

# Current reviews of allergy and clinical immunology

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## Parasites and asthma/allergy: What is the relationship?

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Asthma prevalence is increasing in Western industrialized countries. The infectious theory of asthma onset hypothesizes that lower levels of IL-12 result in reduced  $T_H1$  stimulation and failure of the neonate to deviate from its  $T_H2$  bias at birth. Helminthic infections may influence  $T_H2$  immune responses and hence immune development. Although ecologic data would support a protective effect of parasitic infection on asthma development, this may be due to other exposures. To date, there is no conclusive evidence that parasitic infection protects against asthma development. (*J Allergy Clin Immunol* 2000;105:205-10.)

**Key words:** *Parasites, helminths, asthma, allergy, genetics, atopy, IgE*

Asthma prevalence has been increasing at an astounding rate in Western industrialized countries.<sup>1</sup> Population-based estimates are consistent with an increase in prevalence of about 5% per year. This would translate into roughly half a million new cases of childhood asthma in the United States alone on a yearly basis. Because asthma is associated with the highest rates of hospitalization emergency department visits and days lost from school of any chronic disease of children, this astounding increase has a major public health impact. Studies done in the 1980s suggested that asthma and bronchitis prevalence rates were substantially different between East and West Germany and suggested the hypothesis that the higher rates of allergy and asthma seen in West Germany were associated with greater affluence and that childhood asthma was a disease of medical progress associated with various aspects of lifestyle in Western industrialized countries.<sup>2</sup> Further support for this hypothesis has been lent by prevalence surveys that have contrasted asthma prevalence in poor rural countries of Africa and Asia, where asthma prevalence is low, with the substantially higher prevalence seen in Europe and the Americas.<sup>3</sup>

These basic facts of asthma epidemiology have result-

ed in an infectious theory of asthma onset (Fig 1). This hypothesis suggests that either a deficit of  $T_H1$  type stimulation, either because of excess antibiotics or natural decrease in bacterial or viral infections, leads to lower levels of IL-12 and hence less  $T_H1$  stimulation and a failure of the neonatal immune system to deviate from its  $T_H2$  bias at birth. An alternative corollary to this theory is that differences in the quality of type of  $T_H2$  immune stimulation in postnatal life, as a result of lack of exposure to helminths, may also contribute to abnormal immune system development.

It is likely that the relationship between infection with helminthic parasites and the development of asthma and allergy is a complicated one. The purpose of this review is to provide background information on how and whether differences in parasitic infection rates could help to explain differences in asthma prevalence seen between developed and undeveloped countries.

### DEFINITION OF ASTHMA

Asthma is a clinical syndrome that is characterized by airway inflammation that is associated with and up-regulates airway responsiveness, resulting in respiratory symptoms and episodic but reversible decrements in lung function.<sup>4</sup> In the majority of asthmatic patients, the major source of inflammation is type 1-mediated allergic hypersensitivity to aeroallergens. Sixty to eighty percent of all childhood asthma in Western industrialized countries is associated with immediate-type hypersensitivity and elevated total and specific IgE levels. Skin test reactivity to environmental aeroallergens and allergic rhinitis commonly accompany these immune system abnormalities. Although the asthma syndrome is strongly associated with the atopic state in Western industrialized countries, there is the dissociation of skin test reactivity and total serum IgE from an asthma diagnosis in Africa and Asia.<sup>5</sup> The meaning of this finding and its significance relative to exposure to helminth infection is unknown. This finding does suggest that the allergy/asthma relationship is not monolithic nor is the disease dependent on allergy for its expression.

### PATHOBIOLOGY OF ASTHMA

Fig 2 details current understanding of the primary effector cells involved in the pathogenesis of asthma.

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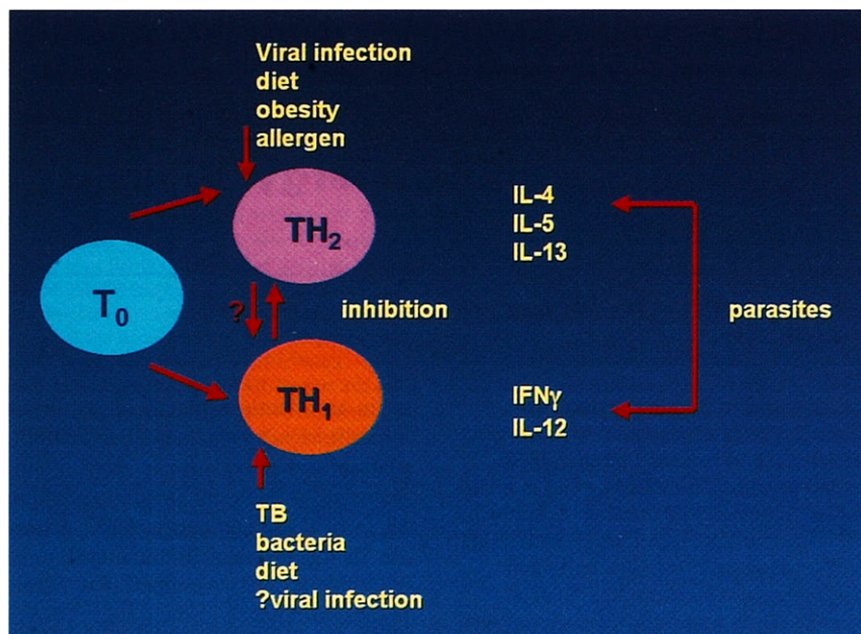


FIG 1. Environmental factors which may influence immune system ontogeny.

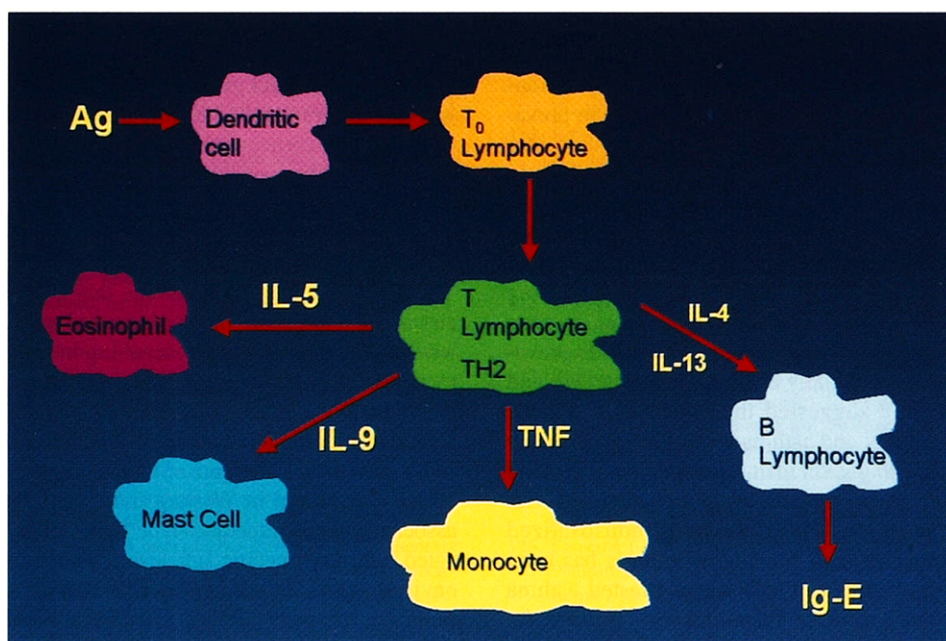


FIG 2. Proinflammatory cytokines and cells involved in airway inflammation in asthma.

Dendritic cells, the antigen-presenting cells located within airways and in the respiratory mucosa, present antigen initially to naive  $T_0$  helper cells, which differentiate into  $T_H1$  and  $T_H2$  clones. Asthma is believed to be the result of an excess of  $T_H2$  CD4-positive T cells that are responsive to the  $T_H2$  cytokines IL-4 and IL-5. These T cells, in turn, interact and signal a variety of inflammatory effector cells, including B cells, which produce IgE; mast cells, which degranulate themselves and also bind IgE;

eosinophils; and neutrophils. The complex cytokine network (detailed in Fig 2) controls the signaling and activation of these inflammatory cells.

## PATHOBIOLOGY OF HELMINTH INFECTION

At first glance, infection with intestinal helminths appears to be similar to the inflammatory response initiated by environmental allergens. The CD4-positive T cell

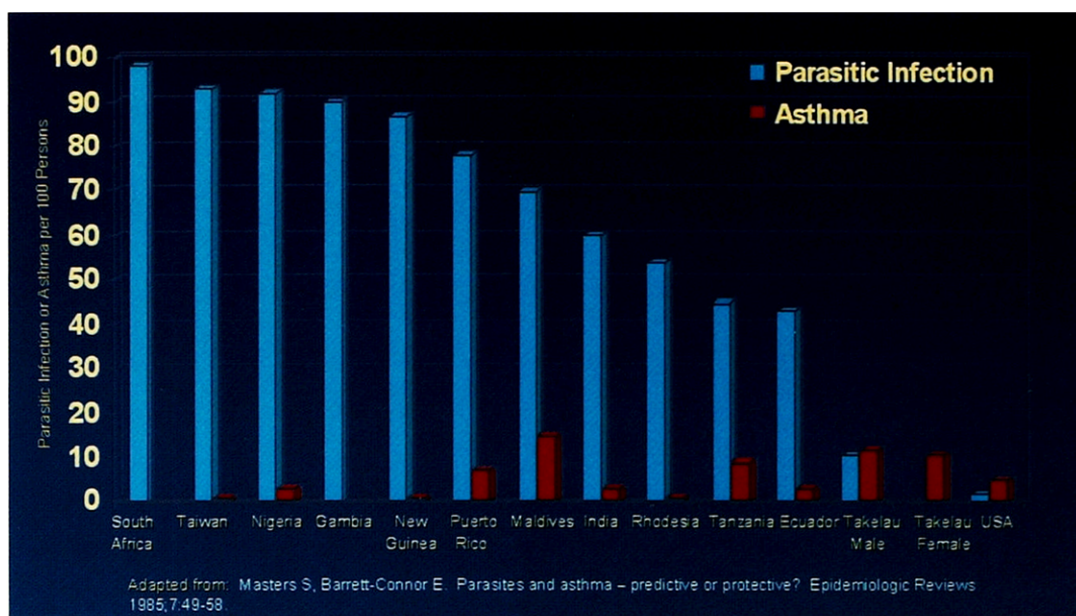


**FIG 3.** Prevalence of asthma and intestinal parasites by country. (Adapted from Masters S, Barrett-Conner E. Parasites and asthma—predictive or protective? *Epidemiol Rev* 1985;7:49-58.)

plays a central role in regulating the inflammatory responses against helminthic parasites, especially intestinal nematodes.<sup>6</sup> At least in animal models, CD4-positive T cells from parasite-sensitive animals can adoptively transfer immunity to parasitic infection. Clearly, T cells can function to recruit and activate effector cells, the same effector cells that are present in allergic reactions. Parasitic antigens are a stimulus for induction of antiparasite IgE antibodies. A mast cell degranulates when the IgE antibody affixed to its surface interacts with antigen. High concentrations of IgE can saturate the more than 100,000 Fc receptor IgE binding sites on each mast cell to prevent binding of other IgE molecules. Extremely high levels of IgE are produced after infection with intestinal nematodes.<sup>7</sup> The extremely high levels of IgE induced by helminths are in contrast to the weak antigenicity associated with aeroallergens. This may account for the paradoxical finding of extremely high total serum IgE levels in rural, non-Western, nonindustrialized countries and the absence of large numbers of asthmatic subjects.

There is a growing body of evidence to support IgE-mediated mechanisms to prevent and control parasitic infection. IgE Fcε receptor 2 complexes can induce cell activation and release reactive oxygen intermediates and platelet-activating factor and from eosinophils major basic protein and eosinophil peroxidase.<sup>8</sup> In general, antiworm IgE antibodies are low in children who are continually reinfected and high in adults who remain uninfected.

An increase in peripheral blood and tissue eosinophils is common in helminthic infection, especially in those with a tissue-invasive phase.<sup>9</sup> There are, at present, only limited data to support a protective role for eosinophils against helminthic infections in vivo. For example, there

is limited evidence that immune expulsion of nematodes can be partially delayed by treatment with antieosinophil serum.<sup>10</sup> In general, the thought is that peripheral blood eosinophilia reflects rather than determines worm burden. It is clear that pathobiologic mechanisms associated with IgE-mediated hypersensitivity are similar in asthma and in helminthic infection. What remains unclear is the role of parasitic infection in asthma and atopy. In an evolutionary sense, it seems likely that the human organism evolved immediate-type mucosal hypersensitivity to respond to the wide variety of parasites present in the environment. This is consistent with the idea that it is not so much that parasites prevent atopy or asthma but that the removal of parasites leaves a highly evolutionary-conserved immune mechanism without its usual target antigens. The hypothesis would be that the IgE response to common aeroallergens is a default present in the absence of helminths and other parasites.

## EPIDEMIOLOGIC DATA LINKING PARASITES AND ASTHMA

As alluded to above, there is an ecologic relationship between asthma prevalence and parasitism.<sup>11</sup> Countries with high asthma prevalence are more likely to be Western, urban, and industrialized without parasites, whereas countries with low asthma prevalence are likely to be rural, nonurban, non-Western, and with high rates of parasitic infection. These ecologic data typified by Figs 3 and 4 are correlational at best. It is probable that factors associated with parasitic infection (ie, exposure to farm animals, different diet, exposure to bacterial infections, decreased antibiotic usage, etc) may account for this inverse relationship rather than parasites per se. It seems

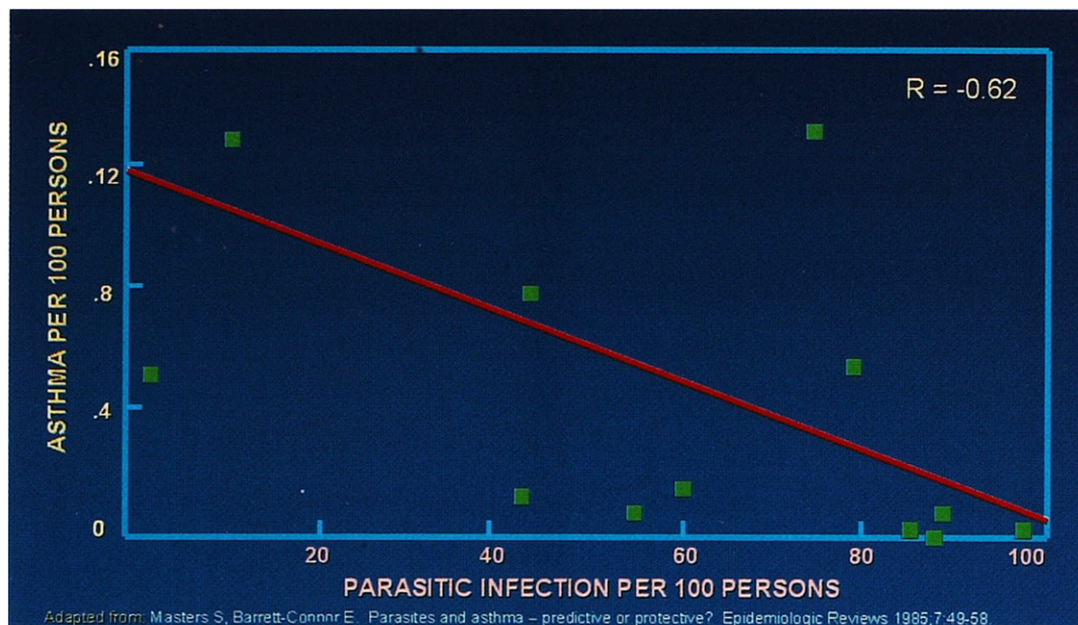


**FIG 4.** Parasites and asthma. (Adapted from Masters S, Barrett Conner E. Parasites and asthma—predictive or protective? Epidemiol Rev 1985;7:49-58.)

likely that ecologic data are hypothesis generating but certainly not proof of an inverse relationship between higher parasitism rates and lower asthma prevalence.

Although there are a large number of case control studies that examine the relationship of parasites to asthma, these studies are inconclusive for a variety of reasons.<sup>12-18</sup> First, these investigations involve selecting a group of asthmatic patients and comparing them with nonasthmatic control subjects, usually of similar age and sex, and examining stool of both groups for ova and parasites. These studies cannot assess the directional relationship between parasitic infection and the occurrence of asthma. In addition, most of these studies are relatively small. Thus, given that asthma is rare in countries where parasitic infection is common, these studies may lack power to detect a significant protective relationship. In only 1 of the 7 studies that used the case control method was the occurrence of intestinal parasites in asthmatic subjects significantly greater than that seen in nonasthmatic control subjects.

## EXPERIMENTAL DATA LINKING PARASITES AND ASTHMA

### Helminths causing asthma

One hypothesis is that helminthic infection actually causes asthma. There are a wide variety of data from the medical literature suggesting that exposure to *Ascaris*, for example, leads to the development of asthmatic symptoms.<sup>19</sup> In addition to these data, Tullus<sup>20</sup> reported in a cross-sectional study that almost 100% of a group of Canadian asthmatics living in a nonendemic area were infected with intestinal nematodes. This report was criticized for the small size of the control group, the relative-

ly infrequent stool examinations for control subjects, and possible observation bias with regard to stool examination for parasites. A subsequent report refuted the work presented in this article.<sup>21</sup> There seems to be little question that certain helminthic infections, particularly *Ascaris lumbricoides* and *Strongyloides stercoralis*, are associated with pulmonary infiltrates with eosinophilia associated with wheezing, elevations in IgE, and episodic airflow obstruction. Despite this clinical association, there is no clear-cut epidemiologic evidence that helminthic infection causes asthma and if the ecologic data are to be believed, the evidence is clearly in the opposite direction.

### Helminthic infection in established asthma

What about the course or role of helminthic infection in already established asthma? Lynch, working in Venezuela, has coauthored a number of articles on this particular topic.<sup>22,30</sup> An anecdotal example of such an effect has been provided by Turton,<sup>31</sup> who recounted how his long-standing and severe hay fever did not recur after he infected himself experimentally with hookworm. The mast cell-binding hypothesis, suggesting that very high levels of total IgE stimulated by helminthic infection can saturate mast cell IgE FC receptors and prevent binding by allergen, raises the possibility that helminthic infection might actually improve asthma in some situations.

Lynch et al<sup>27</sup> evaluated the effect of regular anti-helminthic treatment for a period of 22 months on aspects of the allergic phenotype in children in the slum area of Caracas, Venezuela. Treatment of helminthic infections in this uncontrolled study resulted in a significant decrease in total serum IgE levels, which was accompanied by an increase in skin test reactivity and

serum levels of specific IgE antibody to environmental aeroallergens. The application of the Prausnitz-Kustner passive transfer test and an analysis of specific IgE antibody levels indicated that polyclonal stimulation of IgE synthesis by helminthic parasites results in mast cell FC receptor saturation of suppression of specific IgE responses. This inhibited allergic reactivity, which was reversible by reactivation of the helminthic infection. Lynch had subsequently gone on to demonstrate that such effects can be modified by the degree of parasite burden, socioeconomic status, diet, and other environmental factors.<sup>22-27</sup>

For example, helminthic infection of low intensity can nonspecifically potentiate the synthesis of IgE antibody against environmental allergens and thus enhance allergic reactivity. In contrast, the excess polyclonal IgE stimulated by more intense helminthic infection can suppress the allergic response by producing mast cell saturation and inhibition of specific IgE synthesis. Although the presence of parasitic infection can modify the allergy phenotype, the same is not true for asthma. With regard to asthma, Lynch et al evaluated the effect of regular anti-helminthic treatment with albendazole for 1 year on a group of asthmatic patients in an endemic area for parasites. The number of asthmatic crises, need for maintenance therapy with inhaled steroids, and use of inhaled  $\beta$ -agonists were compared both with those in the year before the study for the treated patients and for those in a group of asthmatic subjects evaluated in parallel in whom parasitic infections were not controlled.<sup>29</sup> Significant improvement in all these indicators of clinical status occurred in the treatment group, not only for the period of antihelminthic administration but also for the year following. However, after 2 years without treatment the severity of asthma reverted to the initial state. No significant changes were observed in the control group over the entire period of evaluation. Thus, although patients' total serum IgE levels that were elevated at the beginning of the study were significantly diminished by antihelminthic administration, specific IgE antibody levels and positive skin test results for house dust mites also decreased. It could be speculated that these results could be the result of nonspecific effects of the treatment or a direct result of eradication of the parasite.

## PARASITES, ASTHMA, AND GENETICS

One of the intriguing questions is whether asthmatic individuals may have some genetic predisposition to be protected from infection with intestinal parasites. Because helminths have been present for thousands of years, humans have evolved an immunologically efficient mechanism for surviving in the presence of infection with these organisms. Thus individuals who are genetically the most resistant to helminthic infection may be the ones who have the most severe allergy, atopy, and asthma in its absence. In this regard, individuals with a genetic predisposition to higher IgE levels (which is not necessarily asthma) may be more resistant to helminthic infection

than individuals who are not susceptible to the development of atopy. It is important to recognize that there are a number of factors besides genetic susceptibility that determine infectivity—age at exposure, worm burden, type of parasite, number of different helminths present, socioeconomic status, and diet—and all contribute to infectious status. Longitudinal investigations are the only method suitable for testing whether genetic susceptibility confers resistance to the onset of parasitic infection. Cross-sectional and case control data are totally inadequate to address this hypothesis. To date, there are no data that bear on this interesting and important question.

Currently, it remains unclear whether the same or different genetic loci are important for determining asthma and susceptibility to parasitic infection. Certainly, there is suggested evidence that the genetics of IgE-mediated hypersensitivity may play an important role both in susceptibility to parasites and asthma. One piece of suggestive data is that the chromosomal area 5q31-33, the cytokine-rich region on chromosome 5q, is known to be linked to total serum IgE level and has also been localized as the region controlling the intensity of infection to *Schistosoma mansoni*.<sup>32</sup> The cytokine IL-5 is in the cytokine cluster chromosome 5q, and segregation analysis has indicated that a major gene that controls IL-5 production in humans is associated with susceptibility to infection to *S mansoni*.<sup>33</sup> In the mouse model, mice with a known mutation for the C $\epsilon$  gene were incapable of making IgE when infected with *S mansoni* or increased worm burden and decreased inflammatory response to this infection.<sup>34</sup> Finally, the Fc $\epsilon$  R1- $\epsilon$  polymorphism on chromosome 11q13 is the  $\beta$  chain of the high-affinity IgE receptor gene, which has been an asthma candidate gene identified by linkage studies.<sup>35</sup> A polymorphism in this receptor is associated with total serum IgE levels in parasitized Australian aborigines. This polymorphism explains 12% of the total residual variation in total serum IgE level. These data suggest the importance of genetic factors in determining susceptibility to parasitic infection and also potentially to asthma.

## CONCLUSION

It would appear that IgE-mediated hypersensitivity is a primary immune mechanism involved in combating helminthic infection. Absence of helminthic infection results in no obvious target antigen for this branch of the immune system, hence the default to aeroallergen sensitivity. Thus, in a broad evolutionary sense, absence of parasites may be associated with increased aeroallergen sensitivity. This is consistent with the dissociation between very high IgE levels and small or nonexistent skin test reactivity to aeroallergens in non-Western, underdeveloped countries. The only known immunologic mechanism by which high levels of parasitic infection can consistently prevent aeroallergen response is through the blocking antibody theory where extremely high levels of IgE bind mast cell FC receptors, preventing aeroallergen from triggering these responses. Viewed in this way, it

seems unlikely that helminthic infection is clearly protective or a preventive for asthma. Indeed, the ecologic data notwithstanding, a variety of other environmental factors including diet, antibiotics, bacterial infections, and exposure to farm animals all could contribute to immune system ontogeny and to an integrated immune response. All these factors are different between western and non-Western countries. Finally, there is a great need to understand the exact mechanisms by which there is a discrepancy between total IgE response and skin test response in parasitized individuals. What is the role of IgG4 in modulating the response to helminths? An additional and unusual feature of helminthic infection is that, although total IgE levels and eosinophils are high, actual respiratory mucosal inflammation is exceedingly rare. Thus there may be specific aspects of the immune response, as yet undiscovered, that are different between the response to helminths and the response to aeroallergens. The epidemiologic and clinical data can point to the areas of discrepancy, but these cannot be resolved without further basic research into the mechanisms of the immune response. Viewed in this way, the decrease in helminthic infection cannot be seen as causally related to the asthma epidemic, but helminthic infection may provide substantive clues as to immune system functioning which, if understood, would help to explain how other environmental exposures are contributing to the increased asthma burden in Western industrialized countries.

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