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Exposure to ambient bioaerosols is associated with allergic skin diseases in Greater Taipei residents[☆]

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ABSTRACT

Allergic skin diseases may result from various types of chemical and biological allergens. This study investigated the association between ambient bioaerosol exposure and allergic skin diseases by using the exposure data obtained from land use regression models and interpolated data. Data on daily average outpatient visits for atopic dermatitis (ICD-9-CM 691.8) and contact dermatitis and other eczema (ICD-9-CM 692.9) between November 2011 and August 2012 were obtained from the National Health Insurance Research Database. A generalized estimating equation was used to analyze the associations between the skin diseases and ambient bioaerosol levels. The results indicated that during the study period, contact dermatitis and other eczema were more prevalent than atopic dermatitis in the study area. Most cases were observed in districts of Taipei City and 3 major districts of New Taipei City, namely Xinzhuang, Banqiao, and Xindian. In univariate analysis, most bioaerosols were positively associated with both skin diseases. After adjustment for air pollution and sociodemographic factors, exposure to total fungal spores was significantly associated with atopic dermatitis in males (relative risk [RR] = 1.12; 95% confidence interval [CI] = 1.05–1.19). Contact dermatitis and other eczema had significant relationships with *Cladosporium* in males (RR = 1.07; 95% CI = 1.02–1.14) and with *Aspergillus/Penicillium* in females (RR = 1.04; 95% CI = 1.02–1.07). Meteorological parameters, namely wind speed, temperature, and rainfall, were also significantly associated with skin diseases. Our findings reveal that exposure to ambient bioaerosols is a significant and independent risk factor for allergic skin diseases.

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1. Introduction

Skin allergy is a common disease that can deteriorate quality of life, work efficiency, and academic performance (Civelek et al., 2011; Kieć-Swierczyńska et al., 2008; Magnavita et al., 2011). Common skin diseases, such as atopic and contact dermatitis, are prevalent worldwide in both children and adults (Simon and Kernland Lang, 2011). Approximately 6.7% of Taiwanese children experience atopic dermatitis, for which various risk factors have been reported (Wang et al., 2007, 2016). Previous studies have found that apart from a genotypic background (Chang et al., 2012), these skin diseases are associated with factors such as

socioeconomic status, lifestyle, and dietary intake. These factors are positively and significantly correlated to case number and symptom severity (Apfelbacher et al., 2011; Karadag et al., 2007). The other crucial determinants are environmental factors, of which temperature, relative humidity, indoor environmental conditions, and everyday chemical and biological agents can induce skin symptoms (Lee et al., 2007; Sybilski et al., 2015; Wang et al., 2007).

Among the environmental factors, bioaerosols have been widely reported as risk factors for many diseases such as asthma, allergic rhinitis, and infections as well as skin allergies (Atkinson et al., 2006; Burge and Rogers, 2000; Harley et al., 2009; Macher, 1999). Most atopic patients have a positive skin reaction to bioaerosols, such as fungal, dust mite, and pet allergens, in the skin prick test (Codispoti et al., 2015; Mimura et al., 2014; Reponen et al., 2012). These allergens can activate the immune system and induce the skin reaction process, thus presenting common symptoms on patient skin, such as redness, swelling, itching, and skin dryness

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(Fischer et al., 1999; Simon and Kernland Lang, 2011).

Personal exposure assessment of bioaerosols is commonly conducted in indoor and occupational environments because of the availability of sampling equipment and electricity. In addition, environmental conditions in these environments are more stable than those in ambient environments (Garcia et al., 2013; Kallawicha et al., 2015a; Madsen et al., 2009; Wang et al., 2015). In a large-scale area, researchers typically use the data from one or a few fixed-site monitoring stations to estimate personal exposure (Atkinson et al., 2006; Chao and Lee, 2013; Chen et al., 2011, 2014a; Lierl and Hornung, 2003). To more accurately characterize the spatiotemporal distribution of ambient bioaerosols, we have successfully developed land use regression (LUR) models to estimate the levels of several bioaerosols in the Greater Taipei area in previous studies (Kallawicha et al., 2015b, 2015c). These models explained approximately 45%–60% of variation in ambient fungal spore distributions, and the results were comparable with other air pollution studies that applied LUR models to estimate ambient pollutants (Adam-Poupart et al., 2014; Chen et al., 2010; Kashima et al., 2009; Rivera et al., 2012; Saraswat et al., 2013). However, the LUR models of other ambient bioaerosols (i.e., endotoxins and total bacteria) were less ideal (Kallawicha et al., 2015b).

In this present study, we investigated the association of skin diseases with ambient bioaerosol exposure. We focused on the outpatient visits of “atopic dermatitis” and “contact dermatitis and other eczema” of the residents of Greater Taipei. The exposure levels were derived from the LUR models and bioaerosol monitoring results of previous studies (Kallawicha et al., 2015b, 2015c).

2. Materials and methods

2.1. Health care facility visit data

Health care data were obtained from the National Health Insurance Research Database (NHIRD) through the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. The National Health Insurance program covers more than 99.9% of Taiwan residents and has contracts with more than 97% of health care providers nationwide (Lee et al., 2010; Lu and Hsiao, 2003; National Health Insurance Administration, 2014). To protect patient privacy, information related to patient identity or care provider is scrambled before inclusion in the NHIRD and is further scrambled before being released to researchers. Therefore, informed consent did not need to be obtained from the study patients. Because patient addresses are unavailable in the NHIRD, we considered the location of the visited facilities as the exposure location of the patients. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes were used to identify the health outcomes of interest. The health outcomes were the number of outpatient visits for allergic skin diseases, including atopic dermatitis (ICD-9-CM 691.8), and contact dermatitis and other eczema (ICD-9-CM 692.9), at each district in the Greater Taipei area during the study period. The Greater Taipei area map is shown in Supplement Material, Fig. S1.

2.2. Bioaerosol exposure data

The exposure levels were derived from previously collected data (Kallawicha et al., 2015b, 2015c). Briefly, ambient air samples were collected from 44 representative sites across the Greater Taipei area. Four sampling campaigns were conducted between November 2011 and August 2012, with each campaign lasting 1–2 weeks. LUR models for bioaerosols were developed and cross-validated. Potential bioaerosol determinants (i.e., land utilization and social and environmental parameters) were included during

model construction. We used validated LUR models to estimate the exposure levels of total fungal spores and major fungal taxa in each district of the Greater Taipei area. The LUR models were validated using the leave-one-out cross validation method with cross-validation R^2 ($CV-R^2$) ranging from 0.38 to 0.57. Various studies used the LUR with similar $CV-R^2$ to estimate air pollutant levels (Adam-Poupart et al., 2014; Chen et al., 2010a; Kashima et al., 2009; Rivera et al., 2012; Saraswat et al., 2013). Because of the relatively low $CV-R^2$ of the LUR models for bacterial aerosols (total bacteria $CV-R^2 = 0.11$ and endotoxin $CV-R^2 = 0.31$), we used the spatial interpolation technique (ordinary kriging) from a geographic information system to estimate the bacterial and endotoxin concentrations in each district during the study period (Kallawicha et al., 2015b, 2015c).

2.3. Environmental data

Meteorological data, namely temperature ($^{\circ}\text{C}$), rainfall (mm), relative humidity (%), and wind speed (m/s), were obtained from 49 monitoring stations of Taiwan's Central Weather Bureau. From 18 monitoring stations of Taiwan's Environmental Protection Administration, we obtained atmospheric pollutant data, including particulate matter with aerodynamic diameters of ≤ 10 and ≤ 2.5 μm (PM_{10} and $\text{PM}_{2.5}$, respectively), carbon monoxide (CO), ozone (O_3), nitrogen oxides (NO_x , NO, NO_2), and sulfur dioxide (SO_2). Because the monitoring stations were not evenly distributed in every district, the ordinary kriging technique was used to interpolate the data, and the average of each environmental parameter was calculated for each Greater Taipei district.

2.4. Sociodemographic data

Sociodemographic data included the size and density (person/ km^2) of the population, the percentage of the population (age >15 years) with a higher education, the percentage of aboriginals, the 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 the urbanization level of each district (Liu et al., 2006).

2.5. Statistical analysis

We used a paired t -test to examine the difference between the average numbers of male and female outpatient visits. The effect of bioaerosol exposure on skin diseases was assessed by using multivariate Poisson models with generalized estimating equations. The numbers of outpatient visits to the health care facilities in each district of the Greater Taipei area were used as the dependent variables. The independent variables included bioaerosol levels, meteorological parameters, and air pollutant concentrations. Because of the limitation of data accessibility and availability, only the average outpatient visit numbers for each district during each seasonal sampling campaign were obtained. To avoid the effects of weekends or holidays, we only included normal working days when counting outpatient visits. Each potential predictor variable was analyzed in the univariate model. To approximate normality, ambient bioaerosol concentrations were transformed using the base-10 logarithm in the regression analysis. The variables with a p value ≤ 0.2 were included in further multivariate analysis. Social demographic factors and air pollutants with a p value < 0.05 were adjusted in the final model. Relative risks (RRs) were calculated for significant bioaerosols and meteorological parameters ($p < 0.05$). Bioaerosol RRs were calculated on the basis of a 10-fold increase. Statistical analyses and data processing were performed using Microsoft Excel 2007 and PROC GENMOD in SAS (v. 9.2, SAS

Institute, Cary, NC, USA), and ArcGIS (v.9.3, Esri, Redlands, CA, USA) was used for spatial analyses.

3. Results

According to the NHRI data, outpatient visit numbers of females were higher than those of males for contact dermatitis and other eczema; however, this difference was not statistically significant ($p > 0.05$). The distributions of outpatient visit numbers for both diseases were illustrated in Supplement Material, Fig. S2. Outpatient visits for both skin diseases were high in most Taipei City districts and in 3 New Taipei City districts, namely Xinzhung, Banqiao, and Xindian, which are mainly business and residential areas (see Supplement Material, Fig. S3).

Table 1 shows the distributions of bioaerosol levels and environmental parameters in the Greater Taipei area during the study period. Bioaerosol concentrations were not normally distributed; positive (right) skewness was observed. Table 2 shows the univariate regression analysis results of the associations between bioaerosol concentrations and skin diseases. Most bioaerosols were positively associated with both skin diseases; however, total bacterial levels had negative correlations with skin diseases.

In multivariate analysis, after adjustment for sociodemographic data and atmospheric pollutants, several fungal spore levels were associated with skin diseases (Table 3). In males, the number of visits for atopic dermatitis increased with the number of total fungal spores (RR = 1.12; 95% confidence interval [CI] = 1.05–1.19). Exposure to *Cladosporium* spores increased the risk of contact dermatitis and other eczema (RR = 1.07; 95% CI = 1.02–1.14) in males, whereas in females, this risk was increased by exposure to *Aspergillus/Penicillium* spores (RR = 1.04; 95% CI = 1.02–1.07). Meteorological parameters were also significantly associated with skin diseases. Temperature was positively associated with atopic dermatitis in females, and wind speed and rainfall had positive associations with contact dermatitis in males and females, respectively. Although endotoxins and total bacteria were associated with skin diseases in the univariate analysis, the associations were nonsignificant in the multivariate analysis after adjustment for other potential confounding variables.

4. Discussion

Most previous studies have used data from limited monitoring stations to estimate the bioaerosol levels and examine the health effects (Adams et al., 2014; Bonetta et al., 2010; Chao et al., 2002; Chen et al., 2014a, 2014b; Degobbi et al., 2011; Docampo et al., 2011). However, the spatiotemporal variations of bioaerosols were ignored, resulting in less accurate exposure assessment. The present study applied validated predictive models to estimate the bioaerosol exposure levels in the Greater Taipei area to overcome the limitations of previous studies, which had a limited number of monitoring stations.

During the study period, more patient visits were made for contact dermatitis and other eczema than for atopic dermatitis, possibly because of the multiple etiologies of contact dermatitis and other eczema. Symptoms can be induced by various types of allergens, such as chemical agents, personal care products, and biological agents (Shih et al., 2015; Thyssen et al., 2014; Wang et al., 2010). The accuracy of the physician diagnosis is another crucial concern that contributes to the higher visit numbers of contact dermatitis and other eczema. Because the ICD-9-CM code of contact dermatitis and other eczema does not provide the specific cause of this skin disease, all cases with ICD-9-CM 692.9, even those less likely to be caused by bioaerosol exposure, were counted and included in the analysis. This diagnosis concern is considered a limitation of our study and other studies that use a secondary database to investigate the association between potential risk factors and adverse health outcomes, particularly those with multiple etiologies. This limitation is inevitable for all bioaerosol-related skin disease cases to be recorded.

According to our results, exposure to fungal spores was positively associated with atopic dermatitis and contact dermatitis and other eczema. This finding is consistent with our hypothesis that bioaerosol exposure aggravates skin allergies. In the univariate analysis (Table 2), most bioaerosols showed positive and significant association with both skin diseases; however, negative associations were observed with bacterial levels. More specifically, most bioaerosols were positively associated with contact dermatitis and other eczema in both males and females, but were correlated with atopic dermatitis only in males. Because the concentrations of these

Table 1
Distributions of bioaerosol levels and environmental parameters in the Greater Taipei area during November 2011 and August 2012.

Variables	Mean	Median	SD	Min	Max
Bioaerosols^a					
Total fungal spores (spores/m ³)	1412.85	582.57	1750.34	27.97	11599.54
Ascospores (spores/m ³)	327.16	111.60	338.85	1.81	1412.48
<i>Aspergillus/Penicillium</i> (spores/m ³)	309.15	74.50	452.10	1.58	2526.73
Basidiospores (spores/m ³)	276.61	194.55	314.80	3.51	2229.35
<i>Cladosporium</i> (spores/m ³)	66.59	34.00	60.73	3.81	219.27
Total bacteria (cells/m ³)	28797.34	29923.35	14603.43	3156.09	71958.00
Endotoxin (EU/m ³)	2.52	1.74	2.17	0.32	12.13
Meteorological parameters					
Temperature (°C)	22.27	21.76	3.72	17.27	28.63
Relative humidity (%)	81.84	82.63	6.35	63.35	94.15
Wind speed (m/s)	1.74	1.60	0.67	0.63	5.31
Rainfall (mm)	0.35	0.40	0.22	0.03	1.08
Atmospheric pollutants					
PM ₁₀ (μg/m ³)	33.64	32.48	12.10	13.75	59.78
PM _{2.5} (μg/m ³)	18.37	16.06	9.16	5.18	36.75
O ₃ (ppb)	23.53	24.02	8.58	9.96	51.08
CO (ppm)	0.62	0.55	0.24	0.12	1.19
NO ₂ (ppb)	17.72	17.41	8.64	2.12	36.31
NO (ppb)	15.13	14.27	6.57	4.52	29.61
NO _x (ppb)	35.11	33.98	12.86	10.51	61.60
SO ₂ (ppb)	2.96	2.58	0.90	1.86	5.75

^a The validated land use regression models were used to estimate the concentrations of fungal spores; the spatial interpolation technique (Ordinary Kriging) was used to estimate the concentrations of total bacteria and endotoxin.

Table 2
Univariate predictors of skin diseases: Bioaerosol concentrations.

Predictor	Sex	Atopic dermatitis β coeff.	Contact dermatitis and other eczema β coeff.
Total fungal spores	Male:	0.1095	0.0952
	Female:	—	0.1502
Ascospores	Male:	0.0883	0.054
	Female:	—	0.1084
<i>Aspergillus/Penicillium</i>	Male:	0.0815	0.0886
	Female:	0.0852	0.1192
Basidiospores	Male:	0.0853	—
	Female:	—	0.043
<i>Cladosporium</i>	Male:	0.1271	0.0855
	Female:	—	0.1437
Endotoxin	Male:	0.1338	0.0581
	Female:	—	0.1452
Total bacteria	Male:	—	−0.2144
	Female:	−0.2407	−0.1297

*The β coefficients with a p value ≤ 0.2 are listed and those with a p value < 0.05 are in bold.

bioaerosols, namely total fungal spores, Ascospores, *Aspergillus/Penicillium*, Basidiospores, *Cladosporium*, and endotoxins, were highly correlated (Spearman correlation coefficients = 0.69–0.93), we could not include these variables simultaneously in the same multivariate models. Therefore, we only included the most significant bioaerosols in the final regression models (Table 3). Further investigation of possible disease mechanisms underlying the individual and integrated effects of bioaerosols is required.

The final multivariate models indicated that fungal spores were significant risk factors for allergic skin diseases, even after adjustment for various atmospheric pollutants and sociodemographic data. With a 10-fold increase in fungal spore concentrations, *Aspergillus/Penicillium* caused a 4% increase in daily visits for contact dermatitis and other eczema in females (RR = 1.04; 95% CI = 1.02–1.07), and *Cladosporium* caused a 7% increase in daily visits for contact dermatitis and other eczema in males (RR = 1.07; 95% CI = 1.02–1.14). Total fungal spores caused a 12% increase in daily visits for atopic dermatitis in males (RR = 1.12; 95% CI = 1.05–1.19). Total fungal spores included assorted spores that were recovered from the air samples. As mentioned, many prevalent fungal taxa were highly related, and we could not differentiate the risk contribution of each taxon. Some less prevalent taxa may also play a role in exacerbating skin allergy symptoms; however, we could not evaluate their effects in this study. Many studies have reported that *Aspergillus/Penicillium* and *Cladosporium* are common outdoor allergens because of their allergenic properties (Blatter et al., 2014; Codispoti et al., 2015; Fernandez et al., 2011; Fischer et al., 1999; Gaitanis et al., 2012), particularly their potency to cause respiratory diseases (Atkinson et al., 2006; Chen et al., 2011, 2014b; Harley et al., 2009).

We observed an apparent sex difference in the effect of fungal taxa on skin diseases. The differential results have been previously discussed with possible reasons such as physiological characteristics, immunological response, and genetics (Chen et al., 2010b; Kim

et al., 2006; Verthelyi, 2001). The specific mechanism is unknown; however, distinct pollutant exposure may also play a role in this difference. The distinct activity patterns between males and females result in different pollutant exposure. Males tend to have higher exposure to outdoor allergens, while females tend to spend more time indoors, especially in Asian countries (Cranney et al., 2016; Gall et al., 2015; Huang et al., 2016). Therefore, this study found that females were more sensitive to indoor allergens (i.e. *Aspergillus/Penicillium*), but males were more susceptible to *Cladosporium*, which is more prevalent outdoors (Chen et al., 2014a; Wu et al., 2004). More studies are needed to clarify the true mechanism.

Previous studies in Taiwan have indicated that exposure to ambient air pollutants (SO_2 , CO, PM_{10} , and NO_x) and other indoor environmental conditions (e.g., visible indoor mold, water leakage, and the presence of cockroaches) can induce symptoms of atopic dermatitis and eczema (Lee et al., 2007; Wang et al., 2007). These studies have included numerous variables at the individual level collected using questionnaires, such as socioeconomic status, parental disease history, and indoor environmental factors, which could not be obtained in our study because of the availability of secondary database. However, our results highlighted the independent association between ambient fungal spore exposure and these allergic skin diseases as the baseline for further investigation.

Our univariate analysis revealed significant associations between meteorological factors, namely temperature, wind speed, rainfall, and relative humidity, and skin diseases (data not shown). Among these variables, temperature, wind speed, and rainfall remained significant in the final multivariate models. Studies have reported various results (Park et al., 2013; Silverberg et al., 2013; Vocks et al., 2001). One possible explanation was discussed in a cohort study of children with atopic eczema; warm and humid weather can increase sweating, which cause skin irritation (Langan et al., 2006). Another study also indicated that high temperature

Table 3
Relative risks of increases in outpatient visits for skin diseases associated with the predicted bioaerosol levels.

Variables	Atopic dermatitis RR (95% CI) ^a	Contact dermatitis and other eczema RR (95% CI) ^a
Male		
Total fungal spores	1.12 (1.05, 1.19)	—
<i>Cladosporium</i>	—	1.07 (1.02, 1.14)
Wind speed	—	1.08 (1.02, 1.14)
Female		
<i>Aspergillus/Penicillium</i>	—	1.04 (1.02, 1.07)
Temperature	1.03 (1.01, 1.04)	—
Rainfall	—	1.22 (1.11, 1.34)

^a Adjusted for atmospheric pollutants and sociodemographic factors.

and low humidity can induce skin dryness, which is a clinical symptom of eczema (Sargen et al., 2014). Patients from various geographical areas may exhibit differing clinical manifestations because of the climatic differences. An alteration in climatic proved to relieve eczema symptoms in Norwegian children; Byremo et al. (2006) reported that the symptoms of patients who moved from an arctic–temperate area to a subtropical area significantly improved in 4 weeks of observation. The effect of temperature in this present study was observed only in female atopic dermatitis cases, probably because female skin is more sensitive to temperature changes which lead to skin irritation (Gazerani et al., 2006).

Other crucial variables significantly associated with skin diseases in our study were the hospital density and number of physicians per 100,000 people. We observed higher numbers of visits in districts that had more hospitals and physicians. These positive associations were significant in both the univariate and multivariate analyses for both skin diseases (data not shown). The effect of these variables increased the number of visits 0.1%–4%. Thus, these variables cannot be neglected from the analysis and must be adjusted in the models to determine the true effects of other predictor variables.

5. Conclusion

According to our review of relevant literature, this is the first study to use exposure levels from LUR models to investigate the associations between ambient bioaerosol exposure and allergic skin diseases. Our findings reveal that exposure to ambient bioaerosols was a significant and independent risk factor for atopic dermatitis and contact dermatitis and other eczema. Total fungal spores, *Aspergillus/Penicillium*, and *Cladosporium* were crucial ambient bioaerosols, which increased the risk of these skin diseases. Furthermore, temperature, wind speed, and rainfall were crucial predictors of outpatient visits for allergic skin diseases. Sex-related differences were observed among these associations. Investigating the underlying disease mechanism and causal effects in future studies is crucial for verifying the association between ambient bioaerosol exposure and allergic skin diseases. However, our findings could draw public attention toward avoiding ambient bioaerosol exposure to reduce individual symptoms and achieve the desired quality of life.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.envpol.2016.06.057>.

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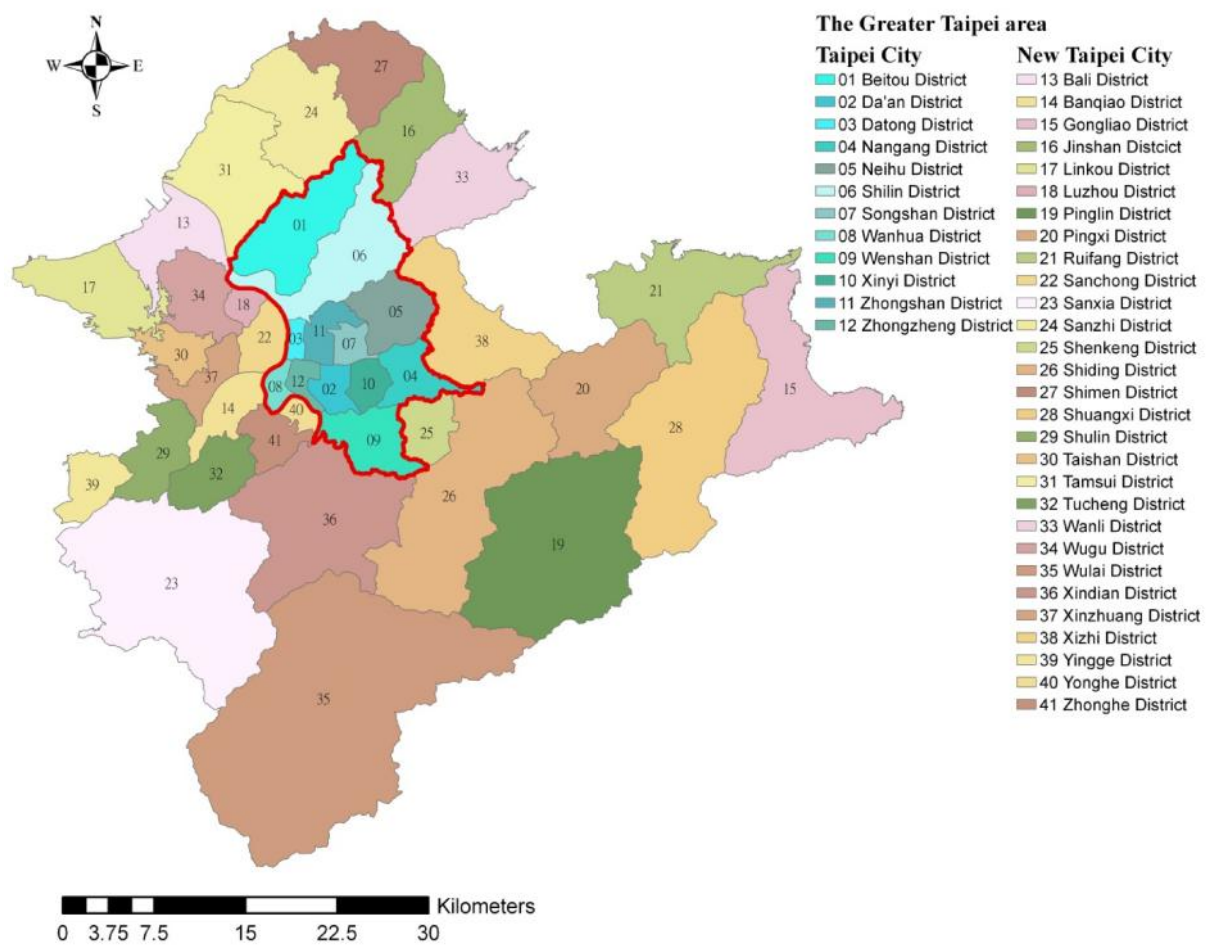
Supplemental Materials

Exposure to ambient bioaerosols is associated with allergic skin diseases in Greater Taipei residents

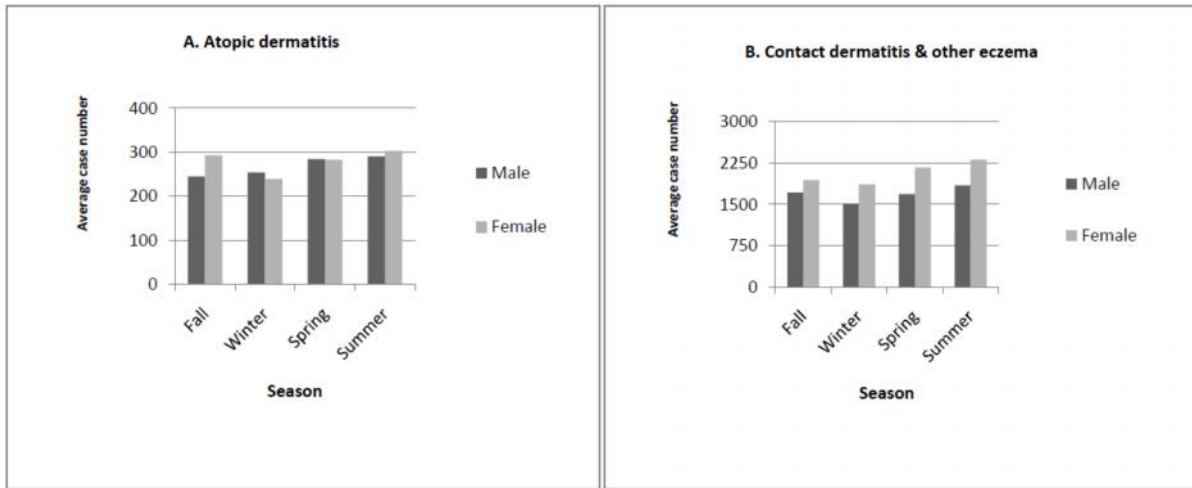
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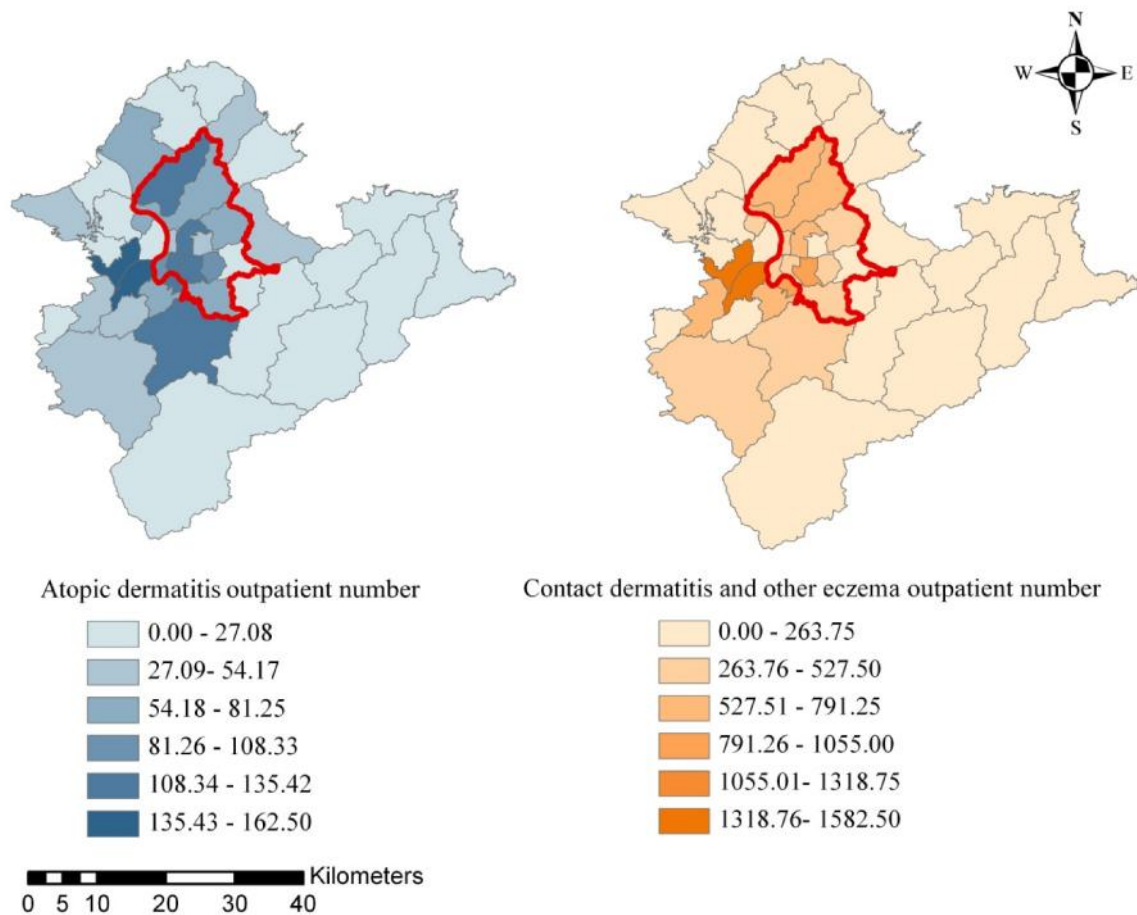
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