# Trends in the outpatient-visits and allergens of allergic rhinitis in Chongqing, China from 2008 to 2017

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### Research

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# Abstract

Background The prevalence of allergic rhinitis (AR) has increased globally. This study was conducted to investigate the changing trends of AR's outpatient visits and inhaled allergens, also the possible association between air pollution and AR visits in Chongqing, China.

Methods We analyzed all the skin prick test results from patients diagnosed as AR in Departments of Otolaryngology of the first affiliated hospital of Chongqing Medical University during 2008 to 2017. The trend of AR visit rate and inhaled allergens was observed. Then, air quality data were acquired from the Chongqing Municipal Environmental Protection Monitoring Center. We explored the effects of air pollutants ($SO_2$, $NO_2$, $PM_{2.5}$, $PM_{10}$, CO and $O_3$) on outpatient visits for AR.

Results From 2008 to 2017, the ratio of AR outpatient visits increased. The number of polysensitization was more than that of monosensitization. However, the rate of mono-specific sensitization to dust mite allergen was on the increase, especially in patients of 20–39 y. No correlations were found between AR visits and pollutants, while mono-mite-sensitized AR visits were significantly correlated with the concentrations of atmospheric $SO_2$, $PM_{10}$ and $PM_{2.5}$.

Conclusions the rising trends in AR visits reflect both a real increase in the occurrence and a more effective diagnosis of cases. Increment in mono-mite sensitization implies the rising trends of new AR cases. The significant correlation between mono-mite-sensitized AR visits and concentration of $SO_2$, $PM_{10}$ and $PM_{2.5}$ supports opinion about an influence of atmospheric pollutants on mite induced immune response in AR.

# 1. Introduction

Allergic rhinitis(AR), a common chronic inflammatory disease in upper airways, affects about 10–40% of the population worldwide (1). AR is an IgE-mediated immunologic response to environmental allergens, characterized by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose, eyes, oral mucose. Furthermore, AR is a known risk factor for comorbid conditions, including asthma, rhinosinusitis, nasal polyposis and sleep disorders, resulting in important medical and social problems (2). Globally, the prevalence of AR appears to be steadily risen in the past few decades and AR is an increasing challenge to public health worldwide (3, 4). In China, the prevalence of AR and profiles of AR-related comorbidities were significantly increased. Self-reported AR prevalence in China has increased from 11.1–17.6% over a 6-year period (5, 6). AR has negatively imposes a considerable burden on society.

Skin prick test (SPT) is a standardized test widely used in the diagnosis of AR. It provides information about the presence of specific IgE to protein and peptide antigens (allergens). Aeroallergen sensitization varies widely between geographical areas, depending on exposure (7–9). Meanwhile, gender (10, 11) and age (12–14)may modify sensitization patterns. Additionally, climate changes could affect sensitization profiles by altering aeroallergen distribution, amount, germination rate, and allergenicity (8, 15). Identification of common aeroallergens is necessary, in order to educate the patient on what allergens to avoid and also help find the best formulation of allergen immunotherapy for effective AR treatment. Thus,

exploring the trend and variation of aeroallergens is meaningful for the establish of AR management strategy.

As we all known, the etiology of AR is multifactorial. Both genetic and environmental factors play key roles (16). However, large increases in the prevalence of AR within a short period of time are unlikely to be explained by variations in the genetic background. Increasing evidence implicates that environmental factors are more and more important in the pathogenesis of AR, which might explain the more aggressive nature of the symptoms of AR, such as air pollution, lifestyle changes, exposure to new allergens. Among them, air pollution attracts high attention.

Air pollution, it is a major and constantly rising hazard in the environment associated with large increases in medical expense and morbidity. Air pollution refers to ozone($O_3$), nitrogen dioxide($NO_2$), sulfur dioxide($SO_2$) and particulate matter(PM), and so on. Their harmful effects on respiratory system have acquired much awareness. Recent studies have demonstrated an association between high levels of air pollution and an increased risk of allergic sensitization and prevalence of rhinitis (17). Moreover, epidemiological and experimental studies suggest the increase in atmospheric pollutant ($NO_2$, $SO_2$, $PM_{10}$, etc.) levels could be one of the possible explanations for the current increase in the prevalence of AR (18–20). Therefore, gaining a better understanding of the association between air pollution and allergens may be an important research task.

Despite this, to the best of our knowledge, few previous study have focused on the changing trends of AR's outpatient visits and allergens, also the interactions between air pollution and AR. Thus, in this study, we carried out a time-series analysis on monthly AR outpatient visits in our department and the change of inhaled allergens during 2008 to 2017. Then, we aimed to assess the possible effects of air pollutants on outpatient visits for AR. To our knowledge, the study is the first one to undertake such a 10-year's comprehensive analysis for Chongqing, and even the first one for China.

## 2. Materials And Methods

Study population and case definition of AR

Monthly numbers of AR outpatients between 2008 and 2017 were obtained from the Departments of Otolaryngology-Head and Neck Surgery, the first affiliated hospital of Chongqing Medical University. This hospitals are Class-Three, Grade A-level tertiary university hospitals located in the central districts in Chongqing city. It is a both comprehensive teaching and researching medical center. The diagnosis of AR was based on the evaluation of a patient's medical history, physical examination and skin prick test(SPT, trying to find the possible allergen).

The monthly numbers of all clinical visitors in the Departments of Otolaryngology-Head and Neck Surgery were extracted from the medical records of the first affiliated hospital of Chongqing Medical University.

The monthly AR ratio= (number of AR patients /number of outpatients)×100%.

Chongqing city

Chongqing is one of the four municipalities in China. It is also an important industrial and commercial center of the southwest region with a population of about 40 million. The major air pollution source in Chongqing is automobile exhaust emissions, such as domestic heating systems and motor traffic. This study examined the trend of AR patients' inhaled allergen positive rate from 2008 to 2017 in the first affiliated hospital of Chongqing medical university, then explore its correlation to air pollution levels in Chongqing area for the recent 10-year period.

Allergens and SPTs

All patients were tested for the common inhalant allergens. These allergens included Dermatophagoides pteronyssimus, Dermatophagoides farina, humulus pollen, artemisia pollen, cat hair, dog hair, cochroach, feather, yeast and tobacco. Meanwhile, yeasts and tobacco. The positive control(1% histamine) and negative control(normal saline solution) and all the allergens were manufactured Allergopharma(hamburg, Germany).

SPTs were performed as follows. The forearm skin was sterilized with an alcohol swab and was introduced the reagent at constant 2.5cm intervals. The cutting edge of the lancet was held flush with the skin, and pricks were administered with consistent intensity and depth. After 15minutes, the results were read and scaled from 1 to 4 according to the size of the wheal and flare size (+1, >negative control, < 5mm; +2, 5-7mm;+3, 7-10mm; +4, >10mm, and/or pseudopods).

Air pollution data

Air quality data were acquired from the Chongqing Municipal Environmental

Protection Monitoring Center. The data provided as average values from the data of 9 monitoring stations distributed across Chongqing. We obtained the concentrations of $SO_2$, $NO_2$, $PM_{2.5}$, $PM_{10}$, CO and $O_3$ on monthly: 1) air quality: sulfur dioxide($SO_2$), industry- related air pollution indication; 2) nitrogen dioxide ($NO_2$), traffic-related air pollution indication; 3)$PM_{2.5}$ and $PM_{10}$, surrogates of complex mixture of air pollutants.

Statistics analysis

The data were categorized and analyzed using SPSS Statistics,Version 17.0. The regression analysis was adapted to evaluate the correlations between the rates of AR outpatient visits and time, also the rates of mono-sensitization to mite in AR patients and time from 2008 to 2017. The Pearson correlation coefficients were performed to assess the relationship among pollutants. Moreover, to investigate relationships between AR and ambient air pollution levels, non-parametric generalized additive model (GAM) was used to analyze the highly non-linear or non-monotonic exposure-response relationship between air pollutants and monthly outpatient visits for AR. A P-value <0.05 was considered statistically significant.

# 3. Results

3.1 Trends in the rates of AR outpatient visits between 2008 and 2017

During the 10 years, a total number of 917240 outpatients attended the Department of Otolaryngology-Head and Neck Surgery at the first affiliated hospital of Chongqing Medical University. 20534 of these were diagnosed with AR. Figure 1a showed the monthly number for outpatients, clinical visit for AR and the AR ratio. It demonstrated that there were seasonal variations in AR ratio from 2008 to 2017. The monthly number for outpatients and clinical visit for AR gradually increased every year. The AR ratios showed one peak during every year and it was in August and September; 7,10,11 showed sub-maximum AR ratios; Meanwhile, 2,3 showed the lowest ratios of AR visits. In Figure 1b, we saw that the AR ratios increased after an apparent period of stability during 2008-2012. In Figure 1c, the regression analysis showed that the AR ratio were in cubic function curve relation with time(R=0.650, F=28.313, p<0.01). According to age, patients in 20-39 y showed stronger increase in the rates of AR outpatient visits(Figure 1d).

3.2 Trends in the aeroallergen of AR outpatient visits between 2008 and 2017

As shown in Figure 2, in the AR patients, the dermatophagoides farine and dermatophagoides pteronyssinus yielded the highest number of positive responses(mean=95.653% and 95.668%) followed by humulus pollen(mean=67.852%) and artemisia pollen(mean=58.603%). Meanwhile, yeasts and tobacco yielded the least(36.581%, 33.223%). It demonstrated that dermatophagoides farine and dermatophagoides pteronyssinus were the most common allergens in Chongqing area. Moreover, the positive rates of artemisia pollen and humulus pollen showed an obviously decreasing tendency from June 2014 and then the positive rate of cockroach showed the third highest from February 2015.

3.2 Trends of mono-sensitization to mite and poly-sensitization in AR during 10 years

As shown in Figure 3a, firstly, this study showed that polysensitization was always very common as about 4/5-2/3 of patients were sensitized to poly allergens. Secondly, we found that the rate of mono-specific sensitization to dust mite allergen(including dermatophagoides farine and dermatophagoides pteronyssinus) was on the increase again after an apparent period of stability from 2008-2013. In 2008, 9.755% of the overall AR patients had a positive prick test for only dust mite allergen(including dermatophagoides farine and dermatophagoides pteronyssinus), while 36.353% of them were sensitized

to dust mite allergen in the 2017. In 2008, the poly sensitized subjects in AR patients were 90.245%, while they were 63.647% in the 2017. In Figure 3b, the regression analysis showed that the rate of mono-sensitization to mite presented increase as cubic function curve(R=0.789, F=63.701, p<0.01). According to age, the results demonstrated that patients in 20-39 y showed stronger increase in the rate of mono-sensitization(Figure 3c).

3.4 Characteristics of air pollutants

Figure 4a demonstrated the data for the monthly air pollution variables($SO_2$, $NO_2$, CO, $O_3$, $PM_{2.5}$, $PM_{10}$) in Chongqing during 2013-2017. The results showed that, monthly average concentrations of $PM_{10}$ varied from 51 ug/m$^3$ to 191 ug/m$^3$; $PM_{2.5}$ varied from 27 ug/m$^3$ to 138 ug/m$^3$; $SO_2$ varied from 7 ug/m$^3$ to 45 ug/m$^3$; $NO_2$ varied from 14 ug/m$^3$ to 57 ug/m$^3$; $O_3$ varied from 19 ug/m$^3$ to 153 ug/m$^3$; CO varied from 523 ug/m$^3$ to 1770 ug/m$^3$. The concentrations of $SO_2$ and $PM_{2.5}$ showed slow decrease from January 2013 to December 2017. During winter(heating period), the concentration of $SO_2$ was higher.

Pearson correlation coefficients of air pollutants were shown in Table 1. $SO_2$, $NO_2$, $PM_{10}$, $PM_{2.5}$ and CO had significant positive correlations with each other(p < 0.05), whereas $O_3$ had a significant negative correlation with the other five air pollutants. This correlation was consistent with previous reports(21,22) and attributed to the stationary fossil fuel combustion-related pollutants($SO_2$ and PM) and the traffic-related pollutant $NO_2$ (23). $PM_{10}$ and $PM_{2.5}$ were highly correlated (correlation coefficient r = 0.938). $PM_{10}$ were moderately correlated with $SO_2$(r=0.591) and weakly correlated with CO(r=0.381); $PM_{2.5}$ were strongly correlated with $SO_2$(r=0.738) and moderately correlated with CO(r=0.424); $NO_2$ were moderately correlated with CO(r=0.482).

3.5 Exposure-Response associations between air pollutants and AR outpatient visit

In this study, we used non-parametric generalized additive model (GAM) to analyze the exposure-response relationships for air pollutants with outpatient visits for

AR during Chongqing city in 2008-2017. Firstly, we evaluated the association between air pollutants and the AR outpatient visit(Table 2a). No significant correlations were found between the AR visits and the concentrations of $SO_2$, $NO_2$, CO, $O_3$, $PM_{2.5}$, $PM_{10}$. Moreover, we explored the relationships for air pollutants with outpatient visits for mono-mite-sensitized AR.

According to the statistical results, the mono-mite-sensitized AR visits were significantly correlated with the concentration of atmospheric $SO_2$, $PM_{10}$ and $PM_{2.5}$. However, there was no obvious correlation between the mono-mite-sensitized AR visits and other air pollutants, including $NO_2$、CO、$O_3$. In the multiple influencing factors GAM models, the contribution of the $SO_2$, $PM_{10}$ and $PM_{2.5}$ to the mono-mite-sensitized AR visits was 67.4% with significant impacts on the change of mono-mite-sensitized AR visits. Based on the analysis of the effect of multi-factors on the change of mono-mite-sensitized AR visits, there were linear relationships between mono-mite-sensitized AR visits and $PM_{2.5}$, $PM_{10}$ concentrations, and non-

linear relationship between mono-mite-sensitized AR visits and $SO_2$ concentration(Table 2b). Figure 4b showed the exposure-response relationships for the concentration of $SO_2$, $PM_{10}$ and $PM_{2.5}$ with outpatient visits for AR.

# 4. Discussion

In this study, we analyzed the results of SPT and studied the associations between major air pollutants and AR visits over a period of 10 years. The main findings as follows: 1) The changes in the outpatient visits of AR have occurred during recent 10 years. The ratio of AR outpatient visits increased during 2008-2017 and the AR attendance in 20-39 y was highest, followed by that of in 40-59 y; 2) The number of polysensitization is more than that of monosensitization, while the rate of mono-specific sensitization to dust mite allergen is on the increase in the decades, especially in patients of 20-39 y; 3)No correlation was found between the AR visits and pollutants, while the mono-mite-sensitized AR visits were significantly correlated with the concentrations of atmospheric $SO_2$, $PM_{10}$ and $PM_{2.5}$.

The results of our study covering a recent 10-year span showed a significant increase in the outpatient visits of AR. From 2008 to 2017, the rate of AR visits obviously increased from 1.51 % to 2.57 % in the overall visit. Noticeably, subjects in the 20-39y age group showed a stronger increase when comparing with other age groups. Although the number of AR outpatient visit was influenced by many factors, our findings also support the idea that the prevalence of AR in Chongqing area appears to be increasing during the 10 years, especially in young adults. These trends correspond to those found in some other Asian countries (24,25) and European. To our knowledge, in China, this is the first time to report the yearly increased rate of AR outpatients visits during recent 10 years.

In this study, our analysis documents that during recent 10 years, the rate of mono-sensitization(positive prick test to dust mite only) was on the increase gradually again after an apparent period of stability during 2008 to 2012. It is of interest to note that the positive responses to SPT are largely dominate by a single allergen, dust mite. A total of about 80-90% of AR patients reacted against the allergen and about 20%-35% of the patients reacted only to it. Reports from China and other countries with similar tropical climates such as Singapore, Malaysia, Thailand, Indonesia and Vietnam have also identified dust mite as a major allergen (26-30). Our findings are in line with these observations that dust mite is the most common allergen in Chongqing. Based on these research and our results, "mite fever", instead of "'hay fever", may be a more accurate term in the tropical setting. Hence, we think that "dust mite sensitization" may be both a true and potentially useful measure of "atopy" in these tropical area.

Interestingly, the significant increment in mono-specific sensitization against dust mites has been observed, especially in the class of 20-39 years. It is therefore an open question what the reason is. Firstly, polysensitization is an immunological phenomenon. The increasing number of sensitizations seems to characterize the natural history of allergic patient and may represent a typical evolution of allergy (31). A recent study supported an immunological hypothesis for explaining the trend to develop polysensitization: a functional defect of T regulatory cells (32). Children with persistent monosensitization produced higher

quantity of IL-10 and IFN-γthan children developing polysensitization (32). Therefore, we think that the obviously rising trends of mono-sensitization may suggest obviously increased new cases of AR in Chongqing area. Secondly, studies showed that each allergen was able of causing a different immunological, inflammatory, functional, and clinical pattern, probably depending on own biological property (33,34). Thus, we speculate that they may be two different categories for monosensitization to mite and polysensitized AR patients. Furthermore, we think that it's a valuable explorance to search the differences between them, including clinical features, immune pathophysiology and heredity.

Recent years, the nature of the relationship between industrial air pollution and atopic diseases is always subject to debate. On the one hand, studies have shown an association between high levels of air pollution and an increased risk of allergic sensitization and prevalence of rhinitis (35,36); the increase in atmospheric pollutant ($NO_2$, $SO_2$, $PM_{10}$, etc.) levels could explain the current increase in the prevalence of AR (37,38); both Zhan FY, et al (21) and Chen CC, et al (22) reported that strong associations exist between daily concentration of the air pollutants and the daily number of outpatients for AR and higher levels of ambient air contaminants enhance the risk of elevated frequency of clinic visits for AR. On the other hand, contradictory findings have been published for the $NO_2$, $O_3$ and $PM_{10}$ levels based on some long term studies (39). In our research, no significant correlations were found between the AR outpatient visits and the concentrations of $SO_2$, $NO_2$, $CO$, $O_3$, $PM_{2.5}$, $PM_{10}$. It is in line with observations that the decline in ambient air pollution levels is not associated with an increase in the incidence of asthma and other allergic diseases (41-42). We think that, besides greater exposure to known and unknown risk factors, the rising trends of AR outpatients visits could partly result from the more effective diagnosis of allergic diseases and patients' enhanced awareness of the need to seek medical help.

Furthermore, when we explored the relationships for air pollutants with outpatient visits for mono-mite-sensitized AR. Significant correlations between mono-mite-sensitized AR visits and the concentration of atmospheric $SO_2$, $PM_{10}$, $PM_{2.5}$ were found. Dermatophagoides farinae and D. pteronyssinus are the most prevalent mite species in Chongqing area. The high humidity and ambient temperatures are certainly ideal for their propagation (43). Recent study demonstrated that there may be some correlations between pollutant and dust mite. For example, Canbaz D. et al. reported that indoor pollutant hexabromocyclododecane enhances house dust mite-induced activation of human monocyte-derived dendritic cells (44). Thus, we speculate that the atmospheric pollutants may have an impact on mite induced immune response in AR, which might elaborate the correlation between air pollution and mono-mite-sensitized AR visits.

In summary, our data from the first affiliated hospital of Chongqing Medical University suggest that the rising trends in AR outpatient visits reflect both a real increase in the occurrence and a more effective diagnosis of previously underdiagnosed cases. Increment in mono-specific sensitization implies the rising trends of new AR cases. Our observation concerning the significant correlation between mono-mite-sensitized AR visits and concentration of atmospheric $SO_2$, $PM_{10}$ and $PM_{2.5}$ supports opinion about an influence of atmospheric pollutants on mite induced immune response in AR.

# Declarations

## Author's contributions

Yang Shen, Su-Ling Hong designed and organized the study and wrote the manuscript. Qi-Yuan Zou, Jia Li and Xia Ke collected the clinical data. Yang Shen and Hou-Yong Kang analyzed the data. Yang Shen wrote the paper. All authors read and approved the final manuscript.

## Acknowledgement

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

The study has been approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Written informed consent was obtained from every participant.

## Funding

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# Tables

Table 1. Pearson correlation coefficients of air pollutants, Chongqing, 2013-2017

| | $SO_2$ | $PM_{10}$ | $NO_2$ | CO | $PM_{2.5}$ | $O_3$ |
|---|---|---|---|---|---|---|
| $SO_2$ | 1 | 0.629** | 0.189 | 0.260* | 0.757** | -0.373** |
| $PM_{10}$ | | 1 | 0.278* | 0.462** | 0.948** | -0.57** |
| $NO_2$ | | | 1 | 0.497** | 0.292* | -0.482** |
| CO | | | | 1 | 0.502** | -0.538** |
| $PM_{2.5}$ | | | | | 1 | -0.591** |
| $O_3$ | | | | | | 1 |

\* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed)

Table 2. The results of GAM model test between AR outpatient visits(a), mono-mite-sensitized AR visits(b) and muli-pollutant factors

(a).

| Pollutant | Estimated degree of freedom | Reference degree of freedom | F | P |
|---|---|---|---|---|
| $SO_2$ | 1 | 1 | 1.932 | 0.1708 |
| $PM_{10}$ | 1.390 | 1.663 | 2.304 | 0.1973 |
| $NO_2$ | 1 | 1 | 0.310 | 0.5804 |
| CO | 4.258 | 5.136 | 2.065 | 0.0796 |
| $PM_{2.5}$ | 1 | 1 | 3.680 | 0.0608 |
| $O_3$ | 1.166 | 1.307 | 1.180 | 0.3682 |

(b)

| Pollutant | Estimated degree of freedom | Reference degree of freedom | F | P |
|---|---|---|---|---|
| $SO_2$ | 2.243 | 2.794 | 5.953 | 0.00151 |
| $PM_{10}$ | 1 | 1 | 6.222 | 0.01615 |
| $NO_2$ | 1 | 1 | 1.614 | 0.21020 |
| CO | 1 | 1 | 1.331 | 0.25444 |
| $PM_{2.5}$ | 1.027 | 1.050 | 7.227 | 0.00845 |
| $O_3$ | 6.193 | 6.772 | 1.949 | 0.05777 |

# Figures
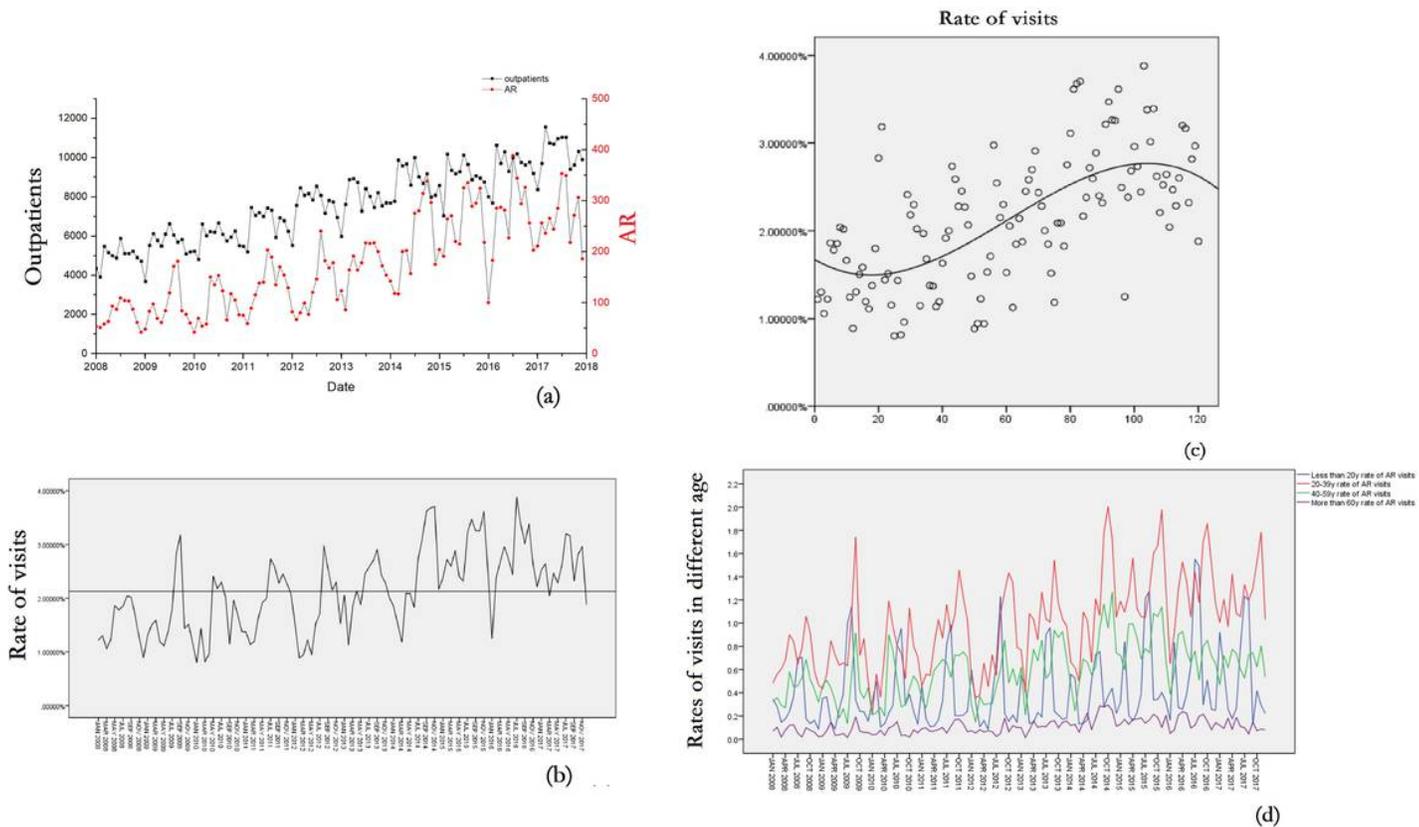
**Figure 1**

Monthly number for outpatients(a), clinical visit for AR(a), the AR ratio(b) and the regression analysis of AR ratio(c), the rates of AR outpatient visits in different age groups(d).
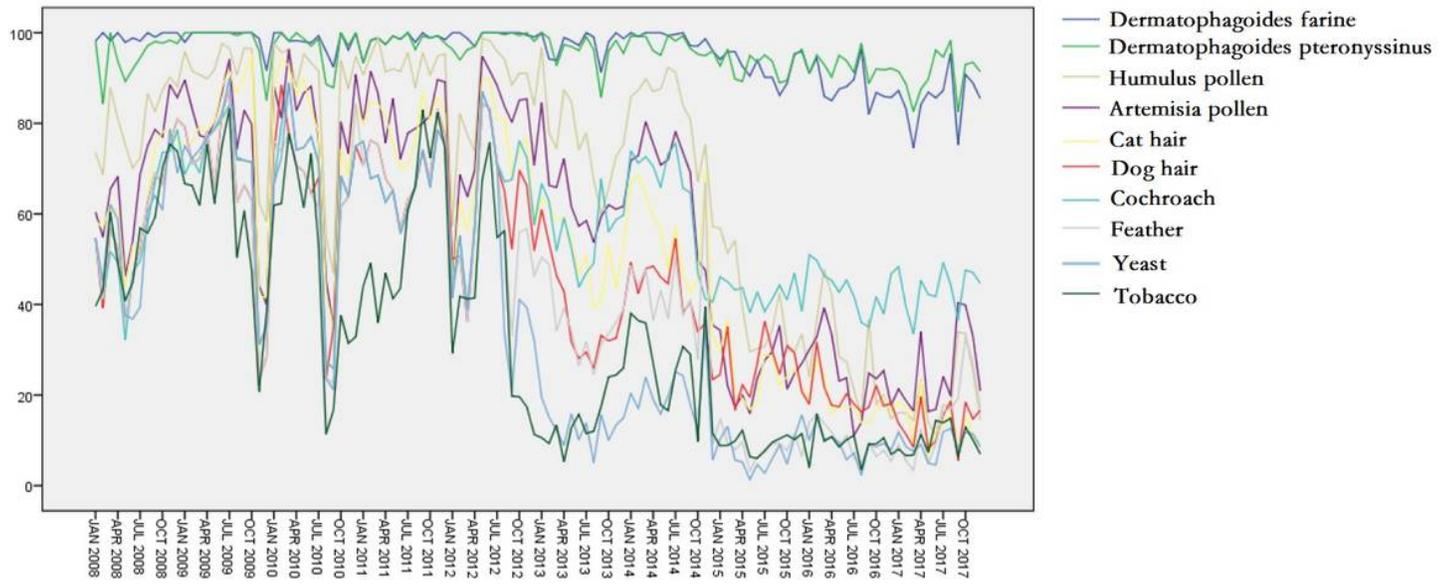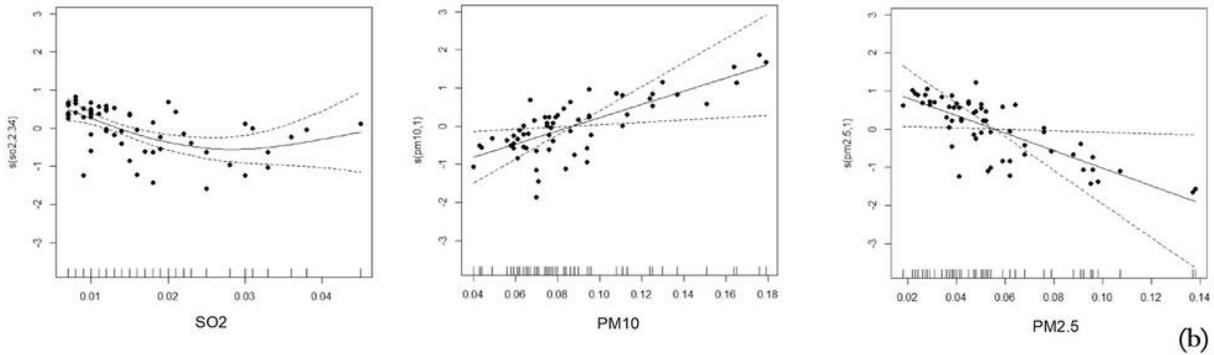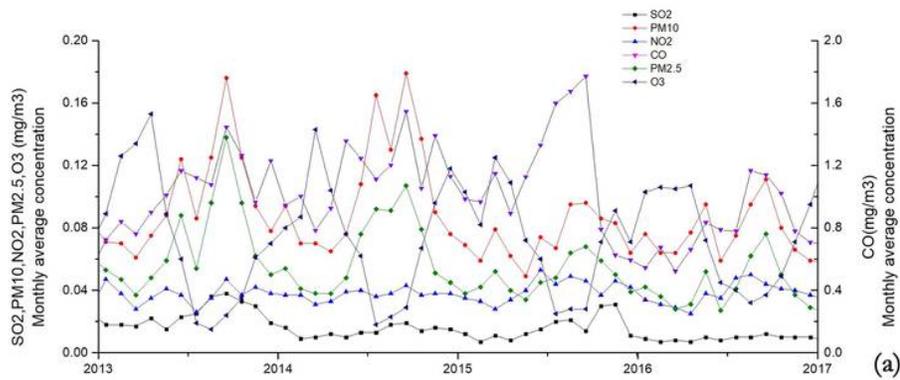
**Figure 2**

Trends in the aeroallergen of AR outpatient visits between 2008 and 2017.

(a)

(b)

(c)
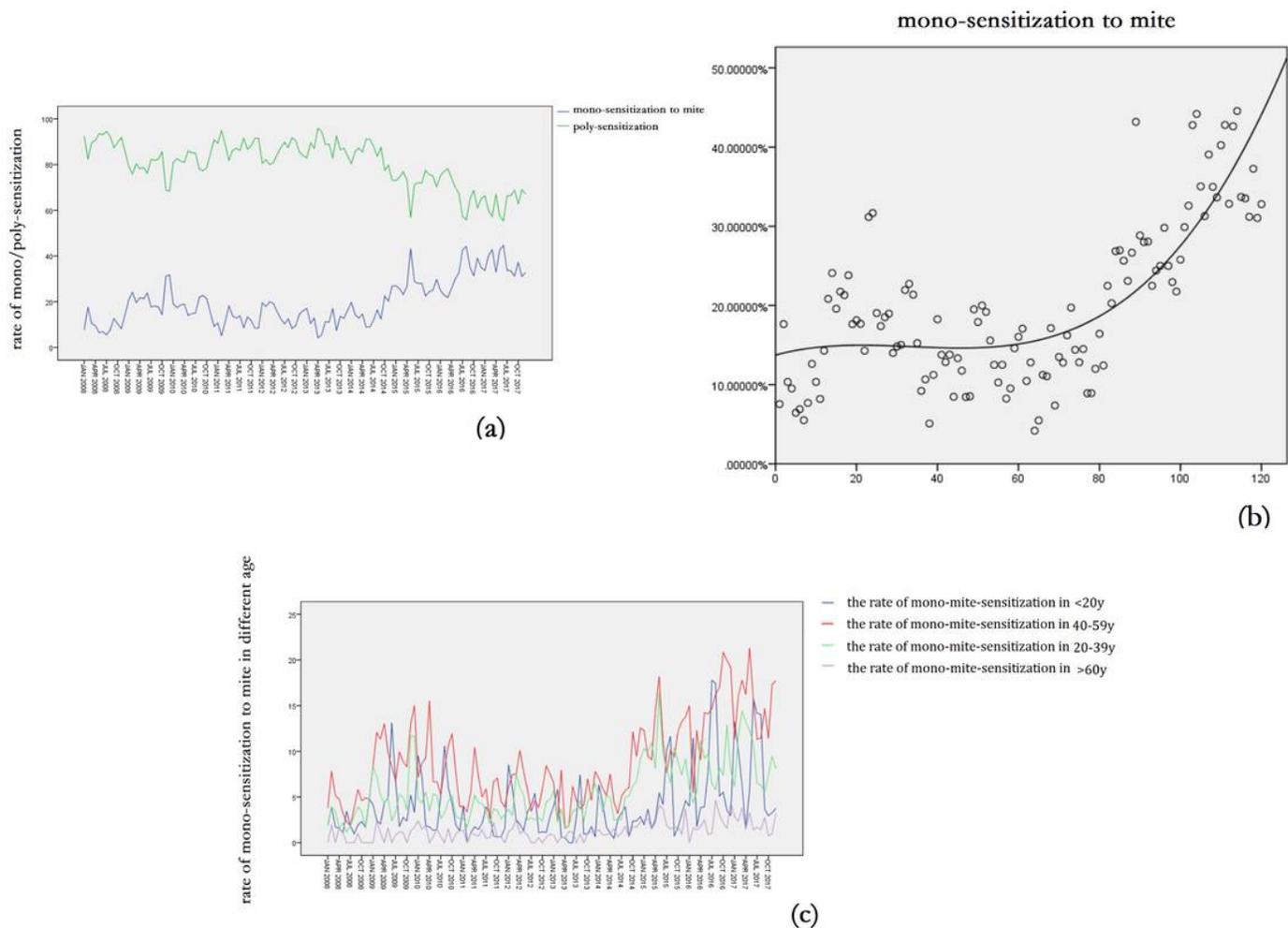
## Figure 3

Trends of mono-sensitization to mite and poly-sensitization in AR between 2008 and 2017(a); The rates of mono-sensitization to mite in different age groups(b).

**Figure 4**

Monthly air pollution variables(SO2, NO2, CO, O3, PM2.5, PM10) in Chongqing during 2013-2017(a), exposure-response relationships for the concentration of SO2, PM10 and PM2.5 with AR outpatient visits(b).

## Supplementary Files

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