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EDITORIAL

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Time for Awareness: How does Global Warming Affect Respiratory Health

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Global warming is increasingly posing an escalating peril to human health. Following the industrial revolution beginning in the mid-19th century, human activities such as fossil fuel and biomass combustion have led to the accumulation of greenhouse gases which, in turn, absorb thermal radiation from the earth´s surface and trap the heat, that would otherwise be reflected into space, within the atmosphere (1). Consequently, the planet is warming up, with the most significant temperature spikes being observed within the last half-century. On one hand, increased temperatures cause the amount, intensity, and type of rainfall to become variable, leading to excessive precipitation and flooding. On the other hand, increased humidity contributes to heat stress and increases the likelihood of desertification. The risk of wild fire increases fivefold, and the frequency of sand and dust storms, especially in the Middle East, North Africa, and Pacific region, increases (1-3). In dry conditions, dust and particulate pollutants become more prevalent and pose a threat to human health. Increasing temperature, humidity and gaseous pollutants prolong pollen seasons and lead to the formation of more allergenic species (1). In addition, gaseous pollutants, which are also consequences of fossil fuel and biomass combustion, trigger a rise in the concentration of allergens in the atmosphere and alter the chemical properties, thereby increasing their allergenicity (1, 4, 5).

Urban areas experience a phenomenon known as urban heat island effect, where they exhibit higher temperatures than surrounding rural areas due to increased heat absorption and evaporation variation secondary to reduced vegetation in cities. Evidence shows that next to UV radiation, elevated temperatures lead to increased ozone levels, which are the main component of photochemical smog formed at ground level by the reaction of sunlight with nitrogen oxides (6). The presence of higher levels of particulate and gaseous air pollution in urban areas accentuates the risk of heat stress (7). The interaction between air pollution and climate change is synergistic, and causes a vicious cycle (6). A very recent project has shown that high temperatures combined with high air pollution levels contribute to an increase in deaths from lung diseases across 148 European cities (8).

All these exposures pose a risk to the integrity of the respiratory epithelial barrier, which is one of the surfaces of the body in contact with the external environment (4). The barrier is formed by the respiratory epithelial cells by connecting to each other with tight junctions and adherent junctions. It is further strengthened by airway mucus secretion, ciliary movements, and immunomodulatory molecules (9). The activity of neuronal cells and transient receptor potentials (TRP) in the mucosal lining also play a role in the maintenance of the barrier (9, 10).

Global warming have well-documented direct and indirect effects on the respiratory system (Figure 1), increasing the risk of premature death from respiratory disease. Heat and heat waves influence the thermoregulatory system, causing an increase in tidal volume and respiratory rate. This might be detrimental to patients with respiratory disease, who are no longer able to increase their minute

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ventilation and therefore have an increased risk of thermodysregulation and heat stroke (1, 11). On a molecular basis, warm air activates TRP channels, causing a cholinergic response that increases specific airway resistance and triggers reflex bronchoconstriction (11). In addition, heat waves might cause damage to cilia (12). In a mouse model, it was shown that the ciliary beat frequency of upper and lower respiratory epithelial cells decreased and the cells even died due to protein denaturation at 50 degrees and above (13), but more studies are needed to explain the effect of heat stress on ciliary movement. Heat stress has also been shown to lead to altered mucus production, disrupted epithelial barriers, airway hyperreactivity, activated Th2-prone inflammatory response, and increased levels of IL-4, IL-1ß, IL-6, and TNFα in a mouse model (14). Heat shock proteins (HSPs), so-called chaperones, have also been shown to be activated. Some of them help cells to adapt to heat and protect them from injury and apoptosis (e.g., HSP70, HSP72, HSP90), while others induce epithelial barrier damage (e.g. secreted HSP90α) and contribute to T2 inflammation when secreted extracellularly (e.g. HSP70) (15-17). All these molecular changes contribute to clinical manifestations of heat stress such as increased prevalence and exacerbation risk of asthma and allergic rhinitis (AR).

On the other hand, excess water accumulating in the atmosphere due to increased humidity secondary to extreme temperatures causes heavy rains, thunderstorms, and floods, further increasing humidity, and increasing indoor mold contamination and house dust mite levels. These airborne allergens have protease activities that disrupt respiratory epithelial barriers, increase permeability, and cause cilia dysfunction, thus leading to respiratory complications such as development and exacerbation of AR and asthma (18). Secondary to heavy rainfall and thunderstorms, pollen grains are mechanically broken down and sub-pollen particles are easily drawn into the lower airways, triggering asthma attacks (19). Similar to mold and house dust mite, pollen also has protease activity that results in increased epithelial permeability by breaking down occludin, claudin, and E-cadherin and initiating the allergic airway inflammatory response, facilitating the presentation of allergens, and paving the way for new sensitizations (20).

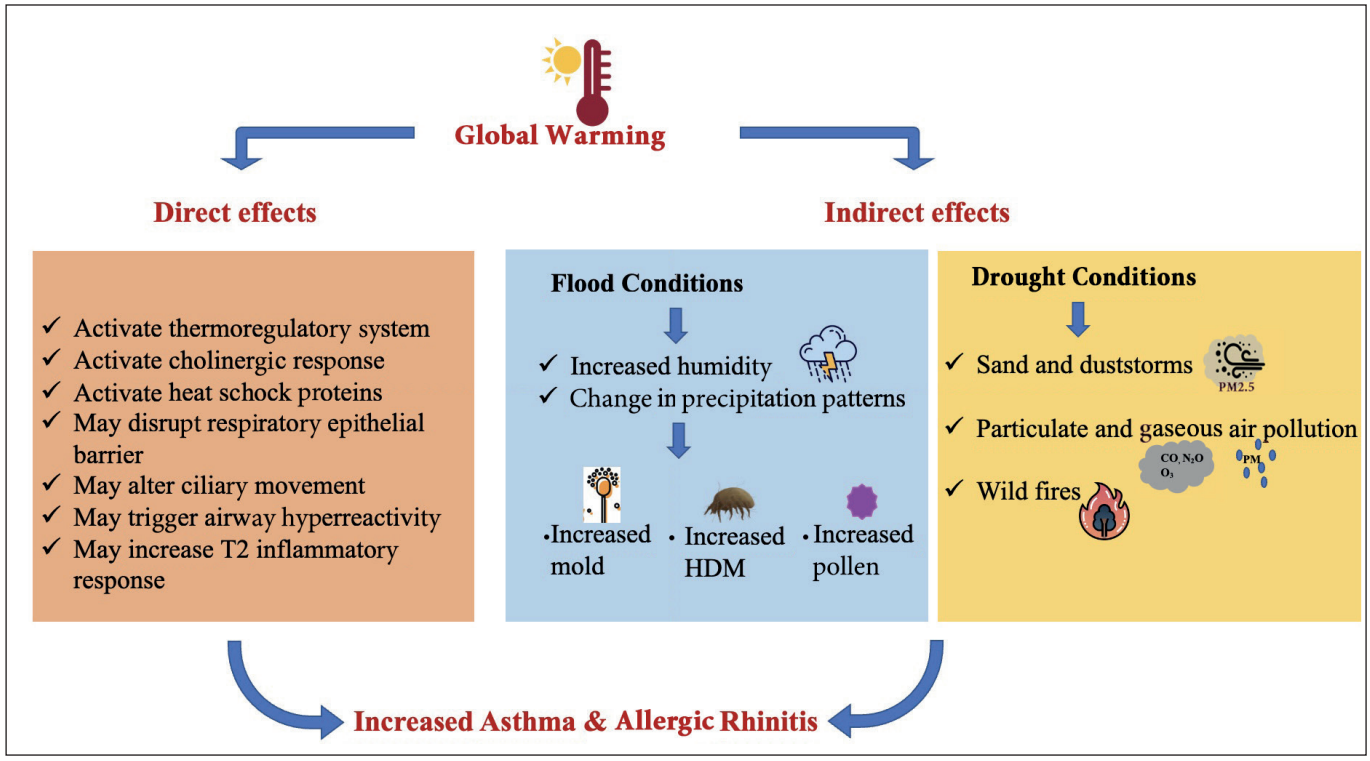

Figure 1. Direct and indirect effects of global warming.
CO_2: *Carbon dioxide,* ***HDM:*** *House dust mite,* ***N_2O:*** *Nitrous oxide,* ***O_3:*** *Ozone,* ***PM:*** *Particulate matter.*

Particulate matter (PM), especially $PM_{2.5}$, which is one of the important components of sand and dust storms, vegetation fires and general air pollution, disrupts respiratory epithelial barriers by breaking down tight junction proteins, increases paracellular permeability, causes ciliary loss and dysfunction, and increases mucus secretion (21). As an ultimate result, this aggravates AR and asthma. Ozone, another major threat to the respiratory system, damages alveolar cells and destroys epithelial barriers of the respiratory system, inducing mucociliary function, ROS production, and neutrophil migration. It increases inflammatory cytokines such as IL-17A, TNF-α, IL-1α and IL-1β, and activates TRPV1 channels (22). As a result, the risk of AR and asthma incidence and even respiratory mortality increases due to chronic particulate matter and ozone exposure.

In addition, climate change may increase the spread of infectious diseases such as the flu and RSV, and of vector-borne disease. Thereby it may cause the spread of diseases to new areas, where they have not been known before (i.e., Malaria, because Anopheles are now moving north.) Changes in temperature and humidity can alter disease transmission patterns and increased pollution can impair the first line defense of upper airways, disrupt epithelial barriers, generate reactive oxygen species, change the balance between inflammatory and anti-inflammatory macrophage polarizations, weaken antiviral immune responses, and increase susceptibility to infection (23).

In conclusion, it has been shown that global warming has significant effects on the respiratory system and is intricately linked to the emergence or exacerbation of respiratory diseases. It is crucial to monitor these effects through long-term analyses and standardized experimental models, to take collective action to reduce greenhouse gas emissions, to mitigate the impact of climate change on public health, to determine appropriate policies, and to increase public awareness.

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