

# Lung Function Trajectories and Associated Mortality among Adults with and without Airway Obstruction

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## Abstract

**Rationale:** Spirometry is essential for diagnosis and assessment of prognosis in patients with chronic obstructive pulmonary disease (COPD).

**Objectives:** To identify FEV<sub>1</sub> trajectories and their determinants on the basis of annual spirometry measurements among individuals with and without airway obstruction (AO) and to assess mortality in relation to trajectories.

**Methods:** From 2002 through 2004, individuals with AO (FEV<sub>1</sub>/VC < 0.70, *n* = 993) and age- and sex-matched nonobstructive (NO) referents were recruited from population-based cohorts. Annual spirometry until 2014 was used in joint-survival latent-class mixed models to identify lung function trajectories. Mortality data were collected during 15 years of follow-up.

**Measurements and Main Results:** Three trajectories were identified among the subjects with AO and two among the NO referents. Trajectory membership was driven by baseline FEV<sub>1</sub>% predicted (FEV<sub>1</sub>%pred) in both groups and also by pack-years in

subjects with AO and current smoking in NO referents. Longitudinal FEV<sub>1</sub>%pred depended on baseline FEV<sub>1</sub>%pred, pack-years, and obesity. The trajectories were distributed as follows: among individuals with AO, 79.6% in AO trajectory 1 (FEV<sub>1</sub> high with normal decline), 12.8% in AO trajectory 2 (FEV<sub>1</sub> high with rapid decline), and 7.7% in AO trajectory 3 (FEV<sub>1</sub> low with normal decline) (mean, 27, 72, and 26 ml/yr, respectively) and, among NO referents, 96.7% in NO trajectory 1 (FEV<sub>1</sub> high with normal decline) and 3.3% in NO trajectory 2 (FEV<sub>1</sub> high with rapid decline) (mean, 34 and 173 ml/yr, respectively). Hazard for death was increased for AO trajectories 2 (hazard ratio [HR], 1.56) and 3 (HR, 3.45) versus AO trajectory 1 and for NO trajectory 2 (HR, 2.99) versus NO trajectory 1.

**Conclusions:** Three different FEV<sub>1</sub> trajectories were identified among subjects with AO and two among NO referents, with different outcomes in terms of FEV<sub>1</sub> decline and mortality. The FEV<sub>1</sub> trajectories among subjects with AO and the relationship between low FVC and trajectory outcome are of particular clinical interest.

**Keywords:** prognosis; chronic obstructive pulmonary disease; FEV<sub>1</sub>; natural history

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

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## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Lung function trajectories have received increased attention during the past decade. However, the few publications on long-term follow-up of lung function in chronic obstructive pulmonary disease usually include a limited number of lung function tests during the observation period or include selected patient populations. Some studies provide mean or median decline estimates without illustrating trajectories. In addition, hardly any studies evaluating long-term lung function development and survival in chronic obstructive pulmonary disease are population based.

### What This Study Adds to the

**Field:** Our prospective population-based study, including repeated measurements of FEV<sub>1</sub>% predicted over 10 years, identified three lung function trajectories with different outcomes in terms of initial FEV<sub>1</sub>, subsequent FEV<sub>1</sub> decline, and mortality among adults with airway obstruction. A majority belonged to the trajectory “FEV<sub>1</sub> low with normal decline,” and compared with them, those in the trajectories “FEV<sub>1</sub> high with rapid decline” and “FEV<sub>1</sub> low with normal decline” had increased mortality. Among nonobstructive referents, two trajectories were identified: a small group with FEV<sub>1</sub> high with rapid decline had increased mortality compared with FEV<sub>1</sub> high with normal decline. The different trajectories among those with airway obstruction are clinically relevant and suggestive of diverse underlying disease mechanisms for which future studies may reveal new treatable traits.

The global burden of chronic obstructive pulmonary disease (COPD) is high, with an expected overall prevalence of about 10% (1). A cornerstone in the diagnosis of COPD is the confirmation of chronic airway

obstruction (AO) by spirometry and assessment of severity on the basis of FEV<sub>1</sub>% predicted (FEV<sub>1</sub>%pred) (2). Decline in FEV<sub>1</sub> is an important prognostic marker, and a rapid decline is associated with both a high burden of disease and mortality (3).

Although there is no gold standard for defining a rapid decline in FEV<sub>1</sub>, a limit of at least 60 ml/yr was discussed in a classic paper by Fletcher and Peto published in 1977 (4).

Decline in FEV<sub>1</sub> among individuals with COPD should be evaluated across several years to identify a reliable measure, as lung function values may naturally fluctuate between examinations performed at shorter time intervals (5). On the basis of large samples of patients with COPD, such estimates of mean or median rate of decline have been presented from both primary care and pharmacological trials (6, 7). Still, the well-known underdiagnosis of COPD (8) entails the need for population-based studies in which individuals across all severity stages of COPD can be identified to further unravel lung function changes over time. By using two time points of lung function measurements, it has been shown that not only a rapid but also a normal rate of decline in FEV<sub>1</sub> among individuals with submaximally attained lung function may contribute to the development of COPD (9). In addition, prognosis differed between groups, and both all-cause and respiratory mortality were higher in COPD associated with a maximally attained FEV<sub>1</sub> followed by a more rapid FEV<sub>1</sub> decline than in COPD associated with submaximally attained lung function but a normal rate of FEV<sub>1</sub> decline (10). Besides presenting mean rates of decline in COPD, the importance of identifying different lung function trajectories in the population has been increasingly highlighted in recent decades, revealing diverse clinically meaningful endpoints from childhood to middle age (11) and also among adults (12). However, there is a lack of longitudinal data from population-based COPD cohorts, especially studies including repeated lung function measurements, which are of importance to provide further insights into the natural history of COPD.

Thus, the overall aim of this study was to identify lung function trajectories and their determinants, on the basis of annual spirometry measurements, in a long-term study including adult individuals with and without AO sampled from the general population. A further aim was to evaluate

prognosis, assessed as mortality, in relation to lung function trajectories.

Some of the results of this study have been previously reported in the form of an abstract (13).

## Methods

### Study Population

The first four OLIN (Obstructive Lung Disease in Northern Sweden) adult population-based cohorts were recruited in 1985, 1992 (age-stratified samples), 1993, and 1996 (random samples) using postal questionnaire surveys, in total comprising about 30,000 individuals. Random and stratified samples of responders were invited to clinical examinations initiated the year after the postal questionnaire surveys (14). Previously examined individuals from the four cohorts were invited to reexaminations from 2002 through 2004, after which we identified the present study population (14), all individuals with AO (FEV<sub>1</sub>/VC < 0.70, *n* = 993 cases) together with 993 age- and sex-matched nonobstructive (NO) referents. This study population (*n* = 1,986) constitutes the longitudinal OLIN COPD study and has since 2005 been invited to annual examinations including spirometry and a structured interview following a validated questionnaire (14). The 2002–2004 clinical examinations constitute the baseline (recruitment), and the last clinical follow-up included in the present paper was conducted in 2014. The Swedish National Board of Health and Welfare provided data on all-cause mortality during 15 years of follow-up from baseline. Ethical approval was given by the Regional Ethics Committee at Umeå University, and the study was performed according to the Declaration of Helsinki.

### Spirometry at Baseline and at Each Clinical Examination

Spirometry was performed in accordance with the American Thoracic Society guidelines (15) using the same set of dry volume spirometers, the Mijnhardt Vicatest 5 (Mijnhardt), throughout. VC was defined as the highest of FVC and slow VC, and VC was used as the denominator when defining AO as FEV<sub>1</sub>/VC < 0.70 before bronchodilation (i.e., modified Global Initiative for Chronic Obstructive Lung Disease criteria) (2). Subjects with FEV<sub>1</sub>/VC < 0.70 were also invited to bronchodilation testing, using 4 × 0.2 mg salbutamol. The Swedish OLIN

reference values for spirometry (16) were used.

**Definition of Variables at Baseline**

Pack-years of cigarette smoking was defined as (number of cigarettes smoked per day/20) × number of years.

Respiratory symptoms during the past 12 months included productive cough

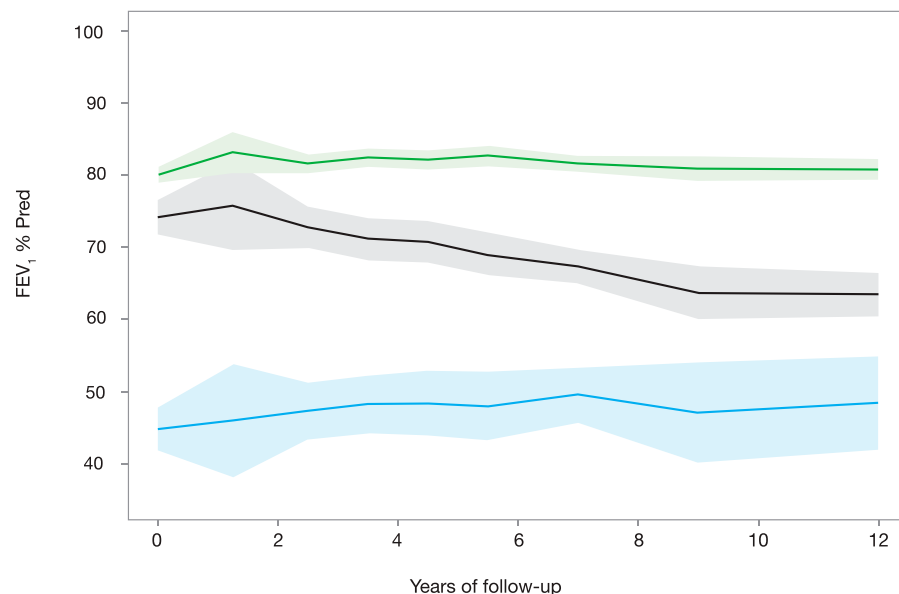
(cough with phlegm most days for at least three months), recurrent wheeze (usually having wheezing and whistling in the chest), and dyspnea (modified Medical Research Council Dyspnea Scale score ≥ 2).

Any respiratory symptom was defined as any of the aforementioned respiratory symptoms during the past 12 months.

Any exacerbations were defined as healthcare contact because of respiratory symptoms during the past 12 months.

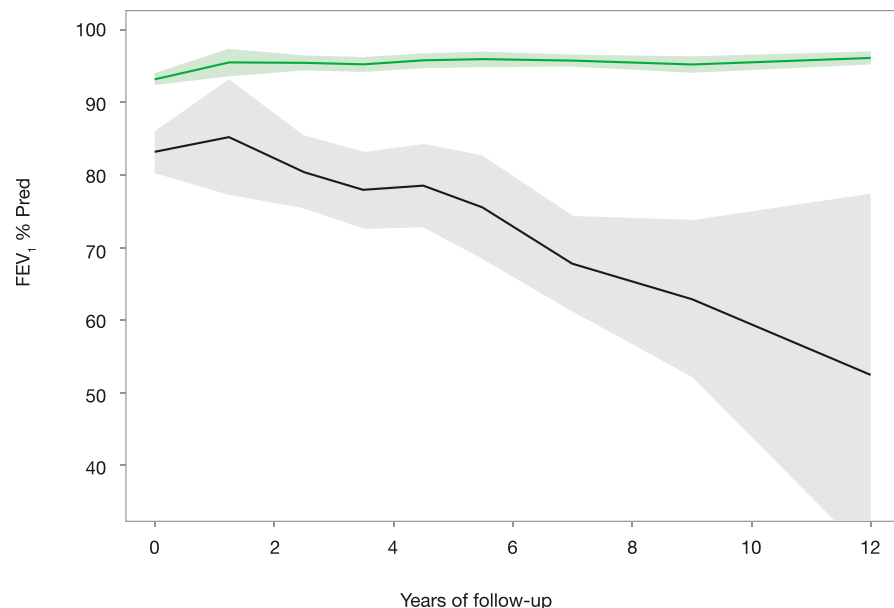
**Definitions of Time-Varying Variables Collected at Baseline and at Each Examination**

Height and weight were measured before spirometry in indoor clothing without shoes.



**Airway obstruction**

- **T1<sub>AO</sub> FEV<sub>1</sub> high with normal decline**  
n = 790, 79.6%  
Crude baseline FEV<sub>1</sub> (mean): Post-BD 80.1% pred
- **T2<sub>AO</sub> FEV<sub>1</sub> high with rapid decline**  
n = 127, 12.8%  
Crude baseline FEV<sub>1</sub> (mean): Post-BD 73.1% pred
- **T3<sub>AO</sub> FEV<sub>1</sub> low with normal decline**  
n = 76, 7.7%  
Crude baseline FEV<sub>1</sub> (mean): Post-BD 40.1% pred



**Nonobstructive**

- **T1<sub>NO</sub> FEV<sub>1</sub> high with normal decline**  
n = 960, 96.7%  
Crude baseline FEV<sub>1</sub> (mean): Pre-BD 92.8% pred
- **T2<sub>NO</sub> FEV<sub>1</sub> high with rapid decline**  
n = 33, 3.3%  
Crude baseline FEV<sub>1</sub> (mean): Pre-BD 80.6% pred

**Figure 1.** FEV<sub>1</sub>% predicted (FEV<sub>1</sub>%pred) trajectories estimated using joint-survival latent class mixed models separately among 993 individuals with airway obstruction (AO) (FEV<sub>1</sub>/VC < 0.70) and 993 nonobstructive (NO) referents without AO (FEV<sub>1</sub>/VC ≥ 0.70) at baseline. The solid lines represent the observed means of FEV<sub>1</sub>%pred, and the shaded areas represent 95% confidence intervals of the means. For subjects with AO who participated in bronchodilation testing, the highest FEV<sub>1</sub>%pred values from pre- or postbronchodilation testing were used as outcomes. For the NO referents, pre-BD FEV<sub>1</sub>%pred values were used as outcomes. BD = bronchodilatory; T1 = trajectory 1 (FEV<sub>1</sub> high with normal decline); T2 = trajectory 2 (FEV<sub>1</sub> high with rapid decline); T3 = trajectory 3 (FEV<sub>1</sub> low with normal decline).

**Table 1.** Characteristics at Baseline by Trajectories of FEV<sub>1</sub>% Predicted Separately among Individuals with and without AO

Characteristic at Baseline	AO			NO		
	T1 <sub>AO</sub> (FEV <sub>1</sub> High with Normal Decline) (n = 790)	T2 <sub>AO</sub> (FEV <sub>1</sub> High with Rapid Decline) (n = 127)	T3 <sub>AO</sub> (FEV <sub>1</sub> Low with Normal Decline) (n = 76)	T1 <sub>NO</sub> (FEV <sub>1</sub> High with Normal Decline) (n = 960)	T2 <sub>NO</sub> (FEV <sub>1</sub> High with Rapid Decline) (n = 33)	P Value*
<b>Clinical characteristics</b>						
Age, yr, mean (SD)	65.4 (11.5)	57.7 (9.3)	70.8 (8.0)	64.1 (11.3)	72.8 (9.4)	<0.001
Age, yr, range	25–85	32–83	52–83	27–84	53–83	—
Male sex	51.4	81.1	43.4	54.2	66.7	0.156
Pack-years, mean (SD)	16.9 (14.9)	31.9 (14.6)	25.6 (15.5)	13.3 (12.5)	8.8 (9.6)	0.130
Nonsmokers	28.0	0.0	22.4	47.9	45.5	—
Former smokers	48.8	0.0	50.0	39.4	42.4	—
Current smokers	23.2	100.0	27.6	12.7	12.1	0.940
BMI, kg/m <sup>2</sup> , mean (SD)	26.2 (4.1)	25.7 (3.9)	25.6 (5.2)	26.6 (3.9)	25.6 (3.1)	0.150
<b>BMI categories</b>						
Underweight	0.8	1.6	5.3	0.5	0.0	—
Normal weight	43.2	46.5	43.4	36.3	45.5	—
Overweight	40.3	40.2	34.2	46.6	48.5	—
Obesity	15.8	11.8	17.1	16.6	6.1	0.376
Parental smoking before school age	53.4	65.4	56.6	49.8	51.5	0.846
Maternal smoking during pregnancy	4.0	7.9	2.6	4.4	0.0	0.219
Productive cough	38.2	63.0	56.6	22.8	36.4	0.070
Recurrent wheeze	45.8	58.3	72.4	18.3	33.3	0.030
Dyspnea (mMRC score ≥ 2)	22.5	22.0	75.0	9.2	15.2	0.252
Any respiratory symptoms <sup>†</sup>	69.0	79.5	93.4	41.0	51.5	0.230
Any exacerbation last 12 mo	18.0	18.9	52.6	9.1	6.1	0.553
Any airway medication use last 12 mo	32.5	25.2	82.9	10.0	12.1	0.691
Self-reported asthma diagnosis, ever	31.9	20.5	44.7	11.1	18.2	0.211
Postbronchodilator <sup>‡</sup> FEV <sub>1</sub> increase of ≥200 ml and ≥12% Lung function at baseline, mean (SD)	16.0	10.8	3.2	N/A	N/A	—
FEV <sub>1</sub> pre-BD						
Liters	2.28 (0.73)	2.49 (0.73)	0.98 (0.32)	2.81 (0.80)	2.31 (0.72)	<0.001
% predicted	75.7 (13.9)	69.6 (15.6)	37.7 (10.9)	92.8 (12.9)	80.6 (17.3)	<0.001
FEV <sub>1</sub> post-BD						
Liters	2.41 (0.74)	2.61 (0.73)	1.04 (0.32)	N/A	N/A	—
% predicted	80.1 (13.6)	73.1 (15.3)	40.1 (11.2)	N/A	N/A	—
VC pre-BD						
Liters	3.55 (1.06)	4.06 (1.00)	2.15 (0.68)	3.61 (1.01)	3.01 (0.93)	0.001
% predicted	86.7 (14.1)	85.7 (14.9)	58.8 (13.4)	87.9 (12.5)	75.9 (16.2)	<0.001
VC post-BD						
Liters	3.59 (1.05)	4.11 (0.99)	2.19 (0.68)	N/A	N/A	—
% predicted	87.7 (13.7)	86.8 (14.6)	59.8 (13.4)	N/A	N/A	—
FEV <sub>1</sub> /VC pre-BD, z-score	-1.6 (1.0)	-2.6 (1.3)	-4.2 (2.3)	0.63 (0.82)	0.71 (0.93)	0.587
FEV <sub>1</sub> /VC post-BD, z-score	-1.1 (1.1)	-2.2 (1.3)	-3.8 (2.4)	N/A	N/A	—

*Definition of abbreviations:* AO = airway obstruction; BMI = body mass index; mMRC = modified Medical Research Council Dyspnea Scale; N/A = not applicable; NO = nonobstructive; pre-BD = prebronchodilator value; post-BD = highest of pre- and postbronchodilator values; T1 = trajectory 1; T2 = trajectory 2; T3 = trajectory 3. Data are presented as column percentage unless otherwise stated. Mean pack-years of smoking is calculated among ex-smokers and current smokers. <sup>†</sup>Chi-square test for proportions, ANOVA for means. <sup>‡</sup>Any of productive cough, recurrent wheeze, attacks of shortness of breath, or dyspnea (mMRC score ≥ 2). <sup>§</sup>Results from bronchodilatation testing available for 846 subjects with AO.

**Table 2.** Determinants of FEV<sub>1</sub>%Pred Trajectory Membership Separately among Individuals with and without AO Using Joint Latent-Class Mixed Models

LC Part of the Model: Baseline Determinants of Trajectory Membership	AO			NO		
	T2 <sub>AO</sub> (FEV <sub>1</sub> High with Rapid Decline)	T3 <sub>AO</sub> (FEV <sub>1</sub> Low with Normal Decline)	T2 <sub>NO</sub> (FEV <sub>1</sub> High with Rapid Decline)	Coef (SE)	P Value	P Value
	Coef (SE)	Coef (SE)	Coef (SE)	Coef (SE)	P Value	P Value
Age	-0.08 (0.04)	0.055	0.10 (0.02)	0.21 (0.04)	<0.001	<0.001
Male sex	1.60 (0.64)	0.013	-0.11 (0.34)	2.16 (1.29)	0.744	0.095
Pack-years	0.07 (0.03)	0.001	0.03 (0.01)	0.06 (0.07)	<0.001	0.385
Current smoking	12.77 (37.02)	0.730	0.50 (0.39)	2.84 (1.41)	0.205	0.045

*Definition of abbreviations:* AO = airway obstruction; Coef = coefficient from joint latent-class mixed models; FEV<sub>1</sub>%pred = FEV<sub>1</sub>% predicted; LC = latent class; NO = nonobstructive; T1 = trajectory 1; T2 = trajectory 2; T3 = trajectory 3.

All variables listed in the table were included in the models, and all models are also adjusted for squared height. Trajectory 1 (FEV<sub>1</sub> high with normal decline) is used as the reference category in the model of determinants of trajectory membership among those with airway obstruction (T1<sub>AO</sub>) and among the NO referents (T1<sub>NO</sub>).

Body mass index (BMI) was calculated (weight [kilograms] divided by height [meters] [2]) and categorized as underweight (<18.5 kg/m<sup>2</sup>), normal weight (≥18.5–24.9 kg/m<sup>2</sup>), overweight (≥25–29.9 kg/m<sup>2</sup>), and obesity (≥30.0 kg/m<sup>2</sup>).

Smoking status was divided into never-smokers, ex-smokers (for at least one year), and current smokers.

### Statistics

The combined longitudinal and survival data were analyzed using joint latent-class mixed models (J-LCMM) (17), enabling a data-driven approach to identify subgroups with different lung function trajectories (*see the online supplement for further details*) while accounting for different survival patterns across subgroups. The J-LCMM analyses were performed using the *lcmm* package in R (R Core Team). FEV<sub>1</sub>%pred was used as the longitudinal outcome variable in the models, and covariates were included to analyze associations with trajectory membership (baseline age, sex, height, pack-years, and smoking habit) and longitudinal FEV<sub>1</sub>%pred (baseline age, sex, height, pack-years and the time-varying covariates, smoking habit, and BMI category) on the basis of previous evidence and clinical experience. For subjects with AO who participated in bronchodilation testing, the highest FEV<sub>1</sub>%pred values from pre- or postbronchodilation testing were used as the outcome. For the NO referents, prebronchodilatory FEV<sub>1</sub>%pred values were used as the outcome. For a description of the survival part of the model, *see the online supplement*. Models identifying two, three, or four trajectories were constructed, and the models with the lowest values of the Bayesian information criterion were chosen among subjects with AO and NO referents, respectively, and presented as main results, while the discarded models are described in Figures E1–E4 in the online supplement.

Differences in characteristics at baseline among the identified trajectories were analyzed using chi-square testing and ANOVA, as appropriate, using SPSS (version 26; IBM). A significance threshold of  $P < 0.05$  was chosen. Individual annual decline estimates in terms of prebronchodilatory FEV<sub>1</sub> (milliliters) are estimated by subjectwise linear regression with time as a covariate. Differences in 15-year all-cause mortality among the identified trajectories were analyzed using Cox proportional-hazards

**Table 3.** Determinants of FEV<sub>1</sub>%Pred Trajectory Shape Separately among Individuals with and without AO Using Joint Latent-Class Mixed Models

MM Part of the Model: Longitudinal Modeling of Determinants of FEV <sub>1</sub> %pred	AO		NO	
	Coef (SE)	P Value	Coef (SE)	P Value
Baseline age	-0.10 (0.05)	0.026	-0.04 (0.04)	0.293
Baseline male sex	-2.01 (1.05)	0.056	-0.80 (0.84)	0.339
Baseline pack-years	-0.20 (0.04)	<0.001	-0.10 (0.04)	0.008
Current smoking (time varying)	-0.55 (0.47)	0.232	0.26 (0.50)	0.606
Overweight (BMI 25–30 kg/m <sup>2</sup> ) (time varying)	-0.29 (0.30)	0.345	-1.18 (0.26)	<0.001
Obesity (BMI > 30 kg/m <sup>2</sup> ) (time varying)	-1.92 (0.47)	<0.001	-2.73 (0.38)	<0.001

*Definition of abbreviations:* AO = airway obstruction; BMI = body mass index; Coef = coefficient from joint latent-class mixed models; FEV<sub>1</sub>%pred = FEV<sub>1</sub>% predicted; MM = mixed models; NO = nonobstructive.

All variables listed in the table were included in the models, and all models are also adjusted for squared height. Smoking, overweight, and obesity were included as time-varying covariates in the longitudinal analysis of determinants of FEV<sub>1</sub>%pred.

models including sex, age, pack-years of smoking, and overweight and obesity at baseline as covariates. Hazard ratios (HR) with 95% confidence intervals (CI) and survival functions for each trajectory were estimated.

### Sensitivity Analysis

J-LCMM were also applied to the subsample of individuals with postbronchodilatory (post-BD) AO (post-BD FEV<sub>1</sub>/VC < 0.70; *n* = 736 of 993 cases) at baseline. Differences in 15-year all-cause mortality among trajectories were analyzed using similar Cox proportional-hazards models as in the main analyses. These results are presented in the online supplement.

## Results

The lung function trajectories are based on a total of >11,000 data points for FEV<sub>1</sub>%pred, and the number of observations at each time point is presented in Table E1. Trajectories among the subjects with AO and NO referents are illustrated in Figure 1 and the corresponding raw data plots in Figures E5 and E6.

### FEV<sub>1</sub> Trajectories among Individuals with AO

The three identified FEV<sub>1</sub>%pred trajectories among individuals with AO are illustrated in Figure 1, and additional characteristics at baseline are presented in Table 1. AO trajectory 1 (T1<sub>AO</sub>), FEV<sub>1</sub> high with normal decline, consisted of 790 individuals with a mean age of 65.4 years, 51.4% of whom were men and 23.2% of whom were current smokers. The mean FEV<sub>1</sub> at baseline was higher and the prevalence of any respiratory

symptom lower than in the other trajectories. AO trajectory 2 (T2<sub>AO</sub>), FEV<sub>1</sub> high with rapid decline, consisted of 127 individuals, 100% of whom were current smokers, with a higher proportion of parental smoking before school age (65.4%), a lower mean age (57.5 yr), and a higher proportion of men (81.1%) than in the other trajectories. The mean FEV<sub>1</sub>%pred at baseline was 73.1, and 79.5% of subjects reported any respiratory symptoms, whereof productive cough was most common. AO trajectory 3 (T3<sub>AO</sub>), FEV<sub>1</sub> low with normal decline, consisted of 76 individuals with the highest mean age (70.8 yr), 43.4% of whom were men and 27.6% of whom were current smokers. The proportions with dyspnea (75.0%), any respiratory symptoms (93.4%), and any exacerbations (52.6%) were higher than in the other trajectories. Both mean FEV<sub>1</sub>%pred, VC% predicted and FEV<sub>1</sub>/VC at baseline were lower than in other trajectories. Ever having had an asthma diagnosis was most commonly reported in T3<sub>AO</sub>, by 44.7%, while the proportion with significant bronchodilation response was the lowest at 3.2%. The prevalence of obesity was slightly higher in T3<sub>AO</sub> compared with T1<sub>AO</sub> and T2<sub>AO</sub> (17.1% vs. 15.8% in T1<sub>AO</sub> and 11.8% in T2<sub>AO</sub>).

Regarding determinants of FEV<sub>1</sub>%pred, age and pack-years of smoking at baseline and the time-varying variable obesity were significantly associated with lower FEV<sub>1</sub>%pred (Tables 2 and 3).

### FEV<sub>1</sub> Trajectories among Referents without AO

The two identified FEV<sub>1</sub>%pred trajectories among the NO referents are illustrated in Figure 1, and characteristics at baseline are

presented in Table 1. NO trajectory 1 (T1<sub>NO</sub>), FEV<sub>1</sub> high with normal decline, consisted of 960 individuals characterized by a mean age of 64.1 years, 12.7% of whom were current smokers, 46.6% overweight, and 16.6% obese; their mean FEV<sub>1</sub>%pred was 92.8% at baseline. NO trajectory 2 (T2<sub>NO</sub>), FEV<sub>1</sub> high with rapid decline, consisted of 33 individuals with a higher mean age (72.8 yr), 12.1% of whom were current smokers, 48.5% overweight, and 6.1% obese; their mean FEV<sub>1</sub>%pred was 80.6% at baseline. Any respiratory symptoms were similarly common in T1<sub>NO</sub> and T2<sub>NO</sub>, at 41.0% and 51.5%, respectively.

Pack-years of smoking at baseline and the time-varying variables overweight and obesity were significantly associated with lower FEV<sub>1</sub>%pred (Tables 2 and 3).

### Annual Rate of FEV<sub>1</sub> Decline for Each Trajectory

In Table 4, subject-specific rates of decline in prebronchodilatory FEV<sub>1</sub> are presented as loss of milliliters per year and also using different cutoffs to define accelerated decline. Among those with AO, the mean estimated annual FEV<sub>1</sub> decline was 27 ml in T1<sub>AO</sub>, 72 ml in T2<sub>AO</sub>, and 26 ml in T3<sub>AO</sub> (*P* < 0.001), and the distribution of individual decline estimates by trajectory is illustrated in Figure 2. The proportions with annual FEV<sub>1</sub> decline of at least 30 ml were 49.3% in T1<sub>AO</sub>, 90.7% in T2<sub>AO</sub>, and 47.1% in T3<sub>AO</sub> (*P* < 0.001).

Among the NO referents, the mean estimated annual FEV<sub>1</sub> decline was 34 ml in T1<sub>NO</sub> and 173 ml in T2<sub>NO</sub> (*P* < 0.001), and the proportion with annual FEV<sub>1</sub> decline of at least 30 ml was 54.6% in T1<sub>NO</sub> and 96.0% in T2<sub>NO</sub> (*P* < 0.001) (Table 4 and Figure 2).

**Table 4.** Annual Decline in Prebronchodilatory FEV<sub>1</sub> by Trajectory, Separately among Individuals with and without AO and at Least Two Measurements of FEV<sub>1</sub>

	AO			NO		
	T1 <sub>AO</sub> (High FEV <sub>1</sub> with Normal Decline) (n = 690)	T2 <sub>AO</sub> (High FEV <sub>1</sub> with Rapid Decline) (n = 108)	T3 <sub>AO</sub> (Low FEV <sub>1</sub> with Normal Decline) (n = 51)	T1 <sub>NO</sub> (High FEV <sub>1</sub> with Normal Decline) (n = 861)	T2 <sub>NO</sub> (High FEV <sub>1</sub> with Rapid Decline) (n = 25)	P Value
Annual decline in FEV <sub>1</sub> , ml						
Mean (SD)	-27 (55)	-72 (49)	-26 (68)	-34 (34)	-173 (172)	<0.001
Median (IQR)	-29 (-48 to -11)	-69 (-96 to -49)	-30 (-50 to -3)	-32 (-50 to -18)	-123 (-183 to -100)	—
Categories of annual decline in FEV <sub>1</sub> , ml						
≥30-ml decline, %	49.3	90.7	47.1	54.6	96.0	<0.001
≥40-ml decline, %	33.0	82.4	41.2	38.1	92.0	<0.001
≥50-ml decline, %	22.8	73.1	23.5	24.6	92.0	<0.001
≥60-ml decline, %	15.4	58.3	13.7	15.6	88.0	<0.001
≥70-ml decline, %	11.4	49.1	13.7	9.9	88.0	<0.001
≥80-ml decline, %	8.7	39.8	13.7	6.2	88.0	<0.001
≥90-ml decline, %	6.2	29.6	9.8	4.3	84.0	<0.001

Definition of abbreviations: AO = airway obstruction; IQR = interquartile range; NO = nonobstructive; T1 = trajectory 1; T2 = trajectory 2; T3 = trajectory 3. Individual decline estimates in terms of FEV<sub>1</sub>% predicted and milliliters per year are estimated by subjectwise linear regression with time as a covariate.

**Fifteen-Year All-Cause Mortality for Each Trajectory**

Among individuals with AO, the crude mean survival was 12.3 years (95% CI, 12.0–12.6 yr) in T1<sub>AO</sub>, 11.9 years (95% CI, 11.1–12.7 yr) in T2<sub>AO</sub>, and 7.0 years (95% CI, 5.9–8.0 yr) in T3<sub>AO</sub>. The corresponding figures in the NO group were 12.9 years (95% CI, 12.6–13.1 yr) in T1<sub>NO</sub> and 6.8 years (95% CI, 5.3–8.3 yr) in T2<sub>NO</sub>. Crude mortality rates per 1,000 person-years were 34.3 in T1<sub>AO</sub>, 38.6 in T2<sub>AO</sub>, and 126.7 in T3<sub>AO</sub>, with corresponding figures of 25.8 in T1<sub>NO</sub> and 138.1 in T2<sub>NO</sub>. Among subjects with AO, survival curves illustrate a higher hazard for 15-year all-cause mortality in T2<sub>AO</sub> and T3<sub>AO</sub> than in T1<sub>AO</sub> (adjusted HRs, 1.56 [95% CI, 1.12–2.15] and 3.45 [95% CI, 2.63–4.52], respectively), when adjusted for age, sex, pack-years and BMI categories. Also among the NO referents, the hazard for 15-year mortality was higher in the trajectory with rapid decline in FEV<sub>1</sub> (T2<sub>NO</sub>) than in that with normal decline in FEV<sub>1</sub> (T1<sub>NO</sub>) (adjusted HR, 2.99 [95% CI, 2.03–4.40]) (Figure 3).

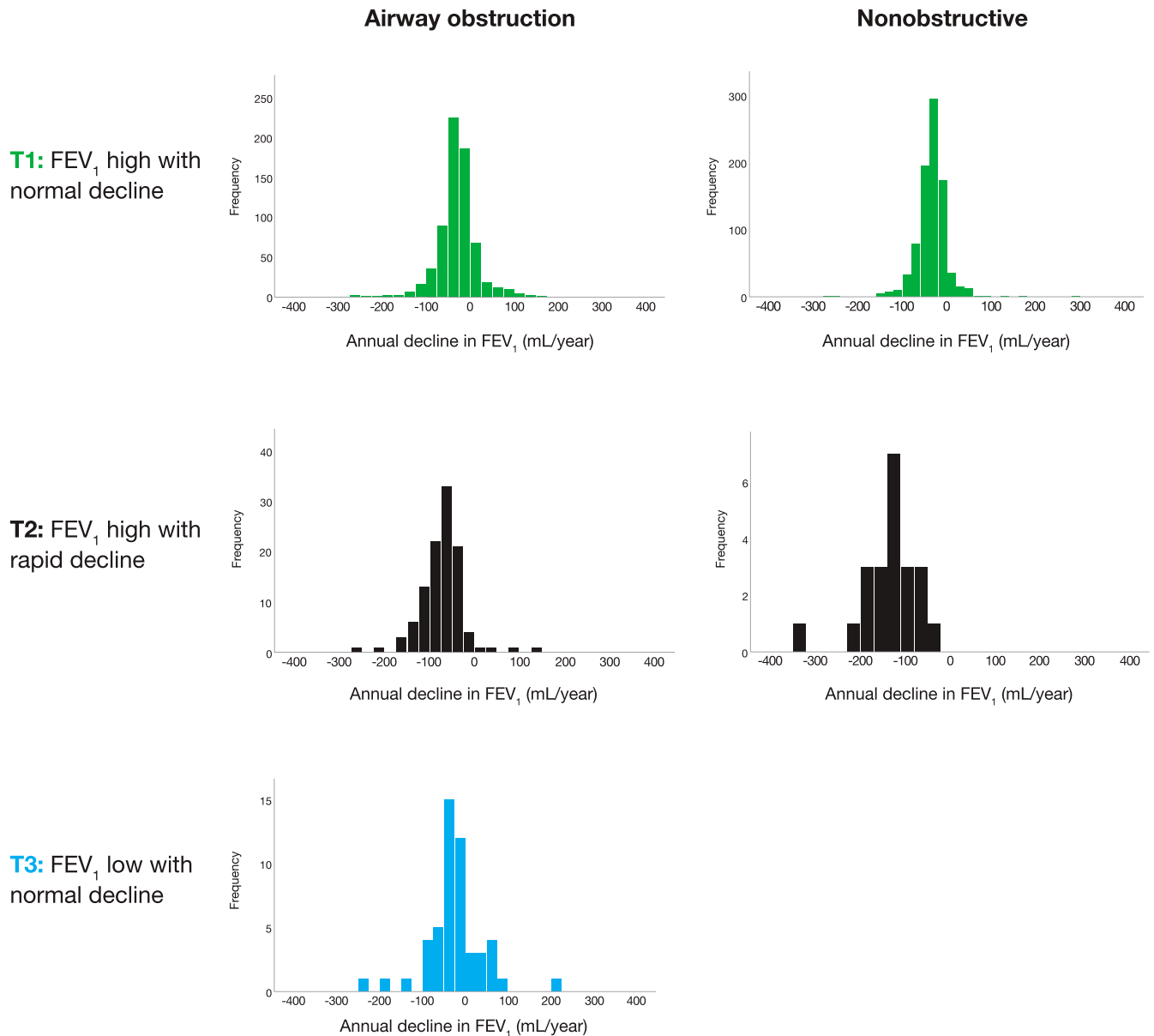
**Sensitivity Analysis**

The separate analysis among 736 individuals with post-BD obstruction confirmed the main findings in terms of both trajectory shapes and survival (see Figure E7).

**Discussion**

In this prospective, population-based case-referent study including repeated lung function testing across more than 10 years of follow-up, data-driven analyses identified three lung function trajectories with clinically different outcomes in terms of both FEV<sub>1</sub> decline and mortality among those with AO, while two trajectories were identified among the NO referents. Among individuals with AO, T2<sub>AO</sub> (FEV<sub>1</sub> high with rapid decline) (mean, 72 ml/yr) had 56% increased mortality, and T3<sub>AO</sub> (FEV<sub>1</sub> low with normal decline) (mean, 26 ml/yr) had 245% increased mortality compared with T1<sub>AO</sub> (FEV<sub>1</sub> high with normal decline). Among the NO referents, the small group of individuals in T2<sub>NO</sub> (FEV<sub>1</sub> high with rapid decline) (mean, 173 ml/yr) had 199% increased mortality compared with T1<sub>NO</sub> (FEV<sub>1</sub> high with normal decline).

Among subjects with AO in the present study, a majority (79%) belonged to T1<sub>AO</sub> (FEV<sub>1</sub> high with normal decline), with an



**Figure 2.** Histograms of individual prebronchodilatory FEV<sub>1</sub> decline (ml/yr) estimates within each of the trajectories, separately among individuals with airway obstruction (FEV<sub>1</sub>/VC < 0.70) and referents without airway obstruction (FEV<sub>1</sub>/VC ≥ 0.70) at baseline. T1 = trajectory 1; T2 = trajectory 2; T3 = trajectory 3.

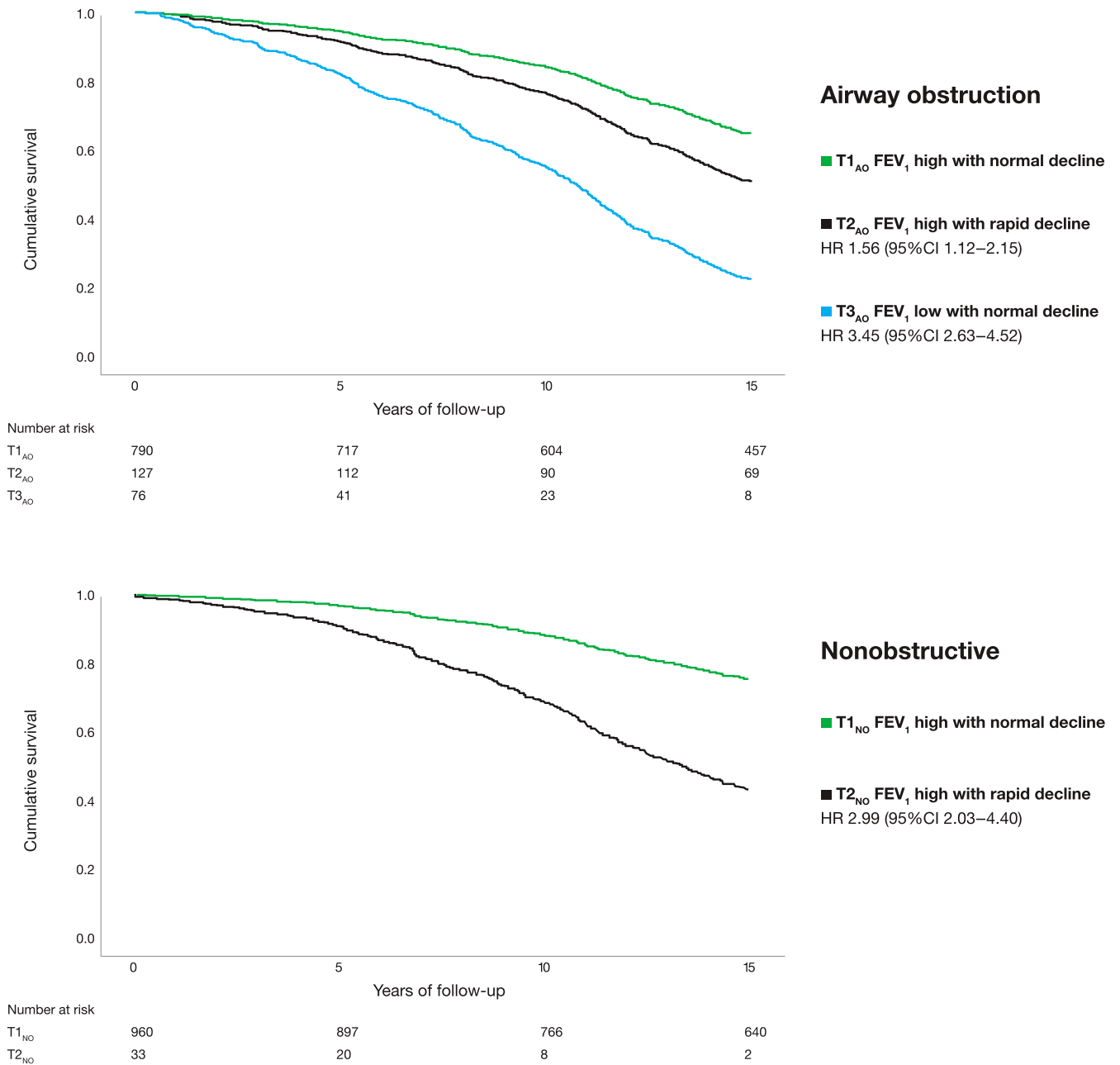
estimated mean FEV<sub>1</sub> decline of 27 ml/yr. Our results thus indicate that on a population level, a majority of those with AO aged 25–85 years at baseline maintain fairly normal lung function. For comparison, about 80% remained in the same Global Initiative for Chronic Obstructive Lung Disease stage during 4–8 years of follow-up of a COPD cohort (18), indicating a good prognosis with respect to lung function decline in the majority of patients. Besides preserved lung function, T1<sub>AO</sub> also had the

best survival among those with AO in the present study, although the mortality rate was slightly higher than that of T1<sub>NO</sub> (i.e., referents with high FEV<sub>1</sub> with normal decline).

In contrast, T2<sub>AO</sub> (FEV<sub>1</sub> high with rapid decline) was a smaller group (12.8% of subjects with AO) than T1<sub>AO</sub>, but the majority in this trajectory fulfilled the criterion for rapid decline suggested by Fletcher and Peto (4). All individuals in this trajectory were current smokers at baseline,

predominantly men, but with the lowest mean age of all trajectories and a higher hazard of death than subjects in T1<sub>AO</sub>. Studies focusing on lung function trajectories in COPD have been increasingly highlighted during the past decade (19), and there are, for comparison, a few studies including longitudinal lung function data in patients with COPD. In the Normative Aging Study, four distinct FEV<sub>1</sub> trajectories were identified using data-driven modeling. These trajectories were then applied to a subsample





**Figure 3.** Survival functions for each trajectory and HRs with 95% CIs (T1 as reference), estimated using Cox regression models including sex, age, pack-years of smoking, and overweight and obesity as covariates, separately among 993 subjects with AO and 993 age- and sex-matched NO referents. AO = airway obstruction; CI = confidence interval; HR = hazard ratio; NO = nonobstructive; T1 = trajectory 1 (FEV<sub>1</sub> high with normal decline); T2 = trajectory 2 (FEV<sub>1</sub> high with rapid decline); T3 = trajectory 3 (FEV<sub>1</sub> low with normal decline).

of smoking men from the COPDGene study, resulting in 17% of subjects being assigned to the trajectory with the most rapid decline in FEV<sub>1</sub> (20). In two other studies including patients with COPD with at least three lung function measurements over 10–12 years, the groups with the most rapid decline in lung function constituted 18–30% of the patients,

with a mean FEV<sub>1</sub> decline of 78–86 ml/yr (21, 22). The proportion with rapid FEV<sub>1</sub> declines in these studies of patients with COPD (20–22) was slightly higher than in the present study. However, the AO group in our population-based study included mainly individuals with mild to moderate airflow limitation, known to be largely

underdiagnosed (8) but still representative of individuals with AO on a societal level. Thus, our results highlight that case finding with repeated lung function measurements among smokers, regardless of age, may identify individuals with rapid lung function declines and a worse prognosis at earlier stages of disease and may also be useful for

the detection of early COPD (23) with an unfavorable prognosis.

T<sub>3AO</sub> (FEV<sub>1</sub> low with normal decline) included 76 individuals with a mean FEV<sub>1</sub> decline of 26 ml/yr. Among the AO trajectories, mean age and proportions of respiratory symptoms and exacerbations were highest and survival was worst in T<sub>3AO</sub>. Besides the lowest FEV<sub>1</sub>%pred, in this trajectory VC% predicted was also lower than in T<sub>1AO</sub> and T<sub>2AO</sub>. In a recently published study, different trajectories were observed in a cohort followed from 7 years to middle age (24). The mixed lifetime spirometry pattern (having both low FEV<sub>1</sub>:FVC and low FVC) was associated with childhood illnesses, and when reaching middle age, these subjects had the highest prevalence of COPD and biomarkers indicating increased inflammation. Taken together across the lifespan, the previous study (24) and T<sub>3AO</sub> in the present study indicate that obstruction with accompanying low VC may indicate the most severe form of COPD. Our assumption is that T<sub>3AO</sub> includes individuals with low maximally attained lung function or previous periods with rapid decline to which earlier life events or childhood disadvantages, including asthma, may have contributed (25–27). Future studies on causes of death could potentially reveal underlying reasons besides respiratory causes for the increased mortality of this trajectory.

We hypothesize that the observed three well-separated trajectories among subjects with AO represent clinically relevant underlying biological mechanisms. Several biomarkers have been associated with COPD pathogenesis, such as reduced concentrations of CC16 (club cell protein 16) and sRAGE (soluble receptor for advanced glycation end-products), different interleukins, and other inflammatory markers (28). Also, genetics and epigenetics may play a role in accelerated lung aging and early COPD (29, 30). In addition, early life events may affect lung function development into adulthood (31). However, the biomarker pattern in COPD is heterogeneous, and different biological processes can be involved in patients with similar degrees of airflow limitation (32), but there are few studies evaluating biomarkers in relation to long-term outcomes. The present study offers clinical aspects to the understanding of lung pathogenesis in COPD, and we propose future studies specifically on

biological mechanisms in relation to these lung function trajectories.

Smoking, assessed by pack-years at baseline and the time-varying variable current smoking, was not unexpectedly associated with both trajectory membership and FEV<sub>1</sub>%pred. Furthermore, parental smoking before school age was most common (65%) in the rapid-decline trajectory (T<sub>2AO</sub>), which is in line with previous studies showing associations between parental COPD and more severe COPD in the offspring (33). However, the relationship between parental smoking and smokers with COPD is difficult to disentangle, as it may mirror familial smoking behaviors but also lower socioeconomic status (34) or a genetic predisposition to the harmful effects of smoking (33).

In COPD, underweight and malnutrition have been observed as risk factors associated with increased mortality (35, 36). However, it has been increasingly recognized that obesity is also common among subjects with COPD (37–39), and in the present study, obesity was associated with more rapid FEV<sub>1</sub> declines in both individuals with AO and NO referents. Even though obesity is a recognized treatable trait in COPD (39, 40), it has rarely been evaluated in relation to changes in lung function. In selected populations of pharmacological COPD trials, higher BMI was, on the contrary, associated with reduced lung function loss among men (41). Further studies are needed to disentangle the relationship between BMI or BMI changes and lung function decline in COPD.

Among NO individuals, we identified two well-defined and delimited lung function trajectories, and the great majority (96.7%) belonged to T<sub>1NO</sub> (FEV<sub>1</sub> high with normal decline), thus with declines in FEV<sub>1</sub> comparable with that of a population sample (42, 43). A strikingly deviant pattern was observed in the small group belonging to T<sub>2NO</sub> (FEV<sub>1</sub> high with rapid decline). This trajectory membership was driven by older age and was associated with a substantially increased hazard for death compared with T<sub>1NO</sub>. The underlying biological mechanisms may be heterogeneous in this small group.

There are previous population-based studies on lung function among adults with long-term follow-up. However, because of a

prevalence of COPD of about 10% (1), the total number of individuals with COPD in these studies is limited (11, 12). Furthermore, in most studies on lung function decline, the annualized estimates are based on two or a few lung function measurements divided by the time of follow-up to yield an average (5, 9, 23, 44). Some pharmacological COPD trials have provided repeated measurements of lung function (6, 45, 46), but they generally include highly selected COPD populations, most often with moderate to severe disease, providing results not generalizable to the COPD spectra in society. Both baseline lung function and rapid decline matter for prognosis (44), and there is evidence showing that low peak lung function in early adulthood is associated with mortality (47). However, lung function groups are most often predefined, and thereafter prognosis is assessed, and an important contribution of our study is the data-driven modeling using FEV<sub>1</sub>%pred to illustrate lung function trajectories, in contrast to studies of predefined groups.

We further want to highlight the following strengths of our study. The population-based design includes a large sample of individuals with AO who, together with age- and sex-matched NO referents, have been followed with annual clinical examinations over several years. The age distribution in the study sample is reasonable for clinically relevant COPD. The standardized methods were ensured by specifically trained personnel, the use of the same spirometers, adherence to guidelines for lung function testing, and, besides lung function, the collection of time-dependent variables such as smoking habit and BMI at each examination. Mortality during the observation period was taken into account by the data-driven modeling of the trajectories. Among the individuals with AO, three trajectories were clearly delimited from one another, all with distinctively different mortality rates, and the findings were confirmed in sensitivity analyses performed in cases with post-BD FEV<sub>1</sub>/VC < 0.70. The results provide another important piece of the puzzle to understand the complex syndrome of COPD, still to be evaluated in relation to clinical phenotypes and underlying disease mechanisms.

The study also has weaknesses. First, spirometry findings are limited to adult life, and we can only make assumptions, on the

basis of data from birth cohorts (11, 26, 27), regarding an association between T3<sub>AO</sub> and earlier life events. Second, medication was not accounted for and may have affected rates of decline in lung function (48). Last, the AO population in this study is likely to be representative of AO in the source population, whereas the original study design with age and sex matching does not imply a corresponding representativeness for the NO referent group. Thus, the lung function trajectories in the NO group are not considered generalizable to the general population but rather aid in highlighting

differences between individuals with AO and NO referents that are unrelated to age and sex.

### Conclusions

In this prospective, population-based study including repeated clinical examination across more than 10 years, we identified three different FEV<sub>1</sub> trajectories among subjects with AO and two among the NO referents. The trajectories were clinically distinguishable between as well as within the groups in terms of initial FEV<sub>1</sub>, subsequent FEV<sub>1</sub> decline, and mortality.

The well-separated different FEV<sub>1</sub> trajectories among subjects with AO and the relationship between low FVC and trajectory outcome are of particular clinical interest. Future studies may reveal tools for both preventive measures and new treatable traits. ■

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