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Lung function in an Australian population: contributions of polygenic factors and the *Pi* locus to individual differences in lung function in a sample of twins

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Summary. A study of lung function in 203 twin pairs aged 18–34 years living in Sydney detected significant genetic variation in females and males. There was no evidence of family environmental effects in either sex and most of the repeatable variation in females was heritable. However, there was evidence for systematic environmental differences between males affecting lung function so that the heritability was lower in males (about 0·6) than females (about 0·8). An effect of smoking on lung function was detected but accounted for less than 3% of the variance. Lung function in females was greater in the M subtype heterozygotes at the *Pi* locus than in the M subtype homozygotes or in other *Pi* phenotypes with low α_1-antitrypsin activity. The *Pi* polymorphism accounted for approximately 9% of the total variance in female lung function. No effect of the *Pi* locus was found in males.

1. Introduction

A characteristic feature of lung-function measurements which has emerged from prospective studies of human populations is their value in predicting longevity (Dawber, Meadors and Moore 1951, Ashley, Kannel, Sorlie and Masson 1975). Indeed, the quality of ventilatory function has been used to provide an indicator of physiological health (Webster and Logie 1974) and of age-dependent physiological impairment (Gibson, Adena, Craft, Rawson and Webster 1979 a, Webster and Gibson 1979).

There is evidence for a genetic component in lung-function variation (Feinleib, Garrison, Fabsitz, Christian, Hrubec, Borhani, Kannel, Rosenman, Schwartz and Wagner 1977), and some environmental factors and daily habits which impair performance have been detected. Of particular importance is the well-documented detrimental effect of cigarette smoking on lung function (Woolcock and Berend 1977), causing a greater decline with age in smokers than in non-smokers. It is also known that there is a more marked rate of decline of lung function in subjects with bronchitis and emphysema (Fletcher and Peto 1977), both of which are diseases associated with air pollution and urbanization (Colley and Reid 1970).

In a study of physiological and biochemical traits in a large sample of the Sydney urban population, forced expiratory volume ($FEV_{1\cdot0}$) and forced vital capacity (FVC) were found to decline with age in males and females and to be lower in current smokers than in non-smokers or past smokers (Gibson, Gallagher, Johansen and Webster 1979 c). There was also evidence that decrements in lung function in smokers and non-smokers were non-randomly distributed in the Sydney metropolitan area, apparently in relation to the amount of land set aside for industrial purposes (Gibson and Johansen 1979).

In line with the overall aim of detecting the various causes of impaired lung function in the Sydney population, a study of spirometry in a sample of twins was carried out to assess the heritable component of the variation. The contribution to this heritable component made by segregation at a specific locus (*Pi*) was also investigated. The *Pi* locus codes for α_1-antitrypsin, and some rare *Pi* phenotypes which have deficiencies in

this enzyme have been associated with disorders of lung function (Mittman 1972, Fagerhol and Cox 1981).

2. Sample and methods

Subjects were 203 pairs of twins in the age range 18–34 years (mean age 23·1 years) of European extraction who were living in the Sydney area and were recruited through the Australian NH & MRC Twin Registry. The majority of twins were born in Australia; those born overseas had lived in Sydney for most of their lives. All twins were typed for red blood cell antigens with the antisera: anti-A, A_1, B, C, c, D, E, e, M, N, S, s, Fy^a, K and Jk^a. The twins were also typed for the serum enzyme α_1-antitrypsin (*Pi*) by iso-electric focusing as described by Clark and Martin (1982). Twins were diagnosed as dizygotic on the basis of a difference in sex, at least one marker locus or, in a few cases, large differences in height, colouring or other morphological features. In 11 remaining cases of doubtful zygosity 3 more genetic markers (Hp, Gc, PGM-1) were typed. It is possible, however, that there are a few pairs diagnosed as monozygotic who on still further typing would prove to be dizygotic.

Forced expiratory volume at one second ($FEV_{1\cdot0}$) and forced vital capacity (*FVC*) at body temperature, prevailing atmospheric pressure and water vapour saturation were measured using a Vitalograph (Garbe and McDonnell 1964) with the subject standing. All subjects were tested in the morning and the best of two tests was recorded. A nose clip was not used. Height (stadiometer) was also measured (without shoes) and details of smoking history and habits were obtained in a self-report questionnaire.

The sex and zygosity distribution of the tested twins (none of whom had a severe respiratory complaint, e.g. asthma) is shown in table 1. There were no significant differences in the distribution of age in the five twin groups. Forty-one pairs of twins returned for a second testing session between 2 and 17 months (mean 4·5 months) after the first visit. For the purposes of calculating repeatability of measurements, the zygosity composition of this repeat sample was ignored but it included 46 males and 36 females.

Table 1. Sex and zygosity composition of twin sample.

MZF	MZM	DZF	DZM	DZO	Total
42	41	44	38	38	203

3. Results

Relationships with age and height

It is a general finding from population samples that lung function decreases with age and is positively correlated with height (Cole 1975, Gibson, Gallagher, Johansen and Webster 1975 b). The correlation of lung-function variables with age is not strong in these twin data and only the correlation with FEV in males is significant ($P<0·01$) (table 2). This is probably due to the small age range represented. Correlation with height, however, is marked and highly significant in all cases (table 2).

Thus, before the effect of smoking on lung function was examined, a compound variable, FEC, was computed in which FEV was corrected for the effects of regression on height and age. In a previous study (J. B. Gibson and M. A. Adena, in preparation)

Table 2. Correlations with age and height.

	Age		Height	
	$FEV_{1\cdot0}$	*FVC*	$FEV_{1\cdot0}$	*FVC*
Males	−0·20**	0·00	0·49***	0·54***
Females	−0·08	−0·02	0·44***	0·64***

**0·001<*P*<0·01, ***P<0·001.

of a large Sydney sample (13 135) of healthy individuals (i.e. nonsmokers with no respiratory disorders), $FEV \times 10^4/\text{height}^2$ (*FEVHT*) was regressed on age.

It was found that the slope and intercept of the *FEVHT* with age regression for the whole twin sample did not differ significantly from that obtained in the large Sydney sample. Similarly, regressions for subpopulations grouped by sex and smoking did not differ significantly between the two data sets. Accordingly, the regression equations derived from the large general population sample were used to calculate individual *FEC* values for the twins, as:

Males: $FEC = FEVHT - (1\cdot8532 - 0\cdot0105969 * \text{Age})$
Females: $FEC = FEVHT - (1\cdot5546 - 0\cdot0098665 * \text{Age})$

FEC, then, is a measure of the deviation in lung function from that found in healthy non-smoking members of the population. Means of *FEV* and *FVC* are significantly greater in males than in females, as are the variances of these two variables (table 3). The differences in standard deviations may reflect range and variance differences in height of the sexes. This seems likely, as after correction for age and height (*FEC*) the standard deviations are equal.

Table 3. Means and standard deviations of males and females. Significance of differences between sexes is indicated.

	Males (N=196)		Females (N=210)	
	Mean	SD	Mean	SD
FEV	4·77***	0·69*	3·46	0·57
FVC	5·63***	0·70*	4.00	0·61
FEC	−0·08***	0·19	−0·02	0·19

*0·01<*P*<0·05, **0·001<*P*<0·01, ***P<0·001.

Comparison of smokers and non-smokers

Twins were classified as smokers if they stated that they were a current cigarette smoker (there were no cigar or pipe smokers) or had only given up smoking since their last birthday. Consumption was rated as cigarettes smoked per day - 0 (none), 1(<10), 2(10–20), 3(20–40), 4(>40). Three smoking variables were considered: years smoked (*Y*), consumption rating (*C*) and their product (*YC*). The correlations between lung function and smoking variables are shown in table 4. Partial correlations controlling for age differed only trivially from these. Because *Y* and *C* are so highly correlated, entering both variables in a regression equation yields multiple correlations with lung-function variables scarcely any higher than the bivariate correlations tabled.

Table 4. Correlations between *FEV, FVC, FEC* corrected for height and age *(FEC)*, years smoked *(Y)*, cigarette consumption (*C*) and their product (*YC*).

	Females ($N=210$)					
	FEV	*FVC*	*FEC*	*Y*	*C*	*YC*
Males ($N=196$)						
FEV	—	0·79***	0·85***	−0·12*	−0·12*	−0·14*
FVC	0·76***	—	0·54***	−0·02	−0·02	−0·01
FEC	0·85***	0·58***	—	−0·11	−0·17**	−0·13*
Y	−0·13*	0·00	−0·08	—	0·79***	0·94***
C	−0·09	0·06	−0·12	0·78***	—	0·81***
YC	−0·15*	−0·01	−0·12	0·92***	0·84***	—

One-tailed significance tests: *$P<0·05$, **$P<0·01$, ***$P<0·001$.

Table 5. Means and standard deviations for *FEV* (age and height corrected) by cigarette consumption.

Cigarettes/ day	Females			Males		
	N	Mean	SD	*N*	Mean	SD
None	121	0·004	0·197	116	−0·063	0·164
<10	27	−0·033	0·149	18	−0·058	0·197
10–20	43	−0·072	0·200	45	−0·095	0·191
>20	19	−0·077	0·193	17	−0·158	0·318

Correlations between lung function and smoking are small in this age group and account for, at most, 3% of the variance in FEV, even after the removal of age and height effects. Nevertheless, of the 18 lung function–smoking correlations tabulated, 16 are negative and 7 of these are statistically significant. The trend for *FEC* to decrease with increasing consumption is illustrated in table 5, and it can be shown, for example, that based upon expected numbers from this table, the relative risk of a female having an *FEC* value in the bottom 5% of the sample, is more than double if she is a heavy smoker (rating 3) than if she is a non-smoker.

Alpha-1-antitrypsin and lung function

Table 6 gives FEC values for the various *Pi* phenotypes which were detected in our sample. *Pi* phenotypes have been divided into three groups on the basis of α_1-antitrypsin activity. One group contains several low-activity variants which individually are relatively rare (Cook 1974). The other two groups comprise subtypes of the M phenotype, all of which have α_1-antitrypsin activities in the normal range. However, the group of three M heterozygotes have higher means and lower variances than the group of three M homozygotes (Beckman and Beckman 1980).

In the following statistical tests on these data, the residual degrees of freedom have been taken as half those available if each individual is presumed to represent an independent observation. This adjustment on account of the genetic similarity of co-twins in fact provides conservative tests for any differences in *FEC* values, because dizygotic co-twins will on average only share genotypes identical by descent at half their loci.

The two sexes are not homogeneous in their distributions of FEC values across the

Table 6. Means and standard errors (with sample sizes in parentheses) for *FEC* in males and females of various *Pi* genotypes†.

	FEC ± SE			
Pi	Males		Females	
M subtype homozygotes				
M_1M_1	0·013 ± 0·022	(79)	−0·065 ± 0·022	(91)
M_2M_2	−0·055 ± 0·028	(5)	0·098 ± 0·137	(3)
M_3M_3	0·039 ± 0·084	(2)	—	
Mean	0·010 ± 0·020	(86)	−0·060 ± 0·022	(94)
M subtype heterozygotes				
M_1M_2	0·004 ± 0·034	(32)	0·058 ± 0·035	(30)
M_1M_3	0·009 ± 0·073	(5)	0·126	(1)
M_2M_3	−0·052 ± 0·036	(7)	0·165 ± 0·108	(2)
Mean	−0·004 ± 0·026	(44)	0·067 ± 0·032	(33)
Low-activity variants				
M_1S	−0·011 ± 0·061	(13)	−0·047 ± 0·036	(20)
M_2S	0·340 ± 0·028	(3)	−0·080 ± 0·099	(9)
M_1Z	0·138 ± 0·062	(4)	0·048 ± 0·046	(5)
M_2I	—		−0·051	(1)
SS	0·289	(1)	—	
SZ	−0·134 ± 0·034	(2)	—	
Mean	0·063 ± 0·046	(23)	−0·042 ± 0·033	(35)

†FEC for one M_1D male was +0·043. The α_1-antitrypsin activity of M_1D has not been reported.

three phenotypic classes ($F_{2,154} = 4{\cdot}31$, $P<0{\cdot}02$). There are significant differences between the groups in females ($F_{2,79} = 4{\cdot}84$, $P<0{\cdot}02$) but not in males ($F_{2,75} = 1{\cdot}01$, $P>0{\cdot}05$). In females the high-activity M heterozygotes have greater lung function than the other two groups and the *Pi* polymorphism accounts for approximately 9% of the total variance in lung function in females.

Genetic analysis

The repeatability for the lung-function measurements, expressed as intraclass correlation coefficients, represents the upper limit to any heritability estimate (Falconer 1981), since one minus this value is an estimate of the proportion of variation due to measurement error. There are no differences in the repeatabilities between sexes (table 7). The repeatability of *FVC* is marginally higher than that for *FEV*, but that for FEC is lower than *FEV*, which is what we should expect for a compound variable where errors are compounded.

The correlation of individual monozygotic pair absolute differences with their corresponding pair sums is now well established as a test for one class of systematic genotype × environment interactions (Jinks and Fulker 1970, Clark, Jardine, Martin, Stark and Walsh 1980, Clark, Jardine, Jones, Martin and Walsh 1981 a, Clark, Jardine, Martin, Stark and Walsh 1981 b). Such interactions may confound any model for the additive action of genetic and environmental effects but can usually be removed by transformation of the scale of measurement. This test was carried out on the lung function variables and, of six correlations calculated, the only significant interaction found was a correlation of −0·31 ($P<0{\cdot}05$) for *FEC* in monozygotic males. This would indicate that males with genotypes predisposing to low *FEC* values are most susceptible to environmental influences. The marginal significance of the interaction, however, does not justify transformation and experience indicates that this would rarely alter the results of model fitting (Martin and Eysenck 1976).

Table 7. Repeatabilities of lung-function measurements and their approximate standard errors.

	Females ($N=36$)	Males ($N=46$)
FEV	0·82 ± 0·06	0·83 ± 0·04
FVC	0·90 ± 0·04	0·90 ± 0·03
FEC	0·71 ± 0·08	0·70 ± 0·07

Table 8. Observed mean squares used for model fitting.

		Observed MS		
Statistic	d.f.	*FEV*	*FVC*	*FEC*
MZM_b	40	0·6256	0·7318	0·04063
MZM_w	41	0·1874	0·1512	0·01625
MZF_b	41	0·6112	0·7853	0·06444
MZF_w	42	0·0461	0·0806	0·00570
DZM_b	37	0·8404	0·6785	0·06897
DZM_w	38	0·3217	0·3172	0·02880
DZF_b	43	0·3601	0·4200	0·04413
DZF_w	44	0·2800	0·1364	0·02896
DZO_b	37	0·4572	0·5851	0·05283
DZO_w	37	0·2407	0·3717	0·02101

The relative importance of genetical and environmental factors on variation in lung function was estimated by fitting models by iterative weighted least-squares to between- and within-pairs mean squares from monozygotic and dizygotic twins (see Clarke *et al.* 1981 a, b). Mean squares and their degrees of freedom are given in table 8: the within-opposite sex pairs mean squares have been corrected for the mean sex difference and the corresponding degree of freedom removed.

Models fitted to the data include a source of individual environmental variance (E_1) which subsumes error variance. Models can also include sources of common environmental variance shared by co-twins but differing between pairs (E_2) or additive genetic variance (V_A) or both. The appropriateness of different models is tested by the chi-square criterion. A model is only elaborated if a simpler one fails or if a significant improvement in fit is achieved by adding a further parameter.

These analyses show that variation in lung-function variables can be explained by individual environmental and additive genetic variation, although the proportions are different in males and females for some variables. In none of these variables is it necessary to include family environmental variation. This is not to say that there are no E_2 influences, merely that they are not large enough to be detected against a background of predominantly E_1 and V_A variance.

The model fitted to all ten mean squares is shown in table 9 and includes a different individual environmental effect for males and females (E_{1_m} and E_{1_f}), different additive genetic effects for males and females (V_{A_m}) and V_{A_f}) and a parameter $V_{A_{mf}}$ which estimates the covariation of additive genetic effects acting on a trait in males and females (Eaves 1977, Clark *et al.* 1981 b). If the genetic effects acting in males are quite different from those acting in females then $\hat{V}_{A_{mf}}$ will be zero. If the genes acting in males and females are the same but produce scalar differences in the two sexes, then the correlation between the effects

Table 9. Model for the covariance of genetic and of environmental effects in mean squares of dizygotic opposite-sex twin pairs.

	E_{1_m}	E_{1_f}	V_{A_m}	V_{A_f}	$V_{A_{mf}}$
MZM					
between	1	·	2	·	·
within	1	·	·	·	·
MZF					
between	·	1	·	2	·
within	·	1	·	·	·
DZM					
between	1	·	$1\frac{1}{2}$	·	·
within	1	·	$\frac{1}{2}$	·	·
DZF					
between	·	1	·	$1\frac{1}{2}$	·
within	·	1	·	$\frac{1}{2}$	·
DZOS					
between	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
within	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$-\frac{1}{2}$

$V_{A_m} = V_A$ effect for males; $V_{A_f} = V_A$ effect for females; $V_{A_{mf}}$ = covariance of additive genetic effects in males and females. Similarly for E_1.

$$R_{V_A} = \frac{\hat{V}_{A_{mf}}}{\sqrt{\hat{V}_{A_m} \cdot \hat{V}_{A_f}}}$$

will be unity.

The estimates for the five parameters, and their significance are shown in table 10 for all three lung-function measures. All are highly significant. The value of $R_{V_{A_{mf}}}$ is also shown and is not significantly different from one for any variable; for *FVC*, it is not significantly different from zero either. The value of χ^2_5 (10 mean squares, 5 parameters estimated) assessing the fit of the model is given and an adequate fit is obtained in each case. Finally, the heritabilities and their standard errors are shown for males and females. Heritability is lower in males than in females for all three variables. In females they are of the same order as the repeatabilities (table 7), but in males, heritabilities are appreciably lower; this indicates that systematic environmental factors influence variation in lung function in males but not in females.

Table 10. Results of model fitting to lung-function data.

	FEV	*FVC*	*FEC*
$\hat{E}_{1_m}$	0·185***	0·154***	0·0169***
$\hat{E}_{1_f}$	0·050***	0·074***	0·0061***
$\hat{V}_{A_m}$	0·289***	0·343***	0·0218***
$\hat{V}_{A_f}$	0·290***	0·267***	0·0316***
$\hat{V}_{A_{mf}}$	0·290**	0·168	0·0338***
$\hat{R}_{V_{A_{mf}}}$	1·00	0·55	1·28
χ^2_5	9·47	5·87	8·21
h^2_m	0·61 ± 0·09	0·69 ± 0·07	0·56 ± 0·10
h^2_f	0·85 ± 0·04	0·78 ± 0·05	0·84 ± 0·04

**0·001<P<0·01, ***P<0·001.

4. Discussion

The main finding from this twin study is that genetic effects account for the major portion of variance in lung function both before and after associations with age and height have been taken into account. Our heritability estimates of lung function (0·56 – 0·69 in males, 0·78 – 0·85 in females) are similar to those obtained in other twin samples of sufficient size to obtain a reliable partitioning of variance. For example, a study of cardiovascular disease risk factors in 514 pairs of male twins aged 42–56 found a heritability of 0·74 for vital capacity and 0·50 for *FEV* (Feinleib *et al.* 1977). The similarity of the heritability and repeatability estimates in our sample of females implies that the only environmental effects on lung function are not repeatable between occasions and may be due to measurement error. In males, however, where heritability estimates are consistently lower than their corresponding repeatabilities, some systematic individual environmental effects (E_1) appear to be important. It is interesting that there is no evidence that family environmental effects (E_2) are important in either sex.

In the age range of our sample (18–34 years), effects of smoking on lung function can be detected but contribute, at most, 3% of the total variance in *FEV*. Since there is a genetic component of variance in cigarette consumption (J. D. Mathews, M. C. Hannah and N. G. Martin, in preparation), we cannot even assume that this 3% will all be detected as environmental variance. The small effect of smoking in our sample is not surprising, for in a study of more than 9000 cigarette smokers and 6000 ex-smokers living in Sydney and who attended a health screening clinic, a significant average decrement in lung function was only found in subjects in their late thirties and older (Gibson *et al.* 1979 c). Their study also showed that lung function in females was less affected by cigarette smoking than in males and this may contribute to the lack of evidence for an E_1 effect in the female twins. It may be that the amount and nature of exercise and other daily habits contribute to E_1 in male twins, but it is surprising that there is no evidence for such effects in females.

A relationship between a deficiency in the serum enzyme α_1-antitrypsin and obstructive lung disease (Eriksson 1965) is well documented (Kanner, Benzelti, Kaluber, Smith and Golden 1979) and similar associations have been found with other respiratory complaints, including the common cold (Martin, Oakeshott, Clark and Carr 1983). However, there has not been agreement about the relationship of enzyme activity or *Pi* phenotypes with lung function in healthy subjects. Our data show significant differences in *FEC* between α_1-antitrypsin-activity groups in healthy females, with the high-activity M heterozygotes having greater lung function than either the M homozygotes or the rarer low-activity phenotypes. However, we found no such differences in males. We estimate that about 9% of total variance, or 11% of the heritable variance in females, is attributable to polymorphism at the *Pi* locus.

In previous studies of *Pi* in relation to lung function, this effect could not have been found because M was not subtyped. Gulsvik and Fagerhol (1979) found no differences in spirometry (vital capacity, $FEV_{1\cdot0}$ and $FEV_{25\text{-}75\%}$) between *Pi* phenotypes M, MS and MZ in more than 1000 subjects aged 15–70 drawn from the population of Oslo. Other studies have shown small losses of elastic recoil and a decrease in maximal flow rates in MZ compared with M phenotypes (Hall, Hyde, Schwartz, Mudholkar, Webb, Chausey and Townes 1976, Larsson, Dirksen, Sundstrom and Eriksson 1976). Horne, Clarke and Barnett (1980) detected lower average values of $FEV_{1\cdot0}/FVC$ ratios and mid-maximum expiratory flow rates in MZ males in a sample of Saskatchewan grain buyers who had prolonged exposure to high

levels of grain dust. We have not been able to detect lower lung function in low enzyme activity phenotypes, but this may be because we have tested a relatively young sample compared with previous studies and because we excluded individuals with symptoms of respiratory disease.

The indication that α_1-antitrypsin-activity levels may be related to spirometry in symptomless subjects is intriguing, particularly in view of the low mean age of our twin sample. Overall, the data have shown that both polygenic and single locus genetic factors affect lung function in the Sydney population and that these must be taken into account, along with the effect of daily life habits, in any attempt to partition the phenotypic variation in relation to detected environmental heterogeneity in the region.

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Zusammenfassung. Eine Untersuchung der Lungenfunktion von 203 Zwillingspaaren in Sydney des Alters 18–34 Jahren entdeckte signifikante genetische Variation bei Frauen und Männern. Es gab keinen Hinweis auf familiäre Umweltwirkungen in einem Geschlecht, und der größte Anteil der wiederholbaren Variation bei Frauen war erblich. Es gab jedoch Hinweise auf systematische Umweltunterschiede zwischen Männern, die die Lungenfunktion dergestalt beeinflußten, daß die Heritabilität bei Männern (etwa 0·6) niedriger war als bei Frauen (etwa 0·8). Eine Auswirkung des Rauchens auf die Lungenfunktion wurde gefunden, was jedoch für weniger als 3% der Varianz verantwortlich war. Die Lungenfunktion bei Frauen war bei den Heterozygoten des Untertyps M des Lokus Pi größer als bei den M-Homozygoten oder bei anderen Pi-Phänotypen mit niedriger a_1-Antitrypsin-Aktivität. Der Pi-Polymorphismus erklärte etwa 9% der Gesamtvarianz der weiblichen Lungenfunktion. Bei Männern wurde keine Wirkung des Pi-Lokus gefunden.

Résumé. Une étude de la fonction pulmonaire chez 203 paires de jumeaux âgés de 18 à 34 ans vivant à Sydney a détecté une variation génétique significative chez les femmes et les hommes. Il n'y avait pas de signe d'effets de milieu familial dans aucun des sexes, et la plus grande part de la variation répétable chez les femmes était héritable. Cependant, il y avait une trace de différences systématiques de milieu entre hommes influant sur la fonction pulmonaire de sorte que l'héritabilité était plus basse chez l'homme (environ 0,6) que chez la femme (environ 0,8). Un effet de l'habitude de fumer sur la fonction pulmonaire a été détecté mais assumait moins de 3% de la variance. La fonction pulmonaire chez les femmes était plus élevée chez les hétérozygotes de sous-type M au locus *Pi* que chez les homozygotes de sous-types M ou chez les autres phénotypes *Pi* à activité faible d'α-$_1$-antitrypsine. Le polymorphisme *Pi* assumait environ 9% de la variance totale de la fonction pulmonaire féminine. Aucun effet du locus *Pi* n'a été trouvé chez les hommes.