



Invited Commentary: Is Indoor Mold Exposure a Risk Factor for Asthma?

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A remarkably consistent association between home dampness and respiratory symptoms and asthma has been observed in a large number of studies conducted across many geographic regions (1–10). In a recent review of 61 studies, it was concluded that dampness was a significant risk factor for airway effects such as cough, wheeze, and asthma, with odds ratios ranging from 1.4 to 2.2 (8). Positive associations have been shown in infants (4, 5), children (1, 2, 10), and adults (6, 7, 9), and some evidence for dose-response relations has also been demonstrated (11). Although it has been concluded that the evidence for a causal association between dampness and respiratory morbidity is strong (3, 8), this evidence is based mainly on cross-sectional studies and prevalence case-control studies; few prospective studies have been conducted (12). Therefore, it is not clear whether indoor dampness causes or only exacerbates preexisting respiratory conditions such as asthma. Interestingly, a recent large European multicenter study in adults showed not only a significant homogenous association across centers between self-reported mold exposure and asthma symptoms but also a higher prevalence of asthma in centers with high self-reported indoor mold exposures (9); this suggests that dampness/moldiness may potentially be involved in the primary causation of asthma.

It is not clear whether molds are merely markers of dampness or are causally related to the symptoms associated with dampness (12, 13). Assessment of exposure to molds in most studies has invariably been done by questionnaire, and it is unknown to what extent questionnaire reports of mold growth correlate with exposure to relevant mold components. The studies that have included objective measurements of mold exposure have generally involved culturing spores from indoor air (14) or from settled dust (15); only a few of these studies showed a positive association between measured exposure and asthma or asthma-like symptoms (see reviews by Verhoeff and Burge (13) and Garrett et al. (14)). Perhaps more importantly, very few longitudinal

studies have been performed that have included exposure measurements. Thus, the study by Belanger et al. in this issue of the *Journal* (16) is one of the first to address the issue of mold exposure and asthma development in a birth cohort study. Belanger et al. measured a number of indoor exposures early in life, including mold exposure, both by questionnaire and by measuring total airborne culturable spores, and studied the association with wheeze and cough at 12 months of age. Interestingly, the strongest association was found for mold exposure, whether it was assessed by questionnaire (odds ratios = 1.55–2.27; $p < 0.05$) or by measured exposure (per 20 colonies, odds ratios = 1.10–1.23; $p < 0.05$ only in children whose mothers had asthma), whereas no associations or only minor associations were found for indoor allergen levels. Mold effects were most pronounced among infants whose mothers had asthma, which suggests potential differences in susceptibility to these exposures for children with and without asthmatic mothers. In a previous article, Gent et al. (17) showed in the same infants that high levels of measured *Penicillium* were significantly associated with both wheeze (relative risk = 2.15; $p < 0.05$) and persistent cough (relative risk = 2.06; $p < 0.05$). No associations were observed for other mold species. These results thus suggest that early mold exposure may increase the risk of asthma (with perhaps a larger risk for children of asthmatic mothers). However, these findings should be interpreted with caution because of the poor predictability of early wheeze and cough in asthma development (18). In addition, infants were selected on the basis of having an older asthmatic sibling; therefore, it is not clear whether results can be extrapolated to a “normal,” low(er)-risk population. Finally, although the associations with reported exposure were “confirmed” by measured mold exposure, it is debatable whether a one-time measurement of airborne culturable mold spores qualifies as a valid measure of chronic exposure (see below).

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Exposure assessment

So where do we go from here for studies of indoor mold exposure and asthma? Improved exposure assessment is clearly one of the priorities. Exposure to molds in the indoor environment is most frequently studied by counting culturable spores in settled dust or in the air, but this approach has serious drawbacks. These include poor reproducibility, selection towards certain species, and the fact that dead molds or mold components are not detected, even though they may have toxic/allergenic properties. Perhaps the most important problem, one that has rarely been acknowledged in the studies published to date, is that air sampling during a period of more than 15 minutes is often not possible, whereas air concentrations usually vary a great deal over time. The few studies that have included repeated exposure measurements of mold either in air or in settled dust have shown considerable temporal variation in concentrations, even over very short periods of time (19, 20). Variability in isolated genera was even more substantial (20, 21).

It has been suggested that a ratio of 3–4 of the within- and between-home variance of exposure, which appears realistic for indoor culturable molds (20), requires 27–36 samples per home for reliable estimation of average exposure in an epidemiologic study with less than 10 percent bias in the relation between a health endpoint and the exposure (22, 23). This suggests that unless many samples per home are taken, culturable sampling will probably provide a very poor quantitative measure of exposure, resulting in a nonspecific bias towards the null. This may explain why most studies that have included culturable mold measurements did not find any association with symptoms (in contrast to reported mold). Nonetheless, a significant association with measured exposure (based on measurement of airborne colony-forming units) was found by Belanger et al. (16). This is particularly surprising, since samples were taken for only 1 minute, a period that is unlikely to be sufficient for obtaining a valid measure of exposure during the previous 12 months. The lack of precision in exposure assessment may have contributed to the fact that only one significant association with wheeze was found and only in those children whose mothers had asthma, whereas no associations with cough were found, in contrast to self-reported mold exposure, which was more consistently associated with respiratory symptoms. On the other hand, overreporting of visible mold growth by asthmatics (or their parents) may result in differential misclassification leading to overestimation of the association with asthma (24), although other studies have demonstrated that such bias is unlikely to occur (9, 25).

More recently, other non-culture-based methods of measuring mold concentrations in the indoor environment have been described that may provide more valid measures of exposure. These are based on measurement of specific mold markers in dust or air, such as ergosterol (26, 27) or genus-specific extracellular polysaccharides (28). Other agents such as $\beta(1\rightarrow3)$ -glucan (29, 30) are being measured because of their potential pathogenic potency (see below). Measurements of specific mold components in house dust vary less (compared with airborne sampling) and appear to be stable even over periods of 12 months or longer (21),

suggesting that for those measures only one sample or a few samples may be sufficient. However, although these measures can be made more precisely (with less variation), it is not clear how well they represent long-term airborne exposures.

Causal mechanisms

If mold exposure is a risk factor for asthma, what are the likely mechanisms? Molds are known to produce immunoglobulin E-inducing allergens, and some studies have shown a higher prevalence of mold sensitization among subjects living in damp buildings (6) and among severe asthmatics (31). In addition, in a large European multicenter study, an association between mold sensitization (*Alternaria alternata* and *Cladosporium herbarum*) and asthma severity was demonstrated (32), and allergic responses to molds have been shown in relation to outdoor air exposures to *Alternaria* in desert environments (33). However, the evidence that immunoglobulin E allergic responses play a major role in indoor respiratory symptoms is still very limited. This may be because mold allergens and immunoglobulin E directed against these allergens are very difficult to measure, since the production of mold allergen in nature is highly variable. Alternatively, nonallergic mechanisms may be more important. Nonallergic airway inflammation has been suggested mainly in relation to exposure to $\beta(1\rightarrow3)$ -glucans, nonallergenic fungal cell wall components that have been suggested to be involved in mold-related respiratory symptoms (34, 35). However, the evidence of a causal role for $\beta(1\rightarrow3)$ -glucan is still very limited. Mycotoxins have recently received considerable attention with regard to the presumed (but as yet not confirmed) relation with a number of cases of infant pulmonary hemorrhage in the United States (reviewed by Kuhn and Ghannoum (36)), but there is currently no evidence that mycotoxins are involved in asthma causation. Finally, it has been hypothesized that indoor mold volatile organic compounds may play a role by causing airway irritation, but the evidence for this is weak (37).

The hygiene hypothesis

Although the main focus has been on adverse health effects of mold exposure, some evidence suggests that microbial exposures early in life may protect against atopy and asthma in some circumstances. The “hygiene hypothesis” postulates that growing up in a more hygienic environment with less microbial exposure may enhance atopic (T helper 2 cell) immune responses, whereas microbial pressure would drive the response of the immune system—which is known to be skewed in an atopic T helper 2 cell direction during fetal and perinatal life—into a nonatopic (T helper 1 cell) direction, potentially protecting against atopy and asthma (38, 39).

In addition to infectious microorganisms (40–43), exposure to microbial agents such as bacterial endotoxin has also been suggested to be protective (39, 44, 45). Interestingly, like fungal exposures, endotoxin exposure has long been associated only with adverse health outcomes, including nonallergic asthma (46). The apparent discrepancy in the potential

role of endotoxin may be related to the timing (prenatal and neonatal vs. child and adult life) and dose of exposure. Currently no studies have linked mold exposure to any protective effects, but the possibility cannot be excluded, since few birth cohort studies including assessment of mold exposure early in life have been conducted, and those that have been published (including the study by Belanger et al. (16)) have only followed the infants for a relatively short period of time. It will therefore be interesting to see the results of continued follow-up of such cohorts into the age groups where atopy and asthma can be more reliably established.

Conclusions

In summary, there is consistent evidence that dampness exacerbates preexisting respiratory conditions such as asthma, but it is not clear whether it also *causes* these conditions. Mold exposure has been suggested to play a role, but current knowledge regarding indoor mold exposure and asthma is still very limited because of 1) the fact that specific causal mold components have not yet conclusively been identified, 2) the lack of valid quantitative exposure assessment methods for molds, and 3) the relative lack of prospective cohort studies studying the role of molds using valid exposure assessment methods. Traditionally applied culture methods provide important qualitative information but are only semiquantitative at best. The development of better exposure assessment methods that can practicably be used in epidemiologic studies is therefore a priority. It would also be interesting to study whether mold exposure early in life might protect against atopy and asthma, as has been suggested for exposure to bacterial endotoxin. Therefore, prospective cohort studies using improved exposure methods are crucial to enable us to better understand the effects of indoor mold exposure on asthma development and exacerbation.

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