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The Effects of Air Pollution, Land-use Types, and Normalized Difference Vegetation Index on Atopic Diseases at 12 Months among Children in the Greater Taipei Area

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An abstract of
A thesis submitted to the Faculty of the
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Abstract:

Background: In Taiwan, the prevalences of asthma, atopic dermatitis, and allergic rhinitis have been increasing, causing a heavy economic burden. Air pollution, land-use types, and normalized difference vegetation index (NDVI) may be associated with atopic diseases. This study aims to investigate the relationships between the outcome of atopic diseases at 12 months and exposure of air pollution, land-use types, and NDVI in the Taipei Greater area.

Methodology: This retrospective cohort study is a secondary analysis of data from multiple sources. Participant and outcome data were obtained from self-reported questionnaires about 360 babies and their parents as part of the Longitudinal Examination across Parental and Postpartum Health in Taiwan (LEAPP-HIT) project (1). LEAPP-HIT data were combined with air pollution, land-use type, and NDVI data from the Environmental Protection Agency's (EPA) air quality monitoring stations, National Land Surveying and Mapping Center, and US space Agency's Moderate Resolution Imaging Spectroradiometer global planting database. Chi-square Tests, Student's T-tests, and Wilcoxon Signed-Rank Tests were first performed to select potential variables for the logistic regression model selection. Logistic regression analysis was then performed to build the univariate and multivariate logistic regression models. After that, the bi-pollutant analysis was performed to provide evidence for the air pollutant in multivariate logistic regression model.

Result: From 2011 to 2014, a total of 360 mothers had reported the atopic disease status for their children aged 0-12 months in Taipei, Taiwan. Under stepwise logistic regression model selection, NO_2 concentration during the second trimester ($p < 0.001$), playground within 1000

meters (p = 0.01), and NDVI within 750 meters during child's 0-12 months (p=0.01) were all significantly associated with atopic diseases at 12 months. When stratified by sex, the effect estimate of NO_2 concentration during the second trimester on atopic disease was significantly higher among male babies. In addition, NO_2 concentration during the second trimester remained significant when input in the bi-pollutant models with other pollutant indicators.

Conclusion: This study identified potential environmental risk factors of these atopic diseases and may have important environment policy implications on improving public health in Taiwan.

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Chapter 1: Introduction

Background of the Problem

Atopy refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies upon exposure to environmental proteins (pollen, house dust mite, and food allergens) resulting in such diseases as atopic dermatitis (AD), allergic rhinitis (AR), and asthma (2). The worldwide prevalences of AD and AR are 1% to 3% (3) and 10% to 30% (4) for adults, respectively, and 15% to 20% (3) and up to 40% (4) for children, respectively. As for asthma, the World Health Organization (WHO) has estimated a total of 235 million people, most predominantly children in low- and lower-middle-income countries, have asthma (5).

Despite high socioeconomic status and universal healthcare, Taiwanese people continue to suffer from higher prevalence of AD, AR, and asthma (6). Studies have shown that the prevalences of these atopic diseases are increasing in Taiwan. In three epidemiological survey studies with children from Taichung, the prevalence of asthma was 2.19% in 1987, 3.54% in 1994, and 6.99% in 2002 (7). The same increased pattern has been observed for AR and AD; the prevalence of AR was 5.1% in 1987, 12.46% in 1994, and 27.59% in 2002 and the prevalence of AD was 1.1% in 1987, 1.88% in 1994, and 3.35% in 2002 (7). Data from the Taiwanese National Health Insurance Research Database (NHIRD) shows that many Taiwanese people are suffering from AD, AR, and asthma. From 2000 to 2007, the NHIRD's 8-year prevalences of AD, AR, and asthma were 6.7%, 26.3%, and 11.9%, respectively (8). The NHIRD's prevalences of AD, AR, and asthma for children and adolescent were higher—9.6%, 37.8%, and 15.7%, respectively (8).

To understand the cause of the increase in AD, AR, and asthma prevalences, researchers have proposed air pollution as a potential environmental risk factor. Air pollution is the presence of such noxious substances as PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, O_3, and Pb in the air at levels that

impose health hazards (7). According to the WHO, air pollution, using 2016 Global Burden of Disease (GBD) data, is responsible for millions of deaths and illnesses every year globally. Outdoor air pollution alone causes 4.2 million premature deaths annually (9). This accounts for 29% of deaths and disease for lung cancer, 17% for acute lower respiratory infection, 24% for stroke, 25% for ischemic heart disease, and 43% for chronic obstructive pulmonary disease (10). Similarly, household air pollution, using 2016 GBD data, increases the rate of respiratory illnesses, cancer, and eye problems, causing 3.8 million premature deaths annually (11).

Several previous studies have identified a link between atopic diseases and air pollution. For asthma and air pollution, Brunst et al's (2015) Cincinnati Childhood Allergy and Air pollution Study, a prospective birth cohort study with 762 children in the greater Cincinnati, Ohio metropolitan area, found that children with high average traffic-related air pollution (TRAP) exposure from birth to age 7 had a significantly increased risk of asthma (aOR = 1.71; 95% CI, 1.01–2.88) (12). Hsu et al's (2015) urban pregnancy cohort study with 736 children and 986 enrolled pregnant women at Brigham and Women's Hospital, Boston Medical Center, and affiliated community health centers found that pregnant women who had high exposure of $PM_{2.5}$ during gestational weeks 16 to 25 carried an increased risk of asthma for boys at age 6 (13). Ghering et al's (2010) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study, a prospective birth cohort study with 3,863 children aged 0-8 in the north, west, and center of the Netherlands, found that children aged 0-8 years who were exposed to NO_2, $PM_{2.5}$, and "soot" had increased odds of having asthma (14). For AD and air pollution, Morgenstern et al's (2008) German Infant Nutritional Intervention and Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in East and West Germany Studies, prospective birth cohort studies with 2,860 children aged 4 year and 3,061 children aged 6 in

Munich metropolitan area, found that NO_2 was positivity associated with AD (OR: 1.18; 95% CI:1.00–1.39) (15). Kim et al's (2017) panel study with 177 children with AD in Seoul metropolitan Area, Korea found that PM_{10}, NO_2, and O_3 were associated with AD symptoms. When PM_{10} (μg/m3), NO_2 (ppb), and O_3 (ppb) increased by 10 units, the risk of AD symptoms increased by 3.2% (95% CI: 1.5-4.9), 5.0% (95% CI: 1.4-8.8), and 6.1% (95% CI: 3.2-9.0), respectively (16). Pénard-Morand et al's (2010) cross-sectional study with 4907 children from six French communities (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Strasbourg and Reims) who did not move their residence during the previous three years, used a 3-year averaged concentration and found that exposure of benzene (OR: 1.11; 95% CI:1.00–1.28), PM10 (OR: 1.15; 95% CI: 1.03–1.33), NOx (OR: 1.11; CI: 1.00–1.26), and CO (OR: 1.14; 95% CI: 1.01–1.29) among children aged 9 to 11 was significantly associated with AD symptoms in the last one year (17). For AR and air pollution, Hwang et al's (2006) nationwide cross-sectional study with 32,143 Taiwanese school children in Taiwan found that the prevalence of AR was significantly associated with SO_2 (aOR: 1.43; 95% CI: 1.25-1.64), CO (aOR: 1.05; 95% CI: 1.04-1.07) , and NOx (aOR: 1.11; 95% CI: 1.08-1.15) (18). Teng et al's (2017) time-series study with 23,344 AR outpatients records in Changchun, China further proved that $PM_{2.5}$ and PM_{10} associated with the development of AR (19). Lee et al's nationwide survey of respiratory diseases and symptoms with 800 middle schools in Taiwan found that after adjusting for age, parental education, and history of atopic AD, physician-diagnosed AR was associated with CO, NOx, and O_3 (20).

Taiwan Atopic Diseases Problem

Since the 1990s, the Taiwanese government has implemented numerous emissions control strategies to improve air quality. These strategies include creating the gasoline vapor recovery

program, employing air pollution control devices for highly reactive volatile organic compounds, limiting hazardous air pollutants from industries, controlling fugitive particulate emissions from stationary sources, putting up strict vehicle emission standards, and setting up on-road vehicle measures (21). These emission control measures have reduced levels of air pollutants, including NOx, SO_2, and $PM_{2.5}$; however, severe pollution events, which mainly involve $PM_{2.5}$, continue to occur in Taiwan, putting many of its citizens at risk (21). At the same time, the prevalences of atopic disease continue to increase. One possible reason is that some Taiwanese medical doctors don't follow asthma guidelines and don't have enough knowledge to treat asthma patients (22). Also, there is a need for identifying early-life risk factors and having an early management program for AD, but Taiwan lacks a consensus on AD prevention and management (23).

Increasing the prevalences of AD, AR, and asthma continue to impact Taiwan economically. The 2002 economic burden study with 1001 patients reported that 21.1% diagnosed AR and 26.4% asthma patients went to see a specialist (24). The loss of productivity was 40% for diagnosed AR patients and 28% for diagnosed asthma patients. Every year the annual direct and indirect costs are projected to be US$9,000 per patient for AR and US$7,500 per patient for asthma (24). Similarly, a survey study from the National Taiwan University Hospital with 191 adult patients reported that the AD patients had a weekly productivity loss of 43.41% (US$180.5 per person) (25).

Statement of the Problem

According to the WHO, air pollution, using 2016 GBD data, kills about seven million people every year globally and causes such illnesses as lung cancer, lower respiratory infection, stroke, ischemic heart disease, chronic obstructive pulmonary disease, and eye problems (9–11).

In Taiwan, severe air pollutants were generated from industries, scooters, and cars. Every day many Taiwanese get exposed to different air pollutants. While the current air pollution policies have shown to be effective, more efforts are still needed to improve these policies. At the same time, many Taiwanese suffer from atopic diseases. The prevalences of atopic diseases continue to grow every year, imposing a huge economic burden on Taiwan (24).

There is limited research that has investigated the association of atopic diseases and air pollution in Taiwan. Many studies related to this topic were done outside of Taiwan and tended to focus on traffic-related air pollution (26). These studies did not use land-use types and Normalized Difference Vegetation Index (NDVI) data with air pollution at the same time to assess how green space and land-use types may contribute to the increase of atopic diseases. Some studies used land-use types with air pollution, but many of these studies only focused on major roadways. Such land-use types as farmland, forest, and playground were ignored, despite potentially providing a good explanation for the increase of atopic diseases. Also, only a few studies were done using NDVI data (27–31). There is only one study in Taiwan reporting the association of atopic diseases and green space, but it did not incorporate any air pollution and land use type data (31). Moreover, the results of these existing studies were different and inconsistent. Therefore, there is a need to assess the association between air pollution, NDVI, and land-use types together to explore the cause of the increase in atopic disease prevalence, which will provide more research evidence for the possible causes of atopic diseases to the global research community, and provide opportunities of doing more of this research in Taiwan.

Purpose of the Study

The aim of this project is to evaluate the relationships of air pollution concentrations, land-use types, and NDVI with atopic diseases among 360 children aged 0-12 months in Taipei, Taiwan.

Significance Statement

There is a lack of information about the relationships between air pollution concentrations, land-use types, and NDVI. As this knowledge gap persists, the prevalence of atopic diseases continues to increase, putting more and more Taiwanese people at risk of atopic diseases. This is the first study to look at air pollution, land use types, and NDVI, as well as controlling for other sociodemographic characteristics to determine if any of these potential risk factors have a significant association with atopic diseases prevalence in Taiwan. The results of the current project will help researchers gain more information about the factors that contribute to the development of these atopic diseases globally. More importantly, the results will be shared with the Taiwanese government to help them strengthen health and environmental policies for improving the health of the Taiwanese people.

Definition of Terms

	Asthma	"A chronic inflammatory airway disease, characterized by coughing, wheezing, dyspnea and chest tightness, that may originate in early life" (32)
AD	Atopic dermatitis	"A chronic relapsing inflammatory skin disease mostly occurring in early childhood" (33)
AR	Allergic rhinitis	"A common chronic inflammatory disease in the upper airways" (34)
WHO	World Health Organization	
NHIRD	National Health Insurance Research Database	
GBD	Global Burden of Disease	
NDVI	Normalized Difference Vegetation Index	A graphical indicator measured by the difference between near-infrared and red lights to assess whether or not the observed target area contains live green vegetation
IgE	immunoglobulin E	

Chapter 2: Comprehensive Review of the Literature:

Over the past few decades, the prevalence of atopic diseases (atopic dermatitis, allergic rhinitis, and asthma) has been increasing worldwide. The prevalences of AD (during 2017) and AR (during 2014) are 1% to 3% (3) and 10% to 30% for adults (4), respectively, and 15% to 20% (3) and up to 40% (4) for children, respectively. Different studies have reported different asthma prevalence, but according to the World Health Organization (WHO), a total of 235 million people from the 2016 GBD data have suffered from asthma worldwide (https://www.who.int/news-room/q-a-detail/asthma). To understand the cause of the increase in atopic diseases prevalence, researchers have studied the associations of asthma, AR, and AD with several risk factors, including air pollution (CO, NO, NO_2, NO_x, SO_2, PM_{10}, and $PM_{2.5}$) (13–15,17–19,35–39), Normalized Difference Vegetation Index (NDVI) (40,41), land-use types (road, farm, and factory) (42–46), and demographic characteristics (sex, education, environmental smoking, and parental atopy) (13,14,17,18,36,39,41,43,47). These risk factors have been showed to have an association with asthma, AR, and AD.

Air Pollutants

CO

The results for the association of CO and atopic diseases vary depending on the type of atopic disease. Pénard-Morand et al (2010) did a cross-sectional study on the long-term air pollution exposure with asthma and allergies using 4,907 randomly selected children aged 9-11 from 108 schools in six French cities (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Strasbourg and Reims). The analysis showed that CO was significantly and positively associated with lifetime asthma (OR: 1.21; 95% CI: 1.03-1.54) and lifetime AD (OR:1.08; 95% CI: 1.00-

1.21), but not with lifetime allergic rhinitis (OR: 1.05; 95% CI: 0.89-1.30) among the 4,907 children who resided at their current address for the past 3 years (17). In consistent with the association of CO and AD, Lee et al's 2008 nationwide survey study with Taiwan Environmental Protection Administration (EPA) air pollution and climatic data from 55 monitoring stations in Taiwan reported that the prevalence of AD among girls in a total population of 317,926 middle-school students was associated with CO (RR: 1.10; 95% CI: 1.00-1.22) (36). Also, Teng et al's 2017 time-series study with 23,344 AR outpatient records, and air pollution data in Changchun, China reported that there was no association between AR and CO (RR:0.99; 95% CI: 0.907-1.053) for 1 Standard Division increase of CO (19). However, another Taiwanese study on the relation of air pollution and AR reported a different result. Hwang et al's 2006 nationwide cross-sectional study with 32,143 Taiwanese school children, air pollution monitoring, and questionnaire data in Taiwan reported that the prevalence of allergic rhinitis was significantly associated with CO (aOR = 1.05, 95% CI: 1.04, 1.07) (18). This difference might be due to the study methods because the cross-sectional study conducted by Pénard-Morand (2010) et al had doctors examining their cohorts for atopic conditions while the nationwide cross-sectional study conducted by Hwang (2006) et al relied on questionnaires.

NO

Most of the studies did not include NO for analysis, and for those that did, the results were different. A case-control cohort study conducted by Clark et al (2010) using 1999-2000 outpatient and hospitalization records, regulatory monitoring data, and land use regression models (LUR) with 3,482 children in British Columbia reported that the LUR derived NO was associated with the elevated risk of asthma in utero (aOR: 1.05; 95% CI: 1.02-1.09) and during the first year of life (aOR: 1.03; 95% CI: 1.00-1.07) (37). Differently, an intervention study

conducted in Vancouver, Canada used LUR with 186 children and reported that NO increased the development of asthma, but this increase was not significant (OR: 1.2; 95% CI: 0.9-1.7) (48).

NO_2

Many researchers studied the association between NO_2 and atopic diseases. Deng et al's (2016) survey study with 2598 preschool children aged 3-6 years and air quality monitoring center data looked at the association of outdoor air pollution during trimesters of pregnancy and childhood atopic diseases. The results showed that the incidence of asthma, AR, and AD were 6.8%, 7.3%, and 28.6%, respectively. These incidences were associated with NO_2—OR = 1.63 (95% CI: 0.99–2.70) for asthma, OR = 1.69 (95% CI: 1.03–2.77) for AR, and OR = 1.37 (95% CI: 1.04–1.80) for AD (47). Similarly, Teng et al (2017) studied only the association of AR and NO_2 and reported that the prevalence of AR was significantly associated with NO_2 (RR: 1.111; 95% CI: 1.058-1.165) (49). Differently from Deng et al (2016), Morgenstern et al's (2008) prospective birth cohort studies with 5,921 children aged 4-6, questionnaires, GIS-based regression models, and air pollution data in the Munich metropolitan area, reported different results for AR and asthma. The analysis showed that NO_2 was not associated with AR (OR: 1.05; 95% CI: 0.77–1.45) and asthma (OR:1.04; 95%, 0.67–1.39) (15). These results were different because Morgenstem et al (2008) incorporated land-use type data, specifically road data, into the analysis.

NOx

NOx seemed to have an association with most of the atopic diseases. Hwang et al (2006) reported that the prevalence of allergic rhinitis was significantly associated with NOx (aOR: 1.11, 95% CI: 1.08, 1.15) (18). Looking back at Pénard-Morand et al's 2010 cross-sectional study showed that NOx in the past year was positively associated with asthma (OR: 1.32; 95%

CI: 1.00-1.89) and AD (OR: 1.11; 95% CI: 1.00-1.26) but not with lifetime AR (OR: 1.02; 95% CI: 0.88-1.32) (17). This difference between Hwang et al's 2006 and Pénard-Morand et al's 2010 studies might be due to the difference of the sample size, 32,143 children vs. 4,907 children.

SO_2

Many studies did not have a consistent result for SO_2. Deng et al (2016) reported that SO_2 was not associated with AR (aOR: 1.17; 95% CI: 0.90-1.50) and AD (aOR: 1.08; 95% CI: 0.93-1.26) during the entire pregnancy. SO_2 was significantly associated with asthma (aOR: 1.43; 95% CI: 1.10-1.85) in the single-pollutant model but not in the multi-pollutant model (aOR: 1.00; 95% CI: 0.65-1.56) (47). As in Pénard-Morand et al's (2010) cross-sectional study, only SO_2 was associated with lifetime asthma (OR: 1.26; 95% CI: 1.11-1.42) (17). SO_2 had no association with lifetime AR (OR: 1.13; 95% CI: 0.95-1.34) and lifetime AD (OR: 0.95; 95% CI: 0.81-1.12) (17). When Taiwanese studies were observed, Lee et al (2008) reported that SO_2 was not associated with the prevalence of flexural AD for both Taiwanese school girls (RR: 0.98; 95% CI: 0.92-1.06) and boys (RR: 0.93; 95% CI: 0.86-1.00), which matched the result from the first two studies (36). However, Hwang et al (2006) reported that SO_2 was significantly associated with AR (aOR: 1.43; 95% CI: 1.25-1.64) (18).

PM_{10}

PM_{10} were investigated in many studies, but the results were different from study to study. Deng et al (2016) reported that PM_{10} was not associated with childhood asthma (aOR: 0.89; 95% CI: 0.68-1.16), AR (aOR: 0.99; 95% CI: 0.76-1.29), and AD (aOR: 1.01; 95% CI: 0.87-1.17) during the entire pregnancy (47). Lee et al (2008) and Hwang et al (2006) both focused on AD and AR in Taiwanese school children and supported these results. Lee et al

(2008) reported that PM_{10} was not associated with childhood flexural AD for boys (RR: 0.91; 95% CI: 0.81-1.02) (36). Hwang et al (2006) reported that PM_{10} was not associated with the prevalence of AR (aOR: 1.00; 95% CI: 0.99, 1.02) (18). Differently, Pénard-Morand et al (2010) had the opposite results, reporting that PM_{10} had an association with lifetime Asthma (OR: 1.28; 95% CI: 1.06-1.51), lifetime AD (OR: 1.13; 95% CI: 1.01-1.24), and lifetime AR (OR: 1.20; 95% CI: 1.01-1.44) (17). Also, Kim et al (2013) did a long-term study to look at the clinical effects of outdoor air pollution on skin symptoms among 22 AD patients in Seoul, Korea. The result showed that increasing PM_{10} by 1 $\mu g/m^3$ was significantly associated with a 0.44% increase in AD symptoms (95% CI: 0.12-0.77%) (38).

$PM_{2.5}$

$PM_{2.5}$ was often found to be associated with asthma and AR. In asthma studies, Hsu et al's 2015 urban pregnancy cohort study with 736 children and 986 enrolled pregnant women at Brigham and Women's Hospital, Boston Medical Center, reported that increased $PM_{2.5}$ exposure level at 16-25 weeks of pregnancy was associated with early childhood asthma development (13). Similarly, Gehring et al's 2010 Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study, a prospective birth cohort study with 3,863 children aged 8 in Netherlands, reported that $PM_{2.5}$ was associated with the incidence of asthma (OR, 1.28; 95% CI, 1.10–1.49), prevalence of asthma (OR, 1.26; 95% CI, 1.04–1.51), and prevalence of asthma symptoms (OR, 1.15; 95% CI, 1.02–1.28) (14). As in AR studies, Teng et al (2017) reported that $PM_{2.5}$ was associated with AR (RR: 1.102; 95% CI: 1.055-1.151) (19). Chen et al's 2018 nationwide study with 30,759 preschool Chinese children along with questionnaires and health data in China reported that an increase of 10 $\mu g/m^3$ of the annual $PM_{2.5}$ was positively associated with the prevalence of allergic rhinitis (OR, 1.20; 95% CI, 1.11-1.29) (39). For AD, Gehring et al (2010)

did not find any association between $PM_{2.5}$ and AD for both non-movers (OR: 1.03: 95% CI: 0.89-1.21) and movers (OR: 0.97; 95% CI: 0.84-1.12) during the first 8 years of life (14).

Normalized Difference Vegetation Index

NDVI is a graphical indicator measured by the difference between near-infrared and red lights to assess whether or not the observed target area contains live green vegetation. To calculate an NDVI value of a target area, researchers will subtract the reflected near-infrared light by the absorbed red light, and then, divide that value by the sum of reflected near-infrared and absorbed red lights. This index is ranging from -1 to +1. An NDVI value close to +1 means there is green vegetation, while below zero means there is water, and close to zero means there is no green vegetation (50).

Some studies showed that NDVI was associated with atopic diseases. Andrusaityte et al's 2016 nested case-control study with 3294 mothers and their 4-6 year-old children in Kaunas city reported that an increased IQR in NDVI buffer zone 100 increased the risk of asthma (OR: 1.43; 95% CI: 1.10-1.85) (40). To understand this situation, Andrusaityte et al (2016) explained that green space facilitates homeostasis, which put positive effects on the central and autonomic nervous and endocrine systems. Healthy people who live or walk in a forest environment would have an increase in immune function. However, the result would be different for people with poorly controlled asthma, chronic airway inflammation, and episodic respiratory symptoms because they have dysfunction alveolar macrophage phagocytic immune response. When green space facilitates homeostasis, it might have a different effect on these people (40).

In another study, Furetes et al (2014) used the "German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development" (GINIplus) and the "influence of Life-style factors on the development of the Immune System

and Allergies in East and West Germany plus the influence of traffic emission and genetics" (LISAplus) prospective birth cohorts with 5,803 people in a buffer zone of 500 meters in Germany to assess greenness and allergies (41). In urban areas, Furetes et al (2014) reported that greenness was positively associated with eyes and nose symptoms (OR: 1.15; 95% (1.01-1.31). Differently, in rural areas, greenness was negatively associated with AD (OR: 0.75; 95% CI: 0.60-0.93), eyes and nose symptoms (OR: 0.71; 95% CI: 0.56-0.89), and aeroallergen sensitization (OR: 0.78; 95% CI: 0.65-0.94) (41). To explain this, Fuertes et al (2014) pointed out that the vegetation in urban areas might be more seminatural or artificial, causing those areas to have a high rate of allergenicity. Also, these urban areas had a high concentration of $PM_{2.5}$, which could enhance the pollen allergenicity. As in rural areas, nature and agriculture might protect these areas against allergy development (41).

Land-use Types

The current study includes such land-use types as rice, dryland, fruit, aquaculture, pasture, greenhouse, forest, road, provincial road, freeway, railway, state road, commercial, factory, house, school hospital, power, social welfare, gas, park, playground, and sport. We think road, farm, and factory might be the land-use types that contribute to atopic diseases. Therefore, we did literature review for these land-use types below.

Road

Studies related to the association of atopic diseases and air pollution often looked at the distance of their cohorts to major roads. Brown et al's (2012) survey study with 204 asthmatic children aged 6-17 in Atlanta, GA reported that asthmatic children who lived closer to a major roadway had an increased frequency of wheezing and increased generalized airway and systemic

inflammation. The reason was that major roadways have traffic-related air pollutants and these pollutants function as airway irritants in children (42). In another study, Miyake et al's (2012) survey study with 5,652 students aged 12-15 in Osaka, Japan reported that shorter distance of residence (less than 100-meter) from major roads was associated with the increased prevalence of wheeze (OR: 1.27; 95% CI: 1.01-1.71), AD (OR: 1.24; 95% CI: 1.02-1.51), headache (OR: 1.40; 95% CI: 1.15-1.17, and tiredness (OR: 1.28; 95% CI: 1.09-1.49) (43). Similarly, Yi et al's (2017) cross-sectional survey study with 31,576 children in Seoul, South Korea reported that atopic AD was associated with major roads within 150-meter (aOR: 1.15; 95% CI: 1.01-1.32), 300-meter (aOR: 1.17; 95% CI: 1.03-1.34), 500-meter (aOR: 1.16; 95% CI: 1.01-1.34) (44).

Farm

Some studies reported that living in a farm might be protective against some atopic diseases. Remes et al's (2003) cross-sectional study with 366 farmers' and 344 non-farmers' children (7,981 total) aged 13-14 in eastern Finland reported that living on a farm had an association with a decreased prevalence of allergic rhinoconjunctivitis (OR: 0.79; 95% CI: 0.63–0.99), but not with asthma (OR: 1.01; 95% CI: 0.72–1.41), wheeze (OR:1.09; 95% CI: 0.75–1.56), and AD (OR:1.07; 95% CI: 0.90–1.28) (51). As in Leynaert et al's 2001 European Community Respiratory Health Survey Study with 5,703 non-farmers and 548 farmers in Belgium, France, Netherlands, Sweden, and New Zealand, they reported that adults who grew up on a farm when they were a child had a lower risk of atopic sensitization (OR = 0.76, CI 95% = 0.60–0.97) (45). To explain this, Leynaert et al (2001) pointed out that only parents who do not have a history of atopic disease choose to live on a farm. Those families who have atopic diseases would move out and live in urban areas (45).

Factory

A study in Korea used cross-sectional studies data to look at the effects of environmental pollution in a population of 35,530 adults aged 20 living near industrial complex areas (46). In this study, Eom et al (2018) reported that people who lived near the industrial complexes had a high rate of cough (OR: 1.18; 95% CI: 1.06-1.31) and sputum production (OR: 1.13; 95% CI: 1.03-1.24) (46). When Eom et al (2018) looked at the people who lived inside the industrial complexes, the prevalence of acute eye disorders was 40% higher and the prevalence of lung and uterine cancer was 3.45 times and 1.88 times higher. There were no clear explanations for other conditions, but for coughing, Eom et al explained that the rate of coughing was high because there were air pollutants in the areas. When these pollutants entered the lung and bronchi, the body would force the person to cough to remove the contaminants (46).

Demographic Characteristics

Sex

Most atopic diseases and air pollution research studies controlled for sex; however, the results for males and females were different depending on the geographic regions, demographics, and atopic diseases studied. Hsu et al (2015) reported that the association between $PM_{2.5}$ and asthma development was significantly higher in boys compared with girls (OR: 1.62 CI: 1.07-2.45) (13). As in Deng et al's (2016) cohort study, the result showed that AR was associated with postnatal exposure of NO_2 and PM_{10} in boys [(OR: 2.06; 95% CI: 1.23-3.44) and (OR: 1.57; 95% CI: 1.02-2.42)] but not with girls [(OR: 1.14; 95% CI: 0.62-2.07) and (OR: 1.28; 95% CI: 0.75-2.20)] (35). For AD, Lee et al (2008) looked at the association of AD with SO_2, CO, 03, PM_{10},

and NOx and reported that flexural AD associated with CO (RR: 1.10; 95% CI: 1.00-1.22) and NOx (RR: 1.11; 95% CI: 1.02-1.21) for only girls (36).

Educational Level

Many studies controlled for educational level, but the results were different depending on the type of atopic disease. Soh et al's (2018) longitudinal cohort study with 953 children aged 2 in Singapore reported that education level did not have any association with child's respiratory health (p=.760) (52). However, Lee et al (2008) reported that having more than 12 years of education was associated with flexural AD in both boys (OR: 1.73; 95% CI: 1.56-1.92) and girls (OR: 1.52; 95% CI: 1.37-1.65) (36). To explain this significance, Lee et al (2008) noted in the discussion that educated parents might be more aware of their children health problems and might be more likely to report it (36).

Smoking

Smoking was controlled for in almost all research studies. Soh et al (2018) controlled for passive smoking, and it was not significant with the child's respiratory health outcome (p=0.462) (52). On the other hand, Lee et al (2008) reported that flexural AD was associated with parent's active smoking habit in both boys (OR: 1.35; 95% CI: 1.10-1.65) and girls (OR: 2.07; 95% CI: 1.48-2.89). Lee et al (2008) controlled for environmental tobacco smoke (ETS) at home as well and reported that flexural AD was not associated with ETS at home in both boys (OR: 0.96; 95% CI: 0.89-1.04) and girls (OR: 1.02; 95% CI: 0.94-1.11) (36). Similar to Lee et al (2008), Deng et al (2016) reported that ETS was not associated with AD (p=0.316), AR (p=0.310), and asthma (p=0.762) (36,47). According to Lee et al, parents with AD children might consider the health risk of their children seriously and end up preventing themselves from being exposed to ETS. Still, these studies recommended to control for both firsthand and secondhand smokes.

Atopy

The rates of atopic diseases tended to be higher for children whose parents had a history of atopic diseases. Jedrychowski et al's 2011 prospective cohort study with 469 women and their babies in New York City and Krakow reported that AD symptoms increased in the group of children whose mothers were atopic (IRR 1.35, 95% CI 1.04–1.75) (53). In the trimester air pollution study, Soh et al (2018) reported that only maternal atopy was significantly associated with respiratory conditions ($p=0.005$) (52). Also, Deng et al (2016) reported that the prevalences of asthma ($p<0.001$), AD ($p<0.001$), and AR ($p<0.001$) were higher for children with parental atopy. According to Deng et al (2016), parents with atopic diseases could pass their atopic genetic markers to their children, causing their children to have atopic diseases (47).

Relevance to the Study

Some research studies have reported inconsistent associations between air pollutants (i.e., CO, NO, NO_2, NOx, SO_2, PM_{10}, and $PM_{2.5}$) and atopic diseases. The current study will analyze all of these pollutants in the univariate logistic model. If any of these pollutants become significant ($p<0.2$) in the univariate model, they will be the main covariates for the study. From above, not a single study has used land-use types and NDVI data with air pollution altogether. This study will include variables from both of these data in the univariate and multivariate models. As for land-use types, most studies tend to focus on road. The dataset has data on other land-use types, and all of these variables will be included in regression analyses. Also, most the air pollution and atopic diseases research studies have controlled for sex, education, environmental smoking, and parental atopy. The study will consider adjusting for these variables regardless of their significance in the final regression model.

Chapter 3: Manuscript

Introduction:

Atopy refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies upon exposure to environmental proteins (pollen, house dust mite, and food allergens) resulting in such diseases as atopic dermatitis (AD), allergic rhinitis (AR), and asthma (2). The prevalences of asthma, AD, and AR have been increasing in both developed and developing countries (33,54–57), leading to a heavy economic burden and poor quality of life (58,59). Despite the high socioeconomic status and universal healthcare, Taiwanese continue to suffer from atopic diseases (60), where the prevalences were 2.19% in 1987, 3.54% in 1994, and 6.99% in 2002 for asthma; 5.1% in 1987, 12.46% in 1994, and 27.59% in 2002 for AR; and 1.1% in 1987, 1.88% in 1994, and 3.35% in 2002 for AD (7). These prevalences continue to grow after 2002. Using Taiwanese National Health Insurance Research Database (NHIRD) from 2000-2007 has reported that the adult prevalences of AD, AR, and asthma are 6.7%, 26.3%, and 11.9%, respectively (8). The child prevalences of AD, AR, and asthma for children and adolescent are higher—9.6%, 37.8%, and 15.7%, respectively (8).

As the prevalences of these atopic diseases keep increasing, Taiwan continues to face a heavy economic burden. The 2002 economic burden study with 1001 patients reported that 21.1% diagnosed AR and 26.4% asthma patients were seen by a specialist (24). The loss of productivity was 40% for diagnosed AR patients and 28% for diagnosed asthma patients. Every year the annual direct and indirect costs are projected to be US$9,000 per patient for AR and US$7,500 per patient for asthma (24). Similarly, a survey study from National Taiwan University Hospital with 191 adult patients reported that the AD patients had a weekly productivity loss of 43.41% (US$180.5 per person) (25).

Several studies have linked the association of atopic diseases to air pollution; however, the results are still inconsistent on the literature. Pénard-Morand et al's (2010) cross-sectional study among 4,907 children aged 9-11 in French reported that CO was not significant with lifetime allergic rhinitis (OR: 1.05; 95% CI: 0.89-1.30) (17). On the other hand, Hwang et al's (2006) nationwide cross-sectional study among 32,143 Taiwanese school children in Taiwan reported the opposite (aOR = 1.05, 95% CI: 1.04, 1.07) (18). Clark et al's (2010) case-control cohort study among 3,482 children in Canada reported that NO was associated with the elevated risk of asthma in utero (aOR: 1.05; 95% CI: 1.02-1.09) (37). Differently, Carlsten et al's (2011) intervention study among 186 children in Canada reported that NO was not significant with the development of asthma (OR: 1.2; 95% CI: 0.9-1.7) (48). Deng et al's (2016) survey study among 2598 preschool children aged 3-6 years in China reported that NO_2 was associated with the increased incidences of asthma, AR, and AD—(OR: 1.63; 95% CI: 0.99–2.70) for asthma, (OR:1.69; 95% CI: 1.03–2.77) for AR, and (OR: 1.37; 95% CI: 1.04–1.80) for AD (47). At the same time, Morgenstern et al's (2008) prospective birth cohort study among 5,921 children aged 4-6 in Germany reported that NO_2 was not associated with AR (OR: 1.05; 95% CI: 0.77–1.45) and asthma (OR:1.04; 95%, 0.67–1.39) (15).

Land-use types may play a role in the contribution of atopic diseases. Brown et al's (2012) survey study among 204 asthmatic children aged 6-17 in the USA reported that asthmatic children who lived closer to a major roadway had an increased frequency of wheezing and increased generalized airway and systemic inflammation. Remes et al's (2003) cross-sectional study among 366 farmers' and 344 non-farmers' children (7,981 total) aged 13-14 in Finland reported that living on a farm was association with the decreased prevalence of allergic rhinoconjunctivitis (OR: 0.79; 95% CI: 0.63–0.99), but not with asthma (OR: 1.01; 95% CI:

0.72–1.41), wheeze (OR:1.09; 95% CI: 0.75–1.56), and AD (OR:1.07; 95% CI: 0.90–1.28) (51). Eom et al's (2018) cross-sectional study among 35,530 adult in Korea reported that people who lived near the industrial complexes had a high rate of cough (OR: 1.18; 95% CI: 1.06-1.31) and sputum production (OR: 1.13; 95% CI: 1.03-1.24) (46).

In addition, Green environments may produce certain allergens, such as fungi, spores, or pollens; therefore, normalized difference vegetation index (NDVI) may contribute to atopic diseases (31). Andrusaityte et al's (2016) nested case-control study among 3294 mothers and their 4-6 year-old children in Lithuania reported that an increased IQR in NDVI buffer zone 100 increased the risk of asthma (OR: 1.43; 95% CI: 1.10-1.85) (40). Similarly, Hsieh (2019) matched case-control study among children aged 0-17 in Taiwan reported that increased risk of asthma in preschool children aged 0-5 years was associated with the surrounding greenness (30,31). More studies are still needed for this association of NDVI and atopic diseases because the results from the literature are still inconsistent (27–31).

To address these knowledge gaps and inconsistency of the existing findings, this study was designed to investigate the associations between these risk factors and atopic diseases in Taiwan.

Methodology:

Study Design and Sample:

This retrospective cohort study is a secondary analysis of data from multiple sources. 500 participants were taken from the Longitudinal Examination across Parental and Postpartum Health in Taiwan (LEAPP-HIT) project. Initiated in 2011, LEAP-HIT is a longitudinal prospective cohort study that assessed infant and child development and mother's mental health

during pregnancy and postpartum in exposure to heavy metals (e.g., Hg, Pb, Cd, As), firsthand and secondhand smoke, and indoor and outdoor air pollutants (e.g., PM_{10}, $PM_{2.5}$, O_3, HCHO, and NO_2) at the Taipei Medical Hospital, Mackay Memorial Hospital, and Taipei City United Hospital in Taipei, Taiwan (1). When pregnant women came to these hospitals for their parental visits, they and their partners were invited to participate in the study. The eligibility criteria were: 1) the gestation week for the pregnant women must not exceed 16 weeks at the time of the invitation, 2) both pregnant women and their partners must plan to have the baby, 3) both parents must read and write in Chinese, 4) both parents must agree to stay in the study until at least 6 months after birth, 5) both parents must provide consent to the study (1). This study focused on the sub-set of 360 children (and their parents) from whom data on atopic diseases was collected.

Data Collection for Participants:

In the LEAP-HIT project, self-reported questionnaires were created and used for mothers, fathers, and babies. Once the pregnant women and their partners consented to the study, both mothers (using the mother's questionnaires) and fathers (using the father's questionnaires) were engaged in the first trimester, second trimester, third trimester, one month after birth, six months after birth, and twelve months after birth. Child health was assessed at one month after birth, six months after birth, and twelve months after birth using the child's questionnaires filled out by mothers and/or fathers. Throughout the whole pregnancy, mother's and father's questionnaires were carried out by interviewers who had been trained to follow standardized protocols in acquiring questionnaires during hospital visits. From 0-12 months after birth, interviewers did home visits to carry out the mother's, father's, and child's questionnaires (1).

Both parents' sociodemographic information (including age, education level, employment status, monthly household income, and marital status) and parent disease history

information (including asthma, rhinitis, and atopic diseases) were obtained through questionnaires during the first trimester. Current smoking status (yes or no) was assessed longitudinally and obtained through questionnaires for both parents from the first trimester to twelve months after birth. The interviewers also asked mothers about secondhand smoke exposure at home and in the workplace during and after pregnancy.

As for children, demographic data (including sex, date of birth, birth season, and weight) and atopic data (yes or no) were assessed and obtained at six months after birth and twelve months after birth (1). Atopic diseases is the outcome of the study. Parents were asked if their child had any atopic conditions (including asthma, allergic rhinitis, and atopic dermatitis).

Exposure Assessment

In addition to the questionnaires, outdoor air pollution concentration, land-use types, and NDVI data were acquired and combined with the LEAPP-HIT data to assess the environments. Hospital medical records were used to obtain each child's home addresses. Interviewers reconfirmed all child's home addresses with the parents during self-reported questionnaires at the hospitals and homes.

Outdoor Air Pollution Concentration Assessment

Outdoor air pollution concentrations and geographic information of CO, NO, NO_2, NOx, SO_2, $PM_{2.5}$, and PM_{10} were obtained from 18 continuous Environmental Protection Agency (EPA) air quality monitoring stations in the Greater Taipei area (https://taqm.epa.gov.tw/taqm/tw/default.aspx) (61). The locations of these EPA air quality monitoring stations can be found on Map 1. Study participants' addresses, EPA air pollution concentrations, and geographic information were rendered using ordinary kriging spatial interpolation combined with a spherical semi variogram in ArcGIS 9.3 to generate the average

CO, NO, NO_2, NOx, SO_2, $PM_{2.5}$, and PM_{10} concentrations for each participant for the following periods: the entire first trimester (gestational week 1-12), second trimester (gestational week 13-28), third trimester (gestational week 29-birth), all trimesters, six months after birth, and twelve months. These data were exported for use in SAS Version 9.3.

Land-use Types

We assessed land-use types, specifically park green space, forests, commercial, airport, residential use area, general roads, provincial roads or expressways, national highways, all roads, railway, high-speed railway lengths, railways, and road-related facilities, using data from the National Land Surveying and Mapping Center. The current study assessed how these land-use types could contribute to atopic diseases by mapping each child's home to each of the closest land-use types. Using established method (Wu et al., 2014; Wu et al., 2017), buffer zones within 100 meters, 250 meters, 500 meters, 750 meters, 1,000 meters, 1,500 meters, and 2,000 meters were created for each child's home (62,63). Within each buffer zone, each child's home was mapped to each of the nearest land-use types and the distance was recorded.

Normalized Difference Vegetation Index

We assessed whether or not the observed target area contained live green vegetation, used NDVI, a graphical index measured by the difference between near-infrared and red lights. This index ranges from -1 to +1. An NDVI value close to +1 means there is green vegetation, while below zero means there is water, and close to zero means, there is no green vegetation (50). In this study, the NDVI data were taken from the US space Agency's Moderate Resolution Imaging Spectroradiometer global planting database using MOD13Q1 V5 from the Terra satellite (61). The satellite computed an NDVI value for each child's home every 16 days at 250-meter spatial resolution from the first trimester to twelve months after birth within buffer zone 100 meters, 500

meters, 750 meters, 1,000 meters, 1,500 meters, and 2,000 meters. Excel and SAS Version 9.3 were used to calculate each buffer zone average NDVI for the entire first trimester, second trimester, third trimester, all trimesters, 0-6 months, 6-12 months, and 0-12 months.

Data Analysis

To examine which variables were associated with twelve months after birth child atopic diseases, we conducted Chi-square Tests, Student's T-tests, and Wilcoxon Signed-Rank Test . Specifically, chi-square tests were performed on categorical variables (e.g., sex, birth season, mother's educational level, mother's smoking status, father's education level, father's smoking status) from the first trimester, second trimester, third trimester, all trimesters, six months after birth, and twelve months after birth. Normality was checked for all continuous variables (e.g., birth weight, mother's maternal age, family income, the concentration of CO, NO, NO_2, NOx, SO_2, PM_{10}, and $PM_{2.5}$ from pregnancy to 12 months after birth, NDVI with buffer zone 100 to 2000). Student's T-tests were performed on normal continuous variables (pooled), and Wilcoxon Signed-Rank Tests were performed on non-normal continuous variables (two-tailed).

All the significant variables from the tests above were first used in univariate logistic regression models to access the association between 12-month atopic diseases individually with a p-value less than 0.2. The p-value cut off was selected to accommodate the limited size of study population, as demonstrated previously (2).

From the univariate logistic regression model analysis, NO_2 concentration during the second trimester was significant and had a negative impact of atopic diseases (beta: 0.0834; p-value: 0.1022). Therefore, NO_2 concentration during the second trimester was retained as the main pollutant covariate. In the multivariate logistic regression analysis, this pollutant covariate was forced with the other covariates that were significant in the stepwise model selection process

with a p-value of 0.05. Sometimes a covariate in the land-use types had more than one buffer zones that were significant (e.g. forest within 150 meters to forest within 1000 meters). A spearman correlation test was then conducted between this covariate and all buffer zones that were significant. If these buffer zones were highly correlated, the biggest buffer zone for that covariate would be used in the stepwise model selection process because it covered more children. The same thing was done for the NDVI covariates. After that, the multivariate logistic regression model was built, and according to the literature, sex, family income, history of atopy, and firsthand and secondhand smoking were adjusted (13,14,17,18,36,39,41,43,47). Interquartile range (IRQ) was used in calculating the effect estimates for each air pollutants.

To assess how the other pollutants (CO, NO, NOx, SO_2, PM_{10}, $PM_{2.5}$) may contribute to the increase of atopic diseases, they were included in the final multivariate logistic regression model. Levels of each pollutant from the first trimester, second trimester, third trimester, all trimesters, 0-6 months, 6-12 months, and 0-12 months after birth were replaced with NO_2 levels during the second trimester individually in the final multivariate logistic model. To confirm that the other pollutants did not have much contribution in the final multivariate logistic regression model, a two-pollutant logistic model was used. Specifically, CO, NO, NOx, SO_2, PM_{10}, $PM_{2.5}$ concentrations during the second trimester were added in the final adjusted multivariate logistic model per IQR with NO_2 concentration during the second trimester individually to see which pollutant was the one contributing to the increase of atopic diseases. All air pollutant concentrations at all trimesters and 0-12 months were highly correlated. CO, NO, NOx, SO_2, PM_{10}, $PM_{2.5}$ concentrations during the second trimester were chosen for the two-pollutant model to match the time period for the NO_2 concentration during the second trimester. Stratification of

baby's gender was also done for final adjusted multivariate logistic and two-pollutant logistic models. All of these analyses were done using SAS Version 9.3 and R Package 3.6.2.

This study was approved by the participating hospitals and both the Affiliated Hospital Joint Human Research Ethics Committee and the Human Body Testing Communities of the Medical Center in Taipei, Taiwan (1). The analyzer was approved by the Taipei Medical University's Institutional Review Board to be added to the current study. All data had been de-identify and required no further approval from Emory University's Institutional Review Board for this analysis.

Results:

From 2011 to 2014, a total of 360 mothers had reported the atopic disease status for their children aged 0-12 months in Taipei, Taiwan. Table 1 shows the demographic and prenatal characteristics. Thirty-one (8.61%) children (16 males and 15 females) had an atopic disease condition while three hundred twenty-nine (91.39%) children (185 males and 144 females) did not have any atopic disease conditions. Among these characteristics, the baby's birth season ($p=0.12$), Maternal education ($p <0.0001$), maternal age at delivery ($p=0.17$), family monthly income ($p=0.16$), and maternal history of atopy ($p=0.1$) were significant predictors of atopic diseases at 12 months at the 0.2 α level.

Table 2 shows the air pollutant concentrations during the entire pregnancy and 0-12 months after birth from all 18 EPA monitoring stations in Taipei, Taiwan. During the entire pregnancy period among all study participants, the average air pollutant concentrations were 651.49 ppb for CO, 12.96 ppb for NO, 21.51 ppb for NO_2 , 34.47 ppb for NOx, 3.22 ppb for SO_2, 46.00 $\mu g/m^3$ for PM_{10}, and 25.71 $\mu g/m^3$ for $PM_{2.5}$, respectively. The average air pollutant

concentrations at 12 months after birth were 658.56 ppb for CO, 12.83 ppb for NO, 21.35 ppb for NO_2, 34.19 ppb for NOx, 3.34 ppb for SO_2, 45.40 $\mu g/m^3$ for PM_{10}, and 23.30 $\mu g/m^3$ for $PM_{2.5}$, respectively.

Univariate logistic regression models were built for each of the covariates that were significant under the Chi-Square, Student's T, and Wilcoxon Signed-Ranked tests shown in Table 3. Among the air pollutants, NO_2 during the second trimester (p=0.10) was significant with atopic diseases at 12 months under a p-value of 0.2 for significance and had an unprotective effect of atopic diseases (beta = 0.08). For the univariate associations between land-use types data and atopic disease, dryland within 2000 meters (p=0.09), forest within 1000 meters (p=0.16), provincial road within 1500 meters (p=0.15), state road within 800 meters (p=0.19), water within 1000 meters (p=0.19), factory within 2000 meters (p=0.17), powerplant within 1500 meters (p=0.18), social welfare within 2000 meters (p=.12), and playground within 1000 meters (p=0.15) were significant with atopic diseases at 12 months. As for the NDVI data, NDVI with a buffer zone of 750 meters during the child's 0-12 months (p=0.10) was significantly associated with atopic disease at 12 months. Among the demographic characteristics, maternal history of thyroid dysfunction (p=0.09), history of atopy (p=0.11), kidney disease (p=0.10) during early pregnancy, age at birth (0.17), father's history of diabetes (p=0.17), anemia (p=0.1), height (p=0.11) were significant with atopic diseases at 12 months.

Using the stepwise logistic model selection, the final multivariate logistic model is selected and shown in Table 4. NO_2 concentration during the second trimester ($p < 0.001$), playground within 1000 meters (p = 0.01), and NDVI within 750 meters during child's 0-12 months (p=0.01) were all significantly associated with atopic diseases at 12 months under a p-value of 0.05 for significance. Based on the literature review, the final multivariate logistic

model was adjusted for family income, father smoking status, history of atopy, maternal smoking status, gestational weeks, secondhand smoking status before and during pregnancy, history of atopy, and baby's sex, as shown in Table 5 (1,3,4,6,10–12,14,16). After the adjustment, NO_2 concentration during the second trimester ($p < .001$) remained significant and its beta remained relatively the same (unadjusted beta = 0.21 and adjusted beta = 0.20).

According to the literature review, some research studies found the risk of atopic diseases to be higher for boys compared to girls (13,64) while other studies found the opposite (56). To explore the role of baby's sex in modifying this association, we stratified the data by baby's sex using the adjusted final multivariate logistic model showed in Table 6 and 7. The NO_2 concentration during the second trimester was higher for boys (beta = 0.26) compared to girls (beta=0.20). Also, the NO_2 concentration during the second trimester was only significantly associated with atopic disease among boys (p=0.01) but not girls (p=0.09).

The results of the bi-pollutant models were shown in Table 8, where NO_2 and each of the other air pollutants were put in the full model simultaneously. NO_2 concentration during the second trimester remained significant while that other pollutant did not (Figure 1). When the models were further stratified by the baby's sex, NO_2 remained significant when another pollutant was put inside the model among boys (Table 9). In addition, PM_{10} or PM_{25} became significant when put in the bi-pollutant model with NO_2 (Table 9). For girls, NO_2 became un-significant (Table 10).

When the final adjusted multivariate logistic model was conducted for each pollutant at different time periods, NO_2 concentration during the second trimester (OR: 3.29, 95% CI: 1.46-7.43) and NOx concentration during the second trimester (OR: 2.15; 95% CI: 1.02-4.51) are

significant with atopic diseases at 12 months (Table 11 and Figure 2). As for 0-12 months of air pollutant levels, none of the pollutant concentrations are significant (Table 12 and Figure 3).

Discussion:

This study investigated the relationships of atopic diseases at 0-12 months, air pollution, land-use types, and NDVI. In the multivariate logistic regression model, NO_2 concentration during the second trimester, playground within 1000 meters, and NDVI within 750 meters during child's 0-12 months were significantly associated with atopic diseases at 12 months. Our study then adjusted for family income, father's smoking status, father's atopy, infant's gestational weeks maternal smoking status, maternal secondhand smoking before and during pregnancy, and maternal atopy. After the adjustment, NO_2 concentration during the second trimester remained significant with a unprotective effect estimate.

Significant Primary Exposures and Covariates

Air Pollution

Our analysis showed that NO_2 concentration during the second trimester was associated with atopic diseases at 12 months. In the bi-pollutant model, NO_2 concentration during the second trimester continued to associate with the outcome when CO, NO, NO_2, NOx, SO_2, and PM_{10}, or PM_{25} during the same time period was added in the adjusted multivariate logistic regression model (Table 8). From Figure 1, NO_2 concentration during the second trimester was the only pollutant associated with atopic diseases at 12 months. This significance of NO_2 was consistent with several previous studies. Deng et al's (2016) survey study among children aged 3-6 years in China reported that NO_2 exposure during the first trimester was associated with AD (OR: 1.54; 95% CI: 1.14–2.09); NO_2 exposure during the second trimester was associated with

asthma (OR: 1.72: 95% CI: 1.02–2.97); and NO_2 exposure during the third trimester was associated with AR (OR: 1.77: 95% CI: 1.09–2.89) (64). Clark's (2010) case-control study among children aged 3-4 years in Canada reported that a 10 μg/m3 increase in NO_2 exposure during pregnancy was associated with the development of childhood asthma (OR: 1.10; 95% CI: 1.05–1.15) (65). In addition, Liu et al's (2016) retrospective cohort study among preschool children in China reported that NO_2 exposure during pregnancy was associated with AR (OR: 1.73; 95% CI: 1.26-2.38) (66) and lifetime-ever AD (OR: 1.53; 95% CI: 1.21-1.94) (67).

Air pollution exposure during the pregnancy period puts children at risk of atopic diseases at 0-12 months. The NO_2 concentration in the multivariate logistic regression model was during the second trimester. When each pollutant at a different time period was placed inside the adjusted multivariate logistic regression model without NO_2, some pollutants (NOx during the second trimester and PM_{10} during the first trimester) during the pregnancy period were significantly associated with atopic diseases at 12 months but not with the pollutants during the 0-12 months period (Table 11, Table 12, Figure 2, and Figure 4). This association between air pollution exposure during pregnancy and atopic diseases is biologically plausible. According to Deng et al (2016), pregnant women should avoid air pollution exposure during pregnancy because the fetal skin structures and respiratory airways of their children are developing during pregnancy (68–70). If these women are exposed to air pollution, the toxic pollutants might cause negative effects on these developments, reducing the capacity to fight infections and increasing the risk of allergic manifestations later in life (71–73). Furthermore, the harmful effects of toxic pollutants might cause oxidative stress and inflammation by decreasing placental blood flow and reducing nutrients to the fetus (74). This situation leads to allergic diseases (inflammatory disorders). Especially for AD, the reactive oxygen and reactive nitrogen species produced by air

pollution exposure during pregnancy might damage the skin barrier, putting the children at risk of AD (33,75). Also, allergic diseases are dominated by T helper 2 (Th2) mechanisms. The harmful effects of toxic pollutants might increase the Th2 responses in the immune system during fetal development and after birth (76).

Normalized Difference Vegetation Index

The findings for the association between greenness and atopic diseases are still inconsistent depending on the place, population, and focused atopic disease of the study (27–31). Our analysis showed that NDVI within a buffer zone of 750 meters during child's 0-12 months was associated with atopic diseases at 12 months. This result was similar to Hsieh et al's (2019) matched case-control study among children aged 0-17 in Taiwan and Andrusaityte et al's (2016) nested case-control study among children aged 4-6 in Lithuania. Hsieh (2019) reported that increased risk of asthma in preschool children aged 0-5 years was associated with the surrounding greenness (30,31). As the level of greenness increased from 0% to 80%, the risk of asthma occurrence increased significantly (31). In Andrusaityte's (2016) study, an increased IQR in NDVI buffer zone 100 was associated with the risk of asthma (OR: 1.43; 95% CI: 1.10-1.85) (30).

To possibly explain this association, the Taiwanese forest information showed that Taiwan has put such policies as tree-planting activities, carbon reduction projects, and green building regulations in place to support sustainable development (31). From 2005 to 2012, the overall green coverage increased by 1.2 times, and nearly 60% of Taiwan is currently covered by forest (77). Green environments may produce certain allergens, such as fungi, spores, or pollens (31). Many parts of Taiwan are already covered by forest, and its green areas continue to

increase gradually. This situation might possibly explain the reason NDVI was associated with atopic diseases at 0-12 months.

Hsieh's (2019) study was in the same location and had a similar age population to our study. According to Hsieh, young children are more vulnerable to the risk of atopic diseases, especially asthma in Taipei because their homes are surrounded by greenness, and they have to stay at home. Adult children aged 6-17 have to go to school. Therefore, older children spend less time at home and become less vulnerable to the risk of atopic diseases (31).

Land-use Types

There hasn't been a study that has information about the association of atopic diseases and playgrounds. Our analysis showed that a playground within 1000 meters was associated with atopic diseases at 0-12 months. The green areas in Taiwan have been increased dramatically and children are living in a green surrounding environment (31). Playgrounds are often located in a green area, especially in a park. Specifically, in Taipei, children's playgrounds are located in all thirteen parks from all twelve districts (78). Akpinar's (2017) cross-sectional study among children aged 1-12 years in Turkey reported that living close to an urban green space was associated with more frequency of physical activity for children aged 1–6 years (79). From Hsieh et al's (2019) matched case-control study, younger children tend to be surrounded by green area. In our study with this information, the parents may take a walk at a park that has a playground and stroll their child with them. Those children who old enough and able to play may be taken out to a playground area surrounded by greenness. Consequently, the children might be exposed to the fungi, spores, or pollens from the green environment, causing them to have allergic reactions. More studies are still needed for this association.

Adjustment of Covariates

Previous studies controlled for family income (30,80), sex (30,31,64,67,81,82), parental atopy (30,64,67,83,84), parental firsthand and second smoking status (30,64,67,82,84), and total number of weeks of infant's gestation (65). Therefore, our study adjusted for family income, father's smoking status, father's atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before and during pregnancy, and maternal atopy. Especially for smoking status in our study, although most female participants did not smoke, many of them were exposed to secondhand smoke. As such, we had to control for both firsthand and secondhand smoke. Even after adjusting for these covariates, NO_2 concentration during the second trimester remained significant and maintained similar unprotective effect estimate.

Stratification by Sex

Some studies stratified their data by sex, and the results among these studies remain inconsistent (64,81,82). The results yielded from the final adjusted multivariate logistic regression model indicated that the effect estimate of NO_2 concentration during the second trimester on atopic disease was significantly higher among boys compared to girls. Even in the bi-pollutant model, NO_2 concentration during the second trimester remained significant for boys but not girls. From a previous study, Deng et al's (2016) cohort study reported that AR was associated with postnatal exposure of NO_2 in boys (OR: 2.06; 95% CI: 1.23-3.44) but not with girls (OR: 1.14; 95% CI: 0.62-2.07) (64). This difference might be linked to the different lung function growth rates and differences in airway size (64). Importantly, the difference could be the immune response in male and female. Channappanavar et al's (2018) animal study in mice in the USA reported that women are more immunity to infection than men because female sex

hormone estrogen plays a role in immunity and the two female X chromosomes contains immune-related genes (85).

Chapter 4: Conclusion, Limitation, and Recommendation

Conclusion:

In conclusion, our retrospective cohort study showed that exposures to NO_2 during the second trimester, playground within 1000 meters, and NDVI within 750 meters during child's 0-12 months were significantly associated with atopic diseases at 12 months. There have been inconsistencies in associations found between atopic diseases, air pollution, land-use types, and NDVI in the literature. The results of the current project may help researchers gain more information about what factors may contribute to the development of these atopic diseases. Importantly, these results may have important environment policy implications for improving public health in Taiwan specifically.

Limitations

There are several limitations to our study. This study is a retrospective cohort study with low birthweight babies. As a result, it was not possible to assess each mother's exposure to air pollution during pregnancy or after the birth of their child. However, our study was able to get a rough estimate of exposure to air pollution using Taipei's EPA air pollution monitoring data and geographic information in ArcGIS's spatial interpolation (61). Additionally, parents' and children's information were collected using questionnaires, which may have recall biases. Our study team used medical records to minimize these possible recall biases. Furthermore, the current study's atopic diseases include asthma, AR, and AD and did not focus on each of these atopic diseases separately. While the study results showed that NO_2 concentration during the second trimester, NDVI within 750 meters during 0-12 months, and playground within 1000 meters were associated with atopic diseases at 0-12 months, we cannot determine which specific atopic diseases were associated with the environmental risk factors identified. Finally, the

duration of this study was short. Some children may not have developed any atopic disease conditions within the 0-12 months period but could have later. Future research should use a longer period to identify potential additional cases.

Recommendation for Future Study

Future research should have longer study periods of at least 5 years, aim to engage a larger sample of children, and disaggregate the outcome to identify specific atopic diseases. The current study's outcome was atopic diseases at 0-12 months. Atopic diseases may take a little longer than one year to be developed. With a small sample size, our study had only 31 children with an atopic disease condition. As a result, many variables were insignificant. Having a longer period to assess the outcome and more children in the sample would help to strengthen the multivariate logistic model. Finally, future studies should disaggregate the outcome to ask about each atopic disease separately. The current study aggregated all atopic diseases, and consequently, it was not clear which atopic disease was associated with NO_2 concentration during the second trimester, playground within 1000 meters, and NDVI within 750 meters. Focusing on each of the atopic diseases separately would allow the results to be more specific and allow the Taiwanese government to know where to strengthen the health and environmental policies for improving the health of the Taiwanese people.

Tables, Figures, and Maps:

Table 1: Demographic & Prenatal Characteristic of Cases and Controls

Characteristics	Cases		Controls		p
	n (or mean)	% (or SD)	n (or mean)	% (or SD)	
Baby's sex					–
Male	16	51.61%	185	56.23%	
Female	15	48.39%	144	43.77%	
Baby's birth season					0.12
Spring	7	22.58%	102	31.00%	
Summer	11	35.48%	83	25.23%	
Fall	13	41.94%	109	33.13%	
Winter	0	0%	35	10.64%	
Baby's birth weight (g)	3141.07	352.98	3101.7	429.71	0.62
Baby's height (cm)	50.52	2.13	50.16	2.27	0.41
Baby's head circumference (cm)	33.67	1.1	33.62	1.62	0.88
Maternal educational					<.0001
High school and below	3	9.68%	21	6.40%	
College and above	28	90.32%	307	93.60%	
Mother smokes	1	3.23	6	1.86	0.6
Mother drinks during pregnancy	1	3.23%	17	5.23%	0.63
Mother has history of atopic diseases	13	41.94%	91	28.09%	0.1
Infant's gestational weeks	38.42	1.2	38.46	1.52	0.67
Maternal age at delivery	33.9	3.01	32.97	3.6	0.17
Father's educational level					0.89
High school and below	4	12.90%	33	10.06%	
College and above	27	87.10%	295	89.94%	
Father smokes	10	33.33%	91	28.80%	0.6
Father drinks during pregnancy	14	46.67%	161	50.63%	0.68
Father has history of atopic diseases	8	26.67%	92	28.93%	0.79
Family Monthly Income					0.16
< $ 2,000 USD	8	26.00%	57	17.33%	
$2,000 to $3,000 USD	11	35.48%	175	53.19%	
> $3,000 USD	12	38.71%	97	29.48%	
Total	31	100.00%	329	100.00%	

Note: Because some variables have missing observations, the total cases and controls will not always be 31 and 329.

*p values of Chi-Square Test for categorical variables, Student's T-test for normal continuous variables (pooled), and Wilcoxon Signed-Rank Test for non-normal continuous variables (two tailed)

Table 2: Air Pollutant Concentrations during Entire Pregnancy & 0- 12 Month after Birth

Entire Pregnancy							
Pollutants	N	Mean	SD	Median	Min	Max	IQR
CO (ppb)	360	651.49	53.65	657.03	444.72	831.19	66.18
NO (ppb)	360	12.96	2.34	13.15	6.47	26.43	2.66
NO_2 (ppb)	360	21.51	3.58	22.22	7.22	27.70	4.31
NOx (ppb)	360	34.47	4.77	35.79	16.20	52.87	5.98
SO_2 (ppb)	360	3.22	0.47	3.22	2.28	4.71	0.69
PM_{10} (ug/m^3)	360	46.00	4.01	45.82	34.18	55.81	5.21
PM_{25} (ug/m^3)	360	25.71	2.44	26.14	14.81	30.66	3.12
0-12 Months After Birth							
Pollutants	N	Mean	SD	Median	Min	Max	IQR
CO (ppb)	360	658.56	52.49	661.30	326.74	812.25	49.24
NO (ppb)	360	12.83	2.14	13.27	3.74	17.14	2.82
NO_2 (ppb)	360	21.35	2.84	21.58	10.33	27.64	3.17
NOx (ppb)	360	34.19	3.84	35.10	14.07	41.18	5.03
SO_2 (ppb)	360	3.34	0.38	3.37	2.48	4.42	0.59
PM_{10} (ug/m^3)	360	45.40	3.01	45.23	38.06	54.45	3.60
PM_{25} (ug/m^3)	360	23.30	3.20	23.22	15.71	31.37	4.94

Table 3: Univariate Logistic Model under a P-value of 0.2 Significance for Stepwise Model Selection

Variables	Beta Estimate	SE	P Value
NO_2 concentration during 2nd trimester	0.08	0.05	0.10
Dryland within 2000 meters	1.22E-06	7.15E-07	0.09
Forest zone within 1000 meters	4.87E-07	3.50E-07	0.16
Provincial road within 1500 meters	-2.20E-06	1.52E-06	0.15
State road within 800 meters	-6.25E-06	4.80E-06	0.19
Water within 1000 meters	-1.09E-06	8.32E-07	0.19
Factory within 2000 meters	-5.10E-07	3.72E-07	0.17
Powerplant within 1500 meters	-2.00E-05	1.70E-05	0.19
Social welfare within 2000 meters	1.50E-05	9.89E-06	0.12
Playground within 1000 meters	3.59E-06	2.47E-06	0.15
Maternal history of thyroid dysfunction during early pregnancy	1.04	0.59	0.08
Maternal history of atopy	0.61	0.38	0.11
Maternal history of kidney disease during early pregnancy	2.36	1.43	0.10
Maternal age at birth	0.08	0.06	0.17
Baby's Birth Season	-0.04	0.19	0.83
Father's history of diabetes	1.69	1.24	0.17
Father’s history of anemia	2.38	1.43	0.10
Father's Height	-0.06	0.03	0.11
NDVI within 750 meters during 0-12 months	1.78	1.33	0.18

Table 4: Multivariate Logistic Model from Stepwise Model Selection using a P-value of 0.5 Significance

Variables	Beta Estimate	SE	P Value
NO_2 concentration during 2nd trimester	0.21	0.07	<0.001
Playground within 1000 meters	7.66E-06	2.95E-06	0.01
NDVI within 750 meters during 0-12 months	4.44	1.63	0.01

Table 5: Adjusted Multivariate Logistic Model from Stepwise Model Selection

Variables	Beta Estimate	SE	P Value
NO_2 concentration during 2nd trimester	0.20	0.07	<0.001
Playground within 1000 meters	7.93E-06	0.00	0.01
NDVI within 750 meters during 0-12 months	4.05	1.70	0.02

Adjusting for family income, father's smoking status, father's atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before and during pregnancy, maternal atopy, and baby's sex

Table 6: Adjusted Multivariate Logistic Model from Stepwise Model Selection for Boys

Variables	Beta Estimate	SE	P Value
NO_2 concentration during 2nd trimester	0.26	0.11	0.01
Playground within 1000 meters	9.69E-06	0.00	0.01
NDVI within 750 meters during 0-12 months	6.37	2.32	0.01

Adjusting for family income, father's smoking status, father's atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before and during pregnancy, and maternal atopy

Table 7: Adjusted Multivariate Logistic Model from Stepwise Model Selection for Girls

Variables	Beta Estimate	SE	P Value
NO_2 concentration during 2nd trimester	0.20	0.11	0.09
Playground within 1000 meters	7.22E-06	0.00	0.20
NDVI within 750 meters during 0-12 months	0.21	2.96	0.94

Adjusting for family income, father's smoking status, father's atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before and during pregnancy, and maternal atopy

Table 8: Two Pollutants in Final Multivariate Logistic Model per IQR during the Second Trimester

	Variables	Beta	P-value	OR	95% CI	
NO_2 + CO	NO_2	1.26	0.00	3.5370	1.4991	8.3449
	CO	-0.20	0.58	0.8218	0.4139	1.6317
NO_2 + NO	NO_2	1.27	0.00	3.5584	1.5728	8.0509
	NO	-0.26	0.31	0.7688	0.4625	1.2778
NO_2 + Nox	NO_2	1.79	0.02	5.9913	1.3955	25.7216
	Nox	-0.75	0.31	0.4733	0.1115	2.0083
NO_2 + SO_2	NO_2	1.18	0.00	3.2583	1.4694	7.2253
	SO_2	-0.08	0.80	0.9193	0.4808	1.7579
NO_2 + PM_{10}	NO_2	1.60	0.00	4.9767	1.8543	13.3569
	PM_{10}	-0.69	0.11	0.4998	0.2144	1.1654
NO_2 + PM_{25}	NO_2	1.27	0.00	3.5494	1.5673	8.0381
	PM_{25}	-0.29	0.40	0.7499	0.3861	1.4564

Note: Adjusting for playground within 1000 meters, NDVI within 750 meters during 0-12 months, family income, father's smoking status, father's history of atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before pregnancy, maternal secondhand smoking during pregnancy, and maternal history of atopy

Table 9: Two Pollutants in Final Multivariate Logistic Model per IQR during the Second Trimester for Boys

	Variables	Beta	P-value	OR	95% CI	
$NO_2 + CO$	NO_2	1.92	0.01	6.85	1.61	29.09
	CO	-0.64	0.28	0.53	0.17	1.68
$NO_2 + NO$	NO_2	2.08	<0.001	7.96	1.89	33.49
	NO	-0.91	0.06	0.40	0.16	1.04
$NO_2 + Nox$	NO_2	3.88	0.01	48.42	2.69	870.41
	Nox	-2.59	0.06	0.07	0.01	1.10
$NO_2 + SO_2$	NO_2	1.43	0.02	4.16	1.22	14.17
	SO_2	0.25	0.61	1.28	0.49	3.32
$NO_2 + PM_{10}$	NO_2	3.62	<0.001	37.34	4.52	308.24
	PM_{10}	-2.92	<0.001	0.05	0.01	0.34
$NO_2 + PM_{25}$	NO_2	1.89	<0.001	6.62	1.94	22.58
	PM_{25}	-1.18	0.03	0.31	0.10	0.91

Note: Adjusting for playground within 1000 meters, NDVI within 750 meters during 0-12 months, family income, father's smoking status, father's history of atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before pregnancy, maternal secondhand smoking during pregnancy, and maternal history of atopy

Table 10: Two Pollutants in Final Multivariate Logistic Model per IQR during the Second Trimester for Girls

	Variables	Beta	P-value	OR		95% CI
NO_2 + CO	NO_2	1.19	0.09	3.28	0.82	13.18
	CO	-0.12	0.83	0.89	0.31	2.56
NO_2 + NO	NO_2	1.15	0.09	3.15	0.85	11.73
	NO	-0.05	0.90	0.95	0.45	2.03
NO_2 + Nox	NO_2	1.24	0.27	3.46	0.39	30.97
	Nox	-0.14	0.90	0.87	0.10	7.45
NO_2 + SO_2	NO_2	1.31	0.05	3.69	1.02	13.31
	SO_2	-0.70	0.19	0.50	0.17	1.42
NO_2 + PM_{10}	NO_2	0.66	0.38	1.93	0.44	8.37
	PM_{10}	0.79	0.19	2.20	0.68	7.06
NO_2 + PM_{25}	NO_2	0.85	0.23	2.33	0.58	9.34
	PM_{25}	0.65	0.20	1.91	0.71	5.13

Note: Adjusting for playground within 1000 meters, NDVI within 750 meters during 0-12 months, family income, father's smoking status, father's history of atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before pregnancy, maternal secondhand smoking during pregnancy, and maternal history of atopy

Table 11: Rate Ratios & 95% CIs OF Air Pollution Concentrations from the Final Adjusted Logistic Multivariate Model per IQR

	Trimester 1			Trimester 2			Trimester 3			All Trimester		
Pollutants	OR	95% CL		OR	95% CL		OR	95% CL		OR	95% CL	
CO (ppb)	1.3533	0.6908	2.6512	1.3097	0.7388	2.3215	0.6558	0.3321	1.295	1.0996	0.6541	1.8487
NO (ppb)	1.2261	0.7013	2.1438	0.9689	0.6159	1.5242	0.7176	0.4361	1.1807	0.9301	0.5815	1.4876
NO_2 (ppb)	1.7507	0.8799	3.4833	3.2074	1.4556	7.0672	0.9493	0.4848	1.8587	1.8309	0.9153	3.6623
NOx (ppb)	1.6655	0.8192	3.3864	2.1489	1.0229	4.5147	0.7956	0.4182	1.5136	1.402	0.7494	2.6227
SO_2 (ppb)	1.336	0.8596	2.0764	1.1246	0.6508	1.9433	1.1573	0.7025	1.9065	1.3542	0.7501	2.4447
PM_{10} (ug/m3)	2.027	0.9748	4.2149	1.1088	0.5824	2.1111	0.5192	0.2579	1.0452	1.1507	0.6613	2.0022
PM_{25} (ug/m3)	1.5742	0.8232	3.0102	1.0901	0.5972	1.9898	0.5573	0.3187	0.9746	0.8878	0.5105	1.5442

Note: Adjusting for playground within 1000 meters, NDVI within 750 meters during 0-12 months, family income, father's smoking status, father's history of atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before pregnancy, maternal secondhand smoking during pregnancy, and maternal history of atopy

Table 12: Rate Ratios & 95% CIs OF Air Pollution Concentrations from the Final Adjusted Logistic Multivariate Model per IQR

	0-6 Month			6-12 Month			0-12 Month		
Pollutants	OR	95% CL		OR	95% CL		OR	95% CL	
CO (ppb)	0.8356	0.4991	1.3992	0.9958	0.5726	1.7319	1.148	0.7758	1.6988
NO (ppb)	0.8203	0.4897	1.3739	0.8212	0.5202	1.2962	0.8968	0.5483	1.4671
NO_2 (ppb)	1.0725	0.607	1.8951	1.5516	0.8193	2.9383	1.4339	0.7787	2.6404
NOx (ppb)	0.9399	0.5211	1.6954	1.1966	0.6386	2.2421	1.1686	0.6218	2.1964
SO_2 (ppb)	0.9292	0.692	1.2476	1.1494	0.684	1.9314	0.9104	0.4741	1.7482
PM_{10} (ug/m3)	1.2158	0.5844	2.5293	0.6864	0.3264	1.4435	0.9629	0.5503	1.6848
PM_{25} (ug/m3)	0.6649	0.3255	1.358	0.8122	0.4338	1.5208	0.7837	0.411	1.4943

Note: Adjusting for playground within 1000 meters, NDVI within 750 meters during 0-12 months, family income, father's smoking status, father's history of atopy, maternal smoking status, infant's gestational weeks, maternal secondhand smoking before pregnancy, maternal secondhand smoking during pregnancy, and maternal history of atopy

Figure 1: Two Pollutants Model using the Final Adjusted Multivariate Logistic Model Per IQR

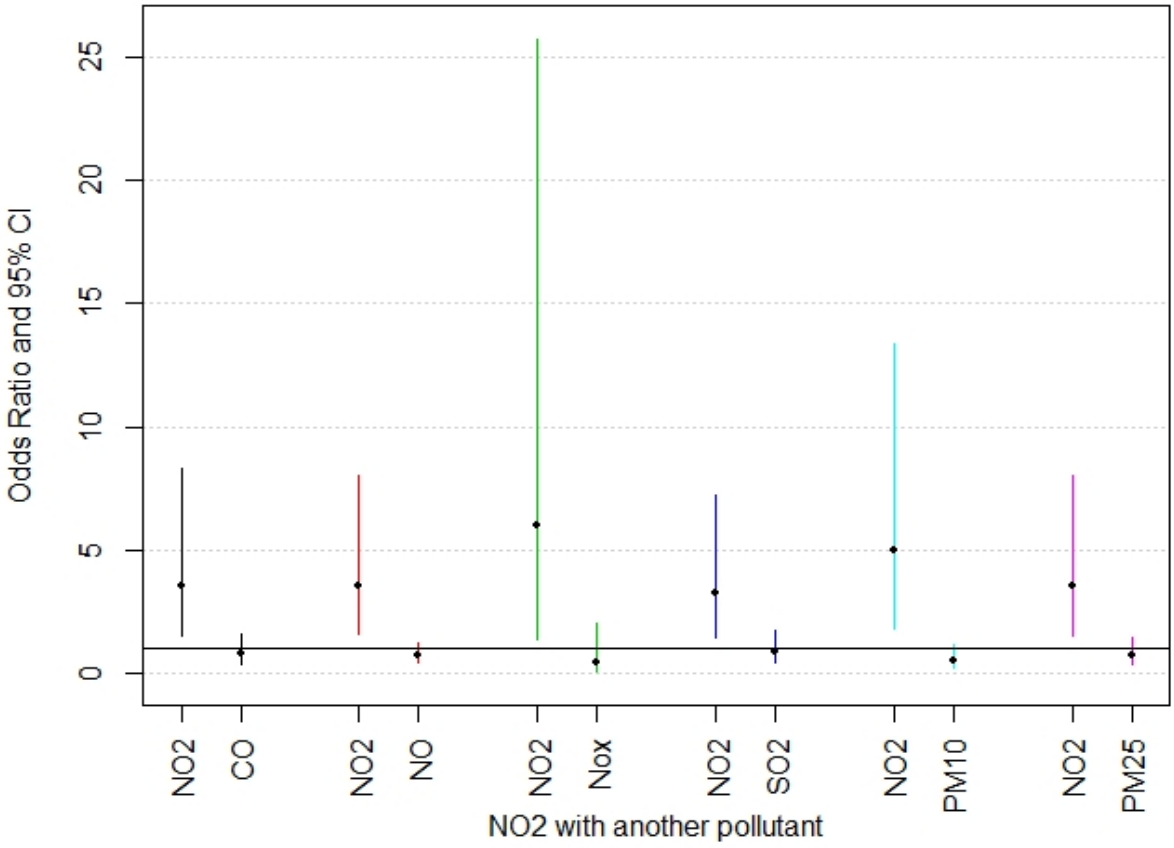


Figure 2: Single Pollutant in the Multivariate Logistic Model per IQR for Trimesters

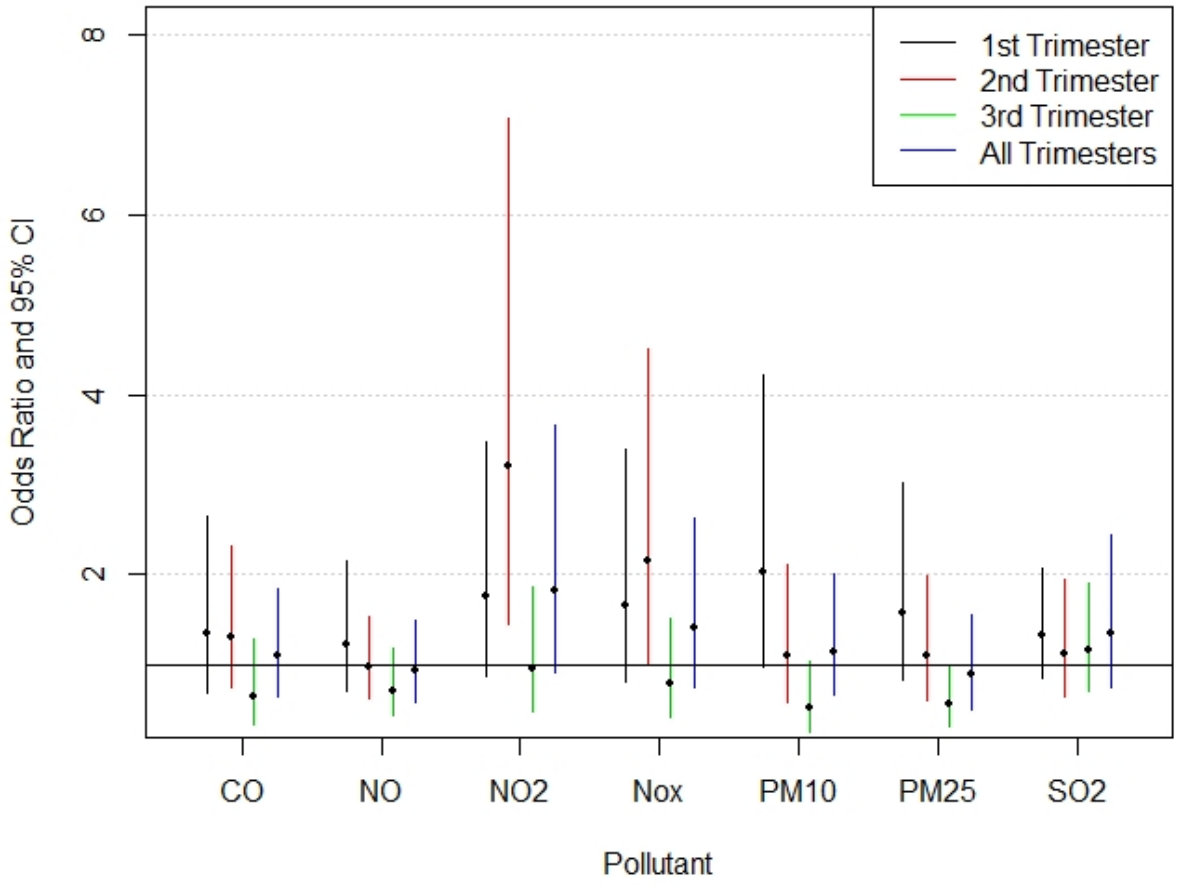
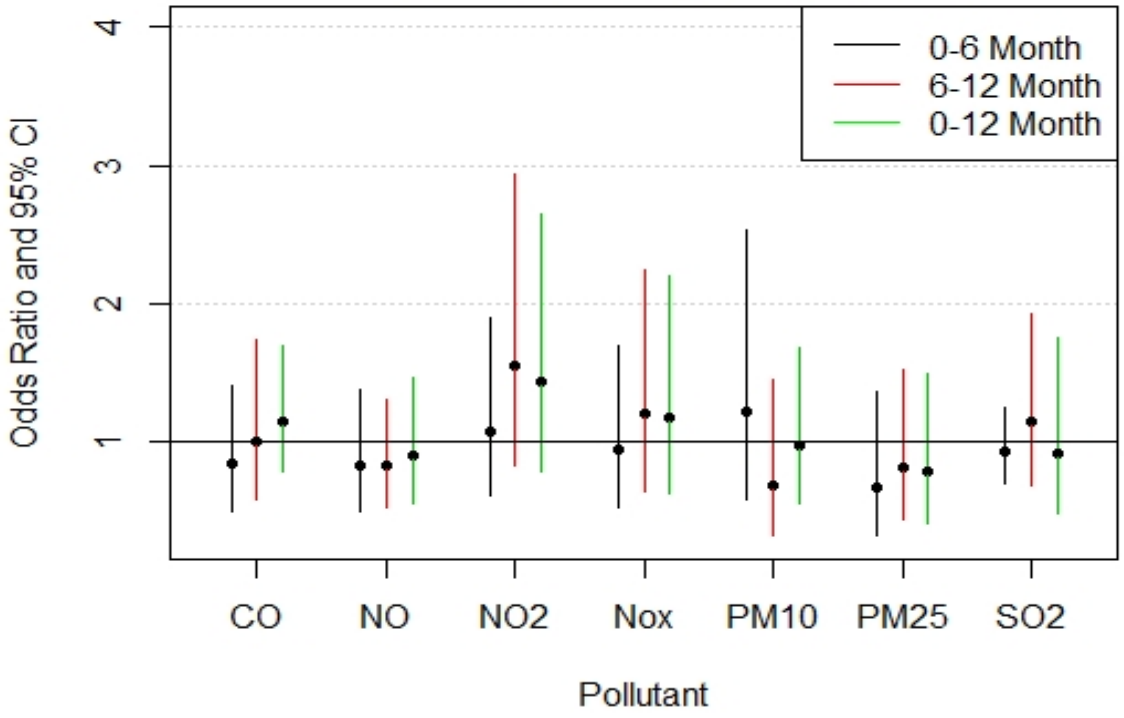
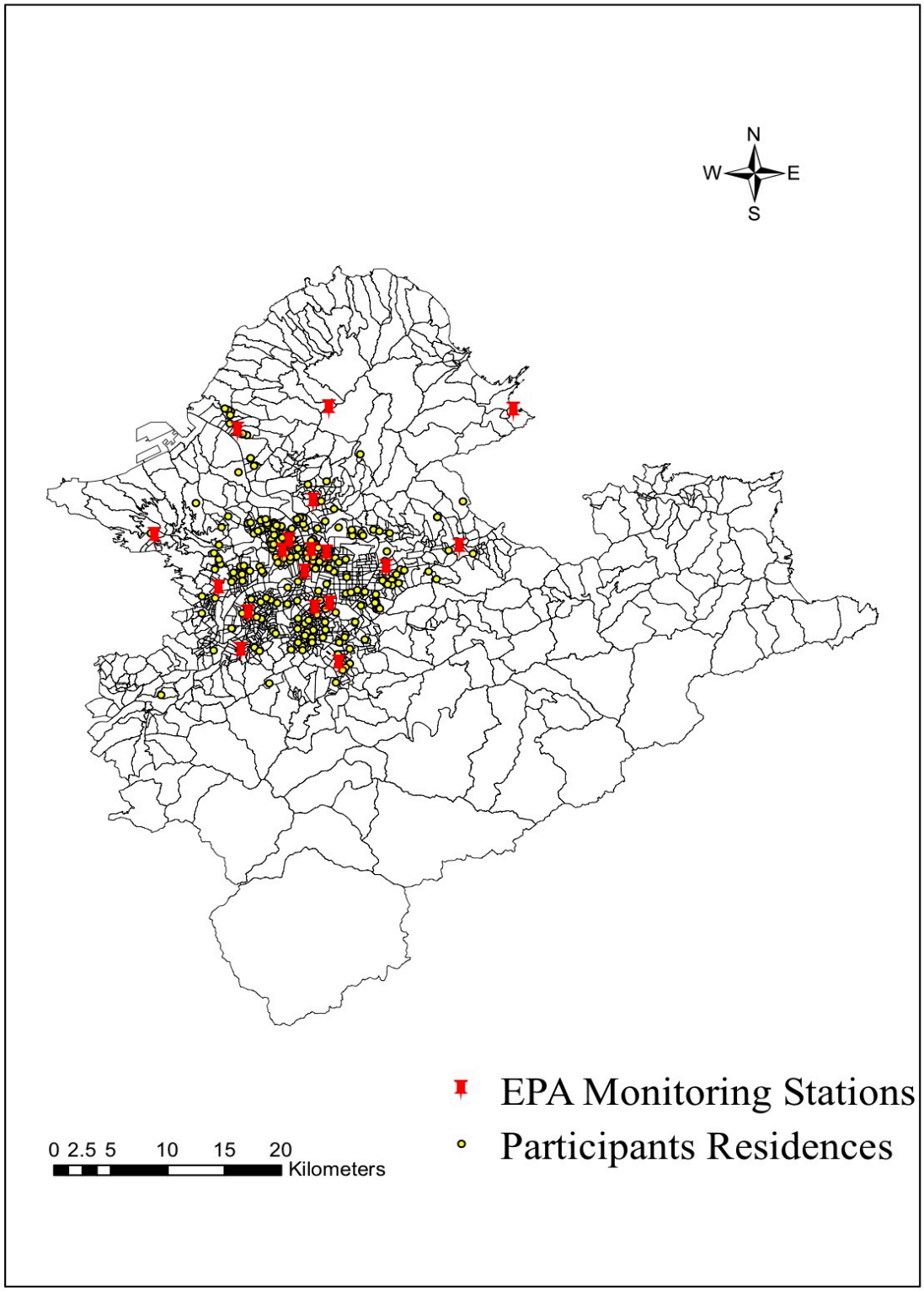


Figure 3: Single Pollutant in the Final Adjusted Multivariate Logistic Model Per IQR during 0-12 Months



Map 1: EPA Monitoring Stations and Participant Residences



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