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Environmental Effects on Immune – Mediated Diseases: A Literature Review and Comprehensive Analysis

Genc Sulcebe[1*], Arbi Pecani[2]

[1] Unit of Immunogenetics, University of Medicine, Tirana, and Academy of Sciences of Tirana, Albania
[2] University Hospital "Shefqet Ndroqi," Faculty of Medicine, University of Medicine, Tirana, Albania

Abstract

Environmental factors significantly impact human health, particularly in immune-mediated diseases resulting from immune system dysregulation. This review synthesizes current research on the influence of air and water pollution, climate change, urbanization, and other environmental stressors on immune health, aiming to elucidate underlying mechanisms that could inform public health strategies. Air pollution, recognized as a primary environmental health risk, is associated with various immune-mediated diseases, including asthma, allergies, and autoimmune disorders, with pollutants such as PM2.5, nitrogen dioxide, and ozone exacerbating inflammatory responses. Children, whose immune systems are still developing, are especially vulnerable. Additionally, water pollutants, including heavy metals and microbial contaminants, contribute to immune dysregulation and chronic inflammatory diseases, while endocrine-disrupting compounds (EDCs) interfere with hormonal regulation, further impacting immune responses. Climate change aggravates these risks by worsening air quality, extending pollen seasons, and altering ecosystems. These changes contribute to an increase in allergies and autoimmune diseases. Biodiversity loss also affects immune development, as reduced microbial exposure may weaken immune resilience, particularly in early childhood. Furthermore, urbanization and indoor air

Address for correspondence: Genc Sulcebe*, Unit of Immunogenetics, University of Medicine, Tirana, and Academy of Sciences of Tirana, Albania. E-mail: gencsulcebe@gmail.com

pollution—linked to cooking fuels, tobacco smoke, and household products—pose health risks through prolonged exposure to harmful substances, leading to chronic inflammation and immune dysregulation.

The review also addresses emerging concerns about pesticide exposure, particularly in agricultural regions. Recent studies indicate a strong association between pesticides and cancer risk, notably for colorectal and pancreatic cancers, with some data suggesting pesticide exposure could pose a greater cancer risk than smoking. This underscores the necessity for stringent regulations and public health measures to mitigate exposure.

In conclusion, these findings highlight the profound impact of environmental factors on immune health and disease development. Targeted interventions, regulatory policies, and continued research are essential to mitigate these risks and protect public health. This synthesis provides an evidence base to support preventive measures aimed at reducing environmental exposures, thereby fostering resilience against immune-mediated diseases and promoting community well-being.

INTRODUCTION

The interplay between environmental factors and human health has garnered increasing attention in recent years, particularly regarding immune-mediated diseases. These conditions, which arise from dysregulation of the immune system, can be influenced by a variety of environmental exposures, including air and water pollution. This literature review aims to synthesize existing research on how environmental pollutants affect immune responses, potentially exacerbating or triggering these diseases. By examining a wide range of studies, this analysis seeks to illuminate the mechanisms through which environmental factors impact immune health, providing insights that could inform public health strategies and preventive measures.

IMPACT OF AIR AND WATER POLLUTION ON IMMUNE-MEDIATED DISEASES

Air and water pollution are global challenges that highly impact people's health. Despite their well-known implications in cardiovascular and respiratory diseases, recent evidence prompts an important role of these factors even in immune-mediated diseases. The complex interplay between air and/or water pollutants and the immune system is characterized by an impaired balance between tolerance and immune activation (1). Therefore, individuals exposed continuously to high pollution levels are at increased risk of immune-mediated diseases.

In this paper, we explore the cascade through which air and water pollutants influence the immune system, affecting both the development and exacerbation of immune-mediated diseases. Clarifying these pathways is crucial to public health policy and individual preventive measures. Air and water pollutants share common mechanisms for developing immune-mediated diseases but also have differences in this regard (2). Air pollutants are inhaled, directly affecting the lung-associated immune response, while water pollutants are ingested or can enter the body through the skin, thus affecting the gastrointestinal-associated immune response and systemic circulation. Numerous mechanisms and different immune cell types are involved in activating inflammatory responses to these pollutants.

Air pollutants and immune response

Air pollution is Europe's top single environmental health risk, significantly contributing to premature death and illness (3). Recent European Environment Agency (EEA) evaluations identify fine particulate matter (PM2.5) as the cause of the most substantial health impacts. Moreover, increasing levels of pollutants like CO2 and particulate matter, together with environmental stressors such as wildfires, flooding, and extreme weather, impact the immune system and make people more susceptible to allergies, asthma, and other immune-mediated diseases (4).

Most Europeans live in areas, especially cities, where air pollution can reach high levels. Both

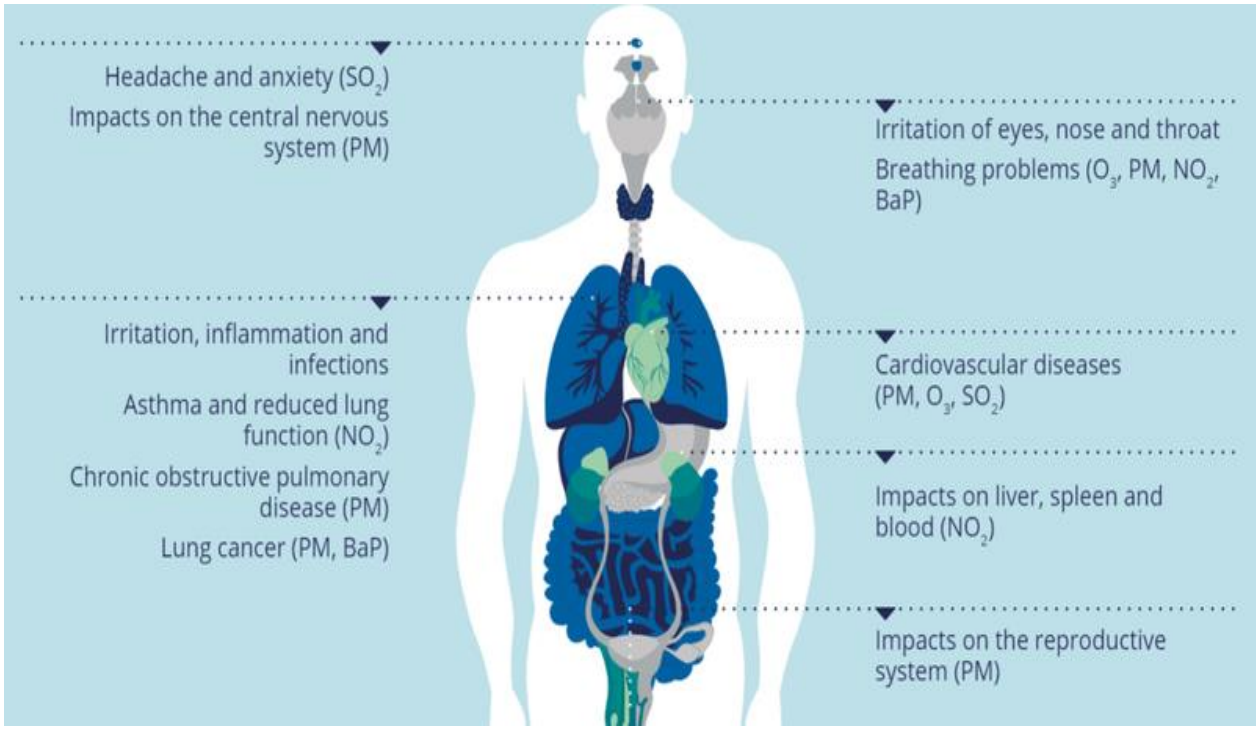

Figure 1. Infographic on effects of air pollutants on human health from EEA

short- and long-term exposure to air pollution can lead to a wide range of diseases (2), including stroke, chronic obstructive pulmonary disease, trachea, bronchus and lung cancers, aggravated asthma, and lower respiratory infections.

The World Health Organization (WHO) provides evidence of links between exposure to air pollution and type 2 diabetes, obesity, systemic inflammation, Alzheimer's disease and dementia (5). The International Agency for Research on Cancer has classified air pollution, particularly PM2.5, as a leading cause of cancer (6). A recent global review found that chronic exposure can affect every organ in the body, complicating and exacerbating existing health conditions (5,6).

Children and adolescents are the most vulnerable to air pollution since their bodies, organs, and immune systems are still developing. Air pollution damages health during childhood and increases the risk of developing diseases later in life, yet children can do little to protect themselves or influence air quality policies (4).

Particulate matter with a diameter of 2.5 μm or less (PM2.5) and those of a diameter10 μm or less (PM10), ozone (O3), nitrogen dioxide (NO2), benzo[a]pyrene (BaP) and sulfur dioxide (SO2) are the most significant air pollutants toward the development of health problems and premature mortality. In 2021, 97% of the urban population was exposed to concentrations of fine particulate matter above the health-based guideline level set by the World Health Organization (7).

Air pollutants, such as particulate matter (PM) and nitrogen dioxide (NO2), can activate macrophages and epithelial cells of the lungs toward the production of interleukin-6 (IL-6) and

tumor necrosis factor-alpha (TNF-α) with high pro-inflammatory effects resulting in recruit of other immune cells to the site of inflammation (3). On the other hand, ozone exposure (O3) activates neutrophils, which further release reactive oxygen species (ROS) and inflammatory cytokines, which enhance inflammation and tissue damage (8). Sulfur dioxide (SO2), a gas produced by burning fossil fuels, activates epithelial cells of the respiratory tract that release interleukin-8 (IL-8) as well as prostaglandins and leukotrienes that will further contribute to airway inflammation and exaggerated response (9). Furthermore, volatile organic compounds (VOCs) as formaldehyde and benzene, activate the dendritic cells of the lungs that directly initiate an immune response by presenting antigens to T cells. Some VOCs can directly interact with mast cells, leading to membrane depolarization and calcium influx, releasing histamine and contributing to allergic symptoms (10). Air pollutants can also induce epigenetic changes in cells. Alteration of DNA methylation patterns, histone modification, and microRNA dysregulation are the most common epigenetic changes evidenced in respiratory epithelial cells targeted by air pollutants, directly affecting gene expression related to inflammation and oxidative stress (11).

Climate change

Climate change affects immune regulation through increased allergens from altered plant distribution and longer pollen seasons, worsened air quality due to intensified wildfires and dust storms, expanded ranges of vector-borne diseases, heightened heat stress susceptibility, waterborne disease risks from altered water quality, and compromised nutrition due to impacts on food production and availability (10). Climate change-induced events significantly impact immune regulation and human health by altering the exposome—the cumulative lifetime exposures of individuals. This disruption can lead to immune dysregulation, triggering conditions like allergies, asthma, autoimmune diseases, and cancers. Vulnerable populations are particularly at risk due to factors that heighten susceptibility (10).

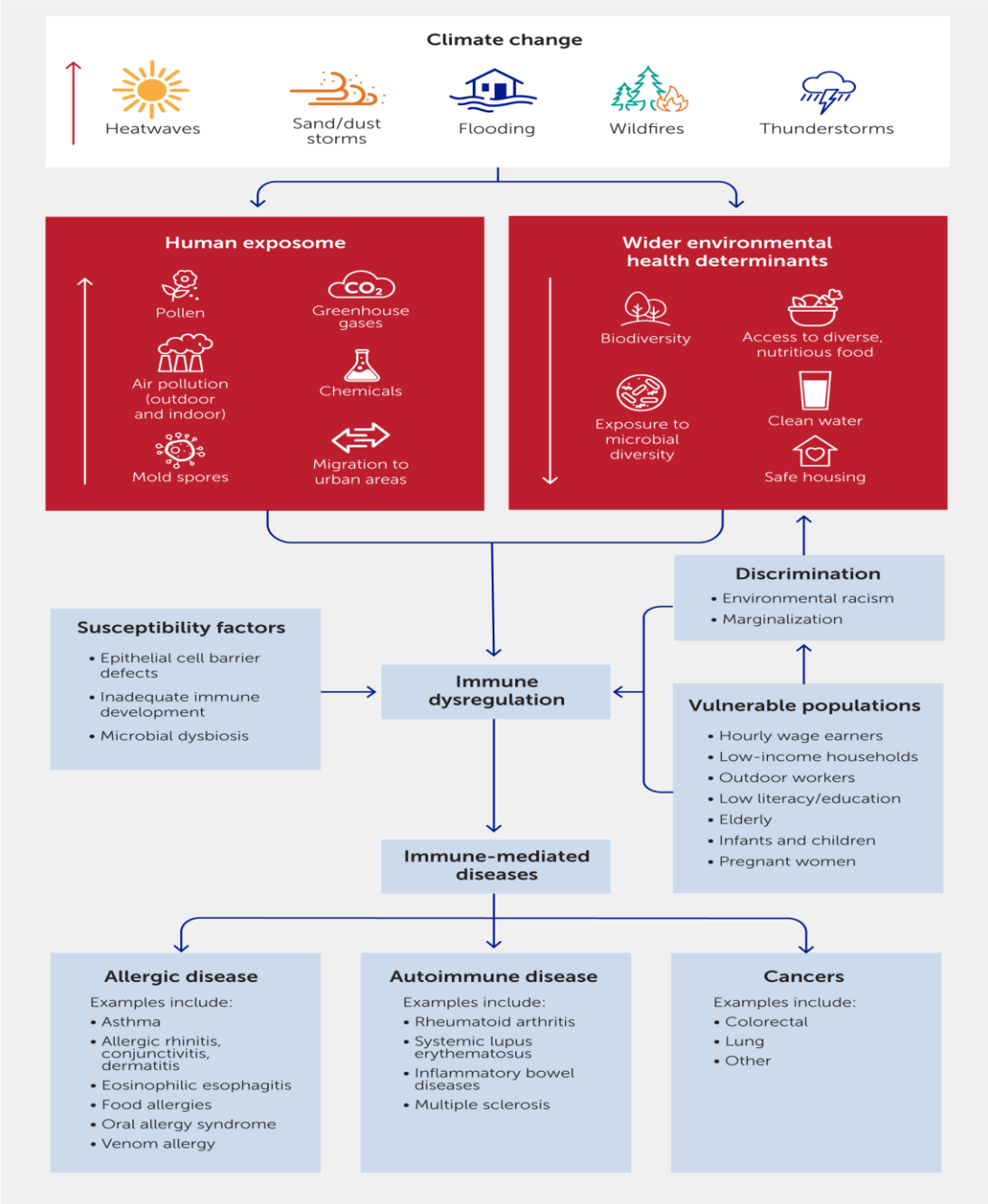

Figure 2. Effects of climate change-related events on immune dysregulation and human health through immune-mediated conditions from Agache I et al.

Increased prevalence of allergies due to environmental factors

The increased prevalence of allergies, particularly in developed countries, has been linked to several factors, including changes in lifestyle, environmental exposures, and alterations in immune system development. Lack of exposure to diverse microbial environments (due to improved hygiene practices, urbanization, and reduced contact with natural environments) may result in a skewed immune response towards allergic reactions instead of tolerating harmless substances (12). City life involves reduced exposure to natural environments and microbial diversity associated with diets rich in processed foods and low in fiber, which directly affect gut microbiota and immune system development (13). Even air pollution and poor indoor environmental quality can trigger allergic reactions and exacerbate symptoms in sensitized individuals. In general, allergic diseases have a genetic component, but environmental factors can influence gene expression through epigenetic mechanisms associated with increased susceptibility to allergies, even in individuals without a strong genetic background (14). Higher temperatures associated with climate change can affect the distribution and allergenicity of pollen-producing plants. This can extend pollen seasons and exacerbate allergic rhinitis and asthma (15). Elevated carbon dioxide (CO2) levels in the atmosphere, a key driver of climate change, can stimulate plant growth and pollen production. This phenomenon, known as the CO2 fertilization effect, can lead to higher pollen counts and greater allergenicity of pollen grains. Climate change alters the geographic distribution of plants and facilitates the spread of invasive plant species that may produce allergenic pollen. These species can outcompete native plants and contribute to pollen-related allergies (14, 16).

On the other hand, heat waves or heavy rainfall can influence plant growth and pollen release patterns toward a sudden increase in pollen concentrations or alter the timing of peak pollen production, affecting allergy symptoms (15, 16). During thunderstorms, pollen grains can be ruptured into small particles that can be easily inhaled and stimulate severe asthma attacks in predisposed individuals, called thunderstorm asthma (17). Thus, addressing climate change and implementing adaptive strategies are crucial in reducing the burden of climate change-driven allergies on public health.

Indoor air pollution

Indoor air pollution can originate from several sources within buildings or enclosed spaces, significantly affecting the immune system and overall health. There are different sources of indoor air pollution, like tobacco smoke, that contains numerous harmful chemicals, carcinogens, and irritants. Cooking stoves that use solid fuels can release PM, CO, and NO2, damaging human health. The materials used to build the houses can contain VOCs (painting, carpets), formaldehyde (adhesives, furniture), and asbestos (especially in older buildings). Even household products (cleaning agents, personal

care products) and biological agents (mold, mildew, or dust mites) can be a serious cause of indoor air pollution with important effects on the immune system (18). Poor indoor air quality is associated with different health risks, like pulmonary (asthma, chronic obstructive pulmonary disease, bronchitis, pneumonia), cardiovascular (hypertension, stroke, heart diseases), neurological (behavioral issues and cognitive impairment), and of course, cancer. Radon and formaldehyde are classified as a human carcinogen (19).

Urbanization

Urbanization is strongly associated with higher levels of air and pollution attributed to industrial activities (smoke and effluents), ongoing constructions, and vehicle emissions. Higher population density, noise pollution, social inequalities, and psychosocial stressors are more prevalent in urban environments. Chronic stress can dysregulate the immune system through effects on neuroendocrine pathways (e.g., hypothalamic-pituitary-adrenal axis) and immune cell function, promoting inflammatory responses and contributing to autoimmune conditions (20). All these factors can collectively induce chronic low-grade persistent inflammation and dysregulate immune responses that contribute to developing and progressing immune-mediated diseases such as rheumatoid arthritis, inflammatory bowel diseases, and multiple sclerosis (21).

Heat stress

Certain populations, such as the elderly, children, and individuals with pre-existing health conditions, are more susceptible to the detrimental effects of heat stress on the immune system mostly due to its impact on physiological processes and immune cell function. Exposure to high temperatures can trigger systemic inflammation and oxidative stress in the body. This inflammatory response involves the release of cytokines and other immune signaling molecules, which are intended to repair tissue damage and restore homeostasis. Moreover, heat stress can directly affect immune cell function by impairing the migration and activity of neutrophils and macrophages, which are crucial for the initial response to infections and tissue repair (22). Heat stress can cause immune cell dysfunction by inducing apoptosis, subsequently reducing the number of circulating lymphocytes and altering cytokine production. Heat stress can compromise the integrity of the skin and mucosal barriers, making individuals more susceptible to microbial infections. This is particularly relevant for skin pathogens and respiratory infections (23). Heat stress induces the production of heat shock proteins (HSPs), which act as molecular chaperones and play a crucial role in protecting cells from stress-induced damage. HSPs also have immunomodulatory functions, influencing the activation and function of immune cells (24).

BIODIVERSITY LOSS AND THE IMPACT ON THE IMMUNE SYSTEM DEVELOPMENT

Pollution, climate change, overexploitation of resources, and habitat destruction result in the global reduction of the variety and number of species, with significant implications for the ecosystem and human health. Exposure to microbial diversity, especially during childhood, is crucial for the human immune system as it shapes its response, lowering the risk of allergic and autoimmune diseases in the future. The "hygiene hypothesis" suggests that decreased exposure to diverse microbes may contribute to the rise in immune-mediated diseases mainly observed in developed countries (25). This hypothesis underscores the importance of early-life exposure to microbial diversity for immune system maturation. Furthermore, dysbiosis and reduced microbial diversity are associated with chronic low-grade inflammation, which contributes to metabolic disorders such as obesity, diabetes, and cardiovascular diseases (26).

ENDOCRINE DISRUPTING COMPOUNDS AND THEIR EFFECT ON IMMUNE-MEDIATED DISEASES.

Endocrine Disrupting Compounds (EDCs) are chemicals found in various products of everyday use that affect the endocrine system in terms of hormone production, metabolism, and signaling (27). EDCs (such as bisphenol phthalates, etc.) mimic or block hormones, significantly affecting immune-regulating hormones (cortisol, estrogen, testosterone), directly affecting immune response and promoting inflammation. Chronic inflammation can be the first step toward developing many immune-mediated diseases and/or a strong contributor exacerbating a present disease. EDCs can alter gene expression and the gut microbiome; both affect immune cell differentiation and function, potentially predisposing humans to immune disorders (28). On the other hand, EDCs exposure during fetal life or early childhood can interfere with the maturation of immune cells in the thymus, leading to long-term alterations in immune functions and increasing the susceptibility to immune-mediated diseases (27, 28).

WATER POLLUTANTS AND IMMUNE RESPONSE

Heavy metals (lead, mercury, cadmium, arsenic) are the most common water pollutants that significantly impact human health. Heavy metals can suppress the immune system by inhibiting lymphocyte proliferation, macrophage phagocytic activity, and cytokine production. The impaired balance of cytokines and regulatory T cells leads to decreased immune tolerance and increased chances of infections. Some heavy metals, such as arsenic and cadmium, have genotoxic effects by damaging DNA and altering cellular signaling pathways, resulting in immune-mediated disorders and cancers (29). On the other hand, microbial pollutants like viruses (hepatitis A), bacteria (E. coli), and protozoa (Giardia)

trigger the innate immune response once recognized by the pattern recognition receptors on the antigen-presenting cells. Soon after, there will be an induction of adaptive immune response leading to activation and proliferation of antigen-specific T and B cells associated with excessive inflammation and the development of chronic diseases (30). Organic compounds like pesticides (chlorpyrifos, atrazine) weaken immune surveillance mechanisms by impairing the phagocytic activity of macrophages and suppressing the cytotoxic activity of NK cells, known for their important role in detecting and eliminating infected and/or tumor cells. Pesticides can also act as haptens for allergy sensitization to develop or exacerbate an autoimmune disease (31).

Sewage and wastewater

After being used, water becomes wastewater. Wastewater can be domestic (water from toilets, sinks, showers) or from commercial, agricultural, or industrial use. It also includes rainwater that washes oil, grease, road salt, debris, or chemicals from the ground into waterways (32). Reports show that 80% of wastewater re-enters the ecosystem without treatment or reuse. In 2024, the WHO found that 1.5 billion people worldwide lacked access to basic sanitation facilities such as toilets or latrines, with 419 million people openly defecating outside (33).

Agriculture mostly contributes to water pollution through rainwater. When it rains, fertilizers, animal waste, and pesticides get washed from farms into waterways, contaminating them. Chemical pollutants, such as pesticides, fertilizers, and heavy metals, can cause serious health problems if ingested (32). Ingesting chemical toxins from contaminated water may lead to serious health risks, including cancer, hormone disruption, altered brain function, damage to the immune and reproductive systems, and cardiovascular and kidney problems. Moreover, swimming in contaminated water can also trigger rashes, pink eye, respiratory infections, and hepatitis (34). Ingesting microplastics can occur via drinking water or through eating contaminated seafood. People have also discovered them in salt, beer, and other food items. Studies show microplastics may cause oxidative stress, inflammatory reactions, and human metabolic disorders (35). However, further research is needed to confirm these effects.

Drinking water containing chemical waste

Pregnant women whose household tap water had higher levels of lithium had a moderately higher risk of their offspring being diagnosed with autism spectrum disorder, according to a new study led by a UCLA Health researcher (36, 37). Lithium is a metal naturally found in rocks and soils and can sometimes be found in drinking water, mainly from the weathering of lithium-containing minerals in older bedrock or where groundwater interacts with saline water. A study published in JAMA Pediatrics identifies for the first time naturally occurring lithium in drinking water as a possible environmental risk factor for autism (37). Some experimental research

indicated lithium, which is among several naturally occurring metals often found in water, could affect an important molecular pathway involved in neurodevelopment and autism. The researchers found a similar relationship between increased lithium levels and a higher risk of autism diagnosis when subtypes of the disorder broke the data down. They also found that the association between lithium levels and autism risk was slightly stronger for those living in urban areas compared to smaller towns and rural areas (37).

In summary, air and water pollution significantly impacts immune-mediated diseases through direct inhalation, immune dysregulation, epigenetic modifications, allergic reactions, waterborne contaminants, and effects on vulnerable populations. Mitigating pollution levels through regulatory measures, public health interventions, and environmental policies is crucial to reducing the burden of immune-mediated diseases and promoting overall health and well-being.

PESTICIDES, THE NEW TOBACCO THREAT FOR CANCER RISK.

Pesticides have significantly transformed agriculture especially, by enhancing production yields. On the other hand, pesticides present also a serious public health risk, due to their association with neurological disorders and various cancers. While many previous studies have concentrated on specific populations with known pesticide exposure, a recent comprehensive investigation sought to evaluate cancer risks related to pesticide use across a broader U.S. demographic (38, 39).

By employing a model that integrated data on pesticide usage, cancer incidence rates, and various influencing factors, researchers uncovered regional disparities in cancer risk linked with agricultural pesticide exposure. The findings indicated that the Midwest, known for high corn production, experienced the most pronounced increase in cancer cases—an estimated additional 154,541 annually, with particular spikes in colorectal and pancreatic cancers (38).

Notably, this study revealed that pesticide exposure was linked to a higher cancer risk than smoking in several instances, especially for non-Hodgkin lymphoma. Despite certain limitations, such as incomplete county data and the omission of seasonal worker exposure, the research underscores the critical need to evaluate pesticide risks alongside those of smoking (38).

Addressing these risks is vital for public health policy and agricultural practices, ensuring that the benefits of enhanced crop production do not come at the expense of community health. Future research should aim to fill the gaps identified in this study, focusing on comprehensive data collection and the inclusion of vulnerable populations to inform safer pesticide use and regulatory measures.

CONCLUSIONS

This review highlights the significant impact of environmental factors on immune-mediated diseases, illustrating how pollutants and other exposures can disrupt immune function and contribute to disease prevalence. The evidence suggests that air and water pollution play critical roles in exacerbating conditions such as autoimmune disorders and allergies. On the other hand, the loss of biodiversity poses a significant threat to immune system development, potentially compromising health by disrupting the complex interactions between ecosystems and human immunity. Furthermore, endocrine-disrupting compounds significantly impact immune-mediated diseases by altering hormonal balance and immune responses, highlighting the urgent need for regulatory measures and further research to protect public health. Recently, it has been pointed out that pesticides have emerged as a formidable cancer risk comparable to tobacco, necessitating urgent public health action and stricter regulations to mitigate their harmful effects on human health.

By synthesizing diverse studies, we emphasize the need for continued research into the mechanisms of these environmental influences, as well as the importance of public health interventions to mitigate exposure. Ultimately, understanding these relationships is crucial for developing strategies that protect immune health and improve overall community well-being.

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