Evaluation of Respiratory Health among Employees in a Water-Damaged Office Building– Connecticut

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Health Hazard Evaluation Report
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NIOSH *National Institute for Occupational Safety and Health*

The employer shall post a copy of this report for a period of 30 calendar days at or near the workplace(s) of affected employees. The employer shall take steps to insure that the posted determinations are not altered, defaced, or covered by other material during such period. [37 FR 23640, November 7, 1972, as amended at 45 FR 2653, January 14, 1980].

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ACKNOWLEDGMENTS

Abbreviations

µg	Micrograms
A_w	Water activity
BR	Building-related
CFU	Colony forming units
CI	Confidence interval
EU	Endotoxin units
FEV_1	Forced expiratory volume in the 1st second of exhalation
FVC	Forced vital capacity
GM	Geometric mean
GSD	Geometric standard deviation
g	Gram
IL-8	Interleukin-8
IQR	Interquartile range
Ln	Natural logarithm
m^2	Meter squared
mg	Milligram
mg/mL	Milligrams per milliliter
mL	Milliliter
ng	Nanogram
NIOSH	National Institute for Occupational Safety and Health
OR	Odds ratio
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
SD	Standard deviation

Highlights of the NIOSH Health Hazard Evaluation

The National Institute for Occupational Safety and Health (NIOSH) received a union request for a health hazard evaluation at a state office building in Connecticut because of ongoing problems with water intrusion. The occupants were concerned about respiratory symptoms, asthma, hypersensitivity pneumonitis, and sarcoidosis in association with the building. Exposure to dampness and mold in indoor environments is a known public health hazard.

What NIOSH Did

- NIOSH investigators visited the facility in July 2001 for an initial tour of the building.
- We offered health questionnaire surveys to all employees in 2001, 2004, 2005, and 2007.
- We provided the following medical tests in 2002, 2004, and 2005 to selected groups of employees:
    - Spirometry (breathing tests)
    - Methacholine challenge testing or bronchodilator testing for asthma
    - Skin allergy testing
    - Exhaled breath condensate to test for signs of inflammation (2002)
    - Exhaled nitric oxide (for allergic asthma) (2002)
    - Nasal nitric oxide (for nasal allergy) (2005)
    - Nasal lavage to test for signs of inflammation (2005)
- We conducted environmental surveys in 2002, 2004, 2005, and 2007 and analyzed dust samples, including:
    - Culturable mold
    - Culturable bacteria
    - Endotoxin (a component of cell walls of some bacteria)
    - Ergosterol (a component of cell walls of mold)
    - Glucan (a component of cell walls of mold)
    - Actinomycetes (a bacteria sometimes associated with allergic lung disease)
    - Dog and cat allergens

What NIOSH Found

- Employees had at least twice the rate of chest symptoms and asthma compared to the U.S. population.
- Employees were 7.5 times more likely to develop asthma after starting to work in the building compared to their asthma risk before they worked in the building.
- Employees with higher exposure to mold or endotoxin had higher risk of respiratory symptoms or physician-diagnosed post-occupancy asthma compared to those with lower exposure within the building.

- Employees starting to work in the building after completion of major remediation (January 2004 or later) were less likely to report symptoms while employees starting to work in the building before completion of major remediation were persistently more likely to report symptoms.
- Employees who had medical tests in both 2002 and 2005 did not show overall improvement in respiratory health.
- There was an increased risk of developing building-related asthma symptoms in any one of the later (2004, 2005, and 2007) surveys among those who reported building-related nasal or sinus symptoms in the 2001 survey compared to those who did not report building-related nasal or sinus symptoms.
- There were lower microbial levels in 2004 and 2005 compared to 2002 following major remediation, but higher levels in 2007.
- There was a lower proportion of hydrophilic (water-loving) fungi among all fungi following remediation in 2004, but the proportion increased in 2005 and 2007, consistent with recurrent water incursion.

What Managers Can Do

- Initiate a routine maintenance program for evaluation of water damage in the building, including regular observational assessment of water stains, mold growth, mold odors, and dampness, and systematic evaluation of window leaks, roof leaks, and functionality of exterior walls.
- Promptly repair all water incursions once they are identified.
- Ensure proper housekeeping procedures and establish regular maintenance schedules.
- Use proper containment measures during water damage remediation and building repairs.
- Keep building occupants updated with information regarding environmental and health issues in the building.
- Initiate ongoing medical surveillance for building-related disease.
- Relocate occupants with building-related chest and nasal symptoms.

What Employees Can Do

- Promptly report water incursions and other building problems to management.
- Report persistent symptoms associated with being in the building environment to management and seek medical evaluation for diagnosis and management, including consideration of restriction from working at implicated workstations or in the building.

SUMMARY

NIOSH found that indices of water damage, such as mold and endotoxin concentrations in vacuumed dust,were associated with building-related respiratory symptoms and asthma. Remediation efforts temporarily lowered water damage indices but did not result in improved health in those employees already affected. Medical surveillance can motivate relocation of affected employees. Ongoing water incursion may be partly due to the pre-1987 building design which did not include a continuous drainage plane behind the brick veneer.

In July 2001, NIOSH received a health hazard evaluation request from a local union representing employees at a state office building in Connecticut. There had been reports of asthma, hypersensitivity pneumonitis, and sarcoidosis occurring among occupants in the building. The building, which had a reported history of water incursion and damage, was originally built in 1985 and purchased by the state of Connecticut from a private company in 1994. Two agencies had been in the office building since the building was purchased, with Agency A occupying the 5th, 6th, and upper floors (14th–20th) and Agency B on the lower floors (7th–12th floors). In 2005, another state agency, Agency C, relocated to the 6th floor of the building. The first four floors are used for parking.

NIOSH conducted an initial health survey in 2001 and medical and environmental surveys in 2002. After these surveys, the building underwent major remediation between 2002 and early 2004, with additional remediation through 2007. After major remediation was completed, NIOSH conducted the first follow-up health questionnaire survey in 2004 and two additional follow-up surveys in 2005 and 2007. NIOSH also performed follow-up medical surveys in 2004 and 2005 on a subset of employees, and conducted follow-up environmental evaluations in 2004, 2005, and 2007. NIOSH invited all occupants to participate in the health questionnaire surveys offered in 2001, 2004, 2005, and 2007.

Results of the 2001 health questionnaire survey indicated elevated prevalences of asthma and lower respiratory symptoms in the building compared to national and state data. There was a 7.5 times increased incidence of adult-onset asthma after building occupancy compared to before occupancy. Some occupants reported new-onset sarcoidosis and hypersensitivity pneumonitis. From the initial 2001 health and 2002 environmental surveys, NIOSH found that occupants with relatively higher exposure to fungi or endotoxin (a cell wall component of Gram-negative bacteria) in the building had a greater risk of respiratory symptoms and post-occupancy physician-diagnosed asthma in an exposure-dependent way, and that occupants with exposure to both higher mold and higher endotoxin levels in the building had an even greater risk of respiratory illnesses than the summation of the individual risks of higher mold and higher endotoxin concentrations.

Throughout the follow-up surveys conducted after the major remediation was completed, NIOSH continued to find elevated

rates of symptoms and disease in the building. Rates of lower respiratory symptoms and asthma remained elevated when compared to national and state data. However, the new onset of diseases such as asthma, hypersensitivity pneumonitis, and sarcoidosis appeared to decline after 2001 or 2002. Respiratory and non-respiratory complaints were higher among occupants who had worked in the building for longer time periods (hired prior to 2004), compared to occupants with shorter occupancy times (hired in 2004 or later). In general, we observed no overall improvement in respiratory health, as reflected in symptom scores, overall medication use, spirometry abnormalities, or sick leave when we compared 97 employees' paired medical data from 2002 and 2005. In addition, occupants who reported building-related nasal or sinus symptoms in the 2001 survey had a higher risk of developing building-related lower respiratory symptoms (wheeze, chest tightness, attacks of shortness of breath, cough, or awakened by an attack of breathing difficulty) in any one of the three follow-up surveys. In this repeated measurement analysis, data suggest that employees with rhinosinusitis symptoms that were not associated with building occupancy did not have an increased risk of building-related asthma symptoms.

The levels of total culturable fungi in the building decreased in 2004 and 2005 compared to 2002 levels, but increased in 2007. This increase in 2007 occurred on all 15 occupied floors and was mostly attributable to an increase in hydrophilic fungi (fungal group requiring high moisture content to survive and grow on substrates). Repeated measurement analysis showed a significant effect of remediation in floor dust levels in 2004 and 2005 for total and hydrophilic fungi and for endotoxin in 2004, after major remediation was completed between 2002 and early 2004. However, this remediation effect disappeared in 2007, which suggests inadequate ongoing remediation.

In summary, this office building with a long history of water incursion is associated with excess respiratory disease among employees. Extensive remediation of water damage temporarily lowered indices of microbial contamination but the building continued to have recurrent water incursion in 2007 and 2008 as documented in consultant reports. Although new employees occupying the building between 2004 through 2007 had fewer respiratory complaints, previously affected employees, on average, did not regain their respiratory health. Employees should seek medical guidance quickly if they develop symptoms. Ongoing medical surveillance can provide health data to guide management decisions about relocation of affected employees and risk

management of continued building occupancy in relation to remediation and productivity costs.

Keywords: NAICS 921130, 922190, 923130 (Public Finance Activities; Other Justice, Public Order, and Safety Activities; Administration of Human Resource Programs), indoor air pollution, indoor air quality, mold, endotoxin, asthma, hypersensitivity pneumonitis, sarcoidosis, dampness, water damage

INTRODUCTION

On July 17, 2001, the National Institute for Occupational Safety and Health (NIOSH) received a health hazard evaluation request from the Administrative and Residual Employees Union representing employees at a state office building in Connecticut. In response to this request, NIOSH investigated respiratory diseases perceived to be work-related among building occupants. This final report presents the findings and recommendations from the initial survey in September 2001 and all subsequent medical and environmental surveys done by NIOSH at this building from April 2002 through August 2007 and will serve to closeout this evaluation.

The building was constructed in 1985 and has been owned and managed by the state since 1994. The building houses three state agencies: Agency A, Agency B, and Agency C. Agencies A and B moved into the building shortly after it was purchased by the state, and Agency C moved to the building in 2005. The facility is a 20-floor office building with parking garages on the bottom four floors and a lobby/cafeteria/mezzanine area on the 5th floor. Agency B occupies the lower floors (floors 7–12) while Agency A is on the 5th, 6th and upper floors (floors 14–20). Since 2005, Agency C employees have also occupied the 6th floor. On average, approximately 1,300 people work in the building.

Since 1994, employees working on the 15 occupied floors of the building have reported recurrent water damage and respiratory health complaints. The building had problems with water incursion through leaks in the roof, around windows, and through the sliding doors of terraces on the upper floors. There had been plumbing leaks on many floors, which had damaged interior walls. The building was found to be operating at negative pressure relative to the outdoors, which may have exacerbated water incursion. Water damage and mold contamination were worst on the upper floors. Some individuals had been diagnosed with post-occupancy onset asthma, hypersensitivity pneumonitis, or sarcoidosis and had been temporarily relocated to another facility. Hypersensitivity

pneumonitis is a lung disease in which the immune system reacts with inhaled microorganisms, forming inflammation or scars called granulomas. Cases of the disease sometimes co-exist with cases of asthma in damp office buildings. Sarcoidosis is an immune-mediated granulomatous multisystem disease of unknown cause.

Internal and external repairs to the building began prior to the health hazard evaluation request in 2001, but major remediation was undertaken in 2002 and considered complete by early 2004. Additional remediation continued through 2007 as intermittent water incursion had occurred after the major remediation. Between 2000 and 2002, carpets and partitions were cleaned, water-stained walls and carpets were replaced, wallpaper and any underlying mold in the bathrooms were removed, and high-efficiency filters were added to the heating, ventilating, and air conditioning system. Major remediation on the building envelope was done between 2002 and early 2004. By the end of 2003, a 7.5 million dollar repair to the exterior of the building had been completed, which included repairing the building envelope and replacing the roof and sheetrock. An environmental management system to control mechanical systems was also added in 2004. Finally, a systematic cleaning of all floor surfaces and furnishings was accomplished with high-efficiency particulate filter vacuums in early 2004.

After receiving the health hazard evaluation request in July 2001, NIOSH performed an initial health questionnaire survey in September 2001, an environmental evaluation in April 2002, and medical testing in June 2002. After completion of major repairs, NIOSH returned for three follow-up health questionnaire and environmental surveys in August 2004, 2005, and 2007. Since 2001, NIOSH investigators have provided results, scientific findings, and recommendations through 12 interim reports/letters to both management and union officials based on observations and cross-sectional and repeated measurement analyses on health questionnaire, medical, and environmental data. These interim reports are available upon request from NIOSH's Division of Respiratory Disease Studies in Morgantown, West Virginia.

The purposes of this final report are: 1) to summarize and discuss the findings from our evaluations during this six-year period (2001–2007); 2) to inform how the health status of occupants and the building environment changed over this period of time; and 3) to examine the impact of remediation in terms of occupant health and environmental indices. We also make recommendations on assessing the occupants' ongoing health and monitoring the building environment.

Health Questionnaire Surveys

We conducted four cross-sectional health questionnaire surveys in 2001, 2004, 2005, and 2007 (Figure 1). To ascertain the health status of employees in the building, all persons working in this state office building were invited to participate in each of the four surveys. In 2007, we also invited current employees who had participated in an earlier survey and were now working at another location to participate. In the first two surveys (2001 and 2004), NIOSH staff supervised self-administered paper versions of the questionnaire in small groups. In 2005 and 2007, the questionnaire was self-administered electronically and run from a secure site at the Centers for Disease Control and Prevention in Atlanta, Georgia. If employees did not have Internet or e-mail access, we mailed each of them a paper copy of the questionnaire. All surveys included questions on health symptoms in the last 12 months and 4 weeks, if the symptoms changed when away from the building, medical diagnoses, demographic and smoking information, and work history. We defined building-related symptoms as those that improved when away from the building. Later surveys (2004–2007) included additional questions on the number of work days lost due to respiratory and non-respiratory problems, perceptions about the building's environment, and on the home environment. In the 2007 questionnaire, we included a module on quality of life, which contained questions from the SF-12® Health Survey, and questions regarding medication use for upper and lower respiratory symptoms. Questions on health symptoms and medical diagnoses in the NIOSH questionnaires were derived from the American Thoracic Society standardized respiratory symptom questionnaire, the 3rd National Health and Nutrition Examination Survey, and the Environmental Protection Agency Building Assessment Survey and Evaluation (questionnaires available upon request). Non-participant surveys were done in both 2004 and 2007 to assess responder bias.

Medical Surveys

Selection of Invitees for Medical Surveys

We conducted medical surveys, which included an extended health questionnaire and medical testing, in 2002, 2004, and 2005, but not in 2007 due to the low participation rate during the 2005

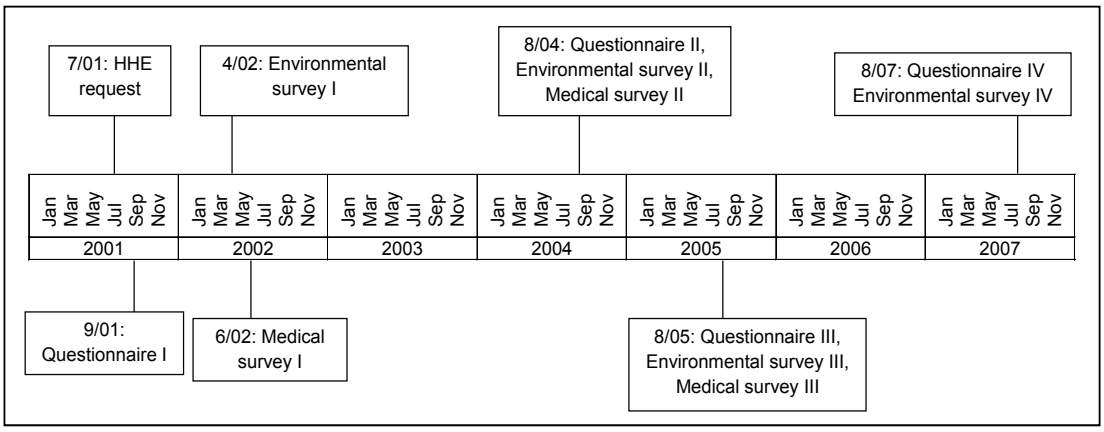

Figure 1. Timeline of health questionnaire, medical, and environmental surveys.

survey (Figure 1).

We selected respiratory case and comparison groups based on the responses to the initial health questionnaire survey in 2001 and invited them to participate in the June 2002 medical survey. We defined the respiratory case group as those participants who reported one or more of the following: three or more of five asthma symptoms (wheeze, chest tightness, attacks of shortness of breath, coughing, and awakened by an attack of breathing difficulty) occurring weekly in the last 4 weeks; two or more hypersensitivity pneumonitis symptoms (fever and chills, flu-like achiness or achy joints, and shortness of breath hurrying on the level or walking up a slight hill) occurring weekly in the last 4 weeks; current physician-diagnosed asthma occurring after building occupancy; or physician-diagnosed hypersensitivity pneumonitis or sarcoidosis. We defined the comparison group as having none of the symptoms listed above in the last year, nor any of the specified diagnoses. On the basis of these criteria, we identified 202 employees who met the case definition and 154 employees who met the comparison group definition. The extended health questionnaire was administered by a trained interviewer on a computer and included questions on health symptoms and medical diagnoses, an extensive module on medication use, quality of life questions from a standardized questionnaire (SF-12 Health Survey), home and work environment, work history, demographic questions, and smoking history (questionnaires available upon request). The 2002 medical testing included spirometry, methacholine challenge testing or bronchodilator testing, allergen skin prick testing, exhaled nitric oxide, and exhaled breath condensate, which are detailed below.

In 2004, the cases and comparison group employees originally invited to participate in the 2002 medical survey, and still currently employed in the building, were offered a repeat extended health questionnaire and medical testing (spirometry, methacholine challenge testing or bronchodilator testing, and allergen skin prick testing, which are detailed below). Fifteen employees who had not been part of the original invitees, but who had volunteered to take part in the 2002 survey, were also invited in 2004.

In 2005, an extended health questionnaire and the same medical testing as in 2004 was offered to the cases and comparison group employees defined in the 2001 survey and still currently employed in the building, employees who had not been part of the original invitees, but who had volunteered to take part in the 2002 and 2004 surveys, and participants in the 2004 health questionnaire survey who met the respiratory case or comparison group definitions. We also randomly selected 300 employees (about 20 employees on each floor of the building) to participate in the extended health questionnaire, allergen skin prick testing, and two additional tests–nasal nitric oxide and nasal lavage, which are detailed below. Of these 300 employees, 139 were part of the group offered all medical tests.

Written informed consent was obtained from each subject before each medical visit. All medical tests were approved by the NIOSH Human Subjects Review Board.

Spirometry

NIOSH technicians performed spirometry tests (breathing tests) using a dry rolling-seal spirometer interfaced to a personal computer and following American Thoracic Society guidelines (ATS 1995), with an abnormal test result being defined as being below the lower limit of normal (Hankinson et al. 1999). Each participant's largest FVC and FEV_1 were selected for analysis. Obstruction was defined as an FEV_1/FVC ratio and FEV_1 below the lower limits of normal with a normal FVC. Borderline obstruction was defined as an FEV_1/FVC ratio below the lower limits of normal with a normal FEV_1 and FVC. Restriction was defined as an FVC below the lower limit of normal with a normal FEV_1/FVC ratio. A mixed pattern (obstruction and restriction) was defined as an FEV_1/FVC ratio, FEV_1, and FVC below the lower limits of normal. Employees with evidence of airways obstruction or a mixed pattern were administered albuterol; a bronchodilator medication used to treat obstructive lung diseases such as asthma,

and were then re-tested to see if the obstruction was reversible. Reversible obstruction was defined as an improvement in the FEV_1 of at least 12% and at least 200 mL after administration of albuterol.

Methacholine Challenge Testing

The methacholine challenge test measures the presence and degree of non-specific bronchial hyper-reactivity which is common among persons with asthma. To detect bronchial hyper-reactivity, methacholine challenge testing was performed using standardized techniques (Crapo et al. 2000) with five different doses (0.125, 0.5, 2.0, 8.0, and 32.0 mg/mL) of methacholine. Five breaths of nebulized methacholine were administered for each dose, starting with 0.125 mg/mL, and spirometry was measured after the fifth breath. If the highest FEV_1 after any dose was greater than 80% of the highest baseline FEV_1, the next higher dose of methacholine was administered. If FEV_1 dropped more than 20% of the baseline value, no further methacholine was given. We calculated the provocative concentration of methacholine that causes an interpolated 20% decline in FEV_1 from baseline (PC_{20}). Categories of bronchial hyper-reactivity were defined as follows (Crapo et al. 2000):

- PC_{20} less than or equal to 4.0 mg/mL – bronchial hyper-reactivity
- PC_{20} between 4.1 and 16.0 mg/mL – borderline bronchial hyper-reactivity
- PC_{20} greater than 16 mg/mL – normal

Skin Prick Testing

Skin prick allergy testing was done with commercially available extracts of seven common indoor and outdoor allergens: dust mite mix, German cockroach, cat hair, grass mix, ragweed mix, common weed mix, and Eastern tree mix. In addition, we tested for sensitivity to three commercially available mold mixes: *Dematiaceae*, *Aspergillus*, and *Penicillium*. The Greer DermaPIK method was used for the skin allergy testing. The Greer DermaPIK is a plastic, single use device with six tiny tines arranged at the tip in a 2 millimeter circle for epicutaneous allergy skin testing. The allergens were placed on the forearm of the subject, along with a positive (histamine) and negative control (glycerin in water). After

15 minutes, each response wheal length and width was measured to the nearest millimeter and recorded. For each wheal, the mean diameter (average of the length and width) was calculated. A positive reaction to an allergen was defined as an average diameter at least 3 millimeters larger than the negative control and greater than 25% of the average diameter of the positive control. For the purposes of this study, atopy was defined as at least one positive skin test on allergy testing (excluding the mold mixes).

Exhaled Nitric Oxide

Nitric oxide gas, produced by various cells within the respiratory tract, is detectable in the exhaled air. In persons with poorly controlled allergic asthma, exhaled nitric oxide concentrations are high. Nitric oxide was measured off-line using standardized techniques (ATS 1999), and the procedure has been documented elsewhere (Akpinar-Elci et al. 2008). For this report we compared mean levels between participants based on symptomatic status. We also used a cut-off point of 9 parts per billion or greater as higher than normal (Kharitonov et al. 1997). However, the upper limit of normal exhaled nitric oxide has not yet been established.

Exhaled Breath Condensate

Exhaled breath condensate testing was being evaluated as a noninvasive way of measuring inflammation in the airways. Exhaled breath condensate was collected over a 15 minute period from subjects using previously published techniques (Mutlu et al. 2001). We measured IL-8 and nitrite in the exhaled breath, which may represent biomarkers of pathological processes such as inflammation in the lungs (Kharitonov and Barnes 2001). Nitrite was measured per manufacturer's recommendations using an ozone chemiluminescence nitric oxide analyzer (Model 280, Sievers, Boulder, Colorado), and IL-8 was measured using a chemiluminescent immunoassay (QuantiGlo, R & D Systems, Minneapolis, Minnesota).

Nasal Nitric Oxide

In 2005, we tested for nasal nitric oxide to look for inflammation in the upper respiratory airways. Nasal nitric oxide was measured on-line using standardized techniques with a rapid-response chemiluminescence analyzer (Sievers Instruments model 280,

Boulder, Colorado) according to the 2005 American Thoracic Society guidelines (ATS 2005). Three measurements were recorded from each nostril. A two-point calibration was done each day using nitric oxide-free gas and 45 parts per million nitric oxide precision gas. We asked pre-test questions to exclude possible confounding factors for nitric oxide measurements such as smoking within the last hour, any nitrate containing food within the last two hours, or having a recent respiratory infection. We rescheduled those who had a positive response to any one of these confounders. Subjects completed five repeated humming maneuvers, immediately before measurement. A latex nasal olive connected to a filter and a respirator tube with a connector was gently introduced into the right naris. Each subject closed his/her velum by holding his/her breath throughout the measurement. Room air entered through the left nostril and was aspirated from the right nostril at 5 liters per minute constant transnasal flow. To achieve a plateau of nasal nitric oxide, 20 to 30 seconds of breath holding was sufficient (ATS 2005; Maniscalco, Sofia et al. 2003; Maniscalco, Weitzberg et al. 2003; Vural et al. 2002).

Nasal Lavage

We also conducted nasal lavage (washing) testing in 2005 to determine if markers of inflammation were associated with self-reported symptoms in subjects. We used collection methods for nasal lavage fluid as described by Hirvonen et al. (1999). Fluid recovered in the collection plate from the nares was combined and the volume was measured. Nasal lavage fluids were centrifuged for 10 minutes at a relative centrifugal force of 600 x gravity. The supernatant fluids were separated from the cell pellets, divided into aliquots, and frozen on dry ice for shipment back to the laboratory. In the laboratory, the supernatant fluids were stored at -80 degrees Celsius until analysis. Cell pellets were suspended in 30 mL Cytolyte® (Cytyc Inc., Marlborough, Massachusetts), and stored at 4 degrees Celsius. Cell /Cytolyt® samples were vortexed for 10 minutes and then centrifuged for 10 minutes at 600 x gravity. Cell pellets were resuspended in 20 mL Preservcyt®(Cytyc Inc.) and cytology slides made using a Thin Prep Processor®(Cytyc Inc.) using the mucoid sample setting. The volume of sample transferred to the glass slide was recorded. Slides were stained (Diff Quick Stain Kit, IMEB Inc., San Marcos, California), and inflammatory cells were counted on > 20 visual fields. Counts for each cell type were adjusted for fraction of total sample used, area of the visual field, and total area of the cytology spot to provide a semi-quantitative assessment of nasal inflammatory cell content.

Albumin (Bethyl Labs, Montgomery, Texas), myleoperoxidase (Assay Designs, Ann Arbor, Michigan), IL-8 (R&D, Minneapolis, Minnesota – chemiluminescent ELISA), and eosinophilic cationic protein (Phadia AutoCap (CAP) System, formerly Pharmacia, Uppsala, Sweden) immunoassays were performed according to the manufacturer's instructions on each nasal lavage supernatant fluid, in duplicate.

Reporting of Individual Medical Testing Results

After each medical survey, letters providing individual test results and interpretations of spirometry, methacholine or bronchodilator testing, and skin prick testing were mailed to each participant's home address. For individuals with abnormal results, guidance and recommendations for additional medical follow-up were provided.

Environmental Surveys

We conducted environmental sampling at four different time points during the study period: April 2002, August 2004, August 2005, and August 2007. Additionally, in December 2001, we collected carpet dust samples from the 17th floor, just prior to the carpet being replaced to compare levels of microbial agents in the new carpets to the old carpets. In April 2002, we collected both carpet and chair dust samples from workstations of 338 case and comparison group employees, including re-sampling the 17th floor. If a case or comparison group employee had moved during the past 12 months, we also collected a sample from the employee's previous workstation. In August 2004, we collected dust samples from the workstations of the 2002 case and comparison groups if they were still employed in the building (n = 279). Before the 2004 survey, we received current seating plans from the agencies and compared the employee names we had from the previous 2002 survey for the selected locations. If a selected employee had changed workstations, we changed our sample to the new location. In August 2005, we randomly selected 300 workstations stratified by floor and collected floor dust samples if the selected workstations were occupied. In August 2007, we re-sampled 150 of the 300 locations sampled in 2005. Information on the number of workstations by floor is detailed in Table 1. The number of workstations with repeated samples by floor during the four environmental surveys is shown in Table 2.

Table 1. Number of sampled workstations by floor and survey*

Floor	Total no. of unique sampled workstations over four surveys†	No. of sampled workstations in the 2002 survey	No. of sampled workstations in the 2004 survey	No. of sampled workstations in the 2005 survey	No. of sampled workstations in the 2007 survey
Total	689	338	279	297‡	150
5	24	4	6	20	4
6	60	30	23	21	10
7	55	30	22	21	11
8	39	21	16	19	11
9	53	26	22	21	12
10	51	28	25	21	10
11	40	16	15	21	11
12	44	19	14	21	10
14	57	30	23	20	10
15	54	27	25	20	10
16	32	8	7	21	10
17	79	58	46	21	14
18	50	20	20	21	12
19	44	20	14	22	12
20	7	1	1	7	3

*** No workstation was sampled more than once in any given survey year.**
† Workstations sampled at least once during the four surveys.
‡ We were not able to identify correct workstations for three employees.

Table 2. Number of sampled workstations by number of replicate samples and floor*

Floor	Total no. of unique sampled workstations over four surveys†	No. of sampled workstations with one sample	No. of sampled workstations with two replicate samples	No. of sampled workstations with three replicate samples	No. of sampled workstations with four replicate samples
Total	689	379	261	33	16
5	24	15	8	1	0
6	60	38	20	2	0
7	55	30	22	2	1
8	39	19	14	4	2
9	53	32	17	1	3
10	51	22	26	2	1
11	40	20	18	1	1
12	44	28	14	0	2
14	57	35	18	4	0
15	54	30	21	2	1
16	32	20	10	2	0
17	79	31	37	10	1
18	50	30	18	1	1
19	44	25	16	1	2
20	7	4	2	0	1

*** No workstation was sampled more than once in any given survey year.**
† Number of dust samples taken from the same workstation across the four surveys.

In 2002 and 2004, both chair and floor dust samples from each workstation were collected. In 2005 and 2007 only floor dust samples were collected.

In the 2002, 2004, and 2007 environmental surveys, floor or chair dust was collected onto polyethylene filter socks (Midwest Filtration Company, Fairfield, Ohio) with a crevice tool and a L'il Hummer™ backpack vacuum (100 CFM, 1.5 horse power, Pro-Team Inc., Boise, Idaho). Each crevice tool for an individual sampling location was cleaned with isopropyl alcohol before sampling. For each sampling location, one chair (seat, back support, and armrest) was vacuumed for 3 minutes and a 2 m^2 carpeted floor area within the workstation (around where the chair was located) was vacuumed for 5 minutes using different crevice tools. The samples were sealed in plastic bags and transported to the laboratory where collected dusts in the filter socks were emptied into 50 mL pyrogen-free conical tubes. Hair, fluff, and other larger objects were removed from the samples, which was then homogenized by rotation on a 360-degree rotary arm shaker at 65 rotations per minute for 2 hours. The dust samples were then weighed, partitioned, and sent for analyses of culturable fungi, endotoxin, ergosterol, cat allergen, and dog allergen. The samples for fungi were cultured with malt extract, dichloran glycerol 18, and cellulose agars at room temperature for 7–10 days. Total culturable fungi were reported as CFU per mg dust and also per m^2 (for floor samples) or per chair (for chair samples) by multiplying the resulting CFU per mg value by the total amount of dust collected in each floor (or chair) sample and then dividing by 2 m^2 for floor samples. Dog and cat allergens were analyzed with an enzyme-linked immunosorbent assay, and reported as µg per mg dust, and also as per m^2 or per chair. Endotoxin samples were analyzed with the Limulus amoebocyte lysate assay using kinetic QCL methods (Chun et al. 2002), and the results were reported as EU per mg dust, and also as per m^2 or per chair. Ergosterol was analyzed with gas chromatography-mass spectrometry and reported as ng per mg dust, and also as per m^2 or per chair. In 2005, we used the High Volume Small Surface Sampler to collect floor dust in the cyclone catch cup from 2 m^2 carpeted areas. The collected dust samples in 2005 were processed in the same way as above and analyzed for all the microbial agents except for ergosterol. The 2005 and 2007 dust samples were also analyzed for (1→3)-β-D-glucan and culturable bacteria [Gram-positive and Gram-negative bacteria].

We reviewed 12 unpublished building assessment reports by environmental consultants and newsletters by the building

management since 2000 to obtain historical information on water damage and remediation. We defined remediation activity as elimination of sources of water infiltration, such as building exterior (window and balcony) repairs and roof coping or replacement, or replacement of water-damaged materials such as carpet and wallboard. Building exterior repairs around window openings included construction activities, such as brick caulking, window flashing, parapet coping, and plastic barrier repair. We did not include surface cleaning as a type of remediation because a thorough cleaning was done on all the floors of the building in 2004. We considered an employee's workstation as "remediated" if the workstation was within 15 feet of a remediated section of exterior or interior walls. We considered all workstations on the floor as "remediated" where an entire floor carpet was replaced. All the workstations on the 19th and 20th floors directly underneath the roof were considered "remediated" when the roof was replaced or repaired. We used a linear regression model that accounted for correlation of repeated measurements within the same sampled workstations across the surveys to examine remediation effectiveness on total and hydrophilic levels of culturable fungi, including the fraction of hydrophilic fungi, as well as endotoxin and cat and dog allergens (Cho et al. 2011).

Statistical Analysis

Since participants may have reported different dates of diagnoses, dates of birth, and building occupancy dates in different questionnaires, the dates used for our analyses were set taking into account all dates reported. The date reported most frequently in the questionnaires was the one used. If there was not one date reported most frequently, we used the date given in the earliest questionnaire completed.

Definitions of Health Outcomes

We defined epidemiological asthma ("epi-asthma") as having either post-occupancy current asthma or having at least three or more lower respiratory symptoms (wheeze, chest tightness, coughing, attacks of shortness of breath, or being awakened by an attack of breathing difficulty) at least once a week in the last 4 weeks. We defined "asthma symptoms" as having two or more lower respiratory symptoms occurring one or more times per week in the last 4 weeks, and "BR asthma symptoms" as asthma symptoms with at least one symptom which improved when away from the

building. Hypersensitivity pneumonitis symptoms ("hypersensitivity pneumonitis-like symptoms") were defined as having two or more of the following: fever and chills, flu-like achiness or achy joints, or shortness of breath while hurrying on the level or walking up a slight hill ("shortness of breath on exertion") at least one or more times per week in the last 4 weeks. Nasal symptoms included stuffy, itchy, or runny nose, or sneezing, and sinus symptoms consisted of sinusitis or sinus problems. "Rhinosinusitis symptoms" consisted of one or more nasal or sinus symptoms occurring at least once every week in the last 4 weeks. We defined "BR rhinosinusitis symptoms" as rhinosinusitis symptoms with at least one symptom which improved when away from the building.

Cross-Sectional Data Analysis

For the health questionnaires in all four survey years, we compared lower respiratory, nasal, sinus, and eye symptoms, as well as physician-diagnosed asthma, to data from the U.S. adult population based on the third National Health and Nutrition Examination Survey (CDC 1996). We also compared asthma prevalences to the adult population in Connecticut, based on data from the Behavioral Risk Factor Surveillance System (CDC 2007). Finally, we compared the prevalence of work-related symptoms occurring weekly in the last 4 weeks to U.S. office workers in buildings without known indoor air quality problems (Environmental Protection Agency Building Assessment Survey Evaluation study) (Erdmann and Apte 2004; Brightman et al. 2008). We calculated 95% CIs using a method which assumes that the observed data are from a Poisson distribution (Kahn and Sempos 1989). The results and discussion of these analyses have been sent to requestors as interim letters and reports which are available upon request.

Major remediation was reportedly completed by early 2004. Thus, we examined whether remediation had an impact on the health status of employees. We compared the prevalence of symptoms in two groups of employees using 2005 and 2007 health questionnaire survey participants–persons who were in the building prior to January 2004 (long-term), and those who came to the building in January 2004 or later (short-term).

For environmental and epidemiologic analyses, we grouped culturable fungi into either "hydrophilic fungi" ($A_w \geq 0.9$, A_w: the amount of free or available water in substrates), "mesophilic fungi" ($0.8 \leq A_w < 0.9$), either "hydrophilic or mesophilic" ($A_w \geq 0.8$),

or "other fungi" (not meeting either mesophilic or hydrophilic classifications) (Burge and Otten 1999; Flannigan and Miller 2001; Grant et al. 1989).

We examined the association between exposure to microbial agents in the building and employees' respiratory illnesses. For the cross-sectional epidemiologic analysis using all 888 initial 2001 health questionnaire participants, we calculated floor averages for fungal and endotoxin measurements and ranked them into tertiles (low, medium, or high exposure floors). Then, we assigned participants from the 2001 questionnaire to one of the tertiles based on the floor they spent the majority of their time on, since not all participants had individual workstation measurements (Park et al. 2006). We used logistic regression models, adjusting for age, gender, race, smoking status, and tenure in the building.

We performed an additional analysis using only 323 participants who met the respiratory case or comparison group definitions (as defined above) from the 2001 survey. In this analysis, we used individual workstation measurements for fungi, endotoxin, ergosterol, and cat and dog allergens as their personal exposures (Park et al. 2008). We used logistic regression models, adjusting for age, gender, race, smoking status, and tenure, using both single and multiple microbial measurements as exposures of interest in the model.

To determine adult-onset asthma incidence rates in the years before and after major remediation was completed, we did an incidence rate analysis using the 2007 cross-sectional survey participants and calculated person-time at risk for three different time periods: from 16 years of age to building occupancy, from building occupancy to January 1, 2004 (when major remediation was reportedly completed), and from January 1, 2004 to the 2007 survey date. For participants with physician-diagnosed adult-onset asthma, time at risk ended on the month and year of diagnosis. Participants with childhood asthma (diagnosed before age 16) did not contribute any time at risk.

We also used logistic regression models to analyze results from the 2007 questionnaire and environmental surveys. As we did for the 2001/2002 cross-sectional study analysis, we assigned all 2007 health questionnaire survey participants to low, medium, or high exposure tertiles, based on the floor where they spent the majority of their time. We adjusted the models for the same parameters, with the exception of race, which wasn't significant in the final model.

Repeated Measurement Data Analysis

To evaluate trends in symptom prevalence over time among those who participated in all four surveys, we used repeated measure models to identify significant differences between survey years.

To evaluate trends of newly reported cases, we used all four health questionnaire surveys to identify reported post-occupancy onset asthma, hypersensitivity pneumonitis, and sarcoidosis in the building by year since the building was occupied in 1994.

To examine changes of participants' health over time, we analyzed persons who participated in both the 2002 and 2005 medical surveys (n = 97) (Iossifova et al. 2011). In this analysis, we redefined respiratory cases based on 2002 questionnaire responses, using the same criteria as those used for the 2001 health questionnaire survey.

We examined the effect of remediation on both qualitative species and quantitative fungal information in the floor dust, including the proportion of fungi classified as hydrophilic or mesophilic. From our review of 12 unpublished building assessment reports by environmental consultants and newsletters by the building management since 2000, we obtained historical information on water damage and remediation. Remediation activities considered in this analysis included work related to eliminating sources of water and replacing damaged building materials. For the repeated measurement analysis, we used more complex regression models to account for a random effect of employees' workstations with environmental samples (Cho et al. 2011).

We also examined the prevalence of lower respiratory, rhinosinusitis, throat, eye, skin, and systemic symptoms among persons who participated in all four health questionnaire surveys (n = 258). In this analysis, we categorized the symptomatic participants into two groups based on time of symptom occurrence–the recent and frequent symptom group: those who reported respiratory symptoms occurring one or more times per week in the last 4 weeks; and the less recent symptom group: those who reported respiratory symptoms in the last 12 months but not in the last 4 weeks.

In three subsequent cross-sectional surveys after the initial evaluation of the building, we examined whether occupants who reported BR rhinosinusitis symptoms in 2001 were more likely to

develop physician-diagnosed asthma or BR asthma symptoms than those with no BR rhinosinusitis symptoms. We also examined how microbial exposures interacted with the presence of BR rhinosinusitis symptoms in the development of asthma or BR asthma symptoms in the building occupants during the subsequent 6 years of follow-up.

We performed repeated measurement analysis using logistic regression models to examine the associations between 2002 microbial exposure and respiratory health using all four health surveys. These models account for within-participant variability based on repeated measurements of health symptoms for each subject.

To examine whether the odds of BR respiratory symptoms in the last 4 weeks changed over time, we used logistic regression models with repeated measurements of health where survey year was considered continuous (coded 1, 4, 5, and 7), after controlling for microbial exposures (fixed 2002 floor averages of total fungi, ergosterol, and endotoxin), age, gender, race/ethnicity, smoking status, and duration of building occupancy. Time trends for BR respiratory symptoms in the last 4 weeks were reported as ORs (95% CIs).

To examine whether BR respiratory symptom severity at the individual level changed over time, we created a symptom severity score variable by coding "0" for no BR respiratory symptom, "1" for those who reported BR 'less recent' symptoms, and "2" for those who reported BR 'recent and frequent' symptoms for each survey. We used the same logistic regression models with repeated measurements where symptom score was considered a continuous dependent variable and survey year was considered a continuous independent variable, after controlling for microbial exposures, age, gender, race/ethnicity, smoking status, and duration of building occupancy.

We reported all results as ORs with 95% CIs. There is an increased risk of association if the OR is greater than one, whereas an OR of one shows no association. A 95% CI means that there is a 95% chance that the true estimate is somewhere between the lower and upper limits. The OR is considered statistically significant if the CI does not contain one.

All data analyses for this final report were done using SAS® System for Windows, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Health Questionnaire Surveys (2001-2007)

Participation and Demographics

Participation in the health questionnaire surveys ranged from 60% to 67% for the four surveys. The total number of employees participating in at least one survey was 1,494, of whom 900 (60%) participated in more than one. Seventeen percent (n=258) participated in all four surveys. Demographics of survey participants were similar for the 4 years studied, with the exception of tenure which increased over the four surveys, as would be expected (Table 3).

Table 3. Participation and characteristics of participants in the four health questionnaires (2001–2007)

Outcome	2001 (n = 888)	2004 (n = 771)	2005 (n = 797)	2007 (n = 762)
Participation	67%	67%	66%	60%
Age (mean ± SD)	45.9 ± 8.7	47.8 ± 8.0	48.6 ± 7.8	48.6 ± 8.4
Gender				
Female	59% (519/887)	58% (446/770)	55% (442/797)	57% (438/762)
Building tenure (mean ± SD)*	5.9 ± 1.9	8.0 ± 3.0	8.7 ± 3.3	9.4 ± 4.6
Race				
White	77% (651/844)	78% (592/760)	81% (625/776)	80% (594/747)
Black	18% (156/844)	18% (136/760)	15% (118/776)	17% (126/747)
Other	4% (37/844)	4% (32/760)	4% (33/776)	4% (27/747)
Ethnicity				
Hispanic	6% (52/857)	6% (47/763)	7% (55/790)	7% (57/762)
Smoking status				
Current	14% (124/888)	11% (87/766)	11% (85/769)	9% (69/738)
Former	26% (235/888)	27% (205/766)	28% (214/769)	28% (205/738)
Never	60% (529/888)	62% (474/766)	61% (470/769)	63% (464/738)

*** Assumed continuous building tenure; 64 participants left the building and returned sometime between 2001 and 2007.**

Initial Cross-Sectional Health Questionnaire Survey in 2001

From the initial cross-sectional survey in September 2001, we found an excess of respiratory symptoms and physician-diagnosed asthma reported among participants. In comparison with the U.S. adult population, wheezing, lifetime asthma, and current asthma were 2.2 to 2.5 times higher than expected ($p < 0.05$). Nasal and eye symptoms were also significantly elevated in the building, but to a lesser extent (1.5–1.6 times higher). The rate of post-occupancy asthma was 7.5 times higher than the rate of pre-occupancy adult-onset asthma, indicating a large increase in asthma incidence in the period after building occupancy (Cox-Ganser et al. 2005).

Subsequent Cross-Sectional Health Questionnaire Surveys in 2004, 2005, and 2007

NIOSH conducted three subsequent cross-sectional surveys offered to all employees in 2004, 2005, and 2007. Rates of lower respiratory symptoms and asthma remained elevated when compared to national rates.

Long-term employees (who occupied the building prior to January 2004) comprise the majority of the participants; approximately 88% or 1272/1447 had been in the building prior to January 2004. Only about 12% (175/1447) had come to the building in January 2004 or later. Figure 2 shows lower respiratory, rhinosinusitis, and hypersensitivity pneumonitis-like symptoms for these two groups of employees. The long-term employee group had a higher prevalence of symptoms in both the 2005 and 2007 surveys, although only rhinosinusitis symptoms in 2005 and hypersensitivity pneumonitis-like symptoms in 2007 were significantly higher. We did not perform the same analysis with the 2004 survey results because we had only a small number ($n = 12$) of short-term employees for the comparison.

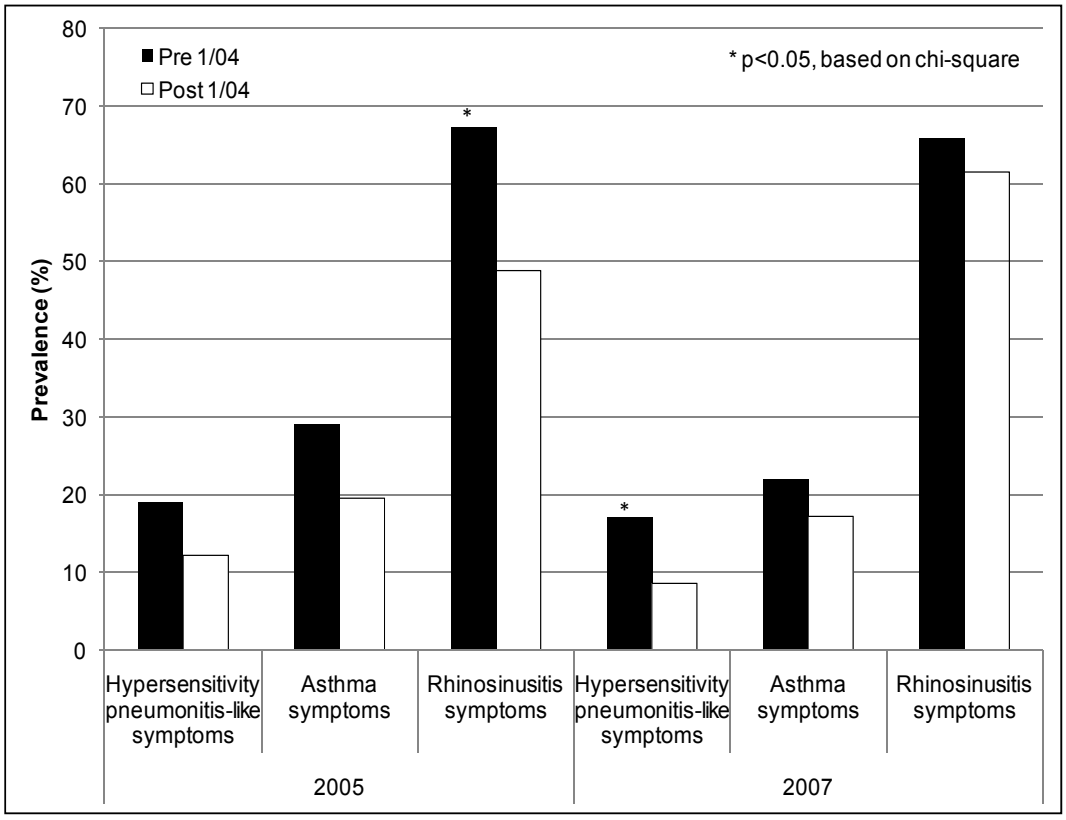

Figure 2. Comparison of respiratory symptoms prevalence by occupancy status (2005 and 2007).

Incidence Rate Analysis Using the 2007 Health Questionnaire Survey Participants

Using the 2007 health questionnaire survey results, we compared the incidence rate of post-occupancy adult-onset asthma, both before and after major remediation was completed, with the incidence rate of pre-occupancy adult-onset asthma. We found the rate between building occupancy and January 2004, when major remediation was reportedly completed, to be the highest, with a rate of 16.0 cases per 1,000 person-years. This was approximately 5.5 times higher than the pre-occupancy rate which was 2.9 cases per 1,000 person-years. The asthma incidence rate for the period between January 2004 and the end of the study period was 12.0 cases per 1,000 person years, which was lower than before remediation, but still 4.1 times higher than the pre-occupancy adult-onset asthma rate. Both post-occupancy adult-onset rates were significantly higher than the pre-occupancy adult-onset rate ($p < 0.001$).

Repeated Measurement Analysis of All Four Surveys

Figures 3, 4, and 5 show the prevalence of respiratory and other symptoms among employees who participated in all four health questionnaire surveys (n = 258) by the less recent, and recent and frequent symptoms groups. The decrease in less recent symptoms from 2001 to 2004 was significant at $p < 0.05$ for wheeze, cough, and shortness of breath on exertion, and marginally significant at $p < 0.10$ for chest tightness, attacks of shortness of breath, and awakened with breathing difficulty. The increase in less recent symptoms from 2004 to 2005 was significant at $p < 0.05$ for chest tightness, cough, and shortness of breath on exertion, and marginally significant at $p < 0.10$ for fever and chills. The decrease in less recent symptoms from 2005 to 2007 was significant at $p < 0.05$ for chest tightness and marginally significant at the $p < 0.10$ level for sinus symptoms.

Recent and frequent symptoms did not tend to show decreases in 2004 as compared to 2001. However, there were indications of increases in these symptoms from 2001 to 2005. This was significant at the $p < 0.05$ level for wheeze, attacks of shortness of breath, shortness of breath on exertion, nose and sneezing symptoms, and rash or itchy skin. The trend toward decreases in 2007 as compared to 2005 was significant at $p < 0.05$ for awakened with breathing difficulty and rash or itchy skin, and marginally significant at $p < 0.10$ for attacks of shortness of breath and nose and sneezing symptoms.

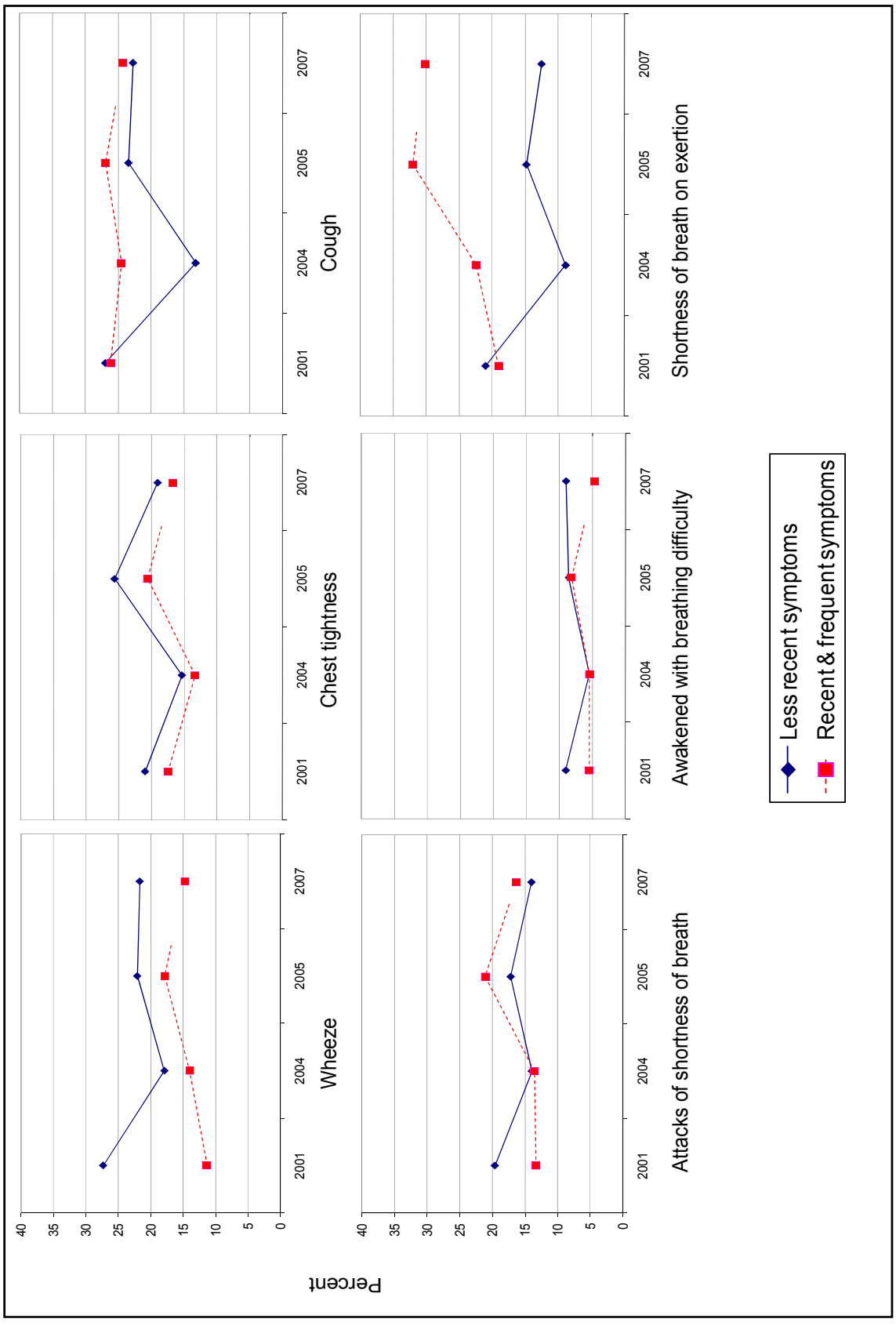

Figure 3. Prevalences of lower respiratory symptoms among those who participated in all four surveys by recent and frequent and less recent symptoms groups.

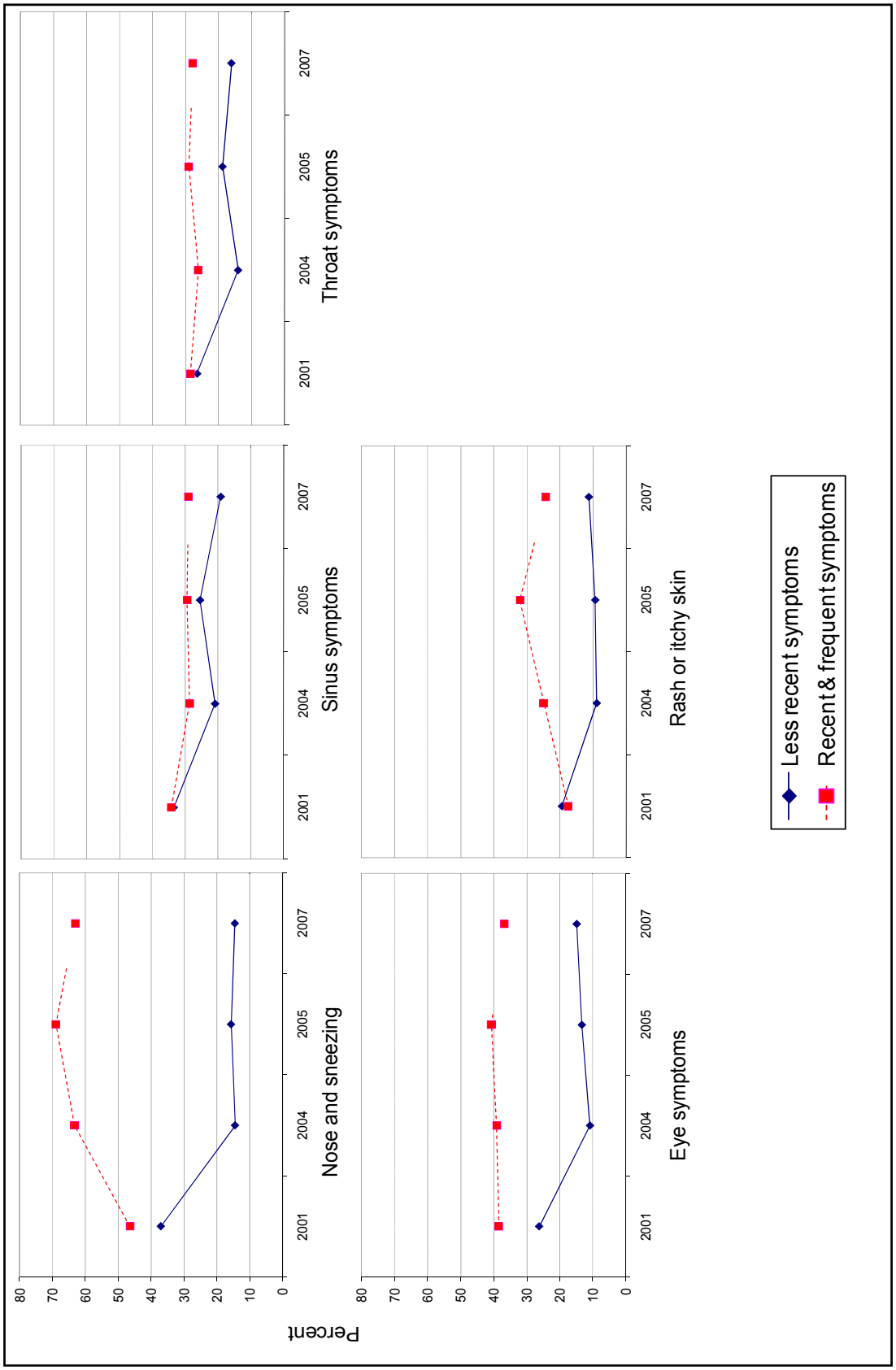

Figure 4. Prevalences of rhinosinusitis, throat, eye, and skin symptoms among those who participated in all four surveys by recent and frequent and less recent symptoms groups.

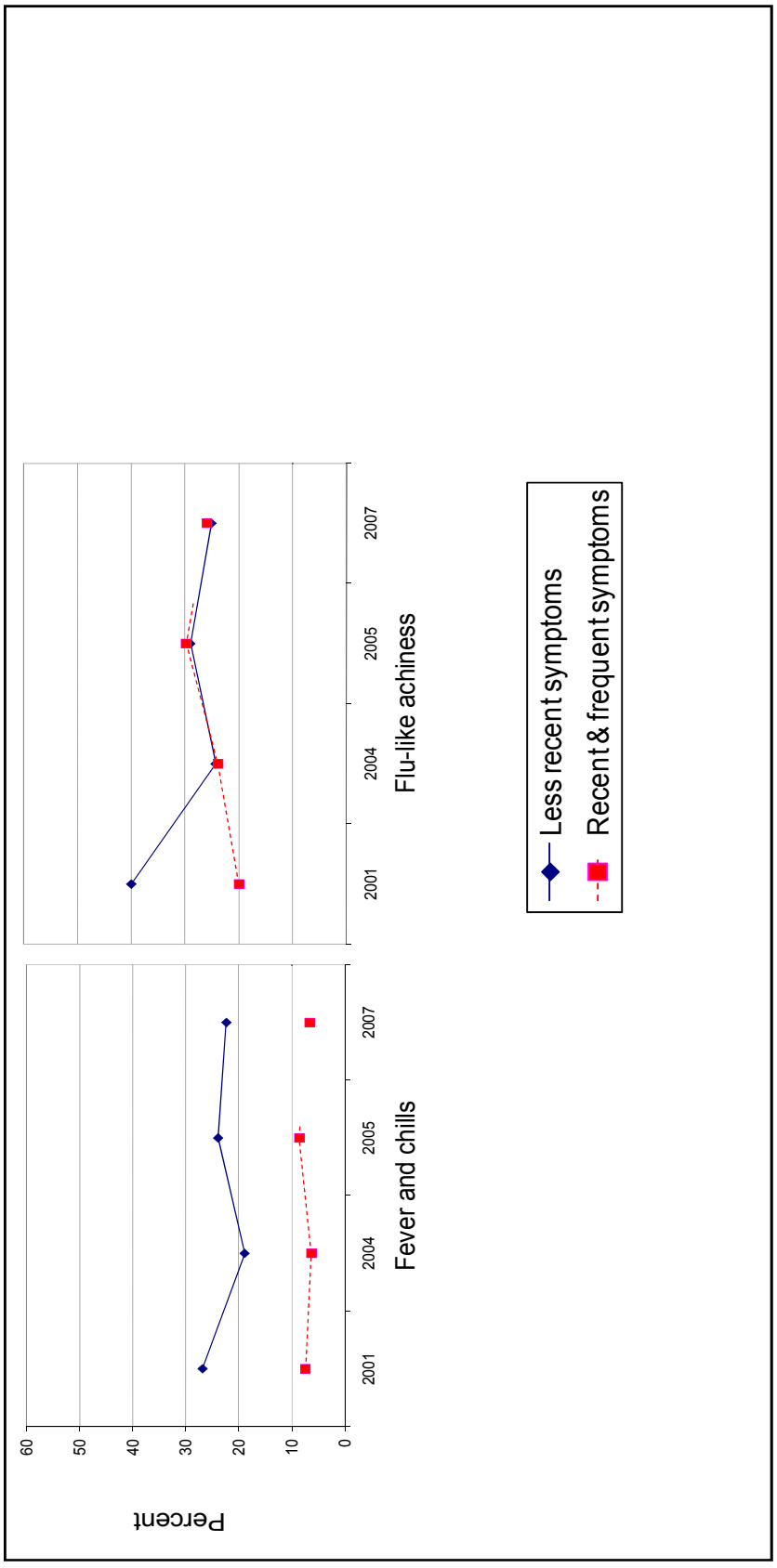

Figure 5. Prevalences of systemic symptoms among those who participated in all four surveys by recent and frequent and less recent symptoms groups.

Figures 6, 7, and 8 show the frequency of physician-diagnosed post-occupancy asthma, hypersensitivity pneumonitis, and sarcoidosis by diagnosis year. Through August 2007, a total of 145 post-occupancy asthma cases had been reported (Figure 6). The number of new asthma diagnoses peaked in 2000 and decreased since then.

There have been a total of 27 hypersensitivity pneumonitis cases and 10 sarcoidosis cases reported through August 2007 since the building was occupied in 1994 (Figures 7 and 8). Incident hypersensitivity pneumonitis and sarcoidosis cases were highest in 2001 and have decreased since then. By August 2007, there were only two post-occupancy asthma cases and two hypersensitivity pneumonitis cases that had been reported for that year. No new sarcoidosis cases had been reported during 2006 and the first 8 months of 2007.

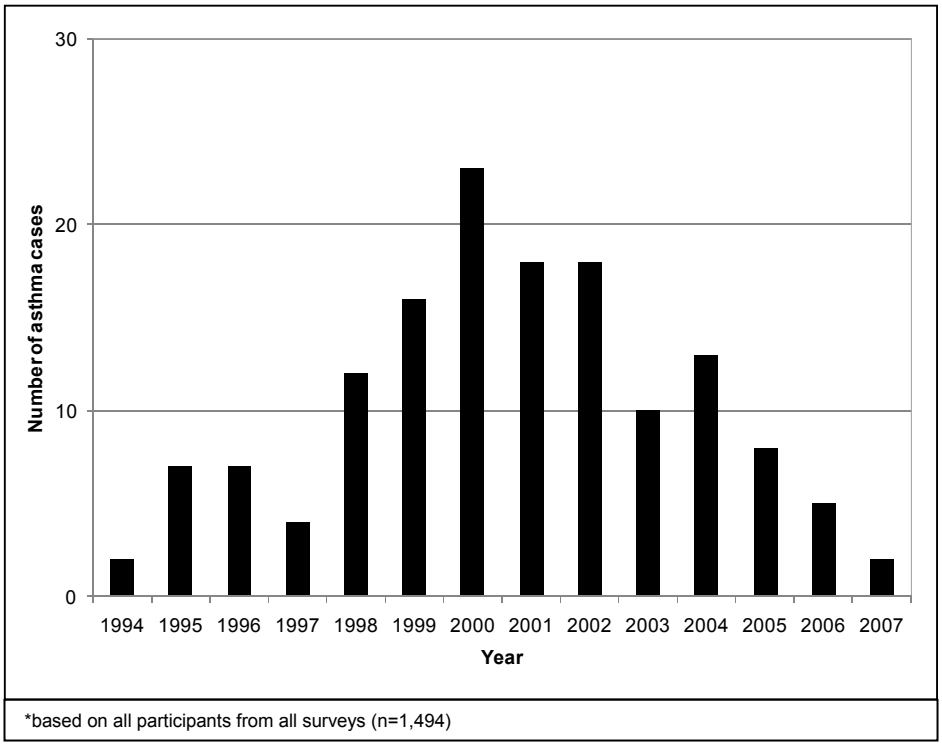

Figure 6. Frequency of post-occupancy asthma diagnoses by year.*

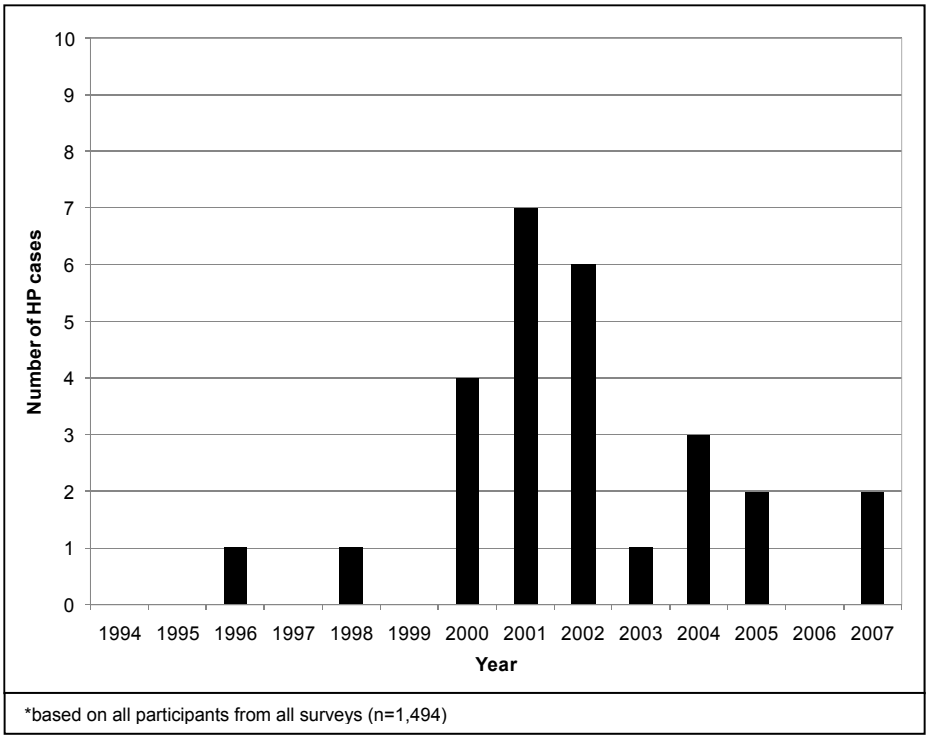

Figure 7. Frequency of hypersensitivity pneumonitis diagnoses by year.*

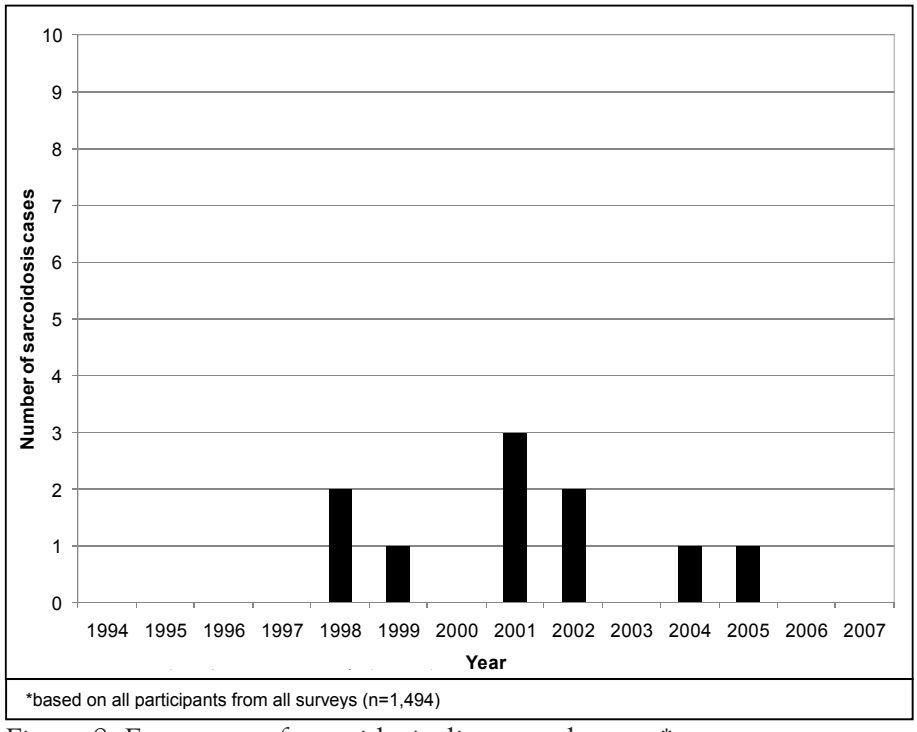

Figure 8. Frequency of sarcoidosis diagnoses by year.*

Among the 1,494 employees who participated in one or more surveys, 322 (22%) reported at least once ever being diagnosed with asthma. In comparison with prevalences reported from the 2007 Behavioral Risk Factor Surveillance System in the state of Connecticut, after adjusting for gender, the risk of ever being

diagnosed with asthma was 1.5 times greater among occupants in the building (95% CI 1.3–1.7).

The percentage of participants who reported current asthma by survey year ranged between 12% and 16% (Figure 9). Percentages are based on the number of participants that answered the question on physician-diagnosed asthma that was still present at the time of that particular survey.

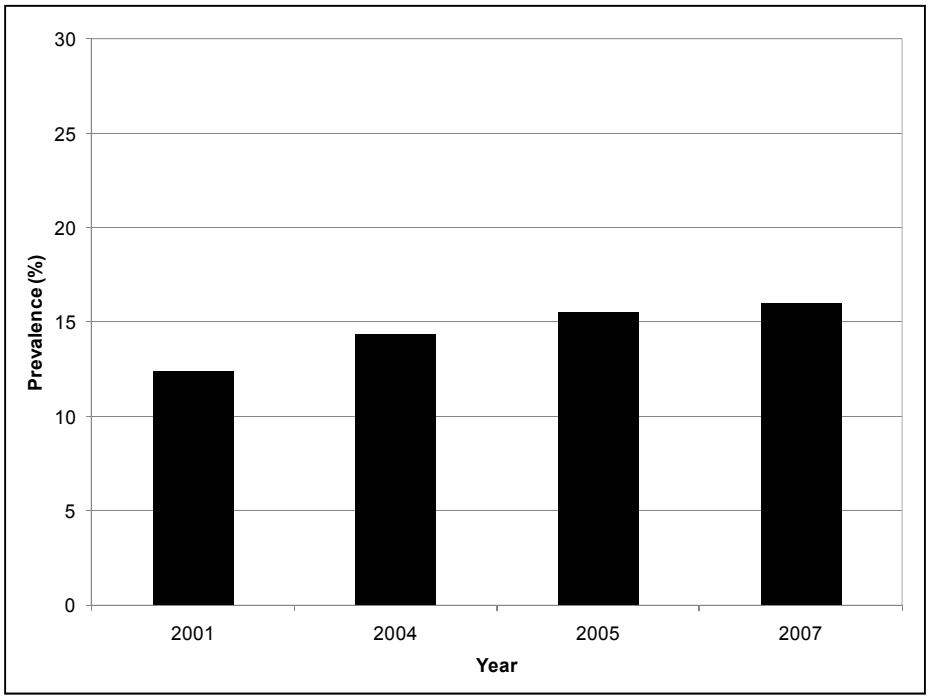

Figure 9. Prevalence of current asthma by survey year.

From the analysis examining progression of rhinosinusitis symptoms in the initial survey to lower respiratory illnesses in the three subsequent surveys, we found that participants who reported BR rhinosinusitis symptoms in the initial 2001 survey were about twice as likely to have developed BR asthma symptoms (Table 4) in later surveys. The 2001 BR rhinosinusitis symptom group was also two times more likely to report new physician-diagnosed current asthma in later surveys but we did not obtain statistical significance due to the small number of new asthma cases (n=20). Polytomous logistic regression analysis showed that 2001 BR rhinosinusitis symptoms increased the risk for developing BR asthma symptoms by about twice, but not for developing non-BR asthma symptoms in any of the follow-up surveys. On the other hand, the group with non-BR rhinosinusitis symptoms tended to have an increased risk for developing non-BR asthma symptoms, but not for developing BR asthma symptoms.

Table 4. Crude and adjusted odds ratios for developing BR asthma symptoms by follow-up survey in the 2001 BR rhinosinusitis symptom group* compared to the 2001 comparison group*

Year of follow-up survey	Crude OR (95% CI)	Adjusted OR (95% CI) Demographics†	Adjusted OR (95% CI) Demographics and Environmental Exposure‡
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 (0.86, 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 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.**
† Race, gender, age, smoking status, and year of building occupancy
‡ Tertile exposure (low/medium/high) is based on the rank order of floor-specific geometric means (per m^2 area) of culturable fungi, ergosterol, and endotoxin measured in the 2002 environmental survey.
§ $p < 0.05$

Medical Surveys (2002–2005)

Participation and Demographics

There were 522 persons who participated in at least one medical survey between 2002 and 2005. Approximately one-third (35% or 185/522) participated in more than one survey. Only 76 (15%) participated in all three surveys.

In 2002, there were 248 participants (233 from the 2001 respiratory case and comparison groups, along with 15 volunteers) among those who were eligible for the medical survey. Participation was higher in the respiratory case group than the comparison group (70% vs. 59%, respectively).

In 2004, 196 employees completed the medical testing. Among these participants, 144 persons had been originally selected as part of the respiratory case or comparison groups in 2001, seven had volunteered to participate in the 2002 medical survey, and 45 employees volunteered in 2004.

During the 2005 survey, 339 employees participated in at least one

part of the medical survey. Of these, 229 were part of either the original 2001 or 2004 respiratory case or comparison groups, 56 were volunteers in 2005 or from earlier medical surveys, and 54 were from the randomly selected group.

Participation in the medical surveys ranged from 46% in 2005 to 68% in 2002 (Table 5). In general, the characteristics of the participants were similar across the three surveys, with the exception of age and building tenure, both of which increased, as would be expected.

Table 5. Characteristics of participants in the three medical survey questionnaires (2002–2005)

Outcome	2002 (n = 248)	2004 (n = 196)	2005 (n = 339)
Participation	68%	60%	46%
Age (Mean ± SD)	46.9 ± 8.4	47.7 ± 7.7	49.2 ± 7.5
Gender			
Female	61% (152/248)	65% (127/196)	59% (199/339)
Building tenure (Mean ± SD)	6.7 ± 1.7	8.6 ± 2.1	9.3 ± 2.8
Race			
White	74% (183/248)	78% (153/196)	79% (269/339)
Black	19% (47/248)	18% (35/196)	17% (58/339)
Other	7% (18/248)	4% (8/196)	4% (12/339)
Ethnicity			
Hispanic	7% (17/248)	5% (10/196)	4% (13/339)
Smoking status			
Current	13% (32/248)	13% (25/196)	9% (30/339)
Former	28% (70/248)	27% (52/196)	31% (105/339)
Never	59% (146/248)	61% (119/196)	60% (204/339)

Initial Medical Survey in June 2002

On the basis of the results from the September 2001 survey, we decided to return to the building to conduct a more extensive questionnaire and medical testing in 2002. As noted in the methods, 356 employees were selected and invited to participate based on the presence or absence of various symptoms, and physician-diagnosed asthma, hypersensitivity pneumonitis or

sarcoidosis. Among the participants, the respiratory cases had a higher prevalence of abnormal breathing tests and medication use (Cox-Ganser et al. 2005).

Allergen skin prick testing was done to determine the percentage of participants that were atopic or had allergies to any one of the three mold mixes. Cox-Ganser et al. (2005) reported that over half of the participants in the 2002 medical survey were atopic. There was no difference in the prevalence of atopy between the respiratory case group and the comparison group. However, persons who reported pre-occupancy asthma were significantly more likely to be atopic than persons with no reported history of asthma or that had developed asthma after being in the building ($p < 0.05$). Persons with post-occupancy asthma were significantly less likely to have a reaction to any of the mold mixes (Cox-Ganser et al. 2005).

Exhaled nitric oxide concentrations were not significantly different between the respiratory case and comparison groups, although participants with physician-diagnosed current asthma who had never smoked had significantly higher levels of exhaled nitric oxide (Interim Letter IV, available upon request). However, among non-smokers, levels of IL-8 were positively associated with several symptoms (cough, any lower respiratory symptom, BR lower respiratory symptom, sneezing, runny nose, any nasal symptom, and any sinus symptom) and physician diagnosed asthma (Akpinar-Elci et al. 2008).

Subsequent Medical Surveys in August 2004 and August 2005

Details on lung function testing and medication usage for the 2004 and 2005 medical surveys can be found in the Interim letter VII (available upon request). The prevalence of abnormal lung function tests and medication use was higher among participants in the respiratory case group when compared to the comparison group as we found from the initial medical survey, showing that self-reported symptoms correlated well with objective lung tests and medication use.

In the two subsequent surveys, we did not find any significant change in atopic status among participants who had an allergic skin test during the 2002 survey and another test in either 2004 or 2005 (Interim letter VII, available upon request).

In 2005, nasal nitric oxide or nasal lavage collection was completed by 153 invited employees (51%). Of these 153 participants, 147 had interpretable nasal nitric oxide results. Of the 146 employees that participated in nasal lavage testing, 142 had results reported for eosinophilic cationic protein, IL-8, myeloperoxidase, or albumin. We found some association between upper airway symptoms and nasal inflammatory markers after adjusting for age, gender, race, smoking status, atopic status, and the use of any allergy medication in the last four weeks. Nasal congestion was marginally associated ($p < 0.10$) with IL-8 and significantly associated with myeloperoxidase ($p < 0.05$). Blowing out thick mucus was also associated with higher levels of IL-8 and eosinophilic cationic protein. We also found that participants who reported systemic symptoms, such as chills, flu-like achiness, or fatigue, had higher levels of nasal inflammatory markers, including IL-8, eosinophilic cationic protein, myeloperoxidase, and neutrophils. There was no statistically significant association between nasal nitric oxide levels and symptoms.

Repeated Measurement Analysis of Medical Surveys

From the analyses of those who participated in both the 2002 and 2005 medical surveys, we observed no overall improvement over the interval in respiratory health, as reflected in symptom scores, overall medication use, spirometry abnormalities, or sick leave for either the 2002 respiratory case group (n = 54) or the 2002 non-case group (n = 43) (Table 6). Four employees went from borderline bronchial hyper-responsiveness to bronchial hyper-responsiveness; six developed abnormal spirometry; three reported incident post-occupancy current asthma, and four were newly diagnosed with hypersensitivity pneumonitis. Among the 2002 non-case group, the number of participants with lower respiratory symptoms increased from 16 in 2002 to 23 in 2005. However, the 2002 respiratory cases relocated in the building had a decrease in medication use and sick leave in 2005 compared with the non-relocated cases (Iossifova et al. 2011). Poorer quality of life was reported more frequently among the 2002 respiratory case group. There appeared to be some marginal improvement in emotional health among the 2002 respiratory case group in 2005, whereas the 2002 non-cases reported more limitations in physical activities in 2005 compared to 2002 (Table 7).

Table 6. Health characteristics among participants in both the 2002 and 2005 surveys, using only paired data from 2002 respiratory cases* and 2002 non-cases followed up in 2005

Medical test	Respiratory cases in 2002 (n = 54)	Respiratory cases in 2005 (n = 54)	Non-cases in 2002 (n = 43)	Non-cases in 2005 (n = 43)
Bronchial hyper-responsiveness or positive bronchodilator test, % (n)	0	7% (2)	0	6% (2)
FVC % predicted	96.1%	95.5%	100.8%	101.9%
FEV_1 % predicted	93.6%	92.7%	99.9%	99.7%
FEV_1/FVC ratio	78.1%	77.2%	79.0%†	77.4%†
Abnormal spirometry, % (n)	18% (8)	20% (9)	0†	11% (4)†
LRS‡ point scale, mean (SD)	5.7 (3.6)	5.7 (3.8)	0.9 (1.4)	1.5 (2.4)
Work-related LRS‡, % (n)	52% (28)	50% (27)	7% (3)	17% (7)
Medication use scale, mean (SD)	1.7 (2.8)	1.1 (2.1)	0.2 (0.7)	0.3 (1.2)
Oral steroid use in last 12 months, % (n)	22% (12)†	7% (4)†	5% (2)	0
Inhaled steroid use in last 4 weeks, % (n)	15% (8)	13% (7)	2% (1)	2% (1)
Beta-agonist use in last 4 weeks, % (n)	22% (12)	22% (12)	0	7% (3)
Post-occupancy current asthma, % (n)	33% (18)	37% (20)	0	2% (1)
Respiratory sick leave days, mean (SD)	4.6 (6.4)§	6.3 (15.6)¶	2.9 (9.6)**	2.0 (5.7)††

*** Respiratory cases were redefined based on 2002 questionnaire responses, using the same criteria as those used for the 2001 health questionnaire survey.**

† Change in health characteristic from 2002 to 2005 within a group was significant ($p < 0.05$).

‡ LRS: Lower respiratory symptoms (wheeze or whistling in the chest, chest tightness, shortness of breath, and cough occurring in the last 4 weeks).

§ Results after excluding an outlier who missed 110 days due to respiratory symptoms in 2005 are given as 4.2 (5.6).

¶ Results after excluding an outlier who missed 110 days due to respiratory symptoms in 2005 are given as 4.3 (6.2).

**** Results after excluding an outlier who missed 60 days due to respiratory symptoms in 2002 are given as 1.5 (3.2).**

†† Results after excluding an outlier who missed 60 days due to respiratory symptoms in 2002 are given as 1.6 (5.0).

Table 7. Quality of life among participants in both the 2002 and 2005 surveys, using only paired data from 2002 respiratory cases* and 2005 non-cases followed up in 2005

Health characteristic	Respiratory cases in 2002 (n = 54)	Respiratory cases in 2005 (n = 54)	Non-cases in 2002 (n = 43)	Non-cases in 2005 (n = 43)
General health fair to poor, % (n)	17% (9)	15% (8)	7% (3)	0
Emotional health has limited kinds of activities, % (n)	41% (22)†	28% (15)†	9% (4)	2% (1)
Emotional health has limited accomplishments, % (n)	50% (27)†	37% (20)†	17% (7)	14% (6)
Physical health has limited kinds of activities, % (n)§	48% (26)	41% (22)	0‡	12% (5)‡
Physical health has limited accomplishments, % (n)§	54% (29)	43% (23)	7% (3)	14% (6)
Limited in climbing stairs, % (n)	48% (26)	57% (31)	9% (4)	19% (8)
Limited in moderate activities, % (n)	30% (16)	31% (17)	5% (2)	5% (2)

*** Respiratory cases were redefined based on 2002 questionnaire responses, using the same criteria as those used for the 2001 health questionnaire survey.**
† $p < 0.10$, change from 2002 to 2005 within a group was marginally significant.
‡ $p < 0.05$, change from 2002 to 2005 within a group was significant.
§ $p < 0.05$, change from 2002 to 2005 between groups was significant.

Environmental Results

Comparison of Floor Dust Fungi Before and After the 17th Floor Carpet Replacement

In December 2001, we collected floor dust samples from 61 locations on the 17th floor before the carpet was replaced. In April 2002, we returned to resample the 17th floor. We did not find a substantial reduction in fungi levels or in the types of fungal taxa (Interim letter III, available upon request).

Initial Environmental Survey in 2002

In April 2002 we returned to the building to sample workstations for respiratory cases and comparison group employees we had identified from the September 2001 survey. We were able to collect 338 floor dust samples and 327 chair dust samples from 323 employees' workstations. We were not able to locate workstations of the other 29 participants. We identified 67 fungal species in the floor dust and 69 fungal species in the chair dust, along with unidentified species of *Penicillium*, yeasts (*Rhodotorula* and *Sporobolomyces*), and non-sporulating fungi. The GM of culturable fungi in floor dust was significantly lower than in chair dust (7,700

CFU/g vs. 11,000 CFU/g, respectively). However, the levels of endotoxin and ergosterol were significantly higher in floor dust than chair dust. More detailed information on the findings of the environmental survey in April 2002 can be found in the article by Park et al. (2008).

Follow-up Environmental Surveys in 2004, 2005, and 2007

In general, the GMs of the microbial agents in the floor dust showed increasing trends across the 4 surveys with the lowest levels in 2002 (Table 8). The levels of cat and dog allergens (μg/m^2) significantly decreased in the 2004 and 2007 surveys compared to the 2002 survey mostly due to an increasing percentage of samples below the LOD. The GMs of total culturable fungi (CFU/m^2) in floor dust were 8 to 16 times higher in the 2007 survey as compared to those in the 2002, 2004, and 2005 surveys due to the increased levels of hydrophilic and mesophilic fungi, such as *Phoma herbarum*, yeasts, *Aureobasidium pullulans*, *Cladosporium* species, *Alternaria alternata*, and *Epicoccum nigrum*. For ergosterol, the primary sterol in the cell membrane of filamentous fungi and yeasts, the GM in 2007 was more than twice that in 2002.

GMs of endotoxin in the 2005 and 2007 surveys (12,800 and 12,000 EU/m^2, respectively) were about 5 times higher than that of the 2002 survey (2,700 EU/m^2). For Gram-negative bacteria, the difference in GMs (CFU/m^2) in floor dust between 2005 and 2007 was more than one order of magnitude, which was mainly driven by increased levels on floors 14–17 in 2007 (data not shown).

The upper floors where water leaks mainly occurred had significantly ($p < 0.05$) higher levels of hydrophilic fungi than the lower floors, except for the 2004 survey (Figure 10). Levels of Gram-negative bacteria on the upper floors were higher than those on the lower floors in 2007.

Table 8. Overall building average levels of microbial agents and cat and dog allergens in floor dust samples across 4 surveys

Environmental parameter	2002 N	2002 GM (GSD)	2004 N	2004 GM (GSD)	2005 N	2005 GM (GSD)	2007 N	2007 GM (GSD)
Total culturable fungi (CFU/m^2)	328	2,000 (5.5)	279	4,100 (4.0)	296	2,400 (5.5)	150	31,900 (4.0)
Ergosterol (ng/m^2)	334	126.2 (3.9)	246	177.7 (3.0)	–	–	143	304.9 (2.1)
Culturable Gram-negative bacteria (CFU/m^2)	–	–	–	–	291	1,800 (10.5)	148	28,000 (65.4)
Endotoxin (EU/m^2)	338	2,700 (4.8)	276	6,100 (5.4)	294	12,800 (5.6)	142	12,000 (2.7)
Cat allergen (Fel d 1) (µg/m^2)	314	0.7 (2.9)	277	0.4 (3.4)	282	0.7 (4.1)	148	0.3 (6.2)
Dog allergen (Can f 1)(µg/m^2)	314	0.6 (3.2)	277	0.3 (3.6)	282	0.5 (4.2)	148	0.4 (3.9)

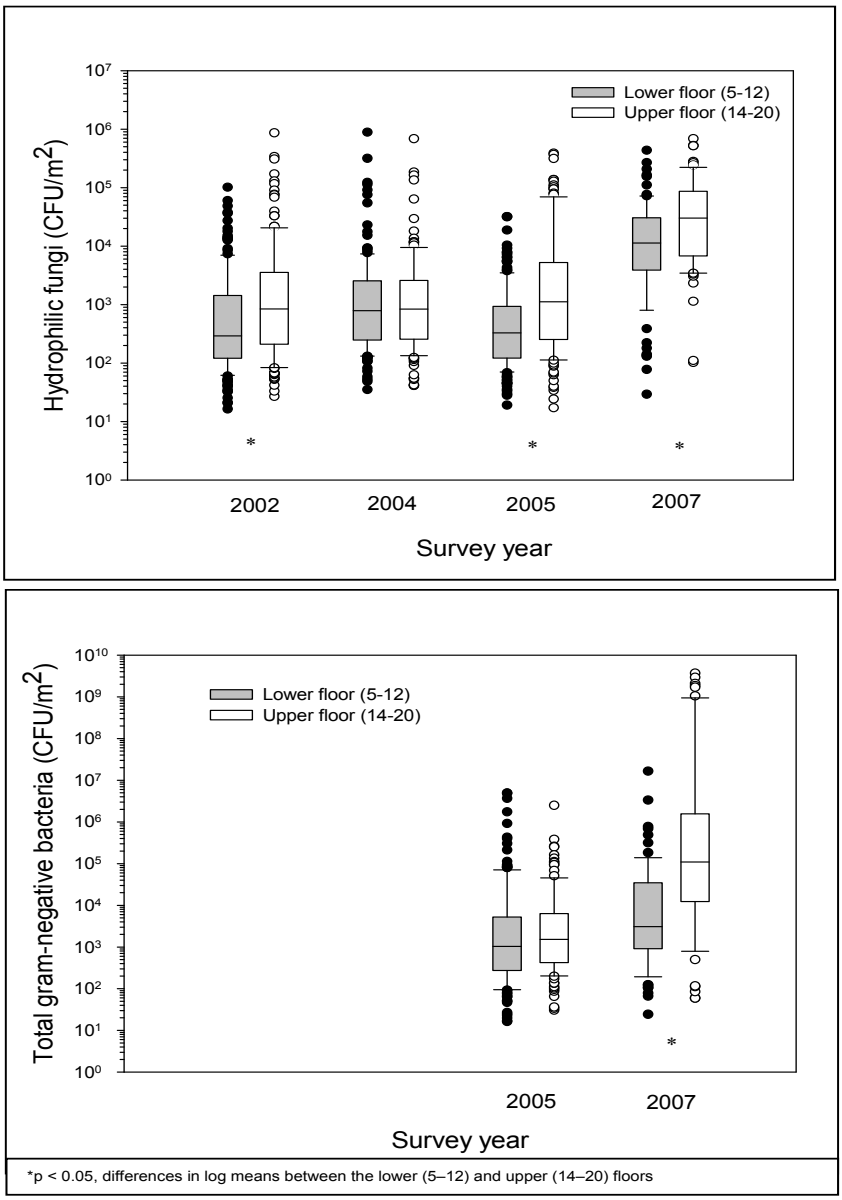

Figure 10. Observed levels of fungi and bacteria on the lower vs. upper floors by survey. No data available on Gram-negative bacteria in the 2002 and 2004 surveys. Each box plot: an IQR with median, upper and lower whiskers: upper and lower boundaries (3rd quartile /1st quartile ± 1.5 IQR).

More details on environmental results for 2004, 2005, and 2007 can be found in Interim letters VII and X, available upon request.

Repeated Measurement Analysis of Environmental Surveys–Effect of Remediation

We examined the effects of remediation on levels of culturable fungi in floor dust collected during the four cross-sectional environmental surveys. From these repeated measurement analyses,

we found significantly lower levels of total and hydrophilic fungi at remediated workstations than at non-remediated workstations in both 2004 and 2005 after completion of major remediation in early 2004 (Table 9). The remediation effect, however, disappeared by 2007. This finding was also supported by results from the qualitative analysis of fungal species that the fraction of hydrophilic to total fungal concentrations was lowest in 2004, increased again in 2005 and was highest in 2007 (Figure 11). The average fungal level in 2007 was ten-fold higher than those in previous surveys (Cho et al. 2011).

Table 9. Adjusted mean levels of microbial agents* and mean fractions of hydrophilic fungi in floor dust by remediation and survey year

Microbial agent	Remediation	2002 Adjusted mean	2004 Adjusted mean	2005 Adjusted mean	2007 Adjusted mean
Total fungi (CFU/m^2)	Yes	1,251	2,773	1,000	36,326
Total fungi (CFU/m^2)	No	2,265†	4,405†	2,561†	29,733
Hydrophilic fungi (CFU/m^2)	Yes	331	461	218	16,624
Hydrophilic fungi (CFU/m^2)	No	837†	1,118†	783†	13,244
Ergosterol (ng/m^2)	Yes	160	178	–	250
Ergosterol (ng/m^2)	No	109†	158	–	314
Endotoxin (EU/m^2)	Yes	6,007	3,671	11,051	11,242
Endotoxin (EU/m^2)	No	1,938†	6,035†	11,500	10,861
Cat allergen (µg/m^2)	Yes	0.50	0.27	0.33	0.24
Cat allergen (µg/m^2)	No	0.72‡	0.42†	0.71†	0.26
Dog allergen (µg/m^2)	Yes	0.40	0.21	0.28	0.48
Dog allergen (µg/m^2)	No	0.57‡	0.25	0.54‡	0.37
Hydrophilic fungi fraction§	Yes	0.37	0.24	0.27	0.58
Hydrophilic fungi fraction§	No	0.49	0.35	0.41	0.58

*** GMs of microbial agents estimated using regression models for repeated measurements: a random effect of workstation and fixed effects of survey, floor, remediation, and remediation by survey interaction. Remediation was a time-varying covariate in the models. In the 2005 survey, workstations on only the 6th floor were considered "remediated".**
† $p < 0.05$, in comparisons of the remediated and non-remediated workstations for each survey.
‡ $p < 0.1$, in comparisons of the remediated and non-remediated workstations for each survey.
§ Defined as concentration of hydrophilic fungi (CFU/g) divided by that of total fungi (CFU/g) in each dust sample; mean hydrophilic fractions were estimated using a generalized linear mixed-effects model with a logit link function conditional on the binomial distribution of the fraction.

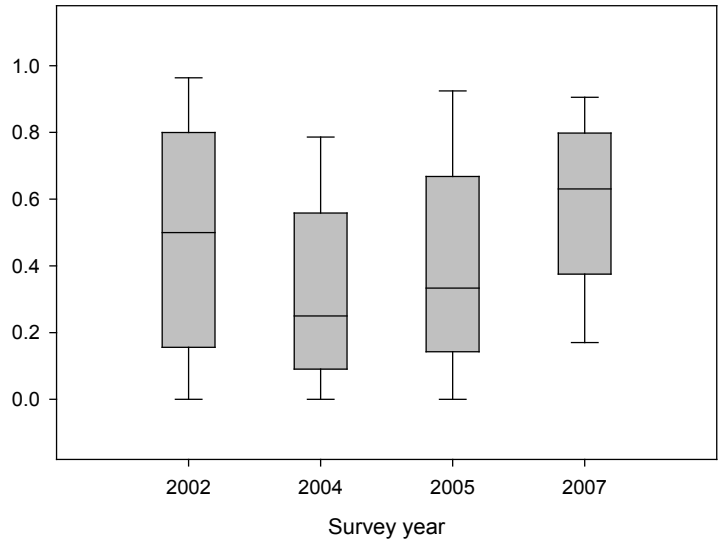

Figure 11. Box plots for fractions of hydrophilic fungi in total fungi concentrations across 4 surveys. Each box plot: an IQR with median, upper and lower whiskers: upper and lower boundaries (3rd quartile /1st quartile ± 1.5 IQR)

Association between Exposure to Environmental Microbial Agents and Occupant Health

Cross-Sectional Analyses of Associations between Microbial Exposure and Health

In data analyses using responses from the case and comparison groups (n = 356) selected from the 2001 health questionnaire joined with data from the April 2002 environmental evaluation, we were able to demonstrate a linear exposure-response relationship between fungi, ergosterol, endotoxin, and cat allergen levels with the presence of asthma (post-occupancy asthma or epi-asthma) or being a respiratory case (Tables 10–11) (Park et al. 2008). Hydrophilic and mesophilic fungi showed a much stronger relationship with health outcomes than fungi with A_w less than 0.8. Although cat allergens were mildly associated with health outcomes, dog allergen levels showed no association. In general, there appeared to be a stronger association with floor dust than with chair dust samples. In models with multiple environmental parameters, the associations remained for total and hydrophilic fungi, and to a lesser extent, ergosterol (data not shown). For a more detailed description of associations, please refer to the article by Park et al. (2008).

Table 10. Association* of floor dust samples with respiratory case status, epi-asthma, and post-occupancy current asthma, adjusted for age, sex, race, smoking status, and building tenure

Environmental parameter	Odds Ratios (95% CI) Respiratory case	Odds Ratios (95% CI) Epi-asthma	Odds Ratios (95% CI) Post-occupancy asthma
Total culturable fungi	1.66† (1.19, 2.33)	1.72† (1.21, 2.46)	1.56‡ (0.96, 2.53)
Fungi with $A_w \geq 0.80$	1.66† (1.17, 2.38)	1.69† (1.15, 2.47)	1.72† (1.03, 2.88)
Fungi not classified as $A_w \geq 0.80$	1.11 (0.80, 1.54)	1.21 (0.84, 1.72)	0.80 (0.47, 1.37)
Hydrophilic fungi	1.73† (1.20, 2.51)	1.80† (1.20, 2.69)	2.19† (1.23, 3.89)
Ergosterol	1.56† (1.13, 2.16)	1.60† (1.13, 2.28)	1.37 (0.87, 2.17)
Endotoxin	1.60† (1.09, 2.37)	1.54† (1.01, 2.34)	1.40 (0.79, 2.50)
Cat allergen (Fel d 1)	1.33‡ (0.96, 1.83)	1.35‡ (0.95, 1.92)	1.16 (0.72, 1.88)
Dog allergen (Can f 1)	1.18 (0.85, 1.65)	1.09 (0.76, 1.57)	1.01 (0.62, 1.65)

*** ORs and 95% CIs were computed based on change of the IQR range in the environmental variable. The number of samples for each model varies. Units of the environmental variables are as follows: CFU/m² for fungi in floor dust; EU/m² for endotoxin in floor dust; ng/m² for ergosterol in floor dust; and µg/m² for allergen in floor dust.**

† $p < 0.05$

‡ $p < 0.10$

Table 11. Association* of chair dust samples with respiratory case status, epi-asthma, and post-occupancy current asthma, adjusted for age, sex, race, smoking status, and building tenure

Environmental parameter	Odds Ratios (95% CI) Respiratory case	Odds Ratios (95% CI) Epi-asthma	Odds Ratios (95% CI) Post-occupancy asthma
Total culturable fungi	1.37† (1.02, 1.85)	1.58† (1.13, 2.20)	1.67† (1.07, 2.60)
Fungi with $A_w \geq 0.80$	1.31† (1.00, 1.72)	1.46† (1.09, 1.97)	1.56† (1.05, 2.30)
Fungi not classified as $A_w \geq 0.80$	1.09 (0.76, 1.56)	1.11 (0.75, 1.64)	1.20 (0.67, 2.18)
Hydrophilic fungi	1.45† (1.07, 1.97)	1.63† (1.16, 2.28)	1.85† (1.19, 2.89)
Ergosterol	1.38‡ (0.98, 1.93)	1.54† (1.05, 2.26)	1.63‡ (0.95, 2.81)
Endotoxin	1.10 (0.82, 1.48)	1.09 (0.79, 1.52)	1.15 (0.71, 1.87)
Cat allergen (Fel d 1)	1.21 (0.91, 1.63)	1.37‡ (1.00, 1.88)	1.55‡ (1.00, 2.39)
Dog allergen (Can f 1)	1.26 (0.86, 1.83)	1.20 (0.78, 1.83)	1.10 (0.61, 2.00)

*** ORs and 95% CIs were computed based on change of the IQR range in the environmental variable. The number of samples for each model varies. Units of the environmental variables are as follows: CFU/m² for fungi in floor dust and CFU/chair for fungi in chair dust; EU/m² for endotoxin in floor dust and EU/chair for endotoxin in chair dust; ng/m² for ergosterol in floor dust and ng/chair for ergosterol in chair dust; and µg/m² for allergen in floor dust and µg/chair for allergen in chair dust.**

† $p < 0.05$

‡ $p < 0.10$

To examine the association between the environment and health using all 2001 health questionnaire participants (n = 888), we classified participants' exposure as low, medium, or high based on their occupied floor and floor-specific means of fungi and endotoxin. In these analyses, we were also able to document an increased risk of lower respiratory symptoms and rash or itchy skin with higher levels of fungi (Figure 12). Other upper and non-respiratory symptoms showed little or no association. For endotoxin exposure, we found employees in the medium tertile of exposure to endotoxin had the greatest amount of risk for some lower respiratory symptoms, rhinosinusitis and throat symptoms, and some non-respiratory symptoms (Figure 13). Although to a lesser extent, employees in the highest tertile group were also significantly more likely to have symptoms than the lowest tertile group (Park et al. 2006).

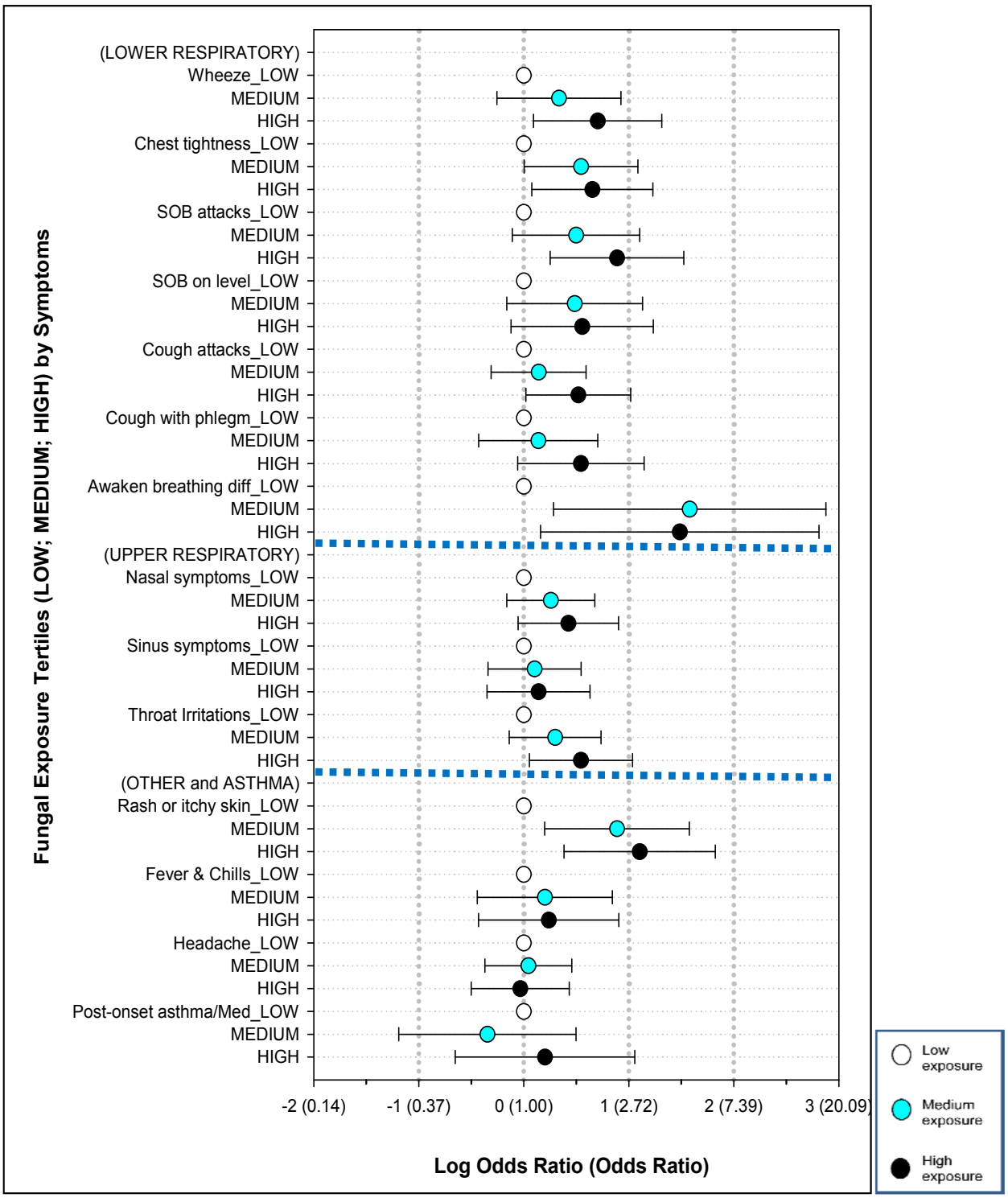

Figure 12. ORs for BR symptoms in the last 12 months by tertile exposures to fungi, 2001/2002 surveys. SOB: shortness of breath; Post-onset asthma/Med: post-occupancy onset of asthma with use of asthma medications.

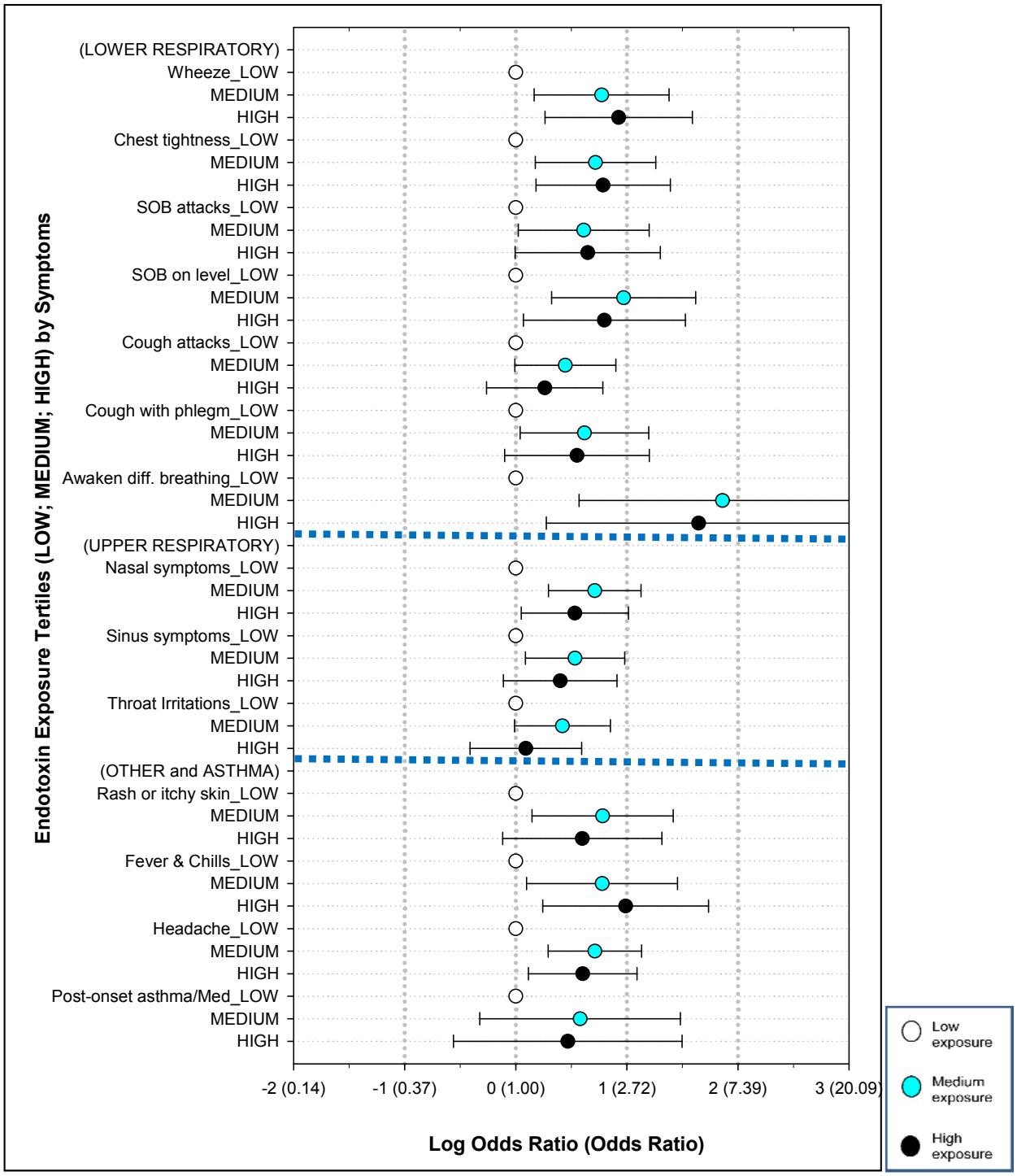

Figure 13. Odds ratios for BR symptoms in the last 12 months by tertile exposures to endotoxin, 2001/2002 surveys. SOB: shortness of breath; Post-onset asthma/Med: post-occupancy onset of asthma with use of asthma medications.

In 2007, we documented an increased risk of BR lower respiratory symptoms and post-occupancy asthma among participants in areas with high levels of ergosterol, endotoxin, and to a lesser extent, total fungi (Interim letter X, available upon request).

Repeated Measurement Analyses of Associations between Exposure and Health

In the logistic regression model examining the progression of BR rhinosinusitis symptoms to BR asthma symptoms or asthma, adjusted for 2001 BR rhinosinusitis symptoms, demographics, and all three initial 2002 environmental exposures (total fungi, endotoxin, and ergosterol), the medium and high tertile exposures to fungi in dust significantly increased the odds of developing BR asthma symptoms in any one of the follow-up surveys (Table 12) in an exposure-dependent manner. In this model, the effect of initial fungal exposure (measured by culturable fungi in the 2002 floor dust, but not follow-up survey exposure) on BR asthma symptoms in any of the follow-up surveys was independent of the effect of 2001 BR rhinosinusitis symptoms, and the odds from fungal exposure was higher than that from 2001 BR rhinosinusitis symptoms. Exposure to ergosterol or endotoxin in 2002 did not increase the odds of developing BR asthma symptoms. To increase analytical 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 the logistic regression model with the four-level interaction variable combining the binary 2001 BR rhinosinusitis symptom status with the binary fungal exposure of the initial 2002 survey, we found an interaction on an additive scale between fungal exposure and BR rhinosinusitis symptoms. The odds 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 = 7.3, 95% CI = 2.7, 19.7) than the comparison group with higher exposure (OR = 3.5, 95% CI = 1.4, 8.8), the BR rhinosinusitis symptom group with lower exposure (OR = 2.4, 95% CI = 0.6, 10.3), or even a summation of these two ORs (Park et al. 2011, submitted).

Table 12. Increased odds* for developing BR asthma symptoms in any of the follow-up surveys in relation to initial 2002 microbial exposures based on measurements in floor dust and interaction between the presence of BR rhinosinusitis symptoms and initial fungal exposure

Independent variables in the model (reference group)	OR (95% CI) Main effect model†	OR (95% CI) Reduced model†	OR (95% CI) Interaction model‡
BR rhinosinusitis (comparison)	2.18 (1.31, 3.64)§	2.14 (1.29, 3.55)§	–
Culturable fungi (low exposure)			
Medium	3.60 (1.46, 8.88)§	3.08 (1.39, 6.81)§	–
High	4.80 (1.85, 12.44)§	3.45 (1.59, 7.46)§	–
BR rhinosinusitis by fungal exposure (comparison/lower exposure)†			
Comparison/higher exposure	–	–	3.45 (1.36, 8.75)§
BR rhinosinusitis/lower exposure	–	–	2.44 (0.58, 10.27)
BR rhinosinusitis/higher exposure	–	–	7.31 (2.71, 19.70)§
Ergosterol (low exposure)			
Medium	0.66 (0.22, 2.00)	–	–
High	0.69 (0.25, 1.93)	–	–
Endotoxin (low exposure)			
Medium	1.22 (0.47, 3.16)	–	–
High	0.79 (0.31, 2.01)	–	–

*** All models were adjusted for year of building occupancy and demographics (age, gender, race, and smoking status).**
† Main effect model included all three exposure variables from the initial environmental survey. Reduced model included only culturable fungi as an environmental exposure variable.
‡ For the interaction model, medium and high tertiles of fungi were grouped into higher exposure for binary fungi variable. Then, the four-level categorical variable was created by combining BR rhinosinusitis symptom (presence/comparison) and binary fungi (lower/higher) variables.
§ $p < 0.05$

In the analyses using repeated measurements of environmental and health data accounting for within-person variability, we found significant associations between microbial exposure and respiratory health consistent with those from the cross-sectional analyses (Table 13). Our trend analyses, controlling for the individual respondent's initial health status in 2001, were based on two different types of health outcomes (recent and frequent symptoms and less recent symptoms) to examine changes of occupants' health status. The results of these analyses showed that the prevalence of symptoms occurring at least once per week in the last 4 weeks (recent and frequent symptoms) were generally not improved in the survey years since 2001 (Table 14). Prevalences of wheeze, asthma symptoms, shortness of breath on exertion, and nasal symptoms occurring more than once per week in the last 4 weeks tended to increase in subsequent survey years. These findings from the repeated measurement analysis were consistent with the trends observed in the prevalence analyses of these symptoms over the survey years using all four health questionnaire survey participants (n = 258) (Figures 3–5). Our symptom severity score analysis

was based on repeated measurements which indicated that the individual symptom severity for wheeze and shortness of breath on exertion tended to worsen in follow-up surveys. However, fever and chills and throat irritation symptom severities improved during the 6 years of the study (Table 14).

Table 13. Risks for BR respiratory symptoms by microbial agent, based on 2002 exposure*

BR symptoms	OR (95% CI) Total fungi	OR (95% CI) Ergosterol	OR (95% CI) Endotoxin
Wheeze	1.27† (1.04, 1.54)	1.15† (1.01, 1.32)	1.35† (1.01, 1.82)
Chest tightness	1.33† (1.10, 1.60)	1.18† (1.03, 1.36)	1.35† (1.02, 1.78)
Attacks of shortness of breath	1.33† (1.10, 1.62)	1.16† (1.02, 1.33)	1.39† (1.04, 1.86)
Cough attacks	1.26† (1.07, 1.49)	1.18† (1.05, 1.31)	1.11 (0.87, 1.42)
Awakened by breathing difficulty	1.50† (1.10, 2.05)	1.28‡ (1.00, 1.63)	1.40 (0.87, 2.24)
Asthma symptoms	1.30† (1.10, 1.54)	1.19† (1.06, 1.33)	1.32† (1.02, 1.69)
Nasal symptoms	1.20† (1.03, 1.40)	1.17† (1.07, 1.28)	1.35† (1.08, 1.69)
Sinus symptoms	1.08 (0.91, 1.29)	1.09 (0.98, 1.21)	1.15 (0.89, 1.50)
Throat irritation	1.20† (1.01, 1.42)	1.20† (1.08, 1.34)	1.15 (0.90, 1.47)

*** Estimated from regression models for repeated measurements, after controlling for effects of survey, age, gender, race/ethnicity, smoking status, and duration of building occupancy. ORs (95% CIs) were computed based on the change of the IQR for total culturable fungi (Ln CFU/m^2) (0.84 for 2002 fungi); ergosterol (Ln ng/m^2) (0.46 for 2002 ergosterol); endotoxin (Ln EU/m^2) (1.66 for 2002 endotoxin).**
† $p < 0.05$
‡ $p < 0.1$

Table 14. Time trends for BR symptoms in the last 4 weeks and changes in symptom severity over time

BR symptoms	ORs (95% CI) for BR symptoms in last 4 weeks*	Coefficient for symptom severity†
Wheeze	1.16‡ (1.05, 1.29)	0.023‡ (Worsening)
Chest tightness	1.00 (0.91, 1.10)	-0.011 (No change)
Attacks of shortness of breath	1.04 (0.94, 1.16)	0.002 (No change)
Cough attacks	1.05 (0.97, 1.15)	-0.0001 (No change)
Awakened by breathing difficulty	0.97 (0.81, 1.16)	-0.003 (No change)
Asthma symptoms	1.08§ (1.00, 1.18)	N/A
Shortness of breath on exertion	1.17‡ (1.06, 1.29)	0.024‡ (Worsening)
Flu-like achiness	1.00 (0.90, 1.11)	-0.008 (No change)
Fever and chills	0.97 (0.83, 1.12)	-0.015‡ (Improving)
Hypersensitivity pneumonitis-like symptoms	1.06 (0.96, 1.18)	N/A
Nasal symptoms	1.12‡ (1.04, 1.20)	0.015 (No change)
Sinus symptoms	1.01 (0.93, 1.10)	-0.011 (No change)
Throat irritation	0.99 (0.91, 1.08)	-0.026‡ (Improving)

*** Time trends for BR respiratory symptoms estimated from regression models for repeated measurements, including 2002 floor averages of total fungi, ergosterol, and endotoxin (continuous), survey year (continuous coded as 1, 4, 5, and 7), age, gender, race/ethnicity, smoking status, and duration of building occupancy variables. ORs are shown in one-year increments.**

† Symptom score was based on the severity of BR respiratory symptom at the individual level and was coded as 0 (no symptom), 1 (12-month symptom only), and 2 (4-week symptom) by survey. Coefficients for symptom severity were estimated from regression models for repeated measurements, including 2001 floor averages of total fungi, ergosterol, and endotoxin (continuous), symptom severity score (continuous), age, gender, race/ethnicity, smoking status, and duration of building occupancy variables. If the coefficient is positive and significant, it was defined as worsening in symptom severity and if the coefficient was negative and significant, it was defined as improving.

‡ $p < 0.05$

§ $p < 0.1$

Discussion

Our four cross-sectional surveys during a 6-year period in this office building with a long history of water damage demonstrated relationships between exposures to dampness-related agents in the building and the adverse effects on occupants' health from both cross-sectional and repeated measurement analyses. Prevalences of lower respiratory symptoms and asthma in the building occupants were higher compared to national and state data. The substantially increased incidence rate of asthma onset after occupancy in the building compared to that before occupancy provided strong evidence of involvement of the building environment in occupants' respiratory illnesses. The risk of respiratory illnesses in the occupants increased in relation to higher levels of microbial agents (fungi and endotoxin in floor and chair dust) in the building. The respiratory cases relocated in the building had a decrease in medication use and sick leave. These findings suggest that removing or decreasing occupants' exposure inside the building is important to protect occupants from building-related illnesses.

Our findings of the association between exposure to dampness-related agents and various respiratory symptoms are consistent with findings from the 2004 Institute of Medicine report and the 2009 World Health Organization guidelines, which conclude that there is sufficient evidence of an association between damp indoor environments and upper respiratory symptoms, wheeze, cough, and exacerbation of asthma symptoms (Institute of Medicine 2004, World Health Organization 2009). In addition, the World Health Organization guidelines further concluded that there is sufficient evidence of an association between exposure to dampness-related agents and the development of asthma, which is also consistent with the findings from our evaluations of the building. The World Health Organization guidelines reported that there is clinical evidence to support that mold and other microbial measures can increase the risk of developing hypersensitivity pneumonitis and chronic rhinosinusitis (World Health Organization 2009). This conclusion is also consistent with our findings on the occurrence of hypersensitivity pneumonitis and rhinosinusitis symptoms related to this damp building.

During the 6 years we studied the building, building management placed much effort on repairing water leaks and replacing damaged building materials, including carpets and dry wall. Indeed, prevalences of symptoms among persons who occupied the building after major remediation was completed in 2004 were consistently lower when compared to longer term employees (those who occupied the building prior to 2004). This may indicate some positive effects of remediation on lowering the prevalence

of symptoms among new employees. This positive remediation effect was also observed in the analyses of new onset of diseases. We found the number of diagnoses of post-occupancy asthma, sarcoidosis, and hypersensitivity pneumonitis cases appeared to be decreasing by 2007. By the time our survey ended in October 2007, two post-occupancy asthma diagnoses, two hypersensitivity pneumonitis cases, and no sarcoidosis cases had been reported for that year. This is considerably lower than between the years 2000 and 2002 before the major remediation, when cases of asthma, hypersensitivity pneumonitis, and sarcoidosis reached their peak. However, this decrease in the number of cases reported could have been due to the study ending before the end of the year in 2007 and the lack of follow-up time. The decrease in new diagnosis of post-occupancy asthma cases was also confirmed by the incidence density analysis on the 2007 survey data which takes the amount of follow-up time into account. However, even though there was a decline, the rate of post-occupancy asthma diagnosed between 2004 and 2007 was still 4.1 times higher than the pre-occupancy adult-onset asthma rate. Our other repeated measurement analyses examining changes of BR symptom severity (no symptom, less recent symptoms, or recent and frequent symptoms) showed alleviation in symptom severity for acute symptoms such as fever/chills and throat irritation symptoms, which may also indicate a remediation effect.

On the other hand, consistently higher symptom prevalence in longer term employees even after the major remediation was completed implies that respiratory symptoms in those with chronic exposure to the damp building environment may not be easily improved. In this building population, the majority (79%) of participants occupied the building before 2001 and this subpopulation appeared to have contributed to the overall increased burden of BR respiratory illnesses among building occupants. This persistently high prevalence contributed by the longer term employees was also reflected by our findings in the repeated measurement analysis that risks of wheeze or shortness of breath on exertion significantly increased and that the severity of those symptoms also significantly increased over the survey years. Another repeated measurement analysis of symptoms and objective medical tests also indicated that a subgroup of the longer term employees (97 employees who participated in both 2002 and 2005 medical surveys) did not generally show improvement in respiratory health, as reflected in symptom scores, overall medication use, spirometry abnormalities, or sick leave. In addition, our analysis on the progression of upper to lower respiratory symptoms among another subgroup of longer term employees showed that the

building occupants who reported BR rhinosinusitis symptoms in the initial 2001 survey were about twice as likely to develop asthma or BR asthma symptoms in subsequent survey years despite remediation. The effect of BR rhinosinusitis symptoms on asthma development was independent of that of mold or other dampness-related exposures. This finding may imply that once nasal and sinus symptoms develop due to exposure to dampness-related agents in building environments, the symptoms tend to progress to more severe and chronic illnesses such as asthma symptoms or asthma. Furthermore, the risk was much increased if those with rhinosinusitis symptoms were exposed to higher fungal levels or dampness-related agents in the building. These findings may indicate that controlling exposure through remediation during the early stages of water damage in a building is important to prevent onset of upper respiratory illnesses and their progression to chronic lower respiratory illnesses.

In many instances of water damage in modern buildings, finding sources of water leaks and damage at an early stage is difficult unless the building is being routinely and carefully monitored. In water-damaged buildings with hidden sources, occupant reports of health symptoms provide valuable information on the building environment and the occupants' potential exposure to building-related contaminants. If building management cannot implement remediation immediately after sources of water damages are identified, relocation of affected occupants should be seriously considered. Our study demonstrated substantial improvement in the health of relocated respiratory cases by the reported decrease in medication use and sick leave. Therefore, close communication between management, physicians, and occupants in relation to building-related health symptoms and the environmental conditions of occupied spaces is crucial to prevent occupant illnesses due to dampness-related exposures in buildings.

Although there were some indications of improvement in BR symptoms among the occupants, we generally found no improvement in risks and severity for many of the respiratory and non-respiratory symptoms as discussed earlier. This mixed result of remediation effects on occupants' health might be explained by partially successful remediation. Our repeated measurement analyses on environmental microbial agents indicated that the major remediation completed between 2002 and early 2004 had significantly decreased microbial levels in remediated workstations in 2004 and to a lesser degree in 2005, but not in 2007. The remediation effect in the 2004 survey was most evident as shown by the substantial decrease in the proportion of hydrophilic

fungi to total fungi, but the proportion started to increase in 2005, and further increased in 2007 where both the level and the proportion were eventually higher than that in 2002. Rates of lower respiratory symptoms and asthma remained elevated when compared to national and state data in all follow-up surveys conducted after the major remediation. Indeed, after the major remediation was completed in early 2004, ongoing water leaks from exterior windows on the upper floors (16–19) and leaks in the corner offices on the18th floor located directly below corner balconies of the 19th floor, had been documented by a consultant (Silver Petrucelli & Associates, Inc.). Another unpublished consultant report (Turner Building Science, LLC) noted that the building envelope was constructed according to a pre-1987 design: the envelope relied primarily on brick sealants between the window assembly and the brick veneer to keep wind-driven rain out of the structure. This older design does not have continuous drainage planes behind the brick veneer, which eventually leads to penetration of rainwater into the building. These findings emphasize that complete building diagnosis, including building inspections for water incursion to ascertain water sources, is essential because incomplete remediation eventually allows persistent water leaks. Recurring microbial proliferation and dissemination even after remediation is likely to adversely affect occupants with building-related illnesses and produce new cases.

Studies have indicated that workers with occupational asthma who continue to be exposed to the causative agent generally do not improve and may even deteriorate (Chan-Yeung and Malo 1993), and that those with shorter exposure durations tended to have higher rates of recovery (Rachiotis et al. 2007). However, exposure cessation is not always curative since many workers with occupational asthma can be left with permanent asthma symptoms and lung function abnormalities (Chan-Yeung and Malo 1993). A recent review article concluded that exposure cessation has been found to be more likely than exposure reduction to result in some degree of improvement in asthma symptoms and lung function abnormalities (Vandenplas et al. 2011). In a study which examines the effect of dampness remediation on students' health, it was found that remediation may be effective in terms of preventing new illness, but not eliminating symptoms in previously affected occupants (Haverinen-Shaughnessy et al. 2004). Our findings from the multiple cross-sectional evaluations are consistent with the literature in that affected occupants with long histories of exposure to increased levels of microbial or other dampness-related agents did not improve as a group in their respiratory symptoms, especially chronic ones such as wheeze and shortness of breath on exertion,

regardless of remediation. Overall, our findings emphasize that early detection of various signs of dampness and mold through routine and thorough inspection is essential; however, once the building is damaged by moisture incursion, immediate and complete remediation is vital for protecting occupants' health from potential dampness-related exposure.

There are limitations to this work. Our repeated measurement analysis on the progression of upper to lower respiratory symptoms and asthma was based on multiple cross-sectional surveys of participants. Occupants who participated in 2004 or 2005 but not in 2007, and who did not report building-related asthma symptoms or asthma diagnosis in the earlier surveys, might have developed the symptoms or had the diagnosis since their last survey that we did not ascertain in 2007. Therefore, there may be an underestimation in identifying building-related asthma symptoms or diagnoses reported in the follow-up surveys. However, this underestimation is not likely to change our conclusions because we obtained similar results when we analyzed only respondents who participated in all four surveys. The healthy worker effect might have also resulted in an underestimation of health outcomes in the follow-up surveys because some of the occupants with building-related respiratory disease had left employment or relocated to facilities outside the building before the follow-up survey. Another limitation in our repeated measurement analysis is the loss of 30% of the initial 2001 respondents in the follow-up surveys. However, the demographics and prevalences of rhinosinusitis symptoms were similar among non-participants and participants in follow-up, which may imply minimal participation bias.

In our surveys we were unable to characterize personal workstation dust exposure for each health questionnaire participant. We assigned exposure based on floor-specific means of the microbial measurements in some epidemiologic analyses of this report, which might have produced exposure misclassification in some occupants. However, unless selection of sampling locations within the floors was biased, assigning exposure to individuals based on their floor and using tertiles of floor-specific means was not likely to be influenced by individual health response, implying that the potential exposure misclassification is likely to be non-differential, if any. 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

DISCUSSION (CONTINUED)

within specific floors. Misclassification of exposure which is independent of participants' health generally decreases the strength of association. Even with this potential attenuation, we were able to demonstrate associations between exposure and health.

CONCLUSIONS

From our study of this building over a 6 year period, we documented an excess of respiratory illnesses in the building. Physician-diagnosed asthma, wheeze, attacks of shortness of breath, and nasal and eye symptoms were significantly higher when compared to national and state data. However, the new-onset of diseases such as asthma, hypersensitivity pneumonitis, and sarcoidosis have in general been declining since 2000 or 2001. In addition, persons who have been in the building for a shorter period of time (2004 or later) appear to have a lower prevalence of respiratory and non-respiratory symptoms. Despite some improvement, the longer term employees (hired before 2004) still showed no overall improvement in their health and even had increased risks of BR respiratory symptoms and post-occupancy asthma. They also had a higher risk of developing BR asthma symptoms if they had already developed BR nasal or sinus symptoms and remained in the building with relatively higher exposures to mold or other dampness-related agents. Although there had been continuous efforts to remediate water damage during the study period, it appeared that the initial success demonstrated in 2004 was not maintained. After three years, the remediation effect on the building environment and occupants' health was minimal. This may be due to the effects of longer-term employees on the burden of disease among building occupants, only partially successful remediation, or a combination of the two.

Water damage in this building is a public health problem with a substantial burden of disease associated with the building. There is a potential for ongoing water incursion due to the pre-1987 building design which did not include a continuous drainage plane behind the brick veneer. Continued attention to finding and remediating sources of water incursion is essential in such circumstances. Occupants should be informed of continued environmental and health issues, have the option of medical surveillance, and be relocated to dry work spaces at the onset of symptoms to avoid potentially long-term chronic respiratory disease.

RECOMMENDATIONS

On the basis of these findings from our evaluations and data analyses, we recommend the following:

1. Continue a routine maintenance program for evaluation and repair of water damage in the building, including regular observational assessment of water stains, mold growth, mold odors, and dampness, and systematic evaluation of window leaks, roof leaks, and functionality of exterior walls.
2. Continue to communicate with occupants regarding indoor environmental complaints (water damage, water stains, indoor air quality, etc.) and BR health complaints.
3. Initiate a surveillance program to monitor occupants' symptoms and new onset of possible building-related illnesses, with appropriate clinical referral for diagnostic tests, follow-up, and consideration of need for relocation.
4. For those persons with BR symptoms or illness, remove dampness problems and sources of microbial contamination from their work environment, or relocate to another area of the building or a different building.
5. Continue to practice daily or routine cleaning and housekeeping protocols, including HEPA vacuuming, to more efficiently remove potential microbial agents or other contaminants, and to minimize accumulation of dust in floor carpet and other surfaces.
6. Reconsider the following recommendation as given in Turner Building Science, LLC report from December 2005: "Evaluate a Redesign of the Exterior Envelope of the Facility to More Permanently Stop Rain Intrusion with a Redundant, Continuous Drainage Plane/Air Barrier/ Insulation Layer System, Installed from the Interior."
7. Advise employees of the availability of this report, and place the report on the website as was done with the interim reports.

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Acknowledgements and Availability of Report

The Respiratory Disease Hazard Evaluation and Technical Assistance Program of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6), or Section 501(a)(11) of the Federal Mine Safety and Health Act of 1977, 30 U.S.C. 951(a)(11), which authorizes the Secretary of Health and Human Services, following a written request from any employers or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

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The Respiratory Disease Hazard Evaluation and Technical Assistance Program also provides, upon request, technical and consultative assistance to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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Acknowledgements and Availability of Report (continued)

Copies of this report have been sent to employee and management representatives at the Connecticut Agencies housed in the building, the Unions represented in the building, and the OSHA Regional Office. This report is not copyrighted and may be freely reproduced. The report may be viewed and printed at www.cdc.gov/niosh/hhe/. Copies may be purchased from the National Technical Information Service (NTIS) at 5825 Port Royal Road, Springfield, Virginia 22161.

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