

Household mold as a predictor of asthma risk: Recent progress, limitations, and future directions

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Asthma prevalence in the United States increased dramatically from 1980 through 1997 and has continued to increase, albeit at a slower pace, over the past decade.¹ Some have speculated that this upward trend is, at least in part, related to modern housing construction, which tends to increase indoor exposures. Installation of central heating systems and highly insulated windows has been shown to decrease air-exchange rates, increase indoor temperature and absolute humidity, and increase levels of mold in carpet dust.² The presence of mold spores in the indoor environment is not in itself a problem when the source is the normal interchange of outside air and when the amount and types of spores inside are the same or less than outside. However, in the setting of inadequate or poorly maintained ventilation systems that might not provide enough air for dilution or dehumidification and the presence of water in materials or condensation from high humidity, mold can actively grow on indoor substrates, potentially adding unhealthy chemicals and bioaerosols to the indoor air.³

There is now a fairly robust body of evidence suggesting that living in moldy households increases the risk of childhood asthma. Early cross-sectional and case-control studies had reported an association between asthma development and household moldiness crudely measured by identifying moldy odors or signs of water damage in homes. Investigators from the Cincinnati Childhood Asthma and Air Pollution Study have strengthened the evidence for causation in a series of articles that have observed significant relationships between mold levels collected in household dust during infancy and subsequent development of recurrent wheeze and asthma at 1,⁴ 3,⁵ and 7⁶ years of age. The prospective design of this birth cohort study minimized the potential for recall bias that can occur in cross-sectional and case control studies (eg, parents might be more likely to recall moldy odor if their child has asthma). Instead of relying on subjective identification of moldy households, dust samples were assayed by polymerase chain reaction (PCR) for common mold species. A quantitative and standardized designation of moldiness for each household was used called the Environmental Relative Moldiness Index (ERMI). The ERMI is a method to quantify household moldiness based on the difference in levels of 26 mold species common to water-damaged homes (group 1 molds) and 10

mold species commonly found in homes irrespective of the degree of water damage (group 2 molds).⁷ These studies extended and reinforced the validity of findings from earlier studies but did not identify specific molds that might be mediating this effect.

In a new analysis of Cincinnati Childhood Asthma and Air Pollution Study data, Reponen et al⁸ have now identified 3 group 1 molds, *Aspergillus ochraceus*, *Aspergillus unguis*, and *Penicillium variable*, which together were most informative in predicting increased risk of asthma by 7 years of age. This analysis demonstrated that infants living in homes with increased dust levels of these 3 molds were more than twice as likely to have asthma compared with infants living in households with lower mold levels. The authors were careful to use multiple statistical models to identify the most informative molds and have shown that these results were robust across models. Because the overall statistical approach was exploratory, however, it will be important to validate the importance of this 3-mold grouping in a hypothesis-driven study with data from a different cohort.

The mechanism by which exposure to molds might result in the development of asthma was not obvious from this study because only 12% of children demonstrated skin test sensitivity to mold at 7 years of age. As the authors note, the 3 most informative molds were not included in the skin prick tests and in fact are not included in commercially available mold panels. As such, one could speculate either that sensitization occurred in a defined manner specifically to these untested molds or that the effects of mold exposure occurred without sensitization.

In this context, recent studies have reported that mice exposed to chitin, a structural element found in mold cell walls, demonstrate eosinophilic lung inflammation despite the lack of allergic sensitization.⁹ Similarly, in ovalbumin-sensitized and challenged mice, co-exposure with fungal metabolites gliotoxin and patulin results in an augmented eosinophilic airway response and greater airway hyperreactivity.¹⁰ These animal studies support a non-IgE-mediated adjuvant-like effect of mold exposure that can increase the magnitude of the airway inflammatory response to other allergenic exposures. An important implication of the present study is that children with negative skin test results to standardized mold panels might nevertheless reside in households with increased mold levels and continue to be at risk for mold exposure-related asthma.

Despite important advances from the Cincinnati Childhood Asthma and Air Pollution Study cohort and other recent studies, more work needs to be done before mold measurements can be used to effectively guide targeted environmental interventions and prevent asthma development. Although the identification of 3 specific molds resulted in improved predictive models compared with subjective reports of moldiness or ERMI, model performance with the 3-mold grouping was still relatively modest, with an area under the curve of 0.73. As such, it might be assumed that a cutoff set to maximize sensitivity would result in marginal

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specificity and that many and perhaps most of the households targeted for home remediation (at significant expense) based on high dust mold levels would, in fact, be at low risk for developing asthma due to mold exposure.

There are a number of reasons why house dust mold levels might have limited predictive ability. Endotoxin studies have demonstrated that significant measurement error can occur with dust sample measurements because levels tend to vary within a household and often are poorly correlated with airborne exposures.¹¹ In addition, personal exposures are often localized to a subject's breathing zone ("personal cloud effect"), varying with each individual's behavior within a microenvironment, and often are significantly higher than predicted by area-wide sampling.¹² As such, 2 individuals in 2 different households with similar levels of house dust mold might be exposed to very different mold levels. Studies with secondhand smoke and ambient air pollution have demonstrated that biological responses to 1 exposure might depend on concurrent exposures.¹³ In households with water damage and poor ventilation, multiple exposures can occur concurrently with mold, including house dust mite allergen, cockroach allergen, and endotoxin. In this setting health responses to high mold levels in a low-endotoxin microenvironment might be substantially different than responses to high mold levels in a microenvironment with high endotoxin levels. Optimizing the predictive value of mold measurements might also require the identification of relevant gene-environment interactions to identify infants who are most susceptible to developing asthma with high mold exposure.

This study and others highlight the importance of the environment and, more specifically, indoor air quality on asthma development. In addition to mold, exposure to endotoxin, cockroach, house dust mite, and secondhand smoke have all been associated with asthma development. Taken together, these studies suggest that at least part of the solution to the increasing trend in asthma prevalence might lie in mitigating home exposures. Until an optimized approach to targeted home remediation is found, the most effective strategy might be to promote public policies that encourage building "asthma-friendly" homes with features such as foundations and building envelopes designed to prevent water intrusion and the incorporation of efficient and effective

ventilation systems.¹⁴ These and other public policy interventions designed to decrease secondhand smoke exposure might be the most practical way to reduce the effects of high indoor exposures and perhaps flatten or reverse the upward trend in asthma prevalence over time.

REFERENCES

1. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. *Natl Health Stat Report* 2011;(32):1-14.
2. Hirsch T, Hering M, Bürkner K, Hirsch D, Leupold W, Kerkmann M-L, et al. House-dust-mite allergen concentrations (Der f 1) and mold spores in apartment bedrooms before and after installation of insulated windows and central heating systems. *Allergy* 2000;55:79-83.
3. Guidance for clinicians on the recognition and management of health effects related to mold exposure and moisture indoors. Available at: <http://oehc.uchc.edu/CIEH.asp>. Accessed July 1, 2012.
4. Cho SH, Reponen T, LeMasters G, Levin L, Huang J, Meklin T, et al. Mold damage in homes and wheezing in infants. *Ann Allergy Asthma Immunol* 2006;97:539-45.
5. Vesper SJ, McKinstry C, Haugland RA, Iossifova Y, Lemasters G, Levin L, et al. Relative moldiness index as predictor of childhood respiratory illness. *J Expo Sci Environ Epidemiol* 2007;17:88-94.
6. Reponen T, Vesper S, Levin L, Johansson E, Ryan P, Burkle J, et al. High environmental relative moldiness index during infancy as a predictor of asthma at 7 years of age. *Ann Allergy Asthma Immunol* 2011;107:120-6.
7. Vesper S, McKinstry C, Haugland R, Wymer L, Bradham K, Ashley P, et al. Development of an environmental relative moldiness index for US homes. *J Occup Environ Med* 2007;49:829-33.
8. Reponen T, Lockey J, Bernstein DI, Vesper SJ, Levin L, Hershey GKK, et al. Infant origins of childhood asthma associated with specific molds. *J Allergy Clin Immunol* 2012. ■■■■■.
9. Van Dyken SJ, Garcia D, Porter P, Huang X, Quinlan PJ, Blanc PD, et al. Fungal chitin from asthma-associated home environments induces eosinophilic lung infiltration. *Immunology* 2011;187:2261-7.
10. Schütze N, Lehmann I, Bönisch U, Simon JC, Polte T. Exposure to mycotoxins increases the allergic immune response in a murine asthma model. *Am J Respir Crit Care Med* 2010;181:1188-99.
11. Park JH, Spiegelman DL, Gold DR, Burge HA, Milton DK. Predictors of airborne endotoxin in the home. *Environ Health Perspect* 2001;163:322-8.
12. Rabinovitch N, Liu AH, Zhang L, Rodes CE, Foarde K, Dutton SJ, et al. Importance of the personal endotoxin cloud in school-age children with asthma. *J Allergy Clin Immunol* 2005;116:1053-7.
13. Rabinovitch N, Silveira L, Gelfand EW, Strand M. The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. *Am J Respir Crit Care Med* 2011;184:1350-7.
14. Krieger J. Home is where the triggers are: increasing asthma control by improving the home environment. *Pediatr Allergy Immunol Pulmonol* 2010;23:139-45.