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Ambient air pollution and low birth weight - are some women more vulnerable than others?

Nadja Westergaard[a], Ulrike Gehring[b], Rémy Slama[c], Marie Pedersen[a,d,*]

[a] Centre for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[b] Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[c] INSERM/Centre National de la Recherche Scientifique (CNRS), Université Grenoble Alpes Joint Research Center, Grenoble, France
[d] Danish Cancer Society Research Center, Copenhagen, Denmark

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ABSTRACT

Background and objectives: Ambient air pollution is controllable, and it is one of the greatest environmental threats to human health. Studies conducted worldwide have provided evidence that maternal exposure to ambient air pollution during pregnancy enhances the risk of low birth weight at term (TLBW, < 2500 g among infants born ≥ 37 completed weeks of gestation), a maker of intrauterine growth restriction (IUGR), and suggest that some subgroups of pregnant women who are smoking, of low or high body-mass index (BMI), low socioeconomic status (SES) or asthma are more vulnerable towards the effect of ambient air pollution. The aim of this commentary is to review the published literature on the association between ambient air pollution and TLBW regarding increased vulnerability for the above-mentioned subgroups.

Results: Although more than fifty epidemiological studies have examined the associations between ambient air pollution and TLBW to date, we only identified six studies that examined the potential effect modification of the association between ambient air pollution and TLBW by the above listed maternal risk factors. Two studies assessed effect modification caused by smoking on the association between ambient air pollution and TLBW. The adjusted odds ratio (OR) for TLBW associated with exposure to ambient air pollution were in one study higher among women who smoked during pregnancy, as compared to the OR of non-smoking women, while in the other study the association was in the opposite direction. The association of ambient air pollution and TLBW were higher among women characterized by extreme BMI (two studies) and low SES compared to non-obese women or women of higher SES (four studies), respectively. Only one study reported the estimated effects among asthmatic and non-asthmatic women and no statistically significant effect modification was evident for the risk of TLBW associated with ambient air pollution.

Conclusion and recommendations: The current epidemiologic evidence is scarce, but suggests that pregnant women who are smoking, being underweight, overweight/obese or having lower SES are a vulnerable subpopulation when exposed to ambient air pollution, with and increased risk of having a child with TLBW. The limited evidence precludes for definitive conclusions and further studies are recommended.

1. Introduction

The health consequences associated with exposure to ambient air pollution are numerous, observed at all ages and in populations from all over the world, even in areas with relative low exposure levels (World Health Organization, 2016a). During the entire life course we are exposed, but exposure during vulnerable periods of exceptional high rates of development and growth, such as the first nine month of life are generally recognized as more critical than at later time periods (Bearer, 1995; Kim et al., 2016; Makri and Stilianakis, 2008; Rich et al., 2009). Prenatal exposure to ambient air pollution has been linked with a wide range of adverse birth outcomes although heterogeneity between studies exists (Dadvand et al., 2013; Hannam et al., 2014; Mendola et al., 2015; Pedersen et al., 2013a; Stieb et al., 2012; Tu et al., 2016). The evidence of an association between maternal exposure to ambient air pollution and term low birth weight (TLBW, < 2500 g among infants born ≥ 37 completed weeks of gestation) is rather consistent (Dadvand et al., 2013; Habermann and Gouveia, 2014; Lavigne et al., 2016; Pedersen et al., 2013a; Stieb et al., 2016). Another commonly used indicator of intrauterine growth restriction (IUGR), which has

* Corresponding author at: University of Copenhagen, Department of Public Health, Centre for Epidemiology and Screening, CSS, IFSV, CES Øster Farimagsgade 5, 1014 Copenhagen, Denmark.
E-mail address: mp@sund.ku.dk (M. Pedersen).

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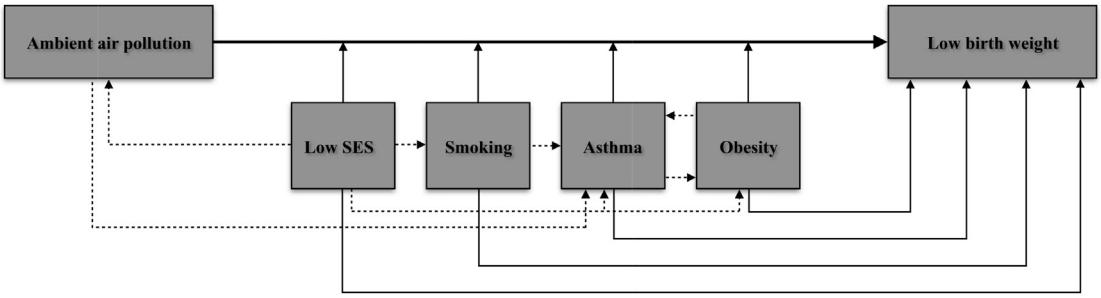

Fig. 1. Effect modifiers of the ambient air pollution - low birth weight relationships.

been associated with ambient air pollution, is small for gestational age (SGA, is often defined as < 10th percentile of the expected gestational age and sex-specific birth weight) (Chernausek, 2012; Gray et al., 2014; Maisonet et al., 2004; World Health Organization, 2012). Recently, ultrasound with Doppler has been used to identify IUGR prenatally and opened new opportunities for studies investigating the impact on early IUGR (Aguilera et al., 2010; Hansen et al., 2008; Iñiguez et al., 2016; Khalil and Thilaganathan, 2016; Malmqvist et al., 2017; Ritz et al., 2014; Roma et al., 2015; Slama et al., 2009; Smarr et al., 2015). Intrauterine growth is influenced by multiple additional factors, which could interact with exposure to ambient air pollution and each other (Valero De Bernab et al., 2004). More than 30 maternal characteristics such as lifestyle factors including overweight/obesity, underweight, diet, physical activity, drugs, alcohol, smoking, residence environment and socioeconomic status (SES) have been associated with an increased risk of TLBW (Valero De Bernab et al., 2004). Some of these risk factors can be hypothesized to modify the association between ambient air pollution and TLBW (Fig. 1). A better understanding of the interplay between known and potential, but yet unknown risk factors, are of importance for prevention of TLBW and development of ambient air quality guidelines. The objective of this commentary is to examine whether pregnant women who were smoking during pregnancy, of low or high body-mass index (BMI), having lower SES or asthma, are a vulnerable subpopulation, with a higher risk of having a child with TLBW, when exposed to ambient air pollution as compared to women, who are not characterized by these risk factors.

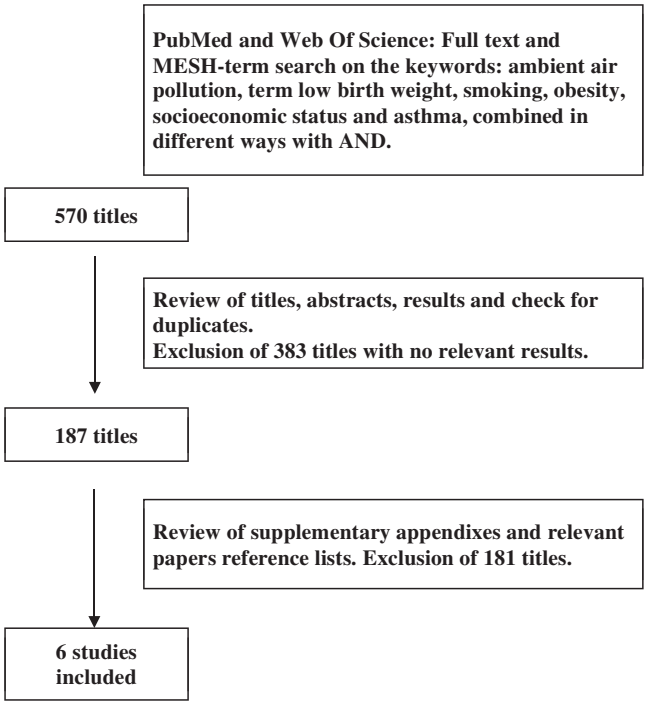

Fig. 2. Literature search and identification of included studies.

2. Materials and methods

Peer-reviewed epidemiological studies available in PubMed and Web Of Science by August 21st 2016 written in English reporting potential effect modification of the association between ambient air pollution and TLBW by a priori selected maternal characteristics (i.e. smoking, obesity, SES and asthma) were identified by carefully checking the full text, tables and results presented in supplemental tables. Keywords used for the literature search and the inclusion/exclusion process are described in (Fig. 2). We selected these maternal characteristics as they are relative common, modifiable and possible contributors to heighten vulnerability towards exposure of ambient air pollution.

3. Results

The characteristics of the six studies that we use as an illustration for this commentary are summarized in (Table 1). Most studies assessed particulate matter with aerodynamic diameter of < 2.5 μm ($PM_{2.5}$) and the results of mean exposure at full pregnancy and effect modification caused by smoking, pre-pregnancy BMI and low SES associated with TLBW are presented in (Table 2). Additional results for other pollutants are summarized in the supplementary appendix (Table S1).

Effect modification by smoking was examined in two studies with inconsistent results (Table 2). The adjusted odds ratio (OR) for TLBW associated with $PM_{2.5}$ was higher in smokers than in non-smokers (1.26 vs. 1.14), but the 95% confidence interval (CIs) was overlapping in an European study and the *P*-value for interaction was not statistical significant ($P = 0.31$) (Pedersen et al., 2013a). In a Japanese study, likewise the adjusted OR for TLBW associated with SO_2 was higher in smokers than non-smokers (2.64 vs. 1.55) (Table S1) while for suspended particulate matter (SPM) the adjusted OR was lower in smokers than in non-smokers (0.99 vs. 1.12) (Table 2) (Yorifuji et al., 2015). None of the interactions reached statistical significance.

Results concerning the effect modification by maternal obesity showed the same tendency in the two studies identified (Table 2). Laurent et al. (2014) found that obese women (BMI > 35 kg/m^2) had a higher OR for TLBW of 1.24 compared to the OR of 1.04 observed among normal weight women (BMI 20–24.9 kg/m^2) when exposed to $PM_{2.5}$. Pedersen et al. (2013a) likewise found that the OR for TLBW associated with exposure to $PM_{2.5}$ was higher in obese women (BMI > 30 kg/m^2) compared to normal weight women (BMI > 18.5– < 25 kg/m^2) (1.26 vs. 1.15, (Table 2)). However, underweight women (BMI < 18.5 kg/m^2) had an OR for the association of TLBW and $PM_{2.5}$ of 1.40 while the OR was 1.15 among women with normal pre-pregnancy weight (BMI 20–24.9 kg/m^2) and the *P*-value for interaction was 0.34 (Pedersen et al., 2013a). Studies evaluating exposure to NO_2 and O_3 also showed a marginally increased risk of TLBW for the obese mothers (BMI > 35 kg/m^2) as compared with those of normal weight (BMI 20–24.9 kg/m^2), in this study no risk of TLBW was found for women with underweight (BMI ≤ 19 kg/m^2) compared to normal

Table 1
Characteristics of the included studies.

Design	N	Time period	Exposure period and level	Location	Outcome	Exposure models	Pollutants	Effect modifiers evaluated	Covariates	Inclusion/exclusion criteria	Reference
Cohort study	960,945	January 1th 2001–December 31th 2008	Trimester, full pregnancy Mean exposure of $PM_{2.5}$: 17.41 μg/m^3 SD: 3.69	Los Angeles County (California, USA)	TLBW	Dispersion model for tracking PM, monitoring stations measuring data in 2000–2008 for NO_2, O_3. Traffic density: annual daily traffic count. Birth certificates were geocoded to maternal residence	NO_2, O_3, $PM_{2.5}$, $PM_{0.1}$	Diabetes, hypertension, maternal race/ethnicity, median block income, preeclampsia, pre-pregnancy BMI, SES (maternal educational level)	Age, GA, parity, sex, trimester primary care began[c]	Excluded: multiple births, birth defects, unknown birth defects status, missing information of GA, implausible combinations of BW and GA, infants born before 260 or after 308 estimated days of gestation	Laurent et al., 2014
Cohort study	818,400	January 1th 2005–Marts 31th 2012	Trimester, full pregnancy Mean exposure of $PM_{2.5}$: 9.07 μg/m^3 SD: 1.70	Ontario (Canada)	PTB, SGA, TLBW	$PM_{2.5}$ was assigned on satellite-derived estimates of single year (1998–2012). NO_2 was obtained from a LUR model (2005–2011). O_3 was assigned by postal codes based on a surface, were an interpolation technique made realistic estimates on O_3 in warm periods (2005–2009)	NO_2, O_3, $PM_{2.5}$	Asthma, diabetes, gestational diabetes, heart disease, hypertension maternal preeclampsia status	Age at delivery, cigarette smoking during pregnancy, month of birth, parity, post secondary education previous caesarean section delivery, SES, sex, visible minority, year of birth[c]	Included: women who had an address with a postal code, giving birth in hospitals, live born, non-planned C-section, singleton birth	Lavigne et al., 2016
Prospective cohort study	74,178	February 11th 1994–June 2th 2011	Trimester, full pregnancy Mean exposure of $PM_{2.5}$: 16.5 μg/m^3 SD: 3.85	Denmark, England, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Spain and Sweden	BHC, TBW, TLBW	LUR model for estimation of NO_2, NO_x, $PM_{2.5}$, $PM_{2.5}$ absorbance, $PM_{2.5-10}$, and PM_{10} plus traffic density and traffic load at the major road near residence address	NO_2, NOx, $PM_{2.5}$, $PM_{2.5}$ absorbance, $PM_{2.5-10}$ PM_{10}	Parity, SES (maternal education), Sex, Smoking[b]	Age, education level, GA, height and weight, parity, season of conception, sex, smoking[c]	Included: singleton pregnancies resulting in live born children with known BW, GA and sex to women living in the ESCAPE study areas. Excluded: women for whom > 25% of values for LUR estimates or daily monitoring of air pollution were missing for the whole pregnancy period and for each trimester	Pedersen et al., 2013a, 2013b
Cohort study	2,928,515	1999–2008	Full pregnancy Mean exposure of NO_2: 13.4 ppb SD:8.1	Canada	PTD, SGA, TBW, TLBW	LUR model for estimation of NO_2 across Canada accounting for background, regional and local spatial variation. LUR predictions of $PM_{2.5}$ combined with Bayesian Maximum Entropy interpolation	NO_2, $PM_{2.5}$	Smoking	Age, GA, marital status, maternal place of birth, neighborhood SES, parity, percent visible minority, season, sex, urban/rural residence, year of birth	Included: singleton births. Excluded: births with missing covariate data	Stieb et al., 2016
Cohort study	322,981	2003–2005	Trimester Mean exposure of $PM_{2.5}$ in	North Carolina (USA)	SGA, TLBW	$PM_{2.5}$ and O_3 concentrations were	O_3, $PM_{2.5}$	SES (Educational level)	Age, area, marital status, month	Excluded: non-singleton births, unknown	Vinikoor-Imler

(continued on next page)

Table 1 *(continued)*

Design	N	Time period	Exposure period and level	Location	Outcome	Exposure models	Pollutants	Effect modifiers evaluated	Covariates	Inclusion/exclusion criteria	Reference
			3. trimester: TLBW: 14.28 μg/m^3 SD: 3.00 SGA: 14.22 μg/m^3 SD: 3.01			obtained by a hierarchical Bayesian model of AP, combined data from air monitors with modeled AP estimates from EPA's CMAQ model. Birth records was geocoded to residence address			prenatal care began, parity, race and ethnicity, sex, smoking, urban-rural continuum codes[c]	GA, < 20 weeks, or > 45, GA implausible for birth weight, chromosomal anomalies, maternal age < 15 and > 50 years or unknown, residence at birth outside North Carolina or missing, addresses not geocodable	et al., 2014
Nationwide longitudinal study	44,109	10th and 17th of January or the 10th and 17th of July 2001–2015	Full pregnancy Mean exposure of SPM in April–December 2000: 32.4 μg/m^3 SD: 8.6, October 2000–June 2001: 29.6 μg/m^3 SD: 8.2	Japan (multiple locations)	TLBW	Air pollution data for NO_2, O_3, SO_2, SPM during the 9 month before birth were obtained from nearest general monitoring stations. CO measured by roadside stations	CO, NO_2, O_3, SO_2, SPM	Smoking	Age, educational level, GA, month of birth, parity, paternal income, residential area, sex, unemployed[a]	Included: children born after 37 gestational weeks and those who were singleton births	Yorifuji et al., 2015

Abbreviations used: AAP: Ambient air pollution; BHC: Birth head circumference; BW: Birth weight; CO: Carbon monoxide; GA: Gestational age; PTD: Preterm delivery; TLBW: Term low birth weight; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; O_3: Ozone; $PM_{0.1}$: Particulate matter with aerodynamic diameter of < 0.1 μm; $PM_{2.5}$: Particulate matter with aerodynamic diameter of < 2.5 μm; $PM_{2.5–10}$: Particulate matter with aerodynamic diameter of < 2.5–10 μm PM_{10}: Particulate matter with aerodynamic diameter of < 10 μm; PTB: Preterm birth; SD: Standard deviation; SES: Socioeconomic status; SGA: Small for gestational age; SO_2: Sulphur dioxide; SPM: Suspended particulate matter.

[a] Adjusted in individual characteristics: sex, gestational week, maternal age at delivery, maternal smoking status, maternal educational attainment, month of birth, parity, paternal income. Municipality-level: Residential area, proportion of unemployed workers over 15 years in each municipality, per capita tax income in each municipality.

[b] We calculated new results of the estimated effect of maternal pre-pregnancy BMI on the association between $PM_{2.5}$ and TLBW for the ESCAPE study population.

[c] Covariates refers to those kept in models.

Table 2
Effect modification caused by maternal smoking, BMI and socioeconomic status on the association of $PM_{2.5}$ and term low birth weight.

Characteristics	Group	N	n (cases)	Adjusted OR	95%CIs	Reference
Smoking (yes vs. no)	All	50,151	675	1.18	(1.06, 1.33)	Pedersen et al., 2013a, 2013b[a]
	Smoker	6237	180	1.26	(1.07, 1.48)	
	Non-smoker	43,914	495	1.14	(1.02, 1.28)	
	All	44,109	2219	1.07	(0.99, 1.15)	Yorifuji et al., 2015[b]
	Smoker	7647	476	0.99	(0.82, 1.21)	
	Non-smoker	36,204	1726	1.12	(1.01, 1.24)	
BMI (kg/m^2)	All	938,629	29,479	1.02	(1.01, 1.03)	Laurent et al., 2014[c]
	≤ 19	24,304	843	0.87	(0.77, 0.99)	
	20–24.9	84,131	1943	1.04	(0.97, 1.12)	
	25–29.9	52,278	1051	1.02	(0.93, 1.11)	
	30–34.9	23,780	423	1.14	(0.99, 1.31)	
	> 35	14,074	272	1.24	(1.04, 1.47)	
	All	50,151	675	1.18	(1.06, 1.33)	Pedersen et al., 2013a, 2013b[a]
	< 18.5	2348	71	1.40	(0.99, 1.99)	
	> 18.5– < 25	36,000	479	1.15	(1.01, 1.30)	
	> 25– < 30	8726	85	1.31	(1.00, 1.71)	
	> 30	3077	40	1.26	(0.84, 1.89)	
SES (Education)	All	938,629	29,479	1.02	(1.01, 1.03)	Laurent et al., 2014[c]
	< 8 grade	115,793	2802	1.06	(1.03, 1.09)	
	9th. - HS	450,535	11,488	1.02	(1.01, 1.04)	
	College	372,301	15,189	1.01	(0.99, 1.02)	
	All	50,151	675	1.18	(1.06, 1.33)	Pedersen et al., 2013a, 2013b[a]
	Low	6967	144	1.25	(1.03, 1.28)	
	Middle	20,442	284	1.23	(1.10, 1.39)	
	High	22,742	247	1.10	(0.94, 1.28)	
	All	297,043	6398	1.01	(0.97, 1.06)	Vinikoor-Imler et al., 2014[d]
	< HS	65,261	2015	1.02	(0.97, 1.07)	
	> HS	146,562	4361	1.02	(0.95, 1.10)	

Abbreviation used: CIs: Confidence intervals; HS: High school; $PM_{2.5}$: particulate matter with aerodynamic diameter of < 2.5 μm; SES: Socioeconomic status.

[a] Effect estimates correspond to a 10-$\mu g/m^3$ increment of full pregnancy mean exposure to $PM_{2.5}$. We calculated new results of the estimated effect of maternal pre-pregnancy BMI on the association between $PM_{2.5}$ and TLBW for the ESCAPE study population. The *P*-value for interaction (Wald's test) for smoking was 0.31, the one for BMI was 0.34 and the *P*-value for SES was 0.41.

[b] Data represent suspended particulate matter (SPM); effect estimates correspond to a 11 $\mu g/m^3$ increment of full pregnancy mean exposure to SPM; *P*-value for interaction was 0.13.

[c] Effect estimates correspond to a 5.82 $\mu g/m^3$ for full pregnancy mean exposure to $PM_{2.5}$. No *P*-value for interaction was available.

[d] Effect estimates correspond to a 3.5 $\mu g/m^3$ increment pr. interquartile range exposure to $PM_{2.5;}$ No *P*-value for interaction was available. Results are presented as risk ratios. No data for TLBW at full pregnancy was available we selected data for 3. Trimester because of the intensive growth of the fetus in this period.

weight women (BMI 20–24.9 kg/m^2) (Laurent et al., 2014) (Table 2 and Table S1).

Four studies reported results of effect modification analyses of SES on the association between ambient air pollution and TLBW (Table 2 and Table S1). In two out of three studies women with low education had higher OR for TLBW associated with exposure to ambient air pollution with $PM_{2.5}$ compared with the OR for women with high education (Laurent et al., 2014; Pedersen et al., 2013a), but the differences were small. Stieb et al. (2016) presented the effect of NO_2 between women with high and low income and found the highest ORs for TLBW among the women characterized by low income (0.98 vs. 1.04), ($P = 0.0509$) (Table S1). Vinikoor-Imler et al. (2014) found no difference for $PM_{2.5}$ between women of low versus high education (Table 2), but in terms of exposure to O_3, women with low educational level had lower OR than women with high education (1.96 vs. 2.20) (Table S1).

To the best of our knowledge only one study to date has reported the effect modification of maternal asthma on the association between exposure to ambient air pollution and TLBW and no differences were found (Lavigne et al., 2016) (Table S1).

4. Discussion

There is suggestive epidemiological evidence of a potential effect modification by maternal smoking, low and high BMI and low SES, but the reported evidence is sparse, inconsistent and the subgroup analyses are limited in their size. As far as we are aware only one study at to date has examined effect modification by maternal asthma, and no difference between women with or without asthma was observed. Publication bias is likely to be important as effect modification analyses are most commonly not part of the main analysis and may be limited by study size.

The biological mechanisms underlying the association between ambient air pollution and TLBW are not entirely understood. Ambient air pollutants may trigger systemic, pulmonary and placental inflammation, oxidative stress, endothelial and cardiovascular changes (Kannan et al., 2006; Shah and Balkhair, 2011; Vadillo-Ortega et al., 2014), which may result in pregnancy-induced hypertensive disorders (Pedersen et al., 2016, 2014), decreased trans-placental nutrient and gas exchange and thereby restrict the intrauterine growth of the placenta and the fetus (Arroyo et al., 2016; Backes et al., 2013; Dadvand et al., 2013; Hannam et al., 2014; Kannan et al., 2006; Malmqvist et al., 2017; Mendola et al., 2015; Pedersen et al., 2013a; Rich et al., 2009; Stieb et al., 2012; Tu et al., 2016; Veras et al., 2008).

Pregnancy involves multiple physiological and behavioral adaptions that can results in higher exposure to ambient air pollution such as inhalation of more air and certain time-activity changes (Adam et al., 2016; Arroyo et al., 2016; Choi and Perera, 2012; Kannan et al., 2006; Vaughan and Fowden, 2016). The pregnant women and her unborn child are considered to be more vulnerable towards exposure to ambient air pollution due to pregnancy-related physiological adaptions and the intense prenatal growth and development (Arroyo et al., 2016; Backes et al., 2013; Shah and Balkhair, 2011; Wang et al., 2016). The lower maternal immune system defense, the higher blood-volume, heart rate and nutritional requirements of the co-existence of the child among other increases the maternal sensitivity to oxidative stress, inflammation and exposures that interfere with the immune, cardiovascular and respiratory system thus heightens the vulnerability to exposure of ambient air pollution (Backes et al., 2013; Casanueva and Viteri, 2003; Kannan et al., 2006; Lakshmanan et al., 2015; Risom et al.,

2005; Vadillo-Ortega et al., 2014; Vaughan and Fowden, 2016; Wang et al., 2016). The pregnancy-related increased vulnerability to ambient air pollution exposure might be exacerbated by other maternal risk factors modifying the defense system and/or contributing to oxidative stress, inflammation and toxicity of the immune, cardio-vascular and respiratory system. A number of factors contributing to vulnerability towards exposure to air pollution in the general population have been identified and reviewed for example by Makri and Stilianakis (2008) and Sacks et al. (2011).

Tobacco smoking is similar in many ways to ambient air pollution. It causes several of the same biological responses and has been associated with similar adverse human health effects, including TLBW (Aycicek and Ipek, 2008; Valero De Bernab et al., 2004). Pedersen et al. (2013a) found that the population attributable risk (PAR) of TLBW associated with exposure to ambient air pollution exposure were similar in size to the PAR associated with maternal smoking during pregnancy, because only 12% of women were actively smoking during pregnancy and 91% were exposed to air pollution levels of $PM_{2.5}$ higher than the WHO guideline levels of 10 $\mu g/m^3$. Inhalable, ultrafine particles and toxic chemical compounds are present in tobacco smoke at higher doses than in the ambient air pollution and for instance nicotine can cause vasoconstriction that may affect the placental perfusion and potentially exacerbate the effect of ambient air pollution and increase the risk of TLBW (Aycicek and Ipek, 2008; Backes et al., 2013; Hayes et al., 2016; Valero De Bernab et al., 2004). It is therefore plausible that active smoking could act synergistically with the exposure to ambient air pollution and increase the risk of TLBW as indicated in the European study (Pedersen et al., 2013a), as well as the exposure of SO_2 indicated in the Japanese study (Yorifuji et al., 2015). On the other hand active smoking can result in higher metabolism and nonsmokers may in that perspective be more sensitive to exposure of ambient air pollution than smokers, which could explain the findings of lower risk in smokers observed in the Japanese study (Yorifuji et al., 2015). Differences in European and Japanese culture and the study designs used may contribute to the differential findings. The European study relied on a more accurate exposure assessment and extensive control of potential confounders such as individual BMI and SES than the Japanese study. Self-reported smoking habits, which can be bias, was used in both studies, but information on smoking habits from early pregnancy was used in the European study while the Japanese study used smoking status after birth as a proxy for smoking status during pregnancy, which may have resulted in misclassification. Finally, residual confounding by smoking quantity and unmeasured smoking-related habits cannot be ruled out.

Overweight and obesity was a potential effect modifier in two studies (Laurent et al., 2014; Pedersen et al., 2013a) and suggestive evidence of a higher risk was likewise observed for underweight women (Pedersen et al., 2013a). These findings are of importance, since prevalence of obesity is growing in the population of women in the fertile age (Knight-Agarwal et al., 2016; Lakshmanan et al., 2015; Scott-Pillai et al., 2013). Obesity is a worldwide epidemic with estimates of 600 million obese and 1,9 billion overweight adults in 2014 (World Health Organization, 2016b). The obesity problem has long persisted in high-income countries, but the prevalence is now increasing in low- and middle-income countries, especially in urban areas (World Health Organization, 2016b). Overweight and obesity may be more prevalent in low SES women and among women living in areas with high ambient air pollution, but urbanization may cause a more equitable distribution of exposure to people in all socioeconomic positions, but individual differences depending on countries has been described (Généreux et al., 2008; Gray et al., 2014; O'Neill et al., 2003; Panasevich et al., 2016). Underweight could reflect unhealthy lifestyle such as low or unhealthy intake of food or morbidity, which could contribute to the suggestive higher risk observed in one of the studies that included this subgroup (Pedersen et al., 2013a).

High maternal BMI is associated with both restricted and excessive fetal growth (Ahmad and Iman, 2016; McDonald et al., 2010). Maternal obesity further enlarges the risk of developing pregnancy-related complications as gestational diabetes mellitus, hypertension and pre-eclampsia (Ahmad and Iman, 2016; Carlson et al., 2015), all individual risk factors for TLBW and related to increased inflammatory levels, with potential to modify the relations between exposure to ambient air pollution and TLBW (Ahmad and Iman, 2016; Dubowsky et al., 2006; Lakshmanan et al., 2015; Rodríguez-Hernández et al., 2013). Obesity entails an increased amount of adipose tissue in the body, which has endocrine functions, and produces adipokines. Adipokines increases the blood levels of tumor necrosis factor-alpha, interleukin-6, resistin, plasminogen activator inhibitor, leptin and reduces the levels of adiponectin, which might affect the angiogenesis, appetite, blood pressure, insulin sensitivity, immunity, lipid metabolism and hemostasis (Ahmad and Iman, 2016; Rodríguez-Hernández et al., 2013). Obese pregnant women have higher levels of free fatty acids and triglyceride, than pregnant women with normal weight, leading to an increased amount of reactive oxygen species causing cell damage, and a chronic low-grade inflammation in the body (Carlson et al., 2015). The consistent low-grade inflammation may result in increased amounts of white blood cells and systematic inflammatory markers when exposed to ambient air pollution (Lakshmanan et al., 2015). The obese mothers vulnerability to ambient air pollution, might be explained by the presumption of both obesity and ambient air pollution having inflammatory effects, which acts synergistically on the pregnant body (Lakshmanan et al., 2015).

Concerning SES three out of four studies conducted in different parts of the world consistently reported that women of low SES had a somehow higher risk of TLBW associated with ambient air pollution than women of higher SES. Panasevich et al. (2016) found a decrease in birth weight for highly educated women, and a birth weight decrease in cities compared to rural areas in a Norwegian study. This may reflect that families with more than one child more often move from the city to suburban and rural areas and that women with lower education tend to get more children than those of higher education. Similar, highly educated women residing in wealthier and more polluted areas, where found to be significantly more exposed to ambient air pollution in the city of São Paulo, Brazil (Habermann and Gouveia, 2014). Erickson et al. (2016) showed a positive association with high education and birth weight and a negative association with birth weight and rural settlement when exposed to $PM_{2.5}$. The heterogeneous results might be explained by more well-educated mothers having a longer commute time and have more activities in central and more polluted parts of the cities (Panasevich et al., 2016). Differences in the criteria for stratifying on SES in the individual studies (Table 2) as discussed in studies on air pollution and asthma could have contributed to the heterogeneity in the results (O'Lenick et al., 2016).

Only one study addressed maternal asthma and it reported no effect modification of exposure to ambient air pollution on TLBW and the tendency was consistent to all pollutants assessed (Lavigne et al., 2016) (Table S1)). In the same study from Ontario, Canada Lavigne et al. (2016) found that maternal asthma modified the association between O_3 and preterm birth (born before 37 completed weeks of gestation) with a 12% increased odds in the asthmatics compared to non-asthmatics who had only a 2% increased odds associated with O_3. In a Swedish study Olsson et al. (2013) likewise found that asthmatic women had an increased risk of preterm delivery when exposed to O_3 as compared to the non-asthmatics. Stronger associations between ambient air pollution and preeclampsia have been reported in asthmatic women (Mendola et al., 2016). Asthma is a condition characterized by chronic inflammation (Rodríguez-Hernández et al., 2013) and maternal asthma increases the risk of TLBW and preeclampsia (Mendola et al., 2016, 2013; Murphy et al., 2006). Asthma treatment depends on the difficulty of symptoms, which often consists of a combination of anti-inflammatory medication such as corticosteroids and beta-2 agonists (Lange, 2015; Lange et al., 2016). Studies have found that pregnant

asthmatic women have low or missing compliance in relations to medical treatment, which complicates investigations of the relations of asthma medication and adverse birth outcomes (Bakhireva et al., 2008; Enriquez et al., 2006; Murphy and Schatz, 2014). Future investigations of effect modification by maternal asthma need to address the use of asthma medications and the severity of the asthma conditions.

The study from Ontario, Canada reported potential effect modification by other maternal co-morbidities including hypertension, heart disease, diabetes, preeclampsia and gestational diabetes mellitus. Especially, the associations between exposure to NO_2 and preterm birth were found to be stronger in women who suffered by these conditions (Lavigne et al., 2016).

Smoking, BMI, SES and asthma may interact not only with the ambient air pollution-TLBW dose-response relationship, but also with each other as illustrated in Fig. 1. Smoking and obesity are established risk factors for asthma (Leiria et al., 2015; Pinedo et al., 2009; Siroux et al., 2000; Stapleton et al., 2011; Sutherland et al., 2008). Severe asthmatic women may have difficulties during physical activity and thereby higher risk of overweight and obesity. Obesity decreases the lung function and increases the airway resistance which enlarges the need for anti-inflammatory treatment (Gruchała-Niedoszytko et al., 2013; Leiria et al., 2015; Sutherland et al., 2008). Obesity and smoking may be related as both characteristics are more prevalent among lower SES (Beauchamp et al., 2014; Monteiro, 2004). Multiple potential explanations have been proposed such as lack of understanding of the harmful effects of smoking, increased exposure to stress and lack of motivation to quit (Hiscock et al., 2012; O'Lenick et al., 2016).

Since road traffic is the main source of both ambient air pollution and noise, mutual confounding could be of concern (Tétreault et al., 2013). Gehring et al. (2014) has reported statistically significant effects of both air pollution and noise on birth weight in a study from Canada while Dadvand et al. (2014) found that noise had no effect on birth weight in a study from Spain and this was also supported by a Danish study (Hjortebjerg et al., 2016). Exposure to road traffic noise has been associated with higher BMI in adults (Christensen et al., 2016; Oftedal et al., 2015). Noise is a stressor and may alter homeostasis with both neural activation and disturbed sleep, that may cause endocrine changes with increased cortisol levels and higher levels of the appetite hormone ghrelin and lower levels of leptin, which increases appetite and the accumulation of fat in visceral tissues.

This commentary is not a complete review of all potential effect modifiers, the four characteristics we focused on in this case are common, modifiable and biological plausible contributors to heighten vulnerability towards exposure of ambient air pollution, and they are in this commentary used as an illustration to stress the need of further research. We believe it is likely that several additional factors could interact with the ambient air pollution-TLBW relationship for example characteristics related to the maternal residence such as the degree and quality of the surrounding greenness (Hystad et al., 2014), population density and other characteristics of the built environment (e.g. neighborhood walkability, distance to nearest park and distance to nearest road) (Hystad et al., 2014; Laurent et al., 2013), temperature and other meteorological factors (Arroyo et al., 2016; Dadvand et al., 2014; Pereira et al., 2012), as well as area-specific SES (Dadvand et al., 2012). Depending on the study area, the physical environmental and socioeconomic factors may be highly correlated with each other and the level of ambient air pollution at the residential level, which can complicate studies of their independent and joint effects (Dunton et al., 2009). In certain heterogenic areas, individual characteristics such as ethical/race (Stieb et al., 2016), genes (Gray et al., 2014), maternal morbidity (e.g. metabolic, autoimmune and cardiovascular diseases), lifestyle factors (e.g. poor diet (Kannan et al., 2006; Pedersen et al., 2013b) and sleep and certain time-activity patterns, stress/traumatic life events) as well as co-exposure to air pollutants occurring inside the residence or elsewhere during work/study and commute may or may modify the association between exposure to ambient air pollution and TLBW. Finally interactions between ambient air pollutants from different sources are often not well studied. Our understanding of how these multiple factors interact with each other and how they may potentially modify the ambient air pollution-TLBW association is very limited and deserves further investigations.

5. Conclusion

The current epidemiologic evidence is scarce, but suggests that pregnant women who are smoking, being underweight, overweight/obese or having lower SES are a vulnerable subpopulation when exposed to ambient air pollution, with and increased risk of having a child with TLBW. The limited evidence precludes for definitive conclusions and further studies are recommended.

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