






Long-Term SGRQ Stability in a Cohort of Individuals with Alpha-1 Antitrypsin Deficiency-Associated Lung Disease

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Background: Health-related quality of life (HRQoL) assessments such as St. George's Respiratory Questionnaire (SGRQ) are often used as outcome measures to evaluate patient-perceived changes in health status among individuals with lung disease. Several factors have been linked to deterioration in SGRQ, including symptoms (dyspnea, wheezing) and exercise intolerance. Whether these findings apply to individuals with alpha-1 antitrypsin deficiency (AATD) remains incompletely studied. This longitudinal study examines the trajectory of SGRQ scores in a cohort of United States individuals with AATD-associated lung disease and defines factors associated with longitudinal change.

Methods: Individuals with AATD-associated lung disease enrolled in AlphaNet, a disease management program, who had ≥ 3 SGRQ measurements collected between 2009 and 2019, and baseline data for clinically important variables were included in these analyses. Data collected after lung transplants were excluded. Mixed-effects model analyses were used to evaluate the changes in SGRQ total and subscale scores over time and by modified Medical Research Council (mMRC) Scale, use of oxygen, age, sex, productive cough, and exacerbation frequency at baseline. Sensitivity analyses were conducted to examine the potential effect of survivor bias.

Results: Participants ($n=2456$, mean age 57.1 ± 9.9 years, 47% female) had a mean SGRQ total score of 44.7 ± 18.9 at baseline, 48% used oxygen regularly, and 55% had ≥ 2 exacerbations per year. The median length of follow-up was 6 (IQR 3–9) years. The SGRQ total score and subscales remained stable throughout the observation period. Age, mMRC categories, presence or absence of productive cough, frequency of exacerbations, and use of oxygen at baseline were significantly associated with the rate of change of SGRQ total ($p < 0.0001$).

Conclusion: We observed long-term stability in HRQoL and an association between the rate of change in SGRQ and baseline mMRC, exacerbation frequency, productive cough, and use of oxygen in this cohort of individuals with AATD-associated lung disease.

Keywords: COPD, alpha-1 antitrypsin deficiency, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease with continuous lung function decline due to ongoing exposure to risk factors, persistent airway inflammation, and aging.¹ People with alpha-1 antitrypsin deficiency (AATD) are predisposed to developing early-onset COPD with typically basilar emphysema, especially when exposed to smoking and other environmental risk factors.^{2,3} Because the cardinal symptoms of dyspnea, chronic productive cough, and wheezing do not usually go away, COPD is generally associated with impaired health-related quality of life (HRQoL). In affected individuals, these symptoms prevent regular physical and social activities, limit exercise capacity, and affect mood and sleep.^{4,5} Studies show that HRQoL deteriorates with COPD severity,⁶ and health status assessment

is often used to assess treatment interventions for managing chronic lung disease.⁷ Thus, HRQoL is a key measure of the burden of chronic lung disease.

The burden of AATD-associated lung disease is often more pronounced than in COPD without AATD due to the development of pulmonary symptoms at a younger age, leading to significant impairment in quality of life.⁸ COPD is usually diagnosed later in life when coping with other aging-related chronic illnesses is prevalent.^{9–11} Younger age at onset of pulmonary symptoms in individuals with AATD is often associated with worse psychological and clinical outcomes related to physical and social limitations.¹²

Our previous research showed associations between HRQoL and clinically meaningful aspects of AATD in cross-sectional analyses.¹³ The objectives of this study were to describe the longitudinal changes in HRQoL in a cohort of individuals with AATD-associated lung disease and to evaluate demographic and clinical factors associated with changes in patient-perceived quality of life over time.

Material and Methods

Study Population

This longitudinal study included participants of AlphaNet, a not-for-profit health management organization for individuals with AATD in the United States who are prescribed augmentation therapy.^{8,14} AlphaNet participants are followed regularly (typically monthly) by AlphaNet Coordinators, individuals with AATD who have specialized training. Coordinators provide education and support, connect AlphaNet participants with various disease-related resources, and collect data to assist disease management.

Inclusion and Exclusion Criteria

Data for the current study were collected between 2009 and 2019 via structured telephone interviews. AlphaNet participants were included in this study if they reported having lung disease, had 3 or more SGRQ measurements, and provided data for the following variables at baseline: age, sex, mMRC, frequency of exacerbations, oxygen use, and whether they had productive cough in the year prior to enrollment. Data collected after receiving lung transplants were excluded from the analyses.

HRQoL Measure

HRQoL was measured using the SGRQ, a multi-dimensional, standardized instrument that has been validated for telephone administration.^{15,16} The SGRQ was designed to measure the impact of obstructive airway disease on patients' overall health and daily activities. It contains 50 items and is divided into three sections: symptoms, measuring distress caused by pulmonary symptoms; activity, describing physical activities that cause or are limited by dyspnea; and impact, assessing social and psychological effects of the disease. SGRQ total score is a summary measure of health status. The total score and the three separate domain scores were calculated for each participant. The SGRQ scores range from 0 to 100, where 0 indicates the best, and 100 represents the worst self-perceived health status. At baseline, the SGRQ was administered during a separate telephone interview scheduled after the baseline assessment had been completed (in order to minimize participant burden) and approximately annually thereafter.

Key Baseline Variables

The modified Medical Research Council (mMRC) dyspnea scale was used to assess self-reported breathlessness.¹⁷ It measures the degree of disability that dyspnea imposes on individuals' daily activities. The mMRC dyspnea scale ranges from grade 0 to 4 (0 = "I only get breathless with strenuous exercise"; 1 = "I get short of breath when hurrying on level ground or walking up a slight hill"; 2 = "On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking"; 3 = "I stop for breath after walking about 100 yards or after a few minutes on level ground"; 4 = "I am too breathless to leave the house, or I am breathless when dressing"). The frequency of exacerbations was measured via the following question at baseline: "Over the past year, how frequently have you experienced worsening (exacerbations or flares) of your lung problems?" with possible responses: "every

month/every 3 months/every 4 months/every 6 months/once/never.” For the purposes of the present analyses, we grouped the responses to this question into 3 categories: “none/one/two or more” exacerbations, which align with a clinically relevant categorization of exacerbations. Another key pulmonary symptom – productive cough – was assessed using the following question: “Over the past 2 years, have you coughed up sputum/mucus from your lungs on a daily basis for at least 3 months each year?” In addition, data on oxygen use were collected and analyzed.

Analyses were conducted under a protocol approved by the University of Kentucky Institutional Review Board (#43435) with a waiver of informed consent due to the retrospective analysis of existing data. The data was accessed in compliance with relevant data protection and privacy regulations.

Statistical Analysis

We expressed values for categorical variables as frequencies and proportions and for continuous variables as means, standard deviations (SD), medians, and interquartile ranges (IQR). Mixed-effects models with random intercepts and random slopes¹⁸ were used to estimate the mean annual change in SGRQ total and domain scores over time. The association between baseline mMRC, exacerbation frequency, productive cough, oxygen use, sex, age and the longitudinal change in SGRQ scores was evaluated. These variables were chosen a priori based on their clinical relevance and consistent association with SGRQ scores in existing COPD research. Mixed-effects models are robust for use in unbalanced datasets in longitudinal analyses.¹⁹ An unstructured covariance matrix was selected as the best fit for the data. We performed missing data analysis by comparing the characteristics of individuals who were included in analyses to individuals who were excluded due to missing data.

To address a potential effect of survivor bias and dropouts on the longitudinal SGRQ estimates, we performed sensitivity analyses by stratifying the overall cohort in quartiles by the length of their participation in the study: ≤ 3 years, >3 and ≤ 6 years, >6 and ≤ 9 years, and >9 years. We compared the slope of change in the SGRQ total across these four groups. We also evaluated the correlation between the first SGRQ score at baseline and the length of follow-up.

The significance level for all analyses was set at 0.05. SAS 9.4 was used to perform the analyses.

Results

Participant Cohort

Of the 4694 AlphaNet participants considered for the study, 2456 (52.3%) individuals met the study inclusion criteria and were included in these analyses (Figure 1). The mean length of follow-up was 6.2 ± 3.2 (median 6, IQR 3–9) years. During this time, the study participants provided an average of 5.5 ± 2.4 SGRQ total measurements with an average of 1.4 ± 0.9 years between the observations. There was no significant difference in the length of follow-up by use of oxygen or reporting productive cough at baseline. A shorter length of follow-up was observed in older individuals, males, people with 2 or more exacerbations, and worse grades of breathlessness on mMRC at baseline (data not presented).

Characteristics of the study participants at baseline are presented in Table 1. The mean age of the cohort was 57.1 ± 9.9 years; 46.6% were women, and 97.1% were non-Hispanic White race. At baseline, 47.9% reported regularly using oxygen, 43.8% reported having a daily productive cough for at least 3 months each year over the past 2 years, and 55.4% had 2 or more exacerbations in the past year.

Baseline SGRQ Scores of the Cohort

The average baseline SGRQ total score was 44.7 ± 18.9 . The means of the subscale scores at baseline were: symptoms 46.8 ± 22.7 , activities 63.5 ± 24.6 , and impact 33.3 ± 18.9 . Baseline SGRQ total and subscale score means by demographic and clinical characteristics at baseline are presented in Table 2. The baseline SGRQ total score had a positive dose–response relationship with the number of exacerbations and mMRC grade. There was no difference in mean SGRQ scores by sex. SGRQ total score had an inverse association with age; older individuals reported a lower score, indicating a better quality of life among older participants. The mean SGRQ total score was not significantly associated with the alpha-1 variant (Supplemental Table 1).

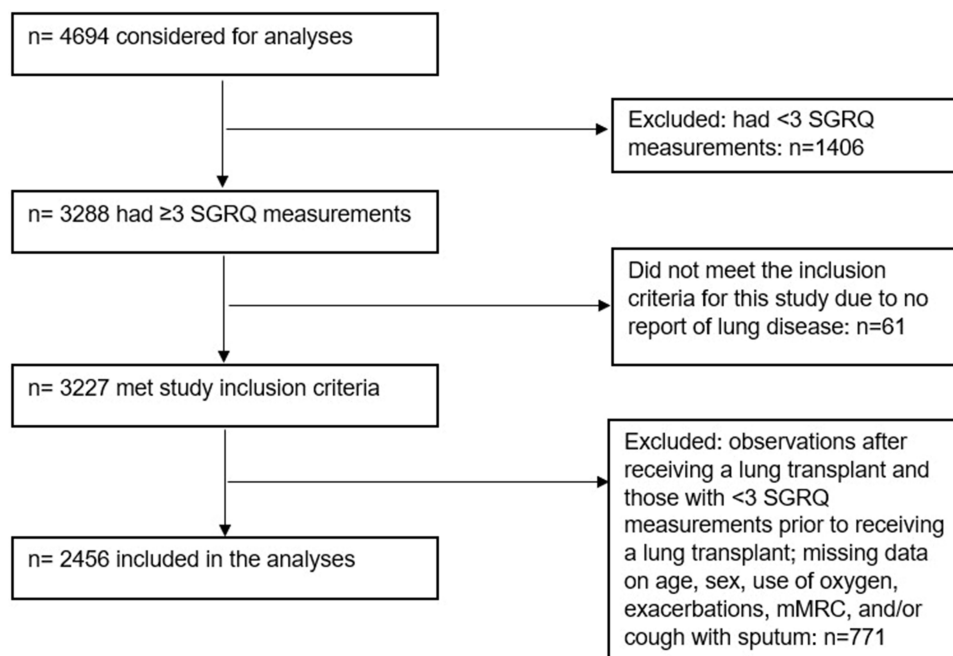


Figure 1 Consort diagram of the study participants.
Abbreviation: SGRQ – St. George’s Respiratory Questionnaire.

Longitudinal Changes in SGRQ Scores

Overall, HRQoL remained stable over time. SGRQ total and impact domain scores showed no significant change over time (Figure 2). The SGRQ activity score showed a slight deterioration over time, with an annual increase of 0.25 units/year. SGRQ symptoms score showed a minor improvement of –0.32 units/year.

Table 1 Baseline Characteristics of the Study Participants, n=2456

Patient characteristic	n (%)
Age, years	
Mean (SD)	57.08 (9.90)
Median (IQR)	57 (50–64)
Age, years	
<50	572 (23.29)
50–65	1391 (56.64)
>65	493 (20.07)
Female	1144 (46.58)
Race/ ethnicity	
Black or African-American	21 (0.86)
Hispanic or Latino	18 (0.73)
Non-Hispanic White	2386 (97.11)
Other	16 (0.65)
Unknown/missing	16 (0.65)
Regular use of oxygen	1177 (47.92)
Frequency of exacerbations in the past year	
0	572 (23.29)
1	523 (21.29)
2 or more	1361 (55.42)

(Continued)

Table 1 (Continued).

Patient characteristic	n (%)
mMRC ^a , mean (SD)	2.31 (1.32)
Median (IQR)	2 (1–4)
mMRC ^a	
0	210 (8.55)
1	609 (24.80)
2	492 (20.03)
3	502 (20.44)
4	643 (26.18)
Daily productive cough for at least 3 months each year over the past 2 years	1076 (43.81)
Self-reported level of comfort with knowledge about Alpha-1	
No	110 (4.51)
Somewhat comfortable	1153 (47.27)
Very comfortable	1176 (48.22)
Data available n=2439	
Alpha 1 variant	
ZZ ^b	1444 (70.40)
SZ	186 (9.07)
MZ	316 (15.41)
Other ^c	105 (5.12)
Data available n=2051	
SGRQ scores at baseline	
SGRQ Total, mean (SD)	44.68 (18.86)
Median (IQR)	45 (31–59)
SGRQ Symptoms, mean (SD)	
Median (IQR)	46.81 (22.72)
Data available n=2441	46 (30–64)
SGRQ Activities, mean (SD)	
Median (IQR)	63.46 (24.55)
Data available n=2454	66 (48–86)
SGRQ Impact, mean (SD)	33.30 (18.92)
Median (IQR)	32 (18–46)
Number of SGRQ measurements, mean (SD)	5.53 (2.35)
Median (IQR)	5 (3–8)
Number of years of follow-up, mean (SD)	6.20 (3.16)
Median (IQR)	6 (3–9)

Notes: ^aModified Medical Research Council scale: 0--I only get breathless with strenuous exercise; 1--I get short of breath when hurrying on level ground or walking up a slight hill; 2--On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking; 3--I stop for breath after walking about 100 yards or after a few minutes on level ground; 4--I am too breathless to leave the house, or I am breathless when dressing. ^bIncludes ZZ, ZNull, NullNull; ^cIncludes FF, FM, FS, FZ, IM, IS, IZ, MS, and other; Data presented in n (%) unless otherwise noted.

Abbreviations: SGRQ- St. George's Respiratory Questionnaire; SD-standard deviation; IQR- interquartile range.

Figure 3 shows annual changes in the mean SGRQ total and subscale scores by mMRC grade based on mixed-effects model analyses. Individuals with higher mMRC grades at baseline had greater improvement in their HRQoL over time compared to those with lower mMRC grades and better SGRQ at baseline. The annual slopes of the SGRQ total score by mMRC grades are presented in Figure 4 (p-value for interaction mMRC grade*time <0.0001). Similarly, individuals reporting a higher number of exacerbations at baseline had a greater change in their SGRQ total score (although the p-value for interaction exacerbation frequency*time =0.064).

Most SGRQ subscales showed stable trajectories across the demographic and clinical characteristics of interest (Supplemental Figures 1–6). SGRQ symptoms subscale score showed greater improvement over time in individuals

Table 2 Baseline SGRQ Total and Subscales Scores by the Participants' Demographic and Clinical Characteristics

	SGRQ Total Score, Mean (SD) n=2456	SGRQ Symptoms Domain, Mean (SD) n= 2441	SGRQ Activity Domain, Mean (SD) n=2454	SGRQ Impact Domain, Mean (SD) n=2456
Age, years				
<50	49.2 (20.5)	52.4 (23.8)	66.8 (26.1)	38.2 (20.5)
50–65	44.7 (18.3)	46.7 (22.2)	63.5 (24.2)	33.3 (18.5)
>65	39.5 (16.9)	40.5 (21.3)	59.5 (23.2)	27.6 (16.4)
Sex				
Female	44.5 (19.4)	46.3 (22.9)	62.7 (25.2)	33.5 (19.7)
Male	44.8 (18.4)	47.2 (22.6)	64.1 (24.0)	33.1 (18.2)
Regular use of oxygen				
No	39.8 (18.5)	43.9 (22.7)	56.4 (24.3)	29.1 (18.2)
Yes	50.0 (17.8)	50.0 (22.3)	71.1 (22.4)	37.8 (18.6)
Frequency of exacerbations in the past year				
0	36.5 (16.7)	37.3 (20.6)	55.1 (23.9)	25.6 (16.0)
1	40.2 (18.0)	40.9 (21.3)	58.9 (24.9)	29.3 (17.7)
2 or more	49.8 (18.4)	53.1 (22.1)	68.7 (23.4)	38.1 (19.1)
mMRC				
0	26.0 (14.5)	32.1 (20.0)	37.9 (21.5)	17.4 (13.6)
1	34.3 (15.6)	38.8 (20.6)	49.6 (21.8)	24.2 (15.3)
2	43.4 (15.8)	44.8 (21.5)	63.1 (20.0)	31.7 (16.6)
3	50.1 (16.5)	51.8 (22.8)	70.6 (20.7)	37.8 (17.2)
4	57.3 (16.1)	56.8 (20.8)	79.6 (19.2)	44.7 (18.3)
Daily productive cough for at least 3 months each year over the past 2 years				
No	40.7 (18.2)	40.2 (21.7)	60.2 (24.6)	29.7 (18.0)
Yes	49.8 (18.4)	55.3 (21.2)	67.7 (23.8)	38.0 (19.1)

Abbreviations: SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council scale; SD, standard deviation.

reporting having productive cough at baseline compared to those not reporting this symptom (p-value for interaction productive cough*time =0.0002).

There were significant differences between total and subscale SGRQ trajectories by baseline age. SGRQ total score annual slopes are shown in Figure 5. Individuals younger than 50 years at baseline started the follow-up period with a significantly worse SGRQ total score but demonstrated a greater improvement in HRQoL over time (annual slope = -0.28/year). Older

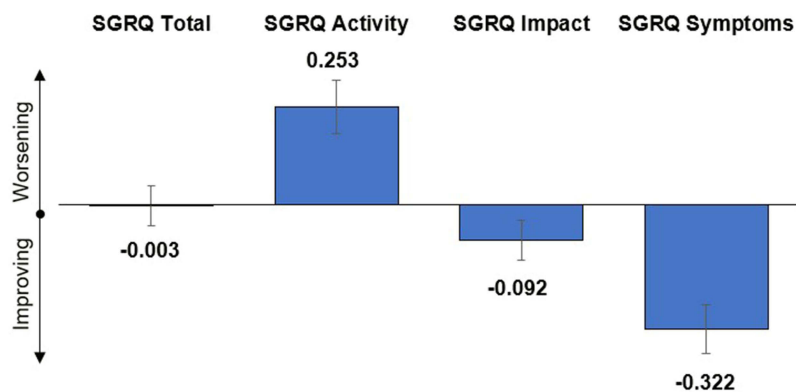


Figure 2 Annual changes in the mean SGRQ total and subscale scores.

Abbreviations: SGRQ – St. George's Respiratory Questionnaire; Error bars reflect standard errors.

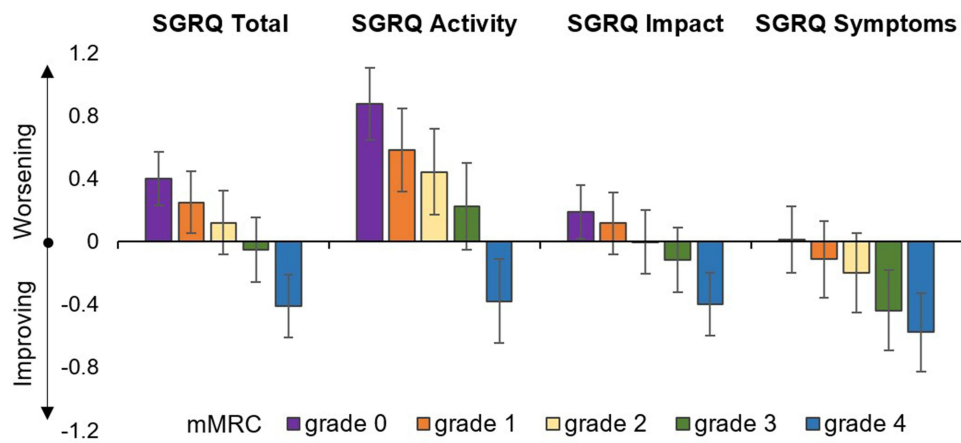


Figure 3 Annual change in the mean SGRQ total and subscale scores by mMRC grade.

Notes: Error bars reflect standard errors.

Abbreviations: SGRQ, St. George’s Respiratory Questionnaire; mMRC, modified Medical Research Council dyspnea scale.

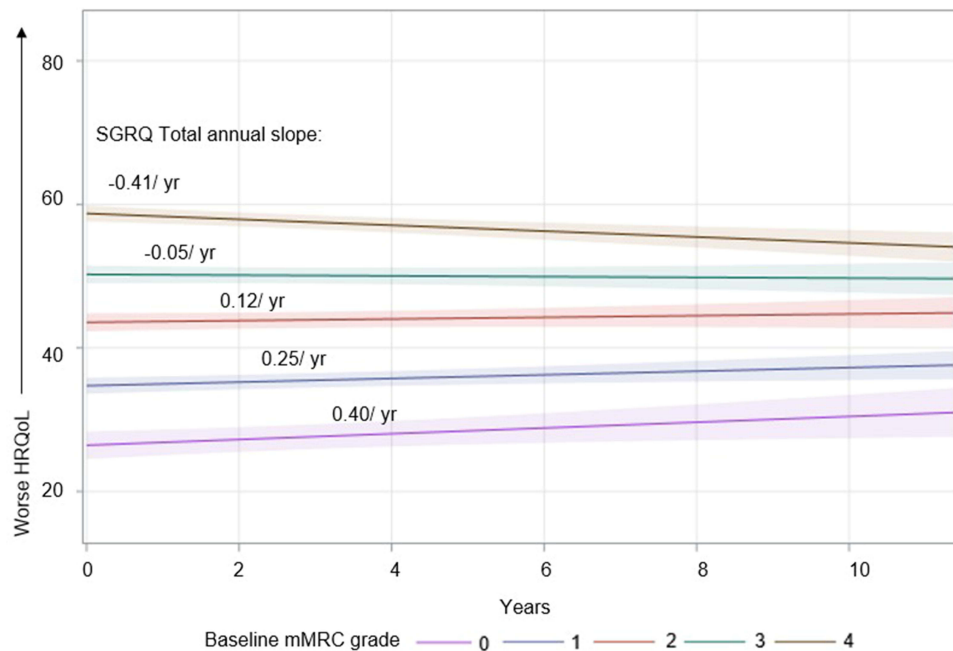


Figure 4 SGRQ Total score longitudinal trajectories by baseline mMRC grade.

Notes: SGRQ Total score Least Square Mean (LSM) and (95% CI) for mMRC grade 0: 26.4 (26.9–30.1), grade 1: 34.7 (34.9–36.8), grade 2: 43.6 (43.0–45.0), grade 4: 50.2 (48.5–50.6), grade 5: 58.7 (55.5–57.4); shaded areas indicate 95% confidence intervals.

Abbreviation: SGRQ- St. George’s Respiratory Questionnaire; mMRC – modified Medical Research Council dyspnea scale.

individuals had significantly better self-perceived HRQoL at baseline but showed gradual deterioration over time (annual slope = 0.35/year), the p-value for interaction baseline age groups*time = 0.0005. Similar slopes were observed for SGRQ activity and impact subscale scores (p-value for interaction baseline age groups*time = 0.0003 and 0.0006, respectively). SGRQ symptoms subscale score trajectories showed gradual improvement for all age groups over time, with a greater improvement in younger adults (p-value for interaction baseline age groups*time = 0.046).

Missing Data Analyses

The comparison of select demographic and clinical characteristics between individuals included and excluded from this study due to data unavailability on key variables and having had lung transplants are presented in [Supplemental Table 2](#).

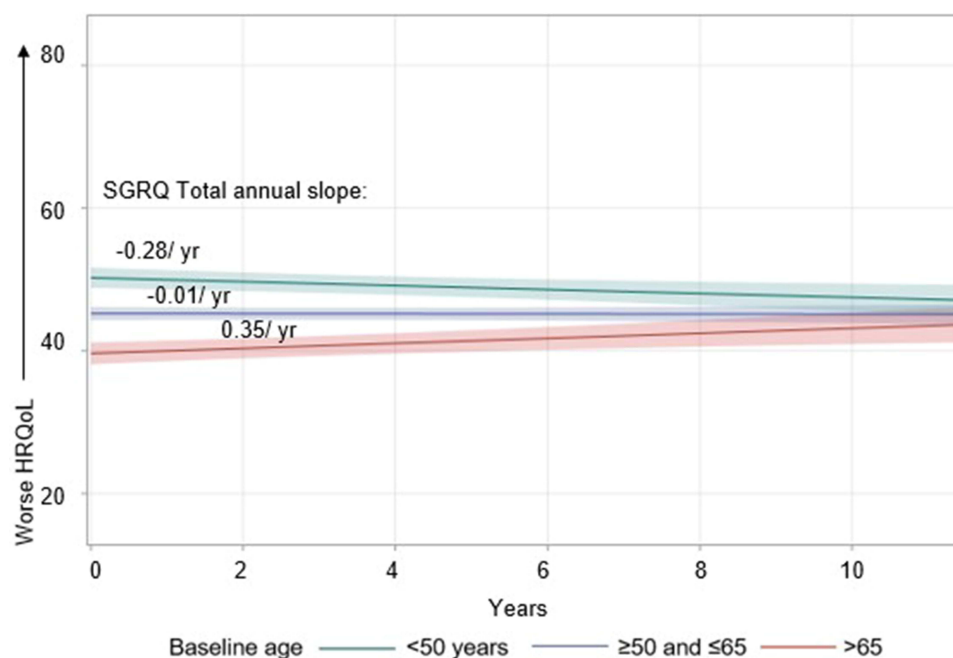


Figure 5 SGRQ Total score longitudinal trajectories by baseline age.

Notes: SGRQ Total score Least Square Mean (LSM) and (95% CI) for baseline age <50 years: 50.2 (48.8–51.7), ≥50 and ≤65 years: 45.2 (42.1–48.4), >65 years: 39.6 (36.1–43.2); shaded areas indicate 95% confidence intervals.

Abbreviation: SGRQ – St. George's Respiratory Questionnaire.

Individuals excluded were older, had higher mMRC, had a higher frequency of oxygen use, and were less comfortable about their AATD knowledge. Excluded individuals had, on average, higher (worse) SGRQ total, activities, and impact scores at baseline compared to the individuals included in this study.

Sensitivity analyses

On correlation analyses, we found no association between baseline SGRQ total and subscale scores and the number of years of follow-up ([Supplemental Table 3](#)). In mixed-effect model analyses, individuals who contributed 3 or fewer years to the study demonstrated an annual increase in SGRQ total score of 1.00/year, >3 and ≤6 years had 0.30, >6 and ≤9 years 0.17, and >9 years -an improvement of -0.22/year.

Discussion

The present study demonstrates stable HRQoL trajectories over time among individuals participating in a health management program for people with AATD-associated lung disease in the United States who are prescribed augmentation therapy. The annual change in the SGRQ total score was well below the minimal clinically important difference (MCID) of 4 points. Previous studies show similar findings in patients with COPD^{20,21} and AATD-associated lung disease,²² although other research reports a greater rate of worsening of HRQoL in participants with AATD not on augmentation therapy.²³ SGRQ symptoms subscale scores showed slight improvement over time, indicating reduced distress caused by pulmonary symptoms. SGRQ activity subscale scores worsened slowly over time, reflecting the physical activities that cause or are limited by dyspnea. SGRQ impact subscale scores, assessing social and psychological effects of the disease, remained stable. Similar changes in SGRQ subscales were previously reported in a group of patients with AATD-associated lung disease not on augmentation therapy.²²

These clinically negligible changes in total SGRQ and its subscales over long periods of time suggest that the SGRQ and likely other respiratory-specific quality-of-life tools will not be good measures of therapeutic efficacy in clinical trials in AATD. Whether this is reflective of the slow progression of emphysema that characterizes this disease or the sensitivity of the HRQoL tools employed remains to be defined. However, the other possibility is that disease management may impact SGRQ

trajectories in a beneficial direction. An early study by Campos et al and a recent meta-analysis suggest that disease management may influence SGRQ trajectories.⁸ Campos et al examined changes in SGRQ trajectories before and after the first year in which AlphaNet implemented its disease management program; findings in this smaller cohort of AlphaNet participants showed a slowing in the rate of worsening of the activity subscale score in the first year of disease management.⁸ In a recent meta-analysis, self-management programs in individuals with COPD showed significant improvements in all aspects of HRQoL, measured by SGRQ, and improved exercise capacity.²⁴

We observed that individuals with worse dyspnea at baseline, reflected by higher mMRC scores, had gradually improved HRQoL over the duration of the observation period. Individuals with no or low levels of dyspnea remained largely stable. Specifically, the SGRQ symptoms subscale showed a lowered burden of pulmonary symptoms and improved health quality across all grades of dyspnea.

In this cohort, individuals with AATD-associated lung disease are younger than usual non-AATD-related COPD patients. In fact, almost a quarter of our study population is younger than 50 years at baseline. We observed significantly worse HRQoL perceived by younger participants at the beginning of the observation period. This might be associated with higher quality of life expectations at younger ages or greater self-perceived burden of pulmonary symptoms and associated distress. Indeed, younger individuals in our cohort self-reported a higher degree of disability that dyspnea imposes on daily activities, measured by mMRC. Our findings agree with previous studies that identified a similar inverse relationship between HRQoL and age in people with COPD,^{25–27} and AATD-associated lung disease.^{9,12} However, it is worth noting that other studies have found no association between HRQoL and age in people with COPD.^{28,29} Over time, younger participants showed significant improvement in HRQoL, specifically in the symptoms and impact domains. This may be related to the benefits of participation in the health management program on the social and psychological burden of the disease. Specifically, AlphaNet coordinators regularly contact the program participants, coordinate their services, and provide disease-related education and support.

Older participants in our study reported better HRQoL at baseline compared to younger individuals. Trajectories of SGRQ total and subscale scores in people over 65 years showed gradual worsening over time, except for the symptoms subscale, which remained stable. The activities subscale showed the greatest increase in older individuals, reflecting the impact of dyspnea on their regular physical activities. This is an important insight since the capacity to perform physical activity is closely linked to an individual's self-perceived dyspnea burden.³⁰ Indeed, shortness of breath often leads to inactivity and physical deconditioning and impacts mobility. These findings are consistent with a study that found a significant association between dyspnea in people with COPD and the physical health component of HRQoL and a moderate association with a mental health component of HRQoL measured using the SF-36 instrument.³¹

Other clinical features of COPD, including oxygen use, exacerbation frequency, and cough, are associated with baseline differences in SGRQ, as would be expected. However, we were surprised to see that longitudinal changes in SGRQ and SGRQ subscales were minimal and produced nearly parallel trajectories, as shown in the graphs in [Supplementary Figures 1-6](#). This is unlike usual COPD, in which exacerbations drive decrements in quality of life over time. Further analysis of exacerbations in AATD seems warranted since the impact of disease management may be attenuating the expected SGRQ decline.

Strengths and Limitations

The findings of our study should be evaluated in view of its strengths and potential limitations. One of the main strengths of our study is the large study population consisting of individuals with AATD and rich clinical and HRQoL data collected in this cohort over many years. All individuals in this study participate in AlphaNet's disease management program, which presents an exceptional opportunity to assess HRQoL in this unique, geographically diverse population with AATD-associated lung disease. Our study included a high number of follow-up SGRQ measurements, which is a definite strength of a longitudinal study, allowing for a robust statistical analysis.

One of the limitations of our study is the unavailability of data on some factors, such as pulmonary function, potentially associated with HRQoL. Recall bias and reporting bias cannot be excluded due to the self-reported nature of the data used in this study. Further, our study population consisted of participants of AlphaNet who received tailored disease-specific education and resources about the improvement of the quality of their lives. Therefore, the findings of

this study may not be generalizable to the general population of people with AATD-associated lung disease. In addition, individuals who were excluded from analyses tended to be older and in worse health, as indicated by higher mMRC scores, higher likelihood of using oxygen, and worse SGRQ scores at baseline. Thus, our findings may not generalize to all participants in AlphaNet. Also, our sensitivity analyses found an association between longitudinal change in HRQoL and length of study follow-up. This suggests that deterioration in HRQoL may be associated with early study withdrawal and potential “healthy survivor” bias when the sickest individuals tend to discontinue follow-up. This differential dropout has been documented in other COPD studies.^{32,33} Considering the unavailability of mortality data for these analyses, we were not able to ascertain the vital status of the dropouts. Therefore, interpretations from this study and other real-world registry data should be evaluated with caution.^{34,35}

Conclusions

HRQoL is an important patient-reported measure of respiratory health in AATD-associated lung disease, considering the absence of a cure and the emphasis on disease management. We observed long-term stability in HRQoL and an association between the rate of change in SGRQ and key baseline parameters of COPD severity, such as mMRC, exacerbation frequency, productive cough, and use of oxygen in individuals with AATD-associated lung disease participating in a disease management program.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Radmila Choate reports research support for AlphaNet. Dr Kristen Holm is affiliated with AlphaNet and reports personal fees from AlphaNet, outside the submitted work. Dr Robert Sandhaus is affiliated with AlphaNet and reports contract payments to AlphaNet, Inc. for Disease Management Services from Grifols and CSL Behring; grants to AlphaNet for Disease Management Services from Takeda, grants from Vertex for investigations in multicenter clinical trial at National Jewish Health and Inhibrx. In addition, he is also the data monitoring committee member for Takeda Alpha-1 liver therapy trial, advisory committee member for Grifols, CSL Behring, Beam, Kooro Bio, Intellia, ADARx, ARespo, Evolve, and Vertex. Some of these companies paid travel expenses. Dr David Mannino reports personal fees from AstraZeneca, GlaxoSmithKline, Regeneron, and Genentech, outside the submitted work. Dr Charlie Strange is a medical director of AlphaNet and reports personal fees and/or non-financial support from AlphaNet and Inhibrx. He also reports grants/personal fees from Grifols, Takeda, CSL Behring, Dicerna, from Inhibrx, and Vertex, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet*. 2004;364(9434):613–620. doi:10.1016/S0140-6736(04)16855-4
2. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis*. 2016;3(3):668. doi:10.15326/jcopdf.3.3.2015.0182
3. Eden E. Asthma and COPD in alpha-1 antitrypsin deficiency. evidence for the Dutch hypothesis. *COPD*. 2010;7(5):366–374. doi:10.3109/15412555.2010.510159
4. Zamzam MA, Azab NY, El Wahsh RA, Ragab AZ, Allam EM. Quality of life in COPD patients. *Egypt J Chest Dis Tuberculosis*. 2012;61(4):281–289. doi:10.1016/j.ejcdt.2012.08.012
5. Jones P, Wijkstra PJ. Quality of life in patients with chronic obstructive pulmonary disease. *Europ Respir Monograph*. 2006;38:375.
6. Ståhl E, Lindberg A, Jansson S-A, et al. Health-related quality of life is related to COPD disease severity. *Health Qual Life Outcomes*. 2005;3(1):1–8. doi:10.1186/1477-7525-3-56
7. Jenkins C, Rodriguez-Roisin R. Quality of life, stage severity and COPD. *Eur Respir Soc*. 2009;33(5):953–955. doi:10.1183/09031936.00019009
8. Campos MA, Alazemi S, Zhang G, Wanner A, Sandhaus RA. Effects of a disease management program in individuals with alpha-1 antitrypsin deficiency. *COPD*. 2009;6(1):31–40. doi:10.1080/15412550802607410
9. Holm KE, Borson S, Sandhaus RA, et al. Differences in adjustment between individuals with alpha-1 antitrypsin deficiency (AATD)-associated COPD and non-AATD COPD. *COPD*. 2013;10(2):226–234. doi:10.3109/15412555.2012.719049
10. Kwon H-Y, Kim E. Factors contributing to quality of life in COPD patients in South Korea. *Int J Chronic Obstr*. 2016;103–109. doi:10.2147/COPD.S90566
11. Lazarus RS, DeLongis A. Psychological stress and coping in aging. *Am Psychologist*. 1983;38(3):245. doi:10.1037/0003-066X.38.3.245
12. Holm KE, Plaufcan MR, Ford DW, et al. The impact of age on outcomes in chronic obstructive pulmonary disease differs by relationship status. *J Behav Med*. 2014;37(4):654–663. doi:10.1007/s10865-013-9516-7
13. Choate R, Holm KE, Sandhaus RA, Mannino DM, Strange C. Health-related Quality of Life in alpha-1 antitrypsin deficiency-associated COPD. *Am J Respir Crit Care Med*. 2023;208(ja):1132–1134. doi:10.1164/rccm.202304-0697LE
14. Alphas Serving Alphas. AlphaNet. Available from: <https://www.alphanet.org/>. Accessed december 15, 2022.
15. Jones P, Quirk F, Baveystock C. The St George's Respiratory Questionnaire. *Respir Med*. 1991;85:25–31. doi:10.1016/S0954-6111(06)80166-6
16. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis*. 1992;145(6):1321–1327. doi:10.1164/ajrccm/145.6.1321
17. Williams N. The MRC breathlessness scale. *Occup Med*. 2017;67(6):496–497. doi:10.1093/occmed/kqx086
18. Pinheiro JC, Bates DM. Linear mixed-effects models: basic concepts and examples. *Mixed Effects Models S S-Plus*. 2000;3–56.
19. Schielzeth H, Dingemans NJ, Nakagawa S, et al. Robustness of linear mixed-effects models to violations of distributional assumptions. *Meth Ecol Evolut*. 2020;11(9):1141–1152. doi:10.1111/2041-210X.13434
20. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. Longitudinal deteriorations in patient reported outcomes in patients with COPD. *Respir Med*. 2007;101(1):146–153. doi:10.1016/j.rmed.2006.04.001
21. Ferrari R, Tanni SE, Caram LM, Naves CR, Godoy I. Predictors of health status do not change over three-year periods and exacerbation makes difference in chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. 2011;9(1):1–10. doi:10.1186/1477-7525-9-112
22. Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological, and health status measurements in α 1-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med*. 2001;164(10):1805–1809. doi:10.1164/ajrccm.164.10.2106036
23. Stolk J, Ng W, Bakker M, et al. Correlation between annual change in health status and computer tomography derived lung density in subjects with α 1-antitrypsin deficiency. *Thorax*. 2003;58(12):1027. doi:10.1136/thorax.58.12.1027
24. Cannon D, Buys N, Sriram KB, Sharma S, Morris N, Sun J. The effects of chronic obstructive pulmonary disease self-management interventions on improvement of quality of life in COPD patients: a meta-analysis. *Respir Med*. 2016;121:81–90. doi:10.1016/j.rmed.2016.11.005
25. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5):1418–1422. doi:10.1164/ajrccm.157.5.9709032
26. Ferrari R, Tanni SE, Lucheta PA, Faganello MM, RAFd A, Godoy I. Gender differences in predictors of health status in patients with COPD. *J Bras Pneumol*. 2010;36(1):37–43. doi:10.1590/S1806-37132010000100008
27. Martinez CH, Diaz AA, Parulekar AD, et al. Age-related differences in health-related quality of life in COPD: an analysis of the COPDGen and SPIROMICS cohorts. *Chest*. 2016;149(4):927–935. doi:10.1016/j.chest.2015.11.025
28. Hynninen MJ, Pallesen S, Nordhus IH. Factors affecting health status in COPD patients with co-morbid anxiety or depression. *Int J Chron Obstruct Pulmon Dis*. 2007;2(3):323.
29. Ekici A, Bulcun E, Karakoc T, Senturk E, Ekici M. Factors associated with quality of life in subjects with stable COPD. *Respir Care*. 2015;60(11):1585–1591. doi:10.4187/respcare.03904
30. Ries AL. Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. *Am J Med*. 2006;119(10):12–20. doi:10.1016/j.amjmed.2006.08.003
31. Justine M, Tahira F, Mohan V. Health-related quality of life, lung function and dyspnea rating in COPD patients. *Monaldi Arch Chest Disease*. 2013;79(3–4). doi:10.4081/monaldi.2013.5209
32. Jones PW, Anderson JA, Calverley PM, et al. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res*. 2011;12(1):1–8. doi:10.1186/1465-9921-12-71
33. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–1554. doi:10.1056/NEJMoa0805800
34. Vasakova M, Sterclova M, Moğulkoç N, et al. Healthy survivor bias in patients with idiopathic pulmonary fibrosis in clinical registries. *Eur Respir Soc*. 2021.
35. Elston DM. Survivorship bias. *European Respiratory Journal*. 2021; 58: PA477. doi:10.1183/13993003.congress-2021.PA477

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