



Risk effects of high and low relative humidity on allergic rhinitis: Time series study

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ARTICLE INFO

Keywords:

Allergic rhinitis

DLNM

Relative humidity

ABSTRACT

Background: The relationship between environmental factors and allergic rhinitis (AR) has become a focal point recently. However, few studies have investigated the adverse effects of both high relative humidity (RH) and low relative humidity. Moreover, the lagged effect and disease burden of RH on AR were also neglected.

Objectives: To explore the association of both high and low RH on daily AR hospital outpatients, and to quantify the corresponding disease burden attributable to RH.

Methods: In our study, we define 95th as high RH and 5th as low RH. A distributed lag non-linear model (DLNM) combined with a Poisson generalized linear regression model were applied to analyze the relationship between RH and hospital outpatients for AR. All patients were retrieved from Anhui Provincial Children's Hospital (n = 37,221) from January 2015 to December 2016. Daily meteorological and air pollutant data were collected by Hefei Meteorological Bureau and Environmental Protection Agency. Subgroup analyses were conducted by gender and occupational groups.

Results: Acute adverse effects of high and low RH on AR were explored respectively, with an increase of daily AR outpatients when encountered high and low RH. The low RH presented a risk effect at current day and lasted up to the eighth day. However, high RH began to appear a risk effect on the fourth day. Notably, the fraction of hospital outpatients attributable to low RH was 5.22% (95% CI: 1.92%, 8.33%) and high RH was 4.07% (95% CI: 1.13%, 7.30%) in the backward perspective. Additionally, male and students appear to be more sensitive to the effects of low RH.

Conclusion: This study suggests that both high and low RH are potential trigger for AR hospital outpatients in Hefei, China. Our studies might offer valuable messages to health practitioners and useful direction to decision-makers respectively.

1. Introduction

Allergic rhinitis (AR) is one of the most common allergic disorders (Casale TB and MS., 2004; Feng et al., 2017), a chronic inflammatory reaction of the nasal mucosa, often accompanied by sneezing, flowing nose, nasal itching and nasal congestion (Lai et al., 2005). It was estimated that nearly 10%–25% of the world's population was suffering from AR every year. Over the past few decades, the morbidity of AR has risen worldwide (von Mutius et al., 2006; Wang et al., 2016; Zhang and Zhang., 2014). Most of the reports indicated that genetic and environmental factors were crucial reasons for its incidence (Wang et al., 2015;

Zihlif et al., 2013). As the mechanism of genetic factors were more stable but uncontrollable, many environment factors gradually attracted more and more attention (Ganiban et al., 2007). But, with the development of the hygiene hypothesis, risk factors about environmental exposure for AR have become gradually difficult and complex to interpret (Martinez, 2001).

Recently, more and more attention has been paid to the influence of environmental factors on AR (Lin and Zacharek, 2012). As a crucial indicator of meteorological factor, relative humidity (RH) has been gradually used to explore the risk effects on AR. Jo et al. found that a significant increase in AR cases with lower RH (Jo et al., 2017), but the

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<https://doi.org/10.1016/j.envres.2019.03.040>

Received 4 December 2017; Received in revised form 1 January 2019; Accepted 17 March 2019

Available online 19 March 2019

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risk of specific humidity range values were not mentioned. In America, Silverberg et al. found that rhinitis prevalence was significantly with lower RH (first quartile (24.3%, 62.8%) logistic regression, $P < 0.01$). At the same time, they also found that high RH were also associated with a higher morbidity of rhinitis. (Silverberg et al., 2015). However, the lagged effect of RH on AR was neglected. Additionally, another study even found no significant association between humidity and AR in Australian (Hughes et al., 2011), which possibly indicated that the RH effects may depend on different geographical environments. Thus, it still not clear whether both high and low RH could increase the risk of AR onset in our area.

The present study aims to examine the relationship between RH and hospital outpatients for AR, and explore the possible modification of the RH-AR associations by individual characteristics.

2. Materials and methods

2.1. Study area

We carried out this study in Hefei, a city with rapid political, economic, cultural development, located in central China (32°52'N, 117°17'E), between the Yangtze River and the Huaihe River. The total area of the city's administrative region is 11408.48 square kilometers (including Chaohu water area of 769.5 square kilometers). It belongs to the subtropical humid monsoon climate.

2.2. Data collection

The daily AR outpatients were collected by Anhui Provincial Children's Hospital from the period of January 1, 2015 to December 31, 2016, and we only included children living in the Hefei area. The cases were incorporated according to the International Classification of Disease, 10th version (ICD-10) for allergic rhinitis (ICD-10, J30). They were classified as sex and occupational groups. Daily meteorological data, such as relative humidity (%), mean wind (m/s), and mean temperature (°C) 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 $PM_{2.5}$ ($\mu g/m^3$), SO_2 ($\mu g/m^3$) and NO_2 ($\mu g/m^3$).

The study was approved by the University of Anhui Medical Research Ethics Committee.

2.3. Statistical analysis

We used distributed lag non-linear model (DLNM) combined with a Poisson generalized linear regression model to evaluate the effect of RH on AR (Gasparrini et al., 2017). A model was designed, in which long-term trend, day of week (DOW), $PM_{2.5}$, mean temperature, mean wind speed, public holiday and seasonality were regarded as the potential confounders. Accounting for the lowest Akaike Information Criterion (AIC), 9 days lag were designed to show the immediately and cumulative effects about RH on AR. The model is as follow:

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

$$\text{Log}(\mu_t) = \alpha + \beta \text{Humidity}_{t,l} + \text{ns}(\text{Mean temperature}_{t,l}, 5) + \text{ns}(\text{Mean wind speed}_{t,l}, 5) + \text{ns}(PM_{2.5,t,l}, 4) + \text{ns}(\text{Time}_t, 8) + \eta \text{DOW}_t + \nu \text{Holiday}_t$$

In our model, where t was the day under surveillance. μ_t was the daily AR patients on day t . l was the lag days. α was the model intercept. $\text{Humidity}_{t,l}$, $\text{Mean temperature}_{t,l}$, $\text{Mean wind speed}_{t,l}$ and $PM_{2.5,t,l}$ were the cross-basis matrix generated by DLNM, β was vector of coefficients for $\text{Humidity}_{t,l}$. $\text{ns}()$ describes a natural cubic spline. Accounting for the lowest AIC, the degree of freedom was five (5df) that was used to adjust for $\text{Mean temperature}_{t,l}$ and $\text{Mean wind speed}_{t,l}$. The degree of freedom was four (4df) that was used to adjust for $PM_{2.5,t,l}$.

Long-term trend and seasonality were controlled by the 8df per year for time. DOW was also controlled as a categorical variable with a reference day of Sunday. In all cases, the AIC and analysis of residuals were used to assess the model fit and choice of df, and to check the autocorrelation of the model (Barnett et al., 2017).

We plotted the relationship between RH and AR outpatients for more intuitive expression after the basic model was designed. To show the risk effects of RH on AR, we counted the RRs at specific RH (5th and 95th percentiles), compared to the reference RH (64%–76% percentiles). Compared with the previous study (median as a reference value), the method can reduce the bias and then better evaluate the relationship between RH and AR (Guo et al., 2011). The effects of lag were investigated with specific days (from lag 0 to lag 9) and cumulative lag days (lag 0–0 to lag 0–9).

Specifically, RH and lagged effects were comprised using a “natural cubic spline–natural cubic spline” method. The DLNM included lags up to 9 days for other confounders (e.g., Mean temperature, Mean wind speed $PM_{2.5}$, SO_2 , and NO_2).

Under the framework of DLNM, attributable fraction of hospital outpatients about AR for high and low RH were calculated. We selected the minimum value as the reference to calculate the attributable risk and 95% confidence interval (CI) of attributable fraction were obtained by applying Monte Carlo simulating method, which is in detail described elsewhere (Gasparrini and Leone, 2014).

In addition, we carried on subgroup analyses by gender (male and female) and occupational group (kindergarten children, scattered children and students).

To check the robustness of our findings, sensitivity analysis was carried out by changing the freedom of calendar day (6–8 df/year), mean temperature (3–5 df), mean wind speed (3–5 df) and $PM_{2.5}$ (3–5 df) in the DLNM. Additionally, we perform sensitivity analyses to put NO_2 and SO_2 , respectively. We used the R statistical environment (version 3.3.3) with the “dlnm” package to fit the regression model to all data analysis (Gasparrini et al., 2010). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Result

3.1. Data description

During period of our study, a total of 37221 cases for AR were included during January 1, 2015 to December 31, 2016 in our analyses. More patients were male (25039 cases, 67.27%). The average values of daily mean temperature, RH, mean wind speed, and $PM_{2.5}$ were 16.7 °C, 73.7%, 1.9 m/s and 61.6 $\mu g/m^3$.

Summary statistics for contaminants, meteorological variables and AR outpatients were presented in Table 1. The correlation coefficient was not beyond 0.6, showing that we can put them into the subsequent modeling for analysis (Supplementary Figure. 1.).

3.2. Overall effects

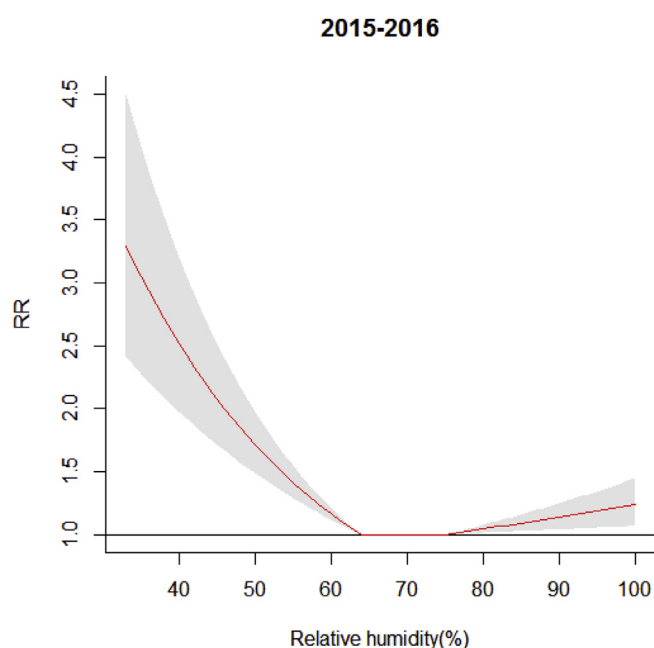
An overall picture of the effect of RH on AR was revealed in Fig. 1, shown the RRs along RH compared to a reference range (corresponding to the 64%–76%). A vital effect of RH was observed. It presented negative correlation between RH and AR under 64th percentile. After going to 76th percentile and latter, it showed positive correlation. Additionally, the effect of RH was more significantly from 33% to 64% on AR.

Accounting for clearly reflecting the relationship between RH and lag on AR, we plotted the single-day lagged effects at 9 days (Fig. 2). The lagged effect of low RH appeared on the first day and lagged up to the eighth day on AR hospital outpatients, but the effect of high RH began to emerge on the fourth day. More detailed information was presented in the Appendix Table 1.

Table 1

Summary statistics for daily weather condition, pollution condition and AR counts of Hefei, China, 2015–2016.

Group	sum	Mean $\pm$ SD	min	max	Frequency distribution						
					p (5)	P (10)	P (25)	(P50)	P (75)	P (90)	p (95)
Relative humidity (%)	/	75.8 $\pm$ 12.6	33	100	52.5	59.0	68.0	76.0	85.0	93.0	95.0
Mean temperature (°C)	/	16.9 $\pm$ 9.0	−5.9	33.7	2.6	4.3	8.9	18.0	24.4	27.8	30.3
Mean wind (m/s)	/	1.9 $\pm$ 0.8	0.8	5.9	0.9	1.1	1.4	1.8	2.3	3.0	3.3
PM _{2.5} (μg/m ³)	/	61.6 $\pm$ 36.2	6	242	20	25	37	54	77	107	131
Total	37221	50.9 $\pm$ 18.7	0	116	26.5	30.0	38.0	48.0	60.0	80.0	87.0
Male	25039	34.3 $\pm$ 13.4	0	82	17	20	25	32	42	54	61
Female	12182	16.7 $\pm$ 6.7	0	40	7	9	12	16	21	26	29
Kindergarten children	11503	15.7 $\pm$ 6.2	0	43	7	9	12	15	19	28	28
Scattered children	13892	19.0 $\pm$ 7.3	0	47	8	10	14	18	24	29	32
Students	11826	16.2 $\pm$ 10.6	0	54	4	5	8	13	23	37	37

**Fig. 1.** Overall effects of exposure-response associations between RH and AR hospital admissions occurrence in Hefei, 2015–2016.

3.3. Effects of cumulative lagged effects on specific percent

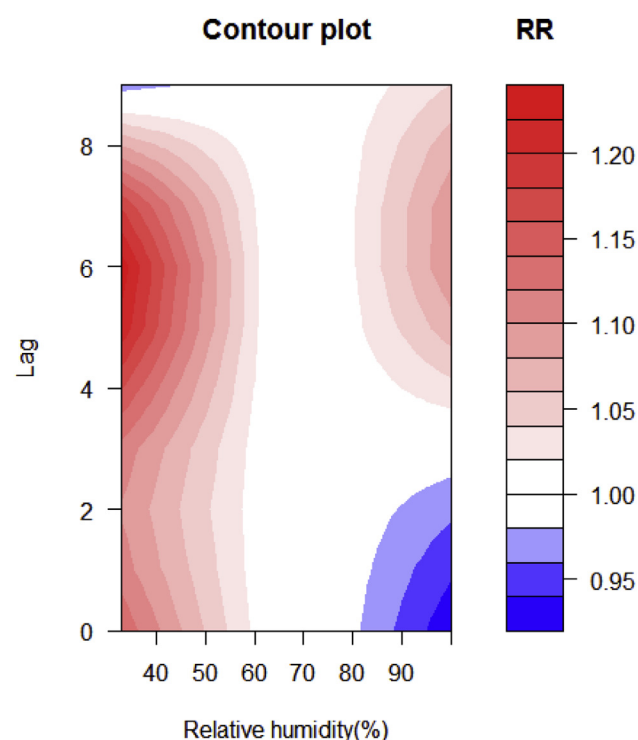
Table 2 showed the RRs of both high and low RH on AR onset over different lagged days through calculating the 95th and 5th percentiles relative to the reference 64%–76%. For the cumulative lagged effects, the 5th percentile humidity occurred the risk effects immediately. For the 95th percentile, the risk effects began to appear on the eighth day.

3.4. Attributable risk

The comparison of the two contributions clearly indicates that low RH might be responsible for most of hospital outpatients for AR attributable to RH, with backward equal to 5.22% (95% CI: 1.92%, 8.33%) and 4.07% (95% CI: 1.13%, 7.30%) for high RH. Estimates of forward attributable risk are very similar, and as expected their sum is equal to the overall burden (Fig. 3).

3.5. Subgroup analyses

In our subgroup, it showed that the lagged effect on AR by different genders and occupational groups, comparing the 95th percentile (93%) and the 5th percentile (53%) to the 64%–76%. For low humidity, male seemed to be more sensitive to the effects of low RH, compared with

**Fig. 2.** A contour plot of the relative risks (RR) of AR hospital admissions along the RH (with reference at 64%–76%) and lag periods. Here the legends respectively (from the left) are: lag periods, RH, and levels of relative risks (RR).**Table 2**

Relative risks of AR cases for specific RH (5th and 95th percentiles) at various lag days, with the reference value of 64%–76%.

Multi-day lag	Cumulative effects	
	95 th percentile (93%)	5 th percentile (5%)
0–0	0.95 (0.92, 0.97)	1.05 (1.02, 1.08) ^a
0–1	0.91 (0.87, 0.95)	1.09 (1.03, 1.14) ^a
0–2	0.89 (0.83, 0.94)	1.12 (1.06, 1.23) ^a
0–3	0.88 (0.82, 0.94)	1.17 (1.10, 1.24) ^a
0–4	0.90 (0.83, 0.98)	1.23 (1.15, 1.32) ^a
0–5	0.95 (0.87, 1.03)	1.32 (1.22, 1.42) ^a
0–6	1.01 (0.92, 1.11)	1.42 (1.30, 1.54) ^a
0–7	1.08 (0.98, 1.19)	1.50 (1.37, 1.65) ^a
0–8	1.14 (1.03, 1.26) ^a	1.54 (1.40, 1.71) ^a
0–9	1.17 (1.05, 1.30) ^a	1.53 (1.37, 1.71) ^a

^a P < 0.05.

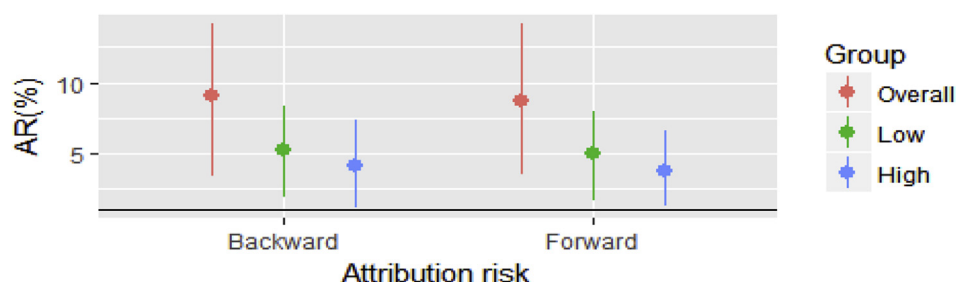


Fig. 3. Total AR hospital admissions fraction (%) attributable to RH, computed backward and forward, showed as components from low RH and high RH with 95% confidence intervals (CI).

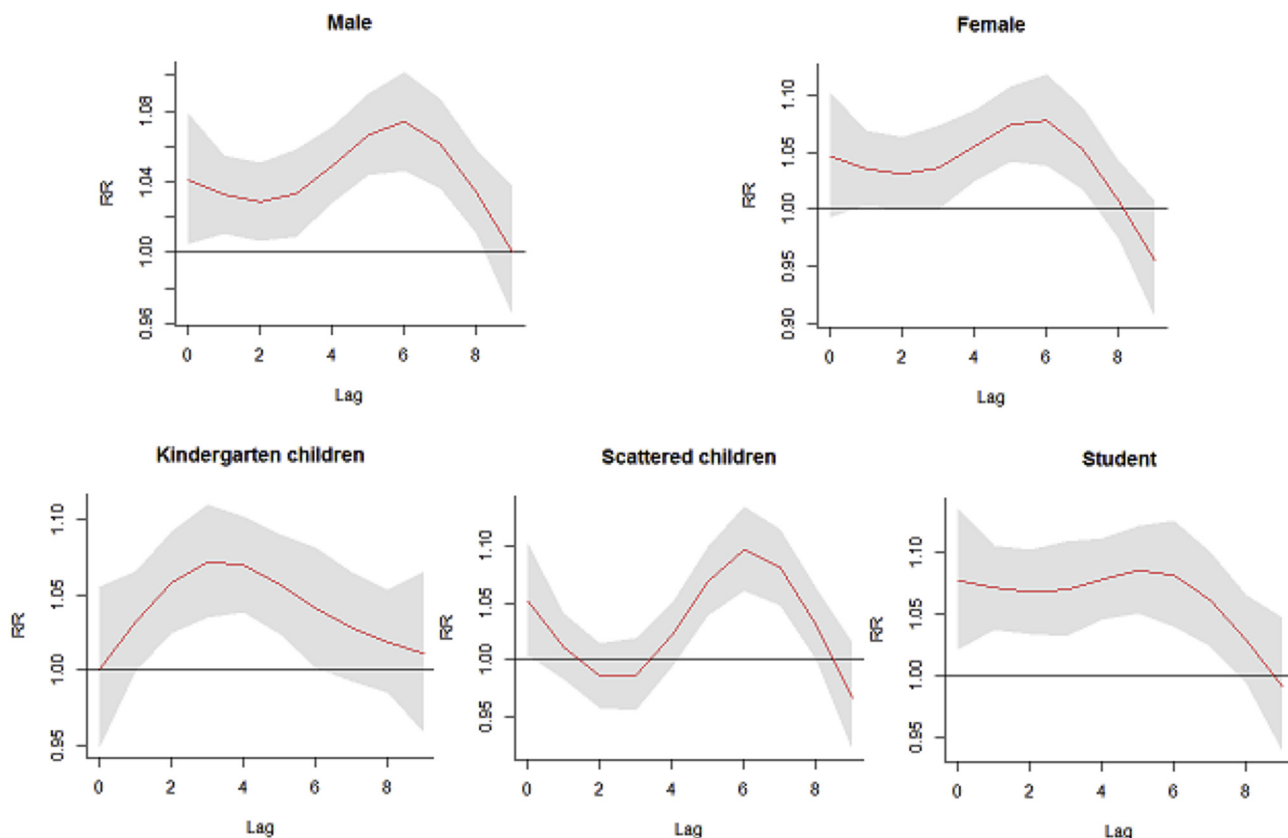


Fig. 4. Lag-specific effects on AR hospital admissions by gender, kindergarten children, scattered children, and students at 5th percentile of RH (reference at 64%–76%).

female patients. When stratified by kindergarten children, scattered children and student groups, significantly association was observed on students. However, for high RH, there were no obvious differences among different groups (Fig. 4 and Fig. 5).

3.6. Sensitivity analyses

Sensitivity analyses were conducted to affirm whether our results were robust to the specification of variables and model selection in this model. We conducted the following sensitivity analyses: (1) varying the df (6–8 per year) for time to adjust for seasonality and long-term trend; (2) modifying (3–5) df for mean wind speed, mean temperature, and pollutants. (Supplementary Fig. S2–S7). Additionally, Supplementary Fig. S8 shows that there was no apparent autocorrelation of model residuals, and Supplementary Fig. S9 indicates that model residuals were independent over time.

4. Discussion

In the present study, we explored both the non-linear and lagged effects of RH on hospital outpatients for AR in Hefei, China, and yielded several notable findings. It indicated that both high and low RH were statistically associated with AR hospital outpatients in Hefei, China. In general, the effect of low RH on AR hospital outpatients emerged on the current day, but the effect of high RH began to appear on the fourth day. Moreover, the attributable risk of low RH was higher than high RH.

Previous studies have reported the relationship between RH and AR hospital outpatients, and the results was inconsistent. For example, a Turkey study documented that low RH was connected to an increased risk of AR outpatients (Yalcin et al., 2013). However, another study in America found that high RH might be regarded as a potential risk factor for AR onset (Silverberg et al., 2015). In this study, we found the risk effects of both high and low RH on AR, especially at lower RH under 64%. Therefore, it is noticeable that the risk effects of both high and low RH on AR hospital outpatients might be presented in the Hefei area,

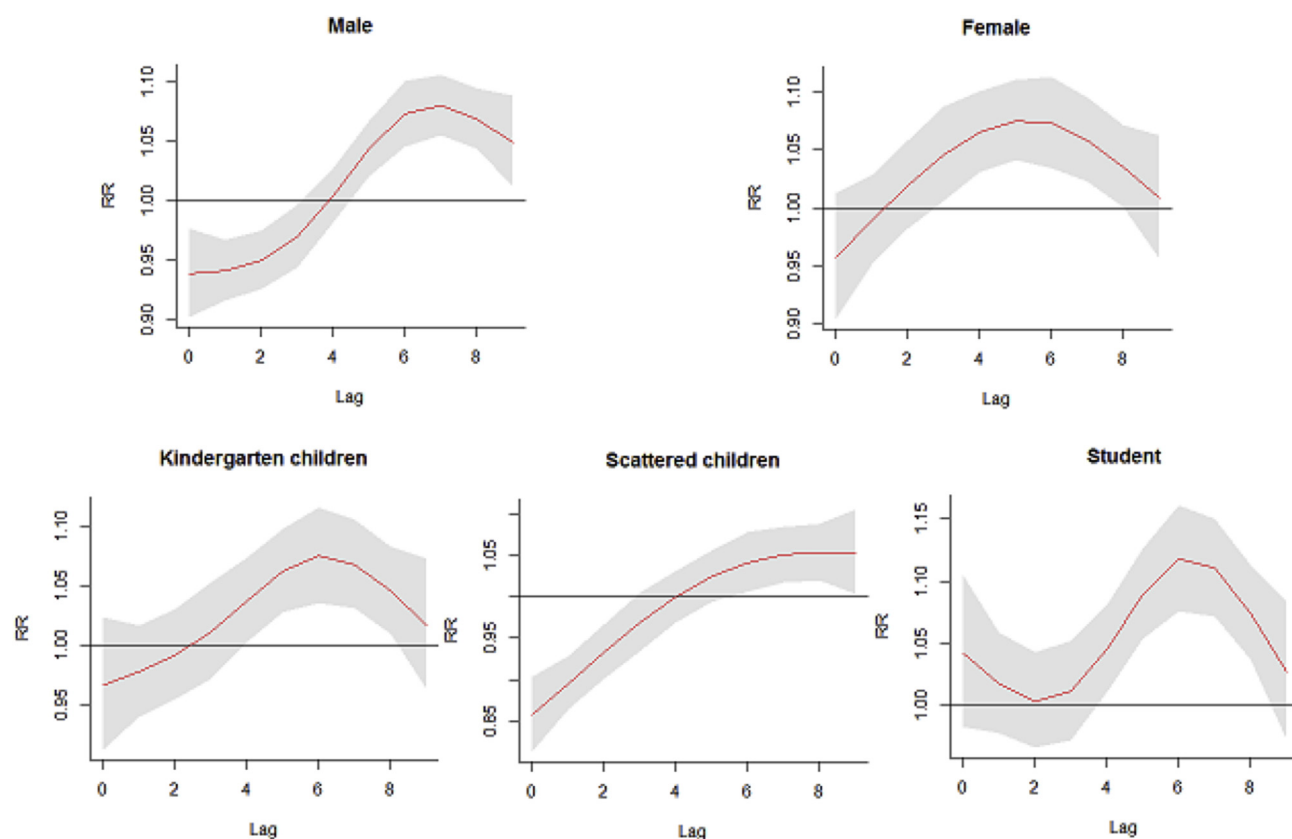


Fig. 5. Lag-specific effects on AR hospital admissions by gender, kindergarten children, scattered children, and students at 95th percentile of RH (reference at 64%–76%).

and this issue should be researched in the future.

The relationship between RH and AR outpatients was investigated by only a few studies, which confined us to straightly compare the results with others. Liu et al. reported that the effect of RH may be the risk factor on AR (Liu et al., 2014). However, in California, Shusterman et al. found that the risk of AR onset attributed to RH decreased (Shusterman, 2016). Both they were not provided the impact of RH about specific risk range on AR. Few studies have emphasized the information about potential delayed effects. Additionally, there are some considerable factors that can explain for the different results in these studies, such as sampling window of environmental variables, geographical location, cohort, sample size and so on. In order to better capture the effects of RH on AR, DLNM was used to quantify both delayed effects and non-linear exposure-response relationship.

In our study, both high and low RH were risk factors. This may be due to following reasons. Firstly, in the case of low humidity, it was conducive to the spread of many allergens (Jones and Harrison, 2004), led to nasal injury and reduce the barrier role of nasal mucosa to allergen. Secondly, for high RH, it was beneficial to the growth and reproduction of allergen (Zhang et al., 2016). Many researches have shown that allergens has a great harmful effect on AR, and humidity can also change concentration and activity of pollen, fungus and other inhaled allergen, then induced AR (Bernstein et al., 2005; He et al., 2015). By our overall effect diagram, we caught the risk effect of low humidity may higher than high RH, suggesting a role of allergen release and dispersion as a higher risk factor for AR onset.

In our subgroup analysis, for different sex susceptibility to allergic rhinitis, the conclusions were inconsistent. Studies have shown that under low humidity conditions, the incidence of females was higher than that of males (Yalcin et al., 2013), and there was also the opposite conclusion of the study (Lee et al., 2003). In our study, Male patients presented to be more vulnerable to the low RH, which might play

outdoors activities more often or be partly due to differential body composition and thus exposed more to the outdoor RH change.

This study further revealed that students were more sensitive to RH-related AR outpatients than other groups. They may be more active and accessible to more allergens, compared with kindergarten children and scattered children. In addition, as the academic burden increases, students are under greater psychological pressure, which might be a potential factor.

Several strengths of our study should be mentioned. Firstly, to our knowledge, this study was better to quantify the RH and investigate both high and low RH on AR. Secondly, through DLNM, we controlled several important mixed factors (mean temperature, mean wind speed, $PM_{2.5}$, SO_2 and NO_2) to explore the lagged effect.

Nevertheless, there are some limitations as follows. Firstly, This is an ecological study, and thus some biases due to exposure misclassification may be inevitable. Secondly, we only included data from a representative children's hospital in Hefei, which means that our findings should be generalized to other regions with caution. However, the findings of this study may encourage a large scale and multi-centre study in future researches.

5. Conclusion

Our study provides evidence that both high and low RH were significantly associated with AR. Low RH had greater risk effects on AR outpatients in different groups. So, a better health alert system is indispensable to decrease the AR morbidity. We are eager to hope that guardian, medical staff and public health sector should take appropriate measures to control and prevent AR onset when encountered unsuitable RH.

Conflicts of interest

The authors declared no competing interest.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81773518).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2019.03.040>.

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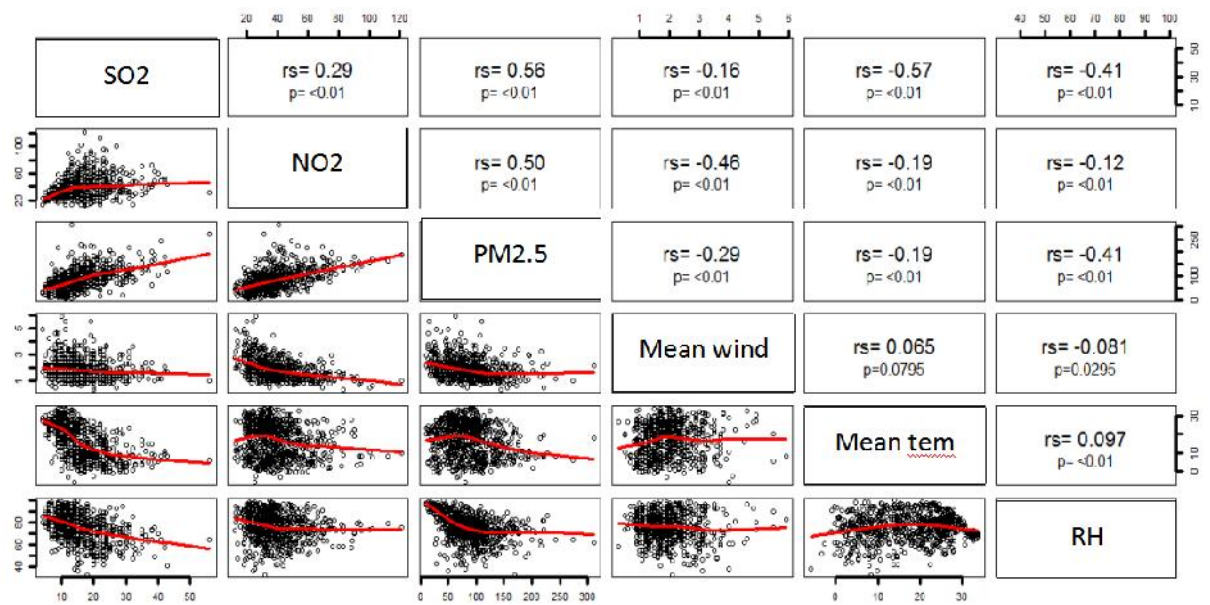


Fig. S1. Spearman's correlation between daily weather conditions, air pollutants and allergic rhinitis in Hefei, China, from 2015–2016.

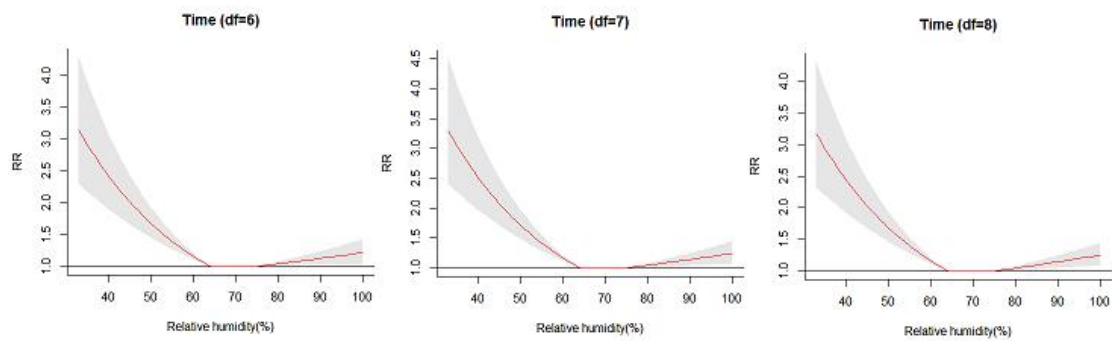


Fig. S2. The overall effects of RH on AR when varying the df (6-8 df/year) for time.

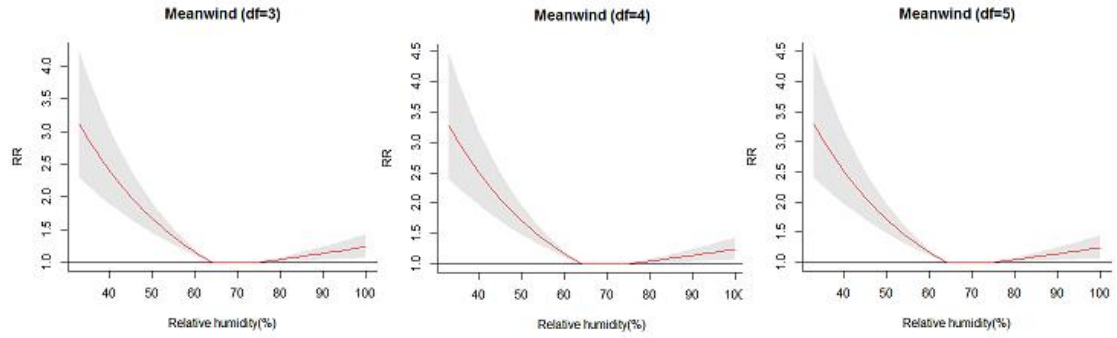


Fig. S3. The overall effects of RH on AR when varying the df (3-5) for Mean wind.

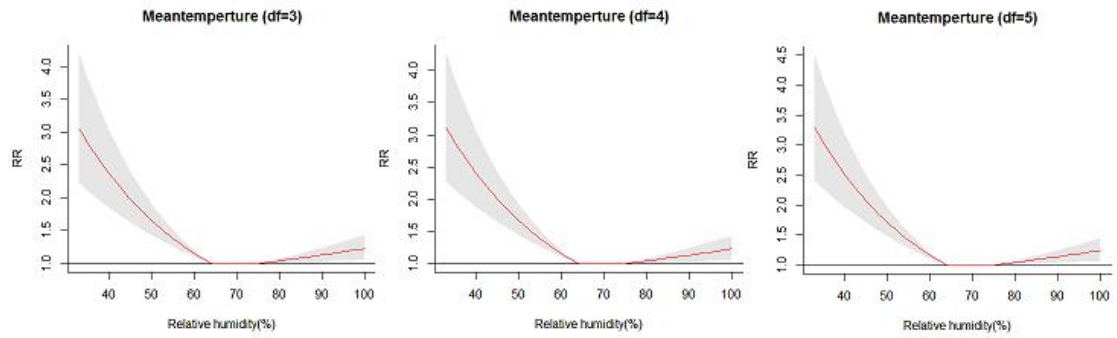


Fig. S4. The overall effects of RH on AR when varying the df (3-5) for mean temperature.

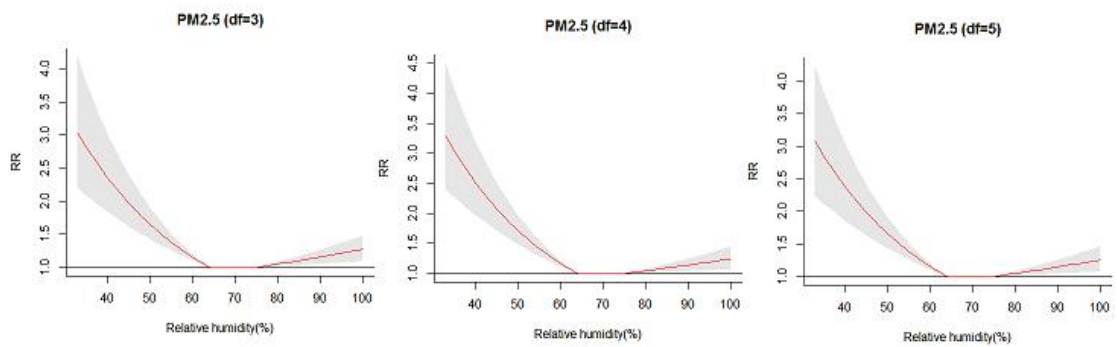


Fig. S5. The overall effects of RH on AR when varying the df (3-5) for $PM_{2.5}$.

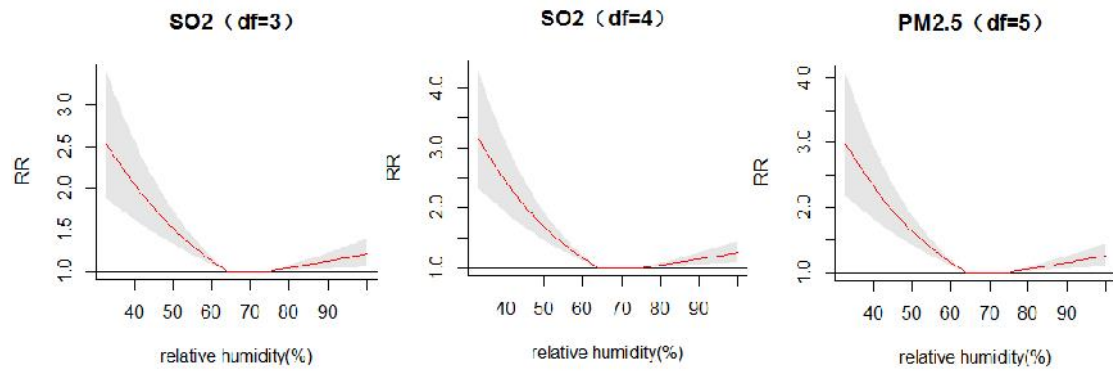


Fig. S6. The overall effects of RH on AR when varying the df (3-5) for SO₂.

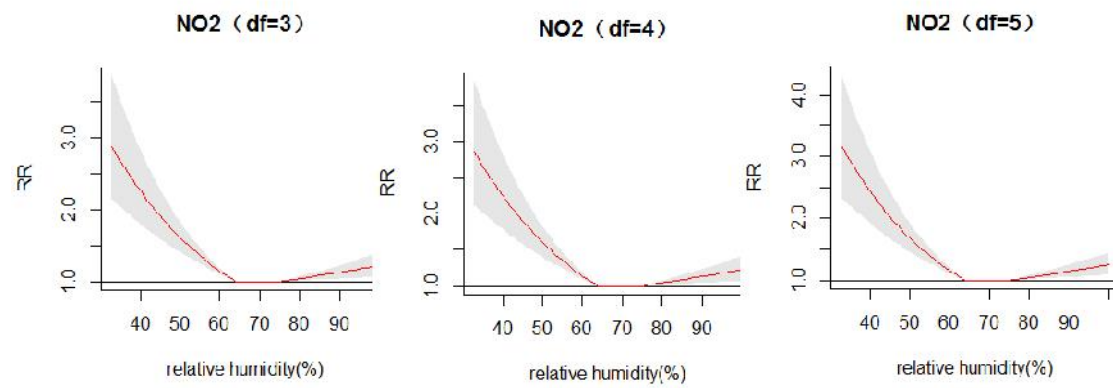


Fig. S7. The overall effects of RH on AR when varying the df (3-5) for NO₂.

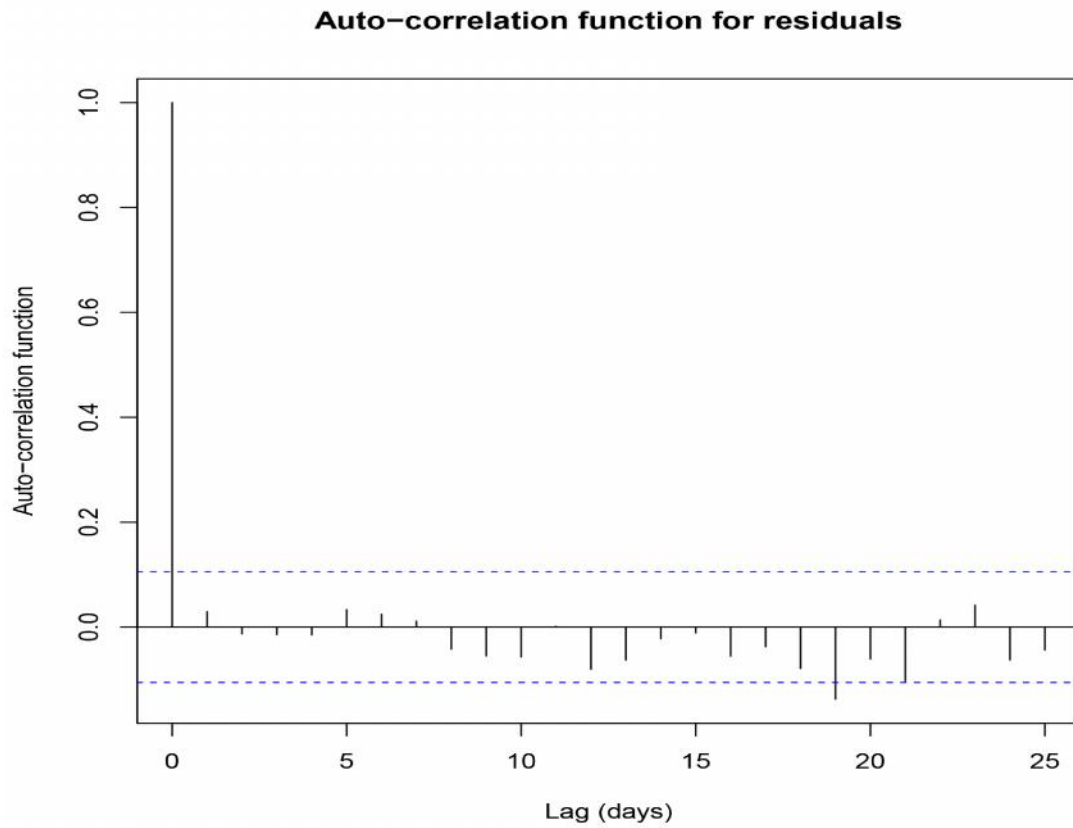


Fig. S8. Auto-correlation function for residuals of DLNM model

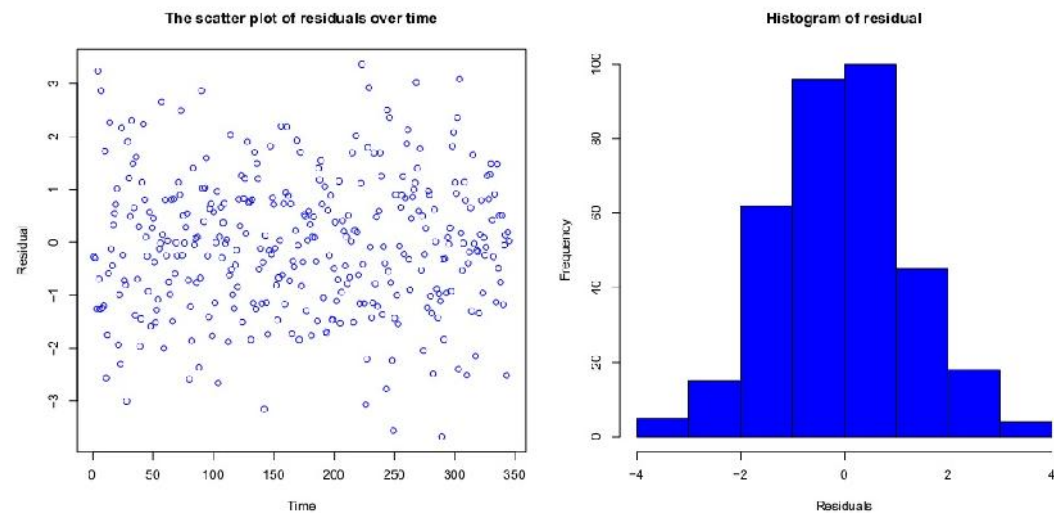


Fig S9: Scatter plot of residuals and histogram of residuals for DLNM model

Appendix table 1 Relative risks of AR cases for specific RH (5th and 95th percentiles) at various lag days, with the reference value of 64%-76%.

Single-day lag	Single effects	
	95 th percentile(93%)	5 th percentile(53%)
0	0.95(0.92, 0.97)	1.05(1.02, 1.08)*
1	0.96(0.94, 0.98)	1.04(1.02, 1.06)*
2	0.97(0.96, 0.99)	1.03(1.02, 1.05)*
3	0.99(0.98, 1.02)	1.04(1.02, 1.06)*
4	1.02(1.01, 1.04)*	1.05(1.04, 1.07)*
5	1.05(1.04, 1.07)*	1.07(1.05, 1.09)*
6	1.07(1.05, 1.09)*	1.08(1.05, 1.10)*
7	1.07(1.05, 1.08)*	1.06(1.04, 1.08)*
8	1.05(1.03, 1.07)*	1.03(1.01, 1.05)*
9	1.03(1.00, 1.06)*	0.99(0.96, 1.02)

*P < 0.05