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REVIEW

A time for everything and everything in its time – exploring the mechanisms underlying seasonality of COPD exacerbations

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Abstract: Across Europe, COPD affects 23 million people leading to annual health care costs of ~€25.1 billion. This burden is particularly severe during winter months in association with the peak incidence of exacerbation events. Seasonal variation in the health status of patients with COPD places additional and often critical pressure on already strained health care resources. COPD exacerbations are characterized by worsening day-to-day symptoms of an individual and often triggered by respiratory infections, but the process by which this occurs in a seasonal fashion is likely to be multifactorial. In this review, we discuss recent population studies that highlight the impact of seasonality in COPD and review the proposed biological mechanisms underlying this. An appraisal of the role of the host susceptibility and response, environmental triggers and the biology of respiratory pathogens is detailed. The impact of each aspect is considered, and an integrated model of the context for the whole individual and society in general is explored.

Keywords: COPD exacerbation, seasonality, pollution, weather

Introduction

Life on earth is intimately linked to the level of energy (ultraviolet [UV], visible, and infrared radiation) received from the sun, and the variations in the angle of earth's rotational axis on its elliptic course gives rise to various seasons. Seasonality affects all forms of life as they adapt to overcome the environmental challenges associated with this cycle.[1] Variations in the mammalian reproductive cycle are among the best documented biological phenomena studied in relation to seasonality, with the level of fertility changing at certain times of the year to improve the chances of survival of offspring.[2] However, there is evidence that many other physiological functions and human disease-related conditions exhibit similar seasonal and also circadian patterns, for example, cardiovascular,[3] physiological state,[4] autoimmune,[5] cutaneous,[6,7] and psychiatric disorders.[8]

The association of COPD with seasonality is notable.[9,10] Individuals with COPD recognize that they are more likely to experience exacerbations in winter, with 30% of COPD patients being frightened of this season.[11] Indeed, some of the more affluent patients with chronic conditions such as COPD and rheumatoid arthritis holiday in sunnier climates during winter, a fact evidenced by the presence of websites encouraging extended winter holidays for this population.[12] This perceived risk is supported by evidence from clinical studies[9,10] demonstrating an increased incidence of COPD exacerbations in the winter months in temperate climates, but not in warmer

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tropical environments. The underlying mechanisms for this variance are not clear, suggesting a variety of factors including host biology, environmental conditions, and pathogen alteration.

In this review, we set out to identify our current understanding of the factors that influence COPD exacerbation seasonality and suggest avenues where further research may reduce risk and improve outcomes.

Importance of seasonality in COPD exacerbation rates

The GOLD guide defines a COPD exacerbation as an acute event characterized by the worsening of a patient's respiratory symptoms that is beyond normal day-to-day variation and leads to a change in medication.[13] However, COPD exacerbations are not always easily demarcated due to the heterogeneity of factors precipitating the event, the variation in the patient's perception of an exacerbation, and biological response to the precipitating factor(s) in terms of severity and duration of symptoms. This leads to differences in the criteria used by studies to define both the disease itself and the presence of an exacerbation.

Allowing for this variation, a systematic search, on the PubMed and Embase libraries, using the search terms of "seasonality" and "COPD exacerbations" identified seven separate studies showing a seasonal variation in COPD exacerbations.[9,10,14–19] A large international multicenter study, the TORCH trial, has shown that seasonality in temperate climates increases the rate of exacerbations, with an almost twofold increase in winter compared with summer months.[9] This is further supported by extrapolation of results from the POET-COPD study which documented a 116% increase in exacerbation rates from December to February when compared with June to August in a study of 7,376 patients over 12 months.[19] Recent data from the SPIROMICS cohort study additionally challenged the concept that individuals can be categorized as either frequent or infrequent exacerbators. Over a 3-year period, many individuals varied on an annual basis in their exacerbation events, suggesting that external influences are important in an individual's risk of exacerbation.[20,21]

This seasonal variation in exacerbation incidence has a corresponding effect on hospital admissions in many different health care systems[22–24] and is also associated with an increase in mortality.[25] Therefore, a greater understanding of the factors that contribute to these seasonal increases in exacerbation rates should provide opportunities to protect patients and reduce the burden on already overstretched health care systems.

Host physiology

The immune system plays a key role in infectious exacerbations of patients with COPD. How seasonality affects this process is complex and multifactorial.

Seasonal effects on gene expression and cytokine pattern – length of day

Dopico et al have highlighted that seasonality affects the expression of genes such as *ARNTL*, which is known to be associated with the immune response.[1] This study used cohorts of patients recruited for studies with a variety of long-term conditions including asthma and type 1 diabetes.[26,27] The authors were able to show that the expression of anti-inflammatory genes was altered by the time of year. Importantly, those more highly expressed in June, July, and August in the northern hemisphere were seen to be raised in December, January, and February (corresponding to the equivalent day lengths and climatic conditions) in the southern hemisphere. This difference was also reflected by the presence of circulating immune cells, which were increased during the winter period in the UK. In equatorial climates where day length and temperature were less variable, there was still evidence of seasonal immune variation linked to rainfall, reflecting the period with the highest incidence of infection.

This relationship may deliver an evolutionary advantage by priming the immune system during the highest risk period for infection. However, other smaller studies have suggested reduced cell-mediated immunity and T-cell function during winter and/or periods spent in colder climates,[28,29] and the overall effects of the winter season on cutaneous and/or systemic immune function may result from a combination of individual effects due to alterations in the length of daytime, exposure of skin to sunshine, body/skin temperature, and hormonal changes. Animal studies support a role for photoperiodic variation in the immunological response.[30] Changes are controlled by the hypothalamic suprachiasmatic nucleus which responds to light via the nocturnal pineal melatonin rhythm (MEL); as day length alters throughout the year, the MEL signal changes in a predictable and reproducible way, resulting in higher levels of melatonin during winter. Melatonin blocks differentiation of Th17 cells (resulting in less interleukin [IL]-17A expression) and induces the production of Treg1 cells (with a consequential increase in IL-10 production[31]), thus permitting an exacerbation. The change in circulating immune cells in these cohort studies[1,26,27] has previously been reproduced in studies of rodents maintained under artificial light conditions mimicking short and long days. In vivo studies in Siberian hamsters demonstrated that the inflammatory response to a bacterial challenge or wound

healing partially varied with the time of year in which the challenge took place. The prevailing cytokine profile also varies in these rodents leading to a change in strength of their immune response.[30] Specifically, circulating levels of IL-1β, IL-6, and tumor necrosis factor α were reduced following lipopolysaccharide challenge in animals under short day conditions.[32,33] Equivalent responses in COPD patients may result in greater risk of exacerbation in short winter days as early local immune defenses would be impaired.[34]

The role of hormonal effects

Animal models highlight the role for hormonal changes in photoperiodicity and immune function, which could alter the susceptibility to COPD exacerbations. In particular, thyroid, pituitary, and gonadal hormones have been implicated in the response to photoperiodicity.[30]

Gonadal hormones have been investigated to determine whether there is a seasonal variation in their impact on immunity, given their established influence on reproductive cycles as a result of day length.[30] These studies have shown conflicting responses. Castration was shown to cause a rise in levels of CD3+T-lymphocyte numbers that were similar, although less profound, to the effect seen in male Siberian hamsters maintained in short daylight conditions.[35] However, the practical benefit of gonadal hormones in the skin inflammatory response associated with photoperiodicity via lymphocyte proliferation has not been confirmed as testosterone supplementation failed to alter the effect of day length.[36]

Seasonal variations in thyroid hormones have also been demonstrated to alter the reproductive cycle.[37–39] The active component, triiodothyronine (T_3), has been established as a key regulator of many different processes in the immune system.[40,41] The effect of photoperiodicity on the role of thyroid hormones was investigated in animal models via its influence on DIO3 mRNA, DNMT3B mRNA, and DIO3 promotor methylation in different tissue types.[30,42–44] This showed that day length does alter the synthesis of T_3 in different tissue types.

Such changes in immune function in response to seasonal hormone variations have so far only been studied in animal models. Prospective studies of the impact of seasonal variations in thyroid levels on the risk of infectious exacerbations in COPD are warranted since they may contribute to the increased exacerbation rates seen in the winter.

Effects of variation in day length

Photoperiodicity is not the sole controlling mechanism for seasonality in the immune system as Dopico et al showed that there was an equivalent rise in white cell numbers during the wet season in equatorial climates.[1] These wet periods are associated with the highest rates of parasitic infections. Thus, while there is no change in day length or significant temperature alterations in the tropics, there is still an advantage of seasonal variability in certain biological responses, supporting the concept of a seasonal change in immunity.[45]

Intriguingly, data showed that there was a reduction in the equivalent seasonal variation in an Icelandic cohort of patients.[1] An explanation for this may be the requirement of the MEL rhythm to have a period of downregulation to be effective, as seen in rodents.[30] The extreme latitude of Iceland leads to almost 24-hour daylight in the summer, thereby losing the time for downregulation. These findings suggest a greater complexity in control of the immune response to seasonality than it being a simple reflection of the photoperiod.

Environmental factors

Temperature

In the general population, extremes in temperature are associated with an increase in morbidity and mortality.[46] This effect is also seen in the respiratory disease setting; for example, in 48 patients with COPD, there was an association with patient-reported quality-of-life scores and hours of warmth.[47] There is a complex interaction between lower temperatures seen in the winter and the increase in mortality rate observed. In the UK population, the average temperature for the preceding 13 days has been shown to be associated with national mortality rates, particularly in those with preexisting lung disease.[48] The influence of cold weather on respiratory complaints is supported by a study from China showing increased health care attendance during periods of lower temperatures.[49] This is not a simple linear response to cold weather since countries with warmer average temperatures have an even greater increase in mortality with a comparable fall in temperature.[50] An explanation for this may be that in colder climates there is better adaption in terms of both quality of housing and personal clothing to cope with those changes.[25] This explanation is supported by the findings of a study of children with asthma, where housing improvements led to a reduction in asthma symptoms.[51] Deprivation has also been shown to have impact on COPD exacerbation rates in the winter. A Scottish study implied that access to warm clothing and housing altered a patient's risk of exacerbating.[52] Despite these findings, a systematic review of European studies did not support the suggestion that housing changes can reduce mortality from respiratory disease.[53]

These inconsistencies related to the impact of cold, environment, and season on respiratory disease, in particular in patients with COPD, are likely a reflection of the complexity of the interplay between a variety of environmental factors and the infectious agent itself and the immune response elicited by the host. Wanka et al have highlighted this by showing that meteorological factors had a significant but nonlinear overlap with pollution findings that made predicting morbidity in asthma or COPD patients difficult.[54]

Precipitation and humidity

The impact of climatic conditions is not solely due to temperature differences. In subtropical climates, the seasonal variation in infection rates remains although there is minimal temperature variation throughout the year. Instead, rates of infection in general, and respiratory viral infections in particular, follow the progress of wet seasons.[55] Where the average precipitation rate was >150 mm per month, there was a rise in seasonal influenza activity, although the effect is less pronounced and reliable than that seen with changes in temperature in temperate climates.[56]

The effects of humidity on exacerbation rates may be linked via viral transmission, with lower humidity levels leading to increased transmission rates.[55–57] Relative humidity (RH) is the water content in a gas mixture, such as the air we breathe, relative to the ability of the gas to hold the water at a given temperature. It is influenced by ambient temperature, which could therefore be the ultimate determinant of infection and associated exacerbations. However, animal models using influenza infection show that where temperature is controlled for, ambient humidity levels alone are sufficient to alter the rate of infection.[58] Rather than RH, absolute humidity (AH), which measures water content regardless of temperature, has been shown to more accurately model viral infection rates in temperate climates.[59]

The relationship between humidity and viral infection rate is not linear. Instead, a rise in infection occurs at low temperatures in association with a low AH, whereas at higher temperatures the reverse is seen.[60] This reflects underlying viral biology with low AH limiting viral envelope disruption at low temperatures. At higher temperatures, the virus is at risk of desiccation, accounting for a protective effect of higher AH. A crossover point therefore exists at which the positive and negative effects of AH are neutral. Based on the global infection rates, this is suggested to be at 24°C, but confirmatory laboratory data are limited with only temperatures <20°C been studied.[60]

Interactions between pollution and seasonal effects

The significance of air pollution on seasonality in COPD exacerbations is integrally linked to weather and temperature. The effects of air pollution are a significant public health concern, with increasing governmental focus on control in both the developing and developed world.[61,62] Airway damage has been shown to occur in children,[63] but eliciting a causative effect for COPD is more difficult. The effect of living closer to high pollution sites did influence disease rates of women in Germany,[64,65] but was not reproduced in an adult population in the UK.[66]

The relationship between air pollution and acute exacerbations of COPD is more established. Large population studies in both European and American cities have shown rises in admission rates and symptomatology in association with increased pollution levels.[67–69] Interestingly, equivalent effects are also seen in more rural locations when pollution levels rise from a low baseline indicating a dose-dependent response regardless of the background concentration of pollutants.[70]

Pertinent to this review, the impact of pollution on mortality is also subject to seasonal variation.[71] National governments have identified significant issues with air quality as a result of pollution in recent years.[72] A large multicenter study in China has shown that there is an association with season, particulate matter (PM), and mortality that follows a biannual pattern, with peaks in mortality in summer and winter.[72] The study reviewed data from 17 large cities to model for any changes seen following a rise in PM by >10 μg/m^3. The greater increases seen in summer as well as winter months may reflect the predominant use of coal-fired power stations for energy generation in China which are required for both winter heating and summer cooling in homes and industries. Curiously, and in contrast with COPD-specific study data where seasonal exacerbation rates are more marked in temperate climates, the mortality impact was more pronounced the closer to the equator the city was located.

Sunlight

Heliotherapy has been used as a treatment for centuries. Its practice proved popular; but even one hundred years ago, it was controversial with the first editorial in the *British Journal of Tuberculosis* being used to question its value.[73] However, UV has a variety of effects on the skin/body, including synthesis of vitamin D, and thus effects on tuberculosis killing by macrophages[74] and local/systemic immunosuppression.

The ability of UV radiation to alter the immune response was eventually documented conclusively in the 1970s. Investigating the impact of UV in skin cancer biology led to the understanding that UV radiation reduces the ability of the immune system to suppress tumor development.[75,76] Further work has shown multiple immune effects from exposure to sunlight leading to reduction in not only local processes such as psoriasis but also systemic conditions including respiratory diseases such as asthma.[77] The UVB wavelengths (290–315 nm) are considered the key components in sunlight responsible for immune modulation, although a role for UVA has also been suggested.[77,78] The amount of solar UVB radiation reaching the earth's surface is dependent on the distance that the radiation travels through the ozone layer in the upper atmosphere. This means that, as a result of the rotational angle of the earth in relation to the sun, reduced levels of UVB exposure are seen at higher latitudes during winter months.[78,79] In addition, cloud cover can attenuate up to 99% of UVB radiation, thus further impacting on levels during winter months at higher latitudes and in the rainy season in equatorial conditions.[80,81]

UV-induced immunosuppression is not likely to be a key determining factor in COPD exacerbations in relation to influenza or viral exacerbations because there is less UV exposure in winter. However, UV light might be relevant via its inhibitory effect on systemic inflammation during summer but not winter when COPD exacerbation occurs. Therefore, enhanced low-level inflammatory processes, which are also energetically costly to control, may contribute to unfavorable alterations in systemic redox status due to increased oxidative stress. The role of oxidative stress in COPD has recently been reviewed and is beyond the scope of this paper, but a specific role for seasonality in this process has not been studied.[82]

UV exposure has also been linked to viral infection partly through this role in immunosuppression. It is recognized to cause viral reactivation of the herpes simplex virus.[83] Solar insolation (ie, the amount of solar radiation reaching the earth's surface) has therefore been incorporated in modeling of environmental factors that influence respiratory viral infection rates. However, the decrease in solar insolation seen in winter months was not found to track infection rates.[59]

The role of sunlight and UV radiation in the regulation of immune system activity has been intrinsically linked to its actions on vitamin D synthesis.[84] While seasonal variation in serum vitamin D levels relates to UV exposure during summer months, a systematic review has highlighted that adequate vitamin D levels are maintained in winter in over 50% of individuals.[6] The role of UVB radiation in this context is to aid the conversion of pro-vitamin D3 (7-dehydrocholesterol) to pre-vitamin D3 (pre-cholecalciferol) before further steps in the liver and kidney convert it to its activated form, 1,25-dihydroxyvitamin D3. However, some of the seasonal deterioration in immune function might be ameliorated by a change in diet.[85] A level of >50 nmol/L is seen as adequate, with some authors considering >75 nmol/L as optimal for the overall well-being of the individual,[6,86] but the precise adequate concentration of vitamin D present in an individual to maintain health is difficult to define and therefore assessing whether seasonal reductions have a clinical effect is challenging.

Vitamin D itself has multiple properties that impact on the immune system. It can drive immune cells such as monocytes, macrophages, and neutrophils to produce antimicrobial peptides including LL-37 and β-defensin 2, which enhance the bactericidal properties of these cells.[87] It also drives differentiation of a variety of different immune cells including dendritic cells, T cells, and monocytes to support specific immune responses, placing it in a key position to alter the inflammatory response seen in COPD exacerbations.[88–90] However, immune cells themselves express the inducible enzyme, CYP27B1 (1α-hydroxylase), so they too can make 1,25-dihydroxyvitamin D3 and cause an autocrine effect at a local level that may alter the immune response independently of sunlight exposure.[91] Its overall impact though remains less clear with a comprehensive systematic review of vitamin D status and ill health, suggesting that the observed low vitamin D levels seen in association with higher mortality may reflect frailty rather than a trigger for illness.[92]

Sunlight exposure or vitamin D supplementation has been proposed as potential therapies. In those with steroid resistant asthma[93] and in those with newly diagnosed disease,[94] the addition of vitamin D to the diet has been shown to improve clinical outcomes as well as in infectious conditions such as tuberculosis.[87,95] A systematic review of asthma exacerbations, including seven separate studies, demonstrated a clinically relevant reduction in steroid use with vitamin D supplementation.[96] Importantly, in the context of COPD, a large meta-analysis showed that vitamin D supplementation reduced acute respiratory tract infections.[97] Although this suggests a role for vitamin D therapy in respiratory conditions in general, other treatment studies have failed to show a clear benefit[95,98] in line with other diseases.[99] This may reflect the low thresholds (<25 nmol/L) used by the positive studies to indicate those individuals requiring treatment. For example,

in a study of muscle strength in COPD where the treatment and interventions arms had levels >40 nmol/L, there was no impact from vitamin D supplementation.[100]

In patients with COPD, a reduction in day length has been shown to be associated with a reduction in the presence of 25-hydroxyvitamin D.[101] However, despite the importance of vitamin D in immunomodulation in experimental model systems, its use in clinical practice remains controversial. In observational studies, low levels of its activated form, 1,25-dihydroxyvitamin D, did not result in an increased frequency of COPD exacerbations[12,101,102] or a reduction in the susceptibility to human rhinovirus (HRV) infection.[101] Subgroup analysis from two separate studies has shown that although infection rates are not altered, the time to exacerbation is increased in those individuals with low vitamin D levels who are given dietary vitamin D supplementation.[103,104] A systematic search of the online databases Embase, Medline, and the Cochrane Library for vitamin D supplementation and COPD exacerbations identifies two separate studies[100,103] and two trials in progress. Those trials to report showed a positive response, predominantly in patients with initial low vitamin D levels. The ongoing randomized controlled trial (PRECOVID trial) of vitamin D supplementation in COPD patients may add further evidence for its use.[105]

A confounding factor in any discussion on vitamin D levels and photoperiodicity is the impact of diet. Historic cultural dietary alteration in indigenous populations in Alaska, for example, developed to account for the inability to synthesize the active form in winter months. With a generational move to Western diets, this seasonal dietary supplementation is being lost which may in turn lead to long-term respiratory health effects.[106] Although seasonal variation in diet in developed countries is relatively limited,[107] the impact on a subset of other micronutrients such as vitamins C and D has not been consistently shown to be altered.[107]

It has been argued that vitamin D may simply be a biomarker of sunlight exposure and that the beneficial effects of sunlight for cardiovascular and metabolic (and perhaps also respiratory) health are due to the release of additional factors from the skin.[108] One such factor may be nitric oxide (NO), and it is conceivable that the increase in COPD exacerbations in the northern hemisphere in winter is linked to the nadir in UV-induced NO release during this time of year.

NO is another immunomodulator induced by UV radiation exposure.[77] NO is a ubiquitous messenger and effector molecule that can be formed by two independent enzymatic routes that depend on the availability of either L-arginine (which is a substrate for nitric oxide synthase, NOS) or nitrate (which can be sequentially reduced to nitrite and NO by a variety of enzymatic and non-enzymatic pathways).[109] In addition, sunlight exposure can liberate NO from preformed storage forms located in the epidermal layer of the skin,[110] possibly leading to alterations in tissue levels during periods of reduced light exposure.[111] Exposure to UV light also drives the synthesis and release of α-melanocyte stimulating hormone (α-MSH), which in turn acts as an anti-inflammatory agent in part by curtailing NO and peroxynitrite production from inducible NOS.[112,113] In patients with COPD, measurements of exhaled NO have been used as a surrogate for exacerbations given its importance in the inflammatory process.[114] It has been shown that exhaled NO levels are raised during winter months, suggesting a degree of active inflammation.[115] This could reflect inter-current viral infection or additionally represent the impact of low α-MSH in response to low UV levels as there are no specific trials looking at this response.

Pathogens

About 50%–70% of COPD exacerbations are triggered by either bacterial or viral infections that stimulate an inflammatory response.[116–120] Many of these infectious agents have also been found to have a seasonal variation in their infection rates. Certain viruses, including respiratory syncytial virus, HRVs, and influenza A and B, along with bacteria like *Mycoplasma pneumoniae* have peaks of incidence in the winter months.[25] The reason for these peaks in infection may relate to both environmental and host factors.

As alluded to earlier, UV radiation, temperature, and humidity have been highlighted as key to viral survival in the environment. For example, the relative proportion of dissolved salts in water droplets has been proposed as a cause for the influence of humidity on infection. Salt levels fall with a drop in humidity as they crystallize out of solution leading to high virion stability.[121] Infectious agents can also be preserved for longer in the cold, thereby increasing the opportunity for patient exposure,[55] and finally UV radiation inactivates viruses by chemically modifying their genetic material.[122] The relative importance of the pathogen versus environmental factors can be seen in a longitudinal study of influenza-related mortality in Chinese cities that covered both temperate and tropical climates.[123] In this 6-year study, overall death rates and influenza-related fatalities were compared between three northern, temperate cities and five southern, tropical ones. In both the regions, there was a seasonal variation in mortality, but it only corresponded with influenza rates in the cooler northern cities, suggesting that weather and temperature were necessary to

create seasonal viral variation rather than a property of the pathogen itself.[123]

Many of the host factors that influence exacerbation rates do so by contributing to the ability of the individual to deal with an infectious challenge. Additional factors that relate to respiratory pathogens include the effect of cold on the nasal epithelium, with cooling, reducing blood flow, and impacting on local immune defenses, including phagocytosis[124,125] and mucocililary clearance.[126] Adenoviruses and corona viruses have similar infection rates throughout the year, suggesting that there is a difference in the reason for susceptibility to infection depending on the infectious agent. Co-infection may account for some of these. Non-typeable *Haemophilus influenzae* is known to influence the severity of the inflammatory response and the clinical consequence in patients who are co-infected with viruses such as HRV.[119,127] It is conceivable, therefore, that many of the seasonal effects we observe in respiratory diseases require the presence of multiple pathogens in the same individual.

Additional research correlating extensive meteorological data including humidity levels and temperature with specific infectious agents in COPD exacerbation might prove helpful in public health strategy.[129,130] Health care services would be better prepared for outbreaks of certain infections if they were found to have predictable patterns in patients with COPD. HRV infections have recently been shown to rise following a fall in average air temperature over the preceding 3 days, suggesting a marker to predict surges in health care demand.[131] Public health services do retrospectively monitor for viral infection patterns. Public Health England data from the most recent respiratory virus surveillance in the UK shows that there are yearly seasonal spikes in infection rates that do correspond to winter months.[128] However, those rates vary on a yearly basis in a manner that does not reflect a linear relationship to temperature alone, highlighting the complex interactions taking place between the individual host, the infectious agent, and the environment.

Conclusion

Seasonality in COPD exacerbation rates clearly has a major impact on both the individual patient and the wider health care system (summarized in Figure 1). Overall, winter excess mortality rates fell in the UK in the last 20 years before the

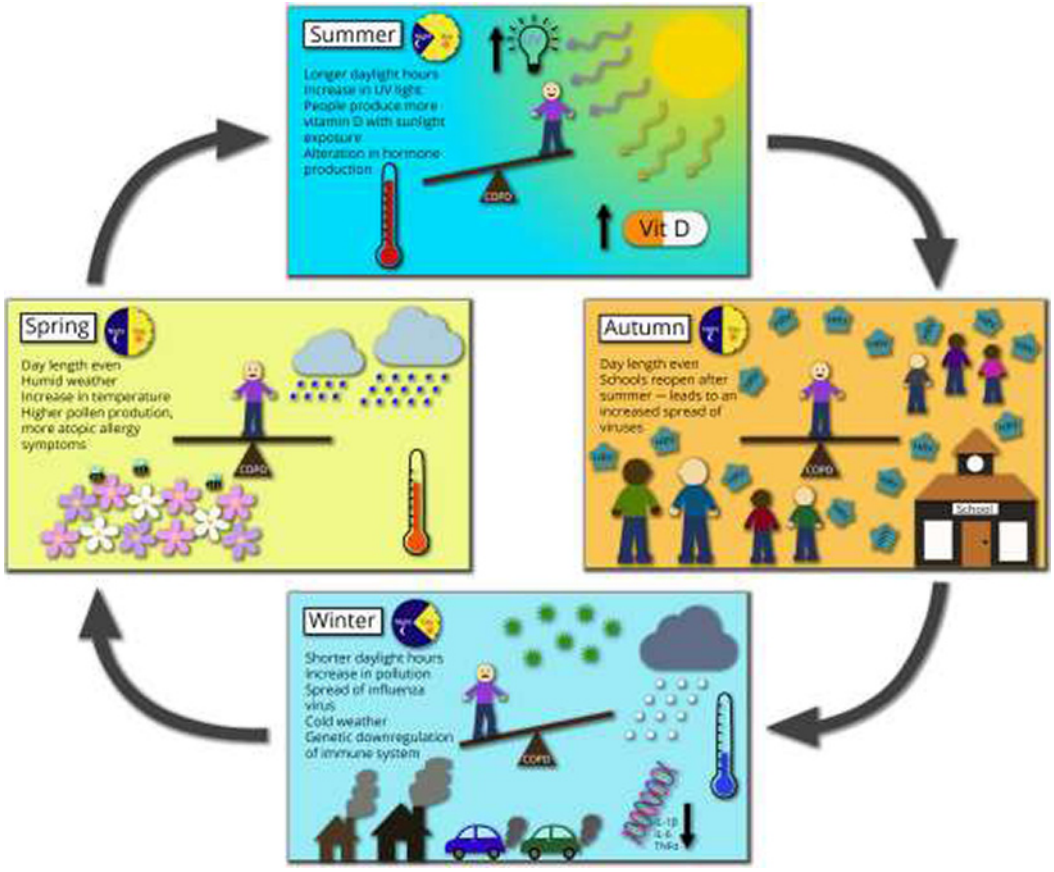

Figure 1 Abridged pictorial representation of factors contributing to seasonal variations in COPD exacerbations.
Abbreviations: UV, ultraviolet; Vit D, vitamin D; IL, interleukin; TNF, tumor necrosis factor.

millennium.[132] However, winter pressures in UK hospitals have significantly increased, stimulating the need for models of prediction and prevention. Therefore, a greater understanding of factors influencing COPD exacerbations during the winter could aid long-term planning strategies.

As outlined in this review, seasonal changes are multifactorial and require research that looks at the issue in its entirety. First, the fundamental biology of the patient in response to seasonality needs to be better understood in order to offer prevention and treatment options. With greater comprehension of the mechanistic events that drive seasonal variations, new targets and avenues for therapeutic intervention could be identified.

In addition, research should be undertaken with a clear knowledge of the changing environmental conditions that patients experience. It is interesting to speculate as to how climate change will impact on these external factors, such as temperature, humidity, pollution levels, and local pathogen rates. In this study, we have discussed the factors separately although they are all clearly interconnected; importantly, with growing climate extremes, there is a risk that this will impact on seasonal variations in exacerbations rates. Given that patients cannot be readily relocated to milder climates during winter weather conditions, it is important to understand how all these factors have an impact together and where any interventions can be targeted. Therefore, large multicenter longitudinal studies are required to provide a research context for health care modeling in order to prioritize limited resources and importantly to offer new opportunities to limit risk-associated exposures for this vulnerable and sizeable patient group.

Disclosure

The authors report no conflicts of interest in this work.

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