

Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is thought to result from an accelerated decline in forced expiratory volume in 1 second (FEV₁) over time. Yet it is possible that a normal decline in FEV₁ could also lead to COPD in persons whose maximally attained FEV₁ is less than population norms.

METHODS

We stratified participants in three independent cohorts (the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort) according to lung function (FEV₁ ≥80% or <80% of the predicted value) at cohort inception (mean age of patients, approximately 40 years) and the presence or absence of COPD at the last study visit. We then determined the rate of decline in FEV₁ over time among the participants according to their FEV₁ at cohort inception and COPD status at study end.

RESULTS

Among 657 persons who had an FEV₁ of less than 80% of the predicted value before 40 years of age, 174 (26%) had COPD after 22 years of observation, whereas among 2207 persons who had a baseline FEV₁ of at least 80% of the predicted value before 40 years of age, 158 (7%) had COPD after 22 years of observation (P<0.001). Approximately half the 332 persons with COPD at the end of the observation period had had a normal FEV₁ before 40 years of age and had a rapid decline in FEV₁ thereafter, with a mean (±SD) decline of 53±21 ml per year. The remaining half had had a low FEV₁ in early adulthood and a subsequent mean decline in FEV₁ of 27±18 ml per year (P<0.001), despite similar smoking exposure.

CONCLUSIONS

Our study suggests that low FEV₁ in early adulthood is important in the genesis of COPD and that accelerated decline in FEV₁ is not an obligate feature of COPD. (Funded by an unrestricted grant from GlaxoSmithKline and others.)

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N Engl J Med 2015;373:111-22.

DOI: 10.1056/NEJMoa1411532

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a major cause of illness and death worldwide.¹ Since the research by Fletcher and colleagues in the 1970s,^{2,3} the prevailing paradigm of COPD pathogenesis has been that, in susceptible persons, exposure to particulate matter — especially tobacco smoke — leads to clinical disease through acceleration of the age-related decline in lung function, as assessed by the forced expiratory volume in 1 second (FEV₁). Subsequent population studies supported this paradigm and led to therapeutic trials aimed at reducing the rapid decline in FEV₁.⁴⁻¹¹ Surprisingly, the observed declines in FEV₁ in these trials and in observational cohorts of patients with COPD have been variable and smaller than anticipated, particularly among persons with the most severe airflow limitation.⁴⁻¹⁶ These observations question the notion that COPD always follows a trajectory of rapid decline in FEV₁ and are consistent with the hypothesis that low maximally attained lung function in early adulthood can also result in COPD later in life, even when the rate of decline in FEV₁ is within the normal range.¹⁷⁻²¹ In fact, this alternative course was already suggested by Fletcher and Peto³ and emphasized by Burrows et al.²² but was never explored in a long-term, prospective investigation. We used data from three large cohort studies to investigate this issue.

METHODS

STUDY DESIGN

In this study, we used data from participants in three large and independent cohort studies, the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort. We used FEV₁ (≥80% of the predicted value [normal FEV₁] or <80% of the predicted value [low FEV₁]) at cohort inception and the presence or absence of COPD at the final cohort study visit to define four trajectories: normal FEV₁ at cohort inception and no COPD at the final visit (trajectory 1), low FEV₁ at cohort inception and no COPD at the final visit (trajectory 2), normal FEV₁ at cohort inception and COPD at the final visit (trajectory 3), and low FEV₁ at cohort inception and COPD at the final visit (trajectory 4). We then determined the extent to which the rate of decline in FEV₁ was an explanatory variable for a diagnosis of COPD at study end for a patient with a normal initial FEV₁ or a low initial FEV₁ at study inception.

STUDY CONDUCT AND OVERSIGHT

The recruitment of participants and the methods used in each of the three cohorts are presented in detail in the Supplementary Appendix (available with the full text of this article at NEJM.org) and are summarized below. Written informed consent was obtained from all participants, and the studies were approved by the relevant ethics review boards. In our analyses, participants were considered to have COPD if they had grade 2 or higher COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹ grading system; grade 2 or higher COPD according to GOLD is defined as a ratio of FEV₁ to forced vital capacity (FVC) of less than 0.70 and an FEV₁ of less than 80% of the predicted value, with the use of the prediction equations from the National Health and Nutrition Examination Survey for the Framingham Offspring Cohort and the Lovelace Smokers Cohort and local prediction equations for the Copenhagen City Heart Study.^{23,24}

FRAMINGHAM OFFSPRING COHORT (FOC)

The FOC as it relates to this study is described in detail in the Supplementary Appendix. We identified 187 current or former smokers, 50 to 65 years of age, who had GOLD grade 2 or higher COPD at the final examination in 1996–1997 and who had undergone spirometry before 40 years of age. Six of these persons started smoking after the study began. We calculated the decline in FEV₁ by measuring the difference (in milliliters) between the first available spirometric measurement and the last measurement obtained at 50 to 65 years of age and dividing the result by the number of years between the measurements. The mean decline in FEV₁ was calculated for persons who had had an FEV₁ of at least 80% of the predicted value on baseline spirometry and for those who had had an FEV₁ of less than 80% of the predicted value on baseline spirometry. In addition, we identified 1662 persons who underwent the first spirometry before 40 years of age, regardless of whether they had COPD at the final examination, and categorized them in one of the four trajectories described above.

COPENHAGEN CITY HEART STUDY (CCHS)

The CCHS as it relates to this article is described in detail in the Supplementary Appendix. The annualized decline in FEV₁ was calculated as the slope between two measurements over the longest observation period. We identified 145 current or

former smokers, 50 to 65 years of age, who had GOLD grade 2 or higher COPD at the final examination in 2001–2003 and who had undergone spirometry before 40 years of age. As in the FOC, we also identified 1242 participants who were 20 to 40 years of age at baseline and who underwent spirometry 25 years later, regardless of whether they had COPD at the final examination, and we categorized them in one of the four trajectories described above.

LOVELACE SMOKERS COHORT (LSC)

The LSC as it relates to this article is described in the Supplementary Appendix. A total of 1553 persons in the LSC who had undergone at least two spirometry tests were included in the current analysis. Decline in FEV_1 was calculated as the slope defined by the first and last data points over all visits. For combined analyses with the FOC and the CCHS, we identified a subgroup of 163 persons who had similar characteristics to patients enrolled in most COPD trials with GOLD grade 2 or higher COPD and an age of 50 to 65 years at the final examination.

STATISTICAL ANALYSIS

We analyzed the combined rate of decline in FEV_1 among the 495 current or former smokers (187 from the FOC, 145 from the CCHS, and 163 from the LSC) who were 50 to 65 years of age and had GOLD grade 2 or higher COPD at the final examination. We report the observed decline in FEV_1 in subgroups defined according to the baseline level of FEV_1 and subsequent annualized decline in FEV_1 . The latter was based on prebronchodilator FEV_1 values and was calculated as the absolute difference in milliliters between FEV_1 values at the two examinations with the longest interval between them. We compared the proportion of persons with declines in FEV_1 of more than 1, 2, or 3 standard deviations (z scores) above the mean decline among persons who had never smoked in the FOC and the CCHS and among former smokers in the LSC. The three cohorts had different mean declines in FEV_1 , but z scores from each cohort made it possible to use a common threshold (e.g., z score >1) to define rapid decline in FEV_1 in the combined analysis. In addition to using z scores, we also used threshold values previously reported in the literature to classify the decline in FEV_1 as “rapid” if the annualized average decline was at least 40 ml per year and “normal” if the annual-

ized average decline was less than 40 ml per year.^{14,25}

We performed a combined analysis of 1622 participants in the FOC and 1242 participants in the CCHS who were younger than 40 years of age at baseline and who also underwent spirometry 10 to 27 years after joining their respective cohorts. In the main analysis, we defined normal or low lung function in early adulthood according to baseline FEV_1 ($\geq 80\%$ or $<80\%$ of the predicted value). The presence or absence of GOLD grade 2 or higher COPD at the final spirometric measurement was the second measure used to define the four trajectories. We report the distribution of participants in these trajectories and compared their characteristics and decline in FEV_1 . Because the assignment to the trajectory categories required attendance at the first and last examinations, the persons who did not attend the last examination, because of death or loss to follow-up, could not be included in the analysis. We also performed a multivariable logistic-regression analysis with incident COPD as the outcome, as described in detail in the Supplementary Appendix.

To estimate the influence of several potential confounders, we performed a number of additional analyses. First, to estimate a potential selection bias, we performed an analysis of hospital admissions for respiratory diseases, admissions for COPD, and survival in the 844 persons participating in the CCHS who attended the first examination in 1976–1978 but did not attend the final examination in 2001–2003 because of death, emigration, or loss to follow-up. These persons could not be assigned to the trajectory category because of the lack of data on final spirometry, but they could be categorized according to their FEV_1 at the baseline examination: less than 80% of the predicted value (305) or at least 80% of the predicted value (539).

Second, to estimate the way in which regression to the mean affected the observed declines in FEV_1 , we analyzed the decline in FEV_1 in the four conceptual trajectory categories using an alternative baseline FEV_1 measurement instead of the measurement from the first examination, which had been used to define these trajectories. We used data from 1091 persons in the CCHS who, in addition to attending the first examination (conducted in 1976–1978) and the fourth examination (conducted in 2001–2003), also attended the second examination in 1981–1983. For these

persons, we compared the declines between the first and fourth examinations (average interval, 25 years) with those between the second and fourth examinations (average interval, 20 years).

Third, we performed a sensitivity analysis using two alternative thresholds to define normal and low maximally attained lung function in the FOC and the CCHS ($FEV_1 \geq 85\%$ and $<85\%$ of the predicted value and $FEV_1 \geq 75\%$ and $<75\%$ of the predicted value). This analysis investigated the effect of the dichotomization on the distribution of participants in the various trajectories.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS IN THE THREE COHORTS

At cohort inception, LSC participants were, on average, 20 years older than the participants in the the FOC and the CCHS (Table 1). In all the cohorts, regardless of the initial FEV_1 , the annual decline in FEV_1 was steepest among persons in whom COPD developed. The highest absolute declines were observed in the CCHS and in the LSC, but when the declines in FEV_1 were compared according to the z scores within each cohort, the persons in the CCHS and the FOC had the greatest declines, a finding that is compatible with the high prevalence of continuous smoking in these cohorts.

RATE OF DECLINE IN FEV_1 AMONG PERSONS IN WHOM COPD DEVELOPED

Table 2 shows the characteristics of the participants who had ever smoked and who had GOLD grade 2 or higher COPD and were 50 to 65 years of age at the final examination, stratified according to their baseline FEV_1 (percentage of the predicted value). The baseline FEV_1 was at least 80% of the predicted value in 20% of the LSC participants, in 44% of the FOC participants, in 49% of the CCHS participants, and in 38% of the participants in the three cohorts combined. In all the cohorts, participants with a baseline FEV_1 of less than 80% of the predicted value had had a slightly higher cumulative exposure to tobacco before the baseline examination than those with an FEV_1 above that threshold, but this difference was not significant. Among persons with COPD at the final examination, the observed decline in FEV_1 and the proportion with a rapid decline in FEV_1 (defined as >2 or >3 SD [z score >2 or

z score >3]) were significantly greater among participants with a baseline FEV_1 of at least 80% of the predicted value than among those with a lower baseline FEV_1 (Table 2). The results of the multivariable logistic-regression analysis with incident COPD at the final examination as the main outcome are presented in Tables S1 and S2 in the Supplementary Appendix.

FEV_1 TRAJECTORIES

Table 3 shows the distribution in the four FEV_1 trajectory categories of the 1622 participants in the FOC and the 1242 participants in the CCHS who underwent spirometry before 40 years of age. Continuous smoking and an early age at the start of smoking were significantly more prevalent among the participants in the trajectories leading to COPD (trajectory 3 and trajectory 4) than among the participants in the trajectories not leading to COPD (trajectory 1 and trajectory 2). After an average observation time of 22 years, 332 persons — 12% of the 2864 participants included in this analysis — had airflow limitation fulfilling the criterion of GOLD grade 2 or higher COPD. Of these 332 persons with COPD, 158 had had normal baseline FEV_1 , which constitutes 7% of the 2207 persons with normal FEV_1 at baseline, whereas 174 had had low baseline FEV_1 , which constitutes 26% of the 657 persons with low baseline FEV_1 ($P<0.001$ for the comparison between participants with an $FEV_1 \geq 80\%$ of the predicted value at baseline and those with an $FEV_1 <80\%$ of the predicted value). Thus, 48% of the 332 persons with COPD at the final examination followed the trajectory from normal baseline FEV_1 to COPD, with an average decline in FEV_1 of 53 ml per year (trajectory 3 in Table 3, and Fig. S4 in the Supplementary Appendix), whereas 52% followed the FEV_1 trajectory from low maximally attained lung function ($FEV_1 <80\%$) at baseline to COPD, with a significantly smaller decline in FEV_1 of 27 ml per year ($P<0.001$) (trajectory 4 in Table 3, and Fig. S4 in the Supplementary Appendix). As seen in Figure 1, the distribution of the observed declines in FEV_1 in the four trajectory categories showed substantial variability and overlap.

Among the 2864 participants in the FOC and the CCHS who underwent spirometry before 40 years of age, 812 reported at both the baseline examination and the final examination that they had never smoked. The average decline in FEV_1

Table 1. Characteristics of Participants 50 to 65 Years of Age with COPD at the Final Examination and All Participants with at Least Two FEV₁ Measurements in the Three Cohorts.*

Characteristic	Lovelace Smokers Cohort		Framingham Offspring Cohort		Copenhagen City Heart Study	
	Participants with COPD at Final Examination (N=163)	All Participants Included in Analyses (N=1553)	Participants with COPD at Final Examination (N=187)	All Participants Included in Analyses (N=1622)	Participants with COPD at Final Examination (N=145)	All Participants Included in Analyses (N=1242)
At baseline examination						
Male sex — no. (%)	39 (24)	336 (22)	97 (52)	765 (47)	83 (57)	587 (47)
Age — yr						
Mean	56±5	56±9	34±4	33±4	36±4	33±5
Range	41–64	31–75	25–40	24–40	25–40	21–40
FEV ₁						
Mean — liters	2.0±0.6	2.5±0.8	2.9±0.7	3.3±0.8	3.1±0.8	3.4±0.9
% of predicted value	66±17	85±19	77±13	89±13	79±15	88±14
Smoking history — pack-yr	49±22	40±21	20±11	16±12	17±9	8±10
Current smoker — no./total no. (%)	104/163 (64)	847/1553 (55)	157/187 (84)	714/1618 (44)	139/144 (97)	697/1239 (56)
FEV ₁ :FVC						
Mean — %	62±5	72±10	81±10	86±9	78±10	83±9
<0.70 — no. (%)	116 (71)	318 (20)	24 (13)	78 (5)	25 (17)	68 (5)
At final examination						
Duration of follow-up — yr						
Mean	4±2	5±2	21±2	21±2	23±4	25±0.4
Range	1–10	1–10	10–27	10–27	14–27	24–27
FEV ₁						
Mean — liters	1.8±0.6	2.5±0.8	2.2±0.5	2.9±0.7	1.9±0.6	2.8±0.8
% of predicted value	63±16	87±20	68±11	91±15	62±15	92±18
Smoking history — pack-yr	49±22	40±21	34±20	24±19	42±21	21±24
Current smoker — no./total no. (%)	35/163 (21)	174/1553 (11)	87/187 (47)	321/1622 (20)	107/142 (75)	448/1220 (37)
FEV ₁ :FVC						
Mean — %	56±10	68±11	63±7	74±7	62±8	76±7
<0.70 — no. (%)	163 (100)	383 (25)	187 (100)	377 (23)	145 (100)	202 (16)
Decline in FEV ₁						
Mean — ml/yr	51±146	19±97	34±22	20±20	51±29	25±23
≥40 ml/yr — no. (%)	81 (50)	476 (31)	60 (32)	180 (11)	95 (66)	258 (21)
z score — no. (%)†						
>1	32 (20)	168 (11)	73 (39)	254 (16)	99 (68)	279 (22)
>2	15 (9)	55 (4)	29 (16)	53 (3)	55 (38)	90 (7)
>3	6 (4)	26 (2)	8 (4)	11 (1)	23 (16)	26 (2)

* Plus–minus values are means ±SD. Chronic obstructive pulmonary disease (COPD) was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹ grading system as grade 2 or higher COPD (a ratio of forced expiratory volume in 1 second [FEV₁] to forced vital capacity [FVC] of <0.70 and an FEV₁ of <80% of the predicted value, with the use of the prediction equations from the National Health and Nutrition Examination Survey for the Lovelace Smokers Cohort and the Framingham Offspring Cohort and local prediction equations for the Copenhagen City Heart Study^{23,24}).

† The z scores are defined according to internal controls in each cohort and describe the decline in FEV₁ 1, 2, and 3 standard deviations above the observed mean decline among former smokers in the Lovelace Smokers Cohort and among those who have never smoked in the Framingham Offspring Cohort and the Copenhagen City Heart Study.

Table 2. Characteristics of Participants 50 to 65 Years of Age Who Had COPD at the Final Examination, Stratified According to the Percentage of Predicted FEV₁ at the Baseline Examination.*

Characteristic	Lovelace Smokers Cohort (N = 163)	Framingham Offspring Cohort (N = 187)	Copenhagen City Heart Study (N = 145)	Combined Cohorts (N = 495)
At baseline examination				
Male sex — no. (%)	8 (25)	42 (51)	47 (66)	97 (52)
Age — yr	54±6	34±4	36±4	38±9
FEV ₁				
Mean — liters	2.6±0.6	3.3±0.6	3.6±0.7	3.3±0.7
% of predicted value	87±6	88±7	91±9	89±8
Smoking status — no./total no. (%)				
Never smoked‡	0/32	1/83 (1)	0/71	1/186 (1)
Former smoker	9/32 (28)	13/83 (16)	3/71 (4)	25/186 (13)
Current smoker	23/32 (72)	69/83 (83)	68/71 (96)	160/186 (86)
Smoking history — pack-yr	47±22	18±9	16±8	22±17
FEV ₁ :FVC — %	72±5	85±7	82±8	82±8
At final examination				
FEV ₁				
Mean — liters	2.1±0.5	2.3±0.5	2.1±0.6	2.2±0.5
% of predicted value	74±8	72±8	65±12	70±10
Smoking history — pack-yr	47±22	34±19	42±20	38±21
Current smoker — no./total no. (%)	7/32 (22)	42/83 (51)	53/70 (76)	102/185 (55)
FEV ₁ :FVC — %	62±6	64±5	62±7	63±6
Decline in FEV ₁				
Mean — ml/yr	150±131	46±18	67±26	72±68
≥40 ml/yr — no. (%)	29 (91)	44 (53)	65 (92)	138 (74)
z score — no. (%)¶				
>1	15 (47)	52 (63)	67 (94)	134 (72)
>2	9 (28)	22 (27)	44 (62)	75 (40)
>3	5 (16)	7 (8)	20 (28)	32 (17)

* Plus-minus values are means ±SD. COPD was defined as GOLD grade 2 or higher COPD.

† The percentage in brackets is the percentage of the total number of participants in the cohort.

‡ Six participants in the Framingham Offspring Cohort who had never smoked at the baseline examination started to smoke before the final examination.

§ P<0.001 for the comparison between the subgroup with a baseline FEV₁ of less than 80% of the predicted value and the subgroup with a baseline level of at least 80% of the predicted value. ¶ The z scores are defined according to internal controls in each cohort and describe the decline in FEV₁ 1, 2, and 3 standard deviations above the observed mean decline among former smokers in the Lovelace Smokers Cohort and among those who have never smoked in the Framingham Offspring Cohort and the Copenhagen City Heart Study.|| P<0.05 for the comparison between the subgroup with a baseline FEV₁ of less than 80% of the predicted value and the subgroup with a baseline level of at least 80% of the predicted value.

among these participants was 18 ml per year. Only 27 of them had COPD at the final examination, which constitutes 8% of all persons with COPD. Of the persons who had never smoked and who had COPD at the last study visit, 7 (26%) followed trajectory 3, whereas 20 (74%) followed the trajectory from low maximally attained lung function ($FEV_1 < 80\%$) at baseline to COPD (trajectory 4). The average decline in FEV_1 among these persons was 37 ml per year and 23 ml per year, respectively.

The analysis of persons who attended the baseline examination of the CCHS but not the final examination showed that participants with an FEV_1 of less than 80% of the predicted value had a significantly greater risk of hospital admissions for respiratory diseases than did those with an FEV_1 of at least 80% of the predicted value (25% vs. 18%, $P=0.02$), as well as a significantly greater corresponding risk of admissions for COPD (9% vs. 4%, $P=0.008$) and of death (32% vs. 25%, $P=0.02$). Additional analyses of the decline in FEV_1 among those who did not attend the final, fourth examination of the CCHS showed a greater decline in FEV_1 in this group between the first and the second examination and between the first and the third examination than in the group of participants who attended the fourth examination (Table S3 in the Supplementary Appendix).

Analysis of the decline in FEV_1 between the second and the fourth examination of the CCHS (average interval, 20 years) that was conducted to investigate the effect of regression toward the mean showed a significantly greater decline in FEV_1 among the persons in trajectory 3 than among those in trajectory 4 (decline of 60 ml per year in trajectory 3 vs. 37 ml per year in trajectory 4, $P<0.001$) (Table S4 in the Supplementary Appendix). A corresponding analysis of the decline in FEV_1 between the second and the third examination (average interval, 11 years) showed a similar pattern, with a greater decline among those in trajectory 3 than among those in trajectory 4, but the difference between these two declines was not significant (27 ml per year and 17 ml per year, respectively; $P=0.37$).

Finally, we observed that the choice of the threshold value defining a normal FEV_1 level at the first examination of the FOC and the CCHS substantially affected the distribution of the participants in the two trajectory categories leading

to COPD. When we used a cutoff value of 85% of the predicted FEV_1 to define a normal FEV_1 in early adulthood, we found that 232 of the 332 participants (70%) who presented with COPD at the final examination were considered to be in the trajectory 4 category (low maximally attained lung function at baseline and COPD at final examination). In contrast, when we used a cutoff value of 75% of the predicted FEV_1 to define a normal FEV_1 , only 126 of the 332 persons (38%) with COPD could be assigned to trajectory 4.

DISCUSSION

The main new finding of this study is that the lung-function value reached in early adulthood seems to be important with respect to the diagnosis of COPD later in life. Our data suggest that approximately half the persons presenting with airflow limitation followed the paradigm that implied a rapid decline in FEV_1 from a normal level of lung function in early adulthood, whereas the other half had a rather normal decline in FEV_1 but started from a low initial value of FEV_1 .

We acknowledge that dichotomizing persons with COPD into two specific trajectories, although conceptually helpful for understanding the natural history of the disease, is artificial. Instead, there exists a wide range of individual trajectories, such that both low maximally attained lung function in early adulthood and a subsequent rapid decline may contribute to COPD.²¹ In addition, it is possible that a single person over time can have periods of rapid decline in FEV_1 followed by periods when the decline is normal or almost normal. If the period of fast decline had already taken place in early adulthood, this person would have been wrongly assigned to the trajectory category of low maximally attained lung function (trajectory 4) in our study, even though a rapid decline in FEV_1 was the main mechanism behind this person's COPD. In addition, our sensitivity analyses showed that the estimation of the contribution of these two conceptual trajectories was strongly affected by the cutoff values chosen for the definition of a normal maximally attained FEV_1 . Nevertheless, even though we cannot precisely estimate the contribution of the trajectory of low maximally attained lung function (trajectory 4 in Fig. 1) to COPD using our study design, our results suggest that this contribution may be substantial

Table 3. General Characteristics and Lung Function of the Participants in the Framingham Offspring Cohort and Copenhagen City Heart Study Combined, According to the Four Lung-Function Trajectories Defined by the Percentage of Predicted FEV₁ at the Baseline Examination and the Presence or Absence of COPD at the Final Examination.*

Characteristic	Trajectory 1 (N = 2049 [72%]) [†]	Trajectory 2 (N = 483 [17%]) [†]	Trajectory 3 (N = 158 [6%]) [†]	Trajectory 4 (N = 174 [6%]) [†]	P Value [‡]			
					Trajectory 1 vs. Trajectory 2	Trajectory 3 vs. Trajectory 4	Trajectory 1 vs. Trajectory 3	Trajectory 2 vs. Trajectory 4
At baseline examination								
Male sex — no. (%)	991 (48)	188 (39)	86 (54)	87 (50)	<0.001	0.44	0.16	0.01
Age — yr	33±5	33±5	34±4	34±5	0.02	0.66	0.01	0.004
FEV ₁								
Mean — liters	3.6±0.8	2.6±0.6	3.4±0.7	2.6±0.6	<0.001	<0.001	0.004	0.78
% of predicted value	95±9	71±9	89±8	69±9	<0.001	<0.001	<0.001	0.002
FEV ₁ :FVC — %	87±7	79±12	85±8	77±9	<0.001	<0.001	<0.001	0.04
Smoking status — no./total no. (%)					0.11	0.03	<0.001	<0.001
Never smoked	740/2043 (36)	153/483 (32)	9/158 (6)	25/173 (14)				
Former smoker	398/2043 (19)	92/483 (19)	16/158 (10)	13/173 (8)				
Current smoker	905/2043 (44)	238/483 (49)	133/158 (84)	135/173 (78)				
Start of smoking before 14 yr of age — no./total no. (%)	61/1253 (5)	11/320 (3)	14/148 (9)	16/146 (11)	0.37	0.70	0.03	0.002
Asthma — no. (%) [§]	29 (1)	8 (2)	6 (4)	20 (11)	0.68	0.01	0.03	<0.001
At final examination								
FEV ₁								
Mean — liters	3.1±0.7	2.6±0.6	2.2±0.6	2.0±0.6	<0.001	0.004	<0.001	<0.001
% of predicted value	97±12	85±13	69±11	63±12	<0.001	<0.001	<0.001	<0.001
Smoking history — pack-yr	19±21	22±22	37±21	37±24	0.04	0.98	<0.001	<0.001
Current smoker — no./total no. (%)	472/2032 (23)	129/480 (27)	89/158 (56)	79/172 (46)	0.10	0.06	<0.001	<0.001
Asthma — no./total no. (%) [§]	38/862 (4)	20/254 (8)	14/70 (20)	9/55 (16)	0.04	0.65	<0.001	0.07
FEV ₁ :FVC — %	77±5	76±5	63±6	62±7	0.38	0.11	<0.001	<0.001
Decline in FEV ₁								
Mean — ml/yr	24±17	2±22	53±21	27±18	<0.001	<0.001	<0.001	<0.001
≥40 ml/yr — no (%)	292 (14)	6 (1)	107 (68)	33 (19)	<0.001	<0.001	<0.001	<0.001
z score — no. (%) [¶]								
>1	367 (18)	7 (1)	118 (75)	41 (24)	<0.001	<0.001	<0.001	<0.001
>2	70 (3)	2 (<0.5)	60 (38)	11 (6)	<0.001	<0.001	<0.001	<0.001
>3	15 (1)	0	21 (13)	1 (1)	0.09	<0.001	<0.001	0.26

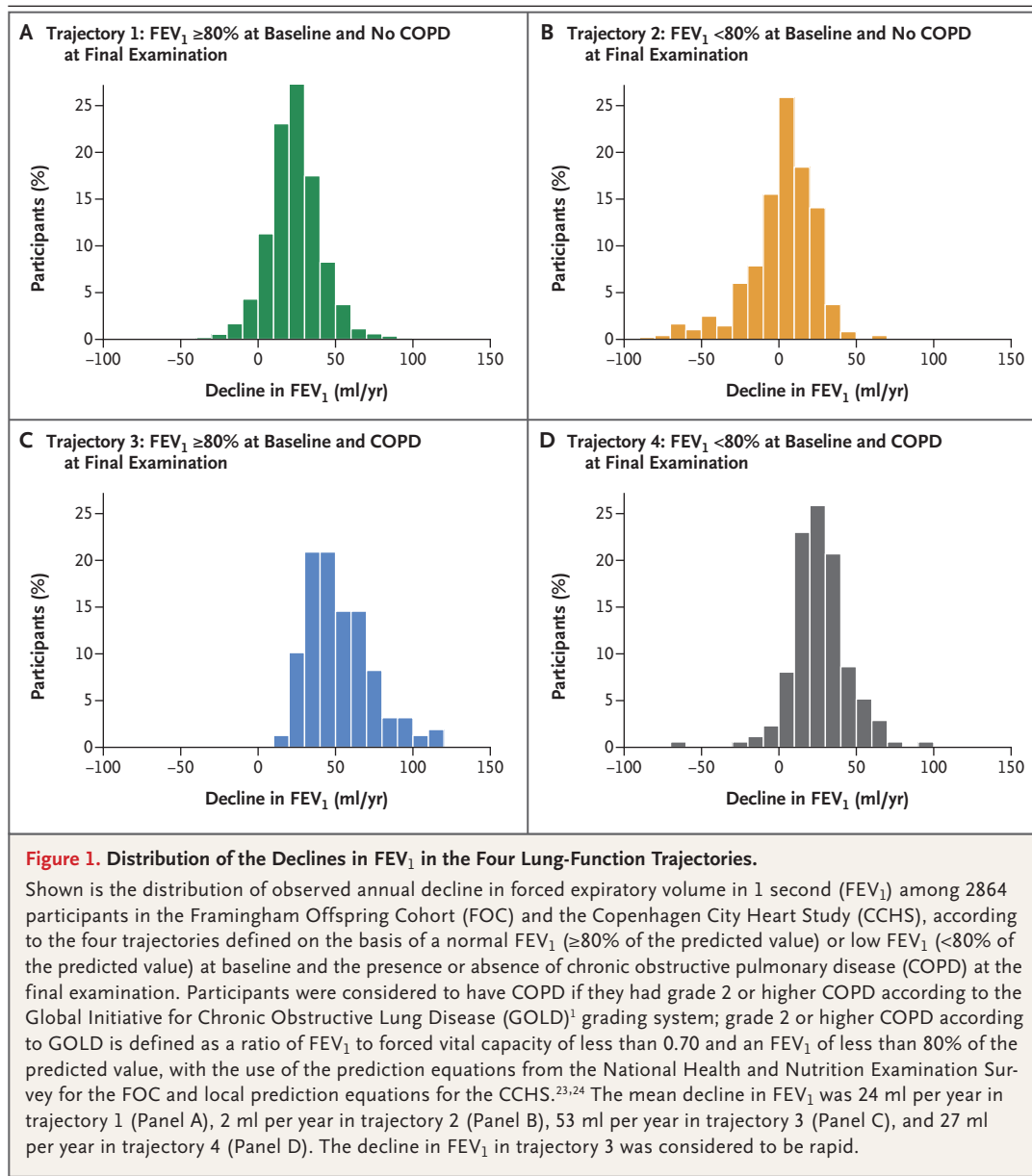
* Trajectory 1 was defined as an FEV₁ of at least 80% of the predicted value at the baseline examination and no COPD at the final examination, trajectory 2 as an FEV₁ of less than 80% of the predicted value at baseline and no COPD at the final examination, trajectory 3 as an FEV₁ of at least 80% of the predicted value at baseline and COPD at the final examination, and trajectory 4 as an FEV₁ of less than 80% of the predicted value at baseline and COPD at the final examination. COPD was defined as GOLD grade 2 or higher COPD. Continuous variables are presented as means ±SD.

[†] The percentage in brackets is the percentage of the 2864 participants included in the analysis.

[‡] P values are based on Fisher's exact test for categorical variables and on analysis of variance for continuous variables.

[§] Asthma was defined according to an affirmative answer to the question "Do you have asthma?" Data on asthma at the final examination were available for the Copenhagen City Heart Study only.

[¶] The z scores are defined according to internal controls in each cohort and describe the decline in FEV₁ 1, 2, and 3 standard deviations above the observed mean decline among those who have never smoked in the Framingham Offspring Cohort and the Copenhagen City Heart Study.



and that populations of patients with COPD comprise persons with different rates of decline in FEV_1 (Fig. 1). This observation is in accord with previous studies and suggests that a substantial proportion of patients with COPD may not have had a rapid decline in FEV_1 , which for decades has been regarded as the hallmark of COPD.^{2,3,12-14}

Persons with a baseline FEV_1 of less than 80% of the predicted value had a risk of COPD in midlife that was more than 3 times as high as the risk among those with a higher baseline FEV_1 (26%

vs. 7%). Studies involving children and young adults have shown that the most important determinant of maximally attained lung function later in life was the lung-function value at a younger age.²⁶⁻²⁹ Svanes et al. observed that childhood risk factors such as maternal smoking, childhood respiratory infections, and childhood asthma were strongly related to the development of COPD in young adults.³⁰ Nevertheless, although our results highlight the important role of maximally attained lung function in early adulthood,

they also indicate that COPD does not develop in approximately 75% of persons with a low maximally attained FEV₁.

Our study has a number of strengths and limitations. Among the former is the replication of findings in large and independent cohorts. The long observation periods in the FOC and the CCHS, as compared with the shorter observation periods in other studies, allowed robust estimates of FEV₁, because the annual decline in FEV₁ was small relative to the high measurement error in the assessment of FEV₁.^{13,31}

The two major potential limitations of our study are the selection bias and the regression to the mean for the estimates of decline in FEV₁. The long observation period in the FOC and the CCHS introduced a selection of healthy persons, which may have resulted in underestimation of lung-function decline. In line with this, we observed that the persons who did not attend the final, fourth examination of the CCHS, because of either death or loss to follow-up, had a greater decline in FEV₁ between the first and the second examination and between the first and the third examination than did the persons who attended the fourth examination (Table S3 in the Supplementary Appendix). Previous analyses of the CCHS indicated that a rapid decline in FEV₁ was associated with higher mortality.³² However, because the persons included in the FOC and CCHS analyses were quite young at baseline, this survivor bias is likely to be smaller than that in most COPD intervention trials, which have enrolled much older patients.^{12,13}

The use of baseline FEV₁ measurement both to classify the participants as having a normal or low initial FEV₁ value and to estimate the subsequent decline in FEV₁ introduced potential problems with respect to regression to the mean.³³ Persons with a higher initial FEV₁ would tend to have a more rapid observed decline in FEV₁ even if there was no association between these two. In contrast, among persons with a low initial FEV₁, regression to the mean would lead to a small decline in FEV₁. Therefore, it would have been preferable to perform multiple FEV₁ measurements at the beginning of the studies to define the true FEV₁ baseline more precisely, as is often done in interventional trials, but we did not have such data. Although regression to the mean undoubtedly affects our findings, the anal-

yses of decline in FEV₁ starting from the second rather than the first examination of the CCHS showed a consistent pattern of a greater decline among persons in trajectory 3 than among those in trajectory 4 (Table S4 in the Supplementary Appendix). This supports our main conclusions and indicates that regression to the mean is not the only mechanism responsible for our findings.

Still another potential methodologic weakness of the FOC and the CCHS concerns the age of the participants at baseline (approximately 35 years). Although this age corresponds to the last part of the “plateau phase” of FEV₁ (i.e., the age at which maximum lung function is attained before the inevitable decline with aging begins to take place), it would have been preferable if the participants had undergone spirometry in their mid-20s, so that the potential influence of an incipient decline in FEV₁ during early adulthood could be avoided.³⁴⁻³⁷

Finally, the appropriateness of the nomenclature used in the present article (i.e., COPD or no COPD) could be misleading, because not all people with a ratio of FEV₁ to FVC of less than 0.70 and an FEV₁ of less than 80% of the predicted value have COPD. We chose the term COPD because it is in common use, but the broader descriptive term “airflow limitation” could be considered by some to be more correct.

In conclusion, the results of this study suggest that the classic trajectory of an accelerated decline in FEV₁ from a normal level is not an obligate feature of COPD and that a substantial proportion of the persons in whom COPD develops have a low FEV₁ level in early adulthood.

The views expressed in this article do not necessarily reflect the opinions or views of the Framingham Offspring Study or the National Heart, Lung, and Blood Institute (NHLBI).

Presented in part at the annual congress of the European Respiratory Society, Munich, Germany, September 6–10, 2014.

The Copenhagen City Heart Study was supported by Glaxo-SmithKline (grant eTrack no. 201589), the Capital Region of Copenhagen, the Danish Heart Foundation, the Danish Lung Foundation, and the Velux Foundation. The funding sources had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript. The Lovelace Smokers Cohort was supported by the State of New Mexico (appropriation from the Tobacco Settlement Fund) and by grants from the National Institutes of Health (RO1s HL068111; ES015482, to Dr. Tesfaigzi; P50HL107165, to Drs. Tesfaigzi and Celli; and K23 HL094531, to Dr. Sood).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the NHLBI for granting access to the Framingham Offspring Cohort database.

APPENDIX

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