CHEST

Original Research

COPD

Clinical Characteristics of Subjects With Symptoms of α_1-Antitrypsin Deficiency Older Than 60 Years*

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Background: **The clinical characteristics of elderly subjects with α_1-antitrypsin deficiency (AATD)-associated COPD have not been described.**

Methods: **The clinical, demographic, health-related quality of life (HRQoL) characteristics and 1-year exacerbation rates of 275 subjects with AATD and COPD receiving augmentation therapy aged > 59 years (mean [± SD] age, 66.3 ± 5.7 years) were compared to those of 354 subjects aged 50 to 59 years (mean age, 54.3 ± 2.8 years) and 293 subjects < 50 years (mean age, 43.9 ± 3.8 years).**

Results: **Older subjects received diagnoses later in life (mean age at diagnosis, 55.0 ± 8.5 years) and had a longer diagnostic delay (mean age at diagnosis, 12.9 ± 14.3 years) than subjects in the other two age groups. Although the proportion of lifetime nonsmokers was higher in the older group, the majority (64%) had significant tobacco exposure but with a longer interval of tobacco abstinence. The mean FEV_1 values (n = 641) were similar between the three age groups, suggesting a slower disease progression in the oldest group. Subjects in the older group were less symptomatic, had less concomitant asthma, and had significantly better scores in most domains of two HRQoL instruments. During follow-up, older subjects had fewer acute exacerbations.**

Conclusions: **Subjects with AATD-associated COPD who reach an older age exhibit a more indolent clinical course than younger affected individuals, possibly related in part to differences in tobacco exposure. This finding supports current guidelines that recommend screening of all patients with COPD for AATD, regardless of their age and prior smoking history.**

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Key words: age groups; α_1-antitrypsin deficiency; COPD; quality of life

Abbreviations: AATD = α_1-antitrypsin deficiency; HRQoL = health-related quality of life; SF-36 = Medical Outcomes Study 36-item short form; SGRQ = St. George respiratory questionnaire

Alpha 1-antitrypsin deficiency (AATD) is a well recognized genetic disorder that predisposes affected individuals to develop early-onset COPD. Susceptible subjects usually receive a diagnosis of obstructive lung disease at a mean age of 44 to 45 years, approximately 8 years after the onset of symptoms.[1,2] Symptomatic AATD has been associated with a marked reduction in life expectancy, with reported estimates of cumulative probability of survival to age 50 years of 52% and to age 60 years of 16%.[3,4]

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Exposure to tobacco smoke and other pollutants is probably the most important factor in the develop-

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ment of symptomatic lung disease and a shortened life expectancy. For example, the median age at death for smokers with AATD was estimated to be approximately 40 years and approximately 65 years for those who have never smoked.[4] Because of these and other studies, clinicians appropriately consider screening young subjects with obstructive lung disease for AATD to institute early effective interventions, such as education, smoking cessation, and, in some cases, specific augmentation therapy with purified α_1-antitrypsin.[1]

Variability in the rate of lung function decline among symptomatic individuals with AATD occurs,[5] and subjects who experience slower lung function decline can be expected to have a delayed onset of symptoms. Delayed diagnosis of AATD in individuals with COPD older than 60 years has been the subject of case reports,[6,7] but it is likely that due to a slower disease progression, many remain undiagnosed in this age group. Since the demographic and clinical features of individuals with symptomatic AATD who live beyond the age of 60 have not been described previously, we analyzed age-associated differences in a large cohort of subjects with symptomatic AATD.

Materials and Methods

The study comprised 1,062 members of AlphaNet, a not-for-profit health management company that coordinates services for patients with AATD in the United States (including the organization and distribution of augmentation therapy) who consent to participate in a disease management program. The data analyzed here correspond to the clinical outcomes recorded during a pre-intervention 12-month control period. For the study, coordinators (all subjects with AATD employed by AlphaNet) were trained by the investigators to participate in the enrollment process and perform follow-up surveys for the study. Given that participants resided throughout the United States, the enrollment process was as follows: AlphaNet members who expressed an initial interest in the study received by mail a package with study details and an informed consent form. In a follow-up telephone call, the coordinators reviewed the study processes and the consent form in detail with potential participants. After this, subjects who agreed to participate mailed their signed informed consent forms directly to the investigators for review and official enrollment in the study. The study and enrollment process was approved by the University of Miami Institutional Review Board.

Study Procedures

Because study participants were distributed throughout the United States, clinical and demographic data were collected through telephone interviews using standardized questionnaires. Data regarding disease exacerbations and health-care resource utilization were collected on a monthly basis by trained AlphaNet coordinators, while disease-specific health-related quality of life (HRQoL) data were collected by experienced surveyors (Qessential Medical Market Research LLC; Exeter, NH) unaware of the results of the other surveys. HRQoL was measured with the disease-specific St. George respiratory questionnaire (SGRQ) at 0, 6, and 12 months of enrollment,[8] and the generic Medical Outcomes Study 36-item short form (SF-36) questionnaire at study entry.[9] Collection of HRQoL information using these questionnaires via telephone has been described previously.[10,11] Results were entered directly at the time of collection into a secure database via an encrypted web-based front end. All surveys were administered between February 2003 and July 2004. In addition, all participants were asked to provide a copy of their genotype/phenotype and antitrypsin level at the time of diagnosis, and a copy of their most recent spirometry result, if performed during the study year, to be utilized for COPD staging according to the criteria of the Global Initiative for COPD.[12]

Measurement of HRQoL

SGRQ domains were scored from 0 (best) to 100 (worst). The SF-36 domains were normalized to the general 1998 United States population on a scale of 0 (worst) to 100 (best), with 50 being the general population mean and SD = 10.[13]

Exacerbations

Exacerbations were defined using the criteria of an expert panel consensus criteria, which was based on medication use and health-care resource utilization.[14] In brief, exacerbations were defined as a sustained worsening of patient condition from the stable state and beyond normal day-to-day variation, that was acute in onset and necessitated a change in regular medication. By this criteria, an exacerbation was categorized as mild if it could be managed in the normal environment with an increase in the usual medication, moderate if it needed additional medical assistance (physician or emergency department visit), and severe if it required hospitalization. Duration of exacerbations was recorded at each monthly questionnaire and used to separate exacerbations that occurred in consecutive months.

Statistical Analysis

The analysis included a cross-sectional analysis of baseline characteristics and a prospective analysis of exacerbations, HRQoL change, and healthcare resource utilization. In order to analyze the characteristics of subjects older than 60 years included in the cohort, subjects were divided into the following three age groups: < 50 years (n = 293), 50 to 59 years (n = 354), and > 59 years (n = 275). Although, differences in measured outcomes were still detected when other age cut-points were used (not shown), this division was arbitrarily chosen to have approximately equal sized age groups. Data were analyzed using statistical software (SAS, version 9.13; SAS Institute; Cary, NC). The χ^2 test was used to compare proportions, and the Student *t* test and analysis of variance with Bonferroni corrections were used to compare quantitative variables between the groups. Variables that did not have a normal distribution were compared with the Mann-Whitney *U* test. The repeat measurement mixed models was employed to compare the changes in HRQoL within and between age groups. All tests were performed two-sided with a significance level of 5%.

Results

Of the 1,062 participants who were enrolled in the study, 34 patients were excluded because of lung transplantation at study entry. During follow-up, 15 patients were excluded because of new lung trans-

plant during the study period, 10 patients withdrew from the study, 6 patients were unavailable for follow-up, and 19 patients died. Subjects not receiving augmentation therapy (n = 42) and with incomplete monthly data collection (n = 14) were excluded from the analysis. Thus, the current analysis of age-related differences in clinical outcomes included 922 subjects receiving augmentation therapy who completed the baseline and HRQoL surveys and all monthly follow-ups for 1 year. The median age of participants was 54 years (range, 34 to 84 years).

Differences in Demographics and Smoking History

The only significant demographic differences observed between age groups were in the proportion of subjects living with children, currently employed, and exposed to tobacco (Table 1). Only a minority of the entire cohort (0.7%) reported current smoking. The proportion of lifetime nonsmokers increased with age and was significantly higher in the older group than in the other two groups. Nevertheless, the majority of subjects in all age groups had a significant history of tobacco use. Among former smokers, tobacco exposure was similar in the three groups; however, subjects in the older group had stopped smoking for a significantly longer interval.

Differences in Diagnostic Experience

Older subjects were diagnosed with AATD at a significantly older age and had a longer diagnostic delay (symptom onset to diagnosis interval) than subjects in the other two age groups (Table 1). No differences were noted by ascertainment status.

Differences in Clinical Features

The major clinical differences among the three age groups are summarized in Table 2. Overall, younger subjects tended to be more symptomatic than older subjects. Of significance, a diagnosis of

Table 1—*Baseline Characteristics According to Age Groups**

Characteristics	All (n = 922)	Age Groups			p Value
		< 50 yr (n = 293)	50–59 yr (n = 354)	> 59 yr (n = 275)	
Demographics					
Age, yr	54.5 ± 9.6	43.9 ± 3.8	54.3 ± 2.8	66.3 ± 5.7	
Male gender	52.6	50.2	51.9	56.4	0.41
White race	99.1	98.6	99.7	98.9	0.43
Lives with partner	73.5	68.3	74.7	77.2	0.09
Lives with children	19.7	43.7	11.9	3.7	< 0.001†‡
Employed	34.4	44.9	40.1	15.4	< 0.001†
Yearly family income					
< $40,000	46.8	49.5	43.3	48.8	0.09
$40,000–$80,000	33.9	33.3	33.8	34.9	
> $80,000	19.3	17.2	22.9	16.3	
Ever smoked	82.1	93.1	86.5	64.3	< 0.001†‡
Smoker characteristics					
Total pack-yr	23.5 ± 14.8	21.4 ± 12.2	24.4 ± 15.9	23.6 ± 16.6	0.76
Age started smoking	17.5 ± 4.2	16.4 ± 3.5	18.0 ± 4.0	18.6 ± 5.3	< 0.001§
Age stopped smoking	37.7 ± 8.7	35.7 ± 5.5	38.9 ± 7.3	40.5 ± 10.5	< 0.001†‡
Quit to study interval	14.6 ± 10	8.0 ± 5.5	15.1 ± 7.7	24.8 ± 11.1	< 0.001†‡
History of environmental exposure‖	23.2	25.5	24.8	18.5	0.2
Diagnostic experience					
Age at diagnosis, yr	45.5 ± 9.5	37.8 ± 5.3	45.0 ± 6.3	55.0 ± 8.5	< 0.001†‡
Symptom to diagnosis interval, yr	8.3 ± 11.1	7.8 ± 9.1	8.3 ± 9.4	12.9 ± 14.3	< 0.001†
Physicians seen before diagnosis, No.	2.6 ± 2.2	2.5 ± 1.9	2.5 ± 2.1	2.6 ± 2.3	0.75
Symptom onset to study interval, yr	17.4 ± 12.4	13.1 ± 9.7	16.7 ± 10.5	23.3 ± 15.3	< 0.001†‡
Diagnosis to study interval, yr	8.9 ± 6.2	6.3 ± 4.6	9.4 ± 6.0	11.4 ± 7.0	< 0.001†‡
Time on augmentation therapy, yr	6.6 ± 4.3	4.8 ± 3.6	6.9 ± 4.3	7.7 ± 4.6	< 0.001†‡
Ascertainment status					
Index case	85.3	85.3	85.1	85.5	0.71
Nonindex case	14.7	14.7	14.9	14.5	

*Values are given as the mean ± SD or %, unless otherwise indicated.
†Significant difference between the group > 59 years of age and each of the two other age groups.
‡Significant difference between the groups 50 to 59 years of age and < 50 years of age.
§Significant difference between the group < 50 years of age and each of the two other age groups.
‖Exposure to biological dust, diesel smoke, mineral dust, metal fumes, or combustion products.

Table 2—*Clinical Features Reported According to Age Groups

Variables	All	Age Groups			p Value
		< 50 yr	50–59 yr	> 59 yr	
Pulmonary diagnoses					
COPD, chronic bronchitis, or emphysema	100	100	100	100	NA
Chronic bronchitis†	28.5	29.7	29.2	26.6	0.69
Asthma	49.6	54.3	50.3	43.0	0.03‡
Bronchiectasis	7.3	4.5	8.8	8.4	0.08
Nonpulmonary diagnoses					
Allergic diseases	64.4	67.3	65.8	59.7	0.22
Hypertension	37.6	25.6	39.7	46.6	< 0.001‡
Arthritic symptoms	12.6	7.5	13.8	16.5	0.02‡§
Vascular disease (stroke, aneurysms)	7.2	6.5	5.2	10.6	0.06
Peptic ulcer disease	6.9	7.5	7.5	5.8	0.7
Diabetes	5.9	5.0	5.2	7.7	0.4
Symptomatic coronary artery disease	5.8	1.0	3.4	13.6	< 0.001‡
Renal disease	4.9	4.5	3.7	6.8	0.3
Common symptoms					
Chronic cough	23.6	25.9	22.8	22.0	0.2
Chronic wheezing/chest tightness	48.1	57.5	46.6	39.5	< 0.001‡§
Dyspnea at moderate/severe exertion	59.2	53.1	53.0	61.8	0.11
Dyspnea at rest/mild exertion	40.6	40.8	41.9	32.2	0.09
Frequent awakenings due to respiratory problems	26.7	36.4	24.5	18.2	< 0.001‡§
Frequently awakes feeling unrested	63.5	71.8	62.0	55.8	< 0.001‡§
Feels fatigued most of the day	67.35	70.6	67.0	63.8	0.22
Limited activities due to dyspnea	65.1	70.1	63.2	62.1	0.19
Unable to work for a living due to pulmonary condition	54.5	51.7	55.2	57.0	< 0.001‡
Exacerbations in prior 12 mo	3.1 ± 2	3.6 ± 2	3.05 ± 2	2.74 ± 2	0.001‖
Spirometry¶					
FEV_1					
L	1.2 ± 0.6 (0.29–3.48)	1.2 ± 0.9 (0.29–2.66)	1.2 ± 0.7 (0.32–3.31)	1.1 ± 0.6 (0.37–3.48)	0.9
% predicted	37.5 ± 19 (10–76)	33.1 ± 15.3 (10–69)	37.4 ± 18.3 (12–76)	38.6 ± 16 (13–75)	0.02‖
GOLD stage					
I/II	19.6	13.8	21.9	21.6	0.11
III	24.9	22.1	21.6	31.9	
IV	55.5	64.1	56.5	46.5	

*Values are given as the mean ± SD (range) or %, unless otherwise indicated. NA = not available.
†Sputum production at least 3 mo a year for at least 2 consecutive years.
‡Significant difference between the group > 59 years of age and each of the two other age groups.
§Significant difference between the group 50 to 59 years of age and the group < 50 years of age.
‖Significant difference between the group < 50 years of age and each of the two other age groups.
¶A total of 641 subjects who had spirometry during the study period.

asthma was reported more often in the younger group. As expected, subjects > 50 years in age reported more nonpulmonary comorbid conditions.

There were no major differences in the long-term respiratory medications used (not shown). Older subjects were more likely to be receiving oxygen therapy (40.1% in the younger group, 49.7% in the intermediate group, and 60.1% in the older group, p = 0.01). No major differences were noted in regular exercise habits between the groups (not shown).

The majority of participants had a spirometry performed during the study year (n = 641,

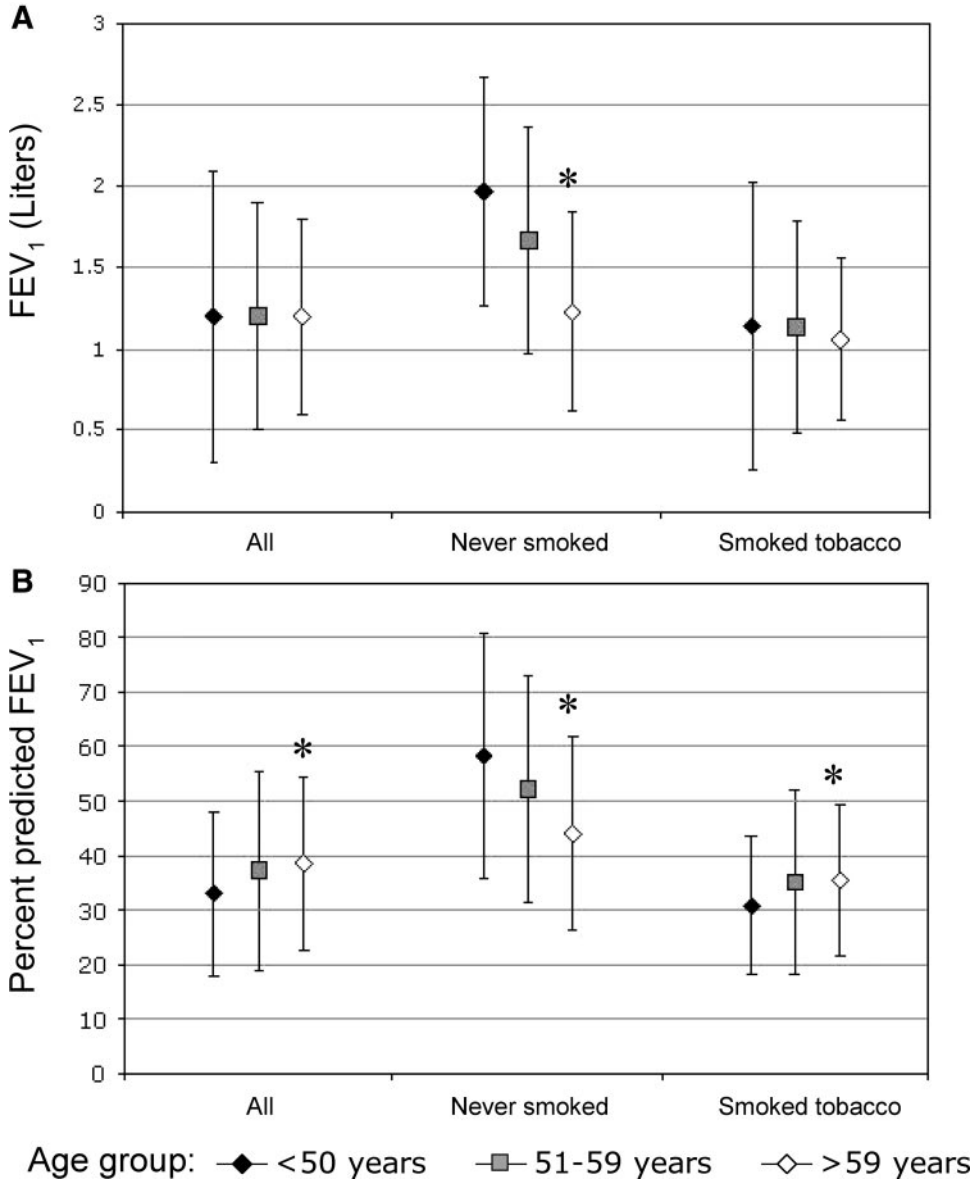

FIGURE 1. Lung function among age groups according to smoking status (n = 641). *Top*, *A*: absolute FEV_1 values (L). *Bottom*, *B*: age-adjusted FEV_1 percent predicted. All values are expressed as the mean ± SD. * = $p < 0.05$ for differences between the oldest and youngest age groups.

69.5%). There were no clinical or demographic differences between subjects who had spirometry vs those who did not (not shown). Overall, no differences were noted among the three age groups in absolute FEV_1 values, but older subjects were categorized as having significantly milder disease based on age-adjusted FEV_1 percentage (Fig 1). Nonsmokers had better lung function values than former smokers ($p < 0.002$). Among nonsmokers, FEV_1 values were significantly lower in the older group.

Baseline HRQoL scores are shown in Figure 2. Compared with the younger group, older subjects had significantly better HRQoL scores, in particular in the total, impacts, and symptom domains of the SGRQ (Fig 2, *left*, *A*), and the mental heath, role emotional, social function, and general health domains of the SF-36 (Fig 2, *right*, *B*). In the most impaired physical domains (activity domain of the SGRQ, and the physical function and role-physical domains of the SF-36), all age groups were affected equally.

Differences in Clinical Outcomes During a 12-Month Follow-up

HRQoL: During the study year, two subsequent SGRQ questionnaires were obtained at 6 and 12

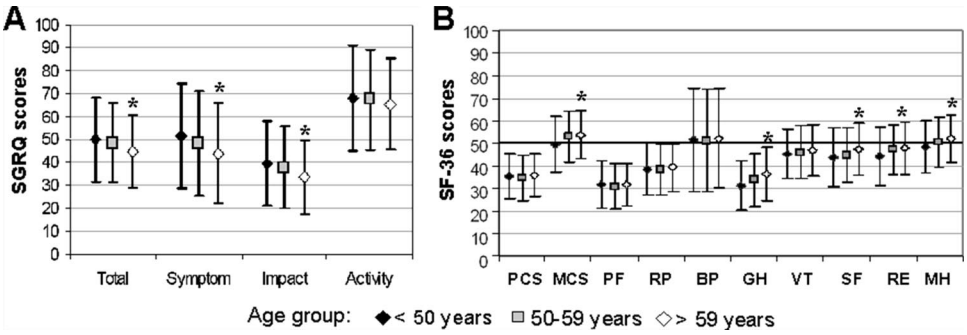

FIGURE 2. Baseline HRQoL scores given as the mean ± SD. *Left*, *A*: SGRQ. *Right*, *B*: SF-36 survey. Value of 50 represents the mean of the general population and each 10-point change represents 1 SD. * = $p < 0.05$ between the youngest (< 50 years) and the oldest (> 59 years) groups. PCS = physical component summary; MCS = mental component summary; PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social function; RE = role-emotional; MH = mental health.

months, and all showed that the older group had better HRQoL (Fig 3). The SGRQ total score did not change by a magnitude that was considered clinically significant (a 4-point magnitude) in any of the three age groups.[15] In the Activity domain, the most severely affected domain, only the oldest group showed a trend toward improvement over time.

Exacerbation Rates: Our cohort experienced a total of 2,268 exacerbations with a mean of 2.45 ± 1.3 exacerbations per subject during the study year, the majority of which were of moderate severity. Similar to the past exacerbation frequency recalled by subjects (Table 2), in the prospective follow-up, subjects in the older group had a lower rate of total exacerbations compared with the other two age groups (Fig 4, *top*, *A*). There were no differences observed in the overall mean duration of exacerbations between age groups (Fig 4, *bottom*, *B*). However, severe exacerbations in older subjects lasted longer than severe exacerbations in the youngest group (23.3 vs 15.9 days, respectively; $p < 0.05$).

Health-Care Resource Utilization: No differences were observed in the rate of emergency department visits, unscheduled physician visits, and hospitalizations among the three age groups during follow-up (Table 3).

DISCUSSION

Our study shows that individuals with symptomatic AATD-associated COPD who reach the age of 60 years or more, represent a group with particular clinical characteristics. These older individuals have less symptomatic AATD, experience fewer acute disease exacerbations and have better HRQoL scores than younger individuals affected with AATD. Due to an apparent slower decline in lung function, the older individuals experience a longer diagnostic delay and receive a diagnosis later in life. These observations complement studies showing variability in lung function decline rates in subjects with AATD. Wencker et al[5] described the term rapid and slow *decliners*; the rapid decliners exhibit the most significant improvements with IV augmentation therapy. Since rapid decliners are likely the ones with shortened life expectancy, subjects in the older group represent a select group of individuals with more indolent but still symptomatic disease (*survivors*). Unfortunately, the true prevalence of slow decliners is unknown since the diagnosis of AATD is likely to be missed in these subjects in view of their less aggressive clinical presentation.

Prior studies have noted that differences in pulmonary involvement and life expectancy with AATD depend on how the diagnosis was ascertained.[4,16] Ascertainment differences were not observed between the three age groups of our cohort. The major clinical determinant likely to explain the age-associated differences that we observed was the amount of tobacco exposure. Several observations have identified tobacco smoke exposure as the most important factor for the development of pulmonary involvement in AATD.[4,17–23] Our findings complement these observations by showing that lower tobacco exposure is associated with slower disease progression and milder COPD-centered outcomes. In the older group, the proportion of lifetime nonsmokers was higher than in the other age groups; and although the majority of older subjects still had significant tobacco exposure, they had a longer interval of tobacco abstinence than the other age groups. Despite this clear association with tobacco, the role of

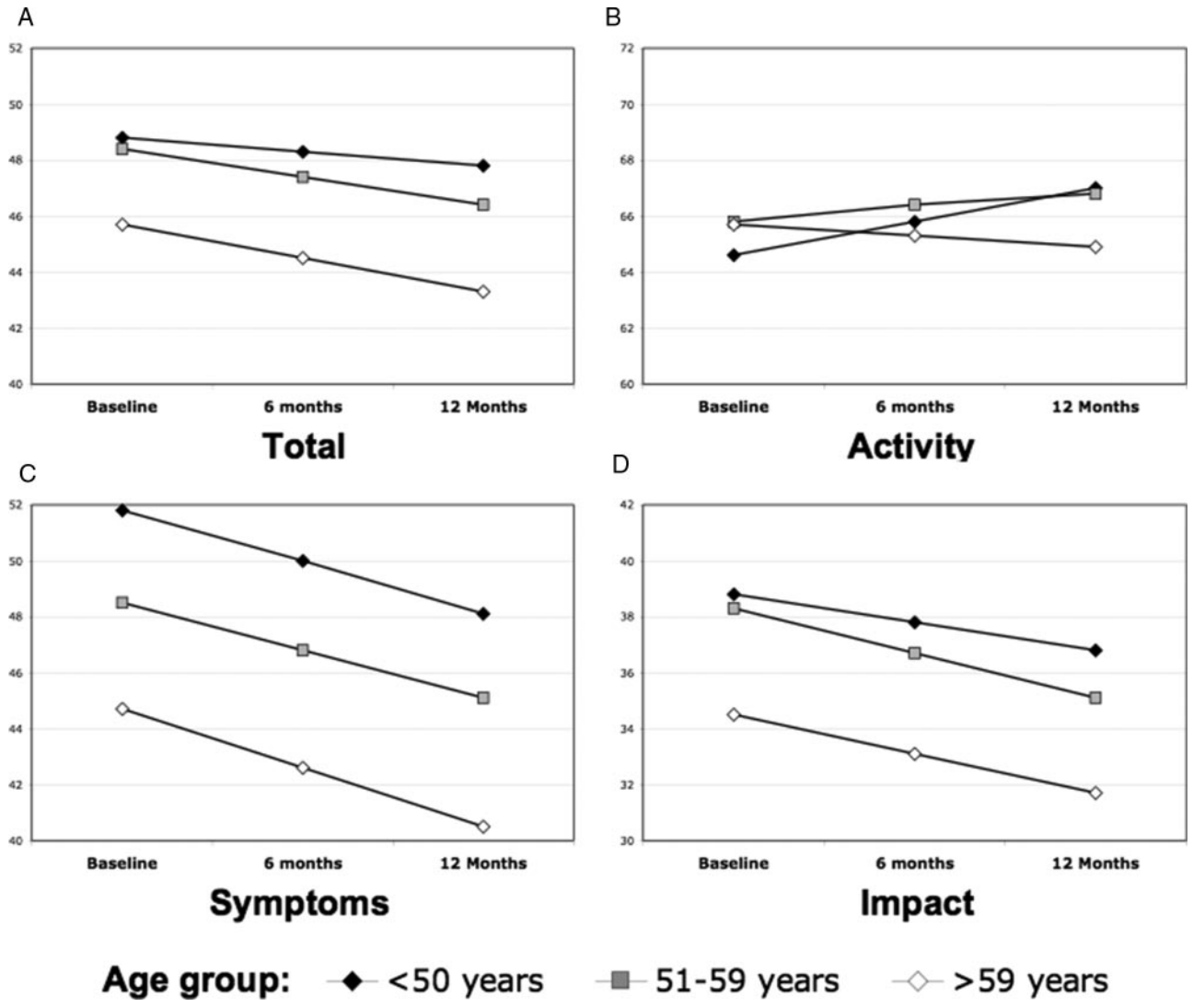

FIGURE 3. Absolute change in SGRQ scores by age group during the 1-year follow-up. *Top left*, *A*: total domain; *top right*, *B*: activity domain; *bottom left*, *C*: symptoms domain; and *bottom right*, *D*: impact domain. Lower scores denote better HRQoL.

other intrinsic (genetic) and extrinsic factors cannot be discarded. Some extrinsic factors that may affect disease progression in AATD include exposure to gases, fumes, dust, and indoor air pollution, as well as the development of asthma, pneumonia, chronic bronchitis, and respiratory illnesses during childhood.[16,24–26] We did not find significant differences in most of these factors among the three age groups studied, except for a higher prevalence of asthma among younger subjects. Although this could be a reflection that a diagnosis of asthma is entertained more often than COPD when a young patient presents with wheezing and airflow obstruction, data from longitudinal studies of patients with COPD and normal levels of α_1-antitrypsin indicate that bronchial hyperresponsiveness is a strong prognostic indicator for FEV_1 loss over time.[12] The possibility that bronchial hyperresponsiveness may increase FEV_1 loss over time has been incompletely explored in AATD.[1,17,27]

Although not based in randomized controlled trials, it is well recognized that augmentation therapy with IV α_1-proteinase inhibitor modifies lung function decline in AATD[1] and may improve survival in subjects with symptomatic AATD.[17] The average duration of augmentation therapy in our subjects was < 8 years, with only a 3-year difference between the youngest and the oldest group, which is unlikely to explain the clinical differences observed.

Our study does not intend to extrapolate the natural history of AATD based on a cross sectional analysis, but to highlight that clinical age-related differences exist. We have been able to perform the current analysis because of the wide age distribution of our cohort, which is usually not observed in

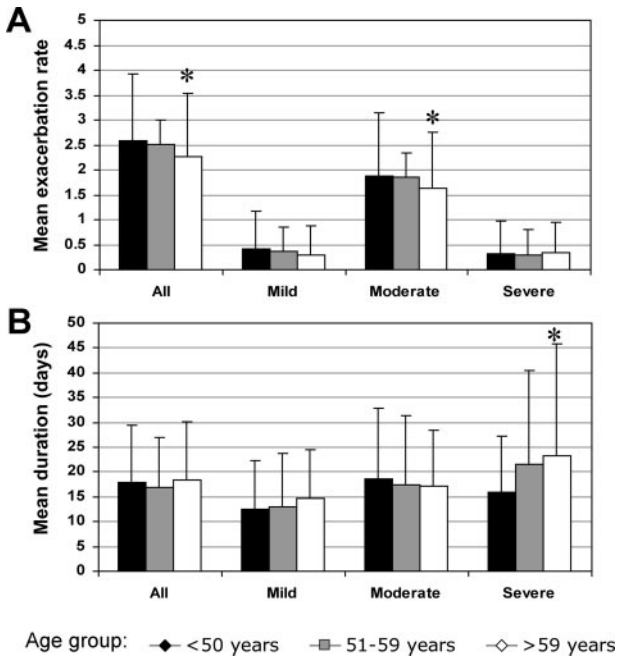

FIGURE 4. Comparison of COPD exacerbations in patients with AATD among different age groups. *Top*, *A*: frequency of exacerbations expressed as mean number of exacerbations > 1 year. *Bottom*, *B*: duration of exacerbations expressed as mean number of days per exacerbation.

cohorts of subjects with COPD not related to AATD.[28–30] In addition, we noted that age differences in some therapeutic attitudes exist, such as the higher prescription of oxygen therapy to older subjects even when younger subjects are equally impaired.

Participation bias, in which subjects with the best health status are more eager to participate in the surveys, could have occurred. If this was the case, the group with the slowest decline in lung function may have been overrepresented, a result which may explain the large number of individuals in the older group. For the purpose of our study, this should not be viewed as a selection bias since it increases the power to analyze the characteristics of these subjects.

Since the study participants were distributed throughout the United States and not available for direct testing, we asked them to provide us with copies of any spirometry test performed during the study year. Spirometry was not available for one third of participants, but these individuals did not differ clinically from the whole group. Since spirometry tests were not standardized, they were used solely for COPD staging and to complement the clinical findings. Although lung function is important in the evaluation of COPD, it is a marker that correlates poorly with other outcomes such as symptoms, ability to function, and HRQoL (patient-centered outcomes).[12,31] Consistent with this finding, despite the clinical differences observed in the study, we found similar absolute FEV_1 values between age groups. We recognize that our study would be more robust if clinical differences were correlated with differences in lung function decline. We anticipate that younger subjects with more symptomatic AATD have the most rapid decline.

The implications of our findings are twofold. First, the results underscore the importance of smoking cessation in patients with AATD. Second, they show that some individuals with AATD exhibit clinical features similar to those of subjects with typical COPD.[28,30,32] Consistent with current screening guidelines,[1] our study supports the notion that screening for AATD should still be considered in all patients with COPD regardless of advanced age or smoking history. This will likely lead to increased detection rates of AATD, including the identification of affected relatives, which will provide the opportunity to more effectively institute preventive measures (*ie*, smoking cessation) and the earlier institution of effective measures, such as augmentation therapy.[17,33]

Table 3—*Health-Care Utilization by Age Group

Variables	Age Groups			p Value
	< 50 yr	50–59 yr	> 59 yr	
ED visits	0.36 ± 0.91	0.32 ± 0.79	0.33 ± 0.76	NS
Unscheduled office visits	1.71 ± 2.89	1.54 ± 2.72	2.04 ± 5.49	NS
Hospitalizations	0.27 ± 0.76	0.24 ± 0.68	0.32 ± 0.76	NS

*Values are given as the mean ± SD per subject per year. NS = not significant; ED = emergency department.

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REFERENCES

1 American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with α_1-antitrypsin deficiency. Am J Respir Crit Care Med 2003; 168:818–900

2 Stoller JK, Sandhaus RA, Turino G, et al. Delay in diagnosis of α_1-antitrypsin deficiency: a continuing problem. Chest 2005; 128:1989–1994

3 Brantly ML, Paul LD, Miller BH, et al. Clinical features and history of the destructive lung disease associated with α_1-antitrypsin deficiency of adults with pulmonary symptoms. Am Rev Respir Dis 1988; 138:327–336

4 Larsson C. Natural history and life expectancy in severe

α_1-antitrypsin deficiency, Pi Z. Acta Med Scand 1978; 204:345–351
5 Wencker M, Fuhrmann B, Banik N, et al. Longitudinal follow-up of patients with α_1-protease inhibitor deficiency before and during therapy with IV α_1-protease inhibitor. Chest 2001; 119:737–744
6 Jack CI, Evans CC. Three cases of α_1-antitrypsin deficiency in the elderly. Postgrad Med J 1991; 67:840–842
7 Korver G, Liu C, Petersen M. α_1-Antitrypsin deficiency presenting with panniculitis and incidental discovery of chronic obstructive pulmonary disease. Int J Dermatol 2007; 46:1078–1080
8 Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145:1321–1327
9 Ware JE, Snow KK, Kosinski M. SF-36 health survey: manual and interpretation guide. Lincoln, RI: QualityMetric Incorporated, 2002
10 Desikan R, Mason HL, Rupp MT, et al. Health-related quality of life and healthcare resource utilization by COPD patients: a comparison of three instruments. Qual Life Res 2002; 11:739–751
11 Anie KA, Jones PW, Hilton SR, et al. A computer-assisted telephone interview technique for assessment of asthma morbidity and drug use in adult asthma. J Clin Epidemiol 1996; 49:653–656
12 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease (GOLD). Available at: www.goldcopd.org. Accessed October 25, 2008
13 Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey. Lincoln, RI: QualityMetric Incorporated, 2002
14 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000; 117(suppl):398S–401S
15 Jones PW. St. George's respiratory questionnaire: MCID. COPD 2005; 2:75–79
16 Silverman EK, Pierce JA, Province MA, et al. Variability of pulmonary function in α_1-antitrypsin deficiency: clinical correlates. Ann Intern Med 1989; 111:982–991
17 Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of α_1-antitrypsin. Am J Respir Crit Care Med 1998; 158:49–59
18 Janus ED, Phillips NT, Carrell RW. Smoking, lung function, and α_1-antitrypsin deficiency. Lancet 1985; 1:152–154
19 Piitulainen E, Eriksson S. Decline in FEV_1 related to smoking status in individuals with severe α_1-antitrypsin deficiency (PiZZ). Eur Respir J 1999; 13:247–251
20 Seersholm N, Kok-Jensen A. Clinical features and prognosis of life time non-smokers with severe α_1-antitrypsin deficiency. Thorax 1998; 53:265–268
21 Seersholm N, Kok-Jensen A, Dirksen A. Survival of patients with severe α_1-antitrypsin deficiency with special reference to non-index cases. Thorax 1994; 49:695–698
22 Seersholm N, Kok-Jensen A, Dirksen A. Decline in FEV_1 among patients with severe hereditary α_1-antitrypsin deficiency type PiZ. Am J Respir Crit Care Med 1995; 152:1922–1925
23 Tobin MJ, Cook PJ, Hutchison DC. Alpha 1-antitrypsin deficiency: the clinical and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z: a survey by the British Thoracic Association. Br J Dis Chest 1983; 77:14–27
24 Mayer AS, Stoller JK, Bucher Bartelson B, et al. Occupational exposure risks in individuals with PI*Z α_1-antitrypsin deficiency. Am J Respir Crit Care Med 2000; 162:553–558
25 Piitulainen E, Sveger T. Effect of environmental and clinical factors on lung function and respiratory symptoms in adolescents with α_1-antitrypsin deficiency. Acta Paediatr 1998; 87:1120–1124
26 Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with α_1-antitrypsin deficiency (PiZZ). Thorax 1997; 52:244–248
27 Eden E, Hammel J, Rouhani FN, et al. Asthma features in severe α_1-antitrypsin deficiency: experience of the National Heart, Lung, and Blood Institute Registry. Chest 2003; 123:765–771
28 Esteban C, Quintana JM, Aburto M, et al. A simple score for assessing stable chronic obstructive pulmonary disease. Q J Med 2006; 99:751–759
29 Miravitlles M, Ferrer M, Pont A, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2-year follow-up study. Thorax 2004; 59:387–395
30 Spencer S, Calverley PM, Burge PS, et al. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004; 23:698–702
31 Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 1997; 155:1283–1289
32 Miravitlles M, Ferrer M, Pont A, et al. Characteristics of a population of COPD patients identified from a population-based study: focus on previous diagnosis and never smokers. Respir Med 2005; 99:985–995
33 Dirksen A, Stockley R, Piitulainen E, et al. Randomized placebo-controlled trial of α_1-antitrypsin (AAT) augmentation therapy with prolastin. Am J Respir Crit Care Med 2008; 177:A419