Original Article

The Association Between Heavy Alcohol Use and Lung Function: A Clinical Study of Adult-Onset Asthma

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What is known about this topic? Little is known about a possible association between heavy alcohol consumption and lung function in patients with asthma, although excessive alcohol drinking has been shown to induce a wide variety of health problems and significant immunomodulatory effects.

What does this article add to our knowledge? In patients with objectively verified adult-onset asthma, heavy alcohol consumption is associated with accelerated loss of lung function.

How does this study impact current management guidelines? Attention should be paid to the assessment of alcohol consumption when treating patients with asthma.

BACKGROUND: In animal studies, alcohol exposure has been reported to damage lungs. However, no human studies exist on the association between alcohol consumption and lung function in asthma.

OBJECTIVE: To evaluate the association between heavy alcohol consumption and lung function decline in patients with adult-onset asthma.

METHODS: In the Seinäjoki Adult Asthma Study, 201 patients were observed for 12 years after the diagnosis of new-onset asthma. Based on detailed questionnaires and laboratory indices of heavy drinking, patients were classified as heavy alcohol consumers or non-heavy alcohol consumers. Spirometry evaluation points were (1) baseline before the initiation of inhaled corticosteroids (ICS), (2) maximum lung function during the first 2.5 years after diagnosis and start of ICS treatment ($Max_{0\text{-}2.5}$), and (3) after 12 years.

RESULTS: Between the asthma diagnosis and follow-up, median (interquartile range) annual decline in FVC was −30 mL (−51 to −11 mL) in heavy alcohol consumers and −5 mL (−26 to 25 mL) in non-heavy alcohol consumers ($P < .001$). This was largely explained by a decline in FVC between $Max_{0\text{-}2.5}$ and follow-up ($P = .041$) and perhaps by a diminished effect of ICS. Annual decline in FEV_1 was −26 mL (−52 to 0 mL) in heavy alcohol consumers and −17 mL (−31 to 6 mL) in non-heavy alcohol consumers ($P = .022$). In multivariate regression analysis, heavy alcohol consumption was a significant predictor of accelerated decline in FVC.

CONCLUSION: In patients with objectively verified adult-onset asthma, heavy alcohol consumption is associated with

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Abbreviations used
BMI- Body mass index
CDT- Carbohydrate-deficient transferrin
GGT- γ-Glutamyl transferase

Key words: *Alcohol consumption; Adult; Asthma; Follow-up; Lung function; FEV_1*

INTRODUCTION

Although many health risks can be induced by heavy alcohol use[1-3] and associated immunomodulatory effects,[4] little is known about the effects of heavy alcohol consumption on asthma. In previous studies, asthma was reported to be associated with a greater risk of having alcohol use disorders.[5,6] For a long time, alcohol has been known to act as a bronchodilator, and it has been proposed to decrease bronchial hypersensitivity in short-term use.[7] However, the effects of long-term alcohol intake on lung health are not clear. In populations consisting mainly of persons without asthma, heavy alcohol intake has been linked to more rapid decline in both FEV_1 and FVC.[8,9] However, alcohol intake has also been linked to possible beneficial effects on lung function and a lower prevalence of restriction.[10,11] A recent review[12] explored the relationship between alcohol consumption and pulmonary function. Whereas heavy alcohol consumption appears to affect pulmonary function negatively, further long-term research is needed to fully understand the relationship. No previous studies on heavy alcohol intake and lung function have focused on patients with asthma.

The prevalence rate of high-risk alcohol consumption is estimated to be approximately 15% to 30% of the population.[13-15] In the United States, heavy alcohol use is defined as eight or more drinks per week for a woman and 15 or more drinks per week for a man (one standard drink corresponds to 14 g of alcohol).[16] Physicians and clinical studies often fail to detect heavy alcohol consumption. Questionnaires are based on self-report, and in general populations such techniques have been suggested to reveal approximately only half of the consumption expected from sales of alcohol.[17] Typically, assessment of alcohol use in most previous studies regarding lung function and alcohol was based solely on data obtained from self-reports. More objective assessment of alcohol use is possible with laboratory markers. γ-Glutamyl transferase (GGT) and alanine aminotransferase have frequently been used as screening tools, but they lack both specificity and sensitivity.[18] Carbohydrate-deficient transferrin (CDT) is a specific marker for alcohol abuse, but it also lacks sensitivity. Elevated levels of CDT typically require a person to take in 50 to 80 g (approximately four to six drinks) of alcohol per day for several weeks. The GGT-CDT index ($GGT\text{-}CDT = 0.8 \times \ln[GGT] + 1.3 \times \ln[\%CDT]$) is the most specific (98%) and sensitive (90%) marker for alcohol abuse compared with GGT, alanine aminotransferase, aspartate aminotransferase, mean corpuscular volume, or CDT alone. The GGT-CDT index is typically elevated when more than 40 g/day of ethanol is used.[18-20]

More information is needed on how heavy alcohol consumption affects patients with asthma and their lung function. Thus, the aim of this study was to evaluate the association of heavy alcohol consumption on lung function in adult-onset asthma.

METHODS

Study design and patients

This study is part of the Seinäjoki Adult Asthma Study (SAAS), a prospective 12-year follow-up study. The study protocol was previously published elsewhere.[21] Patients (n = 256) with the diagnosis of new-onset adult asthma were recruited between 1999 and 2002 (Figure 1). Patients were included in the study if these criteria were fulfilled: (1) new-onset asthma diagnosed by a respiratory specialist, (2) confirmation of the diagnosis by lung function measurements showing variable or reversible obstruction, (3) symptoms of asthma, and (4) age 15 years or older (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). Smokers (current or ex-smokers) and patients with comorbidities were not excluded. We obtained written informed consent to the study protocol, which was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland (R12122).

The study was divided into two parts: collection of the original cohort (baseline) and the 12-year follow-up visit. At the baseline visit, data were collected on symptoms, lung function, demographics, and initial medication.[21] Anti-inflammatory therapy with inhaled corticosteroids (ICS) was started immediately after the baseline visit. Patients were observed for 12 years (mean, 12.2 years; range, 10.8-13.9 years) after the diagnostic visit. During follow-up, patients were actively treated for asthma according to the Finnish Asthma Programme.[22] After the follow-up period, 203 patients (79%) returned to the 12-year follow-up visit. We measured asthma symptoms, disease control, medication, alcohol use, and lung function, and took blood samples. All asthma-related visits and medication information were collected from the whole 12-year follow-up from medical records. Patients also completed Airways Questionnaire 20, a short questionnaire developed to measure the health-related quality of life (HRQoL) of patients with asthma or chronic obstructive pulmonary disease.[23,24] Other variables were measured as previously described[21] and are described in the Supplemental Materials (in this article's Online Repository at www.jaci-inpractice.org).

Lung function evaluation points

We assessed lung function using a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, Calif) according to Finnish reference values[25] and international recommendations.[26] Lung function measurement points were: (1) baseline (ie, time of asthma diagnosis), (2) maximum lung function ($Max_{0\text{-}2.5}$) during the first 2.5 years after diagnosis (ie, after start of ICS therapy) based on the highest prebronchodilator FEV_1 percent predicted, and (3) after 12 years of follow-up (Figure 2). We took lung function measurements after the diagnosis of asthma while patients were receiving medication, without pauses or withholding the therapy. After the initiation of asthma therapy, only prebronchodilator spirometry was

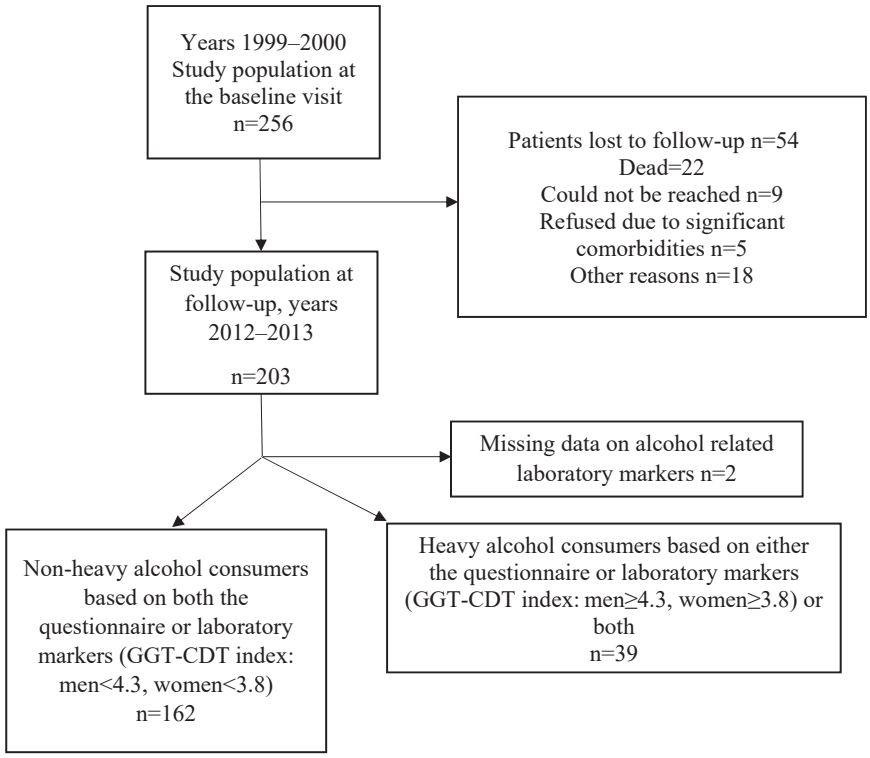

FIGURE 1. Flowchart of the study. *GGT-CDT,* γ-glutamyl transferase—carbohydrate-deficient transferrin.

measured on most patients; therefore, changes in those patients were evaluated.

Assessment of alcohol consumption

Patients were divided into two groups based on alcohol use (heavy alcohol consumption or non-heavy alcohol consumption representing moderate drinkers or abstainers). Patients were considered to be heavy alcohol consumers if the questionnaire data, the GGT-CDT index, or both indicated heavy alcohol consumption. The questionnaires used for gathering quantitative data on hazardous alcohol drinking were the shortened three-item version of the Alcohol Use Disorders Identification Test and the lifestyle risk factor questionnaire described previously in the large National FINRISK study.[27,28] Heavy alcohol users were defined according to the US definitions: men consuming 14 portions/week or more and women drinking 8 portions/week or more.[16] The cutoffs in the GGT-CDT index were 4.3 for men and 3.8 for women.[18]

Statistical analyses

Continuous data are expressed as means (SDs) or medians (interquartile ranges [IQRs]). We compared groups using independent-samples *t* test when analyzing normally distributed data, Mann-Whitney *U* test when analyzing nonnormally distributed data, and Pearson χ^2 test or Fisher exact test when comparing column proportions.

Multiple linear regression analyses were performed to determine the association of heavy alcohol use with lung function decline. To account for potential confounding factors, we included covariates into the analysis stepwise. The model's goodness of fit was assessed using R^2 and *P*. Encompassed covariates were body mass index (BMI) change from baseline to follow-up, age, sex, and smoking history, because these covariates gave the best model of the predictors on lung function decline. Data are presented as the unstandardized β coefficient and 95% CI.

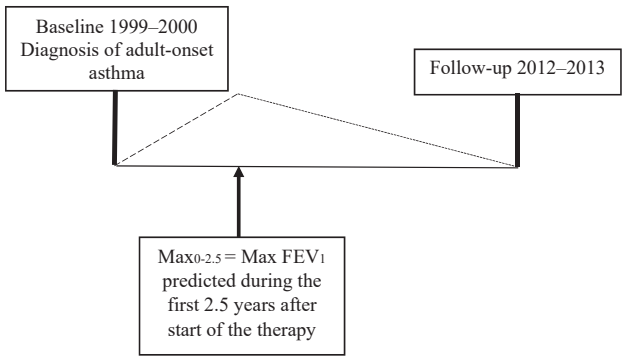

FIGURE 2. Measurement points of lung functions. $Max_{0\text{-}2.5}$ is the point of highest lung function (FEV_1 % predicted) during the first 2.5 years after the start of therapy. First, lung function changes were evaluated between baseline and the follow-up visit. Second, the increase (*dashed line*) after the initiation of corticosteroid treatment as well as the long-term decrease (*dotted line*) in lung function was evaluated. At the baseline visit, patients were mostly corticosteroid-naive and ICS therapy was initiated from that visit.

We performed statistical analyses using IBM SPSS statistics software (version 27, Armonk, NY). *P* less than .05 was regarded as statistically significant. This study is registered at www.ClinicalTrials.gov with Identifier No. NCT02733016 (SAAS).

TABLE I. Main characteristics of study population at baseline and at 12-y follow-up (n = 203)

Demographics and clinical characteristics	Baseline	Follow-up
Age, y (median [interquartile range])	47 (37-56)	59 (49-68)
Female sex, n (%)	118 (58.1)	—
Body mass index, kg/m^2	26.6 (24.1-29.4)	27.9 (24.2-31.2)
Smokers (including ex-smokers), n (%)	103 (50.7)	107 (52.7)
Smoking history, pack-y (of ex- or current smokers)	13 (5-20)	16 (6-30)
Coexisting chronic obstructive pulmonary disease, n (%)	15 (7.4)	34 (16.7)
Atopic, n (%)	68 (33.5)	—
Blood eosinophils × 10^9 L^{-1}	0.28 (0.15-0.41)	0.17 (0.09-0.28)
Total IgE, kU·L^{-1}	84.0 (35.0-174.0)	61.0 (24.0-163.0)
FeNO, ppb	—	11.0 (5.0-19.0)
Pre-BD FEV_1 % pred	82.3 (71.2-92.0)	86.5 (76.0-97.0)
Pre-BD FVC % pred	90.0 (79.8-101.0)	96.8 (15.3)
Pre-BD FEV_1/FVC	0.75 (0.69-0.80)	0.73 (0.67-0.79)
Post-BD FEV_1 % pred	88.0 (76.7-98.9)	90.5 (81.0-98.0)
Post-BD FVC % pred	92.0 (15)	98.1 (15.0)
Post-BD FEV_1/FVC	0.79 (0.74-0.83)	0.75 (0.69-0.81)
Daily ICS, n (%)	16 (7.9)	155 (76.4)

BD, bronchodilator, *pred*, predicted.
Data are presented as n (%), mean (SD), or median (interquartile range).

RESULTS

Patient characteristics

Table I lists the characteristics of the study population (n = 203). Median age of the study population was 47 years (IQR 37-56 years) at asthma diagnosis (baseline) and 58% were female. Half of patients were current or ex-smokers. The proportion of daily inhaled corticosteroid users was 8% at diagnosis and 76% at follow-up. When patients were asked about alcohol consumption, 21% reported that they were abstainers, 72% reported that they were moderate alcohol users, and 6% reported that they were heavy users according to the US definition.[16] However, the GGT-CDT index was elevated in 35 patients (17.9%).

When patients were divided into two groups (heavy alcohol consumption vs non-heavy alcohol consumption) based on both the alcohol use questionnaire and GGT-CDT index, 39 patients were classified as heavy alcohol users (Table II). These patients had a significantly higher mean corpuscular volume, GGT, CDT, and GGT-CDT index than non-heavy users. Patients in the heavy alcohol consumption group reported a median of 6.5 alcohol portions/week (IQR, 0.25-13.0 alcohol portions/week), and non-heavy alcohol consumers, median of 0.5 alcohol portions/week (IQR, 0-2 alcohol portions/week). Patients in the heavy alcohol consumption group were more obese, had more comorbidities, and more often tended to be current or ex-smokers (49% vs 67%; $P = .051$). Heavy alcohol consumers had more unplanned asthma-related hospitalizations (5.6% vs 17.9%; $P = .018$). There were no differences in asthma medication, adherence to ICS treatment, oral corticosteroid use, asthma control, allergy history, blood eosinophil counts, or symptom scores between groups.

Association of heavy alcohol use on lung function

The annual decline in lung function as measured by ΔFVC (mL·year^{-1} or % pred·year^{-1}) and ΔFEV_1 (mL·year^{-1} or % pred·year^{-1}) between diagnosis and follow-up was more rapid in the heavy alcohol consumers compared with the non-heavy alcohol consumers. Because the patients were mostly corticosteroid-naive at baseline, the change in lung function between diagnosis and follow-up includes the effect of ICS therapy started at the time of diagnosis. To dissect the association of alcohol use from the effect of ICS, we separately evaluated the association of alcohol use on lung function change between baseline and $Max_{0\text{-}2.5}$ (ie, the effect of alcohol use on the increasing effect of ICS on lung function) and between $Max_{0\text{-}2.5}$ and follow-up (ie, the effect of alcohol use on long-term lung function decline). There was a nonsignificant ($P = .06$) tendency for reduced ΔFVC (mL year^{-1} or % pred year^{-1}) increase between baseline and $Max_{0\text{-}2.5}$ in heavy alcohol consumers (Table III). In contrast, the annual decline in lung function as measured by ΔFVC (mL·year^{-1} or % pred·year^{-1}) between the $Max_{0\text{-}2.5}$ and follow-up was significantly more rapid in the heavy alcohol intake group (Table III). Figure 3, *A* shows a schematical graph of the lung function change. A similar analysis of ΔFEV_1 revealed no significant differences between heavy alcohol users and non-heavy alcohol users (Table III and Figure 3, *B*).

An increase in BMI can induce a decline in ΔFVC.[31] However, even though the decline is most evident in ΔFVC, there were no significant differences in ΔBMI from baseline to the follow-up visit between the heavy alcohol consumers and non-heavy alcohol consumers. In addition, we found no differences in the Airway Questionnaire 20 score or in adherence to ICS between the groups.[23,24] There were more smokers including ex-smokers in the heavy alcohol consumer group, but no differences in pack-years (Table II). The groups had no significant difference in lung function values at the 12-year follow-up (Table E2).

Factors associated with lung function changes

Spearman's correlation coefficient between the GGT-CDT index and ΔFVC was −0.28 ($P = .01$), suggesting an

TABLE II. Characteristics of study groups at follow-up according to level of alcohol consumption

	Alcohol consumption		
Demographics and clinical characteristics	**Non-heavy (n = 162)**	**Heavy (n = 39)**	***P***
Age, y	58 (14)	58 (11)	.543
Female sex, n (%)	92 (57)	24 (62)	.718
Height	169 (9.3)	167 (10.2)	.281
Body mass index, kg/m^2	27.7 (24.4-30.8)	30.1 (25.5-35.2)	**.008**
Δ Body mass index, kg/m^2	1.0 (2.7)	1.4 (3.7)	.507
Airway Questionnaire 20 score	6.0 (4-9)	7 (4-10)	.379
Smokers (including ex-smokers), n (%)	79 (48.8)	26 (66.7)	.051
Smoking history, pack-y (of ex- or current smokers)	15 (5.3-25.8)	20 (5.1-30.0)	.459
Uncontrolled asthma (%)*	29.6	25.6	.397
Severe asthma (%)†	6.2	5.1	.805
Chronic obstructive pulmonary disease, n (%)	28 (17.4)	6 (15.8)	.813
Comorbidities, n	1 (0-2)	2 (1-4)	**.004**
Daily short-acting β_2-agonist, n (%)	18 (11.1)	5 (12.8)	.781
Daily long-acting β_2-agonist, n (%)	76 (46.9)	19 (48.7)	.860
Daily ICS, n (%)	124 (76.5)	30 (76.9)	.960
Daily add-on drug, n (%) (long-acting β_2-agonist, leukotriene receptor antagonist, theophylline, and/or tiotropium)	82 (50.6)	20 (51.3)	.941
Use of oral corticosteroid courses ever (%)	32.7	33.3	.110
Dispensed oral corticosteroid during 12 y, mg	600 (0-2,257)	600 (0-2,020)	.916
≥1 unplanned hospitalization because of asthma (%)	5.6	17.9	.018
Adherence to ICS over 12 y (%)	74 (39-98)	76 (38-92)	.911
Average dispensed ICS daily dose during 12 y (μg budesonide equivalents/d)	491 (301-796)	611 (323-811)	.712
Short-acting β_2-agonist puffs/wk over 12 y	1.5 (0.6-3.7)	1.7 (1.0-3.1)	.461
Skin-prick positive (%)	52 (34.9)	15 (46.9)	.229
Blood eosinophils × 10^9 L^{-1} at follow-up visit	0.16 (0.10-0.27)	0.20 (0.13-0.28)	.428
Total IgE at follow-up visit, kU·L^{-1}	54 (23-148)	80 (33-305)	.062
FeNO at follow-up visit, ppb	11 (5-20)	8 (5-16)	.114
Pre-BD FEV_1 % pred at baseline	81.5 (67.5-92.2)	84.0 (75.4-94.0)	.143
Pre-BD FVC % pred at baseline	89.0 (76.5-100.0)	92.0 (87.0-103.0)	.111
Pre-BD FEV_1/FVC at baseline	0.75 (0.7-0.8)	0.76 (0.7-0.8)	.265
γ-Glutamyl transferase	28 (22-37)	78.6 (52-119)	**<.001**
% Carbohydrate-deficient transferrin	1.50 (1.40-1.70)	1.80 (1.60-2.0)	**<.001**
γ-Glutamyl transferase-carbohydrate-deficient transferrin	3.2 (3.0-3.5)	4.3 (3.9-4.8)	**<.001**
Mean corpuscular volume	89 (87-92)	91 (89-94)	**.004**
Self-reported heavy alcohol use‡	0	12 (31.6)	**<.001**
Self-reported alcohol portions/wk	0.5 (0-2.0)	6.5 (0.25-13.0)	**<.001**

BD, bronchodilator; *pred*, predicted.
Data are presented as n (%), mean (SD), or median (interquartile range).
*Assessment of asthma control was performed according to the Global Initiative for Asthma 2010 report.[29]
†Assessment of asthma severity was performed according to the European Respiratory Society/American Thoracic Society severe asthma guideline 2014.[30]
‡US definition: men ≥14 portions/wk; women ≥7 portions/wk. Statistical significance was evaluated by independent-samples *t* test, Fisher exact test or independent-sample Mann-Whitney *U* test. Statistically significant *P* values are bolded ($P < .05$).

association. To assess whether heavy alcohol use is independently associated with lung function changes, we carried out multiple linear regression analysis. Heavy alcohol use was associated with a more rapid decline in ΔFVC in adjusted analysis both from baseline to follow-up and from $Max_{0\text{-}2.5}$ to follow-up (Tables IV and V). Other factors associated with faster lung function decline were ΔBMI from baseline to follow up, age, ΔFVC change from baseline to $Max_{0\text{-}2.5}$, and FVC% predicted at baseline (Table IV and V). However, a more rapid decline in ΔFEV_1 was not associated with heavy alcohol consumption in linear regression analysis. Accelerated decline in ΔFEV_1 was associated with increasing age, 10 pack-years or more at follow-up, ΔFEV_1 mL (baseline − $Max_{0\text{-}2.5}$), higher FEV_1 % pred at baseline, higher FeNO at follow-up, and oral corticosteroid use during follow-up (Table VI). All tested variables were not retained in the final multiple regression models. The optimal model was obtained using a selection of variables that were most strongly associated with lung function. Variables that were left out are represented in Tables IV through VI. Additionally, we analyzed an interaction between heavy alcohol use and ΔBMI , but observed no significant effects (eg, for ΔFVC from diagnosis to follow-up: $\beta = -0.263$; $P = .915$).

TABLE III. Lung function change in patients according to their level of alcohol consumption

	Alcohol consumption		
Lung function changes according to alcohol consumption	**Non-heavy alcohol consumption (n = 162)**	**Heavy alcohol consumption (n = 39)**	***P***
Lung function change from diagnosis to follow-up			
ΔFEV_1 from diagnosis to follow-up, mL/y	−16.6 (-31.4 to 6.4)	−25.6 (−51.7 to 0.00)	**.022**
ΔFVC from diagnosis to follow-up, mL/y	−5.1 (−26.2 to 25.1)	−29.3 (−50.9 to −11.1)	**<.001**
ΔFEV_1/FVC from diagnosis to follow-up, ratio/y	0.00 (−0.01 to 0.00)	0.00 (−0.01 to 0.00)	.468
Lung function change from diagnosis to $Max_{0\text{-}2.5}$			
ΔFEV_1 from diagnosis to $Max_{0\text{-}2.5}$, mL	275 (95 to 590)	220 (50 to 480)	.329
ΔFEV_1 from diagnosis to $Max_{0\text{-}2.5}$ (% predicted)	9.0 (3.9 to 18.0)	7.3 (1.0 to 15.0)	.216
ΔFVC from diagnosis to $Max_{0\text{-}2.5}$, mL	310 (0 to 610)	190 (−110 to 490)	.063
ΔFVC from diagnosis to $Max_{0\text{-}2.5}$ (% predicted)	7.4 (1.0 to 13.8)	5.0 (−2.0 to 11.0)	.066
ΔFEV_1/FVC from diagnosis to $Max_{0\text{-}2.5}$ (%)	0.02 (−0.01 to 0.07)	0.04 (−0.02 to 0.07)	.981
Lung function from $Max_{0\text{-}2.5}$ to follow-up			
ΔFEV_1 from $Max_{0\text{-}2.5}$ to follow-up, mL/y	−40.1 (−64.2 to −23.3)	−49.1 (−78.0 to −23.8)	.298
ΔFVC from $Max_{0\text{-}2.5}$ to follow-up, mL/y	−28.5 (−56.4 to -8.1)	−47.7 (−69.0 to −22.7)	**.041**
ΔFEV_1/FVC from $Max_{0\text{-}2.5}$ to follow-up, ratio/y	0.00 (−0.01 to 0.00)	0.00 (−0.01 to 0.00)	.468

Data are presented as medians (interquartile ranges). Lung function change is from $Max_{0-2.5}$ (point of highest lung function during the first 2.5 y after baseline) to 12-y follow-up visit. Statistical significance was evaluated by independent-sample Mann-Whitney *U* test. Statistically significant *P* values are bolded ($P < .05$).

DISCUSSION

In this study, we evaluated the association between heavy alcohol intake and lung function in patients with adult-onset asthma. Our data indicate that heavy alcohol intake is associated with a more rapid decline of FVC compared with that in patients who are non-heavy alcohol consumers. It also might be indirectly linked to a more rapid decline in FEV_1. Most patients were treated with ICS between the baseline (diagnosis) and follow-up, and to dissect the effect of alcohol use from the effect of ICS, we separately evaluated the effect of alcohol use on lung function change between the baseline and $Max_{0\text{-}2.5}$ (ie, the effect of alcohol use on the lung function-increasing effect of ICS) and between $Max_{0\text{-}2.5}$ and follow-up (ie, the effect of alcohol use on long-term lung function decline). Although lung functions were similar at the time of diagnosis between groups, it seems that FVC increases less with the treatment of asthma and decreases more rapidly during the follow-up in heavy alcohol consumers. To the best of our knowledge, this is the first study to evaluate the association between heavy alcohol consumption and lung function in patients with adult asthma.

Little has been previously reported about the effects of heavy alcohol consumption on lung function in patients with asthma. Although the specific effects of excess alcohol consumption on lung tissue have remained largely unknown, previous studies established that alcohol abuse may weaken the lung's immune defenses, leading to increased susceptibility to infections. Chronic heavy drinking may also be expected to impair the lungs' function and lead to an increase in the risk of long-term damage.[32-34] Studies in the general population have indicated that alcohol use may be linked to a decline in lung function, but it has been suggested that smoking explains part of the difference.[8,9,35] In our study, a higher proportion of heavy alcohol consumers were smokers, but no differences in pack-years between the groups and smoking history was not associated with FVC decline in multiple linear regression analysis, despite testing several different smoking variables (smoking in pack-years; 10 pack-years or greater at follow-up; never-, current, or ex-smokers; or ever smokers at follow-up). In addition, no differences existed in the prevalence of coexisting chronic obstructive pulmonary disease between groups. Thus, these suggest that smoking does not explain our findings. Smoking was associated with a more rapid decline in FEV_1 in multiple regression analysis, in line with previous studies.[8,36] However, although our findings support the idea that heavy alcohol consumption is an independent cause of FVC decline, we cannot fully rule out the involvement of smoking or mediation of the effect through modulation of the ICS effect. In addition, underreporting of smoking may have an impact on the results.[37]

We observed the patients for 12 years from the diagnosis to the follow-up visit. Most patients were treated with ICS during the follow-up, and the use of $Max_{0\text{-}2.5}$ as a measurement point enabled us to include the optimal lung function of patients owing to the treatment of asthma. We found a nonsignificant ($P = .063$) tendency for a reduced FVC increase between baseline and $Max_{0\text{-}2.5}$ in heavy alcohol consumers and a significantly steeper FVC decline between $Max_{0\text{-}2.5}$ and follow-up, but no differences in ICS adherence between the groups. A previous study showed that patients with asthma who had substance-related disorders filled prescriptions for controller medications at lower rates compared with patients with asthma who did not have substance-related disorders.[38] According to a systematic review, alcohol consumption is generally associated with decreased adherence to prescribed medications.[39] It is possible that heavy alcohol use might influence the effects of corticosteroid treatment. Alcohol is known to affect hypothalamic—pituitary—adrenal function, and heavy alcohol consumption raises blood cortisol and adrenocorticotropic hormone levels.[40] During abstinence, alcoholics may continue to exhibit attenuated cortisol response for several months.[41] Thus, we cannot exclude the possibility that these effects of alcohol contribute to the current findings.

Few studies have suggested that alcohol consumption is linked to better lung function in the general population. In one such study, patients had less restriction the more they consumed alcohol.[10] In another study, there was no association between lung function and total alcohol use, but a positive association was reported between lung function and self-reported recent and lifetime wine intake. However, wine drinkers probably had a

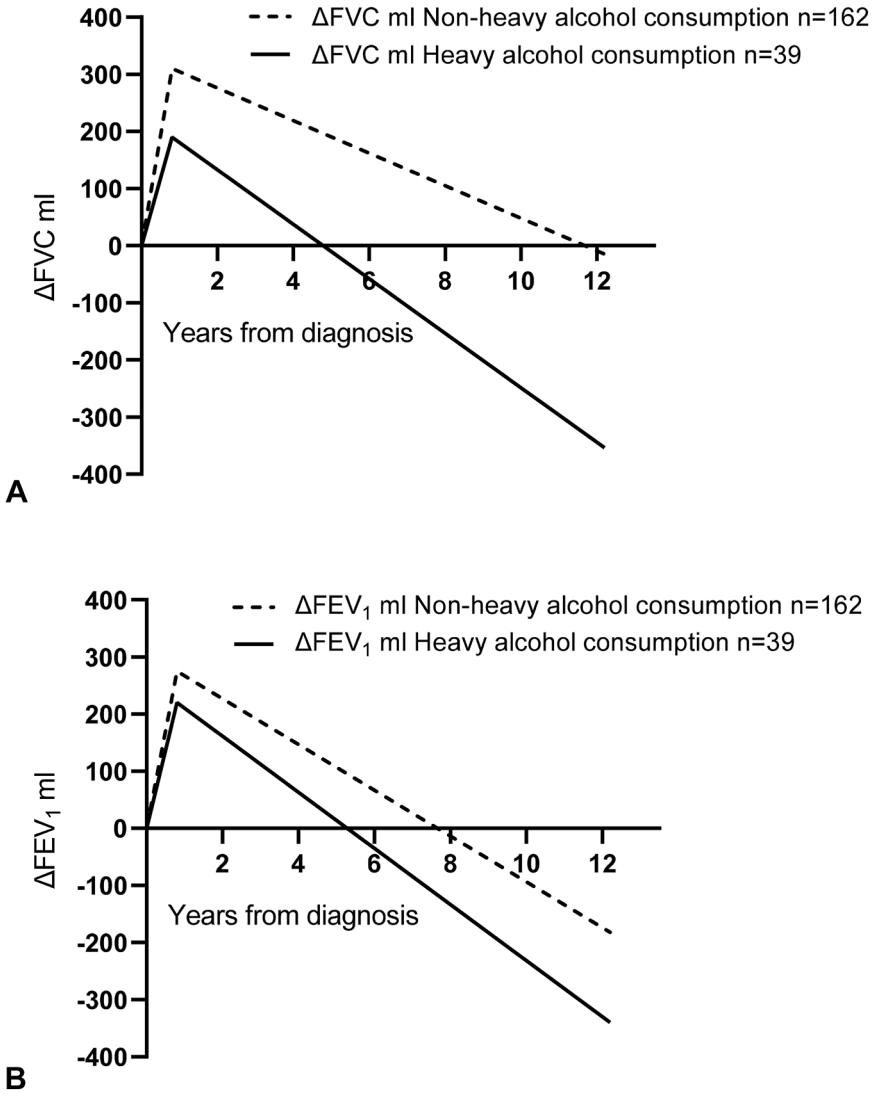

FIGURE 3. (**A**) Changes (ΔFVC) in milliliters during 12 years of follow-up (see Figure 2 for timescale) according to the level of alcohol consumption. Model is based on group medians. $Max_{0\text{-}2.5}$ is the point of highest lung function (FVC % predicted) during the first 2.5 years after baseline and the initiation of ICS therapy. $P = .041$ for the annual change in ΔFVC between $Max_{0\text{-}2.5}$ and the follow-up visit. Statistical significances were evaluated by independent-samples Mann-Whitney *U* test. (**B**) Changes (ΔFEV_1) in milliliters during 12 years of follow-up (see Figure 2 for timescale) according to the level of alcohol consumption. Model is based on group medians. $Max_{0\text{-}2.5}$ is the point of highest lung function (FEV_1 % predicted) during the first 2.5 years after baseline and the initiation of ICS therapy. $P = .022$ for the annual change in ΔFEV_1 between the diagnosis and follow-up visit. Statistical significances were evaluated by independent-samples Mann-Whitney *U* test.

healthier lifestyle, there were more females in the group, and the subjects consumed less alcohol overall.[11] Few studies have shown that moderate alcohol consumption is associated with a positive effect on FVC, but none of these studies concentrated on patients with asthma, and alcohol consumption was based on self-reports.[35,42,43] It is possible that patients with moderate alcohol consumption also have a healthier lifestyle in general.

In most of these studies, alcohol consumption was recorded via questionnaire, and therefore they cannot be considered fully reliable.[17,44] In only one of the studies, the researchers included CDT as a biomarker for heavy alcohol consumption,[9] a specific but less sensitive marker.[18] Questionnaires reveal only about half of the consumption expected from total sales of alcohol,[17] and heavy drinkers tend to underestimate their drinking more.[45] It was also assessed that people who self-identified as lifetime abstainers in one survey had reported alcohol use in previous studies.[46] It is also possible that ex-drinkers quit drinking because of alcohol-related or other medical problems, and this could also increase the likelihood of worse lung function in abstainers' category in these studies. In addition, in most of these studies, patients with asthma were excluded. If patients with asthma were included, the asthma diagnosis was based on self-report. Previous studies on patients with clinically diagnosed asthma are lacking.

TABLE IV. Predictors of annual decline of FVC from baseline to follow-up in multiple linear regression analysis (n = 193)

Predictors	FVC estimated decline ΔmL (95% CI)	*P*
Δ Body mass index (baseline to follow-up)	−2.74 (−4.32 to −1.17)	**<.001**
Age at follow-up	−0.547 (−0.90 to −0.19)	**.003**
Female sex	4.25 (−5.80 to 14.30)	.405
≥10 pack-y at follow-up	−7.97 (−18.44 to 2.51)	.135
ΔFVC mL* (baseline to $Max_{0\text{-}2.5}$)	0.04 (0.03 to 0.05)	**<.001**
FVC % predicted* at baseline	−0.95 (−1.30 to −0.61)	**<.001**
Heavy alcohol use	−14.61 (−26.00 to −3.22)	**.012**

$Max_{0\text{-}2.5}$ is the point of highest lung function (FVC % predicted) during the first 2.5 y after baseline. Statistically significant *P* values (*f* < .05) are bolded. Other variables tested in the multiple regression analysis include height; smoking history in pack-y; ever-smoker at follow-up; never, current, or ex-smoker at follow-up; daily ICS user, Average dispensed inhaled corticosteroid daily dose during 12 y of follow-up (μg budesonide equivalents/day); OCS use (in mg) during 12 y of follow-up; use of oral corticosteroid courses ever; systemic corticosteroids in daily use (for asthma or other indication); adherence to inhaled corticosteroids for 12 y; daily add-on medication (long-acting B_2-agonist, leukotriene receptor antagonist, theophylline, or tiotropium); long-acting B_2-agonists in daily use; short-acting B2-agonists in daily use; blood eosinophils × 109 L^{-1} at follow-up visit; total IgE (kU·L^{-1}) at follow-up visit; FeNO (ppb) at follow-up visit; FeNO at follow-up >20 ppb; atopy; pre-bronchodilator FEV_1 % predicted at baseline; number of comorbidities chronic obstructive pulmonary disease included; patients with at least one comorbidity; coexisting chronic obstructive pulmonary disease (post-FEV_1/FVC < 0.7 and pack-y ≥10); ≥1 hospitalizations during follow-up for any respiratory reason; ≥1 asthma-related hospitalization during follow-up; scheduled asthma contacts (n); contacts owing to respiratory infections or exacerbations; severe asthma according to the ERS/ATS severe asthma guideline 2014; uncontrolled asthma according to the Global Initiative for Asthma 2010 report; and Asthma Control Test scores.
*Pre-bronchodilator values.

TABLE V. Predictors of annual decline of FVC from $Max_{0\text{-}2.5}$ to follow-up in multiple linear regression analysis (n = 190)

Predictors	FVC estimated decline ΔmL (95% CI)	*P*
Δ Body mass index ($Max_{0\text{-}2.5}$ to follow-up)	−1.83 (−3.23 to −0.44)	**.010**
Age at follow-up	−0.60 (−1.01 to −0.18)	**.005**
Female sex	2.12 (−13.28 to 17.52)	.786
Smoked pack-y at follow-up	−0.22 (−0.61 to 0.18)	.276
ΔFVC mL* (baseline to $Max_{0\text{-}2.5}$)	−0.05 (−0.06 to −0.04)	**<.001**
FVC % predicted* at baseline	−1.03 (−1.41 to −0.65)	**<.001**
Height	−0.32 (−1.13 to 0.49)	.434
Heavy alcohol use	−13.51 (−26.22 to −0.82)	**.037**

$Max_{0\text{-}2.5}$ is the point of highest lung function (FVC % predicted) during the first 2.5 y after baseline. Statistically significant *P* values (*f* < .05) are bolded. Other variables tested in the multiple regression analysis include height; smoking history in pack-y; ever-smoker at follow-up; never, current, or ex-smoker at follow-up; daily ICS user, Average dispensed inhaled corticosteroid daily dose during 12 y of follow-up (μg budesonide equivalents/day); OCS use (in mg) during 12 y of follow-up; use of oral corticosteroid courses ever; systemic corticosteroids in daily use (for asthma or other indication); adherence to inhaled corticosteroids for 12 y; daily add-on medication (long-acting B_2-agonist, leukotriene receptor antagonist, theophylline, or tiotropium); long-acting B_2-agonists in daily use; short-acting B2-agonists in daily use; blood eosinophils × 109 L^{-1} at follow-up visit; total IgE (kU·L^{-1}) at follow-up visit; FeNO (ppb) at follow-up visit; FeNO at follow-up >20 ppb; atopy; pre-bronchodilator FEV_1 % predicted at baseline; number of comorbidities chronic obstructive pulmonary disease included; patients with at least one comorbidity; coexisting chronic obstructive pulmonary disease (post-FEV_1/FVC < 0.7 and pack-y ≥10); ≥1 hospitalizations during follow-up for any respiratory reason; ≥1 asthma-related hospitalization during follow-up; scheduled asthma contacts (n); contacts owing to respiratory infections or exacerbations; severe asthma according to the ERS/ATS severe asthma guideline 2014; uncontrolled asthma according to the Global Initiative for Asthma 2010 report; and Asthma Control Test scores.
*Pre-bronchodilator values.

In our study, heavy alcohol consumption was associated with the development of a restrictive lung disorder. A previous study in mice reported that alcohol changes alveolar macrophage function, leading to increased fibrosis and compromised alveolar integrity and therefore impairs pulmonary function.[47] This might explain our findings. Heavy alcohol consumption is also a known risk factor for pneumonia,[48] aspiration pneumonia,[49] and acute respiratory distress syndrome,[32] which can promote lung fibrosis. Unfortunately, in our study, we had no possibility of evaluating signs of mild fibrosis. Chronic alcohol consumption leads to ciliary dysfunction and impairs the function of alveolar macrophages, reducing bacterial clearance and thus affecting pulmonary immune defense.[50] Even though heavy alcohol consumption elevated total IgE levels in blood in previous studies, ethanol seems to dampen type 2 inflammatory response in the lungs.[51,52] In our findings, total IgE levels, FeNO, and blood eosinophils were similar between groups, in line with previous studies.

This study had several strengths. All patients received a diagnosis by a respiratory physician, and the asthma diagnosis was based on typical symptoms and objective lung function measurements. Also, we assessed alcohol consumption by both questionnaires and laboratory markers, which improves identification of heavy alcohol consumption. The use of objective measures strengthens our findings because questionnaires alone are prone to recall bias when assessing alcohol consumption. Questionnaire-based surveys are also typically known to produce underestimates of alcohol consumption.[17,38] The 12-year follow-up is exceptionally long, and the response rate was good, because 79% of patients from the original study cohort returned for the follow-up visit. Smokers and patients with comorbidities were not excluded, which made this a real-life study.[21]

There are some limitations to our study. The number of patients in the heavy alcohol consumption group is low (n =

TABLE VI. Predictors of annual decline of FEV_1 (mL) from baseline to follow-up in multiple linear regression analysis (n = 184)

Predictors	FEV_1 estimated decline ΔmL (95% CI)	*P*
Δ Body mass index (baseline to follow-up)	−1.09 (−2.55 to 0.38)	.144
Age at follow-up	−0.44 (−0.78 to -0.10)	**.011**
Female sex	0.66 (−11.87 to 13.20)	.917
≥10 pack-y at follow-up	−11.67 (−21.26 to −2.08)	**.017**
ΔFEV_1 mL* (baseline to $Max_{0\text{-}2.5}$)	0.05 (0.04 to 0.06)	**<.001**
FEV_1 % predicted* at baseline	−0.57 (−0.87 to −0.27)	**<.001**
Height	−0.67 (−1.35 to −0.08)	**.053**
FeNO at follow-up	−0.32 (−0.59 to −0.04)	**.025**
Oral corticosteroid use during follow-up	−0.02 (−0.04 to −0.01)	**.008**
Heavy alcohol use	−8.00 (−18.55 to 2.55)	.136

$Max_{0\text{-}2.5}$ is the point of highest lung function (FVC % predicted) during the first 2.5 y after baseline. Statistically significant *P* values ($P < .05$) are bolded. Other variables tested in the multiple regression analysis include height; smoking history in pack-y; ever-smoker at follow-up; never, current, or ex-smoker at follow-up; daily ICS user, Average dispensed inhaled corticosteroid daily dose during 12 y of follow-up (μg budesonide equivalents/day); OCS use (in mg) during 12 y of follow-up; use of oral corticosteroid courses ever; systemic corticosteroids in daily use (for asthma or other indication); adherence to inhaled corticosteroids for 12 y; daily add-on medication (long-acting B_2-agonist, leukotriene receptor antagonist, theophylline, or tiotropium); long-acting B_2-agonists in daily use; short-acting B2-agonists in daily use; blood eosinophils × 109 L^{-1} at follow-up visit; total IgE ($kU \cdot L^{-1}$) at follow-up visit; FeNO (ppb) at follow-up visit; FeNO at follow-up >20 ppb; atopy; pre-bronchodilator FEV_1 % predicted at baseline; number of comorbidities chronic obstructive pulmonary disease included; patients with at least one comorbidity; coexisting chronic obstructive pulmonary disease (post-FEV_1/FVC < 0.7 and pack-y ≥10); ≥1 hospitalizations during follow-up for any respiratory reason; ≥1 asthma-related hospitalization during follow-up; scheduled asthma contacts (n); contacts owing to respiratory infections or exacerbations; severe asthma according to the ERS/ATS severe asthma guideline 2014; uncontrolled asthma according to the Global Initiative for Asthma 2010 report; and Asthma Control Test scores.
*Pre-bronchodilator values.

39), which might have led to a loss of power in the analyses. Thus, further clinical studies with larger cohorts are needed. The interaction between BMI and heavy alcohol intake should also be investigated in a larger cohort in future studies, because it may be a significant factor. Although the identification of heavy alcohol consumption was based on both questionnaires and laboratory markers, it is possible we missed some heavy alcohol users, because the laboratory markers and questionnaires are not fully specific and sensitive. Also, alcohol markers were counted only on the follow-up visit, and thus we were unable to assess whether alcohol consumption changed over time. It could be assumed that the tendency to use alcohol is a constant habit, and some alcohol markers also require the heavy use of alcohol for a few months to be elevated.[2,19] In addition, the SAAS is a real-life study of asthma beginning at adulthood, and this study was not powered based on alcohol consumption. Thus, it is possible that some differences were not detected because of a lack of power.

Our data show that in patients with adult-onset asthma, heavy alcohol consumption is associated with an accelerated decline in lung function, especially FVC. Heavy alcohol consumption could be a treatable trait in people with asthma, and more attention should be paid to the assessment of alcohol consumption when treating patients with asthma. More studies on the effects of heavy alcohol consumption on lung function in patients with asthma, and with larger cohorts, are needed.

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ONLINE REPOSITORY

LABORATORY MEASUREMENTS

We measured FeNO with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards (flow rate of 50 $mL \cdot s^{-1}$; NIOX System, Aerocrine, Solna, Sweden).[E1] We collected venous blood and determined white blood cell differential counts. Total IgE levels were measured using ImmunoCAP (Thermo Scientific, Uppsala, Sweden).[E1]

COMPUTATION OF ICS ADHERENCE

We calculated prescribed doses for each patient for each year of follow-up based on medical records.[E2-E4] All drug and dose changes were taken into account individually for each patient and all doses were converted to beclomethasone dipropionate equivalents.[E3] Patients' dispensed doses of ICS were obtained from the Finnish Social Insurance Institution, which records all purchased medication from any Finnish pharmacy.[E2,E4] By comparing dispensed doses with prescribed ICS doses, it was possible to evaluate the adherence of a single patient during the 12-year follow-up, as previously reported.[E2] In the case of ranged doses prescribed (eg, one to two puffs two times daily), we interpreted that patients were adherent when the minimum ICS doses were dispensed.

We calculated 12-year adherence by comparing total cumulative dispensed doses of ICS with the total cumulative 12-year prescribed doses.[E2,E4] To obtain a view on the variability of adherence at long-term follow-up, annual adherence was calculated for each patient individually for each year by dividing yearly dispensed ICS doses by yearly prescribed ICS doses (microgram beclomethasone dipropionate equivalents).[E2-E4]

TABLE E1. Inclusion and exclusion criteria used in Seinäjoki Adult Asthma Study

Inclusion criteria	A diagnosis of new-onset asthma made by a respiratory specialist
	Diagnosis confirmed by at least one of the following objective lung function measurements:
	FEV_1 reversibility in spirometry of at least 15% and 200 mL after 400 μg of salbutamol
	Diurnal variability (≥20% on at least 3 days) or repeated reversibility (≥15%/60 L/min on at least three occasions) during 2-wk PEF monitoring
	A significant decrease in FEV_1 (15%) or PEF (20%) in response to exercise or allergen challenge test
	A significant reversibility in FEV_1 (at least 15% and 200 mL) or mean PEF (at least 20%) in response to trial with oral or inhaled glucocorticoids
	Symptoms of asthma
	Age ≥15 y
Exclusion criteria	Physical or mental inability to provide signed informed consent
	Diagnosis of asthma at age <15 y
	Of note:
	Patients with comorbidities, either other lung disease or any other significant disease, were not excluded
	Patients were not excluded because of smoking, alcohol use, or any other lifestyle factor
	Respiratory symptoms or any other diseases during childhood were not a reason to exclude patients, but a diagnosis of asthma at age <15 y was an exclusion criterion

PEF, peak expiratory flow.
Modified from Kankaanranta et al.[E5]

TABLE E2. Lung function in patients according to level of alcohol consumption

	Alcohol consumption		
Lung functions according to alcohol consumption	**Non-heavy alcohol consumption (n = 162)**	**Heavy alcohol consumption by anamnesis, markers, or both (n = 39)**	***P***
Lung function at time of diagnosis			
Pre-bd FEV_1 L	2.87 (2.3-3.33)	2.86 (2.47-3.52)	.396
Pre-bd FEV_1 % pred	81.5 (67.8-92.2)	84.0 (75.4-94.0)	.143
Pre-bd FVC L	3.73 (3.12-4.41)	3.6 (3.26-4.71)	.514
Pre-bd FVC % pred	89.0 (76.5-100.0)	92.0 (87.0-103.0)	.111
Pre-bd FEV_1/FVC	0.75 (0.7-0.8)	0.76 (0.7-0.8)	.265
Lung function at $Max_{0\text{-}2.5}$			
Pre-bd FEV_1 L	3.22 (2.60-3.84)	3.04 (2.57-4.04)	.872
Pre-bd FEV_1 % pred	91.0 (83.0-102.0)	91.0 (83.0-102.1)	.706
Pre-bd FVC L	4.11 (3.49-4.87)	3.94 (3.26-5.16)	.601
Pre-bd FVC % pred	97.3 (88.0-104.0)	100.0 (87.0-110.0)	.733
Pre-bd FEV_1/FVC	78.1 (73.0-82.3)	81.0 (74.0-83.3)	.221
Lung function at follow-up			
Pre-bd FEV_1 L	2.71 (0.80)	2.66 (0.73)	.760
Pre-bd FEV_1 % pred	87.0 (76.8-96.0)	85.0 (76.0-98.0)	.999
Pre-bd FVC L	3.83 (0.95)	3.63 (1.02)	.261
Pre-bd FVC % pred	97.7 (14.9)	94.8 (16.0)	.295
Pre-bd FEV_1/FVC	0.73 (0.65-0.79)	0.76 (0.68-0.79)	.144

bd, bronchodilator.
Data are presented as n (%), mean (SD), or median (interquartile range).
For lung function change, from $Max_{0\text{-}2.5}$ (the point of highest lung function during the first 2.5 y after baseline) to the 12-y follow-up visit. Statistical significances were evaluated by independent-sample Mann-Whitney *U* test.

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