ASSOCIATION BETWEEN ASTHMA HOSPITAL ADMISSION AND WEATHER TEMPERATURE IN ST. JOHN'S, NEWFOUNDLAND AND LABRADOR, CANADA

By

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Abstract

While temperature changes are associated with increased ER visit and hospitalization for asthma, geography and climate are important moderating factors of this association. To our knowledge, no study has assessed the temperature-asthma hospitalization link in Newfoundland and Labrador (NL). St. John's weather is governed by a marine climate, with vast temperature variations and high winds. We conducted four studies to investigate the association between temperature and asthma hospitalizations among adult asthma patients in St. John's, NL. *Study 1* was a systematic review of the effects of meteorological variables on asthma hospitalization and emergency department (ED) visits in adults. There were 3877 articles identified on initial search. After removing duplicates and irrelevant studies, 19 studies were included. A significant association between temperature and hospitalization among patients with asthma was reported in six studies (31%). In addition, nearly 37% of the studies found that both temperature and relative humidity were associated with asthma hospital admission. Our review suggests that temperature variation can have both a positive (6 studies) or negative correlation (2 studies) with number of asthma related hospital admissions, depending on the season and geographic area. The temperature measurement and the threshold for temperature varied from one study to another. *Study 2*, a time series analysis to examined the daily minimum temperature threshold and its delayed effect on number of daily hospital admission among adult asthma patients. The results of distributed lag non-linear model (DLNM) analyses show the risk of hospitalizations among adult asthma patients increased when the minimum temperature declined below -4°C (RR=1.10; 95% CI: 1.01-1.16) and/or exceeded 14°C (RR= 1.03; 95% CI: 1.01-1.18) on the same day and/or the day after these ranges.

Study 3 was a nested case-control study to assess the effects of extreme temperature on epidemics of hospitalization among adults with asthma. I identified number of hospital admission per day. Cases defined as epidemic days. Epidemic days introduced as days where the observed number of hospital admissions exceeded four standard deviation from the average frequency of distribution daily counts of hospital admissions, and the controls as days within one standard deviation from the average daily hospital admissions. Multivariate logistic regressions showed an epidemic of hospital admission is happening when Daily Minimum Temperature (DMT) exceeds 14.0°C (OR= 1.79; 95% CI: 1.08- 1.86) and declines below -4.0°C (OR= 5.81; 95% CI: 1.12-7.61) within the same day and/or the following day.

Then, to control for individual risk factors, we performed a case-crossover study *(Study 4)* where study subjects were selected from patients who were admitted to the hospital during epidemic days. These patients served as their own controls. The results show extreme warm (DMT > 14.0°C) and cold temperatures (DMT < -4.0°C) are associated with hospital admission among patients with asthma (OR= 1.33; 95% CI: 1.14-1.57 and OR= 1.12; 95% CI: 1.03- 1.23, respectively).

These findings may provide a basis for health authorities to anticipate patient volumes and healthcare demands using weather forecasts to prepare resources and hospital infrastructure accordingly.

General Summary

An important link between temperature and hospital visits for patients with asthma has not adequately been researched in Newfoundland and Labrador (NL) to our knowledge. This study examines the connection between temperature and hospital visits by adult asthma patients in St. John's, NL. The study started with searching for evidence in the current literature about the link between weather variables and hospitalizations of adults with asthma. To be more reflective in a local setting, we examined the effect of daily minimum temperature and its delayed effect on number of daily hospital visits using local data sources in St. John's metropolitan area.

Our study shows that the likelihood of hospital visits by adults with asthma increased when the minimum temperature dropped below -4°C on the same day, or one day before hospitalization. The risk of hospital visits by adults with asthma also increased when the temperature rose above 14°C on the same day or one day before hospitalization. Also, number of hospital admission per day could exceed the expected number resulting epidemic of hospital admission when the minimum temperature reaches the above-mentioned threshold. Our findings suggest that hospitals could use weather forecasts to prepare for higher numbers of asthmatic patients visiting their institution at the same time. Also, provides information for patients with asthma of possible change in their symptoms based on weather forecast.

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List of abbreviation:

CCDSS: Canadian Chronic Disease Surveillance System

CDMS: Clinical Database Management system

Cl: Confidence Interval

CIHI: Canadian Institute for Health Information's

COPD: Chronic obstructive pulmonary disease

DLNM: Distributed Lag Non-Linear Models

DMT: Daily Minimum Temperature

EDVs: Emergency Department Visits

EPA: Environmental protection Agency

GINA: The Global Initiative for Asthma

HAs: Hospital Admissions

ICD: International Classification of Diseases

IgE: Immunoglobulin E

MCP: Medical Care Plan

NAEPP: National Asthma Education and Prevention Program

NCDSS: Newfoundland and Labrador Chronic Disease Surveillance System

NL: Newfoundland and Labrador

NLCHI: Newfoundland and Labrador Centre for Health Information

OR: Odd Ratio

PDAD: Provincial Discharge Abstract Database

PHAC: Public Health Agency of Canada

RR: Relative Risk

WHO: World Health Organization

YYT: St. John's International Airport

Chapter 1: Introduction

1.1.Problem Statement

Asthma is a chronic respiratory disease affecting the airways and lungs. This disease is characterized by wheezing, coughing, and shortness of breath [1]. Asthma is a multifactorial disease, and the etiology of the disease is not fully understood. Many risk factors are associated with increased risk of asthma in the literature [2, 3]. Studies have shown links between asthma-related hospitalization and exercise, respiratory infections, and environmental factors, such as exposure to allergens, tobacco smoke, and indoor and outdoor pollution [5].

Many studies around the world have confirmed associations between weather related variables (e.g., relative humidity, temperature and precipitation) and asthma attacks [2,3]. The relationship between temperature and asthma hospital admission has been consistently reported in previous studies [4,5, 6]. However, the associations between temperature and asthma hospital admission varied by geographic locations, study populations, and climatic characteristics [5]. Thus, it is essential for different geographic locations to conduct locally-based studies to assess the impact of temperature on asthma hospital admission for local public health decision-making [1].

To the best of our knowledge, no previous study has examined the effects of temperature on adult asthma hospital admission in NL. This study aims to determine the effects of weather temperature on hospital admission among adult patients with asthma in St. John's, NL, Canada. St. John's is the capital of Canada's easternmost province, NL, and a city with a cold climate where temperature varies throughout the year.

The results will help healthcare providers and policy-makers predict hospitalization demand for patients with asthma. Asthma hospital admission is preventable [7] by avoiding triggers that may exacerbate symptoms. Patients with asthma will benefit from understanding how weather changes could impact their condition.

This thesis begins with an overview of asthma, its risk factors and epidemiology, asthma-related hospitalization, and the impact of environmental factors on the disease. Chapter two builds on this foundation with a systematic review of the literature surrounding the effect of meteorological variables on adult asthma-related hospitalization and emergency room visits, and a discussion of the current knowledge gap. Chapter three examines the effect of Daily Minimum Temperature (DMT) on number of daily hospital admission for asthma, while Chapter four identifies the epidemic of hospital admission in relation to daily minimum temperature. The fifth and final chapter presents an overall conclusion and recommendation.

1.2.Asthma Overview

1.2.1. Asthma Immunology

Asthma is a heterogeneous disease. This chronic inflammatory airway causing episodes of wheezing, coughing, shortness of breath, chest tightness, and sputum production [1]. Asthma is a reversible airway obstructive disease, and the symptoms subside. It means lung function may go back to normal between attacks [8].

The international consensus report defined asthma as [9] "*Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms which are usually associated with* *widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway responsiveness to a variety of stimuli*."

Asthma primarily involves in the bronchial tree. Bronchial tree is responsible for distributing air throughout the lung until reaching the alveolar sacs. [10, 11]. The smooth muscles of bronchioles can constrict or expand to allow for normal respiration [12]. The bronchi then divide into secondary and tertiary bronchi. The bronchi maintain their wall integrity by smooth muscle and elastic fibers [8]. Asthma causes bronchiolar inflammation, airway constriction, increased resistance, as well as increased mucus secretion that obstruct airways [11].

The airway epithelium is the body's first contact with the external atmospheric environment, and thus plays an important role in the pathogenesis of asthma. In healthy individual, the allergen is trapped in mucus by epithelial layer and moves out of the airway. However, in asthmatics, the epithelial layer is not tight and allows pathogens to enter the body and become sensitized [13]. As a result, these cells (epithelium) interact with environmental triggers to potentially cause airway obstruction and inflammation through the release of multiple cytokines. Epithelial cells also influence several chemokines that attract eosinophils, which play an important role in pathophysiological process of asthma [14].

Several processes underlie asthma and contribute to attacks. The first is airway hyper-responsiveness, an unusually high level of airway sensitivity, causing the bronchioles to constrict and narrow upon exposure to certain airborne substances or environmental conditions [9]. The second is a surplus production of mucus in the airways, further restricting the space reserved for airflow in the lungs. The third pathological process is inflammation of the bronchial tissues [8]. Airway inflammation has a crucial role in the pathophysiology of asthma. Interaction of many cell types and mediators involve in inflammation. Airway inflammation eventually results in the characteristic pathophysiological features of asthma [15].

Most asthmatic have dysregulated epithelial barrier which facilitate translocation of allergens, air pollution and viruses to the airways [16]. In response to allergens, airway epithelial cells release alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which then as a result generate adaptive type 2 immune pathways [16]. TSLP primes dendritic cells to induce the differentiation of naïve T cells into Th2 cells [16]. Th2 cells have a critical role in asthma pathophysiology and contribute to activating B cells via IL-4 to differentiate into plasma cells that generate IgE required for mast cell responses to allergens [16]. For many years, asthma was categorized into two different types based on the presence of airway eosinophilia. Th2 cells play an important role in eosinophilic airway inflammation by generating IL-4, IL-5, and IL-13 [17]. However, the evidence has proven that group 2 innate lymphoid cells (ILC2s) has equally role in type 2 immune responses [18]. Together TH2 cells and ILC2s are responsible in production type 2 cytokines. The alarmins IL-25 and IL-33 can activate group 2 innate lymphoid cells (ILC2s), mast cells, eosinophils, and basophils. Activated ILC2s, like Th2 cells, can produce cytokines such as IL-4, IL- 5 and IL-13 that are important for asthma pathogenesis [21]. IL-5 promotes eosinophil differentiation, they are crucial for B cells maturation and survival. [21]. IL-13, IL-4 are required to lead isotype switch of B cells into plasmacytes producing allergen-specific IgE antibodies [19]. IL-13 induces rapid release of mediators such as histamine, leukotrienes, and prostaglandins [20]. These mediators are responsible for the contraction of smooth muscle cells and mucous secretion, resulting in severe airway obstruction in patients with asthma [21]. IL-13, IL-4, and inflammatory mediators from mast cells, basophils, and eosinophils have effects on airway hyper-responsiveness, smooth muscle hypertrophy, and airway remodeling [18,22] (Figure1).

T helper 17(TH17) also playing a role in some asthmatic patients. The Th17 is different from Th2 response and the primary effector cells are neutrophils [23]. Neutrophil numbers in the airway are only increased in patients with severe asthma, not in patients with mild and moderate asthma; therefore, neutrophils probably have role in some asthma endotype [24].

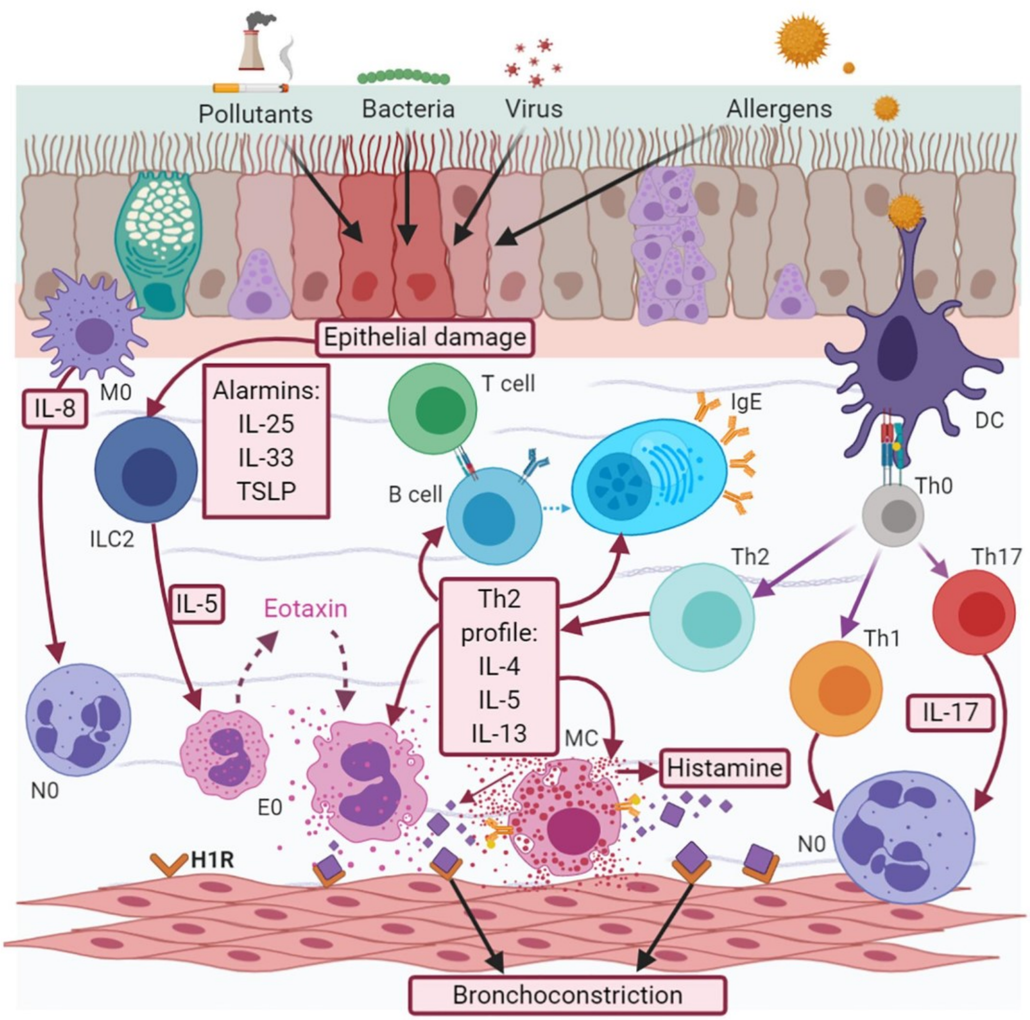

Figure 1: Pathophysiology of asthma. Airway inflammation has a crucial role in the pathophysiology of asthma. Interaction of many cell types and mediators involve in inflammation. Airway inflammation eventually results in the characteristic pathophysiological features of asthma [22].

Traditionally, asthma has been classified into two categories: atopic and non-atopic. Atopic asthma developed the disease in early life and specific immunoglobulin E (IgE) produce to identify allergens. Non-atopic asthma does not present IgE reactivity in serum and developing in later life [25, 16]. However, in the last twenty years, clinicians realized that classifying asthma in just two groups is oversimplified asthma, which could create biases. Asthma has been seen more as a syndrome rather than single disease [16] by defining multiple levels of severity [26]. The NAEPP/GINA guidelines for asthma severity is recommending that if an individual with asthma meets any one criteria for a specific severity category, the subject is assigned to that category despite potential disease heterogeneity within each category [27]. The major assumption with these schemes is that all subjects within a specific asthma severity category share similar disease characteristics. However, asthma is a heterogeneous disease with multiple phenotypes [28]. Patients with asthma differ with respect to factors that triggered attacks, the clinical presentation [29] and patterns of inflammatory responses [28].

1.2.2. Asthma genetic factors

Asthma is a complicated chronic disease, the etiology of asthma is very complex, and many factors are associated with development and exacerbation of asthma. Genetics, allergies, the environment, and infections are often risk factors [2]. Asthma is a hereditary disease passed through the family [5]. For example, identical twins have a higher chance of having asthma compared to non-identical twins, indicating the key role of genetics in the disease. Many genes have been associated with asthma [30].

Over 120 genes have been associated with asthma's susceptibility or its related symptoms [31]. These genes can categorize into distinct subcategories based on their associations within the asthmatic pathway: innate immunity, helper T cell differentiation, epithelial and mucosal immunity, and lung and airway function [32]. Five most commonly known asthma genes are including ADAM33, PHF11, DPP10, GRPA, and SPINK5 [33,34]. These genes have been identified based on positional cloning, which requires no assumptions about likely disease pathogeneses [35,36]. These genes have a known role in mucus production, allergy trigger modification, and airway epithelium reaction to the external environment [37]. Unfortunately, searches for genes involved in asthma are extremely challenging because of the complex pathophysiology of asthma.

1.2.3. Asthma environmental and lifestyle factors

Genetic factors, such as a family history of asthma play an important role in the etiology of asthma, however, it is commonly believed that the underlying causes of most complex diseases, such as asthma, are associated with both genetic and environmental factors, and interactions between gene and environmental factors. Geographic variation in asthma prevalence and incidence also supports the role of the environment as a contributing factor [3]. Besides, for many patients both gene and environmental factors contribute to its inception and evolution [38]. However, many studies have not been able to examine complex interactions between genetic and environmental factors in asthma development [5].

There has been growing evidence in the literature supporting a multifactorial effect of lifestyle on asthma. An increased risk of asthma has been significantly associated with many lifestyle related factors [39], such as diet, exposure to infection early on life, household heating systems, and exercise. For example, tobacco smoke is a risk factor for asthma, consistently reported in people at different age groups [40]. Studies suggest that a healthy diet and nutrition, including fresh fruit and vegetables, may reduce the risk of asthma [41]. Diets rich in fruit, vegetables, fiber, and Omega-3 fatty acids have anti-inflammatory properties [42]. Whereas diet which includes proceed meat, fat, and desserts have pro-inflammatory effects [43].

Physical activity and regular exercise are crucial to a healthy lifestyle. Studies suggest that patients with asthma are less active due to their chronic condition and physical activity generally increases the patient's symptoms of shortness of breath [44]. However, asthmatics with a regular physical activity have shown a reduced asthma symptoms, such as wheezing and shortness of breath, [45] and fewer instances of aggravated symptoms, and asthma-related emergency visits [46].

1.3.Environment & Health

The environment interacts with human health in a variety of ways; studies show many risks and impacts of environmental factors on human health [47]. Environment defined as all physical, chemical, and biological factors external to a person, and all related behavior [48, 23]. It is the exposure to these factors in the environment that influences public health.

Environmental risk factors have effects on disease development, and health outcomes. These effects can be either direct, such as via exposure to harmful agents, or indirect [49,50]. In both developed and developing countries, environmental exposure affects human health. A report from the World Health Organization has estimated that preventable environmental factors contribute to thirteen million deaths annually, 23% of all deaths overall, and 24% of the global disease burden [23]. Environmental risk factors are linked to 25% of all deaths in developing countries, and 17% in developed countries [22].

In prior decades, studies of the impact of environmental factors on human health were mostly focused on associations between chemical toxins, waterborne diseases, and other illnesses such as cancer, with little change in researchers' perspectives regarding the definition of the environment and its effect on human health [51], but research in the field has been invigorated. The definition of environmental health is now much broader, and studies of environmental health are considering health impacts related to broader issues, such as water quality, indoor and outdoor pollution, sanitation and hygiene, harmful chemicals, the ozone layer, and climate change. Although most of these risk factors are preventable and avoidable, 80% of diseases globally are related to them [24].

In addition to a variety of infections and communicable diseases, environmental risk factors also lead to the development of chronic non-communicable diseases and contribute to global mortality [52]. Around two-thirds of the thirteen million deaths caused by environmental risk factors each year are linked to non-communicable diseases [53]. Ambient air conditions such as weather and air pollution, combined with indoor air pollution, account for 3.7 million deaths annually [54]. The impact of the environment on non-communicable diseases has been increasing due to environmental changes, such as climate change [24]. Environmental protection Agency (EPA), and an international opinion from WHO, support the hypothesis that local and regional climate trend may negatively impact human health [55]. The environment and ambient air are a major determinant of chronic respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Studies have been focused on identifying new environmental risk factors associated with asthma and possible solutions [56] and there are very few systematic attempts to evaluate and monitor environmental indicators that relevant to asthma locally and nationally.

1.4.Asthma and the Environment

The etiology of increased risk of Asthma associated with many environmental factors is not fully understood. While many environmental factors have been found to trigger asthma attacks, they may also affect the underlying asthmatic process. These factors affect asthma severity and progression over time. Tobacco smoke, indoor and outdoor air pollution, mold and dampness, animals, and occupational exposures are considered as environmental risk factors. However, level of exposure varies significantly in peoples with different social economic status and the place of living. As an example, some studies suggest high prevalence of asthma in low-income countries are associated with environmental factors [57].

As a respiratory condition, the risk of asthma has been associated with ambient air condition and quality [8]. With the passage of the Clean Air Act in 1960s and other climate action legislation, related research conducted to closely assess the association between air quality, weather, climate and human health [58, 59]. Therefore, number of studies that examined the relationship between those factors and asthma has gradually increased in the literatures.

Literatures suggest meteorological variables and weather conditions are among environmental factors that impact respiratory health, and several studies suggest that weather conditions often exacerbate asthma [60, 61]. Asthma symptoms appear to worsen alongside weather changes, and there are annual trends that accompany the worsening of symptoms during particular seasons and times of the year. For example, cold and dry air causes asthmatic lungs to tighten, leading to a flare in asthma symptoms [62]. This is especially the case during fall and winter; asthma episodes tend to peak at this time, alongside the start of a school year, and cold and flu season. On the other hand, pollen also provokes airways and exacerbates asthma when inhaled, leading to an asthma attack, which is common during spring and pollen season.

Studies have examined weather patterns such as cold spells on asthma exacerbation. During the fall and winter, cold and dry air affects asthma by the irritation of cold air, which leads to bronchospasm of airways [63]. A research from New York City reported an increase in asthma exacerbation in the days following cold spell (three or more sequential days of temperature at the 10^{th} percentile of the daily mean), which is associated with the long-term inflammation process of asthma [64].

Asthma symptoms also worsen with heat and humidity, and literature suggests that hot air contains more water and is heavier and more difficult to breathe [65]. Daily weather, such as warm temperatures and moderate winds may cause more airborne pollen [66]. Another study also suggested a link between daily temperature changes and high relative humidity and asthma exacerbation. Summer thunderstorms, for example, can quickly change weather variables, causing asthma attacks [67] and leading to an increase in asthma-related hospital admission [68].

Recognizing the effect of seasonal weather changes on asthma triggers can help people with asthma better manage their condition. Although asthma is known as a chronic condition with no available cure, its symptoms can be controlled with effective management and treatment. By educating patients about possible triggers, avoiding the triggers, taking prescribed medications, and follow medication instructions, asthma symptoms and the risk of exacerbation can be dramatically reduced.

Tracking asthma symptoms and measuring lung function are effective approaches to managing and treating asthma attacks. Identifying asthma triggers in the environment to avoid them as much as possible could control frequent asthma exacerbation and admission to hospital. Although triggers such as dust, pollen, and viruses are ubiquitous and difficult to avoid, understanding environmental triggers is an important proactive step. Meanwhile, weather variables are among non-allergen triggers and may provoke already inflamed airways, leading to asthma attacks and hospital admission [69]. Local weather forecasts may prove critical for asthmatic patients to gauge the meteorological risks in advance.

1.5.Epidemiology & Burden of Disease

Approximately 300 million people worldwide are living with asthma, and an estimated 100 million more add by 2025 [70]. Asthma prevalence has increased globally in the past several decades [71]. Asthma is a chronic condition in all age groups. Epidemiological studies have found that age and sex are related to asthma prevalence and severity, whereby asthma is more common among young boys, with boys under 18 having a 54% higher rate of asthma than girls of the same age [72, 73]. However, there is also an elevated prevalence among young adults aged 15-34, and adult women.

There are geographic variations in asthma prevalence, incidence and mortality [5]. Asthma prevalence has been reported to be higher in developing countries [74] and the reason is unclear. Study suggests different immunology, genetic, allergies, and exposure to environmental factors such as second-hand smoking in lower-income countries appear to be strongly correlated with higher asthma prevalence [75]. The incidence of asthma in developing countries varies between 3% and 30% in adults depending on geographic location and method of survey [76]. According to the World Health Organization, over 80% of asthma-related deaths occur in low and lower-middle-income countries. This is likely due to a lack of medications, poor asthma management, and limited access to healthcare [11] in developing nations.

The Global Initiative for Asthma (GINA) has estimated that the prevalence of asthma around the world ranges from 1% to 18% of the total population depending on the country and geography

[76]. In one European study, asthma prevalence in adults' reported between 4.9% and 14.3% among men, 5% and 14.9% among women [77]. Meanwhile, the United States' Centers for Disease Control and Prevention (CDC) reported that 7.9% of Americans were living with asthma as of 2013. New Zealand and England have the highest asthma prevalence at 15.1% and 15% of the population, respectively [78].

In 2014, the prevalence of asthma among Canadians was reported to be 2.4 million people or 8.1% of the population [79]. A more recent report from Asthma Canada shows that asthma is the third-most common chronic disease in the country. Asthma is affecting 3.8 million people in Canada. Over 300 Canadians are diagnosed with asthma every day, and asthma attacks account for 250 deaths each year in Canada [68].

One study in Ontario reported a 70.5 % increase in asthma age-sex standardized prevalence from 8.5% in 1996 to 13.3% in 2005. However, during the same period, the age-sex standardized mortality rate was decreased, with a relative decrease of 17.8% ($P < 0.001$) [27]. Another study reported the asthma prevalence rate in Canada as 10.8% while NL prevalence rate reported as 9.5% between 2011 and 2012 [80]. In the same study Nova Scotia reported as 11.8% and New Brunswick as 9.1%.

Globally, asthma is associated with approximately 180,000 deaths annually [81]. These deaths are mostly preventable [82]. Mortality rates for asthma are higher in low-middle income countries where access to medications and specialists is limited [83]. Globally, asthma can cause many days of missing school and workdays. Adjusted-disability life year assigned for asthma rank 22nd worldwide, similar to diabetes and Alzheimer [14].

The economic burden of asthma is significant. The economic burden of disease is classified as direct and indirect cost; indirect cost associate with a reduction in productivity due to sickness and direct costs are associated with the costs of health care utilization, medication, diagnosis, and treatment of asthma. The cost of treating the individual with acute asthma exacerbation has increased in the last decade [84]. The annual financial cost (direct and indirect) attributable to asthma has been estimated to be in the range of $300 to $1,300 per patient per year in Western countries [55]. Canada has been estimated that employed persons with mild asthma have average annual costs of $577 per person, while retired persons are the costliest group with average annual costs of $1,966 per patient [73, 85]. In British Columbia, Canada, asthma-related healthcare costs were estimated at $315.3 million between the years 2002 and 2007 and $435 million in 2008. Concerning population size and currency value, the annual cost of asthma increased by about 10 percent [85]. The indirect cost of asthma in Canada is associated with 50% of the total costs of disease [86]. High economic burden due to asthma-related productivity has been reported in North American and European studies [87]. A study in Europe has reported the indirect costs for asthma are linked to 62.5% of total costs of hospital admission [88]. In 2002, asthma-related direct medical costs were estimated at $9.4 billion in the United States, with an additional $4.6 billion in direct costs and $3.1 billion in costs associated with asthma hospital admission [89].

Asthma is one of the leading causes of hospitalization globally; [5] although asthma hospital admission rates often vary across and even within countries, it is estimated that 20% of asthma patients experience episodes of exacerbated symptoms requiring hospital admission [90]. While most asthma attacks are mild and manageable by the patient, asthma hospitalization is an indicator of the burden of more severe asthma [8] and despite advances in asthma management, asthma-related hospitalization is increasing [91]. In Europe for instance, asthma-related admissions account for 0.6% of hospitalizations [8].

Evidence suggests age and sex-related difference in hospital admission for asthma. Hospitalized patients aged 15 or younger are twice as likely to be male, whereas patients aged 15 years or older are up to three times more likely to be female [92, 93]. Also, women who present to the emergency department with exacerbated asthma symptoms are more likely to be hospitalized than men [94,95].

Asthma-related hospitalizations accounted for 1.2% of total U.S. hospitalizations from 2003 and 2011 [96]. Although asthma-related hospital admission have declined in the past 20 years in Canada [150], the average asthma-related hospitalization rate was reported to be 1864 per 100,000 people from 2006-2009. Atlantic Canada has the hospitalization rate of 774 per 100,000 people for asthma, and NL having 171 admissions per 100,000 people in the same period (2006-2009) [97].

Epidemiological studies from around the world have described an association between environmental factors and asthma-related hospital admission. Air pollution [98], aero-allergens, viral infections [99], and meteorological variables [100] are among environmental factors having an association with asthma-related hospital admission. Weather conditions, including extreme hot and cold temperatures, humidity changes, and wind, have also been linked to asthma-related hospital admission [101, 102] with health effects being lowest at average temperatures, and higher at cold or hot temperature extremes [103]. Some studies have suggested lower minimum temperature is associated with asthma exacerbation in adults leading to hospital admission [56, 57,104].

The association between high temperature and hospital admission in patients with respiratory disease such as asthma is recognized in the literature [105,106]. For example, a study in New York City identified an increase in asthma hospital admission when temperatures exceeded a certain threshold which ranged from 28.9°C–29.4°C [107]. Another study in London reported increases in asthma HAs proportional to every degree Celsius to increase above a threshold, with lags of 0–2 days [108]. However, the threshold for temperature differs across studies, suggesting it varies from region to region based on geographic location [109].

1.6. Medico-administrative Data in Asthma Study

Canada has one of the richest collections of electronic health databases, including administrative health databases, clinical registries, electronic medical records, and health surveys [110]. Medico-administrative databases have many advantages compare to primary data collection in health research, and they are being increasingly used in chronic and infectious disease research and surveillance. [111]. The medico-administrative datasets is often collected for administrative purposes. Thus, contains large numbers of records and sometimes are less expensive for research relative to primary data collection approaches [112].

Although the medico-administrative data were not explicitly collected for research, these data have been used in many studies of health service utilization, program evaluation, health outcomes, and population health surveillance [111]. To conduct unbiased research, it is important to evaluate the quality of the data before conducting the study; the researchers must know about the strengths and limitations of the data to produce unbiased results [113]. When using administrative records, missing, incomplete, or inaccurate data should be considered. Although researchers cannot correct or improve the quality of the data since they usually do not have access to the primary data source, there are approaches to improve the transparency and inferences based on secondary data analysis [114].

Accessing the data typically requires gaining approval from a data custodian and research ethics board, often a time and resource-intensive process that the research team should not underestimate. Safeguarding the data from unauthorized access and disclosure is the main concern for the data custodian [64].

Extraction administrative data is less expensive than primary data collection and often contains demographic and service event records. Administrative data can be even more comprehensive when two or more different datasets are linked, but carefully considering the quality of common identifiers in the datasets is essential [115].

Administrative data have been used in asthma research, including studies of child and adult asthma hospitalization, [116], economics and burden [117], and disease risk factors [118]. The association between air pollution and asthma-related hospital admission has been investigated in previous studies by linking air pollution and health data [53]. Association between hospitalizations and specific weather events, such as thunderstorms or heat waves, links meteorological and hospital admission data investigated in several global studies [31, 59, and 62].

Some studies in Canada conducted by linking health and weather data in Canadian populations to examine the association between weather and asthma hospitalization [119]. However, there is limited study in asthma research by linking administrative and meteorological data in adults Canadian to examine an association between asthma hospitalization and temperature.

Various data sources exist to use for chronic respiratory studies in NL and within Canada. The secondary health data used in this study are listed here and a brief description of each data source can be found in Table 1. The NLCHI has provided us required data by linking:

- Canadian Chronic Disease Surveillance System (CCDSS): To identify patients with asthma based standard case definition.
- Provincial Discharge Abstract Database is formerly known as Clinical Database Management system (CDMS): To extract patients' hospitalization records.
- NLCHI mortality system: To extract dead record of patients during study period.

Table 1: Medico administrative Data source relevant to Asthma in NL.

Data sources	Data availability	Description	Limitations
Provincial Discharge Abstract Database (PDAD) is formerly known as Clinical Database Management system (CDMS) [120]	1995- onward	Contains demographic, clinical and administrative data related to all acute care (inpatient) hospitalizations and surgical daycare cases occurring at acute care facilities (hospitals) in the NL. It is based on data that is collected in the Canadian Institute for Health Information's (CIHI) national Discharge Abstract Database (DAD). Data contains variables; age, sex, Regional Health Authority, hospital of service, place of residence, or reason for hospitalization (i.e. diagnosis). Data can be linked via health insurance number to other data sources. The diagnosis and procedure coding systems governed by CIHI changed from ICD-9 to ICD-10-CA and from CCP to CCI, respectively in October, 2015.	Although not fundamentally different, there are changes from version to version that may impact results. In addition, chronic care services data has not been available for all facilities in the province.
Canadian Chronic Disease Surveillance System (CCDSS) [121]	1995- onward	The Canadian Chronic Disease Surveillance System (CCDSS), formerly the National Diabetes Surveillance System (NDSS) is a network of provincial and territorial chronic disease surveillance systems that submit aggregate data on chronic conditions to the Public Health Agency of Canada (PHAC) for national reporting. The Newfoundland and Labrador Chronic Disease Surveillance System (NCDSS) is the provincial component of the CCDSS and was developed and is maintained by the Centre. This database links health insurance registry information with data on physician claims, mortality and hospital information.	Validity of the diagnosis codes for these disease conditions varied over time. Due to ongoing concerns on completeness and comprehensiveness of the data, the minimum set to meet the case definition criteria may not be properly captured in the data.

		This is a composite database that links records from the MCP Beneficiary Registration File with the MCP Fee-for-Service Physician Claims Database, the NLCHI Mortality System and the Clinical Database Management System. Data is submitted to PHAC at the end of April each year where it undergoes data quality procedures in which the Centre assists. Data is normally available approximately one month later. Data contains variables; sex and five-year age groups for over 20 chronic conditions [121], as well as by postal code of residence after linkage via health insurance number to the MCP Beneficiary Registry File. The CCDSS is a longitudinal, population-based database. Data can be linked via health insurance number to other data sources. There have been slight changes to case definitions for some chronic conditions over the years and the denominator data used for the NL component changed from the Statistics Canada Population Estimates to the MCP Beneficiary Registration File. However, as stated previously the fact that each annual data run of the CCDSS involves re-running data for all years from 1995/96 to latest year of data, comparability of data between years (i.e. trending) is possible.	
NLCHI Mortality system [122]	1991- onward	Contains demographic, administrative, and clinical data related to all deaths that occur in the NL and includes health conditions present at time of death (resident and non-resident). Cause of death information is available and annual data is collected; Statistics Canada carries out a series of	Reporting and release of data is often delayed as data is not available until 18 months after the start of the next calendar year.

		data quality checks. However, Data contains variables; age, place of residence, occurrence of death, antecedent cause of death or other conditions present at the time of death. To identify people, provincial and territorial health insurance registry records are linked using a unique personal identifier to the corresponding physician billing claims, hospital discharge abstract records and prescription drug records.	

1.7.Objective

The overall objective of this thesis is to examine the association between weather temperature and hospital admission among patients with asthma in St. John's between 1996 and 2013. More specifically, this thesis will:

- Summarize and evaluate the effects of meteorological variables on asthma hospitalization and emergency department visits in adults from literature, and identify knowledge gaps.
- Identify the association between minimum temperature, and its delayed effect on number of daily hospital admission among adult patients with asthma in St. John's metropolitan area, Canada.
- Assess the effects of extreme temperature on epidemic of hospitalization among adults with asthma in St. John's metropolitan area, Canada.

1.8.Co-authorship Statement

Chapter two of this thesis was published in the Canadian Respiratory Journal in June 2019, Chapter three was submitted to the Canadian Journal of Respiratory, Critical Care and Sleep Medicine, and Chapter four was submitted to the Heliyon journal.

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This research is a collaborative work, and I would like to acknowledge the contributions of the following co-authors:

Elnaz Bodaghkhani conceptualized the studies, performed data analysis, interpreted the results and wrote the manuscript

- Dr. Shabnam Asghari, my Ph.D. supervisor, who has contributed her guidance on all aspects of this study, including the research proposal, study design, data provision, and writing.
- Dr. Zhiwei Gao, who contributed many influential comments on the manuscripts, methodology, and statistical analyses pertaining to this thesis.
- Dr. Masoud Mahdavian, who contributed significant guidance and insightful comments on the clinical aspects of this study.

Chapter 2: Effects of meteorological factors on hospitalizations in adult patients with asthma: A systematic review.

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2.1.Abstract

Environmental factors such as weather variables contribute to asthma exacerbation. The impact of meteorological factors on asthma-related hospital admissions (HAs) or emergency department visits (EDVs) have been assessed in the literature. We conducted a systematic review to establish a conclusion of whether these findings from the literature are consistent and generalizable or if they vary significantly by certain subgroups.

This study aims to review the effect of meteorological variables on asthma HAs and EDVs in adults, to identify knowledge gaps, and to highlight future research priorities.

A systematic search was conducted in electronic databases such as PubMed, Embase, and CINAHL. All studies published in English were screened and included if they met the eligibility criteria. Two independent reviewers assessed the quality of the studies and extracted the data. The available evidence was summarized and presented using a Harvest plot.

Our initial search returned a total of 3887 articles. After screening titles, abstracts and full texts, 16 studies were included. Thirty-one percent of the included studies (5/16) found that temperature was the only factor associated with asthma hospitalization or EDVs. Six studies (37%) found that both temperature and relative humidity were associated with HAs. Four studies (25%) identified thunderstorms as a possible factor associated with asthma hospitalization in adults.

Our review suggests that HAs and EDVs due to asthma are associated with many meteorological factors. Among the weather variables, changing temperature is the most commonly studied variable. We did not find studies that measured barometric pressure, weather phenomena, or the effect of tornados. To develop effective strategies to protect subjects at risk, further studies are required.

2.2. Introduction

Asthma is a chronic inflammatory condition which is characterized by reversible air flow obstruction [6]. Those affected by this condition may present symptoms such as wheezing, breathlessness, coughing and chest tightness. This chronic condition is highly prevalent, and according to the World Health Organization (WHO) 300 million people around the world have asthma; it is estimated that 100 million more people will be affected by 2025 [123]. While the etiology of asthma is currently unknown, it is believed that factors such as genetics, lifestyle choices and environmental factors contribute to asthma exacerbation which may lead to HAs [124].

Among environmental factors, weather and air pollution play an important role in increasing asthma exacerbations, which requires special care or even hospitalization [125]. Many studies including systematic reviews assessed the effect of pollen, allergens and air pollutions on asthma hospitalization. While many studies indicate that weather factors are positively associated with HAs due to asthma, the exact mechanism is unclear [1, 102,126]. Some studies found temperature and humidity could have an influence on airway function and might affect lung function [127]. One theory suggests that water loss in airways during cold conditions causes inflammation that leads to asthma attacks [2]. Another theory suggests that cold and dry air increases the rate of evaporation of surface fluid in airways [128]. Furthermore, some studies show that changes among weather variables can lead to airway inflammation among people with asthma [3].

Some studies suggest that extreme temperature (both cold and hot) and high winds could increase EDVs and hospitalizations among those with asthma [101,129]. In contrast, other authors did not find any correlation between weather variables and asthma HAs [64]. To our knowledge, there is no review that summarizes the evidence on the effects of meteorological variables on HAs and EDVs among adults with asthma. This review could be important for healthcare demand prediction during weather events. The objectives of this review are (1) to summarize and evaluate the effects of meteorological variables on HAs and EDVs in adults, (2) to identify knowledge gaps, and (3) to highlight future research priorities.

2.3. Methods

2.3.1. Review Question

Our systematic review question "Do weather conditions affect HAs among adults living with asthma?" was defined using the PECO question format where the study **P**opulation is adults (Age ≥18 years) who were diagnosed with asthma according to the asthma definition in the study. **E**xposure of interest includes any weather variables reported in the study. The **C**ontrol groups are adults with asthma who were not exposed to weather variables, and the **O**utcome is any admission to hospital units or emergency departments as reported in the manuscripts.

2.3.2. Data Sources

We searched large electronic databases containing health and medical literature: PubMed (1946 to Dec 2018), Embase via Embase.com (1947 to Dec 2018) and CINAHL via Ebsco (1937 to Dec 2018). Moreover, references of included articles were searched, the articles deemed eligible were included in the review. The search was originally done in November 2017 and updated to included articles published until December 31, 2018.

2.3.3. Search Strategy

A series of relevant terms were identified through consultation between content experts and a librarian. The keywords and Medical Subject Headings (MeSH) for this review fall under the following categories: (1) asthma, (2) hospitalization, and (3) meteorological factors. We included a combination of keywords such as temperature, precipitation, thunderstorm, wind speed and air pressure that could potentially influence HAs and EDVs. See Table 2, a sample search strategy and the key words we used in PubMed.

Table 2: The literature search strategy for PubMed and number of identified articles.

1	**"asthma"[MeSH Terms] OR "asthma"[All Fields] OR ("chronic"[All Fields] AND "respiratory"[All Fields] AND "disease"[All Fields]) OR "chronic respiratory disease"[All Fields] OR "asthma"[Mesh]**	223989
2	"hospitalization"[Mesh] OR "emergency service, hospital"[Mesh] OR (("hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]) AND admission[All Fields]) OR ("length of stay"[MeSH Terms] OR ("length"[All Fields] AND "stay"[All Fields]) OR "length of stay"[All Fields] OR ("hospital"[All Fields] AND "stay"[All Fields]) OR "hospital stay"[All Fields]) OR (("hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]) AND admissions[All Fields]) OR ("length of stay"[MeSH Terms] OR ("length"[All Fields] AND "stay"[All Fields]) OR "length of stay"[All Fields] OR ("hospital"[All Fields] AND "stays"[All Fields]) OR "hospital stays"[All Fields]) OR exacerbation[All Fields] OR exacerbations[All Fields]	481723
3	**"weather"[Mesh] OR meteorological[All Fields] OR ("weather"[MeSH Terms] OR "weather"[All Fields]) OR ("temperature"[MeSH Terms] OR "temperature"[All Fields]) OR ("humidity"[MeSH Terms] OR "humidity"[All Fields]) OR ("wind"[MeSH Terms] OR "wind"[All Fields]) OR ("rain"[MeSH Terms] OR "rain"[All Fields]) OR ("snow"[MeSH Terms] OR "snow"[All Fields]) OR precipitation[All Fields] OR thunder[All Fields] OR ("lightning"[MeSH Terms] OR "lightning"[All Fields]) OR storm[All Fields] OR ("cyclonic storms"[MeSH Terms] OR ("cyclonic"[All Fields] AND "storms"[All Fields]) OR "cyclonic storms"[All Fields] OR "hurricane"[All Fields]) OR ("tornadoes"[MeSH Terms] OR "tornadoes"[All Fields] OR "tornado"[All Fields]) OR ("droughts"[MeSH Terms] OR "droughts"[All Fields] OR "drought"[All Fields]) OR "meteorological concepts"[Mesh] OR ("atmosphere"[MeSH Terms] OR "atmosphere"[All Fields]) OR atmospheric[All Fields] OR "air pressure"[All Fields] OR ("climate"[MeSH Terms] OR "climate"[All Fields]) OR ("seasons"[MeSH Terms] OR "seasons"[All Fields]) OR seasonal[All Fields] OR "thunderstorm"[All Fields] OR thunderstorms[All Fields]**	1298001
4	**1 AND 2 AND 3**	1631
5	**4 AND Publication date to Nov 17, 2017**	1511
6	**4 AND Publication date Nov 17, 2017 – Dec 31, 2018**	120

2.3.4. Inclusion Criteria

Studies included in this review consisted of original research papers from peer-reviewed journals and those published in the English language. We identified studies that focused on HAs or EDVs due to weather factors and looked for adult patients diagnosed with asthma.

Dissertations, audits, policy analyses, book reviews, pilot studies, perspective articles and research at the planning stage (unless provided in the research directory) were excluded. We also excluded studies that evaluated air pollution as the only exposure and those that used a pediatric population as children respond differently than adults to weather changes.

2.3.5. Directory of Identified Studies

A directory of publications was created in RefWorks. We used Mendeley to capture and tag the web-pages' information, which we then imported into RefWorks.

2.4. Study Selection

The eligibility of articles included in this review was assessed in two stages:

Stage 1: Pre-screening

After removing duplicates, the titles and abstracts were screened by one reviewer (EB). We then selected articles that were deemed eligible for full-text review. A random selection of five percent of the articles was assessed by a second reviewer (CM) to assess the validity of the screening. There was 98% agreement, so a second review of the titles and abstracts was unnecessary.

Stage 2: Full-text review

For articles that were found to be relevant in the title/abstract screening phase, the full-text review was performed. Two reviewers (EB and CM) independently checked the full-texts of the articles against the inclusion criteria and fine-tuned the final article selection for data extraction. Any discrepancies were discussed and resolved. Figure 1 shows our PRISMA diagram.

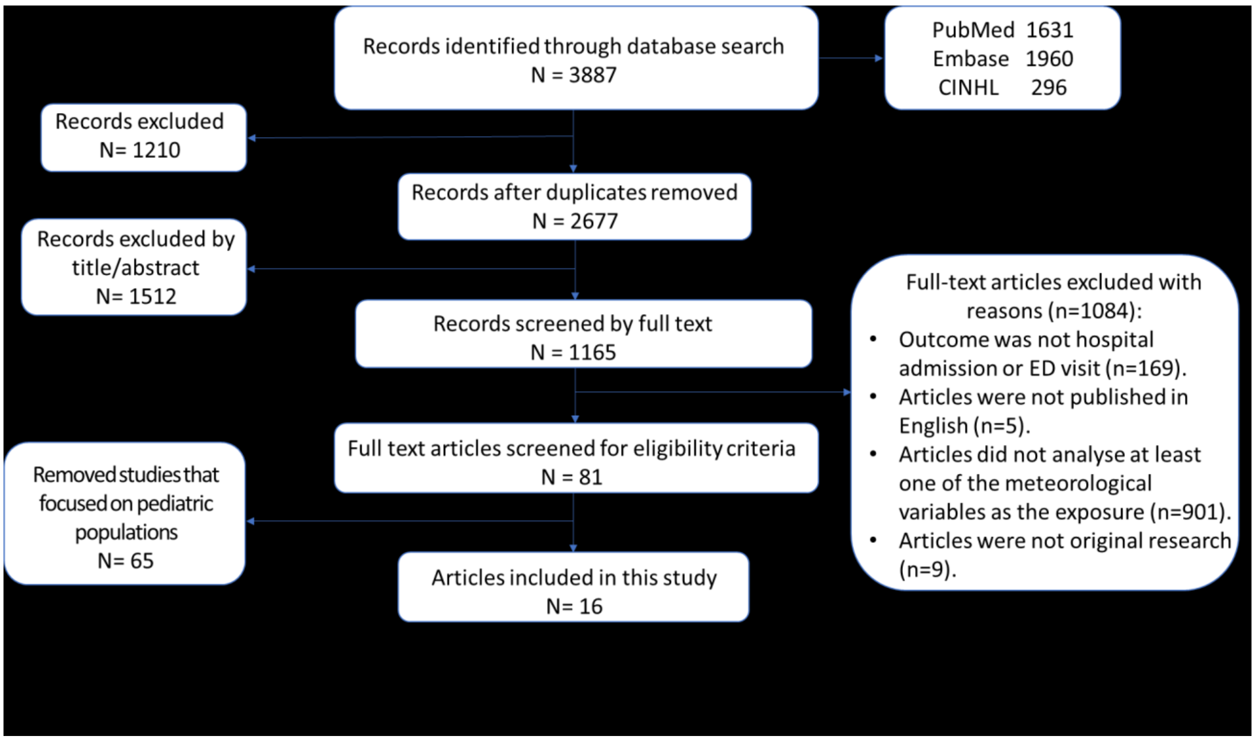

Figure 2: Preferred Reporting items for Systematic Reviews (PRISMA) diagram

2.5. Data extraction

A data extraction tool was developed using Excel. The data extraction tool included the following six characteristics: citations (e.g. authors, publication year, journal, place of study), methodology (e.g. study design, sample size), characteristics of study population (e.g. location of study), meteorological factors (e.g. precipitation, thunderstorms, humidity, temperature), hospitalization (e.g. HAs and EDVs), and study quality.

Data extraction was conducted by two independent reviewers (EB and CM). A calibration test was performed on the first 10% of the reviewed studies. The Kappa index was calculated to assess inter-reviewer agreement (kappa >0.7 was considered a good agreement). The discordant items were reassessed, and the data extraction tool was revised accordingly. The reviewers met weekly to discuss the extracted data and resolve any disagreements. A third reviewer (SA) was invited to mediate if the disagreement did not resolve.

2.5. Quality assessment

We used the Critical Appraisal Skills Program tool (CASP, 2014) to assess the quality and risk of bias of included studies. The tool assesses the study design, the population of study, sample size, statistical methods, confounding variables and biases. We did not exclude low-quality studies from this review, but we kept into account this aspect when summarizing the results.

2.5.1. Synthesis of results and data display

We described all studies that met the eligibility criteria including their quality score. We quantified the frequency of the reported meteorological variables and summarized their effects on HAs or EDVs separately.

We developed a harvest plot to present our systematic review results (Figure 2). A harvest plot is a novel approach to graphically summarize the results of a systematic review of complex and diverse studies [130]. The harvest plot method is flexible by allowing us to display the quantitative data for all studies when it would not be possible to combine in a traditional forest plot [131]. The results of our systematic review show three outcomes (increasing effect, decreasing effect, and no effect) and six weather variables as the exposure which includes temperature, wind speed, fog, rainfall, thunderstorms, and relative humidity. Each row of the plot shows the different exposures examined in these studies. All plots contain a digit at the top of the vertical bar representing the number of studies that examined the factors for the outcome of interest. Each vertical bar of the plot was colored to indicate the effect of that variable on asthma-related admissions (increasing effect, decreasing effect, and no effect) and the size of bar indicates the quality of studies (Good, Fair, Poor).

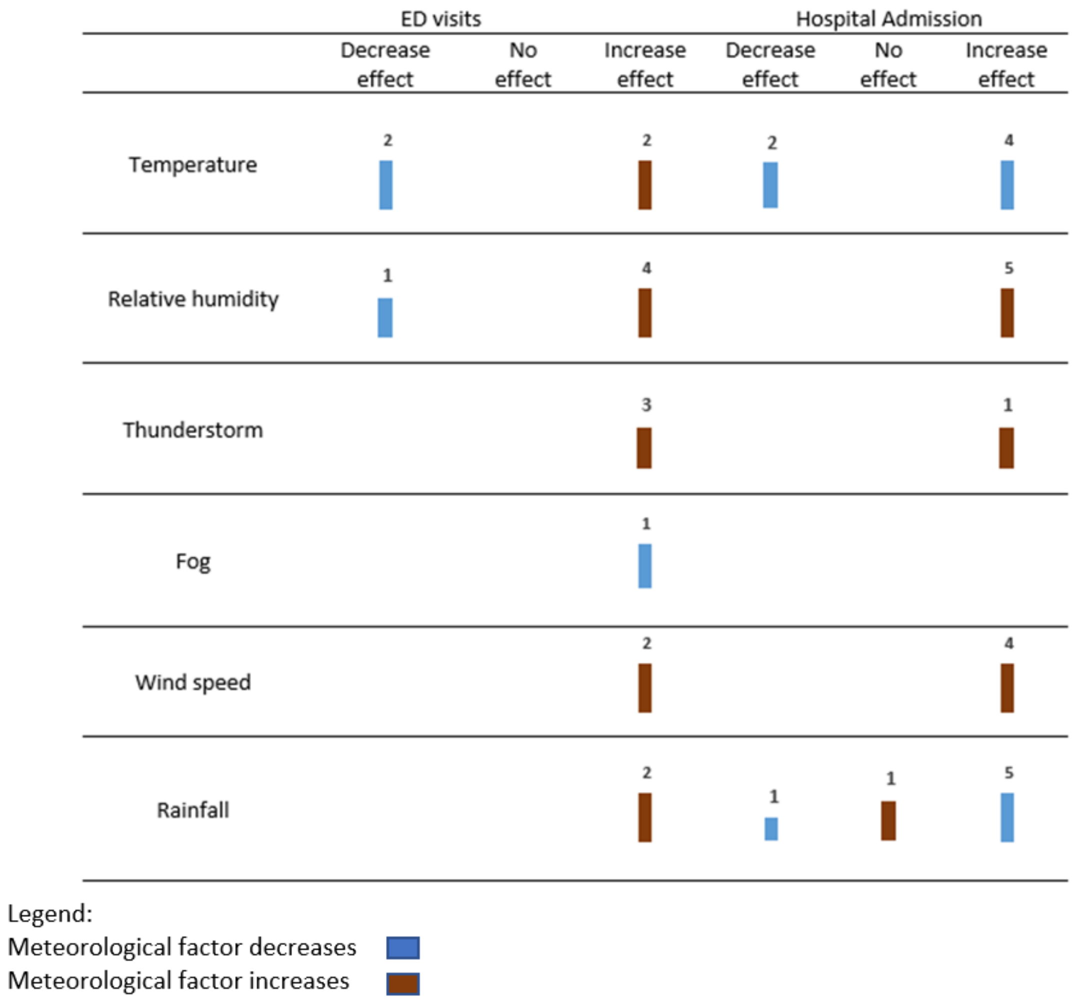

Figure 3: Evidence for the effect of meteorological factors on HAs and EDVs among adults with asthma

The rows indicate all meteorological variables with an effect on asthma-related admissions that were studied in the literature and the three columns show the different effects of each exposure. The numbers on top of each bar indicate the number of studies that investigate the effect of that variable and find that result. The length of each bar shows the quality of the studies (good, fair, or poor). The colors of each bar indicate an increase or decrease in the effect of the variable.

2.6. Results

Our search for asthma-related HAs due to weather factors returned a total of 3877 articles after deduplication. 1512 studies were excluded while screening for titles and abstracts. During full-text review, five studies were excluded because they were not published in English and nine more studies were excluded because they were not original research articles. Eighty-one articles included either adult or pediatric populations. Among them, 65 were excluded as the study population was only children, resulting in 16 studies to be included in this review. Figure 1 shows the PRISMA flow diagram of the included studies.

2.6.1. Study Characteristics

Seven of the 16 included studies were conducted in Asia (five in East Asia), five in the USA, two in Europe and two in Australia (Table 3). Overall, these 16 studies covered 1,144,859 observations, where most articles included at least 50,000 observations each. The mean study period for included studies was 6.5 years with a standard deviation of 7.13 years. Aside from the single study with a case-control design, one ecological study and one cohort study, eight studies in this review used time-series analysis and three conducted case-crossover designs. Articles included in this study used data sources from a health department database (n=9), hospital admission records (n=5), records from an insurance company (n=1) and a dataset from a fire department in Japan. All studies compared the individuals before and after they were exposed to weather conditions. There were no external comparison groups.

2.6.2. Weather variables

As shown in tables 4 and 5, 31% (5/16) of the studies found that temperature was the only factor associated with HAs or EDVs [4, 9, 11,132 and 23]. Nearly 37% (6/16) of the studies found that both temperature and relative humidity were associated with HAs (Table 4) [8, 9, 14,133 21, and 22]. Twenty-five percent (4/16) investigated the effect of thunderstorms as a possible element for asthma hospitalization in adults [134, 18, 24,135]. We did not find any studies that measured weather variables such as barometric pressure, different types of storms (tropical storm, snow storm) and tornados.

2.6.3. Effect of Meteorological factors on Hospitalization

Only one study showed a negative correlation between asthma hospitalization and daily mean temperature (5.79% risk increase, p=0.012) and lower minimum temperature (2.88% risk increase, p= 0.024) during the cold season [20]. This study was conducted in Hong Kong and was adjusted for air pollution, solar radiation and day of the week. Two studies, one in Finland (r= −0.11, p<0.01) [21] and one in China (r=−0.174, P<0.001) [9], have reported that asthmatic symptoms that lead to admission are influenced by daily temperature change during the study period. Five studies found that extremely cold or hot temperatures could trigger asthma attacks that lead to HAs [11, 18, 19, 21, and 23].

2.6.4. Effect of Meteorological factors on EDVs

One study reported that during the summer months, EDVs for asthmatic patients had increased with increasing temperature and humidity [104]. Lower relative humidity was the cause of the increase in EDVs by asthmatic patients in another study [14]. One study [16] reported that rainfall events due to thunderstorms could increase the EDVs for asthmatic patients (Figure 2).

Table 3: Characteristics of studies that examine the effect of meteorological factors on asthma admissions.

			Data source		Measures of effect			Study Outcome		
Author	Objective	Study design	Health data	Climate data	OR	RR	Count	ED[1]	HA[2]	Quality
Abe et al.,2009	Investigate the relationship of weather conditions and asthma exacerbation	Time-series	Tokyo Fire Department, follow-up diagnostic data from emergency physicians	Japan Meteorological Agency	X			X		Good
Anderson et al., 2001	Investigate associations between asthma admissions and thunderstorms	Case Control	Computerized hospital record	Met. Office and Cardiff Airport measurement site.			X		X	Fair
Buckley and Richardson., 2012	Characterize the effect of temperature on EDVs for asthma	Case-crossover	Epidemiologic Collection Tool (NC DETECT)	State Climate Office of North Carolina	X			X		Fair
Delamater et al., 2012 [3]	Investigate the relationships between air pollution, weather conditions, and asthma hospitalizations	Ecological	Healthcare Information Resource Center	Environmental Protection Agency (EPA)			X		X	Fair
Fitzgerald et al., 2014	Investigate whether prolonged periods of very cold temperatures are associated with an	Time-series	New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS)	National Center for Atmospheric Research			X		X	Fair

	increased risk of hospitalization for asthma patients								
Grundstein et al., 2008	Examine the association between thunderstorm activity and asthma morbidity	Time-series	EDV database	Automated surface observing system station	X		X		Poor
Kunikullaya et al., 2017 [3]	Determine the relationship between acute exacerbations of asthma and related HAs due to air pollution and meteorological conditions	Retrospective ecological time-series	Admission recorded by the hospital	Central laboratory of Karnataka State Pollution Control Board and meteorological department		X	X		Fair
Kwon et al., 2014 [3]	Estimate the effect of climate factors and air pollution on asthma hospitalization	Case-cross over	Kangwon National University Hospital and Chuncheon Sacred Heart Hospital	database of the Korea Meteorological Administration	X		X		Fair
Lam et al., 2016	Evaluate associations between asthma hospitalizations and meteorological factors in Hong Kong.	Time-series	Hospital Authority	Single central monitoring station from the Hong Kong Observatory (HKO)		X		X	Fair
Qasem et al., 2008 [3]	Explore which weather factors contribute to	Retrospective time-series study	Medical records from two hospitals (Al-Rashid Allergy Center and	Kuwait Aviation/Meteorology Department		X		X	Fair

	asthma hospitalization while controlling for pollen and spore level in the air in Kuwait		Emergency Department, and Al-Sabah Hospital)						
Qiu et al., 2015	Examine the health effects of environmental triggers on asthma	Longitudinal time series	Hospital Authority Corporate Data Warehouse	Hong Kong Observatory		X	X		Fair
Rossi et al., 1993 [3]	Evaluate the relationships between EDVs for asthma attacks and the meteorological, aerobiological, and chemical characteristics of the outdoor air	Time-series	University Central Hospital	Measured at the meteorological station in the city of Oulu		X	X		Fair
Soneja et al., 2016	Investigate the association between exposure to extreme heat and precipitation events and risk of hospitalization for asthma	Case-crossover	Maryland Department of Health and Mental Hygiene	National Climatic Data Center	X			X	Fair
Zhang et al.,2014	Evaluate the short-term effects of daily mean temperature on asthma HAs.	Time series	Health Insurance System of Shanghai	Shanghai Center for Urban Environmental Meteorology	X	X		X	Good
Andrew et al.,	Assess the demand	Time series	Ambulance Victoria data	Australian Bureau			X		Good

2017	for emergency medical services during epidemic thunderstorm asthma		warehouse and Emergency service telecommunication	of Meteorology
Thien et al., 2018	Investigate the effect of thunderstorm asthma on health services and patient risk factors.	Cross sectional	Ambulance Victoria, the Victorian Department of Health and Human Services Victorian, Australian and New Zealand Intensive Care Society Adult Patient Database, Census data	Australian Bureau of Meteorology

[1] EDVs: Emergency department visits for asthma.
[2] HAs: Hospital admissions for asthma.
[3] Air pollution was considered a confounder in these studies.

Table 4: Studies that examine the effect of Meteorological factors on EDVs.

Meteorological Risk factors										
Location	Author	Sample size	Temp	Relative humidity	Thunderstorm	Fog	Wind speed	Rainfall	Key measures	Results
North America										
North Carolina, USA	Buckley and Richardson., 2012	53,156	YES						Daily min/max temperature	OR for EDVs per 278.15 °K = 1.01, 95% CI: 1.00-1.02
Atlanta, USA	Grundstein et al., 2008	215 832			YES		YES	YES	Total daily rainfall	EDVs 3% higher on days following thunderstorm
Europe										
Oulu, Finland	Rossi et al., 1993	232	YES	YES				YES	Min/max and mean temperature, relative humidity, rainfall	Increased EDVs during the summer due to higher temperature and humidity, (r= -0.11, p < 0.01)
East Asia										
Chuncheon, Korea	Kwon et al., 2014	660	YES	YES		YES	YES	YES	Max/min/mean temp, temperature range, low and mean relative humidity, rainfall, fog present	Low relative humidity increased and fog decreased EDVs. Risk increase: 29.4% (95% CI: -46.3% to -7.2%, P=0.013)
Tokyo, Japan	Abe et al., 2009	643,849	YES	YES				YES	Min temperature and Max relative humidity. Total rainfall	Lower temperature increases EDV by % 1.2
Hong Kong	Qiu et al., 2015	45,896	YES	YES					Daily diurnal temperature range	274.15 °K in diurnal temperature range associated with a 2.49% (95% CI: 1.86% to 3.14%) increase in daily

							EDVs
Victoria, Australia	Andrew et al., 2017	2954	YES		YES	Dropping temperature	41.7 % (95% CI: 39.6% to 43.9%) increase in ER visits due to thunderstorm
Melbourne, Australia	Thien et al., 2018	3365	YES	YES	YES	Plunging temperature and rising humidity	992% increase in asthma-related EDVs

Table 5: Studies that examine the effect of meteorological factors on hospital admission

Effect of meteorological factors on Hospital admissions (H. A)									
				Meteorological Risk factors					
Location	Author	Sample size	Temp	Relative humidity	Thunderstorm	Wind speed	Rainfall	Key measures	Results
Europe									
Cardiff and Newport, UK	Anderson et al., 2001	2000			YES		YES	Min/max temperature and total daily rainfall.	Average daily asthma hospitalization lower in summer time (4.1 May- Sep). More admission on thunderstorm days (p=0.04). No relation ship between rainfall and admission.
North America									
Los Angeles, USA	Delamater et al., 2012	250,000	YES	YES				Max temperature relative humidity	Hospital admission increase in winter, 0.481 per 100,000 admission
New York, USA	Fitzgerald et al., 2014	237,639	YES			YES		Cold spell= 3 days that daily mean temp was less than the 10th percentile for a given month and region.	Hospital admission increased November (mean = 9.6, 95 % CI 5.5, 13.9 %) and April (mean = 5.0, 95 % CI 1.2, 9.0 %)
Maryland, USA	Soneja et al., 2016	115,923	YES				YES	Daily max temperature, Total daily precipitation	Extreme heat increases hospital admission by 3 % (Odds Ratio (OR): 1.03, 95 % Confidence Interval (CI): 1.00, 1.07)

South Asia										
Bangolare , India	Kunikullaya et al., 2017	1768	YES	YES				YES	Max/min/average temp, relative humidity Total daily rainfall	Average daily asthma admission is 4.84 ± 2.91 and has seasonal variation. Increased in cold season. *P=0.015*
Middle East										
Kuwait	Qasem et al., 2008	4353	YES	YES			YES	YES	Daily temperature, relative humidity Total daily rainfall	Hospitalization increased during December due to high temperature (39.7) (P<0.03)
East Asia										
Shanghai, China	Zhang et al.,2014	15,678	YES	YES			YES	YES	Min/max and mean temperature, relative humidity, total daily rainfall	RR: 1.20 (95% confidence interval [CI], 1.01,1.41) in lower temperature
Hong Kong	Lam et al., 2016	56 112	YES	YES			YES		Daily mean temperature and mean relative humidity	Cumulative risk of hospitalization in hot season 1.19 (95% CI 1.06 to 1.34). in cold season, temperature negatively associated.

2.7. Discussion

Our review suggests that temperature variation can have both a positive or negative correlation with asthma HAs, depending on the season and geographic area. The temperature measurement and the threshold for temperature vary from one study to another. Moreover, temperature itself could be influenced by other variables (e.g., wind speed, barometric pressure) which were not taken into account by many studies. Aside from temperature, other weather variables including relative humidity and precipitation [14,136, 137], wind speed [16], and thunderstorms [24] could influence asthmatic patients' condition and the number of HAs.

This study suggests that changes in weather variables could increase EDVs due to asthma. Temperature variation was the most frequently studied factor among the included studies. Thunderstorms [16], rainfall events [15, 2], low temperatures [6, 138], increase in humidity [19] and fungal spores [139] were other variables that could increase EDVs among patients living with this chronic condition. Kwon et al. described a negative relationship between the incidence of fog and EDVs [14]. It is important to note that the definition of weather variables and EDVs have not been consistent across all studies.

Our review has some limitations. First, many studies included in this review did not adjust for the effect of air pollution and pollens where the effect of weather variables was assessed. Air pollution and pollens are known risk factors for asthma exacerbation [21]. A review by D'Amoto et al recommends that changes in weather factors could influence the rate of asthma attacks depending on the intensity and length of the pollen season. Another study by same author reported asthma exacerbations due to the increased pollen in the air during thunderstorms [140].

Other studies indicated a significant increase in the number of patients with bronchial asthma visiting an emergency clinic during December due to fungal spores [20]. A systematic review by

Zheng et al. identified associations between several air pollutants and EDVs due to asthma. This study also showed that weather factors such as wind speed and direction play a key role in air pollution [141].

Only peer-reviewed articles published in English were included, making it possible that we missed studies published in other languages or in the grey literature.

Although there were no limitations to our study design or data collection methods, the studies included in this review are mainly observational studies (time series and case-crossover studies) using secondary data where the data quality is a concern [23, 142].

To our knowledge, this is the first systematic review assessing the effects of meteorological factors on asthma hospitalizations. We identified only 16 studies, 6.25% (1/16) with poor quality, suggesting a lack of available evidence. Estimating a summary effect of meteorological factors on asthma hospitalizations among adults was not possible due to heterogeneity across the studies.

2.8. Conclusion

Information on how particular weather events, such as extreme wind or cold, could affect asthma HAs is essential to predict hospital demands and to help prevent exacerbation among patients with asthma and its consequent HA. Our review shows asthma HAs and EDVs in adults are associated with temperature variability. It also identifies weather variables including relative humidity, rainfall, and wind as factors influencing EDVs and hospitalization among patients living with asthma. Our study suggests the possibility of a gap in the knowledge regarding the effect of barometric pressure, weather phenomena, and tornados. Due to inconsistencies of the methodological approaches and the differences in statistical analyses in the included articles, we were not able to generate a practical policy recommendation. Methodological limitations of the studies and inconsistencies in the study findings show great potential for future research.

2.9.Updated systematic literature search:

Using the same search strategy and the review protocol, we updated the literature search for our systematic review between December 31, 2018 and to October 31, 2020.

2.9.1. Result

There were 678 articles identified, a total of 497 articles after deduplication. At the first stage, by screening the title and abstract, 476 studies were irrelevant (Figure 1).

At the second stage, we screened 21 full-text to assess the eligibility and 17 studies were removed from database, 82% of those had irrelevant outcome, three studies the full text were not available, four studies did not investigate any meteorological factors as exposure, and one study was conducted on pediatric population. Three studies were included in the review covering 696, 236 observations. Table 5 shows characteristics of the included studies. All included studies used secondary data. As it was shown in Table 6, the temperature and relative humidity were defined as main exposure for asthma hospitalization or ED visits. One study investigated the effect of thunderstorm as a possible exposure on asthma hospitalization.

2.9.2. Conclusion

The finding from updated literature search is consistence with our systematic review, and the new studies did not add any new information to our review. The review shows asthma HAs and EDVs in adult are associated with temperature variability. There was inconsistency in exposure measurement and statistical analysis; therefore, we could not generate a policy recommendation. There is great potential for future studies to focus on defining standard exposure definition and a model that applicable to various geographic locations.

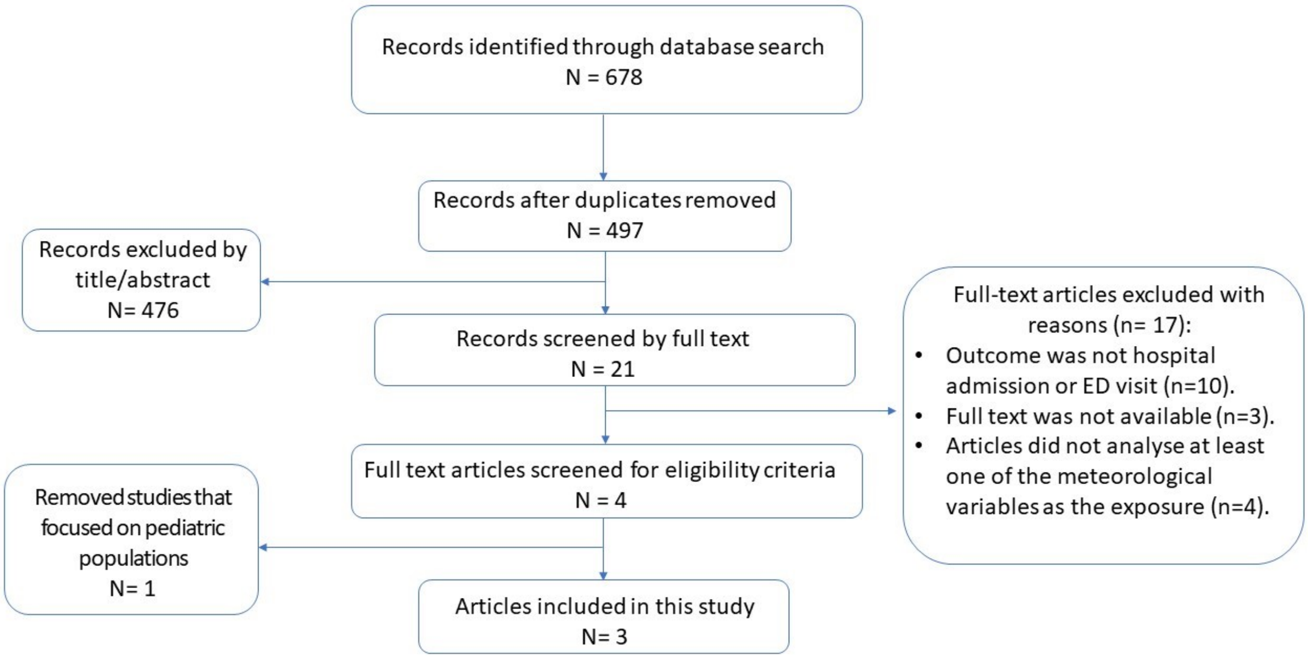

Figure 4: Preferred Repotting items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Table 6: characterizes of studies that examine the effect of meteorological factors on asthma admission and emergency visit.

			Data source		Measures of effect		Study Outcome		
Country	Objective	Study design	Health data	Climate data	OR	RR	ED*	H. A**	Quality
Bannister et al.,2020	Investigate the associated between weather events with epidemic thunderstorm of asthma	Case-control	Victorian Emergency minimum dataset	Australian Bureau of Meteorology	X		X		Good
Wang et al., 2020	Association between diurnal temperature range and hospital admission for chronic respiratory diseases	Time-series	Electronic medical record system of Guangdong Government Affairs Service Center	National Meteorological Information Center of China		X		X	Good
Yu et al., 2008	Associations between metrological factors and asthma exacerbation, emergency room visits	Case-crossover	Taiwan National Health Insurance Research Database	Environmental Protection Agency monitoring stations	X		X		Fair

Table 7: Effect of Meteorological factors on Emergency department (ED)/Hospital admission.

Effect of meteorological factors on Emergency department (ED) /Hospital admission										
			Meteorological Risk factors							
Location	Author	Sample size	Temp	Relative humidity	Thunderstorm	Fog	Wind speed	Rainfall	Key measures	Results
Melbourne, Australia	Bannister et al., 2020	237			YES				Epidemic of hospital admission for asthma with respect to convergence line weather	OR increased from 1 km to 4km within the 48-hr exposure period. 166.3 [95% Cl= 26.8-6707.9]
Taiwan	Yu et al., 2020	25,167	YES	YES				YES	Daily average temperature and total daily rainfall	Each 1 °C increase in temperature was associated with an OR = 0.984 (95% CI 0.970–0.998) and 0.986 (95% CI, 0.973–0.999) for male and female
China	Wang et al., 2020	670,832	YES	YES					DTR = subtracting daily minimum temperature from daily maximum temperature	With increase in DTR, relative risk hospital admission for asthma is higher in hot season 1.09 (95%CI: 1.05 to 1.13)

Chapter 3: Effect of changes in daily minimum temperature on hospital admission among adult patients with asthma, St. John's, Canada, 1996-2013.

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3.1. Abstract

Prior studies suggest that changes in weather temperature affect asthma hospitalizations. However, there is limited evidence regarding how much change is required, and how long the effect remains and continues to influence HAs. In this study, we examined the association between observed daily minimum temperature (DMT) and its delayed effect up to 15 days (lag effect) on the number of daily hospital admissions among asthma patients.

We performed time-series analysis using a Distributed Lag Non-linear Model (DLNM) in order to determine the effect of DMT on the number of HAs of patients with asthma on several subsequent days (lag effect), while controlling for wind speed and precipitation. Potential confounders such as long-term trends, days of the week, holidays and seasonality were controlled by using natural cubic splines. We employed data on HAs and meteorological variables from 1996 to 2013 inclusively, with the study population being patients with asthma living in St. John's, Canada, during this time period.

A total of 44,897 hospital admissions for patients with asthma were recorded. The findings from DLNM indicates that the daily minimum temperatures lower than -4°C was significantly associated with an increased daily number of HAs on the same day (RR=1.10; 95% CI: 1.01-1.19) and one day after (RR= 1.03; 95% CI: 1.01-1.05). In addition, our study showed that an increased daily hospital admission for asthma is associated with a daily minimum temperature that exceeds 14°C on the same day (RR= 1.15; 95% Cl: 1.05, 1.25), as well as one day after (RR= 1.06; 95% CL: 1.03-1.09). No effects were found for lags of 2 days up to 15 days. The results show a higher rate of hospital admission among patients with asthma when DMT declines below the 25^{th} percentile or exceeds the 95^{th} percentile of daily minimum temperature distribution. This study forms a basis for predicting potential changes in healthcare demand, based on forecasted weather.

Keywords: asthma hospitalization, weather condition, asthma epidemiology, environmental epidemiology, daily minimum temperature, Distributed Lag Non-linear Model

3.2. Introduction:

Asthma is a chronic inflammatory condition characterized by a reversible airflow obstruction [1], often presenting as wheezing, breathlessness, coughing and chest tightness. According to the

World Health Organization (WHO), over 334 million people worldwide have asthma, and an estimated 100 million people will join this population by 2025 [143]. Many factors affect asthmatic's condition, from genetics to lifestyle to environmental factors [144] such as weather.

The weather plays a critical role in exacerbating asthma symptoms, which can result in hospitalization [2,145], and prior studies have identified associations between several various meteorological factors and the number of asthma HAs [4, 102]. For example, extreme cold and heat conditions are strongly correlated with asthma attacks leading to hospital admission in adults [146, 145]. Although it is known that sudden changes in weather temperature can affect asthma and increase the likelihood of hospitalization [147], the magnitude of this effect on asthmatic's HAs varies by geographic location, study populations and climate characteristics [148]. Therefore, high temperatures associated with an increased number of HAs in one location may not be generalizable to another location. To our knowledge, there is no unique approach that incorporates frequency and intensity to define the weather temperature threshold across geographic locations. Thus, it is quite necessary for different regions to conduct locally-based environmental epidemiology studies when assessing temperature-related hospitalizations.

The effect of weather temperature on the number of daily HAs is not limited to the time that exposure occurs; its impact can be delayed. Although the literature indicates that temperature has a delayed effect on hospital admission for asthma [149], the latency between temperature change and asthma exacerbation is unclear. It is also unclear whether there is an association between the magnitude of the temperature and time to asthma exacerbation and hospital admission.

In this study, we used distributed non-linear lag models to investigate the number of HAs for asthma in response to different minimum temperatures and lag in St. John's, Canada. St. John's is the most eastern city in the country, at latitude 47.5615° N and longitude 52.7126° W. This city is the capital of and the most populous jurisdiction in NL, Canada. Due to its geographical location, St. John's is subject to marine climate where the weather is prone to sudden change, leading to unpredictable increases and decreases in temperature.

To our knowledge, this is the first study in St. John's evaluating the association between temperature fluctuations and the number of HAs among patients with asthma, despite the high prevalence of the disease in this region [150]. Asthma prevalence was reported as 6.3% in St. John's among adults in 2017 and 2018 [151]. Thus, we performed our study to identify the effect of DMT and its delayed effect on the daily number of HAs among patients with asthma in St. John's, from 1996 to 2013 inclusively.

3.3. Materials & Methods

3.3.1. Data Collection

We conducted analysis using secondary (medico-administrative) data. The study population comprised residents of the St. John's metropolitan area. We confirmed that patients were residents of St. John's by geo-referencing six-digit postal codes according to the Canadian standard from 2016 Census geographic areas [112]. Since the age of majority in NL is 19 years and older and only data for 19 years and older were available for this study, the study population are adults aged 19 years and older who were diagnosed with asthma after 1996.. The cases are identified according to the Canadian Chronic Disease Surveillance System (CCDSS) case definition for medico-administrative databases [152]. A patient was considered to have asthma if there were two physician claims for an asthma diagnosis within two years apart or one hospitalization claim, based on the International Classification of Diseases 9th edition (ICD-9): 493, and 10th edition (ICD-10): J45, J46 (sensitivity of 83.6%; 95% CI: 77.10–89.10) and specificity of 76.5% (95% CI: 71.80–80.80) [153]. Sensitivity is measure the extent of recording the presence of asthma in administrative data when these were present in the chart review data. The algorithm able to identify patients with asthma from patients with other health conditions. Meanwhile specificity is using to determine the extent of reporting absence of asthma condition in the administrative data when asthma were absent in the charts [154].

Canada has universal health insurance, and similar to other provinces, any publicly funded healthcare services used by NL residents are recorded in the medico-administrative data. For this study, we used a de-identified database developed by the NLCHI, which links the Canadian Chronic Disease Surveillance System (CCDSS), Provincial Discharge Abstract Database (PDAD), and NLCHI Mortality System. Patient data used in this study included sex, age, and postal code, as well as date of hospitalization. Data only provide us the overall hospitalization among patients with asthma and not necessary for asthma treatment or other cause of hospitalization.

We obtained the meteorological variables used for this study from Environment and Climate Change Canada. This weather data was collected by weather stations and is publicly available on the department's website. We obtained the daily minimum, maximum, and mean temperatures (°C), total daily precipitation (mm) and daily mean wind speed (km/hr.) during the same period using hourly records from a weather station located at St. John's International Airport. Environment Canada has twelve main weather stations in NL; among these stations, St. John's International Airport (YYT) is nearest to St. John's, and was selected for this study to represent St. John's metropolitan area weather.

Since St. John's has cold climate conditions, we defined the main exposure in this study as DMT. To identify how unusual a specific weather temperature magnitude was, 1st percentiles: -

14°C, 25th percentiles: -4°C, 50th percentiles: 4°C, and 95th percentiles: 14°C of DMT relative to the median temperature used to determine the risk of asthma hospital admission [101].

A daily count of HAs for patients with asthma between January 1, 1996, and December 31, 2013, was obtained from medico-administrative data and linked to meteorological data. We introduced the delayed effects of DMT on hospital admissions as lags. For this study, we measured the lags on the same day (lag 0), one day after (lag 1), five days after (lag 5), and up to 15 days after (lag 15) [155]. This 15-day lag effect was selected based on a previous study showing that the effect of hot and cold temperatures cannot persist after 12 days of lag in patients with asthma that could affect the number of HAs per day [174].

3.3.2. Statistical Methods:

We assessed the correlation between daily asthma HAs and weather variables, including daily minimum temperature, daily maximum temperature, daily mean temperature, wind speed and precipitation, by performing Pearson correlations. We performed time-series analysis using a DLNM to determine the effect of DMT on the number of HAs of patients with asthma on several subsequent days (lag effect), while controlling for wind speed and precipitation. Poisson regression was used to fit the model. To control for seasonal patterns and long-term trends in hospitalization, we used a natural cubic spline function. We also included day-of-week (DOW) and public holidays in the model as covariates. Since we did not have data on the cause of hospital admission we tested the model with other chronic diseases including diabetes, hypertension, and Chronic Obstructive Pulmonary Disease (COPD), to ensure the pattern is specific to patients with asthma.

We performed all statistical analyses by applying the DLNM package in the R statistical environment (version 3.0.1) [156]. This package allows for the simultaneous estimation of different non-linear functions of the associations regarding minimum temperature at each lag period, and also allows for the estimation of non-linear effects across lags [157]. This methodology was developed based on the definition of a ‘‘cross-basis’’ function, a bi-dimensional space of functions specifying the possible non-linear association between minimum temperature and asthma HAs across lag periods. The cross-basis functions are combined from the basic functions for the two dimensions (magnitude temperature and lag), chosen among a set of possible bases [6, 12, 13].

We selected the non-linear cubic splines for the daily minimum temperature effect and up to 15 days lag in the DLNM model for this study [101]. This initial model was set up with natural cubic splines, with 6 degrees of freedom (df) in the lag space and a cubic b-spline with 6 df (three equally spaced knots) in the temperature space [146]. The sensitivity of the model was tested with b-spline having four knots chosen from percentile of DMT distribution (6 df total) in all asthma hospitalization records during the study period [157].

3.4. Results

There was a total of 44,897 hospital admissions for asthma patients (68% female and 33% men) and mean age 48 years (SD= 6.8) old from January 1, 1996, to December 31, 2013 (n= 6,205 days), with an average of eight admissions per day (SD= 4.0). DMT fluctuated between -20°C (minimum) and 20°C (maximum) with a median of 3.98°C during the study period.

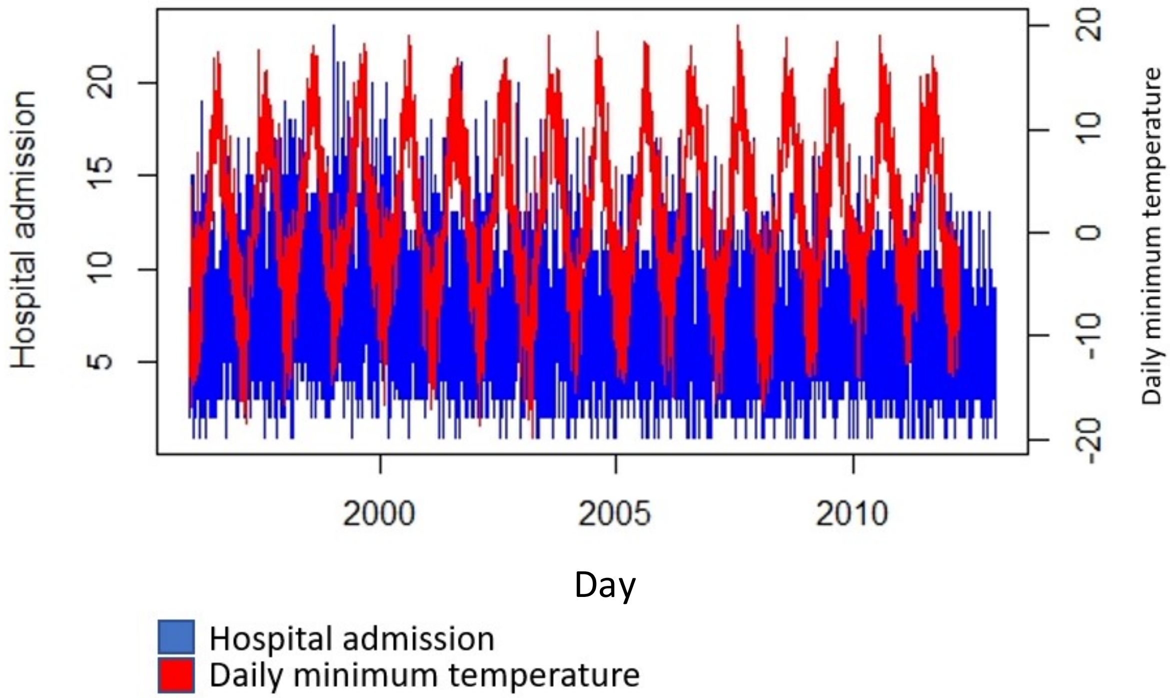

Figure 5: Daily Minimum Temperature & Daily Asthma Hospital Admissions, St. John's, Newfoundland & Labrador, 1996-2013.

Table 8 shows the results of Pearson correlation analyses. Daily asthma hospital admission negatively correlated with daily minimum, maximum and mean temperatures (r=-0.095, r=-0.085, r=-0.092), and positively correlated with precipitation (r=0.020) and wind speed(r=0.53).

Table 8 : Pearson correlations between HAs among patients with asthma & weather variables.

	Hospital Admission	
	Pearson Correlation	95% Confidence Interval
Daily Minimum Temperature	-0.095	-0.12, -0.07
Daily Maximum Temperature	-0.085	-0.11, -0.06
Daily Mean Temperature	-0.092	-0.11, -0.07
Total Precipitation	0.020	-0.004, 0.046
Wind Speed	0.053	0.028, 0.077

Asthma-related hospital admission and DMT over time are illustrated in Figure 5. This figure shows that daily asthma-related HAs fluctuate over the year, between zero and 23 admissions per day. In the same period, the DMT varied between -20°C and 20°C. The number of HAs increased when the minimum temperature was lower.

The three-dimensional plot of daily asthma hospital admission and daily minimum temperature has shown in Figure 6. The figure shows the cold effect starting at about -4 °C between lag 0 and lag 5 days and temperatures over 14°C affects hospital admission at lag 0.

Hospital admission frequency varied seasonally, peaking in the cold seasons (December to May).

Predicted effects along with each temperature (-14°C, -4°C, 4°C, 14°C and 16°C) and predicted lag-specific effects (0, 1, 2, 5, 15) for each temperature are shown in Figure 7. The left side of

Figure 7 displays the changes in relative risk (RR) of daily number of hospital admission at selected lags. At lag 0 and lag 1, the cold temperature below -4°C and warm temperature above 14°C potentially increase RR in hospital admissions (see Table 9). The right side of the same graph indicates the DMT effect at different lags. At daily minimum temperature 4°C, the relative risk of HAs decrease at lag 0 and lag 1.

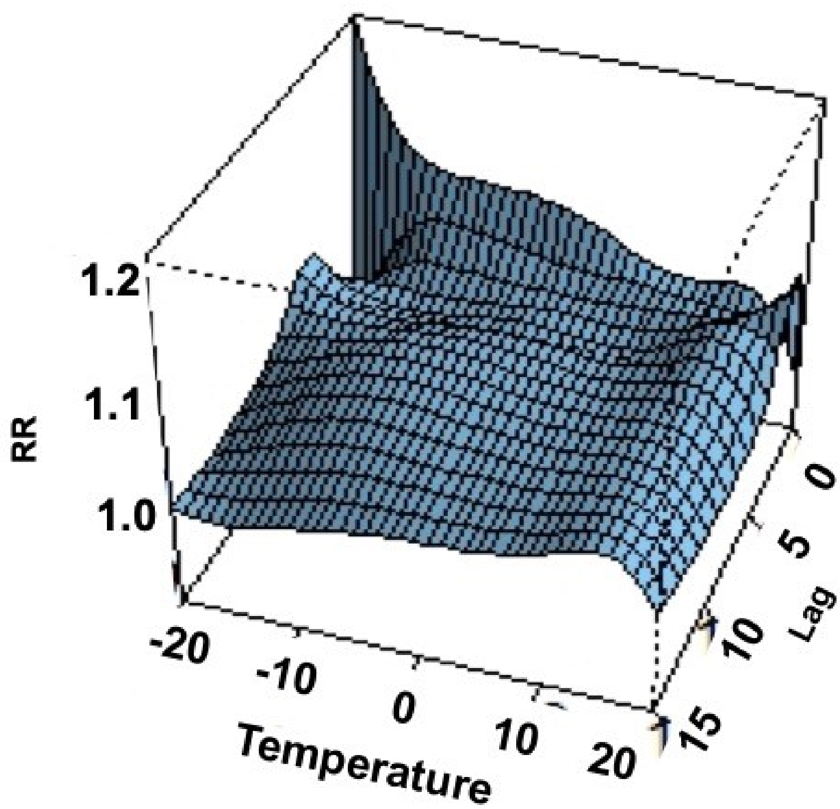

Figure 6: The relative risk (RR) of asthma hospitalizations and daily minimum temperature by lag period, from a DLNM model, adjusted for wind speed, precipitation, day of the week, and time trends in St. John's, NL, 1996-2013.

Table 9 shows daily asthma HAs by DMT day-wise percentiles between 0 and 15 days after changes in DMT controlling for wind speed, precipitation, time trend, and day of the week. As it was shown in this table, the risk of hospital admissions increased on the same day and/or the day after when the minimum temperature declined below -4°C (25th percentile) and/or exceeded 14°C (95th percentile) as compared to other temperature cut points. For example, the relative risk of asthma hospital admissions associated with the 25th percentile of temperature relative to the median temperature was 1.10 (RR =1.10; 95% CI: 1.01-1.19) at lag 0. The effect of DMT on hospital admission was no longer significant two days after a change in DMT.

We did not find any significant association between weather temperature and daily hospital admission when DMT varied within -4°C and 14°C. The analysis didn't show any multi-collinearity within independent variables based on VIF (Variance Inflation Factor) in the model.

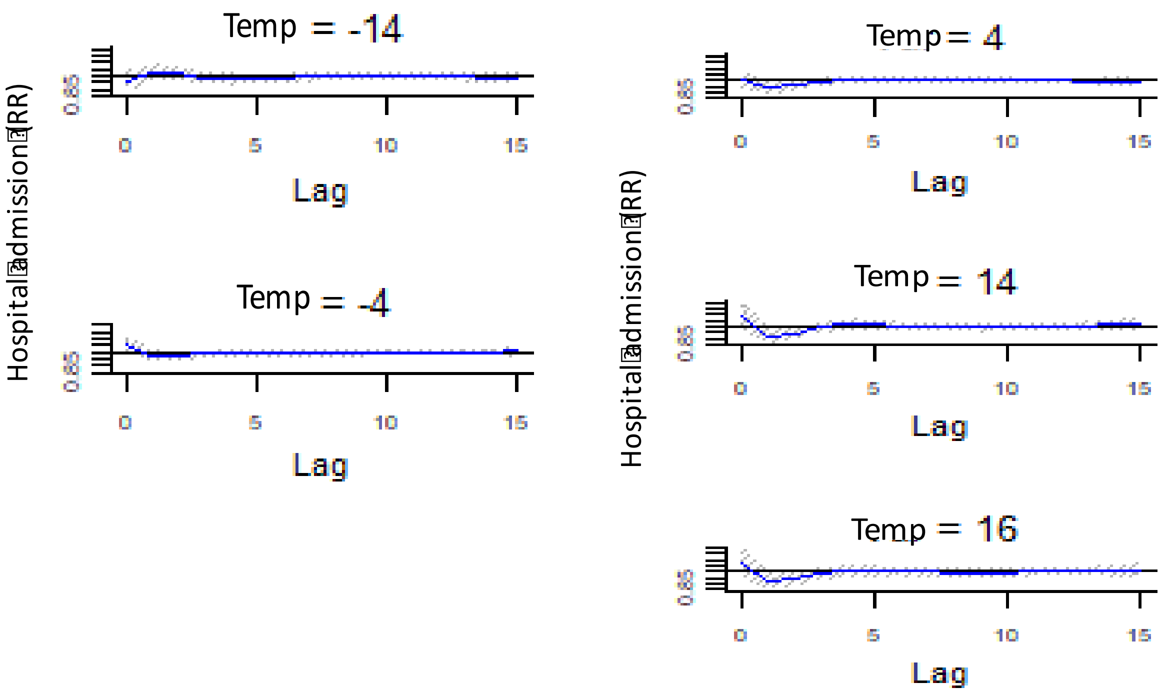

Figure 7: Effect of daily minimum temperature (1st percentiles: -14°C, 25th percentiles: -4°C, 50th percentiles: 4°C, 95th percentiles: 14°C, and 99th percentiles: 16°C) for specific lag (0, 1, 5, 10, 15) with a 95% confidence interval.

Table 9: Relative Risk (RR) of daily hospitalization among patients with asthma associate with selected Daily Minimum Temperature (DMT) cut points and lag period in St John's Canada, 1996-2013.

Lag period	1st Percentile		25th Percentile		95th Percentile		99th Percentile	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
0	1.30	1.27-1.33	1.10	1.01-1.19	1.15	1.05- 1.25	1.13	1.09-1.15
1	1.10	1.04-1.16	1.03	1.01-1.05	1.06	1.03- 1.09	1.08	1.04-1.12
2-5	0.98	0.87-1.03	0.95	0.88-1.10	0.97	0.93- 1.10	0.89	0.86-1.01
6-9	0.99	0.91-1.05	0.98	0.89-1.01	0.94	0.86- 1.09	0.91	0.87-1.03
10-15	0.97	0.85-1.01	0.99	0.92-1.02	0.96	0.89- 1.08	0.94	0.89-1.02

1st percentiles: -14°C, 25th percentiles: -4°C, 50th percentiles: 4°C, and 95th percentiles: 14°C
Median temperature (4°C) is the comparative temperature .The model adjusted for precipitation, daily wind speed, seasonal trends, and day of the week.

3.5. Discussion:

Among 44,897 hospital admissions for patients with asthma that were recorded for the current study, we found an association between DMT and hospital admissions. We also found a significant relationship between the number of daily hospital admissions of patients with asthma and DMT. Daily asthma hospital admissions varied over the study period. The daily minimum temperature effect increased below the 25^{th} percentile and above the 95^{th} percentile of daily minimum temperature distribution. The risk of HAs increased on the same day and/or the day after when the minimum temperature declined below -4°C (25th percentile) and/or exceeded 14°C (95th percentile) as compared to other temperature cut points.

This finding is consistent with the literature. One study by Lam et al. indicated an increase in the risk of asthma hospitalization associated with an increase in temperature within lag 0 and 3 [136]. In Brisbane, a study by Xu et al. found that daily temperature variation was associated with an increase in asthma hospitalization at lag 0-9 days [155]. Meanwhile, Zhang et al. identified a 48% increase in asthma hospitalizations within the 25th percentile of temperature relative to the median temperature at lag 0 [101]. This study also determined that the risk of HAs for asthma increases with low mean temperature. Both low and high temperatures can affect lung function in individuals with chronic respiratory diseases such as asthma, compounded by inflammatory factors and mucus [101, 101].

We also observed that DMT didn't have extended effects on HAs among patients with asthma. The results indicate that DMT could affect admissions on the same day and/or the day after the temperature range. This result was not consistent with other studies; a study in China has reported that hot temperatures had short-term effects, and cold temperature effects lasted for 10-

12 days [155]. However, the association between temperature and asthma hospital admissions is expected to vary by geographic location, since it depends on many other asthma risk factors such as genetic and lifestyle [101].

This study has some limitations. Firstly, because we used secondary medico-administrative data for the analysis, we could not identify the primary diagnosis at the time of admission. Therefore, the cause of a hospital admission may have been misclassified, and the effect of DMT may not be specific to asthma exacerbation. To address this issue, we tested the model with other chronic diseases including diabetes, hypertension, and Chronic Obstructive Pulmonary Disease (COPD). There were no associations between DMT and hospital admissions for diabetes or hypertension. While we found an association for COPD, the pattern was different from asthma. Data showed higher admission rate in winter followed by autumn in general for patients with COPD and number of admission per day did not fluctuated by temperature.

Some studies consider Canadian case definition for asthma an appropriate algorithm to identify cases of asthma for population-based studies using medico-administrative data given the sensitivity of 83.8% % (95% CI 77.1% to 89.1%), specificity of 76.5% (95% CI 71.8% to 80.8%), PPV of 61.5% (95% CI 55.5-67.5), and NPV of 91.3% (95% CI 84.8- 97.8). Sensitivity was used to measure the extent of recording the presence of asthma in administrative data when these were present in the chart review data. The algorithm able to identify patients with asthma from patients with other health conditions. Meanwhile specificity was used to determine the extent of reporting absence of asthma condition in the administrative data when asthma were absent in the charts [158].

Some studies consider Canadian case definition for asthma an appropriate algorithm to identify cases of asthma for population-based studies using medico-administrative data given the

sensitivity of 83.8% % (95% CI 77.1% to 89.1%), specificity of 76.5% (95% CI 71.8% to 80.8%), PPV of 61.5% (95% CI 55.5-67.5), and NPV of 91.3% (95% CI 84.8- 97.8). However, one may question the possibility of misclassification of asthma due to imperfect sensitivity and specificity.

To examine whether misclassification of asthma case definition bias the findings, we repeated the analyses using three other chronic diseases derived from the same database. Our analyses support that the study findings are specific to adults with asthma.

Previous studies also suggested to carry out sensitivity analyses using another validated medico-administrative case definition of asthma, or a primary study of patients living with asthma. Unfortunately, we did not have other databases available to examine the impact of the asthma case definition on the study findings. We hope this study leads to more discussion around how to improve the quality of medico-administrative data. This will eventually strengthen the reputation of these databases and improve the reliability and validity of medico-administrative data for future research and decision-making."

Secondly, I used weather variables from only one weather station to represent conditions across the St. John's metropolitan area and surroundings. However, weather conditions may have varied around the city's census metropolitan area due to topography [62,159]. We could not control for other meteorological factors such as humidity and barometric pressure in the model, due to lack of data availability [160].

There is no unique approach to categorizing extreme weather temperature and identifying weather thresholds in environmental epidemiology [161]. A study calculated temperature deviation index as exposure, in order to identify associations between health exposure and mortality [162]; however, this is not the best approach, since calculated exposure based on several meteorological variables and it is not specific to temperature. Another study defined diurnal minimum temperature as exposure, in order to examine the effect of temperature on childhood asthma [163], which potentially eliminate the effect of extreme temperature on HAs. In this study, choosing the percentile relative to DMT as the main exposure allowed us to capture outliers for climate conditions in St. John's. The exposure is not dependent on other factors in this model [164]. The percentile relative to DMT is merely based on the weather temperature.

Thirdly, small observed correlation suggests the possibility of nonlinear associations or other factors influencing associations between weather variables and hospital admission among patients with asthma. The distributed lag regression model used in this study is a nonlinear and very complex model. It includes many parameters. Its smooth function removes seasonal residual effects and control for time trends. However, due to a lack of available data, we could not control the effect of other asthma risk factors such as viral infection, genetics, and individual risk factors. Although previous studies have investigated the effect of these risk factors on HAs for asthma [165], future studies should consider this limitation. One may suspect the possibility of ecological fallacy, since the weather data were not collected on an individual level, and the study's outcome determined the number of hospitalizations per day. For this study, we assessed the association on group level. As indicated before, the unit of analysis in this study is day, and group level is refer to number of hospital admission per day. The association between HAs and weather temperatures was found to be statistically significant on group level. The study finding is helpful to generate a hypothesis and set the stage for future study. However, it may not enough to confirm the causality.

To our knowledge, no previous study in NL has examined the effect of DMT on adult asthma HAs. Using nearly two decades' worth of data, our study shows there is a higher risk of daily hospital admission when DMT declines below the 25th percentile or exceeds the 95th percentile of DMT distribution. The effect of changes in DMT due to extreme weather could remain or be delayed by up to one day. Our methodology is applicable to other areas; however, studies using local data are required to define the threshold and lag in each geographic location, given variations in climate conditions.

The magnitude of DMT and its delayed effect on HAs for patients with asthma may help healthcare providers and policymakers predict asthma-related hospitalization demand. Moreover, our findings provide beneficial information for patients with asthma, suggesting they should remain aware of changes in the weather and its effect on their condition, limiting outdoor activity when necessary to avoid an asthma attack.

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Chapter 4: Does extreme weather temperature warn of hospital admission epidemics among patients living with asthma?

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4.1. Abstract

The aim of this study is to determine the effects of extreme temperature on epidemics of hospital admission for adults with asthma in the metropolitan area of St. John's, NL, Canada. We used a secondary data analysis, and two approaches to determine the effect of extreme temperature on epidemics of hospitalization among adult asthmatic patients. First, we conducted a nested case-control study to examine the association between extreme temperature and the occurrence of epidemic days. We defined epidemic days as days where the observed number of hospital admissions exceeded four standard deviation of the frequency of distribution daily counts of hospital admissions, and the controls as days within one standard deviation of daily hospital admissions. Then, we performed a case-crossover study where study subjects were selected from patients who were admitted to the hospital during epidemic days. These patients served as their own controls. A conditional logistic regression was performed.

A total of 49665 adults with asthma (68% female, 33% male) from 1996 and 2013 were identified. During the study period there were 6009 epidemic days and 34224 control days. The mean ± standard deviation of hospitalizations on epidemic days was 13.0 ± 1.75, and 7.0 ± 2.08

for control days. The logistic regression found a higher odd of epidemic days when the minimum daily temperature exceeds 14.0°C (Odds Ratio (OR) = 4.00; 95% Confidence Interval (CI): 2.92-5.87) and declines below -4.0°C (OR= 1.43; 95% CI: 1.03-2.03), respectively. These associations were consistent when we applied a case-crossover study.

We found that the number of hospitalizations per day increased among patients with asthma when minimum temperature declines below -4.0°C or rises above 14.0°C. Our findings highlight the potential for developing forecasting models, which could allow the healthcare system anticipate and prepare for increased asthma-related demand due to weather changes.

Keywords: Asthma epidemiology, hospitalization, weather condition, environmental health, minimum temperature.

4.2. Introduction

Asthma is a chronic respiratory disease that effects airways and lungs. Asthma causes symptoms like shortness of breath, chest tightness, coughing and wheezing [166]. According to the World Health Organization, asthma affects more than 339 million people worldwide [167]. Those living with asthma often complain about environmental conditions, especially the weather, as a factor which exacerbates their asthmatic episodes and may lead to hospitalization [168]. Many studies have reported an association between meteorological variables and asthma hospital admission or emergency room visits [169, 101, 132]. The literature also demonstrates that temperature variations [138], cold temperatures [42], warm and humid weather [170] wind speed [171], fog and precipitation [119] can affect hospital admission among individuals with asthma through a variety of potential mechanisms. Asthma is a heterogeneous disease, and it can be affected by weather variables with different proposed pathogenic mechanism. For example temperature changes may cause airway obstructions [22] by increasing the levels of serum total-IgE (immunoglobulin E) and IgG1, inflammatory cells and cytokines [147] that lead to an asthma attack, whereas rising indoor and outdoor pollution may influence asthma by way of related mechanisms that increase the oxidant burden and inflammatory response, or their immune activities [172].

Asthma is one of the leading causes of hospitalization globally [173, 102]. Despite availability of better approaches for diagnosis, new medications, and guidelines for lifestyle interventions, hospitalization due to asthma has trended upward globally during the last century [174, 30]. However, this asthma hospital admission trend also appears to be evolving [148, 96], and there are significant differences in patterns between countries [175]. Variation in hospital admission for asthma among provinces has reported in Canada [176]. The annual asthma hospital admission rate per 100000 persons was reported to be 18.1 (95% Cl: 17.6- 18.6) for adults in Canada in 2017. The same study reported the asthma hospital admission rate as 27.5 (95% Cl: 22.8-33.0) in NL, and 12.3 (95% Cl: 9.9-15.0) in and Nova Scotia which is lowest rate in Canada [150].

Literature suggests that asthma exacerbation requiring hospital admission varies by month of the year and geographical location [2]. The variation in hospital admission among patients during a year has been the subject of many studies, [30,177] where a high frequency of hospital admission is defined as an epidemic day [119,178]. However, there is no one definition for an epidemic of asthma hospital admission; many studies have applied an expected number of hospitalizations per day among patients with asthma based on the prevalence of asthma in a population, and healthcare capacity [138]. According to this approach, an epidemic of asthma hospitalization is broadly defined as a day when the frequency of hospitalization exceeds the expected numbers [119].

Previous studies in Canada and Australia have reported a strong association between asthma hospitalization epidemics and thunderstorms [179,180181]. Others have reported asthma hospitalization epidemics among children and adults, suggesting a possible association between the highest frequency of hospitalization during September, when children return to school, and the spread of viral infections [62, 178,182].

Weather temperature is a common meteorological variable which is measured by all weather stations. Temperature fluctuates throughout the year, and these changes may influence seasonal asthma triggers (e.g., indoor and outdoor pollution, viral infections), potentially leading to asthma hospital admission epidemics [2]. As such, understanding the relationship between asthma hospitalization and temperature variation may be important to predicting patient volume and healthcare demands based on weather forecasts, allocating resources for disease management, and preparing infrastructure to respond to heightened demand.

This study assessed the effects of extreme temperature on hospitalization epidemic days for adults with asthma in the metropolitan area of St. John's. St. John's is the capital of Canada's most easterly province, NL. The city's weather is governed by a marine climate, with vast temperature variations and high winds. The temperature in St. John's can shift substantially in a single day, from freezing morning temperatures to double digit heat in the afternoon. To our knowledge, this is the first study in NL to assess the relationship between extreme temperatures and epidemics of hospital admission.

4.3. Method

4.3.1. Study Design

We used a secondary data analysis, harnessing data on hospitalizations and meteorology, and two approaches to examine the effect of extreme temperatures (warm/cold) on epidemics of hospitalization among patients living with asthma in the St. John's metropolitan area. First, we employed a nested case-control design to examine the association between the effect of extreme temperatures and epidemic days [150, 119]. Then, we performed a case-crossover study where the study subjects were limited to patients who were admitted to the hospital during epidemic days.

4.3.2. Study Setting

The study setting was the St. John's metropolitan area, located at the following geographic coordinates: 47.5615 °N, 52.7126 °W. Weather patterns are diverse, with a single day often featuring elements of multiple seasons experience four seasons in one day, yet seasonal variation in St. John's is small [183]. The temperature can decline to -4 °C or colder during the summer [184] which is short, while the winter season is long. Based on the 2016 Census, St. John's has a population of 205955 people. The land area of St. John's is 804.6 km^2 [185].

4.3.3. Hospitalization Data

We obtained hospitalization data from the NLCHI by linking the following databases: the Canadian Chronic Disease Surveillance System (CCDSS); Clinical Database Management System (CDMS); Medical Care Plan (MCP); and NLCHI Mortality System (MS). These data are not publicly available, and we were granted secondary use of data from NLCHI. The study population consisted of adults aged 19 years or older who were registered with the provincial

MCP, diagnosed with asthma between 1996 and 2013, and who resided in the St. John's metropolitan area. We confirmed that patients were residents of St. John's by geo-referencing six-digit postal codes according to the Canadian standard from 2016 Census geographic areas [113].

St. John's has two hospitals; this study included admission from both hospitals. A patient was considered to have asthma if there were two physician claims for an asthma diagnosis based on the International Classification of Diseases 9th edition (ICD-9): 493, and 10th edition (ICD-10): J45, J46 (sensitivity of 83.6%; 95% CI: 77.10–89.10) and specificity of 76.5% (95% CI: 71.80–80.80). We extracted data regarding hospital admission, age, sex, number of comorbidities (i.e., hypertension; chronic obstructive pulmonary disease; ischemic heart disease; acute myocardial infarction; heart failure and diabetes), and six-digit postal code for each patient. We defined co-morbidities for each case based on the CCDSS case definitions [62].

4.3.4. Meteorological Data

The weather data was obtained from the Environment and Climate Change Canada's St. John's International Airport station. This data is publicly available via the Environment Canada website. Environment Canada has twelve main weather stations in NL. Among these stations, St. John's international airport (YYT) is nearest to St. John's, and was selected for this study to represent St. John's metropolitan area weather. Similar to other Canadian weather stations, weather data is monitored hourly every day at this station. For this study, we extracted all available weather data from 1996 to 2013, inclusive, that was recorded at the YYT weather station. Only hourly measurements of minimum temperature (°C), maximum temperature (°C), mean temperature (°C), precipitation (mm), and wind speed (km/h) were available for this study.

4.3.5. Extreme Weather Temperature

Daily minimum temperature (DMT), or the lowest temperature recorded amongst hourly measurements per day, was considered as the main exposure. We used methodology suggested by Crighton et al and Singleton et al to identify the extreme weather temperature for our study area [178, 96]. For this study, DMT was divided into four cut-points (-4.0 °C>DMT; -4.0 °C≤ DMT <+4.0 °C; +4.0 °C≤ DMT <+14.0 °C and +14.0 °C ≥DMT). The extreme temperature was defined as a minimum daily temperature -4.0 °C>DMT for cold weather and +14.0 °C≥DMT for warm weather. Further details on these cut points are available in our previous work (Bodaghkhani et al., 2020). We also selected a lag period length based on a study by Lin et al. This study suggests a lag period of DMT variation within the 24 hours before the admission day [186].

4.3.6. Nested Case-Control Study

To identify the cases and controls in the analysis, I counted the frequency of hospital admissions per day among all patients with asthma during the study period. In this study, the cases are “epidemic days.” Epidemic days are days when the frequency of daily hospital admission is higher than the expected daily hospital admission. To identify epidemic days, we determined the frequency of hospital admissions per day. Following the methodology suggested by Marks et al., we considered the days where the observed number of admissions was greater than four standard deviation of the frequency of distribution of daily hospital admissions to be epidemic days [5, 119, 182]. Respectively, control days considered as those days where the number of observed attendances were within one standard deviation of the frequency of distribution of daily counts of hospital admission. Controls were selected throughout the year (different days, weeks, months, and season) and could be representative of days with different levels of pollen and dust. A total of 416 epidemic days and 4823 control days identified from 1996 and 2013, inclusive. Therefore, days that hospital admission were between four and one standard deviation are not included in the study.

4.3.7. Case-Crossover Study

To control for individual risk factors, we conducted a case-crossover study where each patient with asthma who was admitted to hospital on epidemic days served as their own control [187]. The individual risk factors may include genetic, different type of asthma, asthma severity, co-morbidities, smoking, and individual allergies. The case-crossover design is a type of case-control study. Case-crossover studies have been conducted elsewhere in the literature to examine the effect of environmental factors such as air pollution, pollen, and precipitation on asthma hospitalization [188]. In this study, we used the case-crossover design to assess the effect of extreme temperature on asthma hospital admission. The case was patient who admitted on epidemic days, while control sampling comprised one week before, and one week after the admission using bi-directional sampling. Thus, controlling for the effect of the day of the week and seasonality [189 , 119]. The study outcome was defined as hospital admission. We set the hazard period to capture the DMT as 24 hours before the admission day. Season is classified according to the astronomical season in the Northern hemisphere, whereby spring starts on March 21, summer starts on June 21, fall starts on September 22 and winter starts on December 22. We compared exposure to extreme weather during the case period and control period.

4.3.8. Statistical Analysis

Descriptive analyses were performed to describe the characteristics of the study population, hospitalization patterns, and meteorological variables. Bivariate analyses, including two sample independent t-tests and chi-square tests were conducted to assess the association between the epidemic of hospital admission and weather variables.

Logistic regression for case-control study applied. The distribution of data is binary. Stepwise selection was applied to build the final model. First, I ran the model with all independent variables (minimum temperature+ maximum temperature+ mean temperature+ wind speed+ precipitation+ season+ day of week+ NLholidays+ weekends).Based on p-value (at P< 0.2). We removed the variables where the P< 0.2. Continued to check the models and compare the AIC in order to achieve the minimum AIC. The model updated with only significant independent variables includes (minimum temperature+ season +Day of week+ precipitation+ wind speed). To check the model performance ROC curve generated, the area under the curve is index of accuracy (area under curve=auc=0.948). Then R^2 calculated (is a statistical measure of how close the data are to the fitted regression line).

For the case-cross over analysis, the daily minimum temperature at the time of hospital admission for each case (the case period) compared with the DMT one week before and one week after the health event (control period). Cases are included only those patients that admitted to the hospital on epidemic days. In order to control for long term trends, the controls selected based on bi-directional sampling, one week before and one week after the case.

Stepwise forward conditional logistic regression for case-cross over study performed to fit the model. First, the model ran with all independent variables (minimum temperature+ maximum temperature+ mean temperature+ wind speed+ precipitation+ season+ day of week+ NLholidays+ weekends). And the model updated with only significant independent variables includes (minimum temperature+ season +Day of week+ precipitation+ wind speed). An odds ratio with a 95% confidence interval was calculated [190 ,191, 192]. A p-value of <0.05 was considered for statistical significance. For the reference group, most normative category choose as a reference group [193]. To control for other variables, including precipitation, wind speed, season, weekdays, and weekends. The collinearity between variables has checked in the final model. All analyses were performed using the R software platform.

4.4. Results

The cohort consisted of a total of 49665 individuals identified with asthma in the St. John's metropolitan area (68% female and 33% men) between January 1st, 1996 and December 31st, 2013. Around 9.6% of records were removed due to a missing value. Table 7 presents the characteristics of 40233 patients hospitalized during the epidemic (n=6009) and control days (n=34224).

Table 10: Characteristics of asthma patients admitted to hospital during epidemic days and control days, St. John's metropolitan area, Canada, 1996-2013.

Characteristics of Hospitalized Patients n= 40233	Epidemic Days n=416	Control Days n=4823	P-Value (Chi-Square)
Sex: n (%)			Not Significant
Female	3993 (66%)	24120 (70%)	
Male	2016 (34%)	10104 (30%)	
Age Group: n (%)			<0.001
19-29	1086 (19%)	6596 (20%)	
30-49	1818 (30%)	9280 (27%)	
50-64	1562 (26%)	8994 (26%)	
65+	1543 (25%)	9354 (27%)	
Number of Comorbidities: n (%)			Not Significant
0	3286 (55%)	17502 (51%)	
1	1615 (26%)	8503 (24%)	
More than Two	1108.0 (19%)	8219.0 (25%)	
Total Patients	6009.0	34224.0	

During the 6205 days of study, the DMT varied between -20.0°C and 20.0°C with a median of 3.9°C. In the same period, the amount of precipitation varied between 0.0mm and 32.0mm a day, and daily wind speed fluctuated between 30.0km/hr. to 165.0 km/hr. Table 2 shows the weather characteristics on epidemic and control days. During the 416 epidemic days, DMT changed between -18.1°C and 18.7°C with a mean ± SD of 0.0 ± 6.9 °C. During the 4823 control days, the minimum temperature varied between -19.8 °C and 20.0 °C with a mean and standard deviation of 1.72 ± 7.64°C.

4.4.1. Hospitalization during the study period

The mean of daily hospital admission was 8.0 (95% CI: 6 - 10), median 7.0, and the range was 0.0-23.0. The number of hospital admissions varied seasonally, with the highest mean daily hospital admission in the winter; mean daily admission = 11.54 (95% CI: 8.17- 14.91). The highest number of hospital admissions were on Wednesdays; mean daily visits of 10.1 (95% CI: 7- 13.2) and the lowest number of admissions occurred on Sundays; mean daily visits 8.06 (95% CI: 5.66 - 11).

The mean number of hospitalizations among epidemic days was 13.0 (95% CI: 12.25-14.75), and the range was 12-23. Among 416 epidemic days, 145 events occurred on Wednesdays, 50 took place in February, and 116 were during the winter. During the control days, the mean number of hospital admissions was 7.0 (95% CI: 4.92- 9.08), with a minimum of 4 admissions and maximum of 11 admissions per day.

Table 11: Characteristics of daily weather in the St. John's metropolitan area on epidemic and control cays, 1996-2013.

Weather Variables	Epidemic Days	Control Days	P-Value *
Daily Minimum Temperature (°C)			
Minimum	-18.10	-19.80	
Mean ± SD	0.01 ± 6.96	1.72 ± 7.64	<0.001
Maximum	18.70	20.00	
Daily Maximum Temperature (°C)			
Minimum	-10.70	-13.70	
Mean ± SD	7.57 ± 8.28	9.46 ± 8.9	Not significant
Maximum	27.70	31.0	
Precipitation (mm)			
Minimum	0.0	0.0	
Mean ± SD	4.56 ± 9.65	4.19 ± 8.73	Not significant
Maximum	99.40	97.20	
Wind speed (km/hr.)			
Minimum	30.0	30.0	
Mean ± SD	48.85 ± 17.30	48.02± 16.97	Not significant
Maximum	122.0	145.0	

** The P value was derived using a two-sample t-test.*

4.4.2. DMT and occurrence of an epidemic of hospital admissions for asthma

The association between DMT and the occurrence of an epidemic of hospital admission for asthma is shown in Table 12. An epidemic of hospital admission is more likely when DMT exceeds 14.0°C or declines below -4.0°C on the same day and/or the following day. The Odds Ratios (OR) were reported as OR= 1.79 (95% CI: 1.08- 1.86) and OR= 5.81 (95% CI: 1.12-7.61), respectively. On the other hand, epidemic days are less likely when the minimum daily temperature is between +4.0°C and +14.0°C on the same day and/or the following day after this range (OR= 0.89; 95% Cl: 0.48-0.99).

To eliminate the effect of multiple hospitalizations (due to disease complications) on the frequency of hospitalization and its pattern, we excluded patients with asthma who had been hospitalized for one year before or after a particular epidemic day. However, the results did not reveal any differences.

Table 12: Association between DMT and occurrence of an epidemic of hospital admissions among adults with asthma, St. John's, 1996-2013, nested case-control design.

Independent Variable		N	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Daily Minimum Temperature	<-4.0 °C	1360	1.96* (1.65-2.01)	1.79* (1.08-1.86)
	-4.0 °C — +4.0 °C	8168	Reference Group	
	+4.0 °C — +14.0 °C	7837	1.42* (1.25-1.99)	0.89* (0.48-0.99)
	>14.0 °C	269	6.81** (2.12-8.52)	5.81** (1.12-7.61)
Season	Winter	11494	1.56 * (1.09-1.92)	1.40* (1.05-1.88)
	Spring	11840	1.68* (1.22-2.01)	1.42 * (1.10-1.85)
	Summer	10174	0.98 * (0.63-1.56)	0.68* (0.50-0.91)
	Fall	11485	Reference Group	
Day of week	Weekdays	4425	Reference Group	
	Weekends	1756	0.12* (0.10-0.25)	0.08** (0.04-0.16)
	NL Statutory Holidays	170	0.86 NS (0.42-2.36)	1.00 NS (0.14-2.87)
Precipitation	Yes	3315	0.96 NS (0.74-1.56)	1.00 NS (0.99-1.01)
	No	2583	Reference Group	
Wind Speed	>40.0 km/hr.	3485	0.86 NS (0.81-1.23)	0.99NS (0.98-1.00)
	<40.0 km/hr.	2292	Reference Group	

NS Not significant (P > 0.05), * P ≤ 0.05, ** P ≤ 0.001

4.4.3. DMT and asthma hospital admissions according to case and control period

Table 13 shows the results of the case-crossover analysis, which examined the association between DMT at four cut points, and admission to hospital. After controlling for wind speed and precipitation, extreme warm and cold temperatures are associated with hospital admission for asthma (OR= 1.33; 95% CI: 1.14-1.57 and OR= 1.12; 95% CI: 1.03- 1.23, respectively). In addition, patients with asthma have smaller odds to be hospitalized when DMT is between +4.0°C and +14.0°C (OR=0.72; 95% CI: 0.68-0.77).

Table 13: Results of case-crossover analyses comparing hospital admission on case period (epidemic days) and control period for adults with asthma, St. John's, 1996-2013.

	Case Period n=6009		Control Period n=12018		Odds Ratio (95% Cl)	P-Value
Daily Minimum Temperature	With Exposure	Without Exposure	With Exposure	Without Exposure		
<-4.0°C	1150	—	3544	—	1.12 (1.03-1.23)	0.02
-4.0°C — +4.0°C	—	1939	—	2852	Reference Group	
+4.0°C — +14.0°C	1262	—	4390	—	0.72 (0.68-0.77)	0.07
>14.0°C	1658	—	1232	—	1.33 (1.14-1.57)	<0.001
Wind Speed						
<40.0 km/hr.	1858	—	9700	—	0.10 (0.09-1.01)	0.30
>40.0 km/hr.	—	4151	—	2318	Reference Group	
Precipitation (mm)						
Yes	1947	—	1651		0.07 (0.06-0.08)	<0.001
No	—	4062	—	10360	Reference Group	
Odds ratios were adjusted for weekdays, weekend, precipitation, and wind speed.						

4.5. Discussion

Our study found an association between extreme weather temperature and asthma-related hospital admission. There is a higher odds of an epidemic of hospitalization occurring among these patients when the weather temperature declined below -4.0°C or exceeded +14.0°C. These findings suggest that, in the St. John's metropolitan area, an epidemic of hospital admission could be expected among patients with asthma during spring and winter weekdays when weather temperatures reach extreme limits. Our findings are consistent with previous studies that evaluated the relationship between asthma hospital admissions and warm and cold temperatures. One study in Hong Kong reported a similar association between temperature and asthma hospital admissions and indicated that the probability of an epidemic of hospitalization increased with warmer summer temperatures and colder winter temperatures [136].

Weather conditions, including extreme hot and cold temperatures, changes in humidity, and the wind, have been previously linked to asthma-related hospital admission [101, 102]. Low and high ambient temperatures are associated with asthma hospital admission and morbidity [194 ,195]. Lower minimum temperature has also been shown to have a positive association with adult asthma exacerbation that leads to hospital admission [93,196 104]. Patients with asthma may develop obstructions upon exposure to cold air, and airway cooling has been shown to speed inflammation and exacerbate the disease by narrowing airways [96].

This study has some limitations. First, we relied on medico-administrative data to identify individuals with asthma, and these data were not collected for the purpose of our research. Use of health administrative data in health research offers important advantages, however the accuracy and coherence of such data has been questioned in the literature and is often reported as a limitation [202]. Asthma can be classified into numerous endotypes and phenotypes [18], however, using secondary data does not allow us to discern between different asthma endotypes and clinical observations during the visit. However, we were able to control for these factors using the case-crossover design, given that each subject serves as their own control. Our study generates a hypothesis that temperature is a factor that causes epidemics for asthma hospital admissions. However, previous studies also suggest that temperature and accompanying air humidity are likely to affect the respiratory epithelium and induce hyperresponsiveness and narrowing of the respiratory airways. Cooling and drying of respiratory epithelium may induce chronic inflammation, which is likely to increase respiratory symptoms [197]. Unfortunately, we did not have the necessary information regarding individual symptoms to identify these relationships. Future studies may focus on individual symptoms by way of patient examination and laboratory testing.

Third, the publicly available meteorological variable did not include all weather variables, such as barometric pressure, fog, and snowstorms. Moreover, some variables, such as relative humidity, were incomplete for the duration of the entire study period. Many studies suggest temperature as the main weather variable [42, 170, 171]. Although extreme temperature may be a proper predictor of asthma hospitalization, further research is required to examine the association between other weather variables, including barometric pressure and humidity.

Temperature may affect many asthma risks factors, including viral infections, pollen, dust, and indoor and outdoor pollution. During cold conditions, individuals with asthma are likely to remain indoors, potentially accruing higher exposure to indoor, airborne particles [119]. Temperature also potentially effects outdoor pollution [104]; some studies have detected evidence that temperature modifies the effect of pollution exposure [198]. Further studies to assess these interactions would be beneficial. With the respect to literature about springtime epidemics in asthma due to pollen sensitivity, we didn't have data on pollen, dust or other air pollutions elements. However, in this project using almost 2 decades data, we were able to select controls throughout the year (days, weeks, month, and season) and could be representative of day with different level of pollen and dust. Ultimately, local wind direction and vegetation type have reported as responsible factors for changes in the concentrations of different airborne pollen [199]. St. John's is the windiest city in North America with average annual wind speed being 24 kilometers per hour. The study region has a cold climate condition with very long and cold winter. The spring usually starts late May/early June [183]. The region could experience even snow in late May. Therefore, pollen sensitivity is less likely to occur during the springtime (According to Astronomical season).

Furthermore, we did not have access to any information regarding the primary cause of hospital admissions, and we were unable to distinguish between planned and unplanned hospital admissions among patients with asthma. The dataset only included overall hospitalizations and did not contain information on patient's symptoms, or how many patients' symptoms were resolved.

We are also only able to identify asthma patients who were admitted to the hospital during the study period. One may question if the pattern surrounding the epidemic of hospital admission is not specific to asthma. We conducted the same analysis for patients with COPD (Chronic Obstructive Pulmonary Disease), diabetes, and hypertension. We found no epidemics of hospital admission for patients with diabetes or hypertension, and while we did identify epidemic days of hospital admission for patients with COPD, these epidemic days followed a different pattern, with the highest admission in the fall. These analyses suggest that the pattern identified here is specific to asthma hospital admission. However, future studies recommending in this regard.

Finally, one may question the effect of missing value on the study findings. We conducted missing value analysis using three approaches: regression imputation, replacing the missing data by mean and multiple imputation. The missing value analysis did not show a significant change in the results when we replaced the missing value by imputed values.

The results of this study suggest that there is a possibility of epidemics in hospital admission for asthma that occur with change in DMT. The result may be a heavy workload and higher demand on epidemic days, which could adversely affect patient safety, quality of care, provider satisfaction and perhaps ultimately, provider retention. This information forms a basis for healthcare providers and policymakers to predict healthcare demand for asthma patients based on forecasted weather. Our study results may be used to guide the development of a smart device application that is connected to Environment Canada and notifies patients of potential risks due to forecasted weather, and healthcare providers regarding upcoming changes in demand.

4.6. Conclusion:

Preventing asthma hospitalizations is important to improve patient outcomes and reduce healthcare costs. Using two decades of data on population-based hospitalizations and meteorology, we found that when the weather temperature declines below -4°C or exceeds 14°C, the number of hospitalizations per day may exceed the expected number, resulting in an epidemic of hospital admissions among patients with asthma. Our findings highlight the potential for such data in forecasting healthcare services demand, and could guide decision makers in implementing cost-effective strategies to prevent and combat asthma hospitalization epidemics. Our findings also provide a foundation for researchers and decision makers to develop smart device applications that examine weather forecast data, warning patients of conditions that may exacerbate their symptoms, and healthcare providers of a potential increase in asthma-related cases.

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Chapter 5: Summary

5.1. Summary and Key Findings of the Thesis

It is essential for a local health authority to have the ability to predict hospital demands caused by particular weather events. It is important to prevent exacerbation symptoms among patients with asthma and its consequent hospital admission. This thesis aimed to investigate the association between meteorological variables and hospital admission among adult patients with asthma in St. John's, Canada.

To identify the current state of knowledge on our topic and further refine our research questions to be more specific to the context of St. John's, this thesis started with a systematic review. The objective of this review was to summarize and evaluate the existing evidence and identify the knowledge gap in peer-review published literature.

The review identified 19 studies assessing an association between weather variables and asthma hospital admission or ED visits [102, 127]. Meteorological variables used in these studies included precipitation, relative humidity, wind, and temperature [132]. Among those variables, temperature variation was the most frequently used meteorological exposure variable [100, 137]; however, these studies showed temperature measurement and the threshold varied from one study to another one. Some studies suggested the use of extreme temperature (cold and hot) in study of asthma hospitalization [1, 5]. The extreme temperature (cold and hot) in these studies was defined based on geography and climate condition [200]. Our review did not find evidence regarding how much change is required and how long the effect remains and continues to influence hospital admission.

This review suggests local climatic effects could predominate a general pattern in a region; and, identification of extreme weather for local climate condition is recommended. Therefore, in the second step, we conducted studies using local medico-administrative and weather data to identify extreme weather for St. John's metropolitan area.

Our review also suggests asthma hospital admission varies between different days and months of a year depending on geographical location. [9, 10, 11]. The variation could propose the possibility of epidemic days of hospitalizations due to extreme temperature. Therefore, in the third step, we assessed the association between extreme temperature and epidemics of hospitalization among patients living with asthma living in St. John's metropolitan area.

The second study was a time series using two decades of metrological and health administrative data. We examined association between meteorological variables and hospital admission among adult patients with asthma. In addition, we examined temperature thresholds and its delayed effect of up to 15 days (lag effect) on asthma hospital admission in St. John's metropolitan area. After controlling for seasonal trend, comorbidities, age and sex, the study showed an association between temperature, precipitation and hospital admission for asthma.

The study also showed, risk of hospital admissions increases when the minimum temperature declined below -4°C and/or exceeded 14°C on the same day and/or one day after these thresholds.

In the third step, we conducted a nested case-control study to determine if an epidemic of hospitalization among patients with diagnosis of asthma is associated with the extreme temperature.

In this study, cases were epidemic days which were introduced as days when the observed number of admissions was greater than four standard deviationof the mean daily admissions during the study period. Controls were days when the number of observed admissions was within one standard deviation of the mean daily admission during the study period. Results from conditional logistic regression indicated an epidemic of hospital admission is more likely to happen when the minimum daily temperature exceeds 14°C and declines below -4°C within the same day and/or the following day in St. John's, Newfoundland, and Labrador.

The nested case-control study did not allow to adjust for the effect of individual risk factors and transience effect of other exposures such as dust, viral infections, and pollen. To control for potential confounders and individual risk factors, a case-crossover study was conducted. In this study, each patient with asthma who was admitted to the hospital on epidemic days served as their own control. The control period account for one week before, and one week after the case period. The findings from case-cross study also supported the association between hospital admission among adult with asthma and extreme weather temperature.

5.2. Limitations

This study has several limitations. For the first study, our systematic review only included peer-reviewed papers; therefore, information from gray literature is not presented. The other issue is publication bias where studies that report significant/favorable results are more likely to be published. In addition, our systematic search focused on peer-reviewed articles in English which make it possible to miss articles that published in other languages. Due to inconsistency in effects, outcomes and methodology among included articles, we were unable to conduct meta-analysis and generate a practical policy recommendation [201].

The other studies reported in this thesis relied on health administrative data. Use of health administrative data offers many advantages; however, the accuracy and coherence of such a data is always under question and often reported as limitation [202].

In our study, the record of hospital admission in asthma patients may be influenced by the accuracy of case definition algorithms [203]. We used CCDSS case definition to identify patient living with asthma. This definition is Canadian standard definition using the International Classification of Diseases (ICD)-9 and ICD-10 codes to identify asthma cases from health administrative data. The asthma case definition has sensitivity of 90% (95% CI [87% to 93%]) and a specificity of 84% (95% CI [80% to 88%]) [204]. Our databases did not have information regarding the cause of hospital admissions, and we could not distinguish between unplanned and planned hospitalizations. We ran the model for non-respiratory chronic conditions (i.e., diabetes and hypertension), we couldn't find any correlation between diabetes and hypertension hospitalization with temperature. Besides, the model ran for COPD, another chronic respiratory disease. We found a different pattern for COPD hospital admission and temperature.

In addition, we couldn't categorize asthma severity in our data. Previous studies demonstrated association between hospital admission and subjects with severe asthma who exposed to environmental exposure [205, 104]. A primary study on patient's primary care visits, ED visits, and tracking asthma patients' medical histories to identify the severity of asthma may provide a clearer picture and future studies can focus on this aspect.

We used historical climate data from the website for Environment and Climate Change Canada, and this information was collected from one weather station (point data). Although several Canadian studies have used this database in asthma research [119, 62,206], station data or point data may not accurately represent a large catchment area. An alternative to the database used for this study would have been a Gridded Climate Dataset, which would be obtained from a satellite and undergo a careful interpolation over a global grid, and thorough analysis for bias and errors. The Gridded Climate data between 1961 and 2003 were available for our analysis. This dataset was only included temperature. We ran the model with the Gridded Climate Data for the available period, our analysis didn't show any difference in the result (data not shown).

In this study we have used historical climate data from St. John's International Airport station. This site is the only station in St. John's metro area that containing historical weather variable for entire study period. Among the other weather stations in NL the St. John's International Airport station is the nearest station to St. John's, the other nearest station is Salmonier Nature Park. With a distance of 65 km, Salmonier Nature Park cannot represent the weather in St. John's metro area. Epidemiological studies are often relying on weather data from the most representing weather station [207, 14]. These studies suggest using data from multiple weather stations does not add value to the regions that don't have complex topography of the cityscapes [208,209].

This study has performed based on a single city with very specific climate condition, so the generalizability of the results is a concern and the result may not be applicable to other locations with different climate. However, the model developed in this study can be used in different geographic locations to identify the temperature threshold and the lag effect [210].

Last, only medico-administrative data between 1996 and 2013 were available at the time the study was conducted. We have requested updated information; however, this process is ongoing, and we have not received updated records from the data custodian at the time of this writing.

5.3. Recommendations for Future Research:

One of the most critical challenges in examining the association between asthma and weather-related factors is the gap between what is known from the research about the effect of weather on asthma and what is applied in health care and decision making. This thesis started with producing evidence-informed theories on weather factors influencing asthma hospitalization using a systematic review. To be more reflective of context and develop evidence for implementation in a local setting, we then further refined our research approach to be more specific to St. John's, Canada. Harnessing insights from existing data sources was a useful strategy to test what we learned in the systematic review and to develop recommendations applicable to local context, and to identify where evidence is lacking and further research is required.

Future research should plan a head for the exchange of knowledge between researchers and knowledge users including decision makers and patients. Engaging patients as part of partnership model with the purpose of developing research that priorities patient's needs, and to optimize the uptake of the evidence into practice is essential to successfully achieve meaningful outcomes [211]. For this research, I received funding from NLSUPPORT to engage patients as partners in my research. Using an integrated knowledge translation approach, I involved patients with lived experience. I discussed my research questions with patient advisors to better capture patients' experience. This information guided my statistical analyses using the NL available data. Working with patient advisors was also useful to develop dissemination strategies appropriate for the target audience. Future research in asthma-weather related could focus on strategies to better capture patient experience during weather events, to combine their experiential knowledge with theoretical knowledge of researcher and to develop strategies for improvements in healthcare and research [8, 212]. This may require interdisciplinary, systematic and programmatic research which includes integrated knowledge translation and implementation science to better identify key priorities in asthma research, develop responsive research question, improve the likelihood of research results, and application of research outcome into practice [213, 214].

Considering the complex and multifactorial causal mechanism that affects weather-related asthma hospitalization, future research should also consider multi-disciplinary approach including collaboration among different stakeholders. Stakeholders in this field includes but not limited to researchers, healthcare professionals, environmental scientists, policymakers, public, and patients. [215].

Improve our understanding of disease through comprehensive and complex data is fundamental [216]. From this perspective, developing asthma-environment-related inventory data with standard definitions locally and nationally to collect/link patient information and environmental factors, performing the assessment of the quality, and transferring this knowledge to potential users may facilitate information development and research [217]. This asthma-environment information and research can then be used to support future program and policy planning [218].

Given the climate conditions and high prevalence of asthma in NL, the potential ability to predict healthcare demand for asthma patients based on weather forecasts highlights the importance of future studies examining certain meteorological variables (e.g., relative humidity, fog, precipitation) and risk of asthma hospitalization across NL. Future research should aim to identify other climate factors and weather variables that associate with adult asthma hospitalization. In addition, identifying associations between metrological factors and asthma hospital admission in children would be beneficial.

Our study was only about hospitalization. We did not have data on asthma exacerbation or other aspect of asthma which could be affected by weather temperature, an increased understanding of the association between meteorological variables and asthma is required to develop medical interventions and inform lifestyle changes that benefit the management of asthma attacks that lead to hospital admissions [119].

In recent years, many technologies have been invented for patients with asthma to keep their treatment information [219]. However, these tools are not sensitive to sudden change in weather condition nor could give a real-time response to change or predict change in symptoms [220]. While the findings from this study need to be verified in other locations, with different climate condition, developing a watch/warning system, which links to Environment and Climate Change Canada may be valuable. The system could notify asthmatic patients and healthcare providers of the impending temperature range that historically associated with an increase in hospital admission for adults with asthma. A similar system for heat-related mortality has been already developed in the United States [221]. Given the results of this study, such a system could be beneficial for asthmatics who are trying to avoid situations where lead to hospitalization. Tracking symptoms and medication, and self-management knowledge especially related to individual action plans are among health technology that can improve asthma management [222]. Of course, much is must to be learned from different stakeholders before such a system can be implemented [223].

5.4. Conclusion:

In Conclusion, environmental factors, particularly weather temperature, play an important role in asthma exacerbation, which often requires immediate care and hospitalization. Preventing asthma hospitalization is important to improve patients' outcomes and reduce health care costs.

Using two decades data on population-based hospitalization and meteorology, our study presented the effect of the minimum temperature on asthma hospital admission at certain thresholds. The results indicate an increase in rate of hospital admission and epidemic of hospital admission among asthmatics is associated with weather temperature. Higher likelihood of hospital admission when minimum temperature declined below -4°C and/or exceeded 14°C on the same day and/or day after these ranges in St. John's metropolitan area. Also, number of hospital admission per day could exceed the expected number resulting epidemic of hospital admission when the minimum temperature reaches the above-mentioned threshold.

Awareness of potential risk factors for asthma that leads to hospital admission is important in the Canadian population. This information may help local healthcare providers and policymakers predict asthma-related hospitalization demand. The findings from this study may provide beneficial information for patients with asthma to reduce the risk of asthma hospitalization, suggesting they should remain aware of changes in the weather and its effect on their condition. For example, one recommendation can be limiting outdoor activity to avoid an asthma attack when the temperature reaches the extreme. To have better understanding of the risk of asthma hospital admission associated with environmental factors, more research is needed. Future research may focus to identify the association between the other weather variables and their thresholds that may influence hospital admission.

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Appendices: Ethic approval

MEMORIAL UNIVERSITY

Faculty of Medicine

Human Investigation Committee
Suite 200, 2nd Floor Bonaventure Place
95 Bonaventure Avenue
St. John's, NL Canada A1B 2X5
Tel: 709 777 6974 Fax: 709 777 8776
hic@mun.ca www.med.mun.ca/hic

June 29, 2011

Dr. Shabnam Asghari
C/o Andrea Pike
Agnes Cowan Hostel Room 419
HSC

Dear Dr. Asghari:

Reference #11.092

RE: **Exploring the Feasibility and Process of Establishing an Online Spatio-Temporal Information System for Chronic Disease in Newfoundland**

This will acknowledge receipt of your correspondence.

This correspondence has been reviewed by the Co-Chair under the direction of the Committee. ***Full board approval*** of this research study is granted for one year effective **May 26, 2011.**

This is to confirm that the Human Investigation Committee reviewed and approved or acknowledged the following documents (as indicated):

- Revised Invitation Letter (E-mail), approved
- Revised Consent Form dated June 3, 2011, approved
- Proposal, approved
- Budget, acknowledged

MARK THE DATE

This approval will lapse on **May 25, 2012.** It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to HIC **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

For a hospital-based study, it is **your responsibility to seek the necessary approval from Eastern Health and/or other hospital boards as appropriate.**

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.
This research ethics board (the HIC) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C.*

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Dr. JF Brunger, PhD
Dr. M. Khraishi, MB, B.Ch., FRCPC
Co-Chairs
Human Investigation Committee

C C VP Research c/o Office of Research, MUN
VP Research c/o Patient Research Centre, Eastern Health
HIC meeting date: July 21, 2011

	Event Form Name	Description
	ICEHR - Post-Approval Document Submission	INTERDISCIPLINARY COMMITTEE ON ETHICS IN HUMAN RESEARCH - Complete this form to submit documents that ICEHR requested in your approval letter, including recruitment scripts or consent forms which require minor revisions; and/or supporting documents such as school board or other organizational permissions.
	GC-REB - Personnel Change Form	GRENFELL CAMPUS RESEARCH ETHICS BOARD - Complete this form to add or remove project team members and/or research staff.
	GC-REB - Amendment Request	GRENFELL CAMPUS RESEARCH ETHICS BOARD - Complete this event form to request additions and/or modifications to an approved protocol, as changes may affect ethical concerns with human participants.
	GC-REB - Adverse Event Report	GRENFELL CAMPUS RESEARCH ETHICS BOARD - Complete this event form to report an adverse event or unanticipated effect.
	GC-REB - Annual Update	GRENFELL CAMPUS RESEARCH ETHICS BOARD - Complete this event form annually, prior to expiration of your clearance, to renew your ethics clearance for another year, or to close your file if the project is completed or terminated.

File No: 20161500

Principal Investigator: Dr. Shabnam Asghari

Project Title: Digital Epidemiology Chronic Disease Tool: Dynamic Visualization of Health data for Chronic Disease in Newfoundland and Labrador (DEPICT)

Events: Drafts

Events: Requiring Attention

Events: Under Review

	Event No	Event Category	Event Submission Date	Event Status
View Event Latest Workflow	20161500 - **382478**	Research Staff Change (ALL REBS - Personnel Change Notification Form)	2017/10/06	Approved
View Event Latest Workflow	20161500 - **382141**	Research Staff Change (ALL REBS - Personnel Change Notification Form)	2017/10/04	Approved

Events: Post Review

	Event No	Event Category	Event Submission Date	Event Status
View Event Latest Workflow	20161500 - **526830**	Ethics Renewal/Study Close Out (HREB - Request for Ethics Renewal/Study Closure)	2021/03/26	Approved
View Event Latest Workflow	20161500 - **492496**	Ethics Renewal/Study Close Out (HREB - Request for Ethics Renewal/Study Closure)	2020/04/17	Approved
View Event Latest Workflow	20161500 - **465585**	Amendment (HREB - Amendment Form)	2019/08/20	Acknowledged

Reminders

Note: My name added as a graduate student. The ethic file renewed annually!