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ORIGINAL RESEARCH

Impact of Air Pollutants and Pollen on the Severity of Nonallergic Rhinitis: A Data-Oriented Analysis

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Background: Rhino-conjunctivitis symptoms are more severe in nonallergic rhinitis (NAR) patients during pollen season than in other seasons. Little is known about the role of pollen and air pollutants on the severity of NAR.

Objective: The aim of this study is to assess the cross-sectional effects of both pollen and air pollutants on NAR patients during the pollen and non-pollen seasons, and to further explore the possible relationship among these triggers.

Methods: A total of 2411 clinically diagnosed NAR outpatients from 2018 to 2019 were recruited for this study. The severity of NAR was measured using rhinoconjunctivitis symptom scores. Associations of daily exposure to pollen, $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3, and rhinoconjunctivitis symptom scores were evaluated using Logistic regression models. Distributed Lag Nonlinear models were used to explore single-day and accumulative Lag effects of environmental factors mentioned above.

Results: During the pollen season, pollen concentration, higher exposure levels of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 increased the severity of NAR group when compared with the low-moderate severity group. The high severity group was associated with lower exposure levels of O_3. However, during non-pollen seasons, no significant association was found in air pollutant metrics, pollen concentration, and severity of NAR. The exposure-severity effects of pollen were different when different ambient pollutants were stratified.

Conclusion: Synergistic effect of pollen and air pollutants, including $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3, might be responsible for aggravating the symptoms of NAR patients during pollen seasons.

Keywords: air pollution, pollen, nonallergic rhinitis

Introduction

As a common inflammatory disease, chronic rhinitis manifests at least 2 nasal symptoms, including itching, sneezing, rhinorrhea, and nasal congestion for more than 12 weeks.[1] With approximately 30% global prevalence, chronic rhinitis could tremendously impair the patients' quality of life and pose a tremendous financial burden to our society.[2,3] Based on its etiology, chronic rhinitis is usually divided into 2 phenotypes, allergic rhinitis (AR) and nonallergic rhinitis (NAR); the former affects 10–40% of the global population,[3] while the latter affects 17–52% of the population in different regions.[4–7] An observational study showed that the prevalence of AR and NAR in a rural area in northern China was 16.78–24.60%.[8]

Although AR and NAR share similar clinical symptoms, their clinical characteristics remain distinctive, especially in different seasons.[9] Unlike AR, the diagnosis of NAR depends on thorough medical history and a series of exclusion tests for allergen sensitization and rhinosinusitis, which leaves this disease underestimated and undervalued. Segboer et al[10] compared the impairment of quality of life between AR and NAR patients and found NAR patients were equally bothered and for some aspects even more affected than AR patients, such as by nasal symptoms, tiredness and lack of

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sleep, demonstrating that the quality of life was significantly impaired in NAR patients. Usually, NAR patients present perennial symptoms, which are associated with environmental factors, such as air pollutants.[11] Our group compared the clinical manifestation of the first-visit NAR patients, who were diagnosed based on positive medical history and negative serum allergen test.[9] However, to our surprise, for NAR patients, the severity of all common rhino-conjunctivitis symptoms, including nasal itching, sneezing, rhinorrhea, nasal congestion, watery eyes, and gritty eyes, was significantly higher during pollen seasons than in other seasons.

Since pollen is usually considered to be associated with a specific allergic response, this observation provokes us to understand what triggers these severe symptoms in NAR patients during pollen seasons. In fact, nonspecific nasal hyperreactivity is one of the most prominent features of NAR.[12] In recent years, studies have shown that environmental factors, such as air pollution and climate change, have a significant impact on human well-being and contribute significantly to various chronic respiratory diseases.[13] With the development of urbanization and industrialization, air pollution has become increasingly severe, and the pollutants were found to be responsible for epithelial barrier dysfunction.[14,15] To date, the association between air pollution and NAR is not yet clear.

To sum up, the aim of the present study was, therefore, to assess the effects of both pollen and air pollutants on NAR patients during the pollen seasons and other seasons, and to further explore the possible relationship among these triggers and understand why such patients experience more severe symptoms during pollen seasons.

Materials and Methods

Data Source and Study Design

The 2411 study participants were first-visit outpatients complaining about suffering with chronic rhinitis from the Otorhinolaryngology and Allergy Department of Beijing TongRen Hospital, China, between January 2018 and December 2019. All the enrolled participants were residents in Beijing. In this retrospective study, chronic rhinitis was diagnosed with more than 2 nasal symptoms, such as rhinorrhea, sneezing, nasal congestion, and itching for more than 12 weeks. NAR was then diagnosed using negative allergen test measured by serum-specific IgE (sIgE; UniCAP system, Phadia, Uppsala, Sweden) using a panel of aeroallergen mixture (house dust mites, trees, weed/grass pollen, molds and animal dander). Upper respiratory infections and chronic rhinosinusitis were excluded by nasal endoscopy. Serum sIgE sensitization tests were performed, and population characteristics and detailed medical history were documented. Clinical information on nasal and ocular symptoms was recorded with a 0-to-3-point visual analog scale (VAS). Total nasal symptom score (TNSS) was calculated as the sum of 4 nasal symptoms (rhinorrhea, sneezing, nasal congestion, and itching). Rhinoconjunctivitis symptom scores were calculated by the sum of TNSS and conjunctivitis scores (gritty eyes and watery eyes), from 0 to 15 points.[8]

The study was approved by the Ethics Committee of Beijing TongRen Hospital and Beijing Institute of Otolaryngology, China, in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants.

Definition of Pollen Season and Concentration of Air Pollutants

Total pollen concentration and various air pollutants in μg/m^3, including NO_2, $PM_{2.5}$, PM_{10}, O_3, SO_2 and CO, were obtained from Beijing Meteorological Bureau. The pollen season was defined based on total pollen grains provided by Beijing Meteorological Bureau as previously reported, beginning from ≥5 pollen grains/m^3 per day for more than 3 consecutive days and ending until <10 pollen grains/m^3 per day for more than 3 successive days.[9] The pollen seasons were March 13th to May 28th and August 20th to October 1st in 2018, and from March 2nd to June 3rd and August 13th to October 2nd, in 2019.[9] Accordingly, the rest of the years was defined as non-pollen seasons.

Statistical Analyses

A descriptive analysis of the basic demographic information of the study population was performed using R: The R Project for Statistical Computing (R 4.1.0 version). Chi-square analysis was used to compare the differences between subgroups. A value of $P<0.05$ was considered to be statistically significant.

The risk was expressed as an odds ratio (OR) per one interquartile range (IQR, Q3 minus Q1) of each air pollutant. During the study period, the IQR levels of air pollutants were 2 (Q1-Q3;2–4) μg/m^3 for sulfur dioxide (SO_2), 16 (23–39) μg/m^3 for nitrogen dioxide (NO_2), 44 (60–104) μg/m^3 for ozone (O_3), 54 (32–86) μg/m^3 for particulate matter ≤10 μm in aerodynamic diameter (PM_{10}), 40(15–55) μg/m^3 for particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$), and 0.44 (0.4–0.84) μg/m^3 for carbon monoxide (CO).

Patients were divided into two groups based on the severity of the disease; patients with rhinoconjunctivitis symptom scores <9 were classified as low-moderate severity group, while patients with scores ≥9 were classified as high-severity group. The OR and 95% Confidence Intervals (95% CI) were estimated by using a multi-variable Logistic Regression model to evaluate the association between pollen exposure, air pollution exposure and the severity of NAR. The distributed lag nonlinear model (DLNM)[16] was used to assess the single-day (lag0-lag14) and accumulative (lag0-1, lag0-2, —-lag0-14) lag effects of pollen and ambient air pollutants during the pollen seasons.

To further understand whether the effects of pollen on the severity of NAR could be modified by air pollutants, a stratified analysis was performed based on the different levels of air pollutant exposure. The cut-off concentrations to classify the low and high exposure levels of PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3 were 50, 35, 50, 80, and 100 μg/m^3, respectively, according to the primary standards of the national air quality standards (GB3095-2012) of China. All data analyzed in this study were performed by using packages "MASS",[17] "dlnm",[16] "tsModel"[18] based on R 4.1.0.

Results

Demographic and Clinical Information of the Study Population

The demographic information of the study population is shown in Table 1. In total, the current study included 2411 NAR patients, with sufficient data on demographic and clinical data. Participants were on an average 34.74 years old, of which

Table 1 Characteristics of the Participants by Levels of Severity in NAR Patients

Variable	Pollen Season		P value	Non Pollen Season		P value
	Low-Moderate Severity (N = 510)	High Severity (N = 1168)		Low-Moderate Severity (N = 275)	High Severity (N = 458)	
Age(y), mean±SD	35.00±8.69	34.47±8.17	0.23	35.89±9.78	34.43±8.38	0.04
Gender(female, %)	237(46.5)	514(44.0)	0.35	127(46.2)	219(47.8)	0.67
Duration of disease (month)	45.86±52.25	48.44±52.72	0.36	45.79±55.49	55.31±55.30	0.025
Nasal Symptoms						
Itching	1.18±0.79	2.51±0.71	<0.001	1.20±0.90	2.56±0.70	<0.001
Sneezing	1.63±0.83	2.76±0.47	<0.001	1.53±0.91	2.78±0.49	<0.001
Rhinorrhea	1.20±0.88	2.50±0.74	<0.001	1.20±0.95	2.48±0.77	<0.001
Congestion	1.39±0.84	2.35±0.78	<0.001	1.37±0.951	2.25±0.91	<0.001
TNSS	5.40±1.71	10.12±1.50	<0.001	5.29±1.96	10.08±1.54	<0.001
Conjunctivitis						
Watery eyes	0.63±0.75	1.81±1.05	<0.001	0.49±0.66	1.71±1.10	<0.001
Gritty eyes	0.81±0.88	2.00±1.04	<0.001	0.71±0.86	1.77±1.05	<0.001
Rhinoconjunctivitis symptom scores	6.12±1.85	12.02±1.87	<0.001	5.89±2.05	11.81±1.90	<0.001
NO_2(μg/m^3), mean±SD	32.73±14.62		-	34.68±13.38		-
$PM_{2.5}$(μg/m^3), mean±SD	43.36±39.23		-	40.49±19.31		-
PM_{10}(μg/m^3), mean±SD	76.14±76.22		-	62.50±26.91		-
O_3(μg/m^3), mean±SD	80.84±31.32		-	93.78±49.47		-
SO_2(μg/m^3), mean±SD	3.94±3.10		-	2.80±1.34		-
CO(μg/m^3), mean±SD	0.63±0.34		-	0.73±0.24		-

Abbreviation: TNSS, total nasal symptom score.

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45.58% were women, and 4.1% had asthma. The average TNSS and Rhinoconjunctivitis symptom scores were 8.56 and 10.03, respectively. In the higher severity category, participants were younger, but the asthma comorbidity was comparable.

During the pollen season, the age and gender distribution, as well as the duration of disease were comparable between the two severity groups. Nevertheless, in non-pollen seasons, patients in the high severity group were younger and had a longer period of disease than the low-moderate severity group; gender distribution remained indistinguishable.

Associations Between Pollen Concentration, Air Pollutants and Severity of NAR

As shown in Figure 1, within pollen seasons, the IQR was higher in the concentration of pollen and air pollutants, and the OR (95% CI) of rhinoconjunctivitis symptom scores, when compared with the low-moderate severity group, were as follows: 1.172 (1.072~1.295) for pollen, 1.101 (1.012~1.213) for PM_{10}, 1.125 (1.008~1.260) for $PM_{2.5}$, 1.283 (1.123~1.471) for NO_2 and 1.198 (1.077~1.339) for SO_2. The low-moderate group was more susceptible to the exposure of O_3 (OR = 0.828 [0.711 ~ 1.339]; P = 0.014). However, no statistically significant association was found in air pollutant metrics, pollen concentration, and the severity of disease during the non-pollen seasons.

Lag Effect of Pollen and Ambient Air Pollutant During Pollen Seasons

Subsequently, we analyzed the single-day and accumulative lag effects of pollen and ambient air pollutants during pollen seasons (Figure 2). Pollen exposure has shown profound effects on the rhinoconjunctivitis symptoms in NAR patients. During the pollen seasons, effects even lasted for 14 days. For PM_{10}, the first-day effect was the most significant and the lag effects remained positive until day 3; for $PM_{2.5}$, the most significant effect also appeared on day 1, and the overall lag effects sustained 6 days. Lag effects for NO_2 lasted 14 days, with relatively higher effects on the first 6 days, which slowly went down afterward. The effect of SO_2 slowly went higher with an increasing lag from 1 to 5 days, and thereafter it decreased from 6 to 14 days. The 3-dimensional graph demonstrates the exposure–outcome relationship for ambient pollen and pollution from lag day 1 to day 14 (Figure 3).

Stratification of Ambient Pollutants

To further analyze the effect of pollen severity at different concentrations of air pollutants, a stratification of ambient pollutants was performed according to the primary standards of the national air quality standards (GB3095-2012) of China (Figure 4). In the current study, stratification of SO_2 was not performed because the concentration was too narrow for stratification. For PM_{10} and $PM_{2.5}$, significant pollen-severity effects and profound lag effects could be found when

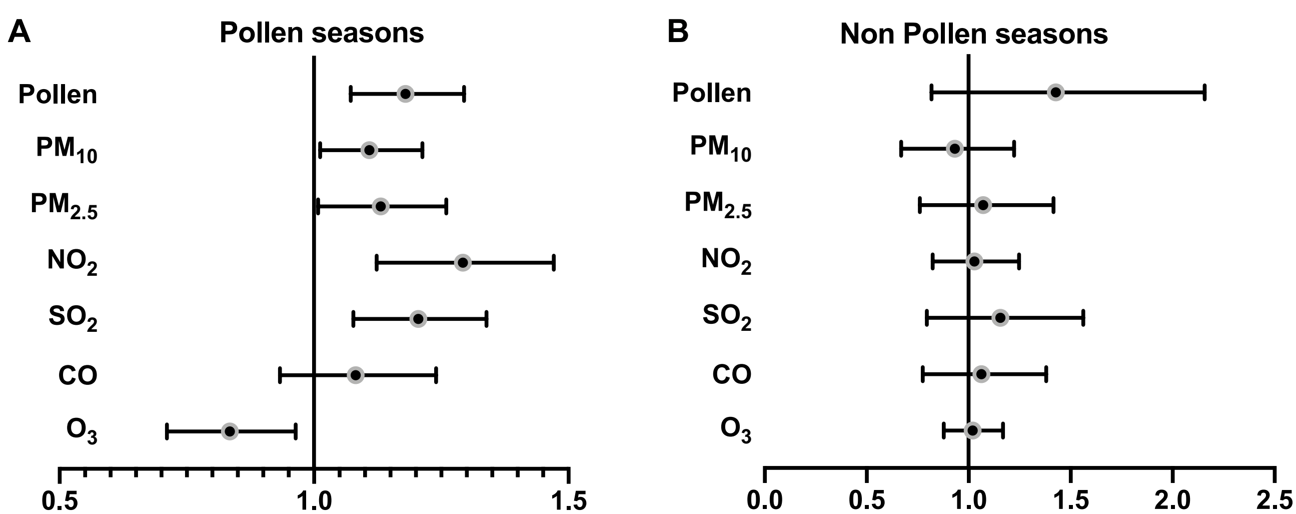

Figure 1 Associations between air pollutant metrics and levels of severity score of NAR, within pollen seasons (**A**) and non-pollen seasons (**B**).

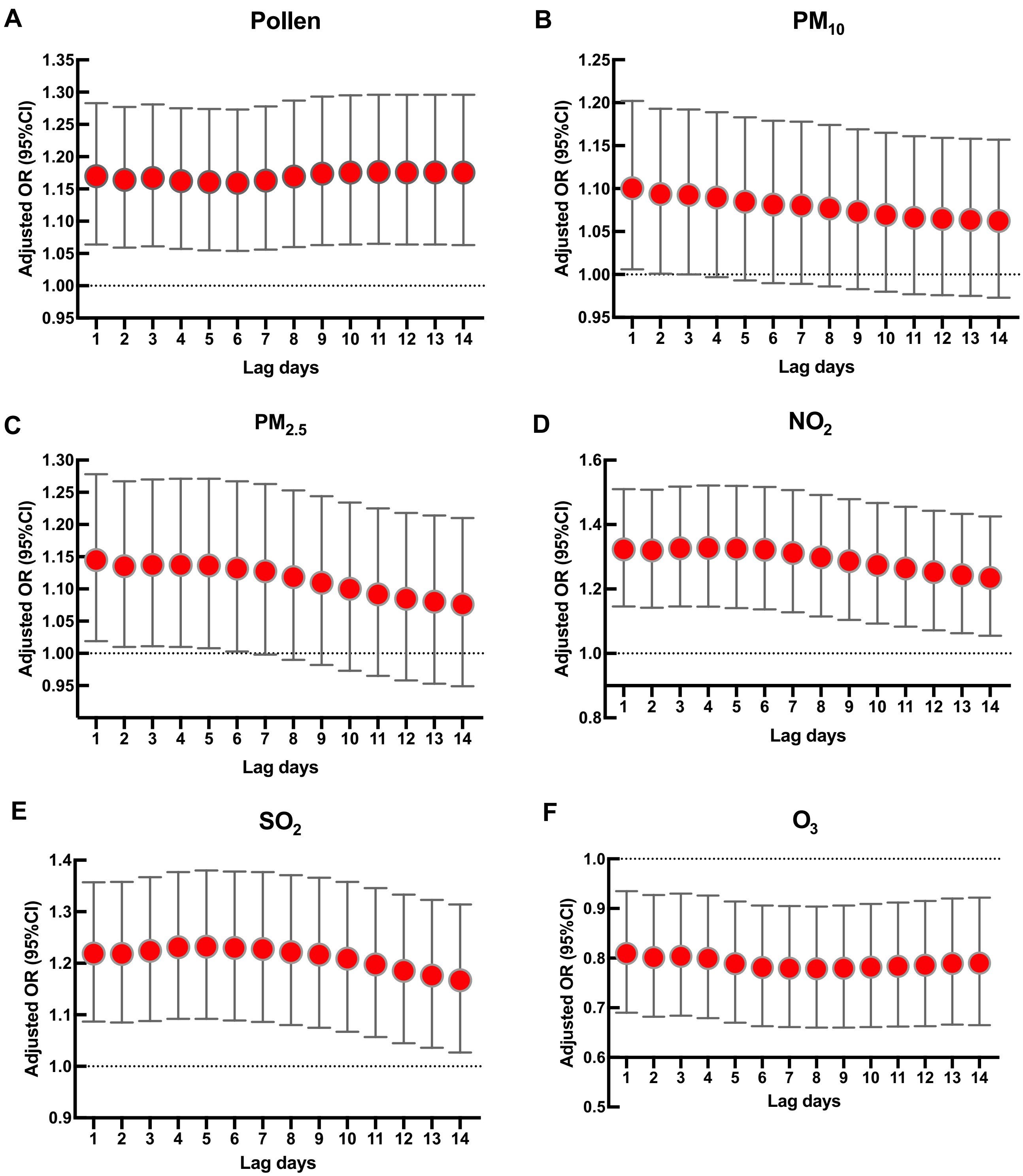

Figure 2 The lag effect of pollen (**A**) and ambient air pollutants including PM_{10} (**B**), $PM_{2.5}$ (**C**), NO_2 (**D**), SO_2 (**E**) and O_3 (**F**) during pollen seasons on the severity of NAR patients.

undergoing high-level of exposure but not low-level of exposure. During low-level exposure of NO_2 and O_3, significant pollen-severity effects and lag effects could be seen; while under high exposure, the effects were indistinguishable between the low-moderate and high severity groups.

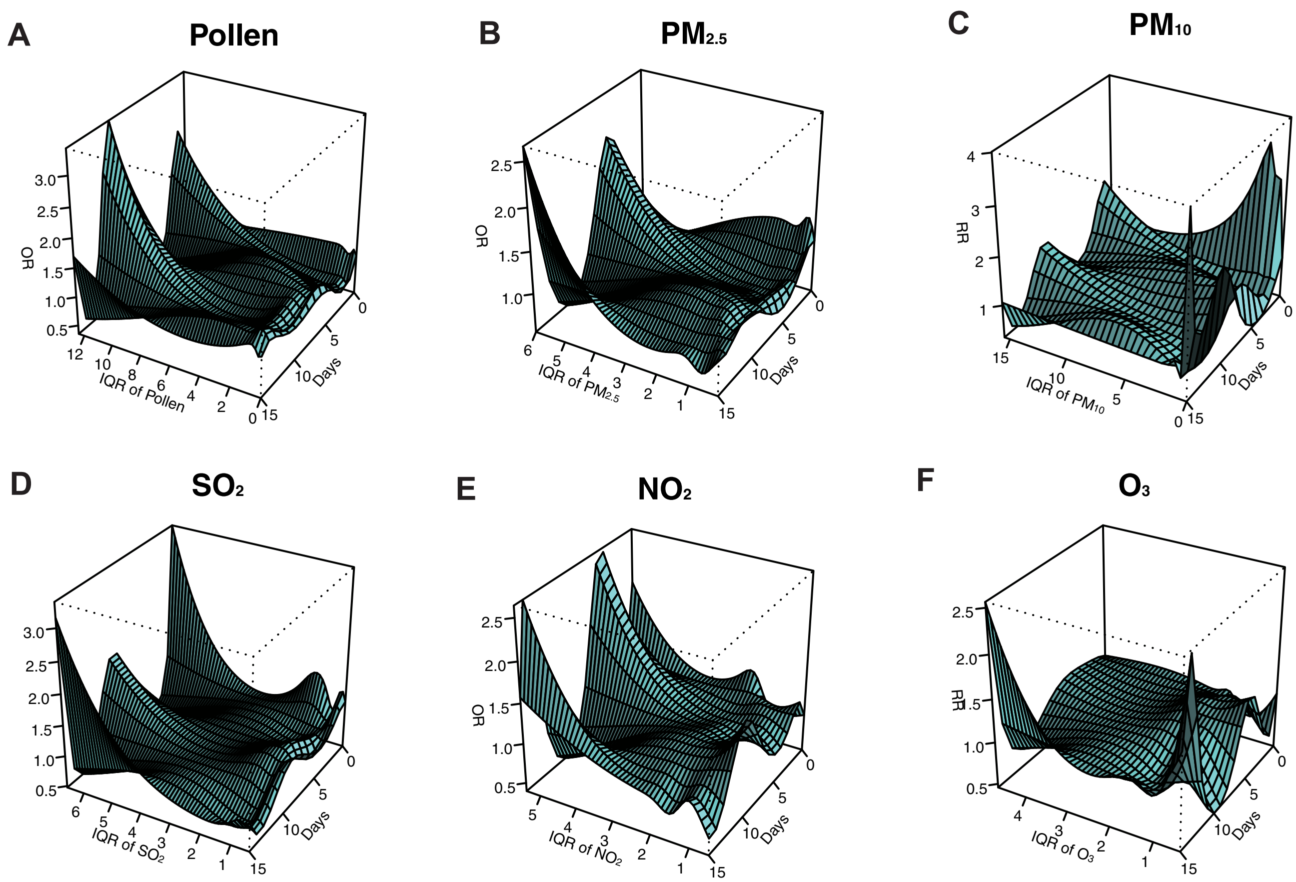

Figure 3 The 3-dimensional graph demonstrates the exposure–outcome relationship for ambient pollen (**A**) and pollution including PM_{10} (**B**), $PM_{2.5}$ (**C**), NO_2 (**D**), SO_2 (**E**) and O_3 (**F**) from lag day 0 to day 14.

Discussion

For a long time, NAR has been hugely underestimated and underrated since the diagnosis of the disease lacks direct objective tests and is mainly dependent on clinical manifestations and exclusion of positive allergen tests.[19] Studies that focused on objective tests in NAR population were limited. The current study is the first real-world study assessing the association of ambient pollen, pollution and severity of the disease.

China is a country with a large number of chronic rhinitis patients. In recent years, chronic rhinitis is emergingly considered an umbrella disease with homogeneous nasal symptoms but with differentiating etiological features.[20] It is estimated that the prevalence of NAR varied from 17% to 52% worldwide.[4–7] One recent study in northern China reported that confirmed standardized prevalence of NAR was 24.60% with help of skin prick test, while the confirmed standardized prevalence of AR was 16.78%.[8] Therefore, the population of NAR patients is much larger than those with AR, although AR is usually considered a more severe disease than NAR. In our previous study, we were intrigued by the finding that the severity of disease in NAR patients was significantly higher during pollen seasons than in other seasons. In the current study, we compared the effects of both pollen and major air pollutants during pollen and non-pollen seasons on the NAR disease severity. We found that in pollen seasons, high pollen concentration alongside high air pollution showed a synergistic effect on the severity of NAR, which might be the reason why NAR patients suffered worse during pollen seasons.

With the development of industrialization, various forms of air pollutants have increased in developing countries. Power generation and traffic have always been major sources of air pollution, which are estimated to contribute towards 3% of the disability-adjusted life years lost globally.[21] There is emerging evidence of the detrimental effects of air

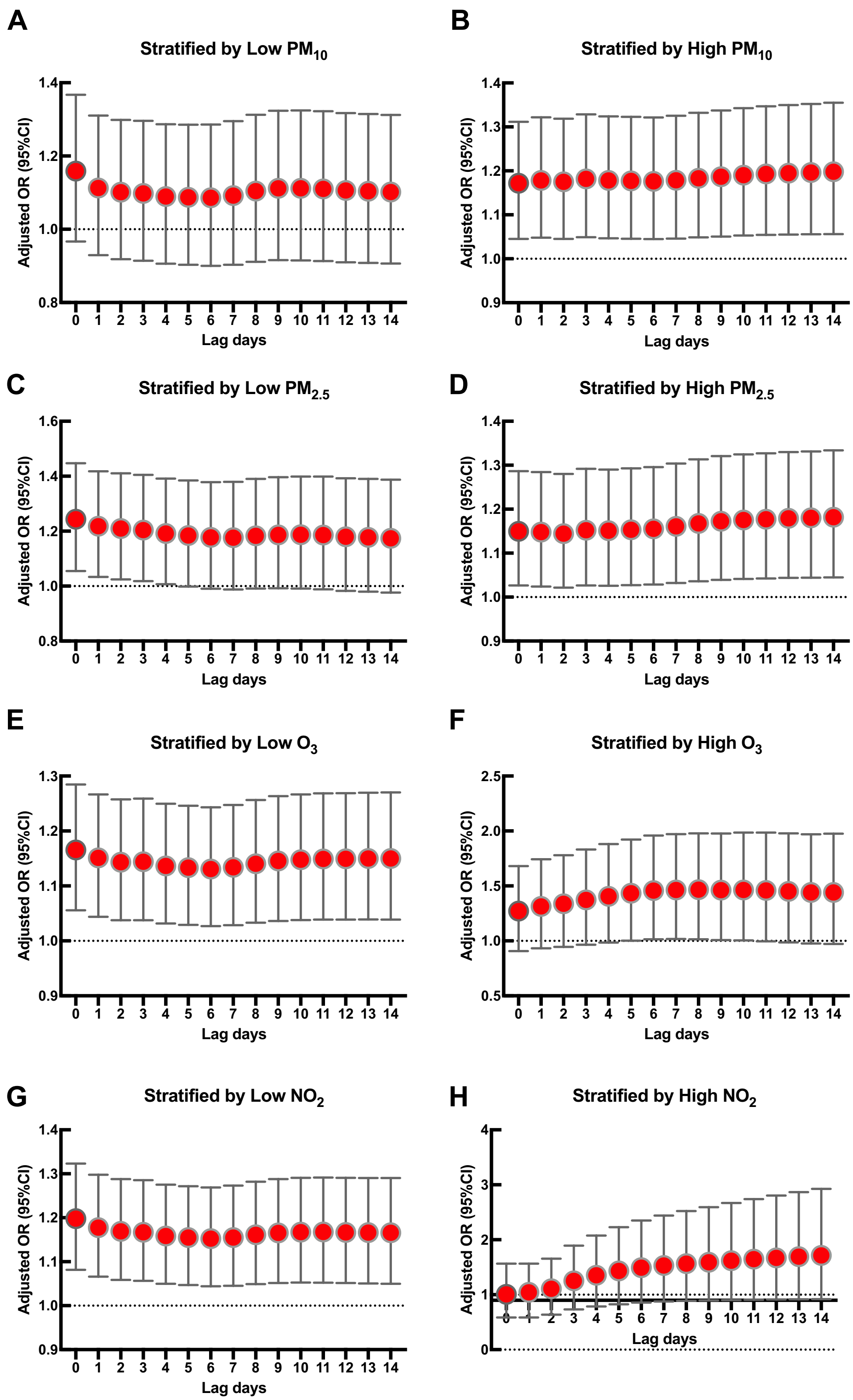

Figure 4 The lag effect of pollen during pollen seasons on the severity of NAR. patients when major ambient pollutants ((**A** and **B**), PM_{10}; (**C** and **D**), $PM_{2.5}$; (**E** and **F**), O_3; (**G** and **H**), NO_2) were stratified.

pollution, such as asthma, allergic rhinitis, chronic obstructive lung disease, cardiovascular diseases, tumors, immune dysfunction, and even mental disorders.[13,22–24] In the current study, we included 6 most common air pollutants, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3, among which, $PM_{2.5}$ and PM_{10} were the best-studied forms of air pollutants. PMs are classified by fractions based on their size; smaller PMs such as $PM_{2.5}$ and ultra-fine particulate matter could easily reach the lower airway and lungs, while larger particles mostly affect the upper airway.[24] It has been proven that air pollution has a huge effect on airway epithelium. A recent genome-wide analysis revealed that the stimulation of organic $PM_{2.5}$ extract activated IL-1 inflammatory pathway, increased mucus secretion and induced airway remodeling in human nasal mucociliary airway epithelial cultures.[25] Xian et al investigated the effects of $PM_{2.5}$ in nasal mucosal tissue using an air–liquid interface culture and found that it led to an epithelial barrier integrity deficiency.[26] A retrospective cross-sectional study in Shanghai reported that exposure to NO_2 and PM_{10} were significantly and positively associated with airway symptoms in 13,335 preschoolers.[27] Apart from PMs, oxidizing gases such as NO_2 and O_3, are also substantial causes of airway diseases. In our study, we found significant pollen-severity effects and profound lag effects even under low exposure of NO_2 and O_3, indicating that these two pollutants should be strictly controlled, especially in pollen season. Li et al reported that black carbon and pollen were associated with oxidative stress in the nasal mucosa and the combination of these two could even aggregate the inflammation.[28] In fact, NO_2 is a relatively weak oxidant, while O_3 is a strong oxidant. In mice and rat models, ozone induced nasal type 2 immunity and aggravated eosinophilic inflammation.[29,30] In our study, we found that even with low exposure to O_3, high symptoms already appeared in NAR patients, indicating that it was a relatively strong symptom inducer.

To date, little is known about the association between air pollutants and the severity of chronic rhinosinusitis, especially NAR. In 2002, a time-series analysis that included 16 NAR patients and healthy volunteers found that O_3 and NO were associated with nasal symptoms.[31] In the current study, we found that air pollutants were significantly associated with the severity of NAR. Consistently, a European cross-sectional study showed that the air pollutants-severity effect was higher in NAR than in AR patients.[32]

Additionally, little is known about the association between pollen concentration and the severity of NAR. Our study implied that pollen, a specific stimulus of patients with allergic diseases such as AR and allergic asthma, is also a strong stimulus to NAR patients. Nonspecific nasal hyperreactivity, a nasal abnormal overactivated reaction towards stimuli, was first considered to be the most prominent and unique characteristic of NAR.[12] Later, a study found that nasal hyperreactivity evaluated by cold dry air stimulation test was comparable between AR patients and NAR patients.[33] For NAR patients, pollen could also induce nasal hyperreactivity, leading to significant nasal symptoms. Moreover, pollen could induce nasal inflammation by being the vector for some strong immunologic and inflammatory effectors. A recent study reported that Artemisia pollen is responsible for airborne endotoxin dispersion, which is capable of inducing airway inflammation.[34] Artemisia annua happens to be the most common and important autumnal pollen allergen in northern China.[35]

However, the current study has some limitations. First, as a retrospective real-world study, only the first-visit clinically diagnosed NAR patients were included in our study. The whole population might be limited by national holidays and the hospital appointment system. Second, as a cross-sectional study, the long-term exposure effects in the same population were unable to be evaluated. Thus, large-scale, prospective studies, and mechanism studies, are needed to further improve the understanding of the synergistic effects of pollen and air pollution. Third, as a real-world study, no nasal provocation test was applied in this study; thus, there might be some local AR patients included into the enrolled subjects.

Conclusion

In summary, this study has provided preliminary information on the synergistic effect of pollen and air pollutants, including $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3, in aggravating symptoms in NAR patients. These results bring us new insights into the management of NAR. Therefore, it is essential to protect NAR patients from pollen, especially during the pollen seasons. Finally, the findings also contribute to understanding the environmental stimuli that directly influence the severity of NAR and thus reemphasize that air pollution needs to be better controlled.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflict of interest.

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