



Relative impact of meteorological factors and air pollutants on childhood allergic diseases in Shanghai, China

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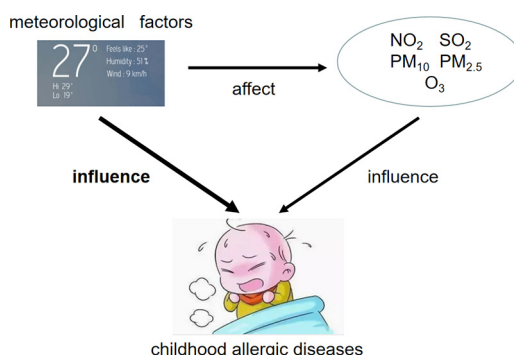
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HIGHLIGHTS

- First study to examine the relative impact of meteorological factors and air pollutants on childhood allergic diseases.
- The relationships between environmental factors and allergic diseases were quantified using 11-year time-series data.
- Meteorological factors played a more important role than air pollutant in the occurrence of these diseases in Shanghai.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Non-optimal weather conditions and air pollution pose a significant threat to children's health. However, the relative impact of different environmental exposures on childhood allergic diseases remains unclear.

Objectives: This study aimed to quantify the relative impact of meteorological factors and air pollutants on childhood allergic diseases in Shanghai, China.

Methods: Data on clinical visits due to childhood asthma, allergic rhinitis (AR) and atopic dermatitis (AD) from 2007 to 2017 in Shanghai were collected from Shanghai Children's Medical Center and Xinhua Hospital. The meteorological data (i.e. daily mean temperature, temperature difference, air pressure, air pressure difference, precipitation, relative humidity, sunshine and wind speed) for the same period were obtained from the Shanghai

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Meteorological factors
Air pollution
Childhood allergic diseases
Adaptive strategy

Meteorological Center. Air pollution data (PM₁₀, PM_{2.5}, NO₂, SO₂ and O₃) were provided by the Shanghai Environmental Protection Agency. Quasi-Poisson regression with distributed lag non-linear models and Poisson regression combined with generalized linear models were used to assess the relative impact of meteorological factors and air pollutants on childhood allergic diseases.

Results: There were a total of 2,410,392 cases of childhood allergic diseases, including 975,771 asthma, 646,975 AR and 787,646 AD. Most of environmental factors were significantly associated with childhood allergic diseases. Daily mean temperature (standard β : -0.076 (95% confidence interval (CI): $-0.086, -0.067$)) and air pressure (standard β : 0.075 (95% CI: $0.068, 0.082$)) seemed to play more important roles than other environmental factors in the occurrence of these allergic diseases. The numbers of these allergic diseases attributable to an interquartile range (IQR) change in meteorological factors also appeared to be greater than those attributable to an IQR change in air pollutants.

Conclusions: Both climatic variation and air pollution were associated with childhood allergic diseases, but the former appeared to play a more important role in the occurrence of these diseases. These findings may have significant implications for the development of tailored strategies to prevent these rapidly-increasing diseases worldwide.

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1. Introduction

Allergic diseases (e.g., asthma, allergic rhinitis (AR) and atopic dermatitis (AD)) are becoming the major child health problems worldwide which lead to a great economic burden and poor quality of life (Asher et al., 2006; GBD, 2016; Ahmed et al., 2018). The International Study of Asthma and Allergies in Childhood (ISAAC) investigated the prevalence of symptoms and severity of asthma, AR and AD in different populations around the world and reported rising global trends in the prevalence of allergic disorders, particularly in highly developed countries (Asher et al., 2006). They found that environmental rather than genetic factors may be the most important drivers of childhood allergic diseases (ISAAC Steering Committee, 1998; Williams et al., 1999).

Asthma, a chronic non-communicable disease characterized by inflammation and reversible obstruction of the airways (GINA, 2017), affects approximately more than three hundred million people worldwide, especially children (GBD, 2016; Kassebaum et al., 2016; Asher and Pearce, 2014; GBD, 2017; To et al., 2010). Wide differences in asthma prevalence have been observed among countries and populations, ranging from 1.5 to 15.6% (Masoli et al., 2004; Van Wonderen et al., 2010). These differences could be a result of complex interactions among environmental and genetic factors (Nishimura et al., 2013; Oh et al., 2016). The prevalence of AR is high, affecting over 10–40% of the population worldwide, and it continues to rise rapidly in recent years (Bousquet et al., 2008; Wang et al., 2016). ISAAC has found a slight worldwide increase in the prevalence of AR among children aged 13–14 years (0.18% per year) and 6–7 years (0.17% per year), as well as >20-fold variation in the prevalence of self-reported AR among countries in the same region and between centers in the same country (GBD, 2016). AD, also known as atopic eczema or eczema, is a chronic inflammatory skin disease mostly occurring in early childhood. Recently, the prevalence of AD is estimated to be 15–20% in children worldwide (Nuttan, 2015). The prevalence of AD in children is still increasing in both developing and developed countries (Ahn, 2014; Williams et al., 2008).

Within the ISAAC studies, Weiland et al. (2004) found that climate may affect the prevalence of childhood asthma and AD. Outdoor relative humidity was negatively associated with asthma symptoms. The prevalence of AD symptoms was also negatively correlated with mean annual outdoor temperature. It has also been found that climatic conditions (and future climate changes) affected the prevalence of childhood AR symptoms (Fuertes et al., 2014). Mounting evidence suggests that long-term exposure to non-optimal environmental factors like high air pollution is associated with the development of childhood allergic diseases (Guarnieri and Balmes, 2014; Kim et al., 2013). It is reported that 8–20% of asthma emergency room visits worldwide could be attributed to ozone (O₃) and 4–9% to PM_{2.5} (Anenberg et al., 2018). However, Anderson et al. (2012) found no evidence of a positive association

between ambient air pollution and the prevalence of asthma as measured at the community level in contrast to reports from within-community studies of individuals exposed to PM_{2.5}, NO₂ and O₃. Indeed, a systematic review and meta-analysis reported that exposure to NO₂, NOx, PM_{2.5}, and PM₁₀ was significantly associated with increased risks of childhood asthma (Khreis et al., 2017). A study conducted in 28 countries in Europe reported that environmental risk exposures were estimated to produce 211,000 disability-adjusted life years (DALYs) in children annually, representing 2.6% of all DALYs in children (Rojas-Rueda et al., 2019). Another study showed that a 1 $\mu\text{g}/\text{m}^3$ reduction in particulate matter concentration would generate nearly \$350 million annually in economic benefits to the US (Williams et al., 2019).

Given that environmental factors affect the development of children's diseases, causing enormous economic burden of families and society and affecting children's health and socio-economic development (Rojas-Rueda et al., 2019; Ahmed et al., 2018; GBD, 2016; Kassebaum et al., 2016; Asher and Pearce, 2014; Asher et al., 2006), a number of studies have been conducted to unveil the relationship between environmental factors and childhood allergic diseases (Anenberg et al., 2018; Passali et al., 2018; Khreis et al., 2017; D'Amato et al., 2014; Sargen et al., 2014). It is of great importance to explore the relative impact of meteorological factors and air pollution on childhood allergic diseases as it can aid in the wise allocation of stretched resources of allergic disease control and prevention. This study aimed to quantify the relative impact of meteorological factors and air pollutants on childhood allergic diseases in Shanghai, China.

2. Methods

2.1. Study participants

This study was conducted in Shanghai, China, a provincial-level administrative region, municipality directly under the Central Government. Shanghai has a subtropical monsoon climate, mild and humid, with four distinct seasons, abundant sunshine and abundant rainfall (Sun et al., 2012; Li et al., 2012). In the past decades, the prevalence of children's allergic diseases including asthma, AR and AD, increased sharply in Shanghai, making Shanghai the city with the highest prevalence rate of childhood allergic diseases in China (Li et al., 2011; Zhang et al., 2013; Liu et al., 2016). In this study, data on clinical visits due to childhood allergic diseases including asthma, AR and AD from January 1st 2007 to December 31st 2017 were collected from Shanghai Children's Medical Center and Xinhua Hospital, two big pediatric hospitals located in Shanghai (Fig. 1, Xinhua Hospital also has a section for adult patients). Principal diagnostic classification of childhood allergic diseases was made according to the tenth version of International Classification of Diseases for asthma (ICD-10, J45-J46), AR (ICD-10, J30) and

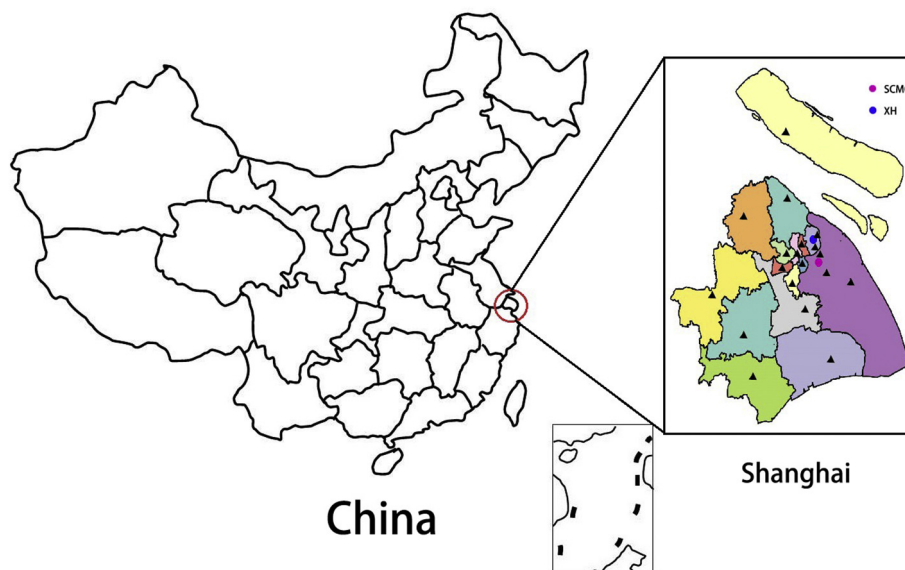


Fig. 1. Locations of two major pediatric hospitals and air quality monitoring stations in Shanghai, China. SCMC: Shanghai Children's Medical Center; XH: Xinhua Hospital; Triangles represent the monitoring stations.

AD (ICD-10, L23). Children were defined as those aged <18 years. We used the first diagnosis upon presenting to the hospital as the method to define childhood allergic disease cases, so each person could only be counted once per day. There were 2,410,392 cases in total, including 975,771 asthma, 646,975 AR, and 787,646 AD. The ethical approval of this project was granted by the Ethics Committee of Shanghai Children's Medical Center (# 18411951600) prior to the data being collected.

2.2. Meteorological factors and air pollution exposure assessment

The meteorological data (daily mean temperature, daily temperature difference, mean air pressure, daily air pressure difference, precipitation, average relative humidity (RH), sunshine hours and average wind speed) from the 1st January 2007 to the 31st December 2017 were obtained from the Shanghai Meteorological Center. The data on daily mean values of ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and airborne particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) or 10 μm (PM_{10}) were supplied by the Shanghai Environmental Protection Agency. Daily mean values of meteorological factors, NO_2 , SO_2 , O_3 , PM_{10} , and $PM_{2.5}$ were calculated using the 24-h monitoring records. Due to the lack of residential addresses of the study subjects, we used the daily averages of air pollutants monitored by many stations distributed in various districts of Shanghai. Monitoring stations were widely distributed in Shanghai, providing monitoring data with considerable geographic coverage (Fig. 1).

2.3. Statistical analysis

A two-stage analysis was conducted. There were three steps in the first stage. Step I: Spearman correlation analysis was used to calculate the correlations between all variables (including environmental factors and childhood allergic diseases). Seasonal decomposition analysis was conducted to assess the seasonal patterns and long-term trends of environmental factors and childhood allergic diseases during 2007–2017. Step II: using Poisson regression allowing for over-dispersion with distributed lag non-linear model (DLNM) (Gasparrini et al., 2010), we examined the relationship between each environmental factor and clinical visits for childhood allergic diseases separately (i.e., one-environmental-factor model) and selected those factors which were significantly associated with the clinical visits of childhood allergic diseases for the analysis of the next step. The environmental factors

examined in this step were daily mean temperature, temperature difference, mean air pressure, air pressure difference, average RH, sunshine hours, precipitation, wind speed, NO_2 , SO_2 , PM_{10} , $PM_{2.5}$ and O_3 . Step III: using the significant environmental factors identified in step II, we built up multivariable models including different sets of covariates using quasi-Poisson regression allowing for over-dispersion with distributed lag non-linear model. Because temperature was highly correlated with air pressure, relative humidity was highly correlated with precipitation, and some of NO_2 , SO_2 , PM_{10} and $PM_{2.5}$ were highly correlated each other, we only chose one from a set of correlated variables each time to build up the models to avoid multicollinearity issues ($r_s \geq 0.7$ would be considered as highly correlated). By comparing all models in step III, we found that the model with mean temperature, RH, wind speed, NO_2 and O_3 or the model with mean air pressure, RH, wind speed, NO_2 and O_3 performed the best (i.e., these two models had the minimum residual deviance). We herewith used mean temperature as an example to elaborate the modelling details. A cross-basis defined by natural cubic spline with four degrees of freedom (dfs) for the space of mean temperature was used. A maximum lag of 21 days was adopted in the analysis after considering the findings of previous studies (Yi and Chan, 2015; Gasparrini et al., 2015) and the reference of Akaike information criterion. Seasonality and long-term trend were controlled by natural cubic spline with 8 dfs in the model. The day of week and public holiday were also controlled as dummy variables.

In the second stage, there were two steps. Step I: we assessed the regression coefficients and standardized regression coefficients in multivariate generalized linear models (GLM). The standard regression coefficient refers to the regression coefficient after eliminating the influence of the unit of the dependent variable Y and the independent variables $X_1, X_2, \dots, X_n$, and the magnitude of the absolute value directly reflects the degree of influence of X_i on Y (Suzuki et al., 2009; Higashi et al., 1998). The equation is as follows:

$$Y \sim \beta_0 + \beta_1 X_1 + \dots + \beta_j X_j + \dots + \beta_J X_J,$$

Standardized $\beta = \beta_j * SDX_j / SDY_j$, SD means standard deviation.

Step II: we calculated the numbers of childhood allergic diseases attributable to an inter-quartile range (IQR) change in meteorological factors and air pollutants. In detail, an increase of IQR in air pollutants and air pressure was adopted to calculate the attributable number, and

meanwhile, a drop of IQR in temperature, RH and wind speed was used to calculate the attributable number to facilitate the comparison between two sets of variables. We used both standardized regression coefficients in multivariate GLM and the numbers of childhood allergic diseases attributable to an IQR change of meteorological factors and air pollutants to assess the relative impact of different environmental exposures in childhood allergic diseases. In the models of the second stage, seasonality and long-term trend were controlled by natural cubic spline with 8 *dfs*, and the day of week and public holiday were also adjusted as dummy variables.

All statistical analyses were conducted using R (version 3.5.1; R Core Team) in which “tseris”, “dlnm” and “splines” packages were mainly used. Statistical significance was set at *p* values ≤ 0.05 (two sides).

2.4. Sensitivity analysis

A series of sensitivity analyses were conducted using alternative *dfs* for calendar time and environmental factors. We used 6–10 *dfs* per year for calendar time and 3–7 *dfs* for environmental factors. DLNM combining other covariates were also performed, such as the model with mean temperature, RH, wind speed, SO₂ and O₃, to compare with the final model and verify it.

3. Results

3.1. Distribution and correlation of childhood allergic diseases and environmental factors

Table 1 presents the summary statistics of childhood allergic diseases, meteorological factors and air pollutants from 1 January 2007 to 31 December 2017. The average value of daily clinical visits for asthma, AR and AD was 243, 161 and 196, respectively. The average value of daily mean temperature, air pressure, sunshine, relative humidity, precipitation and wind speed was 17.3 °C, 1016.0 hPa, 4.9 h, 74.0%, 3.8 mm and 1.5 m/s, respectively. The average value of PM₁₀, PM_{2.5}, NO₂, SO₂ and O₃ was 74.5 µg/m³, 48.3 µg/m³, 49.1 µg/m³, 27.3 µg/m³ and 68.5 µg/m³, respectively.

Table 2 shows the correlations between environmental factors and childhood allergic diseases during 2007–2017. Spearman correlation

coefficients between three allergic diseases were 0.693 (asthma and AR), 0.697 (asthma and AD), and 0.682 (AR and AD). Both asthma and AD were inversely correlated with daily mean temperature, wind speed and SO₂ but positively correlated with daily mean air pressure and NO₂. AR was inversely correlated with SO₂, but positively correlated with O₃. In addition, daily mean air pressure was highly inversely correlated with daily mean temperature (*r*_s = −0.879, *p* < 0.01). Each of NO₂, SO₂, PM₁₀ and PM_{2.5} was positively correlated with others while O₃ was negatively associated with other air pollutants.

3.2. Relationships between environmental factors and childhood allergic diseases

Fig. 2 shows the overall exposure-response relationships of mean temperature, RH, wind speed, NO₂, O₃ and mean air pressure with asthma, AR and AD by using Poisson regression with distributed lag non-linear model. Low mean temperature, RH, wind speed and high levels of NO₂, and O₃ increased the clinical visits for childhood asthma. There was a non-linear trend between air pressure levels and the risk of asthma. Air pressure levels were positively associated with the risk of asthma when air pressure levels were < 1027 hpa. However, there was a downward pattern when air pressure levels reached 1027 hpa or over. Low levels of RH and wind speed and high mean air pressure increased clinical visits for childhood AR. Low temperature, RH, wind speed and high level of NO₂ and mean air pressure increased clinical visits for childhood AD.

3.3. Multivariate GLM results for the relative impact of different environmental exposures on childhood allergic diseases

Table 3 depicts the results of standard regression coefficients (*St_β*) in the multivariate GLM for the relationship between environmental factors and childhood allergic diseases. All three allergic diseases were inversely associated with daily mean temperature and mean wind speed, but positively associated with daily air pressure, NO₂ and O₃. AR and AD were inversely associated with daily RH, but asthma was positively associated with RH. In addition, the values of *St_β* of daily mean temperature (−0.076 (95% CI: −0.086, −0.067)) and mean air pressure (0.075 (95% CI: 0.068, 0.082)) were higher than the values of

Table 1
Daily clinical visits for childhood allergic diseases, meteorological factors and air pollutants from 1 January 2007 to 31 December 2017.

Variables	Mean	Min ^a	P25 ^b	P50 ^b	P75 ^b	Max ^a	IQR ^c
Asthma	243	21	126	212	329	802	203
Allergic rhinitis	161	1	70	132	221	780	151
Atopic dermatitis	196	1	112	180	261	734	149
Meteorological factors							
Mean temperature (°C)	17.3	−5.6	9.5	18.2	24.4	34.8	14.9
Max temperature (°C)	21.4	−3.8	13.8	22.4	28.6	40.9	14.8
Min temperature (°C)	13.9	−7.2	6.1	14.4	21.7	31	15.6
Daily temperature difference (°C)	7.4	0.8	4.8	7.1	9.9	19.5	5.1
Mean air pressure (hPa)	1016.0	992.6	1008.5	1016.0	1023.1	1039.4	14.6
Max air pressure (hPa)	1018.0	996.0	1010.0	1018.0	1026.0	1041.0	16.0
Min air pressure (hPa)	1013.8	984.9	1006.4	1013.7	1020.5	1037.2	14.1
Daily air pressure difference (hPa)	4.6	1.3	3.0	3.9	5.4	20.2	2.4
Sunshine(h)	4.9	0.0	0.0	5.4	8.5	12.5	8.5
Relative humidity (%)	74.0	24.0	67.0	75.0	83.0	100.0	16.0
Precipitation (mm)	3.8	0.0	0.0	0.0	1.6	164	1.6
Wind speed (m/s)	1.5	0.1	1.0	1.5	1.9	6.1	0.9
Air pollutants (µg/m ³)							
PM ₁₀	74.5	6.0	42.2	61.9	92.1	803.8	49.9
PM _{2.5}	48.3	5.0	27.0	41.0	60.0	447.0	33.0
NO ₂	49.1	5.0	34.0	46.0	61.0	153.1	27.0
SO ₂	27.3	5.0	13.0	19.5	34.5	213.9	21.5
O ₃	68.5	7.0	45.4	68.8	85.8	277.9	40.4

Values of meteorological factors were daily average; Values of PM₁₀, PM_{2.5}, NO₂ and SO₂ were daily hourly average; Values of O₃ were computed using 1-h mean concentrations.

^a Min: minimum; Max: Maximum.

^b P25, 25th centile; P50, 50th centile; P75, 75th centile.

^c IQR: interquartile range.

Table 2

Spearman correlations between environmental factors and childhood allergic diseases during 2007–2017.

Variables	Asthma	AR	AD	Mean temp	DTD	Mean AP	DAPD	Sunshine	RH	Precipitation	Wind speed	NO ₂	PM ₁₀	PM _{2.5}	SO ₂
AR	0.693														
AD	0.697	0.682													
Mean temp	−0.290	0.055	−0.412												
DTD	0.016	0.070	0.226	0.039											
Mean AP	0.351	−0.007	0.391	−0.879	0.008										
DAPD	0.104	−0.026	0.168	−0.384	0.036	0.219									
Sunshine	−0.067	0.048	0.100	0.201	0.676	−0.061	−0.169								
RH	−0.079	−0.037	−0.255	0.210	−0.421	−0.327	0.014	−0.592							
Precipitation	−0.043	−0.037	−0.190	0.063	−0.498	0.216	0.154	−0.597	0.602						
Wind speed	−0.154	−0.098	−0.098	0.048	−0.197	−0.080	0.121	0.085	−0.120	−0.001					
NO ₂	0.106	−0.058	0.223	−0.434	0.357	0.360	0.149	−0.001	−0.150	−0.148	−0.470				
PM ₁₀	−0.002	−0.089	0.145	−0.227	0.459	0.189	0.086	0.223	−0.381	−0.355	−0.245	0.709			
PM _{2.5}	0.074	−0.020	0.179	−0.224	0.330	0.143	0.071	0.076	−0.166	−0.200	−0.280	0.655	0.828		
SO ₂	−0.297	−0.437	−0.138	−0.359	0.288	0.333	0.079	0.155	−0.374	−0.292	−0.161	0.687	0.690	0.532	
O ₃	−0.071	0.125	0.024	0.413	0.184	−0.356	−0.168	0.253	−0.134	−0.102	0.151	−0.376	−0.043	−0.075	−0.270

AR: allergic rhinitis; AD: atopic dermatitis; temp: temperature; DTD: daily temperature difference; AP: air pressure; DAPD: daily air pressure difference; RH: relative humidity; $r_s \geq 0.7$ was considered as high correlation; Bold values are statistically significant ($p < 0.05$).

other environmental factors for childhood asthma. The St_β of daily mean air pressure (0.061 (95% CI: 0.054, 0.067)) was higher than the St_β of other environmental factors for childhood AR and the values of St_β of daily mean temperature (−0.157 (95% CI: −0.169, −0.146)) and mean air pressure (0.191 (95% CI: 0.183, 0.200)) were higher than the values of St_β of other environmental factors for childhood AD.

3.4. Numbers of childhood allergic diseases attributable to an IQR change in meteorological factors and air pollutants

Table 4 shows the numbers of childhood allergic diseases attributable to an IQR change in meteorological factors and air pollutants, suggesting that the number of asthma attributable to a drop of IQR in temperature (41,763 (95% CI: 6040, 74,086)), RH (21,594 (95% CI: 8126, 34,155)) in model 1 or the number of asthma attributable to an

IQR change of air pressure (25,762 (95% CI: 2566, 49,313)), RH (57,710 (95% CI: 40,151, 75,686)) in model 2 were much greater than those attributable to NO₂ and O₃. For AR and AD, the number attributable to an IQR change in RH was obviously bigger than those attributable to other environmental factors.

4. Discussion

Our study shows that both meteorological factors and air pollution were significantly associated with childhood allergic diseases, but the climatic variables seemed to play a more important role in the childhood allergic diseases than air pollutants. The values of standard β of climatic variables were apparently greater than those of air pollution, and the numbers of childhood allergic diseases attributable to an IQR change

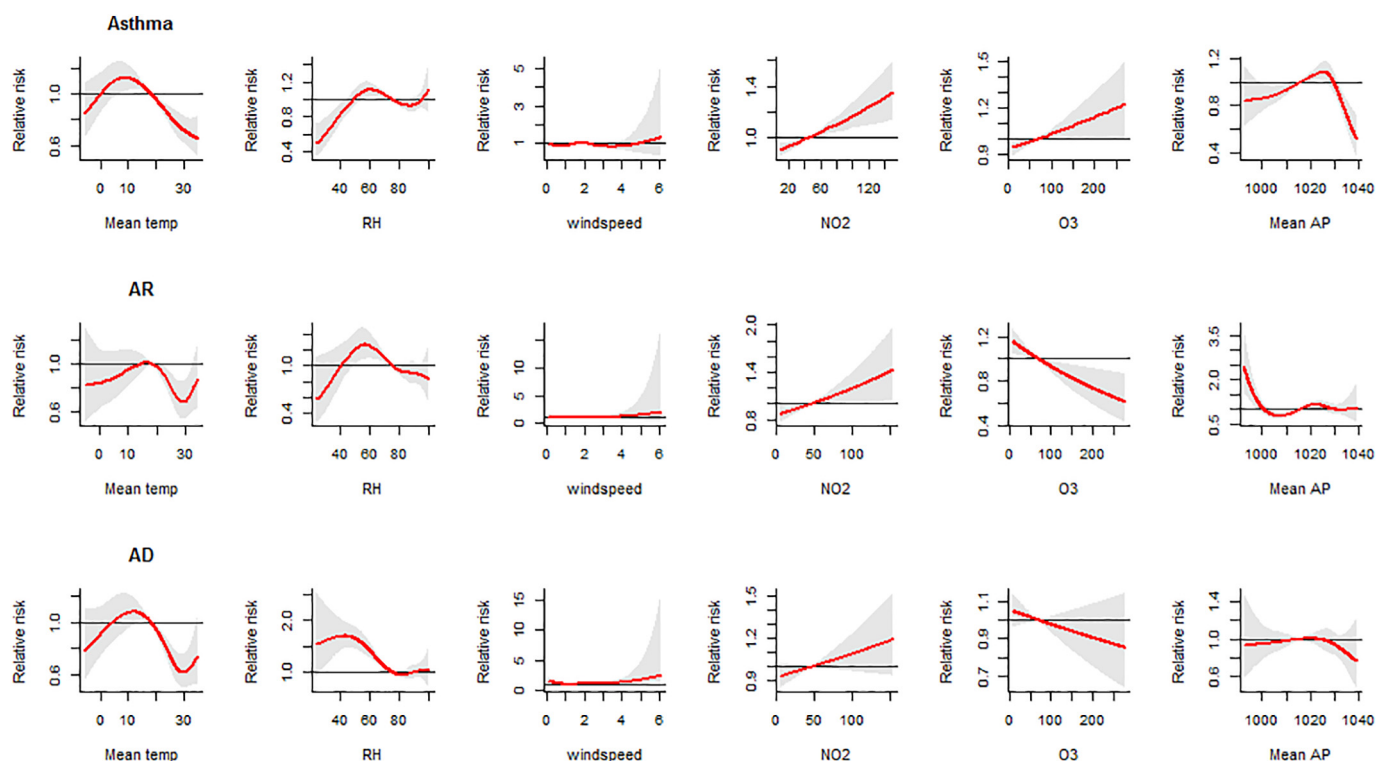


Fig. 2. The overall exposure-response relationships between environmental factors and childhood asthma, AR and AD. AR: allergic rhinitis; AD: atopic dermatitis; mean temp: daily mean temperature; RH: relative humidity; mean AP: daily mean air pressure.

Table 3
Multivariate GLM results for the relationships between environmental factors and childhood allergic diseases after adjustment for confounders.

Variable	Asthma		AR		AD	
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Mean temperature	-0.076 (-0.086, -0.067)		-0.018 (-0.027, -0.009)		-0.157 (-0.169, -0.146)	
Relative humidity	0.004(0.002,0.007)	0.014(0.011,0.018)	-0.028 (-0.031, -0.025)	-0.017 (-0.020, -0.013)	-0.097 (-0.101, -0.093)	-0.070 (-0.074, -0.066)
Wind speed	-0.005 (-0.009, -0.001)	-0.002 (-0.006, 0.002)	-0.004 (-0.008, -0.000)	0.001(-0.003, 0.004)	-0.017 (-0.022, -0.012)	-0.007 (-0.011, -0.002)
Mean air pressure		0.075(0.068,0.082)		0.061(0.054,0.067)		0.191(0.183,0.200)
NO ₂	0.022(0.018,0.026)	0.028(0.023,0.032)	0.032(0.028,0.036)	0.040(0.036,0.044)	0.148(0.143,0.153)	0.164(0.159,0.170)
O ₃	0.007(0.002,0.011)	0.001(-0.004, 0.005)	0.024(0.020,0.028)	0.025(0.021,0.029)	0.110(0.105,0.116)	0.099(0.093,0.104)

Data were presented with St_{β} and 95% confidence interval; St_{β} : standard regression coefficient; AR: allergic rhinitis; AD: atopic dermatitis; mean temperature, relative humidity, wind speed, NO₂, O₃, long-term trends, seasonal trends, the day of week and public holiday effects were controlled in model 1, model 3, model 5; mean air pressure, relative humidity, wind speed, NO₂, O₃, long-term trends, seasonal trends, the day of week and public holiday effects were controlled in model 2, model 4, model 6; Bold means statistical significant ($p < 0.05$).

in meteorological factors were also greater than those attributable to air pollutants.

Even though compelling evidence indicates that both climatic variation and air pollution can affect childhood asthma, AR and AD (Norbäck et al., 2019; Anenberg et al., 2018; Passali et al., 2018; Khreis et al., 2017; Guan et al., 2016; D'Amato et al., 2014; Sargen et al., 2014; Fuertes et al., 2014), no studies have examined the relative impact of climatic variables and air pollutants in childhood allergic diseases to date. Xu et al. (2013) found that both hot and cold temperatures had significant effects on emergency department admissions for childhood asthma in Brisbane, Australia. Children aged 0–4 years were most vulnerable to heat effects, while children aged 10–14 years were most vulnerable to cold effects. Lam et al. (2016) observed that in the cold season, low temperature and humidity were associated with more hospital admissions for asthma in Hong Kong. Another study found that low ambient temperature and RH may aggravate AD symptoms in children (Kim et al., 2017). In addition, adverse effects of NO₂ on AD symptoms were observed. However, none of previous studies has examined the relative role of meteorological conditions and air pollution.

Climatic conditions can directly affect allergic diseases. For instance, low temperature significantly inhibits the body's immune system by reducing lung function and lung capacity (LaVoy et al., 2011) which is conducive to the survival and transportation of respiratory viruses, increased respiratory inflammation, leading to narrowing of the respiratory tract to affect the occurrence and exacerbation of asthma (Kaminsky et al., 2000). In this study, we found that, in general, the lower ambient temperature, the greater the risk for childhood asthma. Similar trend was observed for AD.

Air pollutants, particularly PM, O₃, NO₂, and SO₂, have been shown to have an inflammatory effect on the airways of susceptible subjects, causing increased mucosal permeability, facilitating the penetration and access of inhaled allergens to the cells of the immune system (D'Amato, 2011). There are also data suggesting that air pollution can lead to the development of asthma (Anenberg et al., 2018; Khreis et al., 2017; Guan et al., 2016; Guarneri and Balmes, 2014). Recently,

a study involving 39,782 participants in seven cities across China suggests that outdoor NO₂ and PM₁₀ can increase the risk of asthma, wheeze, rhinitis and eczema among pre-school children (3–6y) (Norbäck et al., 2019). In our study, high level of NO₂ was also a risk for clinical visits of childhood asthma. Similar patterns were found for AR and AD. Therefore, exposure to air pollution may have severe impacts on respiratory health, especially in children. Experimental and clinical studies have demonstrated that asthmatic patients have an increased inflammatory response to air pollutants like PM_{2.5–10} (Rusconi et al., 2011) and especially O₃ (Hernandez et al., 2012). Inflammation and oxidative stress are known mechanisms of the harmful effects caused by air pollution. Additionally, some studies have shown that epigenetic modifications of DNA played an important role in air pollution and childhood asthma (Rusconi et al., 2011).

Real-world evidence has become increasingly important in the literature. Our study based on the information extracted from electronic medical records databases in two pediatric hospitals provides a unique opportunity to address the relative importance of environmental factors in the occurrence of allergic diseases. We found that meteorological factors seemed to play a more important role than air pollutants in childhood allergic diseases in this study. For public health policy development, it is essential to quantify the relative role of meteorological conditions and air pollution, and to design effective community-based allergic disease prevention and control programs. Climate change has been widely recognized as the biggest challenge and opportunity for global health in the 21st century (Watts et al., 2018; Costello et al., 2009; Watts et al., 2015). Human-induced climate change leads to unprecedented temperature increases across the globe and also results in significant changes in precipitation patterns, causing heavy rainfall in some regions and severe droughts in other regions (Watts et al., 2015; IPCC, 2014; Patz et al., 2014; McMichael, 2013). Climate change increases the frequency, intensity and duration of extreme weather events (e.g., heatwaves, floods, bushfires and storms) which pose significant risks to human health (D'Amato et al., 2015). The impact of climate change on the health of vulnerable groups (e.g., children) has attracted

Table 4
Number of childhood allergic diseases attributable to an IQR change in meteorological factors and air pollutants.

Variable	Asthma		AR		AD	
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Mean temperature	41,763(6040,74,086)		–		28,222(-23,822,71,684)	
Relative humidity	21,594(8126,34,155)	57,710(40,151,75,686)	40,051(19,134,60,168)	49,711(28,889,70,573)	54,588(36,679,71,834)	57,710(38,577,75,250)
Wind speed	4710(-5870,14,213)	17,171(2712,30,810)	13,292(-21,858,47,674)	7965(-27,636,43,090)	11,237(-3407,24,773)	17,171(3158,31,398)
Mean air pressure		25,762(2566,49,313)		47,542(-1187,87,435)		–
NO ₂	11,685(5323,18,098)	11,765(1936,21,121)	13,409(858,25,364)	11,531(-1320,22,764)	6836(-2739,16,092)	11,765(2201,22,055)
O ₃	6934(396,13,876)	–	–	–	–	–

Data were presented with number and 95% confidence interval; AR: allergic rhinitis; AD: atopic dermatitis; –: have no risk in model; mean temperature, relative humidity, wind speed, NO₂, O₃, long-term trends, seasonal trends, the day of week and public holiday effects were controlled in model 1, model 3, model 5; mean air pressure, relative humidity, wind speed, NO₂, O₃, long-term trends, seasonal trends, the day of week and public holiday effects were controlled in model 2, model 4, model 6.

a great deal of attention. For example, in recent years, an increasing body of evidence shows that climate change can affect the development of childhood allergic diseases such as childhood asthma, AR and AD (D'Amato et al., 2014; Passali et al., 2018; Sargen et al., 2014). It is also vitally important to curb greenhouse gas emissions through disseminating real-world evidence because climate change will worsen air quality in many parts of the world, which affects a wide spectrum of diseases. Further, it is crucial to develop public health adaptation strategies because overall global emissions continue to rise, and the impacts of climate change will become increasingly severe.

This study has three major strengths. Firstly, to our knowledge, this is the first study to examine the relative importance of meteorological factors and air pollutants in childhood allergic diseases. Secondly, up to 11 years' time-series data were analyzed, with a wide range of meteorological factors and air pollutants. Finally, novel analytic methods were used to explore the association of environmental factors with childhood allergic diseases and their relative role in clinical visits due to these diseases.

Two key limitations in this study should also be acknowledged. Firstly, due to data unavailability, some risk factors (e.g., food, pollen and life events) which may lead to childhood allergic diseases were not included in this study. It is expected that climate change may induce an increase in airborne pollen, an increase of the allergen potency of pollen grains, and variations in the pollen season timing, with an earlier onset and a longer duration. A great number of studies have addressed the strong relations between aerobiology and biometeorology (Beggs and Sikoparija, 2017; Ziska et al., 2019). They have demonstrated the clear short- and long-term influence of meteorological parameters (temperature, relative humidity, rainfall and wind speed) on airborne pollen season. Other studies have demonstrated that meteorological factors such as temperature and relative humidity can affect the physiology, distribution, and amounts of these allergens (van Strien et al., 2004; Piotrowska and Kubik-Komar, 2012). Pollen concentration trends were associated with the overall increasing trend of temperature and inversely associated with the fluctuating trends of relative humidity and rainfall (Bruffaerts et al., 2018). Our study found that childhood allergic diseases were inversely associated with the fluctuating trends of relative humidity, which might be partly explained by higher concentrations of pollen in dry days and lower levels in humid days. Secondly, like other ecological time-series studies, measurement bias is inevitable to some extent because environmental data were collected from monitors at central sites, which could not fully represent personal exposures. Even though this type of measurement error is likely to be non-differential, which may bias effect estimates towards the null (Brenner and Loomis, 1994), the extent of such bias may differ between the measurement of meteorological variables and air pollution. If the exposure misclassification was higher for air pollutants than for meteorological variables, the effect estimates for air pollutants would be more biased towards the null (and hence smaller) than those for meteorological variables. We cannot entirely rule out this potential explanation for our findings.

For the future research directions, prospective cohort studies assessing the associations of a wide range of sociodemographic, behavioral and environmental factors with childhood allergic diseases are warranted. It is also necessary to conduct panel studies with personal monitoring devices to assess the relationship between exposure to environmental factors and childhood allergic diseases. Additionally, it is desirable to distinguish between short- and long-term impacts of environmental exposures on childhood allergic diseases.

5. Conclusions

Both climatic variation and air pollution were associated with childhood allergic diseases, but the former appeared to play a more important role in the occurrence of clinical visits for these diseases. These findings may have important implications for the development of

effective strategies to prevent and treat these rapidly-increasing diseases worldwide, if our findings are confirmed in different populations across different regions.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- Ahmed, A., Hakim, A., Becker, A., 2018. Evaluation of eczema, asthma, allergic rhinitis and allergies among the Grade-1 children of Iqaluit. *Allergy Asthma Clin Immunol* 14, 9. <https://doi.org/10.1186/s13223-018-0232-2>.
- Ahn, K., 2014. The role of air pollutants in atopic dermatitis. *J. Allergy Clin. Immunol.* 134 (5), 993–999. <https://doi.org/10.1016/j.jaci.2014.09.023>.
- Anderson, H.R., Butland, B.K., van Donkelaar, A., et al., 2012. Satellite-based estimates of ambient air pollution and global variations in childhood asthma prevalence. *Environ. Health Perspect.* 120 (9), 1333–1339. <https://doi.org/10.1289/ehp.1104724>.
- Anenberg, S.C., Henze, D.K., Tinney, V., et al., 2018. Estimates of the global burden of ambient PM_{2.5}, ozone, and NO₂ on asthma incidence and emergency room visits. *Environ. Health Perspect.* 126 (10), 107004. <https://doi.org/10.1289/EHP3766>.
- Asher, I., Pearce, N., 2014. Global burden of asthma among children. *Int J Tuberc Lung Dis* 18 (11), 1269–1278. <https://doi.org/10.5588/ijtld.14.0170>.
- Asher, M.I., Montefort, S., Bjorksten, B., et al., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 368 (9537), 733–743. [https://doi.org/10.1016/S0140-6736\(06\)69283-0](https://doi.org/10.1016/S0140-6736(06)69283-0).
- Beggs PJ, Sikoparija B, Smith M. 2017. Aerobiology in the international journal of biometeorology 1957–2017. *Int. J. Biometeorol.* 61(Suppl1):51–58. <https://doi.org/10.1007/s00484-017-1374-5>.
- Bousquet, J., Khaltaev, N., Cruz, A.A., et al., 2008. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63 (Suppl. 86), 8–160. <https://doi.org/10.1111/j.1398-9995.2007.01620.x>.
- Brenner, H., Loomis, D., 1994. Varied forms of bias due to nondifferential error in measuring exposure. *Epidemiology* 5 (5), 510–517 (PMID: 7986865).
- Bruffaerts, N., De Smedt, T., Delcloo, A., et al., 2018. Comparative long-term trend analysis of daily weather conditions with daily pollen concentrations in Brussels, Belgium. *Int. J. Biometeorol.* 62 (3), 483–491. <https://doi.org/10.1007/s00484-017-1457-3>.
- Costello, A., Abbas, M., Allen, A., et al., 2009. Managing the health effects of climate change: Lancet and University College London Institute for Global Health Commission. *Lancet* 373 (9676), 1693–1733. [https://doi.org/10.1016/S0140-6736\(09\)60935-1](https://doi.org/10.1016/S0140-6736(09)60935-1).
- D'Amato, G., 2011. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. *Multidiscip Respir Med* 6 (1), 28–37. <https://doi.org/10.1186/2049-6958-6-1-28>.
- D'Amato, G., Cecchi, L., D'Amato, M., et al., 2014. Climate change and respiratory diseases. *Eur. Respir. Rev.* 23 (132), 161–169. <https://doi.org/10.1183/09059180.00001714>.
- D'Amato, G., Holgate, S.T., Pawankar, R., et al., 2015. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organ J* 8 (1), 25. <https://doi.org/10.1186/s40413-015-0073-0>.
- Fuertes, E., Butland, B.K., Ross Anderson, H., et al., 2014. Childhood intermittent and persistent rhinitis prevalence and climate and vegetation: a global ecologic analysis. *Ann. Allergy Asthma Immunol.* 113 (4), 386–392. <https://doi.org/10.1016/j.anai.2014.06.021>.
- Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. *Stat. Med.* 29 (21), 2224–2234. <https://doi.org/10.1002/sim.3940>.
- Gasparrini, A., Guo, Y., Hashizume, M., et al., 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 386 (9991), 369–375. [https://doi.org/10.1016/S0140-6736\(14\)62114-0](https://doi.org/10.1016/S0140-6736(14)62114-0).

- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388 (10053), 1545–1602. [https://doi.org/10.1016/S0140-6736\(16\)31678-6](https://doi.org/10.1016/S0140-6736(16)31678-6).
- GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390 (10100), 1211–1259. [https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/10.1016/S0140-6736(17)32154-2).
- Global Initiative for Asthma (GINA), 2017. Global Strategy for Asthma Management and Prevention. <http://ginasthma.org/>.
- Guan, W.J., Zheng, X.Y., Chung, K.F., et al., 2016. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. *Lancet* 388 (10054), 1939–1951. [https://doi.org/10.1016/S0140-6736\(16\)31597-5](https://doi.org/10.1016/S0140-6736(16)31597-5).
- Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. *Lancet* 383 (9928), 1581–1592. [https://doi.org/10.1016/S0140-6736\(14\)60617-6](https://doi.org/10.1016/S0140-6736(14)60617-6).
- Hernandez, M., Brickey, W.J., Alexis, N.E., et al., 2012. Airway cells from atopic asthmatic patients exposed to ozone display an enhanced innate immune gene profile. *J. Allergy Clin. Immunol.* 129 (1), 259–261 e1–2. <https://doi.org/10.1016/j.jaci.2011.11.007>.
- Higashi, T., Tamaki, N., Torizuka, T., et al., 1998. FDG uptake, GLUT-1 glucose transporter and cellularity in human pancreatic tumors. *J. Nucl. Med.* 39 (10), 1727–1735.
- IPCC, 2014: Climate change 2014: Synthesis report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Core Writing Team, R.K. Pachauri and L.A. Meyer (eds.)]. IPCC, Geneva, Switzerland, (151 pp).
- Kaminsky, D.A., Bates, J.H., Irvin, C.G., 2000. Effects of cool, dry air stimulation on peripheral lung mechanics in asthma. *Am. J. Respir. Crit. Care Med.* 162 (1), 179–186. <https://doi.org/10.1164/ajrccm.162.1.9806079>.
- Kassebaum, N.J., Arora, M., Barber, R.M., et al., 2016. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 388 (10053), 1603–1658. [https://doi.org/10.1016/S0140-6736\(16\)31460-X](https://doi.org/10.1016/S0140-6736(16)31460-X).
- Khreis, H., Kelly, C., Tate, J., et al., 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ. Int.* 100, 1–31. <https://doi.org/10.1016/j.envint.2016.11.012>.
- Kim, K.H., Jahan, S.A., Kabir, E., 2013. A review on human health perspective of air pollution with respect to allergies and asthma. *Environ. Int.* 59, 41–52. <https://doi.org/10.1016/j.envint.2013.05.007>.
- Kim, Y.M., Kim, J., Han, Y., et al., 2017. Short-term effects of weather and air pollution on atopic dermatitis symptoms in children: a panel study in Korea. *PLoS One* 12 (4), e0175229. <https://doi.org/10.1371/journal.pone.0175229>.
- Lam, H.C., Li, A.M., Chan, E.Y., et al., 2016. The short-term association between asthma hospitalisations, ambient temperature, other meteorological factors and air pollutants in Hong Kong: a time-series study. *Thorax* 71 (12), 1097–1109. <https://doi.org/10.1136/thoraxjnl-2015-208054>.
- LaVoy, E.C., McFarlin, B.K., Simpson, R.J., 2011. Immune responses to exercising in a cold environment. *Wilderness Environ Med* 22 (4), 343–351. <https://doi.org/10.1016/j.wem.2011.08.005>.
- Li, F., Zhou, Y., Li, S., et al., 2011. Prevalence and risk factors of childhood allergic diseases in eight metropolitan cities in China: a multicenter study. *BMC Public Health* 11 (437). <https://doi.org/10.1186/1471-2458-11-437>.
- Li, M., Huang, X., Zhu, L., et al., 2012. Analysis of the transport pathways and potential sources of PM₁₀ in Shanghai based on three methods. *Sci. Total Environ.* 414, 525–534. <https://doi.org/10.1016/j.scitotenv.2011.10.054>.
- Liu, W., Huang, C., Hu, Y., 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.* 92–93, 284–293. <https://doi.org/10.1016/j.envint.2016.04.019>.
- Masoli, M., Fabian, D., Holt, S., et al., 2004. The global burden of asthma: executive summary of the GINA dissemination committee report. *Allergy* 59 (5), 469–478. <https://doi.org/10.1111/j.1398-9995.2004.00526.x>.
- McMichael, A.J., 2013. Globalization, climate change, and human health. *N. Engl. J. Med.* 369 (1), 96. <https://doi.org/10.1056/NEJMc1305749>.
- Nishimura, K.K., Galanter, J.M., Roth, L.A., et al., 2013. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am. J. Respir. Crit. Care Med.* 188 (3), 309–318. <https://doi.org/10.1164/rccm.201302-0264OC>.
- Norbäck, D., Lu, C., Zhang, Y., et al., 2019. Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: synergistic effects between antibiotics use and PM₁₀ and second hand smoke. *Environ. Int.* 125, 252–260. <https://doi.org/10.1016/j.envint.2019.01.036>.
- Nutten, S., 2015. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab* 66, 8–16. <https://doi.org/10.1159/000370220> Suppl 1.
- Oh, S.S., White, M.J., Gignoux, C.R., et al., 2016. Making precision medicine socially precise. Take a deep breath. *Am. J. Respir. Crit. Care Med.* 193 (4), 348–350. <https://doi.org/10.1164/rccm.201510-2045ED>.
- Passali, D., Cingi, C., Staffa, P., et al., 2018. The international study of the allergic rhinitis survey: outcomes from 4 geographical regions. *Asia Pac Allergy* 8 (1), e7. <https://doi.org/10.5415/apallergy.2018.8.e7>.
- Patz, J.A., Frumkin, H., Holloway, T., et al., 2014. Climate change: challenges and opportunities for global health. *JAMA* 312, 1565–1580. <https://doi.org/10.1001/jama.2014.13186>.
- Piotrowska, K., Kubik-Komar, A., 2012. The effect of meteorological factors on airborne Betula pollen concentrations in Lublin (Poland). *Aerobiologia (Bologna)* 28 (4), 467–479. <https://doi.org/10.1007/s10453-012-9249-z>.
- Rojas-Rueda, D., Vrijheid, M., Robinson, O., et al., 2019. Environmental burden of childhood disease in Europe. *Int. J. Environ. Res. Public Health* 16 (6). <https://doi.org/10.3390/ijerph16061084> pii: E1084.
- Rusconi, F., Catelan, D., Accetta, G., et al., 2011. Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. *J. Asthma* 48 (1), 84–90. <https://doi.org/10.3109/02770903.2010.538106>.
- Sargen, M.R., Hoffstad, O., Margolis, D.J., 2014. Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004–2012. *J. Invest Dermatol* 134 (1), 51–57. <https://doi.org/10.1038/jid.2013.274>.
- van Strien, R.T., Gehring, U., Belanger, K., et al., 2004. The influence of air conditioning, humidity, temperature and other household characteristics on mite allergen concentrations in the northeastern United States. *Allergy* 59 (6), 645–652. <https://doi.org/10.1111/j.1398-9995.2004.00470.x>.
- Sun, Y.Z., Li, L.P., Zhou, M.G., 2012. Analysis of the lag-effects of temperature on the five cities' mortality in China. *Zhonghua Yu Fang Yi Xue Za Zhi* 46 (11), 1015–1019 (PMID: 23363923). [in Chinese].
- Suzuki, Y., Oka, K., Ohno, T., et al., 2009. Prognostic impact of mitotic index of proliferating cell populations in cervical cancer patients treated with carbon ion beam. *Cancer* 115 (9), 1875–1882. <https://doi.org/10.1002/ncr.24189>.
- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 351 (9111), 1225–1232 (PMID: 9643741).
- To, T., Wang, C., Guan, J., et al., 2010. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? *Am. J. Respir. Crit. Care Med.* 181 (4), 337–343. <https://doi.org/10.1164/rccm.200907-1035OC>.
- Van Wonderen, K.E., Van Der Mark, L.B., Mohrs, J., et al., 2010. Different definitions in childhood asthma: how dependable is the dependent variable? *Eur Respir J* 36 (1), 48–56. <https://doi.org/10.1183/09031936.00154409>.
- Wang, X.D., Zheng, M., Lou, H.F., et al., 2016. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy* 71 (8), 1170–1180. <https://doi.org/10.1111/all.12874>.
- Watts, N., Adger, W.N., Agnolucci, P., et al., 2015. Health and climate change: policy responses to protect public health. *Lancet* 386, 1861–1914. [https://doi.org/10.1016/S0140-6736\(15\)60854-6](https://doi.org/10.1016/S0140-6736(15)60854-6).
- Watts, N., Amann, M., Ayeb-Karlsson, S., et al., 2018. The lancet countdown on health and climate change: from 25 years of inaction to a global transformation for public health. *Lancet* 391 (10120), 581–630. [https://doi.org/10.1016/S0140-6736\(17\)32464-9](https://doi.org/10.1016/S0140-6736(17)32464-9).
- Weiland, S.K., Hüsing, A., Strachan, D.P., et al., 2004. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup. Environ. Med.* 61 (7), 609–615. <https://doi.org/10.1136/oem.2002.006809>.
- Williams, A.M., Phaneuf, D.J., Barrett, M.A., et al., 2019. Short-term impact of PM_{2.5} on contemporaneous asthma medication use: behavior and the value of pollution reductions. *Proc. Natl. Acad. Sci. U. S. A.* 116 (12), 5246–5253. <https://doi.org/10.1073/pnas.1805647115>.
- Williams, H., Robertson, C., Stewart, A., et al., 1999. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J. Allergy Clin. Immunol.* 103 (1 Pt 1), 125–138 (PMID: 9893196).
- Williams, H., Stewart, A., von Mutius, E., et al., 2008. Is eczema really on the increase worldwide? *J. Allergy Clin. Immunol.* 121 (4), 947–954 e15. <https://doi.org/10.1016/j.jaci.2007.11.004>.
- Xu, Z., Huang, C., Hu, W., et al., 2013. Extreme temperatures and emergency department admissions for childhood asthma in Brisbane, Australia. *Occup. Environ. Med.* 70 (10), 730–735. <https://doi.org/10.1136/oemed-2013-101538>.
- Yi, W., Chan, A.P., 2015. Effects of temperature on mortality in Hong Kong: a time series analysis. *Int. J. Biometeorol.* 59 (7), 927–936. <https://doi.org/10.1007/s00484-014-0895-4>.
- Zhang, Y., Li, B., Huang, C., et al., 2013. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. *Chin. Sci. Bull.* 58, 2504–2512 (in Chinese).
- Ziska, L.H., Makra, L., Harry, S.K., et al., 2019. Temperature-related changes in airborne allergenic pollen abundance and seasonality across the northern hemisphere: a retrospective data analysis. *Lancet Planet Health* 3 (3), e124–e131. [https://doi.org/10.1016/S2542-5196\(19\)30015-4](https://doi.org/10.1016/S2542-5196(19)30015-4).