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Rhinosinusitis and mold as risk factors for asthma symptoms in occupants of a water-damaged building

Abstract Mold exposure in damp buildings is associated with both nasal symptoms and asthma development, but the progression of building-related (BR) rhinosinusitis symptoms to asthma is unstudied. We examined the risk of developing BR-asthma symptoms in relation to prior BR-rhinosinusitis symptoms and microbial exposure among occupants of a damp building. We conducted four cross-sectional health and environmental surveys among occupants of a 20-story water-damaged office building. We defined BR-rhinosinusitis symptom (N = 131) and comparison (N = 361) groups from participants' first questionnaire responses. We compared the odds for the development of BR-asthma symptoms between these two groups over the subsequent surveys, using logistic regression models adjusted for demographics, smoking, building tenure, and first-survey exposures to fungi, endotoxin, and ergosterol. The BR-rhinosinusitis symptom group had higher odds for developing BR-asthma symptoms [odds ratio (OR) = 2.2; 95% confidence interval (CI) = 1.3–3.6] in any subsequent survey compared to those without BR-rhinosinusitis symptoms. The BR-rhinosinusitis symptom group with higher fungal exposure within the building had an OR of 7.4 (95% CI = 2.8–19.9) for developing BR-asthma symptoms, compared to the lower fungal exposure group without BR-rhinosinusitis symptoms. Our findings suggest that rhinosinusitis associated with occupancy of water-damaged buildings may be a sentinel for increased risk for asthma onset in such buildings.

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Practical Implications

Exposure to mold is associated with the development of asthma in damp building occupants, and rhinitis is known to be a risk factor for asthma. However, there is little information about the degree of risk for the progression of rhinosinusitis to asthma owing to mold exposures in damp buildings. Our study of damp building occupants demonstrates that building-related (BR) rhinosinusitis symptoms were a risk factor for the development of BR asthma symptoms and that exposure to mold (fungi) or other dampness-related agents augments risk for the development of BR asthma symptoms among those with BR rhinosinusitis symptoms. Our findings suggest that occurrence of BR upper respiratory illness in water-damaged buildings may presage future endemic asthma.

Introduction

Exposure to indoor dampness and mold is a risk factor for upper and lower respiratory symptoms (Bornehag et al., 2004; Institute of Medicine of the National Academies of Science, 2004). The 2009 World Health Organization (WHO) guidelines concluded that there is clinical evidence of increased risk of chronic rhinosinusitis and allergic fungal sinusitis because of exposure to mold and other microbial agents in damp environments (WHO, 2009). There is also sufficient epidemiologic evidence of association between the development of asthma and indoor dampness-related agents in adults (Cox-Ganser et al., 2009; Karvala et al., 2010, 2011; Park et al., 2008; World Health Organization, 2009).

Comorbidity from nasal symptoms and asthma supports the 'unified airways disease' concept, which suggests the interaction between upper and lower respiratory tracts (Derebery et al., 2008; Krouse et al., 2007). Epidemiologic studies of the general population show that rhinitis is an independent risk factor for asthma (Guerra et al., 2002; Leynaert et al., 1999; Togias, 2003) and that allergic rhinitis may be a risk factor for sinusitis (Bachert et al., 2004). However, there is little information about the degree of risk for the progression of rhinosinusitis symptoms associated

with being in damp buildings during the workday [building-related (BR)] to asthma.

In 2001, the National Institute for Occupational Safety and Health (NIOSH) received a health hazard evaluation request concerning BR diseases in a water-damaged 20-story office building built in 1985 and located in the northeastern United States. The building was occupied by the current tenants in 1994. In response to the request, NIOSH staff conducted an initial cross-sectional health questionnaire survey in September 2001 and an initial environmental survey in April 2002. Building occupants reported that new-onset respiratory and dermatological conditions that they perceived to be BR had occurred as early as initial occupancy in 1994. They complained of an increase in symptom severity and frequency beginning in the fall of 2000. We reported 67 cases of post-occupancy-onset asthma, eight of hypersensitivity pneumonitis, and six of sarcoidosis among 888 participants in the initial 2001 health questionnaire survey (Cox-Ganser et al., 2005). Upper and lower respiratory symptoms were significantly associated with the levels of fungi and endotoxin in floor dust in an exposure-dependent way (Park et al., 2006), and post-occupancy physician-diagnosed asthma was significantly associated with the levels of hydrophilic fungi and ergosterol in floor dust in the cross-sectional analysis of the initial survey data (Park et al., 2008). After major remediation efforts through early 2004, we conducted three subsequent cross-sectional surveys in August 2004, 2005, and 2007 to examine the effect of remediation on occupants' health. Using the initial and three subsequent cross-sectional survey data, we examined (i) whether occupants who reported BR rhinosinusitis symptoms in the 2001 initial survey were more likely to develop BR asthma symptoms or physician-diagnosed asthma in the subsequent surveys than those with no BR rhinosinusitis symptoms in 2001 and (ii) how microbial exposures interacted with the presence of BR rhinosinusitis symptoms at the initial survey in the development of asthma symptoms in the building occupants over the three subsequent surveys.

Methods

Definition of building-related (BR) symptoms

We defined BR symptoms as those that improved when away from the building based on the question 'When away from the building, were your symptoms the same, worse, or better?' We defined BR-rhinosinusitis symptoms as one or more BR nasal symptom (stuffy, itchy, or runny nose), sneezing, or sinusitis or sinus problems occurring one or more times per week in the last 4 weeks. We defined BR-asthma symptoms as two or more asthma-like symptoms (wheeze/whistling, chest tightness, attack of cough, attack of shortness of breath, awakened by attack of breathing difficulty) occurring one or more times per week in the last 4 weeks with at least one symptom being BR. Current asthma was defined as a self-reported physician diagnosis of asthma that was still present at the time of the survey. The non-BR-rhinosinusitis symptom and non-BR-asthma symptom groups' definitions were as above but with no symptoms that improved when away from the building. The same self-administered questionnaire was used in all four cross-sectional surveys, with the first page indicating that consent to participate was implied by completing the questionnaire, as approved by the NIOSH Human Subjects Review Board.

Study population

We selected all participants who did not have BR-asthma symptoms in the initial cross-sectional survey and who participated in any subsequent cross-sectional survey (Figure 1). These selected participants were categorized into a 2001 BR-rhinosinusitis symptom group and a 2001 comparison group (those without BR-rhinosinusitis symptoms) for the investigation of the development of BR-asthma symptoms in the subsequent surveys.

Environmental surveys

In the initial 2002 environmental survey, we had floor dust samples available from 338 workstations. Each dust sample was collected by vacuuming a 2-square-meter carpeted floor area in a standardized way as described previously (Park et al., 2006, 2008). The dust samples were analyzed for culturable fungi, ergosterol (a principal sterol in fungal membranes), and endotoxin (a component of the outer membrane of Gram-negative bacteria), which were used as measures of microbial exposure. In 2004, we collected and analyzed floor dust samples from the 338 workstations we sampled in 2002. In 2005, we collected samples from 300 randomly selected workstations. In 2007, we randomly selected half of the 2005 sampled workstations for sample collection. Details of environmental studies, remediation history, and effect of remediation on the microbial levels in floor dust have been reported in a recent publication (Cho et al., 2011).

Exposure assignment

We estimated floor-specific geometric means (GM) of culturable fungi, ergosterol, and endotoxin in floor dust samples collected from each survey. Using the rank order of these floor-specific means, we categorized all 15 occupied floors into tertile (low, medium, and high) exposure groups for each agent in each survey (Park et al., 2006). To compare the levels of the microbial agents by tertile exposure group and survey,

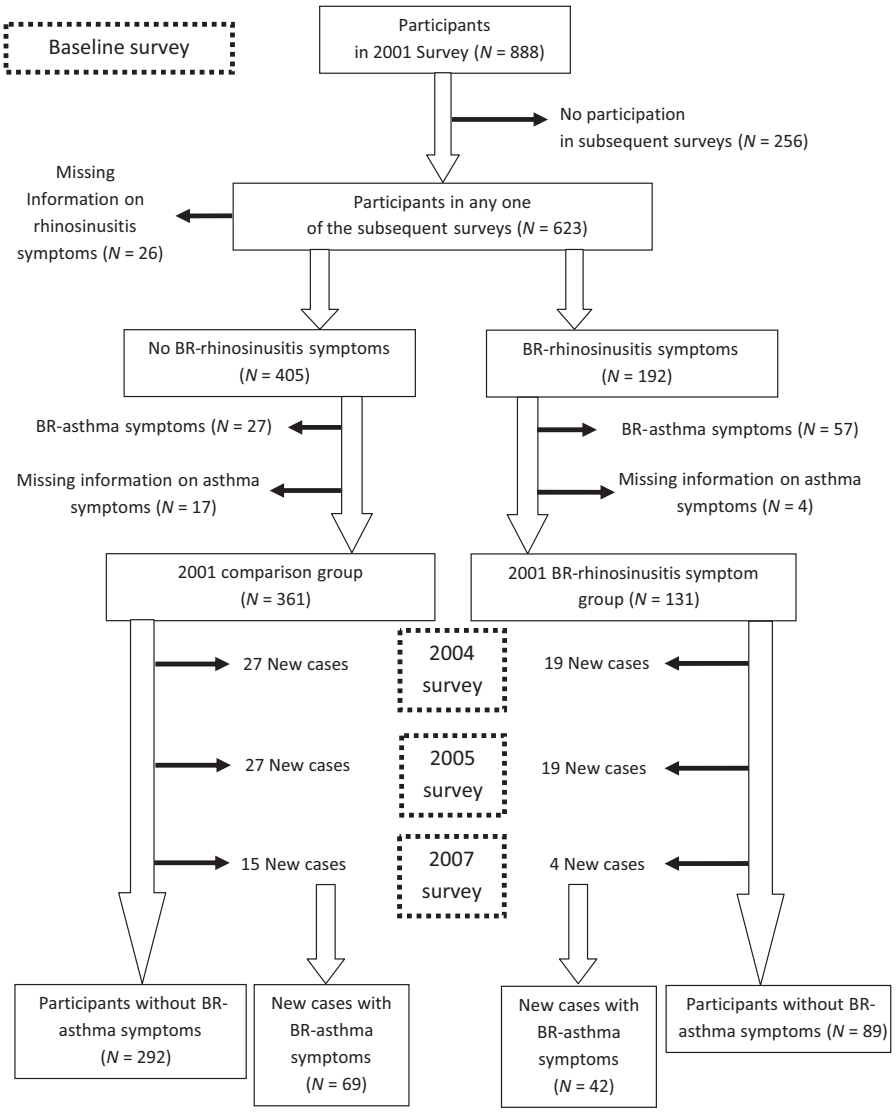

Fig. 1 Study population, identification of building-related (BR) rhinosinusitis symptom and comparison groups, and new cases of BR-asthma symptoms in two groups reported in subsequent cross-sectional surveys

we computed the arithmetic means of the five floor-specific GMs within each tertile. We created a binary fungal exposure variable by combining medium and high tertiles of the initial 2002 environmental survey into one higher-exposure group. We used this binary fungal exposure variable to examine the interaction between the exposures and the presence of BR-rhinosinusitis symptoms in the initial survey on the development of BR-asthma symptoms.

Statistical analysis

We used logistic regression models to examine the associations between the onset of BR-asthma symptoms (in 2004, 2005, 2007, or any one of these subsequent surveys; an outcome variable) and the presence of BR-rhinosinusitis symptoms in the 2001 survey (an explanatory variable). Other explanatory variables included age, gender, race (non-white vs. white), smoking status (never, former, and current smoker), building tenure, and initial survey tertile exposures to culturable fungi, ergosterol, and endotoxin in floor dust. We repeated the models matching the year of fungi, ergosterol, and endotoxin exposures to the year of the outcome variable. We performed analyses both with and without physician-diagnosed asthma cases who had reported no symptoms. We also performed logistic regression modeling with an outcome variable of current physician-diagnosed asthma in any one of the subsequent surveys. Building tenure was estimated based on an assumption that all participants in each health questionnaire survey had continuously occupied the building up to the time of the survey because we had no information on occupancy between surveys (e.g., layoffs and rehiring). We matched the values of explanatory variables of age, smoking status, and building tenure to

the year of the outcome variable being modeled. For participants who did not report BR-asthma symptoms or current asthma in any survey, we used information reported in the last survey for the explanatory variables. We repeated the modeling on the group who participated in all four surveys.

We examined multiplicative (product of two variables) and additive interactions between the initial BR-rhinosinusitis symptom status and the binary fungal exposure of the initial survey in logistic regression adjusted for other explanatory variables. To evaluate additive interaction, we constructed a categorical variable with four levels by combining the initial survey BR-rhinosinusitis symptom status and the binary fungal exposure of the initial survey.

We performed polytomous logistic regressions to examine the associations among non-BR- and BR-rhinosinusitis symptoms (explanatory variables) and asthma symptoms (a three-level outcome variable: asymptomatic, and non-BR- and BR-asthma symptoms).

To examine the potential participation bias, we used the chi-square test to compare initial survey prevalences of BR-rhinosinusitis symptoms in the follow-up survey participants and non-participants. All data analyses were performed using SAS® 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at the P-value ≤ 0.05.

Results

Characteristics of study population

Approximately 70% (623/888) of the 2001 survey participants participated in at least one of the three subsequent surveys (Figure 1). Excluding 84 participants with BR-asthma symptoms in the initial survey and 47 participants with missing information left 492 participants for inclusion in the logistic models. In the BR-rhinosinusitis symptom group, 32.1% (42/131) reported new BR-asthma symptoms, while 19.1% (69/361) of the participants in the comparison group reported such symptoms in any one of the subsequent surveys. Demographics of the 492 participants used for the analyses were similar to those of 265 non-participants in any one of the subsequent surveys (Table 1). Prevalence of BR-rhinosinusitis symptoms was similar in the non-participants (27.6%) and the participants (32.2%) in the subsequent surveys (P-value = 0.2). The demographics of the follow-up survey participants were also similar to those of all the initial survey participants (N = 888) (Cox-Ganser et al., 2005).

Prevalences of BR-rhinosinusitis and BR-asthma symptoms

In the cross-sectional surveys, 36–49% of the participants reported either BR-rhinosinusitis or BR-asthma symptoms in the last 4 weeks (Figure 2). The prevalences of BR-rhinosinusitis symptoms alone ranged from 22% to 30%, with the highest prevalence in 2004. Prevalences of BR-rhinosinusitis symptoms alone were always higher than those of BR-asthma symptoms alone. Prevalences of BR-asthma symptoms ranged from 14% to 22%, with the highest prevalence in 2005.

Table 1 Characteristics in 2001 of subsequent survey participants included in the logistic regression analyses and nonparticipants

Characteristics in 2001	Subsequent survey participants included in regression analyses (N = 492)	Nonparticipants in any one of the subsequent surveys (N = 265)
Age in year, mean ± s.d.	44.4 ± 8.1	49.4 ± 9.6
Race, %		
White	76.4	71.4
Black	14.8	19.2
Other	8.7	9.4
Sex, % female	57.1	60.2
Building occupancy in years, mean ± s.d.	6.0 ± 1.8	5.6 ± 2.2
Smoking status, %		
Current	13.8	11.3
Former	26.0	29.8
Never	60.2	58.9
Physician-diagnosed asthma ever, %	14.2	16.0
Current physician-diagnosed asthma, %	10.2	12.2

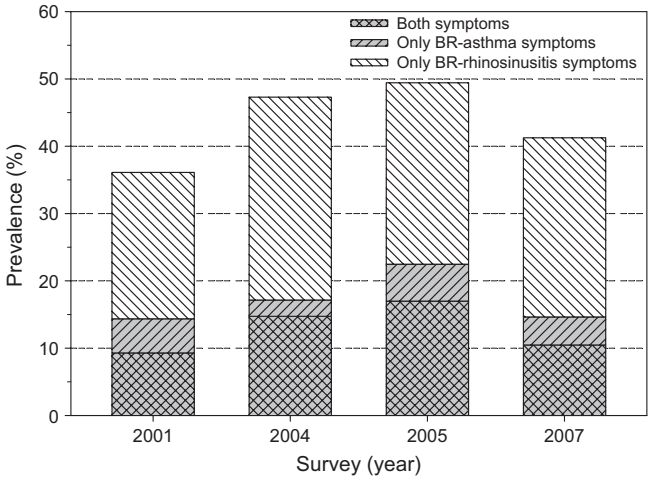

Fig. 2 Prevalence of building-related (BR)-rhinosinusitis and BR-asthma symptoms in all participants of each cross-sectional survey. Prevalence was computed by the number of people with the symptoms divided by the total number of participants (excluding those with missing information on the symptoms) for each survey and then multiplied by 100. Total number of participants is 888 in 2001, 771 in 2004, 797 in 2005, and 762 in 2007. Each type of bar in the stacked bar represents three mutually exclusive symptom groups

Risks of BR-rhinosinusitis symptom for developing BR-asthma symptoms

In unadjusted analyses, the 2001 BR-rhinosinusitis symptom group was approximately twice as likely to

develop BR-asthma symptoms in 2004, 2005, or any one of the three subsequent surveys, compared to the 2001 comparison group (Table 2). The results were similar when the models were adjusted for demographics or for both demographics and initial survey exposures to culturable fungi, ergosterol, and endotoxin (main effect model). The results were similar when we ran the same models after excluding respondents with asymptomatic asthma ($N = 80$) in 2001 (data not shown).

Using the subpopulation of 258 participants who participated in all four surveys, we performed the same analyses with the main effect regression model for the 2004, 2005, 2007, and any of the surveys. We observed the same trend of increased odds with similar magnitude of effect for developing BR-asthma symptoms in the 2001 BR-rhinosinusitis symptom group. The OR for developing BR-asthma symptoms in any of the three subsequent surveys for the 2001 BR-rhinosinusitis symptom group compared to the 2001 comparison group was 2.4 (95% CI = 1.0–5.7; $P = 0.048$).

Polytomous logistic regression analyses showed that 2001 BR-rhinosinusitis symptoms were a significant risk factor (OR = 2.4; 95% CI = 1.4–4.1) for the development of BR-asthma symptoms, but not for non-BR-asthma symptoms in any one of the subsequent surveys; on the other hand, the group with non-BR-rhinosinusitis symptoms tended to have increased, but not significant, odds (OR = 1.8; 95% CI = 0.7–4.8; $P = 0.2$) for developing non-BR-asthma symptoms, but not for BR-asthma symptoms.

We identified 20 new cases of current physician-diagnosed asthma in either the 2001 BR-rhinosinusitis symptom group or the 2001 comparison group. The 2001 BR-rhinosinusitis symptom group had twice the odds of developing current asthma in any one of the subsequent surveys than the 2001 comparison group in both unadjusted (OR = 2.0, $P = 0.14$) and adjusted (ORs = 2.0–2.1, P-values = 0.12–0.17) analyses. The size of effect was similar to that found for the development of BR-asthma symptoms, but they were not statistically significant at $\alpha = 0.05$. Among those who participated in all four surveys ($N = 258$), there were 13 new cases of current physician-diagnosed asthma. Within this subpopulation, the BR-rhinosinusitis symptom group had increased odds of developing physician-diagnosed asthma (unadjusted and adjusted ORs = 2.4–3.2), but they did not reach statistical significance at $\alpha = 0.05$ (P-values = 0.12–0.14) owing to insufficient power.

Table 2 Crude and adjusted odds ratios for developing BR-asthma symptoms by subsequent survey in the 2001 BR-rhinosinusitis symptom group compared to the 2001 comparison group

		Adjusted OR (95% CI)	
Year of follow-up survey	Crude OR (95% CI)	Demographics[a]	Demographics and Environmental Exposure[b]
2004	2.11 (1.11–4.00)*	2.00 (1.02–3.92)*	2.10 (1.03–4.31)*
2005	2.30 (1.30–4.08)*	2.26 (1.23–4.15)*	2.28 (1.19–4.36)*
2007	1.74 (0.87–3.51)	1.76 (0.85–3.63)	1.54 (0.73–3.25)
Any follow-up survey	2.00 (1.27–3.14)*	2.25 (1.39–3.66)*	2.24 (1.34–3.72)*

The 2001 building-related (BR) rhinosinusitis symptom group includes those who reported BR-rhinosinusitis symptoms but no BR-asthma symptoms in the initial 2001 survey, and the 2001 comparison group includes those who had neither BR-rhinosinusitis nor BR-asthma symptoms in the initial 2001 survey.

[a]Race, gender, age, smoking status, and building tenure.

[b]Tertile exposure (low/medium/high) based on rank order of floor-specific geometric means (per m^2 area) of culturable fungi, ergosterol, and endotoxin measured in the initial 2002 environmental survey.

*P-value <0.05.

Effect of fungal exposure and BR-rhinosinusitis symptoms on developing BR-asthma symptoms

In the main effect model with explanatory variables of 2001 BR-rhinosinusitis symptoms, demographics, and all three initial environmental exposures, increasing fungal tertile exposure significantly increased the odds of developing BR-asthma symptoms in 2004 (data not shown) and in any one of the subsequent surveys (Table 3) in an exposure-dependent manner. In this model, the odds ratio of BR-asthma symptoms from initial fungal exposure was independent of the effect of 2001 BR-rhinosinusitis symptoms. The odds ratios for fungal exposure were larger than those for 2001 BR-rhinosinusitis symptoms. However, measurements of ergosterol or endotoxin in the initial environmental survey did not increase the odds of developing BR-asthma symptoms. To increase the statistical power, we excluded the non-significant exposure variables of ergosterol and endotoxin from the main effect model, and the reduced model results showed similar trends to those of the full main effect model. In contrast to the results for initial survey fungal exposure, fungal exposure in the same year of the outcome variable showed no association with BR-asthma symptoms.

We did not find a multiplicative scale interaction ($P = 0.91$) between fungal exposure and the presence of BR-rhinosinusitis symptoms. However, we found indications of an additive interaction effect (Table 3). The odds ratio for developing BR-asthma symptoms with the presence of both BR-rhinosinusitis symptoms and higher fungal exposure within the building at the initial survey was much higher (OR = 7.4, 95% CI = 2.8–19.9) than that for the comparison group with higher exposure (OR = 3.4, 95% CI = 1.3–8.6) or that for the BR-rhinosinusitis symptom group with lower exposure (OR = 2.4, 95% CI = 0.6–10.0).

Average levels of each of the three fungal exposure groups in the initial survey were similar to those in 2004 and 2005, but the levels substantially increased in 2007. The levels of ergosterol were similar in 2002 and 2004 but increased in 2007. The endotoxin levels

Table 3 Increased odds for developing building-related (BR)-asthma symptoms in any of the subsequent surveys in relation to initial microbial exposures based on measurements in floor dust and interaction between presence of BR-rhinosinusitis symptoms and initial fungal exposure

	Odds Ratios (95% CI)		
Independent variables in the model (reference group)	Main effect model[a]	Reduced model[a]	Interaction model[b]
BR-rhinosinusitis symptoms (Comparison)	2.24 (1.34–3.72)*	2.20 (1.33–3.63)*	–
Culturable fungi (Low exposure)			
Medium	3.59 (1.46–8.83)*	3.05 (1.38–6.73)*	–
High	4.92 (1.90–12.72)*	3.47 (1.60–7.49)*	–
BR-rhinosinusitis symptoms by fungal exposure (Comparison/Lower exposure)[b]			
Comparison/Higher exposure	–	–	3.38 (1.34–8.56)*
BR-rhinosinusitis/Lower exposure	–	–	2.39 (0.57–10.03)
BR-rhinosinusitis/Higher exposure	–	–	7.40 (2.76–19.90)*
Ergosterol (Low exposure)			
Medium	0.66 (0.22–1.98)	–	–
High	0.68 (0.24–1.90)	–	–
Endotoxin (Low exposure)			
Medium	1.22 (0.47–3.17)	–	–
High	0.76 (0.30–1.95)	–	–

All models were adjusted for building tenure and demographics (age, gender, race, and smoking status).

[a]Main effect model included all three exposure variables from the initial environmental survey. Reduced model included only culturable fungi as an environmental exposure variable.

[b]For the interaction model, medium and high tertile of fungi were grouped into higher exposure for binary fungi variable. Then, the 4-level categorical variable was created by combining BR-rhinosinusitis symptom (presence/comparison) and binary fungi variable (lower/higher).

*P-value <0.05.

steadily increased until 2005 and stayed similar in 2007 (Figure 3).

Discussion

The literature has shown that the prevalence of upper respiratory symptoms is higher than that of lower respiratory symptoms or illnesses in water-damaged building occupants (Cox-Ganser et al., 2009; Park et al., 2004, 2006; Sahakian et al., 2008; Sudakin, 1998). Our analysis showed that the risk for the development of BR-asthma symptoms was higher in the group of occupants with existing BR-rhinosinusitis symptoms. Additionally, in this building population, the peak prevalence of BR-rhinosinusitis symptoms preceded the peak prevalence of BR-asthma symptoms. We had limited power for investigating the risk factors for new-onset asthma, but it is possible that BR-asthma symptoms are an indication of undiagnosed asthma or of future asthma development. Karvala and colleagues recently demonstrated that damp building occupants with only work-related asthma symptoms without objective evidence of asthma had a more than four-fold increased risk of developing asthma if exposure to damp and moldy workplaces continued (Karvala et al., 2011). In our previous work on this population, we documented a 7.5-fold increase in new-onset asthma in 2001 among occupants since building occupancy (Cox-Ganser et al., 2005) and also found that fungi in floor dust were a risk factor for post-occupancy-onset asthma (Park et al., 2008). Our findings in the present study suggest that occurrence of BR upper respiratory illness in water-damaged buildings may presage future endemic asthma. Furthermore, occurrence of BR upper respiratory illnesses in such buildings should motivate building evaluation and remediation to eliminate dampness and related exposures.

In the present study, we also found an additive interaction between the presence of BR-rhinosinusitis symptoms and fungal exposure for the development of BR-asthma symptoms. This evidence suggests that occupants of water-damaged buildings who are exposed to relatively higher levels of fungi and who have already developed rhinosinusitis have the highest risk for the development of asthma.

The linkage between upper respiratory illness and development of asthma in the general population has been reported in the literature for the past decade (Fox and Lockey, 2003; Guerra et al., 2002; Huovinen et al., 1999; Koh and Kim, 2003; Krouse et al., 2007; Togias, 2003; Volcheck, 2004). In a longitudinal study of the Finnish twin cohort with a 15-year follow-up period, Huovinen and colleagues demonstrated that subjects who reported hay fever 15 years before had 4.3-fold (for men) and 6.0-fold (for women) increased risk of developing asthma (Huovinen et al., 1999). In a nested case–control study within a longitudinal cohort, Guerra and colleagues found that rhinitis was a significant risk factor for adult-onset asthma regardless of the atopic status, and that there may be a synergistic effect of rhinitis and sinusitis on the risk of development of asthma (Guerra et al., 2002). However, little information exists about the risk of development of asthma in

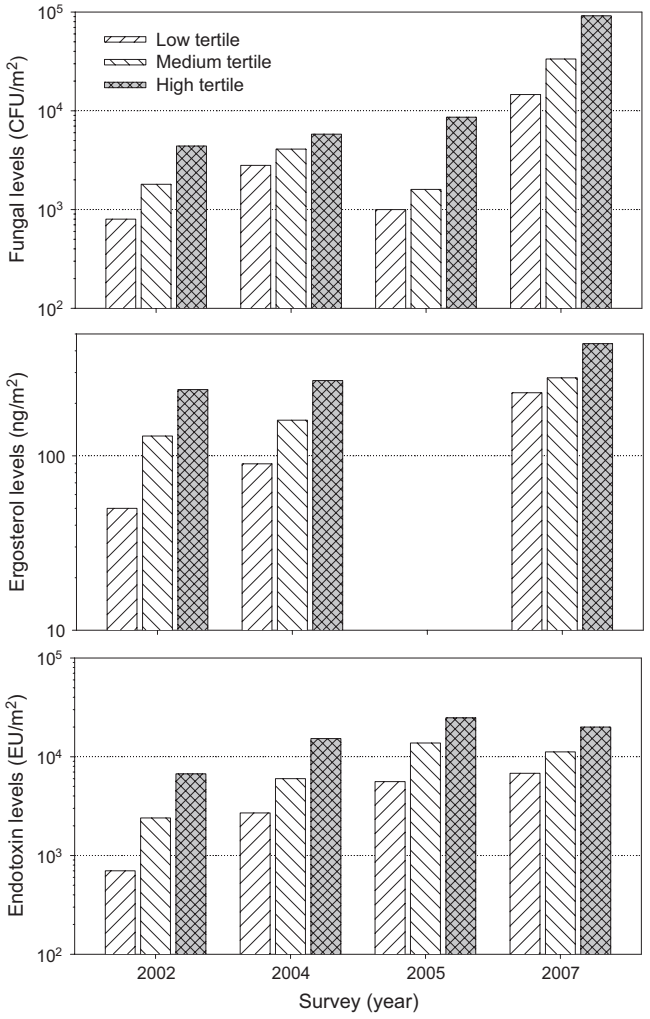

Fig. 3 Average levels of culturable fungi, ergosterol, and endotoxin by survey year and tertile exposure. Each tertile exposure category contains five floors by rank order of floor specific-geometric means of all 15 occupied floors in the building for each survey. Ergosterol was not measured in the 2005 survey. CFU, colony forming unit; ng, nanogram; EU, endotoxin unit

association with dampness and mold or other exposures in occupants who have already developed BR-rhinosinusitis symptoms. Our study indicates that the progression of BR-rhinosinusitis symptoms to BR-asthma symptoms and the progression of non-BR-rhinosinusitis symptoms to non-BR-asthma symptoms likely have independent associated exposures. Microbial or some other exposures related to the damp building environment may uniquely contribute to the progression of BR-rhinosinusitis symptoms to BR-asthma symptoms. Our findings imply that the BR exposures were not involved in the progression of non-BR-rhinosinusitis to non-BR-asthma symptoms; these latter conditions are associated with exposures outside the building.

Our previous study demonstrated that BR upper respiratory symptoms were associated with microbial exposure in occupants of this building (Park et al., 2006). Krouse and colleagues suggested that either allergic or other immunologic (non-infectious) inflammation in the upper airways occurs in rhinosinusitis (Krouse et al., 2007). Exposure to fungal or bacterial proteases may promote the development of rhinosinusitis by damaging nasal epithelium and enhancing antigen passage across the damaged epithelium (Kern et al., 2008). Fungi and bacteria also have pro-inflammatory substances on their cell walls such as $(1 \rightarrow 3)$-β-D-glucan (in fungi), endotoxin (in Gram-negative bacteria), and peptidoglycan (in Gram-positive and Gram-negative bacteria) (Greisner et al., 1998; Huttunen et al., 2003; Trinchieri, 2007), which are present in air and settled dusts in damp buildings and may produce non-allergic responses in building occupants. A 'unified airway model' suggests that pathophysiologic changes in the upper respiratory tract might also affect the lower respiratory tract or *vice versa* (Togias, 2003).

Our environmental data analysis showed that the high- and medium-exposure tertiles, based on floor-specific means of microbial agents at the initial survey, mostly consisted of upper floors, which is consistent with the information provided by building management that historical water damage persistently occurred on those floors (Cho et al., 2011). Thus, the exposure categorization for the epidemiologic analyses was likely to represent historical and relative exposures within the building, although the absolute levels of microbial agents in each tertile at the initial survey did not seem high compared to other published results (Chao et al., 2001; Hines et al., 2000). While major remediation efforts from 2002 through early 2004 did not reduce the absolute levels of exposure in the subsequent surveys, it substantially decreased the fraction of hydrophilic [requiring high water activity (A_w: free water available in a substrate), $A_w \geq 0.9$] to total fungal concentration in 2004. This remediation effect gradually diminished within 3 years, and the fraction in 2007 became higher than that in 2001 (Cho et al., 2011). However, our finding that the initial exposure, but not the subsequent exposures in any of the later surveys, was a significant predictor of BR-asthma symptoms in this subpopulation, may suggest that understanding historical exposure to dampness-related agents in water-damaged building environments is more important than recent exposure in examining natural history of current BR respiratory diseases.

Our study had limitations. Our longitudinal analysis was not based on a prospective cohort study but on multiple cross-sectional surveys of volunteer participants. We did not collect information on when participants may have left employment or rejoined the cross-sectional groups studied in 2004, 2005, and 2007. Thus, we were unable to accurately estimate person-time at risk for incidence density analysis for asthma or BR-asthma symptoms. In this series of surveys, occupants who participated in 2004 or 2005

but not in 2007 and who did not report BR-asthma symptoms or asthma diagnosis might have developed the symptoms or had the diagnosis after their last survey that we did not ascertain in 2007. Therefore, we may have underestimated the prevalence of BR-asthma symptoms or diagnosis reported in the subsequent surveys. However, such underestimation would not be likely to change our conclusions because we obtained similar results when we analyzed only respondents who participated in all four surveys. We may have had some misclassification of the health status of our study population. Some occupants with no BR-symptoms may have had upper and/or lower respiratory health effects associated with the building. For example, people with severe asthma may have had symptoms that no longer improved when away from the building. Healthy worker effects might have resulted in an underestimation of health outcomes in the later surveys because some of the occupants with BR respiratory diseases had left the building. The initial 2001 survey participation was about 70% of the total building occupants, and we lost 30% of the 70% over the three subsequent surveys. Analyses showed that the demographics and prevalences of upper respiratory symptoms were similar in non-participants and participants in the subsequent surveys among the initial respondents. We could not evaluate whether there is any difference in participation in the later surveys because of the development of lower respiratory symptoms. Participation bias is known to have an effect on incidence or prevalence estimates. It has been shown that participation bias may attenuate regression coefficient estimates in longitudinal studies (Wolke et al., 2009), and we used regression analyses to estimate the risk of progression from upper to lower respiratory symptoms. The initial environmental survey was conducted in spring, and all subsequent surveys were performed in late summer. Thus, there could be seasonal differences in pollen counts between the first survey and the others. Although we did not measure any indoor or outdoor levels of pollens, the building had non-operable windows and mechanical ventilation with high-efficiency filters that would keep the pollen levels in the building low. We feel that any seasonal allergy effect on the reporting of BR-symptoms would be minimal. If there is any exposure misclassification in assigning exposure to individuals based on their floor and the tertile of the floor-specific means, it is likely to be non-differential. Sampling locations on each floor appeared to be evenly distributed throughout all spaces within the floor in all four surveys including 2002 and 2004 when the samples were collected from workstations of 2001 participants with and without lower respiratory symptoms or diagnoses, implying that the floor-specific means are a good representation of average exposure of occupants within specific floors (Park et al., 2006). Non-differential misclassification of exposure generally attenuates the strength of association. Even with this potential attenuation, we were able to demonstrate the associations between exposure and health.

In conclusion, our study findings suggest that occurrence of BR upper respiratory illnesses such as rhinitis, sinusitis, or rhinosinusitis in damp building occupants may be a warning for increased risk of developing BR lower respiratory illnesses such as asthma in the future. This is likely to be especially true of buildings that have a cross-sectional asthma excess or increased incidence of asthma since occupancy. Occupants with rhinosinusitis might benefit from relocation to an office environment with less or no water damage. Thus, our study findings suggest that early recognition of increased BR upper and lower respiratory symptoms, identification of water infiltration and damaged areas, and timely effective remediation might have prevented the development of asthma and minimized the burden of respiratory diseases in these occupants of a water-damaged building. Prevention of further illness in other water-damaged buildings with BR respiratory symptoms and occupants with post-occupancy-onset asthma should prompt the consideration of relocation of both those with upper airway and lower airway symptoms and effective remediation before re-occupancy.

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Disclaimer

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