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The Upper Limit of Normal Rate of Lung Function Decline in Healthy Adults in the Framingham Heart Study

Ruchika Sangani, MD,
Pulmonary Center, Boston University Chobanian & Avedisian School of Medicine, Boston, MA

Ming-Ming Lee, MD,
Pulmonary and Critical Care Medicine, Norwalk Hospital, Nuvance Health, Norwalk, CT

Hanfei Xu, MS,
Department of Biostatistics, Boston University School of Public Health, Boston, MA

Josée Dupuis, PhD,
Department of Biostatistics, Boston University School of Public Health, Boston, MA; Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada

George T. O'Connor, MD
Pulmonary Center, Boston University Chobanian & Avedisian School of Medicine, Boston, MA; The NHLBI's Framingham Heart Study Framingham, MA

Abstract

BACKGROUND: Lung function declines over the course of adulthood; however, a consensus on the normal range of decline in an individual's lung function is lacking.

RESEARCH QUESTION: What is the normal range and the upper limit of normal (ULN) decline in lung function in adults without prior tobacco use, occupational dust exposure, or a known diagnosis or symptoms of cardiopulmonary disease?

STUDY DESIGN AND METHODS: A retrospective analysis of healthy individuals who have never smoked (N = 1,305) from the Framingham Heart Study with repeated lung function meeting standards for acceptability and reproducibility was conducted. Longitudinal change was derived using a linear mixed effects model and estimated to a 6-year interval. The ULN decline was defined as the 95th percentile.

RESULTS: The mean follow-up between spirometry examinations was 5.5 years, whereas the mean follow-up between diffusing capacity for carbon monoxide studies was 5.9 years. Decline

CORRESPONDENCE TO: Ruchika Sangani, MD; ruchikas@bu.edu.

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in FEV_1, FVC, and D accelerated with age, whereas decline in FEV_1/FVC decelerated with age. Decline varied with sex, age, and height. Over a 6-year period, the ULN decline in FEV_1 ranged from 383 to 667 mL, and the ULN decline in D_{LCO} ranged from 3.6 to 9.5 mL/min/mm Hg. Overall, male individuals had faster absolute rates of decline than female individuals, whereas relative (%) rates of decline were similar between sexes.

INTERPRETATION: Lung function decline is nonlinear and accelerates with age. In this cohort, the ULN decline over 6 years often exceeded current guidelines for interpreting significant longitudinal change in lung function.

Keywords

epidemiology (pulmonary); FEV_1; longitudinal decline in lung function

Lung function increases in childhood and adolescence and begins to decline in early adulthood as a normal part of aging.[1-3] Estimates of the average rate of lung function decline in adults who do not smoke have been described with initial cross-sectional studies reporting a linear rate of decline in FEV_1 of about 20 to 30 mL/y.[1,4-7] Subsequent cross-sectional and longitudinal studies have demonstrated a nonlinear rate of decline that accelerates with age with an estimated rate of decline in FEV_1 increasing to up to 60 mL/y in older adults.[8-12] Longitudinal studies have also found that the rate of decline in diffusing capacity for carbon monoxide (D_{LCO}) accelerates with age, more than doubling across decades.[13-15]

Although estimates of the population average lung function decline have been reported, the rate of decline for an individual over a given time interval is quite variable due to both biological factors (eg, acute illnesses, environmental exposures, body habitus) and measurement factors (eg, technical quality, test variability, duration of follow-up).[1,11,16-19] In fact, prior studies have shown that within-day coefficient of variation for spirometry ranges from 3% to 11% for a given individual, whereas within-year coefficient of variation for D_{LCO} testing has been found to be up to 9.6%.[20,21] Understanding the normal range of lung function decline over time and establishing an upper limit of normal (ULN) decline may allow for more accurate interpretation of longitudinal changes in lung function. The ULN can be used for not only the early detection of disease, but also the avoidance of unnecessary additional testing and interventions.

In this study, we describe the normal range of both absolute and relative (%) decline in FEV_1, FVC, FEV_1/FVC, and D_{LCO} in a cohort of healthy individuals who never smoked in the Framingham Heart Study (FHS). We also define, for the first time, to our knowledge, the ULN of lung function decline.

Study Design and Methods

Study Design and Study Population

The design and selection criteria for the FHS Offspring, Third Generation, Omni 1, Omni 2, and New Offspring Spouse (NOS) cohorts have been previously described (e-Appendix 1).[22-24] The present investigation included participants from each of these cohorts who had acceptable and reproducible pulmonary function tests (PFTs) from at least two

consecutive examinations. Spirometry data were obtained from examinations 5 (1991-1995), 6 (1995-1998), 7 (1998-2001), 8 (2005-2008), and 9 (2011-2014) for Offspring participants; from examinations 1 (2002-2005) and 2 (2008-2011) for Third Generation participants; from examinations 1 (1994-1998), 2 (1999-2001), 3 (2007-2008), and 4 (2011-2014) for Omni 1 participants; and from examinations 1 (2003-2005) and 2 (2008-2011) for Omni 2 and NOS participants. D_{LCO} data were obtained from examinations 8 and 9 for Offspring participants; examinations 3 and 4 for Omni 1 participants; and examinations 1 and 2 for Third Generation, NOS, and Omni 2 participants. The study was approved by the Boston University Medical Campus institutional review board (H-32132), and all study participants provided written informed consent.

Participants were asked whether they had ever smoked and about prior medical diagnoses at their initial visit and were asked about interim tobacco smoking and medical history at each subsequent examination. Symptoms, physical examination, clinical diagnostic impressions, and occupational history were documented at each visit by a study physician. We defined healthy participants to be those who reported no history of pulmonary disease, atrial fibrillation/flutter, or heart failure; who answered no to all questions about symptoms of dyspnea with exertion, cough, wheeze, or sputum production; who were never reported by an examiner to have a clinical diagnostic impression of any cardiopulmonary conditions; and who had normal baseline PFTs (subsequently discussed). Participants who reported working in a job category (factory/assembly/mechanic, skilled labor, general labor, and heavy labor) classified as high exposure in the University of California San Franicisco COPD Job Exposure Matrix at the time of their baseline examination or follow-up examination were excluded.[25,26] Only PFTs from healthy participants without any history of smoking and without high likelihood of heavy dust exposure by occupational history were included in our analysis. Baseline characteristics and lung function were abstracted from each participant's first contributing examination.

Pulmonary Function Tests

Spirometry from examinations prior to 2002 was performed using a Collins Eagle II spirometer, interfaced to pulmonary function data acquisition and quality control software (S&M Instruments), whereas spirometry and single-breath D_{LCO} measurements after 2002 were performed using a Collins CPL System (nSpire Health, Inc). Spirometers were calibrated daily. Maneuvers were performed prior to bronchodilator administration, with participants wearing nose clips and repeated until at least three acceptable values were obtained or up to a maximum of eight times. Spirometry examinations meeting criteria for three acceptable maneuvers by American Thoracic Society (ATS) standards at time of testing and reproducibility criteria by 2005 ATS standards were included in our primary analysis.[27-29] For D_{LCO} measurements, participants inhaled tracer carbon monoxide and performed a breath hold for 10 to 12 s. The difference between inhaled and exhaled carbon monoxide was used to calculate the D_{LCO}. At least two measurements, > 4 min apart, were obtained from each participant to allow for carbon monoxide washout. A third maneuver was performed if the first two measurements were not acceptable and reproducible within 10% of each other. D_{LCO} measurements meeting acceptability criteria by ATS standards at time of testing and repeatability criteria by 2005 ATS standards were used.[30-32]

The largest FEV_1 and FVC from all acceptable maneuvers, the calculated FEV_1/FVC ratio by dividing these two measurements, and the average D_{LCO} measurement were used in our analyses. Percent predicted values for spirometry were calculated using US National Health and Nutrition Examination Survey III Hankinson reference equations for White patients, and percent predicted values for D_{LCO} were calculated using the reference equation derived by Miller et al.[33-35] These reference equations were used rather than race/ethnic-neutral equations because a large proportion of the participants identified as being non-Hispanic White, and there is minimal difference in the prediction of clinical events between race/ethnic-based and race/ethnic-neutral equations.[34,36] Participants with baseline spirometry less than the lower limit of normal were excluded from both spirometry and D_{LCO} analyses, and those with baseline D_{LCO} below the lower limit of normal were additionally excluded from D_{LCO} analysis.

Changes in spirometry values across the time interval during which the spirometry equipment was changed were not included to avoid the addition of potential measurement inconsistency due to the change in devices. Therefore, participants contributed to a maximum of three spirometry intervals, and all participants contributed to one D_{LCO} interval. Almost all follow-up intervals were within 4 to 7 years and within 5 to 7 years for spirometry and D_{LCO} examinations, respectively. Given that duration of follow-up affects the SE of change, we excluded studies with a shorter or longer interval between examinations.[10]

Statistical Analyses

The absolute and relative (%) decline over 6 years was estimated with use of a linear mixed effects model. The models included adjustment for age, height, and sex to obtain predicted mean and SD for the rate of decline. Random effect terms were included to account for between-individual familial relatedness and within-individual correlation. We performed analyses using R 3.6.0 packages “coxme” and “kinship2” (RStudio). A secondary analysis was conducted using spirometry examinations with at least two acceptable maneuvers that did not necessarily meet reproducibility criteria.

Decline was calculated for strata of age, sex, and height. Participants were classified as short or tall if their height was 1 SD below or above the mean height (by sex), respectively. The ULN 6-year decline was defined as 1.649 SDs above the mean, corresponding to the decline exceeding that experienced by 95% of healthy FHS participants.[34,37] The baseline characteristics of participants were compared based on whether or not they experienced an absolute decline greater than the predicted ULN decline for sequential FEV_1 and D_{LCO} measurements.

Results

Population Characteristics

From a total of 10,239 eligible participants from the five cohorts, 1,305 participants met inclusion criteria for the longitudinal spirometry analysis, and 881 participants contributed to the longitudinal D_{LCO} analysis (Fig 1). Baseline demographic and clinical characteristics of participants are shown in Table 1, and the distribution of interval duration between

sequential examinations is shown in Table 2. The mean follow-up intervals were 5.5 ± 1.0 years for spirometry examinations and 5.9 ± 0.6 years for DLCO examinations. Characteristics according to specific cohorts are shown in e-Tables 1 and 2. Average baseline spirometry values from the ethnically diverse cohorts (Omni 1 and Omni 2) were slightly lower than the largely White cohorts, as expected based on prior literature, as were their percent predicted spirometry values given our use of reference equations for the White, non-Hispanic population.[36] The mean percent predicted baseline PFTs were 102 ± 11 for FEV_1, 103 ± 11 for FVC, 99 ± 5 for FEV_1/FVC, and 100 ± 14 for DLCO.

Decline in FEV_1

The estimated absolute and relative decline in FEV_1 over a 6-year period by strata of sex, age, and height are shown in Table 3 and graphically represented in Figure 2 for participants of average height. The absolute decline in FEV_1 increased with age and height, whereas the relative decline increased primarily with age. The absolute decline in FEV_1 was greater in male participants than in female participants, whereas the relative decline was similar between sexes. The estimated mean absolute decline over 6 years in males ranged, according to age and height, from 147 to 295 mL, corresponding to an estimated mean annual rate of decline ranging from 24.5 to 49.2 mL/y. The estimated ULN decline for male participants over 6 years ranged from 517 to 667 mL, or 12.5% to 16.9%. The estimated mean absolute decline over 6 years in female participants ranged, according to age and height, from 117 to 210 mL, corresponding to an estimated mean annual rate of decline ranging from 19.5 to 35.0 mL/y. The estimated ULN decline for females over 6 years ranged from 383 to 476 mL, or 12.5% to 16.9%.

A total of 30 male participants (5.8%) and 40 female participants (5.1%) experienced a decline in FEV_1 on sequential spirometry that exceeded the predicted ULN. A comparison of baseline characteristics of these participants based on their decline in FEV_1 in comparison with the predicted ULN is depicted by sex in e-Table 3. Although baseline demographics were similar for both sexes, male participants who experienced a decline in sequential FEV_1 testing greater than the predicted ULN had higher baseline lung function than those who did not.

Decline in FVC

Trends in FVC decline were similar with respect to age, height, and sex to that of FEV_1 decline (e-Fig 1, e-Table 4). Estimated absolute decline was greater in male participants than female participants, whereas relative decline was similar between sexes. The estimated mean annual rate of decline ranged from 11.0 to 60.3 mL/y for male participants and from 9.2 to 43.2 mL/y for female participants. The estimated ULN decline over 6 years for male participants ranged from 499 to 796 mL, or 9.7% to 15.4%, and for female participants ranged from 370 to 574 mL, or 10.1% to 16.3%.

Decline in FEV_1/FVC

The estimated decline in FEV_1/FVC decreased with age for both sexes and did not vary with height for either sex (e-Table 5, Fig 3). The mean decline over 6 years ranged from 0.017 for those in their 30s to 0.005 for those in their 70s for male participants, and from 0.021

for a female in their 30s to 0.002 for a female in their 70s. The ULN absolute decline over 6 years ranged, according to age and height, from 0.047 to 0.060 for male participants and from 0.051 to 0.070 for female participants.

Decline in D_{LCO}

The estimated decline in D_{LCO} accelerated with age for both sexes and did not significantly vary by height for either sex (Fig 4, Table 4). The estimated mean decline in D_{LCO} over 6 years ranged, according to age, from 2.2 to 4.0 mL/min/mm Hg for male participants, corresponding to an estimated annual rate of decline ranging from 0.4 to 0.7 mL/min/mm Hg/y. For female participants, the estimated mean decline in D_{LCO} over 6 years ranged, according to age, from 0.3 to 2.1 mL/min/mm Hg, corresponding to an estimated annual rate of decline ranging from 0.05 to 0.35 mL/min/mm Hg/y. The estimated absolute ULN decline over 6 years ranged from 7.4 to 9.2 mL/min/mm Hg, or 21.0% to 29.2% for male participants, and from 3.7 to 5.6 mL/min/mm Hg, or 15.7% to 25.4% for female participants. Both absolute and relative decline were greater for male participants than female participants.

A total of 23 male participants (5.9%) and 15 female participants (3.0%) experienced a decline in D_{LCO} that exceeded the predicted ULN. A comparison of baseline characteristics of these participants based on their decline in D_{LCO} in comparison with the predicted ULN is depicted by sex in e-Table 6. Baseline D_{LCO} testing was significantly higher in the group who experienced a decline greater than the predicted ULN for both sexes.

Secondary Analysis

Longitudinal decline in spirometry was analyzed for all participants (n = 1,484) who had at least two acceptable spirometry maneuvers that did not necessarily meet criteria for reproducibility. This included 179 participants that did not meet criteria for our primary analysis. Results were similar in terms of trends by age and between sexes to results from our primary analysis (e-Tables 7-9), with decline parameters being slightly larger, particularly for older age groups and for the ULN decline.

Discussion

At present, a consensus on how to best interpret longitudinal lung function changes in an individual is lacking. In 2005, the ATS/European Respiratory Society Task Force suggested that a change in FEV_1 or FVC of ≥ 15%, or a change in D_{LCO} of > 10%, from prior testing constitutes clinically significant change.[38] In 2021, the task force remarked on the current paucity of data exploring longitudinal changes in individuals over time and called for further work to be done in this area across all ages and disease states.[39] This study is to our knowledge the largest cohort of healthy individuals who never smoked to have spirometry and D_{LCO} examined in a longitudinal fashion. It is also the first study, to our knowledge, to define an estimated ULN of change for these parameters.

The main findings of this study are as follows: (1) lung function decline is nonlinear and increases with age; (2) the estimated ULN of lung function decline over 6 years in the cohort often exceeded the parameters previously proposed by the ATS/European Respiratory

Society, particularly in older adults and for D_{LCO}; and (3) FEV_1/FVC declines over time; however, the rate of decline decelerates with age.

Our finding that spirometry decline is nonlinear and increases with age agrees with prior studies.[10,25,40-48] In most of these studies, decline parameters were not reported by height and decade-specific age strata, making direct comparison challenging; however, our estimated average annual rates of decline for FEV_1 are similar to prior reports and encompass the median rates of decline presented in a systematic review.[40,47] Our study further supports findings by the systematic review that absolute decline in FEV_1 is greater for males than females, but that relative rates of decline are similar between sexes.[40] Fewer studies have reported sex-specific decline in FVC by age strata. Griffith et al[44] looked at decline in spirometry specifically in adults aged > 65 years and found, similar to our findings, a greater acceleration in FVC decline than that of FEV_1 with increasing age. Inclusion of spirometry that did not meet criteria for reproducibility in our secondary analysis produced similar but slightly larger rates of decline for all parameters. This may further support prior work by Eisen et al[49,50] who showed failure to perform reproducible spirometry was associated with larger rate of lung function decline.

Few studies have looked at longitudinal change in D_{LCO}. Three previous studies were conducted in a similar fashion to ours—longitudinally over an 8- and 9-year period with two consecutive D_{LCO} measurements—and have all similarly found that D_{LCO} decline is nonlinear and increases with age.[13-15] Of these three studies, Sherrill et al[13] reported average rates of decline by decade-specific age strata and sex, observing similar results and trends by sex and age to our findings.

Strengths and Limitations

This study was conducted in a community-based sample with high follow-up rate and detailed clinical, demographic, and exposure history. Given this, we were able to establish a cohort of individuals deemed to be healthy and to have never smoked by strict criteria. By use of the same equipment and PFT protocols across examinations, exclusion of potential occupational confounders, and restriction of our analysis to reproducible data, we were able to minimize variability from technical and environmental factors to the best of our ability.[51] Taken together, our findings reflect the longitudinal change in lung function of particularly healthy individuals.

Our study has several limitations. First, although strict criteria were implemented in determining if participants were healthy, it is possible that some participants may have had subclinical diseases that were not apparent by medical history or symptom questionnaire. Most of the participants did not have chest CT scan, hemoglobin (Hb) measurements, or echocardiogram data available at corresponding examinations to allow for evaluation and exclusion of those with subclinical disease that could affect lung function.

Second, approximately 90% participants reported White, non-Hispanic race and ethnicity, and results may not be generalizable to populations of other backgrounds. Although it has been well described in the literature that Black and Asian populations have lower lung function than White populations for the same age, sex, and height, the change

in lung function parameters over time based on race/ethnicity has not been extensively described.[39,52] One prior study has compared decline in spirometry between Black and White cohorts and found that Black individuals had a slower rate of decline, particularly in older females.[44] The present study was not powered to detect statistically significant differences in lung function decline between race/ethnicity groups; however, it may serve as a valuable comparison when similar work is completed in other populations.

Third, we were unable to include measurements of Hb and carboxyhemoglobin, which are known to impact D_{LCO} results. Given our exclusion of people who smoke, the effect of carboxyhemoglobin is likely negligible. Additionally, prior work has looked at decline in D_{LCO} with and without adjustments for Hb and carboxyhemoglobin levels without a statistically significant change in their findings, implying that our findings would likely be similar for Hb-adjusted D_{LCO} measurement.[15]

Finally, although it is known that those with lower baseline lung function may experience greater changes in lung function as explained by the horse-racing effect, our results suggested that those who experienced decline in the upper 5th percentile of our study tended to have higher baseline lung function.[53] These findings may be explained by regression to the mean.[54] Because the estimated ULN of lung function decline over 6 years has not been previously reported, we are unable to validate our findings in an independent, external population.

Interpretation

This study describes the ULN of lung function decline in a cohort of healthy, individuals who never smoked, stratified by sex, age, and height. This may provide guidance to physicians in interpreting longitudinal lung function and identifying clinically significant changes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

ATS	American Thoracic Society
D_{LCO}	diffusing capacity for carbon monoxide
FHS	Framingham Heart Study

Hb	hemoglobin
NOS	New Offspring Spouse
PFT	pulmonary function test
ULN	upper limit of normal

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Take-home Points

Study Question:

What are the upper limits of normal longitudinal decline in lung function among healthy individuals who never smoked?

Results:

The longitudinal decline in spirometry indices and diffusion capacity accelerates with age and varies by height and sex. This paper provides the mean and upper limit of normal 6-year declines of FEV_1, FVC, FEV_1/FVC ratio, and diffusing capacity for carbon monoxide by strata of age, height, and sex.

Interpretation:

In this cohort of healthy individuals who never smoked, the upper limit of normal decline in lung function measurements over a 6-year period often exceeded current guidelines for interpreting significant longitudinal change in lung function.

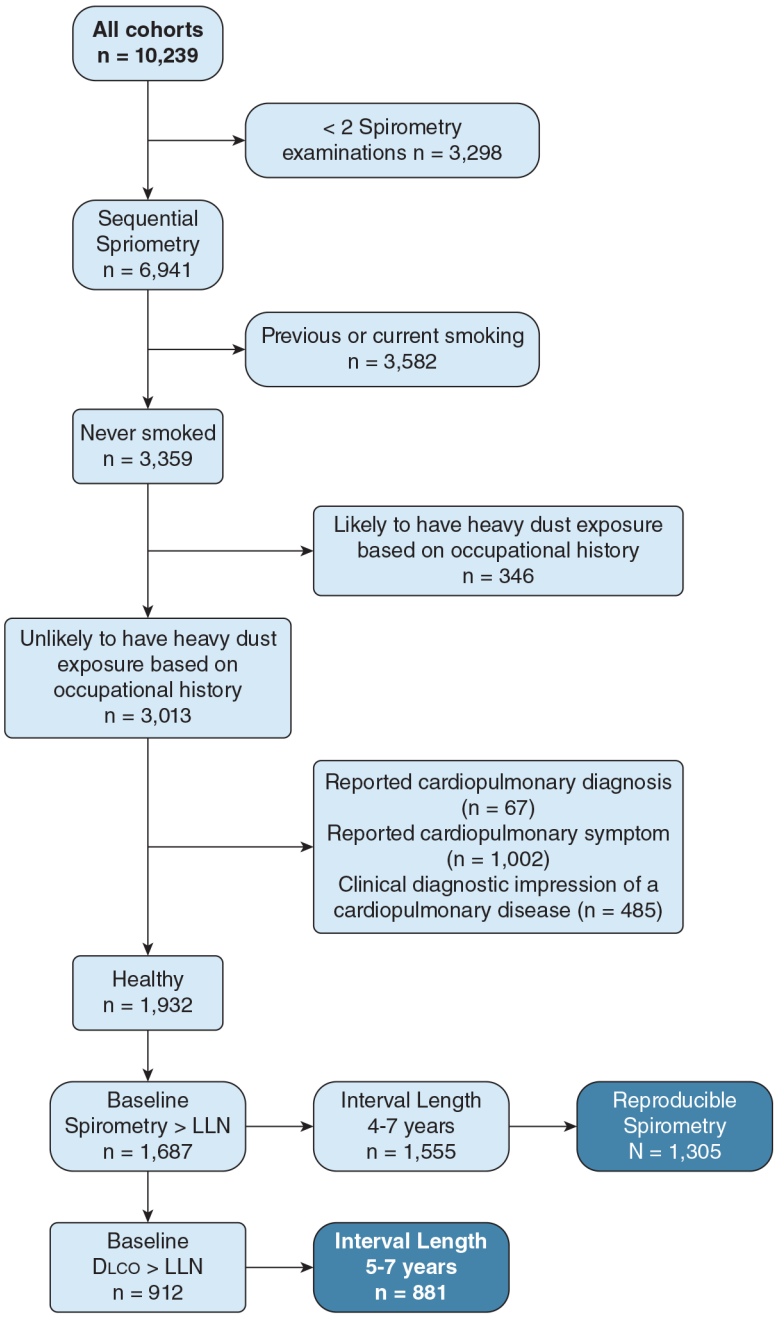

Figure 1 –.

Flowchart illustrating the selection process for eligible participants for inclusion in the primary analyses. DLCO = diffusing capacity for carbon monoxide; LLN = lower limit of normal

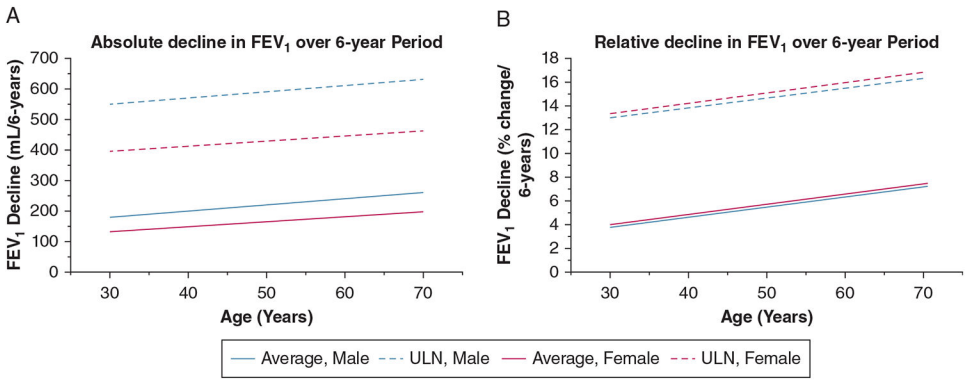

Figure 2 –.

A, Estimated absolute and relative (B) decline in FEV_1 over a 6-y period. Data are presented as average (solid) and ULN (dashed) rates of decline for those of average height, by sex and age. ULN = upper limit of normal.

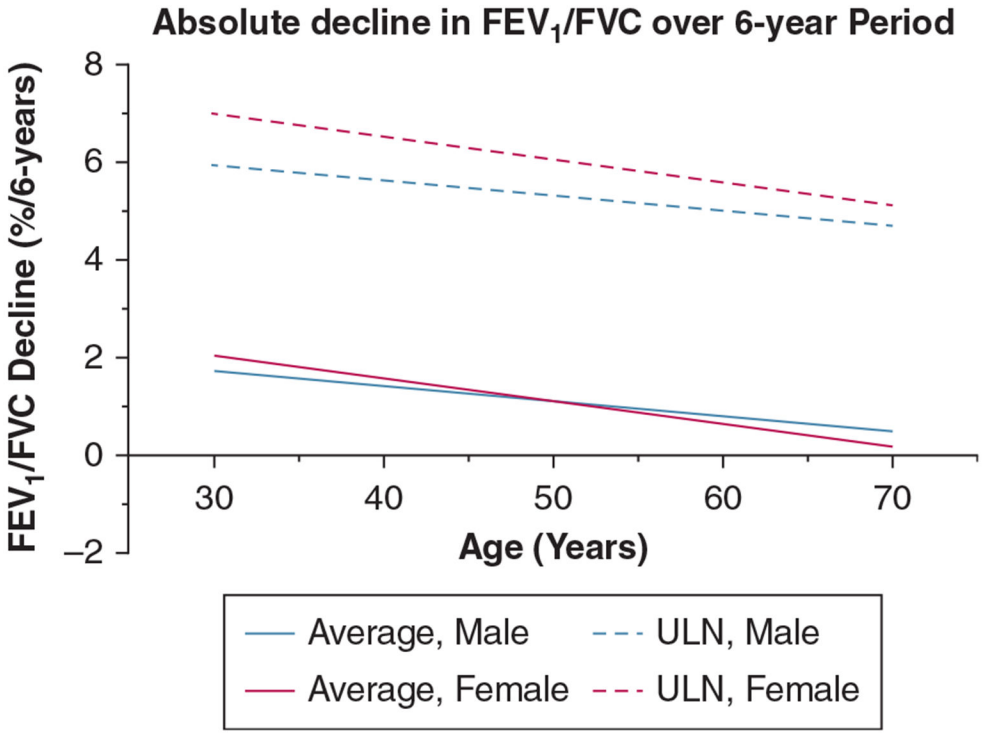

Figure 3 –.

Estimated absolute decline in FEV_1/FVC over a 6-y period. Data are presented as average (solid) and ULN (dashed) rates of decline, by sex and age. ULN = upper limit of normal.

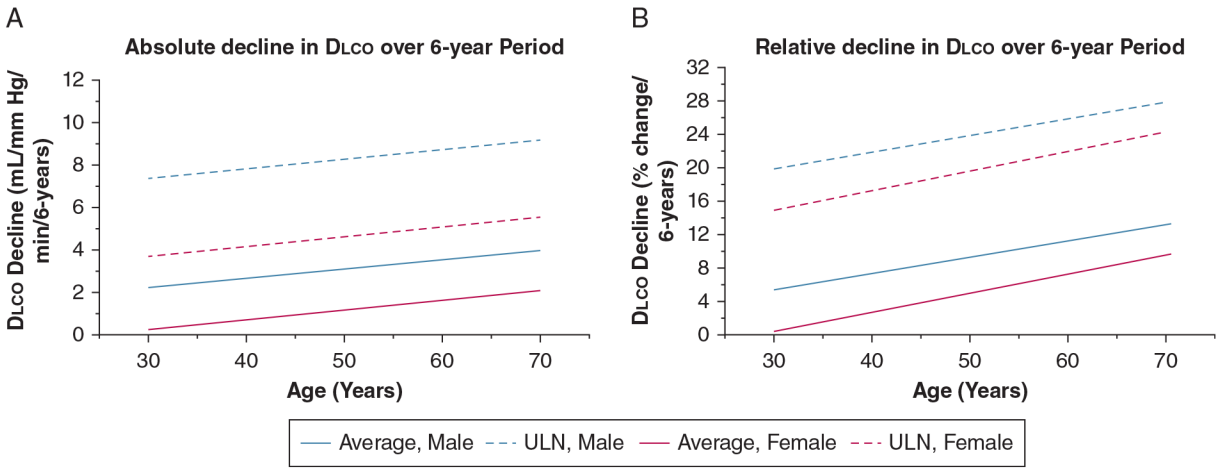

Figure 4 –.

A, Estimated absolute and relative (B) decline in DLCO over a 6-y period. Data are presented as average (solid) and ULN (dashed) rates of decline, by sex and age. DLCO = diffusing capacity for carbon monoxide; ULN = upper limit of normal.

TABLE 1]

Demographic and Baseline Characteristics of the Participants Included in the Primary Analysis

Characteristic	Male Sex (n = 516)	Female Sex (n = 789)
Age, y	44.4 ± 11.3	46.7 ± 12.6
Height, cm	176.6 ± 6.6	162.9 ± 6.3
BMI, kg/m^2	27.3 ± 3.8	25.1 ± 4.5
Self-reported ethnicity		
Hispanic	11 (2)	32 (4)
Non-Hispanic	492 (95)	724 (92)
Unknown	13 (3)	33 (4)
Self-reported race		
American Indian	1 (0.2)	1 (0.1)
Asian	13 (2.5)	25 (3.2)
Black	7 (1.4)	18 (2.3)
Pacific Islander	0 (0)	1 (0.1)
White	484 (93.8)	721 (91.4)
Multiracial	5 (1.0)	9 (1.1)
Unknown	6 (1.2)	14 (1.8)
Cohort		
Offspring	167 (32.4)	300 (38.0)
Third Generation	308 (59.7)	407 (51.6)
New Offspring Spouse	3 (0.6)	7 (0.9)
Omni 1	11 (2.1)	32 (4.1)
Omni 2	27 (5.2)	43 (5.4)
No. of intervals contributed		
1	474 (91.9)	709 (89.9)
2	40 (7.7)	74 (9.4)
3	2 (0.4)	6 (0.8)
FEV_1, L	4.1 ± 0.6	2.9 ± 0.5
FEV_1, % predicted	103 ± 11	102 ± 11
FVC, L	5.2 ± 0.8	3.7 ± 0.6
FVC, % predicted	103 ± 11	104 ± 11
FEV_1/FVC ratio	0.79 ± 0.1	0.79 ± 0.1
DLCO available	387 (75.0)	494 (62.6)
DLCO, mL/min/mm Hg	32.6 ± 5.5	22.3 ± 3.6
DLCO, % predicted	104 ± 14	96 ± 12

Results are presented as mean ± SD or No. (%). DLCO = diffusing capacity for carbon monoxide.

TABLE 2]

Distribution of Follow-Up Intervals of Contributing Examinations

	Interval Follow-Up, y			
	4	**5**	**6**	**7**
Spirometry (n = 1435)				
Male (n = 560)	121 (21.6)	85 (15.2)	283 (50.5)	71 (12.7)
Female (n = 875)	208 (23.8)	139 (15.9)	421 (48.1)	107 (12.2)
DLCO (n = 881)				
Male (n = 387)	…	68 (17.6)	267 (69.0)	52 (13.4)
Female (n = 494)	…	109 (22.1)	311 (63.0)	74 (15.0)

Results are presented as No. (% of total participants in spirometry or DLCO analysis). DLCO = diffusing capacity for carbon monoxide.

TABLE 3]

Estimated Absolute and Relative Rates of Decline in FEV_1 Over a 6-Year Period

		Average Decline in FEV_1				ULN Decline in FEV_1			
		Absolute, mL/6 y		Relative, %/6 y		Absolute, mL/6 y		Relative, %/6 y	
Height	Age, y	Male	Female	Male	Female	Male	Female	Male	Female
Short	30s	146.7	117.2	3.4	3.9	517.3	383.0	12.5	13.3
	40s	166.8	132.6	4.2	4.8	536.8	398.1	13.4	14.1
	50s	186.9	148.0	5.1	5.7	556.8	413.3	14.2	15.0
	60s	207.0	163.4	5.9	6.6	577.2	428.8	15.1	15.9
	70s	227.1	178.7	6.8	7.4	598.1	444.4	16.0	16.8
Average	30s	180.7	132.8	3.8	4.0	550.8	398.4	13.0	13.3
	40s	200.7	148.2	4.6	4.9	570.4	413.5	13.8	14.2
	50s	220.8	163.6	5.5	5.7	590.4	428.8	14.7	15.1
	60s	240.9	179.0	6.4	6.6	611.0	444.3	15.5	16.0
	70s	261.0	194.4	7.2	7.5	632.0	460.1	16.4	16.8
Tall	30s	214.6	148.5	4.2	4.1	584.9	414.1	13.4	13.4
	40s	234.7	163.9	5.1	4.9	604.6	429.3	14.2	14.3
	50s	254.8	179.3	5.9	5.8	624.7	444.7	15.1	15.1
	60s	274.8	194.7	6.8	6.7	645.4	460.2	16.0	16.0
	70s	294.9	210.0	7.7	7.6	666.5	476.0	16.9	16.9

Average height is defined as the average height of the cohort for each sex (177 cm for male participants, 163 cm for female participants), short as being 1 SD below average (170 cm for male participants, 157 cm for female participants), and tall as being 1 SD above average (183 cm for male participants, 169 cm for female participants). ULN = upper limit of normal.

TABLE 4]

Estimated Absolute and Relative Rates of Decline in DLCO Over a 6-Year Period

	Average Decline in DLCO				ULN Decline in DLCO			
	Absolute, mL/mm Hg/min/6 y		Relative, %/6 y		Absolute, mL/mm Hg/min/6 y		Relative, %/6 y	
Age, y	Male	Female	Male	Female	Male	Female	Male	Female
30s	2.2	0.3	5.6	0.5	7.4	3.7	21.0	15.7
40s	2.7	0.7	7.7	2.9	7.8	4.2	23.0	18.1
50s	3.1	1.2	9.7	5.3	8.3	4.6	25.0	20.5
60s	3.6	1.6	11.8	7.7	8.7	5.1	27.1	22.9
70s	4.0	2.1	13.8	10.1	9.2	5.6	29.2	25.4

DLCO = diffusing capacity for carbon monoxide; ULN = upper limit of normal.