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Exacerbations and duration of smoking abstinence are associated with the annual loss of FEV_1 in individuals with PiZZ alpha-1-antitrypsin deficiency

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ABSTRACT

Background: Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder that is associated with a higher risk of chronic obstructive pulmonary disease (COPD) and emphysema. The annual declines in lung function (FEV_1) and transfer factor of the lung for carbon monoxide (TLCO) predict all-cause mortality.
Material and methods: We investigated the longitudinal follow-up data over 11 years (mean follow-up period of 4.89 years) from the German AATD registry and analyzed the relationship between annual loss of FEV_1 and TLCO and sex, age, body mass index (BMI), nicotine consumption, occupational dust exposure, St. George's Respiratory Questionnaire (SGRQ) score, baseline FEV_1 or TLCO, alpha-1-antitrypsin (AAT) serum level, exacerbation frequency and the duration of smoking abstinence by multiple linear generalized estimating equations models (GEE-models).
Results: We evaluated the data of 100 individuals with post-bronchodilator FEV_1 measurements and from 116 individuals with TLCO measurements. The mean overall decline was −54.06 ± 164.62 ml/year in FEV_1 and -0.17 ± 0.70 mmol/min/kPa/year in TLCO. Accelerated deterioration of FEV_1 was associated with occupational dust exposure ($p = 0.026$), shorter duration of smoking abstinence ($p = 0.008$), higher baseline FEV_1 ($p = 0.003$), higher annual exacerbation frequency ($p = 0.003$) and higher frequency of glucocorticoids intake ($p = 0.004$).
Furthermore, patients with an elevated decline in TLCO showed significant impaired health-related quality of life at baseline ($p = 0.039$) and lower AAT serum levels ($p < 0.001$) in multivariate analysis.
Conclusions: Annual decline in FEV_1 is related to the exacerbation rate, occupational dust exposure and the duration of smoking abstinence.

1. Introduction

Alpha-1-antitrypsin -deficiency (AATD) is a genetic disorder that is associated with a reduced inhibition of neutrophil elastase and that leads to a higher risk of chronic obstructive pulmonary disease (COPD). The genotype PiZZ is clinically most relevant and is related to reduced lung functional parameters, reduced transfer factor of the lung for carbon monoxide (TLCO), lower alpha-1-antitrypsin (AAT) serum level and higher mortality [1–3].

Considering the longitudinal course of disease, several studies demonstrated the annual decrease in forced expiratory volume in 1 s (FEV_1) and TLCO as predictors for all-cause mortality [4–7].

The FEV_1 is subjected to physiological variation across the duration of a person's life. In childhood and adolescence, there is a rise in lung function, followed by a plateau phase with stable

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levels of lung function, followed by the start of lung function decline [8,9]. In addition to the lung function, the TLCO undergoes a physiological alteration across lifetime [10]. The decline in FEV_1 as well as the decline in TLCO depends on the initial baseline level: the lower the baseline FEV_1, the less the decline in the follow-up period [11,12].

Prior studies have showed that smoking cessation leads to a normalization of FEV_1 decline towards the values of never-smokers over time [13–15]. However, there is not much data about the effect of smoking cessation on the FEV_1 decline in individuals with AATD. Previous studies showed an association between faster decline in FEV_1 and lower body mass index (BMI), lower reversibility to bronchodilator (BDR), higher exacerbation rate and worse St. George's Respiratory Questionnaire (SGRQ) activity-score in individuals with AATD [11,12].

The aim of this paper was to analyze the change of FEV_1 and TLCO in individuals with AATD over a longer observation period and to identify factors that are associated with rapid decline.

We focused on the association between the duration of smoking abstinence and the decline in FEV_1 and TLCO. In addition, we analyzed the relationship between sex, age, BMI, occupational dust exposure, SGRQ score, baseline FEV_1 or TLCO, AAT serum level, the exacerbation frequency and the annual decline in FEV_1 (ΔFEV_1/yr) and TLCO (ΔTLCO/yr).

2. Material and methods

2.1. Structure of German registry for individuals with AATD

The German AATD registry (AATDR) was established in 2003 and is located at the Saarland University, Homburg. The registry is based on a rolling inclusion of individuals with severe AATD. The registry currently contains the data of 1086 patients (3/2016).

The dataset of AATDR is structured in a similar way to the dataset of the Alpha One International Registry (AIR).

The AATDR includes individuals with severe AAT deficiency, as defined by a known genotype or by low serum concentrations of AAT. Ethical approval for the questionnaires and the data storage concept were granted by the ethics committees of the Marburg University, the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all individuals.

2.2. Questionnaire design

The AATDR baseline questionnaire queries information about basic anthropomorphic data, AATD genotype, smoking habits, COPD exacerbation frequency within the last two years, pulmonary functional parameters, quality of life and pulmonary diseases, e.g. chronic bronchitis, emphysema or asthma bronchiale. The questionnaires are sent to affected individuals or their physicians. Questions on treatment, pulmonary function and the TLCO are answered by the treating physician.

Exacerbations are defined as an excessive worsening of COPD symptoms with a duration of more than two days that required hospitalization or treatment with antibiotics or systemic glucocorticoids. The definition of “exacerbation” was explained in the questionnaires to the participants. We obtained information of exacerbations within the last two years by baseline questionnaires and by follow-up questionnaires. Health-related quality of life data was collected with the SGRQ.

For the analysis of disease progression, we evaluated baseline data from 2004 and follow-up assessments from the years 2006, 2011 and 2015.

2.3. Data analysis

Data from 2004 to March 2016 were compiled and analyzed. At that time, 1086 patients were registered in the database including 876 individuals with PiZZ AATD. For the cross-sectional analysis, data on post-bronchodilator FEV_1 of 413 individuals and on TLCO of 484 individuals were available. Patients with lung transplantation or lung volume reduction in the follow-up period were excluded from the longitudinal study. The longitudinal study population contained 177 PiZZ AATD individuals with available follow-up data about ΔFEV_1/yr or/and about ΔTLCO/yr. We analyzed 100 individuals in the ΔFEV_1 analysis and 116 individuals in the ΔTLCO analysis. For our study, 95 individuals participated in the first follow-up survey (2006), 106 individuals in the second survey (2011) and 61 individuals in the third survey (2015). A number of participants were lost for the follow-up surveys. Reasons cannot be specified in detail (delivery failure of questionnaires due to movements, loss of interest by the participants or missing data about FEV_1 or TLCO, mortality, etc.). Fig. 1 shows the study enrollment process and the numbers of cases of valid data for the investigated variables.

2.4. Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD). The mean values of continuous variables in different groups were compared by independent samples *t*-test. The effects of the analyzed variables on the decline in FEV_1 or TLCO were evaluated by multiple linear generalized estimating equations models (GEE-models). The GEE approach was established by Liang and Zeger (1986) and Zeger and Liang (1986) for the evaluation of longitudinal data [16,17]. Using this model, we could assess multiple follow-up surveys of each individual. The influences of the variables were expressed in univariate analysis and verified by multivariate analysis. Taking into consideration that the baseline FEV_1 may influence the amount of decline in the follow-up period, this parameter was included in some of our multivariate regression models. To avoid multicollinearity in the multivariate analysis, we only included predictor variables which affected the deterioration of FEV_1 or TLCO independently of each other variable. Thus, not all potential confounders (e.g. age) could be considered. We specified the B value which indicates the change in deterioration of FEV_1 (ml/year) or TLCO (mmol/min/kPa/year) for a one-unit increase in the predictor variable. In the binomial predictor variables, B value indicates the difference in loss of FEV_1 (ml/year) or TLCO (mmol/min/kPa/year) between the two groups. Statistical significance was considered for two-sided p values less than 0.05. The analysis was performed using MS Excel and IBM SPSS version 23.

3. Results

3.1. Characteristics of patients

100 PiZZ AATD individuals (male n = 65; female n = 35) with available longitudinal post-bronchodilator FEV_1 data and 116 PiZZ AATD individuals (male n = 72; female n = 44) with available longitudinal TLCO data were analyzed (all together n = 177). 95 PiZZ individuals were available for the first follow-up survey in the year 2006, 106 PiZZ individuals for the second follow-up survey in the year 2011 and 61 PiZZ individuals for the third follow-up survey in the year 2015. The baseline characteristics are summarized in Table 1.

The mean age of the individuals for the longitudinal FEV_1 – and TLCO analysis (n = 177) was 55.2 ± 10.8 years (range: 31–78 years), mean BMI was 24.5 ± 4.4 kg/m^2. Ex-smokers (n = 125; 70.6%) had a

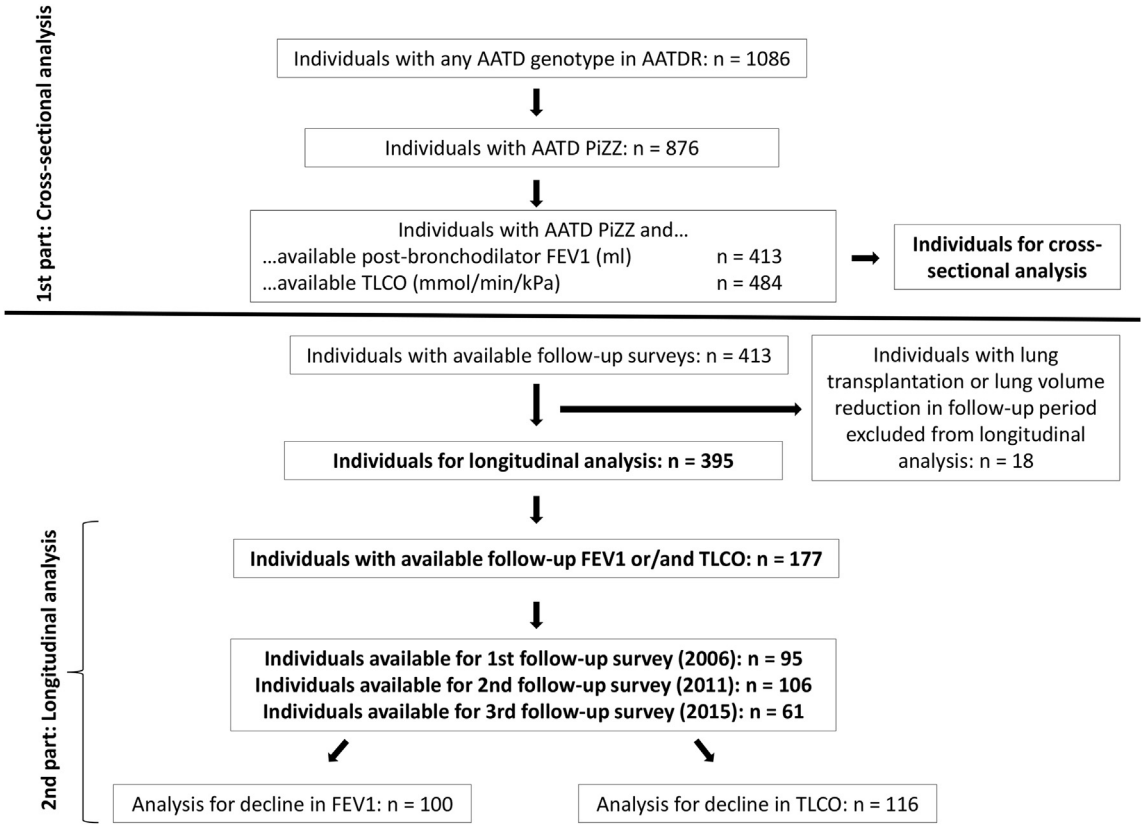

Fig. 1. Flow chart showing study enrollment process (n = 177).

Table 1
Baseline characteristics of individuals for longitudinal analysis.

	Individuals for longitudinal analysis (n = 395) Mean (SD)/n (%)	Individuals with available follow-up FEV_1 or/and TLCO (n = 177) Mean (SD)/n (%)	Individuals available for 1st follow-up survey (n = 95) Mean (SD)/n (%)	Individuals available for 2nd follow-up survey (n = 106) Mean (SD)/n (%)	Individuals available for 3rd follow-up survey (n = 61) Mean (SD)/n (%)
Sex (male)	239 (60.5%)	117 (66.1%)	61 (64.2%)	73 (68.9%)	40 (65.6%)
Age (years)	54.4 (11.6)	55.2 (10.8)	55.7 (10.3)	55.6 (11.0)	53.2 (9.9)
BMI (kg/m^2)	24.4 (4.6)	24.5 (4.4)	24.2 (3.5)	24.9 (4.8)	24.3 (3.6)
Never-smokers	104 (26.3%)	47 (26.6%)	21 (22.1%)	30 (28.3%)	15 (24.6%)
Ex-smokers	281 (71.1%)	125 (70.6%)	72 (75.8%)	73 (68.9%)	44 (72.1%)
Current smokers	9 (2.3%)	5 (2.8%)	2 (2.1%)	3 (2.8%)	2 (3.3%)
Packyears current smokers	25.8 (14.2)	29.2 (11.8)	34.7 (3.3)	31.2 (15.1)	31.4 (15.7)
Packyears ex-smokers	20.3 (14.3)	20.2 (14.0)	21.8 (15.5)	18.5 (12.2)	18.0 (13.2)
Baseline post-bronchodilator FEV_1 (ml)	1595 (674)	1671 (671)	1465 (532)	1759 (716)	1881 (717)
Baseline post-bronchodilator FEV_1 (% pred.)	48.9 (18.1)	51.0 (17.7)	46.4 (15.9)	53.2 (18.7)	55.9 (18.9)
Baseline TLCO (mmol/min/kPa)	4.97 (2.26)	5.06 (2.24)	4.94 (2.26)	5.29 (2.28)	4.96 (1.69)
Baseline TLCO (% pred.)	50.6 (20.2)	51.6 (20.8)	51.0 (21.6)	53.5 (21.1)	50.9 (16.3)

smoking history of 20.2 ± 14.0 packyears; current smokers (n = 5; 2.8%) of 29.2 ± 11.8 packyears. Mean baseline post-bronchodilator FEV_1 was 1671 ± 671 ml (% pred. 51.0 ± 17.7); mean baseline TLCO was 5.06 ± 2.24 mmol/min/kPa (% pred. 51.6 ± 20.8). We compared the individuals that were available for FEV_1 and/or TLCO follow-up assessments (n = 177) with the individuals that were lost during the follow-up period (n = 477). Individuals that were not available for follow-up surveys did not differ significantly from individuals with existing follow-up data in baseline FEV_1 (1526 ± 685 ml vs. 1664 ± 663 ml; p = 0.058), baseline TLCO (5.01 ± 2.54 mmol/min/kPa vs. 4.96 ± 2.29 mmol/min/kPa; p = 0.857), baseline SGRQ (46.89 ± 20.25 vs. 47.22 ± 17.60; p = 0.846) and the exacerbation frequency within the last two years (0.86 ± 1.07 vs. 0.77 ± 1.02; p = 0.339).

3.2. The cumulative nicotine consumption and exacerbation frequency are associated with worse baseline FEV_1 and TLCO in cross-sectional analysis

In the cross-sectional analysis, we evaluated data on all PiZZ individuals with at least one available FEV_1 (n = 413) and/or TLCO (n = 484) measurement (all together n = 654). The baseline FEV_1 (ml) correlated weakly but significantly with age (r = −0.172; p < 0.001), BMI (r = 0.121; p = 0.015), cumulative nicotine

consumption in packyears ($r = -0.147$; $p = 0.003$), the exacerbation frequency ($r = -0.286$; $p < 0.001$) and stronger with the SGRQ score ($r = -0.503$; $p < 0.001$). The baseline TLCO (mmol/min/kPa) was weakly but significantly associated with age ($r = -0.368$; $p < 0.001$), BMI ($r = 0.156$; $p = 0.001$), cumulative nicotine consumption in packyears ($r = -0.144$; $p = 0.002$), the exacerbation frequency ($r = -0.169$; $p < 0.001$) and SGRQ score ($r = -0.356$; $p < 0.001$). Neither the baseline FEV_1 nor the baseline TLCO were significantly dependent on the number of years since quitting smoking ($r = -0.030$; $p = 0.596$; $r = -0.036$; $p = 0.503$).

3.3. The highest decline of FEV_1 is observed in younger individuals (longitudinal analysis)

Analysis of decline is based on 177 PiZZ individuals with available follow-up data on FEV_1 and/or TLCO. The overall mean decline in FEV_1 was −54.06 ± 164.62 ml/year (Fig. 2). Younger individuals (aged 25–39 years) had the highest decline (−147.57 ± 163.59 ml/year), whereas older individuals (≥60 years) showed the lowest loss of lung function in the follow-up period (−34.80 ± 118.09 ml/year) ($p = 0.020$) (Table 2). Similar results were observed in the subgroup of never- and ex-smokers.

Mean overall decline in TLCO was −0.17 ± 0.70 mmol/min/kPa/year (Table 2; Fig. 3). The highest deterioration of TLCO was seen in older individuals (≥60 years) (−0.24 ± 0.89 mmol/min/kPa/year), the lowest decline in younger individuals (aged 25–39 years) (−0.09 ± 0.39 mmol/min/kPa/year) (the difference was not significant).

3.4. Accelerated deterioration of FEV_1 is associated with higher exacerbation frequency and shorter duration of smoking abstinence (longitudinal analysis)

Univariate analysis showed that the decline in FEV_1 was significantly associated with the annual exacerbation rate ($B = -79.110$; $p = 0.003$), the annual intake of glucocorticoids ($B = -78.353$; $p = 0.004$), occupational dust exposure ($B = -61.448$; $p = 0.026$), the duration of smoking abstinence in years ($B = 2.692$; $p = 0.008$) and baseline FEV_1 ($B = -0.050$; $p = 0.003$) (Table 3).

In consideration of several potential confounders, multivariate analysis confirmed the relationship between accelerated decline in FEV_1 and increased exacerbation frequency ($B = -44.877$; $p = 0.014$), the need of glucocorticoids ($B = -43.985$; $p = 0.020$) (both adjusted for sex, dust exposure, augmentation therapy, baseline FEV_1 and years of smoking abstinence) and a shorter duration of smoking abstinence in years ($B = 2.729$; $p = 0.011$)

Table 2
Mean annual decline stratified according to age groups, all individuals. The highest decline in FEV_1 is seen in younger individuals (25–39 years), the highest decline in TLCO is seen in older individuals (≥60 years).

	Mean ΔFEV_1 (ml/yr)	Mean ΔTLCO (mmol/min/kPa/yr)
Overall	−54.06 (164.62) (n = 100)	−0.17 (0.70) (n = 116)
25–39 yrs	−147.57 (163.59) (n = 9)	−0.09 (0.39) (n = 8)
40–59 yrs	−52.66 (191.38) (n = 51)	−0.13 (0.60) (n = 67)
≥ 60 yrs	−34.80 (118.09) (n = 40)	−0.24 (0.89) (n = 41)

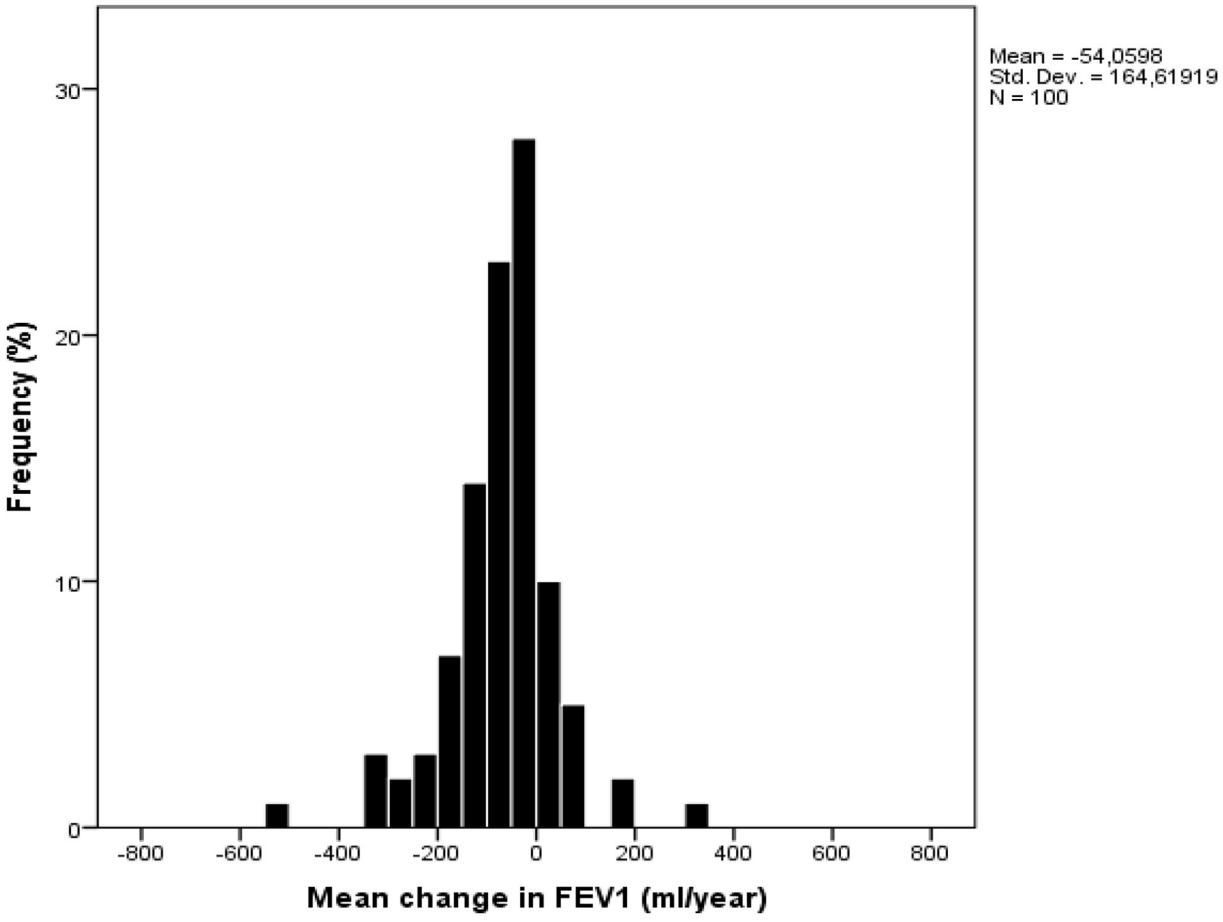

Fig. 2. The mean change in postbronchodilator FEV_1 was −54.06 ml in n = 100 individuals over the follow-up period (average of multiple follow-up surveys for each individual).

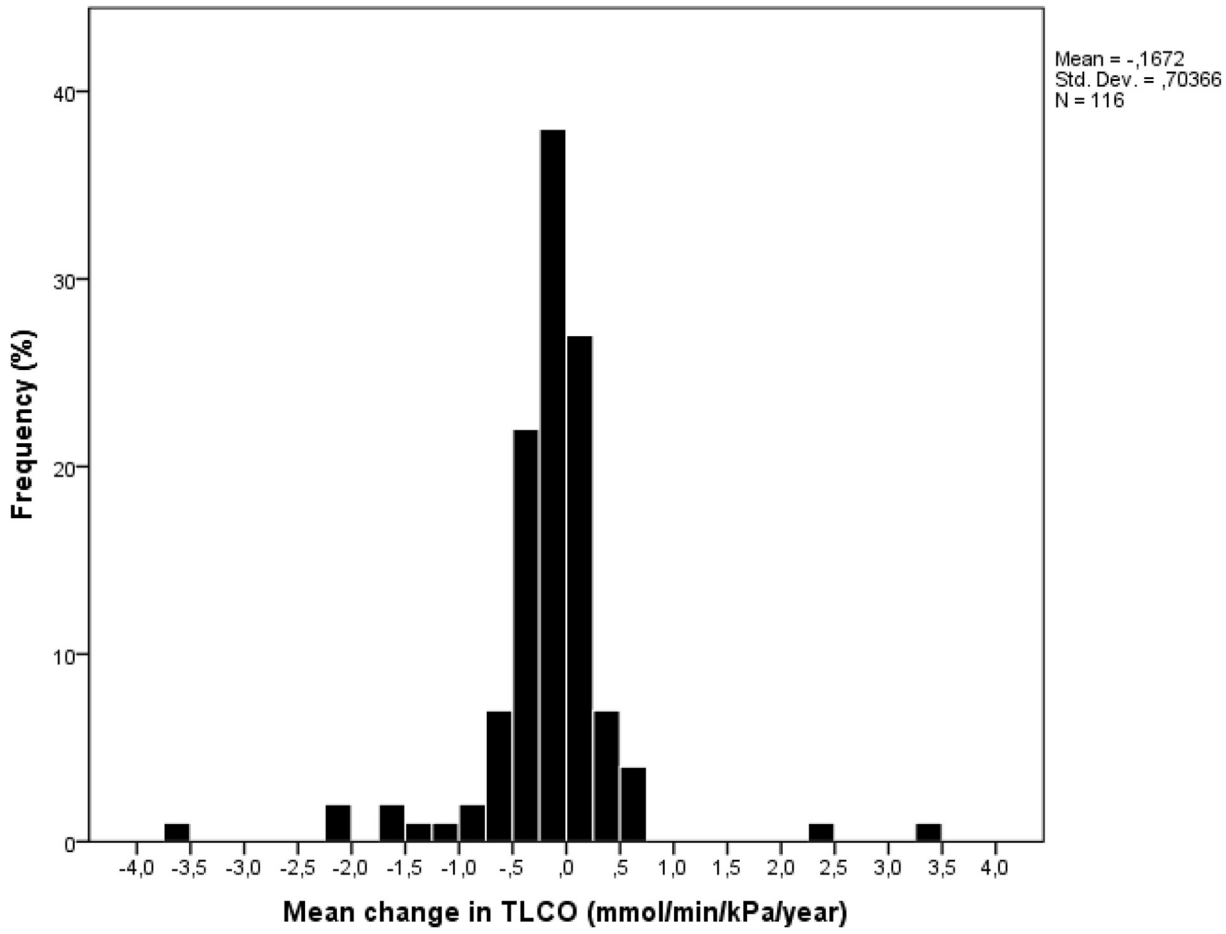

Fig. 3. The mean change in TLCO was −0.17 mmol/min/kPa/year in n = 116 individuals over the follow-up period (average of multiple follow-up surveys for each individual).

(adjusted for sex, dust exposure, augmentation therapy and baseline FEV_1). For example, the B value equal to −44.877 means that a one-unit increase in the annual exacerbation frequency is associated with a change in deterioration of FEV_1 of −44.877 ml/year.

3.5. Increased decline in TLCO is associated with lower baseline quality of life (SGRQ) (longitudinal analysis)

Univariate analysis revealed significant higher rates of decline in TLCO for low BMI (B = 0.023; p = 0.040) and higher SGRQ total-scores (B = −0.008; p = 0.027) at baseline. Multivariate analysis showed a significant relationship between deterioration of TLCO and baseline SGRQ total-score (B = −0.07; p = 0.039) (adjusted for baseline FEV_1, AAT serum level and chronic bronchitis), AAT serum level (B = 0.022; p < 0.001) (adjusted for baseline FEV_1 and chronic bronchitis) and baseline FEV_1 (B = 0.0003; p = 0.020) (adjusted for AAT serum level and chronic bronchitis) (Table 4).

The exacerbation frequency, the need of glucocorticoids or antibiotics or the rate of hospitalizations were not significantly associated with the loss of TLCO.

3.6. Comparison of augmented and not augmented individuals with AATD (longitudinal analysis)

In our study population, most of the subjects (n = 140; 79.1%) received augmentation therapy. A small sample size of 37 (20.9%) individuals reported no augmentation therapy. The differences in mean decline in FEV_1 (augmented: −48.96 ± 168.46 ml/yr (available in n = 85 individuals); not augmented: −82.94 ± 142.51 ml/yr (available in n = 15 individuals)) and TLCO (augmented: −0.15 ± 0.75 mmol/min/kPa/yr (available in n = 87 individuals); not augmented: −0.22 ± 0.53 mmol/min/kPa/yr (available in n = 29 individuals)) between individuals who reported on augmentation therapy and who did not were not significant.

4. Discussion

The main findings of the present study are significant relationships between the annual loss of FEV_1 and the exacerbation frequency and the duration of smoking abstinence. A higher exacerbation frequency and a short duration of smoking abstinence were associated with a faster deterioration of FEV_1. In our analysis, a GEE-model was chosen that enabled the interpretation of longitudinal registry data over 11 years (mean follow-up period of 4.89 years). Using this model, multiple observations for each subject could be assessed and several potential confounders could be included in the analysis.

In contrast to other AATD studies [11,12,18], we analyzed the impact of occupational dust exposure, the duration of smoking abstinence until the baseline lung function measurement after quitting smoking, the frequency of intake of glucocorticoids and antibiotics and the hospitalization rate.

In AATD, data on the age-dependent shape of decline in FEV_1 and TLCO and factors that accelerate the deterioration, is limited

Table 3
GEE-model analysis of variables influencing annual decline in FEV_1 (n = 100). B value indicates the change in deterioration of FEV_1 (ml/year) for a one-unit increase in the predictor variable. In binomial predictor variables, B value indicates the difference in loss of FEV_1 (ml/year) between the two groups. The exacerbation frequency, the glucocorticoids intake and the duration of smoking abstinence are significantly associated with the annual decline in FEV_1 in univariate and multivariate analysis (predictor variables in bold indicate significance in both univariate and multivariate analysis).

Predictor variable	Univariate analysis	Multivariate analysis
	B value (p value) n = 100	B value (p value) n = 100
Sex (male)	−32.704 (p = 0.217)	−44.392 (p = 0.029)
Age (years)	1.853 (p = 0.102)	1.320 (p = 0.267)
Cumulative nicotine consumption (packyears)	0.012 (p = 0.992)	0.060 (p = 0.965)
Chronic bronchitis	36.505 (p = 0.233)	2.504 (p = 0.902)
Emphysema	61.477 (p = 0.387)	26.681 (p = 0.660)
BMI (kg/m^2)	−0.017 (p = 0.992)	1.792 (p = 0.414)
Height (m)	−1.253 (p = 0.332)	−0.996 (p = 0.331)
Weight (kg)	−0.259 (p = 0.575)	0.431 (p = 0.467)
SGRQ total-score	0.198 (p = 0.730)	1.058 (p = 0.020)
AAT serum level (mg/dl)	0.403 (p = 0.591)	−0.051 (p = 0.939)
Exacerbation rate/yr	**−79.110 (p = 0.003)**	**−44.877 (p = 0.014)**
Glucocorticoids/yr	**−78.353 (p = 0.004)**	**−43.985 (p = 0.020)**
Increase of current medication/yr	−28.698 (p = 0.513)	−61.574 (p = 0.004)
Antibiotics/yr	−36.170 (p = 0.328)	−40.472 (p = 0.007)
Hospitalization/yr	18.424 (p = 0.846)	−22.268 (p = 0.479)
Occupational dust exposure	−61.448 (p = 0.026)	−17.104 (p = 0.388)
Duration of smoking abstinence (years)	**2.692 (p = 0.008)**	**2.729 (p = 0.011)**
Baseline FEV_1 (ml)	−0.050 (p = 0.003)	−0.018 (p = 0.306)
Baseline FEV_1 (% pred.)	−1.279 (p = 0.106)	−1.019 (p = 0.159)
Baseline TLCO (mmol/min/kPa)	−1.480 (p = 0.730)	1.174 (p = 0.749)
Baseline TLCO (% pred.)	0.591 (p = 0.323)	0.681 (p = 0.167)

[11,12]. For the analysis, all subjects were stratified into three age groups, because in the general population the decline in FEV_1 and TLCO varies depending on the subjects' age [10,19]. In our study, younger individuals (aged 25–39 years) showed a significant higher mean decline in FEV_1 compared to older subjects (≥60 years). We found no significant differences between the age groups for the decline in TLCO, however, there was a trend for an accelerated decline in older individuals. Viegi et al. found that the annual decline in TLCO is accelerated with higher age in healthy individuals (≥40 years old) [10]. Previous studies on healthy individuals showed a physiological annual change in FEV_1 of approximately −21 ml for non-/ex-smoking persons in middle age (40–59 years) [20]. We could show that middle-aged AATD patients (40–59 years) have an accelerated decline in FEV_1 that is more than 3-times higher compared to healthy persons. AATD subjects from the AATDR have a higher annual decline in FEV_1 (overall −54 ml/year) than individuals with non-AATD COPD from the ECLIPSE study cohort (−33 ml/year in 40–75 year-old ex- and current smokers) or the Lung Health Study (−27 ml/year in ex-smokers) [21,22]. These findings concur with the results from prior AATD studies that found an overall annual deterioration of FEV_1 of −54 ml/year, −50 ml/year, −67 ml/year and −57 ml/year [11,12,23,24].

The present paper investigated several factors that could

Table 4
GEE-model analysis of variables influencing annual decline in TLCO (n = 116). B value indicates the change in deterioration of TLCO (mmol/min/kPa/year) for a one-unit increase in the predictor variable. In binomial predictor variables, B value indicates the difference in loss of TLCO (mmol/min/kPa/year) between the two groups. The SGRQ score, the AAT serum level and the baseline FEV_1 are significantly associated with the annual decline in TLCO in multivariate analysis (predictor variables in bold indicate significance in both univariate and multivariate analysis).

Predictor variable	Univariate analysis	Multivariate analysis
	B value (p value) n = 116	B value (p value) n = 116
Sex (male)	−0.048 (p = 0.640)	−0.316 (p = 0.121)
Age (years)	−0.004 (p = 0.549)	−0.004 (p = 0.482)
Cumulative nicotine consumption (packyears)	0.005 (p = 0.168)	0.004 (p = 0.184)
Chronic bronchitis	−0.153 (p = 0.178)	−0.344 (p = 0.069)
Emphysema	0.279 (p = 0.205)	0.770 (p = 0.151)
BMI (kg/m^2)	0.023 (p = 0.040)	0.008 (p = 0.635)
Height (m)	−0.003 (p = 0.507)	−0.006 (p = 0.226)
Weight (kg)	0.003 (p = 0.386)	−0.001 (p = 0.788)
SGRQ total-score	**−0.008 (p = 0.027)**	**−0.07 (p = 0.039)**
AAT serum level (mg/dl)	0.016 (p = 0.054)	0.022 (p < 0.001)
Exacerbation rate/yr	−0.091 (p = 0.514)	−0.051 (p = 0.724)
Glucocorticoids/yr	−0.091 (p = 0.509)	−0.067 (p = 0.654)
Increase of current medication/yr	0.067 (p = 0.591)	0.079 (p = 0.529)
Antibiotics/yr	−0.101 (p = 0.295)	−0.068 (p = 0.463)
Hospitalization/yr	−0.433 (p = 0.080)	−0.446 (p = 0.098)
Occupational dust exposure	−0.054 (p = 0.662)	−0.214 (p = 0.278)
Duration of smoking abstinence (years)	−0.002 (p = 0.764)	0.003 (p = 0.714)
Baseline FEV_1 (ml)	0.0003 (p = 0.096)	0.0003 (p = 0.020)
Baseline FEV_1 (% pred.)	0.011 (p = 0.075)	0.012 (p = 0.005)
Baseline TLCO (mmol/min/kPa)	−0.019 (p = 0.371)	−0.014 (p = 0.577)
Baseline TLCO (% pred.)	−0.002 (p = 0.407)	−0.002 (p = 0.611)

influence the annual loss of FEV_1 and TLCO. Exacerbations have been identified as a risk factor for worse prognosis in non-AATD COPD [25]. Previous AATD studies showed a relationship between higher exacerbation rate and accelerated decline in FEV_1 [11,12]. Our results confirmed this relationship. In the follow-up, mean decline in FEV_1 was −116 ml/yr in individuals with frequent self-reported exacerbations (≥2/yr) compared to −21 ml/yr in individuals with no exacerbations. Moreover, frequent exacerbation-related glucocorticoids intake correlated with an accelerated decline in FEV_1, which underlines the role of moderate or severe exacerbations on the loss of lung function.

So far, the effect of smoking cessation on the deterioration of FEV_1 has not been investigated in individuals with AATD. It has been shown only in COPD subjects and in healthy individuals that sustained smoking abstinence leads to a return of the rate decline in FEV_1 to that of never-smokers [13–15]. To our knowledge, this is the first paper that revealed that a longer duration of smoking abstinence was associated with a lower decline in FEV_1 in individuals with AATD. This finding was confirmed by multivariate analysis under consideration of several confounders (sex, occupational dust exposure, augmentation therapy, duration of smoking abstinence and baseline FEV_1).

In contrast to the duration of smoking abstinence, the cumulative nicotine consumption in patients' prehistory was not significantly associated with a higher decline in FEV_1. This finding contributes to prior studies that showed a normalization of decline in FEV_1 after quitting smoking in COPD and healthy individuals [13–15]. A comparison between current smokers and ex-smokers in the deterioration of FEV_1 or TLCO was not possible because the number of current smoker in the registry was too small.

The annual decline in TLCO correlated significantly with the baseline SGRQ score. The worse the quality of life score at baseline, the stronger the decline in TLCO in the follow-up. These results underline the role of SGRQ as a good parameter for the estimation of disease progression.

Finally, we investigated the longitudinal follow-up data regarding the AAT augmentation therapy. There was a trend towards lower decline in FEV_1 and TLCO in augmented individuals, however, it was not significant. For a firm conclusion concerning augmentation therapy, the number of not augmented individuals in the registry was too small.

The main strengths of our study are the long follow-up period of 11 years (mean follow-up period of 4.89 years) and the large study group of the AATDR. However, only a part of the study group was available for the follow-up surveys and questionnaires were not filled out completely. This could be a reason for the missing significance in some predictors for the decline in FEV_1 or TLCO. Some more limitations to our study should be noted. First, the findings are based on self-reported information (e.g. exacerbations, lung function data); the quality of these data is likely less as compared to well-controlled clinical trials. Our data might not be representative for all individuals with AATD because individuals with more severe manifestations or increased burden of symptoms might be overrepresented. A part of the baseline study population was lost during the follow-up period. Nevertheless, the individuals that were not available for follow-up assessments did not have significantly worse FEV_1, TLCO and SGRQ at baseline and did not have significantly more exacerbations.

We conclude from our data that AATD individuals have a higher annual deterioration of FEV_1 than healthy subjects or non-AATD COPD individuals. Accelerated decline was associated with frequent exacerbations and glucocorticoids intake as well as a shorter period of smoking abstinence. The longer the period of smoking abstinence, the lower the annual loss of lung function.

List of abbreviations

AATD	Alpha-1-antitrypsin deficiency
COPD	Chronic obstructive pulmonary disease
PiZZ	Protease inhibitor ZZ genotype
TLCO	Transfer factor of the lung for carbon monoxide
AAT	Alpha-1-antitrypsin
FEV_1	Forced expiratory volume in 1 s
BMI	Body mass index
BDR	Airway obstruction: reversibility to bronchodilator/ bronchodilator response
SGRQ	St. George's Respiratory Questionnaire
ΔFEV_1/yr	Annual decline in FEV_1
ΔTLCO/yr	Annual decline in TLCO
AATDR	German alpha-1-antitrypsin deficiency registry
AIR	Alpha One International Registry
GEE-models	Generalized estimating equations models

Ethics approval and consent to participate

The questionnaires and the data storage concept were approved by the ethics committees of the Marburg University and the Landesärztekammer Saarland (SN80/10) and the Data Safety Office of the State of Hessen (all in Germany). A declaration of informed consent was signed by all participating individuals.

Availability of data and materials

The datasets of the AATDR are located at the Department of Internal Medicine V – Pulmonology, Allergology, Intensive Care Medicine, Saarland University Hospital, Homburg, Germany and are available from the corresponding author on reasonable request.

Competing interests

RB, SF and CV have obtained research support and travel sponsoring from Talecris/Grifols and CSL Behring. CV has received honoraria for speaking engagements and for chairing a research prize committee from Talecris/Grifols. PL has received speaker fees from Talecris/Grifols. The authors alone are responsible for the content and the writing of the paper.

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Authors‘ contributions

All co-authors agreed to be accountable for all aspects of the work and reviewed the final manuscript. NB, PL, CV, RB, and SF contributed to conception of the study, patient recruitment and original data collection and interpretation. MS contributed to the patient recruitment. SW performed the statistical analysis.

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