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Combined effects of ambient air pollution and home environmental factors on low birth weight

Chan Lu [a, b], Weishe Zhang [b, c], Xiangrong Zheng [d], Jingchi Sun [c], Lv Chen [a], Qihong Deng [a, b, e, *]

[a] XiangYa School of Public Health, Central South University, Changsha, China
[b] Hunan Engineering Research Center of Early Life Development and Disease Prevention, XiangYa Hospital, Central South University, Changsha, China
[c] Department of Obstetrics, XiangYa Hospital, Central South University, Changsha, China
[d] Department of Pediatrics, XiangYa Hospital, Central South University, Changsha, China
[e] School of Architecture and Art, Central South University, Changsha, China

HIGHLIGHTS

- Air pollution was associated with term low birth weight (LBW) but not with preterm LBW.
- We found term LBW was associated with prenatal exposure to ambient inhalable particle (PM_{10}).
- Term LBW was also related with parental smoking at home during pregnancy.
- Exposure to combined outdoor and indoor air pollution posed the highest risk of term LBW.
- Early pregnancy was identified as the most critical time window for exposure susceptibility.

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ABSTRACT

Background: Low birth weight (LBW) remains a major public health problem worldwide, yet its crucial environmental risk factors are still unclear.
Objective: To examine the association between LBW (term and preterm LBW) and prenatal exposure to ambient air pollution and home environmental factors as well as their combination, in order to identify critical time window for exposure and key outdoor and indoor factors in LBW development.
Methods: A cohort study of 3509 preschool children was performed in Changsha, China during the period 2011–2012. A questionnaire was conducted to survey each child's birth outcome and each mother's exposure to home environmental factors including parental smoking, new furniture, redecoration, mold/damp stains, window pane condensation, and household pets during pregnancy. Maternal exposure to inhalable particulate matter (PM_{10}), industrial air pollutant (SO_2), and traffic air pollutant (NO_2) was estimated during different time windows of gestation, including conception month, three trimesters, birth month, and whole gestation. Associations of term and preterm LBW with ambient air pollutants and home environmental factors were assessed by multiple logistic regression models in terms of odds ratio (OR) with 95% confidence interval (CI).
Results: Term LBW (TLBW) was significantly associated with exposure to ambient PM_{10} during pregnancy, with OR (95% CI) = 1.47 (1.00–2.14) for per IQR increase after adjustment for the covariates and home environmental factors. Specifically, we identified the significant association in early phase of pregnancy including conception month (1.90, 1.09–3.30) and the first trimester (1.72, 1.10–2.69). We further found that TLBW was significantly related with parental smoking at home, OR (95% CI) = 2.17 (1.09–4.33). However, no association was observed for preterm LBW (PLBW). The TLBW risk of ambient air pollution and home environmental factors was independent each other and hence the combined exposure to ambient PM_{10} and indoor parental smoking caused the highest risk. Sensitivity analysis suggested that foetus with younger mothers were significantly more susceptible to risk of indoor parental smoking, while those with smaller house and cockroaches were more sensitive to risk of outdoor PM_{10} exposure.

* Corresponding author. XiangYa School of Public Health, Central South University, Changsha, China.
E-mail addresses: chanlu@csu.edu.cn (C. Lu), qhdeng@csu.edu.cn (Q. Deng).

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Conclusion: Prenatal exposure to combined outdoor and indoor air pollution, particularly in critical window(s) during early pregnancy, significantly increases the risk of term LBW.

1. Introduction

Low birth weight (LBW), birth weight < 2,500 g, is a major public health concern (Blencowe et al., 2012). LBW is not only one of the leading causes of adverse perinatal and neonatal mortality (Bukowski et al., 2007), but also is significantly associated with infant and childhood morbidities that may persist into adult life (Goldenberg and Culhane, 2007; Lakshmanan et al., 2015). Children with LBW increased worldwide over the past two decades (Kana et al., 2017; Shan et al., 2014), most of which occurred in developing countries (Chen et al., 2013). Epidemiological data recently reported a much higher estimated prevalence of LBW (19%) in developing countries compared to developed countries (5%–7%) (Rao et al., 2018). According to the Report from National Health Services Survey of China, the LBW prevalence continuously increased with the scale-up of cities from 2.7% in 2006 to 11.3% in 2011 and then declined to 8.1% in 2017 (Rao et al., 2018). Therefore, LBW has drawn a great attention as a significant health challenge particularly in China owning a huge population, and thus it is necessary to comprehensively identify its crucial risk factors so as to formulate more reasonable and effective health policy and preventive initiatives.

Mounting evidence has linked ambient air pollution exposure with adverse birth outcomes including LBW (Jacobs et al., 2017; Klepac et al., 2018; Shah et al., 2011). Recently, some review studies also suggested possible association between outdoor air pollution and term LBW (TLBW) (Dadvand et al., 2013; Fleischer et al., 2014; Pedersen et al., 2013). However, a few previous studies particularly addressing on traffic-related air pollution were mainly performed in the Western countries (Mariet et al., 2018; Proietti et al., 2013), only limited evidence are from Asian countries (Jacobs et al., 2017). Due to different geography (Hao et al., 2016), meteorological condition (Kloog et al., 2015), and the impact of race and ethnicity, there is a significant variation in the relation between ambient air pollution and fetal growth (Darrow et al., 2011; Gray et al., 2014), and thus data from China characterized by high level and mixed nature of air pollution (Deng et al., 2015, 2016a) warrants further investigations of epidemiological casual inference.

Home environment is another important risk factor for LBW, particularly for pregnant women spending most time indoors. Although emerging evidence suggests that indoor air pollution (IAP) increases the LBW risk (Pope et al., 2010), only little information has been acknowledged for LBW risk of indoor environmental exposures (Harville and Rabito, 2018; Nieuwenhuijsen et al., 2013) including house renovation (Liu et al., 2018), VOC emitting household products (Sørensen et al., 2010), and mold or dampness (Harville and Rabito, 2018), except for solid fuel use and ETS (Abusalah et al., 2012; Khader et al., 2016; Thompson et al., 2011). A majority of pregnant women are heavily exposed to IAP in the low/middle income countries (Kadir et al., 2010), such as China (Deng et al., 2016b). Thus, evidence in the home environment from Asian areas like China would provide further insights on the potential effect of IAP on LBW and its possible mechanisms.

China has experienced serious air pollution from both outdoor and indoor environment over past decades. Given the importance of LBW consequences and the probable impacts of pollution exposure on birth weight, we hypothesized combined outdoor and indoor environmental pollution contributes to LBW in China. In order to test this assumption, we conducted a retrospective cohort study in Changsha, China, which belongs to the nationwide "China-Children-Homes-Health (CCHH)" study with multi centers (Deng et al., 2015; Zhang et al., 2013).

2. Methods

2.1. Study protocol

From September 2011 to January 2012, we performed a questionnaire survey on children's health in 36 kindergartens of Changsha as described in detail elsewhere (Deng et al., 2015). The questionnaires were randomly distributed to all the children in the kindergartens as shown in Fig. 1. All the children in each kindergarten were instructed to own the questionnaires which would be filled by their parents, and then to return it to kindergartens less than one week. A total 3509 valid responses of questionnaires were used in the present work. LBW was defined as birth weight <2.5 kg based on the answer to the question: "What's birth weight (kg) of your child?" We further divided the LBW into two types: term LBW (TLBW) and preterm LBW (PLBW), which was defined as the child's birth weight < 2.5 kg respectively with a gestational age $\geq$37 and < 37 weeks. Maternal exposure in gestation included six-time windows: conception month, 1st, 2nd, and 3rd trimester, birth month, and entire pregnancy, which were respectively defined as the first month of gestation, during 1st-12th weeks, 13th-27th weeks, from the 28th to the last week of pregnancy, during the month when the baby was born, and during the full gestational months.

2.2. Exposure to home environmental factors

Home environmental factors exposure in pregnancy was also assessed by the questionnaire survey (Norbäck et al., 2017, 2018, 2019). We mainly focused on six types of home environmental factors: parental smoking, new furniture, redecoration, mold/damp stains, window pane condensation during winter, and household pets (dogs).

2.3. Assessment of ambient air pollution and temperature

Three air pollutants including sulphur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter $\leq$10 μm in diameter (PM_{10}) were selected in our study. SO_2 was indicated as industrial air pollution, NO_2 as traffic air pollution, and PM_{10} as a surrogate of complex mixture of air pollutants (Kan et al., 2012). Averaged concentrations of PM_{10}, SO_2 and NO_2 during 24-h during 2004–2010 covering the period of maternal exposure in pregnancy for each child were obtained from seven municipal monitoring stations for the three crucial air pollutants (Fig. 1). Data measurements from all stations followed the standard methods set by the State Environmental Protection Agency (EPA) of China: PM_{10} by a tapered element oscillating microbalance (TEOM1400, Rupprecht & Patashnick, USA), SO_2 by ultraviolet fluorescent method (ML/EC9850, Ecotech, Australia) and NO_2 by the chemiluminescent method (ML/EC9841B, Ecotech, Australia). The detailed information

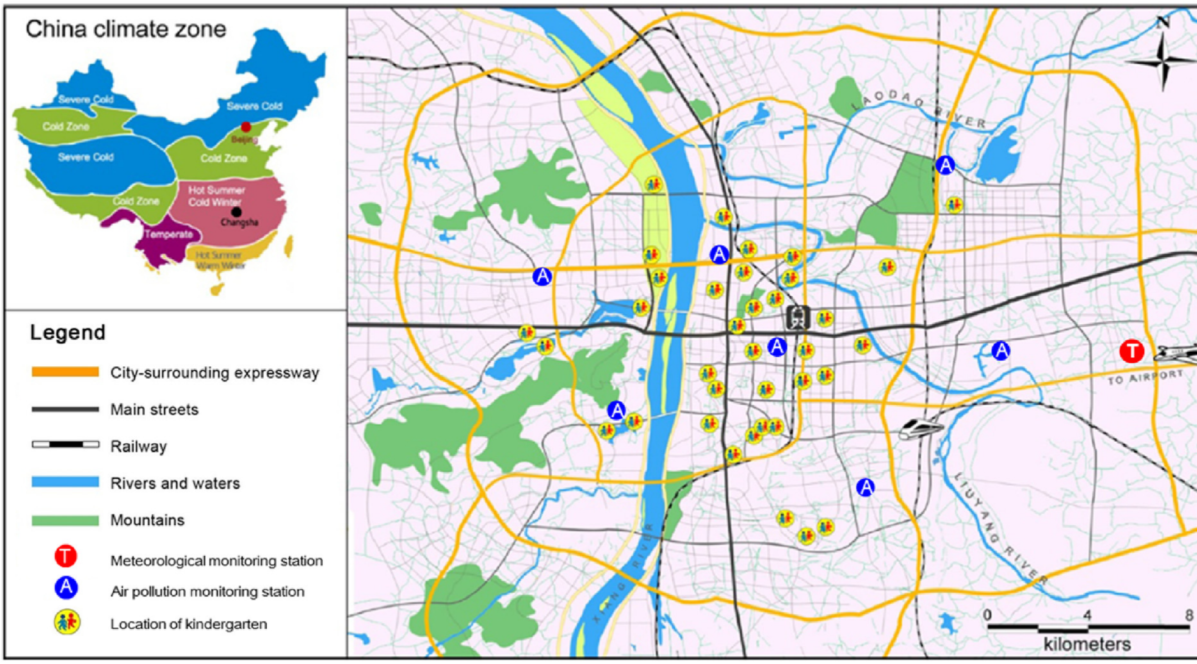

Fig. 1. Distributions of the kindergartens, and stations of air pollution monitoring stations and meteorological parameters in Changsha.

on the surveyed kindergartens and monitoring stations were provided elsewhere (Deng et al., 2015).

The hourly ambient temperature was collected from a meteorological website (www.wunderground.com), and the reported data was based on the airport monitoring station (Fig. 1). Because our studying area is a middle-scale city in China, and thus the temperature from one meteorological station can be efficiently represented as the average temperature of Changsha (Zheng et al., 2018; Zhong et al., 2018).

Maternal exposure to ambient PM_{10}, SO_2, and NO_2 was calculated by an inverse distance weighted (IDW) method as described in our previous work (Deng et al., 2015). Maternal exposures to ambient air pollutants (PM_{10}, SO_2, and NO_2) and temperature were respectively estimated by the means of the three air pollutants during the six-time windows.

2.4. Covariates

The information of potential confounders was collected by the questionnaires. In the present study, the confounding variables contained fetal sex, birth season, maternal productive age, parental atopy, socioeconomic status (SES) indicated by house size, building age, household owner, and cockroaches noted (Table 1). Some previous studies indicated that these confounders were associated with birth outcomes and may also influence associations of LBW with ambient air pollution and home environmental factors (Liu et al., 2018; Wang et al., 2019).

2.5. Statistical analysis

We conducted multiple logistic regression models to investigate the associations of LBW (TLBW and PLBW) with ambient air pollution (PM_{10}, SO_2, and NO_2) and home environmental factors during different time windows with adjustment for potential confounding covariates. Associations in the analysis were calculated as odds ratio (OR) with 95% confidence interval (CI). A p value < 0.05 was considered statistically significant. In our analysis, ambient PM_{10}, SO_2, and NO_2 were included as continuous and categorical variables in the models. In continuous model, OR (95% CI) was calculated for per IQR increase in PM_{10}, SO_2, and NO_2. In category model, the pollution exposure level was classified as four quartiles, and OR (95% CI) was evaluated by different quartiles of exposure to air pollutants with the first quartile as reference. Home environmental factors were included as categorical variables in the model, and their risk of TLBW and PLBW was estimated by setting no parental smoking, new furniture, redecoration, mold/damp stains, window pane condensation, or household pets (dogs) as the reference (OR = 1). All the statistical analyses in our study were performed by SPSS software (version 22.0, SPSS Inc, Chicago, USA).

3. Results

Of 3509 children, 98 (2.8%) were low birth weight, with 45 (1.3%) TLBW and 53 (1.5%) PLBW (Table 1). We observed that the prevalence of TLBW was significantly higher among foetus born in autumn and PTLB prevalence greater in female foetus, older mothers (maternal productive age $\geq$30 years), and house-owner families than male foetus, younger mothers, and non-house-owner families. The prevalence of TLBW among female foetus and families with lower socioeconomic status (SES) (house size $\leq$100 m^2) was also higher compared to male foetus and those with higher SES, although no significance was observed. However, TLBW and PLBW were not related to parental atopy, building age, or cockroaches.

Maternal exposure to ambient air pollutants and temperature in pregnancy was summarised in Table 2. The averaged exposure (mean ± SD) to PM_{10}, SO_2, and NO_2 in each pregnant mother were 109 ± 11, 81 ± 27, and 46 ± 8 $\mu g/m^3$ respectively during whole pregnancy, with slightly variation across different time windows of pregnancy. Furthermore, the averaged individual exposure (mean ± SD) was 18.4 ± 2.3 °C in gestation, with moderate variation between different time windows.

Exposure to home environmental factors was presented in Table 3. About half of parents smoked during pregnancy. Only a few

Table 1
Covariates, demographic information and prevalence of term low birth weight (TLBW) and preterm low birth weight (PLBW) in children (n = 3509).

	Number (n)	(%)	TLBW			PLBW		
			Case (n)	(%)	p	Case (n)	(%)	p
Total	3509	(100)	45	(1.3)		53	(1.5)	
Sex					0.126			**0.041**
Boys	1878	(54)	19	(1.0)		21	(1.1)	
Girls	1631	(46)	26	(1.6)		32	(2.0)	
Birth season					**0.013**			0.208
Spring (March–May)	832	(24)	12	(1.4)		15	(1.8)	
Summer (June–August)	980	(28)	5	(0.5)		19	(1.9)	
Autumn (September–November)	863	(25)	19	(2.2)		7	(0.8)	
Winter (December–February)	834	(24)	9	(1.1)		12	(1.4)	
Maternal productive age (years)					0.793			**<0.001**
<30	2488	(71)	33	(1.3)		26	(1.0)	
≥30	988	(28)	12	(1.2)		27	(2.7)	
Parental atopy					0.688			0.476
No	2983	(85)	39	(1.3)		45	(1.5)	
Yes	462	(13)	5	(1.1)		5	(1.1)	
Socioeconomic status (SES) by house size (m^2)					0.063			0.754
≤100	2070	(59)	33	(1.6)		30	(1.4)	
>100	1391	(40)	12	(0.9)		22	(1.6)	
Building age (years)					0.967			0.959
≤10	1784	(51)	23	(1.3)		26	(1.5)	
>10	1532	(44)	20	(1.3)		22	(1.4)	
Household owner					0.377			**0.029**
No	1189	(34)	18	(1.5)		9	(0.8)	
Yes	2164	(62)	25	(1.2)		36	(1.7)	
Cockroaches noted					0.243			0.869
No	1189	(34)	19	(1.6)		18	(1.5)	
Yes	2141	(61)	24	(1.1)		34	(1.6)	

TLBW: birth weight <2.5 kg with gestational age ≥37 weeks; PLBW: birth weight <2.5 kg with gestational age <37 weeks.
Sum of the number is not 3509 due to missing data. The values $p < 0.05$ were in bold.

Table 2
Descriptive statistics for outdoor air pollution and temperature during different time windows attributed to the children (n = 3509).

	Mean	SD	25% percentile	50% percentile	75% percentile	IQR
Conception month						
PM_{10}	112	23	94	113	129	35
SO_2	85	42	56	76	104	48
NO_2	45	12	35	44	52	17
T	18.0	8.6	11.2	19.8	25.5	14.3
1st trimester						
PM_{10}	111	16	100	110	121	21
SO_2	84	38	58	74	100	42
NO_2	45	11	37	44	52	15
T	18.0	7.8	9.3	18.0	25.6	16.3
2nd trimester						
PM_{10}	110	15	100	108	117	17
SO_2	81	36	57	73	96	39
NO_2	46	11	38	45	53	15
T	18.4	7.3	12.5	18.9	25.0	12.5
3rd trimester						
PM_{10}	107	18	95	106	115	20
SO_2	78	39	50	70	95	45
NO_2	46	10	38	45	53	15
T	18.9	7.7	11.6	19.5	26.0	14.4
Birth month						
PM_{10}	105	23	87	101	121	34
SO_2	77	43	47	67	93	46
NO_2	46	12	37	45	54	17
T	19.0	8.7	12.5	19.9	26.6	14.1
Entire pregnancy						
PM_{10}	109	11	102	108	115	13
SO_2	81	27	60	76	99	39
NO_2	46	8	40	45	51	11
T	18.4	2.3	16.5	18.2	20.3	3.8

PM_{10} ($\mu g/m^3$) = particulate matter ≤ 10 μm in aerodynamic, SO_2 ($\mu g/m^3$) = sulphur dioxide, NO_2 ($\mu g/m^3$) = nitrogen dioxide, T (°C) = temperature.

families had new furniture (12%) and redecoration (5%) at home during pregnancy, while 17% and 47% families reported mold/damp stains and window pane condensation respectively. Merely a small number of families raised pets (dogs) (5%) during pregnancy. We found a significantly higher prevalence of TLBW among the families with parental smoking and without new furniture exposures ($p < 0.05$).

Risk of TLBW and PLBW due to exposure to ambient PM_{10}, SO_2, and NO_2 in pregnancy was provided in Table 4. We found that TLBW was significantly associated with inhalable particulate matter PM_{10} in whole gestation with an OR (95% CI) of 1.46 (1.01–2.11) for IQR increase in PM_{10} after adjusting for the covariates and ambient temperature (basic model), and this association remained significant after further adjusting for all the considered home environmental factors (1.47, 1.00–2.14) (indoor-adjusted model). TLBW was also significantly related with PM_{10} exposure in the conception month and 1st trimester of gestation in the indoor-adjusted model, respectively with ORs = 1.90 (1.09–3.30) and 1.72 (1.10–2.69). However, we observed no PLBW risk of any pollutant exposure. Furthermore, the risk of TLBW at different exposure quartiles of PM_{10} shown in Fig. S1 further demonstrated that high level of PM_{10} exposure increased the TLBW risk with respect to the low exposure level during early pregnancy including conception month and first trimester.

Risk of TLBW and PLBW due to prenatal exposure to home environmental factors was provided in Table 5. It was found that TLBW was significantly associated with indoor parental smoking both in basic and outdoor-adjusted model with further adjusting for all the three ambient air pollutants based on the basic model, respectively with ORs (95% CI) = 2.21 (1.11–4.40) and 2.17 (1.09–4.33). The TLBW risk due to indoor exposure to new furniture, redecoration, mold/damp stains, window pane condensation, or household dogs were not significant. However, no association

Table 3
Prevalence of indoor environmental factors during pregnancy and its associations with TLBW and PLBW (n = 3509).

	Number (n)	(%)	TLBW			PLBW		
			Case (n)	(%)	p	Case (n)	(%)	p
Parental smoking					**0.017**			0.062
No	1689	(48)	14	(0.8)		32	(1.9)	
Yes	1779	(51)	31	(1.7)		20	(1.1)	
New furniture					**0.044**			0.802
No	2389	(68)	33	(1.4)		35	(1.5)	
Yes	431	(12)	1	(0.2)		7	(1.6)	
Redecoration					0.308			0.512
No	2582	(74)	37	(1.4)		44	(1.7)	
Yes	187	(5)	1	(0.5)		2	(1.1)	
Mold/damp stains					0.617			0.326
No	2864	(82)	36	(1.3)		44	(1.5)	
Yes	595	(17)	9	(1.5)		6	(1.0)	
Window condensation					0.246			0.177
No	1748	(50)	27	(1.5)		31	(1.8)	
Yes	1652	(47)	18	(1.1)		20	(1.2)	
Household pets (dogs)					0.426			0.102
No	3309	(94)	44	(1.3)		53	(1.6)	
Yes	164	(5)	1	(0.6)		0	(0.0)	

Sum of the number is not 3509 due to missing data. The values $p < 0.05$ were in bold.

Table 4
Odds ratio (95%CI) of TLBW and PLBW for exposure to outdoor air pollution during different timing windows (n = 3509).

	TLBW		PLBW	
	Adjusted OR I [a]	Adjusted OR II [b]	Adjusted OR I [a]	Adjusted OR II [b]
Conception month				
PM_{10}	1.45 (0.87, 2.41)	1.90 (1.09, 3.30)*	1.14 (0.70, 1.87)	1.23 (0.71, 2.13)
SO_2	0.89 (0.58, 1.39)	1.07 (0.68, 1.68)	1.05 (0.73, 1.51)	1.05 (0.69, 1.61)
NO_2	0.62 (0.36, 1.07)	0.72 (0.40, 1.28)	1.02 (0.59, 1.78)	1.02 (0.55, 1.87)
1st trimester				
PM_{10}	1.53 (0.98, 2.37)	1.72 (1.10, 2.69)*	0.87 (0.56, 1.36)	0.81 (0.49, 1.32)
SO_2	1.11 (0.71, 1.74)	1.30 (0.81, 2.08)	1.10 (0.77, 1.58)	0.97 (0.62, 1.51)
NO_2	0.59 (0.32, 1.06)	0.65 (0.35, 1.21)	1.03 (0.61, 1.77)	0.90 (0.50, 1.64)
2nd trimester				
PM_{10}	1.36 (0.89, 2.09)	1.37 (0.89, 2.12)	1.07 (0.68, 1.68)	1.12 (0.67, 1.89)
SO_2	1.13 (0.68, 1.87)	1.29 (0.77, 2.16)	1.26 (0.83, 1.91)	1.20 (0.73, 1.96)
NO_2	0.58 (0.31, 1.09)	0.58 (0.30, 1.13)	1.01 (0.57, 1.80)	1.00 (0.53, 1.87)
3rd trimester				
PM_{10}	1.31 (0.87, 1.97)	1.23 (0.79, 1.92)	1.27 (0.80, 2.01)	1.55 (0.96, 2.51)
SO_2	0.99 (0.60, 1.62)	1.05 (0.63, 1.75)	1.48 (0.88, 2.50)	1.49 (0.84, 2.65)
NO_2	0.89 (0.49, 1.61)	0.87 (0.47, 1.61)	0.75 (0.40, 1.38)	0.75 (0.38, 1.47)
Birth month				
PM_{10}	1.30 (0.75, 2.25)	1.34 (0.75, 2.38)	1.30 (0.71, 2.40)	1.43 (0.72, 2.84)
SO_2	1.18 (0.77, 1.81)	1.23 (0.79, 1.93)	1.36 (0.86, 2.15)	1.33 (0.80, 2.22)
NO_2	1.03 (0.58, 1.82)	1.03 (0.58, 1.86)	0.96 (0.52, 1.76)	0.91 (0.46, 1.79)
Entire pregnancy				
PM_{10}	1.46 (1.01, 2.11)*	1.47 (1.00, 2.14)*	1.12 (0.76, 1.67)	1.13 (0.73, 1.76)
SO_2	1.11 (0.67, 1.86)	1.28 (0.75, 2.19)	1.25 (0.80, 1.95)	1.10 (0.65, 1.86)
NO_2	0.66 (0.40, 1.09)	0.68 (0.40, 1.16)	1.02 (0.64, 1.61)	0.92 (0.56, 1.54)

OR (95% CI) was estimated by IQR increase for air pollutant during each time window.
*$p \leq 0.05$.
[a] Model I: Models were adjusted for the covariates in Table 1 and outdoor temperature in Table 2 during each time window.
[b] Model II: Models were further adjusted for all the indoor environmental factors in Table 3 based on model I.

was observed between PLBW and any home environmental factor. In addition, we could not obtain the exact ORs of PLBW for indoor exposure to redecoration and household pets (dogs) mainly due to the relative few or no report for preterm LBW among children with these home environmental factors.

The combined effect between indoor and outdoor air pollution on TLBW was assessed by stratification analysis. Table 6 presented that TLBW was significantly associated with exposure to outdoor air pollutants during conception, first trimester, and entire pregnancy only in families with parental smoking at home. On the other hand, Table 7 showed that the association between TLBW and indoor parental smoking was significant only among pregnant mothers with high exposure of outdoor PM_{10} during pregnancy and its critical time windows, which indicated a synergistical effect.

Table 5
Risk of TLBW and PLBW for exposure to indoor environmental factors during pregnancy (n = 3509).

	TLBW		PLBW	
	Adjusted OR I [a]	Adjusted OR II [b]	Adjusted OR I [a]	Adjusted OR II [b]
Parental smoking	2.21 (1.11, 4.40)*	2.17 (1.09, 4.33)*	0.57 (0.30, 1.10)	0.58 (0.30, 1.10)
New furniture	0.20 (0.03, 1.49)	0.20 (0.03, 1.48)	1.64 (0.70, 3.83)	1.69 (0.72, 3.98)
Redecoration	0.46 (0.06, 3.39)	0.44 (0.06, 3.27)	–	–
Mold/damp stains	1.34 (0.60, 2.98)	1.31 (0.59, 2.93)	0.74 (0.28, 1.92)	0.73 (0.28, 1.91)
Window condensation	0.82 (0.43, 1.57)	0.82 (0.43, 1.57)	0.72 (0.38, 1.35)	0.72 (0.38, 1.37)
Household pets (dogs)	0.58 (0.08, 4.28)	0.57 (0.08, 4.25)	–	–

OR: Odds ratio; CI: Confidential interval. OR (95% CI) was estimated according to the reference (OR = 1).
*$p \leq 0.05$.
[a] Models were adjusted for the covariates in Table 1, and outdoor temperature in Table 2 during entire pregnancy.
[b] Models were further adjusted for three outdoor air pollutants exposure in Table 2 during entire pregnancy.

Table 6
Risk of TLBW for exposure to outdoor air pollution during conception month, first trimester, and entire pregnancy stratified by parental smoking during pregnancy (n = 3509).

	Without parental smoking	With parental smoking	Interaction p
Conception month			
PM_{10}	1.14 (0.47, 2.76)	2.84 (1.36, 5.94)**	0.462
SO_2	0.92 (0.43, 2.00)	1.12 (0.64, 1.96)	0.782
NO_2	0.69 (0.25, 1.90)	0.74 (0.36, 1.53)	0.447
First trimester			
PM_{10}	1.49 (0.74, 3.02)	1.94 (1.08, 3.50)*	0.821
SO_2	1.44 (0.69, 3.01)	1.13 (0.61, 2.11)	0.196
NO_2	0.73 (0.25, 2.16)	0.58 (0.26, 1.29)	0.208
Entire pregnancy			
PM_{10}	1.25 (0.64, 2.48)	1.70 (1.05, 2.74)*	0.536
SO_2	1.24 (0.50, 3.11)	1.32 (0.68, 2.58)	0.747
NO_2	0.75 (0.29, 1.94)	0.65 (0.34, 1.25)	0.509

OR (95% CI) was estimated by IQR increase for air pollutant during each time window.
Models were adjusted for the covariates in Table 1, indoor environmental factors in Table 3, and outdoor temperature in Table 2 during each time window.
Interaction p-value was indicated by interaction between parental smoking during pregnancy and exposure to outdoor air pollution during conception month, first trimester, and entire pregnancy on TLBW; bold was indicated as significant interaction with interaction p-value ≤0.1.
*$p \leq 0.05$.
**$p \leq 0.01$.

Table 7
Risk of TLBW for exposure to indoor environmental factors during pregnancy stratified by outdoor PM_{10} exposure during conception month, first trimester, and entire pregnancy (n = 3509).

	Without parental smoking	With parental smoking
Conception month		
Low PM_{10}	1.00	1.31 (0.48, 3.60)
High PM_{10}	1.00	3.40 (1.24, 9.33)*
Interaction p-value		0.146
First trimester		
Low PM_{10}	1.00	1.60 (0.57, 4.50)
High PM_{10}	1.00	2.78 (1.07, 7.20)*
Interaction p-value		0.481
Entire pregnancy		
Low PM_{10}	1.00	1.17 (0.42, 3.30)
High PM_{10}	1.00	3.45 (1.27, 9.39)*
Interaction p-value		0.137

Models were adjusted for the covariates in Table 1, and outdoor temperature in Table 2 during each time window.
*$p \leq 0.05$.
#Interaction p-value was indicated by interaction between parental smoking during pregnancy and exposure to outdoor air pollution during conception month, first trimester, and entire pregnancy on TLBW; bold was indicated as significant interaction with interaction p-value ≤0.1.

Tables 4 and 5 indicated that the risk of TLBW due to exposure to ambient PM_{10} and home environmental factors was independent, because the odds kept consistent after adjustment for each other. Therefore, the risk of TLBW due to the combination of high ambient PM_{10} and with indoor parental smoking was significantly higher, with adjusted OR (95% CI) = 2.89 (1.04–8.04) and 3.61 (1.36–9.59) respectively during conception month and entire pregnancy, than exposure to the combination of low PM_{10} and without parental smoking as shown in Table S1.

The risk of TLBW due to exposure to ambient PM_{10} and parental smoking in the homes in utero stratified by fetal sex and maternal productive age was shown in Fig. S2. We found that the TLBW risk of both ambient PM_{10} and indoor parental smoking exposure was mainly significant in female foetus and younger mothers (maternal productive age <30 years). In addition, we observed a significant interaction between maternal productive age and indoor parental smoking (interaction p-value = 0.089). On the other hand, we detected that low SES (house size $\leq 100\,m^2$) and cockroaches significantly interplayed with PM_{10} exposure respectively during conception month and entire pregnancy on an increase in the risk of TLBW, with interaction p-values = 0.066 and 0.057 individually (Fig. S3).

4. Discussion

According to our best knowledge, the present study is the first to investigate the effect of combination between ambient air pollution and home environmental factors exposure on term LBW (TLBW) and preterm LBW (PLBW). In the present study, we found that TLBW in Changsha was significantly associated with both ambient PM_{10} and indoor parental smoking in utero, especially during early course of pregnancy. The risk of air pollution from outdoor and indoor was independent and thus the combined ambient PM_{10} and indoor parental smoking in pregnancy, particularly during early stage, significantly increased the risk of TLBW. Sensitivity analysis indicated that female foetus and younger mothers were more susceptible to the effects of both outdoor PM_{10} and indoor parental smoking. SES and cockroaches significantly interacted with prenatal PM_{10} on the risk of TLBW.

4.1. TLBW risk of inhalable particulate matter

Evidence in the association between maternal exposure to PM_{10} and TLBW is scarce, and their findings are inconsistent (Jacobs et al., 2017; Ji et al., 2017). In this study, we observed that PM_{10} exposure in utero was associated with an increased risk of TLBW but not PLBW, which is in line with many previous studies (Dadvand et al., 2013; Dibben and Clemens, 2015; Fleischer et al., 2014; Ji et al., 2017; Pedersen et al., 2013; Shah et al., 2011; Tu et al., 2016). A significant association between TLBW and PM_{10} exposure during entire pregnancy was also observed in a recent Scottish Longitudinal Study (SLS) (Dibben and Clemens, 2015) and several international studies including multi-countries (Dadvand et al., 2013; Pedersen et al., 2013). However, some other studies found no association (Araban et al., 2012; Dadvand et al., 2014; Parker et al., 2011). The inconsistent findings from available evidence may be due to different concentration level and pollution sources in different studying areas.

We further detected that effect estimate of ambient PM_{10} exposure was significantly greater during early pregnancy including conception month and first trimester. Although some studies also addressed the trimester-specific exposure, their findings are inconclusive (Araban et al., 2012; Dadvand et al., 2013; Dugandzic et al., 2006; Savitz et al., 2014; Xu et al., 2011). Some human and animal studies have indicated that air pollution exposure affects birth weight mostly during early pregnancy including the 1st week (e Silva et al., 2008) and month (Liu et al., 2003) of pregnancy, which is in line with our study. Our findings can be supported by several studies which also identified a significant TLBW risk due to 1st trimester exposure to PM_{10} (Dadvand et al., 2013; Dugandzic et al., 2006; Romão et al., 2013; Xu et al., 2011) and suspended particle (Yorifuji et al., 2015). These evidences reinforce the findings of the present study, indicating that exposure during early stage of pregnancy is a crucial determinant of LBW. However, some other studies reported a significant association for the second trimester (Romão et al., 2013; Xu et al., 2011) or the third trimester (Capobussi et al., 2016; Dadvand et al., 2014; Romão et al., 2013) exposures, while other studies did not found association for any trimester exposure (Araban et al., 2012; Dugandzic et al., 2006). Because the concentrations of air pollutants were weakly/moderately correlated in different trimester in our study (data not shown) and effect estimates at both 2nd and 3rd trimesters were increased, it is hard to attribute the risk of LBW development merely to 1st trimester and it warrants further investigations.

4.2. TLBW risk of SO_2 and NO_2

Our findings were consistent with some studies which also reported no indication of an adverse effect of SO_2 and NO_2 exposure in whole pregnancy or any trimester on TLBW (Gehring et al., 2011; Michikawa et al., 2017; Stieb et al., 2016; Wilhelm et al., 2012). Our recent work also found significant risk of allergic and infectious diseases which are related to birth outcomes including LBW among preschool children due to SO_2 and NO_2 exposure during early life (Deng et al., 2015, 2016a; 2016b; Lu et al., 2017). However, our study is not consistent with some studies indicating a significant association for SO_2 (Dugandzic et al., 2006; Yorifuji et al., 2015) and NO_2 (Dibben and Clemens, 2015; Pedersen et al., 2013) exposure in utero. Due to the inconsistency among previous studies, the effects of exposure to ambient SO_2 and NO_2 on birth outcomes needs further investigations.

4.3. LBW risk of indoor environmental factors

Other than outdoor air pollution, we also noted that parental smoking during pregnancy can cause TLBW. Our finding is consistent with many studies which suggested that prenatal exposure to indoor active and/or passive smoking could increase LBW risk (Abusalah et al., 2012; Andriani and Kuo, 2014; Hanke et al., 2004; Windham et al., 2000), although some previous study found no risk (Windham et al., 2000). Not only maternal smoking but also secondhand tobacco smoke (i.e., paternal smoking) during pregnancy have been known to increase LBW risk (Banderali et al., 2015). Several studies have shown significant associaitons between maternal smoking during pregnancy and decreased birth weight and increased risk of LBW (Pereira et al., 2017). On the other hand, the findings on LBW risk of paternal smoking are still inconsistent although a significant association has been observed for environmental tobacco exposure in some study (Leonardi-Bee et al., 2008). Our study was inconsistent with a recent Chinese study which found no association between parental smoking during gestation and TLBW (Liu et al., 2018). It has been suggested that nicotine is indeed able to cross the placenta and impact fetal development (i.e., LBW) (Lisboa et al., 2012) through different mechanisms (Banderali et al., 2015; Lee et al., 2015), and therefore preventive measures are need to persuade pregnant mothers to give up active smoking and to also avoid passive smoking exposure since the beginning of gestation (Hanke et al., 2004).

On the other hand, we have not found significant association of LBW with indoor renovation (new furniture and redecoration), mold/dampness (mold/damp stains and window pane condensation), or household pets (dogs) during pregnancy. Our results parallel the findings from several studies in Finland (Ahmed and Jaakkola, 2007), Denmark (Sørensen et al., 2010), and US (Shoaff et al., 2016). A recent Chinese study also found no association of TLBW with household renovation, mold/dampness, or household pets during pregnancy (Liu et al., 2018). However, our findings are inconsistent with some studies which suggested that indoor renovation exposure was significantly associated with reduced birth weight or LBW (Hooiveld et al., 2006), and other studies which reported relationship between indoor mold/dampness and LBW (Harville and Rabito, 2018). Our observed no association between indoor renovation may be ascribed from that the prevalence of these home environmental factors was very low in our study. Environmental risk factors including renovation, mold/dampness, and pets in the home can trigger various fungi growth, including bacteria, dust mites and other biological agents which could contribute to the development of birth outcomes (Harville and Rabito, 2018), although the available findings were inconclusive.

4.4. Susceptibility for TLBW risk of air pollution exposure

In our study, there is synergistic effect between indoor parental smoking and ambient PM_{10} exposure in pregnancy on TLBW, and some populations were more susceptible to their separate effect, such as female foetus, younger mothers, and low SES. The current epidemiologic evidence in the association between TLBW and outdoor air pollution and indoor parental smoking on elevated vulnerability for sensitive population is scarce. Our findings are consistent with a recent review study, which indicates that pregnant women who smokes or has lower SES belong to a vulnerable subgroup when exposed to outdoor air pollution were more likely to deliver a TLBW baby (Westergaard et al., 2017). Some studies found that maternal economic factor was associated with LBW (Abusalah et al., 2012). However, the reason why smoking parents during pregnancy were more susceptible to PM_{10} exposure is unclear, and thus it warrants further studies.

4.5. Strengths

The strength of the present study is that we comprehensively evaluated the effects of ambient air pollution and home environmental factors as well as their combinations on the risk of TLBW and PLBW in different time windows of pregnancy. We observed that TLBW risk began at the early pregnancy, including the conception month and first trimester. Although increasing evidence have linked inhalable particulate matter (PM_{10}) with adverse birth outcomes including LBW, the critical exposure timing window in the development of different type of LBW is still unclear. Another striking finding is that outdoor PM_{10} could interplay with indoor parental smoking in utero especially during early pregnancy so as to significantly increase the risk of TLBW. The potential interaction between ambient air pollution and home environmental factors has not considerably received attentions in regarding to birth outcomes.

4.6. Limitations

There are several limitations of our study which should be acknowledged. First of all, we merely considered inhalable particulate matter, PM_{10}, to present the particulate air pollution. However, the roles of other type of particles (i.e., $PM_{2.5}$ and $PM_{2.5\text{-}10}$) is also important which needs to be further investigated. Secondly, there may be a potential exposure misclassification. We estimated pregnant mother's exposure of ambient air pollution in utero based on the exposure in their child's kindergarten, which would be more accurate by using the home address. In this study, we did not have each family's home address due to that this private question is relatively sensitive in China. Whereas, it is reasonable to assess maternal exposure of ambient air pollution in this way due to that most parents usually send their child in the nearest kindergarten from the home and the mothers are likely to work near the homes or their children's kindergarten. Furthermore, exposure of each air pollutant was calculated using an inverse distance weighted (IDW) method according to the measured data from different monitoring stations for outdoor air pollution. This IDW method may cause exposure bias due to the limited monitoring stations and air pollution sources as well as an ignorance of land use information. Last, we did not measure the detailed number of cigarettes smoking among parents and raised dogs, the concentrations of VOCs emitted from indoor renovation, or quantified the mold/damp stains and window pane condensation. The associations of LBW with indoor parental smoking, renovation, mold/dampness and raised dogs were indirectly assessed by monitoring VOCs concentrations and types/quantity of mold or dampness in the home and their associations with LBW is needed.

4.7. Biological mechanisms

Although the specific biologic mechanisms whereby air pollution (i.e., PM) affects birth outcomes remain to be elucidated, our findings are biologically plausible. Proposed mechanisms underlying the risk of LBW due to air pollution exposure include oxidative stress, placental inflammation, coagulation, endothelial function, and hemodynamic responses (Kannan et al., 2006). Exposure to particles may induce systemic oxidative stress (Donaldson et al., 2001) that can influence the embryo growth adversely at the earliest stage (Mohorovic, 2004), and can also compromise and cross the maternal-fetal blood barrier and ultimately perturb fetal growth and development (Luyten et al., 2018). PM exposure also can induce acute placental inflammation, linked with inadequate placental perfusion (Knottnerus et al., 1990) and impaired exchange for transplacental nutrient (Bobak, 2000), which could result in growth restriction during gestation (Trasande et al., 2016). Particles may also impact platelet, hemoglobin, and white blood cells (WBC) (Riediker et al., 2004), as well as endothelial functions indicated as a pathway for intervening adverse growth in foetus. In addition, particulate matter is possibly related with an increase in blood pressure defined as pregnancy-induced hypertension among pregnant mothers, which may lead to adverse birth outcomes (Kannan et al., 2006).

5. Conclusions

We systematically evaluated the association of term and preterm LBW with prenatal exposure to ambient air pollution and home environmental factors in China. We observed that exposure to both ambient PM_{10} and indoor parental smoking was significantly associated with increased risk of term LBW but not preterm LBW, and the susceptible timing window was early course of pregnancy. Our findings suggest that programs or policies for public education to decrease ambient particulate matter exposure particularly during early pregnancy for expected parents and/or pregnant women could effectively decrease LBW risk. On the other hand, taking initiatives to largely reduce exposure to parental smoking and measures to improve indoor ventilation in the homes to reduce exposure are useful to decrease the prevalence of LBW. Whereas, it warrants further investigations to explore the role of various indoor and outdoor environmental risk factors in the LBW pathogenesis in order to confirm the findings in our study.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2019.124836.

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