycle arrest between G0 and G1 phase and provided evidence that reactive oxygen species (ROS), JNK, and ERK signaling was also involved in these processes; this led not only to a shortening in the embryo's length and reduction of the yolk sac diameter but also to a reduction in the number of somites [59].

5. Conclusions

The present study provides new evidence that prenatal exposure to air pollutants in a cold climate increases the risk of LBW at relatively low levels of air pollution. Our results strengthen the evidence of independent effects of CO and O_3 exposures on the risk of LBW. Our study shows, for the first time, synergistic adverse effects of air pollutants on fetal growth. Our results also indicate the presence of season-specific effects. From the public health perspective, our findings of independent and synergistic adverse effects of low-level air pollution on low birth weight is alarming and underlines the need to reduce air pollution worldwide.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. The effect of air pollution exposure during entire pregnancy per 10 unit increase in concentration on low birth weight less than 3000 g (N = 2517), The Espoo Cohort Study, 1984–1990.

Single Pollutant Model	Low Birth Weight <3000 g		Born in Spring–Summer		Born in Autumn–Winter	
	Cr. RR (95% CI)	Adj. RR (95% CI)	Cr. RR (95% CI)	Adj. RR (95% CI)	Cr. RR (95% CI)	Adj. RR (95% CI)
$PM_{2.5}$ per 10 ug/m^3	0.92 (0.72–1.16)	0.91 (0.71–1.16)	0.95 (0.69–1.33)	0.95 (0.68–1.32)	0.86 (0.60–1.23)	0.86 (0.60–1.23)
PM_{10} per 10 ug/m^3	0.93 (0.75–1.14)	0.92 (0.74–1.14)	0.96 (0.71–1.28)	0.95 (0.71–1.28)	0.88 (0.65–1.21)	0.88 (0.64–1.21)
O_3 per 10 ppb	0.84 (0.58–1.24)	0.79 (0.51–1.25)	0.98 (0.53–1.80)	0.98 (0.53–1.80)	0.64 (0.34–1.22)	0.62 (0.33–1.19)
NO_2 per 10 ppb	0.89 (0.37–2.12)	0.91 (0.37–2.20)	0.87 (0.25–2.98)	0.89 (0.25–3.13)	0.90 (0.26–3.12)	0.91 (0.26–3.20)
CO per 10 ppb	1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.01 (0.98–1.04)	1.01 (0.98–1.04)	0.99 (0.96–1.02)	0.99 (0.96–1.02)
SO_2 per 10 ppb	0.94 (0.54–1.63)	0.94 (0.54–1.65)	0.90 (0.42–1.94)	0.90 (0.42–1.94)	0.98 (0.43–2.21)	0.98 (0.43–2.21)

Table A2. The effect of air pollution exposure during entire pregnancy by comparing the exposure levels below and above the median values on low birth weight less than 3000 g (N = 2517), The Espoo Cohort Study, 1984–1990.

Single and Multipollutant Models	Low Birth Weight <3000 g		Spring–Summer (Warm Season)		Autumn–Winter (Cold Season)	
	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	Crude RR (95% CI)	Adjusted RR (95% CI) [2]	Crude RR (95% CI)	Adjusted RR (95% CI) [2]
$PM_{2.5}(Q_3 \geq 19.5\ \mu g/m^3)$	0.99 (0.80–1.22)	0.98 (0.79–1.22)	1.09 (0.81–1.48)	1.12 (0.82–1.53)	0.88 (0.65–1.21)	0.87 (0.63–1.19)
$PM_{10}(Q_3 \geq 21.15\ \mu g/m^3)$	1.04 (0.84–1.29)	1.04 (0.84–1.29)	1.10 (0.81–1.49)	1.14 (0.83–1.55)	0.98 (0.72–1.34)	0.97 (0.71– 1.32)
NO_2 ($Q_3 \geq 4.41$ ppb)	0.94 (0.76–1.17)	0.96 (0.77–1.19)	0.95 (0.71–1.28)	0.98 (0.72–1.32)	0.93 (0.69–1.27)	0.94 (0.69–1.29)
CO ($Q_3 \geq 295.97$ ppb)	0.92 (0.75–1.14)	0.94 (0.76–1.17)	1.00 (0.74–1.35)	1.03 (0.76–1.39)	0.84 (0.62–1.15)	0.86 (0.63–1.17)
SO_2 ($Q_3 \geq 3.75$ ppb)	1.01 (0.81–1.25)	1.02 (0.82–1.26)	1.04 (0.77–1.41)	1.08 (0.80–1.47)	0.97 (0.71–1.32)	0.96 (0.71–1.32)
O_3 ($Q_3 \geq 23.93$ ppb)	0.91 (0.73–1.13)	0.89 (0.69–1.14)	1.07 (0.76–1.49)	1.08 (0.77–1.52)	0.74 (0.53–1.04)	0.73 (0.52–1.02)

Note: All estimates are from Poisson regression models. CI, confidence interval; CO, carbon monoxide; NO2, nitrogen dioxide; O3, ozone; PM2.5, particulate matter with a diameter up to 2.5 micrometers; PM10, particulate matter with a diameter up to 10 micrometers; ppb, parts per billion; RR, Risk Ratio; SO2, sulfur dioxide; and μg/m3, microgram per cubic meter. [1] Adjusted for season of birth and other confounders (including gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure of pregnant mother, and single parenthood); [2] adjusted for gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure, and single parenthood.

Table A3. The effects of air pollution exposure during entire pregnancy on low birth weight less than 2500 g (N = 2517), The Espoo Cohort Study, 1984–1990.

Single and Multipollutant Models	Low Birth Weight <2500 g		Spring–Summer (Warm Season)		Autumn–Winter (Cold Season)	
	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	Crude RR (95% CI)	Adjusted RR (95% CI)[2]	Crude RR (95% CI)	Adjusted RR (95% CI)[2]
$PM_{2.5}(Q_4 \geq 22.1\ \mu g/m^3)$ [3]	1.42 (0.91–2.21)	1.39 (0.88–2.20)	**2.31 (1.29–4.15)**	**2.31 (1.28–4.16)**	0.67 (0.28–1.57)	0.56 (0.22–1.43)
($PM_{2.5}$ + O_3)	**1.65 (1.04–2.61)**	1.56 (0.98–2.48)	**2.99 (1.62–5.53)**	**2.69 (1.46–4.95)**	0.69 (0.29–1.65)	0.59 (0.23–1.51)
($PM_{2.5}$ + SO_2)	1.09 (0.55–2.15)	1.05 (0.52–2.11)	**2.69 (1.06–6.83)**	2.45 (0.94–6.37)	0.41 (0.14–1.17)	0.34 (0.11–1.07)
$PM_{10}(Q_4 \geq 24.1\ \mu g/m^3)$ [3]	1.30 (0.83–2.04)	1.26 (0.79–2.00)	**2.05 (1.14–3.68)**	**2.00 (1.11–3.62)**	0.63 (0.27–1.49)	0.54 (0.21–1.37)
(PM_{10} + CO)	0.73 (0.39–1.35)	0.71 (0.38–1.32)	0.65 (0.29–1.46)	0.60 (0.26–1.35)	0.64 (0.23–1.81)	0.57 (0.19–1.72)
(PM_{10} + NO_2)	1.15 (0.57–, 2.31)	1.08 (0.52–2.25)	2.39 (0.88–6.48)	2.32 (0.82–6.60)	0.50 (0.17–1.51)	0.42 (0.13–1.35)
NO_2 ($Q_4 \geq 5.1$ ppb) [3]	1.31 (0.83–2.05)	1.30 (0.81–2.06)	1.69 (0.94–3.06)	1.69 (0.93–3.09)	0.92 (0.43–1.97)	0.85 (0.38–1.92)
(NO_2 + PM_{10})	1.18 (0.58–2.37)	1.22 (0.58–2.55)	0.83 (0.30–2.26)	0.83 (0.29–2.40)	1.40 (0.53–3.69)	1.46 (0.52–4.07)
(NO_2 + SO_2)	0.81 (0.38–1.73)	0.78 (0.35–1.73)	1.08 (0.37–3.14)	0.88 (0.27–2.83)	0.57 (0.18–1.76)	0.58 (0.18–1.87)
CO ($Q_4 \geq 329.7$ ppb) [3]	**1.80 (1.18–2.76)**	**1.81 (1.17–2.80)**	**3.40 (1.87–6.18)**	**3.53 (1.93–6.48)**	0.76 (0.34–1.69)	0.67 (0.28–1.59)
(CO + O_3)	**2.01 (1.30–3.10)**	**1.94 (1.25–3.03)**	**4.20 (2.28–7.76)**	**3.92 (2.11–7.30)**	0.78 (0.34–1.75)	0.69 (0.29–1.64)
(CO + PM_{10})	**2.23 (1.24–4.01)**	**2.27 (1.26–4.09)**	**4.64 (2.04–10.55)**	**5.16 (2.24–11.89)**	0.97 (0.37–2.56)	0.91 (0.33–2.56)
(CO + SO_2)	**1.90 (1.00–3.60)**	**1.88 (0.99–3.57)**	**6.10 (2.70–13.76)**	**5.93 (2.59–13.58)**	0.49 (0.18–1.37)	0.45 (0.16–1.33)
SO_2 ($Q_4 \geq 4.7$ ppb) [3]	1.52 (0.98–2.35)	1.51 (0.96–2.36)	**1.83 (1.02–3.29)**	**1.92 (1.06–3.49)**	1.22 (0.61–2.47)	1.12 (0.54–2.34)
(SO_2 + O_3)	**1.82 (1.15–2.89)**	**1.75 (1.10–2.80)**	**2.35 (1.27–4.36)**	**2.34 (1.26–4.35)**	1.33 (0.64–2.76)	1.23 (0.57–2.65)
(SO_2 + $PM_{2.5}$)	1.42 (0.73–2.79)	1.45 (0.73–2.90)	0.83 (0.32–2.11)	0.92 (0.35–2.42)	2.04 (0.86–4.84)	2.03 (0.83–4.93)
(SO_2 + CO)	0.93 (0.48–1.80)	0.94 (0.49–1.82)	0.46 (0.20–1.02)	0.50 (0.22–1.12)	1.89 (0.77–4.62)	1.78 (0.71–4.43)
(SO_2 + NO_2)	1.79 (0.86–3.74)	1.83 (0.85–3.95)	1.72 (0.59–4.98)	2.14 (0.67–6.85)	1.84 (0.65–5.20)	1.64 (0.57–4.70)

Table A3. *Cont.*

Single and Multipollutant Models	Low Birth Weight <2500 g		Spring–Summer (Warm Season)		Autumn–Winter (Cold Season)	
	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	Crude RR (95% CI)	Adjusted RR (95% CI)[2]	Crude RR (95% CI)	Adjusted RR (95% CI)[2]
O_3 ($Q_4 \geq 26$ ppb) [3]	**1.68 (1.09–2.59)**	**1.89 (1.14–3.14)**	**4.47 (2.21–9.02)**	**4.03 (1.96–8.28)**	**1.22 (0.68–2.18)**	1.24 (0.68–2.24)
(O_3 + $PM_{2.5}$)	**1.89 (1.21–2.96)**	**2.05 (1.22– 3.44)**	**6.24 (2.99–13.03)**	**4.95 (2.33–10.49)**	**1.16 (0.64–2.09)**	1.15 (0.63–2.10)
(O_3 + CO)	**1.90 (1.22–2.95)**	**2.05 (1.23–3.43)**	**6.36 (3.09–13.11)**	**4.82 (2.29–10.17)**	**1.19 (0.66–2.14)**	1.20 (0.66–2.18)
(O_3 + SO_2)	**1.97 (1.25–3.11)**	**2.16 (1.28–3.64)**	**5.78 (2.77–12.08)**	**4.99 (2.35–10.61)**	**1.29 (0.70–2.37)**	1.29 (0.69–2.41)

Note: All estimates are from Poisson regression models. 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 micrometers; PM_{10}, particulate matter with a diameter up to 10 micrometers; ppb, parts per billion; RR, Risk Ratio; SO_2, sulfur dioxide; and $\mu g/m^3$, microgram per cubic meter. [1] Adjusted for season of birth and other confounders (including gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure of pregnant mother, and single parenthood); [2] adjusted for gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure, and single parenthood.

Table A4. Joint effect of CO and O_3 and of $PM_{2.5}$ and O_3 during entire pregnancy on low birth weight less than 2500 g, The Espoo Cohort Study, 1984–1990.

CO Entire Pregnancy	O_3 Entire Pregnancy	n/N	% of LBW <2500 g	Crude RR (95% CI)	Adjusted RR (95% CI) [1]	ERR (95% CI) [1]	RERI (95% CI) [1]
Low (<Q_4)	Low (<Q_4)	37/1351	2.74	1	1		
High (>Q_4)	Low (<Q_4)	21/545	3.85	1.41 (0.83–2.38)	1.34 (0.80–2.26)	0.31 (−0.20–1.16)	
Low (<Q_4)	High (>Q_4)	19/532	3.57	1.30 (0.76–2.25)	1.41 (0.73–2.70)	0.41 (−0.27–1.70)	
High (>Q_4)	High (>Q_4)	13/89	14.61	**5.33 (2.94–9.66)**	**5.75 (2.87–11.54)**	**4.75 (1.87–10.54)**	**4.03 (1.61–9.28)**
$PM_{2.5}$ Entire Pregnancy	**O_3 Entire Pregnancy**						
Low (<Q_4)	Low (<Q_4)	38/1327	2.86	**1**	**1**		
High (>Q_4)	Low (<Q_4)	20/569	3.51	1.23 (0.72–2.09)	1.15 (0.68–1.95)	0.15 (−0.32–0.95)	
Low (<Q_4)	High (>Q_4)	23/559	4.11	1.44 (0.86–2.39)	1.56 (0.83–2.92)	0.56 (−0.17–1.92)	
High (>Q_4)	High (>Q_4)	9/62	14.52	**5.07 (2.57–10.01)**	**5.24 (2.53–10.87)**	**4.24 (1.53–9.87)**	**3.53 (1.19–8.70)**

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