



Parental stress and air pollution increase childhood asthma in China

Qihong Deng^{a,b,*}, Linjing Deng^a, Chan Lu^a, Yuguo Li^c, Dan Norbäck^{a,d}

^a School of Energy Science and Engineering, Central South University, Changsha, Hunan, China

^b XiangYa School of Public Health, Central South University, Changsha, Hunan, China

^c Department of Mechanical Engineering, The University of Hong Kong, Hong Kong, China

^d Department of Medical Sciences/Occupational & Environmental Medicine, Uppsala University, Uppsala, Sweden

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ABSTRACT

Background: Although air pollution and social stress may independently increase childhood asthma, little is known on their synergistic effect on asthma, particularly in China with high levels of stress and air pollution. **Objectives:** To examine associations between exposure to a combination of parental stress and air pollution and asthma prevalence in children.

Methods: We conducted a cohort study of 2406 preschool children in Changsha (2011–2012). A questionnaire was used to collect children's lifetime prevalence of asthma and their parental stress. Parental socioeconomic and psychosocial stresses were respectively defined in terms of housing size and difficulty concentrating. Children's exposure to ambient air pollutants was estimated using concentrations measured at monitoring stations. Associations between exposure to parental stress and air pollution and childhood asthma were estimated by multiple logistic regression models using odds ratio (OR) and 95% confidence interval (CI).

Results: Life time prevalence of asthma in preschool children (6.7%) was significantly associated with parental socioeconomic and psychosocial stresses with OR (95% CI) respectively 1.48 (1.02–2.16) and 1.64 (1.00–2.71). Asthma was also associated with exposure to air pollutants, with adjusted OR (95% CI) during prenatal and postnatal periods respectively 1.43 (1.10–1.86) and 1.35 (1.02–1.79) for SO₂ and 1.61 (1.19–2.18) and 1.76 (1.19–2.61) for NO₂. The association with air pollution was significant only in children exposed to high parental stress, the association with parental stress was significant only in children exposed to high air pollution, and the association was the strongest in children exposed to a combination of parental stress and air pollution. Sensitivity analysis showed that the synergistic effects of parental stress and air pollution on childhood asthma were stronger in boys.

Conclusions: Parental stress and air pollution were synergistically associated with increased childhood asthma, indicating a common biological effect of parental stress and air pollution during both prenatal and postnatal periods.

1. Introduction

Asthma is the most common chronic disease in children and the leading cause of pediatric hospitalization worldwide and leads to a heavy economic burden on the family and poor quality of the life (Eder et al., 2006). A rapid increase in the prevalence of childhood asthma has been observed in developing countries, including China (Zhang et al., 2013). Identifying the key causal factors is important to develop prevention measures so as to reduce the rapidly increasing childhood asthma in China.

Although both genetic and environmental factors are responsible for the development of asthma, environmental factors are likely responsible for the rapid increase in the prevalence (London, 2007).

Ambient air pollution has been suggested to be linked with childhood asthma (Guarnieri and Balmes, 2014). Mounting evidence indicates that early-life exposure to traffic-related air pollution (TRAP) in developed countries contributes to the development of asthma in children (Anderson et al., 2013; Brunst et al., 2015; Gasana et al., 2012; Nishimura et al., 2013; Tétreault et al., 2016). Several recent studies in China have showed that exposures to both TRAP and industry-related air pollution (IRAP) were associated with childhood asthma (Deng et al., 2015, 2016a; Liu et al., 2016).

Social environment is another important contributor to childhood asthma (Sandberg et al., 2000). Family or parental stress, such as socioeconomic and psychosocial stresses, may play an important role in their children's health (Shalowitz et al., 2006). Exposure to stress

* Corresponding author.

E-mail address: qhding@csu.edu.cn (Q. Deng).

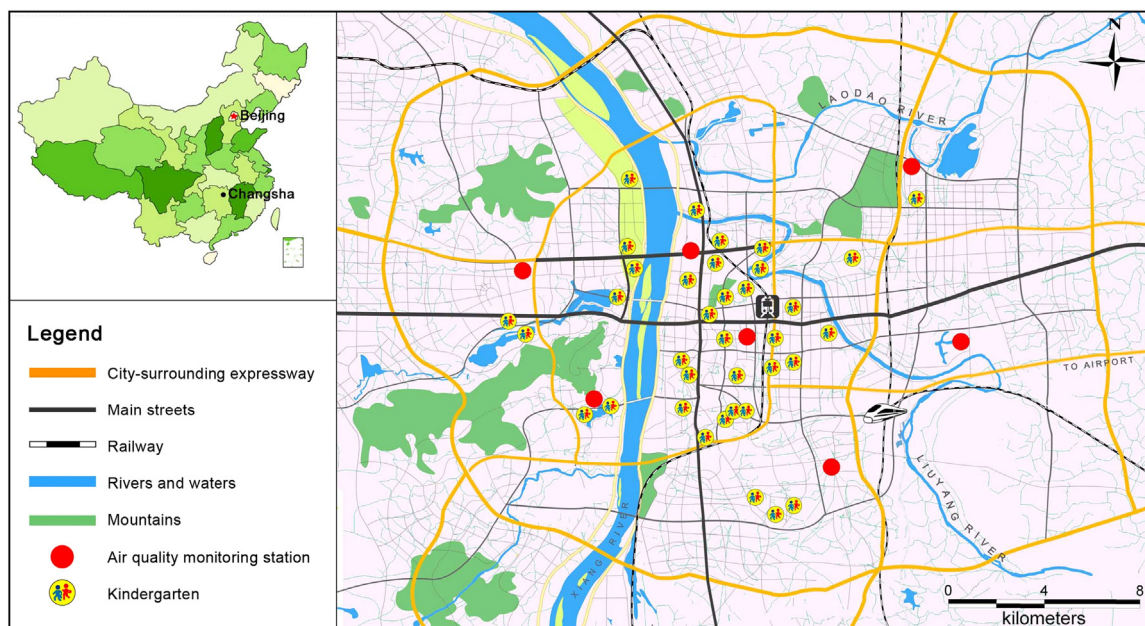


Fig. 1. Distributions of kindergartens and air pollution monitoring stations in Changsha, China.

during pregnancy and early childhood can result in permanently altered changes in stress-response systems, which are thought to play a key role in the programming of respiratory disorders that result in asthma in the later childhood (Lee and Wright, 2016). A growing number of epidemiological studies over the past decade have demonstrated significant associations between prenatal maternal stress and early asthma phenotypes in the children (Cookson et al., 2009; Heinrich, 2015; Lee et al., 2016). Recent systematical reviews and meta-analyses confirmed the link between prenatal stress and the subsequent development of asthma in early childhood (Flanigan et al., 2018; Van De Loo et al., 2016). However, the role of parental stress in childhood asthma in China is lacking and further investigation is warranted to fill the knowledge gap.

Although exposures to air pollution and social stress may increase susceptibility to childhood asthma, there is growing concern about their potential interaction (Chen et al., 2008). Social stress and air pollution often co-exist (O'Neill and Schwartz, 2003), and a recent review found that stress is very likely associated with air pollution, such as low socioeconomic communities face higher levels of air pollution (Hajat et al., 2015). Several recent studies have also observed that children from stressed households are more susceptible to the effects of air pollution on the development of asthma or other respiratory diseases (Bose et al., 2017; Chiu et al., 2014; Clougherty and Kubzansky, 2009; Lee et al., 2018; Shankardass et al., 2009). Strikingly, coinciding with the rapidly increased prevalence of childhood asthma, an increase in air pollution (especially the air pollution episode or haze events) and social stress in China also has been reported (Chen et al., 2014; Huang et al., 2014). Whether the “double exposure” to high air pollution and high parental stress in China contributes to the rapidly increasing of childhood asthma is the focus of this research.

We hypothesize that there is a synergistic effect between exposures to parental stress and air pollution on childhood asthma. To test the hypothesis, we examined not only the role of parental stress in the association between exposure to air pollution and childhood asthma but also the role of air pollution in the association between exposure to parental stress and childhood asthma. We carried out a cohort study in Changsha as part of nationwide multi-center “China-Children-Homes-Health (CCHH)” study (Deng et al., 2015; Zhang et al., 2013). In the present study, parental stress includes socioeconomic stress and psychosocial stress, ambient air pollution includes both traffic- and industry-related air pollutants, and the exposure window includes both

prenatal and postnatal periods.

2. Materials and methods

2.1. Study population

Between September 2011 and January 2012, we conducted a survey for childhood asthma and allergies in the kindergartens in Changsha (Fig. 1). The cohort study protocol was described in detail elsewhere (Deng et al., 2016a). Briefly, we used a self-administered Chinese questionnaire to collect information on health status, exposure to indoor environment risk factors, and lifestyles of the children and their family members. A total of 4988 questionnaires were distributed to the children in 36 randomly selected kindergartens. Children were instructed to have the questionnaire completed by parents and to return it to kindergartens within one week. We received 3897 completed questionnaires (78% response rate). We excluded the following children: 745 children from kindergartens having response rates lower than 50%; 162 children with low birth weight and preterm birth and 10 children with multiple births; 15 children older than 6 years of age; and 65 children younger than 3; and 494 children without information about health outcome were excluded. In total, 2406 questionnaire responses from children aged 3–6 years were used.

2.2. Exposure windows

We considered both prenatal and postnatal exposure windows for each child. Prenatal exposure window was from the conception month to the birth month, and postnatal window spanned from the first month of the first year of life to the last month of last year before survey.

2.3. Exposure to parental stress

Parental stress in the present work was classified into 2 types: socioeconomic stress and psychosocial stress, which were obtained from the parent administered questionnaires. We used housing size to describe parental socioeconomic stress. Housing size has recently become a useful index of socioeconomic status (SES) to predict health outcomes (Butterfield et al., 2011; Juhn et al., 2011), and we further considered it as a kind of socioeconomic stress, as a lower SES is usually related to

higher stress level, particularly in China (Meyer et al., 2008). The housing size was determined according to the question “What’s the size of your house ($\leq 40/41\text{--}60/61\text{--}75/76\text{--}100/101\text{--}150/ > 150\text{ m}^2$)?” The socioeconomic stress was then divided into two levels: low (housing size $> 100\text{ m}^2$) and high (housing size $\leq 100\text{ m}^2$). The larger the housing size, the lower is the stress.

Since our questionnaire has not involved the questions for chronic psychosocial stress in parents, such as anxiety and depression, we evaluated parental psychosocial stress in terms of difficulty concentrating, a main and important symptom of depression, according to American Psychological Association (<http://www.apa.org/helpcenter/work-stress.aspx>). Difficulty concentrating during work was defined according to the question “During the past three months, how often do you have the feeling of difficulty concentrating (weekly/sometimes/never)?” According to the level of difficulty concentrating, psychosocial stress was also divided into two levels: low (never) and high (weekly or sometimes).

We assumed that parental socioeconomic and psychosocial stresses were stable during both prenatal and postnatal periods. The reason is that Chinese Household Registration System (or hukou) has posed severe restrictions on labor mobility (Tong and Piotrowski, 2012) and in the present work we found most children (higher than 70%) have been living in the same house. On the other hand, it was observed that the task-related job stressors, social stressors, and social support remained rather stable over the first 10 years since the young adults worked (Kälin et al., 2014).

2.4. Exposure to air pollution

Three pollutants, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter $\leq 10\text{ }\mu\text{m}$ in diameter (PM_{10}) were chosen as indicators of IRAP, TRAP, and mixture of air pollution, respectively (Deng et al., 2015). The daily (24-h) average concentrations of air pollutants during all children’s pre- and post-natal periods (2005–2011) were obtained from the seven municipal monitoring stations (Fig. 1).

We estimated children’s exposure at kindergartens. Children’s daily exposure to air pollutants at kindergartens was estimated in terms of daily average concentrations obtained at monitoring stations by an inverse distance weighted (IDW) method (Deng et al., 2015). Then, we calculated the monthly mean concentrations of air pollutants at each kindergarten. Finally, child’s prenatal exposure was calculated as average of the monthly mean concentrations of PM_{10} , SO_2 and NO_2 during the full gestational months, and child’s postnatal exposure was calculated as the average of the monthly mean concentrations of the air pollutants during the months from the first year of life to the last year before survey.

2.5. Health outcome

Health outcome is lifetime prevalence of doctor-diagnosed asthma that was defined as an affirmative answer to the question in the questionnaire: “Has a doctor ever diagnosed your child as having asthma?”

2.6. Confounding covariates

Potential confounding variables were obtained from the parent administered questionnaires including personal and indoor environmental factors. The personal covariates included child’s sex, age, breastfeeding, maternal productive age, and parental atopy. Breastfeeding was defined based on the answer to the question: “How long was your child breastfed or fed breast milk (None/ < 1 month/1–3 months/3–6 months/ > 6 months)?” and we divided it into two categories: no or yes. Parental atopy was defined as a history of maternal or paternal asthma and/or allergic rhinitis. The covariates related to indoor environment included environmental tobacco smoke (ETS) at home, indoor new furniture, house redecoration, visible mold/damp

stains at home, condensation on the windows during winter, and household pets (dogs) (Deng et al., 2016b; Norbäck et al., 2018). It was identified in previous studies that these confounders were related to childhood asthma and may influence the effect estimates (Deng et al., 2015).

2.7. Statistical analysis

We used multiple logistic regression models to evaluate the association between pre-/post-natal exposure to air pollutants and parental stress and childhood asthma by adjusting for potential confounding covariates. Associations in the regression analysis were calculated as odds ratios (ORs) with 95% confidence interval (95% CI). The association between childhood asthma and exposure to air pollutants was assessed by either continuous or categorical model. In continuous model, ORs were expressed by per interquantile range (IQR) increase in the exposure level for each pollutant. In categorical model, the exposure range was divided into low ($<$ median) and high ($\geq$ median), and OR at high exposure level was estimated as compared to the low exposure that was set as reference. The association between childhood asthma and exposure to parental stress was assessed by categorical model, during which OR at high parental stress was estimated as compared to the low parental stress. A p value less than 0.05 was considered statistically significant. We finally carried out sensitivity analysis by child’s sex. All statistical analyses were performed by SPSS software (version 16.0, SPSS Inc, Chicago, USA).

Table 1

Covariates, demographic information, and prevalence of asthma among children aged 3–6 years old ($n = 2406$).

	Number	(%)	Case (n)	Prevalence (%)	p-value
Total	2406	(100)	160	6.7	—
Sex					0.002
Boys	1291	(54)	105	8.1	
Girls	1115	(46)	55	4.9	
Age (years)					0.013
3	633	(26)	25	3.9	
4	873	(36)	70	8.0	
5	746	(31)	55	7.4	
6	154	(6)	10	6.5	
Breast-feeding					0.004
No	200	(8)	23	11.5	
Yes	2206	(92)	137	6.2	
Maternal reproductive age (years)^a					0.409
< 30	1717	(71)	110	6.4	
≥ 30	667	(28)	49	7.3	
Parental atopy					< 0.001
No	2149	(89)	106	4.9	
Yes	257	(11)	54	21.0	
Environmental tobacco smoke (ETS) at home					0.963
No	801	(33)	53	6.6	
Yes	1605	(67)	107	6.7	
Indoor new furniture^a					0.169
No	1144	(48)	69	6.0	
Yes	1095	(46)	82	7.5	
House redecoration^a					0.023
No	1561	(65)	96	6.1	
Yes	593	(25)	53	8.9	
Visible mold/damp stains at home^a					0.118
No	1821	(76)	113	6.2	
Yes	583	(24)	47	8.1	
Window condensation^a					0.004
No	1075	(45)	54	5.0	
Yes	1279	(53)	102	8.0	
Household pets (dogs)					0.156
No	2252	(94)	154	6.8	
Yes	154	(6)	6	3.9	

^a Sum of the number is not 2406 due to missing data. The p-values < 0.05 were in bold.

Table 2

Prevalence of parental stress and its associations with childhood asthma (n = 2406).

	Number	(%)	Case	(%)	OR (95% CI) ^a
Socioeconomic stress (housing size)					
Low (> 100 m ²)	978	(41)	56	(5.7)	1
High (≤ 100 m ²)	1403	(58)	103	(7.3)	1.48 (1.02, 2.16)*
Psychosocial stress (difficulty concentrating)					
Low (never)	1231	(51)	70	(5.7)	1
High (weekly or sometimes)	949	(39)	75	(7.9)	1.64 (1.00, 2.71)*
Both socioeconomic and psychosocial stress					
Low	495	(21)	24	(4.8)	1
High	540	(22)	48	(8.9)	2.05 (1.17, 3.58)*

The total number is not 2406 due to the missing data.

^a Adjustment for all the covariates in Table 1.

* p ≤ 0.05.

Table 3

Associations between exposure to air pollutants and childhood asthma (n = 2406).

Air pollutants	OR (95% CI) ^a
Prenatal (during pregnancy)	
PM ₁₀	0.96 (0.73, 1.28)
SO ₂	1.43 (1.10, 1.86)**
NO ₂	1.61 (1.19, 2.18)**
Postnatal (from the first year to the past year of life)	
PM ₁₀	1.45 (1.01, 2.10)*
SO ₂	1.35 (1.02, 1.79)*
NO ₂	1.76 (1.19, 2.61)**

OR (95%CI) was estimated for per interquartile range (IQR) increase in PM₁₀, SO₂, and NO₂.

**p ≤ 0.001.

^a Adjustment for all the covariates in Table 1.

* p ≤ 0.05.

** p ≤ 0.01.

3. Results

Of 2406 children, 160 (6.7%) had a history of doctor-diagnosed asthma. Table 1 shows the lifetime prevalence of asthma stratified by covariates. We found that the asthma prevalence in boys (8.1%), those without breast-feeding (11.5%), and those with parental atopy (21.0%) was significantly higher than the girls (4.9%), those with breast-feeding (6.2%), and those without parental atopy (4.9%). The asthmatic risk for older children was significantly higher than the young children aged 3 years (p = 0.013). Environmental tobacco smoke (ETS) was not associated with childhood asthma, but other indoor environmental factors

(new furniture, redecoration, mold/dampness, window condensation, and household pets) had marginal or significant risk.

The prevalence of parental stress and its association with childhood asthma were shown in Table 2. Children living in houses < 100 m² (58% of sample) had higher prevalence of asthma (7.3%) than those lived in larger houses. The children from families where parents reported difficulty concentrating (39%) had higher asthma prevalence (7.9%) than those from families that reported never having difficulty concentrating. We found that childhood asthma was significantly associated with parental stress with OR (95% CI) = 1.48 (1.02–2.16) for high socioeconomic stress and 1.64 (1.00–2.71) for high psychosocial stress after adjusting for the covariates. Exposure to both high socioeconomic and psychosocial stresses further increased the risk with OR (95% CI) = 2.05 (1.17–3.58).

The statistics of children's exposure to air pollutants was summarized in Table S1 (Please see the file in supplemental materials) and the association between exposure to air pollutants and childhood asthma was shown in Table 3. We found both SO₂ and NO₂ were significantly associated with childhood asthma, with adjusted OR (95% CI) respectively 1.43 (1.10–1.86) and 1.61 (1.19–2.18) during prenatal period and 1.35 (1.02–1.79) and 1.76 (1.19–2.61) during postnatal period for per IQR increase in the exposure level.

The combined effect of parental stress and air pollutants on childhood asthma was examined by stratified analysis. Table 4 showed the association between exposure to air pollutants and childhood asthma was significant only in children with high parental stress, and Table 5 showed the association between parental stress and childhood asthma was significant only in children exposed to high level of air pollution, which indicated a synergistical effect.

The interaction between parental stress and air pollution on the risk of childhood asthma was shown in Table 6. We found the asthmatic risk of high exposure to both parental stress and air pollution was significantly higher than the risk of low exposure to parental stress and air pollution. There is a strong interaction (p < 0.1) between psychosocial stress and exposure to air pollutants during prenatal period, but a strong interaction (p < 0.1) between both socioeconomic and psychosocial stresses and exposure to NO₂ during postnatal period.

We further investigated the association between air pollution and childhood asthma stratified by maternal and paternal psychosocial stresses (the maternal and paternal socioeconomic stresses are the same in a family), as shown in Table 7. We found that paternal stress significantly modified the association during prenatal period, but maternal stress modified the association during postnatal period.

We examined the gender sensitivity for the independent and synergistic effects of exposure to parental stress and air pollution on childhood asthma. Table S2 (Please see the supplemental materials) showed that the asthmatic risks of exposure to air pollution and

Table 4

Associations between exposure to air pollutants and childhood asthma stratified by parental stress (n = 2406).

	Socioeconomic stress, OR (95% CI)		Psychosocial stress, OR (95% CI)	
	Low (n = 978)	High (n = 1403)	Low (n = 1231)	High (n = 949)
Prenatal				
PM ₁₀	0.58 (0.34, 0.99)*	1.16 (0.83, 1.63)	1.16 (0.75, 1.79)	0.77 (0.50, 1.16)
SO ₂	1.20 (0.75, 1.91)	1.51 (1.09, 2.10)*	1.16 (0.77, 1.74)	1.64 (1.11, 2.42)*
NO ₂	1.29 (0.78, 2.12)	1.77 (1.20, 2.61)**	1.18 (0.73, 1.90)	1.93 (1.26, 2.96)**
Postnatal				
PM ₁₀	1.42 (0.79, 2.54)	1.44 (0.89, 2.32)	1.28 (0.74, 2.23)	1.62 (0.95, 2.77)
SO ₂	0.99 (0.60, 1.61)	1.53 (1.07, 2.18)*	1.15 (0.75, 1.78)	1.34 (0.89, 2.01)
NO ₂	1.17 (0.63, 2.20)	2.18 (1.31, 3.64)**	1.31 (0.72, 2.40)	2.03 (1.15, 3.58)*

OR (95%CI) was estimated for per interquartile range (IQR) increase in PM₁₀, SO₂, and NO₂ and adjusted for the covariates in Table 1 (child's sex, age, breast-feeding, maternal productive age, parental atopy, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation, and household pets).

* p ≤ 0.05.

** p ≤ 0.01.

Table 5

Associations between parental stress and childhood asthma stratified by low and high levels of exposure to air pollution (n = 2406).

		Socioeconomic stress		Psychosocial stress	
Pollutants	Exposure level	Low (n = 978)	High (n = 1403)	Low (n = 1231)	High (n = 949)
Prenatal					
PM ₁₀	Low	1	1.13 (0.66, 1.93)	1	1.76 (1.02, 3.05)*
	High	1	1.98 (1.16, 3.39)*	1	1.10 (0.64, 1.89)
SO ₂	Low	1	1.19 (0.67, 2.14)	1	0.72 (0.39, 1.33)
	High	1	1.69 (1.02, 2.81)*	1	2.00 (1.19, 3.35)**
NO ₂	Low	1	1.26 (0.71, 2.25)	1	0.89 (0.49, 1.64)
	High	1	1.68 (1.01, 2.81)*	1	1.80 (1.09, 2.99)*
Postnatal					
PM ₁₀	Low	1	1.46 (0.83, 2.58)	1	1.13 (0.64, 1.98)
	High	1	1.47 (0.88, 2.43)	1	1.64 (0.97, 2.79)
SO ₂	Low	1	1.24 (0.71, 2.16)	1	1.04 (0.59, 1.83)
	High	1	1.72 (1.01, 2.93)*	1	1.78 (1.01, 3.14)*
NO ₂	Low	1	0.96 (0.53, 1.75)	1	0.70 (0.37, 1.33)
	High	1	1.86 (1.13, 3.08)*	1	1.95 (1.18, 3.21)**

Exposure levels were divided into low (< median) and high (≥ median) categories.

OR (95%CI) was adjusted for all the covariates in Table 1.

* p ≤ 0.05.

** p ≤ 0.01.

Table 6

Interaction between parental stress and air pollution on childhood asthma in terms of adjusted odds ratios (95% CI) (n = 2406).

	Exposure level	Stress level	Socioeconomic stress	Psychosocial stress
Prenatal				
PM ₁₀	Low	Low	1	1
	Low	High	1.11 (0.65, 1.89)	1.71 (0.99, 2.96)
	High	Low	0.69 (0.36, 1.31)	1.12 (0.61, 2.08)
	High	High	1.32 (0.73, 2.39)	1.26 (0.67, 2.36)
	Interaction p		.149	0.275
SO ₂	Low	Low	1	1
	Low	High	1.21 (0.68, 2.16)	0.76 (0.42, 1.38)
	High	Low	1.45 (0.79, 2.67)	1.03 (0.58, 1.81)
	High	High	2.41 (1.40, 4.16)**	2.04 (1.23, 3.40)**
	Interaction p		.417	0.015
NO ₂	Low	Low	1	1
	Low	High	1.26 (0.71, 2.22)	0.91 (0.50, 1.64)
	High	Low	1.38 (0.76, 2.51)	1.15 (0.66, 2.00)
	High	High	2.17 (1.28, 3.66)**	2.07 (1.23, 3.47)**
	Interaction p		.559	0.082
Postnatal				
PM ₁₀	Low	Low	1	1
	Low	High	1.56 (0.89, 2.73)	1.09 (0.63, 1.90)
	High	Low	1.39 (0.72, 2.69)	0.95 (0.51, 1.78)
	High	High	1.98 (1.07, 3.67)*	1.58 (0.88, 2.81)
	Interaction p		.808	0.285
SO ₂	Low	Low	1	1
	Low	High	1.29 (0.75, 2.23)	1.05 (0.60, 1.82)
	High	Low	1.14 (0.62, 2.09)	0.95 (0.54, 1.68)
	High	High	1.87 (1.09, 3.19)*	1.61 (0.96, 2.70)
	Interaction p		.534	0.210
NO ₂	Low	Low	1	1
	Low	High	0.97 (0.54, 1.75)	0.76 (0.41, 1.41)
	High	Low	1.32 (0.73, 2.39)	1.18 (0.69, 2.04)
	High	High	2.44 (1.46, 4.06)***	2.29 (1.39, 3.77)***
	Interaction p		.103	0.020

Exposure levels were divided into low (< median) and high (≥ median) categories.

The risk at the low exposure and low stress was set as reference, i.e. OR = 1.

OR (95%CI) was adjusted for all the covariates in Table 1.

* p ≤ 0.05.

** p ≤ 0.01.

*** p ≤ 0.001.

parental stress were both significant in boys only. Table 8 further showed that the asthmatic risks of synergistic exposure to air pollution and high parental stress asthma were also significant in boys only.

4. Discussion

This is the first cohort study to examine the synergistic effect between parental stress and air pollution on childhood asthma. We found that the association with air pollution was significant only in children exposed to high parental stress, the association with parental stress was significant only in children exposed to high level of air pollution, and the association was the strongest in children exposed to a combination of parental stress and air pollution. Sensitivity analysis showed that the independent and synergistic effects of parental stress and air pollution on childhood asthma were stronger in boys. The strength of our study includes: (1) we provided further evidence on the modification of the association between air pollution and childhood asthma by social stress; (2) we newly found that the association between social stress and childhood asthma was modified by air pollution; (3) our findings demonstrated an interactive or synergistic effects between air pollution and social stress on childhood asthma.

In our present work, we considered the housing size as a kind of socioeconomic stress as we hope to find the common and similar effect with the psychosocial stress during work. Housing size was in fact a proxy of parental socioeconomic status (SES). Juhn et al. (2011) first developed the housing characteristics (housing size was the most important component) to measure SES and predict health outcomes. Its utility is qualified by specific social contexts and in concert with other SES indices, and recently housing size has become a useful index of SES to predict health outcomes (Butterfield et al., 2011). It is reasonable to consider housing size as a kind of socioeconomic stress, as a lower socio-economic status (SES) is usually related to higher stress level (Meyer et al., 2008). Growing evidence suggests that exposure to lower SES could increase the risk for mental illnesses, such as depression and anxiety disorders, throughout life (Zimmerman and Katon, 2005). In the recent years, SES has been demonstrated to be associated with symptoms of depression and anxiety, and it was found that symptoms of depression and anxiety are more prevalent among persons with lower compared to higher SES (Lorant et al., 2007; Tracy et al., 2008). A

Table 7

Associations between exposure to air pollutants and childhood asthma stratified by maternal and paternal stress.

	Maternal psychosocial stress (n = 1668)		Paternal psychosocial stress (n = 512)	
	Low (n = 921)	High (n = 747)	Low (n = 310)	High (n = 202)
Prenatal				
PM ₁₀	1.46 (0.89, 2.38)	0.67 (0.42, 1.08)	0.40 (0.14, 1.12)	1.90 (0.68, 5.28)
SO ₂	0.97 (0.62, 1.54)	1.49 (0.97, 2.28)	2.81 (0.94, 8.40)	4.66 (1.18, 18.35)*
NO ₂	1.00 (0.59, 1.70)	1.59 (1.00, 2.51)	2.41 (0.69, 8.38)	8.76 (1.92, 40.01)**
Postnatal				
PM ₁₀	1.17 (0.64, 2.15)	1.62 (0.91, 2.89)	2.24 (0.46, 10.92)	1.61 (0.32, 8.11)
SO ₂	1.06 (0.66, 1.72)	1.33 (0.86, 2.06)	1.72 (0.52, 5.72)	1.69 (0.49, 5.80)
NO ₂	1.11 (0.57, 2.17)	1.93 (1.05, 3.55)*	2.94 (0.57, 15.21)	3.68 (0.59, 22.87)

OR (95%CI) was estimated for per interquartile range (IQR) increase in PM₁₀, SO₂, and NO₂ and adjusted for the covariates in Table 1 (child's sex, age, breast-feeding, maternal productive age, parental atopy, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation, and household pets).

* p ≤ 0.05.

** p ≤ 0.01.

Table 8

Associations between exposure to air pollutants and childhood asthma stratified by parental stress respectively for boys and girls (n = 2406).

	Socioeconomic stress		Psychosocial stress	
	Low	High	Low	High
Boys				
Prenatal				
PM ₁₀	0.46 (0.22, 0.97)*	1.28 (0.83, 1.97)	1.42 (0.80, 2.55)	0.68 (0.39, 1.19)
SO ₂	1.32 (0.70, 2.48)	1.80 (1.20, 2.69)**	1.50 (0.89, 2.53)	1.86 (1.14, 3.04)*
NO ₂	1.48 (0.75, 2.92)	2.11 (1.29, 3.46)**	1.60 (0.86, 3.00)	2.08 (1.19, 3.62)**
Postnatal				
PM ₁₀	1.04 (0.50, 2.18)	1.55 (0.85, 2.83)	1.06 (0.53, 2.12)	1.82 (0.91, 3.63)
SO ₂	1.01 (0.53, 1.91)	1.68 (1.09, 2.60)*	1.41 (0.81, 2.47)	1.40 (0.84, 2.32)
NO ₂	1.40 (0.60, 3.28)	2.62 (1.37, 5.00)**	1.75 (0.78, 3.91)	2.42 (1.17, 5.01)*
Girls				
Prenatal				
PM ₁₀	0.68 (0.31, 1.49)	1.11 (0.63, 1.95)	0.92 (0.47, 1.81)	0.96 (0.51, 1.83)
SO ₂	1.10 (0.55, 2.23)	1.03 (0.57, 1.87)	0.71 (0.36, 1.40)	1.29 (0.65, 2.54)
NO ₂	1.13 (0.53, 2.41)	1.33 (0.69, 2.58)	0.73 (0.34, 1.55)	1.68 (0.84, 3.37)
Postnatal				
PM ₁₀	2.46 (0.87, 6.95)	1.21 (0.54, 2.73)	1.63 (0.64, 4.18)	1.27 (0.53, 3.06)
SO ₂	0.96 (0.44, 2.10)	1.23 (0.65, 2.31)	0.78 (0.38, 1.61)	1.18 (0.59, 2.38)
NO ₂	1.00 (0.38, 2.60)	1.54 (0.65, 3.66)	0.86 (0.33, 2.19)	1.43 (0.57, 3.61)

OR (95%CI) was estimated for per interquartile range (IQR) increase in PM₁₀, SO₂, and NO₂ and adjusted for the covariates in Table 1 (child's sex, age, breast-feeding, maternal productive age, parental atopy, ETS, new furniture, house redecoration, visible mold/damp stains, window condensation, and household pets).

* p ≤ 0.05.

** p ≤ 0.01.

recent review and meta-analysis also found compelling evidence for socioeconomic inequality in depression (Lorant et al., 2003). House has become a significant stressor in China due to its high cost.

We found pre- and post-natal exposures to both TRAP (NO₂) and IRAP (SO₂) were associated with childhood asthma. The association between long-term postnatal exposure to TRAP and childhood asthma were observed in many previous birth cohort studies worldwide, such as in Canada (Clark et al., 2010; Gauderman et al., 2005; Jerrett et al., 2008; McConnell et al., 2010), France (Zmirou et al., 2004), Germany (Morgenstern et al., 2008), Japan (Yamazaki et al., 2014), Netherlands (Brauer et al., 2007; Gehring et al., 2010), Sweden (Gruzjeva et al., 2013), USA (Nishimura et al., 2013), and China (Deng et al., 2015; Liu et al., 2016). Recent systematic reviews and meta-analyses of birth cohort studies also confirmed the association of TRAP with childhood incident asthma (Anderson et al., 2013; Bowatte et al., 2015; Gasana et al., 2012). Only a few studies investigated the asthmatic risk of prenatal exposure to TRAP and our findings were also consistent with these scarce studies (Clark et al., 2010; Deng et al., 2015, 2016a; Hsu et al., 2015; Liu et al., 2016; Sbihi et al., 2016). We further confirmed the recent studies in China that long-term exposure to IRAP (SO₂) was also associated with childhood asthma (Chiang et al., 2016; Deng et al.,

2015, 2016a), although it has been ignored in the developed countries due to its low concentration level (Pénard-Morand et al., 2010).

We found childhood asthma was associated with parental socioeconomic stress, i.e. higher risk of asthma at higher socioeconomic stress or lower socioeconomic status (SES). The evidence for the link between SES and the development of asthma is less clear. Although many studies report asthma to be more prevalent among lower SES children (Almqvist et al., 2005; Galobardes et al., 2015; Hammer-Helmich et al., 2014; Kozyrskyj et al., 2010), several studies found no significant impact of SES on the prevalence of childhood asthma (Hancox et al., 2004). However, a recent review and meta-analysis indicated that lower SES associated with higher prevalence of asthma (Uphoff et al., 2015). A possible mechanism by which SES may modify the effects of air pollution is psychological stress. Several studies suggest that increased severity of asthma among low SES children and adults may be explained by stress.

We found parental psychosocial stress predicted higher risk of asthma in children that was consistent with the findings from many previous investigations (Chen et al., 2006; Sandberg et al., 2004). The literatures mainly focused on chronic psychosocial stress in terms of depression and/or anxiety (Del Giacco et al., 2016; Kozyrskyj et al.,

2008; Lee and Wright, 2016). Recently, there is an increasing body of evidence supporting a causal relationship between prenatal maternal stress and asthma risk in the offspring (Plant et al., 2015). A UK birth cohort observed that maternal anxiety symptoms during fetal life may lead to the development of childhood asthma (Cookson et al., 2009). A recent prospective cohort study in Denmark showed that prenatal depressions in both mother and father were associated with increased risk of asthma in children (Liu et al., 2015). A growing number of studies suggest that maternal stress during pregnancy promotes atopic disorders in the offspring and recent systematic reviews and meta-analyses also suggested a relationship between maternal stress during pregnancy and atopic disorders in the child (Andersson et al., 2016; Van De Loo et al., 2016).

We found that exposure to multiple stressors, both socioeconomic and psychosocial stresses, predicted a higher risk of asthma, which was also consistent with some scarce studies (Chen et al., 2006; Exley et al., 2015; Sandberg et al., 2000). The strongest associations were consistently observed in workers with low educational level or low occupational position, which indicated that stress at work either mediates the association of low socioeconomic status with poorer health or interacts with low socioeconomic status to produce a high risk of poorer health (Wege et al., 2008). The reason may be due to that individuals of low socioeconomic status possess fewer resources to cope with the burden of work and as a result, they may more often experience prolonged or more intense stress (Wege et al., 2008).

We found that children from high parental socioeconomic stress or low socioeconomic status (SES) families were at higher risk of incident asthma due to air pollution. The short-term effect of outdoor air pollution on child hospitalization for asthma was larger in children with higher stress or lower SES has been observed in many countries (Burra et al., 2009; Lin et al., 2004; Neidell, 2004). A US cohort study observed a stronger long-term asthmatic risk among children with low SES as compared to those with high SES (Shankardass et al., 2009). A recent cohort study in Canada observed that children from lower SES households have a higher risk of respiratory diseases due to long-term exposure to air pollution (Cakmak et al., 2016). However, very few studies investigated the association between early life SES and asthma (Braback et al., 2005; Patel et al., 2012). Children from lower SES families may be at higher risk from air pollution, as they tend to live near heavy polluted areas (O'Neill and Schwartz, 2003).

We found that parental psychosocial stress enhanced the effect of air pollution on childhood asthma. Very few studies have assessed the potential role of stress as susceptibility factor in the association between air pollution and childhood asthma (Cooney, 2011). A US cohort study observed that parental stress increased the impact of TRAP on the incidence of asthma in children age 5–9 years (Shankardass et al., 2009). Another US birth cohort study found a positive association between TRAP (NO₂) and asthma only among children with elevated exposure to violence, a social stressor in urban areas (Clougherty et al., 2007). Another Canadian study also found that vulnerability to asthma exacerbations may be heightened in children exposed to higher chronic stress (Chen et al., 2008). A recent birth cohort study found that 'stressful' family events may also increase children's susceptibility to the adverse effect of TRAP exposure (Rancière et al., 2017). On the other hand, very few studies considered effects of prenatal exposures to parental stress and air pollution (Chiu et al., 2014; Exley et al., 2015; Wright, 2007).

We found that paternal psychosocial stress significantly modified the prenatal association between air pollution and childhood asthma. Much attention has been given to the effect of maternal stress on childhood asthma morbidity, whereas little is known about the influence of paternal stress on childhood asthma. It was found that paternal depressive symptoms or lower occupational class contributed to the child's asthma morbidity (Lim et al., 2011; Patel et al., 2012). A recent

study found paternal depression during pregnancy was also associated with childhood asthma (Liu et al., 2015). A US cohort study observed that both maternal and paternal depressions were associated with asthma morbidity in young children (Lange et al., 2011).

We found that the asthmatic risks of exposure to air pollution and parental stress were both significant in boys only. Sex-specific effects of stress on childhood asthma are limited with conflicting results. A recent study found male gender may increase their susceptibility to the adverse effect of early TRAP exposure (Rancière et al., 2017) and another study reported a stronger susceptibility of TRAP modified by parental stress for male children compared to female children (Shankardass et al., 2009). A recent US cohort study found that boys were more vulnerable to maternal stress during prenatal period but girls vulnerable to higher stress during postnatal period (Lee and Wright, 2016). However, another study found that prenatal maternal depression increased asthma in girls but not boys (Turcotte-Tremblay et al., 2014).

The interaction or "synergistic" effect between social stresses and physical pollutants on childhood asthma may due to a common biologic pathway of both exposures (Clougherty and Kubzansky, 2009). It was well known that the air pollution could induce childhood asthma by the mechanism of oxidative stress that resulted in airway inflammation. It was demonstrated that a parent's perceived stress or depression may be transmitted to their child and can be indicative of stress in children (Pearson et al., 2013; Wolf et al., 2008). On the other hand, maternal stress during pregnancy could affect the developing foetus and increased the risk of stress in the offspring (O'Donnell et al., 2013). Psychosocial stress has been linked to inflammation and oxidative stress (Umetsu et al., 2002). Synergistic effects of stress and pollutants are possible because they likely act on common biological systems. A consistent body of evidence indicates that depression is associated with dysregulated inflammation. Recent meta-analyses reported significantly higher levels of the inflammatory markers in depressed subjects compared to controls (Dowlati et al., 2010; Liu et al., 2012). Experimental research also underlined the effects of acute psychosocial stress on inflammatory responses (Steptoe et al., 2007).

Some limitations of this study should be acknowledged. First, we used housing size as a proxy of socioeconomic stress in China. Although it is reasonable to regard it as a kind of stress, housing size is in fact an index of socioeconomic status. We couldn't distinguish the asthmatic risk effects between socioeconomic status and stress. Secondly, we didn't measure the children stress. Previous studies have demonstrated a relationship between parental and childhood stress. Parental stress has been shown to be indicative of stress in children and it was found that a parent's perceived stress may be transmitted to their child (Islam et al., 2011; Wolf et al., 2008). A longitudinal cohort study demonstrated that both prenatal and postnatal parental depression was associated with increased risk of depression in offspring (Quarini et al., 2015). However, the use of parental stress as a proxy for childhood stress limited our ability to distinguish between the effects of parental and personal stresses in the children. The third limitation is we assumed a stable parental socioeconomic and psychosocial stresses. Although it seemed reasonable, parental stress may be changed over time and thus it is better to accurately capture stress in different life domains. On the other hand, we cannot disentangle the effect of parental stresses between prenatal and postnatal periods. The fourth limitation is the potential misclassification of exposure. We estimated children's exposure to air pollution during pregnancy and postnatal life according to their exposure in kindergarten. It will be much better if we could use the home address for prenatal exposure assessment. But in our questionnaire we didn't ask the children's home address because it is a very sensitive and private question in China. However, the exposure assessment was reasonable by considering the situation in China that the parents usually enrolled their children in kindergarten nearest to their home and that parents usually worked near home or kindergartens. In

addition, the monthly average exposure would cause misclassification in exposure in pregnancy. The main reason is that we assessed children's exposure to air pollutants based on monthly average concentrations, because our survey have collected only information about birth month and gestational months of each child.

5. Conclusions

We found that childhood asthma was associated with pre- and post-natal exposure to both air pollution and parental stress, suggesting that both physical toxins and social determinants played an etiologic role in the evolution and trajectory of childhood asthma. Our findings have potentially important implications for both public health and intervention policy. Our study highlights the need to be aware of vulnerability to asthma development in the children who lived in areas with higher levels of air pollution, especially in those families experiencing higher levels of parental stress.

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Competing financial interests

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2018.04.003>.

References

- Almqvist, C., Pershagen, G., Wickman, M., 2005. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin. Exp. Allergy* 35, 612–618.
- Anderson, H.R., Favarato, G., Atkinson, R.W., 2013. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Qual. Atmos. Health* 6, 47–56.
- Andersson, N.W., Hansen, M.V., Larsen, A.D., Hougaard, K.S., Kolstad, H.A., Schläpffen, V., 2016. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy* 71, 15–26.
- Bose, S., Chiu, Y.M., Hsu, H.L., Di, Q., Rosa, M.J., Lee, A., et al., 2017. Prenatal nitrate exposure and childhood asthma: influence of maternal prenatal stress and fetal sex. *Am. J. Respir. Crit. Care Med* 196, 1396–1403.
- Bowatte, G., Lodge, C., Lowe, A.J., Erbas, B., Perret, J., Abramson, M.J., et al., 2015. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and meta-analysis of birth cohort studies. *Allergy* 70, 245–256.
- Braback, L., Hjert, A., F R, 2005. Social class in asthma and allergic rhinitis: a national cohort study over three decades. *Eur. Respir. J.* 26, 1064–1068.
- Brauer, M., Hoek, G., Smit, H., De Jongste, J., Gerritsen, J., Postma, D.S., et al., 2007. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur. Respir. J.* 29, 879–888.
- Brunst, K.J., Ryan, P.H., Brokamp, C., Bernstein, D., Reponen, T., Lockey, J., et al., 2015. Timing and duration of traffic-related air pollution exposure and the risk for childhood wheeze and asthma. *Am. J. Respir. Crit. Care Med* 192, 421–427.
- Burra, T.A., Moineddin, R., Agha, M.M., Glazier, R.H., 2009. Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. *Environ. Res* 109, 567–574.
- Butterfield, M.C., Williams, A.R., Beebe, T., Finnie, D., Liu, H., Liesinger, J., et al., 2011. A two-county comparison of the houses index on predicting self-rated health. *J. Epidemiol. Community Health* 65, 254–259.
- Cakmak, S., Hebborn, C., Cakmak, J.D., Vanos, J., 2016. The modifying effect of socioeconomic status on the relationship between traffic, air pollution and respiratory health in elementary schoolchildren. *J. Environ. Manag* 177, 1–8.
- Chen, E., Hanson, M.D., Paterson, L.Q., Griffin, M.J., Walker, H.A., Miller, G.E., 2006. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. *J. Allergy Clin. Immunol.* 117, 1014–1020.
- Chen, E., Schreier, H.M., Strunk, R.C., Brauer, M., 2008. Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environ. Health Perspect.* 116, 970–975.
- Chen, J., Li, X., Natsuaki, M.N., Leve, L.D., Harold, G.T., 2014. Genetic and environmental influences on depressive symptoms in Chinese adolescents. *Behav. Genet.* 44, 36–44.
- Chiang, T.Y., Yuan, T.H., Shie, R.H., Chen, C.F., Chan, C.C., 2016. Increased incidence of allergic rhinitis, bronchitis and asthma, in children living near a petrochemical complex with SO₂ pollution. *Environ. Int* 96, 1–7.
- Chiu, Y.-H.M., Coull, B.A., Sternthal, M.J., Kloog, I., Schwartz, J., Cohen, S., et al., 2014. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J. Allergy Clin. Immunol.* 133, 713–722.
- Clark, N.A., Demers, P.A., Karr, C.J., Koehoorn, M., Lencar, C., Tamburic, L., et al., 2010. Effect of early life exposure to air pollution on development of childhood asthma. *Environ. Health Perspect.* 118, 284–290.
- Clougherty, J.E., Levy, J.I., Kubzansky, L.D., Ryan, P.B., Suglia, S.F., Canner, M.J., et al., 2007. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ. Health Perspect.* 115, 1140–1146.
- Clougherty, J.E., Kubzansky, L.D., 2009. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ. Health Perspect.* 117, 1351–1358.
- Cookson, H., Granell, R., Joinson, C., Ben-Shlomo, Y., Henderson, A.J., 2009. Mothers' anxiety during pregnancy is associated with asthma in their children. *J. Allergy Clin. Immunol.* 123, 847–853.
- Cooney, C.M., 2011. Stress-pollution interactions: an emerging issue in children's health research. *Environ. Health Perspect.* 119, A431–A435.
- Del Giacco, S.R., Cappai, A., Gambula, L., Cabras, S., Perra, S., Manconi, P.E., et al., 2016. The asthma-anxiety connection. *Respir. Med* 120, 44–53.
- Deng, Q., Lu, C., Norbäck, D., Bornehag, C.-G., Zhang, Y., Liu, W., et al., 2015. Early life exposure to ambient air pollution and childhood asthma in China. *Environ. Res* 143, 83–92.
- Deng, Q., Lu, C., Li, Y., Sundell, J., Norbäck, D., 2016a. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environ. Res* 150, 119–127.
- Deng, Q., Lu, C., Ou, C., Chen, L., Yuan, H., 2016b. Preconceptional, prenatal and post-natal exposure to outdoor and indoor environmental factors on allergic diseases/symptoms in preschool children. *Chemosphere* 152, 459–467.
- Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., et al., 2010. A meta-analysis of cytokines in major depression. *Biol. Psychiatry* 67, 446–457.
- Eder, W., Ege, M.J., von Mutius, E., 2006. The asthma epidemic. *N. Engl. J. Med* 355, 2226–2235.
- Exley, D., Norman, A., Hyland, M., 2015. Adverse childhood experience and asthma onset: a systematic review. *Eur. Respir. Rev.* 24, 299–305.
- Flanigan, C., Sheikh, A., Dunngalvin, A., Brew, B.K., Almqvist, C., Nwaru, B.I., 2018. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. *Clin. Exp. Allergy* 48, 403–414.
- Galobardes, B., Granell, R., Sterne, J., Hughes, R., Mejia-Lancheros, C., Smith, G.D., et al., 2015. Childhood wheezing, asthma, allergy, atopy, and lung function: different socioeconomic patterns for different phenotypes. *Am. J. Epidemiol.* 182, 763–774.
- Gasana, J., Dillikar, D., Mendy, A., Forno, E., Vieira, E.R., 2012. Motor vehicle air pollution and asthma in children: a meta-analysis. *Environ. Res* 117, 36–45.
- Gauderman, W.J., Avol, E., Lurmann, F., Kuenzli, N., Gilliland, F., Peters, J., et al., 2005. Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 16, 737–743.
- Gehring, U., Wijga, A.H., Brauer, M., Fischer, P., de Jongste, J.C., Kerkhof, M., et al., 2010. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am. J. Respir. Crit. Care Med* 181, 596–603.
- Gruzdeva, O., Bergström, A., Hulchiy, O., Kull, I., Lind, T., Melén, E., et al., 2013. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiol* 24, 54–61.
- Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. *Lancet* 383, 1581–1592.
- Hajat, A., Hsia, C., O'Neill, M.S., 2015. Socioeconomic disparities and air pollution exposure: a global review. *Curr. Environ. Health Rep.* 2, 440–450.
- Hammer-Helmich, L., Linneberg, A., Thomsen, S.F., Glümer, C., 2014. Association between parental socioeconomic position and prevalence of asthma, atopic eczema and hay fever in children. *Scand. J. Public Health* 42, 120–127.
- Hancox, R.J., Milne, B.J., Taylor, D.R., Greene, J.M., Cowan, J.O., Flannery, E.M., et al., 2004. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 59, 376–380.
- Heinrich, J., 2015. Can prenatal maternal stress increase the risk of asthma? *Expert Rev. Respir. Med* 9, 379–381.
- Hsu, H.-L.L., Chiu, Y.-H.M., Coull, B.A., Kloog, I., Schwartz, J., Lee, A., et al., 2015. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. *Am. J. Respir. Crit. Care Med* 192, 1052–1059.
- Huang, R.J., Zhang, Y., Bozzetti, C., Ho, K.F., Cao, J.J., Han, Y., et al., 2014. High secondary aerosol contribution to particulate pollution during haze events in China. *Nature* 514, 218–222.
- Islam, T., Urman, R., Gauderman, W.J., Milam, J., Lurmann, F., Shankardass, K., et al., 2011. Parental stress increases the detrimental effect of traffic exposure on children's lung function. *Am. J. Respir. Crit. Care Med* 184, 822–827.
- Jerrett, M., Shankardass, K., Berhane, K., Gauderman, W.J., Künzli, N., Avol, E., et al., 2008. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ. Health Perspect.* 116, 1433–1438.
- Juhn, Y.J., Beebe, T.J., Finnie, D.M., Sloan, J., Wheeler, P.H., Yawn, B., et al., 2011. Development and initial testing of a new socioeconomic status measure based on housing data. *J. Urban Health* 88, 933–944.

- Kälin, W., Keller, A.C., Tschann, F., Elfering, A., Semmer, N.K., 2014. Work experiences and well-being in the first years of professional work in Switzerland: a ten-year follow-up study. In: Keller, A.C., Samuel, R., Bergman, M.M., Semmer, N.K. (Eds.), *Psychological, educational, and sociological perspectives on success and well-being in career development*. Springer, Netherlands, pp. 151–170.
- Kozyrskyj, A.L., Mai, X.M., McGrath, P., Hayglass, K.T., Becker, A.B., Macneil, B., 2008. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. *Am. J. Respir. Crit. Care Med* 177, 142–147.
- Kozyrskyj, A.L., Kendall, G.E., Jacoby, P., Sly, P.D., Zubrick, S.R., 2010. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am. J. Public Health* 100, 540–546.
- Lange, N.E., Bunyavanich, S., Silberg, J.L., Canino, G., Rosner, B.A., Celedón, J.C., 2011. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J. Allergy Clin. Immunol.* 127, 734–740.
- Lee, A., Chiu, Y.H.M., Rosa, M.J., Jara, C., Wright, R.O., Coull, B.A., et al., 2016. Prenatal and postnatal stress and asthma in children: temporal- and sex-specific associations. *J. Allergy Clin. Immunol.* 138, 740–747.
- Lee, A., Hsu, H.H.L., Chiu, Y.H.M., Bose, S., Rosa, M.J., Kloog, I., et al., 2018. Prenatal fine particulate exposure and early childhood asthma: effect of maternal stress and fetal gender sex. *J. Allergy Clin. Immunol.* <http://dx.doi.org/10.1016/j.jaci.2017.07.017>.
- Lee, A., Wright, R.J., 2016. Prenatal stress and childhood asthma risk: taking a broader view. *Eur. Respir. J.* 47, 406–409.
- Lim, J., Wood, B.L., Miller, B.D., Simmens, S.J., 2011. Effects of paternal and maternal depressive symptoms on child internalizing symptoms and asthma disease activity: mediation by interparental negativity and parenting. *J. Fam. Psychol.* 25, 137–146.
- Lin, M., Chen, Y., Villeneuve, P.J., Burnett, R.T., Lemyre, L., Hertzman, C., et al., 2004. Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. *Am. J. Epidemiol.* 159, 294–303.
- Liu, W., Huang, C., Hu, Y., Fu, Q., Zou, Z., Sun, C., et al., 2016. Associations of gestational and early life exposures to ambient air pollution with childhood respiratory diseases in Shanghai, China: a retrospective cohort study. *Environ. Int* 92, 284–293.
- Liu, X., Olsen, J., Pedersen, L.H., Agerbo, E., Yuan, W., Li, J., 2015. Antidepressant use during pregnancy and asthma in the offspring. *Pediatrics* 135, 911–917.
- Liu, Y., Ho, R.C., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF- α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J. Affect Disord.* 139, 230–239.
- London, S.J., 2007. Gene–air pollution interactions in asthma. *Proc. Am. Thorac. Soc.* 4, 217–220.
- Lorant, V., Delière, D., Eaton, W., Robert, A., Philippot, P., Ansseau, M., 2003. Socioeconomic inequalities in depression: a meta-analysis. *Am. J. Epidemiol.* 157, 98–112.
- McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., et al., 2010. Childhood incident asthma and traffic-related air pollution at home and school. *Environ. Health Perspect.* 118, 1021–1026.
- Meyer, I.H., Schwartz, S., Frost, D.M., 2008. Social patterning of stress and coping: does disadvantaged social statuses confer more stress and fewer coping resources? *Soc. Sci. Med* 67, 368–379.
- Morgenstern, V., Zutavern, A., Cyrys, J., Brockow, I., Koletzko, S., Kramer, U., et al., 2008. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am. J. Respir. Crit. Care Med* 177, 1331–1337.
- Neidell, M.J., 2004. Air pollution, health, and socio-economic status: the effect of outdoor air quality on childhood asthma. *J. Health Econ.* 23, 1209–1236.
- Nishimura, K.K., Galanter, J.M., Roth, L.A., Oh, S.S., Thakur, N., Nguyen, E.A., et al., 2013. Early-life air pollution and asthma risk in minority children. The gala ii and sage ii studies. *Stud. Am. J. Respir. Crit. Care Med* 188, 309–318.
- Norbäck, D., Lu, C., Zhang, Y., Li, B., Zhao, Z., Huang, C., Zhang, X., Qian, H., Sundell, J., Deng, Q., 2018. Asthma and rhinitis among Chinese children - indoor and outdoor air pollution and socioeconomic indicators (SEI). *Environ. Int* 115, 1–8.
- O'Neill, M.S., Schwartz, J., 2003. Health, wealth, and air pollution: advancing theory and methods. *Environ. Health Perspect.* 111, 1861–1870.
- O'Donnell, K.J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., et al., 2013. Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology* 38, 1630–1638.
- Pénard-Morand, C., Raherison, C., Charpin, D., Kopferschmitt, C., Lavaud, F., Caillaud, D., et al., 2010. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur. Respir. J.* 36, 33–40.
- Patel, S., Henderson, J., Jeffreys, M., Smith, G.D., Galobardes, B., 2012. Associations between socioeconomic position and asthma- findings from a historical cohort. *Eur. J. Epidemiol.* 27, 623–631.
- Pearson, R.M., Evans, J., Kounali, D., Lewis, G., Heron, J., Ramchandani, P., et al., 2013. Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at 18 years. *JAMA Psychiatry* 70, 1312–1319.
- Plant, D.T., Pariante, C.M., Sharp, D., Pawlby, S., 2015. Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br. J. Psychiatry* 207, 213–220.
- Quarini, C., Pearson, R.M., Stein, A., Ramchandani, P.G., Lewis, G., Evans, J., 2015. Are female children more vulnerable to the long-term effects of maternal depression during pregnancy? *J. Affect Disord.* 189, 329–335.
- Rancière, F., Bougas, N., Viola, M., Momas, I., 2017. Early exposure to traffic-related air pollution, respiratory symptoms at 4 years of age, and potential effect modification by parental allergy, stressful family events, and gender: a prospective follow-up study of the Paris birth cohort. *Environ. Health Perspect.* 125, 737–745.
- Sandberg, S., Paton, J.Y., Ahola, S., McCann, D.C., McGuinness, D., Hillary, C.R., et al., 2000. The role of acute and chronic stress in asthma attacks in children. *Lancet* 356, 982–987.
- Sandberg, S., Järvenpää, S., Penttinen, A., Paton, J., McCann, D.C., 2004. Asthma exacerbations in children immediately following stressful life events: a cox's hierarchical regression. *Thorax* 59, 1046–1051.
- Sbihi, H., Tamburic, L., Koehoorn, M., Brauer, M., 2016. Perinatal air pollution exposure and development of asthma from birth to age 10 years. *Eur. Respir. J.* 47, 1062–1071.
- Shalowitz, M.U., Mijanovich, T., Berry, C.A., Clarkkauffman, E., Quinn, K.A., Perez, E.L., 2006. Context matters: a community-based study of maternal mental health, life stressors, social support, and children's asthma. *Pediatrics* 117, e940–e948.
- Shankardass, K., McConnell, R., Jerrett, M., Milam, J., Richardson, J., Berhane, K., 2009. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc. Natl. Acad. Sci.* 106, 12406–12411.
- Tétreault, L.-F., Doucet, M., Gamache, P., Fournier, M., Brand, A., Kosatsky, T., et al., 2016. Childhood exposure to ambient air pollutants and the onset of asthma: an administrative cohort study in Québec. *Environ. Health Perspect.* 124, 1276–1282.
- Tong, Y., Piotrowski, M., 2012. Migration and health selectivity in the context of internal migration in China, 1997–2009. *Popul Res Policy Rev.* 31, 497–543.
- Turcotte-Tremblay, A.M., Lim, R., Laplante, D.P., Kobzik, L., Brunet, A., King, S., 2014. Prenatal maternal stress predicts childhood asthma in girls: project ice storm. *Biomed. Res Int* 2014, 201717.
- Uphoff, E., Cabieses, B., Pinart, M., Valdés, M., Antó, J.M., Wright, J., 2015. A systematic review of socioeconomic position in relation to asthma and allergic diseases. *Eur. Respir. J.* 46, 364–374.
- Van De Loo, K.F., Van Gelder, M.M., Roukema, J., Roeleveld, N., Merkus, P.J., Verhaak, C.M., 2016. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur. Respir. J.* 47, 133–146.
- Wege, N., Dragano, N., Erbel, R., Jockel, K.H., Moebus, S., Stang, A., et al., 2008. When does work stress hurt? Testing the interaction with socioeconomic position in the Heinz Nixdorf recall study. *J. Epidemiol. Community Health* 62, 338–341.
- Wolf, J.M., Miller, G.E., Chen, E., 2008. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. *Brain Behav. Immun.* 22, 433–441.
- Wright, R.J., 2007. Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. *Paediatr. Perinat. Epidemiol.* 21, 8–14.
- Yamazaki, S., Shima, M., Nakadate, T., Ohara, T., Omori, T., Ono, M., 2014. Association between traffic-related air pollution and development of asthma in school children: cohort study in Japan. *J. Expo. Sci. Environ. Epidemiol.* 24, 372–379.
- Zhang, Y., Li, B., Huang, C., Yang, X., Qian, H., Deng, Q., et al., 2013. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. *Chin. Sci. Bull.* 58, 4182–4189.
- Zmirou, D., Gauvin, S., Pin, I., Momas, I., Sahraoui, F., Just, J., et al., 2004. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. *J. Epidemiol. Community Health* 58, 18–23.
- Zimmerman, F.J., Katon, W., 2005. Socioeconomic status, depression disparities, and financial strain: what lies behind the income-depression relationship? *Health Econ.* 14, 1197–1215.