Does climate mould the influence of mold on asthma?

As a result of short- and long-term climatic shifts, it appears likely that we may witness a rise in temperature and humidity, alterations in quantity and distribution of rainfall and a surge in extreme weather events. These meteorological changes can influence composition, production and spread of aero-allergens, as well as the growth and distribution of plants and other organisms that produce them. In individuals sensitized to these aero-allergens, exposures often result in an allergic response. Thus, it is reasonable to expect that qualitative, quantitative and temporal changes in aero-allergens and subsequent human exposure may result in changes in the occurrence, timing, severity and exacerbations of symptoms in persons with asthma.

The frequency of asthma attacks varies considerably from day-to-day, as indicated by numbers of hospital admissions or accident and emergency attendances for asthma. In many countries there is a predictable seasonal variation, with peak incidence during the early autumn, particularly in children.[1,2] These seasonal fluctuations are thought to be more closely related to the timing of school holidays and circulation of respiratory virus infections, than to seasonal variations in air quality or aero-allergen exposure.[1,3] Superimposed upon the seasonal pattern there are day-to-day variations in attack frequency which have attracted considerable interest in recent years as possible evidence of the adverse effects of outdoor air pollution levels. A recent meta-analysis found clear evidence of effects of PM10 on the occurrence of asthma symptom episodes.[4] Associations between single pollutants and a health outcome such as asthma are often inconsistent. In one review of 16 “methodologically sound” studies, ozone, sulfur dioxide and particles were identified as significant correlates of daily asthma attack rates in no more than half of the reports and one-quarter or less found a significant effect of particulate or nitrogen dioxide levels.[5] Thus, effects of single pollutants should not be interpreted narrowly, but rather as indicative of complex pollutant mixtures, which may vary by location.

Pollens and molds are the two major classes of clinically relevant outdoor aero-allergens. While considerable work has been done to explore the relationships between pollens and allergic disorders, the relationship between molds and asthma is less clear. Mold spores are considerably smaller than pollen grains, ranging in size from 2 to 10 μm and are more abundant.[6] Unlike pollen, mold is not localized to specific geographic regions, although its concentration may be higher in some regions due to specific environmental conditions. Also, unlike pollen, some molds can colonize indoor materials and concentrations of outdoor fungal species in indoor environments may or may not be driven by outdoor concentrations.[6-8] For example, *Alternaria* and *Cladosporium* are universally dominant outdoor fungal species that are detected indoors, while *Penicillium* and *Aspergillus* are universally dominant indoors. Multiple studies have suggested that exposures to *Alternaria*, *Aspergillus fumigatus* and *Cladosporium* may contribute to the development of asthma.[9-11] Further, a sizeable proportion of asthmatics may demonstrate hyperreactivity to one or more mold species.[12,13] At our own institute, 52.5% of adult asthmatics had *Aspergillus* sensitization.[14] Similar results have earlier been reported from a large hospital based study from Kolkata.[15]

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The environmental load of molds is usually inferred from fungal spore counts in ambient air. Due to their small size, spores liberated from fungi can remain suspended in air for long periods, ranging from a few hours to several days. A few studies have assessed spore counts in response to weather and climate changes. An analysis of 8 years spore count data in Denver, USA indicated a positive linear trend in *Cladosporium* spore counts over time, which was positively correlated with average daily temperature, relative humidity and negatively correlated with rainfall.[16] Neither *Alternaria* nor *Epicoccum* showed correlations with meteorological parameters. In another study, *Alternaria* concentrations during 1970-1998 in Derby, UK showed an upward trend, which increased markedly after 1992, with an earlier start date and a longer season over time.[17] In two other British sites, summer temperature was the strongest predictor of the number of days with high *Cladosporium* spore concentrations, while there was a negative relationship between rainfall and spore counts.[18]

The hypothesis that seasonal alterations in outdoor fungal aero-allergen load may contribute to episodic variations in asthma control is an attractive one. Two small studies from California, monitoring total fungal spore count over two different 6 weeks periods, showed significant association between spore count and symptoms severity, peak expiratory flow and as-needed inhaler use, even after adjusting for weather conditions.[19,20] A 13 weeks study on African American asthmatic children in Los Angeles found shortness of breath, wheeze and cough to be associated with fungal spore concentrations.[21] A preliminary study on 24 *Cladosporium* sensitized Danish adults with autumnal asthma, followed up for 11 weeks in peak spore season, showed *Cladosporium* spore count correlated significantly with weekly symptom score and medication use.[22] A prospective study in rural New Zealand showed only a weak association between days of high basidiospore counts and increased nocturnal wakening and reliever medication use in a small population of mild to moderate asthmatics.[23] In two studies from Turkey, outdoor fungi concentrations were significantly correlated with mean monthly asthma score and mean monthly morning and evening peak expiratory flow and climatic conditions among patients with asthma monosensitized to molds.[24,25]

Another study from New Mexico city showed that airborne fungal spore concentrations were significantly associated with asthma attacks in children (but not adults) during both wet and dry seasons.[26] Two studies from Canada have shown that increase in ambient fungal spore (but not pollen grain) count was significantly associated with more emergency visits in asthmatic children, after adjusting for secular trends, weather changes and air pollution.[27,28] Another Canadian study on multi-aero-allergen models of warm season asthma emergency visits between 1992 and 1996 found that *Ascomycetes*, *Alternaria* and small round fungal spores accounted for 4.5%, 4.7% and 3.0% of visits, respectively, at their mean concentrations.[29] A review of 1992-1993 data from London showed that the relative risks for increases in the number of emergency visits and hospital admissions associated with changes in fungal spore concentrations from the lower to upper quartiles were 1.06 (95% confidential interval: 0.94-1.18) and 1.07 (0.97-1.19) respectively in children with asthma; no evidence was found for associations in adults.[30] A number of individual spore taxa, in particular *Alternaria*, *Epicoccum*, *Agrocybe*, mildews, basidiospores and ascospores, were associated with increases in the number of emergency visits and hospital admissions, although the precision of these estimates were low. Analysis of another dataset between 1993 and 1996 from Derby in central England found that asthma admissions increased with *Cladosporium* spore count.[31] Another study evaluating hospital admissions for asthma in Trent during 1987-1994 found some evidence that exceptional rates of admission for asthma tend to occur on days with high total mold spore counts, but no specific taxon was consistently implicated.[32] In a retrospective study in Kuwait, an increase in number of asthmatics visiting an emergency clinic during December was significantly associated with high aerial counts for fungal spores during winter season.[33]

In contrast, a 1 year prospective study on more than 1000 Israeli children presenting to emergency services with asthma exacerbation over 1 year failed to show any correlation between daily airborne spore load and fluctuations in emergency visits.[34] Another 11 months study on a cohort of primary schoolchildren in Australia did not find any evidence for an association between peak expiratory flow and *Alternaria* spore concentrations.[35] A study on children admitted to a Cincinnati Hospital also found no association between asthma visits and daily fungal spore counts.[36]

Perhaps the most convincing evidence of an environmental influence on the incidence of asthma attacks arises from occasional "asthma epidemic days." Breathing cold and dry air is known to result in pulmonary function impairment among asthmatics.[37] More gross climatic events often result in major shifts in ambient aero-allergen loads and can lead to perceptible increases in asthma exacerbations. Most of the patients affected in these documented epidemics are atopic asthmatics and unusual aero-allergen exposures have been implicated in several instances. A striking example occurred in June 1994 when a thunderstorm over England was followed by a 10-fold increase in acute asthma attacks presenting to an emergency service.[38] These thunderstorm-related epidemics were probably due to "aero-allergen pollution."[39] A study from Canada has shown that fungal spore counts doubled and pediatric asthma emergency admissions increased by more than 15% during thunderstorm days, even though ambient concentrations of pollen grains and other air pollutants remained largely same.[40] Large dust-storms over African deserts are known to transport mold spores across continents and mold spores within these dust clouds may seed downwind ecosystems in both outdoor and indoor environments.[41] In New Orleans, it was noted that similar autumn epidemic days tended to be associated with high total spore and pollen counts.[42]

Recent cyclic and extreme weather events have also been implicated in increased mold production. Maximum spore counts were higher and 2-4 weeks earlier after the occurrence of an El Niño event in New England in 1998.[43] An examination of New Orleans housing after Hurricane Katrina exposed extensive mold growth and indoor and outdoor air sampling showed *Aspergillus* spp. and *Penicillium* spp. to be the predominant populations.[44]

Similar data from India is rather sparse. The vast area and geographic/environmental diversity in India suggests that the patterns of airborne fungal spores would vary widely.[45] In general, spores of *Aspergilli-Penicilli*, *Cladosporium, Helminthosporium, Epicoccum* and *Dreschlera* are reported to be common in ambient air in North India. *Aspergilli/Penicilli*, *Cladosporium,* Ascospores, rust and smut spores, *Nigrospora, Periconia, Ganoderma* and *Rhizopus* are major fungal types in Eastern India. *Cladosporium, Aspergilli-Penicilli, Curvularia, Rhizopus* and *Helminthosporium* are common in western India. A study from suburban West Bengal has reported that *Alternaria* spore counts rise during May and June, whereas *Cladosporium* spore counts rise in December.[46] In Delhi, *Cladosporium, Alternaria* and

Aspergillus counts were highest in October to February, April and September to October respectively.[47] *Alternaria* spore counts were highest in May in another report from Meerut.[48]

A small study from West Bengal noted spore concentration increased during early-winter and rainy season and diminished during late-winter and mid-summer and that the number of respiratory allergy cases and the air spora concentrations were positively correlated.[49] Another study from Meerut showed that seasonal fluctuations in number of asthmatics visiting the clinic, as well as symptoms of these patients, were closely related with *Alternaria* spore counts during different months of the year.[48]

Overall, relationship between climate factors and mold species, extent and geography suggests a complex multifactorial mechanism. It appears likely that climate changes can trigger more fungal spore production and alter the distribution timing and pattern. Increased environmental spore load in turn can worsen asthma control in susceptible patients. However, aero-allergen profiles differ greatly in different geographic regions. Moreover, limited availability of extensive aerobiological and epidemiological datasets over long periods presents difficulties in confirming such associations.

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