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A Comparison of Two Methods of Evaluating the Relationship between Fungal Spores and Respiratory Symptoms among Office Workers in Mechanically Ventilated Buildings

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ABSTRACT

Respiratory symptoms are among the most common symptoms reported by workers in mechanically ventilated office buildings. In different studies, the prevalence of nasal problems has been reported in the range of 22%-62% and cough, 18%-41%. Fungal spore exposure has been identified as one possible explanation of these respiratory complaints, exposure arising either as a result of humidification system contamination with fungal species or through local contamination of office carpets, plants, and furnishings. In this study, we compared two approaches to the investigation of this hypothesized association: a repeated measures cross-sectional survey of exposure levels and symptoms under two different ventilation conditions and a nested case-control design within a defined cohort of office workers. The first approach is best suited to the detection of associations attributable to HVAC sources of fungal spore exposure, whereas the latter is best suited to associations related to local fungal spore contamination.

In the four buildings studied, average fungal spore counts were low, in the range of 7.7 to 97.0 ns/m^3*. The highest value observed was 289 ns/m*^{3}*. At these low levels of contamination, there was no difference in fungal spore measurements with the two methodologies. Despite a high prevalence of weekly respiratory and mucosal irritation symptoms among the 1,627 participating building occupants (24%-47%), there was no association between fungal spore count and symptom occurrence.*

INTRODUCTION

Respiratory symptoms are among the most common symptoms reported by workers in mechanically ventilated office buildings. In different studies, the prevalence of nasal problems has been reported in the range of 22%-62% and cough, 18%-41% (Skov and Valbjorn 1987; Burge et al. 1987; Menzies et al. 1990). Since fungal spore sensitivity has been identified as a major cause of allergic rhinitis and a contributing cause of allergic asthma (Salvaggio and Aukrust 1981; Lehrer et al. 1986), it has been hypothesized that exposure to fungal spores in the workplace may be a possible cause of these complaints. In studies of the home environment, associations have been demonstrated between exposure to fungal spores and respiratory problems in children (Burr et al. 1988). In the work environment, associations with fungal spore exposure and the occurrence of specific diseases, such as hypersensitivity pneumonitis, have been demonstrated. However, the role that fungal spore contamination may play in the respiratory and mucosal irritation symptoms of sick building syndrome (SBS) is less certain. Investigations of symptom epidemics in office buildings have lent some support for the etiological role of fungal spores. Elixmann (et al. 1990) found that 135 of 150 patients with complaints of SBS had skin test reactivity to fungal spore antigens traced to a contaminated ventilation system. In one study of factory workers with respiratory complaints, ventilation system contamination with *aspergillus* was associated with a positive serum precipitans among 15% of 1,050 exposed workers in comparison to none of 50 non-exposed controls. Burr et al. (1988) and Burge et al. (1985) have reported similar results, objective and subjective evidence of an allergic response being associated with ventilation system contamination. The question that remains is whether fungal spore exposure can be imputed as a significant contributor to the prevalent respiratory and mucosal irritation complaints that have been systematically noted among office workers in mechanically ventilated office buildings (Skov and Valbjorn 1987; Burge et al. 1987; Menzies et al. 1990).

We compared two different approaches to the investigation of the relationship between fungal spore exposure and symptom occurrence among office workers: (1) a cross-sectional ecological

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approach using building estimates of fungal exposure and (2) a case-control approach using worksite measurements of fungal exposure. The first approach is best suited for the detection of ventilation system sources of fungal spore contamination, the source that has been held responsible in most reported studies to date. If this is a significant contributor to respiratory complaints among office workers, the prevalence of complaints would be higher in buildings with higher fungal spore levels and possibly within the same building under different ventilation conditions. The second approach is most appropriate if local sources of contamination are suspected as the most likely cause of respiratory symptoms among office workers. This possibility is supported by Graveson et al. (1986), who found significant differences in dust-bound mold levels in carpeted and uncarpeted rooms within the same office building. If local contamination were a significant contributor to symptoms, one would expect to find a fairly large range in fungal spore levels in randomly sampled worksite measures and higher fungal spore levels at the worksites of symptomatic as compared to asymptomatic workers. We conducted this investigation as part of a four-building double-blind cross-over study of ventilation conditions and symptom prevalence (Menzies et al. 1991).

OBJECTIVES

The objectives of the study were (1) to compare two methods of evaluating fungal spore exposure in mechanically ventilated office buildings and (2) to estimate the relationship between fungal spore exposure and self-reported symptoms of respiratory and mucosal irritation using the two methods of exposure measurement.

METHODOLOGY

Study Population

Four mechanically ventilated high-rise office buildings in the downtown Montreal area were studied. The study population consisted of a group of employees of major corporate tenants within these building. Using a combination of floor enumeration and employee lists, employees were enumerated and approached to determine their eligibility and willingness to participate in the study. Ineligible workers were defined as those who were on vacation or maternity leave for four or more of the six study weeks, were out of the office at least three of the five days per week (e.g., salesmen), had no fixed work location (e.g., porters), were retired, or had left the company within the first two weeks of the study.

The Experimental Intervention

Two buildings were studied in the spring of 1990 and two in the fall of the same year. The experimental intervention was carried out over a period of six consecutive weeks. It consisted of double-blind manipulation of the ventilation conditions within the building, providing a weekly exposure to one of two ventilation conditions: approximately 50 cubic feet per minute per person (cfmpp) of outdoor air or 20 cfmpp of outdoor air (late afternoon readings of approximately 500 ppm and 1,000 ppm of CO_2, respectively). Ventilation conditions were applied in a randomly ordered sequence within three two-week blocks, with counterbalancing within weeks between the two study buildings to cancel out the effect of weekly weather changes and time trends. The results of this experiment are reported in Menzies et al. (1991).

Measurement of Fungal Spore Exposure

In the two buildings studied in the spring, colony (viable) counts were estimated using agar strips with four minutes of air sampling per measurement[1] (Lab 1) and Sabouraud media and an individual volumetric sampler drawing 35 litres of air per minute continuously for 15 minutes (Lab 2). In the fall, total (spores) counts were also estimated using glycerine-gelatine coated slited and an individual volumetric sampler drawing 10 litres of air a minute continuously for 15 minutes. In the lab, spores were directly counted and identified under a microscope at 400×. After five to seven days, colonies were counted and each morphological type was transferred on a 2% malt medium and submitted to U.V. light for 12-hour cycles) and allowed to sporulate before a sample was taken and examined under a microscope at 1000× for identification. With the sampling time and volume sampled known, counts can be expressed as numbers per cubic metre of air.

Measurement of Symptom Occurrence

At the beginning of the study period, participating workers completed a baseline questionnaire that provided information on the usual conditions of their work and office environment, health condition, and experience with cardinal symptoms of SBS. During the six-week experimental intervention, the same workers completed weekly questionnaires. Each week they were asked to report on the environmental conditions and symptoms (headache; nasal, eye, and throat irritation; cough; fatigue; concentration problems) experienced on the day of questionnaire administration (Wednesday or Thursday).

Method 1—The Ecological Approach

Ventilation System Contamination as a Cause of Respiratory and Mucosal Irritation Symptoms

If ventilation system contamination is hypothesized as the most likely source and cause of respiratory symptoms in SBS, then an ecological design is best suited to the evaluation of the relationship. The approach to measurement is dictated by the underlying supposition that a defined group is at risk because of their exposure to a causative agent. In this study, members of the group at risk are all occupants of a building whose centralized ventilation system may be contaminated with fungal spores. The approach to measurement and analysis is to estimate exposure of the group and their symptom experience. Groups with higher building exposures would be hypothesized to have a greater proportion of symptoms than groups with lower levels of exposure. To estimate group exposure, samples of indoor air were taken at a random sample of locations (worksites) in the building as well as from the hypothesized source of contamination, the building ventilation systems(s). In each of the six study weeks, 3-18 fungal spore measurements were taken from a random sample of worksites as well as from the supply and return air of the building's ventilation system(s). In the spring, samples were taken in each of the six study weeks, providing three weeks of fungal spore data under the two ventilation conditions: outdoor air dampers closed (20 cfmpp) and outdoor air dampers open (50 cfmpp). In the fall, fungal spore data were gathered in two of the six study weeks, providing representation of each ventilation condition in each study building.

The group's experience with symptoms suggestive of mucosal irritation (throat, eye, and nasal irritation) as well as respiratory system problems (cough, shortness of breath) were measured by a weekly questionnaire. The group's experience for each of the

[1] Per litre of distilled water, agar strips composed of agar-agar, 16.0 gms; dextrose (D(+)), 10.0 gms; special peptone, 6.0 gms; KH_2PO_4, 0.5 gms; $M_gSO_4 \cdot 7\ H_2O$, 0.5 gms; Rosa bengal, 0.05 gms; and streptomycin, 0.04 gms.

study weeks was summarized as the proportion of group members reporting one or more of these symptoms (weekly prevalence). The relationship between fungal spore levels and symptom prevalence was examined by correlating weekly building levels of fungal spore counts with weekly prevalence. The group was the unit of analysis. Both parametric and nonparametric methods of estimation were used. Fungal spore exposure was examined using log transformed counts.

Method 2—The Case-Control Approach

Worksite Contamination as a Cause of Respiratory and Mucosal Irritation Symptoms

If local sources of fungal spore contamination are hypothesized to be the source and cause of respiratory complaints, a case-control design, rather than an ecological design, is a more appropriate approach to the evaluation of the association. It is assumed that, if local sources are the primary cause, individual occupants are at varying risk of symptom occurrence as a function of differences in fungal spore exposure in their respective work locations. Therefore, the plan for sampling and measurement is based on the objective of gaining an estimate of the fungal spore exposure of symptomatic workers (cases) and contrasting it with comparable but asymptomatic workers (controls). In this study, symptomatic workers (cases) were defined as participating workers in one of the two fall study buildings who reported having experienced nasal irritation and/or cough and shortness of breath at work at least two to three times per week and who reported that symptoms occurred only in the office environment. Controls were drawn from all other participating workers in the two fall buildings who did not meet the case definition. One control was matched to each case by gender, atopic history, and building location. Cases and controls were defined using data from the baseline questionnaire. Estimates of individual exposure were carried out by sampling the worksites of cases and controls, all samples being taken over a two-day period in the study building with the technician being blind to the symptom experience of the designated worker. The relationship between fungal spore levels and symptom status was evaluated by a paired t-test and a Wilcoxin signed rank test for differences in total spore count. Both raw and log transformed spore counts were used in the analysis. A McNemar test was used to evaluate whether there were differences between cases and controls in the presence or absence of specific fungal spore types.

RESULTS

Study Population

In the spring, 740 of the 840 (88.1%) eligible workers within the first two study buildings participated in the study and, in the fall, 887 of the 977 (90.8%) eligible workers participated. Weekly response rates varied from 71% to 87% in the spring and between 61% and 84% in the fall, the most common reason for nonresponse being that the worker was out of the office for the study week. Cases and controls were drawn from the 693/887 participating workers who had returned the baseline questionnaire by the fourth week of the study. This group represented 89% of all workers who eventually returned the questionnaire. From this group of 693, 163 cases and 163 matched controls were identified. Fungal spore measurements were successfully completed in 106 of these matched case-control pairs. For the remaining 57 pairs, missing data were due to the technician's inability to find the participant's office (50/57), the office was locked (3/57), or the participant had moved (4/57).

Differences in Fungal Spore Measurement as a Function of Methodological Approach

To compare results in fungal spore measurement with the two types of methodological approaches, we used the fall buildings exclusively. In Table 1, it can be noted that the fungal spore levels in both buildings were low, both for estimates produced by the ecological approach and the case-control method. The distribution of fungal spore counts was skewed toward zero. Therefore, both the geometric mean and the arithmetic mean were used to provide a descriptive summary of central tendency. For both methods, the variation in fungal spore levels was more than double the value of the arithmetic mean, suggesting that the distribution may be clumped (rather than random). This type of distribution is consistent with the hypothesis that local sources of contamination may be contributing significantly to estimates produced by random or systematic samples from worksites. Despite the possibility that local sources of contamination may be present and contribute to symptoms, there was no statistically or clinically significant difference in the results that would have been obtained about exposure using the first and second methodology. This conclusion holds for both nonparametric and parametric methods of testing.

Differences in the Estimated Relationship between Fungal Spore Exposure and Symptoms with two Methodological Approaches

Method 1—The Ecological Approach In Table 2, the weekly estimated total spore counts are displayed, as well as the weekly prevalence of respiratory and mucosal irritation symptoms. Comparable measures of fungal spore exposure were produced by both laboratories for buildings A and B. The results from Lab 1 are presented in Table 2, as well as the arithmetic and geometric mean of the observed fungal spore count distribution. With respect to exposure, the first interesting difference is the effect of ventilation condition on fungal spore level. In buildings A, C, and D, fungal spore levels rose when the proportion of fresh air brought into the building was reduced, the opposite effect occur-

TABLE 1
Fungal Spore Count Estimates: Method 1, The Cross-Sectional Ecological Approach, vs. Method 2, The Case-Control Approach

Building	Method #1 HVAC and Floors				Method #2 Cases				Method #2 Controls			
	GM	Mean	sd	range	GM	Mean	sd	range	GM	Mean	sd	range
C	74.5	91.7	55.9	0-267	57.0	74.7	47.3	0-220	61.1	78.1	49.3	0-289
D	63.6	71.9	25.2	22-151	62.7	72.0	39.4	10-160	72.1	78.3	38.3	29-200

Legend:
Mean-arithmetic mean fungal spore count (ns/m^3) sd-standard deviation
GM-geometric mean

TABLE 2
Weekly Fungal Exposure and Prevalence of Respiratory and Mucosal Irritation Symptoms

		Building												
		A n=283			B n=457			C n=534			D n=353			
Ventilation Condition	Test Week	Fungal GM	Fungal Mean	Symptom %p	Fungal GM	Fungal Mean	Symptom %p	Fungal GM	Fungal Mean	Symptom %p	Fungal GM	Fungal Mean	Symptom %p	Overall
Closed	A	20.2	23.6	47	5.7	7.5	35			46			34	
	B	12.3	15.8	38	3.9	8.3	33			40			27	
	C	4.5	7.7	34	5.0	8.8	36	4.9	10.1	38	5.2	7.1	24	
Open	D	10.5	14.7	40	16.6	19.4	45			50			36	
	E	7.0	14.0	42	3.8	4.7	33			40			35	
	F	4.2	10.6	38	18.4	22.3	25	4.4	7.8	39	8.1	8.3	26	
Pearson Correlation (p-value)			r=0.79 (.06)		r= 0.008 (.98)									r=0.28 (.30)
Spearman Rank Order Correlation (p-value)			r=0.61 (.20)		r=0.06 (.91)									r=0.32 (.23)

Legend:
Fungal (Mean) average fungal counts, expressed as cfu/m^3
Symptom (%p): the proportion of all workers in a given study week who reported one or more of the following symptoms: nasal, eye or throat irritation or cough
GM: geometric mean
Test Week: A, B..F represent 1 of the 6 test weeks. The order of ventilation conditions was counterbalanced between buildings, so for example, A closed represents week1 for building A and week 2 for building B
Ventilation Condition: Closed-20cfmpp (approx 1000 ppm CO_2) Open- 50cfmpp (approx 500 ppm CO_2)

ring in building B. The major difference between these buildings was age and filtering systems. Building B was the newest building (less than eight months old) and only pre-filters existed in the ventilation systems. In contrast, the age of buildings A, C, and D was in the range of 4 to 10 years, all having fairly efficient filtering systems. Therefore, we speculate that the observed differences are likely due to a greater abundance of local, indoor sources of contamination in older buildings, producing the relative rise in fungal spore levels with less outdoor air. When a week is used as the unit of analysis, there is no relationship between fungal spore levels and weekly symptom prevalence using both parametric and nonparametric tests of correlation (Pearson's r = .28; Spearman's r = .32). Additional analysis will need to be carried out to adjust for the confounding effects of possible differences in building populations before conclusions in this respect are definitive. A separate analysis was done for the first two buildings, A and B, where sufficient observations existed to estimate building-specific effects. A significant positive correlation was noted in building A but not in building B. Fungal spore species in buildings A and B were similar. *Penicillium* was the most common (A = 71.4% of samples; B = 76.3% of samples), followed by *Cladosprium* (A = 28.6% of samples; B = 21.3% of samples), and *Mycelia* (A = 23.8%, B = 26.3%). Differences in the fungal species present in building A do not provide an obvious explanation for differences in effect. Other possible reasons for this finding will be explored in the discussion.

Method 2—The Case-Control Approach

Key demographic characteristics of cases and controls are summarized in Table 3. It can be noted that there was a higher prevalence of all symptoms among cases in relationship to controls, not just those specific to the respiratory system. With respect to atopic history, cases were more likely to report two or more of the listed conditions used to define the presence or absence of an atopic history. In addition, they were more likely to report asthma, sinus problems, and eczema. In Table 4, differences in total fungal spore counts (viable and nonviable species) between cases and controls are reported. Differences in both the arithmetic and geometric mean are presented. The difference is not significant and is in the opposite direction to that hypothesized using both parametric and nonparametric tests. Controls had slightly higher total fungal spore counts in their office environment than cases. Since a false negative result could have been produced by misclassification of controls, we repeated the analysis using the 42 case-control pairs where the control reported having never experienced either

TABLE 3
Demographics of Cases and Controls

Characteristic	Cases	Controls
Number Complete Data	106/163	106/163
Number Symptoms Reported (max=7)	5.5	3.8
Breakdown of other Reported Symptoms		
Headache	83.0%	69.0%
Fatigue	80.2%	65.1%
Concentration problems	67.0%	56.7%
Throat	84.9%	51.9%
Eye Problems	68.9%	53.8%
Atopic History		
Asthma	11.3%	0.9%
Sinus Problems	31.1%	15.1%
Allergies	34.0%	29.2%
Eczema	11.3%	6.6%
Hayfever	23.6%	27.4%
Gender		
Female	54.7%	54.7%
Male	45.3%	45.3%
Age	37.9 yrs	36.4 yrs

TABLE 4
Mean Fungal Spore Counts—Cases and Controls

	N	Total Fungal Spores (ns/m³)			Difference	Pair t-test (p-value)	Wilcoxin (p-value)
Overall							
		GM	Mean	SD	Case Mean-Control Mean		
Cases	106	57.8	74.2	4.4	raw counts - 4.02	0.51	0.45
Controls	106	64.4	78.2	4.6	log transformed - .047 counts	0.35	0.37
Subset of Cases and Controls where Controls were Asymptomatic for Cough or Nasal Problems						Pair t-test	Wilcoxin
		GM	Mean	SD	Case Mean-Control Mean	(p-value)	(p-value)
Cases	42	47.2	61.3	38.1	raw counts - 24.4	0.01	0.01
Controls	42	69.8	85.8	55.6	log transformed - 0.17 counts	0.05	0.01

cough or nasal problems in any setting. In this subset, the average difference in fungal spore count was 24.4 ns/m³ (raw) and -0.17 (log-transformed). Although this difference is statistically significant ($p = .01$) using both parametric and nonparametric methods, it is again in the opposite direction to that expected: spore counts for controls were higher than for cases. Since there are clinically important differences in the allergenic potential of different fungal species, we also broke down the spore count for cases and controls by species. The results of this analysis are displayed in Table 5. No significant differences exist in the presence of any of the species observed.

DISCUSSION AND CONCLUSIONS

Although no clear-cut threshold has been established in the literature, the fungal spore counts observed in the four buildings in this study are lower than levels previously associated with clinical symptoms. Nevertheless, they are comparable to those reported for mechanically ventilated offices, including those designated as "sick" buildings (Harrison et al. 1990; Holt 1990; Strom et al. 1990). No differences were observed between the two approaches to measurement in this study. Consistent with other studies (Skov and Valbjorn 1987; Burge et al. 1987; Menzies et al. 1990), 25% of participants reported symptoms of upper or lower respiratory irritation at least two to three times per week, only at work. With careful analysis of both viable and nonviable species, we could find no difference in total spore counts or specific species for those who complained of symptoms in comparison to those who did not. At least in this population of workers, there is no difference in the type or level of fungal spore exposure between symptomatic and asymptomatic workers. Similar results were found by Harrison et al. (1990).

It is possible that this lack of association resulted from our methods, which underestimated total fungal spore levels. Since in the four-building ecological approach, only viable spores were included in the analysis of the count (viable spores in our experience representing less than 10% of all spores present), it is reasonable to assume that total spore counts were higher than observed. In addition, certain more allergenic nonviable species may have existed, which cannot be determined in total viable spore count analysis and speciation. Further study of this type of bias in fungal spore estimation is recommended. In the case-control study, despite the lack of differences in fungal spore levels, symptoms among the cases may still have been as a result of fungal exposure, if the cases were sensitized to the antigens. This could be examined by skin testing with antigens specific for the fungal species found in the buildings. Another potential confounding factor is exposure to fungal antigens in other environments, particularly in homes.

TABLE 5
Proportion of Cases and Controls Exposed to Fungal Spores by Type

Spore Type	Cases n	Cases %	Controls n	Controls %
Aspergillus-Penicillium (nv)	102	96.0%	104	98.0%
Cladasporium (nv)	27	25.5%	18	17.0%
Penicillium (v)	21	19.8%	21	19.8%
Cladosprium (v)	19	17.9%	16	15.0%
Mycelia (v)	13	12.3%	14	13.2%
Ganoderma (nv)	13	12.3%	7	6.7%
Aspergillus (v)	8	7.5%	11	10.4%
Ustilago (nv)	9	8.5%	9	8.5%
Alternaria (v)	4	3.8%	5	4.7%
Alternaria (nv)	3	2.8%	2	1.9%

Legend: nv=non-viable spores, v=viable spores

Practical Points

Initial assessment of fungal spore contamination in office buildings could be limited to detailed assessment of the ventilation system, including viable and nonviable spore counts and speciation. The case-control approach to worksite estimates of exposure should be considered under the following circumstances: (1) overall spore counts are ≥300 ns/m^3, (2) no major source is found in the ventilation system, and/or (3) return-air samples are significantly higher than post-filter supply-air samples, particularly at lower ventilation rates, such as in the summer and fall.

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