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Gender-specific differences in effects of prenatal and postnatal environmental tobacco smoke exposure on respiratory symptoms in 23,474 children with and without allergic predisposition: results from 25 districts of northeast China

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Gender-specific differences in effects of prenatal and postnatal environmental tobacco smoke exposure on respiratory symptoms in 23,474 children with and without allergic predisposition: results from 25 districts of northeast China

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To assess the interaction of environmental tobacco smoke (ETS) exposure and allergic predisposition regarding respiratory health among Chinese children, a sample of 23,474 children (6–13 years old) was studied from 25 districts in Liaoning province, China. The results showed that children without allergic predisposition were more susceptible to ETS than children with allergic predisposition. Among children without allergic predisposition, ETS exposure was associated with more respiratory symptoms and diseases in boys than in girls; *In utero* ETS exposure was associated with history of asthma (OR, 1.86; 95% CI, 1.44–2.40) and current asthma (OR, 2.25; 95% CI, 1.48–3.44) only among boys without allergic predisposition. Among children with allergic predisposition, more associations between ETS exposure and respiratory symptoms and diseases were detected in girls. In conclusion, ETS exposure was more evident in boys without family atopy history and more associations were detected in girls with family atopy history.

Keywords: asthma; environmental tobacco smoke; children; allergic predisposition

Introduction

Most studies suggest that there has been a significant increase in the incidence and prevalence of atopic diseases in recent years, especially in non-English language countries (Lee et al. 2007; Pearce et al. 2007; Bjerg et al. 2010). It has been suggested that this increase cannot be explained by genetic factors and/or by improvements in diagnostic methods alone. Lifestyle, environmental factors and/or gene-environmental interactions may play a role (Kabesch 2006; Tsai et al. 2010).

Environmental tobacco smoke (ETS) is a highly prevalent respiratory irritant, and passive smoke consists of a complex mixture of >4,000 different chemicals

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(Lofroth 1989). Children are more vulnerable to ETS than adults, since their respiratory and immune systems are not fully developed. An extensive body of evidence has shown that ETS exposure is associated with respiratory symptoms in children (Dong et al. 2008; Kumar et al. 2008; Gerald et al. 2009; Keil et al. 2009).

However, evidence supporting a causal relationship between involuntary tobacco smoke exposure and asthma induction is inconsistent (Cunningham et al. 1995; Forsberg et al. 1997; Stein et al. 1999; Gilliland et al. 2001; Keil et al. 2009). Also, some authors indicated that the effect of exposure to environmental factors on respiratory symptoms among different races was inconsistent (Peters et al. 1999). There are few studies from the China region, where a large percentage of the population live in crowded apartments. At the same time, in China, the proportion of women smokers (3%) is very low, compared with other developed countries such as the U.S (22%) and Denmark (40%) (Svanes et al. 2004; Yang et al. 2005; Tong et al. 2009), and ETS exposure in China is almost entirely paternal (57% of men smoke) (Yang et al. 2005). Therefore we believed it was necessary to examine involuntary ETS exposure, mainly from paternal smoking, on the health of school-aged children in China. We stratified the data according to parental allergy status to clarify possible interactive effects between the genetic predisposition and ETS exposure.

Methods

Participants and study procedure

The procedures followed were in accordance with Ethical Standards of Responsible Committee on Human Experimentation of China Medical University. 25,897 elementary school children (6–13 years old) were surveyed from 25 districts of seven cities in Liaoning Province, China. A total of 23,474 children responded with a response rate of 90.6%. Liaoning Province is located in northeast China, which includes 14 cities. From April 2007 to May 2008, seven cities (Shenyang, Dalian, Anshan, Fushun, Benxi, Liaoyang and Yingkou) were randomly selected from Liaoning Province. There are five inner-city districts in Shenyang city, four inner-city districts in Dalian city, four inner-city districts in Fushun city, and three inner-city districts in Anshan city, Benxi city, Liaoyang city and Yingkou city, respectively. One elementary school was randomly selected from each district of the selected cities. The resulting 25 elementary schools were included. Local study staff informed participants about the survey at the participating schools. Teachers were given verbal and written instructions, questionnaires with envelope and forms to record questionnaire distribution and collection. After obtaining the written parental consent, parents were invited to a parents' night where teachers explained the study and the conditions of consent. Compliance was strictly voluntary. Parents who wished to participate, completed the questionnaire at home, and returned it (via child) to the teacher in an envelope. Endorsed consent forms were obtained from the parents or guardians of the subjects before their participation in the study.

Questionnaire data

We assessed children's respiratory health and potential risk factors such as exposures to indoor allergens by questionnaire. We included respiratory health-related questions derived from an American Thoracic Society (ATS) Epidemiologic Standardization Project questionnaire, which had been proved to be valid in some

studies (Cunningham et al. 1995; Peters et al. 1999; Zhang et al. 2002; Salo et al. 2004; Lee et al. 2006; Dong et al. 2008). This questionnaire had already been translated into Chinese for previous studies in other Chinese cities (Zhang et al. 2002; Salo et al. 2004; Lee et al. 2006; Dong et al. 2008).

Children's respiratory conditions were determined from questionnaire responses and were defined as follows: (a) *History of asthma*: A "yes" answer to the question "Has a doctor ever diagnosed asthma in this child?" (b) *Current asthma*: Under the condition that the child has been diagnosed asthma, a "yes" answer to the question "Has this child been in an asthma exacerbation in the last two years?" or a "yes" answer to the question "Does this child take medicine or treatment for asthma or asthmatic bronchitis?". (c) *Current wheeze*: A "yes" answer to the question "Does this child's chest ever sound wheezy or whistling, including times when he or she had a cold?" and a "yes" answer to the question "Has this child had 2 or more such episodes in the last 12 months?" (d) *Persistent cough*: The answers to several cough-related questions which indicate that the study child had cough on most days (4 or more days per week) for at least 3 months a year either with or without cold during the last 12 months. (e) *Persistent phlegm*: The answers to several phlegm-related questions which indicate that the study child had been seen congested or brought up productive cough on most days (4 or more days per week) for at least 3 months a year either with or without cold during the last 12 months. (f) *Allergic rhinitis*: A "yes" answer to the question "Has a doctor ever diagnosed allergic rhinitis in this child?" In order to detect the seasonal variation of these asthmatic symptoms, we also asked "In which of the month did this asthmatic symptom usually occur".

Reported ETS exposure was classified in three different ways: (i) Current household exposure, (ii) any passive smoking during the first two years of children's lives, and (iii) any passive smoking during maternal pregnancy (*in utero*) with the child. Smoking by visitors or guests was not ascertained. The current number of household smokers and the current number of cigarettes smoked inside the house per day during workday and day-off were recorded. Three categories were defined: none, 1–10 cigarettes smoked per day, and ≥ 10 cigarettes smoked per day. *Family history of allergy* was defined as any biologic parent or grandparents in whom hay fever or allergies (including allergic dermatitis, allergic conjunctivitis, and eczema) had been diagnosed. *Family history of asthma* was defined as any biologic parent or grandparents in whom asthma or bronchial asthma had been diagnosed. If subjects answer 'yes' to family history of allergy or family history of asthma, then they were defined as allergic predisposition. Unfortunately, blood samplings or skin tests were not performed in our large wide study design.

Statistical methods

The outcome variables in children were defined as persistent cough, persistent phlegm, history of asthma, current asthma, current wheeze, and allergic rhinitis, and the key exposure variables were focused on ETS exposure. To adjust for possible confounding, we also included host-related variables: age, sex, body mass index, breast feeding, study district, home coal use, area per person and parental education level. Home coal use was defined as the use of coal in a household for a cooking and space heating. Area per person was calculated by the equation: area per person = area of residence/family population.

Continuous variables were presented as mean values and standard deviation (SD). Categorical variables were presented as frequencies. Associations between

categorical variables were tested by the use of contingency tables and the χ^2 test. Comparisons between continuous variables between groups were performed by analysis of *t*-test. We developed multivariate logistic regression models containing all predictors with positive effects to respiratory symptoms. Reduced models were then created by removing exposure variables according to the flowing regulation: If the estimated tobacco smoke effects changed by at least 10% when a covariate was included in the base model, the covariate was included in the final model. Finally, we included an interaction term between the ETS exposure and allergic predisposition. Age, body mass index and area per person were included in the models as continuous variables. Sex (boys vs. girls), breast feeding (yes vs. no), home coal use (yes vs. no), parental education levels (< higher school vs. $\geq$ higher school), and study district (defined as dummy variable) were included in the models as categorical variables.

We also studied the independent and joint effects of family atopic diseases and ETS exposure by comparing the risk of asthma in four exposure categories: (i) No family atopy history and no ETS exposure (reference category); (ii) no family atopy history but with ETS exposure; (iii) family atopy history and no ETS exposure; and (iv) both family atopy history and ETS exposure. We calculated adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for each of the six outcome measures. All data were analyzed using SAS (Proc Logistic in SAS System for Windows, Version 8.12). All statistical tests were two-tailed and *p*-values ≤ 0.05 was considered statistically significant.

Results

Of 25,897 eligible participants, 23,474 returned the medical questionnaire (90.6%). The mean age of the children was 9.6 years (SD = 1.80; range 6–13) and 11771 (50.1%) were boys. For all children, the difference of means age between boys and girls were not significant ($t = 1.26$, $p = 0.21$). The characteristics of the participants were shown in Table 1. 13.6% (3199/23474) of children were with allergic predisposition. 1,452 subjects (6.2%) were reported of having history of asthma and 1.8% reported current asthma. Compared with the children without allergic predisposition, percentages of ETS exposure *in utero* (11.4% [365/3199] vs. 7.9% [1596/20275]; $\chi^2 = 45.18$, $p < 0.001$), ETS exposure in first 2 years (33.7% [1077/3199] vs. 22.1% [4479/20275]; $\chi^2 = 204.92$, $p < 0.001$), and current ETS exposure (59.1% [1892/3199] vs. 47.8% [9697/20275]; $\chi^2 = 141.55$, $p < 0.001$) were significantly higher among the children with allergic predisposition. The stratified analysis according to gender shows that the prevalence of history of asthma (7.2% vs. 5.2%; $\chi^2 = 39.44$, $p < 0.001$), current asthma (2.1% vs. 1.5%; $\chi^2 = 15.32$, $p < 0.001$), current wheeze (5.3% vs. 4.1%; $\chi^2 = 16.82$, $p < 0.001$), allergic rhinitis (6.6% vs. 4.7%; $\chi^2 = 39.74$, $p < 0.001$), and persistent phlegm (4.7% vs. 3.9%; $\chi^2 = 8.37$, $p = 0.004$) were significantly higher among boys than among girls (all *p* values < 0.01), except for persistent cough (8.6% vs. 8.0%; $\chi^2 = 3.09$, $p = 0.079$). The proportion of children exposed to ETS during maternal pregnancy and the first two years of life was 8.4% and 23.7%, respectively. Mothers of only 0.2% (51/23474) children were active smokers during pregnancy.

As shown in Table 2, the prevalence of respiratory morbidities was higher in the children with ETS exposed in the first two years or during pregnancy than unexposed children, and was higher in those exposed to current ETS than unexposed children. The prevalence rate of respiratory symptoms increased with the increase in numbers

Table 1. Characteristics and tobacco smoke exposure among elementary school children ($n = 23,474$).

Characteristic	<i>n</i> (%)
Gender	
Boys	11771 (50.1%)
Girls	11703 (49.9%)
Breast feeding	20293 (86.5%)
Home coal use	1799 (7.7%)
Education level of parents < higher school	7528 (32.1%)
Number of room < 3	12927 (55.1%)
Family history of allergy	1951 (8.3%)
Family history of asthma	1602 (6.8%)
Children with allergic predisposition	3199 (13.6%)
Asthma and asthma-related symptoms	
History of asthma	1452 (6.2%)
Current asthma	423 (1.8%)
Current wheeze	1100 (4.7%)
Persistent cough	1954 (8.3%)
Persistent phlegm	1013 (4.3%)
Allergic rhinitis	1316 (5.6%)
Tobacco smoke exposure	
ETS exposure <i>in utero</i>	1961 (8.4%)
ETS exposure in the first 2 years of life	5556 (23.7%)
Current ETS exposure	11589 (49.4%)
Maternal smoking	235 (1.0%)
Paternal smoking	9175 (39.1%)
Number of cigarettes smoked during workday (cigarettes/day) [†]	
0	11885 (50.6%)
1~10	9006 (38.4%)
≥10	2583 (11.0%)
Number of cigarettes smoked during day-off (cigarettes/day) [‡]	
0	11885 (50.6%)
1~10	8649 (36.9%)
≥10	2940 (12.5%)

Values are *n* (%); [†]the number of cigarettes smoked inside the house per day during workday when the child is at home. [‡]the number of cigarettes smoked inside the house per day during day-off when the child is at home.

of cigarettes smoked whether during workdays or during days-off. Among the subjects with ETS exposure, boys were more susceptible to ETS exposure than girls (data not shown). For example, when exposed to ETS *in utero*, the prevalence of history of asthma was significantly higher in boys than in girls (11.0% vs. 7.4%; $\chi^2 = 7.50$, $p = 0.006$). There was also a significant interaction between gender and ETS exposure in the first two years of life for current wheeze (adjusted $OR_{\text{interaction}} = 1.32$, 95% CI, 1.02–1.70, p value of the interaction term = 0.03) and for allergic rhinitis (adjusted $OR_{\text{interaction}} = 1.31$, 95% CI, 1.01–1.69, p value of the interaction term = 0.04).

Logistic regression analyses were performed to evaluate the role of potential confounders on the relationship observed between ETS and respiratory outcomes in children stratified by the status of allergic predisposition. Considering boys and girls together, the effects of ETS exposure on respiratory symptoms differed with regard to susceptible status, with a stronger effect of ETS exposure on some symptoms

Table 2. Percentage of participant with respiratory symptoms and diseases within tobacco smoke exposure categories.

	Persistent cough	Persistent phlegm	History of asthma	Current asthma	Current wheeze	Allergic rhinitis
<i>ETS exposure in utero</i>						
No	1745 (8.1%)	903 (4.2%)	1271 (5.9%)	360 (1.7%)	963 (4.5%)	1125 (5.2%)*
Yes	209 (10.7%)*	110 (5.6%)*	181 (9.2%)*	63 (3.2%)*	137 (7.0%)*	191 (9.7%)*
<i>ETS exposure in the first 2 years of life</i>						
No	1342 (7.5%)	691 (3.9%)	949 (5.3%)	271 (1.5%)	685 (3.8%)	978 (5.5%)*
Yes	612 (11.0%)*	322 (5.8%)*	503 (9.1%)*	152 (2.7%)*	415 (7.5%)*	338 (6.1%)*
<i>Current ETS exposure</i>						
No	800 (6.7%)	395 (3.3%)	578 (4.9%)	165 (1.4%)	395 (3.3%)	623 (5.2%)*
Yes	1154 (10.0%)*	618 (5.3%)*	874 (7.5%)*	258 (2.2%)*	705 (6.1%)*	693 (6.0%)*
<i>Maternal smoking</i>						
No	1912 (8.2%)	988 (4.3%)	1433 (6.2%)	419 (1.8%)	1082 (4.7%)	1296 (5.6%)*
Yes	42 (17.9%)*	25 (10.6%)*	19 (8.1%)*	4 (1.7%)*	18 (7.7%)*	20 (8.5%)*
<i>Paternal smoking</i>						
No	1060 (7.4%)	539 (3.8%)	767 (5.4%)	219 (1.5%)	527 (3.7%)	785 (5.5%)*
Yes	894 (9.7%)*	474 (5.2%)*	685 (7.5%)*	204 (2.2%)*	573 (6.3%)*	531 (5.8%)*
<i>Number of cigarettes smoked during workday (cigarettes/day)[†]</i>						
1 ~ 10	858 (9.5%)*	439 (4.9%)*	641 (7.1%)*	186 (2.1%)*	522 (5.8%)*	525 (5.8%)*
≥ 10	296 (11.5%)*	179 (6.9%)*	233 (9.0%)*	72 (2.8%)*	183 (7.1%)*	168 (6.5%)*
<i>Number of cigarettes smoked during day-off (cigarettes/day)[†]</i>						
1 ~ 10	822 (9.5%)*	426 (4.9%)*	616 (7.1%)*	186 (2.2%)*	496 (5.7%)*	510 (5.9%)*
≥ 10	333 (11.3%)*	193 (6.6%)*	258 (8.8%)*	72 (2.5%)*	209 (7.1%)*	183 (6.2%)*

Values are *n* (%); *Differences between categorical variables were tested with χ^2 test (Yes vs. No), $p < 0.05$. [†]Contrast with the subjects with no current exposure to ETS (1 ~ 10 vs. zero; ≥ 10 vs. zero).

among subjects without allergic predisposition (Table 3). Among subjects without allergic predisposition, maternal passive smoking during any period of pregnancy was associated with an increased risk of history of asthma (OR = 1.64, 95% CI, 1.34–2.00) and current asthma (OR = 1.96, 95% CI, 1.39–2.77). The association of ETS exposure and respiratory health of children increased in strength with the number of cigarettes smoked inside the house per day during workdays and days-off. When the number of cigarettes smoking exceeded 10 per day during day-off, the relationship was significant for history of asthma (OR_{workday} = 2.12, 95% CI, 1.76–2.57; OR_{day-off} = 1.94, 95% CI, 1.61–2.34) and current asthma (OR_{workday} = 2.45, 95% CI, 1.73–3.48; OR_{day-off} = 2.13, 95% CI, 1.50–3.03). Among subjects with allergic predisposition, the association of ETS exposure with history of asthma and current asthma was weaker and not significant except for the ETS exposure in the first two years of age. Even for the persistent cough, persistent phlegm, and current wheeze, most of the adjusted ORs among subjects without allergic predisposition were higher than those among subjects with allergic predisposition.

Also, interaction effects between gender and ETS exposure were estimated firstly among children without allergic predisposition and secondly among children with allergic predisposition. Among the subjects without allergic predisposition, after adjustment for age, body mass index, breastfeeding, parental education, home coal use, area per person and study district, we found a significant interaction between gender and ETS exposure in the first two years of life for persistent cough (adjusted OR_{interaction} = 0.81, 95% CI, 0.64–1.00), and between gender and current ETS exposure for persistent phlegm (adjusted OR_{interaction} = 0.75, 95% CI, 0.56–0.99). However, among the subjects with allergic predisposition, there was an inverse significant interaction between gender and ETS exposure *in utero* for current asthma (adjusted OR_{interaction} = 2.27, 95% CI, 1.01–5.67), and between gender and ETS exposure in the first two years of life for history of asthma (adjusted OR_{interaction} = 1.53, 95% CI, 1.01–2.32), current wheeze (adjusted OR_{interaction} = 1.65, 95% CI, 1.04–2.61), and allergic rhinitis (adjusted OR_{interaction} = 1.70, 95% CI, 1.03–2.81).

Table 4 shows the joint effect of ETS exposure and family atopy history among children. The results indicated that ETS exposure and family atopy in all time periods increase associations of respiratory symptoms and diseases with more increased associations when together. For example, compared with subjects of the reference category, in subjects without family atopy history, ETS exposure *in utero* alone significantly increased the risk of current asthma, with an adjusted OR of 1.96. The effect of family atopy history alone was significant in subjects without ETS exposure *in utero*, with an adjusted OR of 3.85. In the case of the presence of these two factors (both ETS exposure *in utero* and family atopy history), the adjusted ORs of current asthma increased to 5.53 (95% CI, 3.57–8.58), which was higher than the predicted ORs (exposed to ETS *in utero* without family history of atopy + not exposed to ETS *in utero* but with family history of atopy: predicted ORs = [1.96–1] + [3.85–1] + 1 = 4.81). This means that the association from joint exposure to ETS *in utero* and family history of atopy is higher than that predicted from the combination of the separate effects. However, interaction on an additive scale was not statistically significant (*p* value of the interaction term > 0.05) in a logistic regression model. A similar pattern was also observed in history of asthma and asthma-related symptoms.

Table 3. Association of children's respiratory symptoms and diseases with ETS exposure in children with and without allergic predisposition*.

	Persistent cough OR 95% CI	Persistent phlegm OR 95% CI	History of asthma OR 95% CI	Current asthma OR 95% CI	Current wheeze OR 95% CI	Allergic rhinitis OR 95% CI
Children without allergic predisposition ($n = 20,275$)						
ETS exposure <i>in utero</i>	1.37 (1.15–1.63)	1.23 (0.96–1.58)	1.64 (1.34–2.01)	1.96 (1.39–2.77)	1.62 (1.29–2.04)	1.74 (1.44–2.12)
ETS in first 2 years	1.50 (1.33–1.68)	1.36 (1.16–1.61)	1.77 (1.54–2.03)	1.80 (1.39–2.33)	2.06 (1.76–2.40)	1.20 (1.03–1.39)
Current ETS exposure	1.52 (1.37–1.69)	1.61 (1.39–1.86)	1.63 (1.43–1.85)	1.84 (1.44–2.36)	1.97 (1.69–2.29)	1.20 (1.06–1.37)
Maternal smoking	2.35 (1.60–3.46)	2.53 (1.55–4.15)	1.12 (0.60–2.06)	1.22 (0.39–3.86)	1.93 (1.11–3.47)	1.57 (0.90–2.72)
Paternal smoking	1.36 (1.22–1.51)	1.42 (1.22–1.64)	1.43 (1.26–1.62)	1.65 (1.29–2.10)	1.85 (1.60–2.14)	1.09 (0.95–1.24)
Workday [†] 1 ~ 10 ^a	1.44 (1.29–1.61)	1.44 (1.23–1.69)	1.49 (1.30–1.71)	1.68 (1.29–2.19)	1.85 (1.58–2.18)	1.17 (1.02–1.35)
≥ 10 ^b	1.82 (1.55–2.14)	2.22 (1.80–2.74)	2.12 (1.76–2.57)	2.45 (1.73–3.48)	2.40 (1.93–2.99)	1.31 (1.06–1.62)
Day-off [†] 1 ~ 10 ^a	1.46 (1.30–1.63)	1.50 (1.28–1.76)	1.52 (1.33–1.75)	1.75 (1.34–2.29)	1.81 (1.54–2.13)	1.19 (1.03–1.37)
≥ 10 ^b	1.74 (1.49–2.04)	1.97 (1.60–2.43)	1.94 (1.61–2.34)	2.13 (1.50–3.03)	2.48 (2.01–3.05)	1.24 (1.02–1.52)
Children with allergic predisposition ($n = 3,199$)						
ETS exposure <i>in utero</i>	1.10 (0.80–1.51)	1.41 (0.97–2.05)	1.28 (0.95–1.73)	1.43 (0.90–2.25)	1.34 (0.96–1.86)	1.56 (1.15–2.13)
ETS in first 2 years	1.40 (1.13–1.73)	1.72 (1.32–2.24)	1.34 (1.08–1.65)	1.56 (1.11–2.18)	1.62 (1.28–2.04)	0.94 (0.73–1.20)
Current ETS exposure	1.46 (1.17–1.82)	1.59 (1.20–2.11)	1.19 (0.97–1.47)	1.05 (0.75–1.46)	1.39 (1.10–1.76)	0.98 (0.78–1.24)
Maternal smoking	1.99 (0.97–4.10)	2.17 (0.95–4.97)	1.42 (0.65–3.10)	0.52 (0.07–3.81)	1.12 (0.44–2.89)	1.67 (0.69–4.05)
Paternal smoking	1.26 (1.02–1.55)	1.22 (0.94–1.58)	1.14 (0.93–1.40)	1.02 (0.74–1.42)	1.30 (1.04–1.63)	0.95 (0.75–1.19)
Workday [†] 1 ~ 10 ^a	1.46 (1.15–1.84)	1.56 (1.16–2.10)	1.23 (0.98–1.53)	1.03 (0.72–1.47)	1.39 (1.08–1.78)	0.97 (0.75–1.24)
≥ 10 ^b	1.46 (1.07–1.98)	1.69 (1.16–2.47)	1.08 (0.80–1.47)	1.11 (0.69–1.80)	1.40 (1.00–1.96)	1.02 (0.73–1.43)
Day-off [†] 1 ~ 10 ^a	1.38 (1.09–1.75)	1.45 (1.07–1.97)	1.17 (0.93–1.46)	1.06 (0.74–1.51)	1.40 (1.08–1.80)	0.98 (0.76–1.26)
≥ 10 ^b	1.65 (1.24–2.21)	1.93 (1.36–2.76)	1.25 (0.94–1.66)	1.03 (0.64–1.65)	1.37 (0.99–1.90)	0.99 (0.71–1.37)

*Odds ratios with 95% confidence intervals as estimated by logistic regression adjusting for age, gender, body mass index, breastfeeding, parental education, home coal use, area per person, study district. ^acontrast, 1–10 vs. zero; ^bcontrast, ≥ 10 vs. zero.

Table 4. Adjusted ORs (95% CI) of history of asthma and asthma-related symptoms in relation to the joint effect of co-exposure to ETS and family atopy history in elementary children*.

Characteristics	Persistent cough	Persistent phlegm	History of asthma	Current asthma	Current wheeze	Allergic rhinitis
<i>ETS exposure in utero</i>						
Children ^a (reference) [†]	1.00	1.00	1.00	1.00	1.00	1.00
Children ^b	1.37 (1.15–1.63)	1.23 (1.00–1.57)	1.64 (1.34–2.01)	1.96 (1.39–2.78)	1.62 (1.29–2.04)	1.75 (1.44–2.12)
Children ^c	1.88 (1.66–2.12)	2.14 (1.82–2.51)	3.10 (2.73–3.53)	3.85 (3.09–4.80)	3.14 (2.72–3.63)	2.33 (2.02–2.69)
Children ^d	2.04 (1.51–2.77)	2.92 (2.06–4.15)	4.34 (3.27–5.75)	5.53 (3.57–8.58)	4.41 (3.22–6.03)	3.81 (2.86–5.09)
<i>ETS exposure in the first 2 years of life</i>						
Children ^a (reference) [†]	1.00	1.00	1.00	1.00	1.00	1.00
Children ^b	1.50 (1.33–1.68)	1.36 (1.16–1.61)	1.77 (1.54–2.03)	1.80 (1.39–2.33)	2.06 (1.76–2.40)	1.20 (1.03–1.39)
Children ^c	1.81 (1.56–2.10)	1.90 (1.57–2.32)	3.29 (2.84–3.83)	3.75 (2.89–4.86)	3.26 (2.74–3.87)	2.53 (2.16–2.95)
Children ^d	2.53 (2.12–3.02)	3.28 (2.65–4.07)	4.21 (3.51–5.06)	5.62 (4.18–7.57)	5.11 (4.18–6.24)	2.25 (1.81–2.81)
<i>Current ETS exposure</i>						
Children ^a (reference) [†]	1.00	1.00	1.00	1.00	1.00	1.00
Children ^b	1.52 (1.37–1.69)	1.60 (1.38–1.86)	1.62 (1.42–1.85)	1.83 (1.43–2.35)	1.96 (1.69–2.29)	1.20 (1.05–1.37)
Children ^c	1.80 (1.48–2.19)	2.08 (1.60–2.69)	3.63 (3.00–4.39)	5.13 (3.72–7.09)	3.77 (3.01–4.72)	2.63 (2.16–3.20)
Children ^d	2.63 (2.26–3.06)	3.34 (2.75–4.06)	4.28 (3.63–5.03)	5.32 (3.98–7.11)	5.17 (4.29–6.23)	2.51 (2.11–3.00)

*Odds ratios with 95% confidence intervals as estimated by logistic regression adjusting for age, gender, body mass index, breastfeeding, parental education, home coal use, area per person, and study district. [†]All OR are computed to children with no ETS and no family atopy history (reference category). ^ano ETS exposure and without family atopy history (reference category). ^bETS exposure and without family atopy history. ^cno ETS exposure and with family atopy history. ^dboth ETS exposure and with family atopy history.

When stratified analysis by gender, among children without family atopy history, ETS exposure was associated with more respiratory symptoms and diseases in boys than in girls (Table 5). For instance, an association of asthma-related symptoms and *in utero* ETS exposure was identified in boys but not in girls. Even for the ETS exposure during the first two years of life and current ETS exposure, the adjusted ORs in boys were higher than that in girls. ETS exposure during pregnancy was a significant risk factor for history of asthma (OR = 1.86, 95% CI, 1.44–2.40), current asthma (OR = 2.25, 95% CI, 1.48–3.44), and current wheeze (OR = 1.73, 95% CI, 1.29–2.33) only in boys, but in girls, the relationship of ETS exposure during pregnancy and allergic symptoms was not statistically significant.

However, among children with family atopy history, girls were more susceptible to ETS exposure than boys (Table 6). In girls, exposure to ETS during pregnancy and during the first two years of life were both positively associated with history of asthma and asthma-related symptoms. The strongest associations were seen for current asthma (OR = 2.49, 95% CI, 1.33–4.67) and allergic rhinitis (OR = 2.14, 95% CI, 1.64–3.33) with ETS exposure during pregnancy, and for current wheeze (OR = 2.01, 95% CI, 1.44–2.80) with ETS exposure during the first two years of life. But in boys, the relationship of ETS exposure and any allergic symptoms was not identified.

Discussion

In this large cross-sectional study, both prenatal and postnatal ETS exposure was strongly associated with respiratory symptoms among these Chinese children, and ETS exposure was associated with more respiratory symptoms and diseases in subjects without a genetic predisposition than in subjects with a genetic predisposition. This suggests that ETS exposure is an important causal factor for non-susceptible asthma, a condition that deserves far more focus among researchers. In a study of 5,762 school-aged children in 12 Southern California communities, the effects of involuntary tobacco smoke exposure on wheeze were largest in children without a family history of asthma or a family history of atopy, and *in utero* exposure to ETS was positively associated with doctor-diagnosed asthma only in children without family history of asthma (OR = 1.9, 95% CI, 1.0–3.7) (Gilliland et al. 2001). Results from the European Community Respiratory Health Survey (ECRHS) also showed that the associations of maternal smoking with wheeze (OR = 1.23, 95% CI, 1.08–1.40), asthma symptom (OR = 1.24, 95% CI, 1.06–1.44), and chronic bronchitis (OR = 1.21, 95% CI, 1.01–1.44) were significant in non-atopic subjects, but not in atopic subjects (Svanes et al. 2004). On the contrary, in Germany, predisposed children (defined by parental atopy) were at higher risk of asthma and asthma-related symptoms when exposed to passive smoking compared with children whose parents had no atopy, although the difference was not significant (Kramer et al. 2004). A recent cohort study of 1314 children followed for 10 years from birth showed a significant association of allergic sensitization and asthma symptoms with regular maternal smoking only in children with a genetic predisposition (defined by family atopy), but not in the group of children without family history of atopy; and this significant association was only limited to regular maternal smoking not to paternal smoking and irregular maternal smoking (Keil et al. 2009). The failure to demonstrate an association in these children with allergic predisposition may at least in part be explained by a tendency of parents to stop

Table 5. Association of children's respiratory symptoms and diseases with ETS exposure in boys and girls without allergic predisposition*.

	Persistent cough OR 95% CI	Persistent phlegm OR 95% CI	History of asthma OR 95% CI	Current asthma OR 95% CI	Current wheeze OR 95% CI	Allergic rhinitis OR 95% CI
Boys (<i>n</i> = 10,157)						
ETS exposure <i>in utero</i>	1.37 (1.08–1.74)	1.40 (1.00–2.00)	1.86 (1.44–2.40)	2.25 (1.48–3.44)	1.73 (1.29–2.33)	1.76 (1.37–2.27)
ETS in first 2 years	1.65 (1.41–1.94)	1.37 (1.10–1.71)	1.75 (1.46–2.10)	1.93 (1.28–2.90)	2.19 (1.74–2.77)	1.30 (1.03–1.64)
Current ETS exposure	1.66 (1.43–1.92)	1.83 (1.50–2.24)	1.76 (1.49–2.09)	1.86 (1.35–2.55)	2.08 (1.70–2.55)	1.24 (1.05–1.47)
Maternal smoking	2.98 (1.86–4.75)	2.66 (1.44–4.90)	1.60 (0.83–3.08)	1.82 (0.57–5.82)	2.68 (1.42–5.05)	1.76 (0.91–3.40)
Paternal smoking	1.45 (1.25–1.67)	1.55 (1.27–1.89)	1.50 (1.27–1.78)	1.58 (1.16–2.16)	1.88 (1.55–2.28)	1.17 (0.98–1.39)
Workday 1 ~ 10 ^a	1.52 (1.30–1.78)	1.62 (1.30–2.01)	1.62 (1.35–1.95)	1.62 (1.14–2.28)	1.97 (1.59–2.44)	1.21 (1.01–1.45)
≥ 10 ^b	2.17 (1.75–2.69)	2.60 (1.97–3.44)	2.28 (1.78–2.92)	2.73 (1.77–4.21)	2.50 (1.87–3.33)	1.34 (1.02–1.76)
Day-off 1 ~ 10 ^a	1.56 (1.33–1.83)	1.71 (1.38–2.12)	1.66 (1.38–1.99)	1.64 (1.16–2.32)	1.86 (1.50–2.32)	1.24 (1.03–1.49)
≥ 10 ^b	2.01 (1.63–2.49)	2.29 (1.73–3.02)	2.11 (1.65–2.68)	2.54 (1.66–3.90)	2.80 (2.13–3.66)	1.24 (0.95–1.61)
Girls (<i>n</i> = 10,118)						
ETS exposure <i>in utero</i>	1.38 (1.07–1.77)	1.10 (0.77–1.55)	1.36 (0.98–1.89)	1.51 (0.82–2.78)	1.47 (0.98–2.10)	1.74 (1.29–2.34)
ETS in first 2 years	1.34 (1.13–1.59)	1.36 (1.06–1.74)	1.78 (1.46–2.20)	1.71 (1.22–2.40)	1.95 (1.59–2.40)	1.13 (0.92–1.38)
Current ETS exposure	1.38 (1.19–1.61)	1.37 (1.10–1.71)	1.44 (1.18–1.76)	1.79 (1.20–2.67)	1.81 (1.44–2.28)	1.14 (0.93–1.40)
Maternal smoking	1.53 (0.76–3.07)	2.24 (0.97–5.20)	0.26 (0.04–1.91)	— [†]	0.76 (0.19–3.12)	1.19 (0.43–3.28)
Paternal smoking	1.26 (1.08–1.47)	1.25 (0.99–1.58)	1.32 (1.08–1.61)	1.71 (1.16–2.53)	1.80 (1.43–2.25)	0.97 (0.79–1.20)
Workday 1 ~ 10 ^a	1.36 (1.15–1.60)	1.25 (0.99–1.59)	1.31 (1.06–1.63)	1.75 (1.15–2.67)	1.69 (1.32–2.17)	1.11 (0.90–1.38)
≥ 10 ^b	1.48 (1.16–1.89)	1.81 (1.31–2.51)	1.92 (1.43–2.56)	1.93 (1.06–3.52)	2.25 (1.61–3.14)	1.25 (0.90–1.74)
Day-off 1 ~ 10 ^a	1.35 (1.15–1.60)	1.28 (0.98–1.63)	1.35 (1.09–1.67)	1.90 (1.25–2.88)	1.73 (1.35–2.21)	1.11 (0.90–1.39)
≥ 10 ^b	1.48 (1.17–1.86)	1.64 (1.19–2.26)	1.73 (1.30–2.30)	1.46 (0.77–2.72)	2.06 (1.49–2.86)	1.24 (0.90–1.69)

*Odds ratios with 95% confidence intervals as estimated by logistic regression adjusting for age, body mass index, breastfeeding, parental education, home coal use, area per person, study district. [†]Estimate not available due to small number of exposed cases. ^acontrast, 1–10 vs. zero; ^bcontrast, ≥ 10 vs. zero.

Table 6. Association of children's respiratory symptoms and diseases with ETS exposure in boys and girls with allergic predisposition*.

	Persistent cough OR 95% CI	Persistent phlegm OR 95% CI	History of asthma OR 95% CI	Current asthma OR 95% CI	Current wheeze OR 95% CI	Allergic rhinitis OR 95% CI
Boys (<i>n</i> = 1,614)						
ETS exposure <i>in utero</i>	1.14 (0.73–1.77)	1.23 (0.72–2.09)	1.06 (0.70–1.60)	0.87 (0.44–1.73)	0.99 (0.61–1.60)	1.20 (0.77–1.86)
ETS in first 2 years	1.35 (0.98–1.83)	1.75 (1.20–2.55)	1.12 (0.84–1.50)	1.46 (0.93–2.30)	1.36 (0.99–1.89)	0.75 (0.53–1.07)
Current ETS exposure	1.45 (1.06–1.97)	1.48 (0.96–2.20)	1.25 (0.94–1.65)	1.19 (0.76–1.86)	1.42 (1.02–1.97)	0.90 (0.66–1.23)
Maternal smoking	0.45 (0.06–3.41)	0.77 (0.10–5.94)	1.23 (0.35–4.36)	— [†]	1.13 (0.25–5.05)	1.76 (0.49–6.39)
Paternal smoking	1.08 (0.81–1.45)	0.96 (0.66–1.38)	1.07 (0.82–1.41)	1.02 (0.66–1.57)	1.04 (0.76–1.43)	0.86 (0.63–1.17)
Workday 1 ~ 10 ^a	1.50 (1.09–2.08)	1.47 (0.97–2.23)	1.31 (0.98–1.77)	1.16 (0.72–1.87)	1.45 (1.03–2.05)	0.88 (0.63–1.22)
≥ 10 ^b	1.29 (0.83–2.00)	1.53 (0.90–2.60)	1.07 (0.71–1.61)	1.27 (0.67–2.39)	1.33 (0.83–2.12)	0.98 (0.62–1.54)
Day-off 1 ~ 10 ^a	1.49 (1.07–2.07)	1.47 (0.98–2.25)	1.23 (0.91–1.66)	1.16 (0.71–1.89)	1.48 (1.04–2.10)	0.95 (0.68–1.32)
≥ 10 ^b	1.36 (0.90–2.06)	1.50 (0.90–2.51)	1.29 (0.88–1.87)	1.25 (0.68–2.29)	1.28 (0.81–2.00)	0.80 (0.51–1.26)
Girls (<i>n</i> = 1,585)						
ETS exposure <i>in utero</i>	1.06 (0.66–1.68)	1.64 (0.97–2.79)	1.62 (1.06–2.50)	2.49 (1.33–4.67)	1.86 (1.18–2.94)	2.14 (1.68–3.33)
ETS in first 2 years	1.44 (1.06–1.96)	1.73 (1.19–2.52)	1.69 (1.23–2.31)	1.79 (1.08–2.96)	2.01 (1.44–2.80)	1.21 (0.85–1.74)
Current ETS exposure	1.49 (1.09–2.04)	1.74 (1.15–2.61)	1.12 (0.81–1.53)	0.89 (0.54–1.47)	1.36 (1.00–1.93)	1.10 (0.77–1.56)
Maternal smoking	3.20 (1.40–7.34)	2.94 (1.15–7.55)	1.62 (0.60–4.39)	0.88 (0.12–6.71)	1.01 (0.30–3.43)	1.55 (0.45–5.29)
Paternal smoking	1.49 (1.10–2.01)	1.59 (1.09–2.32)	1.24 (0.91–1.68)	1.04 (0.63–1.70)	1.69 (1.21–2.36)	1.08 (0.77–1.53)
Workday 1 ~ 10 ^a	1.42 (1.02–1.98)	1.66 (1.08–2.56)	1.13 (0.81–1.57)	0.86 (0.50–1.48)	1.31 (0.91–1.89)	1.10 (0.75–1.60)
≥ 10 ^b	1.70 (1.10–2.61)	1.97 (1.14–3.40)	1.08 (0.68–1.72)	0.97 (0.47–2.04)	1.54 (0.95–2.48)	1.09 (0.65–1.82)
Day-off 1 ~ 10 ^a	1.29 (0.92–1.81)	1.43 (0.92–2.23)	1.10 (0.78–1.54)	0.93 (0.54–1.58)	1.30 (0.90–1.87)	1.02 (0.70–1.50)
≥ 10 ^b	2.07 (1.38–3.10)	2.62 (1.59–4.31)	1.17 (0.75–1.82)	0.80 (0.37–1.70)	1.56 (1.00–2.48)	1.29 (0.80–2.09)

*Odds ratios with 95% confidence intervals as estimated by logistic regression adjusting for age, body mass index, breastfeeding, parental education, home coal use, area per person, study district. [†]Estimate not available due to small number of exposed cases. ^acontrast, 1–10 vs. zero; ^bcontrast, ≥ 10 vs. zero.

smoking when the child is diagnosed as allergic, as a result of the fact that people avoid exposing their child to something that they believe is a risk factor for allergies. For example, Jaakkola et al. (1994) found a significant lower risk of exposure to ETS at home for atopic children (OR = 0.61) compared with unaffected children. In China, such avoidance behavior may not be seen where there may be a lower awareness of risk factors for asthma/allergies. For example, in this study, 59.1% subjects with a family history of atopy were exposed to current ETS, which was higher than that without family history of atopy (47.8%). The reason for this difference of susceptibility is not known and warrants further studies.

A considerable body of evidence supports the plausibility that maternal smoking had a greater effect than paternal smoking on respiratory symptoms of children, especially for the maternal smoking during pregnancy which had stronger effects than current ETS exposure (Forsberg et al. 1997; Svanes et al. 2004; Hayatbakhsh et al. 2009; Keil et al. 2009; Tsai et al. 2010). Results from the study of 16,000 school-aged Scandinavian children showed that maternal smoking exposure during pregnancy was associated with increases in asthma attacks, dry cough, and asthma treatments. In contrast, current ETS exposure was inversely associated with these end points (Forsberg et al. 1997). Also, children who have been exposed to maternal smoking during pregnancy had a statistically significant reduction in FEF₂₅₋₇₅ and FEV₁ compared with those who were exposed to maternal smoking after pregnancy, and the respiratory function tests in children of mothers who smoked only after pregnancy (but not during pregnancy) were not statistically different from those of non-smoking mother (Hayatbakhsh et al. 2009). However, we did not assess the relation between maternal smoking exposure during pregnancy and atopic diseases because the proportion of maternal smoking is still low. In our study, only 1% of mothers reported smoking, and only 51 (0.2%) of mothers reported active smoking during pregnancy. In Asia, especially in China, according to conventional rules of etiquette, women smoking are considered to be humiliating and discriminated against. So, compared with Western developed countries, the proportion of current women smokers in cities of China is lower. In developed countries, especially in the English-speaking countries, almost 25% of women are smokers. Results from the ECRHS showed that the proportion of maternal smoking was over 40% in Denmark, Iceland and the English-speaking countries, even the proportion of maternal smoking in pregnancy reached 27% in Ireland (Svanes et al. 2004). Differences in the proportion of women smoking could partly explain the high prevalence of allergic respiratory symptoms and diseases observed in the developed countries. But what aroused our great concern is the increase in the percentage of the number of younger and female smokers in recent years. Therefore, we should correctly recognize the association between cigarette smoking and child's health, and emphasize the education for child's health, which will be useful to the prevention of respiratory diseases in children.

In our study, the vulnerability towards exposure to tobacco smoke appeared to differ between boys and girls. In agreement with our findings in children without allergic predisposition, several studies indicate a stronger effect of intrauterine exposure on boys than on newborn girls. There is some evidence that the airways of men and women respond differently to exposure to tobacco smoke products (Cunningham et al. 1995; Stick et al. 1996; Stein et al. 1999; Chen et al. 2005; Hayatbakhsh et al. 2009). This is plausible as there are differences between the airways of boys and girls from early in fetal lung development and throughout life

(Polgar and Weng 1979; Becklake and Kauffmann 1999). Female lungs mature earlier with regard to surfactant production. Throughout life, women have smaller lungs than men, but their lung architecture is more advantageous with a greater airway diameter in relation to the volume of the lung parenchyma. Thus, in childhood airway hyperresponsiveness and asthma is more common among boys than girls. As shown in this study, the stronger association between ETS exposure and respiratory symptoms and diseases in boys, could be related to boys having less mature lungs and relatively narrower airways during childhood. These factors are believed to contribute to the generally higher rates of pulmonary morbidity in boys than in girls, and could possibly also explain a higher susceptibility for damage by exposure to ETS during this age window. Hayatbakhsh et al. (2009) reported that in boys, the most investigated lung function parameters were significantly affected by exposure to passive smoking during the child's entire life, although passive smoking (cumulative dose) in girls was also associated with lung function impairments, the effects were smaller than those in boys and not all significant. A second study in nine-year-old children found that male children with smoking parents had significantly increased bronchial responsiveness (BR) compared to those whose parents did not smoke (OR = 4.3, $p = 0.009$), but no such significant increase in BR was found in female children of smoking parents (OR = 1.5, $p = 0.4$) (Martinez et al. 1988). It is hypothesized that passive smoking, by increasing the frequency of BR and of atopy, may increase the risk of asthma in childhood and particularly in boys. Results from ECRHS (Svanes et al. 2004) showed that in men, ETS exposure in childhood was associated with more respiratory symptoms, but not in women. It has been suggested that the association of paternal smoking and asthma symptom among boys could be explained by boys spending more time with their fathers than girls. However, to our interest, among the children with allergic predisposition, girls were more susceptible to ETS exposure than boys. The reasons for this gender difference are still not fully understood and need to be explored further.

Our study has some limitations. This was a study of respiratory prevalence in children aged between six and 13 years of age, not of respiratory symptom incidence; for example, some of the factors that we studied might have affected respiratory symptoms prevalence through effects on diseases duration rather than disease incidence. Bias could also be introduced if differential changes of environmental exposures showed, for example, some smokers may abstain from smoking when there was a child with asthma symptom in the family. However, large epidemiological studies of asthma often rely on reports on recent symptom history and a physician's diagnosis of asthma because these self-reported measures are cost efficient, practical and their repeatability is generally good (Weissman 2002). At same time, our findings were interesting, regardless of whether the observed associations were caused by effects from incidence or duration.

In conclusion, our data confirm that ETS exposure was associated with respiratory symptoms and diseases in young children regardless of the amount smoked. Even smoking 1–10 cigarettes a day was associated with the parameters (Table 3). Among children without allergic predisposition, boys might be more susceptible to ETS exposure than girls; whereas among children with allergic predisposition, more associations were detected in girls in this group. These observations provide further support for the results of published studies that smoking even very few cigarettes in a day may cause respiratory symptoms and allergic diseases in children. Although genetic predisposition is very prominent in the

occurrence of allergic diseases, environmental factors such as smoking may be more important when genetic predisposition is absent through unknown reasons. These findings reinforce the need to reduce the exposure of young children to ETS.

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