Supplementary material

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1. Method

1.1 Comprehensive description Linear Mixed Effects Model of FEV_1 in %predicted

This description includes the steps that are taken to formulate the final linear mixed effects model. Different models were generated and compared to each other. The models were fitted using the Restricted Maximum Likelihood (REML) approach. Based on the Akaike Information Criteria (AIC) the final and best fitted model for the data was stepwise selected by including one confounding factor at each step. The selection of the included cases is described in the method section of the main text.

In the first linear mixed effects model, the post-bronchodilator FEV_1 %predicted was the dependent variable and modeled by treatment modality, with follow-up duration, sex, age at follow-up moments and packyears. In the model, treatment modality, sex, age at follow-up moments, packyears, follow-up duration, the interaction between treatment modality and follow-up duration, follow-up duration as quadratic factor, and the interaction between treatment modality and follow-up duration as quadratic factor were added as fixed effects. As random effect, the intercept of the subjects and follow-up duration were added. Follow-up duration was also added as repeated effect. The first model showed an AIC of 15960.587

In the second mixed model the same variables were added but follow-up duration was also added as a random effect. This model showed an AIC of 15174.570. Based on this value the decision was made to continue with the second model.

In the third model correlation within countries was added as a confounder, as patients within a country are likely be more homogenous. Country was thereby added as random and repeated effect besides follow-up duration. This model showed an AIC of 15176.426. Because of the small difference in AIC compared to the second model, a chi-squared test was performed based on the log Likelihood, showing no difference between model 2 and 3 (P=0.70). Therefore, the less complicated model 2; without the correlation within countries, was chosen as the best fit model for continuation.

For the fourth and final model, follow-up duration as quadratic factor, and the interaction between follow-up duration and treatment modality were excluded as fixed variable. This model showed an AIC of 15179.733. Again because of the small difference in AIC compared to the second model, a chi-squared test was performed on the log Likelihood, which showed no difference between model 2 and 4 (P=0.16). Model 4 was even less complicated and thus was used as the best fit model for continuation.

To test the effect of therapy, model four was applied for both the augmentation treatment and non-treatment group. Because both were compared to each other, these models were fitted to the

maximum likelihood (ML) instead of the restricted maximum likelihood (REML). The log Likelihood of both models was tested with the chi-squared test to assess any difference in FEV_1 decline between both groups. This test showed no difference between the groups (P=0.71).

1.2 Description of the Linear Mixed Effects Models of FEV_1 in Liters

This description includes the steps which are taken to formulate the final linear mixed effects model for the FEV_1 in Liters (L). The different models were generated with the same methodology as for the FEV_1 %predicted, but a different final model was considered the best fit.

In the first linear mixed effects model, the post-bronchodilator FEV_1 in L was the dependent variable and modeled by treatment modality with follow-up duration, sex, age at follow-up moments and packyears. In the model, treatment modality, sex, age at follow-up moments, packyears, follow-up duration, the interaction between treatment modality and follow-up duration, follow-up duration as quadratic factor, and the interaction between treatment modality and follow-up duration as quadratic factor were added as fixed effects. As random effect the intercept of the subjects and follow-up duration were added. Follow-up duration was also added as repeated effect. The first model showed an AIC of 381.122

In the second mixed model, the same variables were added but follow-up duration was also added as a random effect. This model showed an AIC of -316.177. Based on these values the decision was made to continue with the second model.

In the third model correlation within countries was added as a confounder as patients within a country are likely be more homogenous. Country was thereby added as random and repeated effect besides follow-up duration. This model showed an AIC of -322.408. Because of the small difference in AIC compared to the second model, a chi-squared test was performed on the log likelihood, which showed a significant difference between model 2 and 3 (P=0.00). Therefore, the model with the best AIC, model 3 was the chosen for continuation.

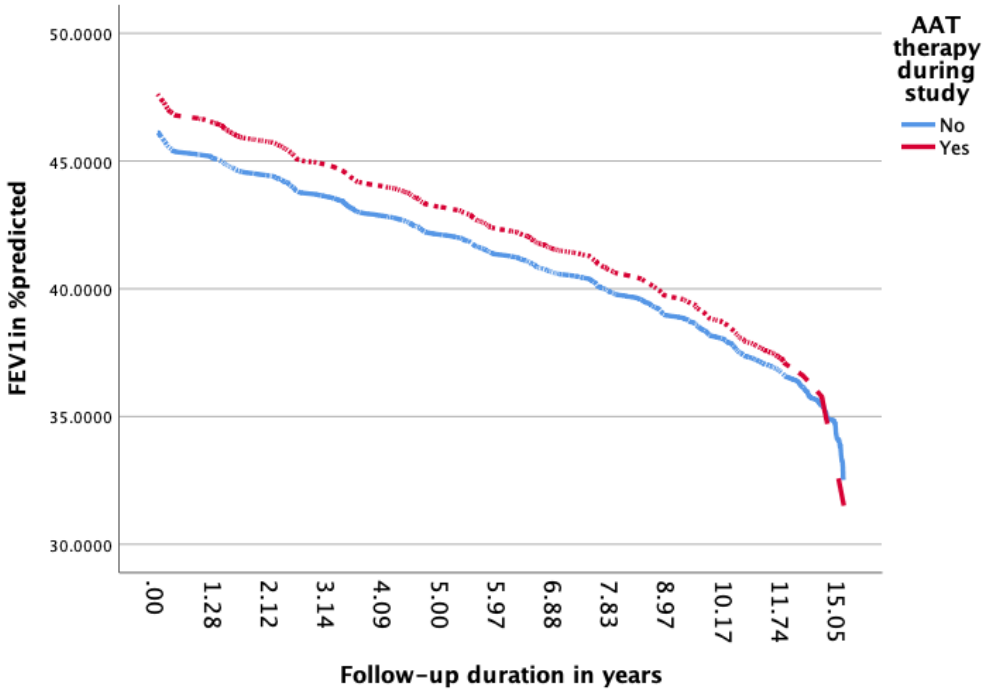
For the fourth and final model, follow-up duration as quadratic factor, and the interaction between follow-up duration and treatment modality were excluded as fixed variable. This model showed an AIC of -328.562. Because of the small difference in AIC compared to the third model, a chi-squared test was performed which showed a significant difference between model 3 and 4 (P=0.05). Model 4 was less complicated and therefore used for continuation.

To test the effect of therapy, model four was applied for both the augmentation treatment and non-augmentation treatment group. Because both models were compared to each other, they were fitted to the maximum likelihood (ML) instead of the restricted maximum likelihood (REML). The log Likelihood of both models were tested by the chi-squared test to assess any difference in FEV_1 decline between groups. This test showed no difference between the two groups (P=0.67).

2. Results

2.1 Graph Linear Mixed Effects Models FEV_1 %predicted

Figure S1. Graph FEV_1 decline in %predicted



Notes: The figure shows the decline in FEV_1 in percentage predicted over the years calculated by the mixed model without confounders, for both groups; untreated and treated.
Abbreviation: FEV_1= post bronchodilator forced expiration in 1 second express as percentage, **AAT**= Alpha-1-antitrypsin

2.2 Results Linear Mixed Effects Models FEV_1 in Liters

Baseline FEV_1 values in liters of all the subjects are summarized in *table S1*. For the additional baseline characteristics see *table 1* in the main text. In the linear mixed effect model analysis only the patients who received augmentation treatment in a country where treatment is available and reimbursed are included in the treatment group and patients who did not receive augmentation treatment from countries where treatment is not available and reimbursed are included in the control group. The mean annual decline in FEV_1 for each group was calculated by applying a mixed model analysis for each group.

Different mixed models were tested based on the likelihood ratio test to define the fixed and random parameters. For the linear mixed effects models, "post-bronchodilator" FEV_1 in liters at the different timepoints is the dependent variable, and as fixed effects we used treatment modality, follow-up duration and the interaction between follow-up duration and treatment, sex, age at follow-up time and packyears of previous smoking. To model the within-patient correlation we used random intercepts and slopes terms. Country was added as a random effect besides follow-up duration.

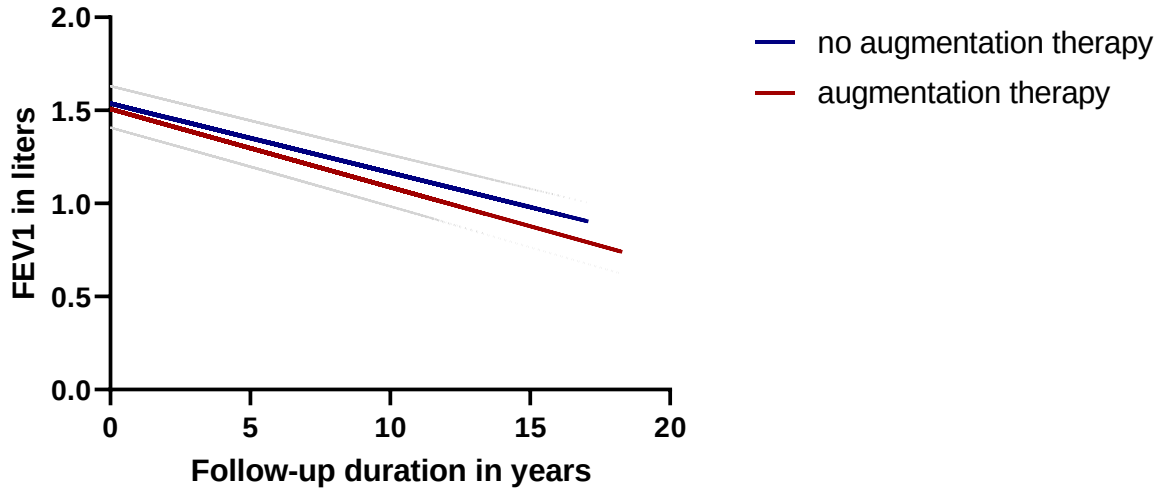
The best fit mixed model analysis showed a mean FEV_1 decline of -0.0291 L per year (95% confidence interval -0.0360 to -0.0223) in the control group and compared to a mean FEV_1 decline of -0.0339 L per year (95% CI -0.0434 to -0.02432) in the augmentation treatment group. The likelihood ratio test showed no difference between the two groups (P=0.67). *See figure S2.*

Table S1. Baseline FEV_1 in liters, stratified per country

	The Netherlands	**UK**	**Italy**	**Germany**	**Spain**
	Not treated N = 59	Not treated N = 187	Treated N=3	Treated N = 116	Treated N= 9
Baseline FEV_1 L (SD)	1.65 (0.39)	1.46 (0.40)	0.90 (0.15)	1.50 (0.42)	1.45 (0.41)

Abbreviation: SD= standard deviation, **FEV_1 L=** post bronchodilator forced expiration in 1 second in liters

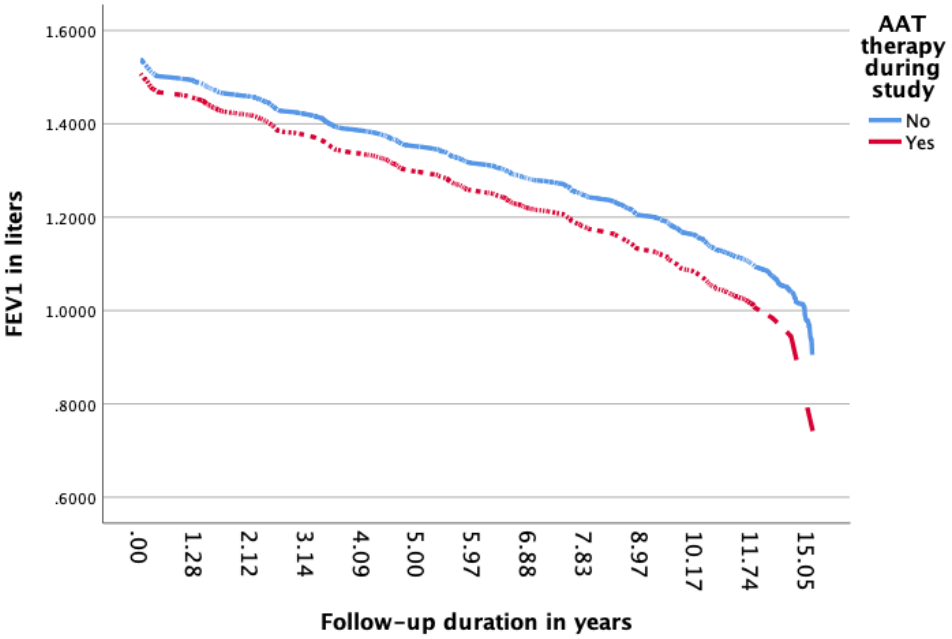
Figure S2. FEV_1 decline in Liters



Notes: The figure shows the decline of FEV_1 in liters over the years calculated by the mixed model without confounders, for both groups; untreated and treated. The confidence interval (CI) of both graphs are overlapping, thereby only the upper CI of the untreated graph and the lower CI of the treated graph is shown. There was no significant difference in decline in FEV_1.

Figure S3. FEV_1 decline in Liters

Notes: The figure shows the decline in FEV_1 in liters over the years calculated by the mixed model without confounders, for both groups; untreated and treated.


1.6000
1.4000
1.2000
1.0000
.8000
.6000
FEV1 in liters
.00
1.28
2.12
3.14
4.09
5.00
5.97
6.88
7.83
8.97
10.17
11.74
15.05
Follow-up duration in years
AAT therapy during study
No
Yes