Outpatient visits for allergic diseases are associated with exposure to ambient fungal spores in the Greater Taipei area

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Abstract

Allergic diseases are prevalent worldwide, and may result from exposure to various substances. Exposure to ambient bioaerosols is a potential risk factor for allergic diseases; however, accurate exposure assessment is challenging due to the limited number of outdoor monitoring stations. In this study, the relationships between ambient bioaerosol exposure and allergic diseases (i.e., acute conjunctivitis, allergic rhinitis, and asthma) were evaluated using validated land-use regression (LUR) models to estimate the exposure levels. Data on the daily outpatient visits were retrieved from the Taiwan National Health Insurance Research Database. The total fungal spore count was associated with acute conjunctivitis in males at the second and third quartiles with relative risks (RRs) of 1.75 (95% confidence interval [CI] = 1.24, 2.48) and 1.32 (95% CI = 1.03, 1.70), respectively. It was also associated with asthma in both sexes when concentration ≥ 95th percentile with RRs = 3.06 (95% CI = 1.89, 4.95) in males and 1.73 (95% CI = 1.08, 2.76) in females. *Cladosporium* was correlated with acute conjunctivitis in females at a concentration ≥ 95th percentile with RR = 2.90 (95% CI = 1.40, 6.04). Basidiospores were associated with allergic rhinitis in males at the third and fourth quartiles with RRs = 1.88 (95% CI = 1.44, 2.45) and 1.49 (95% CI = 1.20, 1.84), respectively. Meteorological parameters including relative humidity and rainfall were also crucial factors associated with the number of outpatient visits. Our results revealed that ambient fungal spores are crucial determinants of allergic diseases. In addition, the use of LUR models is feasible for assessing the exposure of ambient bioaerosols.

***Keywords*:** Bioaerosols; Acute conjunctivitis; Allergic rhinitis; Asthma; Land use regression (LUR)

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INTRODUCTION

Allergic diseases such as allergic conjunctivitis, rhinitis, and asthma are non-communicable diseases that affect individuals worldwide (Bachert *et al*., 2006; Henriksen *et al*., 2015; Lunn and Craig, 2011; Reid and Gamble, 2009). In addition to reducing quality of life, these diseases also affect health care use and expenditure. In Taiwan, the National Health Insurance covers a large proportion of the expenses incurred by these preventable diseases, particularly for pre-school and school children (Chen *et al*., 2010b). Exposure to ambient air pollution has been demonstrated to increase the risk of various morbidities such as asthma, rhinitis, conjunctivitis, eczema, and decreased lung function (Anderson *et al*., 2010; Brauer *et al*., 2007; Chen *et al*., 2013; Chien *et al*., 2014; Chien *et al*., 2012; Mimura *et al*., 2014; Tarigan *et al*., 2017). Gaseous and particulate pollutants are of primary concern, particularly in high-traffic and industrial polluted areas (Aguilera *et al*., 2013; Anderson *et al*., 2010; Becerra *et al*., 2013; Chan *et al*., 2009; Chen *et al*., 2011; Chen *et al*., 2004; Wang and Chau, 2013). However, studies have demonstrated that ambient bioaerosols also critically increase the risk of the allergic diseases (Atkinson *et al*., 2006; Burge and Rogers, 2000; Harley *et al*., 2009; Lovasi *et al*., 2013).

To assess the health impact of ambient bioaerosols, one monitoring station is typically used as the primary source of exposure data (Atkinson *et al*., 2006; Chen *et al*., 2014a; Dales *et al*., 2000; Harley *et al*., 2009; Lierl and Hornung, 2003; Raphoz *et al*., 2010). However, the exposure levels measured at only one or a few monitoring stations cannot be generalized to larger scale areas because of spatiotemporal variation in bioaerosol distributions. In our previous studies, we successfully developed land-use regression (LUR) models to estimate the ambient bioaerosol levels in the Greater Taipei area (Kallawicha *et al*., 2015a; Kallawicha *et al*., 2015b). The data were then used to investigate the associations between exposure to ambient bioaerosols and allergic skin diseases, the results revealing positive relationships (Kallawicha *et al*., 2016).

Recent studies in Taiwan have indicated that the prevalence of allergic diseases and asthma is increasing (Chen *et al*., 2014b; Liao *et al*., 2009; Tsai *et al*., 2006). Ambient bioaerosols could be one of the crucial risk factors for allergic diseases among Taiwanese population. Therefore, in this study, we further investigated the influence of ambient bioaerosols on the allergic diseases—namely acute conjunctivitis, allergic rhinitis, and asthma—among the residents in the Greater Taipei area. Exposure data were estimated using the validated LUR models in addition to previously collected bioaerosol monitoring results (Kallawicha *et al*., 2015a; Kallawicha *et al*., 2015b). The health outcomes were daily outpatient visits for allergic diseases in the Greater Taipei area.

MATERIALS AND METHODS

Health outcome data

Secondary health care facility visit records from the National Health Insurance Research Database (NHIRD) were used in this study; this database covers over 99.9% of the residents in Taiwan. Data were obtained from the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. The number of outpatient visits for allergic diseases was calculated for each district in the Greater Taipei area. The health outcomes of interest were acute conjunctivitis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 372.0), allergic rhinitis (ICD-9-CM: 477), and asthma (ICD-9-CM: 493). The methods were described in detail previously (Kallawicha *et al*., 2016). The average daily outpatient number for each district over the study period in each season (i.e. each sampling campaign) was calculated for the subsequent analysis due to the use restriction of NHIRD.

Bioaerosol exposure levels

The average exposure levels in each district during the study period were estimated using LUR models and previously collected monitoring data (Kallawicha *et al*., 2015a; Kallawicha *et al*., 2015b). In our previous studies, ambient bioaerosol samples were collected from 44 representative sites across the Greater Taipei area between November 2011 and August 2012. We conducted four sampling campaigns during the study period with each campaign lasting 1-2 weeks, including fall (November 21-December 1, 2011), winter (February 13 - 22, 2012), spring (April 16 - 26, 2012) and summer (July 23 - 31 and August 21 - 22, 2012; the discontinuous sampling period was due to a typhoon event). LUR models for total fungal spores, major fungal taxa, total bacteria, and endotoxins were developed by using land utilization data, meteorological parameters, atmospheric pollutants, and important landmarks. These models were validated and had a cross-validation R^2 (CV-R^2) ranging from 0.38 to 0.57. In the current study, the LUR models were used to estimate the levels of total fungal spores and major fungal taxa only because of the relatively low CV-R^2 obtained for total bacteria and endotoxin (Kallawicha *et al*., 2015a). The total bacteria and endotoxin exposure levels were estimated using the spatial interpolation function (Ordinary Kriging) in the geographic information system software ArcGIS version 9.3 (Esri, Redlands, CA, USA).

Environmental variables

Meteorological and atmospheric pollutant data were obtained from 49 monitoring stations of the Taiwan Central Weather Bureau and 18 monitoring stations of the Environmental Protection Administration. The meteorological parameters were temperature, relative humidity (RH), wind speed, and rainfall. Atmospheric pollutants considered were particulate matter with aerodynamic diameters of ≤10 and ≤2.5 μm (PM_{10} and $PM_{2.5}$, respectively), carbon monoxide

(CO), ozone (O_3), nitrogen oxides (NOx, NO, NO_2), and sulfur dioxide (SO_2). Ordinary kriging was used to calculate the average level of each parameter in each district.

Sociodemographic variables

To adjust for the social characteristics of each district, sociodemographic data were obtained from Taiwan Demography Quarterly, the Statistical Abstract of Cities and Counties in Taiwan, and the Taiwan Census. The variables considered included population size and density (persons/ km^2), percentage of population (age >15 years) with higher education, percentage of aboriginals, percentage of elderly population (age > 65 years), number of hospitals, density of hospitals (number of hospitals/km^2), number of physicians per 100,000 people, and urbanization level of each district as previously reported by Liu *et al*. (2006).

Statistical analysis

The difference in outpatient visit numbers between males and females was examined using Wilcoxon Signed-Rank Test. The effect of bioaerosol exposure on the outcome diseases was assessed as previously described (Kallawicha *et al*., 2016). In brief, multivariate Poisson models with generalized estimating equations (GEE) were used with the number of outpatient visits as the dependent variable, and bioaerosol levels, environmental factors, and social demographic variables as independent variables. Univariate analyses were conducted for each health outcome of interest. The bioaerosol concentrations were categorized into quartiles or using the 95th percentile as a cutoff point for analysis. The variables with $p < 0.2$ were included in the further multivariate analysis. Social demographic factors and air pollutants with $p < 0.05$ were adjusted in the final model. Relative risks (RRs) were calculated for significant bioaerosols and meteorological parameters ($p < 0.05$). Statistical analyses and data processing were performed using Microsoft Excel 2007 and PROC GENMOD in SAS (v 9.2; SAS, Cary, NC, USA)

RESULTS

The average outpatient visit numbers for acute conjunctivitis, allergic rhinitis, and asthma during the study period were 15, 15, and 38 cases per day, respectively. Females tended to make more visits than males for each disease in each season; however, the difference was not statistically significant ($p > 0.05$) (Fig. 1). Most visits were reported from the major districts in Taipei city (i.e., Xinyi and Zhongzheng) and New Taipei City (i.e.; Xindian and Zhonghe). The spatial distributions of the average number of outpatient visits for each disease are illustrated in Fig. 2.

The distribution of bioaerosol concentrations across the Greater Taipei area exhibited substantial spatial variation. The concentration of total fungal spores was 1413±1750 spores/m^3 (mean ± standard deviation). More bioaerosol data are provided in Table 1. One-way analysis of variance (ANOVA) and the Kruskal-Wallis test revealed a significant seasonal variation in meteorological parameters and atmospheric pollutants in our study as previously described (Kallawicha *et al*., 2015). The detailed information on environmental parameters were presented in our previous paper (Kallawicha *et al*., 2016).

The univariate analysis results for the relationships between allergic diseases and bioaerosol concentrations at each quartile are listed in Table 2. Both positive and negative relationships were observed. Positive correlations were observed between total fungal spores and acute conjunctivitis in males, and between basidiospores and acute conjunctivitis in both sexes as well as basidiospores and allergic rhinitis in males only. Regarding asthma outpatient visits, most bioaerosols were negatively associated with the number of visits in males; however, total bacteria exhibited significant positive relationships with visit number in both males and females.

Table 3 presents the final models for the studied allergic diseases. The RRs for significant bioaerosols and meteorological parameters, obtained after adjusting for potential confounders (i.e., air pollutants and social demographic factors), are listed. Total fungal spore levels at the second (RR=1.75, 95% confidence interval [CI] = 1.24, 2.48) and third (RR = 1.32, 95% CI = 1.03, 1.70) quartiles were positively associated with acute conjunctivitis in males, whereas a *Cladosporium* level of ≥ 95th percentile was positively correlated with acute conjunctivitis in females (RR = 2.90, 95% CI = 1.40, 6.04). Basidiospore levels at the third (RR = 1.88, 95% CI = 1.44, 2.45) and fourth (RR = 1.49, 95% CI = 1.20, 1.84) quartiles were positively associated with allergic rhinitis in males. For asthma, high concentrations of total fungal spores (≥ 95th percentile) were associated with high RRs in both males (RRs = 3.06, 95% CI = 1.89, 4.95) and females (RR = 1.73, 95% CI= 1.08, 2.76). Meteorological factors, including RH, wind speed, and rainfall were also associated with the studied allergic diseases, mainly acute conjunctivitis. Negative relationships were observed with both RH and rainfall, whereas wind speed exhibited both positive and negative associations with the diseases.

DISCUSSION

In this study, the ambient fungal spores were demonstrated to be crucial risk factors for allergic diseases, namely acute conjunctivitis, allergic rhinitis, and asthma. Although similar results have been reported in other studies (Adhikari *et al*., 2011; Atkinson *et al*., 2006; Behbod *et al*., 2015; Chen *et al*., 2011; Chen *et al*., 2014a; Harley *et al*., 2009), according to our review of the relevant literature, ours is the first study to apply validated LUR models for assessment of fungal exposure levels and to further investigate their impact on these disease outcomes. The use of LUR to assess the exposure levels in this study characterized the spatiotemporal variation of bioaerosols and provided a more accurate exposure assessment of the study area. The LUR models were cross-validated using the leave-one-out cross-validation method with coefficients of determination (R^2) comparable to those in other air pollution studies (Adam-Poupart *et al*., 2014; Chen *et al*., 2010a; Kashima *et al*., 2009; Rivera *et al*., 2012; Saraswat *et al*., 2013).

Our study used National Health Insurance data that included the number of outpatient visits reported from each health care facility in each district of the Greater Taipei area. Similar to previous studies, most cases were reported from the densely populated districts in Taipei City and New Taipei City (Chien *et al*., 2014; Kallawicha *et al*., 2016); therefore, population size and number of hospitals were adjusted in our multivariate analysis (Table 3). In our study, the number of outpatient visits for allergic diseases were relatively low compared with those for allergic skin diseases in the same study area, including atopic dermatitis (ICD-9-CM 691.8) and contact dermatitis and other types of eczema (ICD-9-CM 692.9) (Kallawicha *et al*., 2016). This finding may be attributed to the disease characteristics and treatment methods. Most acute conjunctivitis and allergic rhinitis cases are not severe, and the symptoms can be treated with over-the-counter medication. Similarly, most patients diagnosed as having asthma were suggested by the treating physician to obtain an asthma inhaler and medication. Thus, the outpatient visit records probably contain data for only relatively serious conditions or newly diagnosed asthma cases. In addition, the multiple etiologies of contact dermatitis may have resulted in the higher number of visits which was discussed in our previous report (Kallawicha *et al*., 2016). The data obtained from the NHIRD did not provide information at the individual level because of patient privacy. Thus, the potential causes could not be further scrutinized.

In the univariate analyses, we categorized bioaerosol levels into four quartiles as well as according to cutoff point of ≥ 95th percentile. Both positive and negative associations were observed between bioaerosols and allergic diseases (Table 2). However, after adjustment for the environmental and sociodemographic factors, most relationships became nonsignificant, probably because of covariation between bioaerosols and environmental factors. Various studies have demonstrated that temperature, humidity, wind speed, and environmental pollutants are correlated to ambient bioaerosol concentrations because of growth requirements or the ambient covariation effect (Abdel Hameed *et al*., 2012; Alghamdi *et al*., 2014; Grinn-Gofroń *et al*., 2011; Ho *et al*., 2005). This multicollinearity can influence the association between bioaerosols and health. Thus, nonsignificant effects were observed in the multivariate models.

Among all the bioaerosols, total fungal spores appear to be the most significant and consistent predictors of the studied allergic diseases (Table 3). Total fungal spores exhibited a positive association with acute conjunctivitis in males, with RRs of 1.75 (95% CI = 1.24, 2.48), 1.32 (95% CI = 1.03, 1.70), and 1.36 (95% CI = 0.71, 2.61) for the second, third and fourth quartiles, respectively. The nonsignificant association in the fourth quartile was probably due to a low number of cases in this quartile. The concentrations of total fungal spores were also positively associated with outpatient visits for asthma in both males and females. These positive associations were observed only when the total fungal spore concentrations exceeded the 95th percentile. The RRs were 3.06 (95% CI = 1.89, 4.95) for males and 1.73 (95% CI = 1.08, 2.76) for females. Total fungal spores comprised various fungal taxa recovered in the samples, which included all aerodynamic size ranges and various allergens of fungal spores. Different aerodynamic sizes can settle in different regions of the respiratory tract as well as mucous membranes, and induce distinct symptoms (Fireman *et al*., 2017; Gao *et al*., 2015; Sturm, 2012, 2017). Therefore, the positive association between total fungal spores and number of visits was expected, as demonstrated in previous studies (Atkinson *et al*., 2006; Behbod *et al*., 2015; Dales *et al*., 2000; Meharzi *et al.,* 2017). Although the results of a European cohort study revealed that exposure to diverse fungal taxa could protect against asthma among children living on farms (Ege *et al*., 2011), it appears that overall, very high total fungal concentrations exert adverse effects on patients with asthma. However, we could not elucidate the effect of fungal diversity in this study because the microscopic method could be used to identify fungal spores to only the genus or higher levels based on their morphology. In addition, the biological mechanisms of the antigens and mycotoxins produced by each fungal spore may induce a broad spectrum of symptoms in individuals (Bennett and Klich, 2003; Capasso *et al*., 2015; Klich, 2009; Wong *et al*., 2016). These complex reactions may contribute to diverse observations among studies and warrant for further investigation.

Basidiospores and *Cladosporium* also exhibited positive associations with the studied allergic diseases. These two fungal taxa are prevalent in the outdoor environment, and were recovered in >98% of all samples. Basidiospores were significantly and positively associated with allergic rhinitis in males at the third (RR = 1.88, 95% CI = 1.44, 2.45) and fourth (RR = 1.49, 95% CI = 1.20, 1.84) quartiles. *Cladosporium* was associated with acute conjunctivitis in females when the concentration exceeded the 95th percentile (RR = 2.90, 95% CI = 1.40, 6.04). Outdoor *Cladosporium* spores were reported as a risk factor for rhinitis in a cohort study on the children with parental allergies in the USA (Behbod *et al*., 2015); however, we did not observe this risk in our study. This might have resulted from the use of secondary data in our study, which included cases from all age groups. Age stratification could not be performed because of no or a very low number of cases in each age group for each study district. The associations between these fungal taxa and adverse health effects have also been reported in other studies. The outcomes included asthma (Atkinson *et al*., 2006; Rosas *et al*., 1998), early life wheezing (Harley *et al*., 2009), contact dermatitis (Kallawicha *et al*., 2016), and lung function decline (Chen *et al*., 2014a).

After adjustment for the effect of the ambient air pollution, which varied widely across the study area, we observed that meteorological parameters (i.e., RH, wind speed, and rainfall) were associated with the studied allergic diseases. Ambient humidity (i.e., RH and rainfall) was negatively associated with the number of visits for acute conjunctivitis and asthma. Wind speed, however, exhibited a negative relationship with acute conjunctivitis in males, but a positive correlation in females. These results are inconsistent with those in our previous report, which revealed that these meteorological parameters were positively associated with allergic skin diseases. However, this inconsistent result of the effect of each meteorological parameter on each disease has been reported differently among studies (Kim *et al*., 2011; Park *et al*., 2013; Rosas *et al*., 1998). A possible explanation for the effect of humidity on conjunctivitis was reported in an experimental study to be that an increase in dryness and ocular irritation is caused by low humidity (Wyon *et al*., 2002). Low humidity and high wind speed also enhance the resuspension of particulate matter and facilitate the transportation of aeroallergens attached to particles (Mimura *et al*., 2014); aeroallergens can also exacerbate asthma symptoms (Tang *et al*., 2007). Nevertheless, wind speed may increase or reduce the concentrations of bioaerosols as well as other air pollutants, depending on whether the wind speed causes a dilution or resuspension effect (Burch and Levetin, 2002; Kallawicha *et al*., 2015b; Lin and Li, 2000). Therefore, the impact of wind on the health outcomes can be observed differently.

Although we successfully used the LUR models to estimate the bioaerosol exposure levels in the Greater Taipei area and demonstrated the associations between ambient fungal spores and allergic diseases, several limitations of this study must be discussed. The first limitation was disease etiology. To obtain sufficient data for statistical analysis, we included all cases under the given ICD-9-CM code for each outcome. However, some cases reported by the treating physician might have resulted from other factors not examined in this study (e.g., viral infection). Second, we assumed that the hospital location in each district was the exposure location of corresponding patients, because exact patient addresses could not be obtained due to patient privacy. Thus, we used the data on outpatient visits for each studied disease, which revealed that the visits were usually for minor conditions, and that people tended to visit local clinics or hospitals. This minimized the chances of patients visiting medical centers in different districts.

CONCLUSION

In addition to personal exposure assessment, LUR has been proven to be an alternative method for estimating individual exposure levels. By using this estimation, we demonstrated that exposure to high levels of ambient fungal spores was associated with allergic rhinitis, acute conjunctivitis, and asthma. In addition to total fungal spores, basidiospores and *Cladosporium* are critical risk factors for these outcomes. Meteorological parameters (i.e., RH, wind speed and rainfall) are also significantly associated with the number of medical visits. Our findings highlight the risk of ambient bioaerosol exposure. Future studies should investigate potential dose-response or threshold effects of ambient bioaerosol exposure. Moreover, personal protections strategies are encouraged for atopic and immunocompromised patients to avoid or reduce their exposure to bioaerosols. Decreased symptoms and the severity reduction of diseases can increase patients' quality of life as well as reduce unnecessary medical expenditure.

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FIGURE LEGENDS

Fig. 1. Average number of sex-specific outpatient visits of each disease in each season during November 2011-August 2012

Fig. 2. Spatial distributions of the average outpatient visit numbers of acute conjunctivitis, allergic rhinitis, and asthma in the Greater Taipei area during November 2011- August 2012 (Redline delineates the border of Taipei City)

TABLE TITLES

Table 1. Distribution of bioaerosol concentrations during November 2011 – August 2012

Table 2. Univariate analysis of allergic diseases and bioaerosol concentrations

Table 3. Relative risks of allergic diseases associated with bioaerosol concentrations