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 (viz., 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 the 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 critical determinants of allergic diseases. In addition, using LUR models to assess exposure to ambient bioaerosols is feasible.

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

INTRODUCTION

Allergic diseases such as allergic conjunctivitis, rhinitis, and asthma are non-communicable diseases that affect individuals worldwide (Bachert et al., 2006; Reid and Gamble, 2009; Lunn and Craig, 2011; Henriksen et al., 2015). 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 (Brauer et al., 2007; Anderson et al., 2010; Chien et al., 2012; Chen et al., 2013; Chien et al., 2014; Mimura et al., 2014; Tarigan et al., 2017). Gaseous and particulate pollutants are of primary concern, particularly in high-traffic and industrial polluted areas (Chen et al., 2004; Chan et al., 2009; Anderson et al., 2010; Chen et al., 2011; Becerra et al., 2013; Aguilera et al., 2013; Wang and Chau, 2013). However, studies have demonstrated that ambient bioaerosols also critically increase the risk of allergic diseases (Burge and Rogers, 2000; Atkinson et al., 2006; 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 (Dales et al., 2000; Lierl and Hornung, 2003; Atkinson et al., 2006; Harley et al., 2009; Raphoz et al., 2010; Chen et al., 2014a). However, the exposure levels

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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, b). 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
(Tsai et al., 2006; Liao et al., 2009; Chen et al., 2014b).
Ambient bioaerosols could be one of the crucial risk factors
for allergic diseases among the 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, b). 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, b). 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 the total bacteria and endotoxins (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. The atmospheric pollutants considered
were particulate matter with aerodynamic diameters of $\leq 10$
and $\leq 2.5 \mu m$ ($PM_{10}$ and $PM_{2.5}$, respectively), carbon
monoxide (CO), ozone (O$_3$), nitrogen oxides (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 the 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 $1413 \pm 1750$ spores m$^{-3}$ (mean $\pm$ 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 was 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 the 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, the total bacteria exhibited significant positive relationships with the visit number in both males and females.

Table 3 presents the final models for the studied allergic diseases. The RR$\text{s}$ for significant bioaerosols and meteorological parameters, obtained after adjusting for potential confounders (i.e., air pollutants and social demographic factors), are listed. The 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 $\geq 95^{th}$ percentile

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

<table>
<thead>
<tr>
<th>Bioaerosols*</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Q2 (Median)</th>
<th>Q3</th>
<th>95th P</th>
<th>Q4 (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fungal spores (spores m⁻³)</td>
<td>1412.85</td>
<td>1750.34</td>
<td>27.97</td>
<td>188.44</td>
<td>582.57</td>
<td>2292.89</td>
<td>4130.02</td>
<td>11599.54</td>
</tr>
<tr>
<td>Ascospores (spores m⁻³)</td>
<td>327.16</td>
<td>338.85</td>
<td>1.81</td>
<td>31.79</td>
<td>111.60</td>
<td>614.13</td>
<td>914.41</td>
<td>1412.48</td>
</tr>
<tr>
<td>Aspergillus/ Penicillium (spores m⁻³)</td>
<td>309.15</td>
<td>452.10</td>
<td>1.58</td>
<td>26.67</td>
<td>474.92</td>
<td>1224.96</td>
<td>2526.73</td>
<td></td>
</tr>
<tr>
<td>Basidiospores (spores m⁻³)</td>
<td>276.61</td>
<td>314.80</td>
<td>3.51</td>
<td>34.84</td>
<td>74.50</td>
<td>474.92</td>
<td>1224.96</td>
<td>2526.73</td>
</tr>
<tr>
<td>Cladosporium (spores m⁻³)</td>
<td>66.59</td>
<td>60.73</td>
<td>3.81</td>
<td>10.86</td>
<td>34.00</td>
<td>109.97</td>
<td>168.21</td>
<td>219.27</td>
</tr>
<tr>
<td>Endotoxins (EU m⁻³)</td>
<td>2.52</td>
<td>2.17</td>
<td>0.32</td>
<td>0.87</td>
<td>1.74</td>
<td>3.77</td>
<td>6.84</td>
<td>12.13</td>
</tr>
<tr>
<td>Total bacteria (cells m⁻³)</td>
<td>28797.34</td>
<td>14603.43</td>
<td>3156.09</td>
<td>15161.20</td>
<td>29923.35</td>
<td>39104.38</td>
<td>53210.78</td>
<td>71958.00</td>
</tr>
</tbody>
</table>

All bioaerosol concentrations were estimated using LUR models for each district, except endotoxin and total bacteria that ordinary kriging technique was used; total n = 164 (41 districts x 4 seasons).

*Q = quartile, P = percentile, SD = standard deviation.

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 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 (Atkinson et al., 2006; Harley et al., 2009; Adhikari et al., 2011; Chen et al., 2011, 2014a; Behbod et al., 2015), 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 (Kashima et al., 2009; Chen et al., 2010a; Rivera et al., 2012; Saraswat et al., 2013; Adam-Poupart et al., 2014).

Our study used National Health Insurance data that
Table 2. Univariate analysis of allergic diseases and bioaerosol concentrations.

<table>
<thead>
<tr>
<th>Bioaerosols</th>
<th>Acute conjunctivitis (β (95% CI))</th>
<th>Allergic rhinitis (β (95% CI))</th>
<th>Asthma (β (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Females</td>
<td>Males Females</td>
<td>Males Females</td>
</tr>
<tr>
<td>Total fungal spores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.2469 (-1.4632)</td>
<td>-0.8876 (-0.5083)</td>
<td>-0.1179 (0.8271)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.1593 (-0.8288)</td>
<td>-0.5682 (-0.8202)</td>
<td>-0.2400 (0.2235)</td>
</tr>
<tr>
<td>Q4</td>
<td>0.2802 (-1.2780)</td>
<td>-0.9055 (-0.5938)</td>
<td>-0.4480 (0.3001)</td>
</tr>
<tr>
<td>Ascospores</td>
<td>-0.1199 (-0.8876)</td>
<td>-0.8538 (-0.5293)</td>
<td>-0.1095 (0.7829)</td>
</tr>
<tr>
<td>Q3</td>
<td>-0.0020 (-0.8096)</td>
<td>-0.5569 (-0.8066)</td>
<td>-0.2840 (0.0305)</td>
</tr>
<tr>
<td>Q4</td>
<td>-0.2610 (-1.0806)</td>
<td>-0.7681 (-0.7895)</td>
<td>-0.2570 (0.5922)</td>
</tr>
<tr>
<td>Aspergillus/Penicillium</td>
<td>-0.1935 (0.0586)</td>
<td>0.9403 (0.4691)</td>
<td>-0.0310 (0.6647)</td>
</tr>
<tr>
<td>Q3</td>
<td>-0.1167 (-0.4020)</td>
<td>0.5939 (-0.1229)</td>
<td>-0.1245 (0.1175)</td>
</tr>
<tr>
<td>Q4</td>
<td>-0.1086 (-0.0184)</td>
<td>0.3844 (-0.0349)</td>
<td>-0.3810 (0.1310)</td>
</tr>
<tr>
<td>Basidiospores</td>
<td>0.0234 (0.4994)</td>
<td>0.8058 (0.4649)</td>
<td>-0.2905 (0.4535)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.2297 (0.0272)</td>
<td>0.6585 (0.1420)</td>
<td>-0.6813 (-0.2252)</td>
</tr>
<tr>
<td>Q4</td>
<td>0.0627 (0.4986)</td>
<td>0.5945 (-0.1746)</td>
<td>-0.4768 (-0.2128)</td>
</tr>
<tr>
<td>Cladosporium</td>
<td>-0.1388 (-0.7342)</td>
<td>-0.8539 (-0.5541)</td>
<td>-0.3501 (0.4715)</td>
</tr>
<tr>
<td>Q3</td>
<td>-0.0756 (-1.0678)</td>
<td>-0.6017 (-0.8786)</td>
<td>-0.4514 (-0.0267)</td>
</tr>
<tr>
<td>Q4</td>
<td>-0.0693 (-0.5280)</td>
<td>-0.7015 (-0.6735)</td>
<td>-0.6680 (0.0154)</td>
</tr>
<tr>
<td>Total bacteria</td>
<td>-1.6445 (-0.0273)</td>
<td>-1.0025 (-0.9806)</td>
<td>0.2466 (0.7995)</td>
</tr>
<tr>
<td>Q3</td>
<td>-0.7172 (-0.1860)</td>
<td>-0.9785 (-0.4120)</td>
<td>0.2049 (0.6897)</td>
</tr>
<tr>
<td>Q4</td>
<td>-0.8281 (-0.0039)</td>
<td>-0.3927 (-0.5109)</td>
<td>-0.0198 (0.1191)</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>-0.1848 (-0.6981)</td>
<td>-1.2042 (-0.6307)</td>
<td>0.0702 (-0.0574)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.0839 (-0.0268)</td>
<td>0.08970 (-0.6376)</td>
<td>-0.4066 (-0.7343)</td>
</tr>
<tr>
<td>Q4</td>
<td>-0.3390 (-0.8387)</td>
<td>0.7947 (-0.9672)</td>
<td>-0.039 (-0.3875)</td>
</tr>
</tbody>
</table>

All β coefficients are listed and those with p < 0.05 are in bold; total n = 164 (41 districts × 4 seasons).

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

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Predictor variables</th>
<th>Males (RR, 95% CI)</th>
<th>Females (RR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute conjunctivitis</td>
<td>Total fungal spores</td>
<td>Q1 1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q2 1.75 (1.24, 2.48)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 1.32 (1.03, 1.70)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 1.36 (0.71, 2.61)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cladosporium</td>
<td>&lt; 95th P 0.88 (0.83, 0.94)</td>
<td>1.68 (1.07, 2.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 95th P 2.90 (1.40, 6.04)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>RH</td>
<td>0.50 (0.31, 0.80)</td>
<td>0.28 (0.22, 0.34)</td>
</tr>
<tr>
<td></td>
<td>Wind speed</td>
<td>-</td>
<td>0.16 (0.87, 2.07)</td>
</tr>
<tr>
<td></td>
<td>Rainfall</td>
<td>-</td>
<td>0.24 (0.12, 0.48)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Basidiospores</td>
<td>Q1 1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q2 1.63 (0.88, 2.99)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 1.88 (1.44, 2.45)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 1.49 (1.20, 1.84)</td>
<td>-</td>
</tr>
<tr>
<td>Asthma</td>
<td>Total fungal spores</td>
<td>&lt; 95th P 3.06 (1.89, 4.95)</td>
<td>1.73 (1.08, 2.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 95th P 1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rainfall</td>
<td>0.50 (0.40, 0.62)</td>
<td>-</td>
</tr>
</tbody>
</table>

Total n = 164 (41 districts × 4 seasons).

Adjusted for air pollution and social demographic factors.

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 advised 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 univariable analyses, we categorized bioaerosol levels into four quartiles as well as according to a 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 (Ho et al., 2005; Grinn-Gofroń et al., 2011; Abdel Hameed et al., 2012; Alghamdi et al., 2014). 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 (Sturm, 2012; Gao et al., 2015; Fireman et al., 2017; Sturm, 2017). Therefore, the positive association between total fungal spores and number of visits was expected, as demonstrated in previous studies (Dales et al., 2000; Atkinson et al., 2006; Behbod et al., 2015; Mehrabi 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; Klich, 2009; Capasso et al., 2015; Wong et al., 2016). These complex reactions may contribute to diverse observations among studies and warrant 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 (Rosas et al., 1998; Atkinson et al., 2006), 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 (Rosas et al., 1998; Kim et al., 2011; Park et al., 2013). 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 (Lin and Li, 2000; Burch and Levetin, 2002; Kallawicha et al., 2015b). 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. Using such estimates, we demonstrated that exposure to high levels of ambient fungal spores was associated with allergic rhinitis, acute conjunctivitis, and asthma. In addition to the total number of 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, and future studies should investigate the potential dose-response or threshold effects. Moreover, the implementation of personal protection strategies is encouraged for atopic and immunocompromised patients in order to avoid or reduce their exposure to bioaerosols. Decreased symptoms and a severity reduction of disease can increase patients’ quality of life as well as reduce unnecessary medical expenditures.

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