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REVIEW ARTICLE

Hygiene Hypothesis in Asthma Development: Is Hygiene to Blame?

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Industrialized countries have registered epidemic rates on allergic diseases, such as hay fever, asthma, eczema, and food allergies. The Hygiene Hypothesis was born from work made by Dr. David Strachan, who observed that younger siblings were less susceptible to eczema and asthma, and proposed that this was a result of increased transmission of infectious agents via unhygienic practices within a household. This initial hypothesis was then reframed as the old friends/microbiota hypothesis, implicating non-pathogenic commensal microorganisms as the source of immunomodulatory signals necessary to prevent immune-mediated chronic disorders. Although the hygiene hypothesis is supported by epidemiological research of allergic diseases in certain industrialized settings, it often fails to explain the incidence of asthma in less affluent regions of the world. In this review, we summarize up-to-date information on genetic and environmental factors associated with asthma in different human populations, and present evidence that calls for caution when associating hygiene with the pathogenesis of asthma and other allergic conditions.

Key Words: Hygiene/old friends hypothesis, Asthma, Atopy, Microbiome, Worldwide asthma incidence.

Introduction

In the last 50 years, industrialized countries have been stricken by an epidemic increase in immune-mediated and inflammatory diseases, including hay fever, asthma, eczema, and food allergies (1). This sudden rise in allergic conditions has occurred during a major decrease in the incidence of infectious diseases around the world (2), driven by medical advances in vaccines, antimicrobials and hygiene practices. Although this epidemiological phenomenon had been described before, such as in studies on acute appendicitis in British hospital patients (3,4), and on multiple sclerosis in an Israeli population study (5), it was not until 1989 that it gained disseminated visibility through the work of Dr. David Strachan (6). Dr. Strachan suggested that the decrease in childhood eczema in younger siblings was likely due to increased unhygienic practices with older siblings, augmenting children's exposure to infectious agents within a household (6). This concept was defined as "The Hygiene Hypothesis" and has been tested by a large number of scientific studies.

Although the hygiene hypothesis has been well received by the scientific community and by popular opinion, proper hygiene and cleanliness *per se* have not been associated with a lower risk of immune-mediated conditions (1,7) and indeed protect individuals from the transmission of infectious agents (8). Consequently, there is a need to properly communicate to the public the inaccuracies within the hygiene hypothesis, while still promoting the health advantages driven by exposure to non-pathogenic microbes. This previously proposed modified message (1,7) aims to prevent the increased risk to immune-mediated diseases, such as asthma and allergies, as well as the spread of pathogens and the rise of antimicrobial resistance (1,8).

The hygiene hypothesis was more recently reframed as "the old friends hypothesis" (9), in order to incorporate the importance of the exposure to specific commensal and symbiotic microorganisms, and the development of the microbiome (the community of microbes residing in a host) as the source of microbial stimuli that modulates the immune system and, consequently, protects it from overreacting to non-harmful signals (10–12).

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Asthma is a multifactorial, heterogeneous immune-mediated collection of conditions characterized by bronchial obstruction and chronic airway inflammation (13). Asthma incidence has been reported all over the world. Results from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three showed that, in the span of 5−10 years, many countries have experienced a rise in disease incidence (e.g. Peru, New Zealand and Singapore), while in others it has decreased (e.g. Nigeria, Kuwait and a few centers in Italy and India), or remained stable (e.g. Japan, Tunisia and Argentina) (14). This large, multi-site epidemiological study used consistent methods to define and diagnose asthma in the three phases of the study (including ISAAC Phases One and Two); thus, it is very likely that its results represent accurate dynamics of asthma incidence in the different populations studied.

Given the many risk factors (genetic and environmental) associated with asthma development and progression (Figure 1), the heterogeneity of this disease, as well as the remarkable variation in asthma incidence and hygiene practices around the world, it is highly unlikely that the general considerations of the hygiene hypothesis can be applied to all these geographic-distinct populations, and to all types of asthma. Additional studies showing high prevalence and severity of asthma in low-income countries, including places in Africa, India, South America and the Middle East (38,39), also escape the predictions of the hygiene hypothesis, highlighting the need of specific recommendations for the different human populations. In this review, we propose that while the general concepts of this hypothesis may be used to explain changes in disease incidence in certain industrialized settings, it fails to explain asthma incidence and pathogenesis in other parts of the world. In addition, by limiting our focus on hygiene practices alone, we fail to consider environmental factors (e.g. farming, microbiome, parasites, etc.) that may better explain the sudden increase of asthma incidence in many regions, as well as the rural-to-urban phenomenon, and the high incidence of asthma in non-industrialized settings.

Lessons Learned from Asthma Epidemiology

Epidemiological studies have evidenced how genetic and environmental risk factors influence asthma development (40) (Figure 1). Although it is clear that asthma arises from a combination of factors, the complex gene-environment interactions that likely account for the molecular pathogenesis of asthma are only beginning to be elucidated, and constitute a large gap in our understanding of this disease.

Recent genome-wide association studies (GWAS) have identified several gene polymorphisms associated with an increased susceptibility to asthma (41−44). There is also a strong indication of polygenic determinants for asthma development, which may explain the heterogeneity of phenotypes in human cases (41). However, these genetic factors alone explain only a small proportion of the hereditability of this disease, and they fail to explain the recent epidemic rates of asthma (13,15).

A common observation in many epidemiological studies is the association between disease risk and use of antibiotics, especially during early developmental ages (45−48), including prenatal life (49). These observations

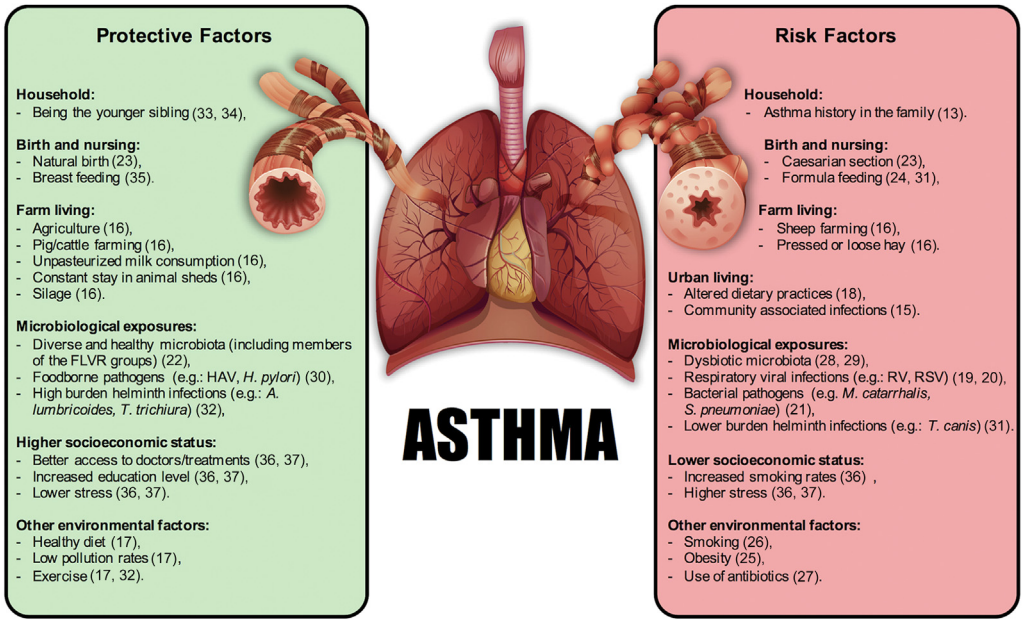

Figure 1. Summary of findings from epidemiological studies of asthma. Protective (green box) and risk-associated (red box) factors for asthma development are described (13,15−37).