

REVIEW ARTICLE

Environmental exposures and asthma morbidity in children living in urban neighborhoods

E. C. Matsui

Division of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

To cite this article: Matsui EC. Environmental exposures and asthma morbidity in children living in urban neighborhoods. *Allergy* 2014; DOI: 10.1111/all.12361.

Keywords

childhood asthma; folate; indoor allergens; indoor pollutants; mouse allergen.

Correspondence

Dr Elizabeth Matsui, Johns Hopkins University, Department of Pediatrics, Allergy & Immunology, CMSC 1102, 600 N. Wolfe Street, Baltimore, MD 21287, USA.
Tel.: +1-410-502-3858
Fax: +1-410-955-0229
E-mail: ematsui@jhmi.edu

Winner of PhARF (Phadia Allergy Research Forum) Award 2012. <http://www.phadia.com/Allergy-Blood-Testing/Learn-more/PhARF/>

Accepted for publication 16 December 2013

DOI:10.1111/all.12361

Edited by: Douglas Robinson

Abstract

A substantial disparity in asthma prevalence and morbidity among urban children compared with their nonurban counterparts has been recognized for more than two decades. Because of the nature of urban neighborhoods, pest allergens, such as cockroach and mouse, are present in high concentrations in US urban housing and have both repeatedly been linked to asthma morbidity in sensitized children. In addition, there is a growing body of evidence demonstrating that concentrations of many pollutants are higher indoors than outdoors in both US and European urban communities and that exposures to indoor pollutants such as particulate matter (PM) and nitrogen dioxide (NO₂) are independently associated with symptoms in children with asthma. Although environmental interventions are challenging to implement, when they reduce relevant indoor allergen and pollutant exposures, they are associated with clear improvements in asthma. Other modifiable risk factors in urban childhood asthma that have emerged include dietary and nutritional factors. Overweight and obese children, for example, may be more susceptible to the pulmonary effects of pollutant exposure. Insufficiency of vitamin D and folate has also emerged as modifiable risk factors for asthma morbidity in children. The identification of these modifiable risk factors for urban childhood asthma morbidity offers a ripe opportunity for intervention.

The high prevalence of asthma and burden of asthma morbidity among urban children in both the USA and Europe has been recognized for more than two decades. During this time, we have developed a greater understanding of the factors that contribute to asthma in urban children, although, disappointingly, we have not made progress in reducing either asthma prevalence or morbidity in this population (1–3).

In both US and European urban communities, higher concentrations of indoor pollutants, including NO_x and PM, have been observed. However, in contrast to the United States, cockroach and mouse allergens are uncommon. In the United States, urban neighborhoods located centrally in a city and characterized by poverty and predominantly populated by race/ethnic minorities are referred to as 'inner-cities'. Several characteristics of inner-city neighborhoods in the USA contribute to a high burden of asthma morbidity. These include the type and condition of housing stock and the proximity to pollution sources such as traffic, psychosocial stressors, and other factors associated with poverty (3).

Indoor allergens

Although common indoor allergens, such as furry pet and dust mite allergens, are present in urban homes and can contribute to asthma morbidity, this review will focus on pest allergens which are more specific to urban neighborhoods. Because of the nature of US inner-city housing, pest allergens are frequently detected in inner-city homes and are often present in high concentrations. The poor housing conditions, and shared walls and floors/ceilings of multifamily dwellings provide an optimal environment for cockroaches, mice, and rats. There are several species of cockroach, but the predominant species in US inner-cities are the German and American cockroaches, with the German cockroach allergen being the most common and the best studied (4–6). These studies have found that cockroach allergen is detectable in 85% of inner-city US homes (4) and that approximately 2/3 of inner-city children with asthma demonstrated skin test sensitivity to cockroach, making them susceptible to the effects of cockroach allergen exposure (4, 7, 8). In fact, cockroach-sensitized children exposed to higher levels of cockroach allergen in their homes have greater asthma

morbidity across a range of morbidity measures than nonsensitized or nonexposed children. Cockroach allergen exposure has also been reported in European urban communities, including high levels in cockroach-infested public housing units in France (9). However, in general, sensitization rates in European studies are much lower than in US studies and may be due to cross-reactivity rather than to a primary IgE response to cockroach (10–12). One study in Poland, however, found that almost a quarter of asthmatic children were sensitized to cockroach and that most of their homes had detectable cockroach allergen. There was also an association between cockroach sensitization and more severe asthma, suggesting that cockroach exposure and sensitization may be clinically relevant in at least some European communities (13).

The role of rodent allergen exposure, however, was not well studied until the past decade. Initial studies reported a prevalence of detectable mouse allergen of 95% in inner-city homes (14), but non-inner-city studies also demonstrated a surprisingly high prevalence of mouse allergen of 75–80% (15, 16). The striking difference between inner-city and non-inner-city homes was in the concentration of mouse allergen found. In suburban homes, concentrations of Mus m 1, the major mouse allergen, were in the range of ng/g of settled dust, while in inner-city homes, mouse allergen concentrations were in the mcg/g range. Studies that have sampled air from bedrooms of children with asthma have found that 85–90% of bedrooms have detectable airborne mouse allergen (17, 18), with 25% having airborne concentrations similar to those found in some laboratory mouse facilities (19). However, it is important to note that mouse allergen, such as other indoor allergens, has a specific geographical distribution with Northeastern and Midwestern US cities having much higher mouse allergen concentrations than Western US cities (20). On an even more granular scale, mouse allergen can also have a specific distribution within a city (21). Whether the geographical heterogeneity of mouse allergen is due to the age or type of housing stock, or other factors, is not known.

Although multicenter studies report mouse sensitization prevalence of 18–22% (20, 22), in some cities, the mouse sensitization prevalence is 50% or more, with higher prevalence found in populations with greater asthma severity (18). Several studies have convincingly demonstrated a strong association between exposure to mouse allergen and asthma morbidity among mouse-sensitized children (18, 20, 23). Not only do sensitized and exposed children have more asthma symptoms and more acute healthcare visits for asthma than nonexposed or nonsensitized children, but they also have higher exhaled nitric oxide levels, worse lung function, and are more likely to have bronchodilator reversibility, demonstrating an effect on pulmonary inflammation and physiology in addition to symptoms and exacerbations (24).

More recent studies have focused on trying to understand the clinical relevance, if any, of mouse allergen levels measured from specific locations within the home. In the Mouse Allergen and Asthma Cohort Study, there was a stronger association between bed mouse allergen levels and asthma-related acute visits than mouse allergen levels in dust samples taken from the bedroom floor or the kitchen and air samples taken from

the bedroom (18). In this study, the shape of the dose–response relationship between mouse allergen exposure and asthma morbidity was also examined. A linear relationship between bed mouse allergen exposure and asthma morbidity was found among mouse-sensitized, but not non-mouse-sensitized, participants (Fig. 1). Taken together, these findings suggest that any incremental reduction in home mouse allergen levels would result in a corresponding reduction in risk of asthma morbidity and that efforts to target the bed exposure compartment may augment the effects of interventions aimed at eliminating the mouse infestation. The role of mouse allergen exposure in causing asthma is less clear than its role in symptoms and exacerbations in inner-city children with established asthma. However, birth cohort studies have found that parental report of mouse exposure in the first year of life, and sensitization to mouse at 2–3 years of age were associated with greater risk of wheeze in early life (25, 26).

There have been only a few studies in European cities examining mouse allergen exposure, and the prevalence of mouse allergen in home dust and sensitization to mouse varied, but was generally lower than that observed in US inner-city populations. In a study of Strasbourg public housing, 60% of homes had detectable mouse allergen, but the concentrations were 1000-fold lower than concentrations observed in US inner-city homes (27). In one Italian study, approximately 5% of patients seen by allergists were sensitized to either rat or mouse, and a much smaller percentage reported mouse infestation (28). One Polish survey of inner-city asthmatics found that 35% were mouse-sensitized and sensitization was associated with detectable mouse allergen in settled dust, although mouse allergen concentrations were still orders of magnitude lower than those observed in US inner-city homes (29).

Indoor pollutants

Although outdoor pollutants have been linked to adverse respiratory effects in urban children with asthma (30) and are

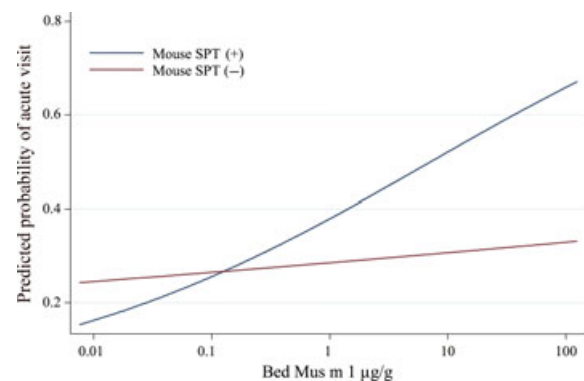


Figure 1 Predicted lines for relationships between bed mouse allergen exposure and predicted probability of an acute visit for asthma. The red line represents children who were not sensitized to mouse and the blue line represents children who were sensitized to mouse. Adapted from (18), Torjusen et al., *Indoor Air*, © 2012 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

known to penetrate indoors and contribute to indoor pollution, there is a growing body of work demonstrating that concentrations of many pollutants are higher indoors than outdoors and that exposure to indoor pollutants is independently associated with asthma symptoms in urban children with asthma.

The best studied indoor pollutants include airborne particulate matter (PM), nitrogen dioxide (NO₂), and second-hand smoke exposure. Airborne particulate matter (PM) is typically measured in different size fractions, so that fine PM is considered PM with an aerodynamic diameter of 2.5 microns or less (PM_{2.5}) and coarse PM is considered PM with an aerodynamic diameter greater than 2.5 microns and up to 10 microns (PM_{2.5-10}). Both fine and coarse PM comprise PM₁₀. Second-hand smoke (SHS) exposure is composed of many substances, which are both particulate and gaseous in nature. SHS contributes predominantly to the fine particle (PM_{2.5}) fraction of airborne particulate matter, and the most commonly measured gaseous component of SHS is airborne nicotine.

Indoor PM concentrations in urban homes are higher than concentrations in nonurban homes (31) and can be as much as twice as high as outdoor concentrations (32–35). Smoking, sweeping, and stove use contribute significantly to both PM_{2.5} and PM₁₀ indoors (32). Both indoor PM_{2.5} and PM_{2.5-10} exposures are associated with more asthma symptoms and rescue medication use in urban children with asthma (32). NO₂ is the byproduct of combustion reactions, and homes with gas-powered appliances have higher levels of NO₂ than homes without gas-powered appliances. Indoor NO₂ levels are also higher than outdoor NO₂ levels in urban homes. In many US cities, gas stoves and heat are prevalent, and some families will use their gas stoves and ovens for heat. In contrast to PM, outdoor NO₂ has little to no influence on indoor NO₂ concentrations. Exposure to indoor NO₂, such as indoor PM, is associated with more asthma symptoms in urban children (36), although one study found that this was only true among nonatopic urban children (37).

Second-hand smoke exposure is relevant in urban childhood asthma as more than half of inner-city US children with asthma live with a smoker as compared to a US national smoking prevalence among adults of 20%. (<http://www.cdc.gov/nchs/fastats/smoking.htm>) Although some studies have reported no effect of SHS exposure on asthma symptoms or asthma-related healthcare use (37), others have found a clear association between SHS exposure and asthma morbidity in children (38), and prenatal and SHS exposures are associated with incident wheeze and asthma in children (39). A recent public smoking ban in UK was associated with a marked reduction in childhood asthma hospitalizations, suggesting a causal link between second-hand smoke exposure and childhood asthma morbidity (40). Another source of indoor pollutants that has been linked to childhood respiratory disease is burning of biomass fuel for cooking, which produces high concentrations of particulate and gaseous pollutants and bioaerosols. Most of the studies focusing on cook stoves have been in developing countries, and use of a variety of alternative fuels and ventilation is associated with lower indoor pollutant concentrations and improved respiratory health (41).

Environmental interventions

Now that a clearer picture of the environmental causes of asthma morbidity in urban children has emerged, there has been greater focus on designing environmental interventions that could serve as an integral part of a patient's asthma management. Intervention studies have focused on targeting-specific allergens, such as cockroach or mouse allergen, or pollutants, such as second-hand smoke exposure. Others have tested the efficacy of a multifaceted intervention tailored to each study participant's panel of triggers, which are identified through allergy testing and assessment of home exposures. Although these interventions are challenging to implement, when they reduce relevant indoor exposures, they are associated with clear improvements in asthma.

The most notable example of a successful environmental intervention is the Inner-City Asthma Study (8), which enrolled 937 inner-city children with atopic asthma. In this randomized controlled trial, the active intervention group received a 1-year, multifaceted environmental intervention that was tailored to the study participants' sensitivities and exposures. The active intervention group had an almost immediate reduction in asthma symptoms that persisted for an additional year beyond the active intervention period, and the improvements in symptoms were associated with the degree of reduction in dust mite and cockroach allergen levels. The findings were striking in that the magnitude of improvement, as compared to the control group, was similar to that observed with controller medication, but unlike controller medications, the effects of the intervention persisted well beyond the active intervention period. This study highlights the feasibility and efficacy of environmental interventions in urban children with asthma and re-enforces the importance of incorporating environmental control practices into the management of urban children with asthma. Although not all aspects of the intervention are relevant to all urban communities, at least some of the interventions should be appropriate for all urban communities.

There have been several randomized controlled trials of indoor pollutant interventions as well. Although the Inner-City Asthma Study environmental intervention trial did not report the effects of the intervention on indoor pollutant levels, it is notable that portable high-efficiency particulate air (HEPA) purifiers were a component of the intervention, so that it is likely that the reductions in allergen levels that were observed were also accompanied by reductions in indoor pollutants, such as PM. In another study, inner-city children with asthma were randomized to a multifaceted intervention or a control group (42). The intervention was similar to the one in the Inner-City Asthma Study, and included deployment of a portable HEPA purifier, but both indoor PM_{2.5} and PM₁₀ levels were measured. This study demonstrated a marked reduction in both PM_{2.5} and PM₁₀ levels as well as an improvement in asthma symptoms in the active treatment group. In a follow-up trial, inner-city children with asthma who lived with a smoker were randomized to one of three groups: (1) two HEPA purifiers and a behavioral intervention aimed at reducing the child's

exposure to SHS, (2) two HEPA purifiers, or (3) control (43). The behavioral intervention was no more effective than the air purifiers, but the air purifier groups had ~40% decline in both $PM_{2.5}$ and $PM_{2.5-10}$ levels and an improvement in some symptoms outcomes. Taken together, these studies indicate that deployment of portable HEPA purifiers not only reduces indoor airborne particulate pollution, but also improve asthma control, even for children living with a smoker. Although these studies provide strong evidence for the incorporation of an individually tailored, multifaceted environmental intervention as an integral part of management of inner-city children with asthma, one question that remains unclear is whether community-level interventions that target the predominant allergen(s) responsible for asthma morbidity in that community would be effective in reducing asthma morbidity. There remain, unfortunately, obstacles to implementation of comprehensive environmental interventions as a part of patient care, perhaps the largest of which is that these services are not covered by health insurance in the USA. This is particularly notable because the population that would arguably have the greatest benefit from environmental intervention is the same population that contributes most to asthma-related healthcare costs, but cannot afford to pay out of pocket for these services. Although these services are covered to some extent in some settings in Europe, access to, and coverage of, these services is not widespread (44).

Other modifiable risk factors and susceptibility factors

There are additional characteristics of low-income, minority children that may contribute directly or indirectly to their disproportionate asthma morbidity. For example, overweight and obesity is more common in inner-city children and adolescents than their non-inner-city counterparts. Approximately 30% of inner-city children with asthma are obese (45, 46), while the percentage of the general population of US children who are obese is 18%. Although the impact of overweight and/or obesity on asthma in this population is not entirely clear, overweight and/or obesity may be associated with more severe disease. There are several biologically plausible mechanisms for a relationship between obesity and worse asthma, but the mechanisms for this association are poorly understood.

In addition, several observations regarding overweight and obese children suggest that they may be more susceptible to the pulmonary effects of pollutant exposure. Overweight and obese children, for example, have greater tidal volumes than their normal-weight counterparts, and pulmonary deposition of airborne pollutants appears to be greater in these children (47). Obesity may also be associated with a reduced capacity to handle oxidative insults such as pollutant exposure, so that inflammatory effects of pollutants are greater in obese patients. Because obesity is associated with resistance to corticosteroids, it is also possible that the inflammatory response induced by pollutant exposure is less responsive to inhaled corticosteroids (48). In fact, some evidence does point to an interaction between weight status and pollutant exposure. In one cohort of inner-city asthmatics, both indoor $PM_{2.5}$ and

NO_2 exposures were associated with more symptoms in overweight and obese children than in normal-weight children (Fig. 2) (46). A large population-based study in China also found that overweight/obese children were more susceptible to the respiratory effects of outdoor pollutant exposure than normal-weight children (49). Given the high indoor pollutant concentrations and high prevalence of overweight/obesity among inner-city children, this combination of risk factors may be responsible for a substantial portion of asthma morbidity.

Inner-city populations are also at risk of insufficiencies or frank deficiencies in micronutrients. Two micronutrients, vitamin D and folate, have emerged as potential modifiable risk factors for asthma morbidity in children in general (50–52). Moreover, inner-city children in particular are at risk of lower vitamin D and folate levels, so that these micronutrients may contribute to asthma morbidity in inner-city children. Psychosocial factors associated with poverty also contribute to asthma morbidity (53). Limited financial resources, low health literacy, and limited emotional support are just some of the many poverty-related factors that are implicated in inner-city asthma.

Conclusions

Urban communities are characterized by a complex environment that has a profound influence on the risk of asthma

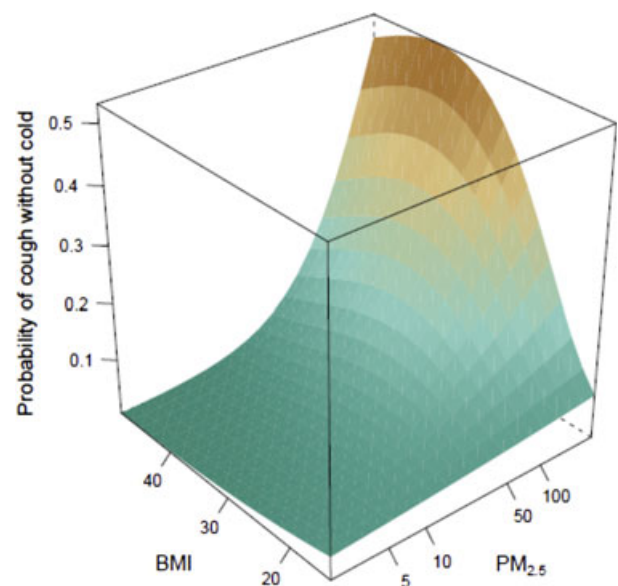


Figure 2 Surface plot of relationships between indoor particulate matter exposure, body mass index, and probability of cough without a cold. Adapted from (46). Reprinted from *Journal of Allergy and Clinical Immunology*, Vol. 131, Lu et al., 'Being overweight increases susceptibility to indoor pollutants among urban children with asthma', pages 1017–1023, copyright 2013, with permission from Elsevier.

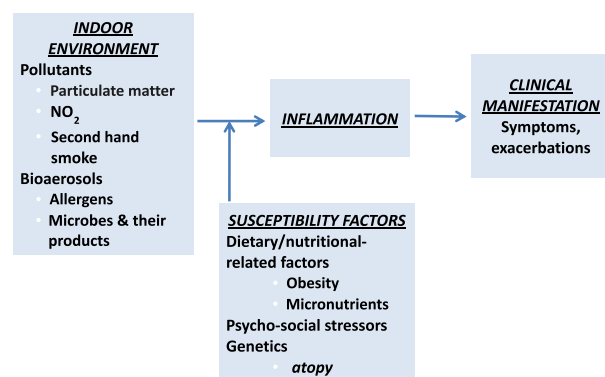


Figure 3 Schematic of complex relationships between environmental exposures, susceptibility factors, and clinical manifestations of asthma.

morbidity, likely explaining a substantial proportion of the high level of morbidity among urban children. Specifically, work over the past decade has provided clear evidence that the pest allergens, pollutants, and poverty-related psychosocial factors play a major role in perpetuating the morbidity in this

population (Fig. 3). The indoor allergens implicated in asthma morbidity are very community-specific, so community-level studies are needed to identify the allergens of greatest public health relevance within any given community. The growing evidence from randomized controlled trials that environmental interventions targeting indoor allergens and pollutants improve asthma should be leveraged to lobby for insurance coverage for these interventions, and future work should focus on refining these interventions and studying the effectiveness of community-level environmental interventions.

Acknowledgments

This work was supported by the National Institute of Environmental Health Sciences (P50ES015903, P01ES018176), the Environmental Protection Agency (R832139), and the National Institute of Allergy and Infectious Diseases (R01AI070630, U01AI083238).

Conflicts of interest

The author was the recipient of the 2012 Phadia Allergy Research Forum Award.

References

- Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. *Natl Health Stat Report* 2011;1–14.
- Mvula M, Larzelere M, Kraus M, Moisiwicz K, Morgan C, Pierce S et al. Prevalence of asthma and asthma-like symptoms in inner-city schoolchildren. *J Asthma* 2005;42:9–16.
- Togias A, Fenton MJ, Gergen PJ, Rotrosen D, Fauci AS. Asthma in the inner city: the perspective of the National Institute of Allergy and Infectious Diseases. *J Allergy Clin Immunol* 2010;125:540–544.
- Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336:1356–1363.
- Eggleston PA, Rosenstreich D, Lynn H, Gergen P, Baker D, Kattan M et al. Relationship of indoor allergen exposure to skin test sensitivity in inner-city children with asthma. *J Allergy Clin Immunol* 1998;102(4 Pt 1):563–570.
- Gergen PJ, Mortimer KM, Eggleston PA, Rosenstreich D, Mitchell H, Ownby D et al. Results of the National Cooperative Inner-City Asthma Study (NCICAS) environmental intervention to reduce cockroach allergen exposure in inner-city homes. *J Allergy Clin Immunol* 1999;103(3 Pt 1):501–506.
- Matsui EC, Ahluwalia SK. The impact of an urban environment on a child's lungs. *Expert Rev Respir Med* 2011;5:465–468.
- 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;351:1068–1080.
- de Blay F, Sanchez J, Hedelin G, Perez-Infante A, Verot A, Chapman M et al. Dust and airborne exposure to allergens derived from cockroach (*Blattella germanica*) in low-cost public housing in Strasbourg (France). *J Allergy Clin Immunol* 1997;99(1 Pt 1):107–112.
- Hirsch T, Stappenbeck C, Neumeister V, Weiland SK, Von Mutius E, Keil U et al. Exposure and allergic sensitization to cockroach allergen in East Germany. *Clin Exp Allergy* 2000;30:529–537.
- Lodrup Carlsen KC, Carlsen KH, Buchmann MS, Wikstrom J, Mehl R. Cockroach sensitivity in Norway: a previously unidentified problem? *Allergy* 2002;57:529–533.
- Liccardi G, Russo M, D'Amato M, Granata FP, De Napoli A, D'Amato G. Sensitization to cockroach allergens in a sample from the urban population living in Naples (southern Italy). *J Investig Allergol Clin Immunol* 1998;8:245–248.
- Stelmach I, Jerzynska J, Stelmach W, Majak P, Chew G, Gorski P et al. Cockroach allergy and exposure to cockroach allergen in Polish children with asthma. *Allergy* 2002;57:701–705.
- Phipatanakul W, Eggleston PA, Wright EC, Wood RA. Mouse allergen. I. The prevalence of mouse allergen in inner-city homes. The National Cooperative Inner-City Asthma Study. *J Allergy Clin Immunol* 2000;106:1070–1074.
- Matsui EC, Wood RA, Rand C, Kanchanaraks S, Swartz L, Eggleston PA. Mouse allergen exposure and mouse skin test sensitivity in suburban, middle-class children with asthma. *J Allergy Clin Immunol* 2004;113:910–915.
- Cohn RD, Arbes SJ Jr, Yin M, Jaramillo R, Zeldin DC. National prevalence and exposure risk for mouse allergen in US households. *J Allergy Clin Immunol* 2004;113:1167–1171.
- Matsui EC, Simons E, Rand C, Butz A, Buckley TJ, Breyse P et al. Airborne mouse allergen in the homes of inner-city children with asthma. *J Allergy Clin Immunol* 2005;115:358–363.
- Torjusen EN, Diette GB, Breyse PN, Curtin-Brosnan J, Aloe C, Matsui EC. Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. *Indoor Air* 2013;23:268–274.
- Matsui EC, Krop EJ, Diette GB, Aalberse RC, Smith AL, Eggleston PA. Mouse allergen exposure and immunologic responses: IgE-mediated mouse sensitiza-

- tion, mouse-specific IgG and IgG4 levels. *Ann Allergy Asthma Immunol* 2004;**93**:171–178.
20. 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.
 21. 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**:284–292.
 22. Phipatanakul W, Eggleston PA, Wright EC, Wood RA. Mouse allergen. II. The relationship of mouse allergen exposure to mouse sensitization and asthma morbidity in inner-city children with asthma. *J Allergy Clin Immunol* 2000;**106**:1075–1080.
 23. Matsui EC, Eggleston PA, Buckley TJ, Krishnan JA, Breyse PN, Rand CS et al. Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Ann Allergy Asthma Immunol* 2006;**97**:514–520.
 24. Torjusen E, Saams J, Peng R, Breyse P, Diette G, Matsui E. Mouse allergen exposure is associated with increased exhaled nitric oxide levels and decreased lung function among mouse sensitized children with asthma. *J Allergy Clin Immunol* 2010;**125**:AB125.
 25. Phipatanakul W, Celedon JC, Sredl DL, Weiss ST, Gold DR. Mouse exposure and wheeze in the first year of life. *Ann Allergy Asthma Immunol* 2005;**94**:593–599.
 26. Donohue KM, Al-alem U, Perzanowski MS, Chew GL, Johnson A, Divjan A et al. Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner-city birth cohort. *J Allergy Clin Immunol* 2008;**122**:914–920.
 27. Muti D, Purohit A, Dazy A, Verot A, de Blay F. Mouse (Mus m1) and rat (Rat n1) allergen levels in dust from private and public houses in Strasbourg, France are lower than houses in the USA. *Eur Ann Allergy Clin Immunol* 2012;**44**:93–95.
 28. Liccardi G, Baldi G, Ciccirelli A, Cutajar M, D'Amato M, Gargano D et al. Sensitization to rodents (mouse/rat) in urban atopic populations without occupational exposure living in Campania district (Southern Italy): a multicenter study. *Multidiscip Respir Med* 2013;**8**:30.
 29. Stelmach I, Jerzynska J, Stelmach W, Majak P, Chew G, Kuna P. The prevalence of mouse allergen in inner-city homes. *Pediatr Allergy Immunol* 2002;**13**:299–302.
 30. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;**121**:1133–1139.
 31. Simons E, Curtin-Brosnan J, Buckley T, Breyse P, Eggleston PA. Indoor environmental differences between inner city and suburban homes of children with asthma. *J Urban Health* 2007;**84**:577–590.
 32. McCormack MC, Breyse PN, Matsui EC, Hansel NN, Williams D, Curtin-Brosnan J et al. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect* 2009;**117**:294–298.
 33. Sousa SI, Ferraz C, Alvim-Ferraz MC, Vaz LG, Marques AJ, Martins FG. Indoor air pollution on nurseries and primary schools: impact on childhood asthma—study protocol. *BMC Public Health* 2012;**12**:435.
 34. Annesi-Maesano I, Hulin M, Lavaud F, Raherison C, Kopferschmitt C, de Blay F et al. Poor air quality in classrooms related to asthma and rhinitis in primary schoolchildren of the French 6 Cities Study. *Thorax* 2012;**67**:682–688.
 35. Hulin M, Caillaud D, Annesi-Maesano I. Indoor air pollution and childhood asthma: variations between urban and rural areas. *Indoor Air* 2010;**20**:502–514.
 36. Hansel NN, Breyse PN, McCormack MC, Matsui EC, Curtin-Brosnan J, Williams DL et al. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environ Health Perspect* 2008;**116**:1428–1432.
 37. Kattan M, Gergen PJ, Eggleston P, Visness CM, Mitchell HE. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. *J Allergy Clin Immunol* 2007;**120**:618–624.
 38. Samir S, Colin Y, Thomas S. Impact of environmental tobacco smoke on children admitted with status asthmaticus in the pediatric intensive care unit. *Pediatr Pulmonol* 2011;**46**:224–229.
 39. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;**129**:735–744.
 40. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. *N Engl J Med* 2010;**363**:1139–1145.
 41. Kodgule R, Salvi S. Exposure to biomass smoke as a cause for airway disease in women and children. *Curr Opin Allergy Clin Immunol* 2012;**12**:82–90.
 42. Eggleston PA, Butz A, Rand C, Curtin-Brosnan J, Kanchanaraks S, Swartz L et al. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Ann Allergy Asthma Immunol* 2005;**95**:518–524.
 43. Butz AM, Matsui EC, Breyse 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 second-hand smoke exposure. *Arch Pediatr Adolesc Med* 2011;**165**:741–748.
 44. de Blay F, Fourgaut G, Hedelin G, Vervloet D, Michel FB, Godard P et al. Medical Indoor Environment Counselor (MIEC): role in compliance with advice on mite allergen avoidance and on mite allergen exposure. *Allergy* 2003;**58**:27–33.
 45. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol* 2010;**125**:584–592.
 46. Lu KD, Breyse PN, Diette GB, Curtin-Brosnan J, Aloe C, Williams DL et al. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. *J Allergy Clin Immunol* 2013;**131**:1017–1023.
 47. Bennett WD, Zeman KL. Effect of body size on breathing pattern and fine-particle deposition in children. *J Appl Physiol* 2004;**97**:821–826.
 48. Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedon JC. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol* 2011;**127**:741–749.
 49. Dong GH, Qian Z, Liu MM, Wang D, Ren WH, Fu Q et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. *Int J Obes (Lond)* 2013;**37**:94–100.
 50. Keet CA, McCormack MC, Peng RD, Matsui EC. Age- and atopy-dependent effects of vitamin D on wheeze and asthma. *J Allergy Clin Immunol* 2011;**128**:414–416.
 51. Matsui EC, Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. *J Allergy Clin Immunol* 2009;**123**:1253–1259.
 52. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. Effect of Vitamin D and inhaled corticosteroid treatment on lung function in children. *Am J Respir Crit Care Med* 2012;**186**:508–513.
 53. Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am* 2011;**31**:19–39.