

New-onset adult asthma in relation to damp and moldy workplaces

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Abstract

Objective Damp and moldy indoor environments aggravate pre-existing asthma. Recent meta-analyses suggest that exposure to such environments may also induce new-onset asthma. We assessed the probability of molds being the cause of asthma in a patient series examined because of respiratory symptoms in relation to workplace dampness and molds.

Methods Altogether 694 such patients had been clinically assessed between 1995 and 2004. According to their histories, they had all been exposed to molds at work and had suffered from work-related lower respiratory symptoms. The investigations had included specific inhalation challenge

(SIC) tests with mold extracts and serial peak expiratory flow (PEF) recordings. Using internationally recommended diagnostic criteria for occupational asthma (OA), we categorized the patients into three groups: probable, possible, and unlikely OA (156, 45, and 475 patients, respectively). The clinical details of 258 patients were analyzed, and their levels of microbial exposure were evaluated.

Results The agreement between the serial PEF recordings and SIC tests (both being either positive or negative) was 56%. In the group of probable OA, mold sensitization was found in 20%. The level of exposure and sensitization to molds was associated with probable OA. At 6 months, the follow-up examinations of 136 patients with probable OA showed that the symptoms were persistent, and no improvement in spirometry was noted despite adequate treatment. Only 58% of the patients had returned to work.

Conclusions Exposure to damp and moldy workplaces can induce new-onset adult asthma. IgE mediation is a rare mechanism, whereas other mechanisms are unknown.

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Introduction

There is an increasing and genuine concern about health effects in association with indoor dampness and mold. Concern has been expressed especially in relation to asthma (Fisk et al. 2007; Mudarri and Fisk 2007; Woodcock 2007). Asthma is a widespread disease in industrial countries, and the incidence does not appear to be decreasing. There is sufficient evidence showing that dampness and mold exposure cause asthma to worsen (Fisk et al. 2007; IOM 2004). Moreover, despite the paucity of high-quality studies on the

association between these exposures and new-onset adult asthma (Jaakkola et al. 2002; Pekkanen et al. 2007; Thorn et al. 2001), the evidence, as assessed in a recent meta-analysis on this issue, strongly supports such an association (Fisk et al. 2007).

For preventive strategies, the evidence connecting ill health to damp and moldy buildings is more than enough (Bornehag et al. 2004, 2001; IOM 2004). There is, however, a need for a medico-legal diagnosis of occupational asthma (OA) in which a causal relationship can be established objectively between exposure at work and the onset of asthma (Vandenplas and Malo 2003). In damp environments, the identification of a specific agent, microbe, or other factor, is a major diagnostic obstacle. It makes the entire health problem elusive and explains why epidemiological studies, as well as case reports on OA caused by exposure to damp environments and microbes, are scarce. In Finland, as in other subarctic countries, the climate puts heavy demands on construction solutions and its execution. Damp buildings constitute a serious and well-recognized domestic, as well as occupational, problem (Nevalainen and Seuri 2005).

According to the Finnish Register on Occupational Diseases, indoor air molds have been the most frequently reported cause of OA since 2001 (Piipari and Keskinen 2005). The Finnish act on occupational diseases requires that the causal association between an exposure and a disease be demonstrated as “probably the principal cause of the disease”. To fulfill these demands, OA is diagnosed in accordance with international recommendations (Fishwick et al. 2008).

Because the causality between exposure to damp and moldy workplaces and asthma is difficult to prove, in Finland patients are referred to the Finnish Institute of Occupational Health (FIOH), which is a reference institute for occupational diseases, for further examination. To support the previous epidemiological evidence on causality between indoor air molds and asthma, we present an assessment of

diagnostic examinations of a series of patients evaluated at FIOH because of suspected mold-induced asthma.

Materials and methods

Patients and study design

During 1995–2004, altogether 2,200 patients with respiratory symptoms related to damp and moldy work environments were examined at FIOH. They were referred to the Institute by occupational health physicians or pulmonologists from all over the country. The suspicion of OA was based on work-related symptoms compatible with asthma (cough, dyspnea, wheeze) and the onset of symptoms temporally associated with exposure to moisture-damaged work environments. Patients with known residential moisture damage were excluded from the study, because of obvious difficulties in discriminating between causative exposures.

The clinical investigations at FIOH included the assessment of specific sensitization to moisture-damage microbes, serial recordings of peak expiratory flow (PEF), and specific inhalation challenge (SIC) tests with commercially available mold extracts. At the time of the study, SIC was a routine procedure and had been carried out on 694 patients, from whom we selected the patients for the present analysis. Informed consent to review patient files was obtained from 676 patients, and for 425 (62.9%) of them, acceptable serial PEF records were available.

For the present analysis, we divided the 676 patients into three categories according to the probability of OA using the diagnostic criteria presented in Table 1. The criteria were consistent with the international diagnostic criteria for OA (Fishwick et al. 2008). Thus, we categorized 156, 45, and 475 patients as having probable, possible, and unlikely mold-induced OA, respectively. We reviewed the clinical details of the 201 patients with probable or possible OA and a sample of patients (57 of 475) with unlikely OA (Fig. 1).

Table 1 Criteria used for allocating patients into different categories according to the probability of occupational asthma (OA)

	Probable	Possible	Unlikely
Exposure to indoor air molds at work	Yes	Yes	Yes
Work-related asthma symptoms	Yes	Yes	Yes
Onset of symptoms or asthma temporarily associated with work in a moisture-damaged environment	Yes	Yes	Yes
Asthma diagnosed	Yes	Yes	Yes or asthma-like symptoms only
Serial PEF measurements at and away from work and a specific inhalation challenge test (SIC)	PEF measurements compatible with OA and/or positive SIC	PEF measurements suggestive of OA and negative SIC	PEF measurements inconsistent with OA (or not performed) and negative SIC

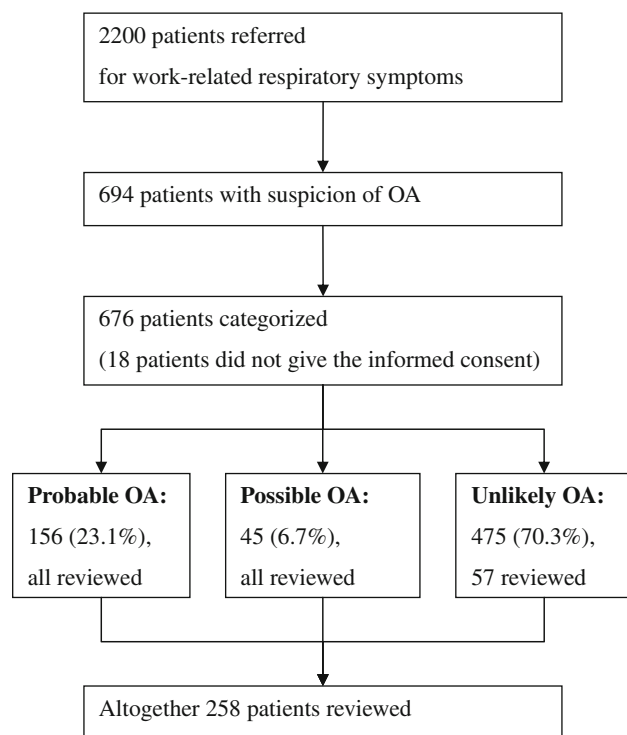


Fig. 1 Distribution of patients with suspected occupational asthma (OA) into categories of the probability of OA

The sample was randomly selected from those for whom an acceptable serial PEF record was available.

Of the patients categorized with probable mold-induced asthma, most of them (136 of 156) had participated in a control examination 6 months after their baseline examination.

The study was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

Evaluation of exposure

An experienced indoor air researcher made a retrospective evaluation of each patient's exposure at work by classifying the intensity of microbial exposure on the basis of the available information in the patient case records. The documents usually included reports on building structure damage and, in most instances, microbial measurements. The moisture damage and microbial growth had been described by indoor air researchers with a background in construction engineering and occupational safety or health service personnel. In most cases, material samples had been analyzed for the presence of microbes, which had been identified. In addition, air samples had been taken for the measurement of microbial air concentrations using six-stage impactors. In the assessment of microbial exposure, only winter-time measurements were considered in the study, as fungal concentrations in outdoor air in the winter are very low in

subarctic countries like Finland. The personal exposure was classified into four categories of exposure to microbes: low, intermediate, high, and not classifiable (Table 2).

We calculated the exposure time on the basis of the first date of employment in a moisture-damaged building, the point of time of water damage, whenever known, or the date when moisture damage had been first reported. We estimated the duration of exposure as <1 year, 1–5 years, 6–9 years, and ≥ 10 years.

Assessment of sensitization

To assess sensitization to molds, skin prick tests (SPTs) and measurements of specific serum immunoglobulin E (IgE) had been carried out using methods reported previously (Sub-Committee on Skin Tests of the European Academy of Allergy and Clinical Immunology 1989; Ceska and Lundkvist 1972).

The SPTs had been carried out with combinations of 29 different commercially available mold allergens (ALK-Abelló A/S, Copenhagen, Denmark) with histamine hydrochloride (10 mg/mL) as a positive control. We defined a positive reaction indicating sensitization as a weal diameter of ≥ 3 mm and equal to or greater than half of that of the histamine reaction. The mold-specific serum IgE antibodies had been determined for the same mold species, if available, using Pharmacia CAP system RAST RIA (Pharmacia, Uppsala, Sweden) until 1996, after which the UniCAP system (Pharmacia & Upjohn, Uppsala, Sweden) had been employed. We defined specific IgE values of >0.35 kU/L as positive.

Sensitization to common environmental allergens had been tested by SPT with the following allergens (ALK-Abelló A/S, Copenhagen, Denmark): pollens of birch, alder, timothy, meadow foxtail, mugwort and dandelion; epithelia of horse, dog, cat and cow; dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*); and molds *Alternaria alternata* and *Cladosporium herbarum*. We defined atopy as the patient having had at least one positive SPT reaction.

We defined atopic history as the patient having had infantile eczema, atopic dermatitis, hay fever, non-occupational allergic rhinitis, or allergic asthma.

Lung function measurements

Flow-volume spirometry had been carried out at FIOH with a pneumotachograph spirometer connected to a microcomputer (Medikro 909 or Medikro 904; Medikro Ltd, Kuopio, Finland). Spirometry had been performed according to guidelines of the European Respiratory Society (Quanjer et al. 1993). The bronchodilator test had been carried out with either rimiterol hydrobromide or (from 1997) salbutamol

Table 2 Classification of personal exposure to microbes

Classification	Definition
Low	An adequate and reliable description of mold damage was available. Single, small mold damage of $<0.5 \text{ m}^2$ was found in the patient's workspace, or limited mold damage ($<1 \text{ m}^2$) was detected in the patient's work environment near the permanent workspace
Intermediate	An adequate and reliable description was available of the mold damage, limited number and area of damage ($<1 \text{ m}^2$), and the total viable concentrations were under 100 cfu/m^3 for airborne fungi and under 10 cfu/m^3 for actinobacteria. Fungal species requiring high water activity were not dominant in the environmental samples
High	An adequate and reliable description of the extent of microbial growth ($>1 \text{ m}^2$) was reported, or total viable concentrations of airborne fungi were $>100 \text{ cfu/m}^3$, or the level of airborne actinobacteria was $>10 \text{ cfu/m}^3$, or fungal species requiring high water activity were dominant in the environmental samples. This category usually included extended moisture and mold damage, for example, in the base floor
Insufficient data	Evidence of exposure to microbes was inadequate or unreliable. Investigations of moisture and mold damage or indoor air measurements had not been undertaken or were not available in the patient files, or the exposure data were not associated with the patient's work area

sulfate. We regarded an increase of 15% or 200 mL in the forced expiratory volume in 1 s (FEV_1) and an increase of 33%, or at least 0.4 L/s, in maximum mid-expiratory flow as significant. The histamine challenge testing had been performed according to the method described by Sovijarvi et al. 1993, with hyperresponsiveness being graded as strong, ($\text{PD}_{15} < 0.10 \text{ mg}$), moderate ($\text{PD}_{15} 0.11\text{--}0.40 \text{ mg}$), or mild ($\text{PD}_{15} 0.41\text{--}1.6 \text{ mg}$). The single breath diffusion capacity for carbon monoxide and specific diffusion capacity had been measured by a Masterlab Transfer or a Compact Lab Transfer device using Finnish reference values (Viljanen et al. 1982).

Serial PEF monitoring

Serial PEF monitoring at and away from work had been carried out according to Burge (1993). PEF graphs had been drawn and the diurnal variations had been calculated (the daily maximum minus the daily minimum divided by their mean), the interpretation of the PEF values being based on direct visual analysis and supported by the percentage decreases in PEF. When allocating patients into diagnostic categories of probability, we adopted the following principles: (1) PEF record compatible with OA = $\geq 20\%$ diurnal variation on at least two work days and relatively more often on workdays than on non-workdays (Liss and Tarlo 1991; Tarlo et al. 2008); (2) PEF record suggestive of OA = no diurnal variations exceeding 20% but the lowest recordings on workdays, or a $\geq 20\%$ change longitudinally across workdays with decreasing values toward the end of the work period; (3) PEF record not compatible with OA = $< 20\%$ diurnal variation with no marked difference between the workdays and non-workdays; (4) PEF record indicating asthma lability = $\geq 20\%$ diurnal variation both at and away from work.

SIC tests

The challenge tests had been carried out according to international guidelines (Subcommittee on 'Occupational Allergy' of the European Academy of Allergology and Clinical Immunology 1992; Cartier et al. 1989). Commercial freeze-dried allergen extracts of *Aspergillus fumigatus*, *Acremonium kiliense*, and *Cladosporium cladosporioides* (for a few tests *Cladosporium herbarum*) had been used (ALK-Abelló). They had been the only mold extracts commercially available for bronchial inhalation tests during the study period. The mold species for SIC had been selected primarily among the species identified in the microbial samples from the workplace. If none of the available species had been identified, the testing had been started with *Aspergillus fumigatus* extract. During the 1990s, an increased serum level of IgG antibodies to molds had been used for selecting fungal allergens for the SIC. At the time, IgG antibodies had been considered a proxy for exposure. Allergen extracts diluted with ALK solvent (ALK-Abelló) had been inhaled with the use of an inspiratory-synchronized dosimetric device (Spira Electro 2) with the following settings: driving pressure 0.2 kPa (2 bars), inhalation time 0.8 s, starting volume 50 mL, inspiratory flow $0.5 \pm 0.1 \text{ L/s}$, and amount of allergen mixture 0.8–1.0 mL. The used starting allergen dilution had been 1:10,000–1:1,000 weight/volume (wt/vol) depending on the severity of the patient's symptoms and the strength of sensitization. The allergen dose had been increased 5- to 10-fold every 15 min if the patient did not react to the previous dose, until the dilution of 1:5 wt/vol had been achieved. The control tests had been carried out with the pure diluent.

After the challenge, the FEV_1 and PEF values had been followed using a pocket-size spirometer (One Flow; STI Medical, St Romans, France) for 24 h according to a protocol described previously (Keskinen et al. 1996).

We regarded a fall in FEV₁ or PEF of $\geq 15\%$ from the pre-challenge value during the first hour after challenge as a significant immediate reaction. Our criterion for a late reaction was a drop of $\geq 20\%$ after more than 1 h after the challenge. We denoted a combination of these reaction types as a dual reaction. A prerequisite for a positive test was the absence of a significant reaction ($\geq 10\%$) to a control challenge test with the pure diluent. The axillary temperature had been routinely followed 1 and 4 h after the SIC, once in the evening and once the next morning.

Statistical analysis

Logistic regression analysis was used for studying the association between atopy in the SPTs and IgE mold sensitization. Odds ratios (ORs) with 95% confidence intervals (95% CIs) are presented. Other proportional data were compared using the χ^2 -test or Fisher's exact test. The significance level was set at 0.05. The analyses were carried out with SAS 9.1 (Cary NC, USA).

Results

Patient characteristics and symptoms

The mean age of the 258 patients was 45.2 (SD ± 8.4). Most of the patients were female (90%) (Table 3). Prior to the investigations at FIOH, asthma had been diagnosed and regular medication initiated for 195 (76%) of the patients. In addition to asthma symptoms, the patients had reported irritative symptoms such as eye irritation and hoarseness. General symptoms, including fatigue and a sensation of elevated temperature, had also been reported (Table 4). The mean duration of the respiratory symptoms before the asthma diagnosis was 3.2 years (SD ± 3.0 , range 0–17.0). The majority of the patients (65%) had never smoked (Table 3).

Exposure

According to their work histories, all of the patients had been exposed to molds. In most instances (66.3%), the exposure had taken place in schools, hospitals, various office environments, or day care centers (Table 3). Correspondingly, most of the patients were teachers, nurses, office workers, or children day care workers, which explains why the majority of the workers were female.

In the analysis of the exposure data, the level of exposure was classified as high or intermediate for 79.0% of the patients. For 15.1%, the exposure classification was not made due to insufficient data. The duration of exposure exceeded 5 years for 69.0% of the patients (Table 3). The

level of exposure was significantly higher in the probable OA group than in the unlikely OA group ($p = 0.049$).

Sensitization

Atopy (i.e., sensitization to at least one common environmental allergen in the SPTs) was determined for 33.2% of the patients (Table 3). Atopy was equally distributed among the three categories of OA. An elevated level of serum total IgE was significantly more common in the probable and possible OA categories than in the unlikely OA category.

Sensitization to molds, as demonstrated by either SPT or serum IgE, was determined for 15.4% (39 of 254) of the patients (Table 3). Altogether 26 of these 39 patients (66.7%) were atopic according to the SPTs. Atopy significantly increased the risk of sensitization to molds (OR 6.5, 95% CI 3.0–14.0). Sensitization to molds occurred the most often among the patients in the probable OA group (Table 3). The association between mold sensitization and OA category was statistically significant ($p = 0.019$).

In the SPTs with mold extracts, *Aspergillus fumigatus* induced a positive reaction the most often (25 of 36 patients, 69.4%), followed by *Cladosporium cladosporioides* and *Rhodotorula rubra* (seven positive reactions each), and *Acremonium kiliense* and *Penicillium expansum* (five positive reactions each). One-third of the patients with positive SPTs to molds (13 of 36 patients) displayed a positive reaction to more than one mold.

For the patients with a high, intermediate, or low level of exposure, the IgE sensitization to molds occurred in 9 of 99 (9.1%), 17 of 97 (17.5%), and 4 of 15 (26.7%) patients, respectively.

Lung function

In the baseline examinations at FIOH, most of the patients (88.8%) showed mild or moderate obstruction in the spirometry (Table 5). Some degree of hyperresponsiveness was present in 44.7% of the patients, whereas bronchial reactivity was normal in 55.3%.

Serial PEF records of acceptable quality at and away from work were available for 193 (74.8%) of the 258 patients included in the analyses. According to interpretations of the PEF records, 47 (24.3%), 77 (39.9%), and 69 (35.8%) were compatible, suggestive, or not consistent with OA, respectively.

SIC tests

The SIC was positive for 133 patients. The positive bronchial reactions were immediate in 35 patients (26%), dual in 35 patients (26%), and late in 63 patients (47%). The

Table 3 Clinical characteristics of the patients

	All (<i>n</i> = 258)	Probable OA (<i>n</i> = 156)	Possible OA (<i>n</i> = 45)	Unlikely OA (<i>n</i> = 57)	
Mean age, year $\pm$ SD	45.2 $\pm$ 8.4	45.4 $\pm$ 8.4	46.4 $\pm$ 7.2	43.9 $\pm$ 9.4	
Gender					
Female, <i>n</i> (%)	233 (90.3)	138 (88.5)	42 (93.3)	53 (93.0)	
Male, <i>n</i> (%)	25 (9.7)	18 (11.5)	3 (6.7)	4 (7.0)	
Smoking status, <i>n</i> (%)					
Current smoker	60 (23.3)	32 (20.5)	12 (26.7)	16 (28.1)	
Ex-smoker	30 (11.6)	15 (9.6)	6 (13.3)	9 (15.8)	
Never smoker	168 (65.1)	109 (69.9)	27 (60.0)	32 (56.1)	
Type of workplace, <i>n</i> (%)					
Hospital, health clinic or similar	74 (28.7)	49 (31.4)	13 (28.8)	12 (21.1)	
School, college	51 (19.8)	32 (20.5)	4 (8.9)	15 (26.3)	
Office	46 (17.8)	23 (14.7)	9 (20.0)	14 (24.6)	
Day care center, kindergarten	21 (8.1)	8 (5.3)	8 (17.8)	5 (8.8)	
Kitchen	8 (3.1)	4 (2.6)	3 (6.7)	1 (1.8)	
Production plant	7 (2.7)	5 (3.2)	2 (4.4)	0	
Laboratory	7 (2.7)	4 (2.6)	1 (2.2)	2 (3.5)	
Military forces, police	7 (2.7)	4 (2.6)	2 (4.4)	1 (1.8)	
Other	37 (14.3)	27 (17.3)	3 (6.7)	7 (12.3)	
Level of exposure, <i>n</i> (%) ^a					
Low	15 (6.8)	8 (6.0)	2 (6.1)	5 (9.4)	<i>p</i> = 0.176
Intermediate	101 (46.1)	56 (42.1)	14 (42.4)	31 (58.5)	
High	103 (47.0)	69 (51.9)	17 (51.5)	17 (32.1)	
Duration of exposure, <i>n</i> (%) ^b					
1–5 years	73 (31.3)	39 (27.3)	13 (38.2)	21 (37.5)	<i>p</i> = 0.291
6–9 years	87 (37.3)	61 (42.7)	10 (29.4)	16 (28.6)	
$\geq$ 10 years	73 (31.3)	43 (30.1)	11 (32.4)	19 (33.9)	
Parental asthma, <i>n</i> (%)	40 (15.5)	25 (16.0)	10 (22.2)	5 (8.8)	<i>p</i> = 0.169
Indicators of atopy					
Atopic history, <i>n</i> (%)	72 (27.9)	42 (26.9)	13 (28.9)	17 (29.8)	<i>p</i> = 0.904
Positive SPT to common environmental allergens, <i>n/n_t</i> (%) ^c	82/247 (33.2)	50/151 (33.1)	17/45 (37.8)	15/51 (29.4)	<i>p</i> = 0.685
Elevated serum IgE ($\geq$ 110 kU/L), <i>n/n_t</i> (%)	79/246 (32.1)	52/148 (35.1)	18/43 (41.9)	9/55 (16.4)	<i>p</i> = 0.013
IgE sensitization to molds					
Positive SPT to molds, <i>n/n_t</i> (%) ^d	36/245 (14.7)	29/148 (20.0)	2/45 (4.4)	5/52 (9.6)	<i>p</i> = 0.022
Elevated serum IgE to molds, <i>n/n_t</i> (%)	22/181 (12.2)	18/113 (15.9)	1/30 (3.3)	3/38 (7.9)	<i>p</i> = 0.114
Either positive SPT or elevated serum IgE to molds, <i>n/n_t</i> (%)	39/254 (15.4)	31/153 (20.3)	2/45 (4.4)	6/56 (10.7)	<i>p</i> = 0.019

OA occupational asthma, *n_t* number of tested patients^a The level of exposure could not be evaluated for 78 patients^b The duration of exposure could not be evaluated for 25 patients^c An SPT to common environmental allergens was performed for 255 patients, but for 8 of them, the result could not be interpreted because of dermographism^d An SPT to molds was performed for 253 of the patients, but for 8 of them, the result could not be interpreted because of dermographism

decreases in PEF ranged between 15 and 41%, and the FEV₁ reductions were between 15 and 49% (Table 6). Sensitization to molds, demonstrated either by SPT or specific serum IgE, was present for 30 of the 130 patients (23.1%). (Measurements were not available for 3 of the 133

patients.) Sensitization did not differ in relation to type of reaction (immediate or dual versus late).

The most common mold extract to induce positive reactions in the SIC was *Aspergillus fumigatus* (85 positive tests versus 26 with *Cladosporium cladosporioides*, 19

Table 4 Prevalence of work-related symptoms and respiratory infections

Symptom/disease	All (n = 258)	Probable OA (n = 156)	Possible OA (n = 45)	Unlikely OA (n = 57)
Upper respiratory and ocular symptoms				
Eye irritation	145 (56.2)	92 (59.0)	24 (53.3)	29 (50.1)
Hoarseness	129 (50.0)	79 (50.6)	18 (40.0)	32 (56.1)
Nasal congestion	122 (47.3)	70 (44.9)	25 (55.6)	27 (47.4)
Rhinorrhea	120 (46.5)	72 (46.1)	21 (46.7)	27 (47.3)
Sneezing	46 (17.8)	24 (15.4)	10 (22.2)	12 (21.1)
Lower respiratory symptoms				
Dyspnea	207 (80.2)	121 (77.6)	38 (84.4)	48 (84.2)
Cough	182 (70.5)	110 (70.5)	29 (64.4)	43 (75.4)
Wheeze	49 (19.0)	31 (19.9)	8 (17.8)	10 (17.5)
Asthma symptoms from nonspecific irritants	99 (38.3)	57 (36.5)	21 (46.7)	21 (36.8)
Other symptoms				
Fatigue	109 (42.2)	68 (43.6)	16 (35.6)	25 (43.9)
Fever and chills	108 (41.9)	61 (39.1)	20 (44.4)	27 (47.4)
Dermal symptoms	60 (23.3)	34 (21.8)	12 (26.7)	14 (24.6)
Headache	54 (20.9)	35 (22.4)	8 (17.8)	11 (19.3)
Arthralgia	48 (18.6)	31 (19.9)	10 (22.2)	7 (12.3)
Nausea	14 (5.4)	8 (5.1)	1 (2.2)	4 (7.0)
Myalgia	13 (5.0)	7 (4.4)	1 (2.2)	5 (8.7)
Vertigo	10 (3.9)	6 (3.8)	0	4 (7.0)
Recurrent respiratory infections	105 (40.7)	67 (42.9)	14 (31.1)	24 (42.1)

OA occupational asthma

Table 5 Lung function examinations of study patients in the baseline examinations and in the follow-up 6 months later (patients with probable OA only)

	Probable OA (n = 156)		Possible OA (n = 45)	Unlikely OA (n = 57)
	Baseline examinations	Follow-up examinations	Baseline examinations	Baseline examinations
Spirometry				
Normal	17/156 (10.9)	13/133 (9.8)	2/45 (4.4)	6/57 (10.5)
Mild deterioration	89/156 (57.0)	86/133 (64.7)	31/45 (68.9)	29/57 (50.9)
Moderate deterioration	47/156 (30.1)	32/133 (24.1)	12/45 (26.7)	21/57 (36.8)
Strong deterioration	3/156 (1.9)	2/133 (1.5)	0	1/57 (1.8)
Bronchodilation test				
Negative	134/156 (85.9)	122/133 (91.7)	38/45 (84.4)	52/57 (91.2)
Positive	22/156 (14.1)	11/133 (8.3)	7/45 (15.6)	5/57 (8.8)
Bronchial hyperresponsiveness				
None	74/145 (51.0)	26/50 (52.0)	26/42 (61.9)	35/57 (61.4)
Mild	45/145 (31.0)	15/50 (30.0)	12/42 (28.6)	18/57 (31.6)
Moderate	23/145 (15.9)	9/50 (18.0)	1/42 (2.4)	2/57 (3.5)
Strong	3/145 (2.1)	0	3/42 (7.1)	2/57 (3.5)

Data presented as positive/tested (%)

OA occupational asthma

with *Acromonium kiliense*, and 3 with *Cladosporium herbarum*). Of the mold-sensitized patients, 26 (86.7%) had a positive SIC reaction to the same mold as shown by the SPT or serum IgE measurement.

During the positive challenge test with an active test agent, but not with control agent, a post-challenge rise of

>0.5°C in axillary body temperature had been measured for 11 patients (8.3%, range of maximum temperature 36.6–38.9). All of these increases occurred after the SIC with mold extract (none after the SIC with diluent). In 10 of the patients with an increase in temperature, the pre- and post-challenge diffusing capacity had been measured, but no

Table 6 Magnitude and time of significant FEV₁ and PEF reductions in positive SICs with an active agent

	FEV ₁ reduction (%)	Time of FEV ₁ reduction, hours after challenge	PEF reduction (%)	Time of PEF reduction, hours after challenge
Immediate reaction	22.3 ± 7.2 (15.0–41.0)		22.8 ± 6.3 (15.0–37.0)	
Late reaction	26.4 ± 5.4 (20.0–49.0)	9.6 ± 5.2 (2.0–20.0)	26.3 ± 5.2 (20.0–41.0)	10.4 ± 5.2 (2.0–20.0)

Data presented as mean ± SD (range)

SIC specific inhalation challenge

Table 7 Agreement between serial PEF measurements and specific inhalation challenge tests (SIC)

	SIC positive (n = 69)	SIC negative (n = 124)	
Serial PEF compatible with OA (n = 47)	25 (53.2%)	22 (46.8%)	p = 0.002
Serial PEF suggestive of OA (n = 77)	29 (37.7%)	48 (62.3%)	
Serial PEF inconsistent with OA (n = 69)	15 (21.7%)	54 (78.3%)	

Only those included with both tests available

OA occupational asthma

differences were noted. The type of the bronchial reaction was late for 7 of the 11 patients (immediate for 2 and dual for 2 patients).

Due to the lability of asthma despite optimal treatment, the SIC tests had to be carried out for 40 (16%) of the analyzed patients with ongoing inhaled corticosteroid medication.

Agreement between the serial PEF records and the SIC tests

The agreement between tests (i.e., both the SIC test and serial PEF monitoring were either positive or negative) was 56.0%. When the SIC was positive, the serial PEF monitoring was compatible with or suggestive of OA for 78.3% of the patients. In the case of a negative SIC, the proportion of patients with a PEF record compatible with or suggestive of OA was 56.5% (Table 7).

The comparison between proving specific IgE mold sensitization (SPT or serum IgE measurement) and SIC testing showed a level of agreement of 57.1%. Type I mold sensitization was more common for the patients with the positive SIC test than for the negative SIC test (23.1 vs. 7.3%).

Follow-up examinations

A total of 136 of the 156 patients who were classified with probable OA participated in the follow-up examinations 6 months after the diagnosis. Of these persons, only 79

patients (58%) had returned to work, while 53 patients (39%) were not working currently, and 4 (3%) were attending vocational training. Altogether 13 patients were still exposed to the original damp work environment, and 4 reported moisture damages also in their new work environment.

Nearly all of the patients (98%, 133 of 136) used asthma medication regularly: 43% (59 of 136) using inhaled steroids alone, 35% (48 of 136) using inhaled steroids and a long-acting β_2 -agonist, and 17% (23 of 136) additionally using a leukotriene modifier or theophylline.

For most of the patients (89%), spirometry showed mild or moderate obstruction (Table 5). The histamine challenge test showed no or only mild bronchial hyperresponsiveness for 82% of the patients (Table 5). Asthma medication was continued by all except one patient, asthma lability requiring additive treatment for 23 patients (17%). The symptom status was unchanged for 73 (54%) patients, improved for 60 (44%), and was worse for 3 (2%). None of those still exposed reported improvement in their symptoms.

None of the 11 patients who had reacted with a rise in temperature during a positive SIC reported a deterioration of symptoms in the follow-up examination. The symptoms were unchanged for 6 of them (55%) and had improved for 5 (45%).

Discussion

In accordance with international diagnostic criteria (Bernstein et al. 2006; Fishwick et al. 2008; Newman Taylor et al. 2004), we allocated patients into three categories: probable, possible, and unlikely OA. The discharge diagnoses given to the patient by FIOH were not considered. For 156 patients, we considered the diagnosis of OA probable, for another 45 cases OA was possible, and for 475 OA was unlikely.

Our diagnoses were based on verified mold exposure, work-related asthma symptoms with onset after entrance into the workplace, and lung function changes compatible with asthma. Other causes of asthma were excluded. The work-relatedness of asthma was objectively demonstrated by work-related changes in serial PEF records or SIC tests

with mold extracts or both. Most of the patients ($n = 133$) in the probable OA group displayed a positive reaction in the SIC tests with mold extracts. Thus, these patients fulfilled the diagnostic criteria of OA (Bernstein et al. 2006; Fishwick et al. 2008; Newman Taylor et al. 2004).

Exposure to moist environment or microbes at home is also known to increase the risk of asthma (Thorn et al. 2001). In such cases, the setting of an occupational asthma diagnosis can be considered unfeasible. Patients with residential moisture damage were not included in the study. Therefore, residential exposure to moisture and microbes should not have interfered with the allocation of patients into different categories.

A major obstacle in building-related health problems is the difficulty of identifying a specific causative agent among a multitude of candidates. Much research has focused on fungal spores as the main offending agent, as several mold species have been reported to specifically trigger allergic asthma (Portnoy et al. 2008; Sahakian et al. 2008). Exposure to molds is not restricted to the workplace as molds are ubiquitous in our environment, outdoors as well as indoors, and therefore a reliable quantitative assessment of the exposure is difficult. As Finland is a subarctic country, the outdoor concentrations of airborne fungi are very low in the winter (Reponen et al. 1992). In indoor air, winter-time concentrations are usually below 100 cfu/m^3 in home environments (Reponen et al. 1992), and even lower, under 50 cfu/m^3 , in office environments (Salonen et al. 2007) and school environments (Meklin et al. 2003). Usually, measurements of microbial air concentrations are performed only in the winter, and summer season measurements were not considered in this study. Thus, the contribution of outdoor fungal spores to the indoor air concentrations and flora was probably minimal. In most of our cases, a characterization of the moisture damage, as well as microbial growth, had been undertaken. Exposure to molds could be retrospectively verified from technical and microbial reports. Therefore, we were able to use a rough grading according to the extent and location of the damage. “The high-level category” of exposure showed a statistically significant association with the probable OA category. This finding suggests that the classification into exposure categories had some validity.

In the diagnostics of OA, the SIC test is generally considered to be as close as we can come to a gold standard (Newman Taylor et al. 2004). With respect to dampness and molds at workplaces, the usefulness of the SIC is modest. The exposure situation at work includes a multitude of other components as well (e.g., spores, metabolic products of microbes, toxins, and chemicals emitted from construction and interior materials). Thus, the choice of one or several microbes identified on a single sampling occasion may be totally wrong. A broad spectrum of microbial genera and species can be found on building materials and in indoor

air, and it can fluctuate over time. Sampling microbes on single occasions does not necessarily reveal the relevant species. The usefulness of SIC testing during the study period was, furthermore, severely restricted by the poor commercial availability of testing products. Consequently, a negative SIC test contributed little, if any, information.

For the SIC testing, there had been access to three commercial test extracts (*Aspergillus fumigatus*, *Acremonium kiliense*, and *Cladosporium cladosporioides*), which were not standardized. Extract batches had, from time to time, but not regularly, been tested for endotoxin content. The *Aspergillus* extracts normally had a low endotoxin content. In one batch of *Acremonium*, the endotoxin concentration had been high enough to explain the irritant reactions of a couple of patients after the SIC testing. SIC test agents contain a small amount of proteins and carbohydrates (Esch 2004). The *Aspergillus fumigatus* extract elicited most of the positive reactions in our patients. The rationale for using the *Aspergillus fumigatus* as the primary test extract had been that *Aspergillus* species represent dominant genres in mold-damaged buildings (Simon-Nobbe et al. 2008), and *Aspergillus* species are known to cross-react and also share epitopes with other mold species (e.g., *Cladosporium*) (Horner et al. 1995; Simon-Nobbe et al. 2008; Vojdani 2004).

The mechanism of positive SIC test reactions was considered to be IgE mediated in 23% of the cases. For most of the patients with positive reactions, specific IgE to a microbe was not found, however. In a previous study on rhinitis patients with positive nasal provocation tests with microbial extracts, specific IgE had been determined similarly in a small proportion of patients only (Karvala et al. 2008). The mechanisms behind most of the positive SIC reactions were unknown. Some of them may have even been toxic. Toxins of *Stachybotrys chartarum* have been shown, together with lipopolysaccharides, to synergistically activate interleukin- 1β , and interleukin-18 mediated inflammatory response in human macrophages (Kankkunen et al. 2009).

In the diagnostics of OA, serial PEF recordings have a fairly high sensitivity and specificity when tested against specific challenge tests (Lemiere 2007; Newman Taylor et al. 2004). Acceptable serial PEF records are possible for about two-thirds of those for whom OA is being considered (Lemiere 2007). The percentage in our material was somewhat lower (63%). The likely explanation is that, if occupational health services fail to initiate serial PEF monitoring in association with damp buildings, this chance is often lost. As there is generally a time lag of 1–3 years before a patient arrives for examinations at FIOH, the moisture damage has often already been repaired—sometimes the entire building has been demolished, the work-contract has ended, or the patient simply refuses to go back to the workplace.

By comparison, serial PEF records are superior to SIC testing in reflecting the entire complex exposure situation at

the workplace. Thus, serial PEF recording is the principal and most reliable diagnostic tool available. It is essential that serial PEF monitoring be carried out correctly. It should be initiated without delay, preferably before the start of any anti-inflammatory medication. The reliability of serial PEF monitoring using ordinary peak flow meters has been questioned (Quirce et al. 1995). It may be advisable to use a computerized peak flow meter in order to improve both quality and reliability. Increases in bronchial hyperreactivity (Newman Taylor et al. 2004) or exhaled nitric oxide (Lemiere 2007) over an exposure period may be a way to improve the reliability of PEF recording. While serial PEF records do demonstrate the association with work, the major weakness is that they do not accurately differentiate between work-exacerbated asthma and OA (Chiry et al. 2007). For diagnosing OA, other aspects, like disease history and immunological assessment, have to be included. We had access to SIC results. The overall agreement between the serial PEF monitoring and SIC testing (both being either positive or negative) was 56%. For the patients with a positive SIC test, the agreement with the serial PEF monitoring was 78%. Considering the flaws of the SIC, previously addressed in this discussion, this figure is fairly high.

There are several reasons for possible diagnostic misclassification. The category of unlikely asthma represents work-exacerbated asthma. This group may well comprise cases of OA. As a negative SIC test does not exclude the possibility that some other microbe or agent was the cause of asthma, the uncertainty of the diagnoses was probably greatest in this category, especially if serial PEF recordings were not available. However, all of the patients had been exposed to a damp environment and had suffered from work-related exacerbations and deterioration of their asthma. Therefore, from the point of view of secondary prevention, the distinction between work-exacerbated and OA is less important. Work-exacerbated asthma is at least as great a health problem as OA is, both in terms of severity and socioeconomic implications (Tarlo et al. 2008; Vandenplas and Henneberger 2007).

The hypothesis of our study was that molds, as known sensitizers, may induce new-onset adult asthma in people who work in damp and moldy environments. While fungal spores in indoor air are potential inducers of respiratory health effects, many other factors, like microbial metabolites or compounds from damp building materials, have been suggested (IOM 2004). The heterogeneity of the symptoms related to building dampness and the difficulties in identifying specific causative agents may refer to a multifactorial etiology. Rather than being regarded as one disease, asthma should be considered a syndrome in which genetics, environment, and individual behavior are determinants. The same is naturally true for OA. This feature may explain why such a high proportion of asthma is attributable to work (Toren and Blanc 2009). There may be several

concurrent factors inducing asthma. In such cases, a specific inducer will not be possible to identify despite an excess risk of asthma in a particular environment.

The clinical follow-up of 136 patients with probable OA revealed persistent symptoms despite adequate anti-inflammatory treatment. Spirometry and bronchial hyperreactivity also remained essentially unchanged. Only 58% of the patients were working, which is much lower than our experience with isocyanate-induced asthma (Piiirila et al. 2005). In some cases, moisture damage had not yet been repaired, whereas in other cases, work without exposure to dampness and molds had not been offered. These patients are often very aware of their sensitivity and tend to become symptomatic from re-exposure easily.

In conclusion, our study confirms that exposure to damp and moldy workplaces induces new-onset adult asthma. Specific IgE-mediated sensitization to molds occurs, but in a small proportion of cases only. The mechanisms of asthma remain largely unknown. Due to the complex exposure situation, serial PEF monitoring is the best available diagnostic tool. Specific inhalation challenge tests with microbe extracts are hampered by several serious flaws. The study also corroborates that damp and moldy work environments aggravate symptoms in asthmatics. There is a juridical need to distinguish between work-exacerbated asthma and OA. The accurate separation between the two types of work-related asthma is not always possible, and, from the point of view of prevention, may not be necessary.

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Conflict of interest The authors declare that they have no conflict of interest.

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