

REVIEW ARTICLE

Immunological resilience and biodiversity for prevention of allergic diseases and asthma

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Abstract

Increase of allergic conditions has occurred at the same pace with the *Great Acceleration*, which stands for the rapid growth rate of human activities upon earth from 1950s. Changes of environment and lifestyle along with escalating urbanization are acknowledged as the main underlying causes. Secondary (tertiary) prevention for better disease control has advanced considerably with innovations for oral immunotherapy and effective treatment of inflammation with corticosteroids, calcineurin inhibitors, and biological medications. Patients are less disabled than before. However, primary prevention has remained a dilemma. Factors predicting allergy and asthma risk have proven complex: Risk factors increase the risk, while protective factors counteract them. Interaction of human body with environmental biodiversity with micro-organisms and biogenic compounds as well as the central role of epigenetic adaptation in immune homeostasis have given new insight. Allergic diseases are good indicators of the twisted relation to environment. In various non-communicable diseases, the protective mode of the immune system indicates low-grade inflammation without apparent cause. Giving microbes, pro- and prebiotics, has shown some promise in prevention and treatment. The real-world public health programme in Finland (2008–2018) emphasized nature relatedness and protective factors for immunological resilience, instead of avoidance. The nationwide action mitigated the allergy burden, but in the lack of controls, primary preventive effect remains to be proven. The first results of controlled biodiversity interventions are promising. In the fast urbanizing world, new approaches are called for allergy prevention, which also has a major cost saving potential.

KEYWORDS

allergy prevention, allergy program, biodiversity, immunological resilience, microbiome

1 | INTRODUCTION

From 1950s, the *Great Acceleration* of human activity coincides with the *Anthropocene*, a title suggested for a geological epoch of human impact on earth's ecosystems.¹ Health and life expectancy have improved in high income countries but much at the expense of environment. Population explosion, escalating urbanization, and overuse of natural resources have become the rule. The increase in emissions of greenhouse gases, global warming, massive extinction of species, and pollution are all part of the Anthropocene. We might be losing resilience as individuals and communities and face epidemics of both communicable (fast) and non-communicable (slow) diseases, with unpredictable outcomes.

Dawn of non-communicable diseases was evident in 1960s, when also increase of allergic diseases and asthma became obvious in most developed countries. Indeed, they are good indicators of the modern health hazards, for example, shown in the Finnish and Russian Karelia.² In a relatively short period of time, after the second world war, two geoclimatically and genetically close populations have developed contrasting immunological expression. In Russian Karelia, hay fever was rare, food allergies few and peanut allergy unknown. The contrast is neither explained by hereditary factors nor by air pollution or common chemicals but rather by changes in lifestyle and environment. Understanding the underlying reasons of this disparity would enable measures for prevention. Allergy is not an isolated case but concurrent with the increase of both type I and II diabetes, cardiovascular diseases, obesity, inflammatory bowel diseases, even mental disorders and cancer.³

Resilience is defined as an ability to recover from or adjust to change or misfortune (Merriam-Webster Dictionary). Resilience is multidimensional; immunological, psychological, and societal aspects are all critical. Lack of it may be the main reason for the increasing burden of non-communicable diseases. Lack of the resilient immunity at individual or community level is also obvious during the current COVID-19 pandemic. In general, resilience of the immune system means having the capacity to adapt to challenges by establishing, maintaining, and regulating an appropriate immune response. A resilient immune response is a healthy state: not too passive, not too active, and able to return to homeostasis. It is a fine balance between useful and harmful response, and no response at all. If resilience is lost, disease may follow.

Microbe-immune system interplay is decisive for resilience and the immune homeostasis. If the crosstalk is not versatile enough, dysregulation arises. Reduced contact to environmental microbial diversity is probably the main reason of the compromised immunological resilience of populations living in the modern, urban environment.^{4,5} In logistic regression models, risk factors of the disease in question are evaluated, but the models seldom identify protective factors as explanations or confounders⁶ (Figure 1).

In this paper, we present some of the recent insights of immunological resilience and biodiversity supporting health and preventing allergic diseases.

Future research perspectives

- Knowledge of the determinants of immunological resilience is a prerequisite for primary prevention.
- Controlled and real-world interventions to study both mechanisms and clinical effect of biodiversity.
- Functional capacity of the microbiome, what are the decisive factors: richness, diversity, or composition?
- Transfer of microbiota from the environment to human body.
- Interaction of epigenetic markers with human or environmental microbiota.
- Validation of the cellular effects of biogenic (volatile, organic) compounds in clinical setting.

Milestones

- Recognition of human body as a community of species (holobiont) and genomes (hologenome).
- Insight of epigenetic regulation of immune adaptation under continuous environmental pressure.
- Biodiversity hypothesis of health. Recognition biodiversity as a major determinant of human health (WHO, The Convention on Biological Diversity 2015).
- Evidence-based nature/biodiversity loss, verified by a long-term follow-up (WWF, Living Planet Index 1970–2020).
- Concept of Planetary Health as the health of human civilization and the state of natural systems (The Rockefeller Foundation-Lancet Commission 2015).
- Paradigm shift in allergy prevention, from avoidance to immunological tolerance/resilience. Implementation of the first national programme for prevention (The Finnish Allergy Programme 2008–2018)

2 | DIVERSITY OF LIFE

Biological diversity comes in two flavors. *Structural* biodiversity consists of layers of life, starting from the diversity of ecosystems followed by numerous species living within, and reaching the complex genetic and phenotypic variation between individuals. Biodiversity is also *functional*, indicating complex interactions between species and their biotic and abiotic environment. Microbial diversity has two dimensions, *alpha* and *beta diversity*. In any given sample, *alpha diversity* is a measurement of species richness (number of different taxa) and evenness (abundance of the taxa in question). *Beta diversity* a distance measure between samples and represents the compositional dissimilarity or heterogeneity. Defining and measuring biodiversity accurately is, however, under constant debate.

In early 2021, the Global Biodiversity Information Facility, a database collecting global species occurrence, listed 2,725,553 species

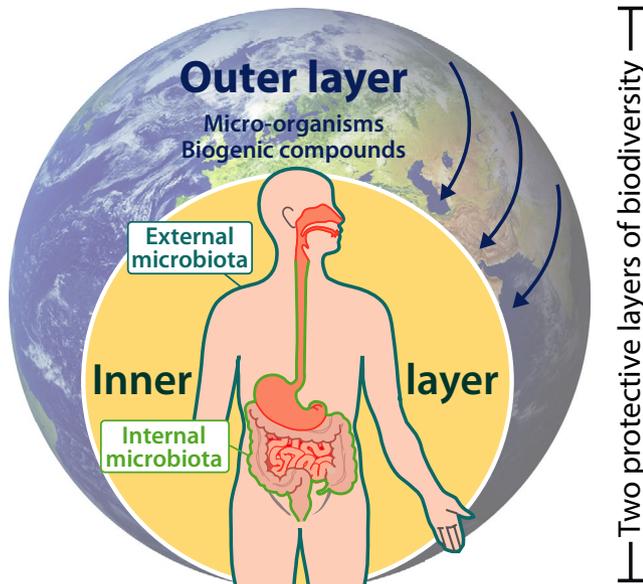


FIGURE 1 Human body is protected by two nested layers of biodiversity. They consist of micro-organisms residing in the living environment and on the external and internal surfaces of the body. The inner layer is dependent on the microbial colonization from the outer layer, from air, soil, and natural waters. In natural environment, humans also breathe biogenic (volatile, organic) compounds with protective cellular functions,⁶ (modified)

in 8 kingdoms of life (gbif.org). The majority of the species are still undescribed or not included to this database. Moreover, those kingdoms or domains representing the biodiversity that is invisible to human eyes, such as in bacteria, archaea, and microscopic fungi, do not have a clear definition of species. While most unknown species belong to these kingdoms, for example, insects are also poorly described. The total number of eukaryotic species, that is, other kingdoms than bacteria, archaea, and viruses, vary somewhere between 5 and 8.7 million.^{7,8} However, when accounting all forms of life, estimates can reach up to 1 trillion species.⁹

2.1 | Environmental microbial exposure

2.1.1 | Urban vs. rural exposure

Microbial exposure and its diversity depend on the environment and living habits.¹⁰ Urban, man-made surface soil materials have poorer microbial communities compared to forest soil.¹¹ Consequently, microbial communities on skin and in airways of children and adults tend to be poorer and more homogenous in urban than in rural individuals.^{4,12,13} This is also evident even in newborns and pets.¹⁴⁻¹⁶ This parallels with overall poverty of both macroscopic and microscopic urban biodiversity (Figure 2).

Within a city, the green areas have a considerable impact on microbial diversity.¹⁷ Macroscopic diversity influences the diversity of microbial communities; species-poor grass fields hold less microbes

than species-rich forested areas both in soil and air.^{18,19} Importantly, revegetation enriches soil microbial communities indicating that urban green spaces can facilitate beneficial microbial exposure.²⁰ Pollutants may shape plant and microbial communities²¹⁻²³ and are associated with negative functional potential of gut microbiota.²⁴⁻²⁶ Thus, exposure to beneficial environmental microbiota can be improved by increasing vegetation and reducing pollution.

2.1.2 | Indoor microbiota

In urban settings, the indoor microbial environment is largely composed by human skin microbiota.²⁷ People are exposed to their own microbes. Indoor microbial composition differs between rural and urban areas,²⁸⁻³⁰ and between homes practicing farming or not.^{10,31} When dirt was collected from doormats, urban dwellers carried indoors less microbiota than their rural counterparts.²⁸ In urban areas, the summertime biodiversity of doormat dirt was at the same level as the wintertime minimum in rural areas.³² The high coverage of built environment around homes reduced the diversity of environmental microbiota carried indoors, but already a backyard rich of plants can make a difference for individual microbiota.^{28,33}

Lifestyle factors have a stronger effect on human microbiome than genetics as shown by studying identical twins.³⁴ While microbial communities differ between Western and indigenous populations such as tribes and hunter-gatherers,³⁵ immigration, for example, from Thailand to United States causes a rather immediate westernization of gut microbiota.³⁶ The analyses of microbiota differences between populations are confounded by a number of factors. Therefore, studying people in the same country but with contrasting lifestyles or environments is likely to give most relevant information.³⁷

2.2 | Biodiversity in health and disease

2.2.1 | Human body as an ecosystem

Lynn Margulis used the concept *Holobiont* to describe the host (animal or plant) of being a community of species subject to continuous evolutionary pressure.^{38,39} Holobiont species are *bionts*, and *hologenome* is the combined genome of the bionts. The concept binds human health tightly with homeostasis of the holobiont (Figure 3).

Natural environment supports human health in a holistic manner. Both visiting natural areas and living in green surroundings associates with physical, mental, and social health. Moreover, a natural living environment associates with reduced risk of mortality to any causes,⁴⁰ also in urban areas.⁴¹

2.2.2 | Infectious diseases

A meta-analysis showed that biodiversity reduced the prevalence of diseases caused either by micro- or macroparasites, consistently in



FIGURE 2 Urban, build environment, and changes in lifestyle (left) have increasingly disconnected children from the natural air, soil, and waters, the evolutionary home of *Homo sapiens* (right). Photos: M. Andersson, J. Haahtela, with permission

plants, wildlife, and humans.^{42,43} Especially vector-borne, generalist wildlife, and zoonotic pathogens are affected by changes to biodiversity.⁴⁴ Interestingly, while diversity of parasites is also declining along other biodiversity,⁴⁵ the risk of zoonoses increases. This may be due to the hampering of ecological mechanisms controlling pest abundance as well as the increased human contact with wildlife.

As biodiversity is lost from ecosystems, the persisting species tend to be those most likely to harbor and transmit pathogens; abundant, widespread, and resilient.⁴³ Therefore, changing species composition, rather than diversity per se, can affect disease risk.⁴⁴ Moreover, even though the individual pathogen load may not change, the risk for an infection is higher in environments with low biodiversity.^{42,43,46} However, for some infectious diseases, measures to improve hygiene, increasing wealth, and targeted biomedical management can be more effective for disease prevention than biodiversity conservation.^{44,47}

2.2.3 | Non-communicable diseases

Biodiversity tends to support well-being and reduce the risk of asthma and allergic diseases.^{4,48} Visiting green environments has been associated with reduced stress and blood pressure.⁴⁹

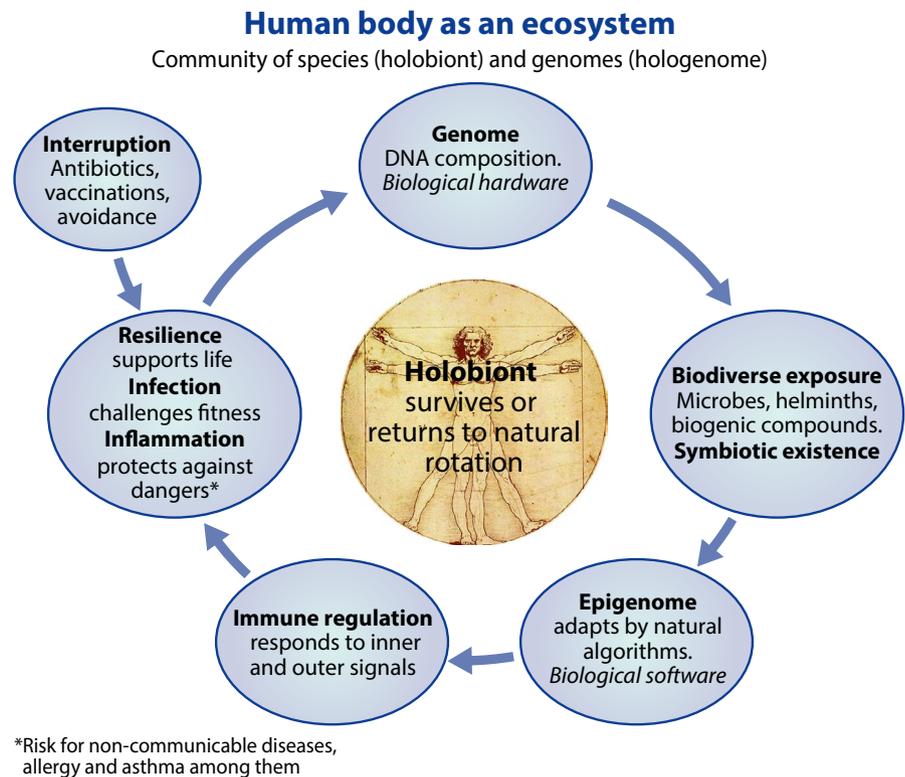
Environmental diversity was associated with reduced risk of asthma in children,⁵⁰ and increasing landscape-level biodiversity with reduced public hospital admissions due to respiratory diseases.⁵¹

All green is not, however, equal in terms of health outcomes. Living next to grassy areas or to coniferous forests has been associated even with an increased risk of asthma in urban children, possibly due to airborne biotic and abiotic contaminants.^{48,52} Even living some hundred meters from a green space does not guarantee exposure to rich environmental microbiota.^{53,54} Nevertheless, diverse vegetation in the immediate surroundings of homes, urban daycares, and schools have associated with reduced allergic sensitization⁴ and improved lung function⁵⁵ suggesting that immediate exposure is of importance.

3 | EPIGENETIC PLASTICITY FOR IMMUNOLOGICAL RESILIENCE

Individuals with specific genotypes have different responses to the same exposure.⁵⁶ This so-called flip-flop pattern results in poor replicability of associations between genotypes and disease, if environmental exposure is not considered. Epigenetic modifications are emerging as promising mechanisms to understand the plasticity of gene-environment interaction.

FIGURE 3 Human body as a community of species and genomes. Biotically diverse exposure calls for epigenetic signaling to modify and adapt immune regulation for resilience. Interruption may degrade or improve resilience. [In the middle, the drawing *Vitruvian Man* by Leonardo da Vinci, from the end of 15th century. Human body is an expression of the microcosm connected to the macrocosm]



Epigenetics refers to mechanisms that perpetuate alternative gene activity in the context of the same DNA sequence.⁵⁷ Epigenetic modifications predispose health or disease by determining regions of the genome accessible to the transcription machinery. Resilience of the immune system depends on epigenetic adaptation throughout life. DNA methylation, histone modifications, and small and long non-coding RNAs (lncRNAs) are hot topics in research.⁵⁸ They play a central role in mediating environmental effects on health and disease (Figure 4).

3.1 | Epigenome-wide studies (EWAS)

A genome-wide DNA methylation study of childhood asthma, including age-matched controls, found 14 asthma associated CpG sites in whole blood which were replicable in independent study cohorts.⁵⁹ Altered DNA methylation profiles were found in eosinophils and cytotoxic T cells. Most of the modified CpG sites were identified at the age of 8 years, but none at birth emphasizing the postnatal environmental exposure in allergic disease.

Genome-wide DNA profiles have been investigated also in nasal epithelial samples.⁶⁰⁻⁶² In the PIAMA birth cohort, the EWAS analysis identified replicable DNA methylation profiles associated with asthma, rhinitis, and sensitization to aeroallergens.⁶⁰ Cardenas et al⁶¹ reported that the differentially methylated regions in nasal epithelium associated with allergic asthma, Th2 signaling, eosinophilia, and airway epithelial defense. Both studies concluded that the nasal epigenome may serve as a biomarker for asthma, rhinitis and airway inflammation.

3.2 | Long non-coding RNAs

lncRNAs are an example of a rather new class of regulatory RNAs transcribed from DNA, but typically not translated into proteins.⁵⁷ lncRNAs are involved in both immune cell development and function.⁶³⁻⁶⁶ Transcriptomics analyses of the Karelian Allergy cohort revealed depressed innate immunity signaling in Russian subjects compared with their Finnish counterparts.² Moreover, the gene-microbe network was richer and more diverse in the Russian subjects. Interestingly, a large part of the up-regulated genes in the Russian subjects were represented by lncRNAs, while one third of the down-regulated genes were immune-related. Indeed, lncRNAs may control host immune responses during microbial infection and Th2 differentiation.^{63,64,66} Differentially expressed lncRNAs may operate as mediators of both gene-environment and gene-microbe interaction, regulating responses not only against microbes but also against foreign proteins released, for example, by pollens.²

3.3 | Interaction with microbiota

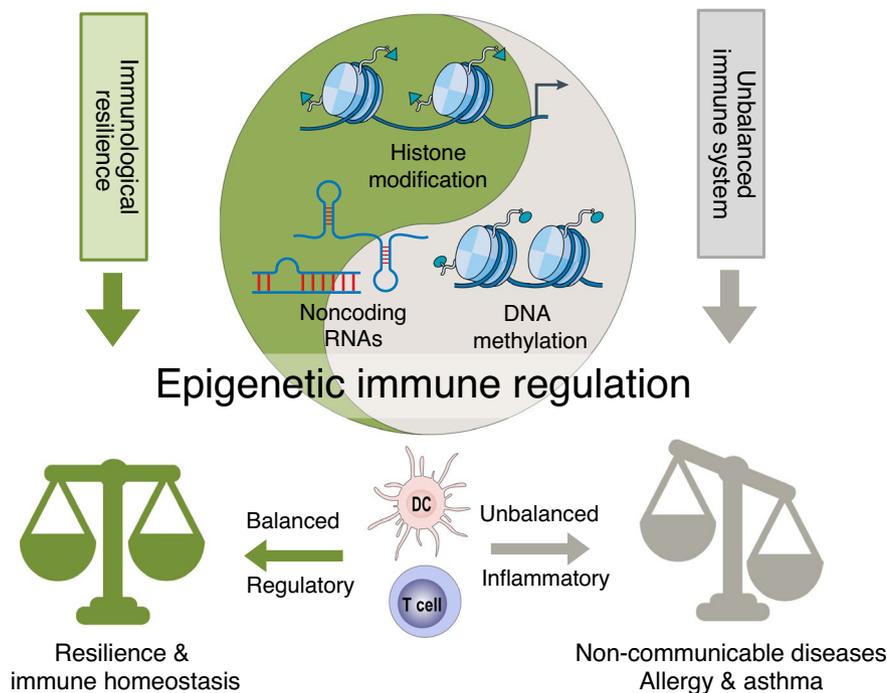
Epigenetic markers may distinguish patient groups, but little is known of their interaction with environmental or human microbiota, or with the immune system in general.⁶⁷ Bacterial products such as peptidoglycans and short chain fatty acids (SCFAs) alter hematopoiesis by increasing neutrophils, macrophages, and dendritic cells.⁶⁸ They modify immune reactivity of both myeloid⁶⁹ and epithelial⁷⁰ cells, potentially through epigenetic reprogramming. A high-fiber diet⁷¹ or exposure to a biodiverse living environment, including

Environmental and microbial diversity



Urban development and changes in lifestyle

FIGURE 4 Epigenetic immune regulation is under a lifetime pressure of complex environmental factors, also called the exposome



soil exposure,⁷² promotes the outgrowth of intestinal bacteria. For example, members of the *Bacteroidetes* phylum generate from dietary fibers epigenetically active, immunomodulatory SCFAs, which inhibit histone modifications.^{71,73} This leads to hyperacetylation of intestinal macrophages and to the differentiation of Th1/Th17 effector T cells or Treg cells.

In mice on a high-fiber diet, SCFAs enhanced generation of dendritic cells, with an impaired ability to activate Th2 effector cells, thus protecting against allergic airway inflammation.⁷¹ *Clostridia* species able to generate SCFAs, associate with the resolution of food allergies.⁷⁴ These microbes also induce colonic Treg cells through histone H3 acetylation and protect against sensitization to food allergens.⁷⁵

Acinetobacter lwoffii induces immune tolerance in both humans and animal models by activating Th1 and Treg differentiation, probably by epigenetic modifications.⁷⁶ In support of this, Brand and coworkers demonstrated that prenatal administration of *A. lwoffii* prevented asthmatic phenotype in the progeny mediated by changes in H4 acetylation of IL4 and IFN γ promoter regions.⁷⁷

The gut microbiome produces diverse neuroendocrine molecules acting as modulators on *gut-brain*, *gut-skin*, or *gut-lung* interaction, in which epigenetic mechanisms like histone modifications and DNA methylation are involved. For example, gut microbiota may influence on cognition and Alzheimer disease through regulation of neural, endocrine, and immune pathways.⁷⁸ One detail is skin itch, which is inhibited γ -aminobutyric acid (GABA) produced by gut *Lactobacillus* and *Bifidobacterium* species.⁷⁹

Taken together, these results suggest that interventions which include epigenetically active microbes or microbial metabolites are useful both for primary and secondary allergy prevention.

The functionally most important epigenetic mechanisms are presented in Table 1.

4 | CONTROLLED AND OPEN INTERVENTIONS

Direct, regular contact with soil or plants diversifies human microbiota,⁸¹ observed both on the skin⁸² and in the gut.³³ For example, children, in similar daycares, who spend several hours a day in natural environment, have more diverse skin microbiota than children with less outdoor activities. However, it is possible that environmental microbes are only transient members of the human microbiota,⁸³ indicating that frequent contact with environmental microbes may be needed for immuno-regulatory effects to arise.

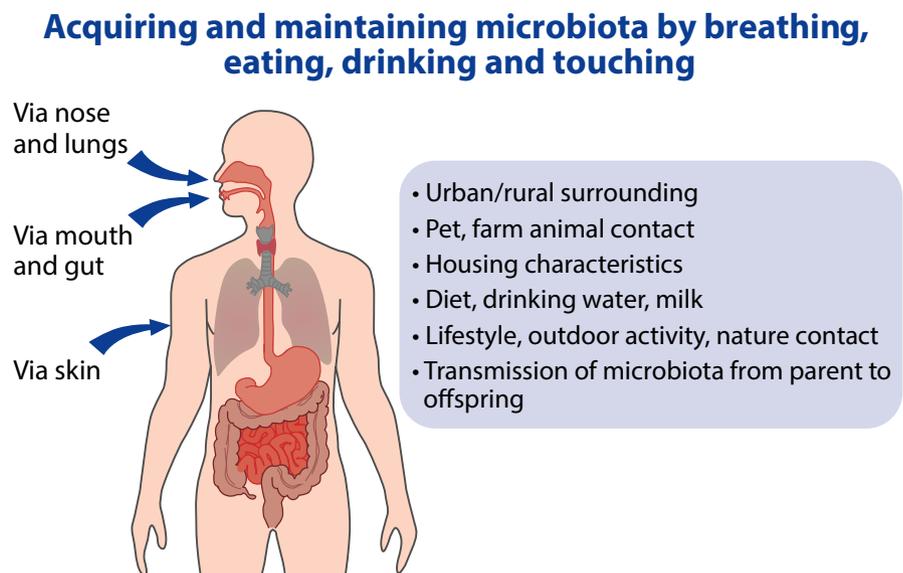
4.1 | Biodiversity interventions

There is an urgent need to test various exposure strategies, ranging from active gardening and outdoor activities to indoor and personalized interventions. A key question is whether we should be

TABLE 1 Epigenetic mechanisms and their proposed functions. The data are mostly based on the review of Q. Zhang and X. Cao⁸⁰

Epigenetic mechanism	Function
DNA methylation and oxidation	<ul style="list-style-type: none"> DNA methylation of CpG dinucleotides is associated with transcription silencing. Methyl-CpG oxidation mediates active DNA demethylation or other functions.
Histone modification <ul style="list-style-type: none"> Acetylation Methylation Phosphorylation 	<ul style="list-style-type: none"> Various roles in transcription regulation.
Nucleosome remodeling	<ul style="list-style-type: none"> Chromatin changes control DNA accessibility and thus the binding of transcription regulators, transcription factors and transcription co-activators.
Non-coding RNAs (ncRNAs) <ul style="list-style-type: none"> Long non-coding RNAs (lncRNAs) Competing endogenous RNAs (ceRNAs) Enhancer RNAs (eRNAs) Circular RNAs (circRNAs) microRNAs (miRNAs) 	<ul style="list-style-type: none"> Divergent roles in cellular responses via RNA-DNA, RNA-RNA and RNA-protein interactions.
RNA modification and "epitranscriptome"	<ul style="list-style-type: none"> Functional modifications in mRNAs and ncRNAs constitute the "epitranscriptome" representing a new layer of epigenetic regulation at the RNA level. The regulatory roles of RNA modifiers in innate immunity and inflammation are still poorly understood.

FIGURE 5 We connect to the environment with senses and activities, and host, what we breathe, eat, drink, and touch. Activities in biotically diverse environment together with unprocessed food provide human body with microbiota for immune regulation,⁸⁴ (modified)



exposed to microbes by ingesting, inhaling, being in skin contact, or by all these means to promote balanced immune homeostasis,⁸⁴ (Figure 5).

Interventions can modify the living environment, change the living habits, or target for both. Studies that enhance nature contacts and follow changes in the commensal microbiota and immune regulation are ongoing, but results have not been published.⁸⁵ Urban citizens want the potential benefits of environmental microbial biodiversity, providing that the efficacy and safety of the nature-based solutions have been shown.⁸⁶⁻⁸⁸

Composition of the microbial communities and their dynamics of transfer in the introduced biodiversity elements are poorly known. When urban volunteers rubbed their hands in gardening soils materials for 20 s and washed hands in tap water, they attained markedly higher microbial diversity on the skin.⁸⁹ In a 2-week intervention, volunteers exposed themselves to a soil-like material, rich of microbes, or just continued life as usual.⁹⁰ The exposure increased the microbial diversity of both skin and stool. The change was associated with the expression of TGF-beta by peripheral blood mononuclear cells.

Standard day care



Biodiversity intervention day care

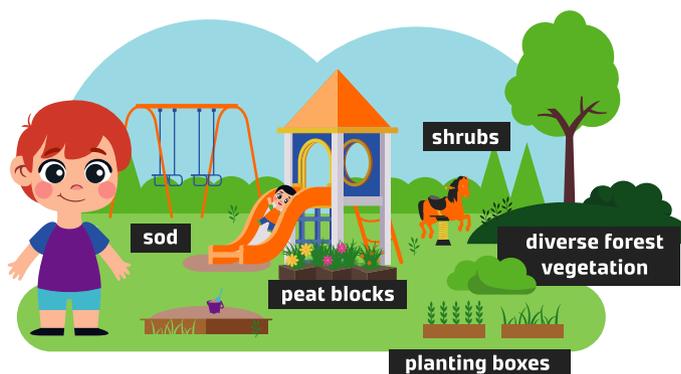


FIGURE 6 In the biodiversity intervention, the daycare yards were enriched with vegetated boreal forest soil blocks, sod, peat blocks, and by gardening the soil for growing vegetables⁹¹

TABLE 2 Practical advice to improve immunological resilience and treatment in the Finnish Allergy Programme (2008–2018)⁹⁷

Primary prevention	Secondary (tertiary) prevention
<ul style="list-style-type: none"> • Support breastfeeding, solid foods from 4 to 6 months • Do not avoid environmental exposure unnecessarily (eg, foods, pets) • Strengthen immunity by increasing connection to natural environment • Strengthen immunity by regular physical exercise • Strengthen immunity by healthy diet (eg, traditional Mediterranean or Baltic type) • Use antibiotics with care. Majority of microbes are useful and support health • Probiotic bacteria in fermented food or other preparations may strengthen immunity • Do not smoke 	<ul style="list-style-type: none"> • Promote regular physical exercise, especially in asthmatics • Promote healthy diet (Mediterranean or Baltic type of diet improves asthma control) • Consider use of fermented food or other preparations, including probiotic bacteria • Consider allergen specific immunotherapy: <ul style="list-style-type: none"> • Allergens as is (foods) • Sublingual tablets or drops (eg, grass pollen, birch pollen, house dust mite) • Subcutaneous injections • Hit early and hit hard respiratory/skin inflammation; find maintenance treatment for long-term control • Do not smoke.

4.2 | Enriching daycare yards

Roslund et al⁹¹ enriched daycare yards with vegetated boreal forest soil blocks, sod, peat blocks, and gardening soil for growing vegetables (Figure 6). The study had two control arms, one without biodiversity intervention and one with nature-oriented daycare. Within 1 month, the diversity of skin microbiota as well as the abundance of *Proteobacteria* were increased in children attending the intervention daycare compared to children in the non-modified daycare. The increased ratio between serum interleukins 10 and 17A indicated activation of immune regulatory pathways. Importantly, the increase of immunomodulatory cytokines and regulatory T cells was associated with a higher diversity of the skin *Gammaproteobacteria*.

5 | THE FINNISH NATIONWIDE ACTION FOR PREVENTION

In Finland (population ca. 5.5 million), several successful national public health programmes have been completed to control respiratory diseases.⁹² The Asthma programme (1994–2004) improved the management by treating asthma primarily as an inflammatory

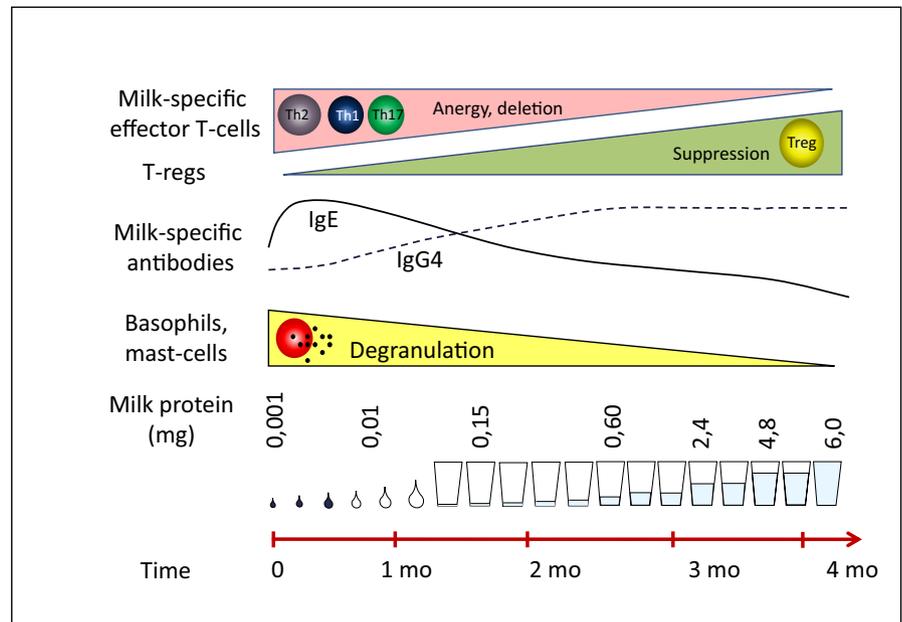
disease.⁹³ For allergic conditions, there are no reports of coordinated action plans to mitigate the burden nationwide. The recent Allergy Programme (2008–2018) was taken to emphasize prevention, tolerance, and nature relatedness^{94,95} (Table 2). The main aim was to transform the strategy from avoidance to tolerance/resilience and focus on allergy health, especially in children.⁹⁶ Severe clinical manifestations were given special attention. A major educational effort both for healthcare professionals and lay public followed.

Indeed, revisiting the allergy paradigm and systematic education mitigated the burden of allergic diseases in the Finnish society.^{97,98} As this real-world intervention lacked controls, the true impact of primary prevention remains to be verified. The Finnish experience is, nevertheless, different from the global trend of asthma and allergy, the burden of which has remained high or is even increasing.^{99–101} This indicates that the current prevention strategies are ineffective and new approaches are required.

5.1 | Case food allergy

In the Finnish Allergy Programme, food allergy guidance and practices were changed with favorable results.^{102,103} The thinking was

FIGURE 7 The immunological changes during the oral immunotherapy (OIT)



based on new knowledge of immunological tolerance. The diversity of foods given at 6 months of age seems to protect from development of food allergies.^{104,105} Most societies have adapted recommending use of solid foods at 4–6 months of age. There is likely an effect of this on the gut microbiome, but more data are required. Interestingly, a recent study indicated that oral immunotherapy (OIT) in peanut allergic adults increased gut microbial diversity.¹⁰⁶ Thus, the gut microbiota seems to shape the host immune system and vice versa.

Dual allergen exposure hypothesis states that immunological tolerance to a food depends on early exposure through the gastrointestinal tract whereas allergic sensitization is more likely, when foods expose the impaired skin barrier.¹⁰⁷ Among infants already sensitized to peanut before 6 months of age, high-dose exposure to peanut resulted in decreased rather than increased risk of peanut allergy.¹⁰⁴ This finding has been repeated with several other foods among children with high risk for allergies.¹⁰⁵ For tolerance induction, there may be a window open between 4 and 6 months of age.¹⁰⁸ In a prospective study, exposure to wheat before the age of 6 months reduced occurrence of allergy as compared with children who were given wheat first after 7 months of age.¹⁰⁹

Early childhood oral tolerance induction is feasible in children who have not yet developed true food allergy for peanut or egg.¹¹⁰ Oral immunotherapy is also a promising therapy for food allergy in older children up to adolescence. Efficacy has been shown in milk, peanut, egg, and wheat allergy. There is still debate about the proportion of patients reaching long-term immunological tolerance.¹¹¹ The immunological changes occurring during the OIT therapy are illustrated in Figure 7.

Atopic march is a cascade of atopic disease in childhood, generally with atopic eczema in early childhood predating other allergic disorders later in childhood. However, only approximately 7% of children with any atopic disease manifestation follow this path during childhood.¹¹²

Genetic factors have a major role in atopic disposition. For example, mutations in the gene coding for the protein filaggrin, linked to epidermal and mucosal homeostasis, predispose to eczema.¹¹³ Children carrying the risk allele for mucosa-associated lymphoid tissue lymphoma translocation gene (MALT1) had the highest risk for peanut allergy.¹¹⁴

The outcome is derived much from the microbiome and environmental factors.¹¹⁵ It is uncertain how much the microbial composition is affected primarily by the type 2 inflammatory response or is the immune deviation caused by a poorly developed microbiome? However, there is a clear association with both atopic eczema, food allergy and early life lung colonization with the microbiome.¹¹⁶

6 | CONCLUDING REMARKS

6.1 | Biodiversity sets limits to human existence

The terrestrial and aquatic ecosystems promote biomass production, stability, and pollination success, produce raw material for processing and manufacturing, support water circulation and freshwater resources, ensure food and support agriculture, sequester carbon from the atmosphere, prevent soil erosion, and provide a place for recreation. A long-term manipulative field experiment in Germany showed that about 45% of different types of ecosystem processes were affected by plant species richness.¹¹⁷ However, the positive biodiversity effect seems to result from several mechanisms acting simultaneously, and functional diversity is even a stronger predictor of a healthy ecosystem than the structural one.¹¹⁸ Loss of biodiversity reduces ecosystem productivity and stability.^{119,120} Now, we are also increasingly aware of the adverse health effects of nature/biodiversity loss, allergic diseases, and asthma as examples.

Human kind has evolved from natural environments, that is from soil and natural waters, but is increasingly affected by built environment and urban space. The fuel for immunological resilience is exposure to biotically diverse life.⁵ Human interaction with macro- and microdiversity is decisive.¹²¹ Urban populations are short of natural experience, not only of exposure to micro-organisms but also to biogenic compounds.^{122,123} The total exposure is also called the *exposome* that can help predict biological responses of the organism to the environment over time.¹²⁴

Immunological resilience is dynamic and derived from exposure through life. The importance of diverse microbial exposure in early life to prevent allergy risk has been reported in both humans and mice.^{125,126} Children, who live on farms, are exposed to a greater variety of environmental micro-organisms and have a lower prevalence of asthma and allergic disorders than children in reference groups.^{10,37} In mouse models of allergic asthma, intranasal instillation of dust extracts from homes with high levels of endotoxins significantly inhibited airway hyperresponsiveness and eosinophilia.³⁷ Furthermore, exposure of mice to microbially rich and diverse soil modified composition of the intestinal microbiota, increased anti-inflammatory signaling in the intestinal epithelium, and protected against experimentally induced allergic asthma.⁷² Skin and epithelial barrier has a constant crosstalk with the environment and dysfunctional barrier predisposes to various health risks.¹²⁷

Resilience is central not only to individuals but to societies and populations by and large.^{128,129} It is strengthened by an environment of multiple options giving room for choices. This is called *redundancy* in the biodiversity discussion. If one option fails, the other may succeed. In a biological or psychological monoculture, the failure of one may mean a failure of all. Biodiversity denotes abundance and even waste instead of extreme effectiveness. Paradoxically, waste creates buffers, that is, resilience. If a population is homogenous in the lack of immunity against COVID-19, it may face extinction. Unpredictable chaos is characteristic to nature. Order and efficacy are the dreams of man.

Prevention is always more cost-effective than medical treatment. World Allergy Organization published already in 2013 a position statement advocating a *Global Allergy Plan* to improve prevention and tolerance.¹³⁰ The Finnish nationwide, real-world intervention, controlled biodiversity interventions, and recent data on environmental epidemiology, microbiome, and epigenetics give credibility to the statement. Several initiatives for prevention are ongoing and new insights presented.¹³¹⁻¹³³ The next step should be systematic implementation studies. Digital transformation in health and care may speed up to obtain results.¹³⁴

Avoidance of allergens causing severe symptoms will remain as good clinical practice but does not solve the public health problem. Probiotic bacteria protect somewhat against atopic eczema, but not generally against IgE-mediated allergies, respiratory outcomes in particular. There are still a number of unknown nutritional¹³⁵ and microbial factors that play a role in building immunological tolerance. For example, rhinovirus infections are associated with exacerbations of asthma. However, early rhinovirus infections as well as certain

other enterovirus infections have associated with decreased risk of IgE-mediated sensitization.¹³⁶ In secondary (tertiary) prevention, allergen specific immunotherapy is effective, but not applicable at population level.

Along with allergy prevention, also measures for other chronic non-communicable diseases have been discussed for a good reason. For example, Nurminen and coworkers found recently that exposure to biodiverse agricultural environment in early life delays the onset of β -cell damaging process among genetically predisposed children and reduces the risk for type 1 diabetes.¹³⁷ Local communities and citizens need guidance to consider both human health and the environment.^{138,139} The Finnish city of Lahti (120 000 inhabitants) is the Green Capital of European Union in 2021.¹⁴⁰ The city is preparing an educational 10-year plan to implement the best practices of public health and environmental care in the spirit of *Planetary Health*, which interconnects human health and the health of the planet.¹⁴¹ The UN Agenda 2030 promotes individual-, community-, and system-level resilience for population well-being to reach the Sustainable Development Goals (SDGs).¹⁴²

6.2 | Money talks

In 2011, the total value of global ecoservices was estimated \$125–145 trillion. They contributed more than twice as much to human well-being than global gross domestic product (GDP).¹⁴³ Furthermore, more than half of the world's total GDP is fundamentally dependent on ecosystem services.¹⁴⁴ Their loss from 1997 to 2011 was worth of \$4.3–20.2 trillion per year.¹⁴³ Only 0.19–0.25% of global GDP is yearly invested to sustain biodiversity.¹⁴⁵ This discrepancy makes no sense ecologically or economically. By protecting global biodiversity, we protect our health, general well-being, as well as our wallets.¹⁴⁶ Although the positive outcome of the Finnish allergy programme initiative was due to several factors, the cumulative, deferred savings of around €1,2 billion during the period from 2007 to 2018 tell of the potential of disease prevention in the health care.¹⁴⁷

CONFLICT OF INTEREST

TH has received personal lecturing fees from GSK, Mundipharma, Orion Pharma, Sanofi, and MJM from GSK, Orion Pharma, outside of the submitted work. AS and HH are stakeholders and members of the board of Uute Scientific Ltd which develops biodiversity-based interventions for the prevention of immune mediated diseases.

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REFERENCES

1. Waters CN, Zalasiewicz J, Summerhayes C, et al. The anthropocene is functionally and stratigraphically distinct from the Holocene. *Science*. 2016;351:aad2622.

2. Ruokolainen L, Fyhrquist N, Laatikainen T, et al. Immune-microbiota interaction in Finnish and Russian Karelia young people with high and low allergy prevalence. *Clin Exp Allergy*. 2020;50:1148-1158.
3. von Hertzen L, Joensuu H, Haahtela T. Microbial deprivation, inflammation and cancer. *Cancer Metastasis Rev*. 2011;30:211-223.
4. Hanski I, von Hertzen L, Fyhrquist N, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. *Proc Natl Acad Sci USA*. 2012;109:8334-8339.
5. Haahtela T. A biodiversity hypothesis. *Allergy*. 2019;74:1445-1456.
6. Ruokolainen L, Lehtimäki J, Karkman A, Haahtela T, von Hertzen L, Fyhrquist N. Holistic view of health: two protective layers of biodiversity. *Ann Zool Fennici*. 2017;54:39-49.
7. Mora C, Tittensor DP, Adl S, Simpson AGB, Worm B. How many species are there on earth and in the ocean? *PLoS Biol*. 2011;9(8):e1001127.
8. Costello MJ, May RM, Stork NE. Can we name earth's species before they go extinct? *Science*. 2013;339:413-416.
9. Locey KJ, Lennon JT. Scaling laws predict global microbial diversity. *PNAS*. 2016;113:5970-5975.
10. Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. 2011;364:701-709.
11. Puhakka R, Rantala O, Roslund MI, Laitinen OH, Sinkkonen A. Greening daycare yards with biodiverse materials affords well-being, play and environmental relationships. *Int J Environ Res Public Health*. 2019;16:2948.
12. Ruokolainen L, von Hertzen L, Fyhrquist N, et al. Green areas around homes reduce atopic sensitization in children. *Allergy*. 2015;70:195-202.
13. Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy*. 2017;47:665-674.
14. Lehtimäki J, Karkman A, Laatikainen T, et al. Patterns in the skin microbiota differ in children and teenagers between rural and urban environments. *Sci Rep*. 2017;7:45651.
15. Lehtimäki J, Thorsen J, Rasmussen MA, et al. Urbanized microbiota in infants, immune constitution and later risk of atopic diseases. *J Allergy Clin Immunol*. 2020. <https://doi.org/10.1016/j.jaci.2020.12.621>
16. Lehtimäki J, Sinkko H, Hielm-Björkman A, Laatikainen T, Ruokolainen L, Lohi H. Simultaneous allergic traits in dogs and their owners are associated with living environment, lifestyle and microbial exposures. *Sci Rep*. 2020;10:21954.
17. Mhuireach G, Johnson BR, Altrichter AE, et al. Urban greenness influences airborne bacterial community composition. *Sci Tot Environ*. 2016;571:680-687.
18. Baruch Z, Liddicoat C, Cando-Dumancela C, et al. Increased plant species richness associates with greater soil bacterial diversity in urban green spaces. *Environ Res*. 2020;196:110425.
19. Mhuireach GÁ, Wilson H, Johnson BR. Urban aerobiomes are influenced by season, vegetation, and individual site characteristics. *EcoHealth*. 2020. <https://doi.org/10.1007/s10393-020-01493-w>. [Epub ahead of print].
20. Mills JG, Bissett A, Gellie NJC, et al. Revegetation of urban green space rewilds soil microbiotas with implications for human health and urban design. *Restor Ecol*. 2020;28:S322-S334.
21. Belz R, Sinkkonen A. Low toxin doses change plant size distribution in dense populations – Glyphosate exposed *Hordeum vulgare* as a greenhouse case study. *Environ Int*. 2019;2019(132):105072.
22. Parajuli A, Grönroos M, Kauppi S, et al. The abundance of health-associated bacteria is altered in PAH polluted soils – implications for health in urban areas? *PLoS One*. 2017;12:e0187852.
23. Roslund MI, Grönroos M, Rantalainen A-L, et al. Half-lives of PAHs and temporal microbiota changes in commonly used urban landscaping materials. *PeerJ*. 2018;6:1-27.
24. Roslund MI, Rantala S, Oikarinen S, et al. Endocrine disruption and commensal bacteria alteration associated with gaseous and soil PAH contamination among daycare children. *Environ Int*. 2019;130:104894.
25. Fouladi F, Bailey MJ, Patterson WB, et al. Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing. *Environ Int*. 2020;138:105604.
26. Vari HK, Roslund MI, Oikarinen S, et al. Associations between land use types, gaseous PAH levels in ambient air and endocrine signaling predicted from gut bacterial metagenome among the elderly. *Chemosphere*. 2021;265:128965.
27. Adams RI, Bateman AC, Bik HM, Meadow JF. Microbiota of the indoor environment: a meta-analysis. *Microbiome*. 2015;3:49.
28. Parajuli A, Grönroos M, Siter N, et al. Urbanization reduces transfer of diverse environmental microbiota indoors. *Front Microbiol*. 2018;9:84.
29. Gupta S, Hjelmsø MH, Lehtimäki J, et al. Environmental shaping of the bacterial and fungal community in infant bed dust and correlations with the airway microbiota. *Microbiome*. 2020;8:115.
30. Shan Y, Guo J, Fan W, et al. Modern urbanization has reshaped the bacterial microbiome profiles of house dust in domestic environments. *World Allergy Organ J*. 2020;13:100452.
31. Kirjavainen PV, Karvonen AM, Adams RI, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nat Med*. 2019;25:1089-1095.
32. Hui N, Parajuli A, Puhakka R, et al. Temporal variation in indoor transfer of dirt-associated environmental bacteria in agricultural and urban areas. *Environ Int*. 2019;132:105069.
33. Parajuli A, Hui N, Puhakka R, et al. Yard vegetation is associated with gut microbiota composition. *Sci Total Environ*. 2020;713:136707.
34. Rothschild D, Weissbrod O, Barkan E, et al. Environment dominates over host genetics in shaping human gut microbiota. *Nature*. 2018;555:210-215.
35. Sonnenburg ED, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. *Nat Rev Microbiol*. 2019;17:383-390.
36. Vangay P, Johnson AJ, Ward TL, et al. US immigration westernizes the human gut microbiome. *Cell*. 2018;175:962-972.
37. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in amish and hutterite farm children. *N Engl J Med*. 2016;375:411-421.
38. Margulis L, Fester R. *Symbiosis as a source of evolutionary innovation*. Cambridge, MA: MIT Press; 1991. ISBN 9780262132695.
39. Simon J-C, Marchesi JR, Mougel C, Selosse M-A. Host-microbiota interactions: from holobiont theory to analysis. *Microbiome*. 2019;7:5.
40. Rojas-Rueda D, Nieuwenhuijsen MJ, Gascon M, Perez-Leon D, Mudu P. Green spaces and mortality: a systematic review and meta-analysis of cohort studies. *Lancet Planet Health*. 2019;3. [https://doi.org/10.1016/S2542-5196\(19\)30215-3](https://doi.org/10.1016/S2542-5196(19)30215-3)
41. Bauwelinck M, Casas L, Nawrot TS, et al. Residing in urban areas with higher green space is associated with lower mortality risk: a census-based cohort study with ten years of follow-up. *Environ Int*. 2021;148:106365.
42. Civitello DJ, Cohen J, Fatima H, et al. Biodiversity inhibits parasites: broad evidence for the dilution effect. *PNAS*. 2015;112:8667-8671.
43. Keesing F, Ostfeld RS. Is biodiversity good for your health? *Science*. 2015;349:235-236.
44. Rohr JR, Civitello DJ, Halliday FW, et al. Towards common ground in the biodiversity–disease debate. *Nat EcolEvol*. 2020;4:24-33.
45. Carlson CJ, Burgio KR, Dougherty ER, et al. Parasite biodiversity faces extinction and redistribution in a changing climate. *Sci Adv*. 2017;3:1-12.
46. Susi H, Laine A-L. Agricultural land use disrupts biodiversity mediation of virus infections in wild plant populations. *New Phytol*.

2020. <https://doi.org/10.1111/nph.17156>. [Epub ahead of print].
47. Wood CL, McInturff A, Young HS, Kim D, Lafferty KD. Human infectious disease burdens decrease with urbanization but not with biodiversity. *Philos Trans R Soc Lond B Biol Sci*. 2017;372:20160122.
 48. Aerts R, Honnay O, Van Nieuwenhuysse A. Biodiversity and human health: mechanisms and evidence of the positive health effects of diversity in nature and green spaces. *Br Med Bull*. 2018;127:5-22.
 49. Lanki T, Siponen T, Ojala A, et al. Acute effects of visits to urban green environments on cardiovascular physiology in women: a field experiment. *Environ Res*. 2017;159:176-185.
 50. Donovan GH, Gatzliolis D, Longley I, Douwes J. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. *Nature Plants*. 2018;4:358-364.
 51. Liddicoat C, Bi P, Waycott M, Glover J, Lowe AJ, Weinstein P. Landscape biodiversity correlates with respiratory health in Australia. *J Environ Manage*. 2018;206:113-122.
 52. Parmes E, Pesce G, Sabel CE, et al. Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: evidence from 9 European cohorts. *Environ Res*. 2020;183:108953.
 53. Uetake J, Tobo Y, Uji Y, et al. Seasonal changes of airborne bacterial communities over Tokyo and influence of local meteorology. *Front Microbiol*. 2019;10:1572.
 54. Baruch Z, Liddicoat C, Cando-Dumancela C, et al. Increased plant species richness associates with greater soil bacterial diversity in urban green spaces. *Environ Res*. 2021;196:110425.
 55. Cavaleiro Rufo JC, Ribeiro AI, Paciência I, Delgado L, Moreira A. The influence of species richness in primary school surroundings on children lung function and allergic disease development. *Pediatr Allergy Immunol*. 2020;31:358-363.
 56. Simpson A, John SL, Jury F, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med*. 2006;174:386-392.
 57. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature*. 2019;571:489-499.
 58. Tost J. A translational perspective on epigenetics in allergic diseases. *J Allergy Clin Immunol*. 2018;142:715-726.
 59. Xu CJ, Soderhall C, Bustamante M, et al. DNA methylation in childhood asthma: an epigenome-wide meta-analysis. *Lancet Respir Med*. 2018;6:379-388.
 60. Qi C, Jiang Y, Yang IV, et al. Nasal DNA methylation profiling of asthma and rhinitis. *J Allergy Clin Immunol*. 2020;145:1655-1663.
 61. Cardenas A, Sordillo JE, Rifas-Shiman SL, et al. The nasal methylome as a biomarker of asthma and airway inflammation in children. *Nat Commun*. 2019;2019(10):3095.
 62. Forno E, Wang T, Qi C, et al. DNA methylation in nasal epithelium, atopy, and atopic asthma in children: a genome-wide study. *Lancet Respir Med*. 2019;2019(7):336-346.
 63. Atianand MK, Fitzgerald KA. Long non-coding RNAs and control of gene expression in the immune system. *Trends Mol Med*. 2014;20:623-631.
 64. Gibbons HR, Shaginurova G, Kim LC, Chapman N, Spurlock CF 3rd, Aune TM. Divergent lncRNA GATA3-AS1 regulates GATA3 transcription in T-Helper 2 Cells. *Front Immunol*. 2018;9:2512.
 65. Heward JA, Lindsay MA. Long non-coding RNAs in the regulation of the immune response. *Trends Immunol*. 2014;35:408-419.
 66. Zhang H, Nestor CE, Zhao S, et al. Profiling of human CD4+ T-cell subsets identifies the TH2-specific noncoding RNA GATA3-AS1. *J Allergy Clin Immunol*. 2013;132:1005-1008.
 67. Woo V, Alenghat T. Host-microbiota interactions: epigenomic regulation. *Curr Opin Immunol*. 2017;44:52-60.
 68. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat Med*. 2010;16:228-231.
 69. Olszak T, An D, Zeissig S, et al. Microbial exposure during early life has persistent effects on natural killer T cell function. *Science*. 2012;336:489-493.
 70. Naik S, Larsen SB, Gomez NC, et al. Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. *Nature*. 2017;550:475-480.
 71. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med*. 2014;20:159-166.
 72. Ottman N, Ruokolainen L, Suomalainen A, et al. Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model. *J Allergy Clin Immunol*. 2019;143:1198-1206.
 73. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol*. 2015;8:80-93.
 74. Bunyavanich S, Shen N, Grishin A, et al. Early-life gut microbiome composition and milk allergy resolution. *J Allergy Clin Immunol*. 2016;138:1122-1130.
 75. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504:446-450.
 76. Fyhrquist N, Ruokolainen L, Suomalainen A, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. *J Allergy Clin Immunol*. 2014;134:1301-1309.
 77. Brand S, Teich R, Dicke T, et al. Epigenetic regulation in murine offspring as a novel mechanism for transmaternal asthma protection induced by microbes. *J Allergy Clin Immunol*. 2011;128:618-625.
 78. Nagu P, Parashar A, Behl T, Mehta V. Gut microbiota composition and epigenetic molecular changes connected to the pathogenesis of Alzheimer's disease. *J Mol Neurosci*. 2021. <https://doi.org/10.1007/s12031-021-01829-3>. [Epub ahead of print].
 79. Akiyama T, Iodi Carstens M, Carstens E. Transmitters and pathways mediating inhibition of spinal itch-signaling neurons by scratching and other counterstimuli. *PLoS One*. 2011;6:e22665.
 80. Zhang Q, Cao X. Epigenetic regulation of the innate immune response to infection. *Nat Rev Immunol*. 2019;19:417-432.
 81. Selway CA, Mills JG, Weinstein P, et al. Transfer of environmental microbes to the skin and respiratory tract of humans after urban green space. *Environ Int*. 2020;145:106084.
 82. Lehtimäki J, Laatikainen T, Karkman A, et al. Nature-oriented day-care diversifies skin microbiota in children—No robust association with allergies. *Pediatr Allergy Immunol*. 2018;29:318-321.
 83. Bateman A. The Dynamics of Microbial Transfer and Persistence on Human Skin. 2017. <https://scholarsbank.uoregon.edu/xmlui/handle/1794/22709>. Accessed September 12, 2019.
 84. von Hertzen L, Beutler B, Bienenstock J, et al. Helsinki alert of biodiversity and health. *Ann Med*. 2015;47:218-225.
 85. Prescott SL, Hancock T, Bland J, et al. Eighth annual conference of inVIVO planetary health: from challenges to opportunities. *Int J Environ Res Public Health*. 2019;16:4302.
 86. Puhakka R, Valve R, Sinkkonen A. Older consumers' perceptions of functional foods and nonedible health-enhancing innovations. *Int J Consum Stu*. 2018;42:111-119.
 87. Puhakka R, Ollila SA, Valve R, Sinkkonen A. Consumer trust in a health-enhancing innovation - comparisons between Finland, Germany and the United Kingdom. *J Int Consum Mark*. 2019;31:162-176.
 88. Puhakka R, Haskins L, Jauho M, Grönroos M, Sinkkonen A. Factors affecting young adults' willingness to try novel health-enhancing nature-based products. *J Int Consum Mark*. 2021:1-18. <https://doi.org/10.1080/08961530.2021.1873887>
 89. Grönroos M, Parajuli A, Laitinen OH, et al. Short-term direct contact with soil and plant materials leads to an immediate increase in diversity of skin microbiota. *Microbiol Open*. 2019;8:1-13.

90. Nurminen N, Lin J, Grönroos M, et al. Nature-derived microbiota exposure as a novel immunomodulatory approach. *Future Microbiol.* 2018;13:737-744.
91. Roslund M, Puhakka R, Grönroos M, et al. Biodiversity intervention enhances immune regulation and health-associated commensal microbiota among daycare children. *Sci Adv.* 2020;6:1-10.
92. Erhola M, Vasankari T, Jormanainen V, Toppila-Salmi S, Herrala J, Haahtela T. 25 years of respiratory health in Finland. *Lancet Respir Med.* 2019;7. [https://doi.org/10.1016/S2213-2600\(19\)30122-5](https://doi.org/10.1016/S2213-2600(19)30122-5)
93. Haahtela T, Herse F, Karjalainen J, et al. The Finnish experience to save asthma costs by improving care in 1987–2013. *J Allergy Clin Immunol.* 2017;139:408-414.
94. Haahtela T, von Hertzen L, Mäkelä M, Hannuksela M, Allergy Programme Working Group. Finnish allergy programme 2008-2018 – time to act and change the course. *Allergy.* 2008;63(6):634-645.
95. von Hertzen LC, Savolainen J, Hannuksela M, et al. Scientific rationale for the Finnish allergy programme 2008–2018: emphasis on prevention and endorsing tolerance. *Allergy.* 2009;64:678-701.
96. Pelkonen AS, Kuitunen M, Dunder T, et al. Allergy in children: practical recommendations of the Finnish allergy programme 2008–2018 for prevention, diagnosis, and treatment. *Pediatr Allergy Immunol.* 2012;23:103-116.
97. Haahtela T, Valovirta E, Bousquet J, Mäkelä M, the Allergy Programme Steering Group. The Finnish allergy programme 2008–2018 works. *Eur Respir J.* 2017;49(6):1700470.
98. Haahtela T, Valovirta E, Saarinen K, et al. The Finnish allergy program 2008-2018: society-wide proactive program for change of management to mitigate allergy burden. *J Allergy Clin Immunol.* 2021. <https://doi.org/10.1016/j.jaci.2021.03.037>. [Epub ahead of print].
99. Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. Online Appendix. Updated 2020. www.ginasthma.org. Accessed December 28, 2020.
100. Mattiuzzi C, Lippi G. Worldwide asthma epidemiology: insights from the global health data exchange database. *Int Forum Allergy Rhinol.* 2020;1:75-80.
101. Dierick BJH, van der Molen T, Flokstra-de Blok BMJ, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. *Expert Rev Pharmacoecon Outcomes Res.* 2020;14:1-17.
102. Erkkola M, Saloheimo T, Hauta-Alus H, et al. Burden of allergy diets in Finnish day care reduced by change in practices. *Allergy.* 2016;71:1453-1460.
103. Savolainen J, Mascialino B, Pensamo E, et al. Structured intervention plan including component-resolved diagnostics helps reducing the burden of food allergy among school-aged children. *Pediatr Allergy Immunol.* 2019;30:99-106.
104. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med.* 2015;372:803-813.
105. Perkin MR, Logan K, Bahnson HT, et al. Efficacy of the enquiring about tolerance (EAT) study among infants at high risk of developing food allergy. *J Allergy Clin Immunol.* 2019;144:1606-1614.
106. He Z, Gouri Vadali VL, Szabady RL, et al. Increased diversity of gut microbiota during active oral immunotherapy in peanut-allergic adults. *Allergy.* 2021;76:927-930.
107. Brough HA, Nadeau KC, Sinder SB, et al. Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? *Allergy.* 2020;75:2185-2205.
108. Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *JAMA.* 2016;316:1181-1192.
109. Poole JA, Barriga K, Donald YM, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics.* 2006;117:2175-2182.
110. Krawiec M, Fisher HR, Du Toit G, Bahnson HT, Lack G. Overview of oral tolerance induction for prevention of food allergy—Where are we now? *Allergy.* 2021. <https://doi.org/10.1111/all.14758>. [Epub ahead of print].
111. Eiwegger T, Hung L, San Diego KE, O'Mahony L, Upton J. Recent developments and highlights in food allergy. *Allergy.* 2019;74:2355-2367.
112. Custovic A, Custovic D, Kljaić Bukvić B, Fontanella S, Haider S. Atopic phenotypes and their implication in the atopic march. *Expert Rev Clin Immunol.* 2020;16:873-881.
113. Clark H, Granell R, Curtin JA, et al. Differential associations of allergic disease genetic variants with developmental profiles of eczema, wheeze and rhinitis. *Clin Exp Allergy.* 2019;49:1475-1486.
114. Winters A, Bahnson HT, Ruczinski I, et al. The MALT1 locus and peanut avoidance in the risk for peanut allergy. *J Allergy Clin Immunol.* 2019;143:2326-2329.
115. Kremski JW, Dant C, Nadeau K. The origins of allergy from a systems approach. *Ann Allergy Asthma Immunol.* 2020;125:507-516.
116. Nibbering B, Ubags NDJ. Microbial interactions in the atopic march. *Clin Exp Immunol.* 2020;199:12-23.
117. Weisser WW, Roscher C, Meyer ST, et al. Biodiversity effects on ecosystem functioning in a 15-year grassland experiment: patterns, mechanisms, and open questions. *Basic Appl Ecol.* 2017;23:1-73.
118. van der Plas F. Biodiversity and ecosystem functioning in naturally assembled communities. *Biol Rev.* 2019;94:1220-1245.
119. Duffy JE, Godwin CM, Cardinale BJ. Biodiversity effects in the wild are common and as strong as key drivers of productivity. *Nature.* 2017;549:261-264.
120. Dainese M, Martin EA, Aizen MA, et al. A global synthesis reveals biodiversity-mediated benefits for crop production. *Sci Adv.* 2019;5:1-13.
121. Rook G, Bäckhed F, Levin BR, McFall-Ngai MJ, McLean AR. Evolution, human-microbe interactions, and life history plasticity. *Lancet.* 2017;390:521-530.
122. Moore MN. Do airborne biogenic chemicals interact with the PI3K/Akt/mTOR cell signalling pathway to benefit human health and wellbeing in rural and coastal environments? *Environ Res.* 2015;140:65-75.
123. Antonelli M, Donelli D, Barbieri G, Valussi M, Maggini V, Firenzuoli F. Forest volatile organic compounds and their effects on human health: a state-of-the-art review. *Int J Environ Res Public Health.* 2020;17:6506.
124. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: early-life events and immune development in a changing world. *J Allergy Clin Immunol.* 2017;140:24-40.
125. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol.* 2010;10:861-868.
126. Gensollen T, Lyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. *Science.* 2016;352:539-544.
127. Akdis C. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol.* 2021. <https://doi.org/10.1038/s41577-021-00538-7>
128. Ran J, MacGillivray BH, Gong Y, Hales TC. The application of frameworks for measuring social vulnerability and resilience to geophysical hazards within developing countries: a systematic review and narrative synthesis. *Sci Total Environ.* 2020;711:134486.
129. Haahtela T, Anto JM, Bousquet J. Fast and slow crises of Homo urbanicus: loss of resilience in communicable diseases, like COVID-19, and non-communicable diseases. *Porto Biomed J.* 2020;5:4.
130. Haahtela T, Holgate ST, Pawankar R, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *WAO J.* 2013;6:3.
131. von Mutius E SHH. Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *Lancet.* 2020;396:854-866.

132. Cevhertas L, Ogular I, Maurer DJ, et al. Advances and recent developments in asthma. *Allergy*. 2020;75:3124-3146.
133. Silva TS, Hageman E, Davis JA, et al. Introducing the ORIGIN project: a community-based interventional birth cohort. *Rev Environ Health*. 2020;45:281-293.
134. Bousquet J, Anto JM, Bachert C, et al. ARIA digital anamorphosis: digital transformation of health and care in airway diseases from research to practice. *Allergy*. 2021;76:168-190.
135. Trikamjee T, Comberiati P, D'Auria E, Peroni D, Zuccotti GV. Nutritional factors in the prevention of atopic dermatitis in children. *Front Pediatr*. 2021;8:577413.
136. Korhonen L, Oikarinen S, Lehtonen J, et al. Rhinoviruses in infancy and risk of immunoglobulin E sensitization. *J Med Virol*. 2019;91:1470-1478.
137. Nurminen N, Cerrone D, Lehtonen J, et al. Land cover of early life environment modulates the risk of type 1 diabetes. *Diabetes Care*. 2021. <https://doi.org/10.2337/dc20-1719>. [Epub ahead of print].
138. Haahtela T, von Hertzen L, Anto JM, et al. Helsinki by nature: the nature step to respiratory health. *Clin Transl Allergy*. 2019;9:57.
139. Halonen JI, Erhola M, Furman E, et al. A call for urgent action to safeguard our planet and our health in line with the Helsinki declaration. *Environ Res*. 2021;193:110600.
140. European Commission. Environment. European Green Capital (europa.eu) 2021.
141. Whitmee S, Haines A, Beyrer C, et al. Safeguarding human health in the anthropocene epoch: report of the Rockefeller foundation-lancet commission on planetary health. *Lancet*. 2015;386:1973-2028.
142. WHO. *Strengthening resilience: a priority shared by health 2020 and the sustainable development goals*. Copenhagen, Denmark: WHO Regional Office for Europe; 2017.
143. Costanza R, de Groot R, Sutton P, et al. Changes in the global value of ecosystem services. *Global Environ Change*. 2014;26:152-158.
144. The World Economic Forum. Nature risk rising: why the crisis engulfing nature matters for business and the economy 2020. <https://www.weforum.org/reports/>. Accessed February 3, 2021.
145. Seidl A, Mulungu K, Arlaud M, van den Heuvel O, Riva M. Finance for nature: a global estimate of public biodiversity investments. *Ecosyst Serv*. 2020;46:101216.
146. Dasgupta P. *The economics of biodiversity: the dasgupta review*. London, UK: HM Treasury; 2021.
147. Jantunen J, Kauppi P, Linna M, Mäkelä M, Pelkonen A, Haahtela T. Astman ja allergian kustannusten myönteinen kehitys jatkui (Positive trend in asthma and allergy costs continues). *Finn Med J*. 2021;76:29-37.(in Finnish, Abstract in English)

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