



UNIVERSITY OF
GOTHENBURG

THE SAHLGRENSKA ACADEMY

Association of birch pollen and air pollution with asthma- control questionnaire scores among individuals with allergic asthma in Sweden.

DATE: 27 September 2021.

Author: Francis Tandoh Amankwaah

Master's Thesis in Public Health Science, 30 hec

Supervisor: Hanne Krage Carlsen

Examiner: Sharon Fonn

Table of Content

PART A	
INTRODUCTION	1
Prevalence of Asthama	1
Causes of Asthma	3
Risk factors and Trigger of Asthma	3
Diagnosis of Asthma	5
Treatment of Asthma	6
Pollen Allergen and Asthma	6
Climate change and Meteorology on Allergic Disease	7
Pollen Allergen, Air Pollution and Allergic Disease	8
ASTHMA SEVERITY AND ASTHMA CONTROL	9
CONCEPTUAL FRAMEWORK	11
Ethics	14
Conclusion	14
REFERENCES	15-17
PART B	18
ABSTRACT	19
INTRODUCTION	20
AIMS OF THE RESEARCH AND RESEARCH QUESTIONS	24
MATERIAL AND METHOD	24
Study Design	24
Study Population	25
Main Outcome Variable	25
Asthma Control Questionnaires	26
Main Exposure and Covariates	27
Variable Calculation	30
Statistical Analysis	30
RESULTS	31
Study Population	31
Characteristic of Study Participants, Waves and Exposure	32
Log Transformation	32

Association between Exposure to Pollen and Asthma Symptoms Control (ACQ-6).....	33
Association between Pollen and Asthma Symptoms Control (ACQ-6) with multi-pollutant models	35
DISCUSSION	36
Importance of Covariates	36
Importance of Lags	37
Compare with other studies	37-41
STRENGTH AND WEAKNESS OF THE STUDY	41
PROPOSED ALIGNMENTS FOR FUTURE STUDIES	42
CONCLUSIONS AND IMPLICATIONS	42
DECLARATION OF CONFLICTING INTERESTS	42
REFERENCES	43-46
TABLES, FIGURES AND APPENDICES	47-55

PART A

INTRODUCTION

Asthma is a chronic respiratory disease that affects both adults and children. It is a complex disease that often starts in childhood. It is known that genomic and environmental factors as well as aberrant immune maturation early in life can contribute to the onset of disease, with great disparity over time and geographical regions.(Von Mutius & Smits, 2020). Asthma is an inflammatory disorder of the respiratory system, particularly of the bronchioles, the major passages for air into the lungs. During an attack, the bronchioles become constricted and the volume of oxygen reaching the alveoli is greatly reduced. The patient feels short of breath and anxious.(McMaster, 2006). Asthma symptoms may include coughing, wheezing, and shortness of breath that can interfere with sleep, exercise, and other normal activity. Severe and prolonged attacks that are untreated may be fatal.(McMaster, 2006)

Prevalence of Asthma

Asthma prevalence has been estimated from surveys using questionnaires, spirometry, and assessment of airway hyperresponsiveness. It was estimated that over 339 million people had Asthma globally in 2016 (Vos et al., 2017) and over 272 million people in 2017, out of this over 99 million and 173 million had asymptomatic and symptomatic asthma respectively(Mazidi, 2019). Though there has been a reduction in the 2016 estimate of the global asthma prevalence, this could be as a result of the use of more advanced methods in diagnosing the disease, improved medication and good controls exhibited by people. However asthma is still one of the commonly reported emergencies cases to most hospitals. Castro and Kraft (2008) reported that increased prevalence of asthma is multifactorial in etiology. They named factors such as obesity, the exposure to allergens, such as mold, dust

mites, and cockroach dust as some of these factors. They further emphasized that increased rate of industrialization leads to pollution and consequently increased airway hyperresponsiveness secondary to exposure to environmental triggers. These are some of the factors that have contributed to the prevalence of asthma globally.

The prevalence of asthma is evidenced to be affected by migration. This principle is known as the “healthy immigrant phenomenon.” This concept suggests that immigrants migrating to higher-income countries tend to be healthier than those born in that country.(Mahmoudi, 2016). The results from systematic review on developing asthma in relation to international immigration suggested an influence of the environment on the development of asthma and allergies throughout the life course. The review revealed that prevalence of asthma and allergic diseases in immigrants was lower than in the host country, and over time converges with the general prevalence in the local population. In the study, the prevalence of asthma was generally higher in second generation than first generation immigrants, and with length of residence in the host country, the prevalence of asthma and allergies increases steadily. (Cabieses et al., 2014). In a different study, asthma prevalence is stable or decreasing in many developed countries but is increasing rapidly in developing countries as lifestyles become westernised.(Papi et al., 2018). This means that social economic status can be associated with to factors of asthma prevalence. It is observed from a study in UK that birth place and education were significant social contributors to risk of adult-prevalent asthma(Shiue, 2013).

In Sweden, an increase of asthma prevalence from 1996 to 2007 was observed, while very few respiratory symptoms displayed an increase in prevalence. This unchanged prevalence of respiratory symptoms and the reduced number of symptoms among asthma patients indicate that a plateau has been reached in the prevalence of asthma and respiratory symptoms (Ekerljung et al., 2010). In a different study, the prevalence of current asthma increased from

1996 to 2016, mainly among the middle-aged and women. The increase was explained by a continuing increase in allergic asthma from 1996 to 2006 and then further from 2006 to 2016, while the prevalence of non-allergic asthma remained stable in all three surveys (Backman et al., 2017).

Causes of Asthma

The causes of the increase in global prevalence of asthma are not well understood. Genetic predisposition, exposure to environmental allergens, indoor and outdoor air pollution, lower respiratory tract infection early in life, airway microbiome makeup, dietary factors and abnormal immunological responses may promote the development of asthma (European Respiratory Society, 2017).

There are a lot of factors that is known to cause asthma in people. It is a disorder that correlates very closely with a number of variables from weather and air quality to presence of allergens to heavy exercise, smoking, stress, and certain environmental pollutants. Heredity is clearly an influence as well; patients with a family history of asthma and atopy are at significantly higher risk of developing asthma than those from families without such a history.(McMaster, 2006). One or more of the causes described above could be the reason through which a person could become asthmatic.

Risk Factors and Triggers of Asthma

Research has found that both genetic and non-genetic factors affect asthma. A number of factors may cause exacerbations in people who have asthma but there is no recognised cause, either biological or environmental, for asthma itself. Thus, when considering nongenetic factors, it is important to distinguish between the triggers of asthma attacks and the causes of the underlying asthmatic process or trait. Both groups of factors may contribute to the

severity and persistence of asthma. (Global Asthma Report 2018). The Global Asthma Report (2018), outlined the following as risk factors for asthma. This include genetic susceptibility, environmental tobacco smoke, air pollution, mould and damp, animals, antibiotics and paracetamol (acetaminophen), occupational exposures, diet and obesity and breastfeeding.

In the treatment and management of asthma, knowing the factors and triggers of asthma is an important domain to the treatment and care of the disease. Comparing studies conducted on risk factors and triggers of asthma, risk factors are considered as factors that lead to the development of asthma while triggers are reported as the things that cause exacerbation of asthma symptoms. In a study that determined whether there is a common asthma triggers globally across region and countries, asthma triggers identified as common across regions fell within three specific categories including allergic triggers (e.g., pet dander and dust mites), physical triggers (e.g., allergic rhinitis and exercise), and environmental triggers (e.g., air pollutants or particulates, tobacco smoke, and weather-related factors)(Vernon et al., 2012). Mahmoudi (2016) also found other triggers that increase the risk of developing asthma including dust mites, mold, and cockroaches. Von Mutius & Smits (2020) reported that genomic and environmental factors contribute to the onset of the disease. Investigating the genetic influence on age at the onset of asthma, genetic factors explain 34% of the variation in the age at onset of asthma, and environmental factors account for 66%. (Thomsen et al., 2010).

Among adults who are current and former smokers, Dumanovsky and Matte (2007) reported that people who are obese reported higher rates of asthma. In children, exposure to passive smoking in childhood significantly predicted asthma (Thomsen et al., 2010). Similarly, environmental tobacco smoking exposure increased chronic bronchitis and three or more episodes of wheezing among children 2 months to 2 years old and asthma among children 2

months to 5 years old (Gergen et al., 1998). As part of environmental tobacco smoking, another study found that the exposure to parental smoking during childhood was significantly associated with asthma assessed in young adulthood (Hu et al., 1997). Asthma among young adults has also been associated with family history of asthma, and visible mold growth at home (Hu et al., 1997). In a study conducted in Turkey, the most important risk factor for occupational asthma among hairdressers was work intensity and atopy. (Akpınar-Elci et al., 2002). Physical activity is reported to have the tendency to influence asthma. Mitchel et al. found that a sedentary lifestyle corresponding to 5 hours or more per day of television is associated with an increase in asthma symptoms in children.

These findings are in support of the Global Asthma Report (2018) conclusion given on factors affecting asthma that environmental factors are much more likely than genetic factors to have caused the large increase in the numbers of people in the world with asthma.

Diagnosis of Asthma

The diagnosis of asthma involves an overall assessment of the patient's medical history, physical examination, and usually a measure of lung function and often a test of response to inhaled bronchodilator (Asher et al., 2020). There is an increasing evidence that identification of the asthma phenotype can be helpful in recommending personalized treatment. The major asthma phenotypes are allergic, nonallergic, infection related, aspirin-associated respiratory disease (AERD), and childhood preasthma phenotype.

In recent years, these have been further classified into (1) trigger induced (including occupational, cigarette smoke induced, air pollution induced, and exercise induced), (2) symptom based (including exacerbation prone, asthma with persistent airflow limitation, cough variant, adult onset, obese), and (3) biomarker based (including eosinophilic and neutrophilic).

Treatment and Prevention of Asthma

Asthma is generally a lifelong disease that is not curable, but treatment with quality-assured essential asthma medicines can effectively control the disease. In view of this making a correct diagnosis is essential for treatment, and improving access to spirometry will help to reduce misdiagnosis. Inhaled corticosteroids are the cornerstone of effective asthma control (European Respiratory Society, 2017). Asthma is treated with bronchodilator drugs that open up the airways or with steroids that suppress the immune response.(McMaster, 2006)

In view of the fact that the causes of most asthma is unknown and there is no effective strategy for primary prevention, epidemiological interventions involving work related asthma show that, in adulthood, early removal of allergens or irritants may lead to better control of the disease and avoiding smoking during pregnancy and avoidance of passive smoke exposure after birth can reduce asthma severity in children. (European Respiratory Society, 2017). Hence a better prevention of asthma is to eliminate or reduce the timing and exposure levels to risk factors and asthmatic triggers.

Relationship between Pollen allergens and Asthma

Pollen is one of the environmental factors that trigger respiratory allergic diseases such as asthma. According to the World Allergy Organisation, pollen allergy is an allergic condition affecting the mucous membranes of the nose and the eyes etc., usually characterized by nasal discharge, nasal congestion, and itchy and watery eyes, itchy nose, inner ears and roof of the mouth, that are caused by a hypersensitivity to airborne pollen, such as the pollen of trees, grasses, and weeds. When the allergen comes in contact with cell-bound immunoglobulin E (IgE) in the tissues of the conjunctiva and nasal mucosa, the tissues release mediators such as histamine or leukotrienes and induce annoying allergic symptoms. Most clinically relevant

pollens are wind-borne, or anemophilous, rather than being from entomophilous plants, which pollinate via insect carriers.(Mahmoudi, 2016)

Effect of Climate Change and Meteorology on Allergic diseases

Meteorological factors can also influence the production and concentration of aeroallergen in the environment which can exacerbate and increase the severity of some allergy diseases. For example, increased in atmospheric carbon dioxide concentration acts as a fertilizer for plant growth. The fertilizing effects of carbon dioxide, as well as increased temperatures from climate change, increases pollen production and the allergen content of pollen grains. This influence the concentrations of airborne pollutants and aeroallergens, and this can exacerbate asthma or other respiratory illnesses (Reid & Gamble, 2009). It is found that seasonal fluctuations in pollen and outdoor air pollutants are associated with asthma-related Emergency Department(ED) visits and that increased spring tree pollen levels likely contribute to a spring asthma peak.(Jariwala et al., 2011)

In a recent study, allergenic plants was in response to higher carbon dioxide levels and warmer temperatures which contributed to the increased production of pollen as well as the appearance of allergenic species in new climactic areas (Barnes, 2018). The findings from a cross-sectional study suggested that ongoing changes in the timing of spring onset, which are related to climate variability and change, are associated with asthma hospitalization. During this study, the early onset of spring was associated with a 17% increase in hospital admissions for asthma and late onset of spring was associated with a 7% increase (Sapkota et al., 2020). Other studies have also established the association between thunderstorm and asthma epidemics and exacerbation during the pollen season by washing down pollen grains and concentrating them in a band of air at ground level (D'Amato et al., 2007). Similar

evidence of association between thunderstorms and epidemics of asthma was established in this study. (Taylor & Jonsson, 2004).

The climate change affect the determinant of health through changes in environmental factors that is mostly related to climate change. Climate change alters local weather patterns including minimum and maximum temperature, precipitation, and storms, all of which affect the burden of allergic disease (Shea et al., 2008). Air pollution and increased exposure to aeroallergens due to climate change may have potentially serious adverse consequences for human health (Demain, 2018). Increase in air and water pollution due to climate change are at the origin of both respiratory infections and aggravation of chronic respiratory diseases, such as asthma and Chronic Obstructive Pulmonary Disease (COPD). Climate change affects the timing, dispersion, quantity and quality of aeroallergens and the distribution and severity of allergic disease (D'Amato et al., 2014)

Association between Pollen Allergens, Air Pollutants and Allergic Diseases

Asthma has been studied for its risk factors, triggers and pollutants association with self reported symptoms and exacerbation. Jariwala et al (2011) indicated that the spring asthma peak is closely associated with increased tree pollen counts and that there exists a significant association between asthma related ED visits and tree pollen concentrations. Another study found that hay fever, symptoms of allergic rhinitis, wheezing, sensitization against pollen, house dust mites or cats, and milk or eggs were associated with outdoor NO₂. The results indicate that traffic-related air pollution leads to increased prevalence of atopic sensitizations, allergic symptoms, and diseases (Krämer et al., 2000). Similarly, traffic-related pollution was associated with respiratory infections and some measures of asthma and allergy during the first 4 yrs of life during a birth cohort study. (Brauer et al., 2007). It is also evident that patients with allergic asthma demonstrated a greater bronchial responsiveness to bronchial

provocation with birch allergen than patients with rhinitis.(Kämpe et al., 2007). Particulate Matter (PM) 2.5 exposure is also found to exacerbate pre-existing asthma and may contribute to developing asthma, allergic rhinitis, and aeroallergen sensitization (Sompornrattanaphan et al., 2020). Exposure to pollens and other aeroallergens may cause allergy, which is a hyperreactivity reaction of the respiratory tract and eye conjunctiva mediated by immunological (mostly IgE-dependent) inflammation.(Marchetti et al., 2017). Exposure to other pollutant is known to induce asthma reactions. The exposure to 0.16 ppm ozone for 7.6 hours with light exercise causes increased airway responsiveness to inhaled mite allergen among people with mild atopic asthma.(Kehrl et al., 1999)

Asthma Severity and Asthma Control

In the management and care of asthma, patients ability to control their asthma with respects to triggers is very imperative to their well being. With patients, they understand their medical conditions better with the symptoms they experience unlike clinicians that will assess both symptoms and severity of the patients. Osborne et al (1999) opined that symptoms are the most important concern of patients with asthma, and they are also an important focus for physicians treating patients with asthma. Especially in asthma care, severity and control maybe confused with, however the two are distinct.

The composite assessment of symptoms, rescue bronchodilator requirements, and lung function is termed asthma control. It is the short term assessment of the adequacy of a treatment and can help to inform whether further intervention or adjustment is needed (Castro & Kraft, 2008). Unlike clinicians that assesses patients asthma considering symptoms, rescue bronchodilator use, lung functions, and asthma exacerbations to effectively manage the condition of patients, the knowledge of patients on their asthma symptoms is a huge step to patients control of their asthma. This knowlodge may border on their prowess to differentiate

asthma symptoms among other symptoms and their efficient use of rescue bronchodilator. Therefore patients perception and awareness of their asthma symptoms influences their ability to take measures to control their asthma.

The severity of a disease is usually considered a function of the inherent intensity of the disease process. (Stoloff & Boushey, 2006). Although closely related, asthma severity and level of control are distinct concepts. A patient with moderate-to-severe asthma can have well-controlled asthma with good management, whereas a patient with relatively mild asthma who is nonadherent to therapy and practices poor allergen control may experience relatively poor control of symptoms.(Vollmer, 2004). In the absence of treatment, severity can be measured by lung function, the intensity and frequency of symptoms, interference with activities, and so on (Vollmer, 2004). This measure of severity is the same as asthma control as measured by control instruments where patient symptoms are used to predict patient asthma conditions by predicting a quantifiable score. Similarly, in research where factors that affects asthma like environment factors such as pollen and pollutants, the accurate measure of asthma is to use asthma control measure.

Castro & Kraft (2008) highlight that asthma severity is a determinant of asthma control, however, medical management can modify the impact of the underlying severity on the level of control while Vollmer (2004) believe that in performing outcomes research, level of control is an outcome of interest, and severity is a confounder for which adjustment may be needed.

Conceptual Framework for Asthma Control

Asthma control can change rapidly in response to triggers or therapy and although it is partially determined by the underlying severity of disease. Asthma severity is a determinant of asthma control; however, medical management can modify the impact of the underlying severity on the level of control (Castro & Kraft, 2008). In this view, the interplay between severity, control and management is important to explaining any composite measure of asthma. According to Castro & Kraft (2008), asthma control incorporates the underlying severity of disease, but also factors in the adequacy of treatment. This framework explains the interplay of asthma control with other factors that affect the disease.

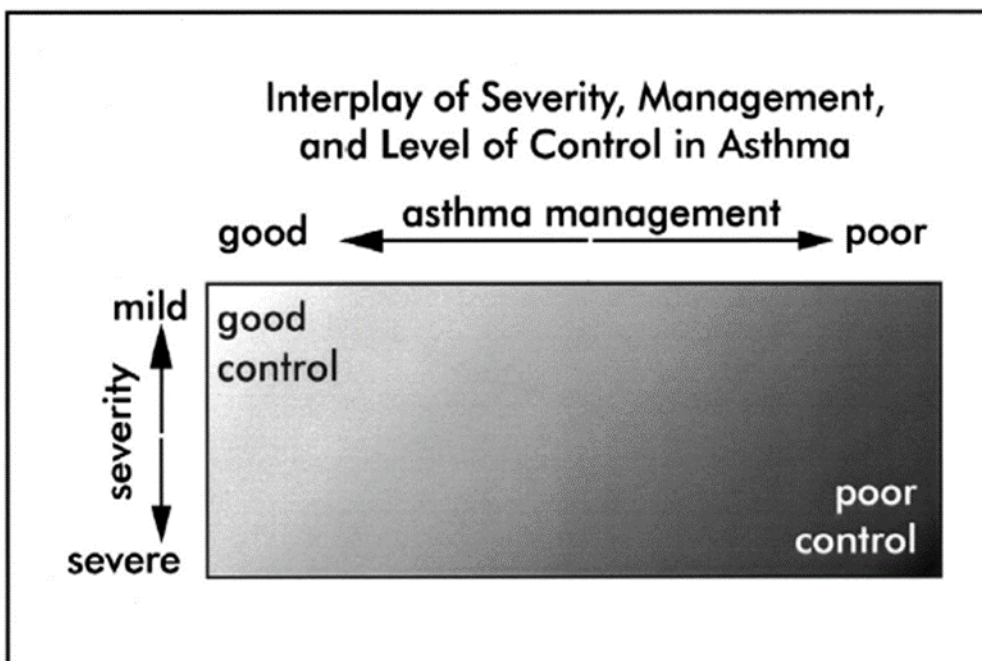


Figure 1.

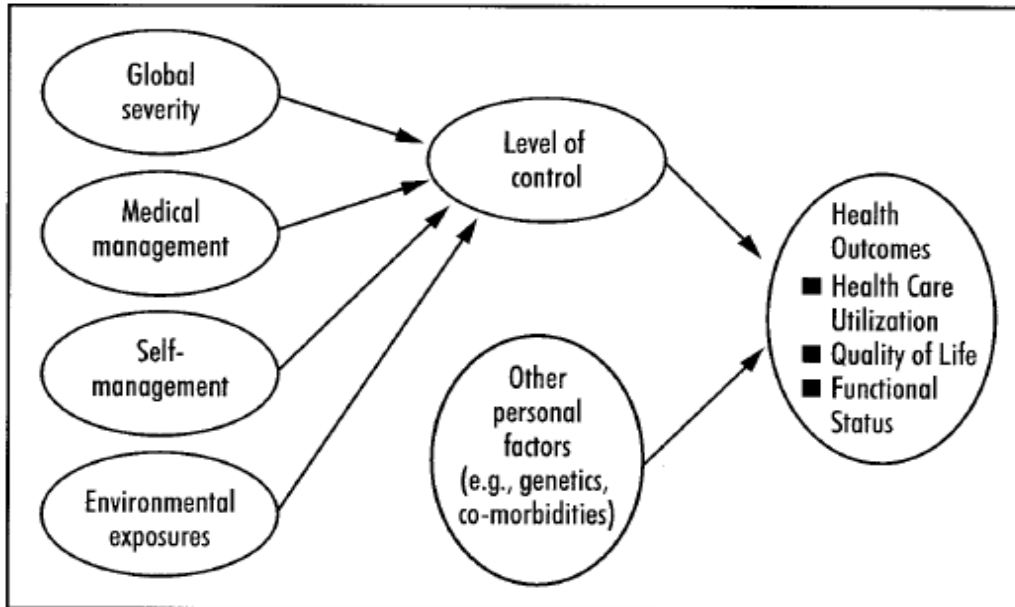
This model was developed by Osborne et al (1999). This model was adopted by Vollmer (2004) and further developed to show other factors in the interplay of asthma control and severity.

To explain asthma control and severity, Osborne et al (1999) modeled this relationship in a plane with asthma severity against asthma management and control. Management here means patients adherence to medications, avoidance of allergen and other factors that induce their asthmatic symptoms.

At any given level of severity, control will tend to improve as management practices improve. Similarly, for any given level of management practices, increasing severity will tend to be associated with worsening control(Vollmer, 2004). This means that it is possible to have severe asthma with good control as a result of good management of factors that affect asthma. It is possible to have moderate or mild severity but poor control and possible for a person with mild severity with poor control to experience frequency exacerbations than the person with very severe asthma.

However, Osborne et al (1999) acknowledges that global severity is a determinant of level of control, but its impact is modulated by medical management, self-management, and environmental exposures. He explained that the level of control, inconjunction with other person factors, determines various health outcomes, including health-care utilization, quality of life, and functional status, the model failed to caputure this. This relationship is what Vollmer (2004) explains with the model he developed to further explore this relationship.

Figure 2 by (Vollmer, 2004) further illustrates the conceptual distinction between severity and control.



In Vollmer (2004) causal model, we see that severity is a determinant of level of control and that its impact is modulated by medical management, patient self-management practices, environmental exposures, and other factors. Level of control, although a legitimate outcome of therapy in its own right, also helps to determine other outcomes, such as health care utilization, quality of life, and functional status. Although severity may influence these outcomes directly, Vollmer (2004) hypothesize, at least in this model, that severity exerts these effects primarily through its influence on level of control.

In this recent study, investigating the impact of birch pollen on people with allergic asthma, the trajectory is better traced from the combination of the two models. Any composite measuring instrument used will follow the

Environmental Exposure → Level of Control → Health Outcome

By scoring their patients symptoms to understand their level of control, we can have knowledge about their asthma situation.

Ethical Consideration:

Ethical consideration permeate all areas of research interest and it borders on respecting the human right of the research participants. In research, participants are entitled to information regarding the disclosure of the nature, duration, and exposure involved (Patel et al., 2016).

This study was conducted in a manner that took into consideration all aspect of ethical considerations pertaining to the design of the study. The study protocol was approved by the Regional Ethical Review Boards at the University of Gothenburg. Participants gave their written informed consent prior to the start of the study and they were permitted to withdraw from the study at any point in time without hesitation. Prior to giving their consent, participants were informed of the intent of the data collection and activities required for their participation. Data collection and storage was done in a manner that ensured privacy, confidentiality and protection of participants data. Participants were assigned identification numbers (ID) through out the data collection and it is difficult to link a particular ID to any participants. The researcher agreed to adhered to all ethical consideration with respect to using the data.

Conclusion

Asthma affect the health of many people and their dialy activities hence expanding the research knowledge on asthma will be great benefit to society. Assessing how a composite measure can accurately be used to predict changes in symptoms among allergic individual with respect to their asthma condition in relation to asthma triggers such as pollen and air pollutants will benefit the endeavor of asthma management among allergic individuals, asthma researchers and clinicians that provide support and care to asthma patients. This research will be imperative to the knowledge of using the asthma control questionnaire to investigate how pollen and air pollution affect people living with asthma.

REFERENCES

- Akpınar-Elci, H. M., Cimrin, C. A., & Elci, C. O. (2002). Prevalence and Risk Factors of Occupational Asthma Among Hairdressers in Turkey. *Journal of Occupational and Environmental Medicine*, 44(6), 585-590. <https://doi.org/10.1097/00043764-200206000-00023>
- Asher, M. I., García-Marcos, L., Pearce, N. E., & Strachan, D. P. (2020). Trends in worldwide asthma prevalence. *The European respiratory journal*, 56(6). <https://doi.org/10.1183/13993003.02094-2020>
- Backman, H., Räsänen, P., Hedman, L., Stridsman, C., Andersson, M., Lindberg, A., Lundbäck, B., & Rönmark, E. (2017). Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. *Clinical and experimental allergy*, 47(11), 1426-1435. <https://doi.org/10.1111/cea.12963>
- Barnes, C. (2018). Impact of Climate Change on Pollen and Respiratory Disease. *Current Allergy and Asthma Reports*, 18(11), 1-11. <https://doi.org/10.1007/s11882-018-0813-7>
- Brauer, M., Hoek, G., Smit, H. A., de Jongste, J. C., Gerritsen, J., Postma, D. S., Kerkhof, M., & Brunekreef, B. (2007). Air pollution and development of asthma, allergy and infections in a birth cohort. *European Respiratory Journal*, 29(5), 879. <https://doi.org/10.1183/09031936.00083406>
- Cabieses, B., Uphoff, E., Pinart, M., Antó, J. M., Wright, J., & Voracek, M. (2014). A Systematic Review on the Development of Asthma and Allergic Diseases in Relation to International Immigration: The Leading Role of the Environment Confirmed. *PLoS ONE*, 9(8). <https://doi.org/10.1371/journal.pone.0105347>
- Castro, M., & Kraft, M. (2008). *Clinical asthma*. Philadelphia : Mosby / Elsevier. <http://lib.ugent.be/catalog/ebk01:1000000000748828>
- D'Amato, G., Liccardi, G., & Frenguelli, G. (2007). Thunderstorm-asthma and pollen allergy.(Author abstract). *Allergy*, 62(1), 11. <https://doi.org/10.1111/j.1398-9995.2006.01271.x>
- D'Amato, G., Cecchi, L., D'Amato, M., & Annesi-Maesano, I. (2014). Climate change and respiratory diseases. In: Eur Respiratory Soc.
- Demain, J. G. (2018). Climate Change and the Impact on Respiratory and Allergic Disease: 2018. *Curr Allergy Asthma Rep*, 18(4), 22. <https://doi.org/10.1007/s11882-018-0777-7>
- Dumanovsky, T., & Matte, T. D. (2007). Variation in Adult Asthma Prevalence in Hispanic Subpopulations in New York City. *The Journal of asthma*, 44(4), 297-303. <https://doi.org/10.1080/02770900701344140>
- Ekerljung, L., Andersson, A., Sundblad, B. M., Ronmark, E., Larsson, K., Ahlstedt, S., Dahlen, S. E., & Lundback, B. (2010). Has the increase in the prevalence of asthma and respiratory symptoms reached a plateau in Stockholm, Sweden? *The international journal of tuberculosis and lung disease*, 14(6), 764-771.
- Gergen, P. J., Fowler, J. A., Maurer, K. R., Davis, W. W., & Overpeck, M. D. (1998). The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics*, 101(2), E8. <https://doi.org/10.1542/peds.101.2.e8>
- Hu, F. B., Persky, V., Flay, B. R., & Richardson, J. (1997). An Epidemiological Study of Asthma Prevalence and Related Factors Among Young Adults. *The Journal of asthma*, 34(1), 67-76. <https://doi.org/10.3109/02770909709071205>
- Jariwala, S. P., Kurada, S., Moday, H., Thanjan, A., Bastone, L., Khananashvili, M., Fodeman, J., Hudes, G., & Rosenstreich, D. (2011). Association between Tree Pollen Counts and Asthma ED Visits in a High-Density Urban Center. *The Journal of asthma*, 48(5), 442-448. <https://doi.org/10.3109/02770903.2011.567427>
- Kämpe, M., Stålenheim, G., Janson, C., Stolt, I., & Carlson, M. (2007). Systemic and local eosinophil inflammation during the birch pollen season in allergic patients with predominant rhinitis or asthma. *Clinical and molecular allergy : CMA*, 5(1), 4. <https://doi.org/10.1186/1476-7961-5-4>

- Kehrl, H. R., Peden, D. B., Ball, B., Folinsbee, L. J., & Horstman, D. (1999). Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol*, 104(6), 1198-1204. [https://doi.org/10.1016/s0091-6749\(99\)70013-8](https://doi.org/10.1016/s0091-6749(99)70013-8)
- Krämer, U., Koch, T., Ranft, U., Ring, J., & Behrendt, H. (2000). Traffic-Related Air Pollution Is Associated with Atopy in Children Living in Urban Areas. *Epidemiology*, 11(1). https://journals.lww.com/epidem/Fulltext/2000/01000/Traffic_Related_Air_Pollution_Is_Associated_with.14.aspx
- Mahmoudi, M. (2016). *Allergy and Asthma: Practical Diagnosis and Management* (2nd ed.. ed.). Cham: Springer International Publishing AG. <https://doi.org/10.1007/9783319308357>
- Marchetti, P., Pesce, G., Villani, S., Antonicelli, L., Ariano, R., Attenu, F., Bono, R., Bellisario, V., Fois, A., Gibelli, N., Nicolis, M., Olivieri, M., Pirina, P., Scopano, E., Siniscalco, C., Verlatto, G., & Marcon, A. (2017). Pollen concentrations and prevalence of asthma and allergic rhinitis in Italy: Evidence from the GEIRD study. *Science of The Total Environment*, 584-585, 1093-1099. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2017.01.168>
- Mazidi, M. (2019). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*.
- McMaster, R. T. (2006). What Causes Asthma? Using the Primary Scientific Literature in Introductory Biology. *Bioscene: Journal of College Biology Teaching*, 33(1), 9-21.
- Papi, A., Brightling, C., Pedersen, S. E., & Reddel, H. K. (2018). Asthma. *The Lancet*, 391(10122), 783-800. [https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)33311-1](https://doi.org/https://doi.org/10.1016/S0140-6736(17)33311-1)
- Patel, N. U., Moore, B. A., Craver, R. F., & Feldman, S. R. (2016). Ethical considerations in adherence research. *Patient preference and adherence*, 10, 2429-2435. <https://doi.org/10.2147/PPA.S117802>
- Reid, C. E., & Gamble, J. L. (2009). Aeroallergens, Allergic Disease, and Climate Change: Impacts and Adaptation.(Report). *EcoHealth*, 6(3), 458. <https://doi.org/10.1007/s10393-009-0261-x>
- Sapkota, A., Dong, Y., Li, L., Asrar, G., Zhou, Y., Li, X., Coates, F., Spanier, A. J., Matz, J., Bielory, L., Breitenother, A. G., Mitchell, C., & Jiang, C. (2020). Association Between Changes in Timing of Spring Onset and Asthma Hospitalization in Maryland. *JAMA Network Open*, 3(7), e207551-e207551. <https://doi.org/10.1001/jamanetworkopen.2020.7551>
- Shea, K. M., Truckner, R. T., Weber, R. W., & Peden, D. B. (2008). Climate change and allergic disease. *J Allergy Clin Immunol*, 122(3), 443-453; quiz 454-445. <https://doi.org/10.1016/j.jaci.2008.06.032>
- Shiue, I. (2013). Associated social factors of prevalent asthma in adults and the very old in the UK. *Allergy (Copenhagen)*, 68(3), 392-396. <https://doi.org/10.1111/all.12091>
- Sompornrattanaphan, M., Thongngarm, T., Ratanawatkul, P., Wongsas, C., & Swigris, J. J. (2020). The contribution of particulate matter to respiratory allergy. *Asian Pacific journal of allergy and immunology*, 38(1), 19. <https://doi.org/10.12932/AP-100619-0579>
- Stoloff, S. W., & Boushey, H. A. (2006). Severity, control, and responsiveness in asthma. *Journal of Allergy and Clinical Immunology*, 117(3), 544-548. <https://doi.org/10.1016/j.jaci.2006.01.005>
- Taylor, P., & Jonsson, H. (2004). Thunderstorm asthma. *Current Allergy and Asthma Reports*, 4(5), 409-413. <https://doi.org/10.1007/s11882-004-0092-3>
- Thomsen, S. F., Duffy, D. L., Kyvik, K. O., & Backer, V. (2010). Genetic influence on the age at onset of asthma: A twin study. *Journal of Allergy and Clinical Immunology*, 126(3), 626-630. <https://doi.org/10.1016/j.jaci.2010.06.017>
- Vernon, M. K., Wiklund, I., Bell, J. A., Dale, P., & Chapman, K. R. (2012). What Do We Know about Asthma Triggers? A Review of the Literature. *The Journal of asthma*, 49(10), 991-998. <https://doi.org/10.3109/02770903.2012.738268>

- Vollmer, W. M. (2004). Assessment of asthma control and severity. *Annals of allergy, asthma, & immunology*, 93(5), 409-414. [https://doi.org/10.1016/S1081-1206\(10\)61406-8](https://doi.org/10.1016/S1081-1206(10)61406-8)
- Von Mutius, E., & Smits, H. H. (2020). Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *The Lancet (British edition)*, 396(10254), 854-866. [https://doi.org/10.1016/S0140-6736\(20\)31861-4](https://doi.org/10.1016/S0140-6736(20)31861-4)
- Vos, T., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Murray, C. J. L. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, 390(10100), 1211-1259. [https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/https://doi.org/10.1016/S0140-6736(17)32154-2)
- Forum of International Respiratory Societies. The Global Impact of Respiratory Disease – Second Edition. Sheffield, European Respiratory Society, 2017.
- The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network, 2018
- World Allergy Organisation, Pollen allergies, Adapting to a Changing Climate (2016) Retrieved: 8/01/2021 url: <https://www.worldallergy.org/UserFiles/file/waw16-slide-set.pdf>

PART B

Association of birch pollen and air pollution with asthma control questionnaire scores among individuals with allergic asthma in Sweden.

DATE: 27 September 2021.

Author: Francis Tandoh Amankwaah

Master's Thesis in Public Health Science, 30 hec

Supervisor: Hanne Krage Carlsen

Examiner: Sharon Fonn

ABSTRACT

Introduction: Asthma is a chronic respiratory disease that affect both adult and children. The disease is as part of the most reported emergency cases to the hospital globally. Over the years asthma prevalence has increased in many countries. In 2016, the disease affected 339 million people globally. To fight asthma, we need to understand the risk factors and triggers that lead to asthma attack and symptoms exacerbation. Investigating the interplay between the risk factors and triggers of asthma is one of the ways to ensure effective asthma management and control.

Aim: This study investigated the association between birch pollen and air pollution with Asthma Control Questionnaire score (aggregate score of reported symptoms) among people with allergic asthma. The study also investigated the association of pollen and ACQ, air pollutants and ACQ and the effect of pollen and air pollutant on ACQ score of participants

Methods: Mixed effect linear regression analyses were performed with independent variables to establish which variables showed an association with the ACQ score. Asthma Control Questionnaires (ACQ) was used as a composite measure, an instrument that aggregate the reported asthmatic symptoms after exposure to pollen and air pollution to investigate this association. The study is panel study that collected data in three waves. Both the outcome and explanatory variable were log transformed for statistical analysis.

Results: In an unadjusted mixed linear model regression with ACQ as the dependent variable and 24 hours of pollen exposure as the explanatory variable, pollen was statistically significantly ($P=0.03$). When other variables like temperature, relative humidity and air pollutants were added to the model air pollutants were not significant. Though air pollutants did not have a directly association on patients ACQ score, when air pollutant meets pollen, pollen become a strong agent to induce symptoms of asthma. In addition, average ACQ was 0.59($SD=0.40$) which signifies that, generally most of the participants had well controlled or managed asthma.

Conclusion: Birch pollen is investigated to have some impact on asthma, even though this association was moderate. Association of air pollutant and ACQ score was insignificant, this notwithstanding pollutant like PM10 could influenced the association between asthma and ACQ (reported symptoms)

Keywords: *Asthma, Birch Pollen and Air Pollution, Asthma Control Questionnaires, Panel study*

Introduction

Asthma is a major noncommunicable disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. It was estimated that more than 339 million people had Asthma globally in 2016. According to WHO estimates, there were 417,918 deaths due to asthma at the global level and 24.8 million DALYS attributable to Asthma in 2016. (WHO, 2020).

Asthma maybe induced by several factors, key among them is asthma caused by allergies. People react to different allergens or allergic triggers such as dust, pollen, molds and inhalation of air pollutants. Out of these allergic triggers, pollen from plant, tree and grass are known for their potency to cause allergic asthma. People exposed to pollen are at the risk of experiencing allergic asthma.

Pollen exposure comes in different seasons and from different plant. Jariwala et al (2011) indicated that the spring asthma peak is closely associated with increased tree pollen counts and that there exists a significant association between asthma related ED visits and tree pollen concentrations. Alaoui et al (2018) also found that allergy to olive pollen existed in the spring season. In Kämpe et al (2007) study, patients with allergic asthma demonstrated a greater bronchial responsiveness to bronchial provocation with birch allergen than patients with rhinitis.

While some studies report association between pollen and asthma, others report no association. For instance, evidence from Marchetti et al (2017) study did not support the assertion that allergic rhinitis and asthma are more frequent in centres with a greater pollen concentration. This suggests that, while pollen exposure is known to trigger acute effects in sensitized individuals, allergen sensitization and the development of allergic diseases may be less influenced by living in areas with a greater pollen concentration.

One major area of concern in studies of Asthma is the effect of co-exposure to ambient air pollution and pollen allergens on asthmatic individuals. Ørby et al (2015) reported that co-exposure to air pollutants and pollen allergens can aggravate the allergic reaction and reduce the threshold at which susceptible individuals are affected. It is revealed in a previous study that, for adult patients, the total weight of chemical variables in the occurrence of respiratory admissions is higher in pollen-related seasons compared to the pollen-free season. This may be explained by the fact that air pollutants can affect allergens, e.g., pollen morphology, and thus change their allergenic potency (Makra et al 2014). This means that there are situations where pollen allergens may genuinely induce asthma symptoms and cases where the induced symptoms are not because of pollen triggers but rather air pollutants that modify the pollen allergens. There may be cases where both pollen and air pollutants have the potency to induce self-reported asthmatic symptoms and cause severe asthma attack.

When asthmatic people are exposed to environmental pollutant, the inherent intensity of their asthma also affect the extent of adverse effects these exposures would have on their condition. In the discussion of the impact, relationship, and association of environmental exposures on asthma with the hope to provide better knowledge in the care and management of disease, a very important aspect of asthma management is hibernated in asthma and environmental pollutants research. That is, how does asthma control and severity affect the impact of these pollutants on people's health and the interplay between asthma severity and control in asthma management. Papaioannou et al., (2015) argued that asthma severity is an inherent characteristic of the patient, and it is defined by the frequency and severity of symptoms as well as the level of treatment that is required to control the symptoms or, in very severe asthma, by non-responsiveness to treatment. They further argued that these characteristics does not necessarily predict response to treatment and so control is easier to quantify and recognise, as both patients and healthcare providers can be taught to quantify

changes in symptoms and lung function (Papaioannou et al., 2015). Guidelines for asthma management have proposed that initial treatment should be based on assessment of asthma severity. The treatments proposed for different degrees of asthma severity are essentially estimates of the intensity of treatment needed to achieve asthma control. (Stoloff & Boushey, 2006). The more severe the disease, the less responsive it is to treatment and so asthma severity can be defined by the minimal amount of medication required to achieve control (Stoloff & Boushey, 2006). Schatz et al., (2005) suggested that symptom frequency is the most prominent determinant of the asthma experience and is thus the minimal essential information necessary to obtain to evaluate a patient's subjective asthma status (Schatz et al., 2005) Even though asthma severity confound the level of asthma control, studies have revealed that asthma severity is measured by the ability to achieve control or minimal medication to achieve control.

To assess the impact of asthma severity and control on how pollutants affect asthma, a composite measure by which control, and severity could be judge is imperative to make headway. In order to provide an accurate assessment of patients asthma, various instruments have been designed to provide a composite measure to assessing asthma control, a lot of which are patient centeric measure. According to (Stoloff & Boushey, 2006) when a disease does not impair current comfort or function but presents a risk of future morbidity or death, assessment of severity, control, and responsiveness is more difficult. They must be assessed through some measure, preferably quantitative, in which deviation from normal has been shown through clinical studies to be related to the risk of adverse events in the future. Hence given the interplay of asthma severity and asthma control, previous study suggest that asthma symptoms are better suited to quantifying the level of current control than for assessment of underlying disease severity(Osborne et al., 1999).

Asthma control is divided into two domains, that is, current impairment and future risk(Castro & Kraft, 2008). When a disease causes discomfort and impairment in the present and also increases the risk of morbidity or death in the future, as asthma does, it cannot be assumed that a treatment that reduces current discomfort- impairment necessarily reduces risks in the future(Stoloff & Boushey, 2006). In view of this, many of these patient centric composite instruments focuses on quantifying the current discomfort and impairment not the future risk. However it only gives indication of how continuous poor control can results in future risk but does not necessarily measure future risk. Some of these instrument are the Asthma Therapy Assessment Questionnaire (ATAQ), Asthma Control Questionnaire (ACQ), and Asthma Control Test (ACT), Test for Respiratory and Asthma Control in Kids (TRACK), Composite Asthma Severity Index (CASI) and others

Expanding what we know about asthma is as good as the management of asthma. Asthma research on risk factors and triggers is a potent way for it effective management and reduction of the disease. Generally, Pollen allergen is known to trigger asthmatic symptoms, however the association between birch pollen and air pollution with self-reported symptoms among individuals with allergic asthma is under researched. This study uses the Asthma Control Questionnaires(ACQ) as a composite measure, an instrument that aggregate the reported asthmatic symptoms after exposure to pollen and air pollution to investigate this association. To the best knowledge of the researcher and articles reviewed, no research has been conducted using the ACQ to investigate the association between birch pollen and air pollution against reported symptoms of asthma. This study aim is to investigate the association between birch pollen and air pollution with the Asthma Control Questionnaires score among individuals with allergic asthma.

Aim of the Research

The aim of this study is to determine whether exposure to pollen and air pollution is associated with self-reported symptoms in individuals with allergic asthma.

Research Questions

- Is there any association between birch pollen exposure and self-reported asthmatic symptoms (ACQ score)?
- What is the association between air pollutants and self-reported asthmatic symptoms (ACQ score)?
- What is the effect of birch pollen and air pollutants on self-reported symptoms of asthma (ACQ score)?

MATERIALS AND METHODS

Study Design

This is a panel study that used a secondary data on birch pollen, air pollution and ACQ responses of participants collected by the department of Environmental and Occupational Medicine at the University of Gothenburg. Birch pollen-allergic individuals were studied in two different pollen seasons and one control season. The first wave with exposure measurement was recorded in April/May 2015, second wave in November (off season of pollen) and the third wave in April/May 2016. The asthma control measurement used for the study analysis is the Asthma Control Questionnaires (ACQ-6). ACQ-6 is a validated six items' questionnaires used to measure asthma control that excludes Forced Expiratory Volume (FEV) measurement.

Study Population

In the original study, 65 participants were involved in the study (41 with birch allergy and asthma and 24 healthy controls). Out of the 65 participants, 38 participants were recruited from Gothenburg, and 27 participants from Umeå. The 41 participants with birch allergy and asthma out of the 65 participants studied, 24 and 17 participants came from Gothenburg and Umeå respectively. Participants from Umeå were recruited from the clinical part of the GA²LEN (Global Allergy and Asthma European Network) study (Jarvis et al. 2012) and in Gothenburg by advertisement at the Gothenburg University and in a local newspaper. The study included a 10-day personal exposure measurement periods at three different occasions for each participant.

In this current study, only the participants with birch allergy and asthma from the original study were studied. Data used in this study involved 40 participants who participated in one wave or more of the 3 waves of exposure data collection. In this study, participants who completed the 6-item ACQ in at least 2 waves were included in the analysis. Two participants had no data for ACQ in all the three waves and three participants had no data for ACQ in wave two and three. These five people were excluded from the study because it is difficult to assess the progress of their asthma control from one wave to another since a single wave or no ACQ data makes it impossible to monitor their asthma progress (**See flowchart in figure 3**). No imputation was made for missing values.

Main Outcome Variable

In the management and care of asthma, asthma severity and asthma control are two important domains used in the assessment and monitoring of the disease (Castro & Kraft, 2008). In this study, the domain of asthma control measurement is the emphasis. The Asthma Control Questionnaires (ACQ) is the instrument used to measure how participants asthma is

controlled. The outcome variable is the ACQ score of asthma using the ACQ-6 questionnaires that excludes the Forced Expiratory Volume (FEV) measurement.

Asthma Control Questionnaires

The Asthma Control Questionnaires is 7 items questionnaires validated to measure control of asthma. Ninety-one asthma clinicians, who were members of international asthma guideline committees, asthma clinicians with measurement expertise and other opinion leaders in asthma management participated in the development of the ACQ.(Juniper et al., 1999). They identified the seven items in the questionnaires as being the most important for determining the adequacy of asthma control. Patients are asked to recall their experiences during the previous week and to respond to the first six questions (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze and rescue short acting b2-agonist use) on a 7-point scale (0=no impairment; 6=maximum impairment). Clinic staff score FEV1% predicted pre-bronchodilator on a similar 7-point scale. The items are equally weighted and the ACQ score is the mean of the seven items and therefore between 0 (well controlled) and 6 (extremely poorly controlled).(Juniper et al., 2005). ACQ has strong measurement properties both as an evaluative and as a discriminative instrument and can be used with confidence in both clinical trials and cross-sectional surveys.(Juniper et al., 1999)

For this study, the shortened version of ACQ-6, is used in this study. ACQ-6 is a validated Asthma Control Questionnaires that excludes the lung function in the ACQ-7. Participants completed the ACQ-6 and each of the six questions are scored on a scale of 0–6 where 0 represents excellent asthma control and 6 represents extremely poor control of asthma. The overall ACQ score from the ACQ-6 was the average of the six responses.

In using the ACQ to identify patients whose asthma is well-controlled, a judicious cut-point is 0.75 and for patients whose asthma is not well-controlled, the judicious cut-point is 1.5

(Juniper et al., 2006). The minimal important difference for the ACQ is close to 0.5 and a change of 0.5 can be considered clinically importance.(Juniper et al., 2005) . Therefore, ACQ score between 0.75 and 1.25 is considered partially controlled asthma. ACQ score of 1.5 has been identified as the best discriminator between patients with asthma who are well controlled and those who are not well controlled.

Ethical Consideration

All participants gave their written informed consent prior to the start of the study. Participants were permitted to withdraw from the study at any point in time. The study protocol was approved by the Regional Ethical Review Boards at the University of Gothenburg (Dnr: 681-14)

Main Exposure and Covariates Variable

The main exposure variable is pollen. Pollen was measured in grain/m³ and matched to the time of participation for each subject at different time intervals of 24 hours, 2 days, 6 days, and 10 days prior to the time the participants filled out the questionnaire. Data on pollen, was a stationary measurement collected as part of routine environmental monitoring.

Personal exposure measurements, samplers, and chemical analysis

Data on pollen, temperature and relative humidity were stationary measurements collected as part of routine environmental monitoring. Both temperature and relative humidity were measured at time intervals of one hour, 1 day, 2 days and 10 days each before clinical visit.

Temperature and relative humidity were stationary measurement from the Swedish Meteorological and Hydrological Institute (SMHI) that provides hourly data on air temperature, relative humidity and wind speed and direction measured centrally in

Gothenburg (57° 71.56 N, 11° 99.24 E) and at Umeå airport (63° 79.47 N, 20°29.18 E), approximately 4 km from the city centre.

In Gothenburg the local environment department provided hourly data on pollutants. Pollen as a stationary measure was measured at the main measurement station in Gothenburg, “Femman” situated at a roof top (height 27 m) in central Gothenburg (57° 42.52 'N, 11° 58.23 'E). In Umeå, they were measured at the former municipality background station at a roof top (height 20 m) located in the city centre of Umeå (63° 79.47 'N, 20° 29.18 'E).

Nitrogen Oxide(NO_x) and ozone

Measurements were performed continuously for 10 consecutive days prior to each individual's scheduled clinical visit. Passive samplers for NO_x and ozone were attached to a fabric cord resembling a necklace and placed as close to the breathing zone as possible. Participants were instructed to wear the samplers all day and place them by the bed when sleeping. In case of precipitation, they were told to shield the samplers from getting wet.

NO_x and ozone were measured with the Ogawa diffusive sampler (Ogawa & Company, Pompano Beach, FL, USA) as 10-day averages of each compound. The Ogawa sampler is cylindrical and has a two-ended design with a diffusion barrier, and a coated filter between two stainless screens on each side. NO_x was collected on one Ogawa badge provided with a filter coated with triethanolamine (TEA) and an oxidizing substance, 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (PTIO) added to oxidize NO to NO₂. The nitrite content of the collection filter was determined by ion chromatography as described previously(Hagenbjörk-Gustafsson et al., 2010). The detection limit was 0.12 µg/m³ for a 10-day sampling period of NO_x.

For ozone measurements another Ogawa badge was used holding collection filters coated with a nitrite-based solution. Ozone oxidizes nitrite to nitrate on the filter and the nitrate content of the filter was after extraction determined by ion chromatography according to a modified method of the standard operation procedure, published by Ogawa (www.ogawausa.com). The nitrate concentration was used to calculate the amount of ozone on each filter. The detection limit was $0.86 \mu\text{g}/\text{m}^3$ for a 10-day sampling period of ozone. In cases where ozone was measured below this level ($n=3$), it was substituted with the detection limit ($0.86 \mu\text{g}$) divided by two, (Schisterman et al., 2006)

The coated filters for NO_x and ozone were supplied by the manufacturer (Ogawa, USA). All samplers were prepared and analyzed at the division of Occupational and Environmental Medicine, Umeå University, Umeå.

Particulate Matter 10 (PM₁₀)

Particulate Matter 10 is any pollution particle in the air either solid or liquid that has a diameter of 10 micrometers or less. In measuring PM₁₀, active sampling of PM₁₀ was performed for 24 hours prior to the clinical visit. Each participant was handed out a backpack equipped with an AirChek® XR5000 personal air sampling pump (SKC Inc., Eighty-Four, PA, USA), mounted with a single-stage Personal Modular Impactor (PMI) sampler for PM₁₀ collection (SKC Inc., Eighty Four, PA, USA) and an airflow of 3.0 L/min. The airflow was calibrated prior to and at the end of the 24-hour sampling period. The PMI sampler was mounted with a 25-mm pre-oiled impaction disc on top of the filter cassette with a 2 μm pre-weighted Millipore PTFE collection filter for gravimetric analysis at Occupational and Environmental Medicine, School of Public Health and Community Medicine at University of Gothenburg, Gothenburg, Sweden. (Haga, S. L., et al., 2021)

Variable Calculation

The pollen measurements and the ACQ score for each participant were log transformed for statistical analysis. Log transforming was done to reduce the skewedness in the data. Mean ACQ score and standard deviation were calculated for the study population. Birch exposure at different lags were 24hours, 48 hours, 6 days, and 10 days of pollen exposure. Other pollutants variable such as particulate matter 10, ozone, and nitrogen oxide were added as covariates. These pollutants were personal exposure measurement. Meteorological factors like relative humidity and temperature were adjusted for and they were stationary measured. Cumulative lag is used to refer the duration of exposure measurement.

Statistical Analysis

Log-log regression, and Mixed linear models with ACQ as the outcome variable and ID as a random effect were used for the analysis. In the log-log regression both ACQ and pollen data were log transformed for the analysis. Statistical analyses were performed with Stata version 16. Mixed Effect Linear regression analyses were performed with independent variables to establish which variables showed an association with the ACQ score. The dependent variable is ACQ score, and the independent variables are the pollen measurements at four different time measurements of 24 hours, 48 hours, 6 days, and 10 days. In the analysis, we first modelled the association of ACQ with pollen, then added temperature and humidity. Finally, we added nitrogen oxide, Ozone and Particulate Matter 10 at lags 0-10 days as covariates in multi-pollutant models. The analysis was adjusted for relative humidity and temperature.

Investigating pollen and air pollution association with asthma, several models were used. In the first model, pollen, temperature, relative humidity, and air pollutants (PM10, NO_x and Ozone) were regressed in mixed effects model at different levels of variable addition with respect to days of exposure. Pollen has 24hours, 2 days, 6 days, and 10 days of measurement.

Both relative humidity and temperature had lag days of 24 hours, 2 days, and 10 days. PM10 was a day measure while NOx and Ozone were 10 days cumulative measure. Mixed effects regression was conducted for 24 hours, 2 days and 10 days exposure in the first model. In each lag, pollen at each lag is regressed without any adjustment to find its association with ACQ score. After, variables are added to the model to find their effects on asthma as shown in table 3.

In the second model, pollen at each lag is regressed in the mixed effect model with air pollutants such as PM10, NOx and Ozone to investigate their association with Asthma.

RESULTS

Study Population

In the original data, information about 40 allergic asthmatic patients were collected from both Gothenburg and Umea. Data on participants exposure to birch pollen, stationary measurement of temperature and relative humidity, ozone, nitrogen oxide (NOx) and PM10 were personal exposure measurement. In addition, individual self-reported symptoms of asthma were measured using the ACQ-6 tool for assessing how well patients' asthmatic condition have been managed.

Out of the 40 participants in the original panel study, 35 participants successfully completed at least two waves' responses out of the three waves of data collection with ACQ-6. Of the five participants excluded from the study, two people had no data on ACQ-6 for all three waves. The remaining three people had no ACQ data for wave two and three. These five individuals were excluded as we had no information on the variables of interest. (See flow chart Figure 3)

Characteristics of study participants, waves, and Exposure

Participants were aged between 27-73 years with an average age of 47.8 years. About 54.3% of participants were male, 65.7% of the participants were living in Gothenburg and 34.3% from Umea. In addition, average ACQ was 0.59(SD=0.40) which signifies that, generally asthma is well controlled or managed among the study participants. (See Table 1)

All the participants completed each wave with respect to pollen measurement at each duration lag with pollen exposure of 10 days and 6days having the highest means and standard deviation of 2.85 ± 2.5 respectively. Pollen exposure of 24hours with the lowest mean of 2.62 and a standard deviation of 2.45. Not all waves were completed for the air pollutants, NOx, Ozone and PM10. (See Table 2)

Log Transformation of data

Figure 4 shows the scatter plot of the original pollen measurements and ACQ illustrating the skewedness in the original data against the plot of the logged transformed pollen and ACQ values. Figure 4. shows pollen data for 24hours and 2 days. The log plots of pollen and ACQ at lag 24hours and lag 2 days shows the plots of each wave. These plots assume some form of normality when compared to the original data (See Figure 4). Similarly, the coefficient of skewedness of the log transformed variables also show improvement approaching normality in the logged data as compared to the original data (skewedness coefficients were 0.54, 0.74, 0.54 and 0.46 for logged pollen variables at lag 24 days, 2 days, 6 days, and 10 days respectively). These coefficients are an improvement in the skewedness coefficient in the original data. Similarly, the logged ACQ variable showed an improvement in skewedness with a coefficient of 0.36.

The researcher acknowledges that in some cases log transformation of variables may not necessarily reduce the skewedness in the data, however in this study the log transformation to some extent has reduced the skewedness in the data.

Association between Exposure to Pollen and Asthma Symptoms Control (ACQ-6)

In an unadjusted mixed linear model regression with ACQ as the dependent variable and 24 hours of pollen exposure as the explanatory variable, pollen was statistically significantly ($P=0.03$) indicating that pollen is associated with ACQ score. Even though there is some significance, this suggests moderate evidence of association between a day exposure to birch pollen and patients reported symptoms of asthma.

When the model was adjusted for temperature as the only covariate, the p-value of pollen was ($P=0.06$). This model showed no statistical significance or evidence of the association between pollen exposure of 24 hours and self-reported symptoms of asthma in P-value. This may suggest that though there are differences in the p-values, the effects on ACQ remain the same, but the estimate is less precise. When the model is adjusted for relative humidity the coefficient of the predictor variable remained the same even though the P-value was not significant (Table 3)

The significance might slightly differ as other covariates are added, however the estimated coefficient of association between pollen and ACQ is similar irrespective of the covariate addition to the model for 24 hours. After PM10 is added to the model, PM10 association with ACQ score was not significant however it changed the relationship between pollen and ACQ. Pollen association with ACQ becomes more significant than in the unadjusted model with ACQ as the dependent variable and pollen as the independent variable. The percentage change in the two coefficient values of pollen in the unadjusted model (coefficient=0.023) and pollen coefficient after adding PM10 to humidity and temperature (coefficient=0.041) is

78% increase. This highlights the potency of pollen with PM10 to change pollen significance after adjusting of temperature and humidity in this study.

For cumulative lags of 2 days and 10 days of pollen exposure, the unadjusted mixed effect regression with ACQ-6 as the outcome and pollen exposure for 2 days and 10 days, they both showed a significant relationship at a p-value of 0.009. The unadjusted model of both lags provides strong evidence of association between ACQ with 2 days exposure and 10 days exposure to birch pollen. In both lags, every 1% increase in the pollen lag resulted in 0.027% increase in self-reported symptoms. The effect of pollen exposure for 2 days and 10 days have same effect on ACQ in the unadjusted model with no covariates.

However, when temperature at 2 days and 10 days are added to the model, the relationship remains significant. Interestingly, though they are strongly significant, there is a very small change in lag of 2 days while 10 days lag remain unchanged in significance from the unadjusted model.

Adding relative humidity as another covariate to temperature in the model, pollen relationship with ACQ is insignificant and as the lag period increase the model shows a decline in the outcome variable for every unit change in the pollen (Table 3).

Association between Pollen and Asthma Symptoms Control (ACQ-6) with multi-pollutant models

Investigating the impact of air pollutants on asthma symptoms in pollen seasons, each pollen lag was placed in the mixed effect model with ACQ as the outcome and pollen lag as the independent variable with 10-day values of Ozone and Nitrogen Oxide (NO_x) as covariate.

At the initial lag of 24 hours of pollen exposure, the association between pollen exposure and ACQ after adjusting for pollutants was not statistically significant (P=0.13). However, exposure lags of 48 hours to 10 days exposure to pollen was statistically significantly associated with ACQ with ozone and NO_x as covariates. The effect of pollen on ACQ

increases as the lag period increases from 24 hours to 48 hours through to 6 days where the significance was higher among the lags and a slight decline at 10 days. After adjusting for ozone and NO_x, every 1% increase in a pollen, ACQ increased by 0.02% after 24 hours of exposure, 0.0275% after 48 hours of exposure, then to a peak of 0.028% after 6 days and then a slight decline to 0.027% after 10 days.

DISCUSSION

The results of this study demonstrate that there is a statistical significance of association between pollen and ACQ score of asthma. The main result of this present study is that seasonal exposure to birch pollen challenges or induces asthmatic symptoms in patients with allergic asthma. The study also found that air pollution in pollen seasons increases the potency of pollen to affect patients' asthma condition. Though air pollutants did not have a directly association on patients ACQ score, when air pollutant meets pollen, pollen become a strong agent to induce symptoms of asthma.

Importance of Covariates

During the study, in the 24 hours lag exposure model, pollen was associated with ACQ scores($p=0.03$) when no variable was added to the model. After temperature was adjusted for, pollen lost its association with ACQ score($p=0.06$). Similarly, when temperature and humidity were adjusted in the model pollen was not associated with ACQ score($p=0.12$) (See Table 3). Interestingly, after adding PM₁₀ to the model of temperature and humidity, pollen association with ACQ score grew stronger($p=0.018$) than the previous significance($p=0.03$). This means that exposure to pollen and PM₁₀ has the tendency to induce asthmatic symptoms within the first 24 hours of exposure. (See Table 3)

Importance of Lags

Unlike PM10, when pollen, NOx and Ozone combined, pollen is not immediately associated with increased ACQ in patients, however as the number of days increases pollen shows increasing effect on asthma, even though previous studies have shown asthma association with NOx, Ozone, and other air pollutants.

There is an interesting trend of behaviour concerning the association between pollen and ACQ score in all lag interval studied. (model 24hours, 2days and 10 days). After adjusting for temperature and humidity in each model, pollen was no longer significantly associated with ACQ, but the effect estimates were rather similar. Accounting for air pollution levels in the model introduces more uncertainty which reduce the model accuracy.

We observed modest association between exposure and outcomes in this study, which is because in this current study, average ACQ was 0.59, which means that generally, almost all the participants had their asthma well-controlled or managed even the pollen season, so exposure to asthma triggers have only moderate asthma control.

Compare with other studies

Comparing our study results with other studies, grass pollen was a strong predictor of asthma hospital admissions and grass pollen had increasing effect on asthma hospital admissions up to a threshold of 30 grains/m³(Erbas et al., 2007). Another study found an association between airborne pollen levels and asthma related emergencies which is independent of the effect of air pollutants and meteorological factors.(Tobías et al., 2003). Even though our study did not involve hospital admissions and emergencies, these findings are consistent with our study results from the unadjusted model of ACQ score and pollen association at the exposure duration of 24 hours, 48 hours, and 10 days. This association between pollen and

ACQ was statistically significant independent of air pollutants and meteorological factors as found in Tobías et al (2003)

In our study, pollen, and humidity at lag 10 days showed association with ACQ score or asthma symptoms. Witonsky et al. (2019) findings revealed that humidity, and grass pollen were shown to have significant associations with asthma related hospitalization. Unlike our study that revealed an association between pollen exposure and ACQ score after 24 hours, Héguy et al. (2008) found that daily increases in emergency department visits from asthma were associated with higher concentrations of pollen from grass species 3 days after exposure. Previous study on air pollution and seasonal asthma during the pollen season suggested that pollen-allergic asthmatic patients living in a more polluted region present more symptoms of seasonal asthma than those living in a city with a low level of pollution (Feo Brito et al., 2007), but we did not test if exposure to different pollution levels would affect the results of the current study. Similarly, there is evidence that tree pollen was a significant cause of hospitalization for asthma in a Canadian community and the burden of acute illness was related to both the potency of the tree pollen and the change in atmospheric concentration(Dales et al., 2008)

Again, our study findings are different from some previous research work in some cases. Unlike our study, where only humidity at lag 10 days was associated with ACQ score, meteorological factors and air pollutants have been shown to have great impact on asthma. Pollutants such as PM10, ozone, nitrogen oxide and other pollutants is widely known to affects asthmatic individuals when they are exposed. In previous research work, emergency room visits for asthma correlated positively with concentrations of NO_x, SO₂ and with high barometric pressure; and negatively with O₃ concentration and minimal and maximal temperature (Garty et al., 1998). Hervás et al (2015) reported that asthma exacerbations were

independently associated with several meteorological factors like pressure, humidity, temperature, and wind. These meteorological factors explain 98.4% of monthly asthma exacerbations according to one study (Hervás et al., 2015).

The ability of pollen to affect or induce asthma condition in patients allergic to pollen is shown in our study, this comes as a support to what other studies have reported on pollen and asthma. Meteorological factors and air pollutants are key factors to induce asthma symptoms and exacerbations, this association was not clearly seen on ACQ score of patients in this study, however its effects on pollen to induce asthma symptoms can be seen from some aspect of the analysis.

Even though the shortened version ACQ-6 was used in this study, the researcher believes that there will be no significant change in the results should the full version be used. This is because in a study to measure and interpret the shortened version of asthma control questionnaire, Juniper et al. (2005) provided strong evidence that when the Forced Expiratory Volume (FEV₁) and b₂-agonist questions are omitted from the original ACQ in clinical trials, the results generated will be very similar to those that would have been generated if the complete questionnaire had been used. The measurement properties (reliability, responsiveness, internal consistency, construct validity and interpretability) of the three shortened versions of the ACQ are very similar to those of the original. In this study only the FEV₁ was omitted which makes it a stronger measure of asthma control than ACQ-5, however in a study that measured asthma control by comparing three classification criteria such as Asthma Control Questionnaire (5-item version; ACQ-5), Global Initiative for Asthma (GINA) and Gaining Optimal Asthma Control (GOAL), patients with GINA controlled, partly controlled and uncontrolled asthma had mean ACQ-5 scores of 0.43, 0.75 and 1.62, respectively. Patients with GOAL totally controlled, well-controlled and uncontrolled asthma

had ACQ-5 scores of 0.39, 0.78 and 1.63. The study showed that percentages of patients considered by GINA criteria to have controlled and partly controlled asthma and by GOAL criteria to have totally controlled and well-controlled asthma are comparable to an ACQ-5 score of ,1.00. (O'Byrne et al., 2010). This means that the shortened version of the ACQ can produce results equivalent to the full version of ACQ and comparable to other asthma control measurements.

The study sample of 35 is very small and makes it difficult to generalise the findings of this research with greater certainty to cover other asthmatic individuals with respect to the exposure variables, duration of exposure and its effect on their asthma. Any attempt to generalise these findings should be done carefully. This is more so because the use of stationary measurements and personal exposure measurement may not capture the true effect of association between ACQ score and air pollutants. This could also reduce the effects of these findings. Furthermore, the underlying severity of participants was not taken into consideration. Asthma severity can influence how participants' exercised control over their asthma, how sensitive they become to monitor symptoms, understand the changing trend of the weather, their environs and adhere to medication instructions. Asthma severity confounds asthma control, and this relationship might have affected our the study findings.

It is also important to draw the differences between the exposure variables, their measurement and how they were treated during the study. The exposure variable like pollen was a stationary measure and it was log transformed for the analysis hence the average pollen for each duration of pollen measurement was very small when compared to the average of each air pollutants. This makes it difficult to compare pollen to any of the air pollutants since they were personal measurement and were not log transformed. These differences will have a significant effect on the study results, affecting the true association among the variables.

However, in all these shortcomings, the association found between ACQ, pollen and other pollutants confirm what other studies have reported concerning asthma and environmental pollutants. A common measure of the exposure variables could have painted a clearer picture of this association.

Strength and Weakness of the Study

The design of the study characterised by the repeated measurement of exposure variables in three waves at different time interval for every single individual coupled with the use of an identical equipment for the measurement of these exposure variables improves the validity of the data collected.

Using a composite measure to investigate how well participants are with their health condition given the presence of the exposure variables can to some extent help us to compare participants based on the score they attain.

When it comes to the control and management of asthma, severity is an important element in treatment and control of asthma. However, in this study the asthma severity of each participant was not taken into consideration as the study data did not include objective disease biomarkers. Hence the results reported in this study does not in any way suggest that because their ACQ score depict a well control score, their disease severity was not intense.

As a potential weakness, since each patient expresses pain or discomfort per their own discretion, patients may report symptoms only when their discomfort exceeds the threshold they can take. So, the outcome is self-reported, which is always a bit unreliable, but we assume that the unreliability is not associated with the exposure because the participants did not know their exposure, so it would not induce systematic error.

Proposed alignments for future studies

Even though ACQ-6 is a validated shortened version of the ACQ-7, and Juniper et al. (2005) provided strong evidence that when the FEV1 and b2-agonist questions are omitted from the original ACQ the results generated will be very similar to those that would have been generated if the complete questionnaire had been used. I propose that future studies should focus on using the completed version of the of ACQ-7 to investigate this interplay of exposures on asthma. Also, future studies should model the severity of participants condition together with environmental exposures to fully unravel the interplay between exposures, and the extent to which this association can cause changes or induce asthma symptoms or cause exacerbation.

Conclusions and Implications

Once again, pollen is investigated to have some impact on asthma, even though this association was moderate, people with asthma should be aware of their environment and what effect their environment have on their condition. The overall ACQ score during the study gives insight that most participants had a well-controlled asthma given the average ACQ score of 0.59. This means that if individuals with allergic asthma have good knowledge on risk factors and, triggers of asthma, this will improve their asthma skills and help them take precautionary measures. This also suggest that adherence to asthma skills, techniques and medication will help improve their health situation. In view of this, patients should not only be made to recall their symptoms in the pursuit of asthma management, but they should be imbued with this knowledge. Future public health campaigns and promotion should focus on educating people on how to management their condition.

Declaration of conflicting interests

The author declares no conflict of interest.

REFERENCES, TABLES, FIGURES AND APPENDICES

REFERENCE

- Akpınar-Elci, H. M., Cimrin, C. A., & Elci, C. O. (2002). Prevalence and Risk Factors of Occupational Asthma Among Hairdressers in Turkey. *Journal of Occupational and Environmental Medicine*, 44(6), 585-590. <https://doi.org/10.1097/00043764-200206000-00023>
- Asher, M. I., García-Marcos, L., Pearce, N. E., & Strachan, D. P. (2020). Trends in worldwide asthma prevalence. *The European respiratory journal*, 56(6). <https://doi.org/10.1183/13993003.02094-2020>
- Backman, H., Räsänen, P., Hedman, L., Stridsman, C., Andersson, M., Lindberg, A., Lundbäck, B., & Rönmark, E. (2017). Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016—results from three population surveys. *Clinical and experimental allergy*, 47(11), 1426-1435. <https://doi.org/10.1111/cea.12963>
- Barnes, C. (2018). Impact of Climate Change on Pollen and Respiratory Disease. *Current Allergy and Asthma Reports*, 18(11), 1-11. <https://doi.org/10.1007/s11882-018-0813-7>
- Brauer, M., Hoek, G., Smit, H. A., de Jongste, J. C., Gerritsen, J., Postma, D. S., Kerkhof, M., & Brunekreef, B. (2007). Air pollution and development of asthma, allergy and infections in a birth cohort. *European Respiratory Journal*, 29(5), 879. <https://doi.org/10.1183/09031936.00083406>
- Cabieses, B., Uphoff, E., Pinart, M., Antó, J. M., Wright, J., & Voracek, M. (2014). A Systematic Review on the Development of Asthma and Allergic Diseases in Relation to International Immigration: The Leading Role of the Environment Confirmed. *PLoS ONE*, 9(8). <https://doi.org/10.1371/journal.pone.0105347>
- Castro, M., & Kraft, M. (2008). *Clinical asthma*. Philadelphia : Mosby / Elsevier. <http://lib.ugent.be/catalog/ebk01:1000000000748828>
- D'Amato, G., Liccardi, G., & Frenguelli, G. (2007). Thunderstorm-asthma and pollen allergy.(Author abstract). *Allergy*, 62(1), 11. <https://doi.org/10.1111/j.1398-9995.2006.01271.x>
- D'Amato, G., Cecchi, L., D'Amato, M., & Annesi-Maesano, I. (2014). Climate change and respiratory diseases. In: Eur Respiratory Soc.
- Dales, R. E., Cakmak, S., Judek, S., & Coates, F. (2008). Tree Pollen and Hospitalization for Asthma in Urban Canada. *International Archives of Allergy and Immunology*, 146(3), 241-247. <https://doi.org/10.1159/000116360>
- Demain, J. G. (2018). Climate Change and the Impact on Respiratory and Allergic Disease: 2018. *Curr Allergy Asthma Rep*, 18(4), 22. <https://doi.org/10.1007/s11882-018-0777-7>
- Dumanovsky, T., & Matte, T. D. (2007). Variation in Adult Asthma Prevalence in Hispanic Subpopulations in New York City. *The Journal of asthma*, 44(4), 297-303. <https://doi.org/10.1080/02770900701344140>
- Ekerljung, L., Andersson, A., Sundblad, B. M., Ronmark, E., Larsson, K., Ahlstedt, S., Dahlen, S. E., & Lundback, B. (2010). Has the increase in the prevalence of asthma and respiratory symptoms reached a plateau in Stockholm, Sweden? *The international journal of tuberculosis and lung disease*, 14(6), 764-771.
- Erbas, B., Chang, J. H., Dharmage, S., Ong, E. K., Hyndman, R., Newbiggin, E., & Abramson, M. (2007). Do levels of airborne grass pollen influence asthma hospital admissions? <https://doi.org/10.1111/j.1365-2222.2007.02818.x>. *Clinical & Experimental Allergy*, 37(11), 1641-1647. <https://doi.org/https://doi.org/10.1111/j.1365-2222.2007.02818.x>
- Feo Brito, F., Mur Gimeno, P., Martinez, C., Tobias, A., Suarez, L., Guerra, F., Borja, J. M., & Alonso, A. M. (2007). Air pollution and seasonal asthma during the pollen season. A cohort study in Puertollano and Ciudad Real (Spain). *Allergy (Copenhagen)*, 62(10), 1152-1157. <https://doi.org/10.1111/j.1398-9995.2007.01438.x>

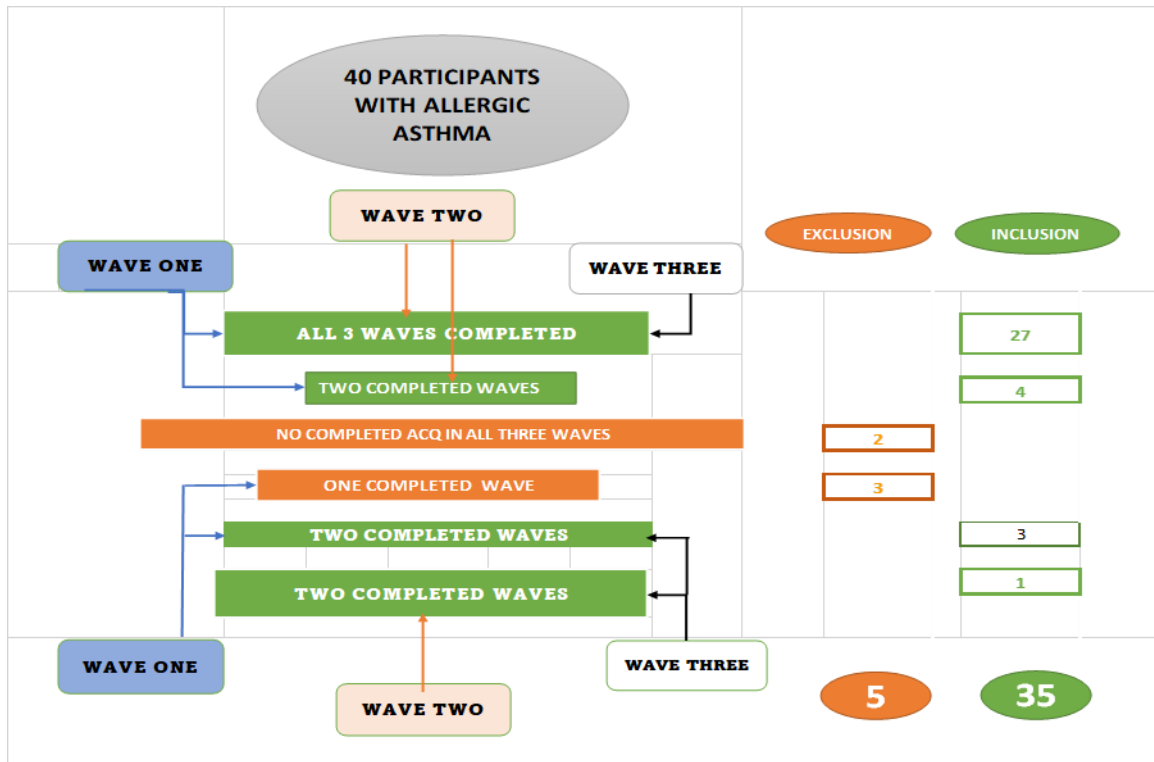
- Garty, B. Z., Kosman, E., Ganor, E., Berger, V., Garty, L., Wietzen, T., Waisman, Y., Mimouni, M., & Waisel, Y. (1998). Emergency Room Visits of Asthmatic Children, Relation to Air Pollution, Weather, and Airborne Allergens. *Annals of allergy, asthma, & immunology*, 81(6), 563-570. [https://doi.org/10.1016/S1081-1206\(10\)62707-X](https://doi.org/10.1016/S1081-1206(10)62707-X)
- Gergen, P. J., Fowler, J. A., Maurer, K. R., Davis, W. W., & Overpeck, M. D. (1998). The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics*, 101(2), E8. <https://doi.org/10.1542/peds.101.2.e8>
- Hagenbjörk-Gustafsson, A., Tornevi, A., Forsberg, B., & Eriksson, K. (2010). Field validation of the Ogawa diffusive sampler for NO₂ and NO_x in a cold climate. *Journal of environmental monitoring*, 12(6), 1315-1324. <https://doi.org/10.1039/b924615k>
- Héguy, L., Garneau, M., Goldberg, M. S., Raphoz, M., Guay, F., & Valois, M.-F. (2008). Associations between grass and weed pollen and emergency department visits for asthma among children in Montreal. *Environmental research*, 106(2), 203-211. <https://doi.org/10.1016/j.envres.2007.10.005>
- Hervás, D., Utrera, J. F., Hervás-Masip, J., Hervás, J. A., & García-Marcos, L. (2015). Can meteorological factors forecast asthma exacerbation in a paediatric population? *Allergol Immunopathol (Madr)*, 43(1), 32-36. <https://doi.org/10.1016/j.aller.2013.07.004>
- Hu, F. B., Persky, V., Flay, B. R., & Richardson, J. (1997). An Epidemiological Study of Asthma Prevalence and Related Factors Among Young Adults. *The Journal of asthma*, 34(1), 67-76. <https://doi.org/10.3109/02770909709071205>
- Jariwala, S. P., Kurada, S., Moday, H., Thanjan, A., Bastone, L., Khananashvili, M., Fodeman, J., Hudes, G., & Rosenstreich, D. (2011). Association between Tree Pollen Counts and Asthma ED Visits in a High-Density Urban Center. *The Journal of asthma*, 48(5), 442-448. <https://doi.org/10.3109/02770903.2011.567427>
- Juniper, E., O'Byrne, P., Guyatt, G., Ferrie, P., & King, D. (1999). Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal*, 14(4), 902-907. <https://erj.ersjournals.com/content/erj/14/4/902.full.pdf>
- Juniper, E. F., Bousquet, J., Abetz, L., & Bateman, E. D. (2006). Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respiratory Medicine*, 100(4), 616-621. <https://doi.org/10.1016/j.rmed.2005.08.012>
- Juniper, E. F., Svensson, K., Mörk, A.-C., & Ståhl, E. (2005). Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory Medicine*, 99(5), 553-558. <https://doi.org/10.1016/j.rmed.2004.10.008>
- Kämpe, M., Stålenheim, G., Janson, C., Stolt, I., & Carlson, M. (2007). Systemic and local eosinophil inflammation during the birch pollen season in allergic patients with predominant rhinitis or asthma. *Clinical and molecular allergy : CMA*, 5(1), 4. <https://doi.org/10.1186/1476-7961-5-4>
- Kehrl, H. R., Peden, D. B., Ball, B., Folinsbee, L. J., & Horstman, D. (1999). Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol*, 104(6), 1198-1204. [https://doi.org/10.1016/s0091-6749\(99\)70013-8](https://doi.org/10.1016/s0091-6749(99)70013-8)
- Krämer, U., Koch, T., Ranft, U., Ring, J., & Behrendt, H. (2000). Traffic-Related Air Pollution Is Associated with Atopy in Children Living in Urban Areas. *Epidemiology*, 11(1). https://journals.lww.com/epidem/Fulltext/2000/01000/Traffic_Related_Air_Pollution_Is_Associated_with.14.aspx
- Mahmoudi, M. (2016). *Allergy and Asthma: Practical Diagnosis and Management* (2nd ed.. ed.). Cham: Springer International Publishing AG. <https://doi.org/10.1007/9783319308357>
- Marchetti, P., Pesce, G., Villani, S., Antonicelli, L., Ariano, R., Attena, F., Bono, R., Bellisario, V., Fois, A., Gibelli, N., Nicolis, M., Olivieri, M., Pirina, P., Scopano, E., Siniscalco, C., Verlato, G., & Marcon, A. (2017). Pollen concentrations and prevalence of asthma and allergic rhinitis in

- Italy: Evidence from the GEIRD study. *Science of The Total Environment*, 584-585, 1093-1099. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2017.01.168>
- Mazidi, M. (2019). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*.
- McMaster, R. T. (2006). What Causes Asthma? Using the Primary Scientific Literature in Introductory Biology. *Bioscene: Journal of College Biology Teaching*, 33(1), 9-21.
- O'Byrne, P. M., Reddel, H. K., Quirce, S., Bateman, E. D., Eriksson, G., Östlund, O., Peterson, S., Sears, M. R., Jenkins, C., Humbert, M., Buhl, R., & Harrison, T. W. (2010). Measuring asthma control: a comparison of three classification systems. *The European respiratory journal*, 36(2), 269-276. <https://doi.org/10.1183/09031936.00124009>
- Papi, A., Brightling, C., Pedersen, S. E., & Reddel, H. K. (2018). Asthma. *The Lancet*, 391(10122), 783-800. [https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)33311-1](https://doi.org/https://doi.org/10.1016/S0140-6736(17)33311-1)
- Patel, N. U., Moore, B. A., Craver, R. F., & Feldman, S. R. (2016). Ethical considerations in adherence research. *Patient preference and adherence*, 10, 2429-2435. <https://doi.org/10.2147/PPA.S117802>
- Reid, C. E., & Gamble, J. L. (2009). Aeroallergens, Allergic Disease, and Climate Change: Impacts and Adaptation.(Report). *EcoHealth*, 6(3), 458. <https://doi.org/10.1007/s10393-009-0261-x>
- Sapkota, A., Dong, Y., Li, L., Asrar, G., Zhou, Y., Li, X., Coates, F., Spanier, A. J., Matz, J., Bielory, L., Breitenother, A. G., Mitchell, C., & Jiang, C. (2020). Association Between Changes in Timing of Spring Onset and Asthma Hospitalization in Maryland. *JAMA Network Open*, 3(7), e207551-e207551. <https://doi.org/10.1001/jamanetworkopen.2020.7551>
- Schisterman, E. F., Vexler, A., Whitcomb, B. W., & Liu, A. (2006). The Limitations due to Exposure Detection Limits for Regression Models. *American journal of epidemiology*, 163(4), 374-383. <https://doi.org/10.1093/aje/kwj039>
- Shea, K. M., Truckner, R. T., Weber, R. W., & Peden, D. B. (2008). Climate change and allergic disease. *J Allergy Clin Immunol*, 122(3), 443-453; quiz 454-445. <https://doi.org/10.1016/j.jaci.2008.06.032>
- Shiue, I. (2013). Associated social factors of prevalent asthma in adults and the very old in the UK. *Allergy (Copenhagen)*, 68(3), 392-396. <https://doi.org/10.1111/all.12091>
- Sompornrattanaphan, M., Thongngarm, T., Ratanawatkul, P., Wongsas, C., & Swigris, J. J. (2020). The contribution of particulate matter to respiratory allergy. *Asian Pacific journal of allergy and immunology*, 38(1), 19. <https://doi.org/10.12932/AP-100619-0579>
- Stoloff, S. W., & Boushey, H. A. (2006). Severity, control, and responsiveness in asthma. *Journal of Allergy and Clinical Immunology*, 117(3), 544-548. <https://doi.org/10.1016/j.jaci.2006.01.005>
- Taylor, P., & Jonsson, H. (2004). Thunderstorm asthma. *Current Allergy and Asthma Reports*, 4(5), 409-413. <https://doi.org/10.1007/s11882-004-0092-3>
- Thomsen, S. F., Duffy, D. L., Kyvik, K. O., & Backer, V. (2010). Genetic influence on the age at onset of asthma: A twin study. *Journal of Allergy and Clinical Immunology*, 126(3), 626-630. <https://doi.org/10.1016/j.jaci.2010.06.017>
- Tobías, A., Galán, I., Banegas, J. R., & Aránguez, E. (2003). Short term effects of airborne pollen concentrations on asthma epidemic. *Thorax*, 58(8), 708. <https://doi.org/10.1136/thorax.58.8.708>
- Vernon, M. K., Wiklund, I., Bell, J. A., Dale, P., & Chapman, K. R. (2012). What Do We Know about Asthma Triggers? A Review of the Literature. *The Journal of asthma*, 49(10), 991-998. <https://doi.org/10.3109/02770903.2012.738268>
- Vollmer, W. M. (2004). Assessment of asthma control and severity. *Annals of allergy, asthma, & immunology*, 93(5), 409-414. [https://doi.org/10.1016/S1081-1206\(10\)61406-8](https://doi.org/10.1016/S1081-1206(10)61406-8)

- Von Mutius, E., & Smits, H. H. (2020). Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *The Lancet (British edition)*, 396(10254), 854-866. [https://doi.org/10.1016/S0140-6736\(20\)31861-4](https://doi.org/10.1016/S0140-6736(20)31861-4)
- Vos, T., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abebo, T. A., Abera, S. F., Aboyans, V., Abu-Raddad, & Murray, C. J. L. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, 390(10100), 1211-1259. [https://doi.org/https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/https://doi.org/10.1016/S0140-6736(17)32154-2)
- Witonsky, J., Abraham, R., Toh, J., Desai, T., Shum, M., Rosenstreich, D., & Jariwala, S. P. (2019). The association of environmental, meteorological, and pollen count variables with asthma-related emergency department visits and hospitalizations in the Bronx. *The Journal of asthma*, 56(9), 927-937. <https://doi.org/10.1080/02770903.2018.1514627>

TABLES, FIGURES AND APPENDICES

Figure 3. Shows how each wave was completed and how many participants completed each wave.



*Colour green shows participants included in the study and the combination of waves they participated. *Colour pink shows participants excluded from the study and the wave they participated.

Table 1. Characteristics of study participants and waves

Characteristics	Sample size(n) (%)	Mean±SD
Wave completed rate		
Wave 1	34 (97.14)	
Wave 2	32 (91.43)	
Wave 3	31 (88.57)	
Age		
27-39	19 (54.29)	
40- 59	9 (25.71)	
60-73	7 (20)	
Average age		47.77 ± 13.35
Sex		
Female	16 (45.71)	
Male	19 (54.29)	
City 1=Goteborg	23 (65.7)	
ACQ-6 score cut-offs		
<0.75	60 (57.14)	
≥0.75<1.5	35 (33.33)	
≥1.5	2 (1.90)	
Uncompleted ACQ	8 (7.62)	
Overall ACQ		0.59 ± 0.40

Abbreviations; SD: Standard deviation, ACQ: Asthma Control Questionnaire, %: percentage

Table 2. Shows summary of Pollen and Air Pollutant Exposure

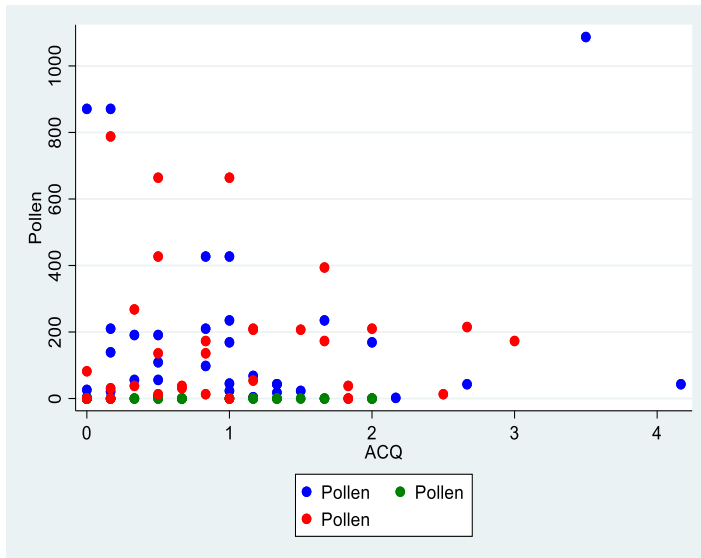
Characteristics	Sample size(n) (%)	Mean±SD
Pollen 24hours		
All Completed waves	105(100)	2.62±2.45
Pollen 2days		
All wave completed	105(100)	2.80±2.48
Pollen 6 days		
All waves completed	105(100)	2.85±2.49
Pollen 10days		
All waves completed	105(100)	2.85±2.48
Wave completed NOx		
Wave 1	34(97.14)	
Wave 2	34(97.14)	
Wave 3	30(85.71)	
Overall average		22.42±12.53
Wave completed Ozone		
Wave 1	35(100)	
Wave 2	34(97.14)	
Wave 3	29(82.86)	
Average		6.58±5.03
Wave completed PM10		
Wave 1	35(100)	
Wave 2	33(94.29)	
Wave 3	27(77.14)	
Average		22.03±30.16

This table shows the wave completion of each exposure variable with their mean and standard deviation. With summary of pollen exposure at each lag, pollen was not described by wave because all waves were completed. Air pollutants such as NOx, Ozone and PM10 were described by waves because not all waves were completed.

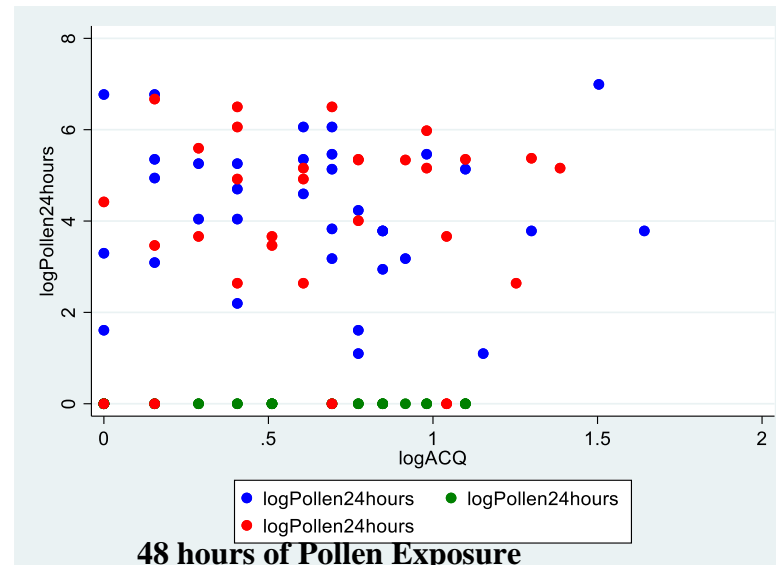
Figure 4. Shows the scatter plot of the original pollen measurements and ACQ illustrating the skewedness in the original data against the plot of logged transformed pollen and ACQ values.

24 hours of Pollen Exposure (Blue== Wave one *Green==Wave two *Red==Wave three)

Raw data Plot of ACQ and Pollen

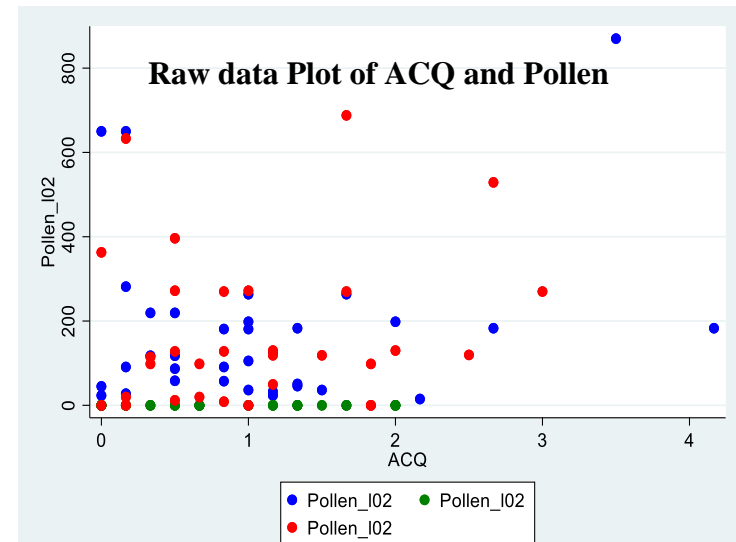


Logged data Plot of ACQ and Pollen



48 hours of Pollen Exposure

Raw data Plot of ACQ and Pollen



Logged data Plot of ACQ and Pollen

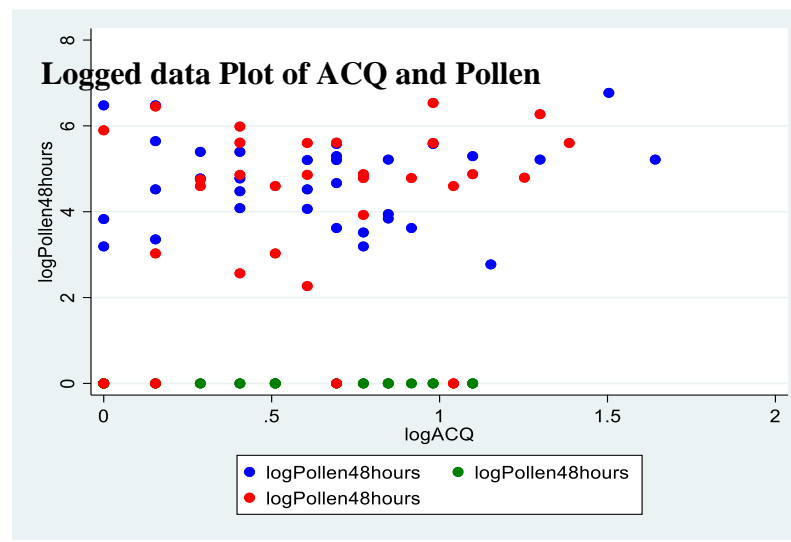


Table 3. Mixed Model regression to assess the association between ACQ, Birch Pollen and Air Pollutants

	Pollen % (CI 95%)	Temperature % (CI 95%)	Humidity % (CI 95%)	Nox % (CI 95%)	Ozone % (CI 95%)	PM10 % (CI 95%)	P-value of pollen
<u>24 hours of Exposure of Variables</u>							
ACQ	0.023(0.0017: 0 .044)	-	-	-	-	-	0.034
	0.023(-0.001: 0.048)	-0.0016 (-0.013 :0.009)	-	-	-	-	0.06
	0.024(-0.0063: 0.054)	-0.001 (-.0146:0.0117)	0.00025(-0.006: 0.007)	-	-	-	0.121
	0.041(.0069: 0.074)	-0.002(-0.015:0.011)	0.003(-0.003: 0.011)	-	-	0.001(-0.001:0.004)	0.018
<u>2 days Cumulative Lag Exposure</u>							
ACQ	0.027(0.0068: 0.047)	-	-	-	-	-	0.009
	0.031(0.0069: 0.054)	-0.0046(-0.0168:0.0076)	-	-	-	-	0.011
	0.018(-0.0123:0 .049)	-0.008(-0.021:0.0052)	-0.0044(-.0118:0.0029)	-	-	-	-
<u>10 days Cumulative Lag Exposure</u>							
ACQ	0.027(0.0069: 0.047)	-	-	-	-	-	0.009
	0.031(0.0077:0 .055)	-0.0082(-.027: 0.0107)	-	-	-	-	0.009
	0.0003 (-0.039:0.039)	-0.0169(-0.037:0.0034)	-0.010 (-0.021:0.00025)	-	-	-	-
	-0.003(-0.043:0.037)	-0.016(-0.036:0.004)	-0.011(-0.022: -0.001)	0.002(-0.004: 0.008)	-	-	-
	-0.006(-0.05:0.037)	-0.017(-0.039: .004)	-0.011(-0.022: -0.001)	0.002(-0.004:0.008)	0.003(-0.011: 0.019)	-	-
			P (0.034)				
			P (0.036)				

Table 3. PM10 was measured in 24hours, and it was included only in the 24hour mixed regression. Ozone and NOx were measured as a 10 day personal measurement and its was only included in the regression model of 10 days lag exposure.

Table 4. Association between Pollen and Asthma Symptoms Control (ACQ-6) with multi-pollutant models

	Pollen % (CI 95%)	NOx % (CI 95%)	Ozone % (CI 95%)	PM10	P-value of Pollen
24 hours					
ACQ	0.020(-0.006:0.047)	0.0017(-0.004:0.0077)	0.0029(- 0.012:0.018)	0.006(- 0.0027:0.003)	0.133
48 hours					
	0.0275(0.0018:0.053)	0.002(-0.0036: 0.0081)	0.00047(- .0146: 0.0156)		0.036
6days					
	0.028(0.0024- 0.0535)	0.0024(- 0.0035:0.0082)	0.00028(- 0.015: 0.0154)		0.031
10days					
	0.027(0.00137:0.053)	0.0023(- 0.0036:0.0082)	0.0004(- .0148: 0.0156)		0.039

Shows the multi-pollutants model and pollen effects on ACQ

Asthma Control Questionnaire

Please answer Questions 1–6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?

- | | |
|-----------------|-------------------------------------|
| 0 Never | 4 Many times |
| 1 Hardly ever | 5 A great many times |
| 2 A few times | 6 Unable to sleep because of asthma |
| 3 Several times | |

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?

- | | |
|----------------------|-------------------------|
| 0 No symptoms | 4 Quite severe symptoms |
| 1 Very mild symptoms | 5 Severe symptoms |
| 2 Mild symptoms | 6 Very severe symptoms |
| 3 Moderate symptoms | |

3. In general, during the past week, how limited were you in your activities because of your asthma?

- | | |
|-------------------------|---------------------|
| 0 Not limited at all | 4 Very limited |
| 1 Very slightly limited | 5 Extremely limited |
| 2 Slightly limited | 6 Totally limited |
| 3 Moderately limited | |

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?

- | | |
|---------------------|---------------------|
| 0 None | 4 Quite a lot |
| 1 A very little | 5 A great deal |
| 2 A little | 6 A very great deal |
| 3 A moderate amount | |

5. In general, during the past week, how much of the time did you wheeze?

- | | |
|---------------------------------|---------------------|
| 0 Not at all | 4 A lot of the time |
| 1 Hardly any of the time | 5 Most of the time |
| 2 A little of the time | 6 All the time |
| 3 A moderate amount of the time | |

6. On average, during the past week, how many puffs of short-acting bronchodilator have you used each day?

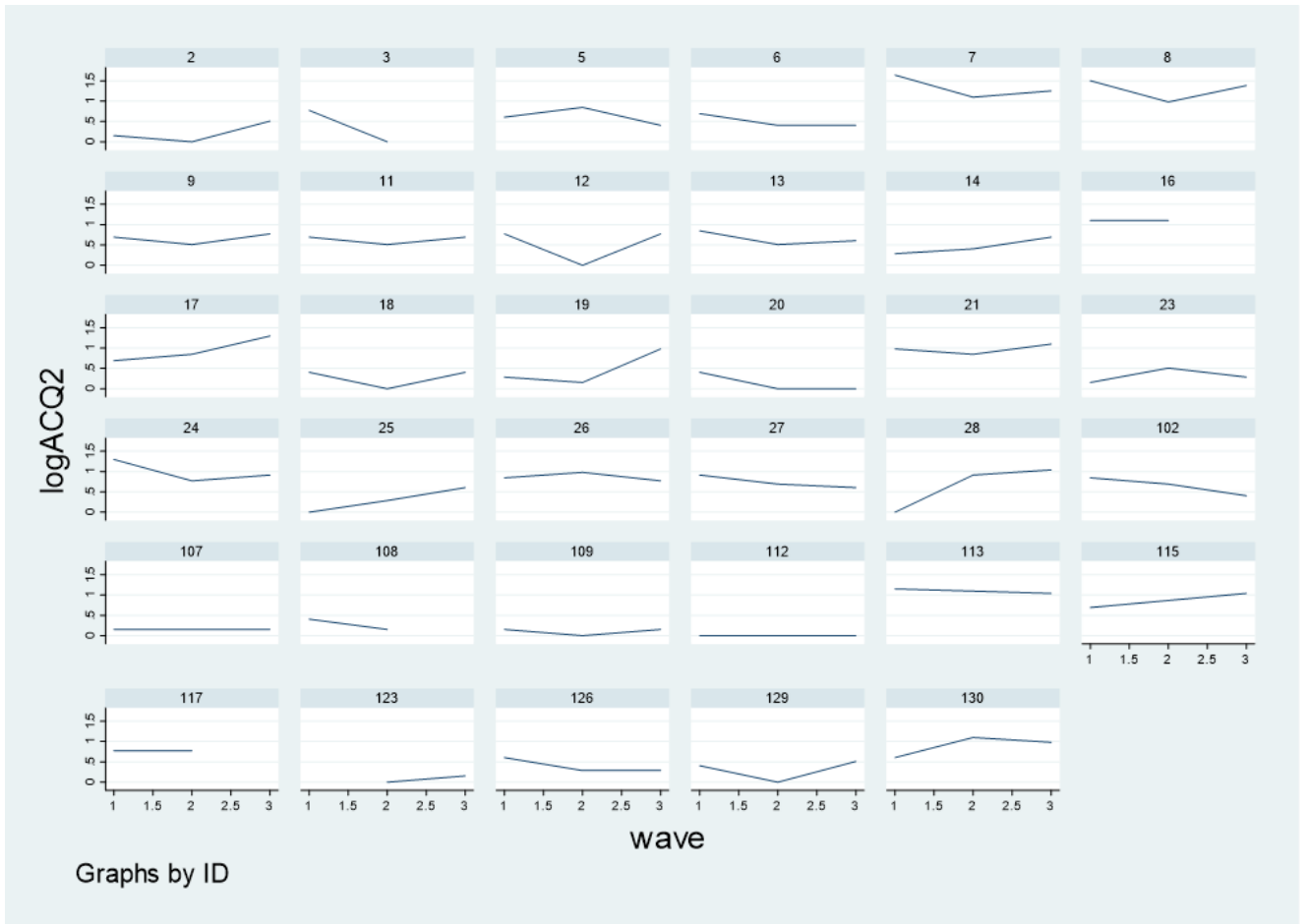
- | | |
|-----------------------|--------------------------------|
| 0 None | 4 9–12 puffs most days |
| 1 1–2 puffs most days | 5 13–16 puffs most days |
| 2 3–4 puffs most days | 6 More than 16 puffs most days |
| 3 5–8 puffs most days | |

To be completed by a member of the clinic staff:

7. FEV₁ prebronchodilator:

- | | |
|-------------------------------|-------------------------------|
| 0 > 95% predicted | FEV ₁ % predicted: |
| 1 95–90% | 4 69–60% |
| FEV ₁ % predicted: | 5 59–50% |
| 2 89–80% | 6 < 50% predicted |
| 3 79–70% | |

(Record actual values on the dotted lines and score the FEV₁% in the next column)



ACQ responses sorted by wave with participants IDs