



The short-term effects of cold spells on pediatric outpatient admission for allergic rhinitis in Hefei, China

Qiang Cheng^{a,b}, Xu Wang^c, Qiannan Wei^{a,b}, Lijun Bai^{a,b}, Yanwu Zhang^{a,b}, Jiaojiao Gao^{a,b}, Jun Duan^{a,b}, Zihan Xu^{a,b}, Weizhuo Yi^{a,b}, Rubing Pan^{a,b}, Hong Su^{a,b,*}

^a Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, Hefei, Anhui 230032, China

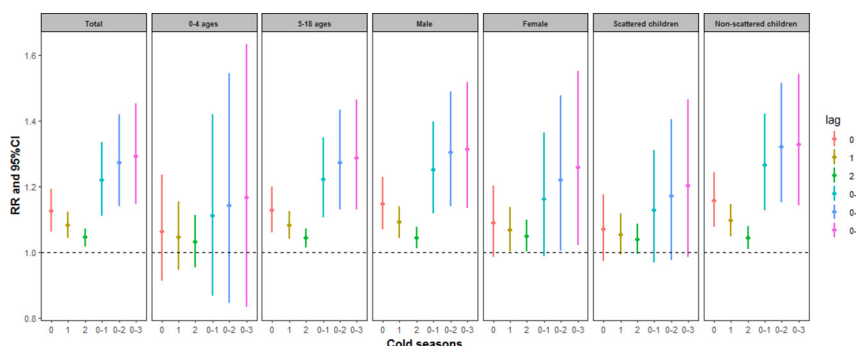
^b Anhui Province Key Laboratory of Major Autoimmune Diseases, Hefei, Anhui 230032, China

^c Anhui Province Children's Hospital, Hefei, Anhui, China

HIGHLIGHTS

- This was the first study to explore the relationship between cold spells and childhood AR.
- Cold spells may significantly increase the pediatric outpatient admission for AR.
- Male children, children aged 5–18 years and non-scattered children may be vulnerable people of AR.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Some studies have reported that cold weather is associated with the development of allergic rhinitis (AR), but the study of extreme cold temperatures and AR is scarce. This study was conducted to find out the optimal definition of the cold spells in Hefei and to explore the relationship between cold spells and childhood AR, further to identify potential susceptible populations.

Methods: Data of daily AR, meteorological variables and air pollutants from January 1, 2014 to December 31, 2016 were collected in Hefei. Poisson generalized linear regression with a distributed-lag nonlinear model (DLNM) was used to explore the relationship between cold spells and daily pediatric outpatient with allergic rhinitis, by comparing the number of the admission during the cold spells with those during non-cold spells in cold seasons (December to April), after adjusting for relative humidity, air pollutants, seasonality, long-term trends, calendar month, holiday and day of the week (DOW).

Results: All definitions of cold spells both had a certain impact on children with allergic rhinitis, and the trend of their effects was similar. The optimal cold spells was defined as the daily average temperature for below 10th with two consecutive days during the study period, and the greatest impact of cold spells was at lag0, with a 12.5% (95%CI: 6.3%–19.1%) increase of AR than non-cold spell days, and its impact could last for 2 days. Male children, children aged 5–18 years and non-scattered children were considered to be more vulnerable to AR in cold spell days.

Conclusions: There was evidence showed that the cold spells may significantly increase the pediatric outpatient admission for allergic rhinitis, especially for male children, children aged 5–18 years and non-scattered children.

* Corresponding author at: Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui Province 230032, China.
E-mail address: suhong5151@sina.com (H. Su).

For the serious threat posed by cold spells, caregivers and health practitioners should strengthen their awareness of the prevention of vulnerable people.

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1. Introduction

The frequency, intensity and duration of extreme weather events are expected to increase due to global climate change (Lionello et al., 2008). At present, the health effects of climate change are increasingly attracting the attention of health practitioners and policy makers (WHO, 2018; IPCC, 2014). It was reported that 48%–74% of the population is expected to be affected by heat waves all the world in 2100 (Mora et al., 2017). Except heat waves, some studies have found that persistent shift of the polar vortices over the past few decades, which may lead to increased cold spells in mid-latitudes (Cohen et al., 2014; Wallace et al., 2014; Zhang et al., 2016). Recently, a study conducted in South Korea and Japan found that the burden of death caused by the cold spells may be higher than that caused by heat waves (Lee et al., 2018). Moreover, the frequency, intensity and duration of cold spells have increased in East Asia, Europe and Australia (IPCC, 2014; H. Kim et al., 2018; E. Kim et al., 2018). Currently, a growing body of studies has reported that cold spells can increase the occurrence of many adverse health outcomes, such as death, cardiovascular events and respiratory diseases (Lee et al., 2018; Ryti et al., 2016; Fitzgerald et al., 2014; Ponjoan et al., 2017). Therefore, it is vital to assess the impact of increased cold spells events on human health for better public health strategies.

Allergic rhinitis (AR) is an allergic respiratory disease characterized by nasal congestion, anterior nasal leakage and posterior rhinorrhea, sneezing, secondary to IgE-mediated inflammation of the nasal mucosa and nasal itching (Pawankar et al., 2013). Epidemiological studies have shown that the prevalence of AR is 10%–40% in the world, which is reported to continually increase (Bjerg et al., 2011; Bousquet et al., 2008; De et al., 2012;). “World Allergy Organization (WAO) white book on allergy, Update” indicated that AR has significant socioeconomic impacts on patients, family members and society, and affects many aspects, including quality of life, physical, psychological and social functions (Pawankar et al., 2013). Meanwhile, AR is widely regarded as one of the factors of asthma, and the prevalence of AR in asthma patients is as high as 95% (H. Kim et al., 2018). Therefore, AR is an ongoing problem in the public health field because of its high prevalence and economic burden (Pawankar et al., 2012; H. Kim et al., 2018). Therefore, identifying the risk factors of AR is significance for the prevention and control of disease.

AR is a multifactorial disease affected by both genetics and the environment (He et al., 2017). Although some previous studies have found some risk factors, such as pollen, dust mites, air pollutants, behavior and lifestyle, which are related to the pathogenesis of AR (Wang et al., 2018; Chen et al., 2016; Hoshino et al., 2015; Wang et al., 2016a). However, due to the global climate change, especially the frequent occurrence of extreme weather, AR as a respiratory disease is more susceptible to extreme cold temperatures. The most recent period, some studies have reported that cold weather is associated with the development of AR (Hyrkäs et al., 2014; Hyrkäspalmu et al., 2018; H. Kim et al., 2018), and the causes were that cold temperature can affect individual's function and ability of working, especially for people with underlying respiratory disease (Harju et al., 2010). However, the study of extreme cold spells and the incidence of AR is scarced. Therefore, to explore the influence of cold spells for AR may help to better identify the risk of AR, so as to reduce its epidemiological and socioeconomic impacts, and

provide accurate reference information for the diagnosis and prevention of AR, and improve the quality of life of the AR patients. Regarding the cold spells, there is no uniform definition up to now, what's more, there is no research on the relationship between cold spells and human health in Hefei. Therefore, the purposes of the study are as follows: (1) to find out the optimal definition of the cold spells in Hefei by fitting different cold spells definitions, so as to provide an important reference for the early warning of the disease; (2) to explore the short-term effects of cold spells on pediatric outpatient admission for AR, and further to identify potential susceptible populations.

2. Materials and methods

2.1. Study population and data sources

Our research was carried out in Hefei, the capital of Anhui Province, which located in the eastern region of China (31°52' N, 117°17' E). It is now governed by 4 districts, 4 counties and 1 county-level city, with a total area of 11,434.25 km². The climatic condition in Hefei was typical subtropical monsoon climates with four distinct seasons.

Daily count of pediatric outpatient admission with allergic rhinitis was obtained from Anhui Province Children's hospital for the period of January 1, 2014 to December 31, 2016, and we only included children living in the Hefei area. The cases were admitted according to the International Classification of Disease, 10th version (ICD-10) for allergic rhinitis (ICD-10, J30). According to the daily admission data of children with allergic rhinitis, we divided the patients into male children and female children, 0–4 years old and 5–18 years old, scattered children and non-scattered children according to different age, gender and forms of care, respectively. The form of care referred to whether the children were sent to the baby room, nursery or kindergarten, elementary school or junior high school. We obtained the approval of the Ethics Committee of Anhui Medical University before collecting allergic rhinitis cases.

Daily meteorological data including average temperature and relative humidity were collected from the Hefei Meteorology Bureau. In the same period, the daily average air pollutant data was obtained from Hefei Environmental Protection Bureau, mainly including PM_{2.5} (μg/m³), PM₁₀(μg/m³), NO₂ (μg/m³), and O₃ (μg/m³).

2.2. Definition of cold spells

There are already various methods to define the cold spells in the world (E. Kim et al., 2018; Wang et al., 2016b; Liang et al., 2018; Ma et al., 2013; Huynen et al., 2001), but there is still no uniform definition of cold spells in China. The main reason is that China is a country with different climatic zones, and the effects of cold spells of different climatic zones may be different. In this study, the daily average temperature was used as an indicator of exposure to determine the effects of cold spells on allergic rhinitis in children, rather than minimum or maximum temperature, due to it can judge the best model fit through the minimum quasi-Poisson Akaike Information Criterion (Q-AIC) standard (Guo et al., 2012), and it can better predict the impact of extreme temperature on morbidity (Xu et al., 2018). And previous studies had shown that the definition of the cold spells for two or more consecutive days provided a more accurate statistical estimate (Tong et al., 2014). So we defined cold spells as the daily average temperature for less than

10th (cold spells < 10%) or 5th (cold spells < 5%), with two or more consecutive days during the study period (Sartini et al., 2016; Liang et al., 2018). In addition, we did not use a lesser percentage of the daily average temperature, due to the number of cold spell days was too short, which was not conducive to the stability of the results.

2.3. Statistical analysis

In order to control the potential biases involved in some extreme summer events, we only limited the analysis of the effects of cold spells on pediatric allergic rhinitis from December to April (the five coldest adjacent months) for every year (Liang et al., 2018). As previous studies had shown that the effect of cold temperature on the morbidity of AR is non-linear and have delayed effects (H. Kim et al., 2018), we used Poisson generalized linear regression with a distributed-lag nonlinear model (DLNM) to explore the relationship between cold spells and daily pediatric outpatient allergic rhinitis (Gasparrini et al., 2010; Wang et al., 2016b; Liang et al., 2018), by comparing the number of the admission during the cold spells with those during non-cold spells in cold seasons.

The Q-AIC was used to select the optimal cold spells definition, degrees of freedom (df) and the model goodness of fit. A model was established in which relative humidity, seasonality, long-term trends, calendar month, holiday and day of the week (DOW), air pollutants were considered to be potential confounders. For air pollutants, though previous studies had found that NO₂, PM₁₀, PM_{2.5} and O₃ had statistically significant effects on the incidence of allergic rhinitis (Chen et al., 2016; He et al., 2017), we only controlled the potential effects of NO₂, PM₁₀, and O₃, rather than PM_{2.5}, for the cold season, there was a high correlation between PM_{2.5} and PM₁₀ by Spearman correlation analysis ($r_s = 0.86 > 0.8$) showed in Fig. S1. The model established is as follows:

Yt~Poisson(μ_t):

$$\text{Log}(\mu_t) = \alpha + \beta \text{CS}_{t,l,3} + \text{ns}(\text{RH}_t, 5) + \text{ns}(\text{PM}_{10t}, 5) + \text{ns}(\text{NO}_{2t}, 5) + \text{ns}(\text{O}_{3t}, 5) + \text{ns}(\text{Time}_t, 6) + \lambda \text{month}_t + \eta \text{DOW}_t + \gamma \text{Holiday}_t$$

In the model, where t is the day of observation; μ_t is the number of pediatric outpatient admission for allergic rhinitis on day t; α is the intercept; CS_t represents the cold spells on day t (0 = non-cold spell days, and 1 = cold spell days); β is the matrix coefficient of the cold spells and a natural cubic spline function with 3 dfs were used to estimate the lagged effects of the cold spell; l is the number of lag days; λ is the coefficient of month_t; η is the coefficient of DOW_t; γ is the coefficient of Holiday_t; ns is the natural cubic spline function; RH_t represent the relative humidity at day t with 5 dfs; a nature cubic spline with 5 df were also used for PM_{10t}, NO_{2t}, O_{3t}, respectively; a nature cubic spline with 6 df per year was used to control the seasonal patterns and long-term trends; While DOW_t indicates that children with allergic rhinitis have differences in working days and weekdays, the chronological variables referenced on the seventh day of the week are used to control the effect of the day of the week; Using Holiday_t as a two-category variable, assigning them “1” (holiday) and “0” (non-holiday) to control the confounding effects of holidays.

In this study we only evaluated the short-term effects of cold spells on AR. Based on the lowest Q-AIC criteria (Huang et al., 2018), we found that the lag and non-linear effects of cold spells on children with allergic rhinitis lasted for 8 days in the optimal definition of cold spells. The single-day lag effect (from lag0 to lag8) and cumulative lag effects (from lag0–0 to lag0–8) were assessed for the effect of cold spells on children with allergic rhinitis, respectively. Furthermore, we conducted the subgroup analyses by gender (male and female), age (0–4 years old and 5–18 years old) and forms of care (scattered children and non-scattered children) to identify the susceptible populations under the optimal definition of cold spells.

Sensitivity analysis was carried out by changing the freedom of calendar day (4–6 dfs/year), relative humidity (3–5 dfs), air pollutants (3–5 dfs) in the DLNM to test the robustness of our findings. We also increased the length of lag days (11–14 days) to verify the stability of the model. All statistical analyses were fitted to the regression model using the R statistical software (version 3.3.3) and the “dlnm” package (Gasparrini et al., 2010). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Data description

A total of 20,689 children with allergic rhinitis aged 0–18 years old were admitted to the hospital in the cold seasons of the study period. Among them, there were more male cases, and the ratio of male cases to female cases is 2.07:1 (13949:6740). Characteristics of daily childhood allergic rhinitis, meteorological variables and air pollution variables in cold seasons (December–April) in Hefei from 2014 to 2016 were summarized in Table 1.

The Spearman correlation coefficients between mean temperature, relative humidity and air pollutions in cold seasons showed in Fig. S1. In the cold season, there was a moderate correlation between the mean temperature and relative humidity of the meteorological variables ($r_s = 0.60$, $P < 0.01$). The mean temperature was negatively correlated with the three air pollutants controlled in this study (NO₂: $r_s = -0.15$, $P = 0.123$; PM₁₀: $r_s = -0.22$, $P < 0.01$; O₃: $r_s = -0.20$, $P < 0.01$). There was also a negative correlation between relative humidity and three air pollutants controlled in this study (NO₂: $r_s = -0.28$, $P < 0.01$; PM₁₀: $r_s = -0.46$, $P < 0.01$; O₃: $r_s = -0.10$, $P = 0.243$). The correlation between the three air pollutants were as follows: NO₂ VS PM₁₀: $r_s = 0.54$, $P < 0.01$; NO₂ VS O₃: $r_s = 0.20$, $P < 0.01$; PM₁₀ VS O₃: $r_s = 0.032$, $P = 0.663$.

3.2. Effects of different definitions of cold spells

Fig. 1 showed that different definitions of cold spells both had a certain impact on children with allergic rhinitis, and the trend of their effects was similar. In general, the most severe effect of cold spells on children with allergic rhinitis occurred on lag0, and its impact can last for 2 days (Fig. 1). Table 2 appeared the cumulative effect on children with allergic rhinitis under different definitions of cold spells, and the maximum cumulative effect occurred at lag0–8. In the different definitions of cold spells, we found that the maximum effect of cold spells on children with allergic rhinitis was 1.252 (95%CI: 1.125–1.393) at lag0 day, and the minimum effect value was 1.081 (95%CI: 0.989–1.180) at lag0 day. According to the Fig. 1 and Table 2, it showed

Table 1

Characteristics for daily childhood allergic rhinitis, meteorological variables and air pollution variables in cold seasons (December–April) in Hefei, China, 2014–2016.

Variables	Mean $\pm$ SD	Frequency distribution				
		Min	P ₂₅	P ₅₀	P ₇₅	Max
Total	45.6 $\pm$ 18.0	0.0	25.0	34.0	43.0	103.0
Male	30.7 $\pm$ 13.0	0.0	22.0	29.0	38.0	71.0
Female	14.8 $\pm$ 6.4	0.0	10.0	14.0	19.0	38.0
Scattered children	17.7 $\pm$ 7.1	0.0	13.0	17.5	22.0	47.0
Non-scattered children	27.9 $\pm$ 13.7	0.0	18.0	25.0	35.0	67.0
0–4 years old	7.0 $\pm$ 6.0	0.0	2.0	5.0	10.0	29.0
5–18 years old	38.6 $\pm$ 16.4	0.0	27.0	36.0	47.0	92.0
Mean temperature (°C)	9.0 $\pm$ 6.0	−5.9	4.5	7.9	13.8	24.1
Relative humidity (%)	72.1 $\pm$ 14.6	33.0	62.0	73.0	83.0	100.0
PM _{2.5} (μg/m ³)	83.9 $\pm$ 46.6	13.0	53.0	73.0	100.8	352.0
PM ₁₀ (μg/m ³)	109.2 $\pm$ 53.9	9.0	73.3	102.0	136.0	374.0
NO ₂ (μg/m ³)	39.0 $\pm$ 16.8	13.0	28.0	36.5	47.0	121.0
O ₃ (μg/m ³)	58.6 $\pm$ 32.3	11.0	37.0	48.0	71.0	193.0

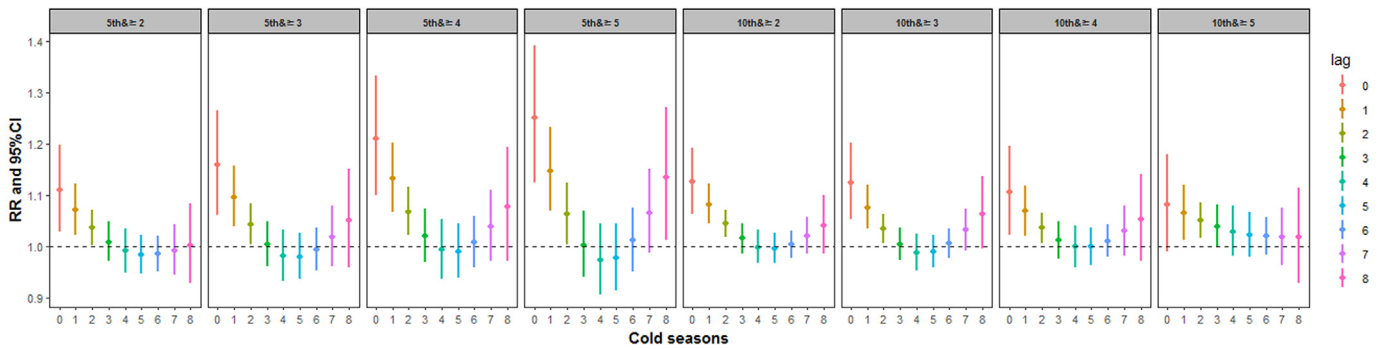


Fig. 1. The effect of cold spells under different definitions on pediatric outpatient admission for allergic rhinitis in cold seasons in Hefei, 2014–2016. Legend: The 10th and 5th which we used to define cold spells, and the “ $\geq n$ ” represented a cold spells lasting n days.

that the confidence interval of the threshold of 10th percentile of the average temperature was narrower than that of 5th percentile of the average temperature. At the same time, based on the 10th percentile of the average temperature, the relative risk of two days of cold spell was the largest, comparing to the longer cold spell duration. Therefore, it was more reasonable to think that the cold spell chart, defined as 10th below the average temperature and lasting for two days, was the most stable. On the other hand, the definition of cold spell days can reach up to 33 days in 2014–2016. So we chose the graph with the most stable and the longest cold spell days as the optimal cold spell definition, which was defined as the daily average temperature for less than 10th with two consecutive days during the study period. Meanwhile, based on the Q-AIC minimum criterion, the model of fit was the best goodness and the Q-AIC value was 3572.136.

3.3. Effects of the optimal cold spells

Table 3 summarized the relative risks (RRs) of cold spells on children with allergic rhinitis with the optimal definition of cold spells. In the single-day lag structure, the adverse effects of cold spells on children with allergic rhinitis occurred from the lag0 to lag2, with the largest RR of AR was at lag0 (RR = 1.125; 95%CI: 1.063–1.191). In the cumulative lag model, the effect of cold spells on children with allergic rhinitis appeared in lag0 to lag0–8, with the maximum cumulative effect of lag0–8 (RR = 1.366; 95%CI: 1.142–1.633).

Figs. 2 and 3 showed the single and cumulative hysteresis effects of cold spells on the different subgroups, respectively. Children aged 5–18 years were more susceptible to allergic rhinitis on cold spells days, however, the effect of cold spells on admission of allergic rhinitis was not statistically significant among children aged 0–4 years. Compared with female children, male children were more susceptible to allergic rhinitis in cold spell days, and their maximum single-day effects

occurred in lag0 (RR = 1.146; 95%CI: 1.069–1.228), which lasted until the second day of lag, and the maximum cumulative lag effect appeared in lag0–8 (RR = 1.374; 95%CI: 1.105–1.708) (Tables S1 and S2). For female children, the single-day effects of cold spells on children with allergic rhinitis appeared at lag1 (RR = 1.067; 95%CI: 1.002–1.137) and lag2 (RR = 1.049; 95%CI: 1.002–1.098) (Tables S1 and S2). In addition, in the subgroups stratified by the forms of care, we only found that the cold spells had significant impact on the non-scattered children, rather than the scattered children. Moreover, in all subgroup analyses, the risks of cold spells on the allergic rhinitis were greatest for non-scattered children (lag0: RR = 1.156; 95%CI: 1.075–1.242; lag0–8: RR = 1.435; 95%CI: 1.147–1.795) (Fig. 2, Tables S1 and S2).

3.4. Sensitivity analysis

Sensitivity analysis showed that the effects of cold spells on total children with allergic rhinitis were robust, by changing the degree of freedom of calendar time (4–6 dfs/year), relative humidity (3–5 dfs), air pollutants (3–5 dfs) one by one in the DLNM (Tables S3–S7). With the increased length of the lag days (11–14 days), the effects of cold spells on total children with allergic rhinitis were also robust (Fig. S2).

4. Discussion

Allergic rhinitis has become a serious allergic respiratory disease, to a certain extent, affecting people's work, study, and life in the world-wide. However, due to the global climate change, especially the frequent occurrence of extreme weather, AR as a respiratory disease is becoming more susceptible to extreme temperatures. To the best of our knowledge, this is the first study to explore the short-term effects of cold spells on children with allergic rhinitis, using Poisson generalized linear regression with a DLNM model. Based on the impact of climate

Table 2
Relative risk of pediatric outpatient admission for allergic rhinitis and the value of Q-AIC under different definitions of cold spells.

Percentile ^a	No. of consecutive days	Days ^b	Q-AIC value	RR(95%CI)		
				lag0	lag0–1	lag0–8
5th	≥ 2	15	3582.750	1.100(1.029–1.197)*	1.189(1.053–1.341)*	1.002(0.928–1.083)
	≥ 3	11	3580.251	1.158(1.061–1.265)*	1.270(1.104–1.460)*	1.358(1.000–1.843)*
	≥ 4	8	3575.129	1.210(1.100–1.332)*	1.371(1.176–1.600)*	1.651(1.149–2.374)*
	≥ 5	6	3574.659	1.252(1.125–1.393)*	1.437(1.207–1.710)*	1.776(1.127–2.800)*
	≥ 2	33	3572.136	1.125(1.063–1.191)*	1.218(1.111–1.334)*	1.366(1.142–1.633)*
10th	≥ 3	21	3577.960	1.125(1.053–1.202)*	1.210(1.090–1.344)*	1.354(1.106–1.657)*
	≥ 4	16	3582.753	1.106(1.022–1.196)*	1.181(1.045–1.335)*	1.353(1.070–1.709)*
	≥ 5	12	3582.548	1.081(0.989–1.180)	1.151(1.003–1.320)*	1.391(1.056–1.833)*

* $P < 0.05$.

^a The threshold cut-off which we used to define cold spells.

^b The number of cold spell days.

Table 3

The total effects of pediatric outpatient admission for allergic rhinitis during cold spells compared with non-cold spell days in cold seasons, 2014–2016.

Single-day lag	Single effects RR(95%CI)	Multi-day lag	Cumulative effects RR(95%CI)
0	1.125(1.063–1.191)*	0–0	1.125(1.063–1.191)*
1	1.082(1.044–1.122)*	0–1	1.218(1.111–1.334)*
2	1.044(1.017–1.072)*	0–2	1.271(1.140–1.418)*
3	1.015(0.986–1.045)	0–3	1.290(1.145–1.454)*
4	0.998(0.966–1.031)	0–4	1.288(1.132–1.465)*
5	0.995(0.966–1.025)	0–5	1.282(1.115–1.475)*
6	1.004(0.978–1.031)	0–6	1.287(1.107–1.495)*
7	1.020(0.985–1.056)	0–7	1.313(1.119–1.540)*
8	1.040(0.984–1.100)	0–8	1.366(1.142–1.633)*

* $P < 0.05$.

factors in different regions, it is important to explore regional optimal cold spell definition. According to perspective of statistics, relative risk and number of days of the cold spells, the results of our study showed that the optimal cold spells was defined as the daily average temperature for less than 10th with two consecutive days during the study period, which would provide an important reference for the early warning of the disease in our area. The findings of our study demonstrated that cold spells may significantly increase the admission of children with allergic rhinitis. In addition, this study had controlled related potential confounders such as air pollutants, and made it more scientific. In order to fully use the early warning information, our study further proposed that the main vulnerable groups of children with allergic rhinitis exposed to cold spell days were male children, non-scattered children and children aged 5–18 years. At the same time, improving interventions targeted at key populations can help reduce the

risk of AR of extreme temperatures and improve prevention and control of disease.

Previous studies had found that the intensity of extreme temperature played a more important role than duration in exploring the association of extreme temperature with health outcomes (Xu et al., 2016; Xu et al., 2018). At the same time, the health effects of the 2 days duration were more harmful than the longer duration (Xu et al., 2016; Xu et al., 2018). More importantly, for cold spells, choosing a relatively high threshold of mean temperature may be more effective for early warning of the disease (Lee et al., 2018). For the selection of the optimal cold spell definition, we mainly based on the perspective of statistics, relative risk and the number of days of the cold spells. First, as stated in the results section, the Q-AIC value of the cold spells defined as the daily average temperature for less than 10th with two consecutive days was minimal and the graph was the most robust. Second, based on the 10th percentile of the average temperature, the relative risk of the cold spell duration of two days was the largest, comparing to the longer cold spell duration. Third, the number of days of the cold spells was the longest between 2014 and 2016. Therefore, it may be more reasonable to define the optimal cold spells as the daily average temperature for less than 10th with two consecutive days during the study period in our area, rather than selecting the average temperature threshold as 5th or longer duration. Meanwhile, this result was consistent with previous studies on extreme temperature and mortality (Lee et al., 2018). However, for 33 cold spell days, it was the total number of cold spell days in three year, so it was not too long.

Although some epidemiological studies have shown that cold temperatures have an impact on the pathogenesis of AR (Hyrkäs et al., 2014; Hyrkäspalmu et al., 2018; H. Kim et al., 2018), it remains unclear, especially for extreme cold temperatures. During the cold spell period, the possible reasons for the increase of pediatric outpatient admission for allergic rhinitis are as follows. First, the change of airway function

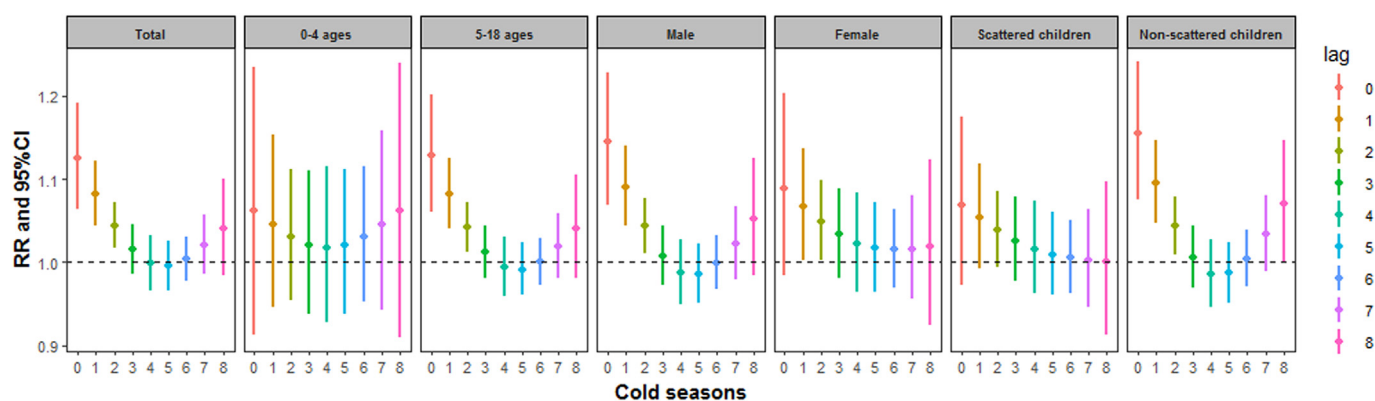


Fig. 2. The single effects of allergic rhinitis in total and different subgroups for cold spells in cold seasons in Hefei, 2014–2016.

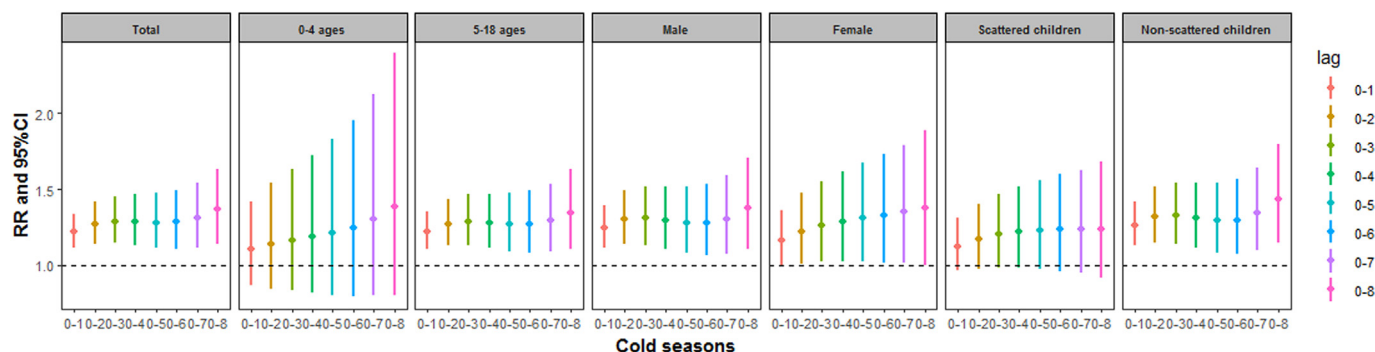


Fig. 3. The cumulative effects of allergic rhinitis in total and different subgroups for cold spells in cold seasons in Hefei, 2014–2016.

was considered to be one of the underlying mechanism that cold temperature affecting children with allergic rhinitis, due to skin cooling or simultaneous cooling and drying of the nasal cavity and airway mucosa while inhaling cold air, resulting in respiratory congestion and rhinorrhea, inflammatory changes and even lower airway bronchoconstriction (Hyrkäs et al., 2014; Hyrkäspalmu et al., 2018). Second, during the cold spell period, the people would reduce their chances of going out, and at the same time it may increase their exposure to allergens, in particular, the using of air conditioners would increase the growth of dust mites and fungus when the doors and windows were closed. Third, when the weather suddenly became cold, immune regulation of children was poor, and it was easy to cause the onset of allergic rhinitis. As expected, for the total children, we found that the cold spells may significantly increase the risk of AR compared to the non-cold spells period in cold seasons in Hefei. We evaluated the short-term effects of cold spells on AR in children, which was the largest in lag0 day. As the number of days increased, the greatest cumulative effect was at lag0–8 days. The results of this study suggested that extreme cold temperatures may be trigger of allergic rhinitis in children. As for the exact etiology and pathogenesis of children with allergic rhinitis in cold spell period, more clinical studies are needed to discover and confirm.

In the subgroup analysis stratified by gender, we found that male children were more sensitive to cold spells effect than female children. A reasonable explanation for this difference may be as follows: compared to female children, male children may have more outdoor activities that make them more likely to be exposed to cold air. We also performed subgroup analysis stratified by age, and the results showed that children aged 5–18 years were more susceptible to allergic rhinitis during cold spell days, which may be due to the educational activities of the education system or the influence of outdoor activities (H. Kim et al., 2018), and their self-protection awareness is poor, and parents pay less attention. However, for children aged 0–4 years, we did not find out that the cold spells have significant adverse effect on them. A possible cause of the above results is that in the cold season, continuous outdoor cold, especially for cold spells days, which can reduce outdoor activities, and parents may be more cautious about children's health, especially for children with respiratory related symptoms (H. Kim et al., 2018). And according to the results of the stratified analysis by forms of care, compared to scattered children, non-scattered children were susceptible to allergic rhinitis during cold spell days. This may be because most of the children in the non-scattered children were students at school, and educational activities in the education system may expose them to more cold air (H. Kim et al., 2018). Therefore, the susceptible population found in the subgroup analysis can provide important clues for child caregivers to take protective measures. Since this was the first study to explore the effect of cold spells on allergic rhinitis in children, no relevant studies were compared with our findings. Moreover, due to climatic conditions, socio-economic conditions and children's ability to adapt are different in different regions (Xie et al., 2017), therefore further more researches are needed in other regions.

The main advantage of this study was that it was the first time to examine the relationship between cold spells and pediatric outpatient admission for allergic rhinitis in Hefei, China. What's more, we conducted a stratified analysis by gender, age and forms of care, which would be helpful to provide timely interventions for the target population. Meanwhile, the limitations of this study are as follows: First of all, this study was a cross-sectional study, which only reflected the association between cold spells and allergic rhinitis in children and did not reveal any causal associations. Next, this study did not use allergen data (pollen, etc.), which may cause certain bias. In addition, our data on childhood AR cases were only from one city and may not be extrapolated to other areas with different weather patterns. More importantly, we did not know the interaction between cold spells and pollutants, but we had controlled the potential impact of air pollutants. Further studies are needed to clarify the interaction effects of cold spells and air pollutants on children with AR.

5. Conclusions

There was evidence showed that the cold spells may significantly increase the pediatric outpatient admission for allergic rhinitis, especially for male children, children aged 5–18 years and non-scattered children. The optimal definition of cold spells was defined as the daily average temperature for less than 10th with two consecutive days during the study period, which would provide an important reference for the early warning of the disease in our area. Further studies are needed to clarify the relationship between cold spells and allergic rhinitis in children in other areas. These results are important for developing appropriate precautions based on specific circumstances, especially for susceptible populations. For the serious threat posed by cold spells, caregivers and health practitioners should strengthen their awareness of the prevention of vulnerable people.

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Conflict of interest

There were no conflict of interest exists in this manuscript, and manuscript is approved by all authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2019.01.237>.

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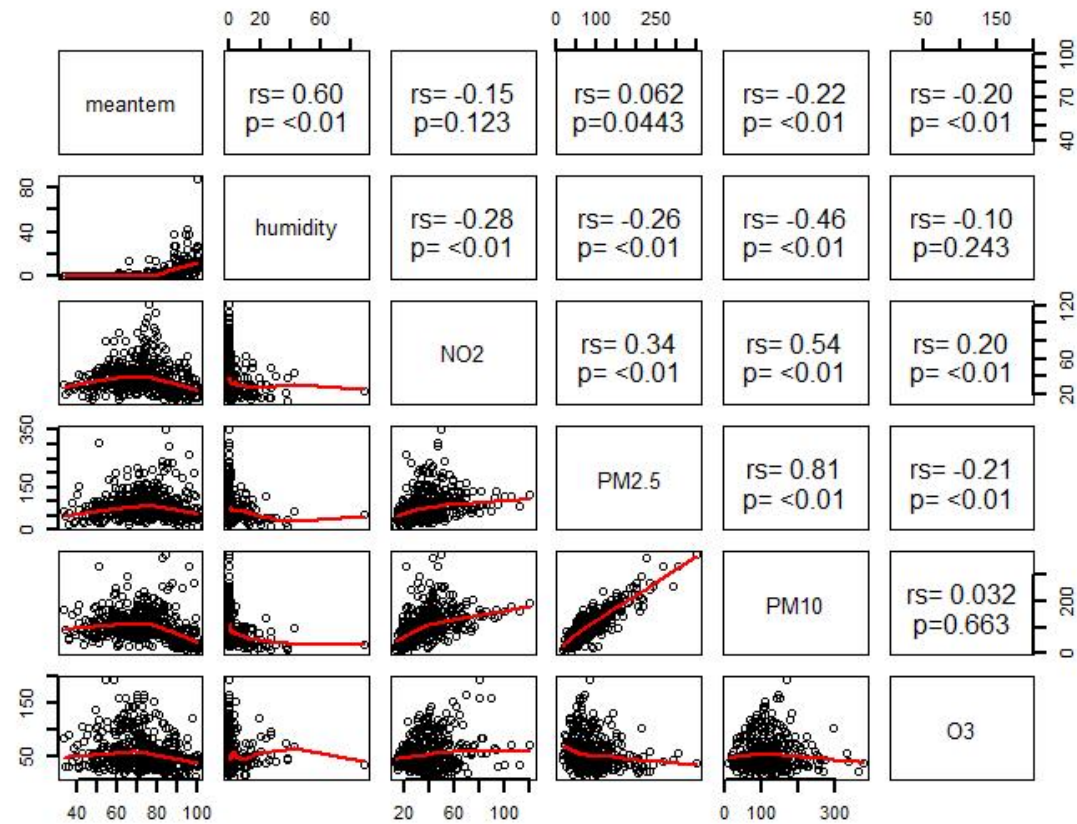


Figure S1. The Spearman correlation coefficients between mean temperature, relative humidity and air pollutions in cold seasons in Hefei, 2014-2016.

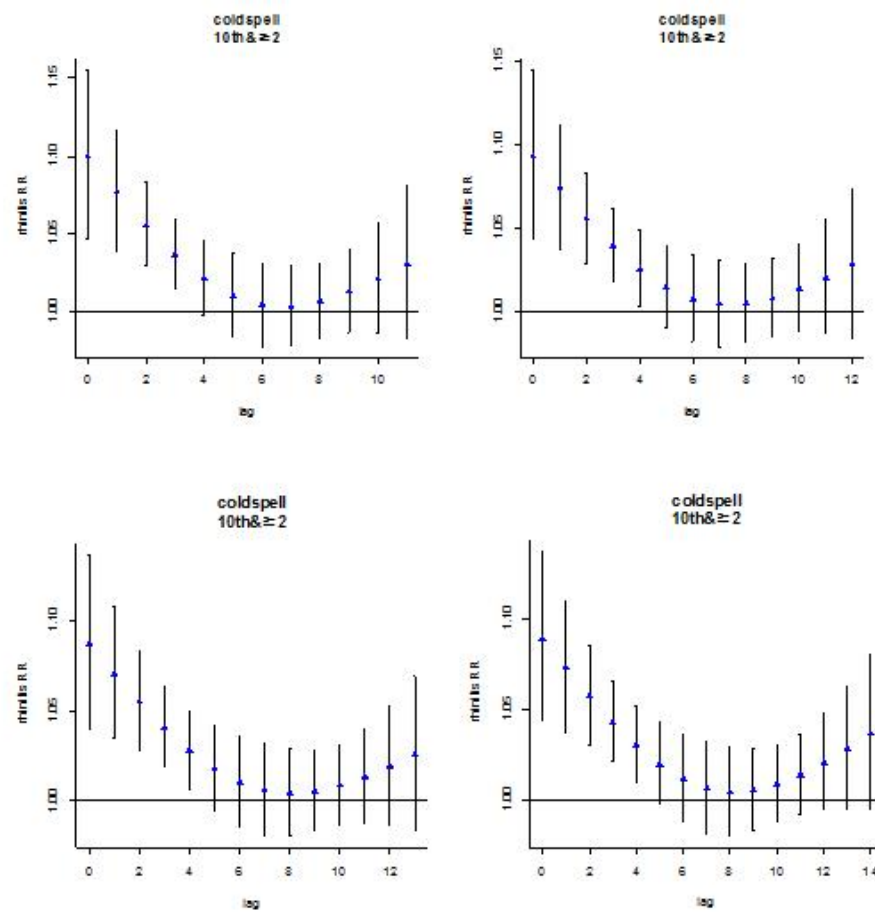


Figure S2. The effect of cold spells on children with allergic rhinitis of different lag days (11-14 days).

Table S1. The single effects of pediatric outpatient admission for allergic rhinitis during cold spells compared with non-cold spell days in cold seasons, 2014-2016.

Group	RR(95% CI)								
	lag0	lag1	lag2	lag3	lag4	lag5	lag6	lag7	lag8
Total	1.125(1.063-1.191)*	1.082(1.044-1.122)*	1.044(1.017-1.072)*	1.015(0.986-1.045)	0.998(0.966-1.031)	0.995(0.966-1.025)	1.004(0.978-1.031)	1.020(0.985-1.056)	1.040(0.984-1.100)
Male	1.146(1.069-1.228)*	1.090(1.044-1.139)*	1.043(1.010-1.077)*	1.007(0.972-1.044)	0.988(0.949-1.028)	0.986(0.951-1.022)	0.999(0.968-1.032)	1.023(0.980-1.067)	1.052(0.983-1.125)
Female	1.088(0.984-1.203)*	1.067(1.002-1.137)*	1.049(1.002-1.098)*	1.033(0.981-1.089)	1.022(0.964-1.084)	1.016(0.964-1.072)	1.015(0.969-1.063)	1.016(0.955-1.081)	1.019(0.925-1.123)
Non-scattered children	1.156(1.075-1.242)*	1.095(1.046-1.146)*	1.043(1.010-1.078)*	1.006(0.969-1.044)	0.986(0.946-1.027)	0.986(0.950-1.024)	1.004(0.971-1.038)	1.034(0.989-1.081)	1.070(0.999-1.147)
Scattered children	1.069(0.973-1.175)	1.054(0.992-1.119)	1.039(0.994-1.086)	1.026(0.977-1.078)	1.016(0.962-1.073)	1.009(0.960-1.061)	1.005(0.962-1.050)	1.002(0.945-1.063)	1.000(0.912-1.097)
0-4 ages	1.062(0.913-1.235)	1.045(0.946-1.154)	1.030(0.955-1.112)	1.020(0.938-1.110)	1.017(0.927-1.115)	1.020(0.937-1.111)	1.301(0.952-1.115)	1.045(0.943-1.158)	1.062(0.910-1.240)
5-18ages	1.128(1.060-1.201)*	1.082(1.041-1.125)*	1.042(1.013-1.072)*	1.012(0.980-1.044)	0.994(0.959-1.030)	0.991(0.960-1.024)	1.001(0.973-1.030)	1.019(0.981-1.058)	1.041(0.980-1.105)

*P<0.05

Table S2. The cumulative effects of pediatric outpatient admission for allergic rhinitis during cold spells compared with non-cold spell days in cold seasons, 2014-2016.

Group	RR(95% CI)								
	lag0	lag01	lag02	lag03	lag04	lag05	lag06	lag07	lag08
Total	1.125(1.063-1.191)*	1.218(1.111-1.334)*	1.271(1.140-1.418)*	1.290(1.145-1.454)*	1.288(1.132-1.465)*	1.282(1.115-1.475)*	1.287(1.107-1.495)*	1.313(1.119-1.540)*	1.366(1.142-1.633)*
Male	1.146(1.069-1.228)*	1.249(1.118-1.396)*	1.303(1.140-1.489)*	1.313(1.135-1.518)*	1.297(1.108-1.517)*	1.279(1.078-1.516)*	1.278(1.064-1.534)*	1.306(1.075-1.587)*	1.374(1.105-1.708)*
Female	1.088(0.984-1.203)	1.161(0.988-1.364)	1.218(1.005-1.476)*	1.258(1.021-1.551)*	1.286(1.026-1.612)*	1.308(1.022-1.673)*	1.327(1.019-1.729)*	1.349(1.017-1.788)*	1.374(1.002-1.885)*
Non-scattered children	1.156(1.075-1.242)*	1.226(1.127-1.421)*	1.320(1.150-1.516)*	1.328(1.143-1.543)*	1.309(1.113-1.539)*	1.291(1.083-1.539)*	1.297(1.074-1.565)*	1.341(1.097-1.638)*	1.435(1.147-1.795)*
Scattered children	1.069(0.973-1.175)	1.127(0.968-1.311)	1.170(0.976-1.404)	1.201(0.984-1.466)	1.221(0.984-1.515)	1.232(0.974-1.559)	1.238(0.961-1.595)	1.241(0.947-1.626)	1.241(0.917-1.681)
0-4 ages	1.062(0.913-1.235)	1.109(0.867-1.419)	1.143(0.846-1.544)	1.166(0.833-1.633)	1.185(0.816-1.722)	1.210(0.800-1.829)	1.247(0.795-1.955)	1.303(0.801-2.120)	1.384(0.801-2.391)
5-18ages	1.128(1.060-1.201)*	1.221(1.105-1.349)*	1.272(1.129-1.433)*	1.287(1.131-1.464)*	1.279(1.113-1.470)*	1.268(1.090-1.474)*	1.269(1.080-1.491)*	1.292(1.088-1.535)*	1.345(1.110-1.631)*

*P<0.05

Table S3. The sensitivity analysis about the changes of *df* for calendar time (4-6) for allergic rhinitis during cold spells in cold seasons.

lag	RR (95%CI)		
	<i>df</i> =4	<i>df</i> =5	<i>df</i> =6
lag0	1.074(1.019-1.132)*	1.118(1.059-1.182)*	1.125(1.063-1.191)*
lag1	1.044(1.011-1.077)*	1.076(1.040-1.114)*	1.082(1.044-1.122)*
lag2	1.017(0.995-1.040)	1.039(1.014-1.065)*	1.044(1.017-1.072)*
lag3	0.996(0.969-1.024)	1.011(0.982-1.040)	1.015(0.986-1.045)
lag4	0.983(0.953- 0.95)	0.994(0.962-1.026)	0.998(0.966-1.031)
lag5	0.979(0.952-1.007)	0.990(0.962-1.019)	0.995(0.966-1.025)
lag6	0.983(0.959-1.007)	0.997(0.972-1.022)	1.004(0.978-1.031)
lag7	0.991(0.960-1.024)	1.011(0.977-1.045)	1.020(0.985-1.056)
lag8	1.002(0.951-1.056)	1.029(0.975-1.086)	1.040(0.984-1.100)
lag01	1.121(1.032-1.218)*	1.204(1.103-1.314)*	1.218(1.111-1.334)*
lag02	1.140(1.035-1.255)*	1.251(1.128-1.388)*	1.271(1.140-1.418)*
lag03	1.136(1.026-1.257)*	1.265(1.131-1.415)*	1.290(1.145-1.454)*
lag04	1.116(1.002-1.243)*	1.257(1.114-1.418)*	1.288(1.132-1.465)*
lag05	1.093(0.973-1.228)	1.244(1.092-1.418)*	1.282(1.115-1.475)*
lag06	1.074(0.950-1.214)	1.240(1.079-1.426)*	1.287(1.107-1.495)*
lag07	1.065(0.937-1.210)	1.253(1.082-1.452)*	1.313(1.119-1.540)*
lag08	1.067(0.926-1.230)	1.289(1.095-1.518)*	1.366(1.142-1.633)*

**P*<0.05

Table S4. The sensitivity analysis about the changes of df for relative humidity (3-5) for allergic rhinitis during cold spells in cold seasons.

lag	<i>RR</i> (95% <i>CI</i>)		
	$df=3$	$df=4$	$df=5$
lag0	1.128(1.069-1.190)*	1.118(1.058-1.181)*	1.125(1.063-1.191)*
lag1	1.075(1.039-1.113)*	1.071(1.035-1.109)*	1.082(1.044-1.122)*
lag2	1.030(1.005-1.056)*	1.031(1.006-1.057)*	1.044(1.017-1.072)*
lag3	0.997(0.969-1.025)	1.002(0.974-1.030)*	1.015(0.986-1.045)*
lag4	0.979(0.949-1.010)	0.986(0.955-1.018)	0.998(0.966-1.031)
lag5	0.979(0.952-1.007)	0.987(0.958-1.016)	0.995(0.966-1.025)
lag6	0.995(0.971-1.019)	1.001(0.975-1.027)	1.004(0.978-1.031)
lag7	1.021(0.988-1.054)	1.024(0.990-1.060)	1.020(0.985-1.056)
lag8	1.052(0.999-1.107)	1.053(0.998-1.110)	1.040(0.984-1.100)
lag01	1.213(1.112-1.324)*	1.197(1.096-1.308)*	1.218(1.111-1.334)*
lag02	1.250(1.126-1.387)*	1.235(1.111-1.372)*	1.271(1.140-1.418)*
lag03	1.246(1.111-1.396)*	1.237(1.103-1.387)*	1.290(1.145-1.454)*
lag04	1.219(1.078-1.340)*	1.220(1.077-1.381)*	1.288(1.132-1.465)*
lag05	1.194(1.044-1.366)*	1.203(1.051-1.378)*	1.282(1.115-1.475)*
lag06	1.188(1.029-1.372)*	1.204(1.040-1.394)*	1.287(1.107-1.495)*
lag07	1.212(1.040-1.413)*	1.233(1.054-1.443)*	1.313(1.119-1.540)*
lag08	1.276(1.076-1.512)*	1.298(1.087-1.549)*	1.366(1.142-1.633)*

* $P<0.05$

Table S5. The sensitivity analysis about the changes of df for O_3 (3-5) for allergic rhinitis during cold spells in cold seasons.

lag	<i>RR</i> (95% <i>CI</i>)		
	<i>df</i> =3	<i>df</i> =4	<i>df</i> =5
lag0	1.106(1.046-1.170)*	1.112(1.051-1.177)*	1.125(1.063-1.191)*
lag1	1.069(1.032-1.108)*	1.074(1.036-1.113)*	1.082(1.044-1.122)*
lag2	1.037(1.011-1.064)*	1.041(1.015-1.069)*	1.044(1.017-1.072)*
lag3	1.013(0.984-1.043)*	1.016(0.987-1.046)	1.015(0.986-1.045)
lag4	0.999(0.967-1.032)	1.002(0.970-1.035)	0.998(0.966-1.031)
lag5	0.998(0.969-1.028)	1.000(0.971-1.030)	0.995(0.966-1.025)
lag6	1.006(0.981-1.032)	1.009(0.983-1.035)	1.004(0.978-1.031)
lag7	1.022(0.988-1.057)	1.024(0.990-1.059)	1.020(0.985-1.056)
lag8	1.041(0.987-1.098)	1.043(0.988-1.101)	1.040(0.984-1.100)
lag01	1.183(1.081-1.294)*	1.195(1.090-1.309)*	1.218(1.111-1.334)*
lag02	1.227(1.102-1.365)*	1.244(1.115-1.387)*	1.271(1.140-1.418)*
lag03	1.243(1.106-1.396)*	1.264(1.123-1.423)*	1.290(1.145-1.454)*
lag04	1.242(1.094-1.408)*	1.266(1.114-1.439)*	1.288(1.132-1.465)*
lag05	1.239(1.079-1.421)*	1.266(1.101-1.456)*	1.282(1.115-1.475)*
lag06	1.246(1.075-1.446)*	1.277(1.099-1.484)*	1.287(1.107-1.495)*
lag07	1.273(1.087-1.491)*	1.308(1.115-1.534)*	1.313(1.119-1.540)*
lag08	1.325(1.111-1.581)*	1.364(1.142-1.631)*	1.366(1.142-1.633)*

* $P < 0.05$

Table S6. The sensitivity analysis about the changes of df for NO₂ (3-5) for allergic rhinitis during cold spells in cold seasons.

lag	RR (95%CI)		
	$df=3$	$df=4$	$df=5$
lag0	1.141(1.079-1.207)*	1.135(1.073-1.201)*	1.125(1.063-1.191)*
lag1	1.091(1.054-1.131)*	1.089(1.051-1.128)*	1.082(1.044-1.122)*
lag2	1.049(1.022-1.076)*	1.049(1.022-1.076)*	1.044(1.017-1.072)*
lag3	1.016(0.987-1.046)	1.018(0.989-1.048)	1.015(0.986-1.045)
lag4	0.996(0.965-1.029)	0.999(0.967-1.032)	0.998(0.966-1.031)
lag5	0.992(0.964-1.022)	0.995(0.966-1.025)	0.995(0.966-1.025)
lag6	1.001(0.975-1.027)	1.003(0.977-1.030)	1.004(0.978-1.031)
lag7	1.017(0.982-1.053)	1.019(0.984-1.055)	1.020(0.985-1.056)
lag8	1.039(0.983-1.097)	1.039(0.984-1.098)	1.040(0.984-1.100)
lag01	1.245(1.138-1.362)*	1.236(1.129-1.353)*	1.218(1.111-1.334)*
lag02	1.306(1.173-1.453)*	1.296(1.164-1.443)*	1.271(1.140-1.418)*
lag03	1.326(1.181-1.490)*	1.319(1.174-1.482)*	1.290(1.145-1.454)*
lag04	1.321(1.165-1.498)*	1.318(1.162-1.494)*	1.288(1.132-1.465)*
lag05	1.311(1.144-1.503)*	1.312(1.144-1.504)*	1.282(1.115-1.475)*
lag06	1.312(1.133-1.520)*	1.316(1.136-1.525)*	1.287(1.107-1.495)*
lag07	1.335(1.141-1.562)*	1.342(1.146-1.570)*	1.313(1.119-1.540)*
lag08	1.386(1.161-1.654)*	1.394(1.167-1.665)*	1.366(1.142-1.633)*

* $P<0.05$

Table S7. The sensitivity analysis about the changes of df for PM₁₀ (3-5) for allergic rhinitis during cold spells in cold seasons.

lag	<i>RR</i> (95% <i>CI</i>)		
	<i>df</i> =3	<i>df</i> =4	<i>df</i> =5
lag0	1.135(1.075-1.199)*	1.126(1.065-1.191)*	1.125(1.063-1.191)*
lag1	1.092(1.055-1.130)*	1.082(1.045-1.121)*	1.082(1.044-1.122)*
lag2	1.054(1.028-1.081)*	1.044(1.018-1.072)*	1.044(1.017-1.072)*
lag3	1.025(0.996-1.054)	1.015(0.986-1.045)	1.015(0.986-1.045)
lag4	1.006(0.974-1.039)	0.998(0.966-1.031)	0.998(0.966-1.031)
lag5	0.999(0.970-1.029)	0.995(0.966-1.025)	0.995(0.966-1.025)
lag6	1.002(0.976-1.029)	1.003(0.977-1.029)	1.004(0.978-1.031)
lag7	1.012(0.977-1.048)	1.019(0.984-1.055)	1.020(0.985-1.056)
lag8	1.025(0.971-1.082)	1.039(0.983-1.097)	1.040(0.984-1.100)
lag01	1.240(1.136-1.353)*	1.219(1.115-1.333)*	1.218(1.111-1.334)*
lag02	1.307(1.178-1.450)*	1.273(1.143-1.417)*	1.271(1.140-1.418)*
lag03	1.339(1.196-1.499)*	1.292(1.149-1.452)*	1.290(1.145-1.454)*
lag04	1.347(1.192-1.522)*	1.289(1.136-1.464)*	1.288(1.132-1.465)*
lag05	1.345(1.177-1.538)*	1.283(1.116-1.473)*	1.282(1.115-1.475)*
lag06	1.348(1.167-1.558)*	1.286(1.108-1.493)*	1.287(1.107-1.495)*
lag07	1.364(1.168-1.594)*	1.310(1.117-1.536)*	1.313(1.119-1.540)*
lag08	1.399(1.173-1.668)*	1.361(1.138-1.627)*	1.366(1.142-1.633)*

* $P < 0.05$