

Atopy, symptoms and indoor environmental perceptions, tear film stability, nasal patency and lavage biomarkers in university staff

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Abstract

Objective Study associations between airway symptoms, complaints on environmental perceptions, atopy definitions and biomarkers including tear film stability (BUT), nasal patency and nasal lavage (NAL). Personal predictors (gender, age, smoking, infections) for the biomarkers as well as associations between the biomarkers were also assessed.

Methods A cross-sectional study of 173 employees in four university buildings, response rate 86%. Tear film break up time (BUT) was measured by a non-invasive method (NIBUT) and self-reported (SBUT). NAL-analysis included eosinophilic cationic protein (ECP), myeloperoxidase (MPO), lysozyme and albumin. Total serum IgE, and specific IgE using Phadiatop® was measured. Data on subjective symptoms, environmental perceptions and background data were collected by use of a questionnaire. Multiple regression analyses were applied.

Results Mean age was 43 years, 21% had weekly ocular, 21% nasal, and 17% laryngeal symptoms. Women had more complaints on environmental perceptions, shorter BUT and less nasal patency. Neither atopy (Phadiatop) nor Total IgE or allergy in the family, but asthma and hay fever was associated with mucosal symptoms or perceptions. Subjects with positive Phadiatop had higher levels of all

NAL-biomarkers. Those with ocular symptoms had shorter BUT. Nasal symptoms were related to respiratory infections and laryngeal symptoms to NAL-lysozyme. Perceiving dry air was associated with lower BUT and reduced nasal volume difference before and after decongestion. Older subjects had greater nasal patency, and less atopy. All NAL-biomarkers were positively correlated. Higher lysozyme level was associated with less nasal patency and greater nasal decongestion.

Conclusions BUT and NAL-lysozyme was associated with ocular, nasal, laryngeal symptoms and indoor environmental perceptions. Ever having had asthma and ever having had hay fever were predictors for symptoms and perceived air quality, respectively. Phadiatop, Total IgE, familiar allergy and ever eczema were not associated to symptoms or perceived environments. Age, gender and Phadiatop were main predictors for ocular and nasal biomarkers.

Keywords Atopy · IgE · Asthma · Rhinitis · Lysozyme · Occupational medicine

Introduction

It is generally believed that “atopic” individuals are particularly vulnerable to inferior indoor environment. However, this has been shown only in few studies and even fewer have used definitions of atopy based on clinical tests. Atopy defined as a positive prick test to any allergen was a significant independent risk factor for reporting at least one SBS-related symptom (Björnsson et al. 1998) although another study using the same definition did not find any association (Muzi et al. 1998). Also, total serum IgE ≥ 100 kU/l has been used as atopic marker when studying association

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between asthma, chronic bronchitis and exposure to irritant agents in occupational domestic cleaning (Medina-Ramon et al. 2005), although the diagnostic sensitivity of this test is low (Simoni et al. 2001; Carosso et al. 2007).

In the early 1920s, the term “atopy” was introduced to designate several phenomena of hypersensitiveness in man (Johansson et al. 2001). This term changed as the scientific field developed and has acquired varying meanings. Today many scientists use the term synonymously with “IgE-mediated”, but particularly paediatricians and dermatologists also consider “atopy” a constitutional trait because IgE-mediated allergy is common in children and young adults and often runs in families. Typical symptoms include asthma, rhinoconjunctivitis, gastrointestinal symptoms and characteristic skin lesions.

“Atopy” has recently been defined as a tendency to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens implying that the term cannot be used until an IgE sensitization has been documented (Johansson et al. 2004). This can be performed by means of testing allergen-specific IgE with a mixture of common inhalant allergens such as in Phadiatop® (Johansson et al. 2005). The presence of IgE antibodies does not necessarily mean clinically active disease but have clinically predictive value for developing characteristic symptoms and to react on allergens corresponding to the specific IgE antibodies (Johansson et al. 2004). Hence, it is of interest to assess the associations between Phadiatop and other subjective and objective markers that are believed to be associated with atopy and to validate definitions of atopy. Also associations with mucosal inflammatory markers, symptoms and complaints on perceived indoor climate are of interest in this context.

There has been an increased use of physiological investigations of the ocular and nasal mucosa to study health effects of occupational and environmental exposure (Franck 1986; Muzi et al. 1998; Kjaergaard and Hodgson 2001; Norbäck and Wieslander 2002). A relatively large inter-individual variation has been observed for these methods, both for measurements of tear film stability as tear film break up time (BUT) (Kjaergaard and Hodgson 2001), nasal patency by acoustic rhinometry (Corey et al. 1998; Wålinder et al. 1999), and biomarkers in nasal lavage (Wålinder et al. 1999). Since the conventional fluorescein method for BUT may give incorrect results, because fluorescein itself has an effect on the tear film stability, a non-invasive tear film break up time (NIBUT) has been developed (Mengher et al. 1985).

Ocular symptoms has been associated to exposures in office environment, female gender, allergic rhinitis, Sjögrens syndrome, use of contact lenses, eye-make-up and certain medication (Wolkoff et al. 2003; Wolkoff et al. 2006). In office workers, a reduced BUT was observed for

females above 40 years, and for those with a history of eye disease (Brasche et al. 2005). Associations between “dry eye”, “office eye” and decreased BUT has been shown (Franck 1986; Wolkoff et al. 2006). In a study of complaints in 14 office buildings across Germany BUT appeared to be the best indicator for self-reported eye symptoms (Brasche et al. 2001). Association between perceiving “dry air” and reduced BUT has been found in laboratory studies among healthy, non-smoking and non-allergic adults (Kjaergaard et al. 2004). However, whether eye irritation such as dry eyes is associated with the perception of dry air after longer duration of office work requires more research (Wolkoff et al. 2006).

In a Swedish study of white-collar workers, males had larger nasal dimensions and higher nasal airway lavage (NAL) concentrations of ECP (eosinophilic cationic protein), MPO (myeloperoxidase) and albumin. Moreover, there was a weak correlation between anterior nasal dimensions and nasal obstruction symptoms (Wålinder et al. 2000). In subjects aged 4–61 years without nasal symptoms, minimum cross-sectional area (MCA) showed weak positive correlations to weight, body mass index, height and age in that order (Millqvist and Bende 1998). In a randomly selected adult population, symptoms of allergy, frequent infections, small anterior nasal dimensions, and a large degree of swelling of the nasal mucosa were related to nasal obstruction symptoms (Grymer et al. 1997). Influence of individual and seasonal variations of biomarkers in NAL was investigated in ten healthy volunteers during 1 year. Men had higher NAL-levels of nitrite, tumor necrosis factor (TNF)-alpha, interleukin (IL)-4, and IL-6. Seasonal differences were detected, with highest TNF-alpha and IL-6 in winter and highest IL-5 in summer. It was concluded that individual variation of the basal level of inflammatory markers is low, while differences between individuals are considerable (Roponen et al. 2003).

Relatively little is known about influence of atopy on ocular and nasal biomarkers. Associations between complaints on perceived indoor environment, ocular and nasal biomarkers have to our knowledge so far not been elucidated in field studies.

The primary aim of this study was to assess the associations between on one-side mucosal symptoms and perceived environments, and on the other side traditional measures for hypersensitivity such as different atopy definitions and new measures in terms of biomarkers. A secondary aim was to study personal predictors for the biomarkers in terms of gender, age, smoking and airway infections as well as associations between the different biomarkers. This study is part of a larger survey about indoor air and health from which data concerning work and home environment have been published elsewhere (Bakke et al. 2007a, b, c).

Material and methods

Study population

A cross-sectional study was performed among university staff from Faculty of Arts and Faculty of Social Sciences working in four approximately 100-year-old buildings. The buildings had been refurbished and supplied with balanced ventilation in 1999–2000. The study was performed in the Norwegian winter season February–March 2004, after the influenza season and before the pollen season. Two specific weeks were chosen by the researchers for the examinations. All employees and master students working in the buildings during the study period were invited to participate. All had regular working place in an office. They were all informed in meetings, one for each building, where the researchers, the safety deputies and head of the department were present. Both oral and written information was given and all participants gave written informed consent. The employees were classified as either office employees with administrative work, or researchers/university teachers. Janitors or cleaning staff were not included in the study, since they were not employed at the institutes. All examinations were performed in offices in their own University building. The subjects were required to be present at their working place at least 1 h before the examination and to fill in a questionnaire on beforehand. The examinations took place within 1 h through the work time. All participants delivered their questionnaires and individual formal permissions. Assessments of NIBUT and PBUT, rhinometry, nasal lavage and blood samples were performed. One and the same researcher performed all eye assessments in the study and another researcher did all the nasal assessments. All blood samples were assessed by the same laboratory. Assessments of all biomarkers were performed blinded. The study was approved by the Regional Committee for Medical Research Ethics of Western Norway and the Norwegian Social Science Data Services. The Ministry of Health and Care Services gave permission to establish a biobank and to transfer the biological material abroad for analysis.

Questionnaire

The participants filled in an extended and modified MM 40 MA questionnaire (Andersson 1998) containing four questions on ocular, nasal and laryngeal symptoms: “Itching, burning or irritation of the eyes”, “Irritated, stuffy or runny nose”, “Hoarse dry throat”, “Cough” and questions about indoor environmental perceptions including “dry air”, “stuffy air”, “temperature too high” and “temperature too low”. These questions were answered by yes (weekly), yes sometimes and not at all. They were also asked about gender, age, respiratory infections the last month (yes/no and

number) and current smoking (yes/no). A person who reported smoking tobacco daily was regarded a current smoker. They were asked following questions concerning hypersensitivity and allergy:

- Have you ever had asthmatic problems?
- Have you ever suffered from hay fever?
- Have you ever suffered from eczema?
- Do allergic diseases occur among others in your family (asthma, hay fever, eczema)?

Blood samples

A blood sample was taken of all participants from the cubital vein with the subject sitting in a chair. The blood was clotted in the tube at room temperature. After a maximum of 2 h the blood was centrifuged. The serum samples were brought to the laboratory and frozen to -25°C . Serum samples were analysed at the Laboratory of Clinical Biochemistry at Haukeland University Hospital for serum IgE (kU/l) and IgE antibody levels by the Immuno-CAP FEIA system (Phadia, Uppsala, Sweden). Allergen-specific IgE was tested for the main inhalation allergens using Phadiatop® (*Dermatophagoides pteronyssinus* (d1), *D. farinae* (d2), birch (t3), timothy (g6), mugwort (w6), cat (e1), dog (e2), horse (e3), and *Cladospodium* (m2)) (Johansson et al. 2005). Results were assessed as negative when the total concentration of the different IgE antibodies was $<0.35 \text{ kU}_\text{A}/\text{l}$ (kU_A = kilounits of specific antigen) or positive when concentration was $\geq 0.35 \text{ kU}_\text{A}/\text{l}$. A positive result was considered marker for “atopy” in line with the clinical definition of an IgE-antibody high responder (Johansson et al. 2004, 2005).

Tear film examination

Tear film stability was studied by assessing non-invasive break-up time (NIBUT) of the tear film by ocular microscopy (Keeler TearScope®, Keeler Instruments, Clewer Hill Road, Windsor, Berkshire SL4 4AA, UK), based on a grid of equidistant circles of light that are blurred by tear film break up (Mengher et al. 1985; Kjaergaard and Hodgson 2001). Contact lens wearers were not assessed. “Self-reported Break Up Time” (SBUT) was assessed by recording the time the subject could keep the eyes open without blinking, when watching a fixed point at the wall (Norbäck and Wieslander 2002). Recording of SBUT were stopped at 30 s in order to keep time schedule. Contact lens wearers were included. The longest of at least three tests for NIBUT and PBUT was registered.

Acoustic rhinometry

Acoustic rhinometry (Rhin 2000; SR Electronics, Denmark) with continuously transmitted wideband noise was applied

to measure nasal patency. This method measures internal dimensions of the nasal cavity at different distance from the nose opening, by means of reflection of ultrasound. Smaller nasal volumes or cross-sectional areas indicate swelling of the nasal mucosa and nasal congestion. The first measurement was after 5 min of rest (sitting); the second was performed 10 min after decongestion (two douches of 140 microgram xylometazolin-hydrochloride each, 5 min apart). By means of acoustic reflection the minimum cross-sectional areas (MCA) on each side of the nose were measured from 0 mm to 22 mm (MCA1) and from 23 mm to 54 mm (MCA2) from the nasal opening. The volumes of the nasal cavity on the right and the left sides were also measured from 0 mm to 22 mm (VOL1) and from 23 mm to 54 mm (VOL2). All mean values were calculated from three subsequent measurements on each side of the nose. Data on nasal dimensions in the present study are presented as the sum of the values recorded for the right side and the left side. The volume difference before and after decongestion (dVOL) was calculated as mean percentage difference of VOL1 and VOL2.

Nasal lavage

Lavage of the nasal mucosa was made with a 20 ml plastic syringe attached to a nose olive. The subjects were standing, with their head flexed ca 30° forward. The room-tempered (20–22°C) sterile 0.9% sterile saline solution was introduced into the nasal cavity. Each nostril was lavaged with 5 ml solution, which was flushed back and forth five times via the syringe at an interval of a few seconds. The fluid was transferred into a 10 ml polypropylene centrifuge tube. Samples were kept on ice and within 300 min the solution was centrifuged at 800 g for 5 min. The supernatant was recentrifuged at 1,400 g for 5 min and immediately frozen to –20°C. Lysozyme was analysed by radioimmunoassay (Venge et al. 1979). The concentrations of ECP, MPO were measured by means of a double-antibody radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden) (Schmekel et al. 1990; Peterson et al. 1991). The intra- and inter-assay coefficients of variation for all three tests were less than 11%. Albumin was measured by the rate nephelometry on an Array protein system (Beckman Instruments). All analyses were performed at the Department of Clinical Chemistry, University Hospital, Uppsala, Sweden.

Statistics

Categorical values were tested with Pearson chi-square tests, and continuous variables were compared using Mann–Whitney *U*-test or rank correlation test (Kendal Tau beta), since the variables were not normally distributed. Multivariate analysis was performed by linear regressions

for biomarkers and logistic regressions for perceptions controlling for age, gender, smoking, number of days with airway infections last month and atopy (positive Phadiatop).

Results

In total, 173 (86%) of the invited staff, participated in the study. Data on Phadiatop, total IgE, NIBUT, SBUT, nasal patency and nasal lavage biomarkers were obtained from 168, 164, 148, 173, 168, and 166 subjects, respectively. Six nasal patency assessments were excluded due to technical reasons. Mean age was 43 years (SD = 13), men were older than women, more women used contact lenses. No other significant gender differences were observed (Table 1). SBUT was not different among contact lenses users compared with the others. In total, 55% had allergy in the family, 37% had atopy defined as a positive Phadiatop, 20% had total IgE ≥ 100 kU/l, 26% had ever had hay fever, 20% had ever had asthma, 41% had ever had eczema, 28% were current smokers and 15% used contact lenses.

In total, 57% reported ocular, 65% nasal and 50% laryngeal symptoms and 41% reported cough weekly or sometimes (Table 2). 52% reported complaints on environmental perceptions about “dry air”, 63% about “stuffy air”, 32% about “temperature too high” and 43% about “temperature too low” weekly or sometimes. Women reported more complaints on perceived indoor environment than men.

Individual predictors for biomarkers, gender, age, smoking, and airway infections

Females had shorter NIBUT and SBUT, smaller anterior and posterior nasal dimensions, and more nasal decongestion by adrenergic spray (Table 3). Older subjects had larger anterior and posterior nasal dimensions. NAL-ECP and NAL-Albumin were associated with number of days with infection last month. No significant associations were found between current smoking and any of the parameters, except for lower nasal volume difference before and after decongestion (dVOL (%): adjusted Beta = –0.12 (–0.21–0.05)).

Associations between different atopy markers, symptoms and perceptions

There were no significant associations between positive Phadiatop and symptoms, or indoor environmental perceptions (Table 4). Stratifying for gender showed the same results. Those with total IgE ≥ 100 kU/l had less ocular symptoms and complained less on perceiving “temperature too high”. Ever having had asthma was associated with more ocular and laryngeal symptoms and cough. Those

Table 1 Gender, age, education, number of days with respiratory infections last month, signs (serum total IgE, NIBUT, SBUT, ECP, MPO, Lysozyme, Albumin, MCA1, MCA2, VOL1, VOL2, dVOL) and percentages of Tot IgE ≥ 100 kU/l, atopy (Phadiatop), allergic disease in the family, ever had asthma, hay fever, eczema, or any of asthma, hay fever or eczema, current smoking and contact lenses use among university staff. Differences in years and infection days (Mean/SD) are tested by *T*-tests for independent samples, signs (Mean/SD) by Mann–Whitney *U*-test and percentages by use of Pearson Chi-square tests

Parameter	Males (<i>N</i> = 81) Mean $\pm$ SD	Females (<i>N</i> = 92) Mean $\pm$ SD	Total (<i>N</i> = 173) Mean $\pm$ SD
Age (Year)	46 $\pm$ 13	40 $\pm$ 13**	43 $\pm$ 13
Education after primary school (Year)	11 $\pm$ 3	10 $\pm$ 3	10 $\pm$ 3
Respiratory infection days	3.3 $\pm$ 4.1	3.8 $\pm$ 4.8	3.6 $\pm$ 4.5
Serum total IgE kU/l	66 $\pm$ 89	93 $\pm$ 307*	80 $\pm$ 233
NIBUT (s)	9.3 $\pm$ 3.4	8.1 $\pm$ 2.4*	8.7 $\pm$ 3.0
SBUT (s)	18.9 $\pm$ 7.6	14.8 $\pm$ 7.3***	16.7 $\pm$ 7.7
ECP (μ g/l)	3.1 $\pm$ 4.7	2.5 $\pm$ 3.9	2.8 $\pm$ 4.3
MPO (μ g/l)	67 $\pm$ 78	59 $\pm$ 64	63 $\pm$ 71
Lysozyme (mg/l)	3.8 $\pm$ 2.5	4.8 $\pm$ 3.2*	4.3 $\pm$ 2.9
Albumin (mg/l)	13.1 $\pm$ 17.1	11.5 $\pm$ 16.1	12.2 $\pm$ 16.5
MCA1 (cm ²)	0.93 $\pm$ 0.27	0.76 $\pm$ 0.23***	0.84 $\pm$ 0.26
MCA2 (cm ²)	0.97 $\pm$ 0.32	0.84 $\pm$ 0.28**	0.90 $\pm$ 0.31
VOL1 (cm ³)	3.6 $\pm$ 0.8	2.8 $\pm$ 0.7***	3.2 $\pm$ 0.8
VOL2 (cm ³)	8.0 $\pm$ 3.0	6.6 $\pm$ 2.4**	7.3 $\pm$ 2.8
dVOL (%)	5.7 $\pm$ 23.4	14.7 $\pm$ 22.6*	10.5 $\pm$ 23.3
	Percentages	Percentages	Percentages
Serum total IgE ≥ 100 kU/l	20	21	20
Atopy (Phadiatop)	36	38	37
Allergic disease in family	51	59	55
Ever asthma	17	22	20
Ever hay fever	24	29	26
Ever eczema	36	42	39
Ever asthma, hay fever or eczema	46	60	54
Ever asthma or eczema	41	51	47
Current smokers	21	33	28
Contact lenses use	9	19*	15

* *P* < 0.05; ** *P* < 0.01;

*** *P* < 0.001

Table 2 In a study of 173 university employees, differences in symptoms and complaints on environmental perceptions found between genders and Phadiatop negative and positive subjects among university staff, weekly or sometimes during the last 3 months (Pearson Chi-square tests)

Parameter	Males (<i>N</i> = 81) %	Females (<i>N</i> = 92) %	Phadiatop negative (<i>N</i> = 103) %	Phadiatop positive (<i>N</i> = 61) %	Total material (<i>N</i> = 173) %
<i>Symptoms</i>					
Ocular symptoms	52	63	57	58	57
Nasal symptoms	62	68	63	70	65
Laryngeal symptoms	42	57	52	47	50
Cough	40	43	41	42	41
<i>Complaints</i>					
Dry air	39	64**	49	61	52
Stuffy air	45	79***	65	62	63
Temperature too high	24	39*	30	37	32
Temperature too low	33	52*	39	48	43

* *P* < 0.05; ** *P* < 0.01;

*** *P* < 0.001

with “ever hay fever” perceived significantly more “dry air” and “temperature too high”. “Ever eczema” was associated with perceiving “temperature too high”. No other significant associations were found for perceived indoor environment and different atopy markers.

Associations between biomarkers, symptoms and perceptions

Lower tear film break up time (BUT) assessed both as NIBUT and SBUT were associated with ocular symptoms

Table 3 In a study of 173 university employees, the relationships between serum total IgE, NIBUT, SBUT, ECP, MPO, lysozyme, albumin and the three variables gender, age and infection days analysed by univariate linear regression. In addition, multiple linear regressions were performed, keeping age, gender, atopy (Phadiatop), current smoking and infection days the last month in the model

Parameter	Gender Beta (95% CI)		Age (per 10 years) Beta (95% CI)		Infection days Beta (95% CI)	
	Bivariate	Adjusted	Bivariate	Adjusted	Bivariate	Adjusted
Serum total IgE	39 (-44 to 98)	36 (-45 to 116)	16 (-11 to 44)	27 (-4 to 58)	-1.8 (-10.3 to 6.6)	-2.1 (-11.0 to 6.8)
NIBUT (s)	-1.2 (-2.1 to -0.2)*	-1.3 (-2.3 to -0.4)**	0.13 (-0.23 to 0.50)	0.10 (-0.26 to 0.46)	0.03 (-0.07 to 0.14)	0.07 (-0.04 to 0.18)
SBUT (s)	-4.1 (-6.4 to -1.9)***	-4.8 (-7.2 to -2.5)***	0.5 (-0.4 to 1.3)	0.3 (-0.6 to 1.2)	0.20 (-0.06 to 0.47)	0.19 (-0.07 to 0.45)
ECP (µg/l)	-0.6 (-1.9 to 0.7)	-0.8 (-2.3 to 0.6)	-0.3 (-0.8 to 0.2)	-0.1 (-0.7 to 0.4)	0.23 (0.07 to 0.38)**	0.19 (0.03 to 0.35)*
MPO (µg/l)	-8.1 (-30 to 14)	-12 (-36 to 11)	-1.6 (-10.0 to 6.7)	1.7 (-7.4 to 10.1)	3.02 (0.46 to 5.59)*	2.61 (-0.08 to 5.29)
Lysozyme (mg/l)	0.97 (0.08 to 1.86)*	0.81 (-0.14 to 1.76)	-0.5 (-0.78 to -0.10)*	-0.2 (-0.58 to 0.15)	0.12 (0.01 to 0.22)*	0.09 (-0.02 to 0.19)
Albumin (mg/l)	-1.6 (-6.7 to 3.5)	-3.0 (-9 to 2.5)	-1.0 (-2.9 to 0.9)	-0.2 (-2.3 to 1.9)	0.77 (0.18 to 1.37)*	0.66 (0.03 to 1.28)*
MCA1 (cm ²)	-0.17 (-0.25 to -0.10)***	-0.14 (-0.22 to -0.06)**	0.05 (0.02 to 0.08)***	0.04 (0.01 to 0.07)*	-0.01 (-0.02 to 0.00)	-0.01 (-0.01 to 0.00)
MCA2 (cm ²)	-0.14 (-0.23 to -0.05)**	-0.15 (-0.25 to -0.04)**	0.02 (-0.01 to 0.06)	0.02 (-0.02 to 0.06)	0.00 (-0.01 to 0.01)	0.00 (0.01 to 0.01)
VOL1 (cm ³)	-0.76 (-0.99 to -0.52)***	-0.62 (-0.88 to -0.37)***	0.18 (0.08 to 0.27)***	0.11 (0.02 to 0.21)*	-0.02 (-0.05 to 0.01)	0.00 (-0.03 to 0.02)
VOL2 (cm ³)	-1.39 (-2.23 to -0.56)**	-1.15 (-2.07 to -0.23)*	0.47 (0.15 to 0.78)**	0.47 (0.13 to 0.82)**	0.02 (-0.08 to 0.12)	0.05 (-0.05 to 0.15)
dVOL (%)	9.0 (1.8 to 16.2)*	8.3 (-0.7 to 15.8)*	-0.7 (-3.4 to 2.0)	-1.6 (-4.5 to 1.2)	0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)

NIBUT Non-invasive break-up time, SBUT "Self-reported Break Up Time", ECP Eosinophil cationic protein, MPO Myeloperoxidase, MCA Minimum cross-sectional area, VOL Volumes of the nasal cavity, dVOL Volume difference before and after decongestion

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 4 In a study of 173 university employees, multiple logistic regression analyses were performed for symptoms and complaints on environmental perceptions (weekly and sometimes versus never) when using different “atopy markers” (Phadiatop pos, serum totalIgE ≥ 100 kU/l, allergy in family, ever asthma, ever hay fever, ever eczema) keeping age, gender, current smoking, and number of days with respiratory infections last month in the models; odds ratios (OR) and confidence intervals

	Phadiatop pos OR (95% CI)	T-IgE ≥ 100 kU/l OR (95% CI)	Allergy in family OR (95% CI)	Ever asthma OR (95% CI)	Ever hay fever OR (95% CI)	Ever eczema OR (95% CI)
<i>Symptoms</i>						
Ocular symptoms	1.18 (0.57–2.46)	0.41 (0.18–0.93)*	1.22 (0.62–2.41)	1.13 (1.01–1.74)*	0.98 (0.46–2.12)	1.81 (0.88–3.72)
Nasal symptoms	1.38 (0.62–3.07)	1.49 (0.61–3.64)	1.45 (0.70–2.99)	2.21 (0.80–6.06)	1.19 (0.51–2.74)	1.38 (0.64–2.97)
Laryngeal symptoms	0.95 (0.45–2.02)	0.77 (0.34–1.75)	1.36 (0.68–2.73)	3.96 (1.58–9.92)**	1.32 (0.60–2.88)	1.07 (0.52–2.19)
Cough	0.90 (0.41–1.97)	0.64 (0.26–1.57)	1.64 (0.79–3.42)	2.99 (1.21–7.42)*	0.73 (0.32–1.64)	0.88 (0.41–1.88)
<i>Complaints</i>						
Dry air	1.62 (0.77–3.40)	1.14 (0.51–2.58)	0.71 (0.36–1.43)	1.29 (0.55–3.02)	2.42 (1.08–5.45)*	1.07 (0.53–2.19)
Stuffy air	0.70 (0.32–1.55)	0.50 (0.21–1.19)	0.99 (0.47–2.07)	0.85 (0.34–2.12)	0.97 (0.41–2.25)	0.84 (0.39–1.82)
Temperature too high	1.26 (0.58–2.74)	0.42 (0.17–0.99)*	1.55 (0.73–3.28)	1.20 (0.51–2.86)	3.48 (1.56–7.76)**	2.23 (1.04–4.77)*
Temperature too low	1.09 (0.51–2.31)	0.63 (0.26–1.49)	1.15 (0.56–2.34)	1.57 (0.67–3.68)	2.09 (0.94–1.10)	0.81 (0.39–1.71)

* $P < 0.05$; ** $P < 0.01$

and perceiving “dry air” in adjusted analyses (Table 5). Lower SBUT was associated with perceiving temperature too low. Lower MCA2 was associated with perceiving “stuffy air”. VOL2 was positively associated with ocular and laryngeal symptoms. The nasal volume difference before and after decongestion (dVOL%) was associated with perceiving less “dry air”. NAL-ECP was associated with cough (OR 1.15, 95% CI; 1.00–1.31).

Associations between different atopy markers and biomarkers

Subjects with positive Phadiatop had longer SBUT, and higher levels of ECP, MPO, lysozyme and albumin (Table 6). None of the other atopy markers were associated with increase of any NAL-biomarkers. Total IgE ≥ 100 kU/l was associated with lower level of MPO. Nasal volume difference before and after decongestion (dVOL%) was positively associated with allergy in family.

Correlations between biomarkers

NIBUT and SBUT were correlated (Tau beta 0.29; $P < 0.001$). All biomarkers in NAL were positively correlated with each other. Higher NAL-lysozyme concentration was associated with less nasal patency (Tau beta -0.15 for MCA1, $P < 0.01$, -0.12 for VOL1 $P < 0.5$) and volume difference after decongestion (Tau beta 0.11; $P < 0.05$). Nasal decongestion was associated with NIBUT (Tau beta 0.14; $P = 0.02$). Total IgE was correlated with SBUT (Correlation coefficient 0.18, $P = 0.001$, Kendall Tau beta).

Discussion

Tear film break up time (BUT), nasal patency, nasal volume difference before and after decongestion and NAL-lysozyme were predictors for ocular, nasal, laryngeal symptoms and environmental perceptions in our study. Perceiving “dry air”, having ocular symptoms and lower BUT were strongly associated. The prevalence of ocular and nasal symptoms was similar to other studies in office and hospital workers using the same symptom questionnaire (Wieslander et al. 1999, 2000). We found that ocular symptoms were associated with reduced tear film stability, measured by two different methods. This is in agreement with previous studies (Franck 1986; Wieslander et al. 2000; Bräschke et al. 2001). In contrast, nasal symptoms were not significantly associated with physiological signs from the nasal mucosa, neither nasal patency nor NAL-biomarkers. Poor correlation has previously been reported between measured nasal patency and nasal obstructive symptoms (Roithmann et al. 1994; Kim et al. 1998). The association between laryngeal symptoms and increased NAL-lysozyme is interesting and should be followed up in future studies.

Our findings does not support that atopy defined by Phadiatop, total IgE, hereditary allergy or previous eczema is predictive for airway symptoms or perceived air quality in terms of “dry” or “stuffy” air in non-industrial indoor occupational environments. Current or previous asthma was associated with symptoms and current or previous hay fever was associated with perceiving “dry air” suggesting that current hyperreactive and hypersensitive airways might be a more important predictor for increased symptoms and perceptions than Phadiatop, IgE or hereditary allergy. This

Table 5 In a study of 173 university employees, different physiological parameters were used as biomarkers. Multiple logistic regression analyses performed for symptoms, complaints (weekly and sometimes versus never) keeping age, gender, current smoking, and number of days with respiratory infections last month in the models; odds ratios (OR) and confidence intervals

Parameter	NIBUT (s) OR (95% CI)	SBUT (s) OR (95% CI)	MCA1 (cm ²) OR (95% CI)	MCA2 (cm ²) OR (95% CI)
<i>Symptoms</i>				
Ocular symptoms	0.81 (0.70–0.94)**	0.95 (0.91–1.00)*	2.82 (0.65–12.2)	3.00 (0.90–10.0)
Nasal symptoms	0.94 (0.81–1.09)	0.99 (0.94–1.04)	1.68 (0.37–7.53)	1.61 (0.46–5.71)
Laryngeal symptoms	0.95 (0.83–1.08)	0.95 (0.91–1.00)*	1.60 (0.39–6.53)	2.66 (0.79–8.97)
Cough	0.98 (0.85–1.13)	1.01 (0.96–1.06)	1.99 (0.45–8.76)	1.08 (0.32–3.63)
<i>Complaints</i>				
Dry air	0.76 (0.64–0.90)**	0.90 (0.86–0.95)***	1.99 (0.48–8.24)	2.55 (0.78–8.39)
Stuffy air	0.99 (0.85–1.15)	0.96 (0.92–1.01)	0.23 (0.05–1.11)	0.16 (0.04–0.59)**
Temperature too high	0.91 (0.77–1.08)	0.97 (0.92–1.02)	0.66 (0.14–3.09)	0.62 (0.18–2.19)
Temperature too low	1.02 (0.87–1.19)	0.93 (0.88–0.98)**	0.90 (0.21–3.93)	0.60 (0.18–2.01)
Parameter	VOL1 (cm ³) OR (95% CI)	VOL2 (cm ³) OR (95% CI)	dVOL (%) OR (95% CI)	
<i>Symptoms</i>				
Ocular symptoms	1.59 (0.96–2.63)	1.19 (1.03–1.37)*	0.48 (0.09–2.55)	
Nasal symptoms	1.31 (0.78–2.20)	1.09 (0.94–1.26)	0.47 (0.08–2.82)	
Laryngeal symptoms	1.32 (0.83–2.10)	1.22 (1.05–1.41)**	0.46 (0.09–2.34)	
Cough	1.31 (0.80–2.14)	1.11 (0.97–1.27)	1.37 (0.26–7.14)	
<i>Complaints</i>				
Dry air	1.57 (0.97–2.53)	1.13 (0.99–1.29)	0.05 (0.01–0.34)**	
Stuffy air	0.80 (0.48–1.32)	0.88 (0.76–1.01)	0.52 (0.09–2.96)	
Temperature too high	0.82 (0.50–1.35)	0.96 (0.83–1.10)	2.48 (0.45–13.7)	
Temperature too low	1.04 (0.64–1.69)	0.98 (0.86–1.12)	1.71 (0.35–8.33)	

NIBUT Non-invasive break-up time, SBUT “Self-reported Break Up Time”, ECP Eosinophil cationic protein, MPO Myeloperoxidase, MCA Minimum cross-sectional area, VOL Volumes of the nasal cavity, dVOL Volume difference before and after decongestion

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

is consistent with a recent finding in Norway that indoor climate at the workplace was stated as the most frequent provoking factor among employees 18–55 years, who had been on sick leave >16 days due to asthma in the years 2000–2003 (Leira et al. 2006). This might also be consistent with findings of association between SBS and atopy defined as past or present asthma, hay fever or atopic dermatitis (Stenberg et al. 1994). Also “atopic manifestations” (any prior history of allergic rhinitis, atopic dermatitis or bronchial asthma) was associated with SBS (Jaakkola et al. 1991). Graudenz et al. 2002 found building related association between respiratory symptoms, symptoms of rhinoconjunctivitis and aging ventilation systems, but this was not associated to familiar atopy or previous diagnoses of asthma or rhinitis. Graudenz et al. 2006 found that individual with allergic rhinitis had different IAQ perceptions compared with controls and perceived more “dry air” particularly at lower indoor temperatures. Individuals with a history of atopy, defined as a history of asthma, hay fever or eczema in childhood, reported a higher prevalence of Sick

Building Syndrome (SBS) symptoms including airway symptoms in the general population (Norbäck and Edling 1991). This association was not found among employees in primary schools (Norbäck et al. 1990b) or among employees in 11 consecutive sick buildings referred for investigation (Norbäck et al. 1990a) although “hyperreactivity” in terms of “easily irritated eyes or respiratory tract during exposure to non-specific irritants (tobacco smoke, exhaust gases, organic solvents)” were associated in both studies. Atopy defined by reporting an allergy to tree or grass pollen or to furry animals, or a history of eczema in childhood was on the other hand associated with SBS among airline crew (Lindgren and Norbäck 2005).

The association between “ever hay fever” and perceiving “dry air” suggest that nasal inflammation increases the sensitivity to irritating effects of indoor air. In particular the symptom “dry eyes” and related ocular-surface effects has been associated to indoor environmental exposure in office building (Wolkoff et al. 2006). Increased air temperature has also been shown to worsen eye irritation symptoms

Table 6 In a study of 173 university employees, multiple linear regression analyses are performed using biomarkers (serum total IgE, NIBUT, SBUT, ECP, MPO, Lysozyme, Albumin, MCA1, MCA2, VOL1, VOL2, dVOL) as dependent variables and different atopy markers (Phadiatop pos, serum total IgE ≥ 100 kU/l, allergy in family, ever asthma, ever hay fever, ever eczema) as independent, keeping age, gender, current smoking, and number of days with respiratory infections last month in the models

Parameter	Phadiatop pos Beta (95% CI)	T-IgE ≥ 100 kU/l Beta (95% CI)	Allergy in family Beta (95% CI)	Ever asthma Beta (95% CI)	Ever hay fever Beta (95% CI)	Ever eczema Beta (95% CI)
Serum total IgE	61 (-22 to 145)	–	–51 (-135 to 32)	–5 (-107 to 98)	–24 (-144 to 97)	1 (-87 to 89)
NIBUT (s)	–0.8 (-1.8 to 0.2)	0.9 (-0.3 to 2.2)	–0.3 (-1.2 to 0.7)	0.4 (-0.8 to 1.5)	–0.1 (-1.4 to 1.2)	0.1 (-0.8 to 1.1)
SBUT (s)	2.8 (0.3 to 5.2)*	2.7 (-0.2 to 5.6)	–1.8 (-4.1 to 0.6)	–0.7 (-3.7 to 2.2)	0.2 (-3.3 to 3.7)	0.0 (-2.5 to 2.5)
ECP (μ g/l)	2.3 (0.9 to 3.8)**	–0.4 (-2.3 to 1.4)	–1.0 (-2.4 to 0.5)	1.4 (-0.4 to 3.3)	0.8 (-2.9 to 1.3)	0.3 (-1.2 to 1.9)
MPO (μ g/l)	32.7 (7.8 to 58)*	–45 (-75 to -15)**	–11.3 (-36.1 to 13.5)	12.0 (18.7 to 42)	–16 (-51 to 19)	–5.6 (-32 to 20)
Lysozyme (mg/l)	1.1 (0.1 to 2.1)*	–0.3 (-1.5 to 1.0)	–0.6 (-1.6 to 0.4)	0.7 (-0.6 to 1.9)	–0.1 (-1.6 to 1.3)	–0.2 (-1.1 to 0.7)
Albumin (mg/l)	7.8 (2.0 to 14.0)**	–7.0 (-14.1 to 0.2)	–3.0 (-8.8 to 2.7)	4.3 (-2.8 to 11.4)	–0.3 (-8.7 to 8.1)	–0.2 (-6.3 to 5.9)
MCA1 (cm ²)	–0.01 (-0.10 to 0.08)	–0.05 (-0.15 to 0.06)	–0.05 (-0.14 to 0.03)	–0.02 (-0.13 to 0.09)	–0.03 (-0.15 to 0.10)	0.04 (-0.05 to 0.13)
MCA2 (cm ²)	–0.01 (-0.10 to 0.12)	–0.06 (-0.19 to 0.07)	–0.07 (-0.18 to 0.03)	–0.04 (-0.17 to 0.10)	–0.03 (-0.18 to 0.13)	0.08 (-0.03 to 0.19)
VOL1 (cm ³)	–0.10 (-0.37 to 0.18)	–0.02 (-0.35 to 0.31)	–0.03 (-0.30 to 0.23)	–0.03 (-0.36 to 0.30)	–0.08 (-0.44 to 0.29)	0.07 (-0.20 to 0.34)
VOL2 (cm ³)	0.37 (-0.59 to 1.34)	–0.28 (-1.45 to 0.89)	–0.25 (-1.19 to 0.70)	0.30 (-0.88 to 1.48)	–0.49 (-1.85 to 0.87)	0.31 (-0.68 to 1.30)
dVOL (%)	–7.4 (-15.4 to 0.6)	7.2 (-2.3 to 16.8)	8.5 (0.8 to 16.2)*	–1.3 (-11.1 to 8.4)	–2.0 (-13.4 to 9.3)	–3.4 (-11.8 to 5.0)

NIBUT Non-invasive break-up time, SBUT “Self-reported Break Up Time”, ECP Eosinophil cationic protein, MPO Myeloperoxidase, MCA Minimum cross-sectional area, VOL Volumes of the nasal cavity, dVOL Volume difference before and after decongestion

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

which also are of interest in view of the association found between “ever hay fever” and both “dry eyes” and perceiving “temperature too high”.

“Ever eczema” was associated with perceiving “temperature too high”. Skin symptoms may be alleviated by lowering room temperature which increases relative humidity (Reinikainen and Jaakkola 2003). A clear-cut inverse correlation was found between aggravating atopic eczema and increasing air temperature in the Swiss high-mountain area (Vocks et al. 2001). This might give some support for avoiding high indoor air temperature in the winter season when the relative humidity is low in order to reduce skin symptoms generally and particularly for person with atopic eczema.

The associations between ocular and laryngeal symptoms and increased posterior nasal volume (VOL2) and between complaining about “dry air” and decreased nasal volume difference before and after decongestion were unexpected and are difficult to explain. These findings should be followed up in future studies.

Gender was a major factor associated with various physiological signs. Females had shorter BUT as assessed by both methods and they had smaller anterior and posterior nasal dimensions, and greater nasal decongestion by adrenergic spray. Shorter BUT in females has been observed in other studies (Wolkoff et al. 2003; Wolkoff et al. 2006; Bräschke et al. 2005). Smaller nasal volumes among women, both anterior and posterior have previously been reported in a study in 411 white-collar workers from Sweden (Wålinder et al. 2000). Younger subjects had less anterior and posterior nasal patency. They also had more atopy, in line with the increase of atopic sensitization in the younger generations (Aberg et al. 1995). In contrast, the Swedish study in white-collar workers could not find any age effect (Wålinder et al. 2000).

We found that 37% had atopy assessed as positive Phadiatop, as compared to 25% in a population of 500 consecutive blood donors from the same region in Norway (Johansson et al. 2005). This might be due to higher prevalence of atopy in the more educated part of the population (Strachan 1996). Among 126 Phadiatop positive blood donors from the same region, 46.8% were positive to timothy, 50.8% to birch, 21.4% to cat and 11.6% to mite (Johansson et al. 2005).

Positive Phadiatop has not previously been used as atopy definition in studies of occupational indoor environmental effects. Atopy defined as a positive prick test to any allergen was significant independent risk factor for reporting at least one SBS-related symptom (Björnsson et al. 1998) although another study using the same definition did not find any such association (Muzy et al. 1998). Phadiatop was strongly associated with all four NAL biomarkers, but not related to nasal patency or nasal decongestion. Moreover, all nasal

biomarkers were associated with each others, and a higher level of lysozyme was associated with decreased anterior nasal patency and increased nasal decongestion. Challenge studies with allergens in sensitised subjects have showed effects on nasal patency (Fisher 1997) and increase of ECP (Beppu et al. 1994; Wilson et al. 1998) and albumin (Wilson et al. 1998) in nasal lavage after exposure. Since the present study was performed in late winter, off pollen season, it is unlikely that the strong effect of atopy on nasal biomarkers was caused by pollen allergen exposure in sensitised subjects. This is supported by self-reported hay fever not being associated with physiological ocular or nasal signs. One possible explanation could be allergic reactions to indoor allergens, such as furry pets, house dust mites or moulds. In future studies, a more detailed allergen testing should be performed.

The study included all staff in four older university buildings. Selection bias is less likely, since the participation rate was high (86%). However, our study is cross-sectional and workers having increased ocular, nasal, laryngeal symptoms and adverse environmental perceptions might have left these environments at an earlier stage leaving back in the population only those that tolerate the environments as a sort of healthy worker effect. On the other hand, the population included relatively high frequencies of subject with subjective and objective markers for allergy and hypersensitivity and many had current or previous asthma or hay fever. Furthermore, those with current or previous asthma or hay fever had more symptoms and complaints on perceived environments. Recall bias may be present, which could affect symptom reporting but cannot affect the physiological measurements. However, the period of symptom reporting was no longer than 3 months. Measurement error or intra-individual variability may have introduced some bias in the investigation, especially for lavage measurements. All assessments were performed by same researcher and same laboratory. For acoustic rhinometry by Rhin 2000, triplicate measurements showed a relative standard error of variation of 7% for MCA1 and MCA2, 6% for VOL1 and 8% for VOL 2 (Wålinder et al. 1997). When the same lavage method and same analytical laboratory was used in an exposure chamber study, a larger day-to-day variability (CV) was found: ECP 69%, lysozyme 42%, MPO 50% and albumin 83% (Wålinder 1999). Misclassification due to measurement error is most likely non-differential, and would result in less power of the study. Thus, we do not believe that our conclusions are seriously influenced by selection response or measurement errors. However, due to the relatively small study size, the power to detect associations for diseases or exposure with a low prevalence was limited.

In conclusion, in office work environment, perceiving “dry air”, having ocular symptoms and lower BUT were

strongly associated. “Ever asthma” and “ever hay fever” were predictors for symptoms and perceived air quality, respectively. Markers of atopy in terms of Phadiatop, Total IgE, familiar allergy and “ever eczema” were not associated to symptoms or perceived environments. Gender was associated to environmental perceptions, BUT and nasal patency. Age was associated to nasal patency. Recent airway infections were predictors for nasal lavage markers. A combined use of questionnaires collecting symptoms and perceived air environmental complaints and measurements of tear film break up time, nasal patency and NAL-markers can be a useful method to study human reactions to the environment.

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