Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases

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The unparalleled burden of a diverse range of chronic noncommunicable diseases (NCDs) is a major global challenge in the 21st century. Chronic low-grade inflammation is a common feature of virtually all NCDs, indicating a central role of the immune system. Furthermore, as the most common and earliest-onset NCD, the epidemic of allergic diseases points to specific vulnerability of the developing immune system to modern environmental change. Indeed, many environmental risk factors implicated in the rise of other NCDs have been shown to mediate their effects through immune pathways. The innate immune system provides a clear example of this convergence, with evidence that physical activity, nutrition, pollutants, and the microbiome all influence systemic inflammation through Toll-like receptor pathways (notably Toll-like receptor 4), with downstream effects on the risk of insulin resistance, obesity, cardiovascular risk, immune diseases, and even mood and behavior. Common risk factors will likely mean common solutions, and interdisciplinary strategies to promote immune health should be an integral part of NCD prevention, with a greater focus early in the life course before disease processes are established. In this context allergic disease provides a very important early target to assess the effectiveness of environmental strategies to reduce immune dysregulation. (J Allergy Clin Immunol 2013;131:23-30.)

Key words: *Allergic disease, early immune development, inflammation, pregnancy and early life, diet and nutrition, microbiome, environmental pollutants and irritants, gene-environmental interactions, developmental origins of health and disease, noncommunicable diseases, obesity, disease prevention*

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Abbreviations used
NCD: Noncommunicable disease
PUFA: Polyunsaturated fatty acid
TLR: Toll-like receptor

Over millennia, our external environment has shaped the myriad elaborate interwoven pathways that maintain constant defense against a diverse range of potential threats. In equal measure our survival has been dependent on evolutionary pressure to limit and regulate immune responses that could be otherwise detrimental to the host. Our complex relationship with the environment is fundamental to understanding the very existence and evolution of the immune system, as well as the reasons for the unprecedented surge in noncommunicable inflammatory diseases in modern times.

A GLOBAL HEALTH CHALLENGE OF PANDEMIC PROPORTIONS

Dramatic environmental and lifestyle changes of the modern age pose a significant threat to human health. An unparalleled increase in a diverse range of chronic noncommunicable diseases (NCDs) is one of the major global challenges of the 21st century. This growing burden of NCDs currently poses the greatest threat to health in both developed and developing regions and is a major barrier to human development. The dominant focus of the NCDs agenda is usually on "the big four": cardiovascular disease, metabolic disease (obesity and type 2 diabetes), cancer, and chronic lung disease. Although both asthma and smoking-related diseases are considered in the context of chronic lung disease, allergic diseases *per se* are typically overlooked in this agenda, despite now being the most common and earliest-onset NCDs in most regions. Already, approximately 30% to 40% of the world's population is affected by 1 or more allergic conditions, with vast personal, social, and economic costs.[1] This needs to be recognized as a major element in the wider public health agenda, with strong efforts toward promoting immune health as an integral part of NCD prevention.

INFLAMMATION AS A COMMON FEATURE OF MANY NCDs: A CENTRAL ROLE OF THE IMMUNE SYSTEM

Chronic low-grade inflammation is a common feature of virtually all NCDs, highlighting the central multisystem interactions of the immune system.[2] The specific vulnerability of the immune system to recent environmental changes is also reflected in

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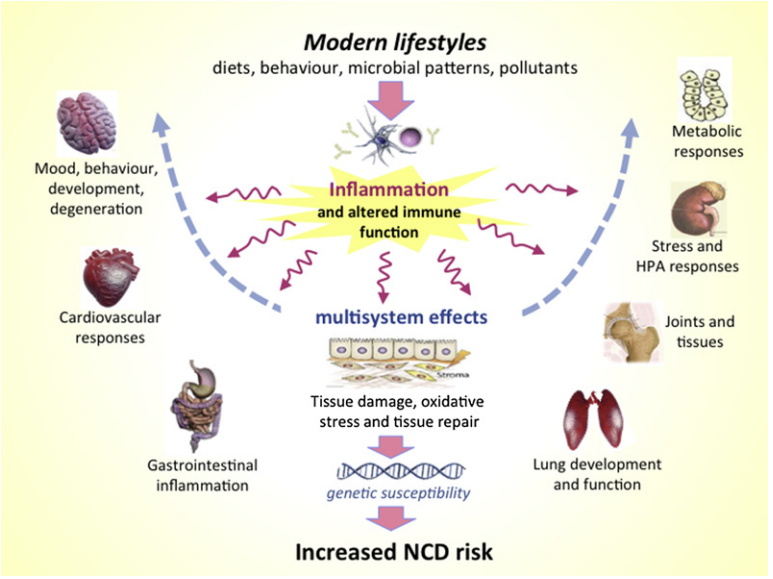


FIG 1. Inflammation: a common element in many NCDs. *HPA*, Hypothalamic-pituitary-adrenal axis.

the dramatic increase in virtually all inflammatory disorders and, in particular, immune diseases, such as allergy and autoimmunity. Furthermore, clinical expression of allergy within the first months of life and detectable immune dysregulation at birth[3] provide clear evidence of very early environmental effects. The risk factors that are specifically associated with early immune dysfunction include modern dietary patterns, environmental pollutants, microbial patterns, and stress.[4,5] These all appear to promote inflammation and are common risks for many NCDs (Fig 1).[2] Reducing the risk of inflammatory responses through lifestyle and environmental interventions is likely to have benefits for the risk and progression of many other NCDs.

Importantly, overcoming the adverse consequences of lifestyle changes will logically require somewhat more holistic approaches than the more focused pharmaceutical approach of immune therapies. Although there remains a clear role for developing better pharmaceutical interventions, holistic approaches are more likely to simultaneously modify a variety of innate immune responses—analogous to the multiple environmental changes currently acting simultaneously on many organ systems to exert chronic inflammatory changes.

As practicing allergists, we must embrace the challenge of more fully understanding the interaction between the environment and immunity. We have the opportunity to be the specialty that leads the way in advising families about the significance of the immune system for many aspects of health, including the limitations of our current understanding. Clinicians often ignore this, and people then seek less rigorous sources for advice. Even if the answers are not clear, we need to be educated so we can put this in context for patients.

EARLY LIFE: A CRITICAL TIME OF RISK AND OPPORTUNITY

Prevention is the ultimate approach to reducing the burden of NCDs, and the greatest potential for this lies in early life. There is already substantive evidence that initiatives to promote a healthy start to life can reduce the risk of both early and later NCDs, with wide social and economic benefits.[6,7] The early environment in both pregnancy and early childhood can determine physiologic, structural, immune, metabolic, and behavioral development and modify response patterns that influence future disease susceptibility.[6,7]

Although many NCDs might not become apparent until later in life, allergic diseases frequently manifest within the first months of life.[8] This is the clearest indication that the developing immune system is exquisitely sensitive to modern environmental pressures, together with mounting evidence that these effects must begin *in utero*.[3] Furthermore, the longer-term implications for this new generation need to be considered. Allergy is a systemic disease associated with systemic release of cytokines and chemokines and with distal recruitment of inflammatory progenitors into the circulation from the bone marrow.[9] Low-grade systemic inflammation has now been clearly linked with the risk for metabolic dysregulation and vascular disease.[10] Although there are some associations between cardiovascular disease and allergic disease in later life,[11,12] the long-term multisystem implications of allergic inflammation in earlier life have not yet been determined, particularly in the current high-prevalence generation yet to reach maturity.

The mandate of the interdisciplinary Developmental Origins of Health and Disease (DOHaD) movement is to promote a life-course approach to disease prevention, beginning with maternal health before conception. It is important to encourage a specific focus on achieving optimal immune development as a core part of the DOHaD agenda because this is likely to be central in reducing the wider burden of NCDs and inflammatory pathology in the future. Studying the early effects of lifestyle interventions on early immune function and allergic disease will provide a useful early barometer in evaluating effectiveness.

COMMON RISK FACTORS MEAN COMMON SOLUTIONS: THE NEED FOR INTERDISCIPLINARY COLLABORATION

Although genetic factors can determine individual susceptibility and patterns of disease, only environmental change can

account for the rapid increase in NCDs. This also suggests common risk factors and the need for common solutions. Moving forward, there is a clear imperative for coordinated interdisciplinary strategies, particularly those focused on early life. There are a number of good examples of immunomodulatory interventions explored for allergy prevention that might have additional multisystem benefits. Anticipating a new collaborative era of preventive medicine, these are considered here in a more interdisciplinary context.

Multisystem benefits of anti-inflammatory ω-3 polyunsaturated fatty acid

With well-recognized anti-inflammatory properties, ω-3 polyunsaturated fatty acid (PUFA)–rich fish oils have been logical interventions for the prevention and treatment of a number of inflammatory conditions. In one of the earliest intervention studies for allergy prevention, we supplemented allergic women with fish oil from 20 weeks' gestation, with immunomodulatory effects in their neonates[13-15] and reduced risk of subsequent allergen (egg) sensitization and eczema severity.[13] More recently, in a much larger, more definitive randomized controlled trial of 706 pregnant women, we observed that fish oil supplementation also achieved a reduction in egg sensitization by 12 months of age in high-risk infants.[16] Rates of atopic eczema (eczema with associated sensitization) were also less in the fish oil group. We also examined the effects of early postnatal fish oil supplementation in high-risk infants (n = 420) from birth to 6 months.[17] The intervention increased infant ω-3 PUFA levels and was associated with decreased allergen-specific T_H2 responses and increased polyclonal T_H1 responses.[18] Although ω-3 PUFA levels at 6 months were associated with lower risk of eczema and recurrent wheeze, there was no effect of the intervention *per se* on the primary study outcomes (intention to treat analysis).[19] However, in a per-protocol analysis, infants who received more than 75% of the intended supplementation (the highest adherence quartile) had a significantly lower prevalence of eczema at 12 months in the fish oil group.[19] These findings suggest that achieving higher ω-3 PUFA levels in infancy gives some protection against allergic outcomes but that postnatal supplementation is not an effective strategy. Even before these more recent large studies, the collective literature appeared to be gathering strength to support an allergy-protective effect of fish oil in pregnancy rather than the postnatal period, as suggested by a 2011 systematic review.[20] The inclusion of additional data from the new studies (above)[16,19] in repeated meta-analyses is expected to provide stronger data that will be better positioned to inform clinical practice recommendations in the very near future.

Notably, these early interventions with fish oil aimed at allergy prevention in early childhood[18,19,21] also have benefits for metabolic programming[22] and reducing cardiovascular risk.[23,24] A recent follow-up of one of these allergy prevention studies at 8 years of age (n = 363) showed that dietary fish oil supplementation over the first 5 years of life reduced the carotid intima-media thickening (as a noninvasive measure of subclinical atherosclerosis) that had been associated with reduced fetal growth.[23] This might be mediated, at least in part, by a reduction in the low-grade systemic inflammation that has been linked directly with the risk for cardiometabolic disease.[25] In keeping with this, we have previously shown that fish oil supplementation in pregnancy decreased neonatal oxidative stress[14] and neutrophil production of leukotriene B_4, which correlated with reduced Toll-like receptor (TLR) 4–mediated inflammatory responses.[15] Furthermore, in addition to immunomodulation[13,18] and allergy reduction,[13,16] we have also seen beneficial effects on aspects of neurodevelopment after both prenatal[26] and early postnatal[27] fish oil supplementation. In summary, restoring the higher ω-3 PUFA levels seen in subjects with more traditional diets is a clear example of an early immunomodulatory intervention that has multisystem benefits.

Effects of the gut microbiome, probiotics, and other microbial products

Changing microbial exposure and diversity remains one of the leading explanations for the increase in rates of many inflammatory diseases. Animal models provide clear evidence that the gut microbiota modulates immune programming and that manipulation of the microbiome can prevent not only allergic disease[28] and autoimmune phenomena[29] but also the risk of obesity, cardiovascular and metabolic disease,[30] and even modulate mood and behavior (Fig 2).[31,32]

Importantly, there is accumulating evidence that many of these multisystem effects are mediated through the immune system (Fig 2). Adverse changes in gut microbiome (induced by the high-fat, low-fiber Western diet) are associated with altered gut barrier function, increased systemic endotoxin levels,[33] and antigenic load and evidence of increased low-grade systemic inflammation (as detected by increased C-reactive protein levels and higher levels of circulating IL-1β, TNF, IL-6, and adiponectin).[34] Microbiota can also directly regulate the host genes involved in lipid metabolism,[35] with associated effects of insulin resistance, food craving, altered lipid profiles, and liver function, eventually transforming the host into a highly efficient lipid-making and lipid storage machine.[30,35-37] A critical role for TLR4 was defined by observations that mice with a loss-of-function mutation in *TLR4* resist becoming obese on a high-fat diet.[38] Long-chain fatty acids can activate TLR4 on macrophage lineage cells or resident cells in the adipose tissue, muscle, brain, and liver to initiate metabolic pathways that promote insulin resistance and oxidative stress.[39,40] These physiologic and metabolic adaptations can be reversed through restoring a more "favorable" gut microbiome.[37] It is also notable that, the positive metabolic effects of exercise are also mediated, in part, through downregulation of TLR4.[41] Even more unanticipated effects of modifying the gut microbiome have been seen with regard to mood, anxiety, and behavior. Germ-free mice respond differently to stress, and in colonized mice, disturbing the gut microflora with antibiotics also alters behavior through changes in brain-derived neurotrophic factor.[31,32,42] A surprising new study has found that addictive behavior is mediated through TLR4 pathways, demonstrating unique and specific links between innate immune pathways and behavior.[43]

At this stage, the long-term effects of early-life strategies have not been investigated in human subjects; however, a new landmark murine study by Cho et al[44] showed that changes in the gut microbiome induced by exposure to antibiotics in early life increased the risk of adiposity, with significant metabolic effects on short-chain fatty acid levels and hepatic metabolism of lipids and cholesterol. Notably, this effect was seen with subtherapeutic doses akin to the antibiotic levels used extensively in agriculture.[44] This underscores the need to more fully examine diverse

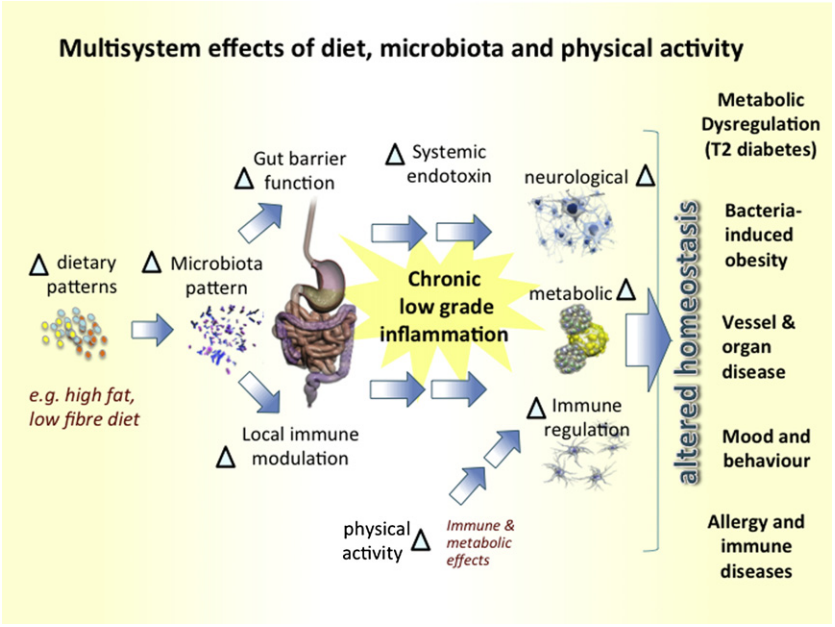


FIG 2. A central role of the immune system in mediating the multisystem effects of diet, physical activity, and the microbiota.

health outcomes in relation to the early microbiome. Existing allergy prevention cohorts with probiotics might provide an opportunity to examine this.

There are now a considerable number of interventions using various probiotic strains in pregnancy, the early postnatal period, or both for allergy prevention.[45] Most of these studies have thus far focused primarily on early outcomes of allergic disease, such as eczema and IgE-mediated food allergy, and approximately half of these showed a significant reduction in the development of eczema (25% to 50%) but no consistent effects on any other allergic outcomes.[45] There is considerable heterogeneity in virtually all aspects of these studies. Several meta-analyses published in the last 12 months have concurred that probiotics reduce the risk of eczema but not other allergic outcome.[46,47] The most recent of these[47] included 13 prevention studies and demonstrated that probiotic treatment reduced the incidence of eczema by 21% (relative risk, 0.79; 95% CI, 0.71-0.88). This effect was still present when the analysis was restricted to studies of patients with IgE-associated eczema.

Thus although the use of specific probiotic supplements has been of interest in assessing the short-term preventive benefits on inflammatory disease in early childhood (ie, allergic disease), slowing the long-term effects of chronic, systemic, low-grade inflammation associated with aging and age-related NCDs requires more sustainable strategies. Ultimately, a more balanced favorable microbiome is likely to be best achieved by establishing more traditional dietary patterns early in life, and this is likely to be of multisystem benefit.

Benefits of anti-inflammatory soluble dietary fiber

Decreasing dietary fiber levels in modern diets has been specifically associated with an increased risk for a number of NCDs, including allergic disease. Soluble fiber (prebiotic carbohydrate) is a major substrate for bacterial growth, selectively stimulating the growth, activity, or both of beneficial members of the gut microbiota, particularly bifidobacteria.[48,49] Of at least equal importance, the resulting fermentation products, short-chain fatty acids, have direct anti-inflammatory effects[50] and promote intestinal integrity through effects on epithelial cell proliferation and differentiation.[51] As anticipated, dietary interventions to increase dietary fiber levels have benefits for both immune[52,53] and metabolic[54] homeostasis, reducing systemic endotoxin levels and antigenic load.[55]

In the context of allergy prevention, initial studies with prebiotics in early infancy have shown promise in infants at both high risk[48,56] and low risk[57] of allergic disease; however, more studies are needed to confirm this, and the results of at least 1 other large-scale multicenter trial are expected soon. Improving intake of soluble dietary fiber is likely to have more global effects on colonization than adding a single probiotic strain. It is also likely to have more multisystem benefits for the longer-term propensity for many other metabolic and inflammatory disease processes. Again, this emphasizes the need to address long-term dietary habits beginning in very early life.

Effects of other dietary exposures

Dietary patterns associated with higher consumption of vegetables, fruits, grains, and legumes and lower intake of saturated fat have been associated with reduced risk for a number of inflammatory diseases.[58] For example, a Mediterranean diet, which is associated with lower rates of cardiovascular disease and obesity,[59] has also been associated with protection against childhood asthma and wheeze,[60,61] particularly higher consumption of vegetables, fruits, legumes, and fish during pregnancy.[61,62] Although the protective elements within these diets are likely to include selenium, zinc, folate, vitamin E, and other antioxidants, the effects of specific supplements have been inconsistent and even paradoxical (as reviewed by Shaheen[58]). These inconsistencies are likely to reflect the inherent complexity of dietary influences or the difficulty in accurately measuring these influences or replicating the

effects with specific supplements. Again, the most logical and sustainable strategies are to promote a healthy balanced diet over the life course.

Multisystem effects of sunlight and vitamin D exposure

Yet another modern behavioral change associated with a broad range of adverse health outcomes (and overall mortality) has been a progressively more sedentary indoor lifestyle and increasing rates of vitamin D insufficiency. The long list of epidemiologic associations with decreasing sunlight exposure includes hypertension, type 2 diabetes, multiple sclerosis, type 1 diabetes (and other autoimmunity), bone disease, some cancers (breast and hematological), susceptibility to infection, food allergy, and asthma.[63,64] Although these relationships can be explained in part by the recognized immunomodulatory effects, studies with vitamin D supplementation have been inconsistent.[65] Although large-scale randomized controlled trials of vitamin D supplementation in pregnancy are still underway, there is also speculation that vitamin D might be a surrogate marker for independent immunomodulatory effects of UV radiation. Indeed, UV radiation mediates direct release of a range of immunomodulatory factors in the skin that promote regulatory cell differentiation in regional nodes and suppression of immune responses at distal sites (as reviewed by Hart et al[66]). Moreover, UVB appears to imprint changes in dendritic cells, which shift from an immunogenic to a more regulatory phenotype (as reviewed by Hart et al[66]). These prostaglandin E_2–mediated effects are systemic and act on bone marrow precursors to reduce inflammatory propensity. Although more studies are needed, this could indicate that the protective effects of some exposure to natural light might be multifaceted and might not be fully compensated by vitamin D supplementation.[66]

Other factors with multisystem effects

A range of other exposures in modern environments are linked with adverse effects on general health and longevity, many with immune effects. These include smoking,[67] persistent organic pollutants and other modern toxins,[68] stress,[69,70] and decreasing physical activity.[71] Although a detailed discussion of each of these is beyond the scope of this review, a number of these exposures have epigenetic effects[72] and might have effects on immune development early in life.

EPIGENETICS, GENETICS, AND EVOLUTIONARY PERSPECTIVES

The T_H2 responses that characterize allergic disease are not inherently pathological and only cause disease when excessive or misdirected. Provoking new thoughts and challenging long-held concepts that T_H2 responses have primarily evolved to defend against helminthes, Palm et al[73] have recently proposed that the very rapid, acute IgE-mediated responses are equally, if not more likely, to have evolved to protect against a broader diverse range of environmental irritants, toxins, venoms, hematophagous fluids (from ectoparasites, such as mosquitoes and ticks), and noxious xenobiotics and phytochemicals. IgE-mediated sneezing, tearing, coughing, vomiting, diarrhea, and itching all serve to rapidly expel or remove these threats, potentially explaining the urgency of the response. These unpleasant symptoms also lead to conditioned avoidance and host aversion to reduce future threat.[73] This perspective might give new insight into the diversity of allergens (plants, mites, venoms, antibiotics, animals, and fungi) that invoke the T_H2 armamentarium.[73] Similarly, the tissue barrier enhancement and repair mechanisms that lead to scarring and fibrosis in asthmatic patients are part of normal mechanisms transiently solicited to restrict penetration, prevent spread, and promote healing.

Although changing patterns of gene-environment interaction are responsible for the increase in rates of allergic disease and many other inflammatory conditions, the mechanisms are not fully clear. Environmental changes must be driving this pandemic, but genetic predisposition remains an important determinant of individual susceptibility. Persistence of genetic polymorphisms that have no functional disadvantage in traditional environments might predispose to disease under radically altered "modern" conditions. There are many diverse pathways and numerous examples of how the disease predisposition conferred by genetic polymorphisms change significantly under different environmental conditions. In the context of allergic disease, the effects of a number of specific genes vary dramatically in relation to changes in relevant exposures, such as cigarette smoking[74] and microbial exposure.[75] Genetic polymorphisms in other functional pathways (eg, vitamin D,[76] folate,[77] and ω-3 PUFA[78] pathways) also modify the host response to the corresponding environmental exposure.

Epigenetic mechanisms provide a clear explanation for changes in gene expression induced by environmental changes. Epigenetic adaption (reviewed in more detail elsewhere[3,79]) allows plasticity of gene expression in response to changeable environmental conditions, and the greatest potential for adaptive programming is in early life, when systems and responses are developing. Although these mechanisms might be intended to ensure survival in anticipation of a potentially hostile environment (eg, fetal imprinting of metabolic responses that conserve energy in a growth-restricted fetus), they can also prime for an increased risk of disease when subsequent environmental conditions are discordant (as seen with cardiovascular and metabolic disease).[80] Although it is less clear how this concept fits other diseases, such as allergy, there is growing evidence that a number of environmental determinants of allergic disease, including environmental pollutants,[81,82] microbial exposure,[83] and dietary nutrients,[84-86] have been documented to mediate changes in phenotype through epigenetic modifications (as reviewed by Prescott and Saffery[3] Martino and Prescott[79]).

Changing environmental exposures can also influence the local tissue milieu during antigen encounter, which critically determines the pattern of effector responses and the efficacy of regulatory mechanisms.[87] There is new evidence that T-cell responses (at any age) are in a state of regulated plasticity, such that the T-cell phenotype can be modulated between effector and regulatory states (rather than a fixed state of terminal differentiation), depending on patterns of gene expression.[88] This fluidity allows adaption to local tissue conditions and is strongly determined by the local tissue milieu.[87] A number of environmental factors implicated in the rise of allergic disease are recognized to alter tissue milieu, including dietary factors,[89] microbial products,[90,91] and pollutants (smoking).[92] Thus it is possible and likely that environmental influences in early life could exert effects on the milieu in various tissues to promote or protect against allergic disease.

These biological perspectives add to our understanding of the mechanisms and pathways, but the ultimate goal is to achieve effective lifestyle interventions. In the wider context the discipline of allergy and immunology has an important role to play in underscoring the adverse effects of modern environmental change on the immune system and how this contributes to many disease processes.

THINKING BEYOND HEALTH TO FIND SOLUTIONS

Our current global health crisis is a major threat to social and economic development worldwide, and it is increasingly important that we (working in health) collaborate with other sectors in finding solutions to the many global challenges facing humanity and our planet. Human health is inexorably linked with the health of our natural environment. Threats, including global warming, decreasing biodiversity, and modern pollutants, have repercussions for food, water, and energy security. Equally, the built environment, social structures, and cultural systems are critical in determining education, equity, and collective behavior, which ultimately influence individuals' opportunities to make healthy choices. Unless we consider the wider social, cultural, and economic determinants of health in this context, we cannot hope to overcome the growing burden of allergy and other NCDs. For this reason, more than ever, it is important that we move toward more interdisciplinary collaboration and more multisectorial engagement to understand and address the complex determinants of health and disease in the modern world. Common strategies will be required to mitigate the growing burden of a broad range of modern diseases, and we need to urgently develop effective strategies to restore traditional dietary and lifestyle patterns, which clearly have many properties that protect not only against allergic disease but also against cardiovascular disease, obesity, diabetes, and many other NCDs.

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