Environmental correlates of impaired lung function in non-smokers with severe α_1-antitrypsin deficiency (PiZZ)

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Abstract

***Background*—Active smoking is the most important risk factor for pulmonary emphysema in subjects with severe α_1-antitrypsin (AAT) deficiency. The aim of this study was to analyse the effects of environmental risk factors other than active smoking on lung function and on respiratory symptoms in non-smoking PiZZ individuals.**

***Methods*—Lifetime exposure to passive smoking, domiciliary use of a kerosene (paraffin) heater or gas cooker, and all occupations since leaving school were reported by 205 non-smoking PiZZ individuals (95 men and 110 women) included in the Swedish AAT deficiency register. Lung function test results and histories of respiratory symptoms (chronic bronchitis, recurrent wheezing, and exertional dyspnoea) were elicited from the AAT register records.**

***Results*—After adjustment for age, agricultural employment and domiciliary kerosene heater usage, but not gas cooker usage or passive smoking, were both associated with significantly decreased lung function. Multiple linear regression analysis showed age, sex, kerosene heater usage, and agricultural employment to be independent determinants of lung function impairment. Age and passive smoking for 10 years or more, both at home and at the work place, were associated with the presence of chronic bronchitis. Age and agricultural employment for ⩾10 years were associated with recurrent wheezing and exertional dyspnoea.**

***Conclusions*—Domiciliary kerosene heater usage and an agricultural occupation therefore appear to be environmental factors associated with decreased lung function in non-smoking PiZZ individuals, and passive smoking is associated with an increased frequency of chronic bronchitis, but not with impaired lung function.**

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Keywords: α_1-antitrypsin deficiency; passive smoking; indoor air pollution; occupational exposure; emphysema

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The relationship between severe α_1-antitrypsin (AAT) deficiency, phenotype PiZZ, and pulmonary emphysema is well known.[1] Smoking is the most important environmental risk factor for the development of emphysema in AAT deficiency.[2 3] Since even non-smoking PiZZ individuals may develop lung disease, it has been suggested that other environmental and/or intrinsic factors may affect lung function in PiZZ individuals.[4 5]

To facilitate study of the natural history, risk factors, and clinical features of AAT deficiency, a national AAT deficiency register was established in Sweden in 1991.[5] All individuals aged 18 years or older living in Sweden and carrying the phenotypes PiZ or Pinull were invited to be included in the register. The initial plasma protein analysis resulting in the final PiZ diagnosis was performed either because of lung disease, other disease (liver, joint symptoms, infection, increased erythrocyte sedimentation rate, etc) or screening (family, neonatal[6] or other screening). Other data for the register were elicited by questionnaire as previously described.[5] Results of lung and liver function tests, diagnosis and treatment are reported regularly by the attending physician while symptoms, smoking habits, occupation, and employment status are reported by the PiZ individuals themselves.

In a previous study of a group of non-smoking PiZZ individuals included in the Swedish AAT deficiency register[5] we found lung function to be significantly decreased in the men and in individuals aged 50 years or more. Moreover, self-reported occupational exposure to gas, fumes or dust, which was more frequent among the men than among the women, was associated with decreased lung function in the older age group. Thus, the results suggested that occupational exposure to airway irritants may be associated with a risk of decreased lung function in PiZZ individuals.

The aim of the present study was to analyse in detail the impact of environmental factors—such as indoor air pollution (passive smoking, domiciliary use of kerosene, and gas stoves) and occupational exposure to airway irritants—on lung function and respiratory symptoms in never smoking PiZZ individuals.

Methods

PATIENTS

All individuals aged 20 years or more included in the Swedish AAT deficiency register up to August 1995 who reported never having smoked regularly were invited to participate in the study. Most of the study participants were included in our previous study.[5] In addition to smoking habits reported in the standard registry questionnaire,[5] detailed questions about

Table 1 Distribution of the respiratory symptoms by sex, age and environmental risk groups

			Chronic bronchitis		Wheezing		Dyspnoea on exertion	
		n	OR	95% CI	OR	95% CI	OR	95% CI
Age group	<50 years	109	1		1		1	
	⩾50 years	96	2.7†	1.2 to 5.8	3.7‡	2.0 to 6.7	9.9‡	5.1 to 19.2
Sex	Men	95	1		1		1	
	Women	110	1.1	0.5 to 2.3	1.7	1.0 to 3.1	1.7	1.0 to 3.1
Passive smoking	0 years	105	1		1		1	
	⩾10 years	71	1.6*	1.3 to 2.4	1.1	0.7 to 1.6	1.2	0.8 to 1.8
Agricultural employment	0 years	175	1		1		1	
	⩾10 years	17	1.6	0.9 to 2.9	1.8*	1.01 to 3.3	1.8*	1.01 to 3.3

*p<0.05; †p<0.01 ; ‡p<0.001 (chi-squared test).

smoking history were included in the present study questionnaire answered by each participant.

The present study questionnaire, sent to 258 individuals who reported that they had never regularly smoked, was answered by 235 (91%). Fifteen of the responders reported a daily consumption of more than one cigarette for a year and another 15 individuals were under 20 years of age. Data for the remaining 205 individuals (95 men and 110 women) were included in the statistical analysis. In 105 individuals (51%) AAT deficiency had been identified during investigation for diseases other than lung disease, 45 (22%) had been identified by screening, and only 55 (27%) because of lung disease.

QUESTIONNAIRE

The present study questionnaire included the following questions: (1) active smoking (yes/no; if yes, the year started and, if ex-smokers, the year they stopped, and the mean daily consumption of cigarettes, cigars or tobacco (grams)); (2) passive smoking since birth (yes/no; if yes, location (home or work place), intensity in days per week, and duration in years; (3) domiciliary kerosene (paraffin) heater usage (yes/no; if yes, duration in years); (4) domiciliary gas cooker usage (yes/no; if yes, duration in years); and (5) education and all occupations since leaving school.

Those reporting daily consumption of more than one cigarette for at least one year during their lives were considered to be smokers (or ex-smokers) and were excluded from the study. For the purposes of statistical analysis the lower limit of passive smoking was one year of either domiciliary exposure to smoking for seven days a week, or exposure at the work place for five days a week. Occasional exposure to smoking in restaurants, lunch rooms or public places was not considered to constitute passive smoking.

All occupations reported by the study participants were classified according to the *Standard Swedish Classification of Occupational Categories* compiled by Statistics Sweden (*Statistiska Centralbyrån*), the National Bureau of Statistics. In each case classification was done without knowledge of the patient's lung function test results or respiratory symptoms, and the number of years spent in each occupational category was noted in the case of any individual who had worked in more than one field.

Self-reported data about respiratory symptoms were elicited from answers to the standard registry questionnaire.[5] Data for the following items were included in the statistical analysis: daily cough with phlegm at least three months per year, called "chronic bronchitis" in this report (item answered by yes/no), recurrent wheezing (yes/no), and exertional dyspnoea (yes/no).

LUNG FUNCTION TESTS

The results of lung function tests including forced expiratory volume in one second (FEV_1) and vital capacity (VC) were elicited from registry records. Lung function test results were expressed as a percentage of reference values published by Berglund and co-workers.[7] Only pre-bronchodilator values were analysed. All lung function tests were performed at the patient's local hospital.

PIZZ DIAGNOSIS

In all cases Pi phenotypes were determined by isoelectric focusing at the Department of Clinical Chemistry, University Hospital, Malmö.[8] All individuals were identified as phenotype PiZZ (though naturally a few cases of PiZ0 cannot be excluded without family studies or DNA analysis, but none was Pi00).

STATISTICAL ANALYSIS

The χ^2 test and Fisher's exact test were used to compare categorical variables. Multiple regression analysis was used in age adjusted correlations between continuous variables. Covariance analysis was used in group comparisons of lung function, with age as the covariate. The Tukey Honest significant difference (HSD) test was used for multiple comparisons.[9]

Table 2 Distribution of sex, mean (range) duration of occupation, and mean (SD) FEV_1 values (% predicted) according to the one-digit level of the Classification of Occupations by Statistics Sweden

Occupation category	M/F*	Duration (years)	FEV_1 (% of predicted)
Technical scientific, teaching	24/18	17 (1–43)	87 (29)
Health care	9/41	13 (1–42)	95 (20)
Administration and office	16/29	15 (1–60)	85 (21)
Commerce and trade	8/24	12 (1–47)	85 (30)
Agriculture	20/10	18 (1–65)	71 (31)
Mining	0/0	—	—
Transport and communication	15/8	10 (1–42)	86 (25)
Industrial production and construction	49/14	14 (1–60)	85 (33)
Service occupations	11/36	8 (1–37)	85 (28)

*M = male, F = female.

Table 3 Mean (SD) age and mean (95% CI) lung function in subgroups according to duration of agricultural employment

	0 years	*1–10 years*	*⩾10 years*
Men/women	75/100	12/1	8/9
Mean (SD) age (years)	46 (18)	42 (18)	62 (16)
FEV_1 (% predicted)	89 (95% CI 85 to 93)**	87 (95% CI 73 to 101)*	59 (95% CI 43 to 76)
VC (% predicted)	90 (95% CI 87 to 93)**	90 (95% CI 78 to 102)*	70 (95% CI 60 to 81)

*p<0.05; **p<0.01compared with the ⩾10 year employment duration subgroup, covariance analysis with age correction.[9]

Results

LUNG FUNCTION AND RESPIRATORY SYMPTOMS IN THE SERIES AS WHOLE

The mean age of the study participants was 47 years (range 20–81). In the series as a whole mean FEV_1 was 86% of predicted (range 14–168) and VC was 88% of predicted (range 32–172). The mean (SD) age of the male subgroup was 44 (18) years, and that of the female subgroup 49 (18) years, the respective mean (SD) FEV_1 values being 80 (30)% predicted and 92 (24)% predicted (p<0.001 after age correction) and the mean (SD) VC values being 86 (22)% predicted and 91 (17)% predicted (p<0.01 after age correction). Mean (SD) FEV_1 was 99 (15)% predicted in subjects aged <50 years and 72 (32)% predicted in those aged 50 years or more (p<0.01).

Chronic bronchitis was reported by 34 (17%), recurrent wheezing by 79 (39%), and exertional dyspnoea by 79 (39%) individuals. The presence of respiratory symptoms related to age and sex are shown in table 1.

PASSIVE SMOKING

Of the 198 subjects for whom data on this item were available, 93 (49%) reported having been "passive smokers" at some time. There was no significant difference in the presentation of the sexes in this group (44 (47%) men and 49 (53%) women). The duration of exposure to environmental smoking was reported to be 1–10 years by 22 of the passive smokers, and more than 10 years by the remaining 71.

There was no significant difference in lung function between the passive smoking subgroups and the unexposed subgroup. However, the prevalence of chronic bronchitis was significantly greater in those exposed for 10 years or more than in the unexposed subgroup (table 1). The prevalence of chronic bronchitis in the subgroup of passive smokers exposed both in the home and at the work place was significantly greater (35% (8/23); p<0.01) than that in the subgroup unexposed to environmental smoking (12% (13/105)) but not compared with that in the subgroup exposed only in the home or at the work place (17% (12/70)).

EXPOSURE TO OTHER INDOOR AIR POLLUTION

Of the 199 subjects for whom data on this item were available, 7% (14/199; eight men) reported domiciliary kerosene heater usage, the mean duration being nine years (range 1–20). As only six subjects reported a duration of kerosene heater usage of 10 years or more, no subgrouping was done according to duration of usage. Lung function and respiratory symptoms of the whole subgroup (n = 14) were compared with those never exposed to kerosene heater emissions (n = 185). The mean (SD) age was 46 (18) years for the unexposed subgroup and 54 (11) years for the exposed subgroup, the respective mean FEV_1 values being 88% of predicted (95% CI 84 to 92) and 65% of predicted (95% CI 44 to 85) (p<0.05 after age adjustment). No significant relationship was found between the duration of exposure and lung function.

Among the men there was no significant difference in lung function between the subgroup exposed to kerosene heater emissions (n = 8) and the non-exposed subgroup (n = 77). The mean (SD) age of the women was 58 (13) years for the exposed subgroup (n = 6) and 49 (23) years for the unexposed subgroup (n = 104), the respective FEV_1 values being 60 (95% CI 21 to 99) and 94% of predicted (95% CI 89 to 92) (p<0.01 after age adjustment).

There was no significant relationship between the use of gas stoves for cooking and lung function. No difference was found in the proportion of subjects with respiratory symptoms between kerosene heater or gas cooker users and non-users.

OCCUPATIONAL CATEGORIES

The numbers of subjects and the duration of employment in the various occupational categories are shown in table 2. Of the series as a whole, 110 (54%) subjects had worked in one category only, 57 (28%) in two, 27 (13%) in three, and five (2%) in four different occupational categories. Six subjects (3%) were students or had never been employed.

For each occupational category the lung function values in three subgroups were compared: those employed in the category for 1–10 years, those employed in the category for ⩾10 years, and the remainder of the series—that is, those never employed in the category.

The category "agriculture" was the only one characterised by significantly decreased lung

Table 4 Multiple linear regression analysis with FEV_1 (% predicted) as the dependent variable, and age, sex, exposure to kerosene heater emissions, and agricultural employment for ⩾10 years as the independent variables

	*β**	*95% C I*	*p value*
All study participants			
Age (years)	−0.7	−0.9 to −0.5	<0.001
Sex (effect of male sex)	−14.9	−21.5 to −8.3	<0.001
Using kerosene heater	−16.2	−29.0 to −3.4	<0.05
⩾10 years in agricultural employment	−18.0	−30.0 to −6.0	<0.01
Men			
Age (years)	−1.0	−1.2 to −0.8	<0.001
Using kerosene heater	−5.8	−11.4 to 23.0	NS
⩾10 years in agricultural employment	−14.6	−32.2 to 3.0	NS
Women			
Age (years)	−0.4	−0.6 to −0.2	<0.01
Using kerosene heater	−28.4	−36.6 to −10.2	<0.01
⩾10 years in agricultural employment	−21.1	−36.9 to −5.3	<0.01

*FEV_1 = Intercept + β*age + β*sex + β*kerosene + β*agriculture. The variance of FEV_1 (% predicted) explained by the variables (R^2) was 35% in the series as a whole, 45% in the men and 26% in the women.

function after adjustment for age when compared with the remainder subgroup (table 3). The age adjusted partial correlation between the employment duration and FEV_1 (% predicted) was –0.40 ($p<0.05$). The prevalence of respiratory symptoms among the subjects employed as agricultural workers is shown in table 1.

Lung function was also analysed separately in the male and female agriculture subgroups. Among the men the difference in lung function was not significant after adjustment for age. As only one female agricultural worker reported an employment duration of <10 years, comparison of lung function was confined to the nine female agricultural workers with employment duration of ⩾10 years and the 100 women never employed in the category. The respective mean (SD) ages were 67 (15) and 48 (17) years, and the respective mean (SD) FEV_1 values were 65 (30) and 94 (22)% predicted ($p<0.05$ after adjustment for age).

No significant subgroup differences in lung function were found in the other occupational categories (table 2).

MULTIVARIATE ANALYSIS OF LUNG FUNCTION

Multiple linear regression analysis was used to determine the impact on FEV_1 (dependent variable) of the independent variables age, sex, passive smoking for ⩾10 years, kerosene heater usage for ⩾10 years, and agricultural employment for ⩾10 years. The results are shown in table 4.

Discussion

In severe AAT deficiency active smoking is the most important risk factor for the development of emphysema, but little is known about other environmental risk factors. In a previous study we found self-reported occupational exposure to airway irritants to be a correlate of decreased lung function in elderly non-smoking PiZZ individuals.[5] The aim of the present study was to analyse the impact of additional environmental factors on lung function and on respiratory symptoms in PiZZ individuals. To avoid the confounding effects of active smoking, only life long non-smokers were included in the study.

The PiZZ individuals in our study were included in the Swedish AAT deficiency register and were living throughout Sweden. Because most (72%) were identified because of some disease state, they did not represent a random sample of PiZZ individuals living in Sweden. The socioeconomic status, which may be a confounding factor, was not taken into consideration. Since information on environmental exposure and occupation was reported retrospectively by the study participants, there is a risk of recall bias. Moreover, in the detailed analysis of all occupations the number of individuals in each occupational category was small. Thus, any failure to demonstrate correlation does not necessarily exclude harmful effects.

Although AAT deficient individuals are known to be particularly susceptible to active smoking, we found no relationship between passive smoking and decreased lung function. However, the subgroup exposed to environmental smoking for 10 years or more was characterised by an increased proportion of subjects reporting symptoms of chronic bronchitis (table 1). Similar results were obtained when the subgroup of those exposed both in the home and at work was compared with the unexposed subgroup. These findings suggest that passive smoking may also be a risk factor for respiratory symptoms in individuals with severe AAT deficiency.

A larger study group is needed to find significantly decreased lung function in passive smokers even when *susceptible* AAT-deficient individuals are studied. Previous population based studies showing harmful effects of passive smoking on lung function and respiratory symptoms have included large numbers of subjects. Leuenberger and co-workers demonstrated a dose-dependent increase of prevalence of respiratory symptoms in subjects exposed to environmental smoke in the SAPALDIA study including more than 4000 never smoking adults.[10] In a study of 1000 adults, including both ex-smokers and never smokers, Xu and colleagues found a dose-dependent decrease in lung function among those exposed to environmental smoking either at home or at work, or both.[11] In large studies of children harmful effects of passive smoking on lung function and respiratory symptoms have been observed.[12 13]

We found a clear correlation between exposure to kerosene heater emissions and decreased lung function (table 4). Kerosene heaters are sources of combustion gases such as carbon monoxide, nitrogen oxides and sulphur dioxide, as well as polycyclic aromatic hydrocarbons, dinitropyrenes, alkylbenzenes, phthalates, hydronaphthalenes, aliphatic hydrocarbons, alcohols and ketones.[14] Cooper and Alberti also investigated sulphur dioxide emissions from kerosene heaters in 14 homes and found a mean concentration of 0.4 (range 0–1.0) parts per million, but no acute effects on lung function,[15] though exposure at that level has been shown to exert detectable acute effects on lung function in asthmatic subjects.[16] Although exposure to kerosene heaters was found to be unrelated to asthma in children in two recent studies[17 18] and to respiratory symptoms in another recent study,[19] cross sectional studies have shown kerosene heater usage to be associated with decreased lung function in primary school children,[20 21] the effect being greater than that of passive smoking.[21] Moreover, in a study of more than 3000 Indian women using various cooking fuels the use of kerosene was associated with lung function impairment which manifested correlation with cooking years and an exposure index.[22] These findings are consistent with those obtained in the present study of a much smaller series, thus demonstrating the appropriateness and increased power of investigating a population of particularly *susceptible* individuals. However, though lung function was significantly decreased in the subgroup exposed to kerosene heater emissions, we found no relationship

between kerosene heater usage and the proportion of subjects with respiratory symptoms.

Agriculture was the only occupational category with significantly decreased lung function (tables 3 and 4). In this subgroup the decrease in lung function was also correlated with employment duration, independent of age. The proportion of subjects with wheezing and dyspnoea on exertion was also significantly increased in the agricultural employment category with an employment duration of $\geqslant 10$ years (table 1). Increased prevalences of asthma and chronic bronchitis among agricultural workers have previously been found in population studies[23 24] where the presence of AAT deficiency was not taken into consideration. Agricultural work in Sweden usually includes exposure both to animals, corpses and dairy products. Although employees were exposed to several known sensitising and non-sensitising risk factors for lung function impairment, because of the small size of this category it was not possible to analyse such subgroups.

There was a preponderance of men both in the agricultural employment category and in the other categories such as metal workers that are associated with risk of exposure to airway irritants. However, after adjustment for age we found no significant differences in lung function or in the proportion of subjects with respiratory symptoms between the male agricultural workers or male metal workers and the remaining men. On the contrary, lung function was significantly poorer in the female agricultural workers than in the remaining women. However, the power of the study to detect occupations with a risk for decreased lung function is reduced. A large proportion of the population, particularly of the men, had been employed in several different occupations with exposure to airway irritants which might affect the lung function either alone or by an additive effect, the "multiple hit" hypothesis.[25] The lack of statistical significance of agricultural employment among the men might therefore result from the fact that comparison was performed against all other men, including a number of individuals exposed to airway irritants. It is also possible that, in AAT-deficient men, lung function is susceptible to other environmental or intrinsic factors not being analysed in the present study.

These findings suggest that kerosene heater usage and agricultural employment are environmental risk factors for lung function impairment in non-smoking PiZZ individuals, and passive smoking is associated with an increased prevalence of chronic bronchitis, but not with decreased lung function.

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