



Impacts of exposure to humidex on the risk of childhood asthma hospitalizations in Hefei, China: Effect modification by gender and age

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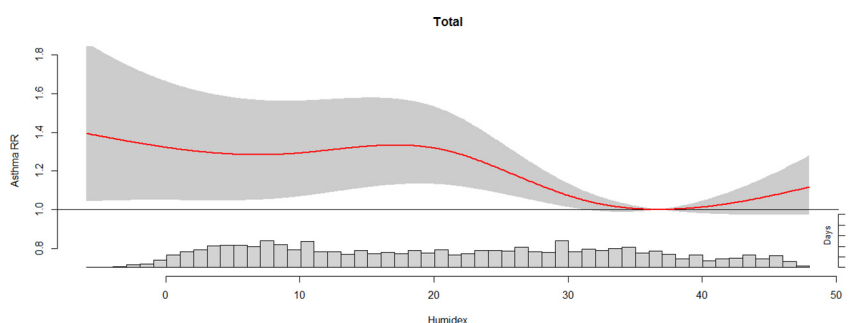
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HIGHLIGHTS

- This is the first study to explore the Humidex-Childhood asthma association in Hefei.
- Low humidex increased the incidence of Childhood asthma.
- Female and school-age children appeared to be more vulnerable to low humidex.
- The adverse effects occurred on lag4, lag5, lag6, lag7.
- Humidex was more significant for prevention and public health than the average temperature.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: With global climate change, there is growing concern about the effects of temperature changes on childhood asthma. However, current research only focuses on the effects of temperature, while ignoring the adverse effects of humidity on children.

Objectives: Our study aimed to quantify the impact of humidex on childhood asthma hospitalizations, which combined temperature and humidity, and further to assess how the effect is modified by individual-factors, such as age and gender.

Methods: Poisson generalized linear models combined with distributed lag nonlinear models were used to estimate the association between daily childhood asthma hospitalizations and humidex from 2013 to 2016. Air pollutants (CO, O₃, and NO₂) and wind velocity were modelled simultaneously using DLNM, as well as day of week, seasonality and long-term trend.

Results: Low humidex was associated with an increased risk of admissions for asthma in children. The adverse effect appeared on the 4th day, with the RR of 1.045 (95%CI: 1.007–1.084) and lasted until the 7th day (RR: 1.045, 95%CI: 1.006–1.085). Compared with the male, there was an immediate effect on female exposed to low humidex. And the female seems to be more sensitive to low humidex. Besides, the significant effects of humidex on children asthma were detected in the children with preschool and school-age, whereas not for the subgroup of infants. And the school-age children are most sensitive to low humidex.

Conclusions: Low humidex was associated with the increased risk of admissions for childhood asthma in Hefei. Children suffering from asthma should avoid exposure to the low humidex environment, especially in female and school-age children. In addition, the index of humidex was more significant for disease prevention and public

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health than the average temperature. These findings may provide epidemiology evidence for formulating precaution guidelines to reduce the risk of childhood asthma hospitalizations.

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1. Introduction

Asthma, as a chronic non-communicable disease, has a serious impact on public health (Cong et al., 2017). There are currently approximately 235 million patients worldwide (<http://www.who.int/mediacentre/factsheets/fs307/en/>) and it is expected that by 2025, there will be an additional 100 million new cases (Masoli et al., 2004). Its remarkable characteristics are coughing, wheezing, difficulty breathing, etc., which were caused by airway inflammation after exposing to the environmental trigger (Aghasafari et al., 2019). According to the Global Burden of Disease (GBD), in 2017, childhood asthma accounted for 0.78%, 2.77% in the China total Disability-Adjusted Life Year (DALYs) among children aged <5, 5–14 years, respectively (<https://vizhub.healthdata.org/gbd-compare/>). In addition, this disease is prone to recrudescence and can't be cured completely at present.

Given the considerable disease burden of childhood asthma and the difficulty of clinical symptom control and intervention, a full understanding about the risk factors of childhood asthma is of great importance to public health. Existing evidence indicates that heredity (Gignoux et al., 2019), allergen (Sheehan and Phipatanakul, 2016) and so on have significant associations with the onset of childhood asthma. However, for now, intervention in genetic susceptibility and allergens are inaccessible for the prevention and treatment of asthma. In recent years, with global climate changing, more and more research has focused on the impact of environmental risk factors on children's health, including temperature, relative humidity, particulate matter with an aerodynamic diameter of $<2.5\ \mu\text{m}$ ($\text{PM}_{2.5}$) (Buteau et al., 2018; Nawrot et al., 2015), Ozone ($\text{O}_{3.8}$) (Strosnider et al., 2019), Nitrogen dioxide (NO_2) (Norback et al., 2019), pollen (Hervas et al., 2015), etc. Especially there are many studies that have explored the association between ambient temperature and childhood asthma hospitalizations (Guo et al., 2012; Son et al., 2014; Soneja et al., 2016; Xu et al., 2013a), but the results of existing research are still controversial, some of them demonstrated that high temperature is positive with increased hospital admissions for childhood asthma, whereas others found that it's low temperature that increases the risk of childhood asthma hospitalizations. And the probable reasons for the inconsistency are followed: 1. there is heterogeneity between studies in different regions; 2. in some research, the effects of pollutants on childhood asthma hospitalizations are not controlled; 3. the existing studies only consider the effects of temperature on asthma, without considering the possible modification of humidity to this effect.

However, existing studies have shown that humidity has a significant impact on the risk of childhood asthma hospitalizations (Li et al., 2013; O'lenick et al., 2017; Zhang et al., 2016a). Therefore, comprehensive assessment of the effects of temperature and humidity on childhood asthma hospitalizations may be more practical. Humidex, which was first proposed by the Canadian Meteorological Agency, can better reflect the combined effects of temperature and humidity and has been applied to assess the effects of temperature and humidity simultaneously on childhood diseases (Zhang et al., 2016b; Zhang et al., 2016c).

Therefore, based on the possible association between temperature, humidity and childhood asthma hospitalizations, we conducted this study with three main purposes: First, to explore the association between childhood asthma hospitalizations and humidex in the city of Hefei, China. Second, to clarify how the effects are modified by individual-level factors, such as gender (male, female), age: infants (0–1 years), preschool children (2–5 years), school-age children (6–18 years). Furthermore, we would like to find out if the composite

index, humidex, is more predictive than the average temperature and plays a more important role in public health.

2. Materials and methods

2.1. Study area

Hefei is the capital of Anhui province which located in the middle of China. There are four municipal districts, with a population of 7.97 million in 2017. Hefei has a typical subtropical monsoon humid climate, with a high humidity throughout the year, experiencing four distinct seasons. The temperature range in Hefei area during the study period was -5.9 to $34.4\ ^\circ\text{C}$. The patient data, meteorological and air pollution data for this study are from the same area and are described in more detail below.

2.2. Asthma data

Daily hospital admissions for childhood asthma were collected from the Anhui provincial children's hospital in Hefei during the period of 2013–2016, including age, gender etc. Diagnosis of asthma was according to the International Classification of Disease, 10th Revision (ICD-10). Daily hospital admissions with the principle cause coded as asthma (ICD-10 codes: J45) among children aged 0–18 years were included in the data analysis (Sheffield et al., 2015). The subjects included in our study were all hospitalized patients. The majority of asthma patients were hospitalized for an average of 5 days.

2.3. Meteorological data

The daily meteorological data are derived from China Meteorological Science Data Sharing Service Network (<http://www.esi.cn>), including daily mean temperature, relative humidity, mean wind velocity, rainfall, sunshine hour etc. The calculation method of daily humidex in Hefei refers to the approach which was provided by CSGNetwork (<http://www.csgnetwork.com/>) in California.

2.4. Air pollution data

Ambient pollution concentration data were obtained from the Environmental Protection Bureau in Hefei. In our analysis, the daily data from ten monitors in Hefei area were used. Daily 24-h mean concentrations of Sulfur dioxide (SO_2), Carbon monoxide (CO), particulate matter with an aerodynamic diameter of $<2.5\ \mu\text{m}$ ($\text{PM}_{2.5}$), particulate matter with an aerodynamic diameter of $<10\ \mu\text{m}$ (PM_{10}), Nitrogen dioxide (NO_2), etc. and daily maximum 8-hour mean concentrations of ozone (O_3) were calculated.

2.5. Statistical analysis

Daily admission for childhood asthma is a small probability event, which is approximate a Poisson distribution. Previous studies have revealed that the effects of changes in humidex on health have nonlinear effects (Zhang et al., 2017). Thus, a Poisson Generalized Linear Models (PGLMs) with a distributed lag nonlinear models (DLNMs) was adopted to estimate the relationship between humidex and childhood asthma hospitalizations in our study (Gasparrini et al., 2010). We first investigated the correlations between humidex and weather indicators or air pollutants with Spearman's correlation test. According to the results of correlation analysis, the possible confounding factors were identified,

which were NO_2 ($r_s = 0.11, p < 0.05$), CO ($r_s = 0.14, p < 0.05$), O_3 ($r_s = -0.12, p < 0.05$), barometric pressure ($r_s = 0.083, p < 0.05$), mean wind velocity ($r_s = -0.085, p < 0.05$). We also observed that the barometric pressure was highly correlated with humidex ($r_s = -0.91, p < 0.05$) (See supplementary Figs. S1, S2). Meanwhile, humidex was calculated from mean temperature and relative humidity. Therefore, in order to avoid the multicollinearity problem, mean temperature, relative humidity, and barometric pressure were not included in the regression model. Then a combination of PGLMs and DLNMs (Armstrong, 2006) was used to explore the association between humidex and childhood asthma hospitalizations. We used the quasi-Poisson Akaike information criteria (Q-AIC) to choose the optimal degrees of freedom (df) (Gasparrini et al., 2010). The models to quantify the relations between humidex and childhood asthma hospitalizations were as follows:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$\begin{aligned} \text{Log}(\mu_t) = & \alpha + \beta H_{t,l} + 4 + \text{ns}(\text{meanwind}_{t,l}, 3) + \text{ns}(\text{O}_{3t,l}, 4) \\ & + \text{ns}(\text{CO}_{t,l}, 4) + \text{ns}(\text{NO}_{2t,l}, 4) + \text{ns}(\text{Time}_{t,l}, 7) + \eta \text{DOWt} \\ & + \nu \text{Holidayt} \end{aligned} \quad (1)$$

where t is the day of observation; μ_t is the daily number of asthma visits on day t ; α is the intercept of model; β is the matrix coefficient of the humidex and a natural cubic spline function with 4 dfs was used to estimate the lagged effects of humidex; $H_{t,l}$ represent the humidex on day t ; ns is the natural cubic spline function in R; $\text{meanwind}_{t,l}, 3$ represent the mean wind velocity on day t with 3 dfs ; $\text{O}_{3t,l}, 4$ represent the ozone on day t with 4 dfs ; $\text{CO}_{t,l}, 4$ represent the carbon monoxide on day t with 4 dfs ; $\text{NO}_{2t,l}, 4$ represent the nitrogen dioxide on day t with 4 dfs . Using a natural cubic spline curve with an annual degree of freedom 7 to control the time trend. DOWt is a categorical variable to control potential confounding effect of the day of week and Holidayt is a categorical variable to control potential confounding effect of holiday (1 for holiday, 0 for work). Maximum lags for DLNMs were chosen by comparing relative risk (RR) using different maximum lags, taking into account the short duration of asthma and the lowest AIC of the model. Therefore we choose the shortest maximum lag (8 days) that could capture a robust lagged effect to assess the association between humidex and childhood asthma hospitalizations (Lam et al., 2016).

Furthermore, we examined significant differences between effect estimates from stratified analyses of potential effect modifier by calculating the 95% confidence intervals (CIs) based on the formula as follows:

$$(\widehat{Q}_1 - \widehat{Q}_2) \pm \sqrt{(\widehat{SE}_1)^2 - (\widehat{SE}_2)^2} \quad (2)$$

where $\widehat{Q}_1, \widehat{Q}_2$ are the estimates for two categories (such as male and female), and $\widehat{SE}_1, \widehat{SE}_2$ represent the corresponding standard errors (Greenstone and Schenker, 2003). Effect estimates were described as relative risk (RR) and 95% confidence intervals (CIs) in daily hospital admissions for childhood asthma. In the present study, where a humidex of 36.8 was selected as the reference, corresponding to the lowest risk of childhood asthma hospitalizations. In order to compare which index, humidex or mean temperature, can highlight the significance of public health interventions, we estimate the attributable fraction and number within the framework of DLNM, using a backward perspective which estimates the risk at time t due to the set of exposure events experienced in the past (Gasparrini and Leone, 2014). The backward attributable risk fraction ($b\text{-AF}_{x,t}$) and number ($b\text{-AN}_{x,t}$) at time t are calculated by Eqs. (3) and (4):

$$b\text{-AF}_{x,t} = 1 - \exp\left(-\sum_{l=0}^L \beta_{xt-l, l}\right) \quad (3)$$

$$b\text{-AN}_{x,t} = b\text{-AF}_{x,t} \cdot n_t \quad (4)$$

where n_t are the number of cases at time t . Through Monte Carlo simulation, the related 2.5th and 97.5th percentiles of distributions are interpreted as 95% empirical confidence intervals (eCI).

All the statistics are completely done in R (version 3.4.1) with packages of “dlnm” and “splines”. For all statistical tests, two-sided p values of <0.05 were considered statistically significant.

2.6. Sensitive analysis

Considering the stability of the model, sensitivity analysis was conducted in our study by (1) Changing df for mean wind velocity (3–5 df /mean wind velocity) and for O_3 (3–5 df/O_3); (2) Changing the degree of freedom for time trends (6–8 df /year); (3) Conducting residual analysis of the final model.

3. Results

3.1. Data description

A total of 32,238 hospital visits aged 0–18 years (3153 aged 0–1 years, 15,508 aged 2–5 years and 13,577 aged 6–18 years) for asthma were collected during the year of 2013–2016 in Hefei. The number of daily mean visits was 22.1, and the maximum was 92. The account of the male and female was 21,711 and 10,527 respectively. The value of daily mean temperature (25, 75percentile), mean humidex (25, 75percentile) and mean relative humidity (25, 75percentile) were 16.8 °C (8.7 °C, 24.6 °C), 21.1 (8.7, 32) and 75% (67%, 85%), respectively. The average concentration of ozone, nitrogen dioxide and carbon monoxide during the study were 67.5 $\mu\text{g}/\text{m}^3$, 34.8 $\mu\text{g}/\text{m}^3$ and 1.0 $\mu\text{g}/\text{m}^3$, respectively. In addition, the number of days of mild contamination during the study was 481 days and the number of days of severe contamination was 92 days. Detailed characteristics of the study population and other variable parameters were shown in Tables 1 and 2.

Fig. 1 presented the time-series distribution of total cases, humidex, temperature and humidity from 2013 to 2016 in Hefei. The case of number, humidex and temperature showed a similar seasonal pattern, but the value of humidex is higher than the mean temperature.

3.2. Relationship between humidex and childhood asthma hospitalizations

Figs. 2 and 3 showed the exposure-response plots of the relationships between humidex and childhood asthma hospitalizations. As shown in Fig. 2, there was a nonlinear statistical association between humidex and childhood asthma hospitalizations. For the whole research population, we mainly found that there was a significant negative association between low humidex and hospital admissions for childhood asthma. Hence, our study primary focuses on the results of the low percentile of humidex (P_{25}) to explore the impact of low humidex on the risk of childhood asthma hospitalizations.

Positive interrelationships between low humidex exposure and daily childhood asthma hospitalizations first appeared on the 4th day,

Table 1

Characteristics of all individuals with hospital admission of childhood asthma in Hefei, China from 2013 to 2016.

Group	Sum	Mean $\pm$ Sd	Frequency distribution				
			P(0)	P(25)	P(50)	P(75)	P(100)
Total	32,238	22.1 $\pm$ 10.3	0	15	21	27	92
Male	21,711	14.9 $\pm$ 7.4	0	10	14	19	57
Female	10,527	7.2 $\pm$ 3.9	0	4	7	9	35
0–1 years	3153	2.2 $\pm$ 2.3	0	1	2	3	16
2–5 years	15,508	10.6 $\pm$ 5.3	0	7	0	3	44
6–18 years	13,577	9.3 $\pm$ 6.6	0	5	8	12	58

Table 2

Descriptive statistics of Meteorological indicators and pollutants across Hefei, China from 2013 to 2016.

Group	Mean $\pm$ Sd	Min	P(25)	P(50)	P(75)	Max
Mean temperature ($^{\circ}\text{C}$)	16.8 $\pm$ 9.2	−5.9	8.7	18	24.6	34.4
Humidex	21.1 $\pm$ 13.4	−5.9	8.7	21	32	48
Rainfall (mm)	21.2 $\pm$ 241.4	0	0	0	0.7	3270
Pressure (Pa)	1013.4 $\pm$ 9.4	994.1	1005.2	1013.4	1020.7	1041.4
Mean wind velocity (m/s)	2.0 $\pm$ 0.8	0.3	1.4	1.8	2.4	6.2
Relative humidity (%)	75.0 $\pm$ 3.2	29	67	76	85	100
NO ₂ ($\mu\text{g}/\text{m}^3$)	34.8 $\pm$ 14.6	8	24	32	42	121
O ₃ ($\mu\text{g}/\text{m}^3$)	67.5 $\pm$ 34.5	7	42	60	87	220
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	73.2 $\pm$ 47.6	7	42	62	90	375
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	106.4 $\pm$ 55.1	0	70	98	131	408
SO ₂ ($\mu\text{g}/\text{m}^3$)	18.2 $\pm$ 8.9	4	12	16	23	73
CO ($\mu\text{g}/\text{m}^3$)	1.0 $\pm$ 0.4	0	0.7	0.9	1.2	4.2

with the RR of 1.045 (95%CI: 1.007–1.084) and lasted until the 7th day (RR = 1.045, 95%CI: 1.006–1.085). The risk of childhood asthma hospitalizations peaked at the lag of 6th day with the RR of 1.117 (95%CI: 1.064–1.173). The effect lasted 4 days and the significant maximum cumulative RR of humidex was at lag07 (RR = 1.356, 95%CI: 1.130–1.629). In contrast to the reference, exposing to low humidex was associated with an increased risk of childhood asthma hospitalizations in our research population (The detailed results were shown in Tables 3, 4).

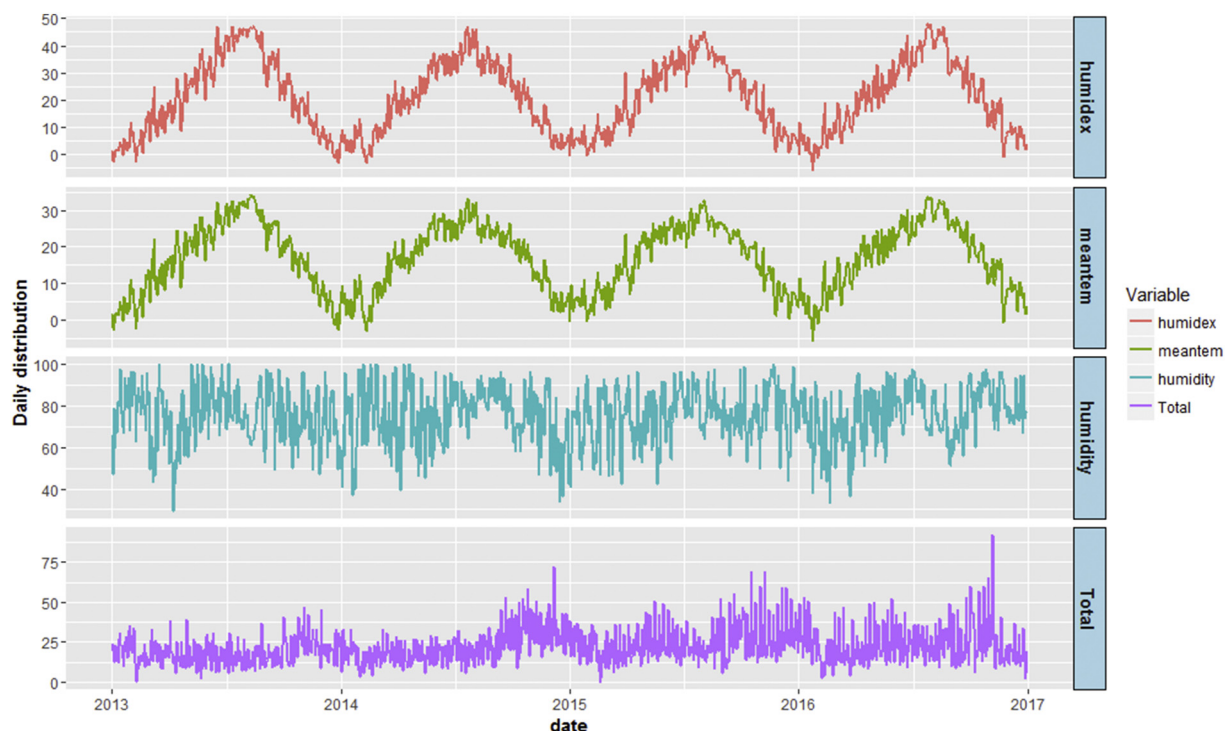
Fig. 4 described results for subgroup analysis of gender, showing that both male and female were vulnerable to the harmful effect of low humidex. The single-day effect of male appeared on days 4–6, and the maximum RR was 1.116 (95%CI: 1.050–1.185) at the lag day 5. While the significant effect of female appeared on the 5th day (RR = 1.118, 95%CI: 1.024, 1.220) and lasted until the 7th day (RR = 1.076, 95%CI: 1.007, 1.150). Interestingly, the maximum single-day RR was 1.186 (95% CI: 1.022–1.376) at lag0. That means there have an immediate effect on female after exposing to low humidex. What's more, the

significant cumulative effect of low humidex on female occurred on the first two days and last four days. While no significant cumulative effect on the male was observed. The female seems to be more sensitive to low humidex in Hefei than the male.

When comparing plots for different age groups, Fig. 5 described results that both preschool children (2–5) and school-age children (6–18) showed the harmful effect of exposure to low humidex. However, significant effects between the two groups occurred at different lag time. And no effect of humidex was detected in the group of infants (0–1 years). Low humidex presented a negative effect on preschool children, with the significant single-day RR occurring on the 5th day and continuing to the 6th day. The risk of childhood asthma hospitalizations peaked at the lag of 6th day with the RR of 1.099 (95%CI: 1.015, 1.172). While in the group of aged 6–18 was first appeared at the day of 4th (1.060, 95%CI: 1.002, 1.222) and continued to the 7th day, with the largest estimates presented on lag 6 (1.179, 95%CI: 1.094, 1.272). In our study, the effect of low humidex on childhood asthma hospitalizations has differences between preschool children and school-age children. The results of our study reported the hazard effect in school-age children was earlier and higher than that in preschool children, suggesting that school-age children were more likely to be exposed to higher risk in the environment with the low humidex (See Table S1).

Based on the optimal models of temperature and humidity index and mean temperature respectively. The attributable risk of humidex is higher than the average temperature showing that the humidex is a better predictor of childhood asthma hospitalizations risk in children than the temperature. (humidex: $b\text{-AF}$ = 15.60%, 95% $e\text{CI}$: 0.63%, 23.95%, $b\text{-AN}$ = 5006; temperature: $b\text{-AF}$ = 12.12%, 95% $e\text{CI}$: 2.50%, 20.61%, $b\text{-AN}$ = 3890) (See Table S2).

Our results were found to be robust by changing the degrees of freedom of the mean wind velocity (3–5), the degrees of freedom of time (6–8), and the degrees of freedom of O₃, (3–5). (See the supplementary materials Figs. S3–S5 for details). The time distribution and histogram of the model residuals are shown in Fig. S6. The figure shows that the residuals of the model are randomly distributed in time, and the residuals follow a normal distribution.

**Fig. 1.** Time series plot for daily childhood asthma cases and meteorological variables in Hefei, 2013–2016.

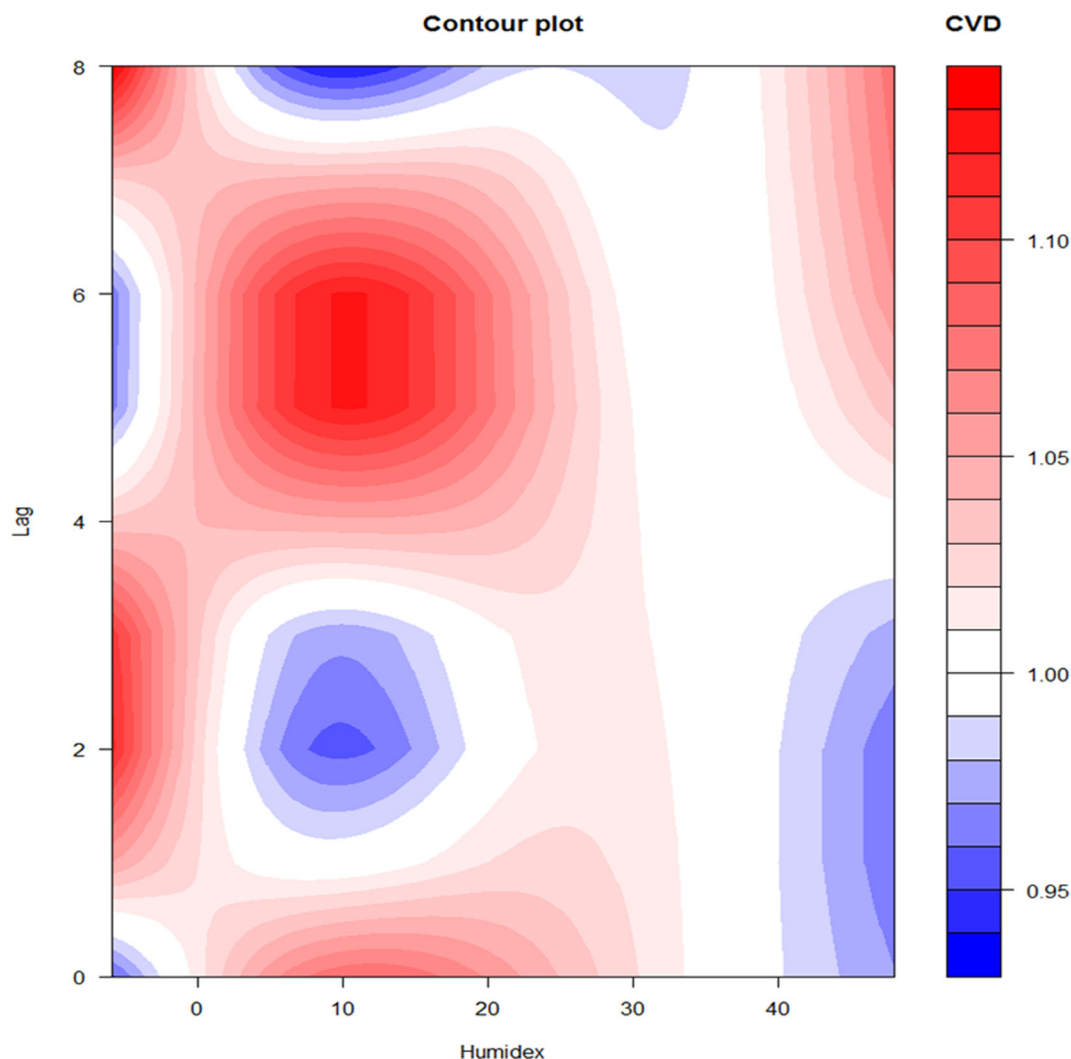


Fig. 2. Heat map for relative risk (RR) of childhood asthma hospitalizations along Humidex and lags produced by DLNM in Hefei, China.

4. Discussion

In recent years, the disease burden of childhood asthma has been increasing rapidly. At the same time, with the in-depth research on the risk of childhood asthma hospitalizations caused by climate change, it is not enough to study the impact of temperature or humidity on childhood asthma hospitalizations from a single level, and it cannot reflect the actual exposure. Thus, it's an urgent need to estimate the combined effects of temperature and humidity. And our study is the first epidemiological studies to quantify the association between humidex and childhood asthma hospitalizations.

In our study, we found that low humidex was associated with the increased risk of admissions for childhood asthma in Hefei. Our findings are similar to a study in Hong Kong that found a significant association between low temperature, low humidity and childhood asthma hospitalizations (Lam et al., 2016). For whole research population, the relative risk of childhood asthma hospitalizations increases to 1.117 (95%CI: 1.064–1.173) for the decrement of humidex (P25:8.7 vs MMT: 36.8) which suggests that low humidex is a significant risk factor for childhood asthma hospitalizations in Hefei. Further in subgroup analysis, our research showed that the female was more susceptible than the male when exposed to low humidex, and the children under 1 year old were least sensitive to low humidex. While school-age children are the most sensitive group to low humidex.

The low humidex, as a mixed effect of temperature and humidity, was associated with the increased risk of admissions for asthma in children, and the biological mechanism is unclear. Previous studies have shown that humidity has a certain degree of modification to temperature (Mostofsky et al., 2014). The underlying mechanism may be due to the combined effects of temperature and humidity on asthma. On the one hand, continuous stimulation of low temperature can cause bronchoconstriction and aggravate airway obstruction in asthmatic patients, and even damage to the airway epithelia (D'amato et al., 2015; Larsson et al., 1998; Sheffield et al., 2015). Besides, a study has shown that immune imbalance is the central link in the pathophysiological mechanism of asthma (Lu et al., 2018). While the body's immunity will be influenced when exposing to low ambient temperatures, which may increase the risk of asthma (Schaller et al., 2006). On the other hand, humidity also has an important impact on the childhood asthma hospitalizations, which will further aggravate the symptom of asthma. When the humidity is in low level, it will cause airway mucosa to dry, increasing the susceptibility to airway bacteria and viruses (Chan et al., 2009; Sheffield et al., 2015). In addition, low temperatures and low levels of humidity also support the survival of viruses like respiratory syncytial virus which will increase the risk of infection-induced triggers (Tang et al., 2010). While in high level, it can dissolve and absorb allergens such as atmospheric pollutants and pathogen spores easily, and aggravate airway damage (Schaller et al., 2006). What's more, children are in a period of growth and development, the body organs

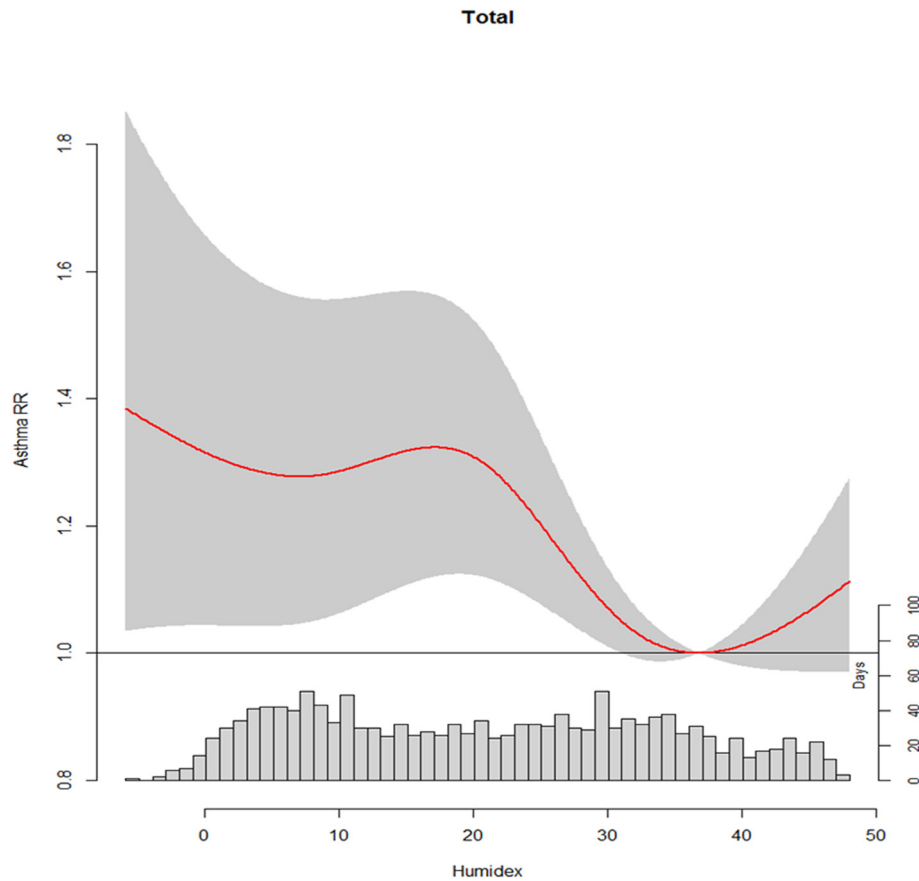


Fig. 3. Overall effects of exposure-response associations between humidex change and childhood asthma hospitalizations in Hefei, 2013–2016.

and immune system are not yet mature, and are more susceptible to external environmental exposure factors and more likely to be injured. However, at present, the underlying pathological mechanisms have not been completely elucidated and further research is needed to provide a shred of biological evidence for this association. Fortunately, we may reduce the incidence of asthma by avoiding exposure to the risk factors. In addition, it is worth noting that epidemiological studies have shown that exercise in low temperatures and humid conditions can significantly increase the risk of acute asthma attacks (Gawlik et al., 2019; Stensrud et al., 2006; Turcotte et al., 2003). Teenagers and athletes are the main susceptible people. This study found that the harmful effects of low humidex may provide basic information for the prevention of exercise-induced asthma and the establishment of early warning systems.

In the subgroup analysis stratified by gender, we found that the female is more likely to be exposed to higher risk in the environment

with the low humidex. Our results were consistent with some epidemiological studies on asthma, which show the incidence of asthma was greater in female than in male, and that females were more likely than males to develop severe asthma (Carey et al., 2007; Walford and Doherty, 2014). A possible explanation is that compared with male children, the female has lower inspiratory muscle strength as well as increased bronchial hyperreactivity, which contributed to the susceptibility of the environment of low humidex (McCallister and Mastronarde, 2008). In addition, the previous study found that female sex hormones and their receptors promote asthma development (Koper et al., 2017). And there are many differences in physical development between males and females before and after puberty, but we don't have an age-stratified analysis of gender in view of group size problems, which may bias our findings.

Age difference is also an influencing factor. The significant association was not detected in the subgroup of infants. While the children

Table 3

The relative risk of childhood asthma hospitalizations associations with 25th percentile of Humidex in Hefei, from 2013 to 2016 (MRH = 36.8).

Time	Singer lagged effects(P_{25} vs MRH)					
	Total	Male	Female	0–1 years	2–5 years	6–18 years
lag0	1.074 (0.987,1.168)	1.024 (0.924,1.135)	1.186 (1.022,1.376)*	0.872 (0.658,1.158)	1.081 (0.957,1.220)	1.120 (0.982,1.277)
lag1	0.998 (0.959,1.039)	0.970 (0.923,1.018)	1.061 (0.989,1.139)	0.967 (0.846,1.106)	1.009 (0.953,1.068)	0.997 (0.936,1.061)
lag2	0.956 (0.909,1.006)	0.943 (0.887,1.003)	0.984 (0.901,1.075)	1.047 (0.884,1.240)	0.967 (0.899,1.039)	0.930 (0.860,1.005)
lag3	0.973 (0.924,1.024)	0.970 (0.910,1.033)	0.980 (0.894,1.073)	1.081 (0.907,1.289)	0.975 (0.905,1.050)	0.952 (0.878,1.031)
lag4	1.045 (1.007,1.084)*	1.046 (1.000,1.093)*	1.044 (0.978,1.113)	1.061 (0.935,1.204)	1.031 (0.979,1.087)	1.060 (1.002,1.222)*
lag5	1.116 (1.062,1.173)*	1.116 (1.050,1.185)*	1.118 (1.024,1.220)*	1.017 (0.860,1.203)	1.091 (1.015,1.172)*	1.174 (1.087,1.267)*
lag6	1.117 (1.064,1.173)*	1.111 (1.046,1.179)*	1.131 (1.038,1.234)*	0.980 (0.830,1.156)	1.099 (1.024,1.179)*	1.179 (1.094,1.272)*
lag7	1.045 (1.006,1.085)*	1.030 (0.984,1.079)	1.076 (1.007,1.150)*	0.955 (0.838,1.088)	1.051 (0.996,1.110)	1.070 (1.009,1.135)*
lag8	0.944 (0.873,1.020)	0.922 (0.838,1.014)	0.992 (0.864,1.138)	0.937 (0.718,1.222)	0.979 (0.875,1.096)	0.922 (0.817,1.040)

MRH: Reference values selected in our study. That is, the humidex corresponding to the minimum risk of childhood asthma hospitalizations.

* $p < 0.05$ indicates statistical significance.

Table 4

The cumulative RRs of childhood asthma hospitalizations associations with 25th percentile of Humidex in Hefei, from 2013 to 2016 (MRH = 36.8).

Time	Cumulative lagged effects(P_{25} vs MRH)					
	Total	Male	Female	0–1 years	2–5 years	6–18 years
lag0	1.074 (0.987,1.168)	1.024(0.924,1.135)	1.186 (1.022,1.376)*	0.872(0.658,1.158)	1.081 (0.957,1.220)	1.120 (0.982,1.277)
lag0-1	1.072 (0.955,1.202)	0.993(0.864,1.142)	1.259 (1.028,1.541)*	0.844(0.575,1.239)	1.090 (0.925,1.285)	1.116 (0.933,1.335)
lag0-2	1.025 (0.907,1.158)	0.937(0.807,1.087)	1.239 (0.999,1.536)	0.884(0.587,1.329)	1.054 (0.885,1.255)	1.038 (0.858,1.256)
lag0-3	0.997 (0.871,1.141)	0.908(0.771,1.071)	1.213 (0.957,1.539)	0.955(0.608,1.502)	1.027 (0.847,1.246)	0.988 (0.800,1.219)
lag0-4	1.041 (0.900,1.205)	0.950(0.795,1.134)	1.266 (0.980,1.637)	1.014(0.621,1.655)	1.060 (0.860,1.305)	1.047 (0.834,1.315)
lag0-5	1.162 (0.995,1.358)	1.060(0.878,1.280)	1.416 (1.077,1.860)*	1.031(0.611,1.739)	1.156 (0.926,1.442)	1.229 (0.965,1.567)
lag0-6	1.298(1.093,1.543)*	1.177(0.955,1.451)	1.602 (1.183,2.169)*	1.010(0.565,1.807)	1.270 (0.993,1.624)	1.450 (1.108,1.897)*
lag0-7	1.356(1.130,1.629)*	1.213(0.971,1.514)	1.724 (1.249,2.378)*	0.965(0.518,1.795)	1.335 (1.028,1.733)*	1.551 (1.167,2.061)*
lag0-8	1.280(1.053,1.555)*	1.118(0.882,1.417)	1.709 (1.213,2.409)*	0.904(0.462,1.766)	1.307 (0.989,1.727)	1.429 (1.057,1.933)*

MRH: Reference values selected in our study. That is, the humidex corresponding to the minimum risk of childhood asthma hospitalizations.

* $p < 0.05$ indicates statistical significance.

aged 2–5 years and children aged 6–18 years were more likely to have a higher risk of asthma hospitalization during days with the low humidex. Possible reasons are as follows: first, for those under 1 year of age, who

are more likely to spend most of their time indoors, but the exact cause is not clear. While the school-age children are lively and the daily average outdoor time is relatively longer and there are more opportunities

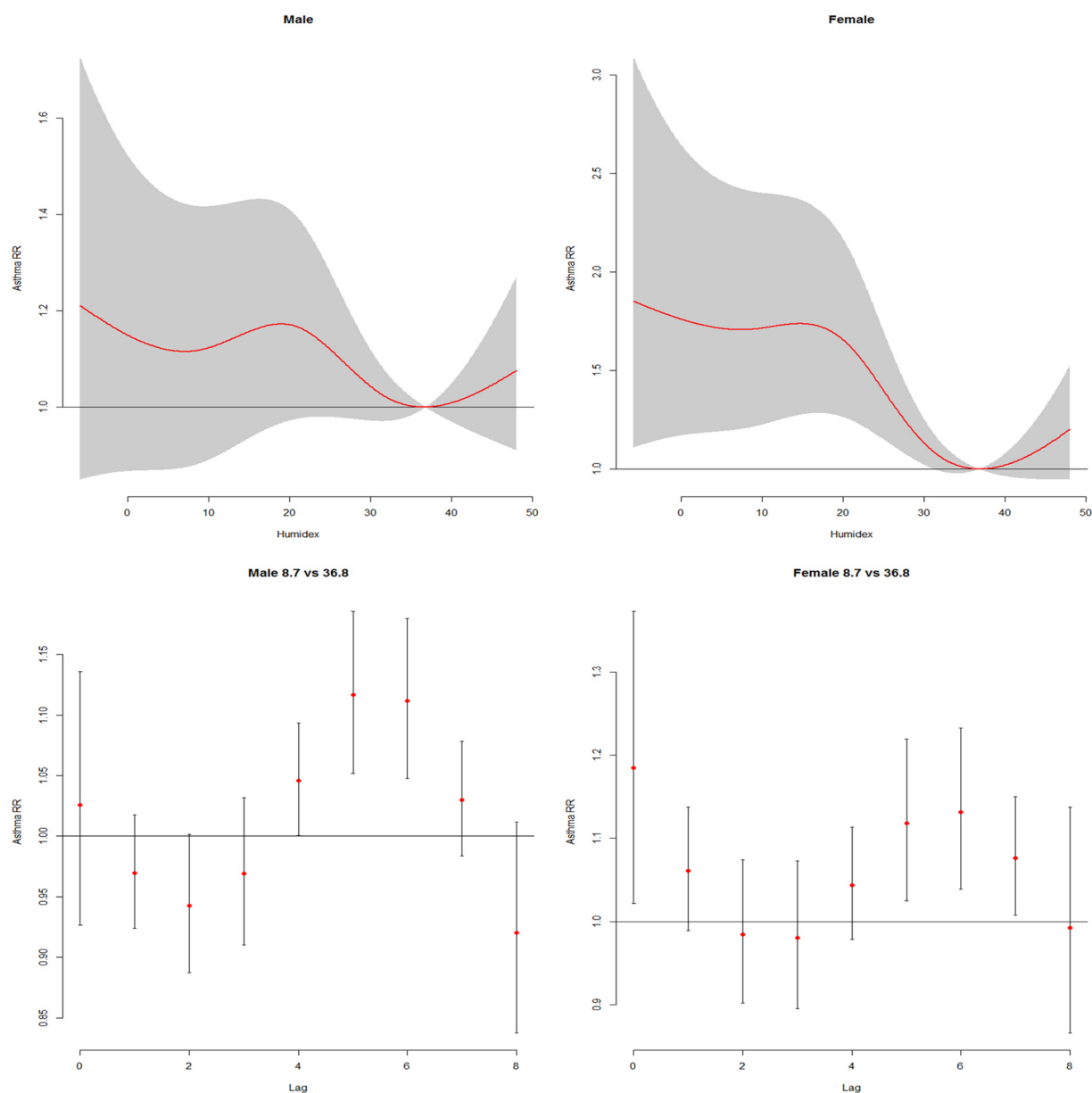


Fig. 4. (left is male; right is female). The combination diagram of the dose-response relationship of the DLNM model of gender and the lag-effects of specific humidex (P_{25}) on childhood asthma hospitalizations with reference of 36.8.

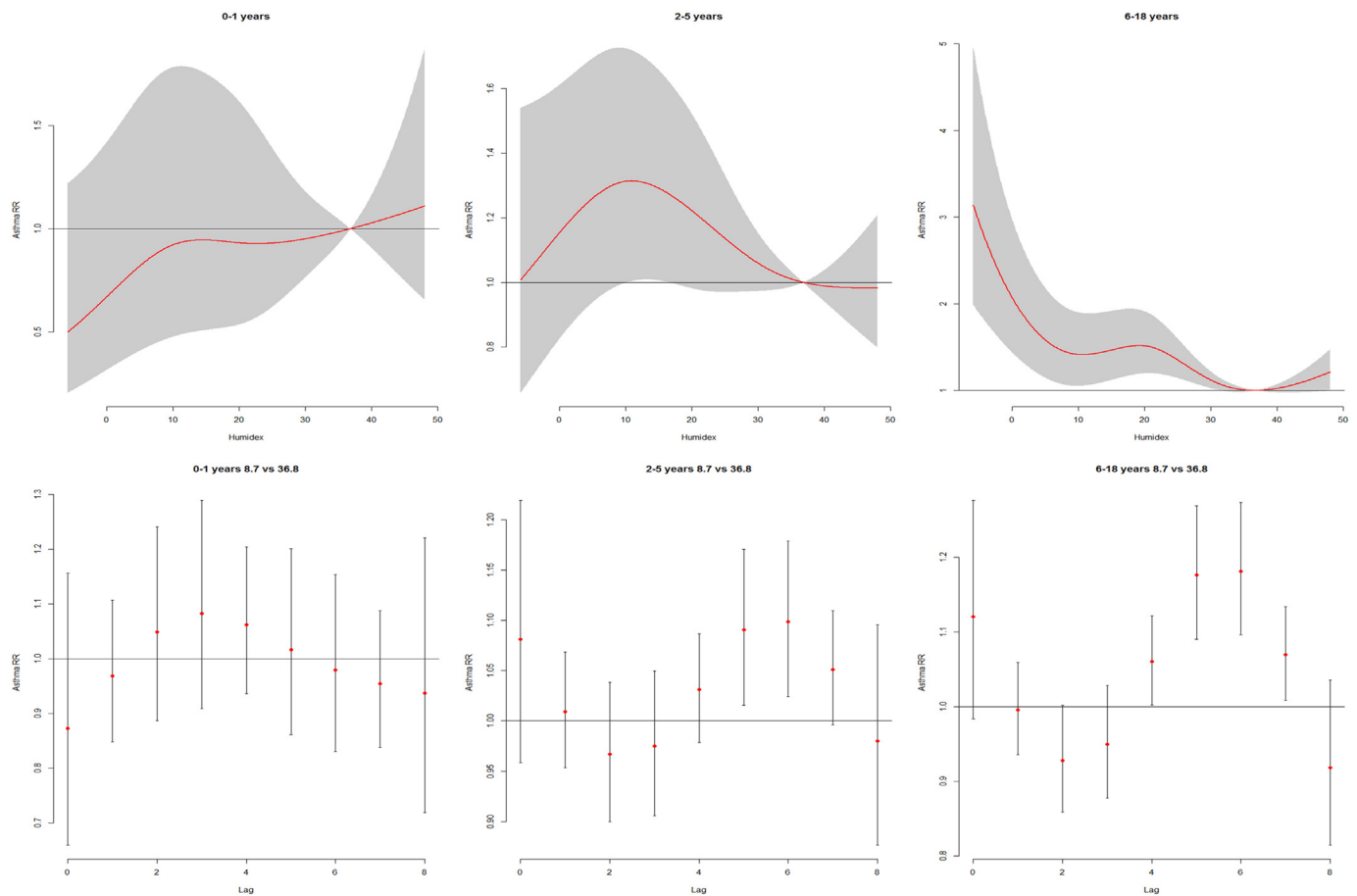


Fig. 5. (Left is 0–1 years old; Middle is 2–5 years old; Right is 6–18 years old). The combination diagram of the dose-response relationship of the DLNM model of age and the lag-effects of specific humidex (P_{25}) on childhood asthma hospitalizations with reference of 36.8.

for exposure to low humidex environment; second, a study in Canada found there was evidence that breastfeeding was protective for asthma (Ye et al., 2012). Children under one year of age may be due to the protective effects of breastfeeding.

In addition, our results suggest that school-age children are more sensitive to the humidex than others. However, so far, no other studies have reported differences in the effect of humidex on childhood asthma hospitalizations among different ages. But our results are similar to some of the findings of studies on childhood asthma hospitalizations and other environmental exposures. A study in Australia found children aged 10–14 years were most vulnerable to cold effects (Xu et al., 2013b). Another study reported a stronger association between hospital admissions for asthma and air pollution in school-age children than in preschool children. Xu et al. found in children ≥ 6 years old, some triggers happened more than that in children 5 years and younger, owing to differences in age (Xu et al., 2016). The results of the above studies suggest that this may be due to differences in physical and psychological aspects of children of different ages, and the intrinsic link is still unclear. Besides, it's noteworthy that the diagnosis of asthma in children under 5 years old is relatively difficult and easily confused with children's wheezing, which may cause instability in the results (Bao et al., 2017).

In the present study, we found that the attribution fraction of the humidex was almost higher than the average temperature, suggesting that using the humidex to assess the association between childhood asthma hospitalizations is more publicly meaningful than using average temperature. Our findings may provide new ideas for exploring the association between the environment and disease in the future.

5. Conclusions

This study provides quantitative evidence that the hospital admissions of asthma in children were associated with low humidex, and there are non-linear and lagged effects of humidex exposure on childhood asthma hospitalizations. Low humidex was associated with the increased risk of admissions for childhood asthma in Hefei. The significant effects of humidex on childhood asthma hospitalizations were detected in the children with preschool and school-age, whereas not for the subgroup of infants. And the school-age children were more likely to be exposed to higher risk in the environment with the low humidex. In gender, compared to the male, we found that the female children are more sensitive to the low humidex. The present findings may provide epidemiology evidence when formulating precaution guidelines for patients with asthma in terms of low humidex environment condition in Hefei. In short, we should focus first and foremost on the prevention of school-age and female children with asthma, and take effective protective measures for healthy children.

6. Strengths and limitations

This study has some advantages. Firstly, to the best of our knowledge, this is the first research to qualify the relationship between humidex and childhood asthma hospitalizations. Secondly, the effect of meteorological factors and pollutants on asthma were controlled in our research, hence our results are relatively reliable. Thirdly, we use daily meteorological data rather than weekly data that would guarantee the accuracy of exposure assessment. There are also several limitations. Firstly, this is an ecological study where potential confounding factors,

such as a spore, pollen, etc. are difficult to control. Secondly, this study is conducted in only one region and the results may not be applicable in other regions. Thirdly, this study lacks specific data on the causes of asthma, such as exercise-induced asthma, which will be further collected for further analysis in the future.

Contributors

P. R. and S.H. designed the study. P.R., G.J., and B.L. conducted the study and analyzed the data. All authors helped interpret the results. P.R. wrote the first draft. All authors contributed to the manuscript revision. Then this was revised critically for important intellectual content by the other author before P.R. incorporated amendments to produce the final draft.

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Provenance and peer review

Not commissioned; externally peer reviewed.

Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2019.07.026>.

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Table S1 the results of the analysis of subgroups

Q-test		RR ₁	RR ₂	L ₁	U ₁	L ₂	U ₂	L ₃	U ₃
2-5 vs 6-18	lag4	1.031	1.06	0.979	1.087	1.002	1.222	/	/
	lag5	1.091	1.174	1.015	1.172	1.087	1.267	-0.14393	-0.02207
	lag6	1.099	1.179	1.024	1.179	1.094	1.272	-0.14021	-0.01979
	lag7	1.051	1.07	0.996	1.11	1.009	1.135	/	/

*L3 and U3 represent the Q test confidence interval of RR values of lag5 and lag6 respectively, and the interval does not contain 0 indicates that it is statistically significant.

Table S2 Backward attributable risk fractions (*b-AF*) and numbers (*b-AN*) of Humidex and Mean temperature

Index		Overall
Humidex	b-AF	15.60% (6.28%, 23.95%)
	b-AN	5006
Mean temperature	b-AF	12.12% (2.50%, 20.61%)
	b-AN	3890

*AF: attributable risk fractions AN: attributable risk numbers

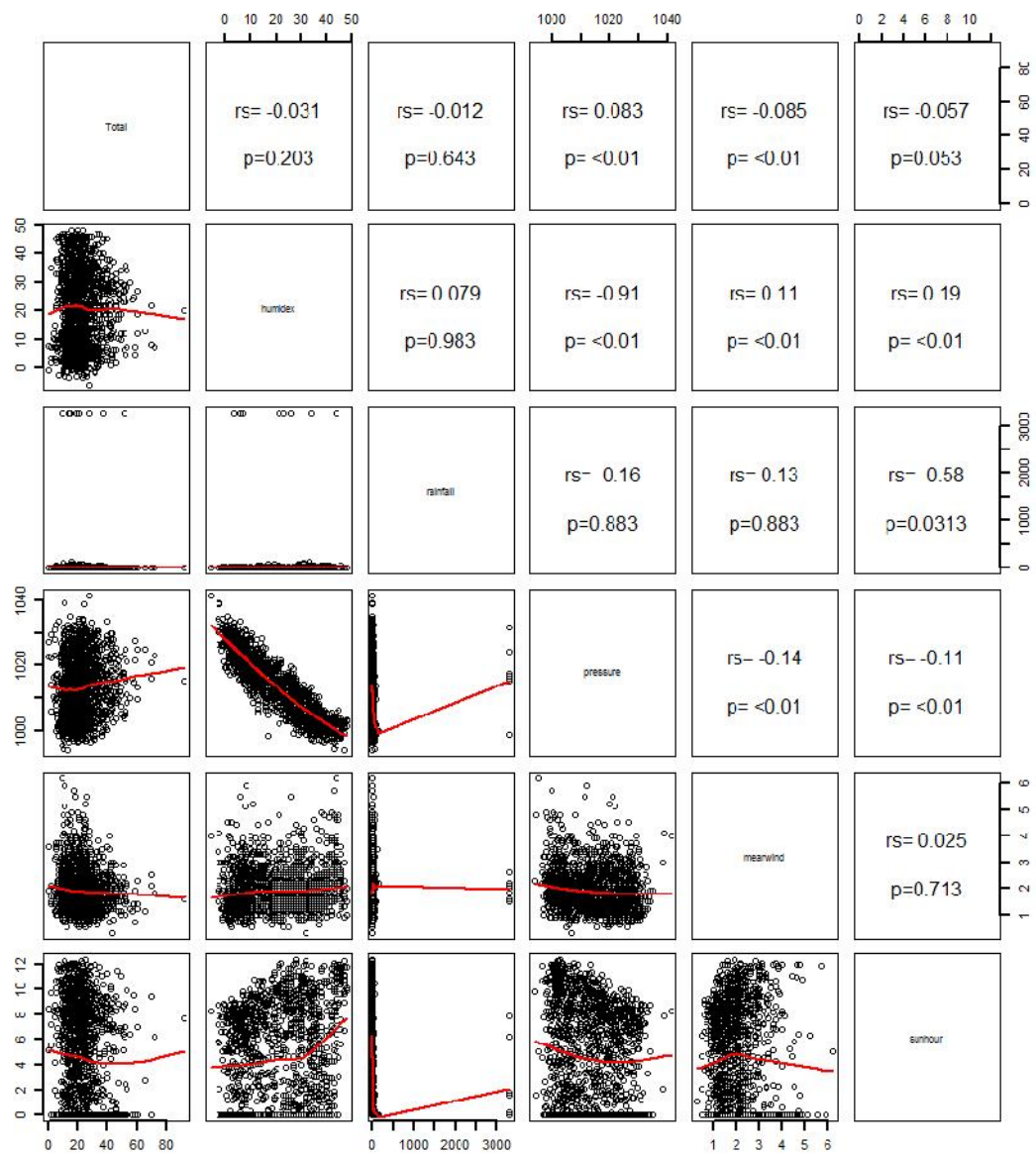


Fig.S1. the Spearman correlation coefficients between daily number of cases, humidex and weather factors from 2013 to 2016 in Hefei.

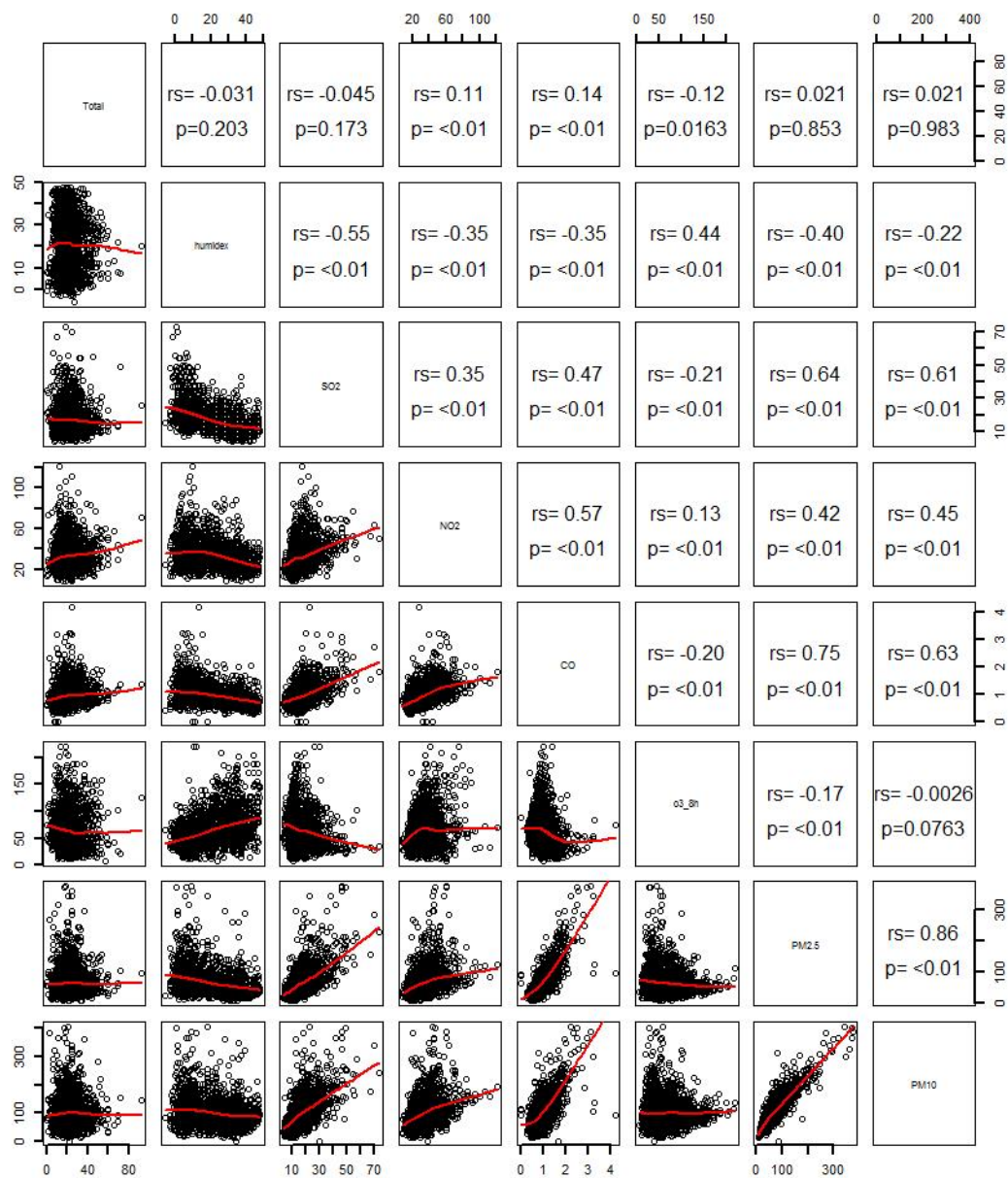


Fig.S2. the Spearman correlation coefficients between daily number of cases, humidex and pollutants from 2013 to 2016 in Hefei.

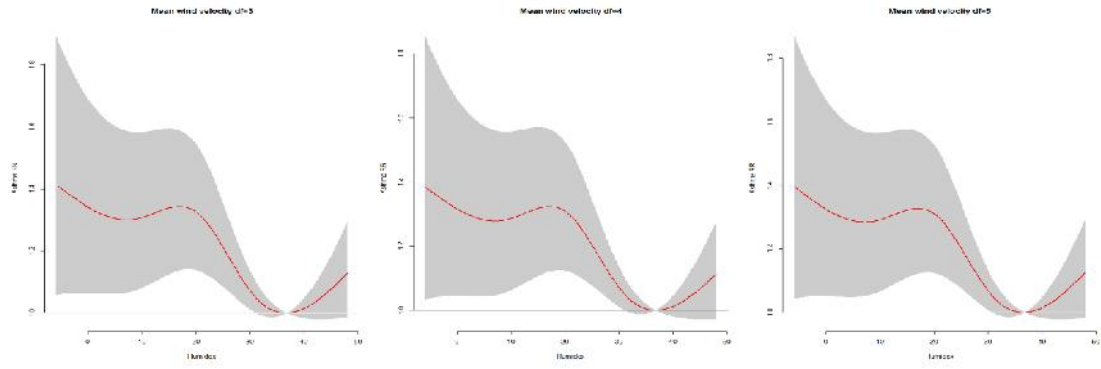


Fig.S3. the overall effects of humidex on childhood asthma when varying the df (3-5 $df/year$) for mean wind velocity.

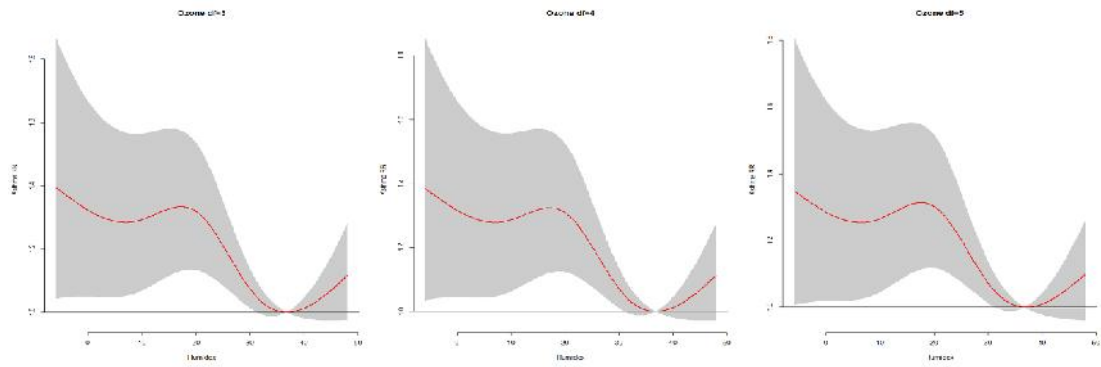


Fig. S4. The overall effects of Humidex on childhood asthma when varying the df (6-8) for time.

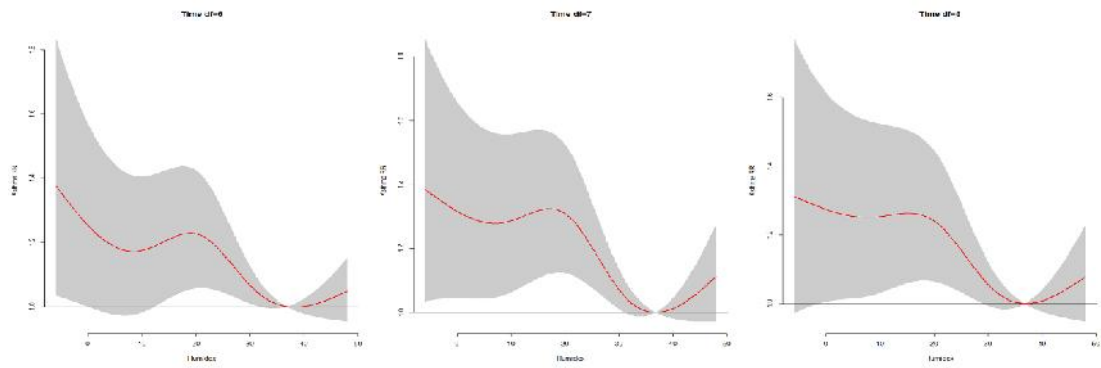


Fig. S5. The overall effects of Humidex on childhood asthma when varying the df (3-5) for Ozone.

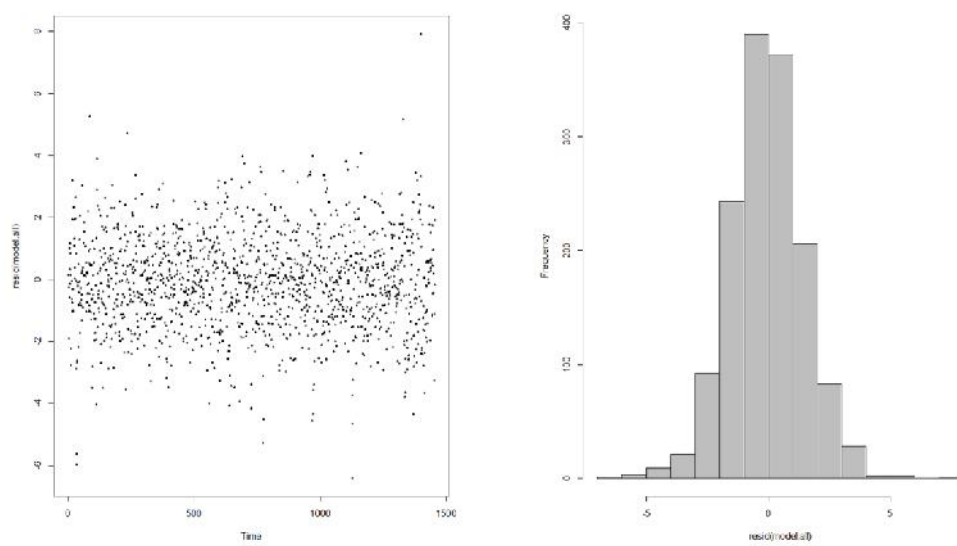


Fig. S6. The temporal distribution of model residuals over time and the histogram of model residuals.

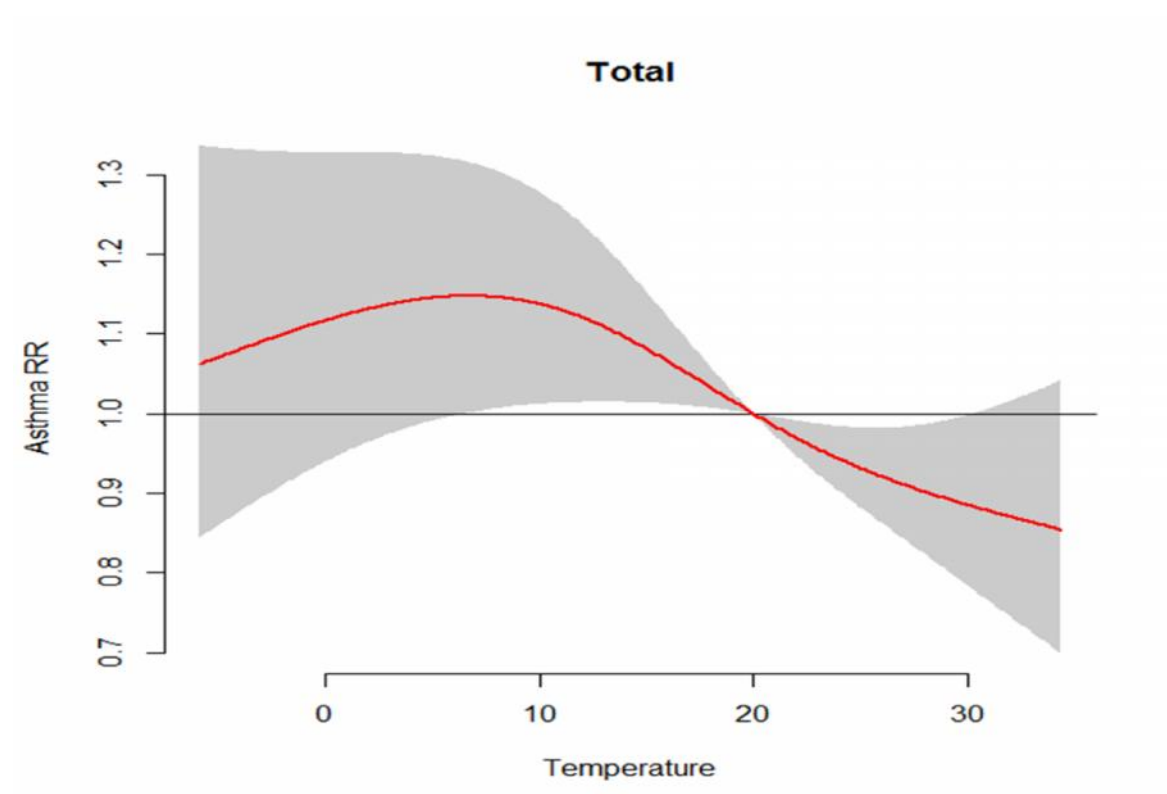


Fig.S7 Overall effects of exposure-response associations between temperature and childhood asthma hospitalizations in Hefei, 2013–2016.

