Association between environmental factors and hospital visits among allergic patients: A retrospective study

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Summary

Objective: **This study investigated correlations between meteorological and environmental factors (MEFs) and allergic rhinitis in childhood (ARC).**

Methods: **Children who received treatment for AR and meteorological data that might have influenced AR in the same time period were included in this study. Daily average maximum values of sulfur dioxide (SO2), nitrogen dioxide (NO_2), and particulate matter (PM10) at 3 a.m. and 8 a.m. were provided by the Shanghai Environmental Bureau for statistical analysis using a generalized additive model (GAM).**

Results: **Outpatient visits for ARC were higher, with a bimodal shape, for daily average temperatures of about 11°C and 21°C. However, increasing humidity was associated with a downward trend in outpatient visits for ARC, suggesting that high humidity had a protective effect on AR. When levels of air pollutants such as O_3, SO_2, and PM10 increased by 10 μg/m^3, AR outpatient visits increased by 1.95%, 1.19% and 0.33%, respectively, suggesting that air pollution might increase the risk of AR episodes.**

Conclusions: **MEFs were significantly correlated with the incidence of ARC.** ***(Asian Pac J Allergy Immunol 2016;34:21-9)***

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Introduction

Allergic rhinitis (AR) typically presents as nasal itching, sneezing, congestion, and discharge; this major nasal disease affects the health, academic performance, and quality of life of children, and may also induce bronchial asthma, nasal sinusitis, nasal polyps, otitis media, allergic conjunctivitis, etc. Both its prevalence and social impacts are high. In recent years, the International Study of Asthma and Allergies in Childhood (ISAAC) reported that the global prevalence of AR, asthma, and atopic eczema showed an overall upward trend.[1] AR incidence accounted for 5%-50% of the total worldwide population,[2] and the incidence rate was 37.74% in China.[3] With the continuous development of society, living environments have undergone tremendous changes, particularly in developing countries, and environmental pollution risen, leading directly to increasing annual incidence of AR. Evidence has shown that meteorological and environmental pollution factors are closely related to the incidence of AR[4-6] and that outdoor air pollution could increase the chances of allergic rhinitis in childhood (ARC).[7,8] Industrial pollutants (sulfur dioxide [SO_2], total suspended particles, and dust sedimentation) have been shown to be predisposing factors for upper respiratory tract infections, and diesel exhaust particles (DEP) and nitrogen dioxide (NO_2) emitted by diesel engines could increase the sensitivity to and incidence of allergic reactions.[9, 10] Exposure to air pollutants including suspended particulate matters with particle size less than 10 and 2.5 μm (PM10 and PM2.5, respectively), nitric oxide (NO), NO_2, ozone (O_3), and pollens, produce chronic effects in the nasal cavity, trachea, and lungs, including increased respiratory symptoms, AR, acute asthma, and other respiratory illnesses.[11,12] Exposure to PM10 results in direct injury to the human respiratory tract.[13] Many countries have established health warning systems to quickly convey accurate meteorological and environmental information to the public, and remind the public to take appropriate preventive measures to reduce the likelihood of disease progression.[14] The large Chinese population with high AR prevalence, long treatment periods, and large family and social economic burdens result in increased social impacts that should be considered by social and medical personnel. Therefore, in this study, we hoped to provide children with AR timely and appropriate risk warning and prevention guidelines based on the established Shanghai ARC-meteorological and environmental factors (MEFs) prediction model and warning system. Corresponding 5-year meteorological and environmental data were analyzed, and time-sequence analytical methods were used to establish a warning data model to forecast levels associated with AR onset, including the meteorological and environmental factors useful for forecasting trends in incidence.

AR can seriously affect the health and life quality of diseased children; treatment costs are expensive and the course long, and some children require lifelong treatment. AR is a social as well as a medical problem. The purpose of this study was to investigate the impacts of MEFs on ARC onset. This preliminary study will form the basis for a future one-year prospective study to verify these findings; further studies will perform appropriate interventions and observe their results. The results of this study provide a reliable theoretical basis for ARC prevention and treatment, guide parents and children to improve their living habits to minimize the impacts of risk factors, and reduce the incidence of respiratory allergic diseases in childhood.

Methods

Outpatient data

Data from outpatient ARC at our hospital were selected among outpatient visits seen by the department of otorhinolaryngology from January 1, 2007 to December 31, 2011; return visits and medication prescriptions were excluded, and data including date of birth, date of visit, and gender were collected. A total of 19,370 patients presenting with AR were included (13,014 men and 6,356 women), aged 2 to 15 years. All enrolled children were diagnosed with AR by four experienced physicians based on their clinical manifestations, topical nasal examinations, and results of allergen testing. Peripheral blood samples were collected from the children. The serum concentrations of total immunoglobulin E (IgE) and allergen-specific IgE (sIgE) antibodies were measured using an AllergyScreen system from Mediwiss Analytic GmbH (Germany) according to manufacturer directions. Serum concentrations of sIgE antibodies for ten common inhalant allergens were measured, including *Dermatophagoides pteronyssinus* (Dp), house dust, mulberry, cat dander, dog dander, cockroach, *Amaranthus retroflexus*, mixed grass pollen (mugwort, ragweed, *Humulus japonicus*, and grey quinoa), mixed tree pollen (oak, *Firmiana simplex*, and willow), and mixed mold (*Penicillium notatum*, branch spore mold, *Alternaria alternata*, *Aspergillus fumigatus*, and *Aspergillus niger*). In addition, nine common food allergens were measured, including egg white, milk, shrimp, beef, mussel, crab, mango, cashew nut, and pineapple. Serum concentrations of total IgE less than 100 IU/mL were considered normal, and sIgE greater levels than or equal to 0.35 IU/mL were considered positive. The quantitative test results of sIgE were divided into six levels according to concentrations: 0: <0.35 IU/mL; 1: 0.35–0.69 IU/mL; 2: 0.7–3.49 IU/mL; 3: 3.50–17.49 IU/mL; 4: 17.50–49.99 IU/mL; 5: 50.00–100.00 IU/mL; and 6: >100.00 IU/mL.

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shanghai Jiaotong University. Written informed consent was obtained from all participants.

Meteorological and atmospheric data

Meteorological data that might affect AR were collected from January 1, 2007 to December 31, 2011 by the Shanghai Meteorological Center as previously described; these analytical factors included the daily average temperature (temperature), relative humidity (humidity), wind speed (wind), and rainfall in Shanghai. Atmospheric levels of SO_2, NO_2 and PM10 were provided by the Shanghai Environmental Bureau (covering six observation sites in Shanghai), and the average maximum values at 3 a.m. and 8 a.m. among the six sites (Xujia, Baoshan, Chongming, Dongtan, Pudong and Jinshan) were used for analysis.

Statistical analysis

A generalized additive model (GAM), an extension of the generalized linear model (GLM),

Table 1. Basic distributions of ARC and meteorological environments

Variables	Mean	SD	Min	P25	Median	P75	Max	MISSING
Outpatient number	29.31	13.854	1	22.00	30.00	38.00	96	178
Average temperature	17.45	9.050	-3	9.60	18.30	25.20	36	0
Average daily relative humidity	64.61	12.768	20	60.00	70.00	70.00	90	0
Average daily wind speed	2.91	0.981	1	2.20	2.80	3.50	7	0
SO_2	39.63	26.068	7	20.00	33.00	52.00	229	31
NO_2	52.65	21.231	11	37.00	50.00	65.00	155	31
o3(8h-max)	43.22	19.717	2	56.80	78.70	107.63	120	7
PM10	80.16	57.99	10	46.00	68.00	101.00	792	31

allowed various parts of GAM's hypothetic functions to be added; this model could handle the complex nonlinear relationships among outcome variables and numerous explanatory variables and it thus was suitable for complex environmental factors-health time-sequence studies. Therefore, this study used GAM as the basic statistical method. In addition, generally under the same environment, the outpatient numbers on the same day would approximately obey the Poisson distribution, so this study used Poisson distribution as the family distribution of regression model. Many similar studies in China and abroad also assumed that the daily numbers of death, outpatient visits, or hospitalizations approximately obeyed the Poisson distribution.

$$\log\mu_l = \alpha + \beta\chi_{t-1} + \eta z_l + s(t, \lambda) + \varepsilon_l$$

In the above equation, χ_{t-1} was the atmospheric composition, z_l was the meteorological factor, $s(t, \lambda)$ was the confounding of other unmeasured factors, and this confounding was assumed to be smooth over time, and could be controlled by the smooth function.

In addition, because the daily outpatient data were time-sequence data, and might be non-independent among observation sites, diagnosis by the fitting model also considered the relevance problem of residual errors; the obtained GAM model was then subjected to residual error analysis, and a residual error-autocorrelogram of each model was then drawn to determine if the residual errors were the randomly stationary. If the values of residual errors' auto-correlated functions were less than 0.1, the residual errors were basically uncorrelated; in other words, they would basically have no effect on the statistical inference of model parameters, but absolute values greater than 0.1 indicated that correlations among the residual errors should be considered. The following GAM + AR (P) calibration model was used for the statistical inference:

$$\log\mu_l = \alpha + \beta\chi_{t-1} + \eta z_l + s(t, \lambda) + \varepsilon_l,$$

$$\varepsilon_l = \gamma_1\varepsilon_{t-1} + \gamma_2\varepsilon_{t-2} + \gamma_1\varepsilon_{t-3}$$

The model's degree of freedom was selected based on the main purpose of this study, which was to estimate the effective value rather than the predictive value of each factor, combined with the value of generalized cross validation (GCV). The punishment splines were used to judge the model's goodness of fit and to select the degree of freedom for each spline function. Because air pollution and meteorological indicators might have delayed effects on the number of hospital emergency cases, this study also set the delayed effect item (retention period effect) as the analytical indicator; the meteorological factors had the largest non-linear correlation coefficient, and the delayed period was included, which had the highest correlation coefficient among the meteorological factors and outpatient visits, into the model. The selection of atmospheric pollutants informed the delay period based on the maximal effect value of each pollutant under controlled weather conditions. $P < 0.05$ were considered statistically significant.

Results

Correlation between seasonal factors and AR incidence

Table 1 shows the basic distribution of ARC and meteorological and environmental factors from 2007 to 2011. In order to understand the fluctuations of meteorological and atmospheric pollutant indicators within this time period, we compared the time-sequence diagram of Shanghai meteorological indicators and atmospheric pollutants from 2007 to 2011 to daily outpatient visits for ARC, which increased slightly each year. The long-term MEF trends were not obvious, but the temperature and levels of O_3, PM, SO_2, and NO_2 showed a seasonal distribution. Interestingly, the seasonal distributions of O_3 and temperature were similar, suggesting a possible correlation between these factors (Figures 1-2). In addition, the average number of monthly ARC emergency visits peaked in spring (April-May) and autumn (October and November. Therefore, the statistical analysis included seasonal factors and long-term trends in the model as confounding factors.

Correlation of meteorological and atmospheric environmental factors

Spearman correlation analysis (Table 2) revealed a strong correlation with atmospheric concentrations; correlation coefficients were greater than 0.5 for NO_2 and SO_2, PM10 and NO_2, and PM10 and NO_2, indicating a moderate correlation; the correlation between O_3 and temperature was also high (r = 0.486), consistent with previous reports. NO_2 was moderately negatively correlated with wind (r > 0.5), for high wind speeds and relatively low pollutant concentrations, suggesting correlations among meteorological and atmospheric variables that were not independent.

Delayed effects

The delay periods were determined by calculating Spearman correlation coefficients between MEFs and outpatient-emergency ARC visits; the final results showed that the temperature on the exact day had the highest correlation coefficient with the outpatient-emergency visits of ARC. The correlation coefficients of 2-day delayed humidity, 3-day delayed wind, and rainfall amount on the exact day had maximal correlation coefficients. O_3, NO_2, and SO_2 levels on the exact day and 6-day delayed PM10 had maximal correlation coefficients (Table 3). Finally, temperature; humidity; and levels of O_3, SO_2, and PM10 were statistically significant (P < 0.05). The results showed that, after controlling for time-related trends, week effects, and other factors, outpatient

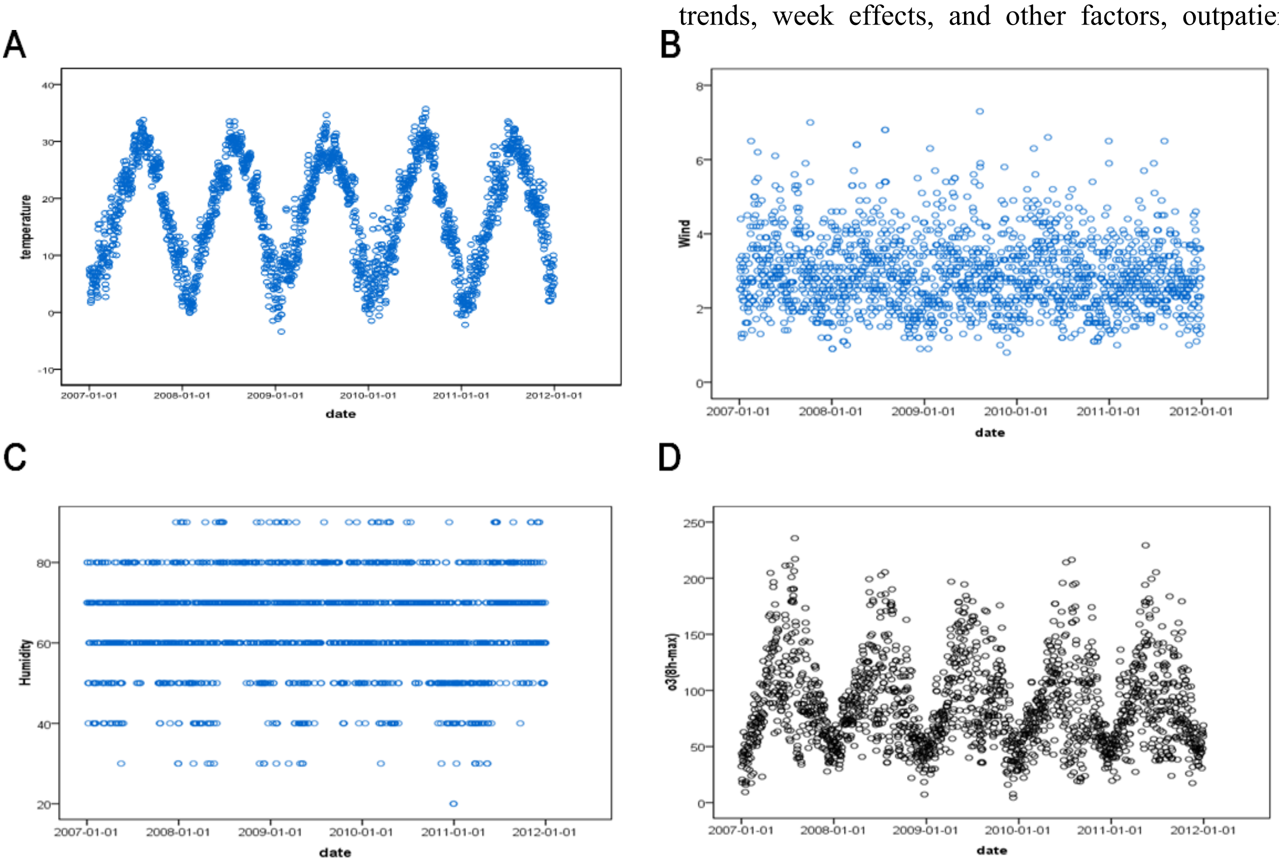

Figure 1. Time sequences of temperature, humidity, wind power and O3 within 2007-2011.
A. Time sequence of temperature within 2007-2011; B. Time sequence of humidity within 2007-2011; C. Time sequence of wind power within 2007-2011; D. Time sequence of O3 within 2007-2011.

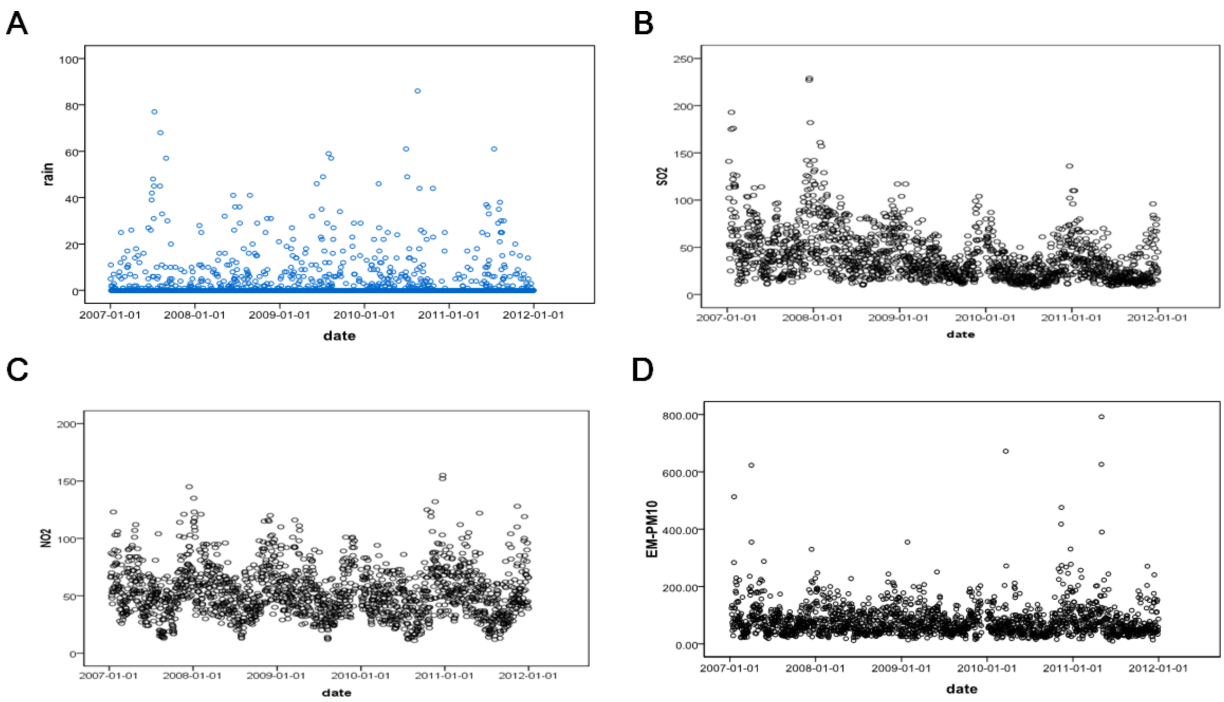

Figure 2. Time sequences of rain amount, SO2, NO2 and PM10 within 2007-2011.
A. Time sequences of rain amount within 2007-2011; B. Time sequence of SO2 within 2007-2011; C. Time sequence of NO2 within 2007-2011; D. Time sequence of PM10 within 2007-2011.

visits for ARC were higher for average daily temperatures of 11°C and 21°C, which exhibited a bimodal distribution. However, with increasing humidity, outpatient visits for ARC decreased, indicating that high humidity had a protective effect on AR. When the air pollutants O_3, SO_2, and PM10 increased by 10 $\mu g/m^3$, outpatient visits for ARC increased by 1.95%, 1.19% and 0.33%, respectively (Table 3, Figure 3), suggesting that air pollution might increase the risk of AR onset.

Discussion

With increased worldwide industrialization, AR-asthma has become a serious allergic disease, affecting patient work, learning, and living.[4-6, 11] Epidemiological studies have reported that AR incidence accounts for 5%-50% of the total world population;[2] the incidence rate in China was about 37.74%.[3] The AR incidence in children 6-7 and 13-14 years of age was 8.5%, and 14.6%, respectively;[1] early childhood living conditions such as the mother's gestational age, multiple pregnancies, low birth weight, family history of allergenic diseases, and race, as well as the surrounding smoking environment, urban living, nutritional status, and air pollution, were all considered risk factors of AR onset.[7,8,15] In the current study, the daily number of outpatient ARC cases slightly increased each year . Based on the time-sequence diagram from Shanghai meteorological indicators and atmospheric pollutants from 2007 to 2011, long-term MEFs trends were not obvious, but temperature and levels of O_3, PM, SO_2,

Table 2. Correlation matrix of MEFs

	Temperature	Humidity	Wind	SO_2	NO_2	O_3	PM10
Temperature	1.000						
Humidity	0.198**	1.000					
Wind	0.090**	-0.005	1.000				
SO_2	0.383**	-0.351**	-0.272**	1.000			
NO_2	-0.383**	-0.215**	-0.507**	0.695**	1.000		
o3(8h-max)	0.486**	-0.272**	-0.056*	-0.011	0.025	1.000	
PM10	-0.277**	-0.217**	-0.277**	0.468**	0.562**	0.024	1.000

$^{**}P<0.01$, $^{*}P<0.05$

Table 3. Analytical results of multivariate model parameters of AR-MEFs

	Estimate	Std. Error	T value	Pr(>|t|)	
(Intercept)	1.1151501	0.1697266	6.57	5.02E-11	***
Ns(temp, 7)1	0.2719054	0.0666801	4.078	4.55E-05	***
Ns(temp, 7)2	0.1172234	0.0831776	1.409	0.158742	
Ns(temp, 7)3	0.1725149	0.0782247	2.205	0.027428	*
Ns(temp, 7)4	0.1160396	0.0835551	1.389	0.1649	
Ns(temp, 7)5	0.0739482	0.0675786	1.094	0.273843	
Ns(temp, 7)6	0.0832075	0.1593722	0.522	0.601604	
Ns(temp, 7)7	-0.0214815	0.0800651	-0.268	0.788468	
Ns(l2humi, 4)1	-0.1703828	0.0603897	-2.821	0.004782	**
Ns(l2humi, 4)2	-0.223784	0.044808	-4.994	5.91E-07	***
Ns(l2humi, 4)3	-0.4057343	0.1409381	-2.879	0.003992	**
Ns(l2humi, 4)4	-0.1779216	0.0395086	-4.503	6.69E-06	***
As.factor(week)1	2.3557959	0.0503923	46.749	< 2e-16	***
As.factor(week)2	2.1768428	0.0506506	42.978	< 2e-16	***
As.factor(week)3	2.0901416	0.0507562	41.18	< 2e-16	***
As.factor(week)4	2.0449764	0.0508186	40.241	< 2e-16	***
As.factor(week)5	2.1924193	0.0506103	43.32	< 2e-16	***
As.factor(week)6	2.2009222	0.0506162	43.483	< 2e-16	***
Ns(date, 42)1	-0.5816783	0.1175663	-4.948	7.51E-07	***
Ns(date, 42)42	0.0577884	0.0666456	0.867	0.385887	
O_3	0.0193459	0.0024634	7.853	4.05E-15	***
SO_2	0.0118577	0.0024728	4.795	1.63E-06	***
l6PM10	0.0032521	0.0008599	3.782	0.000156	***

*, P<0.05, **, P<0.01, ***, P<0.001

and NO_2 showed seasonal distribution (Figures 1-2). Spearman correlation analysis (Table 2) revealed strong correlations among atmospheric pollutant concentrations; correlation coefficients between NO_2 and SO_2, PM10 and NO_2, and PM10 and NO_2, were greater than 0.5 (moderate correlation), and the correlation between O_3 and temperature was also high (r = 0.486), consistent with previous findings. NO_2 was moderately negatively correlated with wind strength (r > 0.5): when the wind was strong, pollutant concentrations were relatively low, indicating a correlation between meteorological and atmospheric variables, and these factors were not independently associated with the average monthly number of emergency visits for ARC. The numbers of emergency visits in spring (April-May) and autumn (October and November) were slightly higher than in other months. Because this study mainly evaluated the relationship between meteorological environmental factors and ARC, seasonal factors were not considered; instead, this study mainly considered the non-pollen stage, and the statistical analysis controlled for seasonal factors and long-term trends included in the model as confounding factors. Correspondingly, analysis of the controlled time trend, week effects, and other factors, revealed that outpatient visits for ARC were higher when the average daily temperatures were 11°C and 21°C, which exhibited a bimodal shape.

Recent studies have reported that outdoor air pollution increases the risk of ARC.[7,8,15,16] Industrial pollution such as SO_2, total suspended particles, and dust sedimentation were predisposing factors for upper respiratory tract infections. SO_2 could cause decreased activities of the mucociliary epithelium in the respiratory system, diminished cilia movement, resulting in an inability to remove local allergens, thus increasing the chances of mucous membranes contacting with the antigens and enhancing the sensitization effects. SO2 could also be adsorbed as a gas sol by the nasal epithelium, thus stimulating an immune response in the nasal mucosa and inducing allergic diseases such as AR, asthma, and others. In addition, SO_2 can promote lipid peroxidation, resulting in damage to the nasal epithelium and exposed nerve endings, which leads to nasal hyper-responsiveness when the nerves are stimulated by allergens.[17] DEP and NO_2 emitted by automotive

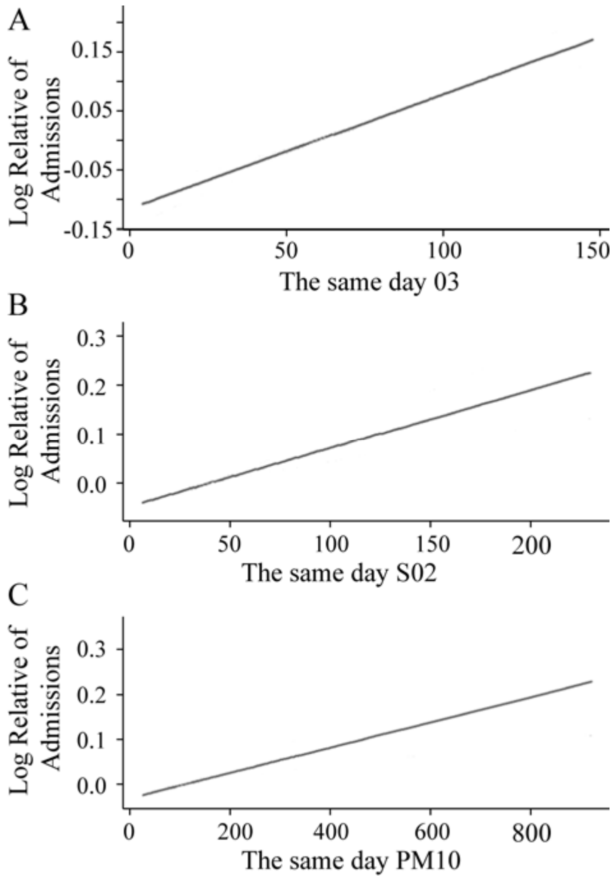

Figure 3. Exposure-response relationships of relative risk degrees of O_3, SO_2 and PM10 with the number of AR patient visits, respectively. A: Exposure-response relationships of O_3 and relative risk degree of AR clinical visits; B: Exposure-response relationships of SO_2 and relative risk degree of AR clinical visits; C: Exposure-response relationships of PM10 and relative risk degree of AR clinical visits.

diesel engines could increase sensitivity and incidence of allergic diseases.[9,18,19] PM10 has direct effects on injury in the human respiratory tract.[10] Research in past decades has substantially increased understanding of the pathogenesis of allergic diseases, including the underlying mechanism involving a Th2-dominant immune response that leads to tissue inflammation and remodeling. Recently, new evidence has also been presented to support the importance of innate immunity at the level of dendritic and epithelial cell response for disease expression; additional types of T-cell responses also likely contribute to disease progression[20,21]. There is now a wealth of evidence linking exposure to outdoor and indoor air pollution, especially airborne PMs, to adverse effects on allergic diseases, where PM's surface materials may target immune regulatory and pulmonary resident cells.[22,23] Several reviews have discussed the potential mechanisms of each individual component associated with PMs; for example, the functional impact of air pollutant gases such as O_3, NO2, and CO has been extensively studied and several recent reviews [24,25] have proposed a series of mechanistic events resulting from PM exposure; their surface chemical and metal components have been used to establish the exposure-disease mechanistic relationship and explain the relationship between particulate air pollutants and allergic diseases. This study showed that levels of atmospheric pollutants O_3, SO_2, and PM10 increased by 10 $\mu g/m^3$, the number of patient visits would increased by 1.95%, 1.19% and 0.33%, respectively (Table 3, Figure 3), suggesting that air pollution might increase risk of AR onset. Research in the United Kingdom showed that short-term acute exposure to environmental O_3 and SO_2 was closely correlated with AR onset.[13] In recent years, the concentration of NO_2, a traffic-related pollutant, has increased every year. NO_2 can increase respiratory tract sensitivity: in 2006, a report from Taiwan found that continuous exposure to environmental NO_2, CO, and SO_2 might increase AR incidence in schoolchildren.[26-28] However, in this study, NO_2 was moderately correlated with the number of ARC patient visits, although the difference was not statistically significant. This study also suggested a less significant correlation between MEFs and NO_2.

A study in Jinan, China reported that increased PM10 and NO_2 concentrations immediately resulted in increased patient visits for AR; however, there was a 3-day delayed effect when SO_2 concentrations increased.[29] In this study, Spearman correlation coefficients of MEFs and outpatient-emergency ARC visits were calculated to determine the delay period; analysis showed that the temperature on the exact day had the maximal correlation coefficient with ARC outpatient-emergency numbers. Low temperatures may cause nasal mucosa irritation, resulting in systolic and diastolic dysfunctions, especially in children. The correlation coefficients were highest for 2-day delayed humidity, 3-day delayed wind, and rain amount on the exact day. Levels of O_3, NO_2, and SO_2 on the exact day and 6-day delayed PM10 had the maximal correlation coefficients, different from findings in Jinan. Moisture may increase aerosolization of pollutant particles, but rainwash could reduce their airborne concentrations air, so the combined action of these two factors, with increasing humidity, likely resulted in reduced AR patient visits, suggesting that the high humidity had a protective effect on AR.

AR results in dysfunction of peripheral immune tolerance, which generates deviated and over-reactive immune reactions towards some "harmless" allergens due to both genetic and environmental factors.[30,31] This study found that MEFs were closely correlated with ARC incidence, but it remains unclear whether increased environmental pollution could lead to the occurrence and development or severity and risk of allergic diseases in subsets of populations with genetic susceptibilities. Additional research on the interactions between genetic and environmental factors could provide important information; however, this research is currently scarce. Future studies will explore the impact of MEFs on ARC, as well as interactive factors such as genetic single nucleic acid polymorphisms and environmental factors, thus providing a reliable theoretical basis for ARC prevention and treatment, increasing the dissemination of related knowledge and guiding parents and children to improve their living habits to reduce exposure to risk factors and incidence of ARC.

Conflict of interest

All authors have no conflict of interest regarding this paper.

References

1. Aït-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy. 2009;64:123-48.
2. Aubier M. Traffic-related pollutants and their impact on allergic respiratory diseases. Bull Acad Natl Med. 2009;193:1303-13.
3. Ballester F, Estarlich M, Iñiguez C, Llop S, Ramón R, Esplugues A, et al. Air pollution exposure during pregnancy and birth size:a prospective birth cohort study in Valencia, Spain. Environ Health. 2010;9:6.
4. Lee SY, Chang YS, Cho SH. Allergic diseases and air pollution. Asia Pac Allergy. 2013;3:145-54.
5. Kennedy DW. The contribution of environmental pollution in the development of allergic rhinitis (AR) and asthma has been previously studied and documented. Introduction. Int Forum Allergy Rhinol. 2014;4:91-2.
6. Dell SD, Jerrett M, Beckerman B, Brook JR, Foty RG, Gilbert NL, et al. Presence of other allergic disease modifies the effect of early childhood traffic-related air pollution exposure on asthma prevalence. Environ Int. 2014;65:83-92.
7. Kaiser H. Risk factors in allergy/asthma. Allergy Asthma Proc. 2004;25:7-10.
8. Marshall GD. Internal and external environmental influences in allergic diseases. J Am Osteopath Assoc. 2004;104:S1-6.
9. Wang KY, Chau TT. An association between air pollution and daily outpatient visits for respiratory disease in a heavy industry area. PLoS One. 2013;8:e75220.
10. Alvarez Miño L, Salazar Ceballos A. Respiratory symptoms and lung function in children aged 6-14 years and their relationship with particulate matter PM10 in Santa Marta, Colombia. Rev Esp Salud Publica. 2013;87:239-46.
11. Silverman RA, Ito K. Age-related association of fine particles andozone with severe acute asthmain New York city. J Allergy Clin Immunol. 2010;125:367-73.e5.
12. MacIntyre EA, Carlsten C, MacNutt M, Fuertes E, Melén E, Tiesler CM, et al. Traffic, asthma and genetics: combining international birth cohort data to examine genetics as a mediator of traffic-related air pollution's impact on childhood asthma. Eur J Epidemiol. 2013;28:597-606.
13. Wood SN, Augustin NH. GAMs with integrated model selection using penalized regression splines and applications to environmental modeling. Ecol Model. 2002;157:157-77.
14. Marno P, Chalder M, Laing-Morton T, Levy M, Sachon P, Halpin D. Cana health forecasting service offer COPD patients anovel way to manage their condition? J Health Serv Res Policy. 2010;15:150-5.
15. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA). Allergy. 2008;63:8-160.
16. Arnedo-Pena A, García-Marcos L, Carvajal Urueña I, Busquets Monge R, Morales Suárez-Varela M, Miner Canflanca I, et al. Air pollution and recent symptoms of asthma, allergic rhinitis, and atopic eczema in schoolchildren aged between 6 and 7 years. Arch Bronconeumol. 2009;45:224-9.
17. Wang Y, An YF, Zhao CQ. Effects of sulphur dioxide inhalation on allergic rhiultis in mice. Chin J Otochinolaryngol Head Neck Surg. 2008;43:509-13.
18. Takano H, Yoshikawa T, Ichinose T, Miyabara Y, Imaoka K, Sagai M. Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. Am J Respir Crit Care Med. 1997;156:36-42.
19. Kobayashi T. Exposure to diesel exhaust aggravates nasal allergic reaction in guinea pigs. Am J Respir Crit Care Med. 2000;162:352-6.
20. Wisniewski JA, Borish L. Novel cytokines and cytokineproducing T cells in allergic disorders. Allergy Asthma Proc. 2011;32:83-94.
21. Licona-Limón P, Kim LK, Palm NW, et al. TH2, allergy and group 2 innate lymphoid cells. Nat Immunol. 2013;14:536-42.
22. Nadeem A, Masood A, Siddiqui N. Oxidant--antioxidant imbalance in asthma: scientific evidence, epidemiological data and possible therapeutic options. Ther Adv Respir Dis. 2008;2:215-35.
23. Comhair SA, Erzurum SC. Redox control of asthma: molecular mechanisms and therapeutic opportunities. Antioxid Redox Signal. 2010;12:93-124.

24. Kim KH, Jahan SA, Kabir E. A review on human health perspective of air pollution with respect to allergies and asthma. Environ Int. 2013;59:41-52.
25. Jang AS. Particulate air pollutants and respiratory diseases. In: Haryanto B. eds. Air Pollution-A Comprehensive Perspective. Publisher: InTech, 2012:153-74.
26. Hwang BF, Jaakkola JJ, Lee YL, Lin YC, Guo YL. Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res. 2006;7:23.
27. Frei T, Gassner E. Trends in prevalence of allergic rhinitis and correlation with pollen counts in Switzerland. Int Biometeorol. 2008;52:841-7.
28. Motta AC, Marliere M, Peltre G, Sterenberg PA, Lacroix G. Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. Int Arch Allergy Immunol. 2006;139:294-8.
29. Wang Y, Zhang Y, Li X. The effect of air pollution on hospital visit for respiratory symptom in urban areas of Jinan (in Chinese). China Environ Sci. 2008;28:571-6.
30. Kim WK, Kwon JW, Seo JH, Kim HY, Yu J, Kim BJ, et al. Interaction between IL13 genotype and environmental factors in the risk for allergic rhinitis in Korean children. J Allergy Clin Immunol. 2012;130:421-6.e5.
31. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong kong from 1995 to 2001. Pediatr Allergy Immunol. 2004;15:72-8.