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HOT TOPIC

Climate Change and Allergic Disease

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Abstract Allergies are prevalent throughout the United States and impose a substantial quality of life and economic burden. The potential effect of climate change has an impact on allergic disorders through variability of aeroallergens, food allergens and insect-based allergic venoms. Data suggest allergies (ocular and nasal allergies, allergic asthma and sinusitis) have increased in the United States and that there are changes in allergies to stinging insect populations (vespids, apids and fire ants). The cause of this upward trend is unknown, but any climate change may induce augmentation of this trend; the subspecialty of allergy and immunology needs to be keenly aware of potential issues that are projected for the near and not so distant future.

Keywords Climate change · Allergies · Allergic disease · Asthma · Rhinitis · Sinusitis · Food allergy · Cost of Illness · Economics

Introduction

The skin, conjunctiva, respiratory and digestive tracts compose a large immunologically active surface that primarily interacts with the external environment. An allergen often triggers an allergic response at multiple sites and is associated with an atopic march in which the allergic response progresses to include multiple allergens and multiple responses. Allergic diseases, including asthma, hay fever, rhinitis, and atopic dermatitis, impact approximately one-third of the population in the U.S. (~100 million individuals) and are associated with significant health care costs and lost productivity that range from over-treatments to significant utilization of health care resources within the medical system. These include urgent care, emergency room visits, and hospitalizations [1, 2]. Data from National Center for Health Statistics/NHANES studies indicate that the prevalence of allergic disease has increased over the past 30−40 years [3], including food allergies [4]. Although the underlying causes of the rising trend of allergic disease are not clear, links have been made to various climate factors (e.g., temperature, precipitation, rising CO_2 concentrations) and their impact on the production and distribution of aerobiological allergens (pollen and mold) [5, 6]. Regardless of the cause, the economic impacts of allergies, including allergic respiratory disorders, and the impact on quality of life are already a well-recognized health care burden; thus, any additional burden generated by climate change needs to be included in future impact assessments (Fig. 1).

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Climate Change

Definition

One of the major issues regarding climate change is understanding the terms being used, There appears to be confusion among the public, government and scientific communities with regard to differences in the meaning of the terminology [7]. By using a statistical analogy, the term "climate" represents the 'mean' and "weather" represents the 'variation around the mean'. *Climate change* reflects

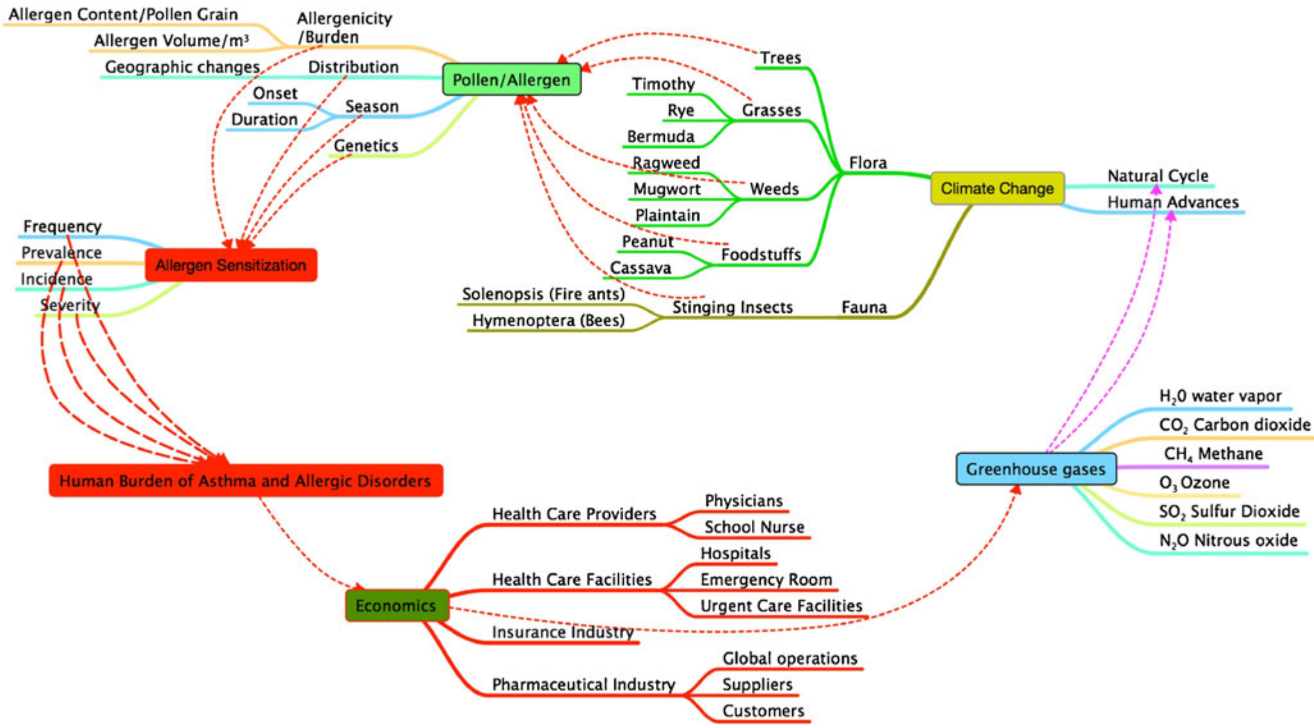

Fig. 1 The cycle of climate and allergic disease. The generation of greenhouse gases, whether due to the nature's own cycle or in combination with man-made sources, generates conditions that promote changes in the climate that affect the flora and fauna associated with allergic disorders. These include alterations in habitats and allergen content of stinging insects to the impact on flora seasonal variations, geographic distribution, and allergen burden (concentration of allergen per grain of pollen or the actual amount of pollen produced per plant), as well as the potential changes in genetics of plants that may lead to the uncovering of novel allergens. Clinically, the exposure would lead to increased allergen sensitization with subsequent increases in frequency, prevalence, incidence, and severity of allergic disorders, including asthma. The end of the cycle is the impact that this would have on cost of illness (economics) through the various participants, including the health care providers and facilities, and pharmaceutical and insurance industries that would also leave a footprint in generating additional greenhouse gases

alterations in weather conditions over time (decades, centuries, millennia) while *weather* represents the day-to-day or *season-to-season* changes that include temperature (increase or decrease), precipitation (rain and snow), wind currents and multiple other meteorological variables.

Intergovernmental Panel on Climate Change (IPCC)

There is increasing agreement among the world's scientists that alterations in greenhouse gas emissions into the lower atmosphere including carbon dioxide are now contributing substantially to the ongoing warming of the earth's surface. It is assumed that these changes have resulted from human activities that are superimposed on ongoing natural variations in the climate. The Fourth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC), a collaboration of more than 2000 scientists from 100 countries, noted that, since 1950, the temperature increase has been, with over 90 % certainty, due to primarily human activity—temperatures have increased 0.7 °C over the 100 years, and it is projected that they will increase by 1.8 to 4.0 °C from 1999 to 2099 [8]. Of note, recent measurements have shown that 2010 has been the hottest year globally in the instrumental record (i.e. since 1860) by the US-based Goddard Institute for Space Studies (NASA), the National Climatic Data Center (US National Oceanic and Atmospheric Administration). The IPCC report concluded that there was "good evidence" that the impact on temperatures and greenhouse gases has affected the timing of the onset of allergenic pollen production, which may influence pollen abundance and/or potency. These factors in turn are likely to increase the frequency of allergies and related respiratory disorders such as asthma [9]

Preliminary Data on the Impact of Pollen Production

The impact that allergenic pollen would have on the development of allergies includes the annual volume of pollen, duration of exposure (onset, closure), intensity of exposure (daily amount), and allergenicity of pollen. In general, it has been appreciated that, for the greatest annual production of aeroallergens, tree pollen is the most abundant, followed by weeds and grasses. Climate change does impact the phenology [the study of plant (and animal) life cycle events that are influenced by seasonal and annual variations in climate] of allergenic plants through alterations in pollen allergenicity, season, distribution, and amount [10–13] (see Table 1). One of the major considerations is that greenhouse gases (e.g., atmospheric CO_2) will absorb energy in the form of heat, which will result in increased surface temperatures and wider fluctuations in weather [11], with changes in plant biomass and pollen production [6] such as short ragweed (*Ambrosia artemisiifolia*) increasing by as much as 60 % [14, 15]. In addition, study associated with the growth of ragweed using different CO2 concentrations suggested that, although the total pollen protein that was harvested from the plants remained unchanged, the AMB a 1 concentrations increased as a function of CO2 concentrations. Relative to pollen grown at current CO2 concentrations (i.e., 370 μmol/mol), pollen grown at futuristic levels such as 700 μmol/mol of CO2 contained 1.6 times more AMB a 1 allergen ($p<0.01$) [16]. Ragweed has one of the longest seasons of aeroallergens and is commonly believed to have the most common prevalence among allergic patients due to increased exposure [17]. In a recent analysis of the National Health and Nutrition Examination Survey, ragweed was the most common allergen, to which 70 % of the United Stated population had sensitivity (unpublished observation by author). Other allergenic plants that have demonstrated climate-induced changes include mugwort, grasses, and trees (including Japanese cedar [18, 19], olive, hazel, longleaf pine, cedar, birch, and alder) [20, 21] . In addition to projected changes in pollen, allergenic fungal spore growth and sporulation (e.g., *Alternaria alternata* [22]) are increased [23]. However, other studies have demonstrated an inverse relationship to allergenicity to increased spore production of *Alternaria* [20, 24]. In general, temperature is a more important variable for spring and early summer pollination of allergenic trees and grasses, while photoperiods (duration of sunlight) are more important for late summer and fall allergenic plants. The impact on pollen will involve dispersion and/or transport, as deposition of ragweed pollen appears to be more local than tree pollen. However, just as some areas will demonstrate increased pollen concentrations, others will show a decrease, such as that noted in European studies between the decreased “hay fever” prevalence (after 1992−1993) and reduced pollen counts [25], and decreased grass (Poaceae) pollen counts [26], coinciding with reduced precipitation. Overall, pollen concentrations have been noted by the International Phenological Gardens in Europe over the past 30 years, with earlier flowering by almost a week since the early 1960s [27] as it relates to grass pollen [28], birch pollen [29], mugwort/*Artemisia* species [11], and *Olea europaea* (olive tree) [30]. The grass pollen season in the northeast United States typically begins in April and ends in October, thus actually having two clear seasonal peaks. An earlier start of the grass pollen season was previously reported [28] in the New York/ New Jersey metropolitan area. Earlier and prolonged release of ragweed pollen season in a transect from Texas northward to Canada found a significant increase in length by 2−4 weeks since 1995 [31]. This has been consistent with the finding from an earlier meta-analysis that suggested a phenologic advance of 5 days per decade for multiple species of plants [32].

There is also the possibility that new aeroallergens may be introduced by intercontinental dispersion of pollen [33] such as ragweed to Europe [34]. Studies into the modeling of many of these allergenic species are presently part of ongoing research, entitled the Global Change Research Program (http://www.epa.gov/ncer/science/globalclimate/) Science to Achieve Results (STAR) initiated by the United States Environmental Protection Agency.

Modeling

Bayesian modeling has incorporated variable selection−parameterization−evaluation−prediction to generate a climate change model and its potential impact on multiple pollen “indices” such as annual production, onset, peak date, and peak value [35]. Three IPCC scenarios representing regionally oriented economic development , rapid economic growth, and a balanced emphasis on all energy sources, and global environmental sustainability with different projections of global annual average CO_2 concentrations [853, 709, and 533 ppm] and temperature (17.7, 17.0, and 16.1 °C) in 2100 were used to generate future pollen indices to assess the risk of human-induced climate change. The predicted averages of annual production and peak value from 2020 to 2100 are 1.1~7.7 times versus the corresponding mean 2000−2009 values, with the onset and peak day advancing by 1~2 weeks (abstract accepted for presentation, ACAAI 2012).

Climate Change Impact on Allergies and Asthma

Allergies

Allergic diseases are the result of an interaction between the immune system and the interplay between genetics and the environment, primarily at the mucosal surfaces, and include rhinitis, conjunctivitis, sinusitis, asthma, urticaria, atopic and contact dermatitis, and gastrointestinal disorders such as food allergy, but also insect sting hypersensitivity [36].

Allergen Sensitization

As a result of climate change, allergen sensitization augmented by increased pollen production, increased duration

Table 1 Significant correlation found between CO_2 concentrations and allergenic pollen concentrations in various countries

Common name [Ref.]	Variables	Phenology	Scientific name	Location/method
Peanut and grain sorghum [66]	Temp 32/22, 36/26, 40/30, and 44/34 °C CO_2 350 and 700 ppm	Elevated temperature decreased germination in both species and elevated CO_2 did not alter pollen longevity	*Arachis hypogaea; Sorghum bicolor*	Controlled laboratory facility in Gainesville, FL, USA. SPAR chamber with natural sunlight
Cowpea [67]	Temp 30/22 and 38/30 °C CO_2 360 and 720 ppm	Elevated CO_2 did not protect pollen from damage by elevated UV/temperature	*Vigna unguiculata*	Controlled laboratory facility in Mississippi, USA SPAR chamber with natural sunlight
Loblolly Pine [68]	Temp ambient summer, not controlled CO_2 ambient and ambient plus 200 ppm	Elevated CO_2 resulted in increased pollen production and pollen production at younger ages and smaller tree sizes	*Pinus taeda* L.	Outdoor plantation plots in North Carolina, USA with vertical CO_2 delivery pipes on plot
grain-sorghum [69]	Temp 32/22, 36/26, 40/30 or 44/34 °C CO_2 350 and 700 ppm	Temperature effects on reproductive processes is more severe at elevated CO_2 concentrations	*Sorghum bicolor* (L.) Moench	Controlled laboratory facility in Gainesville, FL, USA. SPAR chamber with natural sunlight
soybean [70]	Temp 30/22 and 38/30 °C CO_2 360 and 720 ppm	Elevated CO_2 did not protect against damaging effects of increased UV-B and	*Glycine max* L.	Controlled laboratory facility in Mississippi, USA SPAR chamber with natural sunlight
Ragweed [16]		Allergen content increases with elevated CO_2	*Ambrosia artemisiifolia*	
Ragweed [14]	Temp constant 26/21 °C. CO_2 ~380 (ambient) and 700 ppm	Elevated CO_2 increased pollen production, biomass, and flowered earlier	*Ambrosia artemisiifolia*	Glasshouse with controls for CO_2, temperature, and lighting (6 h per day supplemental light)
Ragweed [31]	Temp ambient CO_2 ambient	Increased duration	*Ambrosia artemisiifolia*	Transect that ran from Texas to Canada/ambient observations
Ragweed [71]	Temp ambient CO_2 ambient	Increased duration	*Ambrosia artemisiifolia*	Central Croatia/ambient measurements of pollen levels
Ragweed [72]	Temp ambient CO_2 ambient	Increased concentration	*Ambrosia artemisiifolia*	Northeastern Croatia/ambient measurements of pollen levels
Ragweed [73]	Temp ambient CO_2 ambient	Increased concentration	*Ambrosia artemisiifolia*	Slovakia/ambient measurements of pollen levels
Fireweed [74]; (also called Willowherb)	Temp ambient CO_2 350 and 650 ppm	No effect on pollen tube growth but significant effect on pollen germination probability. Some families increased and others decreased.	*Epilobium angustifolium*	Polyethylene chamber within greenhouse with ambient sunlight and temperature. Also varied nutrient loading in soil and sunlight was supplemented by artificial lighting. Greenhouse located in France or Switzerland.

Table 1 (continued)

Common name [Ref.]	Variables	Phenology	Scientific name	Location/method
Garden Nasturtium [75]; also called Indian Cress or Monks Cress	Temp constant 22/16 °C CO_2 ~380 and 760 ppm	Elevated CO_2 increased nectar secretion rate but did not affect time to flowering, total number of flowers produced, pollen to ovule ratio	*Tropaeolum majus*	Growth cabinets with artificial lighting located in Australia
Rice [76] (cv IR72)	Temp ambient and ambient plus 4 °C CO_2 Ambient and ambient plus 300 ppm	Increased temperature and CO_2 resulted in sterility among pollen grains (less germination)	*Oryza sativa*	Open-top chambers Los Banos, Philippines
Field bean [77]		Increased CO_2 increased number of flowers by 25 %; these flowers remained for 17 % longer time compared to controls	*Vicia faba* L	Open
Japanese cedar [18, 19]	Temp ambient CO_2 ambient	Increased concentration	*Cryptomeria japonica*	Japan/epidemiological study that assessed correlation of temporal trends with patient visits
Birch [78]	Temp ambient CO_2 ambient	Increased concentration	*Betula*	Northwestern Poland/ambient measurements of pollen levels
Birch [79]	Temp ambient CO_2 ambient	Earlier flowering		Switzerland/ambient observations
Grass [80]	Temp ambient CO_2 ambient	Increased concentration		Australia/ambient measurements of pollen levels
Mugwort [81]	Temp ambient CO_2 ambient	Increased concentration	*Artemisia* spp.	Central Croatia/ambient measurements of pollen levels
Alder [82]	Temp ambient CO_2 ambient	Increased concentration	*Alnus glutinosa*	Northwestern Spain/ambient measurements of pollen levels coupled with observations
Cedar [83]	Temp ambient CO_2 ambient		Cupressaceae	Southern Spain/ambient measurements of pollen levels
Alder [84]	Temp ambient CO_2 ambient	Increased duration	*Alnus*	Worcester, United Kingdom; Poznań, Poland/ambient measurements of pollen levels coupled with observations

(Adapted from Blando et al. [21])

of exposure, potential increase in allergenicity and pollutant exposure can act synergistically to stimulate the various genes to generate changes in biomarkers, thus altering the physiology of cells and tissues to generate an atopic disease state [37]. Thus, they can increase the prevalence and enhance allergic response, leading to more severe allergic disorders, including asthma, in the upcoming twenty-first century [38]. Over the past 40 years, allergic rhinitis in the

United States has increased in a continuum from 10 % in 1970 (Bousquet et al. 2008) to 16 % in the 1976−1980 survey (the NHANES II study) (Gergen, Turkeltaub and Kovar 1987 [39]) to 28 % in the 1988−1994 survey (NHANES III) [3] to 30 % in 2000 [40]. Similar rankings were found in Canada, although with a higher prevalence that ranged from 45 to 52 % of the population (Boulet et al. 1997), suggesting that further increases in sensitivity of the population are likely (i.e., more than 50 % prevalence).

Rhinitis

Over the past 30 years, allergic rhinitis prevalence in the US population has increased from 10 % in 1970 to 30 % in 2000 [41], which correlates with the recognition that skin testing positivity prevalence over the same period of time appears to have also increased [3, 39]. Pollen is not the only factor that may play a role in the increasing prevalence of rhinitis, as temperature and humidity also contribute to appropriate nasal function such as eosinophilic infiltration during the late-phase allergic responses [42]. Furthermore, warmer temperatures positively correlate with physician-diagnosed allergic rhinitis [43]. It has been predicted that the number of hay fever sufferers in Japan will increase by 40 % by 2050 because Tokyo's average yearly temperature has already increased by 3 °C since 1890 and is projected to further increase by 3.5 °C by the end of the century [44]. Overall, there have been several indicators that point to climate change as a possible factor in the increase in allergic rhinitis prevalence [44].

Sinusitis

Sinusitis commonly complicates the development of rhinitis, but there have been limited studies focusing on this condition (although an increase would be expected [45], as was noted in an observation performed by the New England Society of Allergy assessment of the clinical impact of an El Nino event) [46]. Some climates are worse than others for individuals with chronic sinusitis due to a variety of environmental factors that appear to be similar to those that would affect allergic rhinitis. Additionally, atmospheric inversions and drops in barometric pressure seem to cause sinus difficulties [47] apart from any effect they may exert on air pollution or allergen concentration such as that seen in extreme weather changes (e.g., those occurring before a rainstorm).

Conjunctivitis

Few studies have noted that pollutants have increased demands for outpatient care for nonspecific conjunctivitis. One study coupled national heath insurance data and those from the environmental protection administration in Taiwan [48]. Unlike other organ systems that are targeted by pollution, the effect on the eye is immediate. Ozone and nitrogen dioxide produced the strongest effects, along with large diameter particulate matter PM10 (not fine particulate matter), with a 2.5 % increase [95 % confidence interval (CI), 0.9−4.1] for a 16.4-ppb (parts per billion) concentration rise in O_3 and a 2.3 % increase (95 % CI, 0.7−3.9) for a 11.47-ppb concentration rise in NO_2. Poor air quality with increasing greenhouse gases along with a projected increase in pollen will increase the prevalence of allergic and potentially dry eye disease, thus expanding the geographic coverage and amount of people affected by the urban eye allergy syndrome [49–51].

Asthma

Scientific evidence supports the "united airway" concept that rhinitis, sinusitis and asthma are expressions of the same inflammatory process that appears in different sites of the respiratory tract at different times and thus increases the severity of the allergic disease process, including asthma [52]. As a result of climate change, increased allergen and pollutant exposures such as diesel exhaust particles increase the primary incidence of allergen sensitization in atopic individuals [37], enhance allergic response, and then increase allergic respiratory disease in the subsequent years [38]. Another climate change variable, temperature, has been reported to be associated with an increase in asthma prevalence. In a New Zealand study, an increase in mean temperature of 1 °C was associated with an increase in asthma prevalence of almost 1 % [53]. In a study comparing a Mediterranean climate versus a subcontinental northern Italian one, the prevalence of asthma increased when the reported annual mean temperature increased along with a decrease in the range of temperature. The report also noted that one of the greenhouse gases, NO_2, was associated with increasing the risk for allergic rhinitis while being exposed to high stable temperatures [54]; similar coastal effects related to increased annual temperatures were noted in another Italian study when compared to subcontinental portions of Italy [55]. Exercise-induced asthma has been reported to be aggravated in birch pollen allergic asthmatics versus non-birch pollen allergic asthmatics because of the warmer and more humid weather in the pollen season in spring [56]. When considering the concept of "one airway–one disease," it should be expected that when the upper respiratory tract would be affected by climate change that an effect would also be seen in the lower airways, leading to increased health care utilization [13, 21].

Food Allergy

The link between global climate change and plant food allergens, such as peanut, and the increase in associated food allergic diseases warrants further investigation [4, 57–59]. Increased CO_2 and temperatures are associated with increased aboveground biomass (similar to poison ivy). However, with several tuber-based foodstuffs, there is a decrease in the underground biomass such as that seen with Cassava (*Manihot esculenta*), the third largest global staple food [60], while the net effects of higher CO_2 may have been slightly positive for rice and soybean.[61].

Contact Dermatitis

More than 100 plant species can induce contact dermatitis, and the development of plant induced dermatitis may also change, as it has been demonstrated that uroshiol potency and content increase when the (poison ivy) plants are exposed to increasing concentrations of atmospheric carbon dioxide. Currently, sensitivity to urushiol occurs in about two in every three people, and amounts as small as 1 ng are sufficient to induce a rash, but previous work done in controlled growth chambers demonstrated that other vines exhibit large growth enhancements from elevated CO(2). While using an intact forest ecosystem to grow poison ivy, photosynthesis, water use efficiency, growth, and population biomass all increased. This suggests that the *Toxicodendron* taxa has the potential to become more abundant and perhaps more "toxic" in the future with the changes associated with climate change [62].

Insect Sting Hypersensitivity

An insect sting hypersensitivity increase has been reported in Alaska based on the analysis of medical insurance datasets that demonstrated statistical significance that appears dependent on increases in annual and winter temperatures, which correlate with stinging insect habitat geographic expansion [63]. The allergic impact of fire ants (*Solenopsis invicta*) may also have climate change implications, as it has been demonstrated that the phospholipase A content of venom is increased in the early summer, corresponding to higher prevalence of anaphylactic events as well as the potential increase in the sting attack rate [64].

Cost of Allergic Disease

A preliminary prediction of cost-of-illness (COI) based on the construct of a new patient value-driven supply chain system indicates that direct and indirect economic costs (and patient care inefficiencies) for allergic and asthma disease will rise significantly, while the quality and delivery of immediate care may suffer. Cost-of-illness research frequently measures the potential economic impacts and burdens of a disease as it attempts to estimate the maximum amount that could potentially be saved or gained if the disease were to be significantly reduced or eradicated. If COI is utilized with cost-effectiveness, cost-benefit analyses combined with other economic analysis methods, the COI economic analysis tends to be more accurate. In addition, new types of COI studies have been introduced due to multiple questions regarding COI effectiveness. These new types of COI approaches include field research by using a bottom−up approach, which involves estimating the quantities of services used for the illness by going prospectively or retrospectively through the patient's records [65]. In order to prepare and draw parallels and polarity between climate change and allergic disease impacts on future economic and supply chain value systems, we developed a simple Bayesian/supply chain economic model. This model provided preliminary results that show a potential 30 % rise within the next decade in medical expenditures related to allergic and asthma disease as climate change impacts continue to rise at the same rate. Additional factors to be included in the Bayesian model are the development of an open formulary or switching to over-the-counter forms of various common prescription medications such as oral antihistamines, ophthalmic agents, and intranasal treatments. Like most global industries with well-developed and optimized supply chains, there is a significant amount of research and development and supply chain optimization that firms conduct to meet consumer needs. To keep pace with the increased need to treat economic impact of asthma, the pharmaceutical industry must manage a complex networks of suppliers, customers and global operations; this will be one of the major management challenges of this century—a challenge shared by most global industries. However, this is a promising introduction to advanced value driven supply chain research that could prove to have major patient and industry operational and financial benefits.

Conclusions

It is the opinion of experts that, even with mitigating programs, the effects of the present concentrations of greenhouses gases and fluorocarbons (even if we were to reduce them to zero) will exert an impact such that the present course will remain for the remainder of the twenty-first century and beyond. The influence of climate change on allergy is unpredictable, as there are various items on both sides of the scale. However, preliminary suspicions by clinical experts indicate that the scale is tipped toward increasing allergies and allergic airway disease, but depending on regions as climate change will have different effects in different regions. As the impact of climate change on allergic diseases emerges, there is and will be increased exposure and sensitization to various allergenic plants that will potentially promote the "allergic march" with increases in the prevalence and sensitivity of the "one airway–one disease", particularly affecting the pediatric population while increasing the persistence of symptoms or the development of new allergies later in the geriatric population. The cost of climate change due to increased severity and number of patients will require advanced modeling to properly mitigate, but more importantly adapt to the needs of the allergic population.

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