

Sarcoidosis, asthma, and asthma-like symptoms among occupants of a historically water-damaged office building

Abstract Sarcoidosis is a granulomatous disease of unknown etiology with evidence of association with exposure to microbial agents. In June 2006, we investigated a sarcoidosis cluster among office workers in a water-damaged building. In the course of the investigation, we became aware of a high rate of respiratory complaints including asthma and asthma-like symptoms. We conducted case finding for physician-diagnosed sarcoidosis and asthma and administered a health questionnaire survey and pulmonary function tests (PFTs) to consenting occupants. We compared prevalence ratios (PRs) to the Environmental Protection Agency's Building Assessment Survey and Evaluation study (BASE) and the National Health and Nutrition Examination Survey (NHANES). We identified six sarcoidosis cases. The current building prevalence is 2206 cases/100,000 population, elevated, compared with the US population range of <1–40 cases/100,000. Of current occupants, 77% (105) participated in the health questionnaire survey and 64% (87) in PFTs. Physician-diagnosed asthma was elevated, compared with the US adult population. Adult asthma incidence was 3.3/1000 person-years during the period before building occupancy and 11.5/1000 person-years during the period after building occupancy. Comparisons with US office workers (BASE) yielded elevated PRs for shortness of breath [PR, 9.6; 95% confidence interval (CI), 6.1–15.2], wheeze (PR, 9.1; 95% CI 5.6–14.6), and chest tightness (PR, 5.1; 95% CI 2.8–9.0). PFT results supported reports of respiratory symptoms and diagnoses. Based on our findings building occupants were relocated.

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Practical Implications

The remission of occupational asthma caused by certain known antigens improves with early diagnosis and removal from exposure. As a suspected antigen-mediated disease, sarcoidosis might also benefit if affected persons are isolated from continued exposure. Our investigation identified a high prevalence of new-onset sarcoidosis, and asthma among workers of a water damaged building with a history of indoor environmental quality complaints. Removal of all individuals from such environments until completion of building diagnostics, environmental sampling and complete remediation is a prudent measure when feasible.

Introduction

In June 2006, the Vermont Department of Health became aware of a possible cluster of sarcoidosis cases among occupants of an office building with a history of water incursion and indoor air-quality-related complaints. Population-based estimates of sarcoidosis prevalence for the United States are not readily available; however, ranges of <1–40 cases/100,000 population have been reported, (Crystal, 2005; Newman et al., 1997) and the most often cited US annual

incidence estimate of sarcoidosis (white race) is 10.9 cases/100,000 (Rybacki et al., 1997). Sarcoidosis is a multisystem granulomatous disease with variable pathogenicity, ranging from an asymptomatic course to systemic involvement. Although sarcoidosis is usually associated with a low mortality rate (1–5%), it can develop into a disabling, chronic condition.

Although the etiology of sarcoidosis has yet to be established, environments with bioaerosols of bacteria, endotoxins, or fungi are associated with granulomatous disease (Newman et al., 2004; Rose et al., 1998).

Respiratory diseases, including sarcoidosis, (Cox-Ganser et al., 2005; Dangman et al., 2005; Kucera et al., 2003) and hypersensitivity pneumonitis (Arnow et al., 1978; Cox-Ganser et al., 2005) have been reported to be elevated among occupants of water-damaged buildings. Additionally, evidence supports an association between exposure to damp indoor environments and asthma and asthma-like symptoms [e.g. wheeze, shortness of breath (SOB), and chest tightness] (Bornehag et al., 2004; Cox-Ganser et al., 2005; Dangman et al., 2005; Institute-of-Medicine, 2004; Jaakkola et al., 2002a,b; Mendell et al., 2006; Nevalainen and Seuri, 2005; Park et al., 2006; Seuri et al., 2000).

The implicated office building was built in 1978 with a three-story addition built in 1991 and houses 136 employees. Visual inspection of the building revealed signs of historic water incursion with approximately 20% of acoustic ceiling tiles exhibiting water-staining. Stains were attributed to roof leaks, pipe leaks, and valve failures in the heat pump system. In addition, we observed condensation between window panes and friable gypsum surrounding windows. Past sewage back-up into carpeted hallways and office spaces as well as entrainment of combustion products from the boiler-room into the occupied spaces have been reported.

In response to requests for assistance, we initiated a health investigation to assess occupational risk and to implement appropriate control measures. In this article, we present the results from our sarcoidosis investigation and our cross-sectional health questionnaire survey and pulmonary function testing (PFT) of current building occupants.

Materials and methods

Study participants

Study subjects included all consenting current and former building occupants. Informed consent was obtained from all study participants and institutional review board approval was obtained in accordance with the guidelines established at the Vermont Department of Health.

Sarcoidosis case definition and case finding

We initiated case finding in June 2006 and ascertained cases through self report and a health questionnaire survey. We also sent letters to former occupants, identified through the building's human resources office, dating back to 1994, asking if those persons had ever received a diagnosis of sarcoidosis. A case was defined as a self-reported physician diagnosis of sarcoidosis in a person who had spent ≥ 20 h/week in the building, with the diagnosis occurring after that person had occupied the building. We interviewed persons who matched our

case definition regarding diagnosis, medical course, potential risk factors, and work history.

Health questionnaire survey

In August 2006, we offered a questionnaire to all 136 current building occupants who had spent ≥ 20 h/week in the building. The questionnaire was developed to assess and compare self-reported health and building-related symptoms and complaints. Questions were derived from two primary sources – the U.S. Environmental Protection Agency (EPA) Building Assessment Survey and Evaluation (BASE) study (Burton et al., 2000; Girman et al., 1995; Womble et al., 1995) and the third National Health and Nutrition Examination Survey (NHANES III; Centers for Disease Control and Prevention, 1996). By completing the questionnaire, participants indicated their consent.

Pulmonary function testing

In September 2006, we offered PFTs to the 136 current employees after obtaining written informed consent. All PFTs were conducted in a 10-day period by NIOSH technicians who followed standard American Thoracic Society (ATS) guidelines for spirometry (American Thoracic Society, 1995). Test results were compared with expected values and 95% normal confidence intervals (CIs; Hankinson et al., 1999). We defined airway obstruction as a low forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio (FEV_1/FVC %) with low FEV_1 . We defined restriction as a low FVC and normal FEV_1/FVC %. A mixed pattern was a low FVC and obstruction (American Thoracic Society, 1995).

To detect bronchial hyperresponsiveness (BHR) among persons with FEV_1 of $\geq 70\%$ predicted value, we performed methacholine challenge testing (MCT) by using standardized techniques (Crapo et al., 2000) with 0.125, 0.5, 2, 8, and 32 mg/ml of methacholine. We reported MCT results as PC_{20} , which is the provocative concentration of methacholine that causes an interpolated 20% decline in FEV_1 from the baseline. We defined BHR as a PC_{20} of ≤ 4.0 mg/ml and borderline BHR as a PC_{20} of 4.1–16.0 mg/ml (Crapo et al., 2000).

Among subjects with baseline $FEV_1 < 70\%$ of the predicted value, reversible bronchoconstriction was ascertained with two puffs of a beta-agonist, followed by spirometry. We defined reversibility as a $\geq 12\%$ increase in FEV_1 over baseline and a minimum 200-ml improvement in FEV_1 (American-Thoracic-Society, 1991).

To detect reduced ability of the lungs to exchange gases, diffusing capacity of the lung for carbon monoxide tests were administered and interpreted by using standard ATS guidelines, (Macintyre et al., 2005) compared with predicted values (Miller et al., 1983).

Nonsmoking-specific equations were applied to all participants, and persons were classified as abnormal if their test results declined below the lower limit of normal.

Definition of combined measure of overall respiratory health

To elucidate the total burden of respiratory illness among building occupants, we increased the sensitivity of our asthma category by broadening the case definition beyond self-reported physician diagnosis. The more sensitive asthma definition included those persons with self-reported physician-diagnosed asthma, questionnaire-indicative asthma (reporting three or more respiratory symptoms of wheeze, chest tightness, SOB, coughing attack, or having been awakened by attack of breathing difficulty), or PFT-indicative asthma (MCT abnormality or reversible obstructive abnormality).

Data analysis

To assess whether rates of respiratory illness were elevated among building occupants, we compared symptom prevalences with three reference populations – the general US population [NHANES III; Centers for Disease Control and Prevention, 1996], a representative sample of US office workers (BASE), (Apte et al., 2000] and Vermont adults [state and county, 2005 Vermont Behavioral Risk Factor Surveillance System (BRFSS); Centers for Disease Control and Prevention (CDC) (2005)]. For NHANES III comparisons, data were standardized for white race, sex, age (17–39 and ≥40 years) and cigarette smoking (current, former, never). We used the Cochran–Mantel–Haenszel test for between-proportion differences (NHANES and BASE), calculated incidence density for adult-onset asthma (aged ≥ 16 years) before and after building occupancy, (Cox-Ganser et al., 2005) and conducted an assessment of intrabuilding clustering of symptoms among current building occupants. Prevalence odds ratios were used to compare the two building sections (original 1978 structure vs. 1991 addition). Sarcoidosis incidence density was calculated as the total number of sarcoid cases identified, divided by the sum of the annual building population for a 15-year period (total person-years). The methods used for statistical analyses of direct two-way comparisons were Fisher's exact test and exact 95% CIs (Hirji et al., 1994).

Results

Participation

Overall participation in the health investigation was 92% (125/136) with 77% participation in the cross-sectional health questionnaire survey and 64% participation in PFTs (Table 1). Demographic characteristics of the building occupants are presented in Table 2.

Table 1 Participation rate (*n* = 136)

Test or survey	Rate (%)
Cross-sectional health survey	77
Pulmonary function testing (PFT)	64
Health survey and PFT	49
Health survey or PFT	92

Table 2 Demographics of health survey participants

Characteristic	Proportion or measure
Female	63.9% (66/105)
White race	97.1% (102/105)
Smoking	
Former	33.0% (33/100)
Current	16.0% (16/100)
Never	51.0% (51/100)
Age [years (mean ± s.d.)]	46.2 ± 12.6
Building occupancy [years (mean ± s.d.)]	7.5 ± 7.8

Sarcoidosis

We identified six cases of sarcoidosis through case finding – three among current building occupants and three among former occupants. Of the six, two persons reported isolated pulmonary involvement, one isolated lymph node involvement, and three with multiorgan involvement. In addition, five of the six reported a biopsy-confirmed diagnosis. All six had received their diagnosis after building occupancy.

On the basis of the building occupant's human resource records, approximately 500 persons had been employed in the building since the first identified illness was diagnosed in 1992. During that time, the 15-year sarcoidosis period prevalence was 1200/100,000 population. The estimated sarcoidosis incidence density for the 15-year period is 294 cases/100,000 person-years at risk (on the basis of 2040 person-years). The current building prevalence is 2206/100,000 population.

Health questionnaire survey

Participants reported high rates of respiratory complaints. Compared with the general US population (NHANES III), prevalence ratios (PRs) for SOB, wheezing, and lifetime asthma ranged from 1.8 to 3.2 ($P < 0.05$; Figure 1, panel a). Nasal symptoms, eye irritation, and sinusitis were also elevated but did not reach a level of statistical significance. Compared with office workers in buildings not known to have indoor air-quality complaints from occupants, PRs for respiratory symptoms during the previous 4 weeks that improved when away from the building were also elevated and included SOB (PR, 9.6; 95% CI 6.1–15.2), chest tightness (PR, 5.1; 95% CI 2.8–9.0), wheezing (PR, 9.1; 95% CI 5.7–14.6), and coughing attack (PR, 3.9; 95% CI 2.5–6.1; Figure 1, panel b).

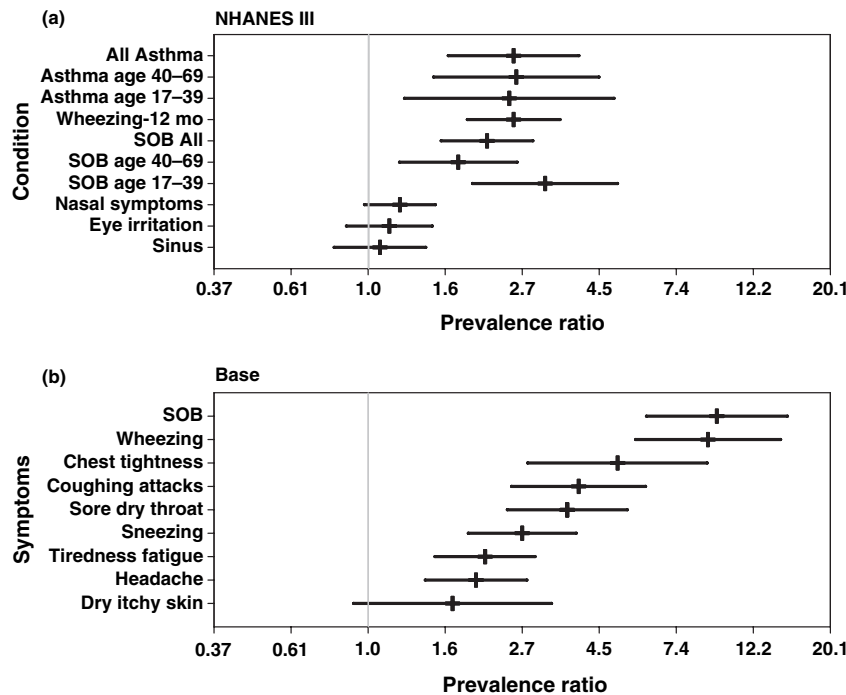


Fig. 1 Comparisons of self-reported symptoms among building occupants and US referent populations – prevalence ratios (PRs) and 95% confidence intervals. Data transformed on natural log scale. SOB, shortness of breath. Panel (a) Comparisons between building occupants and NHANES III. PRs adjusted for age, sex, race, and smoking status. Panel (b) Comparisons between building occupants and US office workers (BASE study participants)

The prevalence of building occupants who reported ever having received a diagnosis of asthma was 20% (21/104). The prevalence of occupants reporting current asthma was 15% (16/104). A comparison with the state and county in which the building was located (BRFSS) provided PRs of 1.6 and 1.3, respectively. In addition, asthma PRs were also elevated compared with the general US population (Figure 1). The prevalence of adult-onset asthma was 15% (16/105), with 56% (9/16) of diagnoses occurring after building occupancy.

An analysis of adult-onset asthma incidence density was conducted on the basis of 2134 person-years at risk before building occupancy and 780 person-years at risk after building occupancy. We identified incidences of 3.3/1000 person-years during the period before building occupancy and 11.5/1000 person-years during the period after building occupancy. The incidence density ratio was 3.6 (95% CI 1.3–9.6), indicating a significant increase in asthma incidence during the period after building occupancy ($P = 0.007$). The age of adult-onset asthma did not differ significantly between building occupants (mean, 37.9; median, 35.4 years) and the state data (mean, 38.8; median, 36.0 years; 2005 state BRFSS data).

Pulmonary function testing

Among the 87 participants receiving PFTs, 32% had at least one abnormal test, with obstructive abnormalities

(obstructive and mixed abnormalities) observed among 13% of participants and BHR among 15% (Table 3). Among persons who participated in both PFTs and the health questionnaire, 29.9% (20/67) had at least one abnormal PFT. Figure 2 shows the symptom reporting

Table 3 Pulmonary function testing of current building occupants – univariate frequencies

Variable	Proportion
Any abnormal lung function ^a	32.2% (28/87)
Spirometry	
Test within normal limits	85.1% (74/87)
Obstructive abnormality ^b	10.3% (9/87)
Reversible obstruction	40.0% (2/5)
Nonreversible obstruction	60.0% (3/5)
Restrictive abnormality	2.3% (2/87)
Mixed abnormality ^c	2.3% (2/87)
Methacholine challenge test	
Abnormal bronchial responsiveness	15.4% (10/65)
PC ₂₀ < 4 mg/ml	4.6% (3/10)
PC ₂₀ 4–16 mg/ml	10.8% (7/10)
Diffusing capacity of the lung for carbon (DLCO) monoxide test determination	
Abnormal	8.1% (7/86)

^aParticipants who had abnormal spirometry or an abnormal DLCO or an abnormal methacholine challenge test.

^bBronchodilator administered to only five of nine subjects with an obstructive abnormality.

^cIncludes obstructive and restrictive abnormalities.

PC₂₀, the provocative concentration of methacholine that causes an interpolated 20% decline in FEV₁ from the baseline.

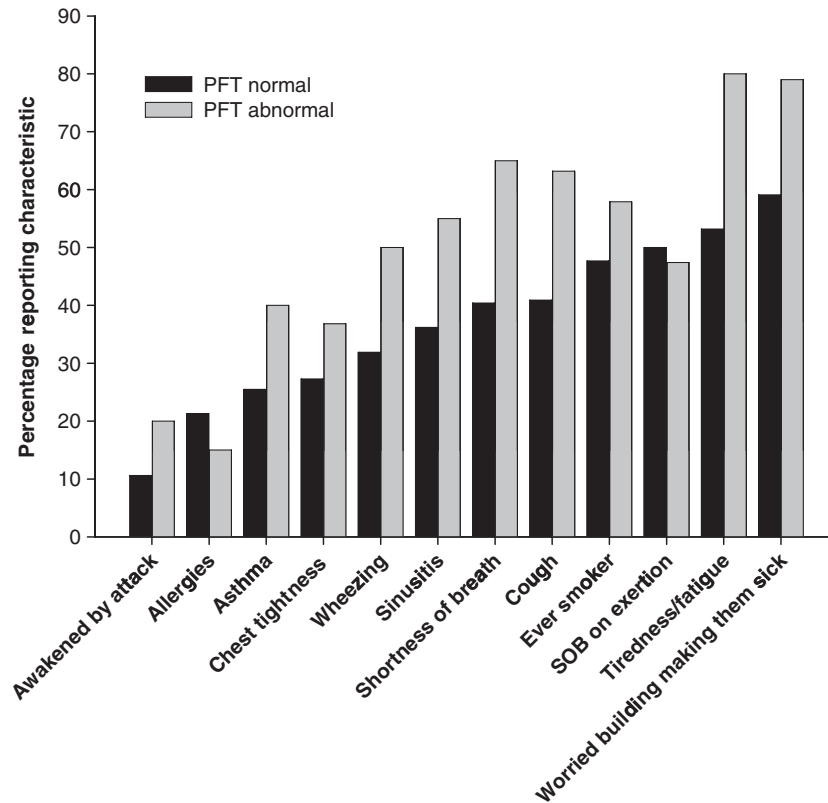


Fig. 2 Symptom reporting among persons with normal and abnormal pulmonary function tests (PFTs). Data are from the 67 persons who participated in both the questionnaire survey and PFT. PFT abnormal defined as any abnormal PFT test, including spirometry, methacholine challenge, diffusion capacity of the lung for carbon monoxide (DLCO), and total lung capacity (See Materials and methods section for specific cut-off values and definitions). Awakened by attack of breathing difficulty during the preceding 12 months

on the health questionnaire among persons with normal and abnormal PFTs.

Combined measures of overall respiratory health

Pulmonary function test-indicative asthma (methacholine challenge or reversible obstructive abnormality) was observed among $\geq 14\%$ (12/87) of PFT participants (not all PFT participants participated in all tests). Questionnaire responses indicative of asthma (three or more of five possible self-reported respiratory symptoms) were observed among 19% (20/104) of participants. In conjunction with physician-diagnosed asthma, the total burden of current asthma among building occupants is an estimated prevalence of 14–34%, depending on case definition applied (Table 4).

Intrabuilding clustering of self-reported symptoms

We conducted an analysis to determine whether spatial aggregations of symptoms could be identified within the building. Substantial differences were observed when the comparison groups were associated with the original 1978 one-story structure or the newer (1991) three-story addition. Overall, occupants of the older

Table 4 Current asthma prevalence by case definition

Physician-diagnosed	15.4% (16/104)
Questionnaire-indicative (three or more respiratory symptoms)	19.2% (20/104)
Methacholine challenge test abnormal	15.4% (10/65)
Pulmonary function test (PFT)-indicative (abnormal MCH or obstruction)	13.8% (12/87)
Questionnaire- and PFT-indicative ^a	34.3% (23/67)
Questionnaire- or PFT-indicative ^b	27.2% (34/125)
Questionnaire- or PFT-indicative ^c	25.0% (34/136)

^aDenominator is those who participated in both the National Institute for Occupational Safety and Health (NIOSH) PFT and health survey.

^bDenominator is those who participated in either NIOSH PFT or health survey or both.

^cDenominator is all building occupants and includes persons who did not participate in health investigation.

section had higher prevalences of multiple symptoms (Table 5). However, no discernable pattern of clustering was apparent among persons reporting physician-diagnosed asthma, questionnaire-indicative asthma, or sarcoidosis with respect to their physical work location within the building (Table 5).

Discussion

We describe an association between occupancy in a water-damaged office building and respiratory mor-

Table 5 Symptom reporting by building location

Symptom	Older section (%) (n = 46)	Newer section (%) (n = 51)	POR	Exact 95% CI	P-value
SOB	55.6	29.4	3.0	1.3–7.0	0.008
Coughing attack	46.3	51.0	0.83	0.3–2.0	0.41
Chest tightness	40.0	23.5	2.2	0.8–5.9	0.07
Wheezing	42.2	37.3	1.2	0.5–3.0	0.39
Awakened by difficulty breathing	10.9	17.7	0.57	0.1–2.1	0.26
SOB on exertion	57.5	29.4	3.2	1.3–8.5	0.006
Physician-diagnosed asthma	24.4	15.7	1.7	0.6–5.6	0.21
Questionnaire-indicative asthma	37.0	23.5	1.9	0.7–5.1	0.11
Influenza-like symptoms	64.4	37.3	3.1	1.2–7.7	0.007
Nasal symptoms	82.9	64.7	2.6	0.9–8.5	0.04
Itchy skin	53.7	33.3	2.3	0.9–5.9	0.04
Itchy eyes	61.0	41.2	2.2	0.9–5.6	0.05
Dry throat	64.4	49.0	1.9	0.8–4.7	0.09
Back pain	84.1	47.1	5.9	2.1–18.5	<0.001
Ever a smoker	46.3	49.0	0.90	0.4–2.2	0.48
Symptoms from building	76.2	69.4	1.4	0.5–4.1	0.31
Worried building making them sick	70.5	69.6	1.0	0.4–2.8	0.56

Older section refers to original 1978 one-story structure, Newer section refers to 3-story 1991 addition. P values are Fisher exact.

POR, prevalence odds ratio; CI, confidence interval; SOB, shortness of breath.

Not all participants responded to all questions.

bilities, including sarcoidosis and asthma. Although background comparison rates are not wholly reliable, estimates of the prevalence of sarcoidosis among the US white population are <40 cases/100,000 population (Crystal, 2005; Newman et al., 1997). In our investigation, the prevalence of sarcoidosis observed among current building occupants was 2206 cases/100,000, which yields a minimum 55-fold increased prevalence with 95% CI lower bound of 11. Furthermore, 25% of all current building occupants had evidence of asthma or asthma-like illness on the basis of PFTs or the questionnaire.

In addition to the temporal association, we observed between building occupancy and onset of asthma, a body of evidence supports an association between exposure to water-damaged buildings and respiratory illnesses, including adult-onset asthma (Bornehag et al., 2004; Cox-Ganser et al., 2005; Dangman et al., 2005; Institute-of-Medicine, 2004; Jaakkola et al., 2002a,b; Jaakkola et al., 2002b; Nevalainen and Seuri, 2005; Park et al., 2006; Seuri et al., 2000). It is biologically plausible that at least some degree of the respiratory burden among study participants can be attributed to the past water damage observed in their workplace. With respect to the cluster of sarcoidosis, however, allocating responsibility to a plausible environmental exposure is more of a challenge because of the lack of established data regarding etiology. Nevertheless, our findings add to a limited body of evidence supporting an epidemiologic association

between sarcoidosis and exposure to indoor water-damaged environments (Dangman et al., 2005; Kucera et al., 2003; Newman et al., 2004).

Recent experimental studies have demonstrated that common microbial constituents of damp indoor environments have the potential to be potent inducers of inflammatory responses (Hirvonen et al., 2005; Murttoniemi et al., 2003). Researchers believe that granuloma formation in sarcoidosis is in response to a presently unidentified antigenic stimulus that induces a local Th1-cell – mediated immune response. Chronic stimulation of macrophages causes the ongoing release of inflammatory cytokines (IL-2, IL-12, IFN- γ , and TNF- α), leading to accumulation of Th1 cells at the site of inflammation. This immunologic cycling contributes to ongoing expansion of the granuloma structure (Richie, 2005).

Prolonged exposure to one or more of the microbial components commonly isolated from damp indoor environments might provide the antigenic stimuli that initiate the immune response responsible for granuloma formation in sarcoidosis. If this model proves accurate, remediation of the environment that fosters the microbial growth should prevent future incident cases that might have occurred through this mechanism and should also aid in remission of those with active sarcoidosis.

As with any public health response that uses an observational study design, potential limitations and biases should be addressed. First, with respect to selection bias, we recruited 92% of the cohort of current building occupants to participate in the health investigation. Because of the high participation rate, selection bias is unlikely to modify our overall conclusions, and sample sizes were sufficient to minimize variation in certain statistical summary measures presented.

Secondly, recall and reporting biases are potential areas of concern in studies of building occupants with known health concerns. If recall bias occurred in the present study (e.g. occupants did not recall a physician diagnosis of asthma), the actual magnitude of respiratory illness we report is an underestimation of the true burden of disease.

Reporting bias occurs when persons report illnesses or symptoms they have not actually experienced or report misdiagnosed conditions. This effect can lead to misclassification of disease and thus to overinflated estimates. The sarcoidosis diagnoses were made by different physicians, and the majority were pathologically confirmed. In addition, we have objective measurements of respiratory health consistent with excess disease that are in agreement with self-reported symptoms and diagnoses obtained from the health questionnaire survey as demonstrated in Figure 2. Additionally, the magnitudes of the measures of effect were elevated such that systematic misdiagnosis of

disease likely would not be occurring at a rate high enough to entirely diminish the statistically significant elevation of illness observed. Overall, these potential biases have not likely been of magnitude great enough to alter our overall conclusions that respiratory morbidities and sarcoidosis were significantly elevated among building occupants, compared with referent populations.

On the basis of our current findings, continued exposure to the building likely increases the risk for experiencing respiratory illness and sarcoidosis, although the exact mechanism is unclear. The remission of occupational asthma caused by certain known antigens improves with early diagnosis and removal from exposure (Douglas, 2005). By analogy, removal

of persons with asthma whose illness onset occurred in this building is prudent. As a suspected antigen-mediated disease, sarcoidosis might also benefit if affected persons are isolated from continued exposure. In the absence of knowledge of the health risk of continued occupancy to those without current building-related complaints, and in view of the high proportion of employees seeking relocation because of respiratory conditions, public health officials in the state concluded that the best course of action was removal of all building occupants until building remediation is completed. Future plans include extensive building diagnostics and remediation, environmental testing, and continued health monitoring of employees.

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