Eur Respir J
1992, 5, 1104–1110

Relationship of upper airways disorders to FEV_1 and bronchial hyperresponsiveness in an epidemiological study

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ABSTRACT: Associations of upper airways disorders (UAD) with forced expiratory volume in one second (FEV_1) and bronchial methacholine response were studied, taking smoking habits into account.

We used epidemiological data drawn from a population of 324 men, aged 27–58 yrs.

Lower FEV_1 level was related to hay fever (p=0.01), usual (p=0.01) and chronic (p=0.02) rhinitis and common cold on the day of examination (p=0.04). Allowance for the major potential confounding factor, tobacco smoking, showed similar results. Bronchial methacholine response was heightened in men reporting hay fever compared to those without (p=0.01) but also in men reporting chronic rhinitis (p=0.06), a group which did not exhibit skin prick test positivity more often than other subjects. Exclusion of asthmatics and taking into account smoking and skin prick test positivity yielded mostly similar results.

Our data support the hypothesis of an association between lung impairment, as assessed by lower FEV_1 and bronchial hyperresponsiveness to methacholine, and different types of UAD, allergic or not.

Eur Respir J., 1992, 5, 1104–1110.

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Keywords: Asthma, bronchial hyperresponsiveness, common cold, lung function, nasal, rhinitis, smoking.

The study was supported by Grant N°88 G/7 from Fond Spécial des Comités Départementaux contre les Maladies Respiratoires et la Tuberculose, Paris, France.

Received: October 4 1991
Accepted after revision April 27 1992

Upper airways constitute the main entrance for air and external aggressions. The air is heated and humidified and a defence mechanism against various external factors is provided, prior to their penetration into the lower airways. However, there are relatively few reports dealing with the relationship between upper and lower airways disorders, except those on allergic rhinitis and asthma or bronchial hyperresponsiveness. Allergic rhinitis and asthma occur either simultaneously or in succession [1–4] and the involvement of bronchial responsiveness in allergic rhinitis is also observable in the absence of prior asthmatic symptoms [5, 6].

An epidemiological study on upper and lower airways diseases among adult men [7] gave us the opportunity to investigate the association of various upper airways disorders (UAD) with forced expiratory volume in one second (FEV_1) and bronchial hyperresponsiveness, after taking into account smoking habits, a factor known to be related to both lung function and bronchial hyperresponsiveness, as well as to some nasal disorders [8]. The assessment of such associations could improve the knowledge of the link between the nose and the lungs.

Materials and methods

Population

Data came from 324 men, aged 27–58 yrs, who were employed in or retired from the Parisian police force and surveyed in 1985–1986, as described in detail elsewhere [7, 9, 10]. Briefly, an on-going epidemiological longitudinal study on the risk factors of respiratory disease had begun in 1980 in a population of 912 working policemen. Among them, 817 had good spirometric tracings. Five years later for practical reasons, it was planned to resurvey only 3 out of 4 of the original population (599 men). The selected sample included all men who, in 1980, had reported a history of asthma (as defined by the answer to the question "Have you ever had asthma attacks?"), wheezing, any perceived hyperresponsiveness symptoms (such as sneezes or runny nose or fit of coughing induced by smoke, cold air and hay), eczema, urticaria and other possible markers for factors of susceptibility to chronic airflow limitation (a total of 306 men), and a similar number (293 men) without

any symptoms, chosen at random from the remaining 511 subjects. Of the 599 men selected, 9 had died, 18 refused to participate, 67 answered a postal questionnaire and 115 were lost to follow-up. Results of this report are restricted to those men who undertook lung function, bronchial methacholine challenge and skin prick tests in the 1985/86 survey (n=324). These men did not differ significantly from those not examined for any criterion of inclusion in the sample, or for age or smoking but they had a significantly higher FEV_1. As four men did not answer the questions on smoking habits, 320 subjects were included in the analyses taking smoking into account.

Questionnaire

Methods in our survey included a questionnaire, methacholine bronchial challenge and skin prick testing to common allergens. For the purpose of this survey, the British Medical Research Council (BMRC) European Coal and Steel Community (ECSC) standardised questionnaire [11] has been extended to determine nasal symptoms and allergy more specifically. In addition to the well-known and extensively used questions on hay fever and usual and chronic rhinitis (3 months each year), we specifically designed new questions for the assessment of other upper airways symptoms on the basis of : i) the "potential" similarity between upper and lower airways diseases; and ii) available data from clinical [4, 12, 13] as well as epidemiological reports [10, 14, 15, 16–18]. The following 11 upper airways disorders (UAD) were then considered: smoke-induced rhinitis, cold-induced rhinitis, exercise-induced rhinitis, hay-induced rhinitis, hay fever, usual rhinitis, chronic rhinitis, watery rhinorrhea, common cold on the day of examination, sinusitis and adenoidectomy. Rhinitis induced by various stimuli such as tobacco smoke, cold air, aspirin, exercise and hay or pollens (briefly, hay-induced rhinitis in this report) allowed assessment of nasal irritative and hyperresponsiveness response [18] (no subject reported aspirin-induced rhinitis). In France, the main hay and pollen season is between February and September [19]. Usual rhinitis with watery secretion was referred to as watery rhinorrhea. The wording of the questions used is given in table 1. The validity (confirmation of reported symptoms by an ear, nose and throat specialist) and reliability of questions on upper airways disorders were previously assessed in a population of 30 and 15 patients, respectively, (unpublished work). The subject interpretation of having a common cold has been validated in a previous survey by the determination of orosomucoid, an acute-phase inflammatory protein. NEUKIRCH *et al* [20] showed a very significant relationship between the level of this protein and the subjective impression of 'common cold' on the questionnaire day independent of smoking.

The daily consumption of tobacco was calculated by considering 1 cigarette, 1 cigarillo, and 1 cigar equal to 1 g, 2 g, and 5 g respectively. Subjects were classified as lifetime nonsmokers, ex-smokers (for at least 1 month) and current smokers.

Table 1. – Upper airways disorders according to asthma and reactor status (n=324)

	Prevalence	Association with	
		Asthma	Reactor status
	%	OR (95% CI)	OR (95% CI)
Nonspecific perceived hyperresponsiveness			
Smoke-induced rhinitis. (When you enter a smoky room does it usually induce sneezes or a runny nose?)	4.6	4.9 (1.6–15.1)*	2.2 (0.7–7.0)
Cold-induced rhinitis. (When you are in contact with cold air, does it usually induce sneezes or a runny nose?)	16.7	1.6 (0.6–4.3)	0.7 (0.3–1.7)
Exercise-induced rhinitis. (Does exertion usually induce sneezes or a runny nose?)	2.8	3.6 (0.8–16.5)	1.7 (0.3–8.1)
Allergic			
Hay-induced rhinitis. (When you are in contact with hay or flowers, does it usually induce sneezes or a runny nose?)	13.9	2.7 (1.1–6.7)*	1.8 (0.8–4.0)
Hay fever	24.7	6.2 (2.9–13.4)†	2.7 (1.4–5.0)†
Other disorders			
Usual rhinitis. (Do you usually have stuffy or runny nose?)	26.2	1.0 (0.4–2.7)	1.1 (0.5–2.1)
Chronic rhinitis. (Do you have stuffy or runny nose on most days for as much as 3 months of the year?)	14.2	1.6 (0.6–4.5)	2.1 (1.0–4.3)**
Watery rhinorrhea. (Do you usually have watery secretion?)	4.6	0.9 (0.1–7.2)	2.2 (0.7–7.0)
Common cold on the day of examination	22.7	1.8 (0.7–4.2)	1.2 (0.6–2.4)
Sinusitis	23.1	1.4 (0.5–3.4)	1.1 (0.6–2.3)
Adenoidectomy	33.3	2.6 (1.2–6.0)*	1.4 (0.7–2.6)

*: $p \leq 0.05$; †: $p \leq 0.001$; **: $p=0.06$; OR: odds-ratio; CI: confidence interval; Reactor status : percentage fall in FEV_1 0f ≥20%.

Drugs taken on the day of examination were also taken into account. Only three men took antihistamines.

Lung function, bronchial challenge and skin prick testing

FEV_1 measurements were performed in a sitting position, with a nose-clip, using a dry spirometer (TLC Test Morgan®), and values were expressed to ambient temperature and pressure saturated with water. Three FEV_1 manoeuvres were performed. In our sample, all tracings satisfied ECSC criteria [21].

The reservoir method was applied for methacholine inhalation challenge [10]. Methacholine aerosol was generated from a 0.02 $mg \cdot ml^{-1}$ solution of methacholine dissolved in saline using an Aerosolan Gauthier device delivering 300μg of methacholine per litre of aerosol, and stored in a bell. After the initial FEV_1 measurement, the seated subject was instructed to inspire the methacholine aerosol slowly, from functional residual capacity (without breath holding). One minute later the FEV_1 was again measured. Four volumes ranging from 1–10 *l* of aerosol were thus administered to the subjects until a 20% decrease from initial FEV_1 was achieved or the maximum dose of 6 mg was given [8]. All subjects who had a 20% fall in FEV_1 were administered salbutamol, and a return to baseline lung function was ensured. Reactor status was defined as a percentage fall in FEV_1 of ≥20% from the highest value of all measures performed. Seven men were unable to perform methacholine challenge because of technical problems.

The highest FEV_1 value was used in the analysis and normalized (FEV_1 score) for age and height as follows:

$$\text{observed } FEV_1 - [a \cdot (\text{age}) + b \cdot (\text{height}) + c] / \sqrt{s^2}$$

where a and b are the age and height regression coefficients respectively, (in the regression of FEV_1 on age and height), c the intercept, and s^2 the residual variance.

Skin prick tests to 2 mixtures of extracts (1/10) of common allergens, a mixture of five grass pollens (Dome Hollister) and a mixture of house dust (95%) and *Dermatophagoides pteronyssinus* (5%) (Stallergens) were performed. The method used consisted of applying drops of allergen solution to the forearm and then pricking through the drops with a lancet (Dome Hollister). A third test was performed with control saline solution. Responses were read 20 min later. Positivity to skin prick tests was defined as the presence of a 5 mm diameter weal, with 3 mm difference between the saline control weal and at least one allergen.

Statistical analysis

Statistical analyses included Chi-squared test in the case of qualitative variables, and paired t-test and the analysis of variance in the case of quantitative variables. The summary Chi-squared test, developed by Mantel-Haenszel for stratified data, was applied to allow for smoking habits. In the case of small numbers, the Fischer's exact test and the adjusted exact test were used [22]. The latter was performed with exact nonparametric statistics using the statistical package StatXact ™. Associations between qualitative characteristics were expressed as odds-ratios (ORs). In the case of the Mantel-Haenszel test, the OR may be regarded as a type of weighted average of the individual odds-ratios, derived from separating the sample into strata according to smoking habits. Finally, a logistic regression model [23] was used to determine the independent (after adjustment for the other factors) effects of various risk factors on the probability of reporting a given symptom.

Results

The prevalences of UAD ranged between 2.8% for exercise-induced rhinitis and 26.2% for usual rhinitis (table 1). Adenoidectomy was a very common operation in this sample, reported by 33% of men. Almost 8% of subjects reported asthma, 15% were reactive to methacholine and 14% were skin prick tests positive. There were more current smokers (40%) than nonsmokers (35%) or ex-smokers (25%). Current smoking was positively related to chronic rhinitis (OR=4.5; p=0.003) and common cold (OR=2.2; p=0.01) but inversely related to hay fever (OR=0.7; p=0.05).

Asthma was related to both a reported diagnosis of hay fever and symptoms of hay-induced rhinitis but also to smoke-induced rhinitis, and adenoidectomy (table 1). As expected, methacholine response was significantly heightened in men reporting hay fever compared to those without (OR=2.7) (table 1). A relationship of borderline statistical significance was also observed between bronchial hyperresponsiveness and chronic rhinitis (OR=2.1; p=0.06).

As expected, the disorders significantly interrelated with each other. The Venn diagram showing the distribution of men according to asthma, bronchial hyperresponsiveness and hay fever and chronic rhinitis, respectively, is given in figure 1. Hay fever and chronic rhinitis were related to each other (OR=2.3). Other disorders associated with increased risk of bronchial hyperresponsiveness without reaching statistical significance were exercise-induced rhinitis (OR=1.7), hay-induced rhinitis (OR=1.8) and watery rhinorrhea (OR=2.2). The association of asthma or bronchial hyperresponsiveness was stronger with the diagnosis of hay fever than with the symptoms of hay-induced rhinitis. Common cold was unrelated to bronchial response to methacholine.

According to analysis of variance, a lower FEV_1 level was associated with hay fever (p<0.01), usual (p<0.01) and chronic (p<0.02) rhinitis, common cold on the day of examination (p<0.04) and hay-induced rhinitis (p=0.09) (table 2). After exclusion of

asthmatic subjects, relationships persisted significantly for usual and chronic rhinitis and common cold. Independent of smoking habits, FEV_1 level was significantly lower in men reporting hay fever ($p<0.01$), usual ($p=0.02$) and chronic ($p=0.02$) rhinitis and common cold ($p=0.06$) compared to those without. As there were several subjects who simultaneously reported chronic rhinitis and hay fever, we included in the previous models the interaction between the two diseases. Similar results were then observed with a lessened statistical significance.

After adjustment for smoking, the association of bronchial hyperresponsiveness persisted with hay fever ($p<0.01$) but not significantly with chronic rhinitis ($p=0.10$) (table 3). Stratification by smoking habits showed that nonsmokers with hay fever displayed significantly greater methacholine responsiveness than nonsmokers without hay fever (table 3). Results changed slightly after exclusion of men reporting chronic rhinitis. Among current smokers, men with chronic rhinitis were slightly more hyperresponsive than those without, but not significantly (OR=2.1) (table 3). This also remained after having excluded the men who reported hay fever. Exclusion of asthmatics did not change previous findings.

Since positive skin prick test was highly associated with bronchial hyperresponsiveness (OR=3.7; $p<0.001$) and asthma (OR=9.0; $p<0.001$) but also with reported diagnosis of hay fever (OR=3.9; $p<0.001$), allowance for skin prick test response was made in studying the relationship between hay fever and bronchial hyperresponsiveness with the logistic regression analysis. The significant predictors of hay fever were then reactor status (OR=2.2; $p=0.02$) and positivity to skin prick test response (OR=3.3; $p<0.001$) (table 4).

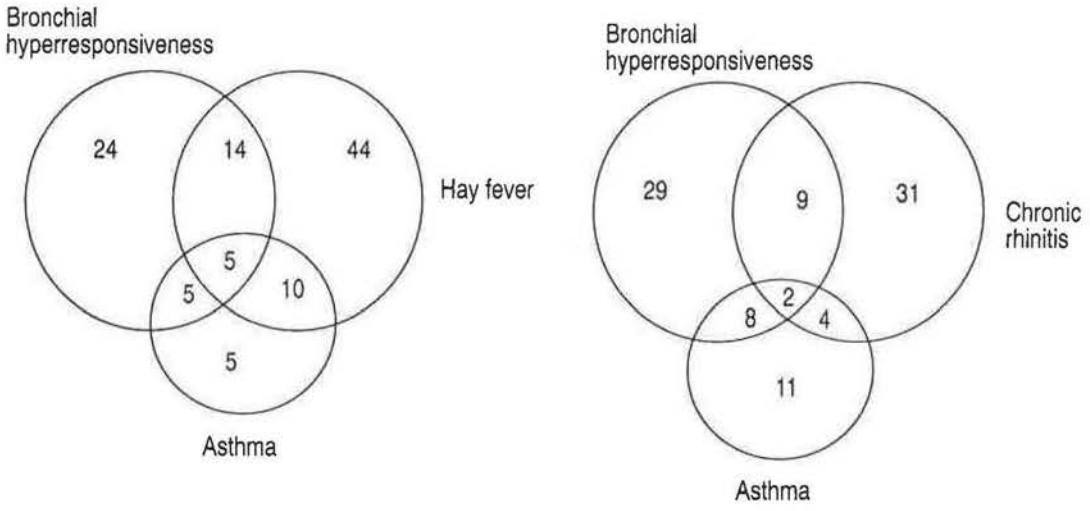

Fig. 1. – Distribution of men according to asthma, bronchial hyperresponsiveness and hay fever or chronic rhinitis. The figures indicate numbers of subjects in each group.

Table 2. – Level of age and height-adjusted FEV_1 score in relation to upper airways disorders

	All men (n=324)			Nonasthmatics (n=299)		
	No	Yes	p	No	Yes	p
Nonspecific perceived hyperresponsiveness						
Smoke-induced rhinitis	0.01±0.98	-0.05±1.24	NS	0.05±0.88	0.35±1.24	NS
Cold-induced rhinitis	0.02±0.99	-0.15±0.91	NS	0.08±0.90	-0.02±0.81	NS
Exercise-induced rhinitis	0.01±0.99	-0.51±0.45	NS	0.08±0.89	-0.52±0.49	0.08
Allergic						
Hay-induced rhinitis	0.03±0.98	-0.24±0.94	0.09	0.09±0.90	-0.09±0.78	NS
Hay fever	0.07±0.93	-0.26±1.09	0.01	0.10±0.89	-0.11±0.89	0.10
Other disorders						
Usual rhinitis	0.08±0.98	-0.24±0.94	0.01	0.14±0.88	-0.15±0.88	0.01
Chronic rhinitis	0.05±0.97	-0.33±1.01	0.02	0.10±0.88	-0.20±0.94	0.04
Watery rhinorrhea	-0.01±0.97	0.02±1.56	NS	0.05±0.89	0.31±0.92	NS
Common cold	0.05±0.98	-0.21±0.94	0.04	0.12±0.90	-0.16±0.82	0.03
Sinusitis	-0.01±0.97	-0.01±1.03	NS	0.06±0.86	0.06±0.98	NS
Adenoidectomy	0.04±0.94	-0.10±1.05	NS	0.06±0.93	0.06±0.78	NS

Mean±SD. FEV_1: forced expiratory volume in one second; NS: nonsignificant. Analysis of variance was used.

Table 3. – Bronchial reactor status in hay fever and chronic rhinitis according to smoking habits (n=320 having reported smoking)

	PD_{20} ≤6 mg %			
	Nonsmokers (n=111)	Ex-smokers (n=82)	Current smokers (n=127)	
Hay fever				
No (n=245)	8.1	10.9	15.4	
Yes (n=73)	28.0	23.1	27.3	
OR	4.4	2.5	2.1	
	p=0.01	NS	NS	
				OR(adj)=2.8 p (adj)=0.01
Chronic rhinitis				
No (n=274)	12.4	13.2	14.9	
Yes (n=46)	16.7	21.4	27.9	
OR	1.4	1.8	2.1	
	NS	NS	NS	
				OR(adj)=1.9 p(adj)=0.10

PD_{20}: provocative dose of methacholine causing a fall in FEV_1 of 20% or more; OR: odds-ratio; (adj): after adjustment for smoking habits (Mantel-Haenszel statistics). Results did not change after exact statistics (StatXact™ application).

Table 4. – Factors associated with hay fever and chronic rhinitis (n=320)

		All		Nonasthmatics	
		OR	95% CI	OR	95% CI
Factors of hay fever					
Reactor status:	Yes *vs* No	2.2	1.10–4.51	3.2**	1.49–6.85
Smoking habits:	Ex *vs* Nonsmokers	1.6	0.84–3.18	1.8	0.59–5.30
	Current *vs* Nonsmokers	0.8	0.38–1.45	0.7	0.32–1.36
Skin prick test positivity:	Yes *vs* No	3.3***	1.66–6.53	2.1	0.89–4.82
Factors of chronic rhinitis					
Reactor status:	Yes *vs* No	1.9	0.84–4.24	2.3*	1.01–5.44
Smoking habits:	Ex *vs* Nonsmokers	3.7*	1.36–10.07	4.4**	1.51–13.04
	Current *vs* Nonsmokers	4.6**	1.80–11.83	4.7**	1.70–13.06
Skin prick test positivity:	Yes *vs* No	1.7	0.66–4.14	1.1	0.38–3.12

*: p≤0.05; **: p≤0.01; ***: p≤0.001; OR: odds-ratio according to the logistic model; 95% CI: 95% odds-ratio confidence interval.

A logistic model with the same potential predictors to determine factors related to chronic rhinitis, indicated that only smoking (OR=3.7; p≤0.05 for ex-smokers and OR=4.6; p≤0.01 for smokers), was significantly associated to chronic rhinitis (table 4). Results did not change for both hay fever and chronic rhinitis after excluding men with a history of asthma, but the odds-ratios observed for reactor status became higher and significant (OR=3.2; p≤0.01 and OR= 2.3; p≤0.05 for hay fever and chronic rhinitis, respectively).

Discussion

In the working population studied, a reduction in FEV_1 was found in men reporting hay fever, common cold on the day of examination, and usual or chronic rhinitis. Furthermore, bronchial methacholine response was heightened, not only in men with hay fever but also in those reporting chronic rhinitis. Findings persisted after exclusion of asthmatics and adjustment for smoking.

The reduction of lung function in patients with allergic rhinitis has been documented previously [24, 25]. The fact that common cold and lowered FEV_1 were highly related, independent of smoking habits, is consistent with our findings in the same population in 1980 [20]. The association between FEV_1 and usual and chronic rhinitis supports the interplay between lung impairment and non-allergic upper airways disorders, since men reporting usual or chronic rhinitis in our sample were not atopic according to skin prick tests to house dust, mite and grass pollens. Whether severe nasal obstruction precedes pulmonary obstructive disease or whether subjects with usual or chronic rhinitis remain a separate, distinct group in these

respects is a subject for longitudinal study. Preliminary results in this same population have shown that cold-induced rhinitis was related to a 5 yr FEV_1 decline [9].

Bronchial hyperresponsiveness is a feature encountered in allergic rhinitis not only among asthmatics [4, 26, 27] but also among non-asthmatics [6, 7, 27]. STEVENS *et al.* [5] observed higher bronchial hyperresponsiveness to methacholine in 567 patients, from their allergic clinic, with rhinitis but without asthma compared to controls. They suggested that allergic rhinitis patients who have bronchial hyperresponsiveness are those who are more likely to develop asthma later. This was prospectively studied by BRAMAN *et al.* [28] in a 4–5 yr follow-up of 40 ragweed-sensitive patients without symptoms of asthma. Allergic rhinitis patients who were hyperresponsive to methacholine were at significantly greater risk of developing asthma than those with normal bronchial challenge. Most studies on the association between allergic rhinitis and bronchial hyperresponsiveness were conducted among nonsmokers in order to consider individuals who are not already exposed to a potential risk factor of bronchial responsiveness [29]. Among the few authors who took into account smoking habits, BUCZO and ZAMEL [30] found, in a sample of 26 selected volunteers without symptoms of asthma and chronic bronchitis, that bronchial hyperresponsiveness was related to nasal allergic symptoms to common environmental allergens in smokers only. They hypothesized that smoking and allergic rhinitis may act synergistically to influence the degree of nonspecific airways responsiveness displayed by individuals. Our population-based data showed a higher than expected percentage of hyperresponsiveness in men reporting hay fever independently of smoking. The relationship of hay fever to hyperresponsiveness was particularly evident among nonsmokers. On the contrary, it is in the group of current smokers that men with chronic rhinitis displayed greater methacholine responsiveness than those without. Hence, bronchial hyperresponsiveness might also be a feature common to non-allergic rhinitis. Discrepancies from the results of BUCZO and ZAMEL [30] might be due to the differences in populations studied and to definitions of nasal symptoms. Contrary to clinical findings [31], but in agreement with population studies [32], no effect of common cold on airway responsiveness was observed in our population. Unexpectedly, we found a strong link between reported asthma and adenoidectomy.

Two patterns can be proposed to explain the association found between upper and lower airways diseases. UAD may be regarded: i) as a stage of lung impairment since upper airways abnormalities might be the first manifestation of a pathological status, which becomes prominent in larger airways over the years); or ii) as another disease, completely separate, also caused by the same risk factors. Factors which are responsible for both upper and lower airways diseases are individual susceptibility, infections, environmental exposure, such as active and passive smoking, allergens, or pollution, and some occupational factors. In two clinical studies, where significantly lower values of maximum mid-expiratory flow rate and maximum terminal flow (potential indicators of obstruction in peripheral lower airways) were found in patients with allergic rhinitis compared to controls [24, 25], the authors hypothesized that lower airways obstruction can be limited primarily to the small airways in such patients. No epidemiological studies have reported on this association. Further investigations are needed to better understand the relationships between upper and lower airways diseases and the underlying mechanisms. They should include nasal functional testing, such as nasal resistance or peak nasal inspiratory flow (PNIF), and should take into account allergic parameters.

Pathological changes in both upper and lower airways might be due to airways inflammation as well as to varying sensitivity of airways to bronchoconstrictive signals, responsible for increased mucosal permeability in airways and enhancement of bronchial hyperresponsiveness [27, 33, 34]. Smoking may play a primary role in such a pathogenic phenomenon.

In conclusion, our findings suggest heterogeneity of upper airways disorders with regard to bronchial hyperresponsivenes and FEV_1.

Acknowledgements: The authors are indebted to the men who participated in the study and wish to thank J. Maccario for help in applying StatXact© statistic.

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