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NIAID, NIEHS, NHLBI, MCAN Workshop Report: The Indoor Environment and Childhood Asthma: Implications for Home Environmental Intervention in Asthma Prevention and Management

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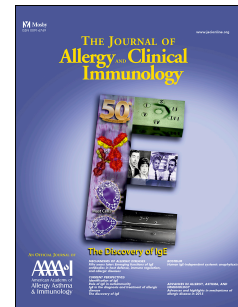
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Abstract:

Environmental exposures have been recognized as critical in the initiation and exacerbation of asthma, one of the most common chronic childhood diseases. The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Environmental Health Sciences (NIEHS), National Heart, Lung, and Blood Institute (NHLBI), and Merck Childhood Asthma Network (MCAN) sponsored a joint workshop to discuss the current state of the science with respect to the indoor environment and its effects on the development and morbidity of childhood asthma. The workshop included U.S. and international experts with backgrounds in allergy/allergens, immunology, asthma, environmental health, environmental exposures and pollutants, epidemiology, public health, and bioinformatics. Workshop participants provided new insights into the biologic properties of indoor exposures, indoor exposure assessment and exposure reduction techniques. This informed a primary focus of the workshop-- to critically review trials and research relevant to the prevention or control of asthma through environmental intervention. The participants identified important limitations and gaps in the scientific methodologies and knowledge, and proposed and prioritized areas for future research. The group reviewed socioeconomic and structural challenges to changing environmental exposure and offered recommendations for creative study design to overcome these challenges in trials to improve asthma management. The recommendations of this workshop can serve as guidance for future research in the study of the indoor environment and on environmental interventions as they pertain to the prevention and management of asthma and airway allergies.

Keywords: asthma; allergy; child health; indoor allergens; pollutants; environmental intervention; clinical trials

Introduction

Many trials aiming to improve asthma outcomes by altering the indoor environment have been conducted over the past two decades in response to observational studies suggesting that indoor environmental exposures influenced childhood asthma incidence and morbidity. The NIH Institutes NIAID, NIEHS and NHLBI, in collaboration with the MCAN, sponsored a joint workshop to discuss the current state of the science with respect to the indoor environment and its effects on the development and morbidity of childhood asthma. The workshop included US and international experts from a variety of relevant disciplines and addressed the unmet need to critically review environmental intervention asthma trials aiming at reducing asthma incidence and improving asthma control. In addition, workshop participants discussed indoor exposure assessment methodologies, and the biologic properties of allergens and indoor pollutants as they relate to the risk of asthma and asthma morbidity, as well as to possible protective effects that some of those exposures may have. This report, authored by all participants, presents the deliberations of the workshop with specific recommendations for current research needs in the field. The workshop was held in 2014, but all authors contributed current

updates in both recommendations and key publications. The authors hope that the report will stimulate the next generation of scientific projects and clinical trials related to the role of the environment in childhood asthma and respiratory allergy.

New insights into indoor exposure assessment

The indoor environment contains numerous exposures with the potential to influence asthma development and morbidity. Exposures include biologics (allergens, bacteria, or fungi), pollutant gases and particulate matter from indoor (e.g. gas stoves and cigarette smoke) and outdoor sources. Infiltrating ambient particulate matter contains a heterogeneous mix of inorganic, organic, and biologic components. (1, 2) Indoor particle sampling can include collection of house dust (vacuumed or swiped from surfaces) or air samples (collected actively or by passive settling). Experience with nasal samplers and other personal monitoring devices for assessment of bioaerosol inhalation exposure is limited. (3-5)

The gold standard for measurement of exposure to individual allergens in dust or air samples has been enzyme-linked immunosorbent assays (ELISA), which have been improved with reduction of assay time and use of amplification to increase sensitivity. In the past decade, for standardized measurement of multiple allergens in epidemiologic studies, ELISA has largely been replaced by fluorescent multiplex array technology, with measurements shown to be reproducible within and between laboratories. (6-8) New laboratory approaches, advances in field sampling equipment and real-time data monitoring, including rapid tests for allergens (9-11) may contribute insight into the spectrum of indoor exposures (Table 1). (6, 7) Technologies for allergen measurement including qPCR, mass spectrometry and allergen biosensors are in development, including those supported by the NIH PRISMS (Pediatric Research using Integrated Sensor Monitoring Systems) program. (12) Mass spectrometry has been used as a high sensitivity method for detection of grass pollen allergens, and is also being evaluated for food allergen detection. (13-15) A first generation of allergen biosensors can measure Der p 1, Der p 2, Asp f 1 and Ara h 1, and advances in personal air sampling methodology have led to new insight into critical allergen exposure locations. (16-19)

For the characterization of indoor microbial communities in dust and air, prior to the availability of culture independent technology enabling metagenomics, environmental microbial taxa were measured either by culture, qPCR of select taxa, or quantification of presence or activity of bioactive indoor pathogen-associated molecular patterns (PAMPs). Gram negative bacteria endotoxin bioactivity has been quantified using both kinetic Limulus amoebocyte lysate (LAL) and recombinant Factor C (rFC) assays. (20-22) Endotoxin and the gram positive PAMP biomarker, peptidoglycan (N-acetyl muramic acid) have been also measured by gas chromatography/mass spectrometry (GC/MS). These methods are now complemented by culture independent metagenomic characterization of communities of microbes originating from a multitude of sources (e.g., humans, pets, mice, cockroaches, dust mites, water, soil, plants, building materials). (23, 24) Amplification and sequencing of select regions (16S rDNA for bacteria; 18S or ITS for fungi) of ribosomal DNA (rDNA), the gene that encodes for ribosomal RNA, yields information on the taxonomic composition of the environmental

microbiome.(23-32) Alternatively, rDNA microarrays can be used to characterize bacterial taxonomic abundance. Microarrays are less agnostic than rDNA sequencing, and may require larger quantities of 16S rDNA. (33) Whole genome shotgun sequencing of all DNA extracted from an environmental sample also yields information on taxonomic composition of bacteria, fungi and viruses, although depth of coverage may be less than for rDNA amplification and sequencing. It also provides characterization of potential function through metagenomics estimation of the proportion of genes detected for given microbial metabolic pathways.(34) All of these metagenomic techniques generate relative abundance data for taxonomic composition or representation of functional pathways, but do not measure total bacterial or fungal microbial load, a task that requires qPCR. Also, they do not adequately address the actual function of household bacteria, and the relevance to that function to metabolic products (including breakdown of household chemicals) that could influence human health, or to colonization of the human microbiome.

Research Priorities

- Analytical/Technological Improvements
 - Personal monitoring devices for allergen, pollutant, and microbial exposures, including capacity for continuous monitoring, real-time data capture and spatial mapping
 - Development of techniques for uncontaminated and unbiased collection, extraction and processing of environmental microbiome samples in air and dust
 - Expansion of methods to measure environmental microbial functional potential and viability
 - Assessment of the metabolism of household chemicals by environmental microbes
- Development of methods for:
 - Quantification of multiple combined as well as individual indoor environmental allergens, microbes, pollutants, and household chemicals (“the exposome”)
 - Assessment of their relevance to human compartmental (e.g., upper airway, lower airway, gut) exposures during critical life stages

Insights into biologic properties of indoor exposures and associations with respiratory allergy and asthma outcomes

Molecular studies of allergens, adjuvants and other environmental stimuli

Allergy is classically manifested by an IgE antibody response to something that is normally considered harmless, typically a protein. The role of allergens in cross-linking pre-formed IgE on mast cells followed by the recruitment of Th2 cells, basophils and eosinophils and resulting in immediate and late allergic responses, is well understood. Given that not all proteins are allergenic, other biologic properties of allergens that are less understood may be responsible for their allergenic potential. Recent studies focus on

the importance of allergen proteases (37) in disrupting airway epithelial barrier integrity and function and allowing for more effective antigen uptake by innate immune cells.(38-40) Also, non-antigenic stimulation of pattern recognition receptors on epithelial cells can produce alarmins like TSLP, IL-33, IL-25 leading to Type 2 immune response polarization. (41, 42)

Human and in-vitro laboratory studies have suggested a variety of adverse or protective airway responses to inhaled allergens modulated by co-exposure to natural adjuvants, (e.g. bacterial components) that depend on dose, timing of exposure and host characteristics. In some mouse models, endotoxin was found to be the primary adjuvant in common house dust for promoting Th17 responses and neutrophilic inflammation characteristic of steroid-resistant asthma, but this microbial product was dispensable for priming the Th2 responses that are associated with allergic asthma.(43) In contrast, bacterial flagellin stimulated strong Th2 responses to ovalbumin, and was an important adjuvant component in some samples of house dust. (44) Thus, in mouse models, microbial ligands found in house dust can act in a dose-dependent manner to direct discrete types of immune responses to inhaled allergens.(45, 46) Human studies support this general notion that concomitant exposure to allergens and microbes can shape the type of immune response to the allergen that develops. (23, 24, 43, 44)

Allergen and microbial exposures may interact with each other and with pollutants, leading to harmful or, in certain cases, beneficial immunologic and clinical effects.(47, 48) Tobacco smoke and other inhalant toxins appear to alter epithelial cell gene expression throughout the respiratory tract and are likely to be important co-factors in immune response to allergens and perpetuation of asthma.(38) Metabolites of microbes and other organisms can also act as adjuvants. For example, chitin, a polysaccharide in allergens, fungi and insects, has been shown to be an adjuvant for Th2 responses.(45, 46, 49)

The effects of allergens, adjuvants and other environmental stimuli on the human airway epithelium can be studied in vitro with the use of primary cell cultures. Nasal brushing yielding upper airway respiratory epithelial cells from the inferior turbinate offers targeted opportunities for epigenetic and gene expression characterization of airway responses potentially relevant to asthma and allergic rhinitis.(50) While it is a minimally invasive procedure, nasal brushing is perceived with variable levels of comfort/discomfort by children and adults.(51) A recent study suggest that gene expression responses to tobacco smoke in the nasal epithelium correlate well with that in lower airway epithelial cells. (52, 53)

Population level studies of allergen exposure

While the prospective relation of home allergen levels to allergy development has been well-studied in specific birth cohorts, including those with clinical trial designs (Table 3), the National Survey of Lead and Allergens in Housing and National Health and Nutrition Examination Survey 2005-2006 were the first US population-level studies of cross-sectional associations between allergen exposures, allergic conditions and sensitization. (54, 55) These surveys indicated that almost half of the US population was sensitized to aeroallergens and that exposure to multiple allergens in homes was common. While many prospective as well as cross-sectional studies show adverse associations of allergens or their sources with allergic sensitization, wheeze or asthma, protective

associations have also been found with exposures to animal allergens or their mammalian sources,(56-60) and in one multi-city disadvantaged urban U.S. cohort study, to multiple allergens including cockroaches and dust mite.(24) Collectively, these findings underscore the need to understand time windows of susceptibility to allergic sensitization and the complex dose-response relationships between allergen exposure, other heritable or environmental co-exposures (e.g., stress, pollutants) and sensitization.

Research Priorities

- Studies on biochemical characteristics, such as protease or lipid binding activity, of a wide variety of allergens, to elucidate their contribution to allergy.
- Studies of individual and combined influences of natural adjuvants, microbial substances, and inhaled irritants and toxicants on immune and airway responses relevant to allergy and asthma, using *in vitro*, *in vivo*, and human studies that take into account dose, timing, vulnerability and susceptibility.
- Studies of airway respiratory epithelial cell responses to environmental stimuli with further development of more consistently comfortable upper airway sampling methods yielding outcomes relevant to the lower airways and asthma.(50)

Exposure reduction techniques: Fundamental concepts/methods and new insights for environmental interventions

Air pollutants found indoors, that can trigger asthma symptoms, originate from outdoor (e.g., traffic) and indoor sources (e.g., secondhand smoke (SHS), gas stove emissions). Elimination of SHS through smoking cessation and home smoking bans should always be considered a first-line indoor environmental intervention for children with asthma. Technologic improvements have been made in the efficacy of High Efficiency Particulate Air (HEPA) particle filtration designed to remove targeted indoor air pollutants such as fine particulate matter (PM_{2.5}). (61) Other than replacement of gas stoves with electric stoves, fewer methods are currently available for indoor NO₂ reduction of indoor or outdoor origin.(62, 63) In homes with smokers, recent home and school-based intervention trials in children report significant reductions in particulate matter with HEPA filter use, (64-66) but without reduction in indoor gases, without consistent reductions in markers of cigarette smoke, and with mixed success in improving child asthma symptoms. The efficacy in reducing indoor pollutants is dependent on room dimensions and building structure and conditions. While air cleaners have been also been used as adjunct interventions in multipronged environmental intervention trials (67) successful in reducing asthma symptoms, their independent contributions to health is uncertain, and the physical settings in which they may reduce exposure sufficiently to contribute to asthma control are also not well defined.

Indoor fungi originate through penetration from outdoors as well as from indoor sources, especially in damp and water damaged buildings.(68-70) They have a multitude of forms, properties and components. Fungi and their irritant or toxicant components can have adverse airway irritant as well as allergenic properties, and asthma symptoms can occur in individuals not sensitized, as well as in those sensitized to fungi.(71, 72) The mechanisms for effects of individual fungal components and interactive effects with other

indoor exposures on airway and immune responses are not well-understood. Paradoxically, some observational birth cohort studies suggest that specific microbial communities or early life diversity of microbial agents, including fungi, may protect against allergy development,(73) but this is not a justification for discouraging fungal remediation in water damaged homes or poorly maintained moldy homes.

In symptomatic patients with asthma, fungal prevention and remediation strategies and their success in reducing exposures or improving health in damp or water damaged buildings can vary by housing stock, climatic region, and resident behaviors. New building materials, ventilation systems, and home furnishings, particularly those harboring humidity, may introduce new challenges requiring novel strategies to minimize fungal growth. While a review of studies to reduce mold in buildings and assess health outcomes recommended “better research, preferably with a randomized controlled study design and with more validated outcome measures,” (74-76) imaginative study designs are needed to fit extreme situations investigators and communities are at times confronted with. In disasters with clear-cut mold damage the health risks can be obvious, but building remediation solutions may be challenging. The post-Hurricane Katrina HEAL study reported improvement of asthma symptoms with implementation of a hybrid intervention with asthma counselors and environmental remediation, but in the midst of post-disaster changes, investigators could not disentangle the extent to which the active study environmental interventions were responsible for the observed fungal reduction or symptom improvement.(77)

A variety of multi-pronged community-based strategies have been used to decrease indoor allergen exposures (78, 79) with varying success in reducing exposure and in improving asthma control. This inconsistency may be due to variable levels of intensity of the intervention, provided resources, participant education, social resources or adherence. More confounders include other changes in environmental exposures, differences in tailoring the interventions to individual sensitivities of the participants, baseline levels of allergens, and effect modification of the intervention health effect by the presence of co-exposures like stress or ETS (i.e., SHS).

While many studies have sampled and tested efficacy of interventions in individual indoor homes, effects of the structure and building components of housing, including multi-unit structures, on exposure are less well studied. In Northeastern and mid-Atlantic cities, asthma prevalence is often high in multifamily low-income housing sites where multiple and interrelated housing-related exposures are present. A few studies have evaluated indoor environmental and respiratory health before and after alterations in single or multifamily homes that undergo ‘green’ construction, renovation or weatherization under construction guidelines aimed to conserve energy while maintaining adequate ventilation, using “environmentally friendly” materials. Such studies take advantage of costly interventions already taking place but have the potential limitations of uncontrolled observational study designs.(80) In one Boston-based study, asthmatic children living in green homes experienced substantially lower risk of asthma symptoms, hospital visits, and asthma-related school absences than children living in conventional public housing.(80) A study of green housing in the South Bronx (81) showed improvements in asthma symptoms and urgent care visits for asthma and a Chicago-based study showed self-reported asthma symptom improvements.(82) However, given the variable application of “green” construction approaches, the potential risks of

responding to financial pressures by reduction of air exchange or inadequate maintenance even in new buildings, and study design limitations, uncertainty remains about which aspects of new construction may improve asthma.

Table 2 offers a summary of selected published studies on exposure reduction and on associations between exposure reduction with asthma control.

Research Priorities

- Well-designed (and, if feasible, blinded and controlled) trials to test the conditions under which free-standing air filtration systems, structural interventions, and other emerging building-level interventions reduce indoor pollutants, allergens, and other contaminants at home or in schools. This is a precondition to assessing whether exposure reduction improves respiratory health.
- Development of effective mold reduction strategies tailored to specific individual risk factors (e.g., poorly controlled asthma) and building, geographic, and climatic factors.
- Tailoring of multipronged strategies for indoor exposure reduction to the specific physical and social situations of urban families and their housing situations. Effective strategies may require changes in physical infrastructure, as well as in building management practices and occupant behavior.
- Assessment, with engagement of building management and construction engineers, of effects of new building approaches (including ‘green’ building) and building characteristics (e.g., humidity, structural integrity) on indoor exposures and health.
- Assessment of effects of housing policy interventions, such as housing mobility programs, on indoor exposures.
- For highly mobile populations or for populations with little control over the structure of their homes, testing of low cost interventions easily transferable from home to home or interventions that can be applied to any home without the need for structural changes.
- Development of novel technologies for particle or gas filtration (including NO₂ reduction) in home and school environments.
- With community engagement, development of interventions that can be applied to low-income populations with limited resources, especially those with high mobility.
- All environmental interventions should include cost-benefit estimations.

Indoor environmental interventions for primary prevention of asthma

Primary prevention of asthma is an enviable goal that, if achieved, could reduce the prevalence of the disease. Of a large number of potentially modifiable risk factors for asthma development identified in the literature, (104) allergen exposure is one that has attracted considerable attention.(105, 106) Observational epidemiologic studies have identified early life allergen exposures as risk factors for subsequent allergic sensitization, and early allergic sensitization is a major risk factor for asthma.(107) However, the concept of allergen avoidance for primary prevention of asthma has been challenged by investigators who argue that this approach is limited by a) the ubiquitous nature of aeroallergens in some ecologic and cultural settings; b) the dominance of genetic factors in influencing the course of asthma; c) the importance of early priming by other factors (microbes or microbial components, in utero smoking, vitamin D, etc.) or,

most recently d) the benefits from early allergen exposure as manifested by studies in food allergy and e) the protective effect against wheezing of high aeroallergen exposure in the first years of life. Evidence for potential benefits of early exposure to allergens or their sources for allergic sensitization, wheeze or asthma have been reported by observational birth cohort studies including the Massachusetts-based Epidemiology of Home Allergens and Asthma Study (EHAAS), the Wisconsin Childhood Origins of Asthma Study (COAST), the Detroit Childhood Allergy Study (CAS) and the Urban Environment and Childhood Asthma (URECA) Study. (24, 56, 58, 108) Most of these observational studies report protective associations with early-life mammalian exposures, especially dogs and associated allergens or microbes. The URECA data indicated that early-life multiple exposures including cockroach and mouse are protective, (24) whereas EHAAS found these two exposures to be risk factors. Multiple differences in cofactors and exposure levels may be responsible for the contrasts in these observational studies.

Dust mite allergen avoidance and prevention studies

Long-term follow up in primary allergen prevention trials focused on house dust mite reduction vary in terms of their success in asthma prevention. (109) The first such study was the Isle of Wight primary prevention study which recruited 120 children and used a multifaceted approach to reduce both common food allergens and house dust mite (HDM) exposure during infancy, with follow-up extending to 18 years. This study has shown a consistent reduction of asthma, but not atopy, in the allergen avoidance group (Figure 1).(110-112) A multifaceted approach for infants with a family history of allergic disease was also tested in the Canadian Asthma Primary Prevention Study (Table 3). The intervention, which began during pregnancy, yielded mixed results with a significant reduction in asthma, but not atopy, at 1, 2 and 7 years. At 15 years of age, the reduction in asthma risk was seen only in females.(113, 114) The Manchester Asthma and Allergy Primary Prevention Study (MAAPPS) tested the effect of stringent indoor allergen avoidance measures in a relatively large (n=291) randomized controlled trial. (115) By age 3 years HDM sensitization was more common in the intervention group and there was no difference between the groups in physician-diagnosed asthma.(116, 117) Finally, in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, 810 allergic mothers were enrolled during pregnancy and randomized to impermeable mattress- and pillow-covers or placebo covers. Apart from a reduction in asthma prevalence at age 2 years, no preventive effect on asthma or allergic sensitization up to 8 years was observed.(118-121)

There are a number of explanations for the inconsistent findings across studies of HDM allergen avoidance. It might be that only a multifaceted intervention is effective.(122) Another potential explanation is that the baseline mite allergen levels in the PIAMA study were so low that further reduction could not have significant clinical effect.(115, 123) It is also possible, but less likely, that genetic variations in Isle of Wight and Canadian children made them more receptive to allergen avoidance (124) or that genes or environmental co-factors in the home, or outside of the home modify either the magnitude or even the direction of the response. Overall, interpretation of these findings is difficult because the relationships between the levels of allergen exposure and their biologic effects are not clear.

Other potentially modifiable environmental factors for asthma prevention

An explanation for protective associations with pets might be that the ecology of the home microbiome is affected by the presence of a pet, which in turn may influence the gastrointestinal microbiome of the infant.(125-127) Whether the microbial ecology of a child's home is affected by outdoor microbes brought in by the pet, or by the pet's own microbiome is unknown (**Figure 1**). The mechanisms through which this protection may occur are unknown, but the role of the microbiome and its biochemical products as modulators of innate immune system responses that may suppress allergy is an area of intense focus.(24, 128) One recent animal model validated the Detroit birth cohort observation that pet dust could be protective against allergic responses.(129)

Asthma disproportionately affects certain ethnic groups, and patterns of allergen and microbial exposure vary according to socioeconomic status, area of residence, and race or ethnicity.(130, 131) For example, non-Hispanic Blacks and Hispanics in the US Northeast are more likely to be exposed to mouse and cockroach allergens (but less likely to be exposed to HDM, dog, and cat allergens) than non-Hispanic whites.(132) In addition, stressful experiences, such as home or community violence, may contribute to the high prevalence of asthma in these communities.(133-135) Such experiences can disturb stress regulation and thus adversely influence immune function and increase susceptibility to asthma.(136) Primary prevention studies in asthma should strive to account for relevant social, cultural and demographic factors, as well as for the role of diet, stress and other lifestyle factors. (137)

Other potentially modifiable factors such as micronutrients, antioxidants and others, which are not considered classic environmental pollutants, allergens, or bioaerosols, are beyond the scope of this article. However, such factors are being actively investigated in the context of asthma prevention. (138-146)

Research Priorities

- Additional observational and animal model validation studies to assess the role of dose, route, timing and pattern of single or multiple exposures, as well as genetic inheritance, in determining the relation of exposure to allergy or asthma development. This will optimize design of asthma prevention trials focused on allergen, pollutant, and microbial exposures.
- Sufficiently powered observational study of multiple early-life environmental influences on asthma and allergy development in diverse communities in the United States. The recent collaboration of U.S. birth cohorts through the NIH-sponsored effort "Environmental Influences on Child Health Outcomes" (ECHO) offers a unique opportunity to achieve this goal; ECHO will facilitate characterization of children manifesting a variety of asthma phenotypes or endotypes that may be differentially influenced by indoor environmental exposures.(147, 148)
- Studies to identify early patterns of human microbiome and its metabolic output in the gastrointestinal tract, the airways and the skin that are associated with the development of allergic diseases, and how they are influenced by the indoor environment, including environmental microbes, their metabolic products, and their functional components.

- Randomized multifaceted environmental interventions for asthma prevention designed to account for each element of the intervention and for social, cultural and other demographic factors.
- Randomized controlled trials (RCTs) that include primary prevention of asthma, through stress reduction measures tailored to ethnic and cultural diversity, and assessment of interactive effects of stress reduction with environmental interventions on asthma development.
- For each of major potentially modifiable factors,
 - Identify the subpopulations that would benefit from the intervention, and subpopulations that might be at adverse risk, or not benefit.
 - Define, develop, refine and test interventions that would be of benefit to most children (e.g., smoking cessation).

Indoor Environmental Interventions for Asthma Management

Although indoor environmental interventions aimed at reducing asthma morbidity have been more successful than those aimed at primary prevention of asthma, questions remain about their role in asthma management. **Table 2** provides an overview of the most recent environmental intervention trials and highlights their findings and limitations in influencing exposure reduction and asthma control. Effective environmental interventions are typically multi-faceted, tailored to the specific exposures and sensitivities of the target subject, and intensive.(84, 150) Publication bias leads to less publication of unsuccessful intervention trials, but the few that have been published suggest that single-allergen interventions and low-intensity efforts are ineffective. One such negative publication (151) exemplifies the challenge of translating an efficacious intervention from a tightly controlled clinical trial setting to a broader population: when the provision of allergen-proof mattress/pillow encasements to adults with asthma was tested in primary care, no effect was found with this untailed intervention. Although the study population was adults, the notion that health benefits observed in tightly controlled RCTs may not easily translate to more “real-world” settings is applicable to environmental interventions in children, too. In addition, families face a number of barriers to remediating environmental exposures, including costs, preferences, home ownership status, life-long behavioral practices, and education. For example, low-income urban populations are highly mobile and have limited resources with which to address environmental concerns. Also, residents often do not control the structure of their buildings since they rent, rather than those who own their homes.

The Inner-City Asthma Study (ICAS) may be the most successful environmental intervention study conducted to date; the intervention was targeted at specific allergen reduction in asthmatic children who were both sensitized and exposed to those allergens, but the intervention was also multi-faceted including integrated pest management targeted to specific allergen sensitivities, provision of HEPA vacuum cleaners, free standing bedroom HEPA filter air cleaners, and allergen-impermeable mattress and pillow covers. Primary trial results reported in 2004 found that the environmental intervention group experienced significant and clinically meaningful reductions in a range of asthma outcomes compared to controls.(84) Benefits were seen up to 12 months after the environmental intervention and cost-effectiveness analysis derived a cost of

\$750 to \$1000 per year per family to implement, a cost they estimated was equivalent to cost of mid-range inhaled corticosteroid and albuterol for a child with moderately severe asthma. This translated to almost \$28 per gained symptom-free day.(152) Because a multi-faceted, patient-tailored, intervention was tested in ICAS, and direct measures of environmental tobacco smoke exposure reduction were not made, it is not possible to determine the relative contribution of individual components of the environmental intervention and exposure reduction to the successful outcome. Notably, both arms of the ICAS (environmental intervention and physician feedback) were successful without other interaction with the health care systems, but optimally environmental control trials should be designed in the context of optimal access to health care, access to medications, and appropriate clinical asthma management.

Research Priorities

- Further define the role of environmental interventions in asthma management by conducting randomized, multifaceted clinical trials designed to account for each element of the intervention and for social, cultural and other demographic factors.
- Determine the most feasible, and cost- and clinically- effective approach to environmental interventions by conducting head-to-head comparisons of various forms of environmental intervention.
- Determine which environmental intervention components can be effectively implemented and the best approaches to implementation. Studies are needed that will test how to effectively implement optimal environmental control schemes into healthcare, public health policy, housing policy, and clinical practice.

Specific, detailed research questions for each priority area in environmental interventions for asthma management described above are listed in **Table 4**. Addressing these research priorities will have clear implications for how healthcare providers, public health agencies, healthcare systems, communities, and insurers implement and support environmental intervention as an integral component of asthma management.

Conclusions

With a focus on indoor allergens, microbes and pollutants, workshop participants assessed current methods, and prioritized new method development for measurement of indoor environmental exposures potentially relevant to asthma development and asthma management. We assessed new insights into the biologic properties of many of these exposures, and prioritized needs for future elucidation of these properties. We reviewed the state-of-knowledge of the efficacy of targeted and multi-pronged environmental interventions in changing environmental exposures, and the social and structural challenges in influencing environment interventions, with recommendations for future directions. Finally, we reviewed the efficacy of primary prevention trials to reduce asthma development by altering the indoor biologic or physical environment, and the efficacy of trials to improve asthma management and asthma control by improving the

indoor home or school environment. For each covered topic, the workshop offered recommendations on research priorities to inform the next generation of asthma prevention or asthma management trials that include environmental components. There was uncertainty as to whether efforts at primary intervention should include a trial of changes in the indoor environment. It is anticipated that the newly funded, U.S.-wide NIH-initiative Environmental Influences on Child Health Outcomes (ECHO) as well as complementary mechanistic studies with functional validation of observational findings might further inform future directions. Ultimately, new trials and translation of trial findings into public policy will need to take into account the family, social, economic and neighborhood context of participants and, for children with established asthma, their access to adequate health care, including appropriate asthma medications.

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Figure Legends**Figure 1**

A schematic model describing presumed relationships between the microbiome and allergic asthma. Adapted with permission from (153)

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 1102 **Table 1. Recent and Emerging Technologies for Indoor Exposure Assessment of Biologic Environmental Exposures**
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	Description/Comments
Allergens	
Fluorescent Multiplex Array(6-8)	Bead-based fluorescent suspension array allows for simultaneous detection of up to 11 allergens. Also being developed for food allergens.
Biosensors(16-19)	Variety of sensor technologies (AAO film, gold nanoparticle, magnetic beads, DNA-stem loop probe). High sensitivity; could be smart phone enabled for personal exposure measures.
Mass Spectrometry(13-15)	Fragmentation of analyte and quantification of mass to charge units. Methods developed for grass pollen, food allergens. High sensitivity, but high throughput capacity is limited; measurements are expensive
Bacteria	
16S rDNA microarrays(33)	Requires higher quantities (~500ng) of 16S rDNA compared to sequencing. Broad range of taxa identifiable, but some rare micro-organisms may be missed.
16S rDNA sequencing(25-28, 33-35)	16S rDNA is amplified and sequenced. Sequencing technologies: Roche 454 pyrosequencing, Illumina HiSeq, MiSeq, Ion Torrent, PacBio. Reference databases for comparison: Greengenes, Ribosomal Database Project (RDP).

Fungi

18S/28S/ITS rDNA sequencing(29, 30, 36)

rDNA from 18S, 28S, or ITS regions is amplified and sequenced.
Sequencing technologies: Roche 454 pyrosequencing, Illumina HiSeq, MiSeq, Ion Torrent, PacBio.
Reference databases (SILVA, FMP) limited but increasing.

All Biologics

Whole genome shotgun sequencing(34)

All DNA from an environmental sample is extracted and sequenced.
More expensive than rDNA methods, often less depth taxonomically for lower abundance microbes.
Offers potential for functional metagenomics (i.e. abundance of microbial metabolic pathway genes).

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Table 2. Select studies on building/home-based exposure reduction and asthma outcomes in children (2000-2017).

Reference	Population	Study design	Exposure focus	Intervention	Exposure outcome	Asthma outcome	Comments
Carter et al. (83)	104 enrolled 6-16 y/o inner-city children with asthma (Atlanta, GA, US)	RCT Single blinded	Dust mite and cockroach allergen	<u>Intervention 1 (n=35)</u> : allergen impermeable covers + effective roach bait, instructions to wash bedding once/wk. in hot water, and education re dust mite and cockroach cleaning measures <u>Intervention 2 (placebo) (n=34)</u> : allergen permeable covers, instructions to wash bedding once/wk. in cold water <u>Control 2 (n=35)</u> : Routine medical care; no home visits [85 completed study; 30/25/30] Significant allergen reduction defined as 70% decrease	No difference between intervention vs placebo in percent attaining 70% decrease in allergen reduction; cockroach allergen reduction measures ineffective	- Decreased acute visits for asthma in those home visited - Decreased acute visits in those allergic to dust mite who had decreased dust mite exposure	Applying allergen avoidance challenging in poor communities because of multiple sensitivities and problems applying protocols in this environment
Morgan et al. (2004) (84)	937 5-11 y/o inner-city children with asthma sensitized to $\geq 1/11$ indoor allergen (7 US cities; ICAS)	RCT	Indoor allergens. ETS	<u>Intervention (n=469)</u> : Multifaceted: 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + remediation with IPM tailored to each child's sensitization /exposure profile <u>Control (n=468)</u> : Evaluation every 6	Reduction in dust mite and cockroach allergen levels	- Decreased asthma symptoms during the intervention year (3.39 vs. 4.20 days) and the year after. - Decreased urgent visits	- Separate effects of each component of intervention unknown; - No direct ETS exposure measures - Cost: \$1500 to \$2000/child-- similar to cost of mid-range ICS & albuterol for a child with moderately severe asthma

				months			
Phipatanakul et al.(2004) (85)	18 mouse infested homes of mouse sensitized inner city asthmatic children (Boston, US)	RCT	Mouse allergen	<u>Intervention (n=12)</u> : Professionally delivered IPM <u>Control (n=6)</u> : No IPM	Reduction (~75%) in settled dust mouse allergen levels in intervention vs. control homes	•No clinical improvement in lung function or symptoms detected	•Insufficient power to detect lung function or clinical response •Unknown what degree of mouse allergen reduction and length of time of reduction required to improve symptoms
Krieger et al. (2005) (86)	274 4-12y/o children with asthma from low income families (Seattle-King County WA, US)	RCT	Multiple asthma "triggers"	<u>Intervention (n=138)</u> : Multifaceted: 5-8 home visits by community health worker over 1 year including home assessment, education, support for behavior change and resources to reduce exposures <u>Control(n=136)</u> : 1 visit, limited resources	N/A	•Increased parent/caregiver actions to reduce exposures •Decreased urgent visits, and increased caregiver QOL •No differences in asthma symptoms between groups	•Separate effects of each component of intervention unknown; •Intervention not tailored to child's sensitivities •Exposures not measured •Projected 4 yr. savings: \$189-\$721
Eggleston et al.(2005)(87)	100 6-12 y/o children with asthma from low income families (Baltimore MD, US)	RCT	PM ₁₀ & PM _{2.5} ; indoor allergens (focus on cockroach, mouse)	<u>Intervention(n=50)</u> : Multifaceted:1 yr. of education + allergen impermeable covers + bedroom HEPA air cleaner + remediation with IPM for mice and for cockroach (if infestation signs or if child sensitized) <u>Control (n=50)</u> : treated at end of 1-yr trial	Reductions of ~39% in PM ₁₀ & PM _{2.5} , and ~50% in cockroach allergen	•Decreased daytime asthma symptoms •No differences in other asthma outcomes, including acute care and quality of life measures.	•Separate effects of each component of intervention unknown; •Population included some children with mild intermittent asthma symptoms and no atopy
Chew et al. (2006) (88)	3 uninhabited water-damaged homes after a major hurricane (New Orleans, LA; US)	Pre-post treatment comparison	Mold (spore counts, cultures, PCR analysis, glucan), endotoxin, and PM	<u>Intervention</u> : Removal of drywall, carpet, insulation, and all water-damaged furnishings	Reductions in mold and endotoxin pre-post, but high levels during clean-up	N/A	•Pre- and during treatment mold and endotoxin levels were orders of magnitudes above those in homes without severe water damage •Adequate respirator use recommended during clean-up

Kercsmar et al. (2006) (74)	62 2-17 y/o children with asthma in homes with mold (Cuyahoga County, IL, US)	RCT	Mold scores; allergen levels	<u>Intervention (n=29) and Control (n=33):</u> asthma action plan, education, individualized problem solving <u>Intervention group only:</u> + Household repairs and modifications	At 6-mo, but not at 12 mo., greater reduction in mold scores in intervention group compared to control	Decreased asthma symptom days and prevalence of exacerbations in intervention compared to control	- Low sample size, limited power --frequency of families moving --complexity of applying for household repairs and working with landlords
Sever et al. (2007)(89)	60 cockroach infested homes (NC, US)	3-arm RCT	Cockroach/ Bla g 1	<u>Intervention 1 (n=20):</u> 12-mo professional entomologist pest control <u>Intervention 2 (n=20):</u> 12-mo contract-based services performed by pest control companies <u>Control (n=20)</u>	Compared to control: <u>Intervention 1:</u> reduction in Bla g 1 (~90%) <u>Intervention 2:</u> No reduction	N/A	Suggest increase education of commercial pest control companies in most effective eradication methods and education of families
Pongracic et al. (2008) (90)	312 5-11 y/o inner-city children with asthma and sensitization to a rodent (subset of ICAS; 7 US cities)	RCT	Rodent allergen/ Mus m 1	<u>Intervention (N=150):</u> ICAS (Inner-City Asthma Study) rodent module: 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + filling rodent access points and setting traps throughout home <u>Control (N=155):</u> 97% received at least 1 other module	80% bedrooms had detectable mouse allergen. <u>Intervention:</u> reduction in mouse allergen (~27%) in bedroom floor but not bed <u>Control:</u> Increase in mouse allergen (~28%)	- No primary outcome (symptom) change - Decreased school absenteeism, nights of child/caretaker waking and caretaker change in plans	- Did not measure rat allergen; cannot evaluate whether findings relate to change in this exposure - Unknown how HEPA air purifier, which most homes received, contributed to these results
Howden-Chapman et al. (2008) (91)	409 households of 6-12 y/o children with asthma (5 New Zealand communities)	RCT	Nitrogen dioxide	<u>Intervention (N=200):</u> Installation of a non-polluting more effective heater (heat pump, wood pellet burner, or flued (vented) gas) before winter <u>Control (N=209):</u> Given replacement heater at end of 1 yr. trial	Reduction in NO ₂ levels in living rooms and bedrooms	- No primary outcome (lung function) improvement - Less health care utilization for asthma and night time awakening - Fewer lower respiratory symptoms	- Engagement with community coordinators - Multiethnic, including Maori, who have greater burden of respiratory disease - Challenges include: --Complex communication --Technical difficulties with Piko (for lung function measurement)

Bryant-Stephens et al. (2009)(92)	264 2-16 y/o children with asthma (Philadelphia PA, US)	Randomized 6-mo Crossover	Dust, pests, pets, ETS	<u>Immediate (n=144) or delayed (n=120) intervention</u> : 6-mo (5 visit) family education+ supplies for trigger reduction (allergen impermeable covers, roach bait, mice traps, cleaning airts, storage bins, replacement for curtains/carpet) given by lay health educators	•Reduction in rodents •Increased use of impermeable covers (measured @ 2.5 mo. post intervention)	•Decreased nighttime wheeze and cough •Decreased ED and inpatient visits (1-yr, not 6-mo post intervention)	•Separate effects of individual interventions unknown •High drop out in the delayed intervention group •The longer in the study, the better the outcome •No skin testing •No formal cost effectiveness analysis (cost ~\$500/home)
Breyse et al. (2011) (93)	49 adults, 29 children from 31 units in a low income 3-building, 60-unit apartment complex (MN, US)	Cross-sectional health survey of pre-immediately post renovation health, followed by survey 12-18 mo. post renovation	Green specifications targeting ventilation, moisture, mold, pests, radon	<u>Intervention</u> : Renovation according to Enterprise Green Communities green specifications, using "healthy Housing" features. New mechanical ventilation installed(94)	•Reduction in energy use (45%) •Tightening of building envelope •Functional exhaust fans •Fresh air @ 70% of ASHRE standard •Lower radon •Annual average indoor CO₂ 982 ppm	Immediately post renovation: •Self-report of cleaner, more comfortable, safer housing •Improvement in overall adult health, in non-asthma respiratory health (adults + children) and in asthma health (adults)	•Potential recall bias •Non-randomized, unblinded study design •Non independence of health reports from residents in same apartment •Potential communication problems with non-English speaking residents •Potential selection bias towards healthier residents •Some retrofitting required as not all renovations worked •Report of health benefits appear fewer in follow up
Butz et al. (2011) (64)	126 children with asthma, residing with a smoker (Baltimore MD, US)	RCT	Indoor PM and ETS exposure	<u>Intervention 1 (n=41)</u> : 6-mo air cleaner <u>Intervention 2 (n=41)</u> : Air cleaner + health coach <u>Control (n=44)</u> : Delayed air cleaner	•Reduction in PM levels •No additional PM reduction with health coach •No air nicotine or urine cotinine reduction	•No change in symptom-free days	•Reduction in PM in homes with smokers not sufficient to meet EPA standards for outdoor air quality •Air cleaners do not reduce nicotine exposure •Limitations: ventilation of household unmeasured, adherence to air cleaner not fully assessed, limited f/up time (6 mo.)
Lanphear et al.(2011) (65)	215 6-12 y/o children with asthma exposed to ≥ 5 cigarettes/day (Cincinnati OH, US)	RCT Double-blinded	Particle counts: $>0.3\mu\text{m}$ $>0.5\mu\text{m}$	<u>Intervention (n=110)</u> : 2 active HEPA air cleaners <u>Control (n=115)</u> : 2 inactive HEPA air cleaners	•Reduction in PM $>3\mu\text{m}$ levels •No air nicotine, cotinine reduction	•Decreased unscheduled asthma visits •No change in asthma symptoms or FENO	•Baseline asthma morbidity and exposures of 2 groups not entirely comparable •Efficacy of HEPA filters may vary by room size, ventilation

Mitchell et al. (2012) (95)	182 4-12 y/o children with moderate to severe asthma living in post Hurricane Katrina flooded areas (New Orleans LA,US)	Observational, pre-post intervention study	Indoor allergens, moisture and mold	<u>Intervention:</u> Individually tailored multi-faceted environmental intervention plus asthma counselor (timing of introduction of counselor varied)	•Reduction in bedroom mold spores and in <i>Alternaria</i> in settled dust	•Reduction (45%) in asthma symptom days •Children with asthma counselor had greater symptom decrease	•Separate effects of individual interventions unknown •Unclear whether mold decrease occurred because of intervention
Hoppe et al. (2012) (96)	Families living in 73 flood/water damaged homes (Cedar Rapids IA, US)	Cross-sectional assessment of homes and health at two levels of remediation (in-progress (n=24) or complete (n=49))	Extensive, (e.g., Mold, bacteria, endotoxin, PM, allergens)	<u>Intervention:</u> Removal of drywall, carpet, insulation, and all water-damaged furnishings	• Levels of mold, bacteria, endotoxin, PM, glucan higher in homes with remediation in progress compared with homes with remediation complete	• Compared to before the flood, residents of in-progress homes reported more allergies • All residents reported more and wheeze and meds for breathing problems	•Cross-sectional •Stage of in-progress clean up variable •Many in-progress families not moved back full time •Potential participation bias
Turyk et al. (2013) (97)	218 <18 y/o children with asthma from 138 families (Chicago IL, US)	Observational, pre-post intervention study		<u>Intervention:</u> Asthma management education, plus individually tailored low-cost asthma home trigger remediation (e.g., allergen impermeable covers, home walkthrough covering reduction in asthma triggers, provision of environmental remediation tools), and referrals to social or medical agencies when appropriate	•Reduction in many environmental triggers	•Lack of improvement in asthma controller use and other asthma management activities •Decreased asthma symptoms, urgent care and ED visits, hospitalization, missed school days, missed work days for caretakers	•Separate effects of individual interventions unknown •Mobility high, unclear how that influenced intervention or outcome •Lack of data on allergen sensitization or lung function
Breysse et al. (2014)(98)	102 low income households in rental properties with 1 or more children with not well-controlled asthma(King Country WA, US)	Observational, pre-post intervention study with historical comparison group		<u>Intervention (n=34):</u> Weatherization plus community health worker(CHW) education <u>Historical comparison group (n=68):</u> CHW education without weatherization	•Reduction in evidence of water damage greater with intervention group, but •No consistent evidence for greater improvement in	•Increased asthma control •Increased caregiver quality-of-life	•Separate effects of weatherization and CHW not demonstrated •Small study size •IPM not used

					intervention vs. comparison group in other environmental exposures		
Colton et al. (2014) (99)	31 low income households in rental housing	Observational comparison of exposures and health in green vs conventional housing, including in those who move between housing types.		<u>Intervention (n=18)</u> : Move from conventional to new buildings designed to green standards. Smoke-free policies and IPM practices employed. <u>Control 1(n=6)</u> : Move from conventional to conventional housing <u>Control 2(n=7)</u> : Live in conventional housing [61 visits including pre and post for 24 who moved]	Green vs conventional housing: • Lower PM _{2.5} , NO ₂ , and nicotine • Fewer reports of mold, pests, inadequate ventilation, and stuffiness	• Fewer sick building syndrome symptoms	• Suggested benefits of move to green housing need further assessment • Number of controls limit pre-post analysis
Colton et al. (2015)(80)	235 households in 3 Boston public housing 188 residents (80%) with 2 visits	Observational comparison of conditions and health in green vs conventional housing. Visits included home inspection and questionnaire.		Visits to Green Units (n = 201) and conventional Public Housing Units (n = 222)	Fewer reports and observations of mold, pests, inadequate ventilation, and secondhand smoke in green compared to conventional housing.	• Fewer asthma symptoms, hospital visits, school absences for children in green compared to conventional public housing.	• Suggested benefits of move to green housing • Effects observed only for children with asthma; effects on adults not certain.
DiMango et al. (2016)(100)	110 adults and 137 children with asthma sensitized and exposed to at least 1 indoor allergen	RCT	Key allergens in vacuumed settled dust (cat, dog, dust mite, cockroach and mouse)	Following optimization of asthma treatment and control, randomization to: <u>Intervention (n=125)</u> : Multifaceted: 40-wk education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner <u>Control (n=122)</u> : education not related to allergen avoidance	• <u>Intervention</u> : reduction in all allergens (cat, dog, dust mite allergens; cockroach, mouse). • <u>Control</u> : reduction in dust mite and mouse allergen (bedroom) and cockroach allergen (kitchen).	• Improvement in asthma control in both arms with no difference between groups.	• Lack of difference between intervention and control groups in achieved allergen reduction may explain lack of effect of active intervention on asthma outcomes • Intervention did not include intensive targeted IPM; post hoc analyses suggested improvement when mouse allergen was reduced • Not powered to assess effects in adults v children

Matsui et al (2017)(101)	350 children and adolescents with asthma sensitized and exposed to mouse allergen (Baltimore MD; Boston MA, US)	RCT	Mouse allergen	<u>IPM+Education Group (n=181)</u> : application of rodenticide, sealing holes that could serve as entry points for mice, trap placement, targeted cleaning, allergen-proof mattress/pillow encasements, portable air purifiers. If infestation persisted or recurred, additional treatments were delivered. <u>Education (n=180)</u> : Written material and demonstration of the materials needed to set traps and seal holes.	•No difference in mouse allergen levels between groups. •~70% reduction in mouse allergen in both groups.	•No difference in asthma symptoms or other asthma outcomes between groups. •Across both groups, reduction in mouse allergen was associated with improvements in asthma symptoms, rescue medication use, acute visits, and mouse-specific IgE.	•Large reduction in mouse allergen observed in education group was unexpected. •Results suggest education alone may be effective in some populations, but study did not include control group that received no education about pest management. •Majority of children's homes continued to have mouse allergen levels above levels previously associated with asthma morbidity.
Rabito et al (2017)(102)	102 5-7 y/o children with moderate to severe asthma in cockroach-infested homes(New Orleans, LA; US)	RCT	Cockroach allergen	<u>Intervention (n=53)</u> : 12-mo with trapping & bait placement at baseline, 1, 3, 6, 9, and 12 mo in areas with evidence of cockroach. <u>Control (n=49)</u> : 12-mo with trapping but no bait placement at baseline, 1, 3, 6, 9, and 12 mo after baseline.	•Fewer cockroaches in intervention homes.	•Fewer asthma symptoms and unscheduled health care utilization. •Fewer with FEV₁<80% predicted.	•Suggested benefits of single intervention with strategic insecticidal bait placement. •Limited by sample size and lack of blinded treatment and blinded assessment personnel.
Murray et al (2017)(103)	286 3-17 y/o mite-sensitized children with emergency hospital attendance for asthma exacerbation (North-West England)	RCT [Age group (3-10 y; 11-17 y) stratified]	Dust mite allergen	<u>Intervention (n=146)</u> : 12-mo with mite-impermeable bed encasings. <u>Control (n=138)</u> : 12-mo with no encasings.	•Lower dust mite (Der p 1) levels.	•Fewer hospital visits with an exacerbation. •No difference in risk of prednisolone use for exacerbation.	•Suggested benefit of single intervention with mite-impermeable bed encasings. •Limited in that all data on exacerbations and oral corticosteroids reported by parents/carers. •No measured adherence to meds or asthma trigger data.

1109 RCT=Randomized controlled trial; ETS=environmental tobacco smoke; IPM=integrated pest management; PM=particulate mass;
 1110 ICS=inhaled corticosteroids; QOL=quality of life; ICAS=Inner City Asthma Study. References (2000-2016) selected by Workshop
 1111 participants as representative and illustrative of asthma management intervention studies in children.

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Table 3: Randomized controlled trials in primary prevention of asthma using HDM allergen avoidance

Studies	Year/s recruited	N	Assessments (Years)	Major findings
Isle of Wight (110-112)	1990	120	1, 2, 4, 8, 18	Reduced asthma and atopy at all ages 1-18
MAAPPS*(109, 115, 116)	1995-1997	291	1, 3, 5, 8, 16	Reduced severe wheezing (infancy) Improved lung function (age 3 years) Increased mite sensitization (age 3 years)
CaPPS(113, 114, 149)	1995	545	1, 2, 7, 15	Reduced asthma (up to age 7 and at age 15 in females only)
PIAMA(118-120)	1996/97	810	1, 2, 3, 4, 5, 6, 7, 8	Reduced asthma at age 2. No effect at other ages.
CAPS(121)	1997-1999	616	18 mo., 3, 5	No difference in asthma, wheeze or atopy. Eczema higher in intervention group.

*Published outcomes of the intervention in MAAPPS available for ages one and three years only

Table 4. Research Questions for Priority Areas for Environmental Interventions and Asthma Management in Children	
Priority: Further define the role of environmental interventions (EI) in asthma management	
• Are the findings from positive trials replicable? Scalable?	
• Are there behavioral interventions that can improve adherence to EI behaviors?	
• How, and in which settings, should EI be implemented? Are EIs effective as a public health intervention delivered at the community or school, rather than health care, level?	
• What populations benefit most from EIs? Should EIs be targeted primarily/only to high morbidity populations, such as low-income and minority children with uncontrolled disease? Are EIs effective in populations that have not been studied (e.g., adults, suburban, rural)?	
• Is further tailoring of the intervention, considering the whole environment (e.g., social stressors) as well as environments not typically studied (e.g., outdoor allergens) more effective than focusing on home and indoor allergens?	
• Do EIs improve asthma outcomes by lowering indoor allergens, by their “bystander” effect on other factors related to asthma (e.g. medication adherence, second hand smoke exposure) or both?	
• Do EIs have beneficial effects above and beyond those obtained by the use of controller medications?	
• Do EIs reduce controller medication requirements/needs?	
• Does EI mitigate the costs and side effects of controller medications?	
Priority: Determine the most feasible, and cost- and clinically- effective approach to EI	
• Which component(s) of EI are clinically effective and cost-effective, in order to maximize clinical effectiveness and limit costs?	
• What is the minimal EI that retains efficacy and what components are required to retain efficacy (e.g., minimum frequency of visits, location of visits, activities performed at visits, duration of intervention?)	

• Are there specific populations for whom the cost-benefit balance is favorable?
• How would coverage of EI by a healthcare system affect asthma morbidity and costs among its pediatric patients with asthma?
• In consideration of cost-effectiveness, which environmental intervention measures are most appropriate for specific populations and what is the optimal duration of a specific intervention?
• What are the benefits of one size fits all EIs, how do they compare to tailored EIs, and how do the cost-benefits compare?
Priority: Determine which EI components can be effectively implemented and the best approaches to implementation (Implementation Science)
• What are the systems obstacles to implementing EIs and how can they best be overcome?
• How should the population that will receive EIs be defined and identified in a non-research setting?
• How should staff be identified and trained (Are community health workers enough? Are more advanced credentials needed? Is professional integrated pest management necessary? How does training used in a clinical trial setting translate to the healthcare or community setting?)
• How can the intervention be supported financially?
• How should tools developed for clinical trials be replicated/developed/adapted for use beyond the clinical trial EI?
• When do adaptations no longer make the EI evidence-based, and what study designs are sufficient to evaluate continued efficacy?

1118
1119
1120

Figure 1:

