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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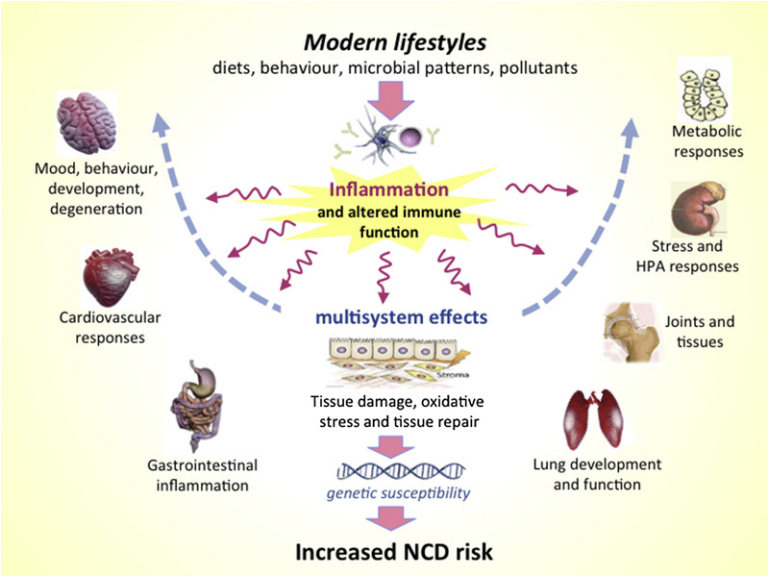

FIG 1. Inflammation: a common element in many NCDs. *HPA*, Hypothalamic-pituitary-adrenal axis.

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