

Original Research**Lung Function Variability in Alpha-1 Antitrypsin Deficiency: Implications for Clinical Trials**

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Abbreviations: AATD- Alpha-1 antitrypsin deficiency; FEV1- Forced expiratory volume in 1 second; DLCO- Diffusing capacity of the lung for carbon monoxide; PFT- Pulmonary function test; NHLBI- National Heart, Lung, and Blood Institute; LMM- Linear mixed-effects models; COPD- Chronic obstructive Pulmonary Disease; FDA- US Food and Drug Administration; FVC- Forced vital capacity; SD- Standard deviation;

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ABSTRACT

Background: Alpha-1 antitrypsin deficiency (AATD) has considerable interindividual variability in lung disease progression. Pulmonary impairment is often measured by forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO). This study aimed to quantify within-person variability in pulmonary function test (PFT) measures and identify baseline factors associated with variability.

Methods: Adult participants with AATD enrolled in the National Heart, Lung, and Blood Institute (NHLBI) Registry (1989-1992) were eligible for inclusion in this analysis if they had three serial PFTs and severe genetic deficiency. PFT variability was evaluated using linear mixed-effects models (LMM) with maximum likelihood estimation. Intra-subject variability was assessed through residual analyses. Baseline predictors, including age, sex, augmentation therapy, liver disease, and FEV1% predicted, were examined as fixed effects.

Results: The analytic FEV1 cohort ($n = 832$) had a mean age of 46.3 ± 10.1 years, 44.4% were female, and 99% were white. Over a mean of 4.4 ± 1.4 years of follow-up, participants completed an average of 5.7 ± 2.0 spirometry tests. FEV1 varied by more than 10% of baseline in 82% of participants and by more than 20% in 55%. DLCO varied by more than 10% in 91% and by more than 20% in 43% of participants.

Conclusions: Substantial individual variability in FEV1 and DLCO was observed in this large AATD cohort. These findings suggest that FEV1 and DLCO are unreliable as clinical trial or stopping rule endpoints in AATD.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a genetic cause of chronic obstructive pulmonary disease (COPD) resulting from mutations in the *SERPINA1* gene.(1) Although pulmonary emphysema is the predominant COPD endotype observed in AATD, airways hyperresponsiveness, chronic bronchitis, bronchiectasis, and normal lung function can occur among individuals with the ZZ genotype, the most common severe deficiency genotype. (2)

Despite a common genetic etiology, there is substantial heterogeneity in disease expression among individuals with AATD. This variability reflects the influence of environmental exposures on lung function, more frequent exacerbations compared with individuals with COPD without *SERPINA1* variants, and differences in therapeutic management.(3) Interpretation of lung function is further complicated by the frequent presence of hyperinflation due to emphysema, as spirometric variables and quantitative measures of emphysema are often poorly correlated, and these relationships can change over time.(4)

Variability in pulmonary function test (PFT) measurements is well recognized (5) and has been described in different patient populations, including those without lung disease and those with COPD or asthma. However, few studies have examined PFT variability specifically in AATD, particularly in individuals with manifestations of lung or liver disease.(6) Historically, various thresholds have been proposed to define clinically meaningful change in lung function over time (for example, absolute change of 100 mL, percent change of 10%, or short-term changes of 12% and 200 mL for forced expiratory volume in 1 second (FEV₁)). (7-11) However, more recent guidelines acknowledge that PFT changes over time depend on multiple factors, including age, sex, baseline lung function, and underlying disease, which limits the generalizability of these thresholds and emphasizes the importance of individualized approaches for accurate interpretation.(12)

Since the 1980s, clinical trial designs in AATD populations have included FEV₁ and DLCO as key outcome measures.(13, 14) However, few studies have demonstrated that available therapies significantly alter these spirometric biomarkers.(15) In part, this may reflect the poor correlation between FEV₁, a measurement of airway flow, and emphysema, an alveolar disease. Moreover, DLCO is known to exhibit marked variability, which has limited its use in most clinical trial designs. More recently, changes in FEV₁ and DLCO have been proposed as stopping rules for some clinical trials in AATD. Stopping rules are designed to prevent study participant harm; however, if they are too rigid, then the validity of trial outcomes can be affected if participants do not get their active or placebo medications.

To address this gap, we aimed to characterize PFT variability and identify subject-related factors associated with PFT changes over time within a large longitudinal cohort of individuals with AATD. The overarching goal of the study was to generate robust evidence on the natural variability of lung function in AATD, with and without liver disease, to improve understanding

of the disease trajectory and disease burden and better distinguish clinically meaningful changes in PFTs over time from PFT variability.

METHODS

This was a retrospective analysis of data from the *Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin*, a longitudinal epidemiological study initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the US Food and Drug Administration (FDA).^(16, 17) The registry protocol was reviewed and approved by the appropriate institutional review board at each of the 37 participating clinical centers. The registry followed individuals with AATD for up to seven years, with annual or semiannual spirometry measurements. Between March 1989 and October 1992, a total of 1,129 individuals of ≥ 18 years of age were enrolled. Of these, 1,026 had a serum AAT level $\leq 11\mu\text{M}$ and 103 had an SZ, ZZ, or ZNull genotype confirmed by DNA gene-probe analysis. Follow-up continued through April 1996. Among all enrolled participants, 927 had at least two postbronchodilator FEV₁ and forced vital capacity (FVC) measurements obtained at least 1 year apart.

Important to this study, rigorous spirometry quality control procedures were implemented across the 37 participating centers in the US and Canada to ensure high-quality, reproducible spirometry results with daily calibration and biologic controls. High reproducibility rates were achieved for both prebronchodilator (95.0%) and postbronchodilator (95.7%) FEV₁ measurements at baseline.⁽¹⁸⁾ Although interpretation strategies for spirometry have changed over the past 30 years, the recommended testing maneuvers have remained largely consistent. Therefore, this dataset was deemed suitable for evaluating longitudinal variability in spirometry and DLCO over time in individuals with AATD. Decisions about treatment with intravenous AAT were made by the participants' physicians, not by the registry. The smoking status of the registry participants was self-reported.

The inclusion criteria for this analysis were a serum AAT level $\leq 11\mu\text{M}$ or an SZ, ZZ, or ZNull genotype confirmed by DNA gene-probe analysis. To generate reliable estimates of lung function slopes, participants were required to have at least three postbronchodilator FEV₁ measurements and three or more DLCO measurements within each 18 months of follow-up. Participants were censored from analysis at the time of lung transplantation. The final analytic sample included 832 individuals with 3 or more spirometry assessments and 586 with 3 or more DLCO measurements (Figure 1).

Predicted and percent predicted values for FEV₁ and FVC were calculated using the Global Lung Function Initiative (GLI) race-neutral reference equations, implemented through the R package *rspi*. Bronchodilator responsiveness was assessed using two approaches: the "Old" criteria, defined as an increase of at least 12% from the pre-bronchodilator value and an absolute change of at least 200 mL, and the "New" method, defined as an increase of at least 15% of the predicted value.

Statistical Analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. Categorical variables were described using frequency and percentage within each category; continuous variables were described using mean and standard deviation (SD). Frequencies and percentages of missing and non-missing observations were reported. Baseline characteristics were summarized for the entire NHLBI cohort, the analytic datasets, and relevant subgroup analyses.

PFT variability was evaluated using linear mixed-effects models (LMM), which are robust to unbalanced data and missing observations under maximum likelihood estimation. Model fit was evaluated using the Akaike information criterion and Bayesian information criterion. Intra-subject variability was quantified through residual analysis, defined as the difference between observed PFT values and model-predicted values (Figure 2). Residual distributions were examined, and subject-level analyses were performed to characterize intra-subject variability. Time to event analyses were performed by Kaplan- Meier methodology.

To evaluate the associations between PFT variability and baseline characteristics, baseline variables of interest (age, sex, augmentation therapy use, presence of liver disease, and FEV1% predicted) were included as fixed effects in the LMMs. Interaction terms were incorporated as appropriate, and AIC and BIC were used to evaluate the best model fit. A sensitivity analysis was performed in the subset of participants who reported never smoking.

Analyses were conducted using SAS (SAS Institute, Cary, NC) version 9.4.

RESULTS

Baseline characteristics of the study population

Of the overall NHLBI dataset (n=1126), 832 participants were included in the FEV1/FVC analytic dataset based on the study inclusion criteria (Figure 1). Baseline characteristics of the participants included in the spirometry analysis were similar to those of the overall registry cohort (**Table 1**). In the spirometry cohort, the mean age was 46.3 ± 10.1 years, 44.4% were female, and 99.0% were white. The majority (76.3%) had a history of smoking. In terms of alcohol use, 16.1% were former drinkers and 63.8% were current drinkers. Liver disease was present in 6.4% of the participants, whereas 83% had lung disease; two participants had undergone liver transplant at baseline. Augmentation therapy was used at baseline by 67.4% of the cohort. Participants completed an average of 5.7 ± 2.0 spirometries over 4.4 ± 1.4 years that were typically performed at 6-month intervals. Baseline characteristics of the DLCO analytic cohort (n=568) were similar.

Baseline characteristics of the FEV1/FVC analytic dataset were evaluated by several parameters: baseline FEV1% predicted ($<50\%$ and $\geq 50\%$), use of augmentation therapy, presence of liver

disease, and bronchodilator responsiveness (defined as $\geq 12\%$ from pre-bronchodilator values and with ≥ 200 ml change, and by a $> 10\%$ change of the predicted FEV1 value) (**Supplemental tables 1.1-1.4**).

FEV1 Variability

In 82.1% of participants (683/832), FEV1 had a 10% or more change from the baseline value on at least one occasion. The frequency distribution of the largest percentage change over time is shown in **Figure 3**. Among all participants whose largest observed change was a decline, the mean largest decline in FEV1 from baseline was 23.5%, while those with their largest FEV1 change as an increase had a mean largest change of 19.4%. The distribution of the number of events with a $\geq 10\%$ or $\geq 20\%$ change in FEV1 from baseline is shown in **Figure 4**. Overall, most participants demonstrated FEV1 variability $\geq 10\%$ from baseline on multiple occasions. When applying varying thresholds of FEV1% change from baseline (**Supplemental Table 1.5**), 44.8% of the cohort still had changes that exceeded a 20% threshold. The frequency distribution of the number of events surpassing the $\geq 20\%$ threshold is also shown in **Figure 4**.

Among all study participants in the spirometry analytic cohort, the mean annual decline in FEV1 was 55 ml, consistent with that reported in the larger NHLBI cohort. We observed a steeper FEV1 decline (-63.33 ml/year) in males compared to females (-44.59 ml/year) ($p < 0.0001$). In addition, younger individuals aged < 39 years had a steeper decline (-69.21 ml/year) compared to those aged > 52 (-45.39 ml/year) ($p < 0.0001$). FEV1 slope was not different between smokers and non-smokers, likely because most individuals had stopped smoking during the NHLBI registry. Detailed results are presented in the supplemental materials (**Supplemental Figures 1.1-1.6**).

Residual-based analysis provided a more precise evaluation of longitudinal differences in FEV1. The baseline lung function value heavily influenced subsequent variability. In the example given in **Figure 2**, a low baseline FEV1 value heavily influenced the chances of a downstream event. This supports the practice in clinical trials of performing spirometry twice at baseline to establish a more robust reference point for slope estimation.

FVC Variability

Based on the largest difference value from baseline per patient, 75.6% of the cohort had one or more events of $\geq 10\%$ change in FVC% from the baseline. Nearly half (47.24%) of the cohort had a decline that was 10% or more from the baseline. The median value of the largest difference per patient in FVC% was -8.87%. The average annual decline in FVC in the overall cohort was 58 ml. We did not observe differences in FVC slopes by sex, age, augmentation therapy, or liver disease at baseline (data not shown).

DLCO Variability

Among the 586 individuals in the DLCO analytic cohort, the mean baseline DLCO was 17.3 ± 7.5 mL/min/mmHg. The majority (91.3%) of the cohort experienced a change from baseline of

$\geq 10\%$, 58.4% of the cohort experienced that change as a $\geq 10\%$ decrease from baseline, and 43.2% experienced a $\geq 20\%$ decrease. The results of the DLCO analysis are included in the Supplemental materials (**Supplemental Figures 2.1- 2.7**).

Kaplan-Meier Analyses

Time to event analyses in **Figure 5** show that half of participants reached a 10% decline in FEV1 at 3.0 years and a 10% decline in DLCO at 2.9 years. Median time to 20% decline occurred at 5.1 years for FEV1 and 5.2 years for DLCO (**Table 2**). The number of participants who met these thresholds appears linear over the 5 years that the majority of participants were being evaluated.

DISCUSSION

Variability in pulmonary function testing remains a major challenge in clinical trials across all obstructive pulmonary diseases. Consequently, marked time and dedication applied to minimizing testing variability have been used, including standardizing spirometry equipment to the same machine and the same operator for study durability. However, these strategies have had limited success, as FEV1 and DLCO are intrinsically affected by participant effort, emphysema, mucus, airway tone, medications, and environmental factors. As a result, large sample sizes are typically required for studies in COPD and asthma to overcome this inherent variability. Further, the FEV1 is an intrinsic target of bronchodilator medications, but not medications that have no bronchodilator activity.

In AATD, FEV1 and DLCO are insensitive biomarkers of disease progression. Emphysema on CT imaging clearly precedes any decline in FEV1 in the natural history of disease. As emphysema develops, lung volumes often increase. The subsequent increase in FVC usually elevates FEV1 in mild disease before FEV1 begins to fall from airways disease and bronchiolar collapse. Lung function also changes during exacerbations, and recovery periods in CT and spirometry may take 6 weeks or longer to show. Thus, the variability in FEV1 does not reproducibly reflect the progression of emphysema. Current state-of-the-art monitoring of PFTs in COPD suggests that measuring more frequently than every 6-12 months does not reveal changes that reflect disease progression. This underscores the need for other, more specific biomarkers of emphysema progression.

In addition, our analysis of inter-subject variability revealed that sex and age significantly influenced pulmonary function decline. Males exhibited a steeper decline in FEV1 and DLCO compared to females, while younger individuals (<39 years) experienced a more pronounced decline in FEV1 than those over 52 years. However, these findings should be interpreted with caution, as the changes are small and may reflect smoking habits common in the 1990s. Further, these observations may be the effect of higher losses if lung function is preserved, since there is more opportunity to lose volume from higher baseline values.

Increases of 10% in either measure are almost as frequent as decreases, highlighting the magnitude of natural variability even under standardized conditions. These findings align with prior observations in AATD cohorts and in COPD, where repeated spirometry frequently fails to capture clinically meaningful decline.(7) For example, studies have shown that spirometric follow-up over five years identifies only about half of patients with rapid FEV₁ decline, and more than half of those with CT-based emphysema progression show no parallel FEV₁ change.(19, 20) Similarly, studies show that both FEV₁ and DLCO exhibit day-to-day variability, with intraindividual variability reaching up to 10% depending on device and test conditions.(21, 22) No technique can be universally applied to improve this natural variability seen in the majority of AATD trials. Alternative biomarkers such as CT densitometry and enhancements to CT scan metrics of airway and alveolar function, which directly quantify lung tissue density and correlate more closely with emphysema progression, may offer greater sensitivity and reproducibility.(23)

The high intrinsic variability of PFTs in AATD reflects several factors: the effort-dependent nature of spirometry, the heterogeneity of lung involvement, and the impact of exacerbations (which occur on average twice yearly in AATD patients),(24) and differences in airway versus alveolar pathology. Furthermore, reliance on single measurements amplifies these effects, and at least three serial PFTs are needed to estimate a reliable slope of decline. Further, the difficulty finding a meaningful clinically important difference (MCID) in usual COPD that requires triangulation with meaningful clinical events is even more difficult in AATD. This study would suggest that an AATD MCID for FEV₁ or DLCO may be an abstract concept.

Historically, AATD clinical trials have used FEV₁ and DLCO as preferred clinical outcome measures. However, few trials have been successful when these outcomes are used. As an example, the original NHLBI Registry showed no difference in FEV₁ slope associated with use of augmentation therapy in the entire cohort (25), despite that fact that mortality differences were present (26).

The current analysis demonstrates that neither FEV₁ nor DLCO is suitable as a stopping rule in AATD clinical trials, due to the high intrinsic variability.(27). There are many reasons that stopping rules can fail to meet the goal of participant safety protection. The most important aspects of this study show a very high intrinsic variability. Further, the natural history of lung function decline suggests that over time all participants would be stopped from receiving drug or placebo. Because the average annual decline in FEV₁ in this cohort was approximately 55 ml, the frequency of reaching stopping thresholds of >10% decline from baseline FEV₁ measures due to natural history progression is high. A more meaningful threshold of at least 20% would better correlate with clinical disease progression, but any threshold also depends on trial duration. Conceivably, a yearly discount in expected values from baseline lung function would be needed to prevent cessation of participation in all study subjects over time. Therefore, adjusting expected lung function over time is a more rational scientific methodology for clinical trial stopping rules

compared to an established 10% stopping rule from baseline that lives throughout the life of a clinical trial.

Our study has some limitations. Clinical care for the NHLBI cohort participants was not centralized and may have led to systematic differences in outcomes depending on the clinical centers and the managing physicians. Other unobserved factors, such as intensity of care received and the daily behaviors of subjects, could have confounded the relationship between pulmonary function change and baseline characteristics. Data on several variables included in this study are self-reported and subject to recall and reporting bias. The NHLBI cohort did not query COPD exacerbations in real time, and some of the observed variability events may reflect exacerbations that would be recognized in a more robust clinical trial design today. Although follow-up visits were delayed up to 6 weeks after exacerbations in the NHLBI study, to attempt to mitigate this, residual effects likely remained. In addition, excluding participants with less than 3 lung function measurements that are at least 6 months apart may have introduced potential selection bias. Thus, the results of this study may not be generalizable to all individuals with AATD. Participants who returned for serial testing (832 for spirometry and 586 for DLCO) represented a subset of the full NHLBI cohort and may differ from others in the AATD populations at large. In general, this population had more lung disease than many of the liver-focused studies today. Additionally, a floor effect exists for both FEV1 and DLCO in which PFTs do not fall as quickly with advanced lung disease.

Since these individuals are included in the NHLBI cohort, the variability is likely to be even higher in those with higher baseline lung function. Our findings demonstrate that higher baseline lung function is associated with substantial variability in FEV1 and DLCO. We were surprised to see that FEV1 variability is nearly identical to DLCO variability in time course and intensity. As such, neither FEV1 nor DLCO are fit for purpose to scientifically serve as effective stopping rules for AATD studies.

In summary, the NHLBI registry represents a herculean effort to enroll and follow the largest number of AATD-affected individuals in a prospective study that has ever been done in this rare disease. The data are robust and remain relevant today, since few new therapies have emerged that may change the natural history of AATD. As gene therapy and RNA-based treatments advance, trial designs should incorporate more robust and biologically relevant endpoints, such as the serum AAT concentration, rather than depending on spirometric or diffusing capacity changes.

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Declaration of Interest

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KEH and RC receive consulting and research income from AlphaNet.

RAS is a medical director for AlphaNet.

DMM is a consultant to AstraZeneca, GlaxoSmithKline, Lilly, Regeneron, Sanofi, Genentech, Chiesi, and Up-to-Date. He is the Chief Medical Officer for the COPD Foundation and a medical expert on behalf of people suing the tobacco and vaping industries.

References

1. Stoller JK, Aboussouan LS. A review of α 1-antitrypsin deficiency. *Am J Respir Crit Care Med*. 2012;185(3):246-59. <https://doi.org/10.1164/rccm.201108-1428CI>
2. Strange C. Airway disease in alpha-1 antitrypsin deficiency. *COPD*. 2013;10(sup1):68-73. <https://doi.org/10.3109/15412555.2013.764404>
3. Turner AM, Ficker JH, Vianello A, et al. Advancing the understanding and treatment of lung pathologies associated with alpha 1 antitrypsin deficiency. *Ther Adv Respir Dis*. 2025;19:17534666251318841. <https://doi.org/10.1177/17534666251318841>
4. Miravittles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α 1-antitrypsin deficiency. *Eur Respir J*. 2017;50(5). <https://doi.org/10.1183/13993003.00610-2017>
5. Berry G. Longitudinal observations. Their usefulness and limitations with special reference to the forced expiratory volume. *Bull Physiopathol Respir (Nancy)*. 1974;10(5):643-56.
6. DeMeo D, Campbell E, Brantly M, et al. Heritability of lung function in severe alpha-1 antitrypsin deficiency. *Hum Hered*. 2008;67(1):38-45. <https://doi.org/10.1159/000164397>
7. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005;2(1):111-24. <https://doi.org/10.1081/copd-200053377>
8. Drummond MB, Schwartz PF, Duggan WT, et al. Intersession variability in single-breath diffusing capacity in diabetics without overt lung disease. *Am J Respir Crit Care Med*. 2008;178(3):225-32. <https://doi.org/10.1164/rccm.200801-090OC>
9. Hathaway EH, Tashkin D, Simmons MS. Intraindividual variability in serial measurements of O_{Leo} and alveolar volume over one year in eight healthy subjects using three independent measuring systems. *Am Rev Respir Dis*. 1989;140:1818-22. <https://doi.org/10.1164/ajrccm/140.6.1818>
10. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948-68. <https://doi.org/10.1183/09031936.05.00035205>
11. Wise RA, Connett J, Kurnow K, et al.. Selection of spirometric measurements in a clinical trial, the Lung Health Study. *Am J Respir Crit Care Med*. 1995;151(3):675-81. <https://doi.org/10.1164/ajrccm.151.3.7881655>
12. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1). <https://doi.org/10.1183/13993003.01499-2021>
13. Rahaghi FF, Miravittles M. Long-term clinical outcomes following treatment with alpha 1-proteinase inhibitor for COPD associated with alpha-1 antitrypsin deficiency: a look at the evidence. *Respir Res*. 2017;18(1):105. <https://doi.org/10.1186/s12931-017-0574-1>
14. Santos G, Turner AM. Alpha-1 antitrypsin deficiency: an update on clinical aspects of diagnosis and management. *Fac Rev*. 2020;9:1. <https://doi.org/10.12703/b/9-1>
15. Edgar RG, Patel M, Bayliss S, Crossley D, Sapey E, Turner AM. Treatment of lung disease in alpha-1 antitrypsin deficiency: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1295-308. <https://doi.org/10.2147/COPD.S130440>
16. McElvaney NG, Stoller JK, Buist AS, Prakash UB. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha1-antitrypsin deficiency. *Chest*. 1997;111(2):394. <https://doi.org/10.1378/chest.111.2.394>
17. The Alpha 1-Antitrypsin Deficiency Registry Study Group. A registry of patients with severe deficiency of alpha 1-antitrypsin. Design and methods. *Chest*. 1994;106(4):1223-32. <https://doi.org/10.1378/chest.106.4.1223>

18. Stoller JK, McCarthy K, Buist AS, et al. Quality control of spirometry testing in the registry for patients with severe alpha-1 antitrypsin deficiency. *Chest*. 1997;111(4):899-909. <https://doi.org/10.1378/chest.111.4.899>
19. Lundquist A, Lindberg A, Eriksson-Ström J, Blomberg A, Backman H. Number of follow-up years needed to identify a rapid decline in FEV1. *Am J Respir Crit Care Med*. 2024;209(1):119-20. <https://doi.org/10.1164/rccm.202309-1664LE>
20. Green C, Parr D, Edgar R, Stockley R, Turner A. Lung density associates with survival in alpha 1 antitrypsin deficient patients. *Respir Med*. 2016;112:81-7. <https://doi.org/10.1016/j.rmed.2016.01.007>.
21. Jensen RL, Teeter JG, England RD, White HJ, Pickering EH, Crapo RO. Instrument accuracy and reproducibility in measurements of pulmonary function. *Chest*. 2007;132(2):388-95. <https://doi.org/10.1378/chest.06-1998>
22. Madsen F, Ulrik C, Dirksen A, et al. Patient-administered sequential spirometry in healthy volunteers and patients with α 1-antitrypsin deficiency. *Respir Med*. 1996;90(3):131-8. [https://doi.org/10.1016/s0954-6111\(96\)90154-7](https://doi.org/10.1016/s0954-6111(96)90154-7)
23. Crossley D, Renton M, Khan M, Low EV, Turner AM. CT densitometry in emphysema: a systematic review of its clinical utility. *Int J Chron Obstruct Pulmon Dis*. 2018;547-63. <https://doi.org/10.2147/COPD.S143066>
24. Choate R, Sandhaus R, Holm K, Mannino D, Strange C. Patient-reported pulmonary symptoms, exacerbations, and management in a cohort of patients with alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis*. 2022;9(4):549-61. <https://doi.org/10.15326/jcopdf.2022.0317>
25. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med*. 1998;158(1):49-59. <https://doi.org/10.1164/ajrccm.158.1.9712017>
26. Stoller JK, Tomashefski J, Crystal RG, Arroliga A, Strange C, Killian DN, Schluchter MD, Wiedemann HP. Mortality in individuals with severe deficiency of alpha1-antitrypsin: findings from the National Heart, Lung, and Blood Institute Registry. *Chest*. 2005;127(4):1196-204. <https://doi.org/10.1378/chest.127.4.1196>
27. Turner AM, Whittkopf P, Wilamowitz-Moellendorff C, et.al. Pulmonary function decline in alpha-1 antitrypsin deficiency: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2026;21:1-16. <https://doi.org/10.2147/COPD.S552227>

Table 1. Baseline Characteristics of the Study Population in the overall cohort, and analytic subsets for spirometry and DLCO analyses

Baseline Characteristics	Overall dataset (n=1126)	FEV1 and FVC analytic sample (n=832)	DLCO analytic sample (n=586)
Age, years, mean ($\pm$ SD)	46.6 (10.5)	46.3 (10.1)	46.0 (10.2)
Sex, female, n (%)	500 (44.4)	369 (44.4)	261 (44.5)
Race, white, n (%)	1117 (99.2)	824 (99.0)	579 (98.8)
BMI, mean ($\pm$ SD)	25.8 (5.4)	26.3 (5.3)	26.3 (5.2)
Current employment status, n (%)	n=1123	n=829	n=585
Employed full-time	477 (42.5)	396 (47.8)	282 (48.2)
Employed part-time	121 (10.8)	99 (11.9)	77 (13.2)
Unemployed (medical reasons)	226 (20.1)	139 (16.8)	91 (15.6)
Unemployed (other reasons)	38 (3.4)	23 (2.8)	19 (3.3)
Retired (medical)	111 (9.9)	70 (8.4)	49 (8.4)
Retired (age)	53 (4.7)	36 (4.3)	25 (4.3)
Full-time homemaker	70 (6.2)	46 (5.6)	30 (5.1)
Other	27 (2.4)	20 (2.4)	12 (2.1)
Marital status, n (%)	n=1122	n=828	n=585
Never married	84 (7.5)	60 (7.3)	47 (8.0)
Widowed	26 (2.3)	14 (1.7)	10 (1.7)
Married	843 (75.1)	637 (76.9)	439 (75.0)
Separated	22 (2.0)	13 (1.6)	12 (2.1)
Divorced	147 (13.1)	104 (12.6)	77 (13.2)
Education, n (%)			
College graduate with advanced training	167 (14.8)	131 (15.8)	99 (16.9)
College graduate	160 (14.2)	123 (14.8)	89 (15.2)
At least 1 yr of college	301 (26.7)	236 (28.4)	165 (28.2)
High school graduate	389 (34.6)	269 (32.3)	186 (31.7)
Completed 10-11 yrs school	64 (5.7)	47 (5.7)	33 (5.6)
Unknown/other	45 (4.0)	26 (3.1)	14 (2.4)
Smoking history, n (%)	n=1122	n=828	n=584
Yes*	857 (76.4)	632 (76.3)	437 (74.8)
Former smoker	728/857 (84.9)	544/632 (86.1)	382/437 (87.4)
Current Smoker	114/857 (13.3)	76/632 (12.0)	47/437 (10.8)
Pack-years	n=798	n=589	n=411
mean (SD)	23.1 (16.5)	22.7 (15.0)	22.4 (15.0)

Alcohol use, n (%)	<i>n</i> =1121	<i>n</i> =828	<i>n</i> =584
Never	254 (22.7)	167 (20.2)	106 (18.2)
Former drinker	195 (17.4)	133 (16.1)	89 (15.2)
Current drinker	672 (60.0)	528 (63.8)	389 (66.6)
Liver disease, n (%)	<i>n</i> =1122	<i>n</i> =828	<i>n</i> =584
Yes	84 (7.5)	53 (6.4)	41 (7.0)
Cirrhosis	29/84 (34.5)	13/53 (24.5)	13/41 (31.7)
Neonatal Jaundice	25/84 (29.8)	19/53 (35.9)	14/41 (34.2)
Hepatitis	42/84 (50.0)	27/53 (50.9)	20 (48.8)
Lung disease, n (%)	<i>n</i> =1121	<i>n</i> =827	<i>n</i> =583
Yes	925 (82.5)	686 (83.0)	482 (82.7)
Emphysema	820/925 (88.7)	601/ 686 (87.6)	419/482 (86.9)
Reversible airways disease	396/922 (43.0)	314/685 (45.8)	220/482 (45.6)
Bronchitis	463/925 (50.1)	346/686 (50.4)	243/482 (50.4)
Liver/lung transplant, yes, n (%)	<i>n</i> =6 lung; <i>n</i> =2 liver at baseline	<i>n</i> =2 liver at baseline	<i>n</i> =0 at baseline
Augmentation therapy, always/sometimes, n (%)	674 (59.9)	561 (67.4)	410 (69.9)
FEV1 % predicted			
<50%		515 (61.9)	343 (58.5)
≥ 50%		317 (38.1)	243 (41.5)
Bronchodilator responsiveness, yes, n (%)		<i>n</i> =814	<i>n</i> =575
<i>old method (≥12% from pre-BD and ≥200ml change)</i>		249 (30.6)	194 (33.7)
<i>new method (≥15% from predicted)</i>		17 (2.1)	11 (1.9)
Number of follow-up visits, mean (SD)		5.7 (2.0)	5.4 (1.9)
Number of follow-up years, mean (SD)		4.4 (1.4)	4.3 (1.4)

Table 2. Time to 10% and 20% decline in FEV1 and DLCO by Kaplan-Meier Analysis

Time to 10% Decline in Years

Quartile Estimates- FEV1				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	5.01000	LOGLOG	4.64000	5.26000
50	3.01000	LOGLOG	2.75000	3.23000
25	1.19000	LOGLOG	1.13000	1.37000

Quartile Estimates- FEV1				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	6.60000	LOGLOG	6.48000	6.87000
50	5.12000	LOGLOG	4.98000	5.37000
25	3.05000	LOGLOG	2.85000	3.24000

Quartile Estimates- DLCO				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	5.78000	LOGLOG	5.08000	6.71000
50	2.91000	LOGLOG	2.44000	3.13000
25	1.20000	LOGLOG	1.09000	1.48000

Time to 20% Decline in Years

Quartile Estimates- DLCO				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	.	LOGLOG	6.44000	.
50	5.17000	LOGLOG	4.69000	5.83000
25	2.16000	LOGLOG	1.96000	2.65000

Figure 1. Study flow for FEV1, FVC, and DLCO analytic cohorts in the NHLBI dataset. A minimum of 3 values were required for inclusion in the current study

Figure 1. Study Flow

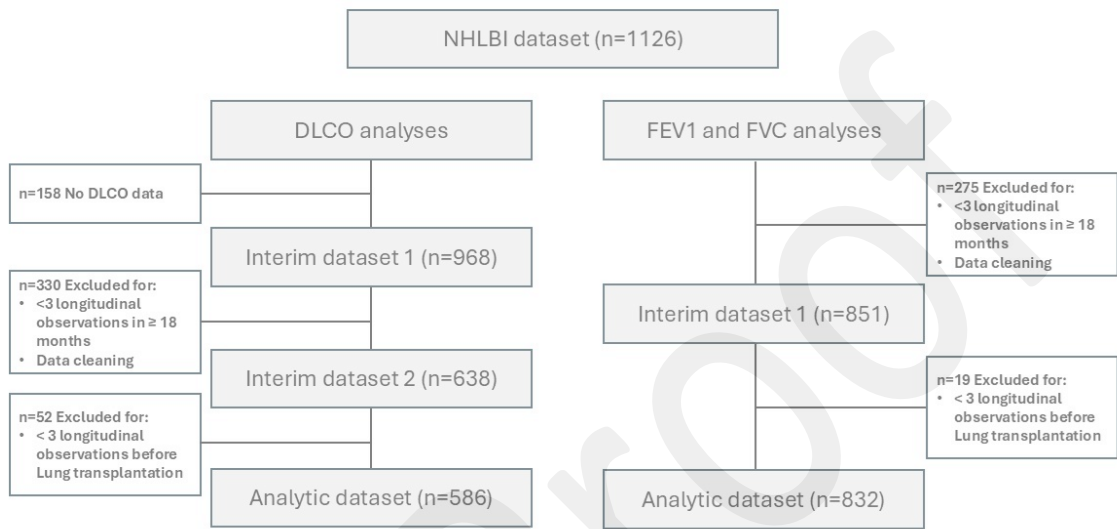


Figure 2. Example of intra-person variability in FEV1 based on a study participant example

A representative patient had a low baseline FEV1 that improved over the following 3 visits. The difference from baseline and the residual differences from the line of regression give differential insight into stopping rules for clinical trials.

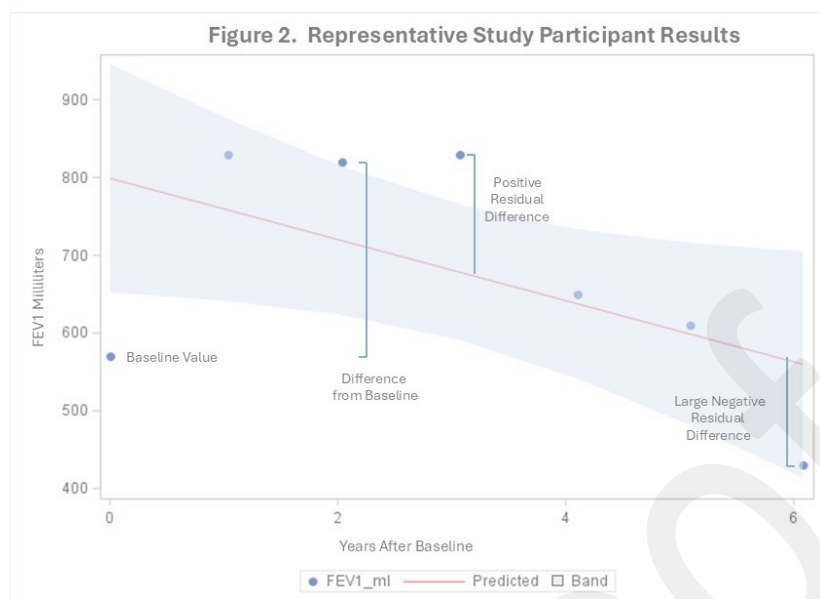


Figure 3. Distribution of the largest % change in FEV1 from baseline, n=832

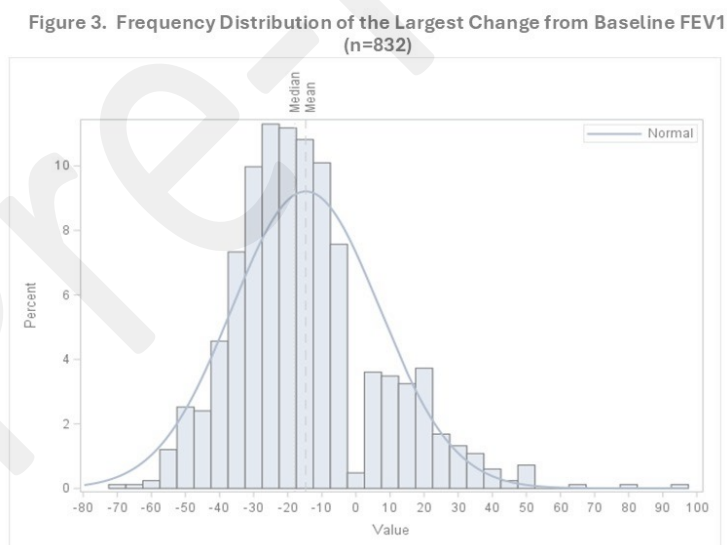


Figure 4 Number of events with a (A) 10% and (B) 20% change in FEV1 from baseline in the analytic sample of n=832.

Figure 4. Distribution of the number of individuals stratified by the number of events with a 10% and 20% change from baseline.

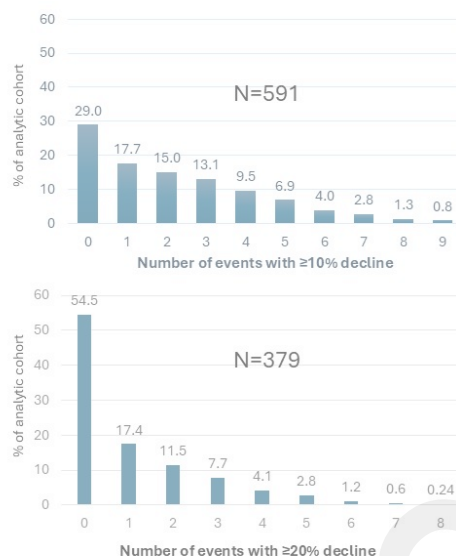
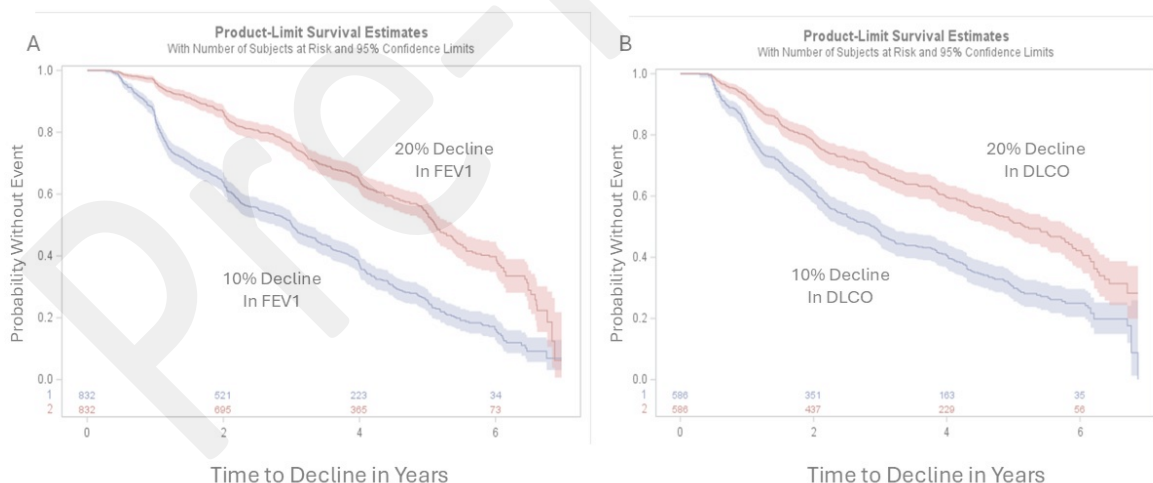


Figure 5. Time to Events of 10% and 20% decline in (A) FEV1 and (B) DLCO

Figure 5. Time to Events of 10% and 20% Declines in (A) FEV1 and (B) DLCO



Online Supplement

Supplemental Table 1.0 Pre- and Post-Bronchodilator Spirometry and DLCO of the analyzed cohort.

Variable	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
PreBronchodilator						
FEV1 (L)	803	1.52	0.98	1.18	0.8	1.92
FEV1 % Predicted	803	45.3	24.0	79.1	62.5	99.4
FVC (L)	803	3.40	1.17	3.25	2.47	4.20
FVC % Predicted	803	81.0	24.0	79.1	62.5	99.4
FEV1/FVC	803	44.8	19.0	39.0	30.0	56.0
FEV1/FVC % Predicted	803	53.2	22.7	46.1	35.5	66.2
PostBronchodilator						
FEV1 (L)	832	1.72	1.06	1.37	0.94	2.25
FEV1 % Predicted	832	50.8	29.8	39.9	28.0	66.0
FVC (L)	832	3.84	1.20	3.71	2.91	4.71
FVC % Predicted	832	90.8	22.0	91.6	74.6	106.1
FEV1/FVC	832	45.2	20.1	39.0	29.0	57.0
FEV1/FVC % Predicted	832	54.0	24.1	46.6	35.2	67.6
DLCO						
DLCO (ml/min/mmHg)	586	17.29	7.45	16.24	11.94	22.04
DLCO % Predicted	586	51.9	20.4	49.2	36.5	65.0

Pre-proof

Supplemental Table 1.1 Baseline characteristics of the FEV1 cohort stratified by baseline FEV1 % predicted

Baseline Characteristics	Baseline FEV1 %predicted	
	<50%	≥ 50%
	515 (61.9)	317 (38.1)
Age, years, mean (SD);	47.2 (9.1)	44.9 (11.5)
Sex, female, n (%)	194 (37.7)	175 (55.2)
Smoking history, yes, n (%) <i>n=828</i>	457 (89.3)	175 (55.4)
Alcohol use, n (%) <i>n=828</i>		
Never	83 (16.2)	84 (26.5)
Former drinker	89 (17.4)	44 (13.9)
Current drinker	339 (66.3)	189 (59.6)
Liver disease, yes, n (%) <i>n=828</i>	32 (6.3)	21 (6.7)
Cirrhosis	6 (18.8)	7 (33.3)
Neonatal Jaundice	12 (37.5)	7 (33.3)
Hepatitis	15 (46.9)	12 (57.1)
Lung disease, yes, n (%) <i>n=827</i>	483 (94.3)	203 (64.4)
Emphysema	464 (96.1)	137 (67.5)
Reversible airways disease	228 (47.2)	86 (42.6)
Bronchitis	243 (50.3)	103 (50.7)
Augmentation therapy, always/sometimes, n (%)	424 (82.3)	137 (43.2)

Note: % represent column%

Supplemental Table 1.2 Baseline characteristics of the FEV1 cohort stratified by use of augmentation therapy at baseline

Baseline Characteristics	Use of augmentation therapy at baseline	
	No	Always/ sometimes
	271 (32.6)	561 (67.4)
Age, years, mean (SD); median (IQR)	44.2 (11.0); 42 (36-51)	47.4 (9.5); 46 (40-53)
Sex, female, n (%)	133 (49.1)	235 (41.9)
Smoking history, yes, n (%) <i>n</i> =828	171 (63.1)	461 (82.8)
Alcohol use, n (%) <i>n</i> =828		
Never	78 (28.8)	89 (16.0)
Former drinker	43 (15.9)	90 (16.2)
Current drinker	150 (55.4)	378 (67.9)
Liver disease, yes, n (%) <i>n</i> =828	16 (5.9)	37 (6.6)
Cirrhosis	5 (31.3)	8 (21.6)
Neonatal Jaundice	12 (37.5)	7 (33.3)
Hepatitis	11 (68.8)	16 (43.2)
Lung disease, yes, n (%) <i>n</i> =827	174 (64.4)	512 (91.9)
Emphysema	125 (71.8)	476 (93.0)
Reversible airways disease	80 (46.0)	234 (45.8)
Bronchitis	90 (51.7)	256 (50.0)
FEV1 % predicted		
<50%	91 (33.6)	424 (75.6)
≥ 50%	180 (66.4)	137 (24.4)

Note: % represent column%

Supplemental Table 1.3 Baseline characteristics of the FEV1 cohort stratified by presence of liver disease at baseline, n=828

Baseline Characteristics	Presence of liver disease*	
	Yes	No
	53 (6.4%)	775 (93.6%)
Age, years, mean (SD); median (IQR)	46.1 (9.4); 45 (39-52)	46.4 (10.2); 45 (39-52)
Sex, female, n (%)	21 (39.6)	347 (44.8)
Smoking history, yes, n (%)	42 (79.3)	590 (76.1)
Alcohol use, n (%) n=827		
Never	9 (17.0)	158 (20.4)
Former drinker	19 (35.9)	113 (14.6)
Current drinker	25 (47.2)	503 (65.0)
Lung disease, yes, n (%) n=827		
Emphysema	46 (86.8)	640 (82.7)
Reversible airways disease	41 (89.1)	560 (87.5)
Bronchitis	23 (50.0)	291 (45.5)
	31 (67.4)	315 (49.2)
FEV1 % predicted		
<50%	32 (60.4)	480 (61.9)
≥ 50%	21 (39.6)	295 (38.1)
Augmentation therapy, always/sometimes, n(%)	37 (69.8)	520 (67.1)

*n=4 missing data on liver disease

Note: % represent column%

Supplemental Table 1.4 Baseline characteristics of the FEV1 cohort stratified by bronchodilator responsiveness at baseline, n=814

Baseline Characteristics	Bronchodilator responsiveness*	
	No	Yes
	565 (69.4)	249 (30.6%)
Age, years, mean (SD); median (IQR)	46.1 (9.4); 45 (39-52)	46.4 (10.2); 45 (39-52)
Sex, female, n (%)	299 (52.9)	64 (25.7)
Smoking history, yes, n (%) n=810	414 (73.7)	204 (82.3)
Alcohol use, n (%) n=810		
Never	122 (21.8)	43 (17.3)
Former drinker	83 (14.8)	46 (18.5)
Current drinker	356 (63.5)	160 (64.3)
Lung disease, yes, n (%) n=810	444 (79.0)	233 (94.0)
Emphysema	388 (87.4)	205 (88.0)
Reversible airways disease	185 (41.7)	125 (53.9)
Bronchitis	216 (48.7)	123 (52.8)
Liver disease, yes, n (%) n=810	37 (6.6)	15 (6.1)
Cirrhosis	9 (24.3)	4 (26.7)
Neonatal Jaundice	16 (43.2)	3 (20.0)
Hepatitis	17 (46.0)	9 (60.0)
FEV1 % predicted		
<50%	336 (59.5)	171 (68.7)
≥ 50%	229 (40.5)	78 (31.3)
Augmentation therapy, always/sometimes, n(%)	364 (64.4)	190 (76.3)

*n=18 missing data on BDR

BDR defined as (≥12% from pre-BD and ≥200ml change)

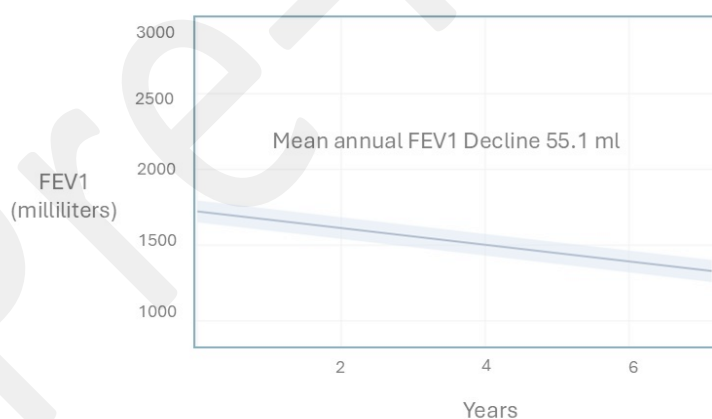
Note: % represent column%

Supplemental Table 1.5 FEV1 stopping rules met with various thresholds

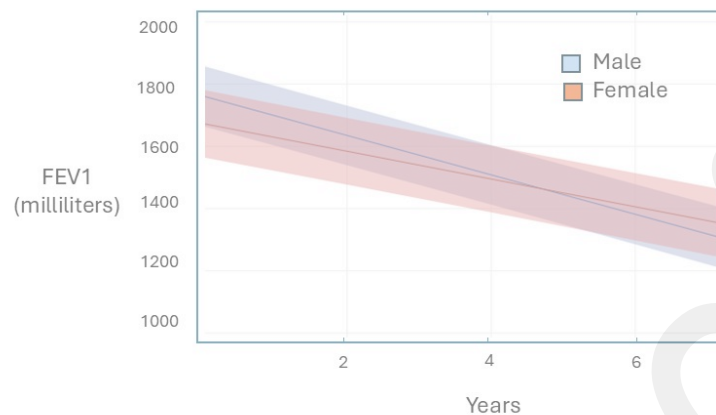
FEV1 change from baseline ¹	n (%)
≥10% decline	
no	274 (32.9)
yes	558 (67.1)
≥15% decline	
no	366 (44.0)
yes	466 (56.0)
≥20% decline	
no	459 (55.2)
yes	373 (44.8)
≥30% decline	
no	642 (77.2)
yes	190 (22.8)

¹ indicates the largest difference in FEV1 value from baseline

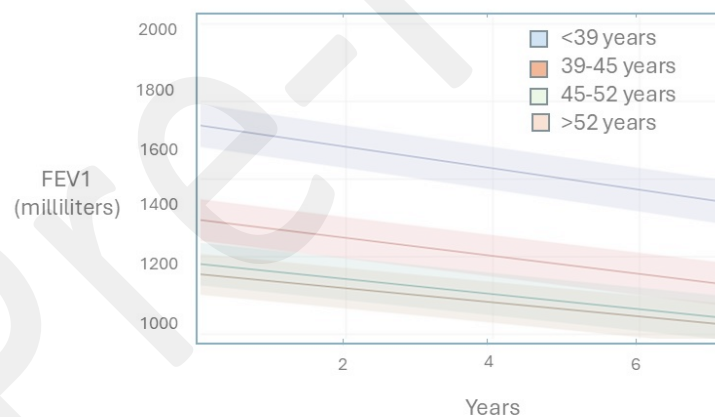
Supplemental Figure 1.1. Linear fit with 95% Confidence Intervals for FEV1 change in milliliters



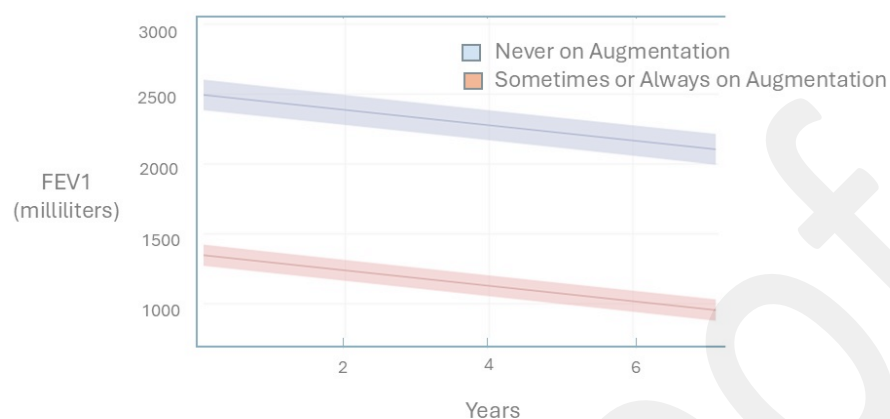
Supplemental Figure 1.2. Linear fit with 95% Confidence Intervals for FEV1 change by sex. Males declined at 63.3 compared to females at 44.6 milliliters/year ($p<0.001$)



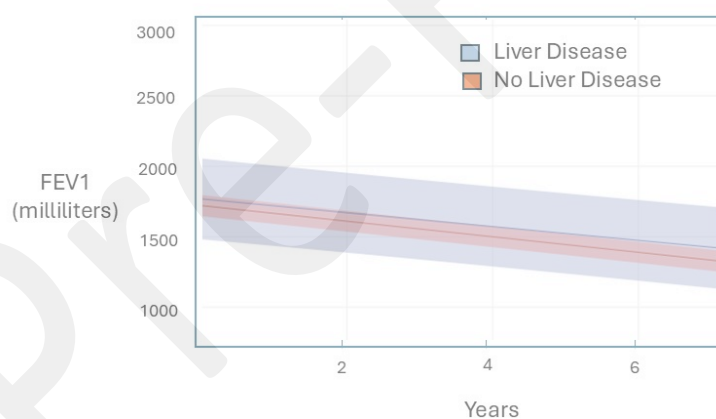
Supplemental Figure 1.3. Linear fit with 95% Confidence Intervals for FEV1 change by age. Younger individuals (<39 years) declined at 69.2 compared to older individuals >52 years at 45.4 milliliters/year ($p<0.0001$)



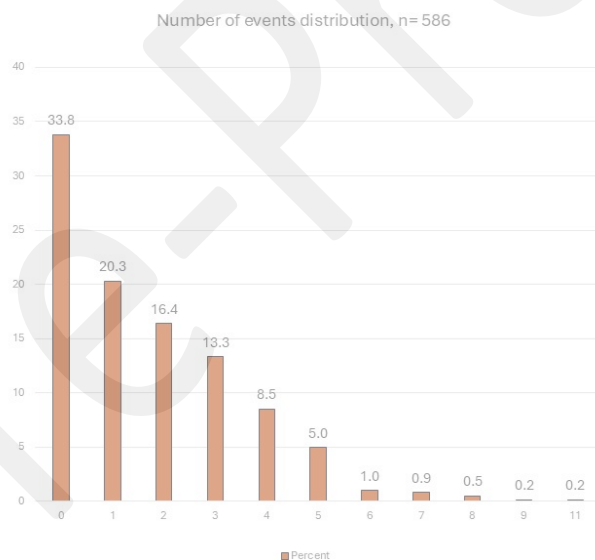
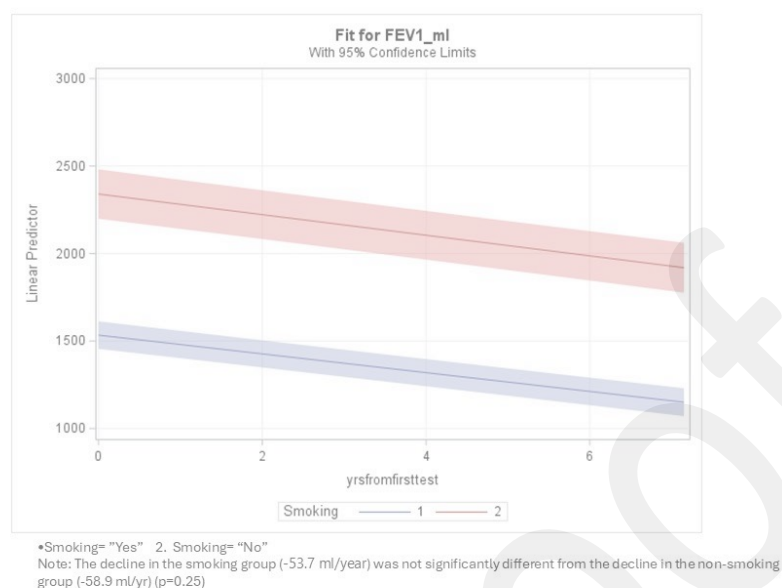
Supplemental Figure 1.4. Linear fit with 95% Confidence Intervals for FEV1 change by augmentation therapy use. There is no difference in FEV1 decline ($p=0.91$)



Supplemental Figure 1.5. Linear fit with 95% Confidence Intervals for FEV1 change by liver disease presence. There is no difference in FEV1 decline ($p=0.44$)

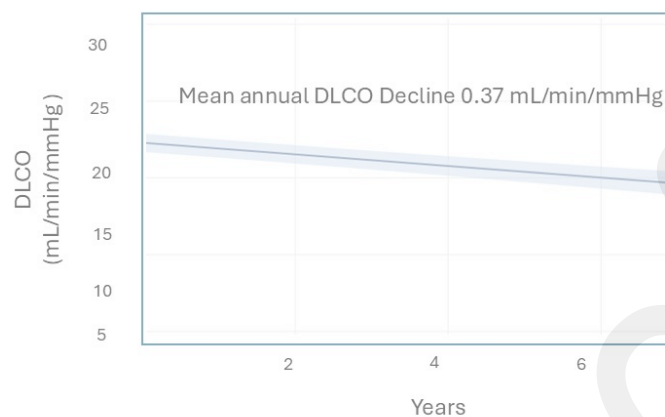


Supplemental Figure 1.6. Longitudinal analysis of FEV1 slope by smoking status

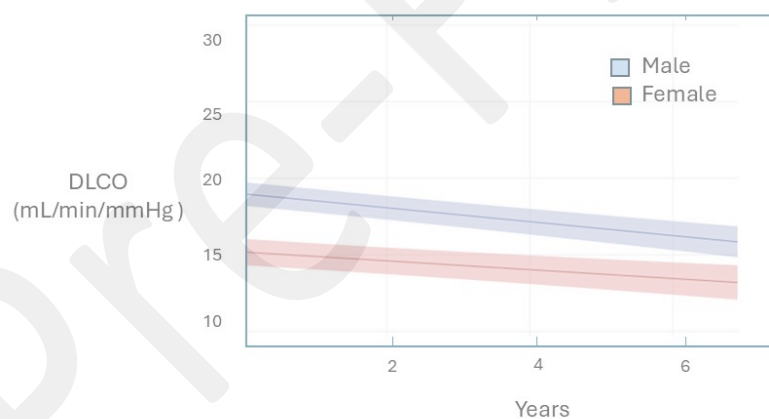


Note: n=388 had 1 or more events of $\geq 10\%$ decline in DLCO from baseline

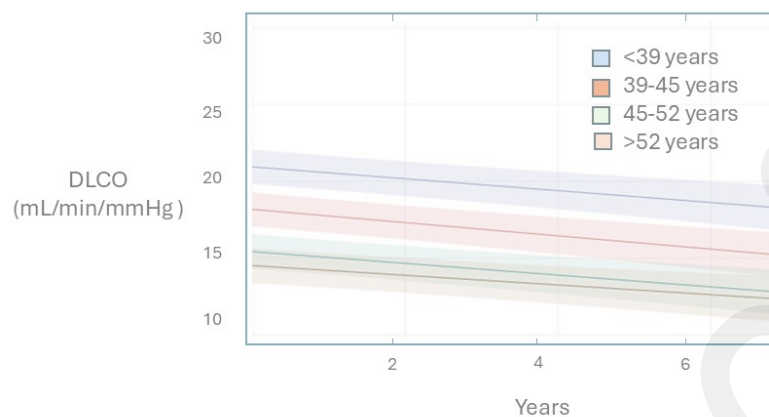
Supplemental Figure 2.2. Linear fit with 95% Confidence Intervals for DLCO change in mL/min/mmHg



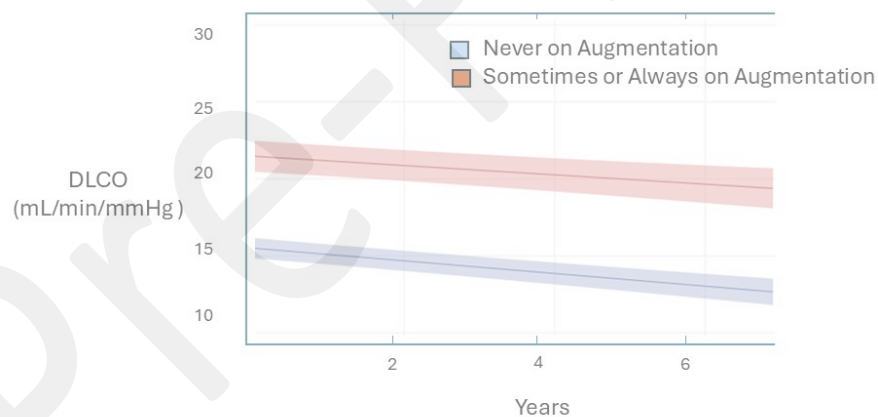
Supplemental Figure 2.3. Linear fit with 95% Confidence Intervals for DLCO change by sex. Males show a steeper slope decline than females ($p=0.04$)



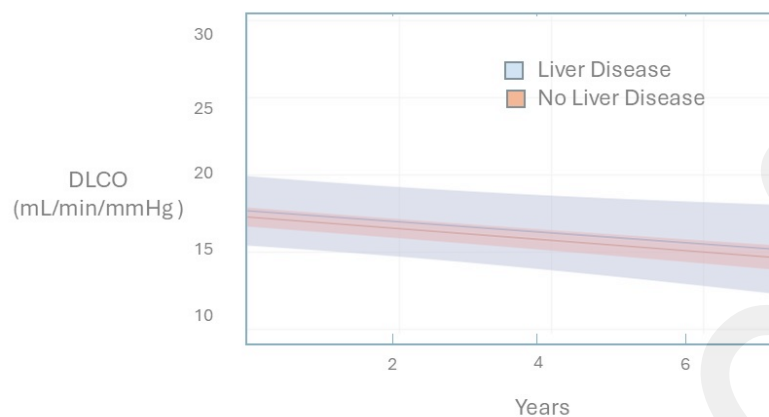
Supplemental Figure 2.4. Linear fit with 95% Confidence Intervals for DLCO change by age. There was no difference in slope ($p=0.80$)



Supplemental Figure 2.5. Linear fit with 95% Confidence Intervals for DLCO change by augmentation therapy. There was no difference in slope ($p=0.22$)



Supplemental Figure 2.6. Linear fit with 95% Confidence Intervals for DLCO change by liver disease. There was no difference in slope ($p=0.91$)



Supplemental Figure 2.7. Longitudinal analysis of DLCO by presence of smoking at baseline

