Peer-reviewed version available at *Appl. Sci.* **2020**, *10*, 6399; doi:10.3390/app10186399

Article

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 and (adjusted RR 1.44, 95% CI: 1.04-2.00) and exposure to O3 in the spring-summer season (1.82, 1.11-2.96). There was also evidence of synergistic effects between CO and O3 (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 PM2.5 and O3 (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 in a cold climate on the risk of LBW at low levels of air pollution.

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 2500g [1]. LBW has been recognized to be 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].

Epidemiological studies in the recent years have reported that retarded fetal growth and LBW are related to several factors, including maternal nutrition, socio-economic environment, lifestyle, and several environmental exposures. 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 SO2 and CO during the second and third trimesters, respectively, increase the risk of low birth weight. 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]). Increase of 5 μg/m3 in prenatal exposure to PM2.5 and PM10 were associated with an 18% and 16% increased risk of LBW, respectively. Even exposure to PM2.5 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 28.1g per 20 ppb of NO2. In a recent original study from our team on the effect of air pollution on pre-term birth, we found an increased risk of PTB with maternal exposure to relatively low levels of air pollution. We also found synergic effects of PM2.5 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 as 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 by 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 climates with relatively low levels of air pollution. None of the previous studies have elaborated on interactions between different pollutants or potential seasonal differences in their effects on fetal growth.

To fill in 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 with specific air pollutants during the entire pregnancy, as well as to elaborate on potential season-specific effects. The high accuracy in both the assessments of exposure and health outcomes provided a unique framework for this study.

2. Materials and Methods

Study population

The source population included all the children of the city of Espoo, Finland, born between January 1, 1984 and March 31, 1990. Espoo is an urban–suburban municipality (population279,000), 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 2,568 children (response rate 80.3%) whose parents filled in the baseline questionnaire of the Espoo Cohort Study. [18-20].

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° x 0.1 ° for the Northern European domain [22]. This dataset was also used as a regional background by Kukkonen et al. [23] for the fine resolution modelling of the concentrations of fine particulate matter (PM2.5) 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 above-mentioned 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 Centre 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 (PM2.5), respirable particulate matter with a dry diameter up to 10 μm (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3).

Outcome of interest

The main outcome of interest was low birth weight, which was defined in the present study as infants weighing less than 3000 g at the time of delivery. We selected a higher than traditional cut point for low birth weight, 3000 g, to increase the number of cases from 30 to 218. This was justified, because it increased the statistical efficiency of our analyses and enabled testing the hypothesis about the effects of air pollution on fetal growth. 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 January 1, 1987.

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).

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 entire pregnancy on the risk of LBW. We compared the risk of LBW among babies with the highest quartile Q4 of exposure with the reference categories of exposure, i.e. those with exposure in the lower exposure quartiles (Q1-Q3). We fitted 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. The interaction was estimated on additive scale because it has public health relevance [37]. The statistical methods of 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 for example as: 1) high CO and low O3 (i.e. A), 2) low CO and high O3 (i.e. B), and 3) high CO and high O3 (i.e. AB), and these were compared to the reference category of 'low CO and low O3' 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 PM2.5 and O3. Estimates for the independent and joint effects were derived from the modified Poisson regression analysis by applying both crude and adjusted models [38]. We applied 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 factors. This can be expressed in terms of ERRs as follows:

RERI= ERR (AB) - ERR (A) - 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 independent and joint effects of other pollutant exposures and their combinations with O3 (i.e. between PM25 and O3; and between CO and O3) on the risk of LWB. For the joint-effects analyses, we chose those pollutants that were not strongly correlated with each other but showed highest increased effect estimate in the multipollutant models

To examine potential modifying effect by 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).

Analyses were carried out using PROC GENMOD procedure in SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA).

3. Results

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 low birth weight, 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 96.0% were not exposed to environmental tobacco smoke during pregnancy.

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

Characteristic	*n* (%)
Total	2568 (100.00)
Birth weight	
<3000g	218 (8.49)
Gender	
boy	1311 (51.05)
girl	1257 (48.95)
Maternal age at delivery (years)[1]	
<25	370 (14.41)
25-30	960 (37.38)
>30	1216 (47.35)
Family socioeconomic status[2,3]	
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	2204 (85.82)
Environmental tobacco smoke exposure of the pregnant mother	
yes	101 (3.93)
no	2467 (96.07)

1 the age of 22 persons was missing

2 (high vs low or medium parental education and occupation)

3 There are 12 missing data in this category

Exposure distribution

Table 2 presents the mean values and distributions of air pollutants in different seasons for the entire pregnancy. The mean concentrations of PM2.5, PM10, CO, NO2, O3 and SO2 during the entire pregnancy were 19.6 μg/m3, 21.4 μg/m3, 295.1 ppb, 4.3 ppb, 3.9 ppb and 23.8 ppb, respectively.

Table 2. Distributions of air pollution 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

Table 3 represents the correlations of the average concentration of air pollutants; in most cases, the correlation is positive, and the lowest Pearson correlation coefficient was found between CO and SO2. For O3, however, there was negative correlation between O3 and CO and SO2 and O3 with coefficient r = - 0.26151 and r = - 0.36899 respectively.

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

Pollutants	PM_{25}	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

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; SO_2, sulfur dioxide.

Table 4 shows the effects of average air pollution exposure during entire pregnancy on the risk of low birth weight. The risk of LBW was increased in relation to the highest quartile of CO in the two-pollutant model that adjusted for PM10 (adjusted RR 1.44; 95% CI 1.04-2.00). The effect estimates of CO show similar pattern among babies born during both spring/summer (aRR 1.61; 1.01-2.55) and autumn/winter (aRR 1.26; 0.78-2.03) when adjusting for PM10 and among babies born during spring/summer in the two-pollutant model that adjusted for O3 (crude RR 1.29, 1.17-3.13). Exposure to O3 was associated with increased risk of LBW among babies born during spring/summer in the single-pollutant model (RR 1.80; aRR 1.80, 1.10-2.94) and in the two-pollutant models adjusting for other pollutants (e.g. adjusting for CO: aRR 1.88, 1.15-3.09). The risk of LBW was also increased in relation to NO2 in the full model and among babies born during autumn/winter, although the lower 95% confidence interval (95% CI) was<1.00 (Table 4). The risk of LBW was not related to PM2.5, PM10 or SO2 exposures in any of the models.

Table 4. The effects of air pollution exposure during entire pregnancy on low birth weight (N=2,298), The Espoo Cohort Study, 1984-1990.

Single and multipollutant models	Low birth weight		Spring-Summer(Warm season)		Autumn-Winter (Cold season)	
	Crude RR (95% CI)	Adjusted RR (95%CI)[a]	Crude RR (95% CI)	Adjusted RR (95% CI)[b]	Crude RR (95% CI)	Adjusted RR (95% CI)[b]
$PM_{2.5}$(Q_4≥22.1μg/m^3)[c]	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_{10}(Q_4≥24.1μg/m^3)[c]	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 ≥ 10.3 ppb)[c]	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)
CO (Q_4 ≥ 406.5 ppb)[c]	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)

Single and multipollutant models	Low birth weight		Spring-Summer(Warm season)		Autumn-Winter (Cold season)	
	Crude RR (95% CI)	Adjusted RR (95%CI)[a]	Crude RR (95% CI)	Adjusted RR (95% CI) [b]	Crude RR (95% CI)	Adjusted RR (95% CI) [b]
SO_2 ($Q_4 \geq 13.3$ ppb)[c]	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)
O_3 ($Q_4 \geq 24.1$ ppb)[c]	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. 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; $\mu g/m^3$, microgram per cubic meter.

[a] 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)

[b] adjusted for gender, maternal age, family socioeconomic status, maternal smoking during pregnancy, environmental tobacco smoke exposure and single parenthood

[c] single pollutant model

The joint effects of air pollution exposure on the risk of low birth weight

Table 5 presents the joint effects between CO and O3, PM2.5 and O3 on the risk of LBW. The assessment of potential effects of simultaneous CO and O3 exposures shows that there is a synergistic effect on the risk of LBW: the joint effect of 'high CO and high O3' exposure on LBW showed 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 O3 at their high exposure levels, when compared to the risk that would have been expected by summing their independent effects. There was suggestive evidence of a synergistic effect of high PM2.5 and high O3 (RERI 0.72, 95% CI: -0.07-3.60), although the 95% CI included the null value (0).

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

		n/N	% of low birth weight	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	ERR (95% CI)[a]	RERI (95% CI)[a]
CO entire pregnancy	O_3 entire pregnancy						
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)**
PM2.5 entire pregnancy	O3 entire pregnancy						
Low (< Q_4)	Low (< Q_4)	17/1320	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 the 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; RR, Risk Ratio;.

[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

Table 6 shows the joint effects of the pollutants on LBW for spring-summer season. The joint effect of high PM2.5 and high O3 was substantially higher during the spring-summer season, an adjusted RR of 4.30 (95% CI: 0.66-10.16), than what would have been expected from their independent effects (1.1 for PM2.5 and 1.8 for O3). The relative risk due to interaction (RERI) was 2.80 (95% CI: 1.36-19.88). These observations should be taken cautiously; despite an increase in adjusted RR, the RR is not significant, apart from RERI. However, the risk based on RERI was statistically significant suggesting that PM2.5 and O3 enhance each other's effects. Interestingly, ozone - either alone or in

combination with the other pollutants - increased the risk for LBW only when the pregnancy takes place more or less during the cold season.

Table 6. Joint effect of CO and O_3, PM2.5 and O3 exposures during entire pregnancy on low birth weight for births in spring and summer (Stratified for season), The Espoo Cohort Study, 1984-1990

CO entire pregnancy	O_3 entire pregnancy	n/N	% of low birth weight	Adjusted RR (95% CI) a	*ERR (95% CI)* [a]	RERI (95% CI)[a]
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)**
PM2.5 entire pregnancy	O3 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)**

Note: All the 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; SO_2, sulfur dioxide.

[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

4. Discussion

Main findings

The results of the Espoo Cohort Study on prenatal air pollution exposures and low birth weight strengthened the evidence that maternal exposure to air pollutants during pregnancy increases the risk of LBW. These are the first findings in a cold climate with relatively low levels of air pollution. Babies with the highest exposure to CO had a 44% (95% CI: 4%-100%) increase in the risk of LBW, and among babies born during the warm season those with the highest exposure to O3 had a 82% increase (95% CI: 11%-196%).

None of the previous studies had elaborated on interactions between different pollutants or potential seasonal differences in their effects on fetal growth. Thus we present novel evidence of synergistic effects between the highest exposures to CO and O3 as well as to PM2.5 and O3. Presence of high average levels of both CO and O3 increased the LBW risk by 108% (27%-394%) more than expected from the independent effects. Corresponding risk increase for PM2.5 and O3 was 72% (95% CI: -7%-260%). The synergistic effects were even stronger among children born in spring-summer season.

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].

Misclassification of prenatal exposure to air pollution was minimized, as we were able to use maternal residential addresses throughout pregnancy period to get an excellent coverage for the exposure assessment. In addition, exposure assessment method used was independent of the outcome assessment, which reduced the likelihood of any major bias.

Both weight and gestational age of the infant, were relevant for the outcome assessment, were primarily based 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. The gestational age was estimated using the last menstrual cycle in combination with the findings in the ultrasound examination.

Our study has several strengths. First, we used the 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 Centre over the study period and applied this information in exposure assessment in the model. In addition, we were able to get mother's residential addresses during entire pregnancy rather than relying solely on the mother's address at the time of delivery. The measurement of 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 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, and ethnicity/race. However, since we adjusted for family socioeconomic status, it is likely to cover for a major part of these missing covariates.

Synthesis with previous knowledge

Our result provide evidence that maternal exposure to carbon monoxide (CO) is associated with an increased risk of LBW in infants. The effect was stronger among the babies born during spring-summer season and in the presence of high exposure to O3. This findings is consistent with the result from a study conducted by Maisonet et al [11] in the US, they found average concentration of a unit of CO (adjusted OR 1.31, 95% CI: 1.06-1.62) to increase the risk of LBW in the 3rd trimester. A population-based retrospective study conducted in Brazil [40] also found an association between CO and LWB during the entire pregnancy (1.33 95% CI: 0.93-1.90). In a systematic review and meta-analysis conducted by Stieb et al. [9], statistically significant association between maternal exposure to CO and risk of low birth weight was reported with a summary-OR of 1.07 (95% CI: 1.02-1.12). In a case-control study conducted in Peru [41], maternal exposure to CO was associated to low birth weight with an adjusted OR of 3.53 per ≥3.82 ppm increase (95% CI 0.95-13.23).

Several epidemiological studies have outlined 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) [42], birth weight as a continuous outcome was negatively associated with 10μg/m3 increase in PM10 (-10.31g, 95% CI: -13.57 to -3.13g) 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]). Increase of 5 μg/m3 in prenatal exposure to PM2.5 and PM10 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 PM2.5 concentrations below the minimum level recommended by the European Union were associated with an increased risk of LBW [12]. Our study reveals a 9% (1.09; 95% CI: 0.79–1.50) and 3% (1.03; 95% CI: 0.74–1.43) increased risk of LBW for prenatal exposure to PM2.5 and PM10 delivery

for babies born during the warm season. Our result is similar to a meta-analysis of 14 original studies conducted by Sapkota et al. [14], the result suggested an increased risk of 9% LBW (1.09; 95% CI: 0.90–1.32) LBW in association with PM2.5 exposure and 2% (1.02; 95% CI: 0.99–1.05) for PM10.

We found no evidence of the effects of exposure to NO2. From our analysis, RR of LBW for NO2 after adjusting for potential confounders during the whole pregnancy was 1.00 (95% CI: 0.78-1.28). The Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health [43] reported a significant association between NO2 and LWB. This result is also consistent with the study by Stieb et al. [44] which reported a similar finding. In a survey by Yorifuji et al. [45] in Japan using multilevel regression analyses to evaluate the relationship between air pollution and LBW, the odd ratio for NO2 was 1.71 (95% CI: 1.18-2.46).

We provide evidence that high exposure to O3 increases the risk of LBW among the babies born in warm season (March-August), but not among babies born in cold season. Our results are in line with the findings by Chen et al. [46]. The Brisbane study with study period of over 10 years also found a similar result in the single-pollutant model for ozone; they assessed the effects of air pollution on birth outcomes using Cox's proportional hazards model yielding hazard ratios (HRs) and 95% confidence intervals (95% CI) associated with an interquartile range (IQR) increase in each air pollutant.

We found that high levels of PM2.5 and O3 exposure during entire pregnancy increase the risk of LBW synergistically with an excess risk of 144% above the additive effect. This result is consistent with our previous study on air pollution and PTB [15] where a 152% excess risk was found in relation to PTB. To the best of our knowledge, ours is the first study to estimate the joint effect of air pollutants on the risk of low birth weight.

Biological plausibility

Studies that have accumulated over the recent years have shown that development and maintenance of uteroplacental circulation in the pregnant mother is a major precondition for a healthy pregnancy outcome, as the latter is highly dependent on the placenta. Healthy placenta can transfer enough oxygen and nutrients that are required for healthy fetal development and energy production from the maternal blood 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]. Although the mechanisms underlying many of the adverse effects related to the air pollutants remain so far unclear. The detailed mechanisms underlying this effect remain unknown. NO2 and SO2 exposures are considered to have some toxic effects on the functional and developmental growth of the exposed fetus. The mechanisms underlying this 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 the 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 is 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, which 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 the inflammatory responses, particulate matter inhaled by the mother can induce a strong adverse reaction in the maternal body. It has been reported that PM2.5 - 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. In general, there are three different of these 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, predicated on cellular stressors that affect the endoplasmic reticulum (ER). Using primary fetal alveolar cells, Che et al. (2014) [57] demonstrated that exposure of these cells to fine particulate matter, contained in cooking oil fumes, can upregulate pro-apoptotic signaling mediators and downregulate anti-apoptotic ones. Specifically, the extrinsic death receptor pathway and the intrinsic mitochondrial pathways were activated [57]. In another study, cultured rat embryos experienced growth retardation when exposed to PM2.5. The authors found both an activation of apoptotic pathways as well as cell cycle arrests between G0 and G1 phase, and provide evidence that reactive oxygen species (ROS), JNK and ERK signaling was involved in these processes; this led not only to a shortening in embryo length and reduction of the yolk sac diameter, but also to a reduction in the number of somites [58].

5. Conclusions

The present study provides new evidence of prenatal exposure to air pollutants in a cold climate on the risk of LBW at relatively low levels of air pollution. Our results strengthen the evidence of independent effects of CO and O3 exposures on the risk of LBW. Our study shows, for the first time, synergistic effects of air pollutants on fetal growth, which is in line with synergistic effects on the risk of preterm birth which we presented recently [15]. Our results also indicate presence of season-specific effects. From public health perspective, our finds of independent and synergistic effects of low-level air pollution is alarming and underlines the need to reduce air pollution worldwide.

Author Contribution: Hamudat Balogun: 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. **Nazeeba Siddika:** Conceptualization, Methodology, Formal analysis, 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, Writing – original draft, Supervision, Funding acquisition.

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

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

References

1. World Health Organization. (2004). *ICD-10 : International Statistical Classification of Diseases and Related Health Problems* : tenth revision, 2nd ed. World Health Organization, https://apps.who.int/iris/handle/10665/42980 (accessed on 21 June, 2020).

2. Barker, D.J. The fetal and infant origins of adult disease. *BMJ* **1990**, *301*, 1111, doi:10.1136/bmj.301.6761.1111.

3. WHO. *Global Nutrition Targets 2025: Low Birth Weight Policy Brief (WHO/NMH/NHD/14.5)*. Geneva: World Health Organization; 2014.

4. United Nations Children's Fund and World Health Organization, Low Birthweight: Country, regional and global estimates. UNICEF, New York, 2004.

5. European Perinatal Health Report. *The Health and Care of Pregnant Women and Babies in Europe in 2010*. http://www.europeristat.com/

6. Vieira, S.E. The health burden of pollution: the impact of prenatal exposure to air pollutants. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2015**, *10*, 1111-1121, doi:10.2147/COPD.S40214.

7. Zhu, X.; Liu, Y.; Chen, Y.; Yao, C.; Che, Z.; Cao, J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis. *Environ. Sci. Pollut. Res.* **2015**, *22*, 3383–3396, doi.org/10.1007/s11356-014-3458-7.

8. Dadvand, P.; Parker, J.; Bell, M.L.; Bonzini, M.; Brauer, M.; Darrow, L.A.; Gehring, U.; Glinianaia, S.V.; Gouveia, N.; Ha, E.H.; Leem, J.H.; van den Hooven, E.H.; Jalaludin, B.; Jesdale, B.M.; Lepeule, J.; Morello-Frosch, R.; Morgan, G.G.; Pesatori, A.C.; Pierik, F.H.; Pless-Mulloli, T.; Rich, D.Q.; Sathyanarayana, S.; Seo, J.; Slama, R.; Strickland, M.; Tamburic, L.; Wartenberg, D.; Nieuwenhuijsen, M.J.; Woodruff, T.J. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ. Health Perspect.* **2013**, *121*, 267-373, doi:10.1289/ehp.1205575.

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

10. Maisonet, M.; Correa, A.; Misra, D.; Jaakkola, J.J. A review of the literature on the effects of ambient air pollution on fetal growth. *Environ. Res.* **2004**, *95*, 106–115, doi.org/10.1016/j.envres.2004.01.001.

11. Maisonet, M.; Bush, T.J.; Correa, A.; Jaakkola, J.J. Relation between ambient air pollution and low birth weight in the Northeastern United States. *Environ. Health Perspect.* **2001**, *109*, 351–356, doi:10.1289/ehp.01109s3351.

12. Pedersen, M.; Giorgis-Allemand, L.; Bernard, C.; Aguilera, I.; Andersen, A.M.; Ballester, F.; Beelen, R.M.; Chatzi, L.; Cirach, M., Danileviciute, A.; Dedele, A.; Eijsden, M.V.; Estarlich, M.; Fernández-Somoano, A.; Fernández, M.F.; Forastiere, F.; Gehring, U.; Grazuleviciene, R.; Gruzieva, O.; Heude, B.; Hoek, G.; De Hoogh, K.; Van den Hooven, E.H.; Håberg, S.E.; Jaddoe, V.W.; Klümper, C.; Korek, M.; Krämer, U.; Lerchundi, A.; Lepeule, J.; Nafstad, P.; Nystad, W.; Patelarou, E.; Porta, D.; Postma, D.; Raaschou-Nielsen, O.; Rudnai, P.; Sunyer, J.; Stephanou, E.; Sørensen, M.; Thiering, E.; Tuffnell, D.; Varró, M.J; Vrijkotte, T.G; Wijga, A.; Wilhelm, M.; Wright, J.; Nieuwenhuijsen, M.J.; Pershagen, G.; Brunekreef, B.; Kogevinas, M.; Slama, R. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). *Lancet Respir. Med.* **2013**, *1*, 695–704, doi:10.1016/S2213-2600(13)70192-9.

13. Shah, P.S; Balkhair, T. Air pollution and birth outcomes: A systematic review. *Environ. Int.* **2011**, *37*, 498–516, doi:10.1016/j.envint.2010.10.009.

14. Sapkota, A.; Chelikowsky, A.P.; Nachman, K.E.; Cohen, A.J.; Ritz, B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Qual. Atmos. Health.* **2012**, *5*, 369-381, doi.org/10.1007/s11869-010-0106-3.

15. Siddika, N.; Rantala, A.K.; Antikainen, H.; Balogun, H.; Amegah, A.K.; Ryti, N.R.I.; Kukkonen, J.; Sofiev, M.; Jaakkola, M.S.; Jaakkola, J.J.K. Synergistic Effects of Prenatal Exposure to Fine Particulate Matter (PM 2.5) and Ozone (O 3) on the Risk of Preterm Birth: A Population-Based Cohort Study. *Environ. Res.* **2019**, *176*, 108549, doi:10.1016/j.envres.2019.108549.

16. Kukkonen, J.; Karl, M.; Keuken, M.P.; Van der Gon, H.A.C.; Denby, B.R.; Singh, V.; Douros, J.; Manders, A.; Samaras, Z.; Moussiopoulos, N.; Jonkers, S.; Aarnio, M.; Karppinen, A.; Kangas, L.; Lützenkirchen, S.; Petäjä, T.; Vouitsis, I.; Sokhi, R. Modelling the dispersion of particle numbers in five European cities. *Geosci. Model Dev.* **2016**, *9*, 451–478, doi.org/10.5194/gmd-9-451-2016.

17. Kukkonen, J.; López-Aparicio, S.; Segersson, D.; Geels, C.; Kangas, L.; Kauhaniemi, M.; Maragkidou, A.; Jensen, A.; Assmuth, T.; Karppinen, A.; Sofiev, M.; Hellen, H.; Riikonen, K.; Nikmo, J.; Kousa, A.; Niemi, J. V.; Karvosenoja, N.; Santos, G. S.; Sundvor, I.; Im, U.; Christensen, J. H.; Nielsen, O.-K.; Plejdrup, M. S.; Nøjgaard, J. K.; Omstedt, G.; Andersson, C.; Forsberg, B.; Brandt, J. The influence of residential wood combustion on the concentrations of PM2.5 in four Nordic cities, *Atmos. Chem. Phys*. **2020**, *20*, 4333–4365, https://doi.org/10.5194/acp-20-4333-2020.

18. Jaakkola, J.J.; Jaakkola, N.; Ruotsalainen, R. Home dampness and molds as determinants of respiratory symptoms and asthma in pre-school children. *J. Expo. Anal. Environ. Epidemiol.* **1993**, *3*, 129-42.

19. Jaakkola, J.J.; Hwang, B.F.; Jaakkola, N. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect.* **2005**, *113*, 357-361, doi:10.1289/ehp.7242

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

21. Sofiev, M.; Kouznetsov, R.; Prank, M.; Soares, J.; Vira, J.; Tarvainen, V. A long-term re-analysis of atmospheric composition and air quality. ITM 2016, **2018**, Springer Proceedings in Complexity, Springer, Cham.

22. Sofiev, M.; Vira, J.; Kouznetsov, R.; Prank, M.; Soares, J.; Genikhovich, E. Construction of the SILAM Eulerian atmospheric dispersion model based on the advection algorithm of Michael Galperin. *Geosci. Model Developm.* **2015**, *8*, 3497-3522. doi:10.5194/gmd-8-3497-2015.

23. Kukkonen, J.; Kangas, L.; Kauhaniemi, M.; Sofiev, M.; Aarnio, M.; Jaakkola, J.J.K.; Kousa, A.; Karppinen, A. Modelling of the urban concentra-tions 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.* **2018**, *18*, 8041–8064, doi.org/10.5194/acp-18-8041-2018.

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

25. Deal, S.B.; Bennett, A.C.; Rankin, K.M.; Collins, J.W. The relation of age to low birth weight rates among foreign-born black mothers: a population-based exploratory study. *Ethn. Dis.* **2014**, *24*, 413-417.

26. Khoshnood, B.; Wall, S.; Kwang-Sun, L. Risk of low birth weight associated with advanced maternal age among four ethnic groups in the United States. *Mat. Child Health J.* **2005**, *9*, 3-9, doi.org/10.1007/s10995-005-2446-4.

27. Roy, P.; Kumar, A.; Kaur, I.R.; Faridi, M.M. Gender differences in outcomes of low birth weight and preterm neonates: the male disadvantage. *J. Trop. Pediatr.* **2014**, *60*, 480-481, doi: 10.1093/tropej/fmu042.

28. Ghosh, R.; Rankin, J.; Pless-Mulloli, T.; Glinianaia, S. Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review. *Environ. Res.* **2007**, *105*, 400-408, doi.org/10.1016/j.envres.2007.03.009.

29. Madden, D. The relationship between low birth weight and socioeconomic status in Ireland. *J. Biosoc. Sci.* **2014**, *46*, 248-265, doi: 10.1017/S0021932013000187.

30. Martinson, M.L.; Reichman, N.E. Socioeconomic inequalities in low birth weight in the United States, the United Kingdom, Canada, and Australia. *Am. J. Public Health*, **2016**, *106*, 748-754, doi:10.2105/AJPH.2015.303007.

31. Ko, T.J.; Tsai, L.Y.; Chu, L.C.; Yeh, S.J.; Leung, C.; Chen, C.Y.; Chou, H.C.; Tsao, P.N.; Chen, P.C.; Hsieh, W.S. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr. Neonatol.* **2014**, *55*, 20-27, doi: 10.1016/j.pedneo.2013.05.005.

32. Sclowitz, I.K.; Santos, I.S.; Domingues, M.R.; Matijasevich, A.; Barros, A.J. Maternal smoking in successive pregnancies and recurrence of low birthweight: the 2004 Pelotas birth cohort study, Brazil. *Cad Saude Publica.* **2013**, *29*, 123-130, doi:10.1590/s0102-311x2013000100015.

33. Miyake, Y.; Tanaka, K.; Arakawa, M. Active and passive maternal smoking during pregnancy and birth outcomes: the Kyushu Okinawa maternal and child health study. *BMC Pregnancy Childbirth*, **2013**, *6*, 157, doi: 10.1186/1471-2393-13-157.

34. Ion, R.C.; Wills, A.K.; Bernal, A.L. Environmental tobacco smoke exposure in pregnancy is associated with earlier delivery and reduced birth weight. *Reprod. Sci.* **2015**, *22*, 1603-1611, doi: 10.1177/1933719115612135.

35. Mohd Zain, N.; Low, W.Y.; Othman, S. Impact of maternal marital status on birth outcomes among young Malaysian women: a prospective cohort study. *Asia Pac. J. Public Health*, **2015**, *27*, 335-347, doi: 10.1177/1010539514537678.

36. Sullivan, K.; Raley, R.K.; Hummer, R.A.; Schiefelbein, E. The potential contribution of marital-cohabitation status to racial, ethnic, and nativity differentials in birth outcomes in Texas. *Matern. Child Health J.* **2012**, *16*, 775-784, doi: 10.1007/s10995-011-0801-1.

37. Rothman, K.J.; Greenland, S.; Lash, T.L. *Modern Epidemiology*, third ed.; Library of Congress Cataloging-in-Publication Data: United States of America**, 2012**; pp71-83.

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

39. https://data.unicef.org/country/fin/ (accessed 22 June, **2020**).

40. Cândido da Silva, A.M.; Moi, G.P.; Mattos, I.E; Hacon Sde, S. Low birth weight at term and the presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study. *BMC Pregnancy Childbirth*, **2014**, *14*, 309, doi:10.1186/1471-2393-14-309.

41. Yucra, S.; Tapia, V.; Steenland, K.; Naeher, L.P.; Gonzales, G.F. Maternal exposure to biomass smoke and carbon monoxide in relation to adverse pregnancy outcome in two high altitude cities of Peru. *Environ. Res.* **2014**,*130*, 29-33, doi:10.1016/j.envres.2014.01.008.

42. Lamichhane, D.K.; Leem, J.H.; Lee, J.Y.; Kim, H.C. A meta-analysis of exposure to particulate matter and adverse birth outcomes. *Environ. Health Toxicol.* **2015**, *30*, e2015011, doi.org/10.5620/eht.e2015011.

43. Panasevich, S.; Håberg, S.E.; Aamodt, G.; London S.J.; Stigum, H.; Nystad, W.; Nafstad, P. Association between pregnancy exposure to air pollution and birth weight in selected areas of Norway. *Arch. Public Health.* **2016**, *74*, 26, doi:10.1186/s13690-016-0138-8.

44. Stieb, D.M.; Chen, L.; Hystad, P.; Beckerman, B.S.; Jerrett, M.; Tjepkema, M.; Crouse, D.L.; Omariba, D.W.; Peter, P.A.; Van Donkelaar, A.; Martin, R.V.; Burnett, R.T.; Liu, S.; Smith-Doiron, M.; Dungadzic, R.M. A national study of the association between traffic-related air pollution and adverse pregnancy outcomes in Canada, 1999-2008. *Environ. Res.* **2016**, *148*, 513-526, doi:10.1016/j.envres.2016.04.025

45. Yorifuji, T.; Kashima, S.; Doi, H. Outdoor air pollution and term low birth weight in Japan. *Environ. Int.* **2015**, *78*, 95-96, doi:10.1016/j.envint.2014.09.003

46. Chen, G.; Guo, Y.; Abramson, M.J.; Williams, G.; Li, S. Exposure to low concentrations of air pollutants and adverse birth outcomes in Brisbane, Australia, 2003-2013. *Sci. Total Environ.* **2018**, *622-623*, 721-726, doi:10.1016/j.scitotenv.2017.12.050.

47. Uvuz, F.; Kilic, S.; Yilmaz, N.; Tuncay, G.; Cakar, E.; Yuksal, B.; Bilge, U. Relationship between preterm labor and thrombophilic gene polymorphism: a prospective sequential cohort study. *Gynecol. Obstet. Invest.* **2009**, *68*, 234-238, doi:10.1159/000237743.

48. Wu, H.; Zhu, P.; Geng, X.; Liu, Z.; Cui, L.; Gao, Z.; Jiang, B.; Yang, L. Genetic polymorphism of MTHFR C677T with preterm birth and low birth weight susceptibility: a meta-analysis. *Arch. Gynecol. Obstet*., **2017**, *295*, 1105-1118, doi:10.1007/s00404-017-4322-z.

49. Perera, F.; Herbstman, J. Prenatal environmental exposures, epigenetics, and disease. *Reprod. Toxicol.* **2011**, *31*, 363-373, doi:10.1016/j.reprotox.2010.12.055

50. Maroziene, L.; Grazuleviciene, R. Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. *Environ. Health*, **2002**, *1*, 6, doi:10.1186/1476-069x-1-6.

51. Tabacova, S.; Baird, D.D.; Balabaeva, L. Exposure to oxidized nitrogen: lipid peroxidation and neonatal health risk. *Arch. Environ Health*, **1998**, *53*, 214–221, doi: 10.1080/00039899809605698.

52. Perera, F.P.; Jedrychowski, W.; Rauh, V.; Whyatt, R.M. Molecular epidemiologic research on the effect of environmental pollutants on the fetus. *Environ. Health Perspect.* **1999**, *107*, 451–460, doi:10.1289/ehp.99107s3451.

53. Salam, M.T.; Millstein, J.; Li, Y.F.; Lurmann, F.W.; Margolis, H.G.; Gilliland, F.D. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. *Environ. Health Perspect.* **2005**, *113*, 1638–1644, doi:10.1289/ehp.8111.

54. Di Cera, E.; Doyle, M.L.; Morgan, M.S.; De Cristofaro, R.; Landolfi, R.; Bizzi, B.; Castagnola, M.; Gill, S.J. Carbon monoxide and oxygen binding to human hemoglobin F0. *Biochem.* **1989**, *28*, 2631–2638, doi.org/10.1021/bi00432a041.

55. Kannan, S.; Misra, D.P.; Dvonch, J.T.; Krishnakumar, A. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. *Environ. Health Perspect.* **2006**, *114*, 1636–1642, doi:10.1289/ehp.9081.

56. Liu, S., Krewski, D., Shi, Y., Chen, Y., Burnett, R. T. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ. health perspect.* **2003**, *111*, 1773–1778, doi.org/10.1289/ehp.6251.

57. Che, Z.; Liu, Y.; Chen, Y.; Cao, J.; Liang, C.; Wang, L.; Ding, R. The apoptotic pathways effect of fine particulate from cooking oil fumes in primary fetal alveolar type II epithelial cells. *Mutat. Re.s Genet. Toxicol. Environ. Mutagen.* **2014**, *761*, 35-43, doi:10.1016/j.mrgentox.2014.01.004.

58. Yuan, X.; Wang, Y.; Li, L.; Zhou, W.; Tian, D.; Lu, C.; Yu, S.; Zhao, J.; Peng, S. PM 2.5 induces embryonic growth retardation: Potential involvement of ROS-MAPK s-apoptosis and G0/G1 arrest pathways. *Environ. toxicol.* **2015**, *31*, 2028-2044, https://doi.org/10.1002/tox.22203.