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Environmental risk factors of rhinitis in early infancy

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Previous studies of allergic rhinitis in children have not documented the environmental risk factors for infants at age one. We examined the relationship of environmental tobacco smoke (ETS) and visible mold exposures on the development of allergic rhinitis, rhinitis and upper respiratory infection (URI) in a birth cohort where at least one parent was skin prick test (SPT) positive. ETS exposure and upper respiratory symptoms were obtained by questionnaires. Visible mold was classified as none, low or high during home visit. Infants had a SPT at age one. After adjustment for potential confounders, exposure to >20 cigarettes per day was associated with an increased risk of developing allergic rhinitis at age one [odds ratio (OR) = 2.7; 95% CI 1.04–6.8] and rhinitis symptoms during the first year (OR = 1.9; 95% CI 1.1–3.2). Infants with low (OR = 1.5; 95% CI 1.1–2.3) or high (OR = 5.1; 95% CI 2.2–12.1) levels of visible mold in their homes were more likely to have more frequent URI during the first year. Older siblings were protective for development of both rhinitis symptoms and allergic rhinitis. This study suggests that ETS exposure, rather than visible mold, is associated with rhinitis and allergic rhinitis in infants. The analysis also suggests that mold may be a stronger risk factor for URI that ETS.

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The prevalence of respiratory allergies in children from birth to 4 yr is 6%, while 4% reportedly have rhinitis (1). A 2004 study of children aged 6–7 yr, however, found that 26% experienced 'sneezing or a runny, or a blocked nose' and 12% reported 'itchy eyes' (2). Rhinitis symptoms (nasal blockage, rhinorrhea, sneezing, nasal itching or rubbing) have been identified in infants as young as 6 months (3). It is estimated that 40% of all children may experience allergic rhinitis (4), including 20% at 2 yr of age, (5).

The impact of environmental exposures on children's respiratory health have also been well documented. About 43% of children aged two through 11 yr are exposed to home environmental tobacco smoke (ETS) (6). There are clear associations with ETS exposure and wheezing, asthma (7, 8), and otitis media in children (7, 9). Other studies on upper respiratory infection (URI) and ETS in children 6 months and older have been contradictory, as ETS has been found to be a risk factor (8, 10) and to have no significant effect (11). Non-allergic rhinitis symptoms have also been associated with ETS exposure in infants as young as 3 months (12).

Adverse respiratory effects from indoor mold exposure also have been observed in children and adults. Mold in the home has been shown to be a risk factor for otitis media in children aged four to five (13), and wheeze or cough in young children (14), and infants (15), as well as within an adult population (16). According to the International Study of Asthma and Allergies in Children (ISAAC), dampness or mold in the home is a risk factor for allergic rhinitis in children aged six and older (17). Mold is also a risk factor for non-allergic rhinitis in children as young as 3 months (12).

Although risk factors for rhinitis and URI in infants have been evaluated, some results are contradictory and most studies failed to examine multiple environmental exposure pathways,

particularly as related to allergic rhinitis. This study evaluated the impact of indoor household exposures to both ETS and visible mold and personal 'exposures' including pet ownership, presence of siblings, daycare attendance and being breastfed on URI and rhinitis symptoms prior to age one and allergic rhinitis at age one.

Methods

Recruitment

Infants enrolled in the Cincinnati Childhood Allergen and Air Pollution Study (CCAAPS) study as of January 2004 (n = 633) were included in this analysis. Infants were identified monthly by county and city birth certificates from early 2001 through 2003. All infants lived in a seven county area of the Ohio Kentucky River Valley. The primary exposure of interest in the CCAAPS study was traffic pollution defined by the proximity of the infant's home to a traffic source. Residential addresses on the birth certificates were geocoded using the EZLocate Extension from TeleAtlas for ArcView 3.2 to determine distance from traffic. Parents of potentially eligible infants were sent a letter explaining the study. Parents were then contacted and interviewed via phone, home visit or mail-in survey. Infants were ineligible if gestation was <35 wk. To be enrolled, parents must have indicated a positive response to at least one of 12 allergy symptoms and had a positive SPT (wheal 3 mm or larger than the negative control) to at least one of 15 aeroallergens. Parents were enrolled at infant's age 7.5 $\pm$ 2.4 months.

Data collection

At the time of the parent SPT, an interviewer-administered questionnaire collected information on smoking habits, family health history, demographics and other covariates. The question used for infant rhinitis symptom collection was adapted from the ISAAC survey for 6–7 yr olds core rhinitis module 'In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu' (18). The infant's respiratory health history from birth to time of enrollment was also collected.

The parent was instructed on the use of monthly diaries to collect information on the infant's upper respiratory symptoms. The parent must have completed at least one diary prior to the child's 12 month clinical exam to be included in this study.

Outcome definitions

On each diary, parents could indicate if their infant had a 'sinus' or 'ear infection' in the past 30 days. An infant was defined as having an URI if the parent indicated a sinus or ear infection *and* antibiotic use on the same diary. The infant was defined as having rhinitis if the parent identified the infant had 'sneezing or a runny or blocked nose not associated with a cold or chest infection' in the past 30 days. The number of times each infant had an URI or rhinitis was summed. At approximately 12 months of age a skin prick test (SPT) was performed on the infant that included the same environmental allergens as performed on the parent. Allergic rhinitis was defined as having rhinitis at least once on any diary and a positive SPT to one or more aeroallergens at the 12 month clinical exam.

Exposure definitions

The main environmental exposure variables of interest were ETS and visible mold. A measure of total ETS exposure was calculated by summing the number of cigarettes smoked daily by each smoker living in the infant's home and categorizing into none, 1–19 cigarettes/day or ≥ 20 cigarettes/day.

Within an average of 3 wk after enrollment, a trained assessor examined each home for visible mold and water damage. 'No mold' homes had no water damage, visible mold, moldy odor or history of mold/water damage. 'High mold' homes were defined as having mold in one room ≥ 0.2 m^2 or a combined area of visible mold and water damage on the same surface ≥ 0.2 m^2 (19). All other homes were defined as having 'low mold.' The CCAAPS exposure of interest, traffic pollution defined by the proximity of infant's home to a traffic source, was excluded from the analysis because it was not significantly associated with any of the outcomes ($p > 0.20$). Other covariates included ownership of a cat or dog and attending a daycare center (yes/no). Breastfeeding practices were defined as never, one to 4 wk, or more than 4 wk, and the number of older siblings was defined as none, one, or two or more. Mother's education level (ever attended college or less) was used as a socioeconomic status indicator. Infant gender and mother's race were collected from the birth certificate.

Data analysis

All analysis was performed using SAS software (version 8.02 for Windows; SAS Institute Inc.,

Cary, NC, USA). Chi-square was used to examine participation bias for infants whose parents did not complete the diaries and therefore were excluded compared with those that were included in the analysis. Simple and multiple regression analysis (unadjusted and adjusted), odds ratios (OR) and 95% Confidence Intervals (95% CI) were generated using a cumulative logit model for the outcomes of rhinitis and URI. Model assumptions were checked by varying outcome level groupings. Binary logistic regression was used for the outcome of allergic rhinitis. All models were carried out using the LOGISTIC procedure, correcting for overdispersion because of correlations between multiple responses by the same subject. Each independent variable was analyzed separately and then in the adjusted models. 'Backward elimination' was performed to remove non-significant variables, unless removal of a variable caused ≥10% change in the coefficients of the two exposure variables. The number of monthly diaries returned was entered as a covariate in the adjusted models to adjust for frequency of response.

Results

As of January 2004, 633 parents participating in the CCAAPS study had returned one or more monthly diaries, with 585 also having home mold classification completed. Of these infants, 495 had a SPT. About one-third (31%) of infants had at least one URI with concurrent antibiotic use, half (49%) experienced rhinitis in their first year of life, 17% were SPT positive to one or more aeroallergen and 9% met the definition of allergic rhinitis.

Table 1 displays the demographics and personal characteristics of the infants. Overall, 29% and 56% were exposed to ETS and visible mold, respectively. About one-third had a dog and one quarter a cat. Most mothers were Caucasian (77.6%) and had attended some college (77.5%). Figs. 1 and 2 display the prevalences of each health outcome with exposures of ETS and visible mold. Fig. 1 shows an increasing prevalence of allergic rhinitis with increasing exposure to ETS, significant with ≥20 cigarette/day exposure. A non-significant increasing trend is observed with rhinitis, and the prevalence of URI is highest in the non-exposed group. Fig. 2 shows that all outcomes were higher in the homes of infants with high visible mold, but only the association with URI was significant.

In the unadjusted analysis, infants exposed to 20 or more cigarettes per day had a significantly increased risk of having allergic rhinitis at age one (OR 2.4, 95% CI 1.1–5.5), while no significant associations were observed with rhinitis or URI. Visible mold was associated with increased URI for those living in 'low mold' (OR 1.4, 95%CI 1.01–2.1) and 'high mold' (OR 3.8, 95% CI 1.7–8.4) homes. Although there was an increase in allergic rhinitis and rhinitis with increasing visible mold exposure, the associations were not significant ($p > 0.05$).

The adjusted analysis of allergic rhinitis, rhinitis and URI is displayed in Table 2. Infants

Table 1. Demographics and personal characteristics of infants

Factor	Number*	%
Visible mold		
None	259	44.3
Low	303	51.8
High	23	3.9
Total no. of cigarettes		
None	449	70.9
1–19	106	16.8
≥20	78	12.3
Siblings		
None	237	37.4
1	219	34.6
≥2	177	28.0
Mother's education (yrs)		
≤12	140	22.5
≥13	481	77.5
African–American maternal race	141	22.4
Male infant gender	333	47.4
Dog ownership	213	33.7
Cat ownership	152	24.0
Attend daycare	58	9.2
No. of weeks breastfed		
None	210	33.2
1–4	56	8.9
>5	367	58.0

*Number of infants may vary because of missing information.

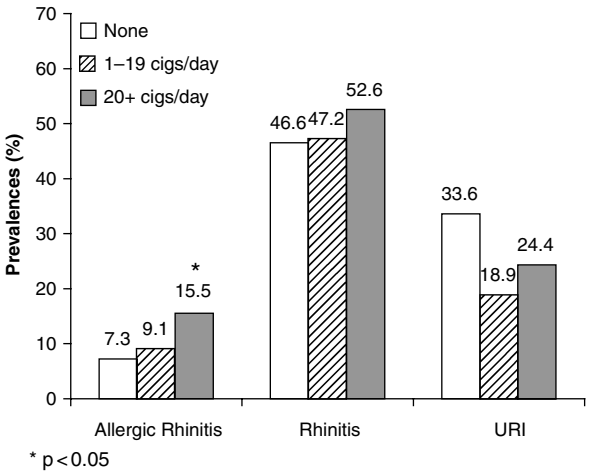

Fig. 1. Prevalences of infant allergic rhinitis, rhinitis and URI by daily ETS exposure.

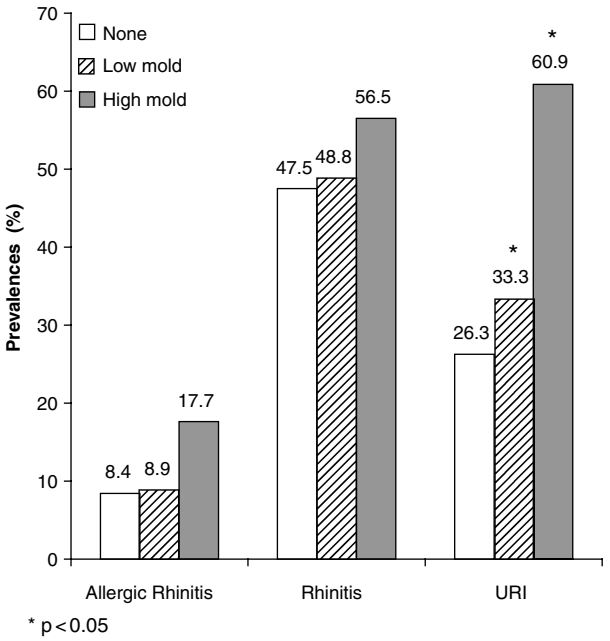

Fig. 2. Prevalences of infant allergic rhinitis, rhinitis and URI by in-home visible mold.

Table 2. Adjusted* associations estimated as odds ratios (OR) and 95% confidence intervals (95% CI) between exposures and upper respiratory symptoms.

	Allergic rhinitis OR (95% CI)	Rhinitis OR (95% CI)	URI OR (95% CI)
Visible mold			
None†			
Low	1.2 (0.6–2.5)	1.1 (0.8–1.6)	1.5 (1.01–2.3)
High	3.2 (0.7–14.8)	1.7 (0.7–3.8)	5.1 (2.2–12.0)
Total no. of cigarettes			
None†			
1–19	0.9 (0.3–2.8)	1.2 (0.7–1.9)	0.6 (0.3–1.1)
>20	2.7 (1.04–6.8)	1.9 (1.1–3.2)	0.8 (0.4–1.6)
Siblings			
None†			
1	0.4 (0.2–0.8)	1.0 (0.7–1.4)	‡
>2	0.4 (0.2–1.03)	0.7 (0.4–0.99)	‡

*Adjusted for mother's education, gender, cat and dog ownership, daycare attendance, breastfeeding and number of diaries returned.
†Reference category.
‡Factor removed by backward elimination.

exposed to 20 or more cigarettes per day compared with the non-exposed were almost three times more likely to have allergic rhinitis at age one (OR 2.7, 95% CI 1.04–6.8). This exposure also doubled the risk of rhinitis (OR 1.9, 95% CI 1.1–3.2).

Infants living in high mold homes were over five times more likely to have URI's than those that lived in homes where mold was not visible (OR 5.1, 95% CI 2.2–12.0). The odds ratio showed consistently rising trends from the low to high mold homes for all outcomes.

Infants with two or more older siblings had decreased rhinitis episodes in the first year (0.7, 95% CI 0.4–0.99). Mother's race, infant gender, cat ownership and breastfeeding practices were not associated with any of the outcomes in the adjusted models. Analysis of infants with rhinitis during the first year and any positive SPT at age one (including food) yielded results similar for allergic (aeroallergen only) rhinitis. The same risk factors for URI were also observed in an analysis of infants that had URI's in the first year regardless of antibiotic use and in a sub-analysis of ear infection only. When the interaction of mold and ETS exposures were evaluated in each multivariate model, no significant relationships were observed.

The infants whose parents returned diaries compared with those that did not were more likely to have mothers that attended college (χ^2, $p < 0.0001$), live in a non-smoking household ($p = 0.002$) and be breastfed ($p = .002$). There were no significant differences, however, with race, gender, number of older siblings, dog or cat ownership, daycare attendance or health of the infant from birth to enrollment.

Discussion

The risk of allergic rhinitis, rhinitis and URI related to the indoor environment in a cohort of infants at high risk for developing allergic disease was assessed. Exposure to ETS was associated with an increased risk of allergic rhinitis and rhinitis during the first year of life, and visible mold was associated with more frequent URI. Having older siblings decreased the risk of both allergic rhinitis and rhinitis at age one.

Our analysis indicated that ETS was a significant risk factor for allergic rhinitis at age one, and to our knowledge this is the first report of this association at that early age. We also showed that ETS was a significant risk factor for rhinitis, as has been observed in children aged 3 months to 5 yr (12), and in children aged 6–7 yr (20).

The ETS exposure became significant in the adjusted analysis only when education level of the mother was entered in the model. This finding suggests that ETS exposure is potentially confounded by the mother's education level. There was also a significant association with increased rhinitis and URI in infants whose mothers had higher education. This finding is supported by the 1999 National Health Interview Survey that found the proportion of children with all types of allergies increases with parent education level (1). Although ETS exposure was associated with allergic rhinitis, it was not associated with

allergic sensitization (regardless of respiratory symptoms) at age one (data not shown), as has been previously reported (21).

Our findings support other studies showing associations with ETS and rhinitis symptoms. In healthy adult test subjects, 15 min of side stream tobacco smoke exposure caused irritation and increase of rhinitis symptoms and nasal resistance, nasal congestion, headache and cough (22, 23). Historically ETS sensitive subjects reported significantly more nose and throat irritation. These studies suggest that in 1-yr-old children, rhinitis symptoms also are aggravated by ETS exposure.

We did not show ETS as a risk factor for URI or otitis media as was found in a 1998 meta-analysis of nine studies (21). Another study in 4–5 yr old children that adjusted for mold at home also found that ETS was not a risk factor for ear infection (13). This finding does not exclude a true association in older children and may also be attributed to access to medical treatment. Mothers in this study that have a college degree have a lower smoking rate (4.2%) than those with some college education (18.6%) or high school or less (31.2%). Those with a higher education may also have better access to medical care and therefore lead to more frequent diagnosis of URI in the non-smoking group, masking any association between URI and ETS.

Our analysis also shows that visible mold is the highest predictor of URI in infants under age one, as has been previously reported in older children and adults. Sinusitis has been positively associated with mold exposure measured by self-report (1.9; 1.15–3.11) and surveyor-assessed report of dampness in the home (1.9; 1.11–3.30) in subjects 16 and older (24). Spengler et al. (25) showed that parental report of household mold was associated with an increased risk of URI (1.7; 1.35–2.25) in older children aged eight through twelve. Significant associations between ear infection and assessor reported mold has been previously reported in children aged four to five (13), as well as infants before 6 months (26).

It has been suggested that effects of mold exposure and lower respiratory infection in infancy are due to non-allergenic fungal spore components or metabolites released from fungi (27). All fungal cell walls contain $(1 \rightarrow 3)$-β-D-glucan, a glucose polymer that has immunosuppressive, mitogenic and inflammatory properties. Mycotoxins are secondary metabolites of filamentous fungi and can be produced by many mold genera, such as Aspergillus, Penicillium, Stachybotrys and Fusarium (28, 29). *In vitro*, it has been shown that exposure of adult human nasal respiratory ciliated epithelium to mycotoxins from Aspergillus fumigatus causes a significant decrease in nasal cilia beating frequency (30), which functions to clear mucous and bacteria from the nose. Both inflammatory and non-inflammatory mechanisms inhibit mucous and bacterial clearing, possibly leading to congestion, runny nose, or trapped infection-causing bacteria (31).

We observed sibling number to have a protective effect on rhinitis and allergic rhinitis. A review in 2000 showed that all studies that investigated sibling number and rhinitis in children 7 yr or older reported a significant negative relationship (32). One study in 2001 described the potential impact of siblings observed with rhinitis in younger children, at a median age of 2.8 yr (33). To our knowledge, this is the first report of the 'sibling effect' with allergic rhinitis and rhinitis in the first year of life.

Although the biological mechanisms of the sibling effect are still unknown, the 'hygiene hypothesis' (34) conceived that increasing hygiene and smaller family size reduced the number of infections in early life, altering the course of allergic disease by promoting a T-helper cell 1 (Th1) pattern of immunity rather than the allergic Th2 pattern (32, 35). Our results show that daycare attendance, not older siblings, is associated with more frequent URI and rhinitis.

Limitations of this study include the outcomes of URI and rhinitis symptoms collected by parental report rather than diagnosed by a health care professional. The outcomes of rhinitis and allergic rhinitis could be attributed to an upper respiratory viral infection rather than a hypersensitivity reaction. We did attempt to limit recall bias, however, by asking parents to complete the diaries every month. Although we assessed visible mold during the in-home evaluation, ETS exposures were collected by parental report of any smoking in the home by a resident.

In conclusion, findings related to infant allergic symptoms and disease demonstrate that the effects of environmental exposures are pronounced in the first year of life. Continued research into measurements of upper respiratory immune function and possible gene-environment interactions might help to better explain these results.

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