

Prevention Is the Best Remedy: What Can We Do to Stop Allergic Disease?



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Allergic diseases such as atopic dermatitis, food allergy, allergic rhinitis, and allergic asthma have been coined the epidemic of the 20th century given the significant rise in prevalence in Western countries in the last century.¹ With urbanization and adoption of a western life style a significant rise in incidence of allergic diseases is now being observed in developing countries. The rapid changes in the epidemiology of these common illnesses affecting a very significant proportion of the general population cannot solely be attributed to genetic factors. Changing environmental conditions interacting with an exposed subject's genomic background are likely to play a major role in this epidemic. Both the loss of protective exposures and the gain of risk factors will affect the prevalence of a given condition. Numerous epidemiologic surveys have identified and characterized relevant environmental exposures and life style factors to deduce potential strategies for prevention of allergic diseases. One example is the overwhelming evidence accumulated over decades of research showing the harmful effects of tobacco smoking and secondhand tobacco smoke exposure, which eventually resulted in political action, that is, the ban of cigarette smoking in public areas. This approach has resulted in measurable significant public health

benefits as exemplified by a significant reduction of asthma hospitalizations.

Given the enormous societal and individual burden caused by allergic illnesses in all age groups, it seems of paramount importance to identify novel strategies to prevent these ailments. The Prevention of Allergy and Asthma Theme reviews the existing evidence in the areas of atopic dermatitis and the atopic march, childhood origins of adult lung disease, immunologic strategies for the prevention of asthma, and the farm studies with particular focus on consumption of unprocessed cow's milk.

There is strong evidence that the prevalence of allergic illnesses is low in children raised on traditional farms. The main sources of protection are the child's early life exposure to farm animals and the consumption of unprocessed cow's milk. Brick et al² discuss in the first Clinical Commentary Review the evidence that consumption of unprocessed cow's milk may indeed prevent the development of allergic sensitization, allergic rhinitis, and asthma. The authors discuss the potential role of milk ingredients such as peptides and fatty acids and the effect of milk processing for its composition and impact. The authors also report the start of an intervention trial with minimally processed cow's milk that will demonstrate whether a microbiologically safe alternative to raw cow's milk will also have preventive properties. It seems noteworthy that very recently a number of experimental studies have confirmed the allergy protective effect of unprocessed cow's milk in a murine house dust mite model of asthma and a murine food allergy model.³ Interestingly, the heat labile fraction of cow's milk was again identified as essential for the protective effect.⁴

In the second Clinical Commentary Review, Beck et al⁵ provide an excellent overview of studies investigating primary prevention strategies for atopic dermatitis and food allergies. Atopic dermatitis is one of the most common inflammatory skin conditions with high prevalence affecting 15% to 30% of children and 2% to 10% of adults. A number of strategies for primary prevention have been suggested, some of them having been tested in randomized clinical trials. The authors critically review the potential benefit of breastfeeding, emollients, microbial exposures, vitamin D and UV light, water hardness, and immunotherapy. As atopic dermatitis may be seen as a first manifestation in what has been termed "the atopic march," the relevance of the findings for halting the atopic march is furthermore considered.

In the third clinical commentary, Van Mason and Portnoy⁶ discuss immunologic approaches to asthma prevention. As pharmacologic and nonpharmacologic factors may influence the immunophenotype, they consider the opportunities for prevention through both approaches. Given the vast amount of observational studies focusing on nonpharmacologic factors that may be associated with a reduced risk of incident asthma, the

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authors rightly caution against overinterpreting any observed associations as definitive evidence of a causal relationship between the factor and incident asthma risk. Dietary factors that have been studied include vitamin D, vitamin E, folate/folic acid, and long-chain fatty acids. For both vitamin D and fish oil, meta-analyses reported little effect on asthma prevention. For vitamin D, a meta-analysis found that vitamin D may confer some protective effect against respiratory infections, but not against incident asthma. One analysis that combined data from 2 randomized clinical trials suggested that there may be some benefit of maternal vitamin D supplementation, however. Although many observational studies suggest an inverse association between maternal folate supplementation and risk of incident allergic disease, including asthma, its enormous success in reducing the risk of spinal cord deformities in offspring precludes the conduct of trials of reduced folate/folic acid intake during pregnancy. Early life folate/folic acid exposure, however, could be an area of future study for primary prevention.⁷ With respect to microbial exposures, the authors summarize the rapidly growing body of observational evidence pointing to exposure to diverse microbes in their environments being associated with reduced risk of asthma and other allergic diseases. Although intervening on the microbial environment may be theoretically possible, this approach requires much greater study. In contrast, there have been multiple randomized clinical trials of maternal and/or infant supplementation with probiotics, which unfortunately have been largely disappointing with respect to asthma prevention. However, the efficacy likely depends on the types of bacteria, doses, and study populations, and additional trials are underway. Overall, randomized clinical trials targeting indoor allergen exposure as primary prevention have also been negative, and this approach has largely been abandoned.

In contrast, there are some promising data pointing to efficacy of allergen-specific immunotherapy (AIT) as preventative among children with established rhinitis, but long-term results are less clear. It is important to note, however, that distinguishing prevention of asthma symptoms from prevention of disease in these trials can be tricky, as it is possible that AIT is simply reducing the frequency and/or severity of symptoms among those with asthma rather than reducing the risk of developing the disease. The authors also review the studies aimed at reducing the risk of respiratory infections, which could serve to reduce the risk of incident asthma and/or reduce exacerbations among those with established disease. Although there is active interest in the potential of biologic agents in primary prevention, there are no data yet, but at least 1 trial is underway.

In the fourth clinical commentary, Grant et al⁸ discuss opportunities to intervene during childhood to prevent lung disease in adulthood and discuss preterm birth, early life viral infections, secondhand smoke exposure and active smoking and e-cigarette use, air pollution exposure, allergen exposure, and dietary factors. Despite the lack of efficacy of asthma controller medications in altering the natural history of asthma and lung function growth, there are clear opportunities to alter the natural history of childhood lung disease through other pathways. As preterm birth is a risk factor for chronic obstructive pulmonary disease (COPD), current efforts to reduce the risk of preterm birth should reduce the risk of COPD in adulthood. We have also made major strides in reducing smoking initiation among children, which should also yield benefits with respect to COPD risk. The reduction of secondhand smoke exposure, such as

achieved through regulation in Scotland, and has been implemented in public housing in the United States, holds promise in reducing the risk of adult lung disease, but long-term data are not yet available. Unfortunately, the recent epidemic of e-cigarette use threatens to undermine the advances in reducing cigarette smoking and secondhand smoke exposure and requires immediate action to mitigate its risks to long-term lung health. Although dietary interventions overall hold some promise for prevention and management of childhood asthma, long-term outcome data are scant. We have also made strides in improving lung function growth through air pollution regulation, and the increased lung function growth observed among cohorts who are growing up in environments with lower concentrations of criteria air pollutants should translate to reduced risk of lung disease in adulthood.⁹ Grant et al¹⁰ also tackle the topic of allergen reduction as a means of preventing long-term consequences of childhood asthma. Although early childhood interventions aimed at indoor allergen exposure reduction have generally failed to reduce the risk of incident asthma, recent data links reduced indoor allergen exposure among sensitized children and adolescents with asthma to improvements in lung function growth, suggesting that allergen exposure reduction may improve pulmonary outcomes in adulthood.¹⁰ These data are drawn from a single observational study and focus on mouse allergen among a low-income and minority population, suggesting that ongoing exposure to unhealthy home environments could lead to poorer outcomes in adulthood. For all of these interventions, however, long-term data are scant and will be critical to determining if the early benefits translate into the predicted long-term benefits.

The reviews for this Theme Prevention of Allergy and Asthma highlight many potential strategies, but it becomes evident that we need more well-powered blinded randomized intervention trials to come up with solid data on which to base general recommendations for the population at large or at-risk individuals.

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