Allergy Asthma Immunol Res. 2023 Nov;15(6):705-724
https://doi.org/10.4168/aair.2023.15.6.705
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Review

Check for updates

Epithelial Barrier Theory: The Role of Exposome, Microbiome, and Barrier Function in Allergic Diseases

Purevsuren Losol,[1,2,3,4] **Milena Sokolowska**,[5] **Yu-Kyoung Hwang**,[1,2] **Ismail Ogulur**,[5] **Yasutaka Mitamura**,[5] **Duygu Yazici**,[5] **Yagiz Pat**,[5] **Urszula Radzikowska**,[5] **Sena Ardicli**,[5] **Jeong-Eun Yoon**,[1,2] **Jun-Pyo Choi**,[1,2] **Sae-Hoon Kim**,[1,2,3] **Willem van de Veen**,[5] **Mübeccel Akdis**,[5] **Yoon-Seok Chang**,[1,2,3*] **Cezmi A. Akdis**[5]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[3]Medical Research Center, Seoul National University, Seoul, Korea
[4]Department of Molecular Biology and Genetics, School of Biomedicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia
[5]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

OPEN ACCESS

Received: Aug 2, 2023
Revised: Sep 18, 2023
Accepted: Oct 7, 2023
Published online: Oct 26, 2023

Correspondence to
Yoon-Seok Chang, MD, PhD
Department of Internal Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Tel: +82-31-787-7023
Fax: +82-31-787-4052
Email: addchang@snu.ac.kr

Copyright © 2023 The Korean Academy of Asthma, Allergy and Clinical Immunology · The Korean Academy of Pediatric Allergy and Respiratory Disease
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
Purevsuren Losol
https://orcid.org/0000-0001-7620-1077
Milena Sokolowska
https://orcid.org/0000-0001-9710-6685
Yu-Kyoung Hwang
https://orcid.org/0000-0002-8025-7134
Ismail Ogulur
https://orcid.org/0000-0001-8282-7762

ABSTRACT

Allergic diseases are a major public health problem with increasing prevalence. These immune-mediated diseases are characterized by defective epithelial barriers, which are explained by the epithelial barrier theory and continuously emerging evidence. Environmental exposures (exposome) including global warming, changes and loss of biodiversity, pollution, pathogens, allergens and mites, laundry and dishwasher detergents, surfactants, shampoos, body cleaners and household cleaners, microplastics, nanoparticles, toothpaste, enzymes and emulsifiers in processed foods, and dietary habits are responsible for the mucosal and skin barrier disruption. Exposure to barrier-damaging agents causes epithelial cell injury and barrier damage, colonization of opportunistic pathogens, loss of commensal bacteria, decreased microbiota diversity, bacterial translocation, allergic sensitization, and inflammation in the periepithelial area. Here, we review scientific evidence on the environmental components that impact epithelial barriers and microbiome composition and their influence on asthma and allergic diseases. We also discuss the historical overview of allergic diseases and the evolution of the hygiene hypothesis with theoretical evidence.

Keywords: Allergy; asthma; barrier; exposome; microbiota; microbiome; environment; exposure; climate; pollution

INTRODUCTION

According to the World Health Organization, approximately 10%–40% of the global population has been diagnosed with at least one of the allergic diseases. Additionally, around 40%–50% of school children have sensitization to at least one allergen.[1] The clinical presentation of atopic diseases often follows a well-described pattern, beginning from atopic dermatitis (AD) and food allergy (FA) in childhood, which can progress to allergic rhinitis (AR) and asthma later in life. This phenomenon is known as the "atopic march (or allergic march)."

Generated by xmlinkpress

Yasutaka Mitamura
https://orcid.org/0000-0001-6389-9285
Duygu Yazici
https://orcid.org/0000-0001-9094-6542
Yagiz Pat
https://orcid.org/0000-0003-4268-4933
Urszula Radzikowska
https://orcid.org/0000-0002-7341-9764
Sena Ardicli
https://orcid.org/0000-0003-2758-5945
Jeong-Eun Yoon
https://orcid.org/0000-0002-2374-1288
Jun-Pyo Choi
https://orcid.org/0000-0001-8925-1786
Sae-Hoon Kim
https://orcid.org/0000-0002-2572-5302
Willem van de Veen
https://orcid.org/0000-0001-9951-6688
Mübeccel Akdis
https://orcid.org/0000-0003-0554-9943
Yoon-Seok Chang
https://orcid.org/0000-0003-3157-0447
Cezmi A. Akdis
https://orcid.org/0000-0001-8020-019X

Disclosure
There are no financial or other issues that might lead to conflict of interest.

The development of allergic diseases has been attributed to complex interactions between genetic and environmental factors. Genetic susceptibility includes an association of well-described gene polymorphisms and allergic disease development.[2] However, this cannot explain the marked increase in the prevalence of allergic diseases in the short time frame of the last 60 years,[3,4] suggesting the important role of modern environmental factors in promoting the development of these diseases. Allergy prevalence varies widely across the globe, with higher rates in developed countries.[5] This could be influenced by several factors, including improved hygiene, changes in dietary habits, the introduction of various toxic chemicals to human lives, and exposure to outdoor and indoor pollutants. A recent meta-analysis of 22 chemical inventories from 19 countries revealed that more than 350,000 new substances had been introduced to human lives since the 1960s, unfortunately with little control over their health effects.[6] Other contributing factors can include climate change and reduced biodiversity. The "epithelial barrier theory" has been reframed to explain how environmental factors and lifestyle changes can impact human health.[7-9]

The "epithelial barrier theory" proposes mechanisms for developing allergic, autoimmune, and neurodegenerative diseases with inflammation and tissue damage. It accepts and embraces the hygiene and biodiversity hypotheses and links them to epithelial barrier defects and microbial dysbiosis. In addition, it demonstrates possible ways of preventing allergic and autoimmune diseases and suggests future research directions.[7] Early studies have studied apoptosis of epithelial cells for damaging the epithelial barrier in eczema and epithelial shedding in asthma and chronic sinusitis.[10-12] Around the same time, we started to understand the key roles of epithelial barriers by keeping away the exposome and washing away the inflammatory cells and cytokines.[13] Following this, epithelial barrier defect has been linked to type 2 response in asthma, chronic rhinosinusitis, and AD.[14-16] The role of interleukin (IL)-4 and IL-13 as well as T helper (Th) 2 cells and type 2 innate lymphoid cells have been reported.[17-19]

This review discusses the role of the exposome, lifestyle changes, and immunosenescence on epithelial barrier defects caused by damaged epithelial cells, dysregulated inflammatory responses, and microbial dysbiosis. It also discusses the evolution of the hygiene hypothesis and the role of epithelial barrier dysfunction in allergic diseases.

EPIDEMIOLOGY OF ALLERGIC DISEASES

A trend data analysis in the UK between 1971–1991 showed an increased prevalence of hay fever and eczema by 260% and 150%, respectively.[4] Since 1990, hospital admissions for allergic diseases (anaphylaxis, FA, urticaria, and angioedema) have increased dramatically (**Fig. 1**).[4] In contrast, hospital admissions for asthma increased from the early 1960s until the late 1980s and have since fallen and stabilized.[4,20-22] Although a plateau has been reached in the prevalence of asthma, AR, and AD in industrialized countries, their prevalence is still on the rise in developing countries.[23,24] The incidence of specific FAs, such as peanut allergy, has increased in Western nations in recent decades.[25] In the Global Asthma Network study conducted between 1993 and 2020, the prevalence of current wheeze decreased in low-income countries and increased in lower-middle-income countries, but was stable in upper-middle-income and high-income countries.[26] The International Study of Asthma and Allergies in Childhood (ISAAC), conducted between 1996–1997 and 2002–2003, demonstrated a significant increase in the percentage of children and adolescents reporting

https://doi.org/10.4168/aair.2023.15.6.705

asthma (**Fig. 1**).[27,28] The variance in the prevalence and severity of asthma, rhinoconjunctivitis, and eczema was observed not only between countries or regions but also between centers within the same country and the same city.[27] Those discrepancies could be explained by differences in environmental exposures, socioeconomic conditions, medical treatment availability, *etc*. In Korean nationwide cross-sectional survey (2008–2017), a 10-year trend study revealed a significant decrease in the prevalence of asthma in infants, preschool children, and the elderly, and in AD in infants and preschool children. Additionally, a significant increase in the prevalence of AR in school-age children, adults, and the elderly, and AD in school-age children and the elderly was observed.[29] A systematic review of studies conducted between 1978 and 2016 demonstrated an increased prevalence of AR, conjunctivitis, AD, and FA among children but an inconsistent pattern of asthma in Korea (**Fig. 1**).[30] After the 2000s, a new wave of allergic diseases is taking place, such as FA and anaphylaxis, eosinophilic gastrointestinal disease, particularly esophagitis and drug hypersensitivity and urticaria.[31-33]

Several lines of evidence have shown that environmental exposures are responsible for the rising prevalence of allergic diseases.[8,34-36] A 10-year follow-up (2008–2018) research conducted in the Polish urban city of Krakow has shown a reduction in the incidence of asthma and AR among children and adolescents, a possible link with improved air quality in the city.[34] While exposure to tobacco smoke and fungi on the house wall increased the risk of asthma, mite sensitization was associated with increased risks of AD, AR, and asthma among kindergarten children in Taiwan.[8] Consumption of certain foods (cereals, pasta, butter, margarine, and potato), physical activity, smoke exposure, and electronic device usage were linked to asthma among young Chinese adults, and parental asthma was the most important intrinsic epidemiological factor for asthma manifestation.[35] Children living in

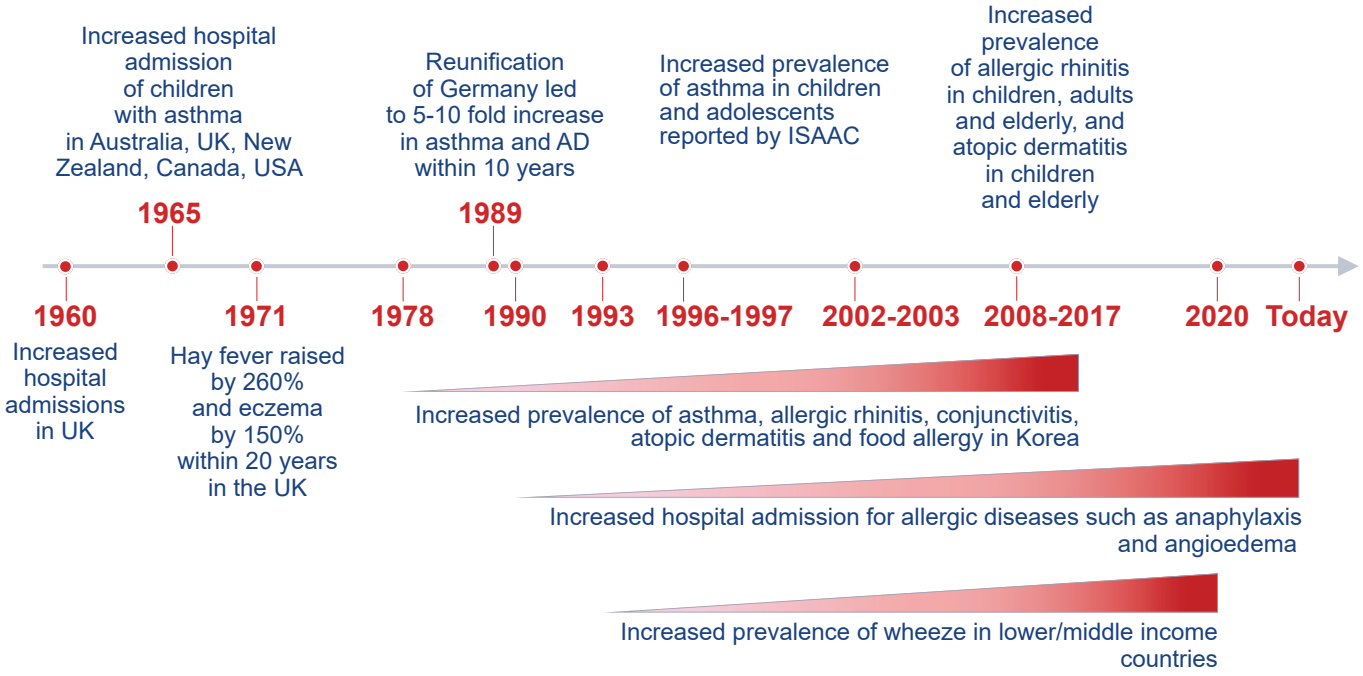


Fig. 1. Epidemiology of allergic diseases. The prevalence of allergies increased to epidemic levels, starting with asthma, as reported in the UK. A nearly 10-fold increase in pediatric asthma was observed in Australia, the UK, New Zealand, Canada, and the USA. Increased prevalence of allergic diseases since 1978 has been reported in different studies.
AD, atopic dermatitis.

https://doi.org/10.4168/aair.2023.15.6.705

areas surrounded by high road density and proximity were at an increased risk of developing atopic eczema, but not asthma or AR, and were more vulnerable to these conditions if they lived in deprived areas in Korea.[36] The prevalence of asthma and allergic diseases varies across countries and throughout the years, which could be influenced by the effects of environmental and lifestyle changes.

EVOLUTION OF HYGIENE HYPOTHESIS

Hygiene hypothesis

In 1989, Strachan[37] proposed the "hygiene hypothesis" to explain that the lower incidence of infection in early childhood limits the opportunity to prevent allergic diseases (**Fig. 2**). The paper observed that British children from larger families were less likely to develop hay fever. This could be related to the combined effect of declining family size, household, and high standard of personal cleanliness. In 1988, a year before the paper by Strachan,[37] Barker first used the term "hygiene hypothesis" when exploring a positive relationship between high

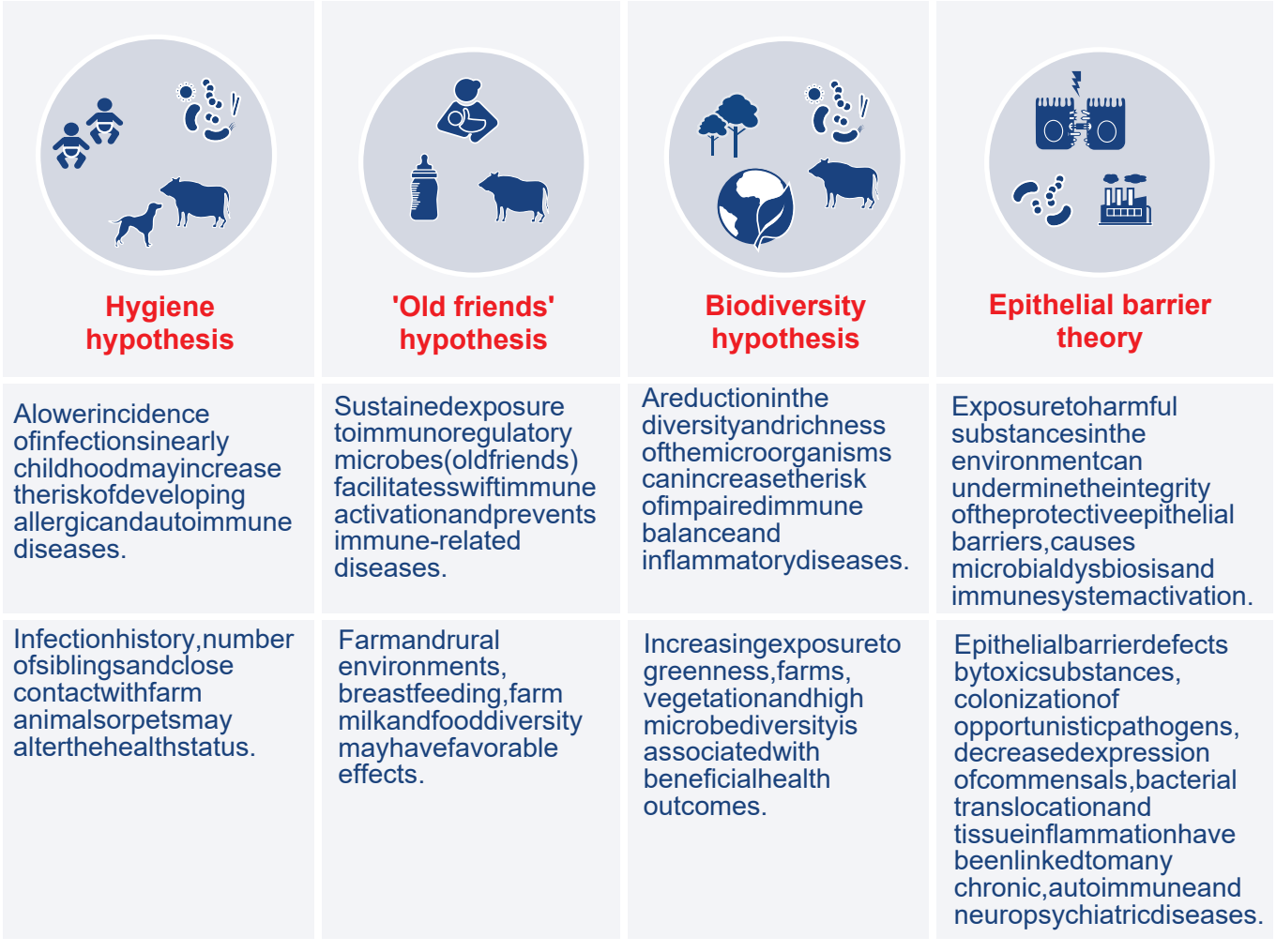


Fig. 2. Hypotheses for the development of allergic diseases. The hygiene hypothesis proposes a relationship between the incidence of allergic diseases and lower exposure to infection. 'Old friends' hypothesis explains the correlation between allergic disease development and exposure to immunoregulatory microbes at early ages. The biodiversity hypothesis defines the link between a biodiverse environment and health. Epithelial barrier theory proposes the interplay between environmental harmful substances and epithelial barrier dysfunction.

https://doi.org/10.4168/aair.2023.15.6.705

rates of appendicitis and particular patterns of food consumption and infectious diseases.[38,39] The findings sparked a surge of interest in the hypothesis, which led to its being explored in various research areas, including autoimmune and allergic diseases. Several birth cohort and family cohort studies reflected the link between allergy occurrence and the number of siblings in the household.[40,41] However, a review of 53 articles assessing the causal effect of the number of siblings on the development of allergy and asthma did not reach a definitive conclusion.[42] Epidemiological data have shown that farm exposure and close contact with the farmyard and animals protect from childhood allergies despite similar genetic ancestries and lifestyles.[43] A study of school children from farming communities, the Amish and Hutterites, found that the Amish who practice traditional farming had a lower prevalence of asthma and allergic sensitization in children than the Hutterites who practice industrial agriculture methods. It has to be noted here that it is not only the farming style that differs between the two communities but also the overall modern versus traditional lifestyle, including processed food as well as laundry detergents and cleaning material usage in Hutterites.[43]

Shortcomings of the hygiene hypothesis have been taken attention during the last few years. For example, water sanitation was established in many Western cities in the 1920s, but the allergy and asthma epidemics started in the 1960s. For the same reason, the protective role of parasite infections has also been questioned. Interestingly, allergic asthma is still rising in "unhygienic" cities in Asia and Africa.[44] Another limitation of the hygiene and biodiversity hypotheses is that probiotics have yet to prove to be a strong alternative for preventing or treating allergies.[45] Migrants moving from developing countries to affluent regions demonstrate a rapid increase in asthma and allergic diseases as well as autoimmune diseases, such as type 1 diabetes and multiple sclerosis.[9,23,24,46,47] Studies of migrants who do not develop allergies and asthma suggest that in-house living conditions are a more decisive factor than general public hygiene.[48] It can be concluded that many of the risk factors associated with FA, AR, AD, and asthma are not directly linked to hygiene but rather to the mode of delivery, antibiotic use, use of different cleaning products, dietary practices, indoor air pollution, and urbanization.[49-51]

"Old friends" hypothesis

In the early 2000s, Graham Rook postulated the "old friends" hypothesis, which explains that immunoregulatory microbes that have been accompanied throughout human existence are recognized by the host innate system as harmless or treated as "old friends" (**Fig. 2**). Continuing exposure to these microbes is necessary for prompt immune activation to prevent immune-mediated diseases. However, reduced exposure to these microbes can cause immune dysregulation.[52] Farm and rural environments are associated with high microbial load and are thought to reduce the risk of allergy by modulating the immune system. Early exposure to farm environments also influences DNA methylation in genes related to asthma and allergy.[53] Nutritional factors, such as breastfeeding, farm milk, and food diversity, may impact both epigenetic modifications and the protective effect of a farm environment on allergic diseases.[54,55] The European cross-sectional study (GABRIEL) showed that early life and long-term exposure to stables and farm milk decreased the development of asthma, hay fever, and atopic sensitization in children living in rural areas.[56] Other European birth cohort studies, Finnish rural-suburban LUKAS and German urban LISA, observed an association between higher bacterial diversity in early life and reduced risk of AR later in childhood.[57] The protective effect of a farming environment on sensitization to common allergens lasts into adulthood, but it may also induce sensitization to farm allergens.[58] It is conclusive that early-life exposure to farming, particularly maternal farming activities during pregnancy or growing up on a farm, shapes lung function development and can benefit allergy.[59,60]

https://doi.org/10.4168/aair.2023.15.6.705

Biodiversity hypothesis

The "biodiversity hypothesis" supports previous hypotheses proposing that more contact with natural environments would enrich the human microbiota that maintains immune balance and prevents inflammatory diseases (**Fig. 2**).[61,62] Biodiversity can be defined as complex interactions between species and their macro- and microenvironments.[63]

A large New Zealand birth cohort suggested that exposure to greenness and vegetation diversity may protect from childhood asthma.[64] Another cross-sectional ecological Australian epidemiology study has shown a positive correlation between natural and biodiverse environments and beneficial respiratory health outcomes.[65] The microbiome in nature is more diverse and dynamic and responds to changes in ecological conditions. This can change the microbiome's balance, significantly impacting the ecosystem and human health. A study has shown that residents in green areas have more diverse and healthy gut microbiota.[66]

Epithelial barrier theory and microbiome

In recent years, there has been a growing understanding of the complex interplay between the epithelial barrier and inflammation. The mechanisms underlying the "epithelial barrier theory" suggest that exposure to harmful substances in the environment can weaken the protective barriers of the skin, airways, and gastrointestinal mucosa, making them prone to bacterial leakage and dysbiosis.[7,67-69] Epithelial barrier defects and microbial dysbiosis have been linked to several immune-related diseases (**Fig. 2**).[70-74] The contribution of the microbes, including bacteria, fungi, viruses, archaea, and other microorganisms, and their interactions with the host are essential for the maturation and regulation of the immune system.[75]

The epithelial barrier theory endorses the biodiversity hypothesis by providing clear reasons for the missing biodiversity in chronic inflammatory diseases. Asthma, CRS, and AD have decreased biodiversity and colonized opportunistic pathogens.[76,77] The first reason for reduced biodiversity is because colonizing opportunistic pathogens such as *Staphylococcus aureus* overwhelm the inflamed areas and cause a decrease in *S. epidermidis* and *S. hominis*.[78] The second reason is a strong antimicrobial response in chronic epithelial barrier leaky areas involving *S. aureus* and other opportunistic pathogens. The third reason is that opportunistic pathogens have a more robust division capacity than commensals. The fourth reason is that toxic substances not only decrease the epithelial barrier function but also affect the microbial composition of chronically affected tissues.[79]

Commensal bacteria colonizing the oral cavity, skin, airway, and intestinal mucosa perform a protective function by mediating host immunity, directly inhibiting pathogen growth, and competing for colonization.[80] Once the epithelial barrier is impaired, opportunistic pathogens begin to dominate to cause decreased commensals and microbial diversity, contributing to the onset or development of many chronic immune-mediated and metabolic disorders.[71,72,81-83] Individuals with chronic rhinosinusitis and asthma present dominant pathogenic genera, such as *Streptococcus*, *Haemophilus*, *Staphylococcus*, and *Moraxella*, in the airway.[36,38,75] However, changes in commensal bacteria with anti-inflammatory and immunomodulatory properties, including *Bifidobacterium spp.*, *Lactobacillus spp.*, and *Akkermansia muciniphila*, have also been documented in their gut microbiome.[37,75,84] The abundance of Clostridia class bacteria in the gut differs between healthy and food-allergic twins.[85] Skin commensal *Acinetobacter* species may protect against allergic sensitization and lung inflammation by tuning the balance of Th1, Th2, and anti-inflammatory responses to environmental allergens.[86]

https://doi.org/10.4168/aair.2023.15.6.705

Major respiratory viruses found in the airways of children and adults with wheezing and asthma exacerbations include human rhinoviruses (RV) and respiratory syncytial viruses.[87,88] Coronavirus disease 2019 pandemics caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the recent changes in diagnosis, treatment, and seasonality of the viruses might change this situation, and a new equilibrium might be set,[89-92] especially for patients with asthma.[93,94] Recurrent viral infections contribute a lot to the temporary epithelial barrier disruption in asthma and AR due to direct effects on various innate immunity mechanisms such as activation of RIG-I inflammasome, damaging infected cells, delaying antiviral responses[93] and disrupting tight junctions (TJ) between the cells.[95,96] Additionally, the interkingdom dynamics between the viruses and bacteria on the mucosal barriers might influence the range of epithelial damage and subsequent type 2 or non-type 2 immune response.[97-99] The type of underlying inflammation at the mucosal barriers might also influence the susceptibility to the infection with RV, SARS-CoV-2, and the subsequent epithelium damage.[100]

EXTERNAL EXPOSOME IN EPITHELIAL BARRIER DAMAGE

Climate change and air pollution

Climate change and global warming are becoming major environmental threats to human health, and the changes are now being recognized as potential risk factors for epithelial barrier dysfunction. Climate change can disrupt the function of epithelial cells by increasing exposure to pollutants, elevating pollen emission, and changing its allergenic properties (**Fig. 3**).[101,102] A retrospective analysis of datasets with 20 years or more from 17 locations across the northern hemisphere showed that increases in daily minimum and maximum temperatures over time were associated with increases in seasonal pollen load and pollen season duration.[103] Allergens, such as pollens and house dust mite exposure, elicit nasal symptoms and suppress innate antiviral immunity by reducing interferon-λ and pro-inflammatory chemokine responses of airway epithelia.[93,104]

Air pollution by ozone, nitrogen dioxide, and diesel exhaust particles induces permeability of human bronchial epithelial cells and facilitates the penetration of allergens and irritants to the submucosa, where they interact with and activate immune cells.[105] Particulate matter (PM) exposures released from wildfires, sand, and dust storms have been associated with asthma, chronic obstructive pulmonary disease, pulmonary embolism, and infections in the lower airway.[106,107] A possible explanation for PM-related asthma relies on the impact on the airway via disruption of epithelial barrier integrity with downstream effects on the immune system.[107] Other extreme weather events, such as thunderstorms during pollen season, have been observed to induce severe asthma attacks and deaths in patients with pollen allergies.[108]

Cigarette smoke induces oxidative stress and epithelial cell death and inhibits epithelial repair processes, leading to several smoke-related lung diseases. Both cigarette smoking and vaping disturb oral, airway, and intestinal microbiota composition and diversity, promoting pathologic changes and impaired mucosal immune responses.[109,110]

Detergents and chemicals

Toxic substances in laundry, dishwashing, and household cleaning detergents can damage the respiratory, skin, and gut epithelium (**Fig. 3**). Professional dishwasher rinse aid caused cellular cytotoxicity and directly impaired barrier integrity of gut epithelial cells by damaging

https://doi.org/10.4168/aair.2023.15.6.705

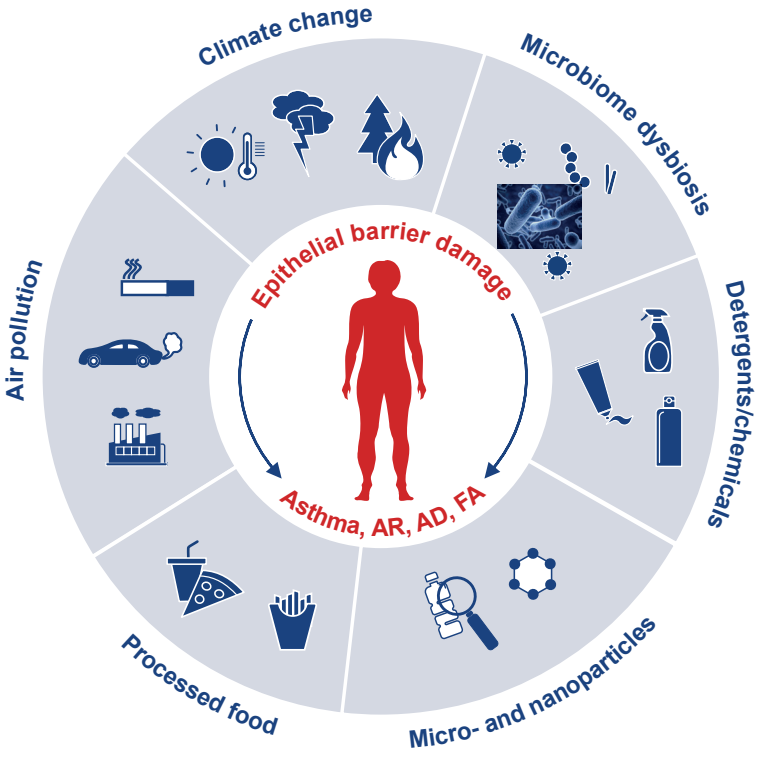


Fig. 3. External exposome factors that can impact the skin, lungs, and gut epithelial barrier defects. Climate change causes extreme weather events and results in the loss of biodiversity. Polluted air leads to changes in the composition and diversity of the microbiome. Processed foods promote the development of intestinal inflammation and microbial dysbiosis. Chemicals damage barrier integrity and increase the risk of infection. Microbial dysbiosis can lead to an overgrowth of harmful bacteria and damage the epithelial barrier. The role of these exposomes in epithelial barrier damage has been well-documented in allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergy.

TJ and adherence junction (AJ) expression in daily exposed concentrations.[111] The alcohol ethoxylates in the rinse aid that remains on washed dishware were identified as a culprit ingredient causing gut epithelial inflammation and barrier damage.[111] In the bronchial epithelial cells, laundry detergents and rinse residue (containing sodium dodecyl benzene sulfonate) directly disrupted TJ barrier integrity.[112,113] Transcriptomic analysis of the study revealed that exposure to laundry detergent at high dilution upregulated genes involved in lipid metabolism, apoptosis progress, and cell damage and downregulated genes involved in cell adhesion.[112]

Toothpaste containing sodium lauryl sulfate (SLS), the most commonly used detergent, to prevent the growth of some microorganisms and to remove plaques, affected the cell viability in oral epithelial cells.[114] SLS is also a frequent ingredient in soaps, cosmetics, and cleansing products. SLS patch on the skin resulted in skin redness, decreased stratum corneum hydration, and skin barrier function.[115] It also disturbed skin microbiota, increasing the abundance of pathogenic bacteria (Staphylococcaceae, Enterobacteriaceae, Pantoea) and decreasing skin commensals (Actinobacteria).

Micro-/nanoplastics

Plastic is used extensively in everyday life and can harm humans and the environment. Microplastics (< 5 mm) and nanoplastics (< 0.1 μm) are commonly present in food products, water, cosmetics, discharged health care products, packaging, household goods, *etc.*[116,117]

https://doi.org/10.4168/aair.2023.15.6.705

Humans are exposed to micro/nano-plastics via inhalation, ingestion, and skin contact. The smaller particles (inhalable fraction) are absorbed via the pulmonary epithelium and reach the systemic circulation. In contrast, microplastics > 150 μm are not absorbed and remain bound to the intestinal mucosal layer, where they induce local inflammation.[116] An advanced *in vitro* model study observed the translocation of micro/nano-plastics across the lung and intestinal epithelial barrier, activation of pro-inflammatory cells, and disrupted barrier integrity after exposure to micro/nano-plastics (**Fig. 3**).[118] Other cell line model studies have shown that airborne nanoplastics (40 nm polystyrene) induce oxidative stress and inflammatory responses, leading to cell death and epithelial barrier destruction in a size- and duration-dependent manner.[119,120] While there is limited research on the ability of nanoplastics to penetrate the skin, polystyrene particles with a diameter of 20–200 nm could infiltrate the top layer of the skin at a depth of 2–3 μm.[121]

Processed foods

Over time, food processing has evolved significantly in parallel with socioeconomic conditions. Modern food processing methods include canning, packaging, freezing, pasteurization, and adding chemicals. There is a substantial amount of evidence to suggest that a Western diet, characterized by high total and saturated fat, refined sugars, low fiber content, and processed foods, is associated with an increased risk of low-grade intestinal inflammation, dysbiosis, and a reduction of gut microbial diversity, and disturbed gut epithelial barrier function (**Fig. 3**).[122,123] Ultra-processed foods (snacks, drinks, sweets, and formulated foods), certain cheeses, oils, and margarine contain high levels of advanced glycation end products (AGEs). A high dietary intake of AGEs and AGE-forming sugars promotes the development of food allergies due to the misinterpretation of a threat from dietary allergens.[124] In Phase Three of the ISAAC, participants consuming fast food more than three times per week had an increased risk of developing asthma, rhinoconjunctivitis, and eczema.[125] Processed foods also contain synthetic colorants and emulsifiers, such as polysorbate 80 and carboxymethylcellulose, to enhance appearance and texture and extend shelf-life. Studies suggest that these products may enhance bacterial translocation across mucosal surfaces, affect the gut epithelial mucous layer, alter microbial composition, and contribute to the development of intestinal inflammation.[126-129] Recent study has shown that commonly used food emulsifiers, polysorbate 20 and polysorbate 80, cause cell death at daily-used concentrations, directly impair barrier integrity of gut epithelial cells, and cause molecular toxicity and proinflammation at lower doses.[129]

EPITHELIAL BARRIER DYSFUNCTION IN ALLERGIC DISEASES

The innate immune responses of epithelial cells are essential for maintaining tissue homeostasis. Epithelial cells facilitate mucociliary clearance, produce antimicrobial peptides and inflammatory cytokines, activate mucosal immune cells, and recruit these immune cells to the site of infection and inflammation, constituting a first physical, chemical, and immunological barrier.[130] Epithelial cells are also involved in tissue repair and remodeling processes by rapidly dividing, migrating, differentiating, secreting growth factors, and degrading extracellular matrix proteins.[131]

Studies have shown that opening the epithelial barrier induces inflammatory responses and increased epithelial permeability, creating a vicious cycle that potentiates dysregulated

https://doi.org/10.4168/aair.2023.15.6.705

subepithelial immune responses and more exposure to allergens and irritants.[70,132] Cell-cell adhesion complexes (TJ, AJ, desmosome) are the key regulators of paracellular permeability.[133] TJs defects and increased epithelial permeability are the main characteristics of chronic airway disease and leaky gut syndrome. Patients with asthma, AD, and FA express lower levels of TJ protein claudin-1 in the skin, bronchial and intestinal epithelium.[134] AR patients have reduced expression of the transmembrane proteins occludin and claudin-7, associated with exposure to second-hand smoke and urban locations.[135] It has also been reported that a high-fat diet and antibiotics affect intestinal permeability via altering microbial composition and disrupting intestinal TJs.[136,137] A perturbed gut integrity and permeability allow bacterial translocation into the circulation as further colonization by opportunistic pathogens makes the host more susceptible to inflammation, tissue damage, and chronic diseases.[138]

Epithelial cells release alarmin cytokines (IL-25, IL-33, and thymic stromal lymphopoietin [TSLP]) in response to allergens and infection. These cytokines prime the immune system to produce type-2 immune responses characterized by activation of mast cells, eosinophils, dendritic cells (DCs), Th2, and innate lymphoid 2 cells. In a functional study, IL-33 potentially drives virus-induced asthma exacerbations by suppressing Th1-innate antiviral response without affecting Th2-response (**Fig. 4**).[139] Clinical trials evaluating the effect of anti-IL-33 and its receptor ST2 and anti-TSLP in inflammatory allergic diseases have shown improvements in asthma exacerbation, inflammatory biomarkers, and lung function.[140]

Epithelial barriers gradually lose integrity with age due to the senescence of epithelial cells, leading to decreased protection from pathogens through the decreased mucociliary

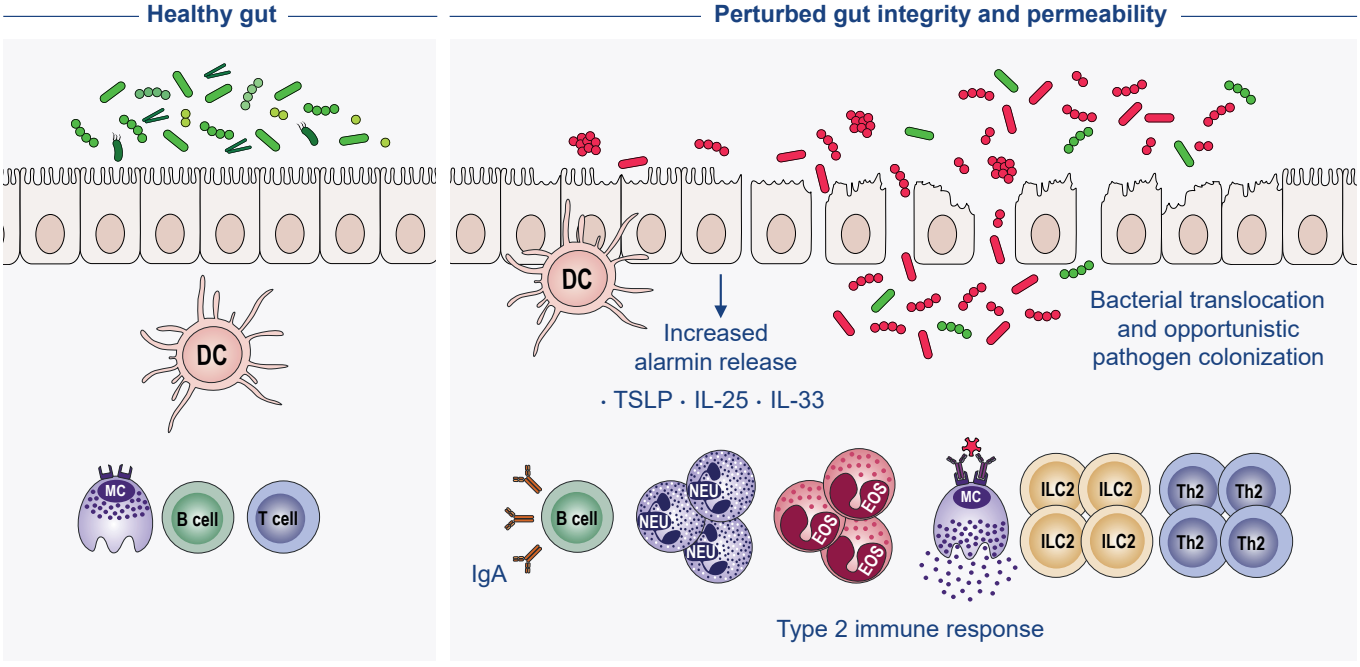


Fig. 4. Mechanisms of epithelial barrier theory. Perturbed gut integrity and permeability facilitate bacterial translocation and opportunistic pathogen colonization. Damaged epithelial cells produce TSLP, IL-25, and IL-33, followed by activation of immune cells. Type-2 cytokines and degranulation of mast cells exacerbate the inflammation and further attenuate barrier function.
DC, dendritic cell; TSLP, thymic stromal lymphopoietin; IL, interleukin; Ig, immunoglobulin.

https://doi.org/10.4168/aair.2023.15.6.705

function and leakiness through the loss of TJs and tissue damage.[141] Senescent epithelial cells increase airway susceptibility to infections or bacterial colonization in aged individuals, exacerbating existing asthma or potentially leading to late-onset asthma.[141] Age-associated alterations in DCs affect the function of epithelial cells. The DCs of the elderly secrete tumor necrosis factor-α that affects the function of primary bronchial epithelial cells, promoting airway inflammation.[142] In addition, aging in the lung is associated with chronic low-grade inflammation, characterized by increased IL-1β, IL-6, and IL-8 expression, that contributes to chronic inflammation, tissue damage, airway obstruction and remodeling.[143-145] Epithelium from asthmatics airways exhibits activated senescent signaling pathways, such as p16 and p21.[146] In human bronchial epithelial cells, TSLP induced p16 and p21 in a dose-dependent manner.[146] Silencing of these cellular senescence pathways inhibited TSLP-induced remodeling, demonstrating a functional role for senescent epithelial cells in airway remodeling.[146] Chronic rhinosinusitis in elderly patients commonly occurs with nasal polyps and is associated with increased levels of pro-inflammatory markers, tissue neutrophilia and bacterial infection.[147,148] The reduction in total and specific serum immunoglobulin (Ig)E levels with aging in patients with AR, asthma, and insect allergy suggests that the proportion of atopy may decrease in older adults.[149] However, the association between serum IgE levels and aging in AD is inconsistent.[150] Skin immunosenescence can cause a systematic type 2 inflammatory response by releasing alarmins from damaged epithelial cells and senescent skin stromal cells.[151] AD patients with this subtype show frequent allergic sensitization to other airborne and food allergens.[152] In addition, age-associated shifts in the microbiome and the microbiome's influence on the aging process have been documented.[150,153-155] The correlation between aging and microbiota composition is well established and suggests lower species richness during childhood, more stability and diversity during adulthood, and loss of some beneficial genera in individuals with advanced ages.[82,153,155]

CONCLUSIONS

In allergic diseases, exposure to harmful environmental substances significantly impacts public health by changing microbial composition and disrupting the skin, respiratory tract, and gut epithelial barrier. Loss of biodiversity and environmental degradation are also directly associated with an increased incidence of allergy. However, as the factors contributing to allergic sensitization and mucosal barrier function are discovered, inventive and rational modifications can be applied to reduce the burden of allergic diseases.

The barrier theory suggests a need for avoidance of the environmental cues and warrants further studies on safe levels of exposure to potentially harmful substances discussed here, such as inhaled and ingested detergents, ingestion of processed foods containing emulsifiers, exposure to PM, diesel exhaust, microplastics, and specific nanoparticles. As Paracelsus said in 1493, "sola dosis facit venenum," translating to all substances are poisons; everything can potentially become toxic; it merely depends on the dose. There is sufficient epidemiologic evidence from *in vitro* and *ex vivo* studies demonstrating that even trace amounts of enzymes and surfactants found in detergents can damage epithelial barriers and increase bacterial translocation. It is recommended that patients with diseases avoid exposure to these substances. There is a need for research into epithelial barriers, immune system, microbiome and environmental interactions, biochemical and molecular mechanisms associated with leaky barriers, and short- and long-term consequences of leaky epithelial barriers to advance our understanding.

https://doi.org/10.4168/aair.2023.15.6.705

ACKNOWLEDGMENTS

We thank Dr. Anna Globinska and Ms. Mandukhai Dulguun for their assistance in generating the figures. This work was partly supported by the Technology Innovation Program (or Industrial Strategic Technology Development Program - 20019505, Development of Microbiome-based Treatment for Asthma) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

REFERENCES

1. Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss M. WAO white book on allergy: update 2013. Geneva: World Allergy Organization; 2013. 248.
2. Radzikowska U, Baerenfaller K, Cornejo-Garcia JA, Karaaslan C, Barletta E, Sarac BE, et al. Omics technologies in allergy and asthma research: an EAACI position paper. Allergy 2022;77:2888-908.
PUBMED | CROSSREF
3. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. BMJ 1997;315:717-21.
PUBMED | CROSSREF
4. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. Thorax 2007;62:91-6.
PUBMED | CROSSREF
5. Dierick BJ, van der Molen T, Flokstra-de Blok BM, Muraro A, Postma MJ, Kocks JW, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. Expert Rev Pharmacoecon Outcomes Res 2020;20:437-53.
PUBMED | CROSSREF
6. Wang Z, Walker GW, Muir DC, Nagatani-Yoshida K. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ Sci Technol 2020;54:2575-84.
PUBMED | CROSSREF
7. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol 2021;21:739-51.
PUBMED | CROSSREF
8. Huang CF, Chie WC, Wang IJ. Effect of environmental exposures on allergen sensitization and the development of childhood allergic diseases: a large-scale population-based study. World Allergy Organ J 2021;14:100495.
PUBMED | CROSSREF
9. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R. Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. BMJ 1992;304:1020-2.
PUBMED | CROSSREF
10. Trautmann A, Akdis M, Kleemann D, Altznauer F, Simon HU, Graeve T, et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. J Clin Invest 2000;106:25-35.
PUBMED | CROSSREF
11. Trautmann A, Schmid-Grendelmeier P, Krüger K, Crameri R, Akdis M, Akkaya A, et al. T cells and eosinophils cooperate in the induction of bronchial epithelial cell apoptosis in asthma. J Allergy Clin Immunol 2002;109:329-37.
PUBMED | CROSSREF
12. Basinski TM, Holzmann D, Eiwegger T, Zimmermann M, Klunker S, Meyer N, et al. Dual nature of T cell-epithelium interaction in chronic rhinosinusitis. J Allergy Clin Immunol 2009;124:74-80.e1.
PUBMED | CROSSREF
13. Akdis CA. Allergy and hypersensitivity: mechanisms of allergic disease. Curr Opin Immunol 2006;18:718-26.
PUBMED | CROSSREF
14. Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-γ and IL-4. J Allergy Clin Immunol 2012;130:1087-1096.e10.
PUBMED | CROSSREF

15. De Benedetto A, Rafaels NM, McGirt LY, Ivanov AI, Georas SN, Cheadle C, et al. Tight junction defects in patients with atopic dermatitis. J Allergy Clin Immunol 2011;127:773-86.e1.
PUBMED | CROSSREF

16. Xiao C, Puddicombe SM, Field S, Haywood J, Broughton-Head V, Puxeddu I, et al. Defective epithelial barrier function in asthma. J Allergy Clin Immunol 2011;128:549-56.e1.
PUBMED | CROSSREF

17. Wawrzyniak P, Wawrzyniak M, Wanke K, Sokolowska M, Bendelja K, Rückert B, et al. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients. J Allergy Clin Immunol 2017;139:93-103.
PUBMED | CROSSREF

18. Sugita K, Steer CA, Martinez-Gonzalez I, Altunbulakli C, Morita H, Castro-Giner F, et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. J Allergy Clin Immunol 2018;141:300-310.e11.
PUBMED | CROSSREF

19. Pat Y, Rückert B, Ogulur I, Yazici D, Pérez-Diego M, Küçükkase OC, et al. Differentiation of bronchial epithelial spheroids in the presence of IL-13 recapitulates characteristic features of asthmatic airway epithelia. Allergy 2022;77:2229-33.
PUBMED | CROSSREF

20. Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. Thorax 2007;62:85-90.
PUBMED | CROSSREF

21. Mitchell EA. International trends in hospital admission rates for asthma. Arch Dis Child 1985;60:376-8.
PUBMED | CROSSREF

22. Krämer U, Schmitz R, Ring J, Behrendt H. What can reunification of East and West Germany tell us about the cause of the allergy epidemic? Clin Exp Allergy 2015;45:94-107.
PUBMED | CROSSREF

23. Grüber C, Illi S, Plieth A, Sommerfeld C, Wahn U. Cultural adaptation is associated with atopy and wheezing among children of Turkish origin living in Germany. Clin Exp Allergy 2002;32:526-31.
PUBMED | CROSSREF

24. Hammond SR, English DR, McLeod JG. The age-range of risk of developing multiple sclerosis: evidence from a migrant population in Australia. Brain 2000;123:968-74.
PUBMED | CROSSREF

25. Lieberman JA, Gupta RS, Knibb RC, Haselkorn T, Tilles S, Mack DP, et al. The global burden of illness of peanut allergy: a comprehensive literature review. Allergy 2021;76:1367-84.
PUBMED | CROSSREF

26. Asher MI, Rutter CE, Bissell K, Chiang CY, El Sony A, Ellwood E, et al. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. Lancet 2021;398:1569-80.
PUBMED | CROSSREF

27. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) phase three: a global synthesis. Allergol Immunopathol (Madr) 2013;41:73-85.
PUBMED | CROSSREF

28. Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J 2020;56:2002094.
PUBMED | CROSSREF

29. Ha J, Lee SW, Yon DK. Ten-year trends and prevalence of asthma, allergic rhinitis, and atopic dermatitis among the Korean population, 2008–2017. Clin Exp Pediatr 2020;63:278-83.
PUBMED | CROSSREF

30. Kang SY, Song WJ, Cho SH, Chang YS. Time trends of the prevalence of allergic diseases in Korea: a systematic literature review. Asia Pac Allergy 2018;8:e8.
PUBMED | CROSSREF

31. Willits EK, Park MA, Hartz MF, Schleck CD, Weaver AL, Joshi AY. Food allergy: a comprehensive population-based cohort study. Mayo Clin Proc 2018;93:1423-30.
PUBMED | CROSSREF

32. Hommeida S, Grothe RM, Hafed Y, Lennon RJ, Schleck CD, Alexander JA, et al. Assessing the incidence trend and characteristics of eosinophilic esophagitis in children in Olmsted County, Minnesota. Dis Esophagus 2018;31:doy062.
PUBMED | CROSSREF

33. Giavina-Bianchi P, Aun MV, Kalil J. Drug-induced anaphylaxis: is it an epidemic? Curr Opin Allergy Clin Immunol 2018;18:59-65.
PUBMED | CROSSREF

34. Mazur M, Czarnobilska M, Dyga W, Czarnobilska E. Trends in the epidemiology of allergic diseases of the airways in children growing up in an urban agglomeration. J Clin Med 2022;11:2188.
PUBMED | CROSSREF

35. Wong QY, Lim JJ, Ng JY, Malipeddi P, Lim YY, Sio YY, et al. An updated prevalence of asthma, its phenotypes, and the identification of the potential asthma risk factors among young Chinese adults recruited in Singapore. World Allergy Organ J 2023;16:100757.
PUBMED | CROSSREF

36. Yi SJ, Shon C, Min KD, Kim HC, Leem JH, Kwon HJ, et al. Association between exposure to traffic-related air pollution and prevalence of allergic diseases in children, Seoul, Korea. BioMed Res Int 2017;2017:4216107.
PUBMED | CROSSREF

37. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259-60.
PUBMED | CROSSREF

38. Morris J, Barker DJ, Nelson M. Diet, infection, and acute appendicitis in Britain and Ireland. J Epidemiol Community Health 1987;41:44-9.
PUBMED | CROSSREF

39. Perkin MR, Strachan DP. The hygiene hypothesis for allergy - conception and evolution. Front Allergy 2022;3:1051368.
PUBMED | CROSSREF

40. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax 2001;56:758-62.
PUBMED | CROSSREF

41. Gupta RS, Walkner MM, Greenhawt M, Lau CH, Caruso D, Wang X, et al. Food allergy sensitization and presentation in siblings of food allergic children. J Allergy Clin Immunol Pract 2016;4:956-62.
PUBMED | CROSSREF

42. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health 2002;56:209-17.
PUBMED | CROSSREF

43. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. N Engl J Med 2016;375:411-21.
PUBMED | CROSSREF

44. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-pacific region. Allergy Asthma Immunol Res 2013;5:251-7.
PUBMED | CROSSREF

45. Fiocchi A, Burks W, Bahna SL, Bielory L, Boyle RJ, Cocco R, et al. Clinical use of probiotics in pediatric allergy (CUPPA): a world allergy organization position paper. World Allergy Organ J 2012;5:148-67.
PUBMED | CROSSREF

46. Leung R. Asthma and migration. Respirology 1996;1:123-6.
PUBMED | CROSSREF

47. Rosenberg R, Vinker S, Zakut H, Kizner F, Nakar S, Kitai E. An unusually high prevalence of asthma in Ethiopian immigrants to Israel. Fam Med 1999;31:276-9.
PUBMED

48. Ernst SA, Schmitz R, Thamm M, Ellert U. Lower prevalence of atopic dermatitis and allergic sensitization among children and adolescents with a two-sided migrant background. Int J Environ Res Public Health 2016;13:265.
PUBMED | CROSSREF

49. Yu JE, Mallapaty A, Miller RL. It's not just the food you eat: ENVIRONMENTAL factors in the development of food allergies. Environ Res 2018;165:118-24.
PUBMED | CROSSREF

50. Milligan KL, Matsui E, Sharma H. Asthma in urban children: epidemiology, environmental risk factors, and the public health domain. Curr Allergy Asthma Rep 2016;16:33.
PUBMED | CROSSREF

51. Losol P, Barcik W. Dietary fiber and fermented food consumption and its link to allergic responses. Allergy 2022;77:2568-70.
PUBMED | CROSSREF

52. Rook GA, Brunet LR. Microbes, immunoregulation, and the gut. Gut 2005;54:317-20.
PUBMED | CROSSREF

53. Michel S, Busato F, Genuneit J, Pekkanen J, Dalphin JC, Riedler J, et al. Farm exposure and time trends in early childhood may influence DNA methylation in genes related to asthma and allergy. Allergy 2013;68:355-64.
PUBMED | CROSSREF

54. Frei R, Heye K, Roduit C. Environmental influences on childhood allergies and asthma - the farm effect. Pediatr Allergy Immunol 2022;33:e13807.
PUBMED | CROSSREF

55. Losol P, Rezwan FI, Patil VK, Venter C, Ewart S, Zhang H, et al. Effect of gestational oily fish intake on the risk of allergy in children may be influenced by *FADS1/2*, *ELOVL5* expression and DNA methylation. Genes Nutr 2019;14:20.
PUBMED | CROSSREF

56. Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001;358:1129-33.
PUBMED | CROSSREF

57. Hyytiäinen H, Kirjavainen PV, Täubel M, Tuoresmäki P, Casas L, Heinrich J, et al. Microbial diversity in homes and the risk of allergic rhinitis and inhalant atopy in two European birth cohorts. Environ Res 2021;196:110835.
PUBMED | CROSSREF

58. Koskela HO, Happonen KK, Remes ST, Pekkanen J. Effect of farming environment on sensitisation to allergens continues after childhood. Occup Environ Med 2005;62:607-11.
PUBMED | CROSSREF

59. Campbell B, Raherison C, Lodge CJ, Lowe AJ, Gislason T, Heinrich J, et al. The effects of growing up on a farm on adult lung function and allergic phenotypes: an international population-based study. Thorax 2017;72:236-44.
PUBMED | CROSSREF

60. House JS, Wyss AB, Hoppin JA, Richards M, Long S, Umbach DM, et al. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. J Allergy Clin Immunol 2017;140:249-256.e14.
PUBMED | CROSSREF

61. von Hertzen L, Hanski I, Haahtela T. Natural immunity. Biodiversity loss and inflammatory diseases are two global megatrends that might be related. EMBO Rep 2011;12:1089-93.
PUBMED | CROSSREF

62. Haahtela T. A biodiversity hypothesis. Allergy 2019;74:1445-56.
PUBMED | CROSSREF

63. Haahtela T, Alenius H, Lehtimäki J, Sinkkonen A, Fyhrquist N, Hyöty H, et al. Immunological resilience and biodiversity for prevention of allergic diseases and asthma. Allergy 2021;76:3613-26.
PUBMED | CROSSREF

64. Donovan GH, Gatziolis D, Longley I, Douwes J. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. Nat Plants 2018;4:358-64.
PUBMED | CROSSREF

65. Liddicoat C, Bi P, Waycott M, Glover J, Lowe AJ, Weinstein P. Landscape biodiversity correlates with respiratory health in Australia. J Environ Manage 2018;206:113-22.
PUBMED | CROSSREF

66. Wu K, Guo B, Guo Y, Han M, Xu H, Luo R, et al. Association between residential greenness and gut microbiota in Chinese adults. Environ Int 2022;163:107216.
PUBMED | CROSSREF

67. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, Turk M, Gorgulu Akin B, Akdis M, et al. Epithelial barrier hypothesis: Effect of the external exposome on the microbiome and epithelial barriers in allergic disease. Allergy 2022;77:1418-49.
PUBMED | CROSSREF

68. Pat Y, Ogulur I, Yazici D, Mitamura Y, Cevhertas L, Küçükkase OC, et al. Effect of altered human exposome on the skin and mucosal epithelial barrier integrity. Tissue Barriers. Forthcoming 2022.
PUBMED | CROSSREF

69. Losol P, Kim SH, Ahn S, Lee S, Choi JP, Kim YH, et al. Genetic variants in the TLR-related pathway and smoking exposure alter the upper airway microbiota in adult asthmatic patients. Allergy 2021;76:3217-20.
PUBMED | CROSSREF

70. Akdis CA. The epithelial barrier hypothesis proposes a comprehensive understanding of the origins of allergic and other chronic noncommunicable diseases. J Allergy Clin Immunol 2022;149:41-4.
PUBMED | CROSSREF

71. Losol P, Sokolowska M, Chang YS. Interactions between microbiome and underlying mechanisms in asthma. Respir Med 2023;208:107118.
PUBMED | CROSSREF

72. Losol P, Choi JP, Kim SH, Chang YS. The role of upper airway microbiome in the development of adult asthma. Immune Netw 2021;21:e19.
PUBMED | CROSSREF

73. Tuli JF, Ramezanpour M, Cooksley C, Psaltis AJ, Wormald PJ, Vreugde S. Association between mucosal barrier disruption by Pseudomonas aeruginosa exoproteins and asthma in patients with chronic rhinosinusitis. Allergy 2021;76:3459-69.
PUBMED | CROSSREF

74. Yamagishi M, Akagawa S, Akagawa Y, Nakai Y, Yamanouchi S, Kimata T, et al. Decreased butyric acid-producing bacteria in gut microbiota of children with egg allergy. Allergy 2021;76:2279-82.
PUBMED | CROSSREF

75. Barcik W, Boutin RC, Sokolowska M, Finlay BB. The role of lung and gut microbiota in the pathology of asthma. Immunity 2020;52:241-55.
PUBMED | CROSSREF

76. Komlósi ZI, van de Veen W, Kovács N, Szűcs G, Sokolowska M, O'Mahony L, et al. Cellular and molecular mechanisms of allergic asthma. Mol Aspects Med 2022;85:100995.
PUBMED | CROSSREF

77. Lunjani N, Hlela C, O'Mahony L. Microbiome and skin biology. Curr Opin Allergy Clin Immunol 2019;19:328-33.
PUBMED | CROSSREF

78. Altunbulakli C, Reiger M, Neumann AU, Garzorz-Stark N, Fleming M, Huelpuesch C, et al. Relations between epidermal barrier dysregulation and Staphylococcus species-dominated microbiome dysbiosis in patients with atopic dermatitis. J Allergy Clin Immunol 2018;142:1643-1647.e12.
PUBMED | CROSSREF

79. Abdurrahman G, Schmiedeke F, Bachert C, Bröker BM, Holtfreter S. Allergy-a new role for T cell superantigens of *Staphylococcus aureus?* Toxins (Basel) 2020;12:176.
PUBMED | CROSSREF

80. Khan R, Petersen FC, Shekhar S. Commensal bacteria: an emerging player in defense against respiratory pathogens. Front Immunol 2019;10:1203.
PUBMED | CROSSREF

81. Pascal M, Perez-Gordo M, Caballero T, Escribese MM, Lopez Longo MN, Luengo O, et al. Microbiome and allergic diseases. Front Immunol 2018;9:1584.
PUBMED | CROSSREF

82. Losol P, Park HS, Song WJ, Hwang YK, Kim SH, Holloway JW, et al. Association of upper airway bacterial microbiota and asthma: systematic review. Asia Pac Allergy 2022;12:e32.
PUBMED | CROSSREF

83. Alemao CA, Budden KF, Gomez HM, Rehman SF, Marshall JE, Shukla SD, et al. Impact of diet and the bacterial microbiome on the mucous barrier and immune disorders. Allergy 2021;76:714-34.
PUBMED | CROSSREF

84. Michalovich D, Rodriguez-Perez N, Smolinska S, Pirozynski M, Mayhew D, Uddin S, et al. Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients. Nat Commun 2019;10:5711.
PUBMED | CROSSREF

85. Bao R, Hesser LA, He Z, Zhou X, Nadeau KC, Nagler CR. Fecal microbiome and metabolome differ in healthy and food-allergic twins. J Clin Invest 2021;131:e141935.
PUBMED | CROSSREF

86. Fyhrquist N, Ruokolainen L, Suomalainen A, Lehtimäki S, Veckman V, Vendelin J, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. J Allergy Clin Immunol 2014;134:1301-1309.e11.
PUBMED | CROSSREF

87. Jartti T, Bønnelykke K, Elenius V, Feleszko W. Role of viruses in asthma. Semin Immunopathol 2020;42:61-74.
PUBMED | CROSSREF

88. Makrinioti H, Hasegawa K, Lakoumentas J, Xepapadaki P, Tsolia M, Castro-Rodriguez JA, et al. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma: a systematic review and meta-analysis. Pediatr Allergy Immunol 2022;33:e13741.
PUBMED | CROSSREF

89. Sokolowska M, Rovati GE, Diamant Z, Untersmayr E, Schwarze J, Lukasik Z, et al. Effects of non-steroidal anti-inflammatory drugs and other eicosanoid pathway modifiers on antiviral and allergic responses: EAACI task force on eicosanoids consensus report in times of COVID-19. Allergy 2022;77:2337-54.
PUBMED | CROSSREF

90. Bravo-Queipo-de-Llano B, Sánchez García L, Casas I, Pozo F, La Banda L, Alcolea S, et al. Surveillance of viral respiratory infections in the neonatal intensive care unit-evolution in the last 5 years. Pathogens 2023;12:644.
PUBMED | CROSSREF

91. Pinky L, DeAguero JR, Remien CH, Smith AM. how interactions during viral-viral coinfection can shape infection kinetics. Viruses 2023;15:1303.
PUBMED | CROSSREF

92. Styrzynski F, Zhakparov D, Schmid M, Roqueiro D, Lukasik Z, Solek J, et al. Machine learning successfully detects patients with COVID-19 prior to PCR results and predicts their survival based on standard laboratory parameters in an observational study. Infect Dis Ther 2023;12:111-29.
PUBMED | CROSSREF

93. Radzikowska U, Eljaszewicz A, Tan G, Stocker N, Heider A, Westermann P, et al. Rhinovirus-induced epithelial RIG-I inflammasome suppresses antiviral immunity and promotes inflammation in asthma and COVID-19. Nat Commun 2023;14:2329.
PUBMED | CROSSREF

94. Sokolowska M, Radzikowska U. How can allergen immunotherapy protect against COVID-19? Am J Respir Crit Care Med 2023;207:1408-10.
PUBMED | CROSSREF

95. Kast JI, McFarlane AJ, Głobińska A, Sokolowska M, Wawrzyniak P, Sanak M, et al. Respiratory syncytial virus infection influences tight junction integrity. Clin Exp Immunol 2017;190:351-9.
PUBMED | CROSSREF

96. Sajjan U, Wang Q, Zhao Y, Gruenert DC, Hershenson MB. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care Med 2008;178:1271-81.
PUBMED | CROSSREF

97. Teo SM, Tang HH, Mok D, Judd LM, Watts SC, Pham K, et al. Airway microbiota dynamics uncover a critical window for interplay of pathogenic bacteria and allergy in childhood respiratory disease. Cell Host Microbe 2018;24:341-352.e5.
PUBMED | CROSSREF

98. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020;75:1564-81.
PUBMED | CROSSREF

99. Losol P, Ji MH, Kim JH, Choi JP, Yun JE, Seo JH, et al. Bronchial epithelial cells release inflammatory markers linked to airway inflammation and remodeling in response to TLR5 ligand flagellin. World Allergy Organ J 2023;16:100786.
PUBMED | CROSSREF

100. Stocker N, Radzikowska U, Wawrzyniak P, Tan G, Huang M, Ding M, et al. Regulation of angiotensin-converting enzyme 2 isoforms by type 2 inflammation and viral infection in human airway epithelium. Mucosal Immunol 2023;16:5-16.
PUBMED | CROSSREF

101. D'Amato G, Chong-Neto HJ, Monge Ortega OP, Vitale C, Ansotegui I, Rosario N, et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. Allergy 2020;75:2219-28.
PUBMED | CROSSREF

102. Davies JM. Grass pollen allergens globally: the contribution of subtropical grasses to burden of allergic respiratory diseases. Clin Exp Allergy 2014;44:790-801.
PUBMED | CROSSREF

103. Ziska LH, Makra L, Harry SK, Bruffaerts N, Hendrickx M, Coates F, et al. Temperature-related changes in airborne allergenic pollen abundance and seasonality across the northern hemisphere: a retrospective data analysis. Lancet Planet Health 2019;3:e124-31.
PUBMED | CROSSREF

104. Gilles S, Blume C, Wimmer M, Damialis A, Meulenbroek L, Gökkaya M, et al. Pollen exposure weakens innate defense against respiratory viruses. Allergy 2020;75:576-87.
PUBMED | CROSSREF

105. D'Amato G, Holgate ST, Pawankar R, Ledford DK, Cecchi L, Al-Ahmad M, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. World Allergy Organ J 2015;8:25.
PUBMED | CROSSREF

106. D'Amato G, Akdis CA. Desert dust and respiratory diseases: Further insights into the epithelial barrier hypothesis. Allergy 2022;77:3490-2.
PUBMED | CROSSREF

107. Noah TL, Worden CP, Rebuli ME, Jaspers I. The effects of wildfire smoke on asthma and allergy. Curr Allergy Asthma Rep 2023;23:375-87.
PUBMED | CROSSREF

108. D'Amato G, Annesi-Maesano I, Cecchi L, D'Amato M. Latest news on relationship between thunderstorms and respiratory allergy, severe asthma, and deaths for asthma. Allergy 2019;74:9-11.
PUBMED | CROSSREF

109. Chopyk J, Bojanowski CM, Shin J, Moshensky A, Fuentes AL, Bonde SS, et al. Compositional differences in the oral microbiome of E-cigarette users. Front Microbiol 2021;12:599664.
PUBMED | CROSSREF

110. Gui X, Yang Z, Li MD. Effect of cigarette smoke on gut microbiota: state of knowledge. Front Physiol 2021;12:673341.
PUBMED | CROSSREF

111. Ogulur I, Pat Y, Aydin T, Yazici D, Rückert B, Peng Y, et al. Gut epithelial barrier damage caused by dishwasher detergents and rinse aids. J Allergy Clin Immunol 2023;151:469-84.
PUBMED | CROSSREF

112. Wang M, Tan G, Eljaszewicz A, Meng Y, Wawrzyniak P, Acharya S, et al. Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells. J Allergy Clin Immunol 2019;143:1892-903.
PUBMED | CROSSREF

113. Saito K, Orimo K, Kubo T, Tamari M, Yamada A, Motomura K, et al. Laundry detergents and surfactants-induced eosinophilic airway inflammation by increasing IL-33 expression and activating ILC2s. Allergy 2023;78:1878-92.
PUBMED | CROSSREF

114. Birant S, Duran Y, Akkoc T, Seymen F. Cytotoxic effects of different detergent containing children's toothpastes on human gingival epithelial cells. BMC Oral Health 2022;22:66.
PUBMED | CROSSREF

115. Leoty-Okombi S, Gillaizeau F, Leuillet S, Douillard B, Le Fresne-Languille S, Carton T, et al. Effect of sodium lauryl sulfate (SLS) applied as a patch on human skin physiology and its microbiota. Cosmetics 2021;8:6.
CROSSREF

116. Hirt N, Body-Malapel M. Immunotoxicity and intestinal effects of nano- and microplastics: a review of the literature. Part Fibre Toxicol 2020;17:57.
PUBMED | CROSSREF

117. Yee MS, Hii LW, Looi CK, Lim WM, Wong SF, Kok YY, et al. Impact of microplastics and nanoplastics on human health. Nanomaterials (Basel) 2021;11:496.
PUBMED | CROSSREF

118. Donkers JM, Höppener EM, Grigoriev I, Will L, Melgert BN, van der Zaan B, et al. Advanced epithelial lung and gut barrier models demonstrate passage of microplastic particles. Microplastics and Nanoplastics 2022;2:6.
CROSSREF

119. Yang S, Cheng Y, Chen Z, Liu T, Yin L, Pu Y, et al. *In vitro* evaluation of nanoplastics using human lung epithelial cells, microarray analysis and co-culture model. Ecotoxicol Environ Saf 2021;226:112837.
PUBMED | CROSSREF

120. Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol Appl Pharmacol 2001;175:191-9.
PUBMED | CROSSREF

121. Campbell CS, Contreras-Rojas LR, Delgado-Charro MB, Guy RH. Objective assessment of nanoparticle disposition in mammalian skin after topical exposure. J Control Release 2012;162:201-7.
PUBMED | CROSSREF

122. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr 2015;114:999-1012.
PUBMED | CROSSREF

123. Bolte LA, Vich Vila A, Imhann F, Collij V, Gacesa R, Peters V, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut 2021;70:1287-98.
PUBMED | CROSSREF

124. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: Food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. J Allergy Clin Immunol 2017;139:429-37.
PUBMED | CROSSREF

125. Ellwood P, Asher MI, García-Marcos L, Williams H, Keil U, Robertson C, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. Thorax 2013;68:351-60.
PUBMED | CROSSREF

126. Chassaing B, Van de Wiele T, De Bodt J, Marzorati M, Gewirtz AT. Dietary emulsifiers directly alter human microbiota composition and gene expression *ex vivo* potentiating intestinal inflammation. Gut 2017;66:1414-27.
PUBMED | CROSSREF

127. Roberts CL, Rushworth SL, Richman E, Rhodes JM. Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. J Crohn's Colitis 2013;7:338-41.
PUBMED | CROSSREF

128. Kwon YH, Banskota S, Wang H, Rossi L, Grondin JA, Syed SA, et al. Chronic exposure to synthetic food colorant Allura Red AC promotes susceptibility to experimental colitis via intestinal serotonin in mice. Nat Commun 2022;13:7617.
PUBMED | CROSSREF

129. Ogulur I, Yazici D, Pat Y, Bingöl EN, Babayev H, Ardicli S, et al. Mechanisms of gut epithelial barrier impairment caused by food emulsifiers polysorbate 20 and polysorbate 80. Allergy 2023;78:2441-55.
PUBMED | CROSSREF

130. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. Immunity 2015;43:29-40.
PUBMED | CROSSREF

131. Croasdell Lucchini A, Gachanja NN, Rossi AG, Dorward DA, Lucas CD. Epithelial cells and inflammation in pulmonary wound repair. Cells 2021;10:339.
PUBMED | CROSSREF

132. Kim SR. Viral infection and airway epithelial immunity in asthma. Int J Mol Sci 2022;23:9914.
PUBMED | CROSSREF

133. Hellings PW, Steelant B. Epithelial barriers in allergy and asthma. J Allergy Clin Immunol 2020;145:1499-509.
PUBMED | CROSSREF

134. Xia Y, Cao H, Zheng J, Chen L. Claudin-1 mediated tight junction dysfunction as a contributor to atopic march. Front Immunol 2022;13:927465.
PUBMED | CROSSREF

135. Nur Husna SM, Siti Sarah CO, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Reduced occludin and claudin-7 expression is associated with urban locations and exposure to second-hand smoke in allergic rhinitis patients. Sci Rep 2021;11:1245.
PUBMED | CROSSREF

136. Nascimento JC, Matheus VA, Oliveira RB, Tada SF, Collares-Buzato CB. High-fat diet induces disruption of the tight junction-mediated paracellular barrier in the proximal small intestine before the onset of type 2 diabetes and endotoxemia. Dig Dis Sci 2021;66:3359-74.
PUBMED | CROSSREF

137. Feng Y, Huang Y, Wang Y, Wang P, Song H, Wang F. Antibiotics induced intestinal tight junction barrier dysfunction is associated with microbiota dysbiosis, activated NLRP3 inflammasome and autophagy. PLoS One 2019;14:e0218384.
PUBMED | CROSSREF

138. Nagpal R, Yadav H. Bacterial translocation from the gut to the distant organs: an overview. Ann Nutr Metab 2017;71 Suppl 1:11-6.
PUBMED | CROSSREF

139. Ravanetti L, Dijkhuis A, Dekker T, Sabogal Pineros YS, Ravi A, Dierdorp BS, et al. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity. J Allergy Clin Immunol 2019;143:1355-1370.e16.
PUBMED | CROSSREF

140. Gauvreau GM, Bergeron C, Boulet LP, Cockcroft DW, Côté A, Davis BE, et al. Sounding the alarmins: the role of alarmin cytokines in asthma. Allergy 2023;78:402-17.
PUBMED | CROSSREF

141. Teissier T, Boulanger E, Cox LS. Interconnections between inflammageing and immunosenescence during ageing. Cells 2022;11:359.
PUBMED | CROSSREF

142. Prakash S, Agrawal S, Vahed H, Ngyuen M, BenMohamed L, Gupta S, et al. Dendritic cells from aged subjects contribute to chronic airway inflammation by activating bronchial epithelial cells under steady state. Mucosal Immunol 2014;7:1386-94.
PUBMED | CROSSREF

143. Meyer KC, Ershler W, Rosenthal NS, Lu XG, Peterson K. Immune dysregulation in the aging human lung. Am J Respir Crit Care Med 1996;153:1072-9.
PUBMED | CROSSREF

144. Moliva JI, Rajaram MV, Sidiki S, Sasindran SJ, Guirado E, Pan XJ, et al. Molecular composition of the alveolar lining fluid in the aging lung. Age (Dordr) 2014;36:9633.
PUBMED | CROSSREF

145. Sunaga N, Kaira K, Tomizawa Y, Shimizu K, Imai H, Takahashi G, et al. Clinicopathological and prognostic significance of interleukin-8 expression and its relationship to KRAS mutation in lung adenocarcinoma. Br J Cancer 2014;110:2047-53.
PUBMED | CROSSREF

146. Wu J, Dong F, Wang RA, Wang J, Zhao J, Yang M, et al. Central role of cellular senescence in TSLP-induced airway remodeling in asthma. PLoS One 2013;8:e77795.
PUBMED | CROSSREF

147. Morse JC, Li P, Ely KA, Shilts MH, Wannemuehler TJ, Huang LC, et al. Chronic rhinosinusitis in elderly patients is associated with an exaggerated neutrophilic proinflammatory response to pathogenic bacteria. J Allergy Clin Immunol 2019;143:990-1002.e6.
PUBMED | CROSSREF

148. Stryjewska-Makuch G, Glück J, Branicka O, Lisowska G. Phenotypes of chronic rhinosinusitis and peripheral blood leukocytes parameters in elderly patients. Medicina (Kaunas) 2023;59:126.
PUBMED | CROSSREF

149. Mediaty A, Neuber K. Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. Immun Ageing 2005;2:9.
PUBMED | CROSSREF

150. Zhou L, Leonard A, Pavel AB, Malik K, Raja A, Glickman J, et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2019;144:144-56.
PUBMED | CROSSREF

151. Chen B, Yang J, Song Y, Zhang D, Hao F. Skin immunosenescence and type 2 inflammation: a mini-review with an inflammaging perspective. Front Cell Dev Biol 2022;10:835675.
PUBMED | CROSSREF

152. Tanei R, Hasegawa Y. Atopic dermatitis in older adults: a viewpoint from geriatric dermatology. Geriatr Gerontol Int 2016;16 Suppl 1:75-86.
PUBMED | CROSSREF

153. Xu C, Zhu H, Qiu P. Aging progression of human gut microbiota. BMC Microbiol 2019;19:236.
PUBMED | CROSSREF

154. Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol 2022;19:565-84.
PUBMED | CROSSREF

155. Lee JJ, Kim SH, Lee MJ, Kim BK, Song WJ, Park HW, et al. Different upper airway microbiome and their functional genes associated with asthma in young adults and elderly individuals. Allergy 2019;74:709-19.
PUBMED | CROSSREF