Online Supplement

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

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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

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

	Baseline FEV1 %predicted	
Baseline Characteristics	**<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 (%) *n=828*	457 (89.3)	175 (55.4)
Alcohol use, n (%) *n=828*		
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 (%) *n=828*	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 (%) *n=827*	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

	Use of augmentation therapy at baseline	
Baseline Characteristics	**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 (%) *n=828*	171 (63.1)	461 (82.8)
Alcohol use, n (%) *n=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 (%) *n=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 (%) *n=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

	Presence of liver disease*	
Baseline Characteristics	**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*	46 (86.8)	640 (82.7)
Emphysema	41 (89.1)	560 (87.5)
Reversible airways disease	23 (50.0)	291 (45.5)
Bronchitis	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

	Bronchodilator responsiveness*	
Baseline Characteristics	**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)

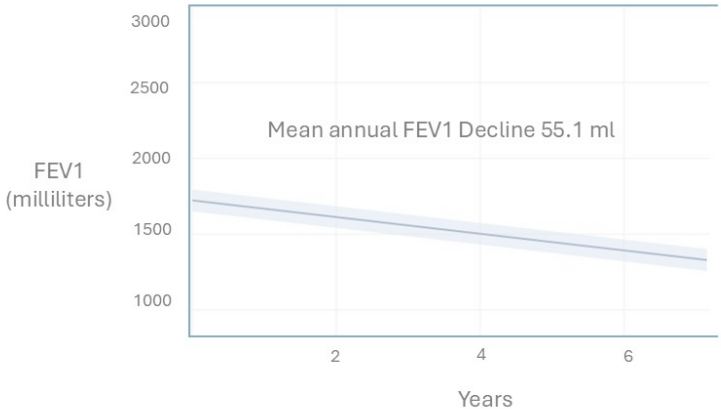
*n=18 missing data on BDR
BDR defined as (≥12% from pre-BD and ≥200ml change)
Note: % represent column%

Supplemental Table 1.5 FEV1 stopping rules met with various thresholds

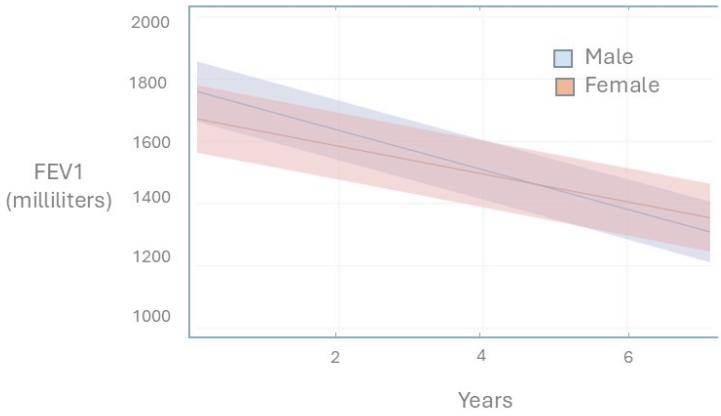
FEV1 change from baseline[1]	n (%)
≥10% decline	
no	274 (32.9)
yes	558 (67.1)
≥15% decline	
no	366 (44.0)
yes	466 (56.0)
≥20% decline	
no	459 (55.2)
yes	373 (44.8)
≥30% decline	
no	642 (77.2)
yes	190 (22.8)

[1] indicates the largest difference in FEV1 value from baseline

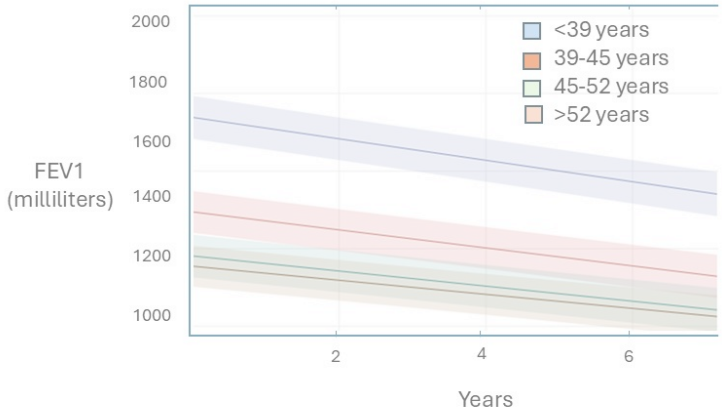
Supplemental Figure 1.1. Linear fit with 95% Confidence Intervals for FEV1 change in milliliters



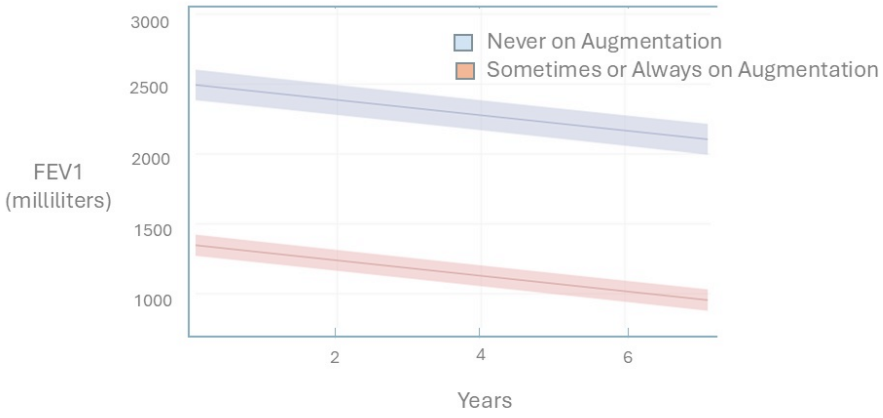
Supplemental Figure 1.2. Linear fit with 95% Confidence Intervals for FEV1 change by sex. Males declined at 63.3 compared to females at 44.6 milliliters/year (p<0.001)



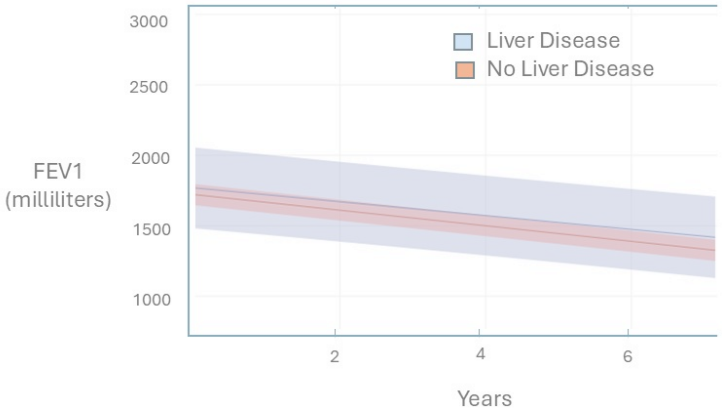
Supplemental Figure 1.3. Linear fit with 95% Confidence Intervals for FEV1 change by age. Younger individuals (<39 years) declined at 69.2 compared to older individuals >52 years at 45.4 milliliters/year (p<0.0001)



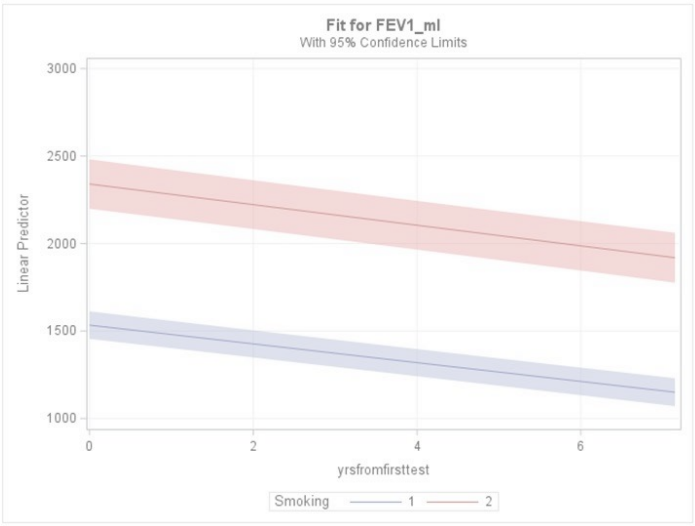
Supplemental Figure 1.4. Linear fit with 95% Confidence Intervals for FEV1 change by augmentation therapy use. There is no difference in FEV1 decline (p=0.91)



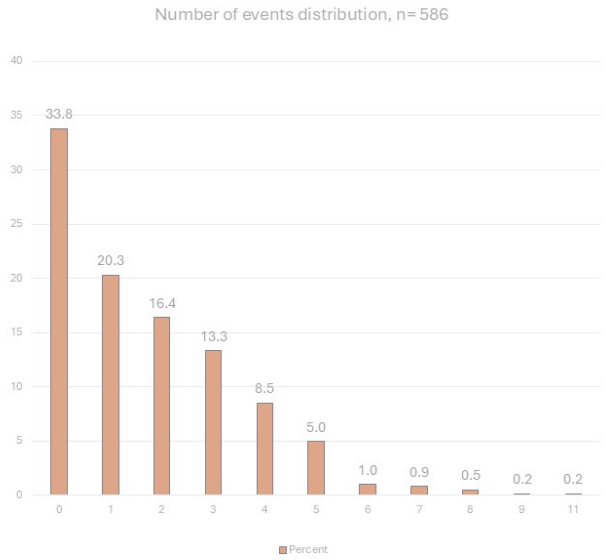
Supplemental Figure 1.5. Linear fit with 95% Confidence Intervals for FEV1 change by liver disease presence. There is no difference in FEV1 decline (p=0.44)



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

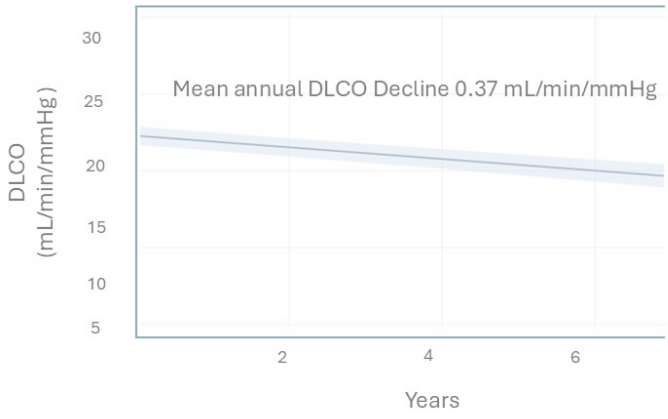


•Smoking= "Yes" 2. Smoking= "No"
Note: The decline in the smoking group (-53.7 ml/year) was not significantly different from the decline in the non-smoking group (-58.9 ml/yr) (p=0.25)

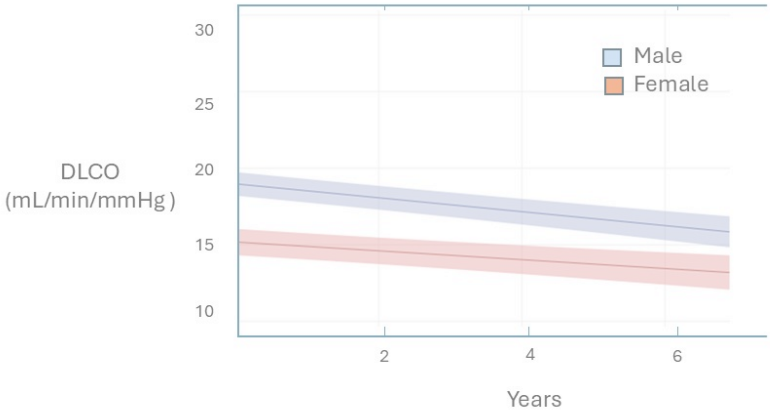


Note: n=388 had 1 or more events of ≥10% decline in DLCO from baseline

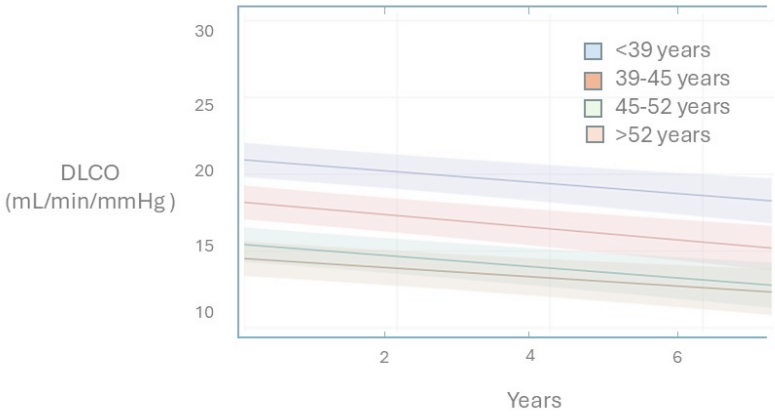
Supplemental Figure 2.2. Linear fit with 95% Confidence Intervals for DLCO change in mL/min/mmHg



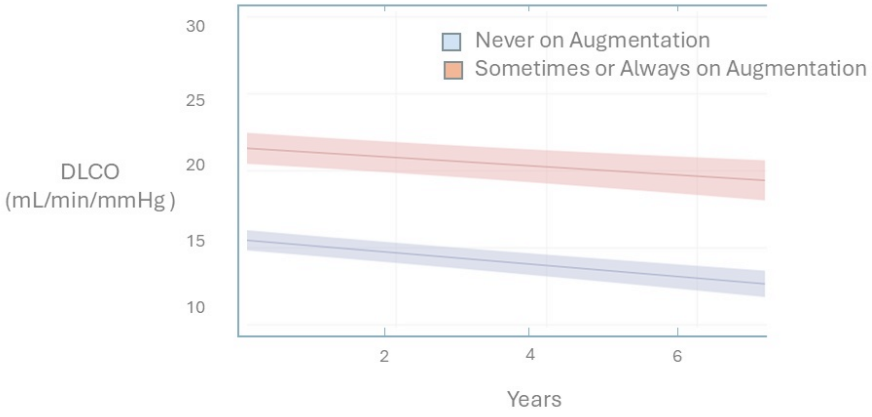
Supplemental Figure 2.3. Linear fit with 95% Confidence Intervals for DLCO change by sex. Males show a steeper slope decline than females (p=0.04)



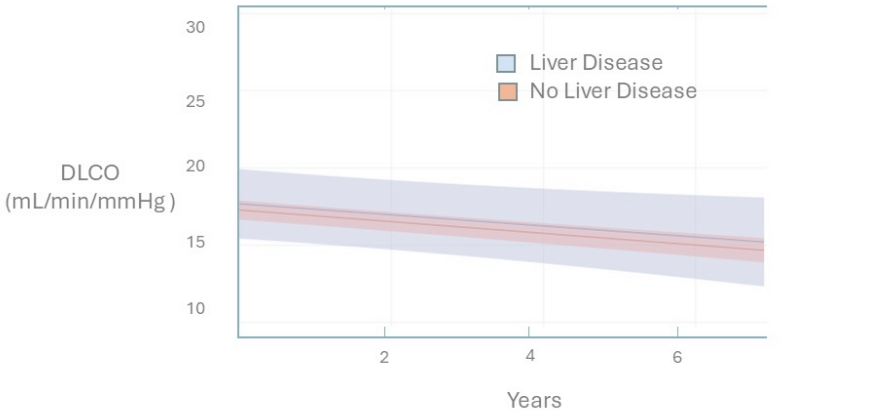
Supplemental Figure 2.4. Linear fit with 95% Confidence Intervals for DLCO change by age. There was no difference in slope (p=0.80)



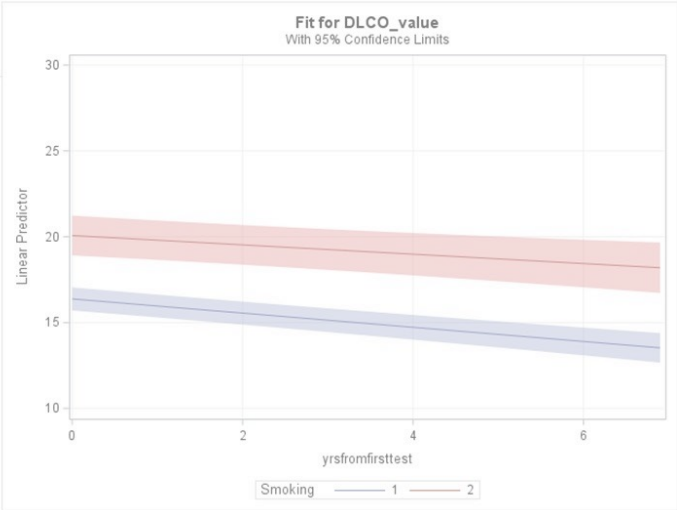
Supplemental Figure 2.5. Linear fit with 95% Confidence Intervals for DLCO change by augmentation therapy. There was no difference in slope (p=0.22)



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



•Smoking="Yes" 2. Smoking= "No"
No significant difference in DLCO slope by smoking (p=0.13)