

# Risk factors for symptom onset in PI\*Z alpha-1 antitrypsin deficiency

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**Background:** In an early study of highly symptomatic patients with PI\*Z alpha-1 antitrypsin deficiency (AAT), tobacco smoking was identified as a risk factor by comparing the age of symptom onset in smokers and nonsmokers. Age of symptom onset has not been well studied in relationship to other environmental exposures.

**Methods:** Environmental exposures were assessed in 313 PI\*Z adults through retrospective self-administered questionnaire. Age of onset of symptoms with and without these exposures were analyzed through survival analysis.

**Results:** Personal smoking was the most important risk factor, associated with earlier onset of cough and wheeze, and showed a dose-dependent relationship with the onset of dyspnea. Childhood environmental tobacco smoke (ETS) exposure was independently associated with younger age of onset of cough. Earlier onset of wheeze was also associated with childhood respiratory infections and family history of emphysema. The report of childhood respiratory infections was associated with childhood ETS exposure, but no statistically significant interactions were noted.

**Conclusions:** We conclude that both personal and secondhand exposure to tobacco smoke in childhood are likely to accelerate the onset of symptoms in AAT deficient patients. Respiratory infections in childhood may also contribute to this risk.

**Keywords:** alpha-1 antitrypsin deficiency, tobacco smoke pollution, respiratory symptoms, lower respiratory illness.

## Introduction

PI\*Z individuals have a severe deficiency of alpha-1 antitrypsin (AAT) and are genetically susceptible to developing chronic obstructive pulmonary disease (COPD) (Black and Kueppers 1978; Larsson, 1978; Tobin et al 1983; Janus et al 1985; Brantly et al 1988; Silverman et al 1989) particularly with personal tobacco use (Larsson 1978; Tobin et al 1983; Janus et al 1985; Brantly et al 1988; Silverman et al 1989). Other reported risk factors include occupational exposures (Piitulainen et al 1997, 1998; Mayer et al 2000b), lower respiratory tract infections (Brantly et al 1988; Silverman et al 1989), and family history of emphysema (Silverman et al 1989). In an early study of highly symptomatic PI\*Z patients, tobacco smoking was identified as a risk factor by comparing the age of symptom onset in smokers and nonsmokers (Larsson 1978). Age of symptom onset has not been well studied in relationship to other exposures.

Childhood environmental tobacco smoke (ETS) exposure has been associated with increased frequency and severity of respiratory infections (Colley et al 1974; Ware et al 1984; Fergusson and Horwood 1985; Tager et al 1993; Chen 1994; Strachan and Cook 1997), respiratory symptoms (Cunningham et al 1996; Ehrlich et al 1996; Jaakkola et al 1996; Withers et al 1998), and diminished airflow (Ware et al 1984; Tager et al 1993) in the general population. A prospective study of PI\*Z children found a greater prevalence of recurrent wheezing at 4 years of age in those with two smoking

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parents. Lower forced expiratory volume in one second [FEV<sub>1</sub>]/forced vital capacity [FVC] ratio was found in that group at 18 years, although no difference in FEV<sub>1</sub> or wheeze was seen (Piitulainen and Sveger 1998). Childhood lower respiratory infections have been associated with respiratory symptoms (Gold et al 1989) and airflow limitation (Gold et al 1989; Shaheen et al 1994; Johnston et al 1998) in the general population. An interaction between the effects of ETS exposure and respiratory infections has been postulated (Gold et al 1989; Strachan and Cook 1997).

We systematically surveyed 313 PI\*Z individuals to examine the relationships of personal tobacco use, childhood ETS exposure, and respiratory infections to age of symptom onset.

## Methods

### Study subjects

The study protocol was approved by the Human Subjects Institutional Review Board of the National Jewish Medical and Research Center. A total of 329 subjects self-reporting PI\*Z phenotype were recruited from four sources. Sixty-two were recruited through a national educational meeting on AAT deficiency (Group 1), 94 from two different outpatient clinics specializing in AAT deficiency (Groups 2 and 3), and 173 through mailings sent out through a national AAT registry (Group 4). The participation rate was 75% in the first two groups. To maintain confidentiality, individuals in Groups 3 and 4 were invited to participate by the other clinic and by the registry themselves, respectively. We do not know how many of these individuals in these two groups chose not to participate. Exclusion criteria were age less than 30 years and diagnosis of lung cancer.

### Survey instrument

The study instrument was a self-administered questionnaire designed for a larger study on occupational and environmental exposures (Mayer et al 2000b). Childhood ETS was assessed by the question "Did you live or work with someone who smoked every day during childhood (age 0–18 years)", and if so, "For how many years" and "Year of last exposure". Participants were considered to have had childhood ETS exposure if they reported 12 or more years of exposure and/or we could verify that they were exposed for the first 6 years of life by comparing the year of birth and the year of last exposure. Personal tobacco use was assessed through standardized American Thoracic Society (ATS) questions (Davis et al 1978). The number of pack-years smoked before

the development of each symptom was calculated. If the individual never developed the symptom, the lifetime number of pack-years was used. Those who reported an age of beginning smoking after the reported age of symptom development were considered to have smoked 0 pack-years, as were the never-smokers. Smokers were grouped by number of pack-years smoked before the development of each symptom: 1–10, 11–20, 21–30, and greater than 30 pack-years. Those with 0 pack-years served as the referent group. Childhood respiratory infection was defined as either pneumonia or recurrent episodes of bronchitis reported in childhood. Family history of emphysema was determined by indication that at least one parent had emphysema.

Symptoms of cough and wheeze were based on questions modified from the ATS-DLD-78 questionnaire (Davis et al 1978). Chronic cough was defined as cough 4–6 times per day or night almost every day, or daily morning cough present 3 or more months per year. Wheeze was defined as "wheeze occasionally, apart from colds." A dyspnea scale modified from the St. George's questionnaire (Jones et al 1992) was used to assess current dyspnea, defined as "breathlessness walking outside, on level ground at your own pace." Age of symptom onset was assessed in individuals with current symptoms through the question: "How old were you when you first started to notice (this symptom) on a regular basis?"

### Statistics

Survival analyses were performed using Cox proportional hazards modeling (Elashoff 1983). The hazard rate may be thought of as the instantaneous odds of developing the symptom at a given age for those individuals who have not developed that symptom before that age. The hazard ratio (HR) is the hazard rate for those in the risk group divided by the hazard rate for those not in the risk group. A separate Cox model was created for outcomes of cough, wheeze, and dyspnea onset. Models were created using only one predictor variable at a time, as well as multivariable modeling of the predictor variables of pack-years of smoking before the development of each symptom, childhood ETS, childhood respiratory infections, and family history of emphysema. Three sets of interaction were also examined in these models. First, exposure variable by age of onset of symptom interactions were included to test for the proportional hazards assumption, ie, that the HR does not vary by age of symptom onset. Plots of differences in log cumulative hazard rates for the exposure group versus age of onset of symptom were also examined to determine if simple interaction terms were adequate to account

for nonproportional hazards. Second, group by exposure variables were included to test for heterogeneity between sampling groups. None of these group interaction terms were significant. Third, exposure interactions were also examined. The main interaction of interest here was between ETS and respiratory infections, controlled for personal smoking. Interactions between personal smoking and respiratory infections, ETS and personal smoking, ETS and family history, and family history and personal smoking were also examined. None of these interactions reached a significance level of  $<0.1$  in the final model, so results are not presented here.

Odds ratios of current symptoms and of respiratory infections given childhood ETS exposure were estimated using logistic regression techniques and chi-square test. Spearman correlation coefficients were used to assess the association between the ages of onset of cough, wheeze, and dyspnea. Differences between groups were assessed by ANOVA. All statistical tests were two-sided and were considered statistically significant at the 5% level. Statistical analyses were performed using JMP (version 3.2, SAS Institute Inc., Cary, NC) and SAS (version 6.12, SAS Institute Inc.).

## Results

### Demographics and prevalence of exposure

The mean age of the participants was 52.9 years and 54% were male. Seventy-one percent ( $n = 223$ ) reported childhood ETS exposure (Table 1). Sixteen individuals were excluded from the analysis due to uncertainty of ETS exposure. Seventy-four

percent of subjects reported they had smoked cigarettes, pipes, or cigars. Only two individuals continued to smoke. Forty-two percent of subjects reported having had recurrent bronchitis and/or pneumonia in childhood. The effects of education and smoking could not be separated, as all of the participants with less than a high school degree were ever-smokers.

Baseline characteristics of the participants in the four recruitment groups are shown in Table 2.

We compared the prevalence of exposure and outcome measures between the four groups. There were no significant differences, other than participants from Group 1 tended to report an earlier age of onset of symptoms, and this was statistically significant for cough, although Group 1 did not report more current symptoms. PI\*Z phenotype was self-reported. The phenotype was verified in 89 of the 128 participants of Groups 1 and 2 (70%). All verified individuals were PI\*Z, except for one PI\*SZ individual.

Individuals with childhood ETS exposure differed in their personal tobacco use from those without ETS exposure (Table 1). Those who were exposed to childhood ETS were more likely to become smokers themselves (77% vs 66%,  $p = 0.031$ ). They were also more likely to begin smoking at an earlier age (16.6 years vs 18.4,  $p < 0.001$ ). There was no difference in the intensity of smoking (19.4 vs 18.7 cigarettes per day,  $p = 0.279$ ).

### Age of onset of symptoms

Our study population was relatively symptomatic with 47% reporting chronic cough, 69% reporting wheeze, and 49%

**Table 1** Baseline characteristics of 313 individuals with PI\*Z alpha-1 antitrypsin deficiency according to presence or absence of childhood ETS exposure

Variable	With childhood ETS exposure (n = 223)	Without childhood ETS (n = 90)	p-value
Age (mean years $\pm$ SD)	52 $\pm$ 10	55 $\pm$ 11	0.057
Gender (male)	53%	61%	0.185
<b>Ever smokers</b>	<b>77%</b>	<b>66%</b>	<b>0.031</b>
Mean number of cigarettes smoked per day (in ever smokers)	19.4 $\pm$ 8.7	18.7 $\pm$ 9.4	0.617
<b>Mean age of beginning smoking</b> (mean years $\pm$ SD)	<b>16.6 <math>\pm</math> 0.3</b>	<b>18.4 <math>\pm</math> 0.5</b>	<b>&lt;0.001</b>
History of prior lower respiratory tract infection	41%	44%	0.634
<b>Family history of emphysema</b>	<b>49%</b>	<b>23%</b>	<b>&lt;0.001</b>
Chronic cough	50%	39%	0.081
Chronic wheeze	71%	66%	0.361
Chronic dyspnea	50%	47%	0.618

**Abbreviations:** ETS, environmental tobacco smoke; SD, standard deviation.

**Note:** **Bold** indicates statistical significance.

**Table 2** Baseline characteristics of 313 individuals with PI\*Z alpha-1 antitrypsin deficiency by recruitment group

Comparison of characteristics between groups	Group 1	Group 2	Group 3	Group 4	p-value
Age (mean years $\pm$ SD)	51.4 $\pm$ 9.4	51.4 $\pm$ 1.26	53.4 $\pm$ 12.0	53.9 $\pm$ 10.5	0.232
Gender (male)	56%	54%	50%	54%	0.956
Ever smokers	80%	69%	65%	74%	0.362
Mean number of cigarettes smoked per day (in ever smokers)	19.9 $\pm$ 10.1	17.4 $\pm$ 7.9	18.8 $\pm$ 10.5	19.8 $\pm$ 8.4	0.441
Mean age of beginning smoking (mean years $\pm$ SD)	17.1 $\pm$ 3.1	17.3 $\pm$ 2.8	16.9 $\pm$ 2.8	17.1 $\pm$ 3.8	0.976
Childhood ETS exposure	69%	69%	75%	72%	0.903
History of prior lower respiratory tract infection	54%	38%	31%	41%	0.206
Family history of emphysema	35%	48%	26%	40%	0.283
Chronic cough	59%	56%	50%	50%	0.609
Chronic wheeze	74%	68%	73%	67%	0.716
Chronic dyspnea	53%	62%	42%	53%	0.151
Mean age of onset of cough	32.6 $\pm$ 11.8	35.1 $\pm$ 14.9	41.0 $\pm$ 13.7	39.7 $\pm$ 14.6	<b>0.039</b>
Mean age of onset of wheeze	36.4 $\pm$ 12.8	39.0 $\pm$ 13.6	39.7 $\pm$ 20.1	40.6 $\pm$ 14.5	0.388
Mean age of onset of dyspnea	37.2 $\pm$ 10.4	39.2 $\pm$ 12.6	41.4 $\pm$ 15.1	42.2 $\pm$ 12.6	0.061

**Abbreviations:** ETS, environmental tobacco smoke; SD, standard deviation.

**Note:** **Bold** indicates statistical significance.

reporting dyspnea. In those who reported current symptoms, the mean age of onset of cough was 37 years, 39 years for wheeze, and 41 years for dyspnea. Ages of symptom onset were highly correlated (all  $p < 0.05$ ):  $r = 0.79$  for wheeze and dyspnea,  $r = 0.71$  for cough and breathlessness, and  $r = 0.69$  for cough and wheeze. In those who developed a symptom, the mean age of onset was 11 years earlier in smokers for cough (35 years  $\pm$  13 vs 46  $\pm$  17,  $p < 0.001$ ), 5 years earlier for wheeze (38 years  $\pm$  12 vs 43  $\pm$  20,  $p = 0.041$ ), and eight years earlier for dyspnea (39 years  $\pm$  10 vs 47  $\pm$  17,  $p < 0.001$ ) with greater variability seen in the never smokers (Table 3). Only onset of cough was earlier in the never-smokers with ETS exposure. Childhood respiratory infections were significantly associated with earlier onset of all symptoms in both

never-smokers and smokers. The odds of currently having each symptom by exposure are shown in Table 4. Results of the Cox proportional hazards modeling for developing symptoms are shown in Table 5.

The onset of cough and wheeze was earlier in smokers compared with never-smokers, with the greatest effect seen in those smoking 1 to 10 pack-years (HR = 2.16, 95% confidence interval [CI] = 1.18–3.96) and (HR = 1.90; 95% CI = 1.10–3.30) respectively. Earlier onset of dyspnea was seen in those smoking more than 10 pack-years with the greatest risk between 20–30 pack-years (HR = 2.71; 95% CI = 1.48–4.97). Family history of emphysema was associated with earlier onset of wheeze (HR = 1.72; 95% CI = 1.20–2.47), but did not remain significant in the final model for cough or dyspnea.

**Table 3** Mean age of symptom onset for childhood ETS exposure, childhood lower respiratory infections, personal smoking, and family history of emphysema

Mean age of onset of symptom $\pm$ SD (p-value)	Cough		Wheeze		Dyspnea	
	Smoker	Never smoker	Smoker	Never smoker	Smoker	Never smoker
Smoking status alone	<b>46 <math>\pm</math> 17</b>	<b>36 <math>\pm</math> 13</b> ( <b>&lt;0.001</b> )	<b>43 <math>\pm</math> 20</b>	<b>38 <math>\pm</math> 12</b> ( <b>0.041</b> )	<b>47 <math>\pm</math> 17</b>	<b>39 <math>\pm</math> 10</b> ( <b>&lt;0.001</b> )
With/without childhood ETS	<b>42/53 <math>\pm</math> 15/11</b> ( <b>0.043</b> )	34/39 $\pm$ 12/14 (0.061)	42/44 $\pm$ 19/20 (0.827)	<b>37/42 <math>\pm</math> 12/12</b> ( <b>0.003</b> )	47/47 $\pm$ 18/16 (0.940)	<b>37/43 <math>\pm</math> 10/9</b> ( <b>0.001</b> )
With/without childhood respiratory infections	<b>36/49 <math>\pm</math> 19/13</b> ( <b>0.011</b> )	<b>32/37 <math>\pm</math> 11/13</b> ( <b>0.040</b> )	<b>35/40 <math>\pm</math> 14/11</b> ( <b>0.018</b> )	<b>32/38 <math>\pm</math> 23/17</b> ( <b>0.018</b> )	<b>39/49 <math>\pm</math> 21/14</b> ( <b>0.013</b> )	<b>36/39 <math>\pm</math> 10/9</b> ( <b>0.045</b> )
With/without family history	44/49 $\pm$ 17/16 (0.386)	33/37 $\pm$ 12/12 (0.049)	41/43 $\pm$ 18/23 (0.731)	36/39 $\pm$ 12/12 (0.058)	45/48 $\pm$ 9/10 (0.808)	38/40 $\pm$ 10/9 (0.137)

**Abbreviations:** ETS, environmental tobacco smoke; SD, standard deviation.

**Note:** **Bold** indicates statistical significance.

**Table 4** Odds ratios of current symptoms for childhood ETS exposure, childhood lower respiratory infections, personal smoking, and family history of emphysema

Symptom	Childhood ETS	Ever Smoker	Childhood respiratory infections	Family history of emphysema
Cough	1.56 (0.94–2.57)	<b>1.78 (1.18–2.94)</b>	1.12 (0.67–1.84)	1.00 (0.62–1.61)
Wheeze	1.28 (0.76–2.15)	<b>2.64 (1.59–4.41)</b>	<b>2.05 (1.21–3.51)</b>	<b>2.03 (1.11–3.21)</b>
Dyspnea	1.13 (0.69–1.85)	<b>2.28 (1.37–3.79)</b>	<b>1.63 (1.00–2.66)</b>	1.03 (0.60–1.49)

**Abbreviations:** ETS, environmental tobacco smoke.

**Note:** **Bold** indicates statistical significance.

In crude analyses, those with childhood ETS exposure had earlier onset of cough in a nonproportional manner, such that the increased risk seen age at 20 (HR = 2.78,  $p = 0.012$ ) gradually diminished by age 45 compared with those without childhood ETS. Earlier onset of wheeze was of borderline significance (HR = 1.34;  $p = 0.058$ ). No increased risk was seen for dyspnea (HR = 1.38,  $p = 0.077$ ). In the Cox proportional hazards model, ETS continued to be associated with earlier age of onset of cough only (HR = 2.11; 95% CI 1.18–3.76). All of the crude analyses for childhood respiratory infections were nonproportional. Risk of earlier onset of cough (HR = 1.98,  $p = 0.024$  at age 20) diminished by age 35, wheeze (HR = 2.67,  $p = 0.001$  at age 20) diminished by age 45, and dyspnea (HR = 2.83,  $p = 0.016$  at age 20) diminished by age 40. In the Cox proportional hazards model, childhood respiratory infections continued to be associated only with earlier onset of wheeze (HR = 1.49; 95% CI = 1.05–2.11.)

Those with childhood ETS exposure were more likely to report respiratory infections in childhood (HR = 1.57; 95% CI = 1.00–4.45). In the Cox proportional hazards modeling, there were no significant interactions between childhood ETS exposure and respiratory infections on age of symptom onset; the largest (HR = 1.96, 95% CI = 0.80–4.83) was seen for onset of dyspnea.

## Discussion

In this study, we found that childhood ETS exposure was associated with earlier onset of cough in individuals with PI\*Z AAT deficiency. Childhood respiratory infections and family history were associated with earlier onset of wheeze. Among those with symptoms, childhood respiratory infections were associated with earlier onset of all symptoms in both smokers and never-smokers. With personal smoking, increased risk of onset of cough and wheeze was noted within the first 10 pack-years. Earlier onset of dyspnea was seen after 10 pack-years with a dose-dependent increased risk up to 30 pack-years.

In an earlier analysis of Groups 1 and 2, we had found a statistically significant association between childhood ETS exposure and earlier age of onset of cough, wheeze, and dyspnea, adjusted for personal smoking, dichotomized as ever- or never-smoker (Mayer et al 2000a). The main reason for recruiting additional subjects for this second study was to increase sample size. We also realized that we had the ability to calculate the number of pack-years smoked before the age on onset of symptoms, thus giving a better measure of the “dose” of personal smoking. We had previously analyzed earlier age of beginning personal smoking in Groups 1 and 2, but we did not find this to be a better or additive predictor. Although there was no overall difference in the number of cigarettes smoked per day between those with and without

**Table 5** Adjusted hazard ratios for the development of symptoms for childhood ETS exposure, childhood lower respiratory infections, pack-years of smoking before onset of symptoms, and family history of emphysema

Risk factor	Cough	Wheeze	Dyspnea
Childhood ETS	<b>2.11 (1.18–3.76)</b>	1.26 (0.83–1.92)	1.00 (0.62–1.59)
Pack-years: 1–10	<b>2.16 (1.18–3.96)</b>	<b>1.90 (1.10–3.30)</b>	1.29 (0.63–2.60)
Pack-years: 11–20	1.00 (0.50–2.00)	1.51 (0.91–2.49)	<b>2.35 (1.34–4.12)</b>
Pack-years: 21–30	1.19 (0.63–2.24)	1.61 (0.98–2.65)	<b>2.71 (1.48–4.97)</b>
Pack-years: >30	1.23 (0.58–2.61)	1.15 (0.62–2.13)	<b>2.20 (1.14–4.21)</b>
Family history	1.26 (0.81–1.98)	<b>1.72 (1.20–2.47)</b>	1.30 (0.85–2.15)
Childhood respiratory infections	1.30 (0.84–1.99)	<b>1.49 (1.05–2.11)</b>	1.45 (0.97–1.98)

**Abbreviations:** ETS, environmental tobacco smoke.

**Note:** **Bold** indicates statistical significance.



childhood ETS, it is possible that these who began smoking earlier also smoked more intensely. A post-hoc analysis revealed this trend ( $p = 0.079$ ). We continued to see a greater association between childhood ETS and age of onset of wheeze and breathlessness in Groups 1 and 2 than in Groups 3 and 4, albeit of borderline significance. It is possible that the earlier reported age of onset of cough and breathlessness could have been contributory, but our analyses for heterogeneity did not reveal any statistically significant differences between the groups.

No statistically significant interactive effect on age of symptom onset was observed between the occurrence of childhood respiratory infections and ETS exposure. It is possible that the sample size conferred inadequate power to detect such an interaction. While we were able to identify those with ETS exposure in early childhood, we lacked information regarding the age at which lower respiratory tract infections occurred, precluding us from confirming other observations (Colley et al 1974; Ware et al 1984; Fergusson and Horwood 1985) that childhood ETS exposure predisposes to infections during the first few years of life. The questionnaire did not distinguish between prenatal, postnatal maternal, or paternal smoking. There remains considerable controversy regarding the relative risk conferred by these different exposure sources (Ware et al 1984; Fergusson and Horwood 1985; Tager et al 1993; Chen 1994; Strachan and Cook 1997). Because of our relatively small sample size, we combined bronchitis and pneumonia in childhood, but these may confer differential risk. As individuals reporting ETS exposure were more likely to also report previous lower respiratory tract infections, these risk factors would be additive in those individuals.

Experimentally, it takes time for the AAT deficiency-associated pulmonary parenchymal destruction to occur (Karlinsky and Snider 1978), which is supported by the observation in epidemiologic studies that few individuals develop symptoms before age 25 (Larsson 1978; Brantly et al 1988; Silverman et al 1989). It is possible that our study participants with current chronic symptoms may have reported respiratory symptoms in childhood that had nothing to do with their genetic disease. Even if they had, a serious detriment to quality of life is posed by the presence of respiratory symptoms during childhood and teenage years in a population at increased risk for an adult life with chronic progressive pulmonary problems.

While we examined the effects of prior respiratory infections and personal tobacco use, there may have been

additional effects from other unmeasured exposures or host factors. For example, increased risk of airflow limitation and chronic bronchitis has been found in smoking first-degree relatives of individuals with severe COPD without AAT deficiency (Silverman et al 1998).

Misclassification and recall bias may have affected our results. It is possible that subjects reporting childhood ETS exposure may have been more likely to recall symptoms and to ascribe them to an earlier age. However, the 6% of subjects reporting dyspnea before age 20 in this series is similar to the 7% with symptoms before age 20 in the study by Brantly and colleagues (1988), but less than the 18% reporting lung trouble before age 16 in the series by Silverman and colleagues (1989), making it less likely that our subjects significantly underestimated their age of onset of symptoms. We may have missed significant childhood ETS exposure outside of the home, biasing our results towards the null. Alternatively, individuals with earlier onset of symptoms may have been more likely to report childhood ETS exposure. This would have led to a selective misclassification of exposure, falsely implicating childhood ETS exposure or increasing the magnitude of its true effect. We attempted to minimize this bias by separating these two questions and nesting them among questions about other current symptoms and environmental exposures, respectively. As there was no real association between childhood ETS exposure and current symptoms, we do not believe current clinical status presented a significant source of bias.

Although we adjusted for personal tobacco use in the Cox proportional hazards modeling, it is possible that some confounding still occurred. Never-smokers may have had a greater tendency to recall ETS exposure than smokers. A "healthy smoker effect" is possible whereby those who chose never to smoke may somehow already have been less healthy than those who did. It is also possible that the effects of personal tobacco use outweighed and obscured the effects of childhood ETS exposure. The mean age of smoking commencement was almost 2 years earlier in those with ETS exposure compared with those without exposure. It is likely the significantly earlier age of onset of wheeze and dyspnea with childhood ETS exposure in smokers only is attributable to the earlier age of beginning smoking. However, it does not account for the earlier age of cough in the never-smokers. Multiple comparisons error is unlikely as childhood ETS exposure had a consistent effect on elevated risk of developing cough, mean age of onset of cough, and odds of currently having chronic cough.

Personal smoking was associated with elevated risk of development of dyspnea beginning after 10 pack-years and increasing in a dose-dependent manner up to 30 pack-years. Decreased risk after 30 pack-years might represent a "survivor effect" whereby those who are able to smoke that long without developing symptoms are less likely to do so in the future. Elevated risk for the development of cough and wheeze during the first 10 pack-years of smoking only was not expected. It is possible that these represent irritant symptoms rather than true AAT deficiency-related pulmonary injury and therefore might occur more quickly, if indeed they are to occur. Post-hoc analysis shows a median of cessation of smoking 7 years after the development of cough, 4 years after the development of wheeze, and 5 years after the development of dyspnea.

In order to achieve adequate statistical power, we recruited study participants from four known populations with this uncommon disorder. As such, there is an inherent risk of selection bias that may limit our ability to generalize our findings to the PI\*Z population as a whole. Fewer subjects in this study reported dyspnea than in a survey of Alpha-1 Association members (90% with dyspnea at mean age 48 years) or participants in the National Heart, Lung, and Blood Institute Registry (90% at mean age 46 years). However, the prevalence of pulmonary symptoms was greater in our study population than in the Swedish Alpha-1 Registry studies (Piitulainen et al 1997, 1998). Our study subjects may have been more symptomatic than an unselected PI\*Z population. Only a portion of the participant phenotypes were verified. We believe that the possible inclusion of individuals with less severe deficiency states, with their expected overall less severe clinical course, would have served only to decrease the power of our study.

## Conclusion

In individuals with severe AAT deficiency, personal smoking was associated with earlier onset of cough, wheeze, and dyspnea. Self-reported childhood environmental tobacco smoke exposure was associated with younger age of cough. Childhood respiratory infections and family history of emphysema were associated with earlier onset of wheeze.

## Acknowledgements

We extend our gratitude and thanks to the Alpha-1 Association and the Alpha-1 Foundation. We especially thank Janis Berend, CNP, RN, Symma Finn, Daniel Laskowski, RPFT/CCRC, Michele Cooper, Heather Davis, Kieran Nelson,

Joy Davis, Stephanie Clancy, and the faculty and staff of the Division of Environmental and Occupational Health Sciences. We thank Zung Vu Tran, Ph.D. for his review of biostatistical methods. We thank Paul Blanc, M.D., M.P.H. for his thoughtful review and recommendations on the manuscript. We also thank Becki Bucher-Bartelson, Ph.D. for her invaluable assistance in the initial phases of this work. Most of all we thank the participants, without whose help this study would not have been possible. This work was funded in part by a grant from the Department of Health and Human Services, United States Public Health service, CDC/NIOSH Grant OH, USA 007454.

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