

Original article

Nasal mucosal histamine reactivity among young students and teachers, having no or prolonged exposure to a deteriorated indoor climate

Background: In a study performed in the spring of 1995, we found a significantly greater nasal mucosal histamine reactivity among teachers, who had worked for several years in a recently renovated moisture-damaged school, than in those in a control school. In the present study we investigated the students who begun their high-school studies at both schools in the autumn of 1995 and compared them with the teachers as regards mucosal reactivity, atopy and symptoms.

Methods: Twenty-eight teachers in the target school, 18 teachers in the control school and 45 students from each school underwent a nasal histamine provocation test and a skin-prick test. They also answered a standardized questionnaire.

Results: The teachers in both schools had more marked nasal mucosal histamine reactivity at the lowest provocation concentrations than the students. The histamine provocation curve of the target school teachers had consistently higher values than that of the students ($P = 0.0001$), but its slope and shape were similar ($P = 0.15$), while the slope of the provocation curve of the control school teachers was flatter. However, there was only a borderline significance in this respect compared to the students ($P = 0.07$). Teachers with a dry and crusty appearance of the nasal mucosa on anterior rhinoscopy reacted more strongly to histamine provocation than those without this finding ($P = 0.0004$). There was a significantly higher frequency of skin-prick test positivity (SPT+) among the students ($P = 0.03$). There were no significant differences in nasal mucosal histamine reactivity between atopic and non-atopic subjects out of pollen season.

Conclusions: Teachers had a significantly greater mucosal histamine reactivity than the students, whereas the latter had a significantly higher frequency of atopy. These results are compatible with an age-related pattern of mucosal reactivity. A crusty appearance of the nasal mucosa seems to predispose to an increase in histamine reactivity. There were no significant differences according to histamine reactivity between atopic and non-atopic subjects.

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Office workers (1, 2), school personnel (3, 4) and the general population (5, 6) commonly complain about poor indoor air quality. Many studies have shown a relationship between staying in damp buildings and irritative symptoms from the mucous membranes of the airways (7, 8).

The indoor environment is also one of many factors discussed as contributing to an increase in the prevalence of atopy in western industrialized countries, mainly in young people (9). However, it is probably much less important than a lower exposure to bacterial infections and changes in eating habits early in life connected with the western lifestyle (10–12).

Many houses built during the last few decades are airtight and poorly ventilated. Irritating volatile organic

and inorganic compounds in the indoor air may, under these conditions, emanate from building materials and act as adjuvant factors for allergic sensitization (13, 14). A high level of indoor humidity may also provide optimal conditions for the growth of mites and allergy to them (15, 16).

IgE-mediated diseases of the airways (asthma and rhinitis) are usually accompanied by a contemporary hyperresponsiveness to non-allergic stimuli, such as cold air, dust and various irritants (17, 18).

It seems likely that an allergic inflammation affects the mucosal sensory nerves, which become hyperreactive (19). However, some studies also indicate a mucosal hyperresponsiveness out of season in patients suffering from seasonal allergy to pollen (20, 21).

Among persons who develop symptoms of chronic rhinitis, the proportion with a non-allergic aetiology increases steadily with age and exceeds 60% after the fifth decade of life (22).

This suggests that age-related changes in mucosal function, at least partly, are responsible for the increase in mucosal reactivity.

Histamine, a non-allergic stimulant, routinely used for nasal provocation induces sneezing, rhinorrhoea and nasal congestion in people with allergic and/or non-allergic rhinitis as well as in healthy persons (23, 24). The nasal congestion can be assessed by various methods i.e. acoustic rhinometry, rhinomanometry or nasal peak flowmetry (25, 26). All of these methods are indirect and the values depend on a combination of mucosal swelling and accumulated secretions in the nasal cavity.

Rhinostereometry is an optical high-precision method which allows direct inspection of the nasal mucosa with the subject held firmly to an individually formed tooth-splint (27). By this method, one could confirm the presence of an increased reactivity to histamine, measured as mucosal swelling, in non-atopic tenants living in a residential area with severe indoor climate problems compared to people living in a control area without these problems (28).

We have previously shown that teachers who had been working for a long time in a water-damaged school with moisture problems had increased mucosal sensitivity of the upper airways subjectively (as shown in questionnaires) and objectively (using nasal histamine provocation) vs. teachers in a control school (29). This was found although the target school had been renovated more than one year before the study. We therefore considered it necessary to do a follow-up study of the students beginning their high-school education at the two schools. This also gave us an opportunity to compare the students and the adult teachers.

In this study we aimed to determine how students in these two schools, beginning their first grade of senior high-school education, differ from the teachers concerning objectively recorded mucosal reactivity, frequency of atopy and occurrence of symptoms.

We also wished to determine whether there was a difference in nasal mucosal reactivity to histamine between atopic and non-atopic subjects (30). The study was done out of the Swedish pollen season.

Material and methods

Study populations

A random sample of teachers who had worked for at least 5 years in the renovated water-damaged school (39 persons) and all teachers in the control school who fulfilled the same inclusion criteria (30 persons) were invited to take part in the study in the early spring of

1995. Twenty-eight and 18 teachers, respectively, accepted and formed two study groups.

A random sample of 180 students (90 from each school), beginning their high-school studies, were asked to participate in the study. Forty-five of them from each school accepted and formed the study groups from the target and the control school.

To judge the presence of a selection bias the students in the first group of randomly selected students (50 at each school), who had declined to participate, were offered a simplified test procedure including a skin-prick test and answering the questionnaire, but without the nasal histamine challenge. Fifty-four (27 from each school) of these students had already undergone the complete investigation and now a further 38 students (19 from each school) agreed to take part in the skin prick test. This means that a total of only eight students gave no information at all in the first selected group. The studies were done in the autumn of 1995 about 2 months after the start of the term.

Questionnaires

A validated standardized questionnaire (MM 040 NA) was used for the teachers and a somewhat modified one (MM 060 NA) for the students (31). They both contained the same questions about the perceived indoor climate, symptoms often referred to in indoor climate research and allergic manifestations specified in Table 2 and some background factors (age, gender, smoking habits, etc.). For the questions about the indoor air quality and symptoms a recall period of 3 months was used and three alternatives were given, 'yes, often' (every week), 'yes sometimes' and 'no, never'. Only the first alternative was interpreted as a positive outcome.

Skin-prick test

All teachers and students underwent a standardized skin-prick test (32). The test panel consisted of allergens against pollen (birch, grass and mugwort), mites (*D. pteronyssinus* and *D. farinae*), furred animals (cat, dog and horse) and moulds (*Claudosporium*, *Alternaria* and *Aspergillus fumigatus*) besides negative and positive histamine controls. Skin-prick test positivity (SPT+) was defined as the formation of a wheal of a mean diameter of at least 3 mm in response to any of the allergens used and atopy as the combination of SPT+ and reported allergic manifestations.

Provocation test

The nasal histamine provocation test in the teachers was done in a single-blind manner at the hospital outside the two schools (29). To simplify transport and avoid unnecessary exposure to cold air before the provocation, the students were investigated in the respective schools.

A standardized provocation test described by Hallén and Juto (33) involves the use of three concentrations of a histamine solution (1, 2 and 4 mg/ml). After 15 min of acclimatization and a further 15 min to assess the stability of the nasal mucosal position, the provocation started with the lowest histamine concentration (1 mg/ml). Recordings of the mucosal position on both sides of the nose were made with rhinostereometry (27) after 5 and 10 min with an increase in the histamine concentration each 10 min.

Anterior rhinoscopy was done before provocation. The findings were divided by the examiner, a physician with considerable experience, into two groups i.e., with or without a dry and crusty appearance of the nasal mucosa.

Statistical analysis

The two study groups of teachers and the two study groups of students, concerning nominally scaled variables, were compared with Fisher's exact test specially adapted for use in small samples (34). An analysis of variance model (ANOVA) for repeated measurements was used to analyse differences in mucosal congestion. It aimed at modelling the growth curves for mucosal swelling as a function of the provocation concentrations of 1, 2 and 4 mg/ml of the histamine solution. The main group factor or 'between subjects' factor was divided into four categories. In the sequel, the factor is denoted simply by the group and it is composed of the fourfold combination of two factors, i.e., school (target or control) and person category (teacher or student). Two 'within subjects' factors were included, i.e., dose (with levels 1, 2 and 4 mg/ml, as defined above) and time (5 and 10 min after each provocation). The 'between subjects' and 'within subjects' factors and interactions between these were the main explanatory variables in the model, but a set of additional variables was also included in the analysis to control for confounding, i.e., as covariate factors (gender, smoking habits and allergic manifestations). We also analysed the effect of a dry crusty appearance of the nasal mucosa. These analyses were done only in the teachers. We introduced crusty appearance as an additional covariate in the analysis of both the baseline values and the whole provocation curve. In all statistical tests, two-sided tests were used with a significance level of five percent. The ANOVA was first done with all interactions included and followed by a sequential search for parsimonious models where interactions of no statistical significance were excluded. Evaluations of the goodness-of-fit of the models were done with Akaike's information index (35).

When a final ANOVA model had been found we tried to describe the basic shape of the provocation curves by slightly reformulating the model. In this model we estimated the linear regression of an increase in swelling per $^2\log$ mg/ml histamine (doses 1, 2 and 4 mg/ml which give the logarithmic values 0, 1 and 2) for each school and category. We also determined the 95% confidence intervals (95% CI) for the estimates of the intercept and slope in these regressions.

In addition we analysed differences in the baseline values (at provocation level 1 mg/ml) with the ANOVA model. Only the 'within subjects' factor time (5 and 10 min) was included in this model, but the school and person category were included as 'between subjects' factors.

In a supplementary ANOVA model, atopy was introduced as an additional factor.

Results

Study population

Table 1 shows a few characteristics of the students and teachers in the two schools. The proportion of boys was higher in the target school than in the control school, but it only reflects the gender ratio in the two schools (47.9% vs. 33.4% boys in the target and control schools, respectively). A description of the teachers with an analysis of the completion rate, has been reported in more detail elsewhere (29).

Some data on the primary randomly selected 100 students are given in Table 2. Fifty-four students took part in the histamine provocation study and 46 declined to participate, mostly because they had no time or did not feel like it.

Table 1. Some personal characteristics of the students and the teachers at the two schools

	Target school (students) <i>n</i> = 45	Control school (students) <i>n</i> = 45	Target school (teachers) <i>n</i> = 28	Control school (teachers) <i>n</i> = 18
Gender (% males)	46.7	28.9	46.4	66.7
Age (mean)	16.1	16.1	51.4	50.6
Smoker (%)	15.6	13.3	7.1	5.6

Table 2. Comparison between students who took part in the histamine provocation test (provocation group) and those who declined to participate (non-provocation group) among the first randomly selected 100 students. Q = questionnaire, P = prick test, Hi = histamine provocation

	Provocation group (Q + P + Hi) <i>n</i> = 54	Non-provocation group (Q + P) <i>n</i> = 38
Gender (male)	21/54 (38.9%)	27/38 (71.1%)
Asthma/hay fever*	13/53 (24.5%)	11/38 (28.9%)
Mucosal symptoms†	6/54 (11.1%)	3/38 (7.9%)
SPT+	18/54 (33.3%)	11/38 (28.9%)

* Questions asked: Have you ever had asthmatic problems? Have you ever suffered from hay fever?

† Questions asked: During the last 3 months have you had any of the following symptoms?

- itching, burning or irritation of the eyes?
- irritated, stuffy or runny nose?
- hoarse, dry mouth?
- cough?

Thirty-eight of these 46 students who declined to participate in the provocation test agreed to have the skin-prick test and answered the questionnaire. There was no selection of students to participate in the histamine provocation study according to reported allergic manifestations (asthma/hayfever), mucosal symptoms or positive skin-prick test (SPT+). The participation rate of girls was higher.

Reported allergy and symptoms

The reported prevalence of allergic manifestations was similar in students and teachers in the target school, but the teachers in the control school reported a somewhat lower prevalence. However, the overall difference between students and teachers was not significant, $P = 0.52$.

(Table 3). Teachers had a higher frequency of mucosal symptoms (21.9%) than students (10.0%), but the difference was only of borderline significance, $P = 0.07$.

Skin-prick test

The frequency of SPT+ and the prevalence of mucosal symptoms are shown in Table 3. The total frequency of SPT+ among the students was much higher than in the

Table 3. The prevalence of symptoms and frequency of atopy (positive skin-prick test) in students and teachers at the two schools

Symptoms (according to questionnaire)	Target school (students) <i>n</i> = 45	Control school (students) <i>n</i> = 45	Target school (teachers) <i>n</i> = 28	Control school (teachers) <i>n</i> = 18
Asthma/hayfever (%)	27.9	24.4	25.0	11.1
Mucosal symptoms (%)	8.9	11.1	25.0	16.7
SPT+ (%)	35.6	35.6	17.9	16.7

adult teachers (35.6% vs. 17.4%, $P = 0.03$). The frequencies of SPT+ teachers and students were similar in the two schools. 75% (6/8) of the SPT+ teachers and 69% (22/32) of the SPT+ students reacted to pollen allergens.

The provocation test

The results of the histamine provocation test in the students and teachers on the provoked side of the nasal cavity are given in Table 4 and Fig. 1. Only small oscillations around the baseline were seen on the control side. The ANOVA analysis of the baseline values (provocation concentration 1 mg/ml) showed a borderline statistical significance for the interaction factor person category and time after provocation, $P = 0.07$, primarily due to an increase in the value at 10 min in teachers at the target school. Of greater relevance and more statistical significance is the difference in the main factor teachers vs. students, $P = 0.0001$, with students having much lower values than teachers (on average, about half the teacher's value).

Since we had previously determined separated provocation curves in the teachers in both schools, from 1 mg/ml to 4 mg/ml (29), it was only necessary to compare the students at the schools with the teachers. The first ANOVA model with all main factors and interactions showed that the interaction group $\times$ concentration level was highly significant, $P = 0.008$, which indicated that the four groups had different provocation curves. Figure 1 shows that the statistical significance is due to two features, i.e., the curves are different in the two groups of teachers and those of the students are much lower than those of the teachers. We therefore did stratified subgroup analyses of the person category (teachers and students separately) and school (target school and control school separately).

The separate analysis of the teachers is mentioned above. Since we found no difference between students in both schools in any respect, they can be viewed as a homogeneous group. Our analysis of each school showed that the provocation curve of the target school teachers had consistently higher values than that of the students, $P = 0.0001$, but its slope and shape were similar, $P = 0.15$. In the control school, however, the slope of the curve was of borderline significance, the interaction category $\times$ provocation concentration had $P = 0.07$.

Table 5 summarizes the essential features of the analysis of the provocation curves. We expressed mucosal swelling as a linear function in the ^{2} logarithms

Table 4. Nasal mucosal congestion in mm (mean and (SD)) induced by three provocation concentrations in high-school students and teachers at the two schools

Provocation concentrations	Target school (students) <i>n</i> = 45	Control school (students) <i>n</i> = 45	Target school (teachers) <i>n</i> = 28	Control school (teachers) <i>n</i> = 18
1 mg/ml				
After 5 min	0.20 (0.28)	0.25 (0.27)	0.50 (0.73)	0.49 (0.54)
After 10 min	0.09 (0.33)	0.15 (0.29)	0.52 (0.75)	0.42 (0.50)
2 mg/ml				
After 5 min	0.50 (0.43)	0.56 (0.40)	0.98 (0.81)	0.82 (0.76)
After 10 min	0.29 (0.50)	0.44 (0.44)	0.88 (0.84)	0.65 (0.67)
4 mg/ml				
After 5 min	0.80 (0.53)	0.82 (0.60)	1.42 (0.83)	0.86 (0.72)
After 10 min	0.53 (0.63)	0.54 (0.60)	1.10 (0.85)	0.59 (0.61)

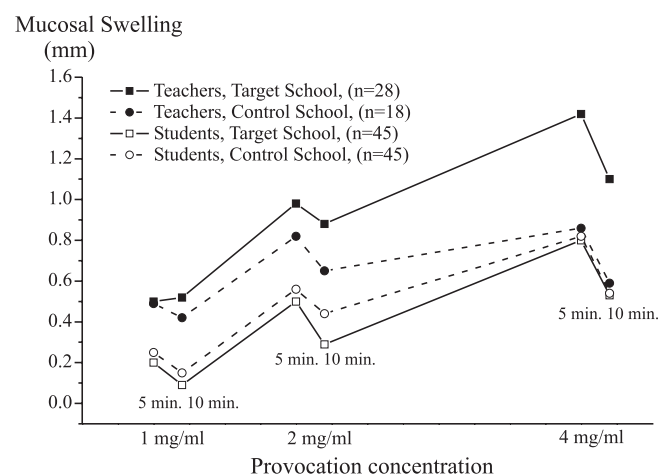


Figure 1. Histamine provocation curves of the teachers and students at both schools.

of the provocation concentration separately for 5 and 10 min. The differences and similarities in intercepts and slopes in the four groups accord with our results from the ANOVA model. Students had less mucosal swelling than teachers, as shown by the intercepts, but there were few, if any, differences between the students in the two schools, as shown by both the intercepts and the slopes. The reactions of the teachers at the control school to the provocation concentration differed considerably from their colleagues at the target school, and those of both groups of students were intermediate

Table 5. linear regression analysis of mucosal swelling induced by histamine provocation (logarithmic values 0,1 and 2) stratified for time after provocation (5 and 10 min) and person category (teachers and students). Estimates of intercepts, slopes and 95% confidence intervals (95% CI)

Time	Category	School	Intercept	95% CI	Slope	95% CI
5 min	Teachers	Target	0.49	0.25–0.73	0.46	0.36–0.57
		Control	0.42	0.13–0.71	0.18	0.05–0.32
	Students	Target	0.20	0.13–0.28	0.30	0.22–0.37
		Control	0.26	0.18–0.33	0.28	0.21–0.36
10 min	Teachers	Target	0.52	0.28–0.76	0.29	0.19–0.39
		Control	0.42	0.12–0.72	0.09	0.03–0.21
	Students	Target	0.08	0.00–0.17	0.22	0.15–0.30
		Control	0.17	0.08–0.26	0.18	0.11–0.25

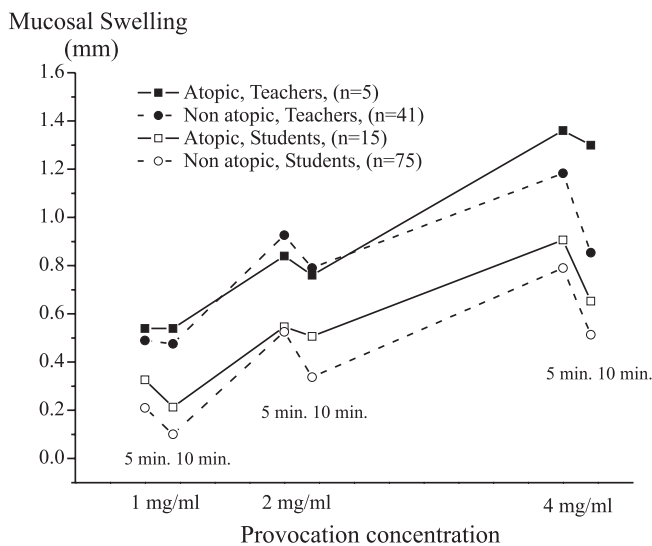


Figure 2. Histamine provocation curves of atopic and non-atopic teachers and students.

compared to the groups of teachers, as assessed by their slopes.

A separate analysis of differences between atopic and non-atopic subjects showed no significant differences in the provocation curves (Fig. 2).

The rhinoscopic examination of the teachers showed that 15 had a dry and crusty mucosa and 31 did not. No significant difference was found between teachers in the target school and those in the control school (10/28 and 5/18, respectively, $P > 0.50$). Among the students less variation was noted in the rhinoscopic findings and only one had such a finding on rhinoscopy, although seven students had a slightly dry mucosa.

When a crusty appearance was included as a covariate in the analysis of the baseline values and of the whole provocation curve (target school vs. control school, teachers only), we found a definite statistical significance for the crusty appearance, $P = 0.002$, in the analysis of baseline values and $P = 0.0004$ in the analysis of the

provocation curves. However, more importantly, the significant difference between the target and control schools in the latter analysis did not disappear with the introduction of a crusty appearance, $P = 0.002$ for the different slopes.

Discussion

The nasal histamine provocation tests differed markedly between teachers and students as regards nasal mucosal histamine reactivity. The fact that even the teachers from the control school showed more marked mucosal swelling in response to the lowest histamine provocation concentrations than the students suggests that age and/or various types of environmental exposures are of importance. Such a mucosal reaction pattern may partly be due to a lowered number of goblet cells (36) and a reduced secretory ability with age (37), which might lead to a lack of protective mucus layer and make the mucosal sensory nerve endings more sensitive to nonspecific stimulation. Among the teachers the curves for mucosal swelling, based on the rhinoscopic findings, rose sharply in those with a dry and crusty nasal mucosa. The development of such a dry mucosa may be constitutional, but it may also be age dependent, and predispose to an increase in mucosal reactivity to histamine.

The difference in provocation curves between teachers from the target and control schools could not be explained by differences in appearance of the nasal mucosa.

It is also noteworthy that in another study, using a somewhat modified histamine provocation procedure, the shape and level of the curve for mucosal swelling in the teachers in the control school resembled that of a group of people living in a residential area with no indoor air problems (28).

The teachers in the control school had only a moderate increase in mucosal swelling when exposed to the highest histamine concentration compared to the students. The marked mucosal reaction to the lowest histamine concentration may induce tachyphylaxis of the neural response during repeated stimulation. This is unlike the teachers in the target school who reacted most to the highest histamine concentration. Their curve for mucosal swelling closely resembled that of the students, but at higher levels.

As expected, the students reported mucosal symptoms less frequently than the teachers in the renovated moisture-damaged school. The difference was of only a borderline significance, but this may have been because of the small number of teachers in the study group.

The frequency of SPT+ was at least twice as high among the students as in the teachers (36% vs. 17%) and comparable to other studies of school children (38). This accords with an increasing frequency of atopy in the western world (7–9) and indicates that the increase in nasal histamine reactivity among the teachers at the

renovated damp school is not related to an increased frequency of manifestations of atopy. Indeed, the relationship between working and/or residing in these buildings and increased mucosal reactivity seems to be due to emissions in the air from the moisture-damaged foundation by microbial growth or chemical degradation of the material (39–41).

No differences in nasal histamine reactivity were found between the students at the two schools. More girls participated in the provocation test, but the frequency of symptoms from the mucus membranes and reported allergic manifestations as well as the frequency of SPT+ did not differ between those who participated in the provocation test and those who declined to do so.

The study was done outside the pollen season and no significant differences in mucosal swelling curves due to histamine provocation were seen between atopic and non-atopic subjects. Although some studies show an increase in nasal mucosal reactivity to histamine challenge among atopic subjects outside the pollen season (20, 21), it seems that the ongoing mucosal inflammation among young atopics during pollen season may disappear almost entirely outside the pollen season. Nor could we find a significant difference in this matter between atopic and non-atopic teachers but the group of atopic teachers (five subjects) is obviously too small to draw any further conclusions.

A limitation of this study was the relatively small number of teachers in both groups. Data in other studies

using the same method, however, indicate that differences between groups can be detected in as few as a dozen subjects (28).

In conclusion we found a significantly greater mucosal histamine reactivity among the teachers than in the students, although the students had a significantly higher frequency of manifestations of atopy. The teachers in the control school showed a higher reactivity to histamine with the lowest provocation concentration and the curve for mucosal swelling was flatter compared to that of the students. In teachers with a dry and crusty nasal mucosa, based on the rhinoscopic findings, the curves for mucosal swelling were markedly increased. The findings accord with an age-related pattern of mucosal reactivity. No significant differences in nasal histamine reactivity was found between atopic and non-atopic subjects out of pollen season.

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