Workshop summary

NIAID, NIEHS, NHLBI, and MCAN Workshop Report: The indoor environment and childhood asthma—implications for home environmental intervention in asthma prevention and management

Diane R. Gold, MD, MPH,[a,b] Gary Adamkiewicz, PhD, MPH,[b] Syed Hasan Arshad, DM,[c] Juan C. Celedón, MD, DrPH,[d] Martin D. Chapman, PhD,[e] Ginger L. Chew, ScD,[f] Donald N. Cook, PhD,[g] Adnan Custovic, MD, PhD,[h] Ulrike Gehring, PhD,[i] James E. Gern, MD,[j] Christine C. Johnson, PhD, MPH,[k] Suzanne Kennedy, PhD,[l] Petros Koutrakis, PhD,[b] Brian Leaderer, PhD, MPH,[m] Herman Mitchell, PhD,[n] Augusto A. Litonjua, MD, MPH,[a] Geoffrey A. Mueller, PhD,[o] George T. O'Connor, MD, MS,[p] Dennis Ownby, MD,[q] Wanda Phipatanakul, MD, MS,[r] Victoria Persky, MD,[s] Matthew S. Perzanowski, PhD,[t] Clare D. Ramsey, MD, MSc, FRCPC,[u] Päivi M. Salo, MS, PhD,[v] Julie M. Schwaninger, MS,[w] Joanne E. Sordillo, ScD,[a] Avrum Spira, MD, MSc, MSc,[x] Shakira F. Suglia, ScD,[y] Alkis Togias, MD,[w] Darryl C. Zeldin, MD,[v] and Elizabeth C. Matsui, MD, MHS[z]

Boston, Mass; Isle of Wight, Southampton, and London, United Kingdom; Pittsburgh, Pa; Charlottesville, Va; Atlanta and Augusta, Ga; Research Triangle Park and Chapel Hill, NC; Utrecht, The Netherlands; Madison, Wis; Detroit, Mich; New Haven, Conn; Chicago, Ill; New York, NY; Winnipeg, Manitoba, Canada; and Rockville and Baltimore, Md

From [a]the Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, and [b]the Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston; [c]the David Hide Asthma and Allergy Research Centre, Isle of Wight, and Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton; [d]the Division of Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh; [e]Indoor Biotechnologies, Charlottesville; [f]the Centers for Disease Control and Prevention (CDC), National Center for Environmental Health, Division of Environmental Hazards and Health Effects | Air Pollution and Respiratory Health Branch, Atlanta; [g]Immunity, Inflammation and Disease Laboratory, [o]Genome Integrity and Structural Biology Laboratory, and [v]the Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park; [h]the Section of Paediatrics and MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London; [i]the Institute for Risk Assessment Sciences, Utrecht University; [j]the Departments of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison; [k]the Department of Public Health Sciences, Henry Ford Hospital & Health System, Detroit; [l]the Department of Pediatrics, NC Children's Hospital, University of North Carolina, Chapel Hill; [m]Yale School of Public Health, Yale School of Medicine, Yale School of Forestry and Environmental Studies, Center for Perinatal, Pediatric and Environmental Epidemiology (CPPEE), New Haven; [n]Rho Federal Systems Division, Rho, Inc, Chapel Hill; [p]Pulmonary Center, Boston University School of Medicine; [q]the Division of Allergy-Immunology and Rheumatology, Department of Pediatrics, Augusta University; [r]Asthma, Allergy and Immunology, Boston Children's Hospital, Harvard Medical School, Boston; [s]the Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago; [t]the Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York; [u]the Departments of Medicine and Community Health Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg; [w]the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville; [x]the Division of Computational Biomedicine, Department of Medicine, Boston University School of Medicine; [y]the Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta; and [z]the Division of Pediatric Allergy/Immunology, Johns Hopkins University, Baltimore.

This workshop was supported by funds from the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases; the Division of Lung Diseases, National Heart, Lung, and Blood Institute; the Division of Intramural Research, National Institute of Environmental Health Sciences; and the Merck Childhood Asthma Network. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of any of the above-referenced National Institutes of Health institutes or the US Centers for Disease Control and Prevention.

Disclosure of potential conflict of interest: D. R. Gold receives grant support and travel support from the National Institutes of Health (NIH). S. H. Arshad receives grant support from the NIH and serves as a consultant for Nutricia. M. D. Chapman receives grant support from the National Institutes of Allergy and Infectious Diseases (NIAID), is an employee of Indoor Biotechnologies, receives royalties from the University of Virginia, and holds stock with Indoor Biotech. A. Custovic serves as a consultant for Novartis, Regeneron/Sanofi, ALK-Abelló, and Boehringer Ingelheim and receives speaker fees from Bayer, Thermo Fisher, and GlaxoSmithKline. U. Gehring receives travel support from the NIAID, National Institute of Environmental Health Sciences (NIEHS), Merck Childhood Asthma Network (MCAN), and National Heart, Lung, and Blood Institute (NHLBI). J. E. Gern receives personal fees from PREP Biopharm, Boehringer Ingelheim, Janssen, and Regeneron. C. C. Johnson receives grant support from the NIAID and travel support from the NIH. S. Kennedy receives travel support from MCAN. B. Leaderer receives travel support from the NIAID. A. A. Litonjua serves as a consultant for AstraZeneca Pharmaceuticals, travel support from the NIH, and royalties from the UpToDate and Springer Humana Press. G. T. O'Connor receives travel support from the NIH, serves as a consultant for AstraZeneca, and receives grant support from Janssen Pharmaceuticals. D. Ownby receives grant support from the NIH. M. S. Perzanowski receives travel support from the NIH and payment for lectures from Indoor Biotechnologies. J. E. Sordillo receives travel support and grant support from the NIH. A. Spira serves as a consultant for Veracyte and AllegroDx Corp, receives grant support from Janssen Pharma, and holds US patents US PTO 20060154278 and S PTO 20120041686. S. F. Suglia receives travel support and grant support from the NIH. E. C. Matsui receives travel support from the NIH; serves as a consultant for Environmental Defense Fund, Church & Dwight; and received payment for lectures from Indoor Biotechnologies. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 1, 2017; accepted for publication April 14, 2017.

Available online May 10, 2017.

Corresponding author: Diane R. Gold, MD, MPH, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115-5804. E-mail: diane.gold@channing.harvard.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2017.04.024

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; National Institute of Environmental Health Sciences; National Heart, Lung, and Blood Institute; and Merck Childhood Asthma Network sponsored a joint workshop to discuss the current state of 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 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 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. (J Allergy Clin Immunol 2017;140:933-49.)

Key words: *Asthma, allergy, child health, indoor allergens, pollutants, environmental intervention, clinical trials*

Many trials aiming to improve asthma outcomes by altering the indoor environment have been conducted over the past 2 decades in response to observational studies suggesting that indoor environmental exposures influenced childhood asthma incidence and morbidity. The National Institutes of Health's National Institute of Allergy and Infectious Diseases, National Institute of Environmental Health Sciences, and National Heart, Lung, and Blood Institute, in collaboration with the Merck Childhood Asthma Network, sponsored a joint workshop to discuss the current state of 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 and the possible protective effects of some of those exposures. 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.

Abbreviations used
ECHO: Environmental Influences on Child Health Outcomes
HDM: House dust mite
HEPA: High-efficiency particulate air
ICAS: Inner-City Asthma Study
NIH: National Institutes of Health
qPCR: Quantitative PCR
SHS: Secondhand smoke

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 (eg, 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 the ELISA, which has been improved by reduction of assay time and use of amplification to increase sensitivity. In the past decade, for standardized measurement of multiple allergens in epidemiologic studies, the 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] might provide insight into the spectrum of indoor exposures (Table I).[6-8,12-28] Technologies for allergen measurement, including quantitative PCR (qPCR), mass spectrometry, and allergen biosensors, are in development, including those supported by the National Institutes of Health (NIH) Pediatric Research using Integrated Sensor Monitoring Systems program.[29] 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.[12-14] A first generation of allergen biosensors can measure levels of 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.[15-18]

For the characterization of indoor microbial communities in dust and air, before the availability of culture-independent technology-enabling metagenomics, environmental microbial taxa were measured by means of either culture, qPCR of select taxa, or quantification of the presence or activity of bioactive indoor pathogen-associated molecular patterns. Gram-negative bacterial endotoxin bioactivity has been quantified by using both kinetic Limulus amebocyte lysate and recombinant Factor C assays.[30-32] Endotoxin and the gram-positive pathogen-associated molecular pattern biomarker peptidoglycan (N-acetyl muramic acid) have been also measured by using gas chromatography/mass spectrometry. These methods are now

TABLE I. Recent and emerging technologies for indoor exposure assessment of biologic environmental exposures

	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[15-18]	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[12-14]	Fragmentation of analyte and quantification of mass to charge units Methods developed for grass pollen and food allergens High sensitivity, but high throughput capacity is limited; measurements are expensive.
Bacteria	
16S rDNA microarrays[25]	Requires higher quantities (~500 ng) of 16S rDNA compared with sequencing Broad range of taxa identifiable, but some rare microorganisms might be missed.
16S rDNA sequencing[19-22,25-27]	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
Fungi	
18S/28S/ITS rDNA sequencing[23,24,28]	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[26]	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 (ie, abundance of microbial metabolic pathway genes)

complemented by culture-independent metagenomic characterization of communities of microbes originating from a multitude of sources (eg, human subjects, pets, mice, cockroaches, dust mites, water, soil, plants, and building materials).[33,34]

Amplification and sequencing of select regions (16S rDNA for bacteria and 18S or ITS for fungi) of rDNA, the gene that encodes for ribosomal RNA, yields information on the taxonomic composition of the environmental microbiome.[19-24,33-36] Alternatively, rDNA microarrays can be used to characterize bacterial taxonomic abundance. Microarrays are less agnostic than rDNA sequencing and might require larger quantities of 16S rDNA.[25] 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 might 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.[26] 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

- Analytic/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 and individual indoor environmental allergens, microbes, pollutants, and household chemicals ("the exposome")
  - Assessment of their relevance to human compartmental (eg, upper airway, lower airway, and 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 preformed IgE on mast cells followed by recruitment of T_H2 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 might 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, nonantigenic stimulation of pattern recognition receptors on epithelial cells can produce alarmins, such as thymic stromal lymphopoietin, IL-33, and 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 coexposure to natural adjuvants (eg, 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 T_H17 responses and neutrophilic inflammation characteristic of steroid-resistant asthma, but this microbial product was dispensable for priming the T_H2 responses associated with allergic asthma.[43] In contrast, bacterial flagellin stimulated strong T_H2 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 that develops to the allergen.[33,34,43,44]

Allergen and microbial exposures can 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 cofactors 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 T_H2 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] Although it is a minimally invasive procedure, nasal brushing is perceived to have variable levels of comfort/discomfort by children and adults.[51] A recent study suggests 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

Although the prospective relation of home allergen levels to allergy development has been well-studied in specific birth cohorts, including those with clinical trial designs, 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. Although many prospective and 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 1 multicity disadvantaged urban US cohort study to multiple allergens, including cockroaches and dust mites.[34] 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 coexposures (eg, stress and 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 by 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 (eg, traffic) and indoor (eg, secondhand smoke [SHS] and gas stove emissions) sources. Elimination of SHS through smoking cessation and home smoking bans should always be considered a first-line indoor environmental intervention for children with asthma. Technological 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 NO_2 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 (Table II)[64-89] 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. Although air cleaners have been used as adjunct interventions in multipronged environmental intervention trials[69] that have been successful in reducing asthma symptoms, their independent contributions to health are uncertain, and the physical settings in which they might reduce exposure sufficiently to contribute to asthma control are not well defined.

Indoor fungi originate through penetration from both outdoor and indoor sources, especially in damp and water-damaged buildings.[90-92] They have a multitude of forms, properties, and components. Fungi and their irritant or toxicant components can have adverse airway irritant and allergenic properties, and asthma symptoms can occur in both subjects who are not

TABLE II. 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 (2001)[68]	One hundred four enrolled 6- to 16-y-old inner-city children with asthma (Atlanta, Ga)	RCT Single-blind	Dust mite and cockroach allergen	*Intervention 1 (n = 35)*: Allergen-impermeable covers + effective roach bait, instructions to wash bedding once per week in hot water, and education re: dust mite and cockroach cleaning measures *Intervention 2 (placebo; n = 34)*: Allergen-permeable covers, instructions to wash bedding once per week in cold water *Control 2 (n = 35)*: 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 percentage 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 challenge in poor communities because of multiple sensitivities and problems applying protocols in this environment
Morgan et al (2004)[69]	Nine hundred thirty-seven 5- to 11-y-old inner-city children with asthma sensitized to ≥1/11 indoor allergen (7 US cities; ICAS)	RCT	Indoor allergens ETS	*Intervention (n = 469)*: Multifaceted: 1 y of education + allergen-impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + remediation with IPM tailored to each child's sensitization/exposure profile *Control (n = 468)*: Evaluation every 6 mo	Reduction in dust mite and cockroach allergen levels	● Decreased asthma symptoms during the intervention year (3.39 vs 4.20 d) 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 midrange ICS and albuterol for a child with moderately severe asthma
Phipatanakul et al (2004)[70]	Eighteen mouse-infested homes of mouse-sensitized inner-city asthmatic children (Boston, Mass)	RCT	Mouse allergen	*Intervention (n = 12)*: Professionally delivered IPM *Control (n = 6)*: 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)[71]	Two hundred seventy-four 4- to 12-year-old children with asthma from low-income families (Seattle-King County, Wash)	RCT	Multiple asthma "triggers"	*Intervention (n = 138)*: Multifaceted: 5-8 home visits by community health worker over 1 y, including home assessment, education, support for behavior change, and resources to reduce exposures *Control (n = 136)*: One visit, limited resources	NA	● 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)[72]	One hundred 6- to 12-year-old children with asthma from low-income families (Baltimore, Md)	RCT	PM_{10} and $PM_{2.5}$; indoor allergens (focus on cockroach, mouse)	*Intervention (n = 50)*: Multifaceted: 1 y of education + allergen-impermeable covers + bedroom HEPA air cleaner + remediation with IPM for mice and for cockroach (if infestation signs or if child sensitized) *Control (n = 50)*: Treated at end of 1-y trial	Reductions of ~39% in PM_{10} and $PM_{2.5}$ 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

(Continued)

TABLE II. *(Continued)*

Reference	Population	Study design	Exposure focus	Intervention	Exposure Outcome	Asthma outcome	Comments
Chew et al (2006)[73]	Three uninhabited water-damaged homes after a major hurricane (New Orleans, La)	Pre-post treatment comparison	Mold (spore counts, cultures, PCR analysis, glucan), endotoxin, and PM	*Intervention*: Removal of drywall, carpet, insulation, and all water-damaged furnishings	Reductions in mold and endotoxin pre-post but high levels during clean-up	NA	• Before 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)[66]	Sixty-two 2- to 17-year-old children with asthma in homes with mold (Cuyahoga County, Ill)	RCT	Mold scores; allergen levels	*Intervention (n = 29) and Control (n = 33)*: Asthma action plan, education, individualized problem solving *Intervention group only*: + Household repairs and modifications	• At 6 mo but not 12 mo, greater reduction in mold scores in intervention group compared with control	• Decreased asthma symptom days and prevalence of exacerbations in intervention compared with control	• Low sample size, limited power — Frequency of families moving — Complexity of applying for household repairs and working with landlords
Sever et al (2007)[74]	Sixty cockroach-infested homes (North Carolina)	Three-arm RCT	Cockroach/Bla g 1	*Intervention 1 (n = 20)*: 12-mo professional entomologist pest control *Intervention 2 (n = 20)*: 12-mo contract-based services performed by pest control companies *Control (n = 20)*	Compared with control: • *Intervention 1*: reduction in Bla g 1 (~90%) • *Intervention 2*: No reduction	NA	• Suggest increase in education of commercial pest control companies in most effective eradication methods and education of families
Pongracic et al (2008)[75]	Three hundred twelve 5- to 11-year-old inner-city children with asthma and sensitization to a rodent (subset of ICAS; 7 US cities)	RCT	Rodent allergen/Mus m 1	*Intervention (n = 150)*: ICAS rodent module: 1 y of education + allergen-impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + filling rodent access points and setting traps throughout home *Control (n = 155)*: Ninety-seven percent received ≥1 other module	• Eighty percent of bedrooms had detectable mouse allergen. • *Intervention*: Reduction in mouse allergen (~27%) in bedroom floor but not bed • *Control*: 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)[76]	Four hundred nine households of 6- to 12-year-old children with asthma (5 New Zealand communities)	RCT	Nitrogen dioxide	*Intervention (n = 200)*: Installation of a nonpolluting, more effective heater (heat pump, wood pellet burner, or flued (vented) gas) before winter *Control (n = 209)*: Given replacement heater at end of 1-y trial	Reduction in NO_2 levels in living rooms and bedrooms	• No primary outcome (lung function) improvement • Less health care use for asthma and nighttime 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)

(Continued)

TABLE II. *(Continued)*

Reference	Population	Study design	Exposure focus	Intervention	Exposure Outcome	Asthma outcome	Comments
Bryant-Stephens et al (2009)[77]	Two hundred sixty-four 2- to 16-year-old children with asthma (Philadelphia, Pa)	Randomized 6-mo crossover	Dust, pests, pets, ETS	*Immediate (n = 144) or delayed (n = 120) intervention*: 6-mo (5-visit) family education + supplies for trigger reduction (allergen-impermeable covers, roach bait, mice traps, cleaning airs, storage bins, replacement for curtains/carpet) given by lay health educators	● Reduction in rodents ● Increased use of impermeable covers (measured at 2.5 mo after intervention)	● Decreased nighttime wheeze and cough ● Decreased ED and inpatient visits (1-y, not 6 mo, after intervention)	● Separate effects of individual interventions unknown ● High dropout rate in the delayed intervention group ● Greater the study length, better the outcome ● No skin testing ● No formal cost-effectiveness analysis (cost ~$500/home)
Breysse et al (2011)[78]	Forty-nine adults, 29 children from 31 units in a low-income, 3-building, 60-unit apartment complex (Minnesota)	Cross-sectional health survey of prerenovation/immediately postrenovation health, followed by survey 12-18 mo after renovation	Green-specifications targeting ventilation, moisture, mold, pests, radon	*Intervention*: Renovation according to Enterprise Green Communities green specifications by using "healthy Housing" features New mechanical ventilation installed[69]	● Reduction in energy use (45%) ● Tightening of building envelope ● Functional exhaust fans ● Fresh air at 70% of ASHRE standard ● Lower radon ● Annual average indoor CO_2 of 982 ppm	Immediately after renovation: ● Self-report of cleaner, more comfortable, safer housing ● Improvement in overall adult health in nonasthmatic respiratory health (adults + children) and in asthma health (adults)	● Potential recall bias ● Nonrandomized, unblinded study design ● Nonindependence of health reports from residents in the same apartment ● Potential communication problems with non–English-speaking residents ● Potential selection bias toward healthier residents ● Some retrofitting required because not all renovations worked ● Report of health benefits appear fewer in follow-up
Butz et al (2011)[64]	One hundred twenty-six children with asthma, residing with a smoker (Baltimore, Md)	RCT	Indoor PM and ETS exposure	*Intervention 1 (n = 41)*: 6-mo Air cleaner *Intervention 2 (n = 41)*: Air cleaner + health coach *Control (n = 44)*: 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 follow-up time (6 mo)
Lanphear et al (2011)[65]	Two hundred fifteen 6- to 12-year-old children with asthma exposed to >5 cigarettes/d (Cincinnati, Ohio)	RCT Double-blind	Particle counts: >0.3 μm, >0.5 μm	*Intervention (n = 110)*: Two active HEPA air cleaners *Control (n = 115)*: Two inactive HEPA air cleaners	● Reduction in PM >3 μm levels ● No air nicotine or cotinine reduction	● Decreased unscheduled asthma visits ● No change in asthma symptoms or FENO values	● Baseline asthma morbidity and exposures of 2 groups not entirely comparable ● Efficacy of HEPA filters can vary by room size, ventilation
Mitchell et al (2012)[80]	One hundred eighty-two 4- to 12-year-old children with moderate-to-severe asthma living in post–Hurricane Katrina–flooded areas (New Orleans, La)	Observational, pre-post intervention study	Indoor allergens, moisture, and mold	*Intervention*: Individually tailored multifaceted environmental intervention plus asthma counselor (timing of introduction of counselor varied)	● Reduction in bedroom mold spores and *Alternaria* species in settled dust	● Reduction (45%) in asthma symptom days ● Children with asthma counselors had greater symptom decrease	● Separate effects of individual interventions unknown ● Unclear whether mold decrease occurred because of intervention
Hoppe et al (2012)[81]	Families living in 73 flood/water-damaged homes (Cedar Rapids, Iowa)	Cross-sectional assessment of homes and health at 2 levels of remediation (in progress [n = 24] or complete [n = 49])	Extensive (eg, mold, bacteria, endotoxin, PM, allergens)	*Intervention*: Removal of drywall, carpet, insulation, and all water-damaged furnishings	● Levels of mold, bacteria, endotoxin, PM, and glucan higher in homes with remediation in progress compared with homes with remediation complete	● Compared with before the flood, residents of in-progress homes reported more allergies ● All residents reported more wheeze and medications for breathing problems	● Cross-sectional ● Stage of in-progress clean up variable ● Many in-progress families not moved back full time ● Potential participation bias

(Continued)

TABLE II. *(Continued)*

Reference	Population	Study design	Exposure focus	Intervention	Exposure Outcome	Asthma outcome	Comments
Turyk et al (2013)[82]	Two hundred eighteen <18-year-old children with asthma from 138 families (Chicago, Ill)	Observational, pre-post intervention study		*Intervention*: Asthma management education plus individually tailored low-cost asthma home trigger remediation (eg, 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, hospitalizations, missed school days, and 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)[83]	One hundred two low-income households in rental properties with ≥1 children with not well-controlled asthma (King Country, Wash)	Observational, pre-post intervention study with historical comparison group		*Intervention (n = 34)*: Weatherization plus CHW education *Historical comparison group (n = 68)*: CHW education without weatherization	● Reduction in evidence of water damage greater with intervention group but no consistent evidence for greater improvement in intervention vs comparison group in other environmental exposures	● Increased asthma control ● Increased caregiver quality of life	● Separate effects of weatherization and CHW not demonstrated ● Small study size ● IPM not used
Colton et al (2014)[84]	Thirty-one 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		*Intervention (n = 18)*: Move from conventional to new buildings designed to green standards Smoke-free policies and IPM practices used *Control 1 (n = 6)*: Move from conventional to conventional housing *Control 2 (n = 7)*: Live in conventional housing (61 visits, including before and after 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 control subjects limits pre-post analysis
Colton et al (2015)[67]	Two hundred thirty-five households in 3 Boston public housing units,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 SHS in green compared with conventional housing	● Fewer asthma symptoms, hospital visits, school absences for children in green compared with 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)[85]	One hundred ten adults and 137 children with asthma sensitized and exposed to ≥1 indoor allergen	RCT	Key allergens in vacuumed settled dust (cat, dog, dust mite, cockroach, and mouse)	After optimization of asthma treatment and control, randomization to group *Intervention (n = 125)*: Multifaceted: 40-wk education + allergen-impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner *Control (n = 122)*: Education not related to allergen avoidance	● *Intervention*: Reduction in all allergens (cat, dog, dust mite allergens, cockroach, and mouse) ● *Control*: 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 might 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 vs children

(Continued)

TABLE II. *(Continued)*

Reference	Population	Study design	Exposure focus	Intervention	Exposure Outcome	Asthma outcome	Comments
Matsui et al (2017)[86]	Three hundred fifty children and adolescents with asthma sensitized and exposed to mouse allergen (Baltimore, Md; Boston, Mass)	RCT	Mouse allergen	*IPM plus education group (n = 181)*: 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. *Education (n = 180)*: Written material and demonstration of the materials needed to set traps and seal holes	● No difference in mouse allergen levels between groups. ● Approximately 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 levels	● Large reduction in mouse allergen observed in education group was unexpected ● Results suggest education alone might be effective in some populations, but the study did not include a control group that received no education about pest management. ● Majority of children's homes continued to have mouse allergen levels greater than levels previously associated with asthma morbidity.
Rabito et al (2017)[87]	One hundred two 5- to 7-year-old children with moderate-to-severe asthma in cockroach-infested homes (New Orleans, La)	RCT	Cockroach allergen	*Intervention (n = 53)*: 12-mo with trapping and bait placement at baseline and 1, 3, 6, 9, and 12 mo in areas with evidence of cockroach *Control (n = 49)*: 12-mo with trapping but no bait placement at baseline and 1, 3, 6, 9, and 12 mo after baseline	● Fewer cockroaches in intervention homes	● Fewer asthma symptoms and unscheduled health care use ● Fewer with FEV_1 <80% of predicted value	● 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)[88]	Two hundred eighty-six 3- to 17-year-old mite-sensitized children with emergency hospital attendance for asthma exacerbation (Northwest England)	RCT (age groups: 3-10 y and 11-17 y stratified)	Dust mite allergen	*Intervention (n = 146)*: 12-mo with mite-impermeable bed encasings *Control (n = 138)*: 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/caregivers ● No measured adherence to medications or asthma trigger data

References (2000-2016) selected by workshop participants as representative and illustrative of asthma management intervention studies in children were used.
ASHRE, American Society of Heating, Refrigerating and Air-Conditioning Engineers; *CHW*, community health worker; *ED*, emergency department; *EPA*, Environmental Protection Agency; *ETS*, environmental tobacco smoke; *FENO*, fraction of exhaled nitric oxide; *ICS*, inhaled corticosteroids; *IPM*, integrated pest management; *NA*, not applicable; *PM*, particulate mass; *QOL*, quality of life; *RCT*, randomized controlled trial.

sensitized and those who are sensitized to fungi.[93,94] Mechanisms for the 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, can protect against allergy development,[95] 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, can introduce new challenges requiring novel strategies to minimize fungal growth. Although 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,"[66,96,97] imaginative study designs are needed to fit the extreme situations with which investigators and communities are at times confronted. In disasters with clear-cut mold damage, the health risks can be obvious, but building remediation solutions can be challenging. The post–Hurricane Katrina Head-off Environmental Asthma in Louisiana study reported improvement of asthma symptoms with implementation of a hybrid intervention with asthma counselors and environmental remediation, but in the midst of postdisaster changes, investigators could not disentangle the extent to which the active study environmental interventions were responsible for the observed fungal reduction or symptom improvement.[98]

A variety of multipronged community-based strategies have been used to decrease indoor allergen exposures,[99,100] with varying success in reducing exposure and improving asthma control. This inconsistency might 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 allergen levels, and effect modification of the intervention

health effect by the presence of coexposures, such as stress or environmental tobacco smoke (ie, SHS).

Although many studies have sampled and tested the efficacy of interventions in individual indoor homes, effects of the structure and building components of housing, including multiunit 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.[67] 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.[67] A study of green housing in the South Bronx[101] showed improvements in asthma symptoms and urgent care visits for asthma, and a Chicago-based study showed self-reported asthma symptom improvements.[102] However, given the variable application of green construction approaches, the potential risks of responding to financial pressures through reduction of air exchange or inadequate maintenance (even in new buildings), and study design limitations, uncertainty remains about which aspects of new construction can improve asthma.

Table II offers a summary of selected published studies on exposure reduction and on associations between exposure reduction and 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 (eg, 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 might 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 (eg, humidity and 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 NO_2 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,[103] allergen exposure is one that has attracted considerable attention.[104,105] 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.[106] However, the concept of allergen avoidance for primary prevention of asthma has been challenged by investigators who argue that this approach is limited by (1) the ubiquitous nature of aeroallergens in some ecologic and cultural settings, (2) the dominance of genetic factors in influencing the course of asthma, (3) the importance of early priming by other factors (eg, microbes or microbial components, *in utero* smoking, and vitamin D), or, most recently, (4) the benefits from early allergen exposure as manifested by studies in food allergy and (5) 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, the Wisconsin Childhood Origins of Asthma Study, the Detroit Childhood Allergy Study, and the Urban Environment and Childhood Asthma study.[34,56,58,107] Most of these observational studies report protective associations with early-life mammalian exposures, especially exposure to dogs, and associated allergens or microbes. The Urban Environment and Childhood Asthma data indicated that early-life multiple exposures, including cockroach and mouse, are protective,[34] whereas the Epidemiology of Home Allergens and Asthma Study found these 2 exposures to be risk factors. Multiple differences in cofactors and exposure levels might 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 (HDM) reduction vary in terms of their success in asthma prevention (Table III).[108-121] 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 allergen and HDM exposure during infancy, with follow-up extending to 18 years. This study has shown a

TABLE III. Randomized controlled trials in primary prevention of asthma using HDM allergen avoidance

Studies	Year(s) recruited	No.	Assessments (y)	Major findings
Isle of Wight[109-111]	1990	120	1, 2, 4, 8, 18	Reduced asthma and atopy at all ages, 1-18 y
MAAPPS*[108,114-116]	1995-1997	291	1, 3, 5, 8, 16	Reduced severe wheezing (infancy) Improved lung function (age 3 y) Increased mite sensitization (age 3 y)
CAPPS[112,113,121]	1995	545	1, 2, 7, 15	Reduced asthma (up to age 7 y and at age 15 y in female subjects only)
PIAMA[117-119]	1996/1997	810	1, 2, 3, 4, 5, 6, 7, 8	Reduced asthma at age 2 y No effect at other ages
CAPS[120]	1997-1999	616	18 mo, 3 y, 5 y	No difference in asthma, wheeze, or atopy Eczema was higher in intervention group

MAAPPS, Manchester Asthma and Allergy Primary Prevention Study; *PIAMA*, Prevention and Incidence of Asthma and Mite Allergy.
*Published outcomes of the intervention in MAAPPS available for ages 1 and 3 years only.

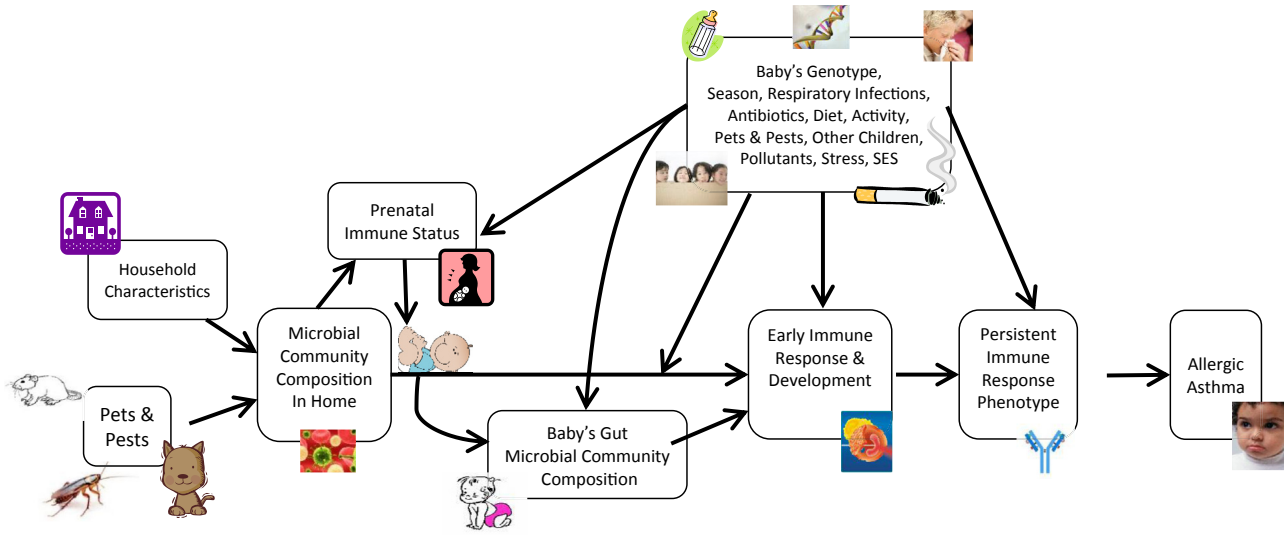

FIG 1. A schematic model describing presumed relationships between the microbiome and allergic asthma. Adapted with permission from Johnson and Ownby.[128]

consistent reduction of asthma, but not atopy, in the allergen avoidance group.[109-111]

A multifaceted approach for infants with a family history of allergic disease was also tested in the Canadian Asthma Primary Prevention Study (Table III). 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 female subjects.[112,113]

The Manchester Asthma and Allergy Primary Prevention Study tested the effect of stringent indoor allergen avoidance measures in a relatively large (n = 291) randomized controlled trial.[114] 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.[115,116]

Finally, in the Prevention and Incidence of Asthma and Mite Allergy 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.[117-119]

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 Prevention and Incidence of Asthma and Mite Allergy study were so low that further reduction could not have significant clinical effect.[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 cofactors in or outside 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 might 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 (Fig 1).[128] The mechanisms through which this

protection can occur are unknown, but the role of the microbiome and its biochemical products as modulators of innate immune system responses that might suppress allergy is an area of intense focus.[34,129] One recent animal model validated the Detroit birth cohort observation that pet dust could be protective against allergic responses.[130]

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.[131,132] 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.[133] In addition, stressful experiences, such as home or community violence, can contribute to the high prevalence of asthma in these communities.[134-136] Such experiences can disturb stress regulation and thus adversely influence immune function and increase susceptibility to asthma.[137] 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.[138]

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.[139-147]

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 the 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 US 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 might be differentially influenced by indoor environmental exposures.[148,149]
- Studies to identify early patterns of the human microbiome and its metabolic output in the gastrointestinal tract, airways, and 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 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 the 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 (eg, 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 II 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 multifaceted, tailored to the specific exposures and sensitivities of the target subject, and intensive.[69,150] 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 untailored intervention. Although the study population was adults, the notion that health benefits observed in tightly controlled randomized controlled trials might not easily translate to more real-world settings is applicable to environmental interventions in children as well. In addition, families face a number of barriers to remediating environmental exposures, including costs, preferences, home ownership status, lifelong 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 because they rent rather than those who own their homes.

The Inner-City Asthma Study (ICAS) might 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 multifaceted, 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 with control subjects.[69] 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 the cost of midrange inhaled corticosteroid and albuterol for a child with moderately severe asthma. This translated to almost $28 per gained symptom-free day.[152] Because a multifaceted and 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

TABLE IV. Research questions for priority areas for environmental interventions and asthma management in children

Priority: Further define the role of EIs 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 EIs 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 (eg, adults, suburban, or rural)?
● Is further tailoring of the intervention, considering the whole environment (eg, social stressors), as well as environments not typically studied (eg, outdoor allergens), more effective than focusing on home and indoor allergens?
● Do EIs improve asthma outcomes by decreasing indoor allergen levels, by their "bystander" effect on other factors related to asthma (eg, medication adherence and SHS 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?
● Do EIs mitigate the costs and side effects of controller medications?
Priority: Determine the most feasible and cost-effective and clinically effective approach to EIs
● Which component(s) of EIs are clinically effective and cost-effective to maximize clinical effectiveness and limit costs?
● What is the minimal EI that retains efficacy, and what components are required to retain efficacy (eg, minimum frequency of visits, location of visits, activities performed at visits, and duration of intervention?)
● Are there specific populations for whom the cost-benefit balance is favorable?
● How would coverage of EIs by a health care 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 with tailored EIs, and how do the cost-benefit ratios 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 nonresearch 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 health care 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 for EIs?
● When do adaptations no longer make the EI evidence-based, and what study designs are sufficient to evaluate continued efficacy?

EI, Environmental intervention.

contribution of individual components of the environmental intervention and exposure reduction to the successful outcome. Notably, both arms of 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, cost-effective, 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 health care, 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 IV. Addressing these research priorities will have clear implications for how health care providers, public health agencies, health care 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 the needs for future elucidation of these properties. We reviewed the state of knowledge of the efficacy of targeted and multipronged 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, US-wide NIH initiative 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.

We thank Dr Floyd Malveaux for his Merck Childhood Asthma Network leadership and support of this workshop.

REFERENCES

1. Habre R, Moshier E, Castro W, Nath A, Grunin A, Rohr A, et al. The effects of PM2.5 and its components from indoor and outdoor sources on cough and wheeze symptoms in asthmatic children. J Expo Sci Environ Epidemiol 2014; 24:380-7.
2. Habre R, Coull B, Moshier E, Godbold J, Grunin A, Nath A, et al. Sources of indoor air pollution in New York City residences of asthmatic children. J Expo Sci Environ Epidemiol 2014;24:269-78.
3. Gore RB, Hadi EA, Craven M, Smillie FI, O'Meara TJ, Tovey ER, et al. Personal exposure to house dust mite allergen in bed: nasal air sampling and reservoir allergen levels. Clin Exp Allergy 2002;32:856-9.
4. Renstrom A, Karlsson AS, Tovey E. Nasal air sampling used for the assessment of occupational allergen exposure and the efficacy of respiratory protection. Clin Exp Allergy 2002;32:1769-75.
5. Graham JA, Pavlicek PK, Sercombe JK, Xavier ML, Tovey ER. The nasal air sampler: a device for sampling inhaled aeroallergens. Ann Allergy Asthma Immunol 2000;84:599-604.
6. Earle CD, King EM, Tsay A, Pittman K, Saric B, Vailes L, et al. High-throughput fluorescent multiplex array for indoor allergen exposure assessment. J Allergy Clin Immunol 2007;119:428-33.
7. Filep S, Tsay A, Vailes L, Gadermaier G, Ferreira F, Matsui E, et al. A multiallergen standard for the calibration of immunoassays: CREATE principles applied to eight purified allergens. Allergy 2012;67:235-41.
8. King EM, Filep S, Smith B, Platts-Mills T, Hamilton RG, Schmechel D, et al. A multi-center ring trial of allergen analysis using fluorescent multiplex array technology. J Immunol Methods 2013;387:89-95.
9. Tsay A, Williams L, Mitchell EB, Chapman MD, Multi-Centre Study G. A rapid test for detection of mite allergens in homes. Clin Exp Allergy 2002; 32:1596-601.
10. Winn AK, Salo PM, Klein C, Sever ML, Harris SF, Johndrow D, et al. Efficacy of an in-home test kit in reducing dust mite allergen levels: results of a randomized controlled pilot study. J Asthma 2016;53:133-8.
11. Tovey ER, Willenborg CM, Crisafulli DA, Rimmer J, Marks GB. Most personal exposure to house dust mite aeroallergen occurs during the day. PLoS One 2013; 8:e69900.
12. Chapman MD, Briza P. Molecular approaches to allergen standardization. Curr Allergy Asthma Rep 2012;12:478-84.
13. Fenaille F, Nony E, Chabre H, Lautrette A, Couret MN, Batard T, et al. Mass spectrometric investigation of molecular variability of grass pollen group 1 allergens. J Proteome Res 2009;8:4014-27.
14. Monaci L, Pilolli R, De Angelis E, Godula M, Visconti A. Multi-allergen detection in food by micro high-performance liquid chromatography coupled to a dual cell linear ion trap mass spectrometry. J Chromatogr A 2014;1358:136-44.
15. Kurita R, Yanagisawa H, Niwa O. Indoor allergen assessment quantified by a thin-layer electrochemical cell and magnetic beads. Biosens Bioelectron 2013; 48:43-8.
16. Sun X, Guan L, Shan X, Zhang Y, Li Z. Electrochemical detection of peanut allergen Ara h 1 using a sensitive DNA biosensor based on stem-loop probe. J Agric Food Chem 2012;60:10979-84.
17. Kim D, Wang SX. A magneto-nanosensor immunoassay for sensitive detection of *Aspergillus fumigatus* allergen Asp f 1. IEEE Trans Magn 2012;48:3266-8.
18. Tsai JJ, Bau IJ, Chen HT, Lin YT, Wang GJ. A novel nanostructured biosensor for the detection of the dust mite antigen Der p2. Int J Nanomedicine 2011;6:1201-8.
19. Kembel SW, Meadow JF, O'Connor TK, Mhuireach G, Northcutt D, Kline J, et al. Architectural design drives the biogeography of indoor bacterial communities. PLoS One 2014;9:e87093.
20. Konya T, Koster B, Maughan H, Escobar M, Azad MB, Guttman DS, et al. Associations between bacterial communities of house dust and infant gut. Environ Res 2014;131:25-30.
21. Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, et al. Cohabiting family members share microbiota with one another and with their dogs. Elife 2013;2:e00458.
22. Taubel M, Rintala H, Pitkaranta M, Paulin L, Laitinen S, Pekkanen J, et al. The occupant as a source of house dust bacteria. J Allergy Clin Immunol 2009;124: 834-40.e7.
23. Amend AS, Seifert KA, Samson R, Bruns TD. Indoor fungal composition is geographically patterned and more diverse in temperate zones than in the tropics. Proc Natl Acad Sci U S A 2010;107:13748-53.
24. Adams RI, Miletto M, Taylor JW, Bruns TD. The diversity and distribution of fungi on residential surfaces. PLoS One 2013;8:e78866.
25. Fujimura KE, Rauch M, Matsui E, Iwai S, Calatroni A, Lynn H, et al. Development of a standardized approach for environmental microbiota investigations related to asthma development in children. J Microbiol Methods 2012;91:231-9.
26. Tringe SG, Zhang T, Liu X, Yu Y, Lee WH, Yap J, et al. The airborne metagenome in an indoor urban environment. PLoS One 2008;3:e1862.
27. Schloss PD, Jenior ML, Koumpouras CC, Westcott SL, Highlander SK. Sequencing 16S rRNA gene fragments using the PacBio SMRT DNA sequencing system. PeerJ 2016;4:e1869.
28. Faino L, Seidl MF, Datema E, van den Berg GC, Janssen A, Wittenberg AH, et al. Single-molecule real-time sequencing combined with optical mapping yields completely finished fungal genome. MBio 2015;6.
29. National Institute of Biomedical Imaging and Bioengineering. Pediatric research using integrated sensor monitoring systems. Available at: https://www.nibib.nih.gov/research-funding/prisms. Accessed February 24, 2017.
30. Alwis KU, Milton DK. Recombinant factor C assay for measuring endotoxin in house dust: comparison with LAL, and (1–> 3)-beta-D-glucans. Am J Ind Med 2006;49:296-300.
31. Milton DK, Feldman HA, Neuberg DS, Bruckner RJ, Greaves IA. Environmental endotoxin measurement: the kinetic limulus assay with resistant-parallel-line estimation. Environ Res 1992;57:212-30.
32. Park JH, Szponar B, Larsson L, Gold DR, Milton DK. Characterization of lipopolysaccharides present in settled house dust. Appl Environ Microbiol 2004;70: 262-7.
33. Fujimura KE, Demoor T, Rauch M, Faruqi AA, Jang S, Johnson CC, et al. House dust exposure mediates gut microbiome *Lactobacillus* enrichment and airway immune defense against allergens and virus infection. Proc Natl Acad Sci U S A 2014;111:805-10.
34. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J Allergy Clin Immunol 2014;134:593-601.e12.
35. Lax S, Smith DP, Hampton-Marcell J, Owens SM, Handley KM, Scott NM, et al. Longitudinal analysis of microbial interaction between humans and the indoor environment. Science 2014;345:1048-52.
36. Meadow JF, Altrichter AE, Kembel SW, Moriyama M, O'Connor TK, Womack AM, et al. Bacterial communities on classroom surfaces vary with human contact. Microbiome 2014;2:7.
37. Chapman MD, Wunschmann S, Pomes A. Proteases as Th2 adjuvants. Curr Allergy Asthma Rep 2007;7:363-7.
38. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. J Allergy Clin Immunol 2014;134:499-507.
39. Lambrecht BN, Hammad H. Asthma: the importance of dysregulated barrier immunity. Eur J Immunol 2013;43:3125-37.
40. Cayrol C, Girard JP. IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. Curr Opin Immunol 2014;31:31-7.
41. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R, et al. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. Nature 2009;457:585-8.
42. Karp CL. Guilt by intimate association: what makes an allergen an allergen? J Allergy Clin Immunol 2010;125:955-62.
43. Whitehead GS, Thomas SY, Cook DN. Modulation of distinct asthmatic phenotypes in mice by dose-dependent inhalation of microbial products. Environ Health Perspect 2014;122:34-42.
44. Wilson RH, Maruoka S, Whitehead GS, Foley JF, Flake GP, Sever ML, et al. The Toll-like receptor 5 ligand flagellin promotes asthma by priming allergic responses to indoor allergens. Nat Med 2012;18:1705-10.
45. Dickey BF. Exoskeletons and exhalation. N Engl J Med 2007;357:2082-4.
46. Mack I, Hector A, Ballbach M, Kohlhaufl J, Fuchs KJ, Weber A, et al. The role of chitin, chitinases, and chitinase-like proteins in pediatric lung diseases. Mol Cell Pediatr 2015;2:3.
47. Eldridge MW, Peden DB. Allergen provocation augments endotoxin-induced nasal inflammation in subjects with atopic asthma. J Allergy Clin Immunol 2000;105:475-81.

48. Matsui EC, Hansel NN, Aloe C, Schiltz AM, Peng RD, Rabinovitch N, et al. Indoor pollutant exposures modify the effect of airborne endotoxin on asthma in urban children. Am J Respir Crit Care Med 2013;188:1210-5.
49. Da Silva CA, Pochard P, Lee CG, Elias JA. Chitin particles are multifaceted immune adjuvants. Am J Respir Crit Care Med 2010;182:1482-91.
50. Zhang X, Lenburg ME, Spira A. Comparison of nasal epithelial smoking-induced gene expression on Affymetrix Exon 1.0 and Gene 1.0 ST arrays. ScientificWorldJournal 2013;2013:951416.
51. Lai PS, Liang L, Cibas ES, Liu AH, Gold DR, Baccarelli A, et al. Alternate methods of nasal epithelial cell sampling for airway genomic studies. J Allergy Clin Immunol 2015;136:1120-3.e4.
52. Zhang X, Sebastiani P, Liu G, Schembri F, Zhang X, Dumas YM, et al. Similarities and differences between smoking-related gene expression in nasal and bronchial epithelium. Physiol Genomics 2010;41:1-8.
53. Poole A, Urbanek C, Eng C, Schageman J, Jacobson S, O'Connor BP, et al. Dissecting childhood asthma with nasal transcriptomics distinguishes subphenotypes of disease. J Allergy Clin Immunol 2014;133:670-8.e12.
54. Salo PM, Arbes SJ Jr, Crockett PW, Thorne PS, Cohn RD, Zeldin DC. Exposure to multiple indoor allergens in US homes and its relationship to asthma. J Allergy Clin Immunol 2008;121:678-84.e2.
55. Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol 2014;134:350-9.
56. Litonjua AA, Milton DK, Celedon JC, Ryan L, Weiss ST, Gold DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. J Allergy Clin Immunol 2002;110:736-42.
57. Ownby DR, Johnson CC. Dogs, cats, and asthma: will we ever really know the true risks and benefits? J Allergy Clin Immunol 2016;138:1591-2.
58. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 2002;288:963-72.
59. Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. J Allergy Clin Immunol 2008;122:114-8, e1-5.
60. Perzanowski MS, Chew GL, Divjan A, Jung KH, Ridder R, Tang D, et al. Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. J Allergy Clin Immunol 2013;131:886-93.
61. Lee WC, Catalano PJ, Yoo JY, Park CJ, Koutrakis P. Validation and application of the mass balance model to determine the effectiveness of portable air purifiers in removing ultrafine and submicrometer particles in an apartment. Environ Sci Technol 2015;49:9592-9.
62. Paulin LM, Diette GB, Scott M, McCormack MC, Matsui EC, Curtin-Brosnan J, et al. Home interventions are effective at decreasing indoor nitrogen dioxide concentrations. Indoor Air 2014;24:416-24.
63. Yoo JY, Park CJ, Kim KY, Son YS, Kang CM, Wolfson JM, et al. Development of an activated carbon filter to remove NO2 and HONO in indoor air. J Hazard Mater 2015;289:184-9.
64. Butz AM, Matsui EC, Breysse P, Curtin-Brosnan J, Eggleston P, Diette G, et al. A randomized trial of air cleaners and a health coach to improve indoor air quality for inner-city children with asthma and secondhand smoke exposure. Arch Pediatr Adolesc Med 2011;165:741-8.
65. Lanphear BP, Hornung RW, Khoury J, Yolton K, Lierl M, Kalkbrenner A. Effects of HEPA air cleaners on unscheduled asthma visits and asthma symptoms for children exposed to secondhand tobacco smoke. Pediatrics 2011;127:93-101.
66. Kercsmar CM, Dearborn DG, Schluchter M, Xue L, Kirchner HL, Sobolewski J, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. Environ Health Perspect 2006;114:1574-80.
67. Colton MD, Laurent JG, MacNaughton P, Kane J, Bennett-Fripp M, Spengler J, et al. Health benefits of green public housing: associations with asthma morbidity and building-related symptoms. Am J Public Health 2015;105:2482-9.
68. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. J Allergy Clin Immunol 2001;108:732-7.
69. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068-80.
70. Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, et al. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. Ann Allergy Asthma Immunol 2004;92:420-5.
71. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. Am J Public Health 2005;95:652-9.
72. Eggleston PA, Butz A, Rand C, Curtin-Brosnan J, Kanchanaraksa S, Swartz L, et al. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. Ann Allergy Asthma Immunol 2005;95:518-24.
73. Chew GL, Wilson J, Rabito FA, Grimsley F, Iqbal S, Reponen T, et al. Mold and endotoxin levels in the aftermath of Hurricane Katrina: a pilot project of homes in New Orleans undergoing renovation. Environ Health Perspect 2006;114:1883-9.
74. Sever ML, Arbes SJ Jr, Gore JC, Santangelo RG, Vaughn B, Mitchell H, et al. Cockroach allergen reduction by cockroach control alone in low-income urban homes: a randomized control trial. J Allergy Clin Immunol 2007;120:849-55.
75. Pongracic JA, Visness CM, Gruchalla RS, Evans R 3rd, Mitchell HE. Effect of mouse allergen and rodent environmental intervention on asthma in inner-city children. Ann Allergy Asthma Immunol 2008;101:35-41.
76. Howden-Chapman P, Pierse N, Nicholls S, Gillespie-Bennett J, Viggers H, Cunningham M, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. BMJ 2008;337:a1411.
77. Bryant-Stephens T, Kurian C, Guo R, Zhao H. Impact of a household environmental intervention delivered by lay health workers on asthma symptom control in urban, disadvantaged children with asthma. Am J Public Health 2009;99(suppl 3):S657-65.
78. Breysse J, Jacobs DE, Weber W, Dixon S, Kawecki C, Aceti S, et al. Health outcomes and green renovation of affordable housing. Public Health Rep 2011;126(suppl 1):64-75.
79. Enterprise. Green communities. Available at: http://www.enterprisecommunity.org/solutions-and-innovation/green-communities. Accessed February 24, 2017.
80. Mitchell H, Cohn RD, Wildfire J, Thornton E, Kennedy S, El-Dahr JM, et al. Implementation of evidence-based asthma interventions in post-Katrina New Orleans: the Head-off Environmental Asthma in Louisiana (HEAL) study. Environ Health Perspect 2012;120:1607-12.
81. Hoppe KA, Metwali N, Perry SS, Hart T, Kostle PA, Thorne PS. Assessment of airborne exposures and health in flooded homes undergoing renovation. Indoor Air 2012;22:446-56.
82. Turyk M, Banda E, Chisum G, Weems D Jr, Liu Y, Damitz M, et al. A multifaceted community-based asthma intervention in Chicago: effects of trigger reduction and self-management education on asthma morbidity. J Asthma 2013;50:729-36.
83. Breysse J, Dixon S, Gregory J, Philby M, Jacobs DE, Krieger J. Effect of weatherization combined with community health worker in-home education on asthma control. Am J Public Health 2014;104:e57-64.
84. Colton MD, MacNaughton P, Vallarino J, Kane J, Bennett-Fripp M, Spengler JD, et al. Indoor air quality in green vs conventional multifamily low-income housing. Environ Sci Technol 2014;48:7833-41.
85. DiMango E, Serebrisky D, Narula S, Shim C, Keating C, Sheares B, et al. Individualized household allergen intervention lowers allergen level but not asthma medication use: a randomized controlled trial. J Allergy Clin Immunol Pract 2016;4:671-9.e4.
86. Matsui E, Perzanowski M, Peng R, Wise R, Balcer-Whaley S, Newman M, et al. Effect of an integrated pest management intervention on asthma symptoms among mouse-sensitized children and adolescents with asthma: a randomized clinical trial. JAMA 2017;317:1027-36.
87. Rabito FA, Carlson JC, He H, Werthmann D, Schal C. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. J Allergy Clin Immunol 2017;140:565-70.
88. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children: a randomised trial of mite impermeable bedcovers. Am J Respir Crit Care Med 2017;196:150-8.
89. Jhun I, Gaffin JM, Coull BA, Huffaker MF, Petty CR, Sheehan WJ, et al. School environmental intervention to reduce particulate pollutant exposures for children with asthma. J Allergy Clin Immunol Pract 2017;5:154-9.e3.
90. Hanson B, Zhou Y, Bautista EJ, Urch B, Speck M, Silverman F, et al. Characterization of the bacterial and fungal microbiome in indoor dust and outdoor air samples: a pilot study. Environ Sci Process Impacts 2016;18:713-24.
91. Sordillo JE, Alwis UK, Hoffman E, Gold DR, Milton DK. Home characteristics as predictors of bacterial and fungal microbial biomarkers in house dust. Environ Health Perspect 2011;119:189-95.
92. Baxi SN, Muilenberg ML, Rogers CA, Sheehan WJ, Gaffin J, Permaul P, et al. Exposures to molds in school classrooms of children with asthma. Pediatr Allergy Immunol 2013;24:697-703.

93. Pongracic JA, O'Connor GT, Muilenberg ML, Vaughn B, Gold DR, Kattan M, et al. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. J Allergy Clin Immunol 2010;125:593-9.
94. Korkalainen M, Taubel M, Naarala J, Kirjavainen P, Koistinen A, Hyvarinen A, et al. Synergistic proinflammatory interactions of microbial toxins and structural components characteristic to moisture-damaged buildings. Indoor Air 2017;27:13-23.
95. Behbod B, Sordillo JE, Hoffman EB, Datta S, Webb TE, Kwan DL, et al. Asthma and allergy development: contrasting influences of yeasts and other fungal exposures. Clin Exp Allergy 2015;45:154-63.
96. Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. Evid Based Child Health 2013;8:944-1000.
97. Chew GL, Horner WE, Kennedy K, Grimes C, Barnes CS, Phipatanakul W, et al. Procedures to assist health care providers to determine when home assessments for potential mold exposure are warranted. J Allergy Clin Immunol Pract 2016;4:417-22.e2.
98. Lichtveld M, Kennedy S, Krouse RZ, Grimsley F, El-Dahr J, Bordelon K, et al. From design to dissemination: implementing community-based participatory research in postdisaster communities. Am J Public Health 2016;106:1235-42.
99. Krieger J. Home is where the triggers are: increasing asthma control by improving the home environment. Pediatr Allergy Immunol Pulmonol 2010;23:139-45.
100. Matsui EC. Environmental exposures and asthma morbidity in children living in urban neighborhoods. Allergy 2014;69:553-8.
101. Garland E, Steenburgh ET, Sanchez SH, Geevarughese A, Bluestone L, Rothenberg L, et al. Impact of LEED-certified affordable housing on asthma in the South Bronx. Prog Community Health Partnersh 2013;7:29-37.
102. Jacobs DE, Ahonen E, Dixon SL, Dorevitch S, Breysse J, Smith J, et al. Moving into green healthy housing. J Public Health Manag Pract 2015;21:345-54.
103. Bousquet J, Gern JE, Martinez FD, Anto JM, Johnson CC, Holt PG, et al. Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MeDALL joint workshop. J Allergy Clin Immunol 2014;133:1535-46.
104. Platts-Mills TA, Rakes G, Heymann PW. The relevance of allergen exposure to the development of asthma in childhood. J Allergy Clin Immunol 2000;105(suppl):S503-8.
105. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 1996;153:141-6.
106. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, et al. Early identification of atopy in the prediction of persistent asthma in children. Lancet 2008;372:1100-6.
107. Bufford JD, Reardon CL, Li Z, Roberg KA, DaSilva D, Eggleston PA, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. Clin Exp Allergy 2008;38:1635-43.
108. Simpson A, Custovic A. Prevention of allergic sensitization by environmental control. Curr Allergy Asthma Rep 2009;9:363-9.
109. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. Lancet 1992;339:1493-7.
110. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. J Allergy Clin Immunol 2007;119:307-13.
111. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. Thorax 2012;67:1046-51.
112. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Arch Pediatr Adolesc Med 2000;154:657-63.
113. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. J Allergy Clin Immunol 2005;116:49-55.
114. Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. J Allergy Clin Immunol 2000;105:252-8.
115. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. Lancet 2001;358:188-93.
116. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. Am J Respir Crit Care Med 2004;170:433-9.
117. Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. Am J Respir Crit Care Med 2002;166:307-13.
118. Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. Pediatr Allergy Immunol 2006;17:329-36.
119. Gehring U, de Jongste JC, Kerkhof M, Oldewening M, Postma D, van Strien RT, et al. The 8-year follow-up of the PIAMA intervention study assessing the effect of mite-impermeable mattress covers. Allergy 2012;67:248-56.
120. Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. J Allergy Clin Immunol 2006;118:53-61.
121. Chan-Yeung M, Dimich-Ward H, Becker A. Atopy in early life and effect of a primary prevention program for asthma in a high-risk cohort. J Allergy Clin Immunol 2007;120:1221-3.
122. Maas T, Kaper J, Sheikh A, Knottnerus JA, Wesseling G, Dompeling E, et al. Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. Cochrane Database Syst Rev 2009;(3):Cd006480.
123. van Strien RT, Koopman LP, Kerkhof M, Oldenwening M, de Jongste JC, Gerritsen J, et al. Mattress encasings and mite allergen levels in the Prevention and Incidence of Asthma and Mite Allergy study. Clin Exp Allergy 2003;33:490-5.
124. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 2006;174:386-92.
125. Fujimura KE, Johnson CC, Ownby DR, Cox MJ, Brodie EL, Havstad SL, et al. Man's best friend? The effect of pet ownership on house dust microbial communities. J Allergy Clin Immunol 2010;126:410-2, e1-3.
126. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Sears MR, et al. Infant gut microbiota and the hygiene hypothesis of allergic disease: impact of household pets and siblings on microbiota composition and diversity. Allergy Asthma Clin Immunol 2013;9:15.
127. Levin AM, Sitarik AR, Havstad SL, Fujimura KE, Wegienka G, Cassidy-Bushrow AE, et al. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity. Sci Rep 2016;6:31775.
128. Johnson CC, Ownby DR. The infant gut bacterial microbiota and risk of pediatric asthma and allergic diseases. Transl Res 2017;179:60-70.
129. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. N Engl J Med 2016;375:411-21.
130. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosh D, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. Nat Med 2016;22:1187-91.
131. Celedon JC, Roman J, Schraufnagel DE, Thomas A, Samet J. Respiratory health equality in the United States. The American Thoracic Society perspective. Ann Am Thorac Soc 2014;11:473-9.
132. Leaderer BP, Belanger K, Triche E, Holford T, Gold DR, Kim Y, et al. Dust mite, cockroach, cat, and dog allergen concentrations in homes of asthmatic children in the northeastern United States: impact of socioeconomic factors and population density. Environ Health Perspect 2002;110:419-25.
133. Olmedo O, Goldstein IF, Acosta L, Divjan A, Rundle AG, Chew GL, et al. Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City. J Allergy Clin Immunol 2011;128:284-92.e7.
134. Suglia SF, Enlow MB, Kullowatz A, Wright RJ. Maternal intimate partner violence and increased asthma incidence in children: buffering effects of supportive caregiving. Arch Pediatr Adolesc Med 2009;163:244-50.
135. Chen W, Boutaoui N, Brehm JM, Han YY, Schmitz C, Cressley A, et al. ADCYAP1R1 and asthma in Puerto Rican children. Am J Respir Crit Care Med 2013;187:584-8.
136. Sternthal MJ, Jun HJ, Earls F, Wright RJ. Community violence and urban childhood asthma: a multilevel analysis. Eur Respir J 2010;36:1400-9.
137. Cacioppo JT, Berntson GG, Malarkey WB, Kiecolt-Glaser JK, Sheridan JF, Poehlmann KM, et al. Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. Ann N Y Acad Sci 1998;840:664-73.
138. Szentpetery SE, Forno E, Canino G, Celedon JC. Asthma in Puerto Ricans: lessons from a high-risk population. J Allergy Clin Immunol 2016;138:1556-8.
139. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol 2011;127:724-33, e1-30.
140. Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, Harshfield BJ, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in

pregnancy for the primary prevention of asthma and allergies in children. Contemp Clin Trials 2014;38:37-50.

141. Sewell DA, Hammersley VS, Devereux G, Robertson A, Stoddart A, Weir C, et al. Investigating the effectiveness of the Mediterranean diet in pregnant women for the primary prevention of asthma and allergy in high-risk infants: protocol for a pilot randomised controlled trial. Trials 2013;14:173.
142. McEvoy CT, Schilling D, Clay N, Jackson K, Go MD, Spitale P, et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. JAMA 2014;311:2074-82.
143. Moreno-Macias H, Dockery DW, Schwartz J, Gold DR, Laird NM, Sienra-Monge JJ, et al. Ozone exposure, vitamin C intake, and genetic susceptibility of asthmatic children in Mexico City: a cohort study. Respir Res 2013;14:14.
144. Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on patients with asthma and allergies. J Allergy Clin Immunol 2014;133:1237-45.
145. Keet CA, Shreffler WG, Peng RD, Matsui W, Matsui EC. Associations between serum folate and vitamin D levels and incident mouse sensitization in adults. J Allergy Clin Immunol 2014;133:399-404.
146. Okupa AY, Lemanske RF Jr, Jackson DJ, Evans MD, Wood RA, Matsui EC. Early-life folate levels are associated with incident allergic sensitization. J Allergy Clin Immunol 2013;131:226-8, e1-2.
147. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. JAMA 2016;315:362-70.
148. Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. Lancet Respir Med 2017;5:224-34.
149. National Institutes of Health. Environmental Influence on Child Health Outcomes (ECHO) Program. Available at: https://www.nih.gov/ECHO. Accessed February 24, 2017.
150. Crocker DD, Kinyota S, Dumitru GG, Ligon CB, Herman EJ, Ferdinands JM, et al. Effectiveness of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. Am J Prev Med 2011;41(suppl 1): S5-32.
151. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. N Engl J Med 2003;349:225-36.
152. Kattan M, Stearns SC, Crain EF, Stout JW, Gergen PJ, Evans R 3rd, et al. Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma. J Allergy Clin Immunol 2005;116:1058-63.