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Allergic Rhinitis: Association with Air Pollution and Weather Changes, and Comparison with That of Allergic Conjunctivitis in Taiwan

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Received: 27 September 2020; Accepted: 20 October 2020; Published: 26 October 2020

Abstract: Allergic conjunctivitis (AC) and rhinitis (AR) are common allergic diseases that may be environmentally related. We used a systematic sampling cohort database, which was applied in an AC study previously, to examine the association of AR with air pollution and weather changes. A case-crossover design coupled with conditional logistic analysis was implemented in the analysis; we identified 140,365 eligible AR subjects, and matched their diagnoses with environmental monitoring data. Unlike AC, the descriptive statistics indicated that AR occurred the most in adults under 50 years old by age (44.7%), and in winter by season (28.7%) ($p < 0.001$); similar to AC, AR occurred more in women than to men. Nitrogen dioxide (NO_2) was found to be positively associated with AR ($p < 0.001$), whereas relative humidity and temperature were negatively related ($p < 0.001$). We found that the risk of AR increased with descending NO_2 levels relative to AC (OR = 0.984, $p = 0.003$) after adjustment for covariates. It is suggested that AR could be triggered or exacerbated by lower levels of NO_2 than is AC. We recommend that AR patients pay extra attention to air pollution and mitigate their allergic problem accordingly.

Keywords: air pollution; allergic conjunctivitis; allergic rhinitis; nitrogen dioxide; relative humidity; temperature

1. Introduction

Allergic conjunctivitis (AC) and rhinitis (AR) are commonly observed allergic diseases that irritate and may even severely affect people's daily lives. By definition, AC is an eye inflammation caused by allergic reactions, and AR is an IgE-mediated inflammatory disease of the nasal mucous membranes triggered by a variety of allergens. AC can be divided into primary and secondary types depending on where the allergic reaction occurs. For the primary type of AC, the allergic reaction occurs in the conjunctivae, whereas secondary AC is usually induced by the IgE-mediation inflammation of AR [1]; perhaps this is the reason why AC is usually considered a comorbidity with AR [2–6].

AC and AR have been becoming prevalent around the world. For instance, a U.S. study based on the National Health and Nutrition Examination Survey III from 1988 to 1994 indicated that 6.4% of the sample population reported ocular allergy symptoms, 16.5% reported nasal symptoms, and 29.7% reported both [7]. A U.K. study examining a group of rural children found that the prevalence of AC, AR, and rhinoconjunctivitis (possessing both ocular and nasal allergic symptoms) was 17.5%, 15.1%, and 13.0%, respectively [8]. An Iranian survey reported that the prevalence of AC and AR in Tehran was 15.9% and 28.3%, respectively, with both symptoms together accounting for 12.3% [5]. It is believed that these numbers are underestimated, because not all patients with the allergic symptoms seek medical treatment [7].

Besides allergens, air pollution is considered to be related to allergic symptoms to a certain extent [9]. A number of studies have found that ambient air pollution and/or weather changes are

associated with AC [10–14] and AR [15–19]; moreover, the emerging climate change is considered to intensify these environmentally related health impacts [20]. Although the reported pollutants are quite different among the studies, nitrogen dioxide (NO_2) is the most commonly found air pollutant that is associated with AC or AR. These associations suggest that NO_2 and/or other pollutants may be effective in triggering or exacerbating AC or AR. A review paper has summarized that air pollution has a significant impact on the ocular surface, but the detailed mechanism remains unclear [21]. As for AR, research has confirmed that diesel exhaust particulate (DEP), which is usually surrogated by NO_2, induces the production of IgE antibodies as well as oxidative stress in the airways to enhance allergic inflammation and to sensitize the airways to following allergen exposure [22–26]. As NO_2 is associated with or may have an impact on both diseases, it is interesting to know whether the associated levels of NO_2 or the susceptibility to NO_2 is different between AC and AR.

We would like to explore such a difference to understand the complexity of air pollution related allergic diseases. Having examined the association of the first occurrence of AC with air pollution and weather changes recently [11], we took advantage by using the same datasets and approaches to find out the association between the first occurrence of AR and environmental factors, and made a comparison of the associated air pollutants in common between AC and AR (e.g., NO_2). Because the secondary type of AC was influenced by AR, we only selected the primary AC data in comparison with the AR result. To our best knowledge, this is the first study to conduct such a comparison, and we expect the result presented herein to help the general public better understand the relations between environmental factors and these common allergic diseases.

2. Materials and Methods

2.1. Inclusion of Subjects

Like the methodology used in the previous study that examined the association between AC and ambient conditions [11], the identical systematic sampling cohort database of the National Health Insurance of Taiwan from 2004 to 2013 was used in this study. AR diagnoses were clinically made and coded following the International Classification of Diseases, the 9th Revision, Clinical Modification (ICD-9 CM) at the outpatient visits; the ICD-9 CM codes of 477.0, 477.1, 477.2, 477.8, and 477.9 identified potential AR subjects. We only selected the patients' first occurrences of AR for the study data to eliminate the possibility that the diagnoses were influenced by the previous symptoms. One year of diagnosis-free period was used for the first occurrence selection, and thus those identified in the first year (i.e., 2004) were excluded. There were 316,819 cases for the first occurrence of AR during the span; after subtraction of those with no environmental monitoring data or insufficient information, the number of AR subjects reduced to 140,365. Meanwhile, there were 100,636 subjects for AC after deduction of ineligible patients [11]. Among the AC and AR groups, there were 27,964 subjects who were included in both, with 11,303 suffering AC earlier than AR and 16,661 having the diagnoses in the reverse order. This study, using secondary data with no identifiable personal information, was granted an exempt review by the Research Ethics Committee of Tzu Chi General Hospital (No: IRB108-90-B, approved on 15 June 2019).

2.2. Environmental Monitoring Data

Environmental data for the study subjects were obtained from the environmental monitoring stations in the neighborhoods of the subjects' clinics or hospitals. We retrieved the data from 73 of the available 76 environmental monitoring stations in Taiwan, which continuously collected air pollutant and meteorological data. The items for collection included carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter with aerodynamic diameter $\leq$ 2.5 and 10 μm ($PM_{2.5}$, PM_{10}), sulfur dioxide (SO_2), relative humidity (RH), and temperature. The monitoring records were open to the public and available from the website of the Taiwan Air Quality Monitoring Network (TAQMN, https://airtw.epa.gov.tw/ENG/default.aspx). The daily average was calculated for each

pollutant or meteorological factor in the analysis, except the 8-hour average was used for ozone, because the ozone-forming reaction (photochemical smog reaction) occurred during the diurnal period of a day. In this study, we downloaded the environmental data covering from 2004 to 2013 for AR subjects from the website for analysis, in addition to those already downloaded for AC subjects in the previous work [11].

2.3. Data Management and Analysis

Descriptive statistics was conducted by stratifying data to sub-groups with several factors (e.g., age, sex, and season), and comparisons using statistical tests (e.g., chi-square test and *t*-test) were performed to find out differences between the sub-groups. Despite no available personal information from the cohort database, the information of locations of subjects' clinics or hospitals at the county or district levels was sufficient for linking the AR diagnoses with environmental monitoring sites in the neighborhood. Statistical analysis of environmental data divided by the case and control periods was performed to show preliminary comparisons of exposures between both.

Following the previous study that examined the AC association with environmental factors [11], we again applied the case-crossover design to the analysis of AR association with air pollution and weather changes, because AC and AR similarly fit the description of "brief exposure to cause a transient change in risk of a rare acute onset disease" [27]. In this design, data for cases and controls were from the same subjects but at different occasions; specifically, exposure for each case period was the average of environmental data on the day of the first AR diagnosis and the two prior days (D_0, D_{-1}, D_{-2}), and that for the controls was the average of environmental data on four different days, one and two weeks before and after the onset of AR (D_{-14}, D_{-7}, D_{+7}, D_{+14}). The bidirectional selection for control days was confirmed to be "resistant to confounding by time trend", which could occur with use of the unidirectional control sampling (i.e., selecting controls only prior to cases) [28]. Using this design intended to assess the short-term exposure of environmental factors, instead of the long-term exposure, which was relatively difficult to assess with quite potential confounding factors. Additionally, using this design could take out confounding effects in the first place, because cases and controls were the same subjects having the virtually identical backgrounds (e.g., age, sex, long-term exposure to allergens or pollution that developed AR). Our selection of control days, weeks away from cases, was similar to that of previous air pollution-related studies [14,29]; other data management was as same as that used in our previous study [11].

Univariate and multivariate conditional logistic regression analyses were conducted for the case-crossover design to learn the significance of association between each air pollutant or meteorological factor and AR, and to identify all the significant factors that were associated with AR, respectively. The correlation among air pollutants and meteorological factors was given in the previous study [11], with pairs of CO/NO_2 and $PM_{2.5}/PM_{10}$ being highly correlated ($\rho > 0.8$); due to collinearity, only one variable of each pair was selected to enter a single multivariate analysis. Environmental data with relatively large variations were shown as levels with each containing 10 units (e.g., ppb, $\mu g/m^3$). As the case and control data were from the same subjects with identical settings in age, sex, and season, there was no need to adjust for covariates in this analysis.

Having learned the associations of AC and AR with environmental factors from our previous study and this one, we applied a multivariate logistic regression analysis to compare the associated air pollutants in common between AC and AR. For the 27,964 subjects having both diagnoses of AC and AR, we allocated them to the AC or AR group according to the early symptom (i.e., 11,303 to AC and 16,661 to AR). By allocating this way we could have independent AC and AR groups for the analysis, which contained a total of 213,037 subjects with 83,975 for AC and 129,062 for AR. Adjustments for covariates were conducted step by step to exclude possible confounding effects. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for performing all the statistical analyses.

3. Results

The descriptive statistics for AC and AR subjects are listed in Table 1. The average age of AR subjects (31.41 years) was significantly higher than that of AC subjects (27.60 years); the breakdown shows that the highest proportion in the AR group were adults younger than 50 years old (19–49 years) that accounted for 44.7%, compared to 38.4% in the AC group. A sex difference is apparent for either group with females making up more than 50%. The most occurrences of AR were present in spring (26.7%) and winter (28.7%), the seasons with allergens and coldness, respectively; whereas AC occurrences were mostly in spring (29.6%) and fall (26.3%), commonly known as allergy seasons. The difference within each stratum was confirmed to be statistically significant for AC or AR ($p < 0.001$), indicating that both allergic diseases were age-, sex-, and season-specific.

Table 1. Statistics of subjects having allergic conjunctivitis (AC) and allergic rhinitis (AR) by age, sex, and occurring between 2004 and 2013.

	AC †	**AR**
Total	100,636	140,365
Age (Mean ± SD)	27.60 ± 21.06	31.41 ± 21.49
	n (%)	*n* (%)
Sex		
Male	44,049 (43.8)	65,469 (46.6)
Female	56,587 (56.2)	74,896 (53.4)
p-value [a]	<0.001	<0.001
Age		
0–6	18,971 (18.9)	23,205 (16.5)
7–18	25,366 (25.2)	24,320 (17.3)
19–49	38,676 (38.4)	62,699 (44.7)
≥50	17,623 (17.5)	30,141 (21.5)
p-value [b]	<0.001	<0.001
Season		
Spring	29,815 (29.6)	37,416 (26.7)
Summer	24,682 (24.5)	28,667 (20.4)
Fall	26,469 (26.3)	34,064 (24.3)
Winter	19,670 (19.6)	40,218 (28.7)
p-value [b]	<0.001	<0.001

[a] two-sample *t*-test; [b] chi-square test; † same subjects used in Zhong et al. [11].

The averages of air pollutant concentrations during the case period are significantly higher than that during the control period for AC and AR ($p < 0.001$), despite the small-scale differences (Table 2). It appears that PM_{10} has the largest differences between the case and control periods, with a relative difference of approximately 1.9% for either AC or AR. As for meteorological factors, RH is in contrast with all air pollutants, showing a significantly lower average in the case period for either disease ($p < 0.001$); temperature, however, resulted in opposite outcomes for both diseases, showing AC and AR case occurrences at higher and lower temperatures than their respective controls.

Table 2. Mean concentrations of air pollutants and meteorological data by case and control periods between 2004 and 2013.

	Case	Control	*p*-Value
Air Pollutant/Weather Factor	**Mean (95% CI)**		
AC (*n* = 100,636)			
CO (ppm)	0.630 (0.628, 0.632)	0.624 (0.623, 0.626)	<0.001
NO_2 (ppb)	20.9 (20.8, 20.9)	20.6 (20.6, 20.7)	<0.001
O_3 8 h average (ppb)	45.8 (45.7, 46.0)	45.0 (45.0, 45.1)	<0.001
$PM_{2.5}$ (μg/m^3)	33.7 (33.6, 33.8)	33.1 (33.0, 33.1)	<0.001
PM_{10} (μg/m^3)	59.3 (59.1, 59.5)	58.1 (58.0, 58.2)	<0.001
SO_2 (ppb)	4.80 (4.78, 4.81)	4.72 (4.71, 4.73)	<0.001
Relative humidity (%)	73.5 (73.4, 73.5)	73.9 (73.9, 73.9)	<0.001
Temperature (°C)	24.1 (24.1, 24.2)	24.0 (24.0, 24.1)	<0.001
AR (*n* = 140,365)			
CO (ppm)	0.636 (0.634, 0.638)	0.632 (0.631, 0.633)	<0.001
NO_2 (ppb)	21.3 (21.2, 21.3)	21.0 (21.0, 21.0)	<0.001
O_3 8 h average (ppb)	44.1 (44.0, 44.1)	43.7 (43.7, 43.8)	<0.001
$PM_{2.5}$ (μg/m^3)	33.7 (33.6, 33.8)	33.2 (33.2, 33.3)	<0.001
PM_{10} (μg/m^3)	59.2 (59.0, 59.3)	58.1 (58.0, 58.2)	<0.001
SO_2 (ppb)	4.76 (4.75, 4.78)	4.70 (4.69, 4.71)	<0.001
Relative humidity (%)	73.7 (73.6, 73.7)	74.1 (74.1, 74.1)	<0.001
Temperature (°C)	22.9 (22.9, 22.9)	23.0 (23.0, 23.0)	<0.001

CI, confidence interval.

From the previous study, we knew that the first occurrence of AC was positively related with NO_2, O_3, and temperature, and negatively with RH [11]. In this study, we found that each air pollutant was positively associated with the first occurrence of AR in the univariate conditional logistic regression analysis ($p < 0.001$, Table 3); in contrast, RH and temperature resulted in the odds ratio (OR) values smaller than 1.0, suggesting that low RH or temperature might have favored the onset of AR. Due to collinearity caused by the high correlation pairs of CO/NO_2 and $PM_{2.5}$/PM_{10} [11], multivariate analyses were conducted separately by a combination of four models containing CO or NO_2 and $PM_{2.5}$ or PM_{10}. The four models derived similar results, among which the one with NO_2 and PM_{10} was presented in Table 3. Among the significant factors that were associated with AR, NO_2 was positively related, whereas RH and temperature were negatively related. Every increase of 10 ppb NO_2 was associated with an additional 7.6% chance of AR occurrence; a 10% increment of RH and an increment of 1 °C in temperature were related to 9.2% and 1.2% reduction in AR occurrence, respectively. Having compared the AC and AR associations with environmental factors, we found that NO_2 and RH were factors in common but in opposite directions, and temperature was associated with AC and AR in opposite directions.

Table 3. Results of univariate and multivariate conditional logistic regression analyses for AR.

Air Pollutant/ Weather Factor	Univariate		Multivariate	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
O_3 8 h (10 ppb)	1.019 (1.014, 1.023)	<0.001	0.995 (0.990, 1.001)	0.105
SO_2 (ppb)	1.017 (1.013, 1.020)	<0.001	0.996 (0.991, 1.000)	0.503
CO (ppm)	1.076 (1.042, 1.110)	<0.001	–	-
NO_2 (10 ppb)	1.071 (1.060, 1.083)	<0.001	1.076 (1.059, 1.093)	<0.001
PM_{10} (10 μg/m^3)	1.019 (1.017, 1.022)	<0.001	1.003 (0.999, 1.006)	0.150
$PM_{2.5}$ (10 μg/m^3)	1.025 (1.020, 1.029)	<0.001	–	-
Relative Humidity (10%)	0.913 (0.905, 0.920)	<0.001	0.908 (0.899, 0.917)	<0.001
Temperature (°C)	0.987 (0.985, 0.989)	<0.001	0.988 (0.986, 0.990)	<0.001

OR, odds ratio; CI, confidence interval.

As NO_2 was the only air pollutant associated with AC and AR in common, it was interesting to differentiate the levels of NO_2 associated with these two allergic diseases; thus, we applied a multivariate logistic regression analysis for the comparison with adjustments for other related factors as covariates. The averages of NO_2 concentrations during the case period were 20.87 and 21.26 ppb for AC and AR, respectively (Table 2), and the result was complied with the AR-to-AC OR (1.052) after adjustment for age, sex and season (Table 4). O_3, a significantly associated factor with AC, and RH, a meteorological factor commonly associated with both diseases, were used in adjustment and did not change the OR value very much (OR = 1.048, Table 4). No significant change in OR was found until the input of temperature, the factor associated with AC and AR in different directions, and the OR turned to be 0.984 after adjustment for temperature (p = 0.003, Table 4), indicating a 10 ppb decrement of NO_2 related to extra 1.6% risk of AR relative to AC; in other words, AR was associated with the lower levels of NO_2 than AC, after controlling for age, sex, season, O_3, RH, and temperature. The derived significance (p = 0.003) was even smaller than the α value that was corrected by Bonferroni method (0.05/7 = 0.07), indicating a true significant effect, other than a result of multiple tests.

Table 4. Estimated risk of AR relative to AC-associated NO_2 levels (10 ppb).

Disease	N	Model 1 [a]	Model 2 [b]	Model 3 [c]	Model 4 [d]
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
AR	129,062	1.052 (1.043, 1.062)	1.047 (1.037, 1.057)	1.048 (1.037, 1.059)	0.984 (0.973, 0.994)
AC (Reference)	83,975	-	-	-	-
p-value		<0.001	<0.001	<0.001	0.003

[a] adjusted for age, sex and season; [b] adjusted for age, sex, season, and O_3; [c] adjusted for age, sex, season, O_3, and RH; [d] adjusted for age, sex, season, O_3, RH, and temperature.

4. Discussion

The age comparison between both diseases indicated that AR occurred to adults and the elderly more prevalently than did AC. A study provided a possible explanation saying that "asymptomatic sensitization to pollens, pets, or house dust mite was significantly associated with onset of rhinitis symptoms" and "for later development of allergic rhinitis" [30]; therefore, it took time for AR to develop and occur in the adulthood. Additionally, aging could be an impact factor because there was a frequent occurrence of dry nose and nasal congestion in the elderly population, resulting in immunosenescence [31].

As for the sex comparison, females accounted for more than 53.4% of AC and AR occurrences, suggesting female predominance in allergic diseases. This observation is quite common and recognized as sex-specific bias in IgE-mediated allergic diseases [32]. Although AR was known to be more prevalent for young boys than girls [15,33], there was a consistent finding, summarized by a number of papers, showing that sex-related AR prevalence was switched from childhood (male predominance) to adulthood (female predominance) [34]. Consequently, in a population with all ages, females are usually the majority who suffer allergic diseases (e.g., AC and AR).

The t-test results shown in Table 2 give a general idea about environmental exposures for cases and controls. Although the minimal but significant difference for each environmental factor comparison might result from the large sample size, it could be a potential difference between exposures of cases and controls. These data complied with those derived from the univariate conditional logistic regression analysis (Table 3) and were further examined by multivariate regression analyses, which showed NO_2, RH, and temperature as significantly associated factors with AR occurrence (Table 3).

Among the seasonal differences in occurrence, a major influential factor between AC and AR was winter, which appeared to be a protector for the former (19.6%, the lowest) but a malignant factor for the latter (28.7%, the highest). This difference was supported by the results of multivariate logistic analyses,

which showed a positive association with temperature (OR = 1.013) for AC [11] and a negative one (OR = 0.988) for AR (Table 3). AR patients are known to be susceptible to cold weathers [33,35,36], especially those with sudden temperature changes [37]. In contrast, AC was hardly influenced by cold weather, probably because coldness did not trigger AC, and also there were relatively few AC-induced allergens present in the cold season.

Our AR results were in support of a previous study conducted in Shanghai, China, which found negative associations of AR with temperature and RH [38]. AR-associated air pollutants identified in that study, however, were $PM_{2.5}$ and PM_{10}, which are different from what this study found (NO_2). The difference in AR-associated air pollutants could be due to diverse patterns of air pollution in the ambient environments. The negative AR association with temperature and RH is reasonable, because warm and humid weather assists with the nose functions of warming and humidifying the inhaled air, and subsequently effects a reduction in AR occurrence. Nevertheless, extremely high humidity may result in an opposite effect. Another Chinese study indicated that, besides low RH, high RH was related with AR hospital outpatient visits, suggesting that high humidity could favor the growth and reproduction of allergen [39], such as molds that grew with indoor dampness [40]. That study, however, indicated a time difference between the effects of high and low RHs on AR, showing a 3-day lag for high RH but an immediate impact for low RH. It is suggested that the effect of high RH on AR may not be as apparent as that of low RH, and this could be the reason why we merely found the negative AR association with RH in this study.

The OR for comparing the NO_2 association with AR to that with AC changed from 1.048 to 0.984 after adjustment for temperature, indicating a significant confounding effect of temperature on the NO_2 associations with both diseases. Having controlled for all covariates, we found that the risk of AR was associated with the relatively low levels of NO_2, compared with that of AC. If NO_2 is truly effective in AC and AR occurrences, it indicates that AR may be triggered or exacerbated at lower levels of NO_2 than AC, with all other affecting factors (covariates) being controlled. NO_2 with CO is usually considered a surrogate of vehicle emissions, which are found to be associated with allergic diseases by a number of studies, but the effects of vehicle emissions on these diseases are not completely known [41]. Of all kinds of vehicle emissions, DEP has been confirmed to likely induce allergic inflammation and to exacerbate AR symptoms when exposure to allergens occurs [22–26]. As for AC, there have been fewer studies that examined this issue, and the detailed mechanism allegedly remains unclear [21]. Two studies using cultured human conjunctival epithelium for testing indicated that DEP exposure increased inflammatory factor expression in human conjunctiva and led to allergic conjunctival responses [42,43]. Thus, DEP, surrogated by NO_2, may actually result in certain inflammatory effects on AC and AR.

Should DEP effects take place, it appears that AR is triggered or exacerbated by lower levels of DEP (NO_2) than AC. The reasons for this are yet to be discovered, but one assumption is that the olfactory epithelium may be more susceptible to DEP than the conjunctival epithelium. With the presumably higher susceptibility, the mechanism of DEP effects on AR should be easier to observe than that on AC; the finding that AR-related papers outnumber AC-related ones seems to be in support of the assumption. In addition, the worldwide finding that prevalence of AR is usually higher than that of AC could be at least partly explained by the assumption, because of the lower threshold for AR occurrence. In terms of exposure, the nose is generally exposed to inhaled air 24 hours a day, whereas the eyes are not exposed during sleep. With the longer time of exposure, the threshold concentrations of triggering matter (e.g., DEP) could be lower.

As mentioned in the previous work of AC analysis, this research using secondary data comes with similar limitations, such as representativeness of subjects, correctness for pairing of disease and environmental information, and lack of personal information [11]; as described in the previous study, these limitations appeared to be minor issues for this type of study. Another limitation was unable to assess allergen exposure for these two allergic diseases due to lack of ambient allergen information. Fortunately, the case-crossover design made exposure conditions of cases and controls

virtually identical, and thus no adjustment was needed for the conditional logistic regression; as for the comparison between risks of AC and AR associated with NO_2, the confounding effect of seasons could be evened out by adjustment in the regression analysis. Note that we used the same database within the same time frame for comparing risks of AC and AR associated with NO_2. This result provides a new direction for studying the effect of air pollution on allergic diseases as well as for intervening to mitigate the impairment.

5. Conclusions

In contrast to AC, AR seemingly occurred the most to adults under 50 years of age and in winter in Taiwan from 2004 to 2013; similarly, women were more susceptible to both allergic diseases. NO_2 was found to be positively associated with AR, whereas RH and temperature were negatively related. Both AC and AR were positively associated with NO_2, and AR was associated with the lower levels of NO_2 after adjustment for age, sex, season, O_3, RH, and temperature. As NO_2 is considered as a surrogate of vehicle emissions (e.g., DEP), it is advised that AR patients pay extra attention to reducing exposures to traffic related air pollution.

Author Contributions: Conceptualization, L.-M.Y.; methodology, C.-J.H.; software, S.-P.H.; validation, C.-J.H.; formal analysis, S.-P.H.; investigation, S.-P.H.; resources, C.-C.T.; data curation, S.-P.H.; writing—original draft preparation, S.-P.H.; writing—review and editing, L.-M.Y.; visualization, L.-M.Y.; supervision, L.-M.Y.; project administration, L.-M.Y.; funding acquisition, C.-C.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Taiwan's Ministry of Science and Technology under Grant No: MOST 105-2621-M-320-001. L.-M.Y. was partly supported by Tzu Chi University Supplement Grant (610400184-08).

Acknowledgments: This study is based in part on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes (Registered number NHIRD-104-452). The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.

Conflicts of Interest: The authors declare no conflict of interest.

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