The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2015 VOL. 373 NO. 2

Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease

Peter Lange, M.D., Dr. Med. Sc., Bartolome Celli, M.D., Alvar Agustí, M.D., Ph.D., Gorm Boje Jensen, M.D., Dr. Med. Sc., Miguel Divo, M.D., Rosa Faner, Ph.D., Stefano Guerra, M.D., Ph.D., Jacob Louis Marott, M.Sc., Fernando D. Martinez, M.D., Pablo Martinez-Camblor, Ph.D., Paula Meek, R.N., Ph.D., Caroline A. Owen, M.D., Ph.D., Hans Petersen, Ph.D, Victor Pinto-Plata, M.D., Peter Schnohr, M.D., Dr. Med. Sc., Akshay Sood, M.D., M.P.H., Joan B. Soriano, M.D., Yohannes Tesfaigzi, Ph.D., and Jørgen Vestbo, M.D., Dr. Med. Sc.

ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is thought to result from an accelerated decline in forced expiratory volume in 1 second (FEV_1) over time. Yet it is possible that a normal decline in FEV_1 could also lead to COPD in persons whose maximally attained FEV_1 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 (FEV_1 ≥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 FEV_1 over time among the participants according to their FEV_1 at cohort inception and COPD status at study end.

RESULTS

Among 657 persons who had an FEV_1 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 FEV_1 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 FEV_1 before 40 years of age and had a rapid decline in FEV_1 thereafter, with a mean (±SD) decline of 53±21 ml per year. The remaining half had had a low FEV_1 in early adulthood and a subsequent mean decline in FEV_1 of 27±18 ml per year ($P<0.001$), despite similar smoking exposure.

CONCLUSIONS

Our study suggests that low FEV_1 in early adulthood is important in the genesis of COPD and that accelerated decline in FEV_1 is not an obligate feature of COPD. (Funded by an unrestricted grant from GlaxoSmithKline and others.)

The authors' affiliations and their membership in the three study cohorts are listed in the Appendix. Address reprint requests to Dr. Lange at the Institute of Public Health, Section of Social Medicine, Copenhagen University, P.O. Box 2099, Øster Farimagsgade 5, DK-1014 Copenhagen K, Denmark, or at peter.lange@sund.ku.dk.

Drs. Lange, Celli, and Agustí contributed equally to this article.

N Engl J Med 2015;373:111-22.
DOI: 10.1056/NEJMoa1411532

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 (FEV_1). Subsequent population studies supported this paradigm and led to therapeutic trials aimed at reducing the rapid decline in FEV_1.[4-11] Surprisingly, the observed declines in FEV_1 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 FEV_1 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 FEV_1 is within the normal range.[17-21] In fact, this alternative course was already suggested by Fletcher and Peto[3] 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 FEV_1 (≥80% of the predicted value [normal FEV_1] or <80% of the predicted value [low FEV_1]) at cohort inception and the presence or absence of COPD at the final cohort study visit to define four trajectories: normal FEV_1 at cohort inception and no COPD at the final visit (trajectory 1), low FEV_1 at cohort inception and no COPD at the final visit (trajectory 2), normal FEV_1 at cohort inception and COPD at the final visit (trajectory 3), and low FEV_1 at cohort inception and COPD at the final visit (trajectory 4). We then determined the extent to which the rate of decline in FEV_1 was an explanatory variable for a diagnosis of COPD at study end for a patient with a normal initial FEV_1 or a low initial FEV_1 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 FEV_1 to forced vital capacity (FVC) of less than 0.70 and an FEV_1 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 FEV_1 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 FEV_1 was calculated for persons who had had an FEV_1 of at least 80% of the predicted value on baseline spirometry and for those who had had an FEV_1 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 FEV_1 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 annualized 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 (≥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 ≥85% and <85% of the predicted value and FEV_1 ≥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 ≥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 FEV_1 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 [FEV_1] to forced vital capacity [FVC] of <0.70 and an FEV_1 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 FEV_1 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 FEV_1 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)	
	≥80% of Predicted FEV_1 (N=32 [20%])†	<80% of Predicted FEV_1 (N=131 [80%])†	≥80% of Predicted FEV_1 (N=83 [44%])†	<80% of Predicted FEV_1 (N=104 [56%])†	≥80% of Predicted FEV_1 (N=71 [49%])†	<80% of Predicted FEV_1 (N=74 [51%])†	≥80% of Predicted FEV_1 (N=186 [38%])†	<80% of Predicted FEV_1 (N=309 [62%])†
At baseline examination								
Male sex — no. (%)	8 (25)	31 (24)	42 (51)	55 (53)	47 (66)	36 (49)	97 (52)	122 (39)
Age — yr	54±6	56±5	34±4	34±4	36±4	36±4	38±9	44±12
FEV_1								
Mean — liters	2.6±0.6	1.8±0.5	3.3±0.6	2.6±0.6	3.6±0.7	2.6±0.6	3.3±0.7	2.3±0.6
% of predicted value	87±6	61±15	88±7	69±10	91±9	68±11	89±8	65±13
Smoking status — no./total no. (%)								
Never smoked‡	0/32	0/131	1/83 (1)	5/104 (5)	0/71	0/73	1/186 (1)	5/308 (2)
Former smoker	9/32 (28)	50/131 (38)	13/83 (16)	11/104 (11)	3/71 (4)	2/73 (3)	25/186 (13)	63/308 (20)
Current smoker	23/32 (72)	81/131 (62)	69/83 (83)	88/104 (85)	68/71 (96)	71/73 (97)	160/186 (86)	240/308 (78)
Smoking history — pack-yr	47±22	50±23	18±9	21±12	16±8	18±10	22±17	32±23
FEV_1:FVC — %	72±5	59±10	85±7	77±10	82±8	74±11	82±8	69±13
At final examination								
FEV_1								
Mean — liters	2.1±0.5	1.7±0.6	2.3±0.5	2.1±0.6	2.1±0.6	1.8±0.6	2.2±0.5	1.9±0.6
% of predicted value	74±8	61±16	72±8	64±12	65±12	58±16	70±10	61±15
Smoking history — pack-yr	47±22	50±23	34±19	35±21	42±20	42±22	38±21	42±24
Current smoker — no./total no. (%)	7/32 (22)	28/131 (21)	42/83 (51)	45/104 (43)	53/70 (76)	54/72 (75)	102/185 (55)	127/307 (41)
FEV_1:FVC — %	62±6	55±10	64±5	61±8	62±7	61±9	63±6	59±10
Decline in FEV_1								
Mean — ml/yr	150±131	27±139§	46±18	24±19§	67±26	37±23§	72±68	28±92§
≥40 ml/yr — no. (%)	29 (91)	52 (40)§	44 (53)	16 (15)§	65 (92)	30 (41)§	138 (74)	98 (32)§
z score — no. (%)¶								
>1	15 (47)	17 (13)§	52 (63)	21 (20)§	67 (94)	32 (43)‖	134 (72)	70 (23)§
>2	9 (28)	6 (5)§	22 (27)	7 (7)§	44 (62)	11 (15)§	75 (40)	24 (8)§
>3	5 (16)	1 (1)§	7 (8)	1 (1)‖	20 (28)	3 (4)§	32 (17)	5 (2)§

* 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 FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 of at least 80% of the predicted value at the baseline examination and no COPD at the final examination, trajectory 2 as an FEV_1 of less than 80% of the predicted value at baseline and no COPD at the final examination, trajectory 3 as an FEV_1 of at least 80% of the predicted value at baseline and COPD at the final examination, and trajectory 4 as an FEV_1 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 FEV_1 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.

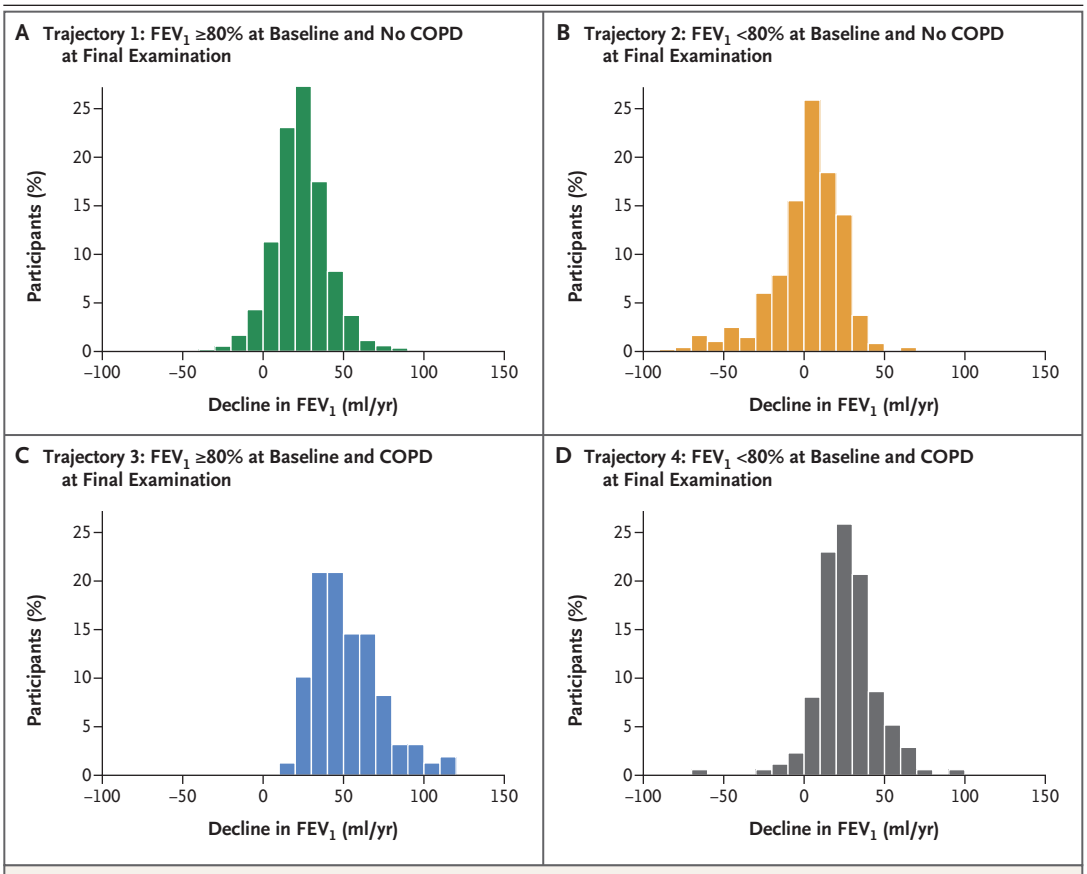

Figure 1. Distribution of the Declines in FEV_1 in the Four Lung-Function Trajectories.

Shown is the distribution of observed annual decline in forced expiratory volume in 1 second (FEV_1) among 2864 participants in the Framingham Offspring Cohort (FOC) and the Copenhagen City Heart Study (CCHS), according to the four trajectories defined on the basis of a normal FEV_1 (≥80% of the predicted value) or low FEV_1 (<80% of the predicted value) at baseline and the presence or absence of chronic obstructive pulmonary disease (COPD) at the final examination. 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 FEV_1 to forced vital capacity of less than 0.70 and an FEV_1 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 FOC and local prediction equations for the CCHS.[23,24] The mean decline in FEV_1 was 24 ml per year in trajectory 1 (Panel A), 2 ml per year in trajectory 2 (Panel B), 53 ml per year in trajectory 3 (Panel C), and 27 ml per year in trajectory 4 (Panel D). The decline in FEV_1 in trajectory 3 was considered to be rapid.

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 FEV_1.

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 FEV_1, because the annual decline in FEV_1 was small relative to the high measurement error in the assessment of FEV_1.[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 FEV_1. 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 FEV_1 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 FEV_1 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 FEV_1 measurement both to classify the participants as having a normal or low initial FEV_1 value and to estimate the subsequent decline in FEV_1 introduced potential problems with respect to regression to the mean.[33] Persons with a higher initial FEV_1 would tend to have a more rapid observed decline in FEV_1 even if there was no association between these two. In contrast, among persons with a low initial FEV_1, regression to the mean would lead to a small decline in FEV_1. Therefore, it would have been preferable to perform multiple FEV_1 measurements at the beginning of the studies to define the true FEV_1 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 analyses of decline in FEV_1 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 FEV_1 (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 FEV_1 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 FEV_1 to FVC of less than 0.70 and an FEV_1 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 FEV_1 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 FEV_1 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 GlaxoSmithKline (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

The authors' affiliations are as follows: the Institute of Public Health, Section of Social Medicine (P.L.), Respiratory Section, Hvidovre Hospital (P.L.), Copenhagen City Heart Study, Frederiksberg Hospital (P.L., G.B.J., J.L.M., P.S.), and the Department of Respiratory Medicine, Gentofte Hospital (J.V.), Copenhagen University, Copenhagen, and University of Southern Denmark, Odense (G.B.J.) — all in Denmark; Brigham and Women's Hospital, Harvard Medical School, Boston (B.C., M.D., C.A.O., V.P.-P.); Servei de Pneumologia, Thorax Institute, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona (A.A.), and Fundació Clínic per a la Recerca Biomèdica (R.F.) — both in Barcelona; Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (A.A., R.F.) and Instituto de Investigación Hospital Universitario de la Princesa, Universidad Autónoma de Madrid (UAM), Cátedra UAM–Linde (J.B.S.) — both in Madrid; Arizona Respiratory Center, University of Arizona, Tucson (S.G., F.D.M.); Universidad Autónoma de Chile, Santiago, Chile (P.M.-C.); University of Colorado, Denver, Denver (P.M.); Lovelace Respiratory Research Institute (H.P., Y.T.) and University of New Mexico (A.S.) — both in Albuquerque; and the Respiratory and Allergy Research Group, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom (J.V.).

The authors constitute the COPD Progression Group. Members of the Copenhagen City Heart Study include Dr. Lange, Mr. Marott, and Drs. Boje Jensen, Schnohr, and Vestbo (Dr. Lange is the responsible author). Members of the Lovelace Smokers Cohort include Drs. Sood, Petersen, Divo, Pinto-Plata, Owen, Guerra, Meek, Martinez, Tesfaigzi, and Celli (Dr. Celli is the responsible author). Members of the Framingham Offspring Cohort include Drs. Agustí, Faner, Celli, Soriano, and Martinez-Camblor (Dr. Agustí is the responsible author).

REFERENCES

1. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.

2. Fletcher CM, Peto R, Tinker CM, Speizer FE. The natural history of chronic bronchitis and emphysema. Oxford, United Kingdom: Oxford University Press, 1976.

3. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1:1645-8.

4. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. JAMA 1994; 272:1497-505.

5. Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999; 353:1819-23.

6. Pauwels RA, Löfdahl C-G, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 1999;340:1948-53.

7. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

8. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000;343:1902-9.

9. Decramer M, Rutten-van Mölken M, Dekhuijzen PNR, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 2005;365:1552-60.

10. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.

11. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332-8.

12. Tantucci C, Modina D. Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis 2012;7:95-9.

13. Tashkin DP. Variations in FEV1 decline over time in chronic obstructive pulmonary disease and its implications. Curr Opin Pulm Med 2013;19:116-24.

14. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184-92.

15. Casanova C, de Torres JP, Aguirre-Jaíme A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med 2011;184: 1015-21.

16. Mohamed Hoesein FA, Zanen P, Boezen HM, et al. Lung function decline in male heavy smokers relates to baseline airflow obstruction severity. Chest 2012; 142:1530-8.

17. Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. Am J Respir Crit Care Med 1996;154: S208-S211.

18. Kerstjens HAM, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax 1997;52:820-7.

19. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med 2013;1:728-42.

20. Sanchez-Salcedo P, Divo M, Casanova C, et al. Disease progression in young patients with COPD: rethinking the Fletcher and Peto model. Eur Respir J 2014;44:324-31.

21. Postma D, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet 2015;385:899-909.

22. Burrows B, Knudson RJ, Lebowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Respir Dis 1977;115:751-60.

23. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.

24. Løkke A, Marott JL, Mortensen J, Nordestgaard BG, Dahl M, Lange P. New Danish reference values for spirometry. Clin Respir J 2012;7:153-67.

25. Petersen H, Sood A, Meek PM, et al. Rapid lung function decline in smokers is a risk factor for COPD and is attenuated by angiotensin-converting enzyme inhibitor use. Chest 2014;145:695-703.

26. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349: 1414-22.

27. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007;370:758-64.

28. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med 2012;185:1183-9.

29. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax 2014;69:805-10.

30. Svanes C, Sunyer J, Plana E, et al.

Early life origins of chronic obstructive pulmonary disease. Thorax 2010;65:14-20.
31. Hnizdo E, Sircar K, Glindmeyer HW, Petsonk EL. Longitudinal limits of normal decline in lung function in an individual. J Occup Environ Med 2006;48:625-34.
32. Baughman P, Marott JL, Lange P, et al. Combined effect of lung function level and decline increases morbidity and mortality risks. Eur J Epidemiol 2012;27:933-43.
33. Bland JM, Altman DG. Some examples of regression towards the mean. BMJ 1994;309:780.
34. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring Cohort. Am J Respir Crit Care Med 2009;180:3-10.
35. Burrows B, Lebowitz MD, Camilli AE, Knudson RJ. Longitudinal changes in forced expiratory volume in one second in adults: methodologic considerations and findings in healthy nonsmokers. Am Rev Respir Dis 1986;133:974-80.
36. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Continuous longitudinal regression equations for pulmonary function measures. Eur Respir J 1992;5:452-62.
37. Kohansal R, Soriano JB, Agusti A. Investigating the natural history of lung function: facts, pitfalls, and opportunities. Chest 2009;135:1330-41.