# Occupational Exposure Risks in Individuals with PI*Z $\alpha_1$-Antitrypsin Deficiency

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**We obtained questionnaire and spirometry data from 128 $\alpha_1$-antitrypsin ($\alpha_1$AT)-deficient individuals with phenotype PI*Z to examine the relationship between chronic respiratory symptoms, airflow limitation, treatment requirements, and semiquantitative estimates of occupational exposure to dust, fumes, smoke, and gas. After adjusting for age, smoking, and prior lower respiratory tract infections, increased prevalence of chronic cough (OR = 4.69, 95% CI = 1.57–13.74, p = 0.006) and having left a job due to breathlessness (OR = 2.72, 95% CI = 1.07–6.92, p = 0.036) were seen in individuals reporting high mineral dust exposure compared with those with no exposure. Subjects reporting high mineral dust exposure also had significantly lower $FEV_1$ (31% predicted for high exposure versus 36% for low and 40% for unexposed, p = 0.032). The excess risk of chronic cough seen with occupational fumes or smoke exposure disappeared after adjusting for mineral dust exposure, but the association with lower $FEV_1$/FVC ratio persisted (p = 0.022). Personal tobacco use was a significant risk factor for most outcome measures, but no interaction with occupational exposure was seen. These results suggest that occupational inhalational exposures are independently associated with respiratory symptoms and airflow limitation in severely $\alpha_1$AT-deficient individuals.**

The contribution of occupational dust, fume, and gas inhalation to development of chronic respiratory symptoms and airflow limitation has been documented in cross-sectional studies in the general population (1, 2), occupational cross-sectional studies (3), occupational cohort studies (4–8), experimental studies (9), as well as rigorous reviews of the literature (10, 11). However, the occurrence and severity of chronic obstructive pulmonary disease (COPD) at a given level of exposure are far from uniform. Many individuals never develop lung disease despite breathing unclean air, whereas others become impaired with comparable levels of exposure. This supports the possibility of a combination of effects from both environmental exposures and genetic factors. From a clinical standpoint, it is difficult to know how to advise patients who are at risk for COPD about the potential effects of occupational exposures on their long-term health.

Individuals with severe $\alpha_1$-antitrypsin ($\alpha_1$AT) deficiency comprise one population known to be genetically susceptible to the development of emphysema, chronic bronchitis, airflow obstruction, and respiratory symptoms (12–17). Persons with phenotype Z (PI*Z) are either homozygous for the Z allele (PI*ZZ) or have one Z allele and have no second allele (Pi*NullZ) (12, 13). PI*Z individuals produce one-tenth of the normal amount of $\alpha_1$AT, which is approximately one-half of what is considered to be the minimum $\alpha_1$AT level required to prevent protease digestion of lung tissue (13, 14). Even among PI*Z individuals, the degree of clinical pulmonary impairment varies greatly (15–18), suggesting that environmental factors may also play a role.

Personal tobacco use is the major environmental risk factor for PI*Z individuals and is associated with younger age of symptom onset (15, 17, 19), greater chronic airflow obstruction (12, 15, 17, 19), increased rate of air flow decline over time (18, 20, 21), and shorter life expectancy (17, 19). Other factors may contribute risk to disease severity in PI*Z individuals, including history of prior lower respiratory tract infections (15, 16) and parental history of emphysema (13). In prior studies, when occupational exposure to dust, fumes, or gas was characterized by the answer to a single dichotomous question, no significant effects were found in two studies that enrolled both smoking and nonsmoking individuals (13, 16). However, in a large study of never-smokers, older males who reported dust, fume, and gas exposure were found to have more severe airflow obstruction (22). A second study in an overlapping cohort by these authors found increased prevalence of wheezing, dyspnea on exertion, and lower $FEV_1$ in never-smokers who had spent at least 10 yr in agricultural employment (27).

In the current cross-sectional study, we further define occupational exposures by using semiquantitative self-reported estimates of occupational and environmental exposure to specific types of dust, fumes, smoke, and gas to assess their relationship to the degree of airflow limitation, chronic respiratory symptoms, and treatment requirements in this genetically susceptible population.

## METHODS

### Study Subjects

The study protocol was approved by the National Jewish Medical and Research Center Human Subjects Institutional Review Board. Subsequently, data were collected from 128 PI*Z volunteers. Study subjects were recruited from two groups. Sixty-one volunteers were enrolled at the May 1998 $Alpha_1$ National Association meeting. One additional subject, too ill to attend the meeting, learned of the study and participated by mail. In addition, a list of 101 PI*Z individuals was supplied to us by the $\alpha_1$AT specialty clinic at National Jewish Medical and Research Center. After three separate mailings of the questionnaire, 66 agreed to participate. The overall participation rate for the two subgroups was 75%. Subjects' phenotypes were self-reported on the instrument described below. To maximize the number of subjects in this study, data from the two sources were combined.

We excluded persons who were less than 30 yr old or who reported having lung cancer. No one was found with the latter condition.

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### Questionnaire

The study instrument consisted of a 12-page, self-administered questionnaire. Demographic and medical information, frequency and amount of personal tobacco use, and occupational and environmental dust, fume, smoke, and gas exposures were obtained. Personal tobacco use was assessed by use of standard American Thoracic Society (ATS) questions (23), allowing us to determine ever-smoking status and lifetime cigarette consumption, in pack-years.

The exposure assessment portion of the questionnaire was designed specifically to obtain semiquantitative estimates of exposure to specific substance categories. Dust, fumes, smoke, gas, and water mist were divided into recognizable subcategories with examples of jobs or environments that typically involve each. Dust was subdivided into (*1*) biological dust (wood, textile, food, bird, animal, and plant) and (*2*) mineral dust (rock, construction, metal, ceramic/clay/chalk, asbestos/fibrous glass, dye, and pulverizing/mixing). Smoke was subdivided into diesel and fire/combustion products. Fumes refers specifically to metal fumes. The questionnaire stipulated that respondents consider only those exposures lasting an average of $\geqslant$ 20 h per week and present for at least 1 yr. Study subjects estimated the duration of each category of exposure in total years and the number of months per year of exposure. Additionally, they were asked to estimate the average amount of each reported exposure in the air immediately around them on a five-point Likert scale, ranging from "none" to "a lot." The respondents also listed the job or hobby that caused the exposure.

Self-reported exposures were examined in three ways. First, we dichotomized subjects into exposed and unexposed to (*1*) any biologic dust, (*2*) any mineral dust, (*3*) any fumes or smoke, (*4*) any gas, or (*5*) water mist. Other nonoccupational environmental exposures listed on the questionnaire were placed into a separate category. Second, we assessed the total number of years of exposure. The total number of years of exposure in each category was obtained by summing the reported years of exposure in each subcategory. Third, the amount of exposure reported on the Likert scale was divided into none, low, and high categories. None was defined as an answer of "no exposure" or a listing of the amount of exposure as "none." Low was defined by an answer of "a little bit" or "a moderate amount" and high by "quite a bit" or "a lot."

Outcome measures on the questionnaire included symptoms (chronic cough, wheeze, dyspnea, impairment of activities due to breathlessness, and having left a job due to breathlessness) and treatment requirements (daily medication use, regular oxygen use, need for surgery). Symptom questions (cough and wheeze) were modified from the ATS-DLD-78 questionnaire (23). Chronic cough was defined by cough four to six times per day or night, almost every day, or daily morning cough, which was present 3 or more mo per year. Wheeze was defined by "wheeze occasionally, apart from colds." Two modified dyspnea scales from the St. George's questionnaire were also used (24). Dyspnea was defined by "breathlessness walking outside, on level ground at your own pace." Impairment due to breathlessness was defined by a positive response of "It stops me from doing 1 or 2 things I would like to do" to the question "What important activities does breathlessness prevent you from doing?" Subjects were also asked if they had ever left a job because of shortness of breath. Daily medication use was defined by the use of prescription medications daily, or almost every day, for treatment of lung disease. Regular oxygen use was defined as having been prescribed oxygen for use with activities, at night, or continuously. History of surgical treatment included lung volume reduction or lung transplantation surgery. History of former and current $\alpha_1$AT augmentation therapy was obtained. Additional questions addressed episodes of bronchitis and pneumonia prior to the onset of symptoms and parental history of emphysema, defined as having at least one parent with a history of emphysema.

### Spirometry

$FEV_1$, as percent predicted, and $FEV_1$/FVC ratio were used as objective outcome measures. At the national meeting, spirometry was performed by a qualified NIOSH-certified technician, in accordance with the ATS guidelines (25). Each individual's percent of predicted was calculated based on his or her age, height, and sex (26). Several individuals at the conference and all of the participants by mail provided copies of their most recent spirometry results obtained at their physician's office or hospital. Spirometry was obtained, on average, within the same month as the questionnaire (range 0–22 mo, with only 9 being greater than 12 mo. Data older than 24 mo were not used). All spirometry reports were reviewed for quality and compliance with ATS criteria.

### Statistics

Statistical analyses were performed on a personal computer using JMP (version 3.2, SAS Institute Inc., Cary, NC) and SAS (version 6.12, SAS Institute Inc.). The distributions of all variables were examined for determination of normality, missing data, and outliers. We examined crude associations between exposure and the presence of symptoms or need for treatment by chi square or by Fisher's exact test. Odds ratios (ORs) and 95% confidence (CIs) were calculated for each. The population was stratified into ever-smokers and never-smokers. If the Breslow–Day Test of Homogeneity of ORs for the smoking strata was significant, the stratum-specific ORs were reported separately. Otherwise, the adjusted OR (Cochran–Mantel–Haenszel technique) was reported.

Logistic regression was used to quantify the relationship between the presence of symptoms and need for treatment and the number of years of exposure and amount of exposure in each exposure category. Multiple logistic models were then constructed using exposure variables found to have a p value less than 0.25 univariately. Each exposure variable was entered into a multiple regression model adjusting for age, pack-years of personal tobacco use, and history of prior lower respiratory tract infections. If colinearity between predictor variables was found, the variable with strongest statistical association was used in the multiple regression model. Confounding and effect modification were assessed. Hosmer–Lemeshow goodness of fit test was applied.

Finally, a best model was constructed using a backward stepping technique with age, pack-years personal tobacco use, history of prior lower respiratory tract infection, and mineral dust exposure forced into the model to find the strongest predictor of each outcome variable.

Similarly, linear regression analysis was performed for the $FEV_1$ and $FEV_1$/FVC ratio outcome variables. In addition, Wilcoxon rank sum test was used to determine if there was a difference in the distribution for these two pulmonary measures between the exposed and unexposed groups. This test was also used to look for a difference in the distribution of the total number of years of exposure and the presence of symptoms and the need for treatment.

All statistical tests were two sided and conducted at the 5% level of significance.

## RESULTS

### Demographics and Frequencies of Exposure

Fifty-five percent of the 128 participants were male. The mean age was 51.5 yr and did not differ significantly between males and females. Sixty-six percent of participants reported one or more exposures to occupational dust, fumes or smoke, mist, or gas. Forty-eight percent reported exposure to biologic dust, 49% to mineral dust, and 24% to fumes and/or smoke (Table 1). Many individuals, especially those in construction and farming trades, reported exposures in more than one category. Among the 49% who reported exposure to mineral dust, 73% also reported exposure to biological dust and 41% reported exposure to fumes and smoke. Coexposure to fumes and smoke was even higher (61%) in those individuals reporting high mineral dust exposure. In contrast, only 24% of individuals reporting high exposure to biological dust reported exposure to fumes or smoke. A list of the job titles reported with the heavy exposure to mineral dust is shown in Table 2. Exposures that were not included in the analysis (due to small numbers include gas [n = 6], water mist [n = 6], and other environmental, nonoccupational exposures [n = 13]). Seventy-six percent reported ever smoking cigarettes, pipes, or cigars. Only one individual was a current smoker at the time of the study. Seventeen individuals reported ever smoking pipes and five reported ever smoking cigars. All of the pipe and cigar smokers, except

one, also reported cigarette smoking. Thus, pack-years of smoking history were reported for cigarettes only.

All of the participants with less than a high school degree reported personal tobacco use. As we were unable to separate the effects due to smoking from those effects of education/socioeconomic status alone, education level was not included in further analyses. Similarly, sex was colinear with occupational exposures, with only five women reporting exposure to fumes and smoke and seven reporting high mineral dust exposure. Therefore, sex was not included in the multivariate analyses.

### Frequencies and Severity of Outcome Measures

Ten percent (n = 13) of the participants had undergone either lung volume reduction or transplantation surgery. Because most participants reported a change in symptoms after surgery, those individuals were not included in the symptom, treatment, or pulmonary function analyses. The small number precluded its use as an outcome measure of disease severity. As a whole, our study population was very symptomatic with significant airflow limitation and treatment requirements. Forty-three percent (n = 49) reported dyspnea, 85% (n = 98) reported impairment due to breathlessness, 43% (n = 50) reported chronic cough, 75% (n = 86) reported wheeze apart from colds, and 41% (n = 47) reported leaving a job due to breathlessness. Eighty-three percent (n = 95) reported daily medication use and 46% (n = 53) reported regular oxygen use. The median $FEV_1$ was 36% predicted (range 12–126) and the median $FEV_1$/FVC ratio was 36 (range 21–86).

### Relationship of Environmental and Occupational Exposure to Outcomes

*Exposed versus unexposed.* We observed a statistically significant crude association of both occupational mineral dust (OR = 2.74, 95% CI = 1.28–5.86) and fumes or smoke (OR = 2.59, 95% CI = 1.05–6.36) exposures and report of chronic cough. Personal tobacco use was not associated with cough (OR = 1.78, 95% CI = 0.74–4.43). Both occupational mineral dust (OR = 2.66, 95% CI = 1.29–5.52) and fumes or smoke (OR = 2.57, 95% CI = 1.12–5.86) exposures were also significantly associated with having had to leave a job due to breathlessness.

After adjusting for age, pack-years of personal tobacco use, and prior lower respiratory tract infections, occupational mineral dust exposure remained significantly associated with chronic cough (OR = 2.95, 95% CI = 1.28–6.81), but not having had to leave a job due to breathlessness (OR = 2.11, 95% CI = 0.97–4.61). Adjusted risk of chronic cough (2.95, 95% CI = 1.08–8.03) with fumes or smoke exposure did not remain significant after additional adjustment for mineral dust exposure. There was no interaction between the two occupational exposures.

Only fumes or smoke was associated with a significantly lower $FEV_1$/FVC ratio, with a median value of 33% in exposed versus 40% in those unexposed (p = 0.003). This association remained significant after adjustment for mineral dust exposure, personal tobacco use, and age (p = 0.022). Again, there was no interaction seen between the two exposures.

Personal tobacco use was significantly associated with the need for daily medications (OR = 2.88, 95% CI = 1.06–7.88), regular oxygen use (OR = 2.50, 95% CI = 1.03–6.09), and having left a job due to breathlessness (2.97, 95% CI = 1.17–7.53). Lower $FEV_1$ (32% predicted versus 56%, $p < 0.001$) and $FEV_1$/FVC ratio (34% versus 41%, p = 0.015) were seen in ever-smokers compared with never-smokers. We found no association between any of the outcome variables and history of parental emphysema, although wheeze achieved borderline significance (OR = 2.72, 95% CI = 0.97–7.60). History of prior lower respiratory infection was associated with chronic cough (OR = 2.52, 95% CI = 1.10–5.76) and wheeze (OR = 4.24, 95% CI = 1.64–10.97), which remained significant and of similar magnitude after adjustment for age, pack-years of personal tobacco use, and mineral dust exposure.

*Total years of exposure.* A significantly greater median number of years of mineral dust exposure was found among those reporting chronic cough (3.5 versus 0 yr, p = 0.015) and having left a job due to breathlessness (7.5 versus 0 yr, p = 0.001), but the difference did not remain significant after adjustment.

*Amount of exposure.* High occupational mineral dust exposure was strongly associated with the presence of chronic cough both before (OR = 4.20, 95% CI = 1.61–10.98) and after adjustment (OR = 4.61, 95% CI = 1.57–13.74) (Table 3). High mineral dust exposure was also associated with an increased crude risk of wheeze (OR = 4.72, 95% CI = 1.01–22.13), but was not significant after adjustment (OR = 4.43, 95% CI = 0.93–21.10). Due to full model instability, presence of wheeze was adjusted for age and pack-years of personal tobacco use only, without history of lower respiratory tract infection. Similarly, high mineral dust exposure was associated with an increased crude risk of having had to leave a job due to breathlessness both before (OR = 3.73, 95% CI = 1.55–8.97), and after adjustment (OR = 2.72, 95% CI = 1.07–6.92).

**TABLE 1**

**PERCENTAGE OF STUDY PARTICIPANTS REPORTING EXPOSURE, MEDIAN TOTAL NUMBER OF YEARS OF EXPOSURE, AND AMOUNT OF EXPOSURE***

| Exposure | Reporting Exposure n (%) | Median Total Years of Exposure (Range) | Amount of Exposure (%) | | |
|---|---|---|---|---|---|
| | | | None† | Low | High |
| Fumes/ smoke | 24 (31) | 0 (0–90)‡ | 75 | 13 | 12 |
| Biological dust | 48 (61) | 0 (0–48)‡ | 52 | 28 | 20 |
| Mineral dust | 49 (63) | 0 (0–135)‡ | 51 | 23 | 26 |
| Personal tobacco use | 76 (97) | 12 (0–62)§ | | | |

* Exposure categories are not mutually exclusive.

† Individuals who indicated exposures, but extimated the amount around them to be "none," are included in this group.

‡ Total years of exposure is the sum of the years reported in each subcategory of the exposure type.

§ In pack-years.

**TABLE 2**

**JOB TITLES REPORTED BY TWO OR MORE STUDY PARTICIPANTS REPORTING HEAVY MINERAL DUST EXPOSURE (n = 32)*†**

| Job Title | No. Reporting |
|---|---|
| Construction‡ | 13 |
| Farmer | 7 |
| Auto (brake) mechanic | 5 |
| Heavy equipment operator/road work | 4 |
| Printing press/linotype operator | 2 |
| Tool/metal grinder | 2 |
| Miner | 2 |
| Sandblaster | 2 |
| Teacher | 2 |
| Foundry worker/solderer | 2 |

* Job titles reported by one individual include painter, dental technician, fireman, warehouse worker, pharmaceutical production worker, fly ash salesman, baker, and office worker.

† Some individuals reported more than one job title.

‡ Includes cabinet maker, boat builder, pipe fitter, boilermaker, heating system installer, dry waller, roofer, electrician, and many also did some soldering or welding.

**TABLE 3**

**CRUDE AND ADJUSTED ODDS OF SYMPTOMS AND NEED FOR TREATMENT (WITH 95% CONFIDENCE INTERVALS) OF STUDY PARTICIPANTS REPORTING HIGH AMOUNTS OF EXPOSURE TO MINERAL DUST COMPARED WITH THOSE UNEXPOSED*,†**

| Symptom/Treatment Requirement | High Mineral Dust Exposure | |
|---|---|---|
| | Crude | Adjusted |
| Dyspnea | 1.13 (0.46–2.79) | 0.96 (0.35–2.59) |
| Cough | 4.20 (1.61–10.98)‡ | 4.84 (1.58–14.83)‡ |
| Wheeze§ | 4.72 (1.01–22.13)‡ | 4.43 (0.93–21.10) |
| Daily medication use | 0.85 (0.26–2.76) | 2.34 (0.46–11.81) |
| Regular oxygen use | 2.06 (0.82–5.22) | 1.94 (0.64–5.86) |
| Left job due to breathlessness | 3.73 (1.55–8.97)‡ | 2.72 (1.07–6.92)‡ |

* Because all individuals reporting high mineral dust exposure reported impairment of activities due to breathlessness, the logistic regression analysis yielded an infinite odds ratio.

† Results of subjects reporting low mineral dust exposure compared with unexposed are not shown as there were no significant differences.

‡ Indicates significance.

§ Model adjusted for age, pack-years, sex, and $\alpha_1$-antitrypsin augmentation therapy. History of lower respiratory tract infection was not included due to model instability.

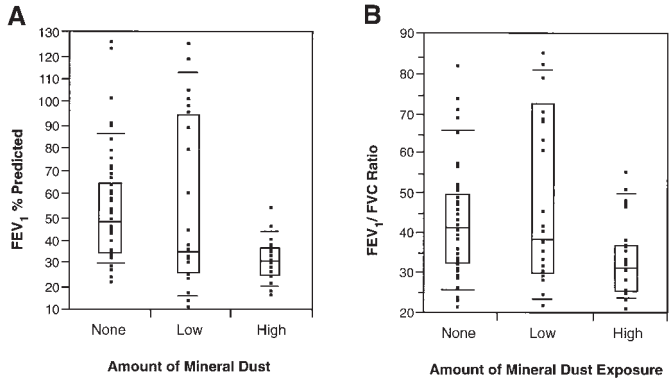


***Figure 1.*** Spirometric measurements and amount of mineral dust exposure. (*A*) Subjects reporting high mineral dust exposure had significantly lower $FEV_1$ (31% predicted for high exposure versus 36% for low and 40% for unexposed, $p = 0.032$) and (*B*) lower $FEV_1$/FVC ratio (31% versus 38% and 41%, respectively, $p = 0.007$).

As all individuals reporting high occupational mineral dust exposure also reported impairment of activities due to breathlessness, no odds ratio could be calculated.

High occupational exposure to mineral dust was associated with a significantly lower $FEV_1$ (31% predicted for high exposure versus 36% for low and 40% for unexposed, $p = 0.032$) and $FEV_1$/FVC ratio (31% versus 38% and 41%, respectively, $p = 0.007$) (Figure 1). No interaction was seen between personal tobacco use and mineral dust exposure. After adjusting for age and pack-years of smoking, $FEV_1$ was significantly lower in individuals with high mineral dust exposure ($p = 0.045$), although $FEV_1$/FVC ratio was not ($p = 0.085$).

We found no association between either total years or amount of biological dust or fumes or smoke exposure. Only three individuals were exposed to high amounts of fumes or smoke, which precluded that analysis.

### Final Multivariate Models

The final multivariate models yielded the single strongest predictor for each of the respiratory symptoms and treatment requirements (Table 4). High mineral dust exposure was the strongest predictor of both chronic cough and having left a job due to breathlessness. History of prior lower respiratory tract infections was the strongest predictor of wheeze. Pack-years of personal tobacco use was the strongest predictor of everything else. We observed a 6.5% decrease in $FEV_1$, percent predicted, for every 10 pack-years of personal tobacco use ($p < 0.001$) and a 2.3% decrease in $FEV_1$/FVC ratio for every 10 pack-years of tobacco use ($p = 0.029$). The effect of personal tobacco use was of similar magnitude both before and after adjustment.

## DISCUSSION

In this study, we have demonstrated for the first time that occupational exposure to mineral dust is independently associated with a dose-dependent increased prevalence of chronic cough, lower $FEV_1$, and lower $FEV_1$/FVC ratio in individuals with $\alpha_1$AT deficiency, phenotype PI*Z. Occupational inhalational exposure also affected quality of life, as measured by having had to leave a job due to breathlessness. Furthermore, we have confirmed and expanded the understanding of the effect of personal tobacco use as a risk factor. Importantly, occupational dust exposure and personal tobacco use contribute independently to the risk of developing more severe symptoms and airflow obstruction.

This study has confirmed that apart from the gene itself, tobacco smoking is still the major risk factor in individuals with PI*Z $\alpha_1$AT deficiency (12, 16–19). Consistent with those previous reports, lifetime history of personal tobacco use, measured in pack-years, was associated with significantly increased risk of dyspnea, impairment of activities due to breathlessness, and lower $FEV_1$ and $FEV_1$/FVC ratio. In addition, our study shows that personal tobacco use increases the

**TABLE 4**

**STRONGEST PREDICTOR FOR EACH SYMPTOM AND TREATMENT REQUIREMENT IN FINAL ADJUSTED MODEL***

| Symptom/Treatment Requirement | Strongest Predictor | Unit (*Pack-years*) | OR (95% CI) |
|---|---|---|---|
| Dyspnea | Personal tobacco use | 10 | 1.49 (1.05–2.11) |
| Impairment due to breathlessness | Personal tobacco use | 10 | 3.09 (1.25–7.68) |
| Cough | High mineral dust exposure | | 4.64 (1.57–13.74) |
| Wheeze | History of lower respiratory tract infection | | 4.16 (1.59–10.90) |
| Daily medication use | Personal tobacco use | 10 | 2.85 (1.34–6.06) |
| Regular oxygen use | Personal tobacco use | 10 | 1.79 (1.20–2.66) |
| Left job due to breathlessness | High mineral dust exposure | | 2.72 (1.07–6.92) |

*Definition of abbreviations*: CI = confidence interval; OR = odds ratio.

* Adjusted for age, pack-years of personal tobacco use, prior lower respiratory tract infection, and mineral dust exposure, except wheeze and impairment due to breathlessness, which were not adjusted for mineral dust due to fill model instability.

PI*Z individual's need for daily medication, regular oxygen supplementation, and likelihood to have left a job due to breathlessness.

This study also confirmed the association of prior lower respiratory tract infections with symptoms of cough and wheeze in patients with PI*Z $\alpha_1$AT deficiency (15, 16). We asked specifically about episodes of bronchitis or pneumonia occurring either in childhood and/or before the onset of regular problems with breathing. In a separate question, participants were asked about episodes of bronchitis or pneumonia occurring after the onset of regular problems with breathing. Thus, we are confident that our questionnaire captured information on the lower respiratory tract infections that preceded the development of chronic cough and wheeze. Ideally, a prospective study design would allow for differentiation between bronchitis and pneumonia to examine the individual contributions of these two clinical entities to disease severity.

Our findings on occupational exposure risks are compatible with a recent study of occupational exposures in 205 never-smoking PI*Z individuals from the Swedish registry (27), in which subjects with at least a 10 yr history of agricultural work were found to have an increased prevalence of wheeze and dyspnea on exertion. In addition, lower $FEV_1$ was found among the female agricultural workers. In general, the disease was less severe in the Swedish group compared with our U.S. cohort. In our study, chronic cough, with or without phlegm, was the strongest correlate of occupational exposure. We also found only a small, though consistent, crude association between the presence of chronic cough and having left a job due to breathlessness and the total number of years of mineral dust exposure. In contrast to the Swedish registry study, we arrived at the total number of years of exposure in each category by summing the number of years in each subcategory. Thus, for a small number of individuals, an impossibly high total number of years was calculated. However, the use of a nonparametric test of ranked values showed that the distribution of years of exposure was consistently higher in the symptomatic groups from beyond the 25th percentile, indicating the difference was not driven by a small number of outliers.

In our study, individuals with high mineral dust exposure as a whole reported high levels of exposure to not only several different types of mineral dust, but also to biological dust and fumes or smoke as well. Thus, high mineral dust exposure may be a surrogate measure of heavy inhalational exposure, rather than an effect unique to mineral dust. The importance of the amount of respirable-size dust (2.5 μm or smaller) has been emphasized (28, 29) as this is the fraction of the exposure that reaches the lower airways, effectively forming the "dose." The amount of respirable dust generated is dictated in large part by the specific activity performed on the job. Self-reported and retrospectively collected data on the "amount of dust in the air right around you" must be considered only a fair surrogate for the actual amount of respirable dust exposure. Although the potential for misclassification of exposure certainly exists, the increased strength of association seen using this crude, self-reported scale of exposure supports its validity.

Unlike previous studies (1, 2, 27), we found no association between occupational exposures and symptoms of dyspnea (measured by presence of breathlessness when walking on the level ground at one's own pace and impairment of activities due to breathlessness). This may be due to our narrow definition of dyspnea. Impairment due to breathlessness was associated with personal tobacco use, a known major risk factor, but only when measured as a continuous variable in pack-years. Dyspnea was also associated with pack-years of smoking, although the effect was small. A smaller effect due to occupational exposures may not have been seen due to a lack of power with the small sample size.

As in any study of this design, selection bias may have affected our results. Study participants were identified through their attending a national educational meeting and through a specialty clinic for $\alpha_1$AT-associated lung disease. Our study population as a whole was highly symptomatic with significant airflow limitation and treatment requirements. The median $FEV_1$ in nonsmokers in our study was 56% predicted, as compared with 84% (22) and 86% (27) in the Swedish registry studies where a large number of participants were identified through other $\alpha_1$AT-associated diseases and familial screening. Our population may have another unidentified genetic or environmental risk factor contributing to the development of chronic respiratory symptoms and airflow limitation. Conversely, there is some risk of survivorship bias, as individuals must have been in adequate health to participate. Additional selection bias may have come from our letter of invitation. We tried to minimize this by specifically asking those without exposures and/or symptoms to participate and by asking questions about exposures before those about symptoms on the questionnaire. In addition, we may have some bias due to the "healthy worker effect," such that those PI*Z individuals able to remain in the workforce may, for some reason, be more healthy. Symptomatic individuals may have chosen to avoid or limit their exposure to occupational dust, fumes, and smoke. Our intent was to capture intolerance of dusty environments through having to leave a job due to breathlessness. It is possible that physical labor demands also played a role.

As described above, we relied on self-reported exposures. It is unknown if any subset of our study subjects systematically differed in their recall of past occupational exposures. A further limitation of our study pertains to sample size. Some exposures and outcomes were reported at low frequencies that precluded their analysis. Further studies using a larger sample size should allow for further differentiation between categories of occupational exposures and examination of some of the less common exposures. Ideally, this larger study would also include a greater proportion of asymptomatic individuals.

Our findings confirm a link between occupational inhalational exposures and chronic respiratory symptoms and airflow limitation in PI*Z $\alpha_1$AT deficiency, independent of the other established risk factors. Although it can be argued that our very symptomatic study population represents a highly susceptible subgroup of PI*Z individuals, consistent findings in the much less symptomatic Swedish registry population (22, 27), argue for a real risk to a sizable proportion of PI*Z individuals. Therefore, it is important to consider the potential clinical implications of occupation for the health of PI*Z individuals. PI*Z individuals should receive counseling about the potential detrimental effects of occupational inhalational exposures on their long-term health. They may choose to avoid occupations/job duties with heavy exposure or to work with employers to protect them from high levels of exposure. They should, of course, also be counseled to not smoke tobacco products. Both occupational inhalational exposures and personal tobacco use are potentially preventable causes of lung function decline and chronic symptoms.

In general population-based screening studies, the prevalence of the *Z* gene is highly variable. The frequency of the PI*Z phenotype is estimated to range from 1 in 3,000 to 1 in 5,000 in the United States (30–33). Based on a U.S. civilian labor force of 138 million workers (34) and a conservative prevalence figure of 1 in 5,000, we estimate that over 27,000 U.S. workers are potentially PI*Z. In addition, the risk to workers with heterozygous $\alpha_1$AT deficiency phenotypes (35, 36) and to

those with other as yet unidentified genetic susceptibility factors is not known. Because we cannot identify all workers who are genetically susceptible to the development of COPD, this is yet another reason to protect the breathing zone of all workers from high levels of dust, fumes, and smoke.

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