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Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with α_1-antitrypsin deficiency (PiZZ)

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Abstract

***Background* – Severe α_1-antitrypsin (AAT) deficiency (PiZZ) is associated with an increased risk of lung emphysema, especially in smokers. The aim of this study was to identify risk factors other than smoking for declining lung function.**

***Methods* – Lung function was studied in 225 self-reported never-smoking PiZZ individuals included in the Swedish AAT deficiency register.**

***Results* – Lung function was poorer in men than in women (mean (SD) forced expiratory volume in one second (FEV_1) 80 (30) versus 88 (17)% predicted) despite the fact that the men were younger (mean (SD) age 45 (18) versus 51 (17) years), and poorer in those aged 50 or older than in those aged under 50 (mean (SD) FEV_1 70 (30) versus 98 (16)% predicted). Self-reported occupational exposure to gas, fumes, or dust occurred more frequently in men than in women. In those aged 50 or older lung function was lower in individuals exposed to airway irritants than those who were not exposed (mean (SD) FEV_1 63 (29) versus 76 (31)% predicted). Male sex, increasing age, and previous symptoms of wheezing were independent risk factors for lung function impairment, and male sex, wheeziness, and occupational exposure to airway irritants were independent risk factors in the subjects aged 50 years or more.**

***Conclusions* – In non-smoking PiZZ individuals lung function declines with increasing age, especially after 50. Men are at greater risk of lung function deterioration than women. Asthmatic symptoms and occupational exposure to airway irritants appear to constitute additional risk factors.**

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Keywords: α_1-antitrypsin deficiency, lung function, occupational exposure, airway irritants

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The plasma level of α_1-antitrypsin (AAT) is controlled by a set of codominant alleles which constitute the so-called Pi (protease inhibitor) system. In individuals with the PiZZ phenotype plasma AAT levels are usually 10–20% of normal, thus implying that the PiZZ phenotype is an important inherited risk factor for pulmonary emphysema.[1]

Cigarette smoking is a well documented additive risk factor for emphysema development.[2] It has been suggested that other genetic and/or environmental factors such as previous lower respiratory tract infections may predispose to emphysema.[3 4]

The natural history of non-smoking AAT-deficient individuals has been poorly documented. In his classic study Larsson showed the clinical course to be milder and prognosis better in non-smokers than in smokers.[2] The annual decline in lung function is also slower in non-smokers than in smokers or ex-smokers.[5] Black and Kueppers were the first to observe the great individual variability in the clinical course and the decline of lung function in non-smoking AAT-deficient patients lacking exposure to airway irritants, and suggested that host factors rather than environmental factors might be determinants of the development of chronic obstructive pulmonary disease (COPD).[6]

The aim of the present study was to identify risk factors other than smoking for declining lung function in a group of PiZZ individuals taken from the Swedish Register. Age, sex, plasma AAT levels, history of pneumonia, wheeziness, and occupational exposure to airway irritants were analysed as risk factors.

Methods

In Sweden a "screening" plasma protein analysis (including – in addition to AAT – albumin, orosomucoid, haptoglobin, ceruloplasmin, IgG, IgA, and IgM) is a frequently ordered test which is used both for suspicion of AAT deficiency in patients with COPD and for investigations of many other clinical symptoms such as increased sedimentation rate, repeated infections, hepatic, renal, and joint symptoms. If AAT levels below normal values are detected, the blood samples are sent for determination of the Pi phenotype to the Department of Clinical Chemistry at the University Hospital, Malmö, which has been the national reference laboratory for the phenotyping procedure in Sweden since 1963 when AAT deficiency was first described.[7] A number of PiZZ individuals without symptoms of lung disease are therefore identified accidentally. The patient's employment conditions are not known at the time of the PiZZ diagnosis.

To facilitate epidemiological and clinical studies of AAT deficiency the Swedish register

of AAT deficiency was started in August 1991 with the aim of including all individuals aged 18 years or over with severe AAT deficiency (PiZZ, Z0 and 00) living in Sweden. After establishing a definite diagnosis of AAT deficiency, attending physicians invite the patients (residents in different counties throughout Sweden) to be included in the register. Clinical examination, blood samples, and lung function tests are performed at the patients' local hospitals, the results being reported to the registry in a yearly questionnaire. The questionnaire consists of two parts: one to be answered by the attending physician, the other by the patient.

Physicians report the following data: (a) characteristics of the patient (sex, date of birth (and death if applicable)); (b) indication(s) for the original plasma protein analysis; (c) type of lung or other disease; (d) date of last chest radiograph; (e) results of serum transferase measurements; (f) results of current and/or older spirometric investigations; (g) treatment for pulmonary disease (including replacement therapy with human AAT); (h) treatment for other diseases; and (i) liver or lung transplantation.

The patient questionnaire is a modified version of the adult respiratory disease questionnaire used in epidemiological research.[8] The following questions are included: (a) number of siblings; (b) number of siblings tested for AAT deficiency; (c) smoking habits until inclusion in the register ("have you ever regularly smoked?" yes/no; if yes, age at starting, age at stopping and average daily consumption (number cigarettes/cigars or grams of pipe tobacco)); (d) occupation; (e) current employment status; (f) occupational exposure to gas, fumes, or dust for at least three months (yes/no; if yes, duration of exposure in years); (g) annual frequency of colds (≤ 1 or ≥ 2); (h) number of attacks of pneumonia prior to inclusion in the register; (i) cough and phlegm (yes/no); (j) occurrence of daily cough or phlegm for at least three months per year; (k) wheeziness (yes/no; if yes, with colds, damp weather, on exertion, other occasions); (l) shortness of breath on exertion; (m) duration (years) of above symptoms; (n) visual analogue scales for self-rating of general health and of capacity for physical exercise.

The follow up period for each individual registered is planned to be at least five years. In December 1994 the total number of patients included was 665, the mean age (range) being 48 (18–89) years at inclusion. Seventy five (11%) were current smokers, 333 (50%) ex-smokers, and 257 (39%) never smokers. The annual increment of new patients to the register is approximately 100, and the refusal rate only 5%.

PATIENTS

This cross sectional study is based on those PiZZ individuals aged more than 20 years included in the Swedish AAT deficiency register up to December 1994 who, at the time of enrolment in the register, had a forced expiratory volume in one second (FEV_1) recording and reported that they had never smoked regularly. Of the 257 non-smokers in the register 25 were younger than 20 years, and in seven cases no FEV_1 recording was available. Thus, the study group consisted of 225 individuals (107 men). The data reported to the register at enrolment were used in the analyses.

Plasma AAT concentrations were measured by radioimmunoassay[9] and Pi phenotypes determined by isoelectric focusing.[10]

The indications for plasma protein analysis leading to PiZZ diagnosis were respiratory disease or symptoms including repeated respiratory tract infections in 65 cases (29%, "lung disease"), other clinical symptoms in 103 cases (46%, "other disease"), family study or screening in 53 cases (23%, "screening"), and unknown in four cases (2%). These subgroups are referred to as "indication subgroups".

The indication subgroup "other disease" consisted of hepatic (13 cases), renal (nine cases), joint symptoms (13 cases), repeated infections other than in the respiratory tract (27 cases), high sedimentation rate (nine cases), and other symptoms (32 cases). Of the 53 individuals in the indication subgroup "screening" 34 were identified by family studies and 19 by different screening procedures including newborn infants,[11] school children, and blood donors. The PiZZ diagnosis was established 0–28 years before the inclusion, the exact date being unknown in some cases.

All patients gave their informed consent to participate in the study which was approved by the ethics committee of the Medical Faculty of the University of Lund.

LUNG FUNCTION TESTS

Standard spirometric tests had been performed for each subject at either the physiological laboratory or the lung department of his/her local hospital. The best of three measurements of FEV_1 and vital capacity (VC) were recorded, and in 41% of the cases recordings were also performed after inhalation of a β_2 agonist. The results of the spirometric tests are expressed as percentages of predicted values according to the reference values of Berglund and coworkers.[12]

STATISTICAL ANALYSIS

The Student's t test and analysis of variance were used to compare the continuous variables between the groups. The Tukey honest significant difference (HSD) test for unequal sample sizes was used for multiple comparisons[13] and the χ^2 test was used to compare the categorical variables. The independent effects of sex, age, AAT levels, pneumonia, wheeziness, and occupational exposure, and the statistical significance of interactions between these effects in determining percentage predicted FEV_1, were established by multiple linear regression. A p value of <0.05 was considered significant.

Table 1 Mean (SD) plasma α_1-antitrypsin (AAT) levels and lung function in 225 PiZZ individuals who had never smoked

	All (n=225)	*Men (n=107)*	*Women (n=118)*	*p value†*
Age (years)	48 (18)	45 (18)	51 (17)	0.010
AAT (g/l)*	0.23 (0.08)	0.22 (0.08)	0.25 (0.09)	0.018
FEV_1 (% predicted	84 (28)	80 (30)	88 (25)	0.028
VC (% predicted)	88 (20)	86 (20)	90 (20)	0.220

FEV_1 = forced expiratory volume in one second; VC = vital capacity.
* Normal range 0.95–1.75 g/l.[9]
† Difference between male and female subgroups, Student's *t* test.

Results

LUNG FUNCTION AND PLASMA AAT LEVELS: AGE AND SEX RELATIONSHIPS

The results of lung function tests and AAT levels are shown in table 1. For spirometric values, prebronchodilator values are shown. A reversibility test was performed in 93 (41%) of the patients. The mean (range) FEV_1 was 2.4 (0.5–6.0) l before and 2.8 (0.6–6.1) l after inhalation of a β_2 agonist, the mean (range) reversibility being 6 (0–80)%. FEV_1 increased from 0.5 to 0.9 litres in one exceptional patient, giving a reversibility of 80%. In 12 other cases the reversibility was ≥15%. The mean FEV_1 (% predicted) was significantly lower in men than in women (p = 0.028) despite the fact that the men were younger (p = 0.010, table 1).

Most of the patients under 50 years of age seemed to have normal lung function, but in those aged 50 years and over there was considerable variability in percentage predicted FEV_1 (fig 1). The spirometric results were therefore analysed separately for the two age groups and the FEV_1 was found to be significantly higher in the younger age group (mean (SD) 98 (16) versus 70 (30)% predicted; p<0.001, Student's *t* test), as was VC (95 (16) versus 81 (21)% predicted; p<0.001).

Plasma AAT levels were higher in women than in men (table 1) and higher in the older patients than in the younger age group (0.25 (0.09) versus 0.22 (0.08) g/l, p = 0.016).

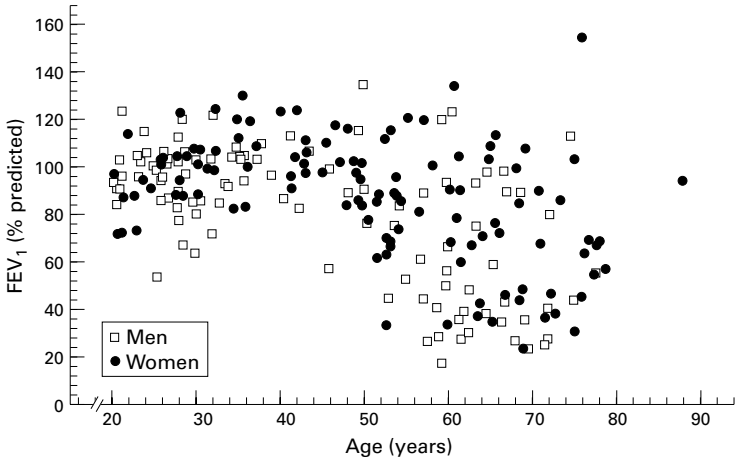

Figure 1 FEV_1 (% predicted) versus age in PiZZ men (n=107) and women (n=118) who had never smoked.

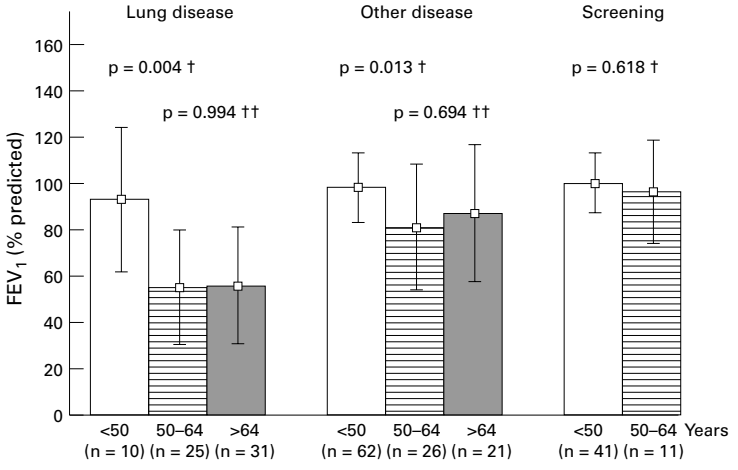

Figure 2 Age and lung function relationships in the indication subgroups "lung disease", "other disease", and "screening". Mean (SD) values of FEV_1 (% predicted) are shown for the age groups <50 years, 50–64 years, and >64 years. In the "screening" subgroup the maximum age was 61 years so the >64 years age group was not applicable.
† Difference between the <50 and 50–64 age groups; †† difference between 50–64 and >64 age groups.

LUNG FUNCTION ACCORDING TO INDICATION FOR AAT TEST

The male/female ratio was 35/30 in the "lung disease" subgroup, 42/61 in the "other disease" subgroup, and 27/26 in the "screening" indication subgroup (p = 0.207, χ^2 test), the mean (range) ages of the three subgroups were 62 (20–89) years, 46 (20–87) years, and 36 (20–61) years, respectively, and the mean (SD) FEV_1 was 61 (29), 92 (22), and 99 (15)% predicted, respectively. When adjusted for age there was a significant difference in lung function between the "lung disease" and the "other disease" subgroups (p<0.001). The "screening" subgroup was excluded from the test because the mean age was only 36 years and the maximum age 61 years.

Before analysing lung function by age, each indication subgroup was split up into three age groups (<50, 50–64, and >64 years) (fig 2). In the "screening" subgroup only age groups <50 years and 50–64 years were applicable. FEV_1 (% predicted) was significantly higher in the <50 years age group than in the 50–64 age group in the "lung disease" subgroup (p = 0.004) and in the "other disease" subgroup (p = 0.013), whereas the difference in the "screening" subgroup was not significant (p = 0.618).

OCCUPATIONAL EXPOSURE TO AIRWAY IRRITANTS

Eleven subjects recorded their occupation as house wife, four were students, and all the other individuals were or had been employed.

Occupational exposure to gas, fumes, or dust for at least three months was reported by 85 individuals (38%, "exposed"), denied by 130 individuals (58%, "non-exposed"), and 10 individuals (4%) did not know.

More of the men than the women reported occupational exposure to airway irritants (52% versus 28%, p<0.001, χ^2 test). The male predominance in occupational exposure to irritants was also present in the indication subgroups "lung disease" (65% versus 38%, p = 0.034) and "other disease" (52% versus 23%, p = 0.006). A similar tendency was seen

Table 2 Mean (SD) lung function values by age and sex in individuals with ("exposed") and without ("non-exposed") occupational exposure to gas, fumes, or dust during at least three months

Age	*Sex*	*Exposed*	*Non-exposed*	*FEV_1 (% pred)*		*VC (% pred)*	
				Exposed	*Non-exposed*	*Exposed*	*Non-exposed*
<50	M&F	39	71	102 (14)	101 (9)	99 (8)	96 (14)
≥50	M&F	46	59	63 (29)*	76 (31)	80 (23)	82 (20)
≥50	M	27	17	54 (28)†	69 (35)	75 (22)	83 (19)
≥50	F	19	42	75 (26)	78 (29)	87 (22)	81 (21)

*p = 0.032 compared with non-exposed group aged ≥50 years (Student's *t* test).
†p = 0.017 compared with non-exposed women (Tukey HSD test).

in the "screening" subgroup (42% versus 28%) but the difference was not significant (p = 0.285).

For the whole population and those below 50 years of age lung function did not differ significantly between the "exposed" and "non-exposed" groups. In contrast, in those aged 50 years and above FEV_1 (% predicted) was lower in individuals "exposed" than in those "non-exposed" to airway irritants (p = 0.032, table 2). Lung function did not differ significantly between the men and women in the "exposed" and "non-exposed" groups with the exception of "non-exposed" women and "exposed" men in the older age group (p = 0.017, table 2). Among the "exposed" individuals the median duration of exposure was eight years (range 1–50) with no difference between the sexes, but the duration of exposure was correlated with age (r = 0.50, p<0.001). Linear regression analysis showed significant correlation between FEV_1 (% predicted) and duration of exposure to irritants (p<0.001), a correlation which disappeared when correction was made for age.

FACTORS INFLUENCING LUNG FUNCTION

In multiple linear regression analysis FEV_1 (% predicted) was used as the dependent variable with sex, age, plasma AAT level, history of pneumonia, wheeziness, and occupational exposure to irritants as the independent variables. The results are shown in table 3. Increasing age (p<0.001), male sex (p = 0.001), and symptoms of wheezing (p = 0.007) were identified as the independent determinants of FEV_1.

An identical analysis was then performed in the two age groups (<50 and ≥50 years). In the younger age group only male sex was a determinant of lung function (p = 0.028), but in the older group male sex (p = 0.025), wheeziness (p = 0.011), and occupational exposure to irritants (p = 0.026) were all independent determinants of lung function (table 3). The interaction effect of sex and occupational exposure to irritants was non-significant (p = 0.659).

Multiple regression analysis was also performed separately for men and women. In women increasing age was the only independent factor influencing FEV_1 (p = 0.008), whereas in men both increasing age (p<0.001) and wheeziness (p = 0.009) had an independent effect on FEV_1.

In the "lung disease" indication subgroup increasing age (p = 0.022) was the independent factor influencing FEV_1 (% predicted), while in the other indication subgroups none of the above factors had an independent effect on lung function.

MEDICAL HISTORY

Forty five percent of individuals reported having had one or more attacks of pneumonia before inclusion in the register. Breathlessness at exertion was reported by 46% and wheeziness by 39%. The mean age at onset of breathlessness was 52 years and of wheeziness was 45 years. Medical history or symptoms did not differ between the sexes.

Wheeziness was reported by 46% of individuals exposed to airway irritants and 34% of those not exposed (p = 0.071). A history of pneumonia was reported by 54% of individuals in the "lung disease" subgroup, 55% in the "other disease" subgroup, and 11% in the "screening" indication subgroup (p<0.001). Shortness of breath at exertion was reported by 85%, 35%, and 23%, respectively (p<0.001) and wheezing by 63%, 35%, and 17%, respectively (p<0.001).

Discussion

In patients with AAT deficiency cigarette smoking is a well documented additional risk factor for emphysema.[2] The aim of our study was to analyse lung function in PiZZ individuals who had never smoked, thus eliminating smoking as a confounding factor. As in previously published studies, most of the patients (77%) were identified because of some disease, but in contrast to several other studies[2 14 15] only 29% were identified because of lung disease.

Table 3 Results of multiple linear regression analysis

	All individuals			*Age ≥50 years*		
	Regression coefficient	*95% CI*	*p value*	*Regression coefficient*	*95% CI*	*p value*
Sex (men v. women)	15	6.8 to 23	<0.001	16	2 to 30	0.025
Age (years)	−0.7	−0.9 to −0.5	<0.001	−0.5	−1.2 to 0.4	0.351
AAT (g/l)	−12	−58 to 34	0.605	19	−57 to 95	0.609
Wheeziness (yes versus no)	12	3.4 to 21	0.007	17	3 to 31	0.012
Pneumonia (≥1 versus never)	0.6	−7.6 to 8.8	0.887	5.0	−9 to 19	0.473
Occupation exposure (exposed versus non-exposed)	6.9	−1.3 to 16	0.106	7.0	2.4 to 12	0.026

Sex age, plasma ATT level, wheeziness, history of pneumonia, and occupational exposure to airway irritants were independent variables and FEV_1 (% predicted) was the dependent variable in all individuals and in the age group ≥50 years. Proportion of variance (R^2) explained by the variables was 34% in the whole population, and 25% in the age group ≥50 years.

It is evident that AAT-deficient individuals who have never smoked are at risk of deterioration in lung function with increasing age (fig 1). Until 50 years of age most AAT-deficient non-smokers seem to have normal spirometric values and only a few of them are identified because of respiratory symptoms. Above this age there are great interindividual differences in lung function, though the mean values decline significantly with age.

To evaluate the effect of ascertainment bias we analysed lung function in the indication subgroups separately (fig 2). The individuals identified for respiratory symptoms or other medical reasons showed a deterioration in lung function after 50 years. In contrast, in the group identified by screening or family studies lung function did not decrease more than expected with age, but this subgroup did not include any individuals older than 61 years and the number aged over 50 was small.

Impairment of lung function in elderly AAT-deficient individuals who have never smoked has been documented earlier, but in those studies the participants were predominantly recruited because of lung disease, or the series was small.[6 14 15]

In our study previous asthmatic symptoms seemed to predispose to impairment of lung function (table 3) but, in contrast to previous reports, a history of lower respiratory tract infections had no effect on lung function.[4]

Our results show that lung function is significantly more impaired in men than in women, a difference which has been discussed before but never verified.[15] Smoking habits have been suggested to be responsible for the male predominance among AAT-deficient individuals suffering from COPD,[3 15] but in our study smoking was an exclusion criterion. We can only speculate about the reasons for the sex differences. The plasma AAT level increased with age and was higher in women than in men, which is in agreement with the findings of earlier studies.[4] The women were significantly older than the men which may explain the sex difference in AAT levels. However, multiple linear regression analysis showed that plasma AAT level was not an independent determinant of FEV_1.

There was a male predominance among individuals reporting occupational exposure to airway irritants ($p<0.001$). The effect of occupational exposure to airway irritants has been investigated in relation to Pi phenotypes in a few studies. Horne and coworkers[16] showed lung function to be poorer in grain workers with the PiMZ phenotype than in those with the PiM phenotype, which may indicate a higher sensitivity to environmental exposure. In our group of non-smokers aged over 50 years lung function was poorer in those individuals who were exposed than in those who were not exposed to airway irritants (table 2). Exposure to irritants was also identified as an independent risk factor for the decline in lung function in this age group (table 3). It is probable that an exposure duration of several years is needed for a deterioration in lung function to be detected by standard spirometric tests which could explain why no effect of exposure was detected in those younger than 50 years. The lack of a statistically significant effect of occupational exposure to airway irritants on lung function in men, women, or the "indication" subgroups may be due to the insufficient number of individuals above 50 years of age in these groups.

Our findings suggest that occupational exposure to airway irritants is a risk factor for a premature decline in lung function in AAT-deficient individuals. However, it should be borne in mind that our questionnaire only included a general question about occupational exposure, and no specific details were elicited of different putative airway irritants. Further studies are needed to determine which employment categories or what other environmental factors may be specific risk factors for lung disease in conjunction with AAT deficiency.

We conclude that, in PiZZ individuals who have never smoked, lung function declines after the age of 50 years. Men are at greater risk of lung function deterioration than women. Previous asthmatic symptoms and occupational exposure to airway irritants appear to constitute additional risk factors.

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