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Complex Interactions of Pollutant and Allergen Exposures and Their Impact on People With Asthma

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ABSTRACT

Pediatric asthma has many causes and can manifest differently in different children and at different times. Understanding the many factors related to the development and exacerbation of asthma is complicated by the complexity of the many environmental exposures related to asthma development and morbidity. Furthermore, the same environmental exposures that may cause increased symptoms at 1 point in time may be protective when the exposure occurs earlier or at high enough levels. We know that environmental exposures such as allergens, irritants, and pollutants are quite complex in their composition; further examination of this complexity may improve our understanding of this complex and highly prevalent disease. *Pediatrics* 2009;123:S160–S167

IN THE PAST 20 years, we have begun to understand that airway inflammation in asthma arises from maladaptation to environmental stresses. In studying this process, we have tended to focus on one mechanism or another (eg, immunoglobulin E [IgE]-mediated responses to biological materials or oxidative stress resulting from ozone or particulates) and have found evidence that each is important. Patients encounter these environmental stresses simultaneously, however, and this simultaneous exposure may enhance responses (ie, adjuvant or priming) or may decrease responses to one of the stressors. We have begun to address the issue of complex responses to simultaneous exposure to other bioactive materials in the hygiene hypothesis.^{1,2} Originally, this hypothesis proposed that the increased prevalence of allergic diseases was related to a population shift in immune responsiveness because infectious illnesses were less prevalent. More recently, researchers found that children had less asthma and allergic disease when they were exposed early in life to endotoxin from Gram-negative bacteria,² a finding that seems to confirm the hygiene hypothesis. This finding, however, could also be an example of effect modification (ie, simultaneous exposure to endotoxin in airborne particulates decreased IgE-mediated sensitization to allergens).

ENVIRONMENTAL ALLERGENS ARE CARRIED ON PARTICLES

Our understanding of environmental allergen exposure depends on continually developing technology that allows us to measure levels of allergenic proteins in the environment. Technological advances have made it possible to test the hypotheses that environmental allergen exposure is related to sensitization, asthma prevalence and severity, and asthma incidence rates. In addition, asthma prevalence and severity have clear dose-response relationships to allergen exposure. Indoor allergen levels measured both in settled household dust and in indoor air are more clearly related to asthma than are outdoor allergen levels³; therefore, many of the data supporting a discussion of interactions between allergens and pollutants refer to indoor allergen exposure. An important corollary of those studies is the demonstration that allergens carried on airborne particles have clearly defined characteristics that are related to their effects on asthma. For example, allergens from house dust mites and cockroaches are found on particles with median diameters of 10 to 30 μm , whereas very few particles $<5 \mu\text{m}$ in diameter carry mite allergens.⁴ Because the larger particles are almost never found in air samples and asthma outcomes are most closely related to allergen concentrations in bedding dust, exposure is assumed to occur through contact with bedding and clothes. Cat, dog, and mouse allergens are readily detected in air samples. These allergens are carried on particles with mass median diameters of 5 μm ; 25% are on particles of $\leq 5 \mu\text{m}$.^{5,6} These smaller particles are usually found in indoor air, regardless of whether there are animals in the home.⁷ In addition, particles of this size are readily inhaled and deposited in pulmonary airways. Fungal spores are large but buoyant and are readily collected and cultured from both indoor and outdoor air.⁸ Although spores have been considered the primary source of fungal allergen exposure, data suggest that allergen levels are low in ungerminated spores⁹ and that hyphae and other fragments may be important sources of fungal allergens.¹⁰

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Key Words

asthma, allergy, pollutants

Abbreviations

DEP—diesel exhaust particle

ETS—environmental tobacco smoke

HEPA—high-efficiency particulate air

IgE—immunoglobulin E

PAMP—pathogen-associated molecular pattern

TLR—Toll-like receptor

Th—T helper

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SIMULTANEOUS EXPOSURE TO ALLERGENS AND POLLUTANTS

The air that suspends allergen-bearing particulates also contains both particulate and gaseous pollutants. Most pollutants that affect asthma seem to do so by acting on airway mucosa or by causing resident macrophages, dendritic cells, lymphocytes, and granulocytes to release cytokines, prostaglandins, and mediators that lead to inflammation. Airborne particulates seem to have a greater and more consistent effect on asthma than do gaseous pollutants, and exposure to these particulates can induce the asthmatic state (incident asthma) and cause exacerbations in individuals with asthma (symptomatic asthma).³ Because allergens and many of the bioactive pollutants described below are carried on particulates, it is possible that these agents contribute substantially to the effects of particulates on asthma.

Like that of diesel exhaust particles (DEPs) and other combustion products, the relative mass of airborne allergens is quite low; for example, animal allergens usually are found in nanogram quantities, and fungal spores rarely are found in concentrations more than a few thousand spores per square meter, compared with microgram quantities of total particulate mass. Bioactive pollutants also are present in very low concentrations, but even these small concentrations can have serious effects on susceptible patients with asthma. It follows that relatively large variations in levels of allergen-containing particles could occur with little or no change in total particulate concentrations. In addition, with the assumption that many particles are aggregates of combustion products, inorganic material, and biological aerosols, it is possible that the pollutants produce an adjuvant effect that increases or decreases IgE-mediated inflammation. Although the chemical composition of outdoor particles has been thoroughly described,¹¹ almost nothing is known regarding the presence of identifiable biological products that can influence airway inflammation.

Many questions remain to be addressed, including the following: What is the composition of indoor and outdoor air particles? Are individual particles found indoors composites of combustion products and bioaerosols (allergens and other biologically derived materials), or is there a heterogeneous mixture of particles that could lead to widely varying exposures to individual components and to interactions among the components? How does simultaneous exposure to components with potent (but not identical) biological activities lead to or prevent incident asthma in a child with asthma or a susceptible child? Is it important to reduce exposure to other particulate components; if it is, how can this be done?

EFFECTS OF AIRBORNE POLLUTANTS AND ALLERGENS ON ASTHMA AND INFLAMMATION

Particulates

Table 1 summarizes the interactions of pollutants and allergens and their effects on sensitization and on asthma. Airborne particulates are present in microgram quantities in both indoor and outdoor air. Particulates <10 μm in diameter are thought to reach the lower airways; those <5 μm in diameter are most easily deposited in the small airways and alveoli and are more likely to be related to inflammatory lung disease. These pollutants are quite heterogeneous, and many of the specific agents described below, such as environmental tobacco smoke (ETS), DEPs, allergens, endotoxin, and fungi, are included in the particulate category. The primary sources of outdoor particulates are road traffic, coal and oil burning, industrial processes, windblown soil, and sea spray.¹¹ Although indoor particulates have been less well studied, they include bioaerosols generated in the indoor environment as well as outdoor or ambient particulates, because more than one half of indoor particulates come from outdoors.^{12,13}

Ambient particulates have been found to have direct inflammatory effects in the airways of animals, as well as

TABLE 1 Air Pollutants, Their Interactions With Allergens, and Effects on Respiratory Disease

Pollutant	Mechanism	Effects on Sensitization	Effects on Asthma
Particulates	Directly induce airway inflammation; activate macrophages and dendritic cells to produce Th2 cytokines	High concentrations decrease sensitization	Increase cough and bronchitis; high concentrations decrease asthma rates
DEPs	Induce airway inflammation; activate epithelia, dendritic cells, and T cells to produce Th2 cytokines	Increase sensitization and total IgE levels	Increase incident asthma rates and asthma symptoms
ETS	Induces airway inflammation; activates epithelia, dendritic cells, and T cells to produce Th2 cytokines	Increases sensitization	Increases incident asthma rates and asthma symptoms in preschool-aged children
Endotoxin	Induces airway inflammation; activates epithelia, macrophages, and dendritic cells to produce Th1 cytokines	Decreases sensitization	Decreases incident asthma rates; increases asthma symptoms
(1 $\rightarrow$ 3)- β -D-glucans	Induce mild airway inflammation; activate neutrophils; increase total IgE levels	Inconsistent effects on sensitization	Increase asthma symptoms
Bacterial DNA	Activates macrophages and T cells to produce Th1 cytokines	Unknown	Unknown
Nitrogen dioxide	Induces airway inflammation	Unknown	Increases asthma symptoms
Ozone	Induces airway inflammation; activates neutrophils; induces Th1 cytokines	Unknown	Increases asthma symptoms

in *in vitro* and *in vivo* studies with human inflammatory cells. Human dendritic cells are activated to produce both T helper (Th) type 2 and Th1 cytokines, and respiratory secretions rapidly accumulate neutrophils and macrophages.^{14,15} In animal models, specific IgE antibody production is augmented, and the resulting inflammation typically is eosinophilic.¹⁶

Epidemiologically, ambient particulates are related consistently to increased respiratory symptoms in persons with asthma.^{17–19} Paradoxically, in highly polluted areas such as East Germany before reunification²⁰ or Third World countries where cooking is performed on indoor fires,²¹ particulate concentrations are related to cough, bronchitis, and acute infections, and asthma is less common than in Western countries. Although there are many reasons why asthma prevalence differs in these countries, the example of East German cities, where air pollution decreased sharply after reunification and this decrease was associated with a significantly lower prevalence of bronchitis and higher prevalences of asthma and allergy, suggests that high levels of pollution may decrease asthmatic inflammatory processes through mechanisms that do not involve Th2 immune responses.²⁰ Once asthmatic inflammation has been established, the patient has markedly increased bronchial responsiveness and begins to respond to lower levels of exposure with increased asthma symptoms and morbidity. The possibility that particulate pollution is related to airway symptoms but somehow protects children from developing asthma may explain why it has been so difficult to find a consistent relationship between ETS and incident asthma in children.^{3,22}

Diesel Exhaust Particles

Diesel exhaust forms very fine particles (0.05–1.0 μm in diameter), but DEPs adhere to ambient particulates and are readily identified microscopically in particulate matter <10 and <2.5 μm .²³ Because we know that ambient particles are in equilibrium with indoor particles and that ~60% of indoor particles come from outdoor sources,¹³ homes in environments such as inner cities and areas near major roadways with heavy diesel traffic might have significant quantities of DEPs in indoor air; however, no studies to date have attempted to identify DEPs in indoor air.

Diesel exhaust contains polycyclic aromatic hydrocarbons such as benzpyrene, quinones, and phenanthrene, which have important biological effects. DEPs activate bronchial epithelia, macrophages, and other immunologic cells *in vitro* to release a number of proinflammatory cytokines, including granulocyte/macrophage colony-stimulating factor (GM-CSF) and interleukin 8 (IL-8),²⁴ and induces these same cytokines in human bronchial challenge.²⁵ In animal models, DEPs are capable of inducing acute lung inflammation,²⁶ in the context of releasing the same cytokines. An even more important observation, made by Diaz-Sanchez et al.,²⁷ was that DEPs instilled into the noses of ragweed-allergic volunteers markedly enhanced the specific IgE antibody response to ragweed allergen. Subsequently, it was found that DEPs did this by causing the production of Th2

cytokines, which influenced T-cell and B-cell maturation and increased IgE production. These experiments and those that demonstrated that IgE-dependent mast cell and basophil activation was enhanced by DEPs have been reviewed.²⁸

Epidemiological studies have shown that increased exposure to DEPs increases allergen-specific IgE antibody levels and both incident asthma rates and exacerbation for individuals diagnosed as having asthma.^{19,29–32} Janssen et al.³² examined schoolchildren in 24 schools located near busy roadways. They found that current asthma symptoms, allergic rhinitis symptoms, and sensitization to pollen allergens were significantly related to the children's proximity to roadways carrying heavy truck traffic, as opposed to those carrying heavy automobile traffic. The association with respiratory symptoms was seen almost exclusively for children with pre-existing bronchial hyperresponsiveness and asthma. Studies such as that assumed that the relationship to road traffic depends on DEPs, although none measured levels of black carbon or other markers of DEPs. In contrast, a study by Jansen et al.³¹ demonstrated close associations between elemental carbon concentrations in ambient air and respiratory symptoms and exhaled nitric oxide levels in adults with asthma and other respiratory diseases, thus supporting the concept that DEPs are the important variable in traffic-related respiratory disease.

Environmental Tobacco Smoke

ETS is composed almost entirely of fine particles (0.2–1.0 μm).³³ Smoking is the single largest indoor source of fine particles in homes with smokers,¹³ and each cigarette adds 1 to 2 $\mu\text{g}/\text{m}^3$ to the indoor particulate matter of <2.5 μm , averaged over a 24-hour period. Containing many of the same polycyclic aromatic hydrocarbons as found in diesel exhaust, these particles cause similar airway inflammation. Not only does cigarette smoke cause inflammation and lung destruction in the high exposures found in smokers' airways, but also ETS causes inflammation, increased allergen sensitization, and increased bronchial hyperresponsiveness in animal models.³⁴ In human nasal challenges with ETS, Diaz-Sanchez et al.³⁵ reported the same effects as seen with DEPs, that is, increased allergen-specific IgE levels, Th2 cytokine production, and mast cell activation. Therefore, we would expect that exposure to ETS in the home would increase rates of incident asthma and exacerbations among patients with diagnosed asthma.

Epidemiologically, ETS has been found to increase incident asthma rates and to cause asthma exacerbations in preschool-aged children with asthma, but the association is less convincing for older children.¹ In a critical review by the Institute of Medicine, the evidence was considered to be insufficient for determination of whether ETS was associated with incident asthma in preschool-aged children.³ Since then, a report on 342 children in a prospective birth cohort study in Germany found that children exposed to parental smoking were more likely to become sensitized to food and inhalant

allergens, but the authors did not comment on whether the children were more likely to develop asthma.³⁶

Pathogen-Associated Molecular Patterns

Pathogen-associated molecular patterns (PAMPs) are a diverse group of molecules that share an origin in microbial agents such as bacteria and fungi and are capable of activating an innate immune response in organisms. The category includes endotoxin, lipoteichoic acid, (1→3)- β -D-glucans, and bacterial DNA. The relationships of PAMPs to allergen sensitization and asthma should be considered in the context of the hygiene hypothesis. According to this hypothesis, the increasing prevalence of asthma and atopic diseases seen throughout the world is related to worldwide decreases in serious infectious diseases and increases in hygienic living conditions.¹ Evidence that environmental endotoxin exposure during infancy also is associated with decreased prevalences of allergy and asthma has emerged. Therefore, PAMPs might be capable of modifying IgE-mediated sensitization to environmental proteins and decreasing the incidence of asthma.

Endotoxin, a constitutive molecule in the cell walls of Gram-negative bacteria, is the most extensively studied and perhaps the most potent of the PAMPs. In indoor environments, endotoxin is readily measured in settled dust, but concentrations may vary >10 000-fold in samples from different homes. Concentrations are highest in farm homes, especially when the residents are engaged in livestock farming.³⁷ Other important variables are the presence of cats, dogs, or mice in homes, older homes, and infrequent vacuuming.³⁸ Although there has been no systematic study of the size of particles carrying endotoxin, endotoxin is measured readily in indoor air, which suggests that at least some is carried on small airborne particles. A report on 3 homes found that the mass median diameter of particles containing endotoxin ranged from 0.15 to 0.28 μ m, which makes even smaller particle size likely.³⁹ Endotoxin activates cells through Toll-like receptor (TLR) 4 and the nuclear factor κ B pathway to increase cytokine formation, especially in monocytes, macrophages, and granulocytes. Endotoxin is a potent stimulus to Th1 cytokine production in a variety of in vivo and in vitro models, with evidence that these effects occur through TLRs on T regulatory cells and dendritic cells.^{40–42} IgE antibody responses in these experiments are suppressed in the presence of high endotoxin levels.

Epidemiologically, children living in homes with high endotoxin levels have been found consistently to have lower rates of sensitization to indoor allergens such as dust mite and cat allergens, as well as to pollen allergens.^{37,41} In addition, incident asthma, allergic rhinitis, and other atopic diseases are less frequent in this population. Individual responses to endotoxin effects have provided one of the strongest examples of what is called “gene-environment interaction.” CD14 is a critical component of the endotoxin-related innate immune response, acting as an important cofactor in the cellular response. Soluble CD14 binds endotoxin, and cell-bound CD14 links with TLR4 to allow cell activation. One poly-

morphism in the promoter region of CD14 (–159/C-T) was associated with lower levels of soluble CD14 and lower levels of IgE sensitization to environmental allergens.^{43,44} Subsequently, it was shown that this genotype was associated with decreased IgE-mediated sensitization among individuals living in environments with relatively low exposure to endotoxin but was associated with greater risk for nonallergic asthma among individuals living in environments with high endotoxin exposure. In a birth cohort at risk for asthma, it was found that the CD14 –159/C-T genotype was associated with increased soluble CD14 levels and lower risks of sensitization and asthma only among individuals who lived in homes with low endotoxin levels; for individuals who lived in homes with high endotoxin levels, this genotype increased the risk for sensitization.⁴⁵ These findings present a perfect example of a gene-environment interaction; the outcome depended on both a particular susceptibility and environmental exposure, and the outcome itself was a modification of the immunologic response to another environmental stimulus. To advise patients properly and to propose appropriate environmental modifications to alleviate the disease burden, we must understand the complexity of the gene-environment interaction.

Another PAMP, (1→3)- β -D-glucans, has been suggested as a contributor to asthma morbidity.⁴⁶ These compounds are complex polysaccharides that are constitutive parts of the cell walls of fungi, bacteria, and certain plants. Although there is no information regarding airborne particle size characteristics, the ease with which airborne levels can be measured in homes and industrial settings (such as agricultural product processors and garbage-handling facilities) suggests that a substantial fraction is carried on small particles. In animal and in vitro experiments with cell cultures, (1→3)- β -D-glucans activate macrophages and neutrophils and induce airway inflammation at high concentrations; however, these effects are more variable and inconsistent than is the case with endotoxin.⁴⁷ The only evidence of the effects on atopy comes from experiments with mice, in which solutions of (1→3)- β -D-glucans instilled in the trachea enhanced subsequent IgE antibody responses to ovalbumin.⁴⁸ Epidemiological studies also are inconsistent but suggest that allergic asthma rates are increased with exposure to higher doses of glucans.⁴⁷

The final PAMP is bacterial DNA, which differs from mammalian DNA in its high content of methylated cytosine-phosphate-guanine residues (CPG). Bacterial DNA has little inflammatory effect by itself, but immune cells respond rapidly through a TLR (TLR9) to augment Th1 responses; therefore, the sequences are called immunostimulatory sequences. When bacterial DNA is administered with an allergen, specific IgE antibody production is decreased and levels of immunoglobulin G antibody to the allergen are increased, producing a Th1 shift.⁴⁹ These methylated cytosine-phosphate-guanine motifs have been found in dust from farm homes and barns; the collected dust synergistically enhances the in vitro effects of endotoxin on peripheral blood leukocytes.⁵⁰ Very little is known about airborne concentra-

tions, and even less is known about the effects on human disease; however, because the concentrations of bacterial methylated cytosine-phosphate-guanine motifs in settled dust correlate with endotoxin concentrations, it is possible that bacterial methylated cytosine-phosphate-guanine motifs are partly responsible for the immunomodulatory effects of endotoxin.⁵⁰

Fungi

Fungi represent a unique bioaerosol whose effects were recognized, in a report from the National Academy of Sciences, as being important to respiratory diseases of individuals and to public health.⁵¹ The mechanism for their respiratory effects is not entirely clear but includes both IgE-mediated inflammation and important nonallergic pathways. A number of fungal allergens have been identified, and positive skin test results for fungal allergens are common for children^{52,53} and adults⁵⁴ with asthma. Sensitization to mold is related to the prevalence of asthma symptoms and asthma severity.⁵⁵ Fungi and their spores are found in home environments, especially damp homes,⁸ and sensitized patients with asthma are significantly more symptomatic in environments with higher levels of culturable fungi.⁵⁶ Clusters of near-fatal asthma have been observed for *Alternaria*-sensitized patients with asthma during the early autumn months in the Midwest, when very high ambient *Alternaria* spore counts occur.⁵⁷ However, indoor dampness and mold also are associated with cough and wheeze in persons without asthma⁵⁸ and persons who are not sensitized.^{55,58} Therefore, fungi must be capable of causing airway inflammation and morbidity through other mechanisms, such as endotoxins, glucans, and exotoxins.⁵¹ Infants of parents with asthma are more likely to have symptoms of asthma in the first year of life if they live in a damp moldy home,^{59,60} and symptomatic infants rarely have evidence of sensitization to fungi. This supports the concept that mold can cause wheezing and asthma through mechanisms other than allergy. This bioaerosol is an example of the importance of both immune and nonimmune environmental stresses in asthma, as well as the potential interactions of different pathways for the same particle.

Gaseous Pollutants

Two gaseous pollutants, that is, nitrogen dioxide and ozone, are particularly important in asthma and atopy. Nitrogen dioxide is a potent respiratory irritant, probably acting as an oxidative agent.⁶¹ Because the airways have effective antioxidant mechanisms, lung inflammation is unlikely with concentrations lower than the current, Environmental Protection Agency-proposed, ambient limits (53 ppb), although recent epidemiological studies suggested that asthma symptoms may be initiated at lower concentrations.^{63–66} Human and animal studies demonstrate that higher concentrations of nitrogen dioxide (100–400 ppb) can induce changes in lung function and increase the asthmatic response to allergen exposure.⁶² Epidemiologically, nitrogen dioxide exposure was related to respiratory symptoms in infants,⁶³

but asthmatic symptoms were not distinguished from other illnesses. Small but significant increases in morning symptoms and ambient nitrogen dioxide levels were seen in a large, multicenter study of urban children with asthma.⁶⁴ Although nitrogen dioxide was originally recognized as a hazardous component of smog, more-recent studies have found health effects related to indoor exposure in homes with gas stoves. Exposure to home settings with high nitrogen dioxide concentrations (inner-city homes or other homes using gas stoves with poor ventilation) has been associated with increased asthma symptoms, usually unrelated to atopy and allergen exposure.⁶⁵ In addition, children with asthma who were exposed to higher levels of nitrogen dioxide in their homes recovered more slowly from upper respiratory illness-related asthmatic episodes.⁶⁶

Ozone is a potent oxidant that causes significant lung injury at high concentrations (>500 ppb) in animals and humans.³³ Lower concentrations (80–400 ppb) induce airway inflammation, with an influx of neutrophilic leukocytes or a mixture of neutrophils and eosinophils, in persons with allergic rhinitis or asthma.^{67,68} Acute experimental exposures to these lower concentrations also increased bronchial hyperresponsiveness in patients with asthma; for example, patients with mild asthma who were exposed to ozone at 160 ppb for 7.6 hours while performing mild exercise demonstrated increased bronchial hyperresponsiveness and an increased response to allergen challenge 18 hours later.⁶⁹ Epidemiologically, ozone concentrations encountered in highly polluted environments such as Mexico City, Mexico,¹⁹ or US inner cities have been related to symptoms in children with asthma.⁶⁴ A cohort study of school-aged children in the Los Angeles, California, area found that children who participated in ≥ 3 outdoor team sports in areas with greater ozone pollution were at greater risk of developing asthma.⁷⁰ Because this correlation was seen with exposure to levels that were generally lower than the National Ambient Air Quality standard (80 ppb), prolonged outdoor exposure and exercise likely increased the risk for asthma in those children. All of these effects can be explained on the basis of inflammation resulting from the direct toxic effects of ozone, and no studies of immunologic effects have been published.

INTERVENTION STUDIES

Two randomized, clinical trials tested interventions that combined indoor allergen reduction and particulate reduction with the use of high-efficiency particulate air (HEPA) filters. Morgan et al⁷¹ reported the results of an environmental intervention conducted in the Inner City Asthma Study. They enrolled 937 children (5–11 years of age) with atopic asthma in 7 major US cities in a randomized, controlled trial of an environmental intervention that lasted 1 year. The intervention included allergen-proof covers for the child's mattress, box springs, and pillows; a HEPA room air cleaner; a vacuum cleaner with a HEPA filter; professional cockroach pest control; and an individually tailored environmental education program. Home environmental exposures were assessed every 6 months, and asthma-related complica-

tions were assessed every 2 months during the intervention and for 1 year after the intervention. The intervention group had fewer days with symptoms, compared with the control group, during both the intervention year (3.39 vs 4.20 days; $P < .001$) and the year afterward (2.62 vs 3.21 days; $P < .001$). Levels of cockroach allergen on the bedroom floor and mite allergen in the bed and on the floor decreased significantly more in the intervention group. Reductions in the levels of cockroach allergen and dust mite allergen (Der f1) on the bedroom floor were significantly correlated with reduced complications of asthma ($P < .001$). Acute care visits attributable to asthma and forced expiratory volume in 1 second values did not differ between the groups during the 2-year study. Changes in airborne pollutants were not reported.

Eggleston et al⁷² conducted a randomized, controlled trial of environmental treatment in the homes of inner-city children with asthma. One hundred children (6–12 years of age) with asthma were assigned randomly to the treatment group or to the control group. The treatment consisted of home-based education, cockroach and rodent extermination, mattress and pillow encasings, and a HEPA cleaner. Outcomes were evaluated through home evaluations at 6 and 12 months, clinic evaluation at 12 months, and multiple telephone interviews. In the treatment group, 68% of subjects had ≥ 1 positive skin test result, 48% reported symptoms in the past month, 84% received cockroach extermination services, and 75% used the air cleaner. More than one half of the homes had a smoker living in the home; therefore, particulate levels were quite high. Despite this, levels of particulate matter of $<10 \mu\text{m}$ decreased by 39% in the treatment group while increasing in the control group ($P < .001$). Cockroach allergen levels in settled dust decreased by 51% in the treatment group and increased in the control group. Daytime symptoms increased in the control group and decreased in the treatment group ($P = .04$). Other measures of morbidity, such as spirometric findings, nighttime symptoms, and emergency department use, did not change significantly.

Only 1 reported trial was directed at moisture and mold avoidance.⁷³ Families were assigned randomly to receive asthma self-management education or education plus household repairs (reduction of water infiltration, removal of water-damaged building materials, and alterations to heating/ventilation/air conditioning systems). The remediation group reported a significant decrease in symptom days, as well as a significantly lower rate of exacerbations requiring acute care visits, compared with the control group. No difference was seen in forced expiratory volume in 1 second values. Visible mold was less apparent in the homes of the remediation group, and mold identifiable with polymerase chain reaction technology was reduced to a significantly greater extent in the remediated homes. Asthma symptoms were reduced more in the intervention group than in the control group, and the intervention group required one half as many acute care visits during the year. Levels of airborne pollutants and fungi were not reported.

Smoking cessation interventions have had limited success in reducing ETS exposure in homes.^{74,75} Success-

ful ETS reduction interventions have included long, repeated interventions with families, with strong behavioral change techniques.⁷⁶ Most trials have focused on low-income or minority families. One trial with a more-general population that included medical office-based counseling and educational materials with limited follow-up monitoring had limited success in reducing air nicotine levels or children's excreted cotinine levels.⁷⁷ A study that used behavioral strategies led by a nurse and feedback with urinary cotinine levels⁷⁸ reported a reduction in urinary cotinine levels and an associated decrease in acute care visits attributable to asthma. Only 4 trials reported respiratory symptom or lung function outcomes, and these showed no effect⁷⁵; none of the trials described levels of particulate exposure.

CONCLUSIONS

Environmental exposure to both allergens and air pollutants is associated with asthma pathogenesis, but through quite different mechanisms. The pollutants most consistently associated with asthma are airborne particulates, perhaps because these particles contain allergens, endotoxin, fungal products, and biologically active combustion products. Simultaneous exposure to all pollutants and allergens is common and may be associated with either increased or decreased asthma prevalence and exacerbations. Endotoxin, for example, may cause respiratory symptoms while decreasing the frequency of allergic sensitization and asthma symptoms. The practical lessons from this discussion are that it is sensible to advise families to stop smoking and to use home air cleaners with HEPA filters to remove particulates and activated charcoal to remove gaseous pollutants. Even more important, health care practitioners should be aware of potential interactions among environmental allergens and should expect to see practical methods for decreasing these environmental exposures in the future.

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