

Sensitization to *Aspergillus fumigatus* and functional outcome of asthma

R. Benghida¹, H. Ghezzi¹, J.-L. Malo¹

Summary

Introduction Despite its high prevalence in the asthmatic population, sensitization to *Aspergillus* has not benefited from as much research interest as other mould species. This study aims at investigating the role of the presence or the absence of *Aspergillus* sensitization in the deterioration of airway calibre in asthmatics over a five-year follow-up period.

Material and methods One hundred and thirty-three asthmatic subjects aged 18 to 40 years were separated into two groups: those sensitized (cases) and those not sensitized (controls) to *Aspergillus* were matched according to the following criteria: age, gender and FEV₁ (% pred). Clinical, functional, allergic and therapeutic parameters were studied.

Results The FEV₁ slope was less pronounced in the group sensitized to *Aspergillus* (-17 ml/year) in comparison to the controls (-27 ml/year). There was also a less noticeable slope of forced vital capacity in the sensitized subjects (-25 ml/year) as compared to the controls (-28 ml/year). None of these differences were statistically significant.

Conclusion We did not find any increase in the decline in FEV₁ or FVC associated with sensitization to *Aspergillus*.

Key-words: Asthma • *Aspergillus* • Forced expiratory volume • Hypersensitivity • Fungi.

Corresponding author: J.-L. Malo
Service de pneumologie (Chest Clinic), Hôpital du Sacré-Coeur de Montréal, 5400 Ouest, boul. Gouin, Montréal, Canada H4J 1C5
malojl@meddir.umontreal.ca

To cite the present paper, use exclusively the following reference:
Benghida R, Ghezzi H, Malo JL. Sensibilisation à *Aspergillus fumigatus* et devenir fonctionnel de l'asthme (full text in english on www.em-consulte.com/revue/rmr). *Rev Mal Respir* 2007;24:23-31.

Rev Mal Respir 2007 ; 24 : e126-33

Introduction

Asthma is a multifactorial disease influenced by many environmental factors that modulate its clinical expression and course: moulds are one of the agents that play an important role. As early as 1698 [1] John Floyer reported the case of an individual who had an attack of asthma in a wine cellar, an environment in which moulds abound. In 1873, Charles Blackley [2] emphasized the role played by two species of moulds (*Penicillium* and *Chaetomium*) in triggering asthma attacks.

More recently *Alternaria alternata*, a common mould that is specific to temperate climates has elicited a certain interest. Harris [3] emphasized the role played by *Alternaria alternata* in triggering allergies in mould-sensitized subjects. O'Hollaren et al [4] showed that 10 out of 11 children and young adults (91%) with respiratory arrest due to asthma had a positive skin-prick test to *Alternaria alternata*, whereas in a control group made up of 99 asthmatics with no case history of respiratory arrest, only 31% were sensitized. The authors also found that these episodes of respiratory arrest coincided with the presence of *Alternaria alternata* in the air. Targonski et al [5] found a 2.16 fold higher risk of death (IC95% =1.31-3.56) in the asthmatic population on the days when the spore counts for moulds exceeded a threshold of 1000 spores per cubic metre.

More recently in the *European Community Respiratory Health Survey*, Zureik et al [6], reported a prevalence of immediate skin-prick sensitization to *Alternaria alternata* and *Cladosporium herbarum* of 17.7% in 1132 asthmatic subjects aged 20 to 44 years. The authors showed an increase in the frequency of sensitization to each of these moulds or to both as the asthma severity score increased, with a score ratio of 2.34 (IC95%=1.56-3.52) between slight and severe asthma.

Aspergillus fumigatus is a ubiquitous microscopic fungus that can colonize the airways and cause several diseases: aspergillus asthma, allergic bronchopulmonary aspergillosis, hypersensitive pneumonia, pulmonary aspergilloma, chronic necrotizing pulmonary aspergillosis and invasive aspergillosis [7]. The prevalence of IgE type sensitization in asthmatic subjects is 20 to 30% according to the studies [8, 9]. The studies show in general that asthmatics have a faster decline in their respiratory function than normal subjects (40 to 50 ml/year) [10-13]. This suggests that *Aspergillus* sensitization causes airway impairment that in turn accelerates the subject's age-related functional deterioration. Although *Aspergillus* sensitization does not directly cause the onset of allergic pulmonary aspergillosis and ultimately bronchiectasis, a condition that can be clinically identified by episodes of poor health with fever and expectoration of plugs of thick, rubbery mucous, one can assume that there is a latent stage during which the airway walls are colonized by *Aspergillus*, even though the subject does not develop bronchiectasis.

Subjects and methodology

Subjects

All the records of asthmatic patients treated by three physicians in the chest clinic were examined (n = 2661); 149 satisfied the selection criteria listed below and were therefore included.

The inclusion and exclusion criteria were as follows:

- At least five years of follow-up with five evaluations at regular intervals during this period.
- Non-smoking subjects or individuals who had smoked less than 10 packet-years.
- Age between 18 and 40 years.
- Skin-prick tests were performed when the subjects were seen for the initial assessment: the *Aspergillus* test had to be positive for the cases (three mm or more with no significant urticaria and a response of 3 mm or more to the histamine phosphate test, 1 mg/ml). The *Aspergillus* test had to be negative for the controls.

The exclusion criteria were:

- Any other chronic pulmonary disorder.
- Urticaria greater than 3 mm in diameter for the allergy tests.

Matching method

The subjects with *Aspergillus fumigatus* sensitization were matched with one or two control subjects according to availability, two in most cases (n = 29) and one in 23 cases. Subjects below the age of 25 were matched for gender, age range (plus or minus two years), percentage of predicted FEV₁ at the initial assessment (maximum discrepancy 10% discrepancy, except for normal values for which a greater freedom was tolerated). Beyond the age of 25, the age criterion was more flexible and the subjects were matched in five-year age ranges. This decreased the total cohort to 133 subjects.

Parameters examined

Clinical data

The subject's clinical and respiratory functional status was recorded in the file at each evaluation.

An "exacerbation" is an asthma attack reported either by the patient or by the clinical practitioner during the course of an assessment, entailing a change in treatment in both cases (initiation or increase in anti-inflammatory drugs).

Functional data

The functional values were based on FEV1 and forced vital capacity (FVC) readings before and after administration of a short acting beta-2 adrenergic agent.

Allergological data

Skin prick tests were performed during the initial assessment. The products and allergens tested were the following: saline, histamine phosphate (1mg/ml), tree pollens, ragweed pollen, a blend of dusts, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, feathers, *Dermatophagoides* (D.) *Pteronyssinus*, *D. Farinae*, cat dander, dog dander, poaceae pollen, various artemesia pollens, various shrub pollens, cockroach calyx, horse dander.

Details of treatments

Anti-asthmatic treatments (bronchodilators, inhaled corticosteroids, oral corticosteroids) were recorded at each check-up. All the subjects included in this study used inhaled corticosteroids, in some cases associated with short or long-term courses of oral corticosteroids.

Statistical tests

Spirometry: the changes in slope were calculated by linear regression for each parameter using R 2.0.1; the software is available free of charge on the CRAN (*Comprehensive R Archive Network*) website. We used a T test for matched values. The decline slopes for the matched controls were estimated using the mean value of both matched controls for the T test on FEV₁ decline, forced vital capacity and the FEV₁ over forced vital capacity ratio. The results for the other allergens were analysed with SPSS version 12, using a T test for independent values (fig. 1).

Results

For a comparable age of about 28 years in both groups, there was no noticeable difference between the *Aspergillus*

sensitized subjects and the controls in terms of gender distribution and tobacco use (table I). In this study the follow-up period was slightly longer for the controls than for the *Aspergillus* sensitized group. The spirometry values were similar in both groups.

Table I.

Basic anthropomorphic, clinical, functional and allergological data.

	Case sensitized to <i>Aspergillus</i> <i>fumigatus</i> (n = 52)	Non -sensitized controls (n = 81)
Sex (M/F)	29(55,8%) /23(44,2%)	52(64,2%) /29(35,8%)
Age (years)	28.7 ± 6.6 (18.2-40.3)	28.2 ± 6.2 (18.0-38.5)
Atopy*	52 (100%)	76 (93.8 %)
Tobacco use (S/ES/NS)****	2(3.8%)/4(7.7%) /46(88.5%)	9(11.1%)/1(1.2%) /71(87.7%)
Dose of inhaled corticosteroids (microgr/ day) at the first check-up**	838.3 ± 621	803.8 ± 609
Follow-up period (months)	118.6 ± 57.1	148.9 ± 57.6
FEV₁ (% predicted)	81.2 ± 20.9	84.5 ± 18.2
FEV₁ /FVC (%)	85.3 ± 6.6	85.6 ± 2.5
Results of the skin-prick tests		
Dust mites	44 (84.6 %)	43 (53.1 %)
Pollens	47 (90.4 %)	64 (79.0)
Moulds	52 (100 %)	19 (23.5 %)
Household pets	46 (88.5 %)	66 (81.5 %)
Exacerbations (/year)	(0.35 ± 0.44)	(0.33 ± 0.32)
Reversibility of FEV₁ (%)***	12.3 ± 15.0 (n=31)	14.8 ± 14.4 (n=52)

*Defined as the presence of a weal = 3 mm in response to at least one of the airborne allergens tested; **in beclomethasone equivalent; ***Defined as post-bronchodilator FEV₁ less pre-bronchodilator FEV₁ divided by pre-bronchodilator FEV₁ x 100; ****Smokers, Ex-smokers, Non-smokers

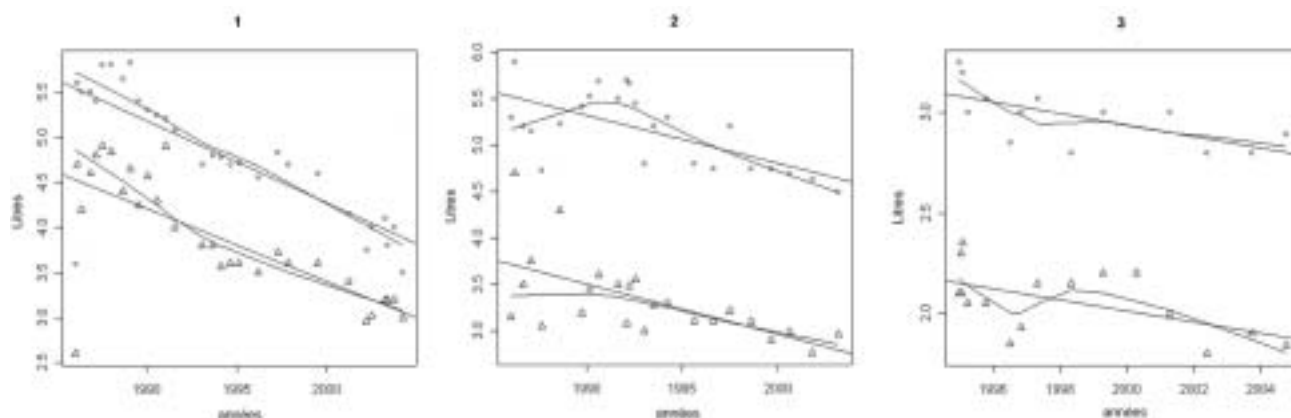


Fig. 1.
Examples of data curves for some patients obtained using R software.

The *Aspergillus* sensitized group tended to be polysensitized to ubiquitous allergens with a higher prevalence of sensitization to dust mites and pollens.

The frequency of exacerbated asthma attacks was identical in both categories of subjects at around 0.3 exacerbations per year. The improvement in spirometry values after administration of a bronchodilator during the initial assessment was more or less identical in both cases, when this reading was available. The *Aspergillus* sensitized subjects did not show any signs of allergic broncho-pulmonary aspergillosis during the follow-up; none reported plugs of thick, rubbery mucous in their expectorations nor had recurrent pneumonia.

We recorded a decline in spirometry values in both groups of subjects (table II). The decline was less accentuated in the *Aspergillus* sensitized group, although with a mean decline of -17 ml/year against -27 ml/year for the control group, this effect was not significant. There was also a non-significant difference between the decrease in FVC in the sensitized subjects and the controls; however this decrease was less noticeable in the sensitized cases, their mean value being -25 ml/year, against -28 ml/year for the controls. We also examined the threshold of positivity to see whether it had any impact on this trend; only the subjects whose skin-prick tests for *Aspergillus fumigatus* were over 6 mm and their matched controls were assessed, using the same method. 17 of the sensitized subjects fulfilled these criteria. The mean decline in FEV₁ was -11 ml/year for this group, whereas for the control population it was -26 ml/year. The annual decline in FVC in this sub-group was -14 ml/year for the sensitized subjects and -24 ml/year for the controls (delta value statistically non-significant).

Although our study was designed as a comparative, matched study we also analysed the relationship between the spirometry decline slopes and sensitization or non-sensitization to ubiquitous allergens, including other moulds. The subjects were not matched for this analysis. table III and table IV show that when the subjects were positive for other moulds and common allergens in the skin-prick tests, the decline in their spirometry slope was less noticeable, although this effect was not significant.

We did not find any statistically significant association between the predicted FEV₁ values at the initial assessment and the FEV₁ decline curve ($r^2=0.02$) (fig. 2). Similarly, there was

no statistically significant association between the number of monthly exacerbations and the FEV₁ slope ($r^2=0.03$) (fig. 3), nor between the number of exacerbations and the forced vital capacity slope ($r^2=0.05$) (fig. 4). We also sought to determine whether there was any statistically significant association between the reversibility of the FEV₁ values recorded during the initial assessment and the FEV₁ decline slope; the correlation coefficient was low and judged non-significant ($r^2=0.04$) (fig. 5).

The FEV₁ curve was smoothed (14) to give a FEV₁ slope for mean age, defined as age at the initial assessment plus half of the follow-up period (fig. 6). This enabled us to identify the mean age below which the slopes seem to show a noticeable difference. We then analysed this sub-group, made up of sixty subjects (mean age below 34 years) twelve of whom were *Aspergillus* sensitized asthmatics, each matched with two controls and twelve others each matched with one control; we found a difference, although the delta value did not reach the normal threshold of statistical signif-

Table III.

Results of the decline slopes for the three spirometric values according to non-sensitization (no) or sensitization (yes) to the other moulds assessed.

		FEV ₁	FVC	FEV ₁ /FVC (%)
Cladosporium				
No	N	94	94	93
	Mean	$-2.56.10^{-2}$	$-2.92.10^{-2}$	$-1.68.10^{-3}$
	SD	$4.56.10^{-2}$	$5.34.10^{-2}$	$6.04.10^{-3}$
	Minimum	-0.1998	-0.2714	-0.0168
	Maximum	0.0869	0.0771	-0.0219
Yes	N	39	39	39
	Mean	$-1.36.10^{-2}$	$-1.65.10^{-2}$	$-6.28.10^{-5}$
	SD	$5.06.10^{-2}$	$5.41.10^{-2}$	$9.10.10^{-3}$
	Minimum	-0.1285	-0.0899	-0.0340
Alternaria				
No	N	80	80	79
	Mean	$-2.39.10^{-2}$	$-2.67.10^{-2}$	$-2.17.10^{-3}$
	SD	$5.09.10^{-2}$	$6.06.10^{-2}$	$6.07.10^{-3}$
	Minimum	-0.1998	-0.2714	-0.0225
	Maximum	0.1477	0.1973	-0.1535
Yes	N	53	53	53
	Mean	$-1.94.10^{-2}$	$-2.36.10^{-2}$	$2.41.10^{-4}$
	SD	$4.15.10^{-2}$	$4.18.10^{-2}$	$8.23.10^{-3}$
	Minimum	-0.1285	-0.1076	-0.0340
	Maximum	0.0871	0.0831	0.0223

FVC: forced vital capacity; N: number of subjects; SD: standard deviation.

Table II.

Mean slopes (l/yr) of spirometric values for *Aspergillus fumigatus* sensitized subjects and matched controls.

	Cases (52)	Controls (81)
FEV ₁	-0.017 ± 0.05	-0.027 ± 0.04
FVC	-0.025 ± 0.06	-0.028 ± 0.05
FEV ₁ /FVC	0.10 ± 0.9	-0.26 ± 0.05

Table IV.
Results of the decline slope for the three spirometric values according to non-sensitization (no) or sensitization (yes) to ubiquitous airborne allergens.

Dust mites				
No	N	46	46	46
	Mean	$-2.14.10^{-2}$	$-2.34.10^{-2}$	$-2.04.10^{-3}$
	SD	$4.46.10^{-2}$	$5.01.10^{-2}$	$6.06.10^{-3}$
	Minimum	-0.1998	-0.2714	-0.01681
	Maximum	0.0871	0.0805	0.0219
Yes	N	87	87	86
	Mean	$-2.24.10^{-2}$	$-2.66.10^{-2}$	$-7.60.10^{-4}$
	SD	$4.89.10^{-2}$	$5.58.10^{-2}$	$7.58.10^{-3}$
	Minimum	-0.1765	-0.2334	-0.0340
	Maximum	0.1477	0.1973	0.0223
Household pets				
No	N	21	21	21
	Mean	$-4.04.10^{-2}$	$-5.36.10^{-2}$	$-2.53.10^{-3}$
	SD	$5.45.10^{-2}$	$5.96.10^{-2}$	$4.66.10^{-3}$
	Minimum	-0.1998	-0.2714	-0.01681
	Maximum	0.0647	0.0125	0.0074
Yes	N	112	112	111
	Mean	$-1.86.10^{-2}$	$-2.02.10^{-2}$	$-9.54.10^{-4}$
	SD	$4.53.10^{-2}$	$5.12.10^{-2}$	$7.45.10^{-3}$
	Minimum	-0.1765	-0.2034	-0.0340
	Maximum	0.1477	0.1973	0.0223
Pollens				
No	N	22	22	22
	Mean	$-2.42.10^{-2}$	$-3.89.10^{-2}$	$-7.76.10^{-4}$
	SD	$5.29.10^{-2}$	$6.13.10^{-2}$	$6.98.10^{-3}$
	Minimum	-0.1998	-0.2714	-0.01681
	Maximum	0.0647	0.0332	0.0223
Yes	N	111	111	110
	Mean ²	$-1.86.10^{-2}$	$-2.28.10^{-2}$	$-1.29.10^{-3}$
		$4.53.10^{-2}$	$5.20.10^{-2}$	$7.14.10^{-3}$
	Minimum	-0.1765	-0.2034	-0.0340
	Maximum	0.1477	0.1973	0.0219

FVC: forced vital capacity; N: number of subjects; SD: standard deviation.

icance ($p > 0.05$) for FEV₁ or for forced vital capacity before the use of bronchodilators.

Discussion

We found no acceleration in the decline of respiratory function related to sensitization to *Aspergillus fumigatus* or other common allergens.

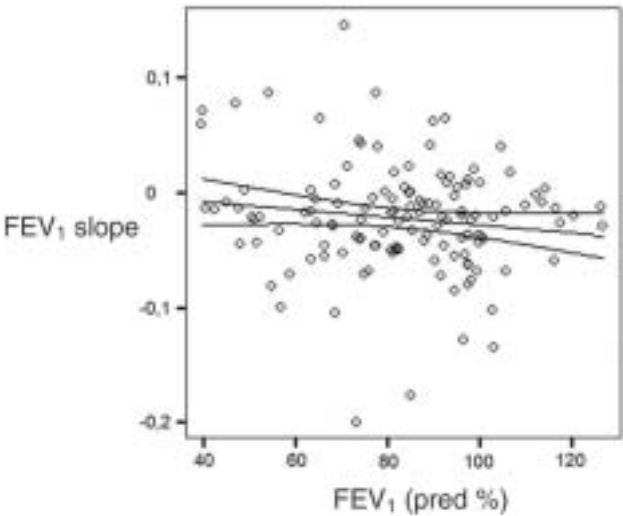


Fig. 2.
Predictive value of predicted FEV₁ percentage and FEV₁ decline slope

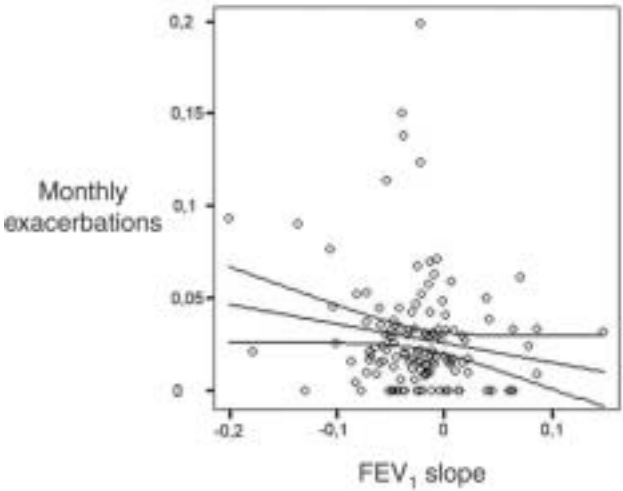


Fig. 3.
Relationship between the FEV₁ decline slope and onset of exacerbations.

Zureik et al's study [6] demonstrated an association (ratio = 2.34; IC95% = 1.56-3.52) between the increase in the degree of severity of asthma, based on a clinical and functional score and sensitization to two moulds: *Alternaria alternata* and *Cladosporium herbarum*. Zureik et al [6] used three indices to identify the degree of severity of asthma: the number of exacerbations during the year preceding the study, the dose of corticosteroids and the calibre of the airways. However, one of these indices, namely the number of exacerbations during the year preceding the study, is an indicator of the control rather than the severity of the disorder as discussed by Cockcroft and Swystun [15]; they drew a

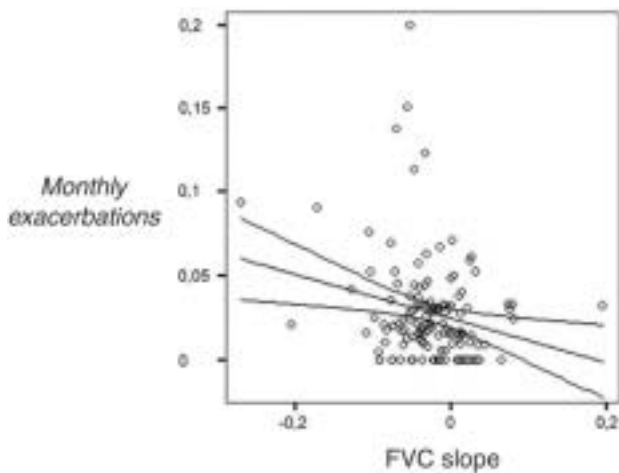


Fig. 4.
Relationship between FVC decline slope and onset of exacerbations.

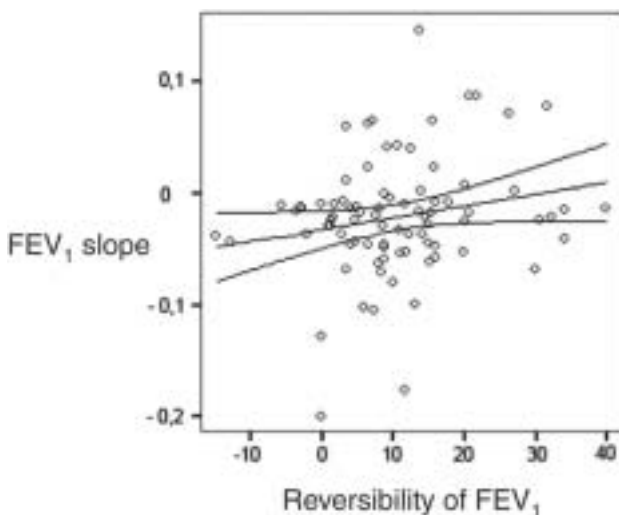


Fig. 5.
Predictive value of reversibility at first check-up on subsequent evolution of FEV_1 .

distinction between the concept of control and severity of asthma. Ross et al [16] based their severity index on the number of visits to the A and E department, and found a positive association in an asthmatic population with significant exposure to moulds, proven by taking samples from their domestic environment (score ratio = 2.8, although this value was not statistically significant). In our longitudinal retrospective study we examined functional decline according to the number of years, which is another relevant indicator for the assessment of asthma.

FEV_1 and FVC values decline from adult age onwards; this is a natural phenomenon, but the decline is more noti-

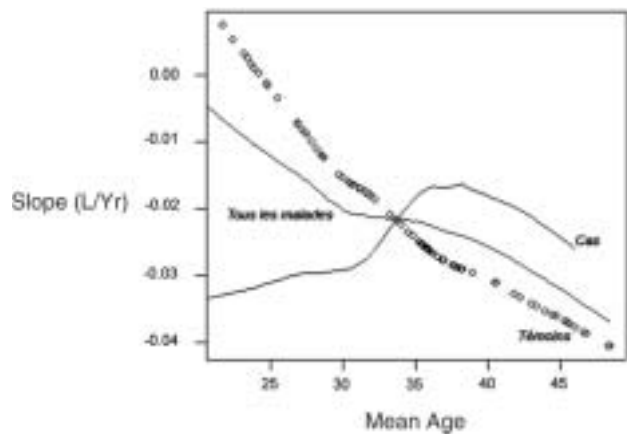


Fig. 6.
 FEV_1 decline slope smoothed out for mean age.

ceable in asthmatics whose basic respiratory function is below normal. In a 15 year longitudinal study Lange et al [17] established that in adult asthmatics (= 20ans) FEV_1 declined faster than in non-asthmatic subjects (38 ml/year versus 22ml/year; $p < 0.001$); these authors also show the role that smoking plays in accelerating the decline. However, we feel that it important to point out that in this study the diagnosis of asthma was based on a questionnaire; the authors assimilated former smokers and non-smokers and no details were reported on the cumulative doses of tobacco exposure. Lastly, it is also important to emphasize that these figures were based on only three spirometric assessments for fifteen years of follow-up. Peat et al [10] carried out an 18 year longitudinal study involving 92 asthmatic adults and 186 controls and found a more noticeable decline in the asthmatics than in the non-asthmatics (50 ml/year and 35 ml/year respectively). Schachter et al [18] studied the functional changes in spirometry in a rural population, assessing the decline at 24 ml/an versus 6 ml/year for a normal subject. In all the studies cited the apparently high degree of variability in the decline in FEV_1 with age can be explained by the different ways these asthmatic populations were recruited and the presence of compounding factors, even if they do all agree in revealing a faster decline in asthmatics. Our study concerned only asthmatics but the decline rates recorded (17 ml/yr for *Aspergillus* sensitized asthmatics and 27 ml/yr for the controls) remain close to the values described in the literature.

Ulrik [19] reviewed all the factors that could potentially contribute to explaining the acceleration in the decline of FEV_1 in asthmatics in detail. These include gender, tobacco use, severity of symptoms, atopy, baseline pulmonary function, the degree of hyper-responsiveness of the airways, response to bronchodilators and treatment. Our goal was to identify the role that *Aspergillus* sensitization alone plays in

the changes in spirometry; we therefore purposely excluded subjects with a history of tobacco use exceeding 10 packet-years in order to avoid the « healthy smoker » bias [20]. It is possible that smoking potentializes the effect of *Aspergillus fumigatus* sensitization. Seymour et al.'s study is interesting in this respect [21]. Using an *Aspergillus fumigatus* sensitized mouse model the authors establish that exposure to secondary tobacco smoke (passive smoking?)* eventually results in a larger accumulation of IgE expressing cells in sensitized mice exposed to the ambient air. They also establish that about 28 days later, in a secondary phase, the Th2 cell cytokines start to drop significantly whilst interferon gamma levels decrease. *Aspergillus fumigatus* sensitized mice exposed to tobacco smoke show a significant decrease in inflammatory cytokines, including interleukin-6, when compared with the sensitized mice that were not exposed to tobacco smoke. This shows that tobacco smoke alters the IgE response, increasing the production of NO and decreasing the production of inflammatory cytokines in *Aspergillus* sensitized mice.

Gender is a factor that remains controversial in terms of its influence on the prognosis for asthma, although most studies tend to demonstrate that the gender effect is not significant. Contradictory results have been reported in studies exploring the impact of age of onset of the disease; thus Ulrik [19] did not consider age of onset as a factor of prognosis in asthma, but emphasized the importance of the severity of the symptoms at onset. Severity has also been the subject of several studies demonstrating that it does have an impact on the decline of spirometric values. However we do not have enough evidence to prove that age of onset, atopy, airway hyper-responsiveness, reversibility in response to beta-mimetics or asthma-related hypersecretion of the mucous membranes have any effect. For example, atopy does not seem to be associated with a faster decline in FEV₁. Many studies, including the research carried out by Annesi et al [22], support this hypothesis. Nevertheless, the results are not always unanimous, since Villar et al [23] showed a faster decline in FEV₁ atopic subjects.

Ulrik [19] emphasized the positive effect that corticosteroids had on this parameter, especially when they were inhaled. In a recent study carried out by Dijkstra et al. [24], on a cohort of 122 asthmatics taken from a population of 281 asthmatic subjects with moderate to severe asthma monitored for a period of 23 years, the authors found that the subjects treated with corticosteroids had a less noticeable decline, especially the males with a decline of 20.6 ml/year less ($p = 0.011$) versus only 3.2 ml/year less for the females ($p = 0.73$). This effect still applies to subjects that smoke less than five packet-years with a decline of 36.8 ml/year for the males ($p=0.0097$) and 0.8 ml/year for the females ($p = 0.94$); the gender difference is statistically significant ($p = 0.045$). The protective effect of inhaled corticosteroids in males who have smoked less than five packet-years is dose dependent to

the extent that the higher the dose, the less noticeable the decline becomes ($p = 0.006$). An anti-inflammatory treatment therefore has a substantial impact. In our study, all the subjects took inhaled corticosteroids throughout the follow-up period.

Sensitization to some allergens also has a significant effect on accelerating the decline in FEV₁. Weiss et al. [25] reported a faster decline in an adult population sensitized to two cockroach calyx allergen extracts *Bla g1* et *Bla g2*, for which they found a decline of 79.8ml/an and 40.81 ml/an respectively.

We matched our subjects according to their spirometry baseline values, thus avoiding the bias known to our English-speaking colleagues as the *Horse-Racing Effect* [26, 27]; in our study the decline in FEV₁ depends on the initial spirometry readings recorded at the beginning of the follow-up. However, this initiative raised another issue, challenging the statistical power of the sample size. We therefore examined the power of our study. Our main spirometric indicator was FEV₁, for which the value to detect a difference of 10 ml/year between our two groups was around 50%. Although this is sufficiently powerful in our eyes, notwithstanding we cannot exclude a possible effect of *Aspergillus* sensitization on the decline in respiratory function. If we include a larger number of subjects we will probably be able to exclude the likelihood of *Aspergillus* sensitization having any effect on spirometric decline more clearly. However, this would be extremely surprising since our data tend, on the contrary, to show a non-significant protective effect.

In our study, the subjects' sensitization to different airborne allergens was documented on the basis of a single test performed at the beginning of the follow-up period. However, an allergy profile can change over a period of time [28] as can the subject's degree of exposure to *Aspergillus*, although this analysis is questionable because the size of the population may render the results non-significant. Lastly, recombinant *Aspergillus* allergens should be considered; they would be relevant to assess the subjects' sensitization initially and during the follow-up since they are easy to characterize and can be standardized.

If sensitization to some moulds seems to make asthma more severe [6, 29, 30], some authors suggest that a certain category of *Aspergillus fumigatus* sensitized asthmatics may develop bronchopulmonary allergic aspergillosis [29], although this has never been formally documented. In our study, the patients were regularly monitored and we did not pick up any clinical or radiological signs suggesting allergic bronchopulmonary aspergillosis during the follow-up period.

A recent study [31] on the decline of spirometry values in a population of asthmatics shows that the decline in FEV₁ and FVC varies in time. The authors demonstrated that the fluctuations they found in the decline of the respiratory function slope were age-related. This is not new because

Ulrik et al. [13] showed a faster decline in subjects with recently diagnosed asthma.

In conclusion, sensitization to *Aspergillus* does not seem to have a deleterious effect on the decline in respiratory function in asthmatics. On the contrary, it would seem to have a protective effect. The factors which do have an adverse effect on respiratory function should therefore be thoroughly explored, especially if they contribute the process of airway remodelling.

Acknowledgements:

The authors would like to thank Mrs. Jocelyne L'Archevêque for her technical assistance in this study.

References

- Floyer J. A Treatise of the Asthma. 1698
- Blackley CH. Experimental research on the cause and nature of *Catarhus Aestivus* (hay fever or hay asthma). 1873
- Harris LH. Experimental Reproducibility of Respiratory Mold Allergy. *The Journal of Allergy* 1941; 12: 279-289
- O'Hollaren M, Yunginger J, Offord K, Somers M, O'Connell E, Ballard D et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991; 324: 359-363
- Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. *J Allergy Clin Immunol* 1995; 95: 955-961
- Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002; 325: 411-418
- Al-Alawi A, Ryan CF, Flint JD, Müller NL. *Aspergillus*-related lung disease. *Can Respir J* 2005; 12(7): 377-387
- Schwartz HJ, Citron KM, Chester EH, Kaimal J, Barlow PB, Baum GL et al. A comparison of the prevalence of sensitization to *Aspergillus* antigens among asthmatics in Cleveland and London. *J Allergy Clin Immunol* 1978; 62(1): 9-14
- Malo J-L, Paquin R. Incidence of immediate sensitivity to *Aspergillus fumigatus* in a North American asthmatic population. *Clinical Allergy* 1979; 9: 377-384
- Peat J, Woolcock A, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987; 70: 171-9
- Ulrik C, Backer V, Dirksen A. A 10 year follow up of 180 adults with bronchial asthma: factors important for the decline in lung function. *Thorax* 1992; 47: 14-8
- Weiss ST. Atopy as a Risk Factor for Chronic Obstructive Pulmonary Disease. Epidemiological Evidence. *Am J Respir Crit Care Med* 2000; 162: S134-S136
- Ulrik CS, Lange P. Decline of Lung Function in Adults with Bronchial Asthma. *Am J Respir Crit Care Med* 1994; 150: 629-34
- Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Statist Assoc* 1979; 74: 829-36
- Cockcroft D, Swystun V. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996; 98:1016-8
- Ross M, Curtis L, Scheff P, Hryhorczuk D, Ramadrisnan V, Wadden R et al. Association of asthma symptoms and severity with indoor bio-aerosols. *Allergy* 2000; 55: 705-11
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339: 1194-1200
- Schachter E, Doyle C, Beck G. A prospective study of asthma in a rural community. *Chest* 1984; 85: 623-30
- Ulrik CS. Outcome of asthma: longitudinal changes in lung function. *Eur Respir J* 1999; 13: 904-918
- Becklake MR, Lalloo U. The 'Healthy Smoker': A Phenomenon of Health Selection? *Respiration* 1990; 57: 137-144
- Seymour BW, Peake JL, Pinkerton KE, Kurup VP, Gershwin LJ. Second-hand smoke increases nitric oxide and alters the IgE response in a murine model of allergic aspergillosis. *Clin Dev Immunol* 12(2), 113-124. 2005
- Annesi I, Neukirch F, Orvoen-Frija E, Oryszczyn MP, Korobaef M, Doré MF et al. The Relevance of Hyperresponsiveness but not of Atopy to FEV1 decline Preliminary Results in a Working Population. *Bull Eur Physiopathol Respir* 1987; 23: 397-400
- Villar MTA, Dow L, Coggon D, Lampe FC, Holgate ST. The Influence of Increased Bronchial Responsiveness, Atopy, and Serum IgE on Decline in FEV1. A Longitudinal Study in the Elderly. *Am J Respir Crit Care Med* 1995; 151: 656-62
- Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, ten Hacken NH, Timens W, Postma DS. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006; 61(2): 105-10.
- Weiss S, O'Connor G, DeMolles D, Platts-Mills T, Sparrow D. Indoor allergens and longitudinal FEV1 decline in older adults: the normative aging study. *J Allergy Clin Immunol* 1998; 101: 720-725
- Peto R. The horse-racing effect. Statistical peculiarities of rates of change of medical parameters observed in progressive studies, with special reference to lung disease. Statistical contributions to environmental problems (Proc IX Int Biometric Conf Vol II) Boston 1976
- Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977; 1: 1645-1648
- Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987; 79: 16-24
- Maurya V, Guignani HC, Sarma PU, Madan.Taruna, Shah A. Sensitization to *Aspergillus* Antigens and Occurrence of Allergic Bronchopulmonary Aspergillosis in Patients with Asthma. *Chest* 2005; 127: 1252-9
- Tunnincliffe WS, Fletcher TJ, Hammond K, Roberts K, Custovic A, Simpson A et al. Sensitivity and exposure to indoor allergens in adults with differing asthma severity. *Eur Respir J* 1999; 13: 654-9
- Connolly CK, Prescott RJ. The Darlington and Northallerton Long Term Asthma Study: pulmonary function. *BMC Pulm Med* 2005; 5: 2.