The Natural History of Chronic Airflow Obstruction Revisited

An Analysis of the Framingham Offspring Cohort

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***Rationale*: Understanding normal lung development and aging in health and disease, both in men and in women, is essential to interpreting any therapeutic intervention.**

***Objectives*: We aimed to describe lung function changes in healthy never-smoking males and females, from adolescence to old age, and to determine the effects of smoking and those derived from quitting.**

***Methods*: Prospective cohort study within all participants of the Framingham Offspring cohort who had two or more valid spirometry measurements during follow-up (n = 4,391; age range at baseline 13 to 71 yr), with a median follow-up time of 23 years.**

***Measurements and Main Results*: To best fit the curves describing FEV_1 changes with age to raw data, we used a generalized additive model with smooth terms and incorporating the subject-specific (longitudinal) random effects. We found that: (*1*) healthy never-smoker females achieve full lung growth earlier than males, and their rate of decline with age was slightly, but not significantly, lower; (*2*) smoking increases the rate of lung function decline, both in males and in females; (*3*) there is a range of susceptibility to the effects of smoking. The presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a group of susceptible smokers; and (*4*) quitting smoking has a beneficial effect at any age, but it is more pronounced in earlier quitters.**

***Conclusions*: Lung function changes from adolescence to old age differ in males and females, smoking has similar deleterious effects in both sexes, and quitting earlier is better.**

Keywords: chronic obstructive pulmonary disease; FEV_1; sex; lung function; natural history

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Determining lung function development, both in health and in disease, remains an important issue, especially to interpret new strategies and drugs targeted to modify the natural history of chronic obstructive pulmonary disease.

What This Study Adds to the Field

Lung function changes from adolescence to old age differ in males and females, smoking has similar deleterious effects in both sexes, and quitting earlier is better.

Chronic obstructive pulmonary disease (COPD) is a major public health problem as it affects 5 to 15% of all adults in industrialized countries, its prevalence increases steeply with age, it affects a growing number of women, and it causes 2.7 million deaths worldwide per year (1, 2).

Tobacco smoking is the main risk factor for COPD, and spirometry is the best tool to diagnose and stage COPD. More than 30 years ago, the UK Medical Research Council (MRC) cohort explored the factors other than smoking that modify lung function decline (3, 4). The MRC was a landmark study, but it has several limitations that are worth noting. First, it did not include women. This is important because the World Health Organization has predicted that a COPD epidemic in females will occur in the next decades (5). Second, the age range of participants (n = 1,136), all of them working men, was 30 to 59 years only, and follow-up time was relatively short (8 yr). Yet, the MRC cohort is often mistaken as representative of the entire human life span. Finally, in the 1960s spirometry was not standardized, and the prevalence of smoking among men was much higher than today. Despite these limitations the so-called Fletcher and Peto diagram (*see* Figure E1 in the online supplement) is widely considered to represent the natural history of COPD (6).

Understanding normal lung development and aging, both in health and disease and in men and women, is considered a research priority in current respiratory medicine (7), and is essential to properly interpret results of eventual therapeutic interventions. It is also important to understand the development of the lungs and the influence of sex.

To overcome these limitations, we recreated the Fletcher and Peto lung function curves using data from the Framingham Offspring cohort (8). It is worth noting that this is a larger cohort that includes males and females, that the age range of participants is much larger (from 13–80 yr), that participants were followed up regularly up to 26 years, and that spirometric measurements were standardized. We used these data to describe lung function changes in healthy never-smoking males and females from adolescence to old age, and to determine the effects of smoking and those derived from quitting. Preliminary results of this research have been presented in abstract form elsewhere (9).

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METHODS

Study Population, Design, and Ethics

The Framingham Offspring cohort was started between 1971 and 1975 and includes 5,124 males and females (8). Participants are the adult children, and their spouses, of the participants in the original Framingham cohort, a seminal study that started in 1948 (10).

The Framingham Offspring participants underwent periodic clinical examinations every 4 years up to exam 7, conducted in 1998. In the analysis presented here, we include data obtained in exam 1 (1971–1975), exam 2 (1979–1982), exam 5 (1991–1995), and exam 6 (1996–1997), all of which had reliable spirometric measurements and relevant clinical information according to internal National Heart, Lung, and Blood Institute–National Institutes of Health standards (10). We included in the analysis all participants with two or more valid spirometry measurements during follow-up (n = 4,391; age range at baseline 13–71 yr). Permission to analyze the Framingham database was obtained from the National Heart, Lung, and Blood Institute–National Institutes of Health according to a prespecified research proposal previously approved by our Institutional Review Board.

Spirometry

Spirometry was performed using a 6L Collins water-sealed bell spirometer connected to an Eagle II microprocessor that provided automatic correction for body temperature, pressure saturated with water vapor conditions, based on calibrations performed daily by technicians. Measurements were obtained with the subject standing and wearing nose clips. Maneuvers were repeated (up to a maximum of 8) until at least three acceptable spirograms were obtained. The largest FVC and the largest FEV_1 from all acceptable maneuvers were selected (10), as per later recommendations (11). No bronchodilator was used in any of the Framingham cohort studies, so all values reported are prebronchodilator (pre-BD).

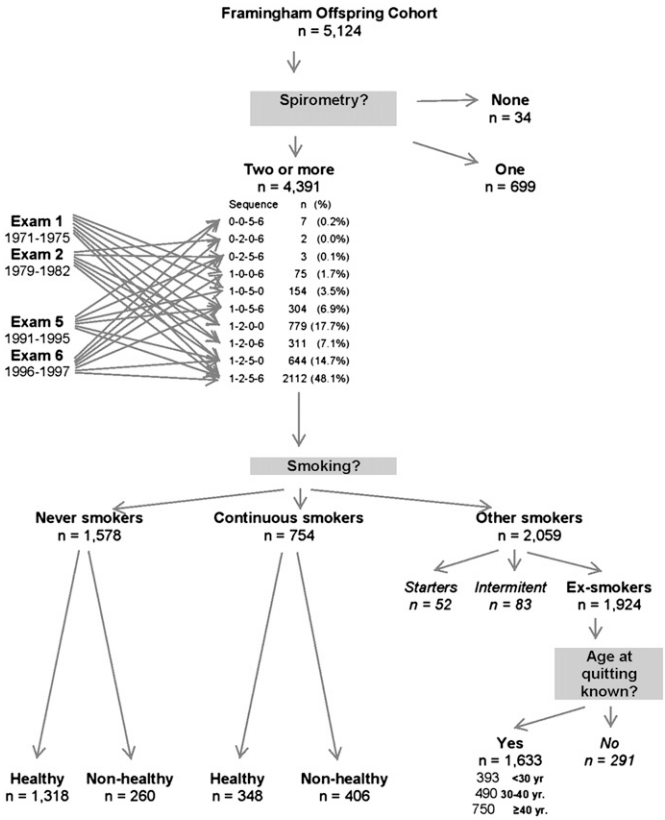

Figure 1. Flow diagram of participants from the Framingham Offspring cohort by available spirometry and smoking information in exams 1, 2, 5, and 6.

Operational Definitions

We considered "never-smokers" those individuals who declared that they never smoked before and during the study, "continuous smokers" those who declared active smoking in all available examinations, and "former smokers" those smokers who declared not smoking during the last year in one of the examinations (10). We did not include in the analysis intermittent smokers. Pack-years were calculated as the number of packs of cigarettes smoked per day times how many years the participant smoked.

We considered "healthy" participants those who reported "No" responses to all questions on dyspnea on exertion, increased dyspnea, nocturnal dyspnea, nocturnal cough or wheezing at exam 1, and/or were never reported by an examiner with a clinical diagnostic impression of asthma, chronic obstructive lung disease, chronic bronchitis, or emphysema during follow-up examinations. By contrast, those fulfilling affirmatively any of these criteria were considered "unhealthy," as per standard published Framingham Original and Offspring cohorts methodology and definitions (10).

We considered airflow obstruction as defined by a pre-BD FEV_1/FVC ratio lower than 0.7 and an FEV_1 value lower than 80% of predicted.

Statistical Analysis

Results are presented as mean ± SD and 95% confidence intervals (95% CI) or percentage, as appropriate. Mean comparisons between groups were analyzed by analysis of variance (followed by *post hoc* test) or Welch's *t* test, as required. To best fit the curves describing FEV_1 changes with age to raw data, we used a generalized additive model (12), with smooth terms and incorporating the subject-specific (longitudinal) random effects. Scatter plots smoother of Gaussian-type like splines are also included. Statistical analysis was performed using R statistical software version 2.6.1 (13) and the package mgcv 1.3–27 (14). In this analysis, we expressed FEV_1 in absolute values (liters) or, as Fletcher and Peto did, as percentage of the predicted value at the age of 25 years (3). To calculate the predicted value at the age of 25, we used the Third National Health and Nutrition Examination Survey (NHANES-III) Hankinson's reference equations for whites (15), according to age, sex, and height, because after reviewing the website and related publications it was assumed that all Framingham Offspring participants were white (10). Because the latter was not always measured when the participant was precisely at the age of 25, we used the closest height available after this age, to avoid using a height value of someone who might be still growing. Finally, to calculate FEV_1 decline in the different study groups we first calculated it in each participant by dividing the difference in milliliters between measurements obtained in the first and last available spirometry in each individual, out of a maximum of four (as per Figure 1 and Table E2) by the time (years) between these measurements, and individual values were averaged. The slope from the first adult measurement (after 20 yr) to the last available lung function measurement was adjusted by body mass index, height, and age for comparisons within groups. A P value lower than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

From the original 5,124 participants at inception of the Framingham Offspring cohort, 4,391 (85.7%) contributed with at least two lung function measurements for this study, and the process of determining smoking status and other related information is presented in Figure 1. A comparison of baseline characteristics with the 699 participants with a single spirometry measurement, not included in later analyses, is presented in Table E3. These participants with only one spirometry measurement had a shorter follow-up, were slightly older (significant only in men), and had a reduced smoking exposure history (all $P < 0.05$) when compared with participants included in this research.

Table 1 presents the demographic and clinical characteristics of the 2,121 males and 2,270 females included in the study at their first examination evaluation. Of them, 1,017 contributed

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PARTICIPANTS WITH TWO OR MORE SPIROMETRIES, AT EXAM 1 OF THE FRAMINGHAM OFFSPRING COHORT

	Male (n = 2,121)	Female (n = 2,270)
Follow-up, years	22.7 ± 2.7	23.1 ± 1.8
Age, years	36.5 ± 10.5	35.6 ± 10.1
Height, cm	176.3 ± 7.2	162.3 ± 6.1
Weight, kg	81.9 ± 12.5	63.3 ± 11.8
BMI, kg/m^2	26.4 ± 3.6	24.0 ± 4.3
Smoker, n (%)		
Current	361 (17.0%)	393 (17.3%)
Former	1,094 (51.6%)	965 (42.5%)
Never	666 (31.4%)	912 (40.0%)
Pack-years*	31.2 ± 24.1	19.0 ± 17.0
FEV_1, L	3.7 ± 0.7	2.7 ± 0.5
FEV_1,% pred	87.8 ± 13.9	90.0 ± 17.5
FVC, L	4.3 ± 0.8	3.2 ± 0.5
FVC, % pred	83.6 ± 11.7	85.6 ± 11.3
FEV_1/FVC	0.85 ± 0.1	0.86 ± 0.1
FEV_1, % pred at age 25	81.7 ± 14.3	83.1 ± 14.0

Definition of abbreviations: BMI = body mass index; % pred = percentage of the predicted value.

Results are presented as mean ± SD or percentage, as appropriate. There were 34 participants of the Framingham Offspring cohort with no spirometry, and 699 with only one spirometry, who did not contribute data to this study.

* Pack-years are calculated for current and former smokers as per the formula (cigarettes smoked per day/20) × years of smoking.

with two lung function measurements, 1,269 with three, and 2,105 with four. Mean age at the time of the first available spirometry was 36 years (range from 13–71 yr) in both males and females. More males were current or former smokers than females ($P < 0.05$), and the mean pack-years were 31.2 for males and 19.0 for females. FEV_1 in absolute values (L) was greater in males than in females. Table 1 also presents FEV_1 and FVC values as percent predicted, as well as percent predicted at age 25 for FEV_1.

FEV_1 Changes in Healthy Never-Smokers

Figure 2 presents FEV_1 changes with age in healthy never-smoking males and females, expressed in absolute values (Figure 2A) and as percent predicted at the age of 25 (Figure 2B). As expected, males had higher absolute FEV_1 values during their lifetime than females (Figure 2A). Three other observations are of note: First, in males, FEV_1 values increased up to a peak at the age of 23 years but not in females in the age range of this study. Second, FEV_1 in females (but not males) plateaus until about the age of 40 years. Third, the annualized rate of decline for healthy never-smoking males (19.6 ml/year; 95% CI, 17.1–22.1 ml/yr) was slightly but not significantly greater ($P = 0.266$) than that observed in females (17.6 ml/yr; 95% CI, 13.8–21.4 ml/yr). Similar results were observed when FEV_1 was expressed as percent of the predicted value at the age of 25 (Figure 2B).

For completeness, the same figures are presented for FVC (Figure E4) and the ratio FEV_1/FVC (Figure E5).

Effects of Smoking

The mean age at starting smoking in this cohort was 17.5 ± 3.6 years in male and 18.8 ± 4.2 years in female participants. Figure 3 compares FEV_1 decline in healthy never-smokers and continuous smokers both in males (Figure 3A) and females (Figure 3B). We observed, first, that smoking reduced the maximal FEV_1 value achieved in males, but not in females. Second, continuous smoking increased the rate of FEV_1 decline (vs. never-smokers), in males (38.2 ml/yr; 95% CI, 33.9–42.6), and

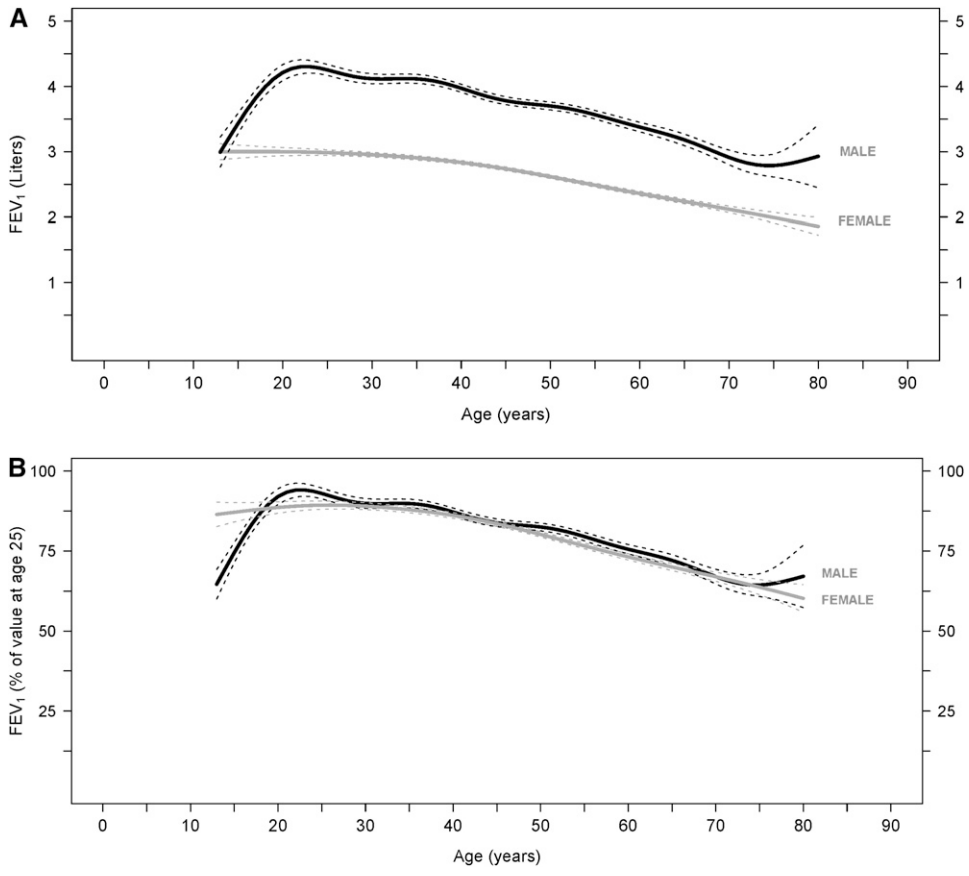

Figure 2. Mean FEV_1 values by age (and 95% confidence intervals [CI]) in male (*black line*) and female (*gray line*) healthy never-smokers, expressed (*A*) in absolute values and (*B*) as percentage of the FEV_1 value at the age of 25. The mean FEV_1 decline value (and 95% CI) for males was 19.6 ml (17.1–22.1) and for females 17.6 ml (13.8–21.4), with a *P* value of 0.266. For further explanation, *see* text.

females (23.9 ml/yr; 95% CI, 20.9–27.0). Third, the rate of FEV_1 decline was higher in continuously smoking males than females ($P < 0.001$). We also confirmed that there is significant variability in the rate of decline of lung function in continuous smokers, both in males (from 8 to 63 ml/yr) and females (from 14 to 49 ml/yr) (first vs. fourth quartiles of lung function decline, data not shown).

It is often acknowledged that only a fraction of smokers (the so-called susceptible smokers) will develop airflow obstruction. According to our definition (pre-BD FEV_1/FVC ratio less than 0.7 and an FEV_1 value less than 80% of predicted), we found that 33.0% of continuous-smoker males and 24.2% of continuous-smoker females developed airflow obstruction during follow-up, higher than the proportions observed in our group of never-smokers, 7.4% of men and 5.6% of women. To further explore the issue of susceptibility to smoking in the Framingham Offspring cohort, we investigated if the presence of respiratory symptoms at baseline and/or a respiratory diagnosis in continuous smokers (unhealthy smokers; *see* operational definitions above) identifies a group of individuals particularly susceptible to smoking. As shown in Figure 4, the rate of FEV_1 decline in unhealthy continuous smokers was increased versus healthy continuous smokers and versus healthy never-smokers, in both sexes ($P < 0.05$).

Effects of Quitting Smoking

Figure 5 presents the effects of quitting smoking at different ages in males (Figure 5A) and females (Figure 5B). Smokers who quit before the age of 30, between 30 and 40 years of age, and after the age of 40 years are compared with healthy never-smokers and continuous smokers. The rate of FEV_1 decline in both male and female smokers who quit before age 30 was indistinguishable from healthy never-smokers. In contrast, smokers who quit after the age of 40 years showed a significantly enhanced rate of decline of FEV_1 versus healthy never-smokers and earlier quitters, but not significantly different from continuous smokers (Figure 5).

DISCUSSION

The main findings in this study were: (*1*) healthy never-smoker females achieve lung growth earlier than males, and their rate of decline with age is slightly but not significantly lower; (*2*) smoking increases the rate of decline of FEV_1 in both males and females; (*3*) there is a range of susceptibility to the deleterious effects of smoking on lung function. The presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a group of susceptible smokers; and (*4*) smoking cessation has a beneficial effect on lung function decline with age, which is particularly evident in early (vs. late) quitters.

Previous Studies

Several previous population-based studies have analyzed lung function decline over time (16–21). To the best of our knowledge, however, this is the first time that a large cohort of both males and females, with a wide age range, is followed for up to 26 years to describe lung function changes from adolescence to old age in healthy never-smokers and to investigate the effects of smoking and smoking cessation.

Our current understanding of the natural history of COPD is mostly based on the seminal publication of Fletcher and Peto from the MRC cohort (3, 4). Based on a limited number of observations, these authors proposed that FEV_1 declines physiologically with age, that this decline was significantly enhanced

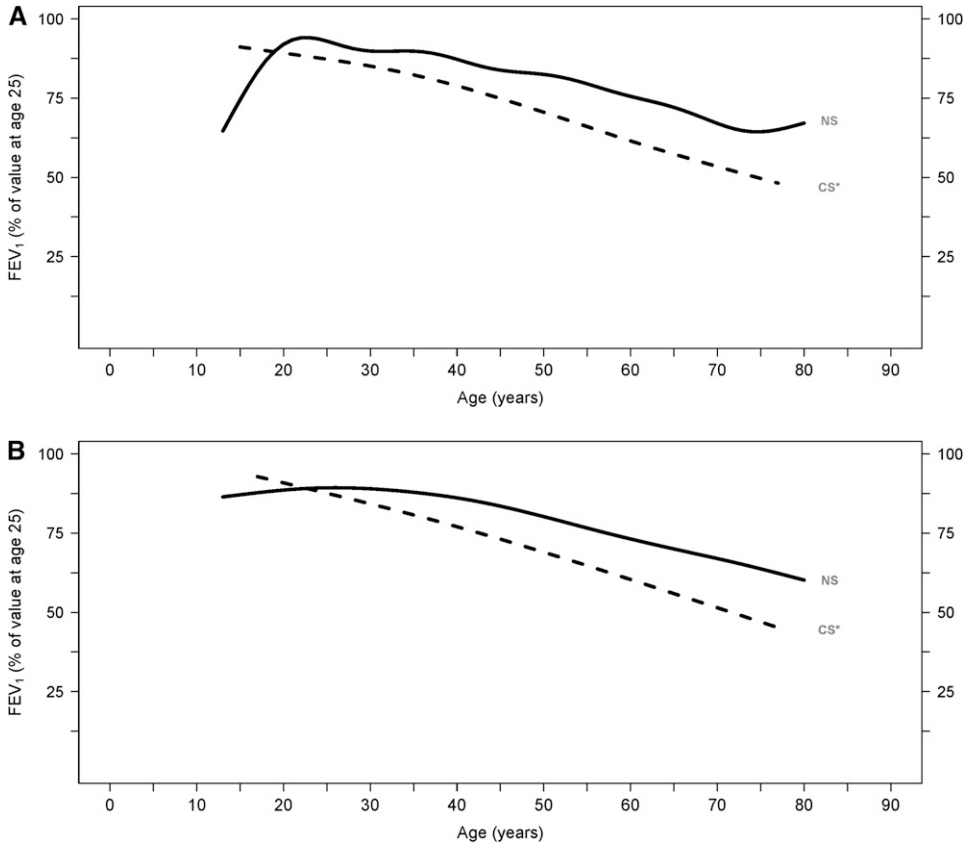

Figure 3. Mean FEV_1 values (expressed as percent of its value at the age of 25) by age, for healthy never-smokers (NS), and continuous smokers (CS). (*A*) Data for males and (*B*) for females. The mean FEV_1 decline value (and 95% confidence intervals) for males was 38.2 ml (33.9–42.6) and for females 23.9 ml (20.9–27.0), with a *P* value < 0.001. $*P < 0.05$ versus healthy never-smokers. For further explanation, *see* text.

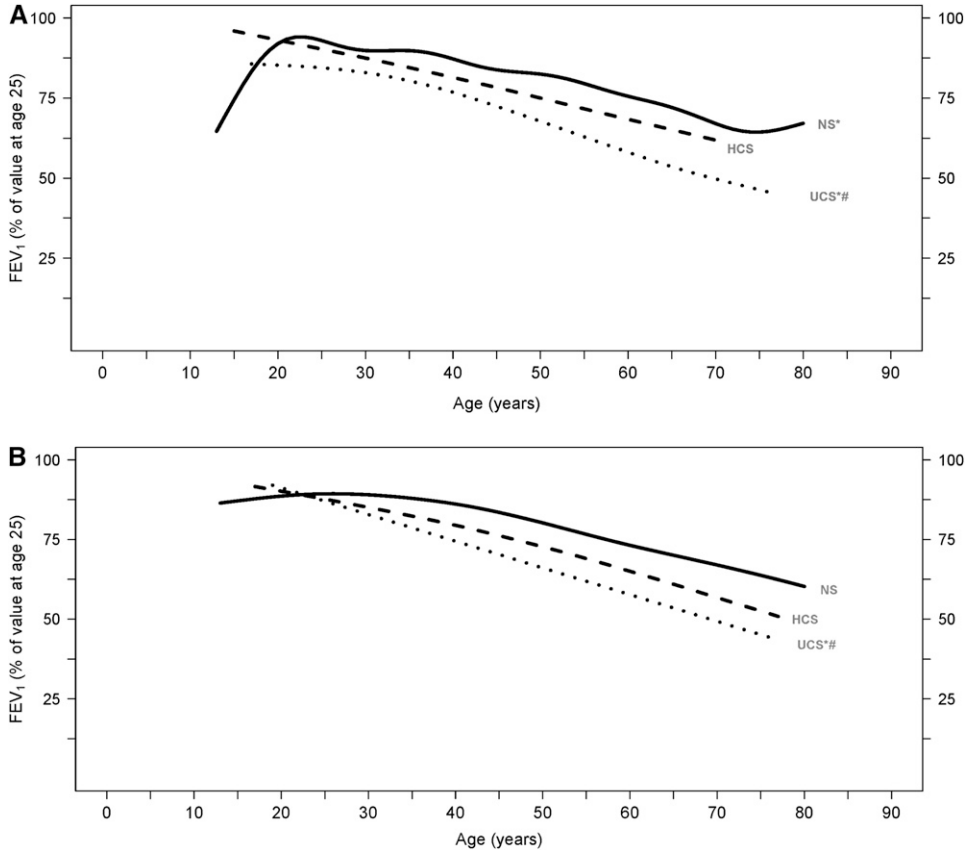

Figure 4. Mean FEV_1 values (expressed as percent of its value at the age of 25) by age, for healthy never-smokers (NS), healthy continuous smokers (HCS), and unhealthy continuous smokers (UCS). (*A*) Data for males and (*B*) for females. The mean FEV_1 decline value (and 95% confidence intervals) for males in each subgroup were 32.5 ml (24.9–40.2) for healthy continuous smokers and 42.3 ml (37.2–47.3) for unhealthy continuous smokers; for females, 17.1 ml (12.9–21.2) for healthy continuous smokers and 30.7 ml (26.3–35.0) for unhealthy continuous smokers. $^{*}P < 0.05$ versus healthy never-smokers. $^{\#}P < 0.05$ versus healthy continuous smokers. For further explanation, *see* text.

in a subgroup of smokers (so-called susceptible smokers) and that the rate of FEV_1 decline would be "normalized" after quitting smoking at any age (3, 4). We believe that our study is the first attempt to recreate that model with data.

Normal Lung Function Growth and Decline

Within the age range studied, we could identify a peak of FEV_1 only in males (Figure 2). This is in keeping with other studies (22) and suggests that females achieve lung growth earlier than males. In these Framingham Offspring participants, males started smoking at a mean age of 17.5 years, when the lung is still growing. This was not the case in females, who started smoking at a mean age of 18.8 years, when their lungs are fully developed. Nowadays, teens start smoking much earlier, which could have even more harmful effects on lung growth.

We also observed that females appear to have a longer FEV_1 plateau phase, as other studies have reported in the past (16, 21–23), and that their annual rate of FEV_1 decline with age was slightly but not significantly lower than in healthy never-smoking males (17.6 vs. 19.6 ml/yr, $P = 0.266$) (Figure 2). The above-mentioned plateau phase refers to pooled group data, but large variability at the individual level and by subgroups of individuals has been reported elsewhere (24). The trend in Figure 2A of a small FEV_1 increase in absolute values in males in the oldest age categories could indicate a healthy survivor bias, or mere variation due to a shrinking sample size, as this trend is not seen in women.

Finally, previous longitudinal studies have published figures of FEV_1 decline in never-smokers that range from 10 to 50 ml/yr (6). Our results are within this range but it is of note that we used a more stringent definition (healthy never-smokers) than most previously published longitudinal studies, which reported results on never-smokers.

Effects of Smoking

Our results confirm that tobacco smoking increases the rate of lung function decline in males and females (16–18, 20, 24–27) (Figure 3). There is also significant variability in the rate of decline of lung function in continuous smokers and, in particular, the rate of FEV_1 decline was slightly but significantly higher in continuous smoking males than females (Figure 3). This is consistent with data from the Tucson respiratory study 20 years ago (28). However, in our study the percentage of continuous smokers developing airflow limitation was similar in males (33%) and females (24%), suggesting that males and females may be equally susceptible to the deleterious effects of tobacco smoking.

Fletcher and Peto reported that phlegm production or infective episodes did not increase lung function decline (3, 4). In contrast we found that the presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a subpopulation of smokers who are particularly susceptible to the deleterious effects in their lungs of smoking, extending the conclusions of a recent large European follow-up study (29). This novel information has important clinical relevance.

Finally, we observed that smoking appeared to reduce the FEV_1 peak in males (Figure 3A). Because we did not identify such a peak in females (Figure 3B) we do not know if this occurred earlier also in this group. In any case, at least in males, our results suggest that smoking during adolescence may reduce lung growth as has been shown by others (27). The clinical importance of this observation is that failure to reach optimal lung growth is a potential risk factor for the subsequent development of airflow obstruction later in life (28, 29).

Effects of Smoking Cessation

Many previous studies have investigated the effects of quitting smoking on lung function decline (16, 28). We found that

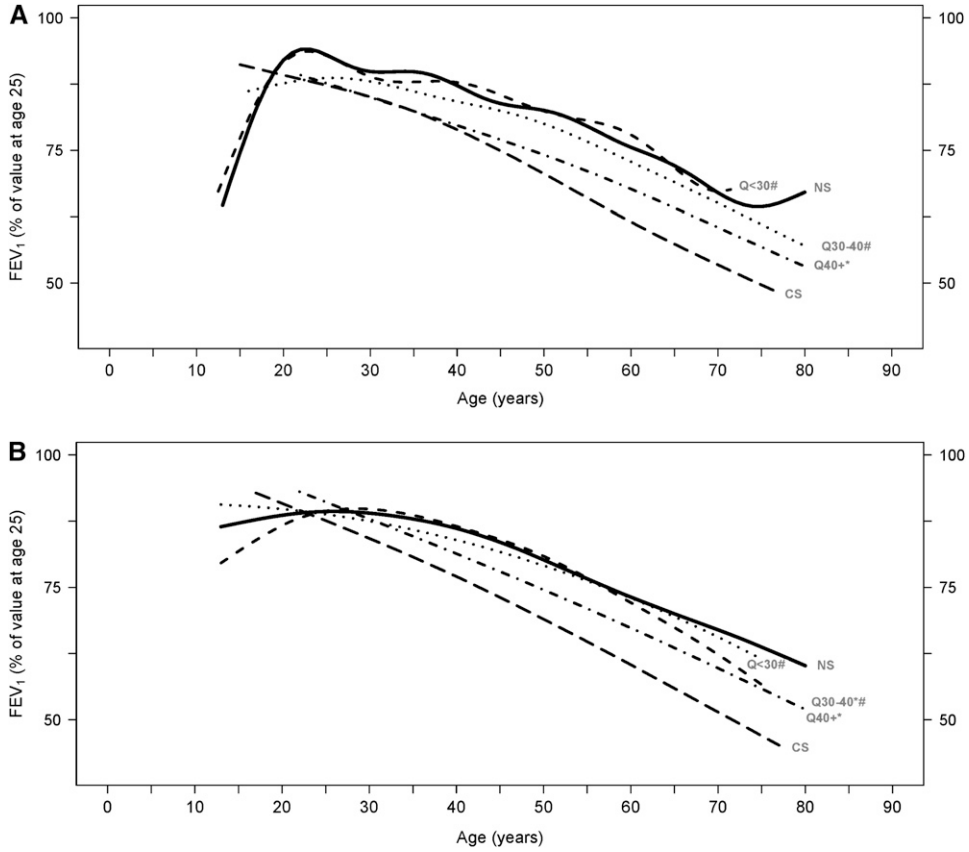

Figure 5. Mean FEV_1 values (expressed as percent of its value at the age of 25) by age in smokers who quit smoking before the age of 30 ($Q < 30$), between 30 and 40 years of age (Q30–40) and after the age of 40 (Q40+). Curves from healthy never smokers (NS) and continuous smokers (CS) are also included for comparison. (*A*) Results in males. (*B*) Results in females. The mean FEV_1 decline value (and 95% confidence intervals) for each curve of quitters for males was 15.5 ml (11.3–19.8) in quitters before the age of 30, 24.0 ml (20.0–28.1) in quitters between 30 and 40 years of age, and 28.9 ml (26.4–31.1) in quitters after the age of 40; for females, 10.4 ml (6.3–14.5) in quitters before the age of 30, 16.5 ml (14.0–19.0) in quitters between 30 and 40 years of age, and 21.0 ml (18.8–23.2) in quitters after the age of 40. $^*P < 0.05$ versus healthy never-smokers (NS). $^{\#}P < 0.05$ versus CS. For further explanation, *see* text.

smoking cessation had a beneficial effect on the rate of FEV_1 decline by age (Figure 5). However, previous studies generally investigated the beneficial effects of quitting in middle-aged individuals only (mean age of about 45 yr) (16, 28, 30). In contrast, our study explored the effects of quitting at younger ages. We found that the rate of FEV_1 decline of smokers (both males and females) who quit before the age of 30 was indistinguishable from that of healthy never-smokers, but it was significantly enhanced (and not different from that of continuous smokers) in those who quit after the age of 40 (Figure 5). The observation that the rate of FEV_1 decline between smokers who quit after the age of 40 and continuous smokers is not significantly different could be due to lack of power, because in Figure 5 in males and also in females, the curves appear to have different slopes. It is not our intention to send a misleading and potentially discouraging public health message by implying that late quitting may not have a beneficial impact on the course of subsequent lung function, as this beneficial effect was elegantly reported in the Lung Health Study (31, 32). On the contrary, all these observations highlight the importance of early quitting and do not support the model proposed by Fletcher and Peto, in which it was suggested that the rate of lung function decline returns to normality after quitting independently of the age of the individual (3, 4).

Strengths and Limitations

Our study has some strengths and potential limitations that deserve comment. Among the former, the inclusion of female participants, its large sample size, its long follow-up time, and the study of individuals both during adolescence and old age are particularly worth noting. Among the latter, we acknowledge that, first, reliable lung function data were available in only four examinations (Figure 1 and Table E2), and that the accuracy of most estimates would have been larger if more spirometries had been available in the same individual, reducing any potential cohort effect (33). Connected with this, there is potential bias due to applying the Hankinson's NHANES-III prediction equations (15), which are more recent, to the Framingham data, but it appears there is no other satisfactory alternative. It is counterintuitive that Framingham healthy, never-smoker participants have on average lower than the 100% expected mean percent predicted spirometry values according to Hankinson's equations. A likely cohort effect is envisioned, as generations grow healthier and leaner, similar to the one demonstrated in the Dutch population (33). Second, all information on smoking and quitting was self-reported and not objectively (biologically) verified, although it has been extensively used to date (10). Third, several potential confounders, such as passive smoking and environmental, occupational, and allergen exposures, were not available and were therefore not taken into account in the analysis. Fourth, one of many ongoing controversies in COPD research is the use of a fixed ratio or a lower limit of normal to diagnose airflow obstruction (34). As per current Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, we used the former, but it is worth noting that spirometric results correspond to pre-BD values, and because the FEV_1/FVC ratio decreases with increasing age, as in Figure E5, any fixed-ratio definition leads to the potential for overestimation of airflow obstruction in older participants and underestimation of airflow obstruction in young participants. Finally, an inherent limitation of any serial spirometric assessment is that individuals who die, or are very sick, cannot possibly contribute more lung function data. This selection bias is strongly related to smoking status, as it can be seen in Table E6. Death was more frequent in continuous smokers (33% of male and 19% of female) than in the respective comparator

groups of never-smokers or intermittent smokers. Accordingly, any results on fast decliners, or other individuals more susceptible to the harmful effects of smoking, are diluted due to this survivor bias. Finally, and not an original objective of our research, we confirm that survival of continuous smokers is much reduced when compared with never-smokers, both in males and in females (Figure E7).

Stanojevic and colleagues (35) have recently proposed a new way of collating and analyzing spirometric data from population surveys, aimed at developing reference ranges that more accurately describe the nonlinear relationship between spirometric lung function and height by age, by means of an extension of the LMS (lambda, mu, sigma) method. We agree that this new modeling technique provides an elegant solution and a statistically robust means of developing continuous reference ranges from early childhood to old age. However, given the limitations stated above, and as we are not pooling different surveys, we decided to sustain the analytical approach as per the original UK MRC study and curves.

There is an urgent need to agree on the interpretative strategies of pulmonary function, at the individual and population levels, and this is a matter of ongoing debate (6). Quanjer and colleagues (36) have elegantly discussed the advantages of using reference equations that use height, age, or other parameters, such as *z*-scores, in schoolchildren and adolescents in particular. We concur with previous investigators (35, 36) that limitations remain for describing the progression of pulmonary function and the natural course of respiratory disease, as highlighted in our research.

Our results provide longitudinal evidence that recreates the Fletcher and Peto lung function curves in males and, for the first time, extends them to females. This allowed us to identify sex differences in normal lung growth and aging. We confirm that continuous smoking enhances the rate of FEV_1 decline and causes airflow obstruction only in a percentage of smokers. Contrary to Fletcher and Peto (3), the presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a particularly susceptible phenotype, which may be helpful in clinical practice. Our results clearly support the benefits of quitting smoking at early ages.

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