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Desert dust and respiratory diseases: Further insight on the epithelial barrier hypothesis.

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Global warming and climate change pose a significant health concern as extreme weather events are becoming more frequent and severe, increasing exposure to environmental factors that aggravate respiratory diseases.^{1,2} Dust storms, also referred to as sandstorms, arise from arid regions when strong winds blow large amounts of loose sand and dirt into other areas. Small sand particles can remain airborne for days and travel long distances. Countries in the path of the sandstorm record a temporary but significant deterioration in air quality. Dust storms mainly originate from North Africa (the Sahara Desert), accounting for over 50% of the total global atmospheric dust, which is almost five times greater than the Arabian Peninsula, the second-biggest source.³

In this issue of Allergy, Bogan et al. reported the adverse effects of atmospheric sand dust particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) on mortality, emergency room (ER) visits, and hospitalizations due to asthma, chronic obstructive pulmonary disease (COPD), lower respiratory tract infections (LRTIs), and pulmonary embolism (PE) in Southeast Turkey.⁴ The 646,665 patients included in the study were admitted to four hospitals in Gaziantep located north of the Syrian Border. Among these, 624,387 were treated in the hospital and discharged, whilst 22,278 patients were hospitalized. A generalized additive Poisson regression model adjusted for confounding factors was used to evaluate the mortality and respiratory morbidity on main and lag effects of dust storms from 0-3 days, particulate matter (PM₁₀) levels, and maximum temperatures. The data

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indicated that dust storms increased the risk for same-day asthma mortality and same-day emergency room visits due to asthma and chronic obstructive pulmonary disease (COPD). Same-day hospitalizations due to asthma and lower respiratory tract infection (LRTIs), 2-day lagged hospitalizations due to COPD, and 3-day lagged hospitalizations due to LRTIs were positively associated with dust storms. In addition, the effect of maximum temperature and PM₁₀ concentration on respiratory indices was investigated.

Several studies have reported the health hazards of dust storms in relation to morbidity, hospitalization, mortality, and at-risk populations. Exposure to dust particles has been implicated in respiratory diseases (asthma and pneumonia), cardiovascular diseases (ischemic heart disease, cerebrovascular disease), COPD, conjunctivitis, and allergic rhinitis.³ Inhaled sand in subjects with airway hyperreactivity contribute to a proinflammatory response. In addition, all-cause hospital admissions had a significant association with the short-term health effects of dust storms.³ Studies conducted in regions with frequent sandstorms, such as in most countries in the Arabian Peninsula, suggest an increased prevalence of asthma in those countries, including Saudi Arabia (25 %),⁶ UAE (15.4 %),⁷ Qatar (19.8 %),⁸ and Kuwait (15.6 %).⁹ Asthma is largely uncontrolled in the Middle East, posing a significant socioeconomic burden and reducing the quality of life. Over 50% of children and 30% of adults have reported an absence from school and work due to asthma.⁵ Military personnel from the United States of America serving in Iraq developed respiratory diseases including asthma.¹⁰

Many factors affect the extent of the hazard posed by dust storms on health, e.g. the size of the PM. The diameter of PM from samples collected in the Saudi Arabian Peninsula ranged from less than 2 μm to 20 μm , with over 85% of dust particles measuring less than 10 μm . Particles smaller than 2.5 μm are a great health concern as they can penetrate deep into the gas-exchange region of the lung. The dust storm particulate matter damage to the lungs can be further aggravated by anthropogenic pollutants such as metals (e.g. cadmium, manganese, and nickel) and sulfur dioxide from car exhausts and industrial emissions.⁶ In addition, mold present in the dust storm can induce severe asthmatic exacerbations and even cause respiratory arrest in children and adolescent asthmatics.³ Similarly, inhalation of pollens during seasonal dust storms has been attributed to increasing asthma exacerbations.³ Such is the case in Japan, where worsening of asthma symptoms was reported during the dust dispersion period in April coinciding with high airborne levels of Japanese cedar pollen. These effects were more prevalent in patients with allergic rhinitis or atopy compared to controls.¹¹

There is a growing global pandemic of allergic, autoimmune and neurodegenerative diseases, representing one of our biggest health challenges today and a prominent change in humanity since its existence (Text box 1).¹² These diseases are currently affecting more than 25% of the global population, in contrast to only 1-2% in the 1960s. The epithelial barrier hypothesis has been proposed to explain the bewildering increase in many chronic noncommunicable diseases observed in the last 60 years. It attributes the origin of these diseases to a defective epithelial barrier triggered by environmental exposure to certain substances, including desert dust as in the study of Bogan et al, laundry and dishwashing detergents, emulsifiers as food additives, microplastics and rising ozone levels. Epithelial barrier damage in the airway, gastrointestinal, and skin epithelium can be induced by epigenetic mutations or exposure to toxic substances (See text box 2). Defective epithelial barriers are associated with the colonization of opportunistic pathogens

and loss of commensals in the affected organs with microbial dysbiosis. An immune response develops against the dysbiotic microbiome leading to a chronic periepithelial inflammation trying to expulse the microbiota that has translocated between and beneath the epithelial barriers. Overall, a chronic vicious cycle develops with the continuum of chronic mucosal and/or skin inflammation that plays a role in the chronicity and exacerbation of the aforementioned diseases. The strong link between the epithelial barrier hypothesis and dust storms is evident by the increased incidence and severity of asthma and COPD attacks during dust storms.

Desert dust contributes to the poor prognosis and mortality of chronic respiratory patients. This is in line with epidemiological evidence demonstrating that even trace amounts of certain toxic substances can damage epithelial barriers and increase bacterial translocation leading to microbial dysbiosis and inflammation in patients with chronic non-communicable diseases. These patients should avoid exposure to such substances as discussed here for desert dust and chronic respiratory diseases. The detrimental impact of desert dust on health will only become more evident with rising global temperatures and climate change as these increase the risk of exposure to barrier-damaging agents and sandstorms. Regulatory authorities should implement environmental measures to reduce global climate change and its associated health hazards, such as air pollution.³

Conflicts of interest:

CA has received research grants from the Swiss National Science Foundation, European Union (EU CURE), Novartis Research Institutes (Basel, Switzerland), Stanford University (Redwood City, Calif), and SciBase (Stockholm, Sweden); he is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic diseases and Asthma, and serves on the Advisory Boards of Sanofi/Regeneron, Novartis, GlaxoSmithKline, and SciBase, and is the Editor-in-Chief of Allergy. GD declares no conflict of interest in relation to this work.

Diseases affected by epithelial barrier defects

Local epithelial barrier defect and microbial dysbiosis directly affect respiratory and gastrointestinal tissues

- *Atopic dermatitis*
- *Asthma*
- *Chronic rhinosinusitis*
- *Allergic rhinitis and conjunctivitis*
- *Eosinophilic esophagitis*
- *Inflammatory bowel disease*
- *Coeliac disease*

Distant autoimmune and metabolic diseases linked to gut barrier defects and microbial dysbiosis

- *Diabetes*
- *Obesity*
- *Non-alcoholic steatohepatitis*
- *Autoimmune hepatitis*
- *Liver cirrhosis*
- *Rheumatoid arthritis*
- *Multiple sclerosis*
- *Systemic lupus erythematosus*
- *Ankylosing spondylitis*

Chronic neuropsychiatric conditions associated with a gut barrier defect and microbial dysbiosis

- *Autism spectrum disorders*
 - *Parkinson disease*
 - *Alzheimer disease*
 - *Stress-related psychiatric disorders*
 - *Chronic depression*
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Pathophysiology of diseases linked to epithelial barrier defects.

- Opening of the skin and mucosal epithelial barriers due to epigenetic changes or exposure to barrier-damaging agents.
 - Colonization of opportunistic pathogens, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*
 - Translocation of microbiota to inter and subepithelial areas
 - Immune response to commensals and opportunistic pathogens concomitant with systemic inflammation
 - Microbial dysbiosis and decreased biodiversity and commensals
 - Inflammation in the periepithelial area and chronicity
 - Immune cells migrating to distant organs from affected barrier areas
 - Defective barrier healing capacity due to inflammation and epigenetic regulation
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