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Authors
Regan, Elizabeth A
Lynch, David A
Curran-Everett, Douglas
et al.

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Original Investigation

Clinical and Radiologic Disease in Smokers With Normal Spirometry

Elizabeth A. Regan, MD; David A. Lynch, MD; Douglas Curran-Everett, PhD; Jeffrey L. Curtis, MD; John H. M. Austin, MD; Philippe A. Grenier, MD; Hans-Ulrich Kauczor, MD; William C. Bailey, MD; Dawn L. DeMeo, MD; Richard H. Casaburi, PhD, MD; Paul Friedman, MD; Edwin J. R. Van Beek, MD; John E. Hokanson, PhD; Russell P. Bowler, MD; Terri H. Beaty, PhD; George R. Washko, MD; MeiLan K. Han, MD; Victor Kim, MD; Song Soo Kim, MD; Kunihiro Yagihashi, MD; Lacey Washington, MD; Charlene E. McEvoy, MD; Clint Tanner, MD; David M. Mannino, MD; Barry J. Make, MD; Edwin K. Silverman, MD; James D. Crapo, MD; for the Genetic Epidemiology of COPD (COPDGene) Investigators

IMPORTANCE Airflow obstruction on spirometry is universally used to define chronic obstructive pulmonary disease (COPD), and current or former smokers without airflow obstruction may assume that they are disease free.

OBJECTIVE To identify clinical and radiologic evidence of smoking-related disease in a cohort of current and former smokers who did not meet spirometric criteria for COPD, for whom we adopted the discarded label of Global Initiative for Obstructive Lung Disease (GOLD) 0.

DESIGN, SETTING, AND PARTICIPANTS Individuals from the Genetic Epidemiology of COPD (COPDGene) cross-sectional observational study completed spirometry, chest computed tomography (CT) scans, a 6-minute walk, and questionnaires. Participants were recruited from local communities at 21 sites across the United States. The GOLD 0 group (n = 4388) (ratio of forced expiratory volume in the first second of expiration [FEV_1] to forced vital capacity >0.7 and FEV_1 ≥80% predicted) from the COPDGene study was compared with a GOLD 1 group (n = 794), COPD groups (n = 3690), and a group of never smokers (n = 108). Recruitment began in January 2008 and ended in July 2011.

MAIN OUTCOMES AND MEASURES Physical function impairments, respiratory symptoms, CT abnormalities, use of respiratory medications, and reduced respiratory-specific quality of life.

RESULTS One or more respiratory-related impairments were found in 54.1% (2375 of 4388) of the GOLD 0 group. The GOLD 0 group had worse quality of life (mean [SD] St George's Respiratory Questionnaire total score, 17.0 [18.0] vs 3.8 [6.8] for the never smokers; $P < .001$) and a lower 6-minute walk distance, and 42.3% (127 of 300) of the GOLD 0 group had CT evidence of emphysema or airway thickening. The FEV_1 percent predicted distribution and mean for the GOLD 0 group were lower but still within the normal range for the population. Current smoking was associated with more respiratory symptoms, but former smokers had greater emphysema and gas trapping. Advancing age was associated with smoking cessation and with more CT findings of disease. Individuals with respiratory impairments were more likely to use respiratory medications, and the use of these medications was associated with worse disease.

CONCLUSIONS AND RELEVANCE Lung disease and impairments were common in smokers without spirometric COPD. Based on these results, we project that there are 35 million current and former smokers older than 55 years in the United States who may have unrecognized disease or impairment. The effect of chronic smoking on the lungs and the individual is substantially underestimated when using spirometry alone.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Genetic Epidemiology of COPD (COPDGene) Investigators are listed at the end of this article.

Corresponding Author: Elizabeth A. Regan, MD, National Jewish Health, 1400 Jackson St, Room K706, Denver, CO 80206 (regane@njhealth.org)

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Cigarette smoking continues to be a common addiction in the United States despite efforts to reduce its prevalence. Approximately 49% of adult Americans 45 years or older are current or former smokers, and approximately 19% of the adult population currently smoke.[1,2] Chronic obstructive pulmonary disease (COPD), a consequence of smoking, is the third leading cause of death in the United States and a major cause of chronic disability.[3] Although COPD is traditionally defined by airflow obstruction on spirometry, smoking-associated effects on the lungs related to COPD also include emphysema, gas trapping, and chronic bronchitis.[4,5] Current thinking that only a minority of smokers will ever develop COPD[6,7] may underestimate the potential for disease and impairment.

Symptoms such as productive cough, dyspnea, and exercise intolerance may be dismissed as normal aging, especially in older former smokers. Information is sparse about effects of smoking on individuals not diagnosed as having COPD (based on spirometry), and data from high-resolution computed tomography (CT) scanning in these individuals are limited.[8-10] Smoking cessation reduces the severity of respiratory symptoms and slows the mean rate of lung function decline but does not eliminate the risk of progressive lung disease.[11]

Studies[8,11-14] document a steady decrease in forced expiratory volume in the first second of expiration (FEV_1) associated with smoking that exceeds normal age-related decline. However, spirometry may be insensitive to early disease or subclinical lung pathology,[15] in part because variation in the maximally attained FEV_1 of young adulthood gives smokers with higher values a greater buffer before declining to defined disease levels.[11,16] Collectively, these considerations suggest that current spirometric criteria for diagnosing impairment due to COPD and identifying smoking-related lung disease may be inadequate.

We postulated that many chronic cigarette smokers (current and former) without spirometric evidence of COPD would have impairments in physical function, quality of life, and respiratory symptoms. We further theorized that high-resolution CT scanning would demonstrate significant lung disease in a substantial fraction of individuals. We studied a well-characterized cohort of smokers enrolled in the Genetic Epidemiology of COPD (COPDGene) cross-sectional observational study who did not meet spirometric criteria[17] for COPD and compared them with a small group of never smokers and with a Global Initiative for Obstructive Lung Disease (GOLD) 1 (mild COPD) group. We chose to use the label GOLD 0, which has been discarded from the GOLD classification, although this group is no longer included in the spirometric categories of the current GOLD classification. Population-based cohorts usually do not have enough diseased individuals for study. In contrast, a disease-specific cohort is not population based and may lack generalizability. We chose to align the 3 segments of the COPDGene cohort that had been recruited from a general population (never smokers, GOLD 0 individuals, and GOLD 1 individuals) to the population-based National Health and Nutrition Examination Survey (NHANES) cohort using spirometry and smoking exposure to enhance the generalizability of our findings.

Methods

Institutional review board approval of the study was obtained at 21 clinical centers. Written informed consent was obtained from all participants. The COPDGene study was funded in September 2007, and the first participants were enrolled in January 2008. Enrollment ended in July 2011. The COPDGene study includes 10 192 individuals 45 to 80 years old with at least a 10 pack-year smoking history, along with a comparison group of 108 never smokers of a similar age range. The details of the planned study design were described previously.[18] Individuals were self-identified as non-Hispanic African American or non-Hispanic white race. Only 2 racial groups were enrolled to provide adequate power for genetic analyses. Smokers were enrolled based on smoking history and were classified using GOLD spirometric criteria based on postbronchodilator spirometry.[17] Recruitment strategies for smokers with COPD included outpatient clinics, word-of-mouth communication to friends and spouses of individuals with COPD, advertisements, and outreach to community groups and churches. Participants were recruited from local communities at 21 sites across the United States. Clinical centers were instructed to not recruit individuals without COPD from pulmonary clinics and to target community sources. The never smokers were recruited from the same sources at 12 centers to reflect a normal aging distribution for CT-based lung changes without any diagnosed lung disease. Additional details of the study methods are described in the eMethods in the Supplement.

This report focuses on the GOLD 0 group (n = 4388), defined as current and former smokers with a normal postbronchodilator ratio of FEV_1 to forced vital capacity exceeding 0.7 and an FEV_1 percentage of at least 80% predicted. They were compared with never smokers (n = 108) and with the GOLD 1 (mild COPD) group (n = 794).

Imaging

Detailed CT protocols for the COPDGene study have been published previously.[18,19] Quantitative analysis of emphysema severity and gas trapping was performed on segmented images using software programs (3DSlicer; http://www.slicer.org and Pulmonary Workstation 2; vidadiagnostics).

Visual Scoring of Chest CT Scans

In total, 300 GOLD 0 CT scans were randomly selected for visual scoring.[20] One hundred scans were randomly selected from never smokers and GOLD 1 individuals. At least 2 and up to 5 readers (D.A.L., J.H.M.A., P.A.G., H.-U.K., S.S.K., K.Y., and J.D.C.) were blinded to group membership and independently read the CT scans. The scans with divergent readings were reread for a consensus score.

Impairments in Smokers

We prospectively defined 7 characteristics of impairment. These included chronic bronchitis, history of severe respiratory exacerbations, dyspnea (modified Medical Research Council dyspnea score[21] ≥2), quantitative emphysema exceeding 5%, quantitative gas trapping exceeding 20%, St George's Respi-

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Table 1. Genetic Epidemiology of COPD (COPDGene) Cohort

Variable	Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)	GOLD 2-4 (n = 3690)
Age, mean (SD), y	62.1 (9.2)	56.7 (8.4)[a]	61.7 (9.0)[b]	63.4 (8.5)
Male sex, No. (%)	34 (31.5)	2320 (52.9)[a]	457 (57.6)[c]	2025 (55.6)[c]
Non-Hispanic white race, No. (%)	100 (92.5)	2581 (58.8)[a]	614 (77.3)[b]	2854 (77.3)[b]
Current smoking, No. (%)	0	2619 (59.7)[a]	443 (55.8)[c]	1501 (40.7)[b]
Pack-years, mean (SD)	0	37.2 (20.2)[a]	45.0 (24.6)[b]	53.0 (27.5)[b]
BMI, mean (SD)	28.2 (5.0)	28.9 (5.8)	27.1 (5.1)[b]	28.1 (6.3)[b]
At least some college, No. (%)	98 (90.7)	2759 (62.9)[a]	539 (67.9)[c]	1920 (58.4)[b]
Continuous Variables Adjusted for Age, Sex, and Race				
BMI >30, No. (%)	34 (31.5)	1615 (36.8)	185 (23.3)[b]	1226 (33.2)[c]
Coronary artery disease, No. (%)	1 (0.9)	329 (7.5)[a]	98 (12.3)[b]	608 (16.5)[b]
Diabetes mellitus, No. (%)	10 (9.3)	507 (11.6)	67 (8.4)[c]	482 (13.1)[b]
Any cancer, No. (%)	8 (7.4)	157 (3.6)	44 (5.5)[c]	249 (6.8)[b]
Comorbid disease score, mean (SD)	0.6 (1.0)	1.0 (1.1)	1.0 (1.1)[a]	1.4 (1.2)[b]
FEV_1 % predicted, mean (SD)	104.0 (11.6)	97.6 (11.8)[d]	91.1 (11.5)[b]	51.0 (16.2)[b]
FVC % predicted, mean (SD)	100.3 (12.0)	96.7 (12.1)[a]	108.6 (12.3)[b]	77.1 (15.9)[b]
Ratio of FEV_1 to FVC, mean (SD)	0.81 (0.05)	0.79 (0.05)[d]	0.66 (0.05)[b]	0.51 (0.10)[b]
Functional residual capacity by CT, mean (SD)	2.6 (0.6)	2.7 (0.7)	3.2 (0.7)[b]	3.8 (1.0)[b]
Total lung capacity by CT, mean (SD)	5.2 (0.9)	5.2 (1.0)	5.7 (1.0)[b]	5.6 (1.1)[b]
Function and quality of life, mean (SD)				
Six-minute walk distance, m	493 (102)	447 (103)[d]	442 (105)[a]	345 (120)[b]
SGRQ total score	7.0 (17.1)	17.6 (17.6)[d]	21.3 (18.0)[b]	43.3 (21.3)[b]
SGRQ impact	4.0 (14.8)	10.9 (15.2)[d]	13.8 (15.6)[b]	32.1 (19.9)[b]
SGRQ symptom	6.6 (21.3)	22.4 (21.8)[d]	28.8 (22.5)[b]	48.0 (25.2)[b]
SGRQ activity	12.4 (24.5)	27.0 (25.1)[d]	30.6 (25.5)[b]	60.4 (28.4)[b]
SF-36 physical component score	52.8 (9.7)	47.4 (9.8)[d]	47.8 (10.0)[a]	37.9 (10.9)[b]
SF-36 mental component score	52.9 (10.9)	49.3 (11.1)[a]	49.0 (11.2)[a]	46.6 (12.5)[b]
Symptoms, No./total No. (%)				
Modified Medical Research Council dyspnea score ≥2	4 (3.7)	1029/4387 (23.5)[a]	175 (22.4)[c]	2447/3677 (66.6)[b]
Chronic bronchitis	0	552 (12.6)[a]	125 (15.7)[c]	1039 (28.2)[b]
Severe exacerbation	0	190 (4.3)[a]	39 (4.9)[a]	837 (22.7)[b]
Bronchodilator responsiveness	5 (4.6)	431/4309 (10.0)	204/783 (26.1)[b]	1341/3668 (36.6)[b]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, computed tomography; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; SF-36, 36-Item Short Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

[a] $P < .05$ compared with never smokers.

[b] $P < .001$ for comparison of GOLD 1 or GOLD 2-4 with GOLD 0.

[c] $P < .05$ only.

[d] $P < .001$ compared with never smokers.

ratory Questionnaire (SGRQ) total score[22] exceeding 25, and a 6-minute walk distance of less than 350 m.

Medication Use

Respiratory medication use in the Gold 0 group was compared between individuals with and without any impairment by category (beta-agonists, inhaled corticosteroids, and inhaled anticholinergics). In addition, individuals who reported medication use were compared with those who did not.

Statistical Analysis

We analyzed discrete data and dichotomous data using χ^2 test or Fisher exact test. For continuous data, we used the *t* test (for normal data) or Wilcoxon rank sum test (for nonnormal data). We considered $\alpha < .05$ to be statistically significant. We estimated least squares means for continuous variables after adjusting for age, sex, race, and group in the basic description of the COPDGene cohort in **Table 1**. We used multiple linear regression to assess the factors predicting respiratory quality of life, as measured by the SGRQ total score, among smokers with normal spirometry. We selected variables for the initial regression model from univariate analyses that demonstrated differences between the study groups and that were associated clinically with quality of life for individuals with COPD. We then refined this initial regression model using backward elimination to eliminate nonsignificant terms. Model fit was assessed using residual plots, which demonstrated that the model was appropriate. We used statistical software (JMP, version 10, and SAS, version 9.2; SAS Institute) to analyze the data.

NHANES Cohort

To assess the generalizability of COPDGene data to the broader population, we used the NHANES population. We

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Table 2. Quantitative Computed Tomography Scoring and Visual Scoring

Variable	Never Smokers	GOLD 0	GOLD 1	GOLD 2-4
Quantitative Computed Tomography Scoring	**(n = 108)**	**(n = 4388)**	**(n = 794)**	**(n = 3690)**
% LAA at −950 Hounsfield units inspiratory, mean (SD) [range] (n = 8472)[a]	1.9 (2.4) [0.02-13.0]	2.0 (2.5) [0.004-25.0]	5.2 (5.7) [0.02-43.0][b]	13.0 (12.8) [0.02-61.9][b]
No./total No. (%) with >5% emphysema	9 (8.3)	428/4110 (10.4)	273/760 (35.9)[b]	2107/3437 (61.3)[b]
% LAA at −856 Hounsfield units expiratory, mean (SD) [range] (n = 7668)[c]	10.2 (9.1) [0.6-53.6]	11.0 (9.7) [0.03-83.4]	20.3 (12.3) [0.36-68][d]	39.2 (20.8) [0.14-87.8][b]
No./total No. (%) with >20% gas trapping	11/105 (10.5)	536/3708 (14.5)	319/678 (47.1)[b]	2419/3123 (77.5)[b]
Airway wall area percentage, mean (SD)[e]				
Segmental airway (n = 8483)	58.4 (2.1)[d]	60.1 (2.9)	60.3 (2.8)[d]	62.9 (3.1)[b]
Subsegmental airway (n = 3053)	62.3 (2.0)[d]	63.1 (2.2)	63.3 (2.1)	65.7 (2.4)[b]
No./total No. (%) with segmental airway wall area percentage >61.2[f]	8 (7.4)[d]	1325/4118 (32.2)	260/760 (34.2)	2448/3440 (71.2)[d]
Visual Scoring in a Subset of Individuals, No. (%)	**(n = 100)**	**(n = 300)**	**(n = 100)**	**(n = 392)**
Definite emphysema	3 (3.0)[b]	72 (24.0)	68 (68.0)[b]	256 (65.3)[b]
Airway thickening	9 (9.0)[b]	92 (30.7)	67 (67.0)[b]	276 (70.4)[b]
Emphysema or airway disease	10 (10.0)[b]	127 (42.3)	81 (81.0)[b]	392 (100)[b]

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; LAA, low attenuation area.

[a] Represents the percentage of LAA at −950 Hounsfield units on inspiratory chest computed tomography scan (near-air density) and is a surrogate for the degree of emphysema. It does not discriminate well between normal lungs and emphysematous lungs at levels below 5%.

[b] $P < .001$ compared with GOLD 0.

[c] Represents the percentage of LAA at −856 Hounsfield units on expiratory chest computed tomography and is a surrogate for gas trapping in the lungs.

[d] $P < .05$ compared with GOLD 0.

[e] Represents the percentage of the total airway cross-sectional area that is tissue (wall).

[f] The 61.2 is the median value for the whole cohort, including those with chronic obstructive pulmonary disease, selected as the reference value for airway wall thickening.

reclassified our participants based on their prebronchodilator spirometry values, extracted an age-similar population from the NHANES, and grouped both cohorts as never smokers, smokers without COPD by GOLD criteria (GOLD 0), and GOLD 1. The objective of this comparison was to determine whether the COPDGene never smokers and GOLD 0 group had spirometry similar to that of individuals from the general population.

We identified non-Hispanic African American and non-Hispanic white individuals 45 to 80 years old from the 2007 to 2010 NHANES data set who were never smokers or who had smoking exposure equivalent to that of the COPDGene cohort (minimum of 10 pack-years of smoking). Members of the NHANES cohort were selected from a total of 20 686 enrolled individuals. We excluded the following groups: individuals younger than 45 years and older than 80 years (n = 14 421), Hispanic or mixed-race individuals (n = 1997), never smokers with abnormal spirometry (n = 711), any individual with missing spirometry (n = 541), smokers whose spirometry was classified as Preserved Ratio Impaired Spirometry (n = 197),[23,24] and smokers with less than 10 pack-years of smoking history (n = 364). The final NHANES cohort for analysis included 2455 individuals.

Results

GOLD 0 Group

The GOLD 0 group was significantly younger and had less smoking exposure than the individuals with COPD in the GOLD 1 through GOLD 4 groups (mean [SD], 37.2 [20.2] pack-years vs 45.0 [24.6] pack-years in the GOLD 1 group; $P < .001$) (Table 1 and eFigure 1 and eTable 1 in the Supplement). The GOLD 0 group had higher proportions of women and non-Hispanic African Americans. Variables in Table 1 were adjusted for age, sex, and race to address those differences. Current smoking was more common in the GOLD 0 group than in the GOLD 1 group (59.7% [2619 of 4388] vs 55.8% [443 of 794], $P < .001$), and body mass index (calculated as weight in kilograms divided by height in meters squared) was higher than in the GOLD 1 group, as was the proportion with obesity (body mass index, >30). Rates for dyspnea and respiratory exacerbations were similar in the GOLD 0 and GOLD 1 groups, while chronic bronchitis was more frequent in the GOLD 1 group. Comorbid diseases were more common in both the GOLD 0 and GOLD 1 groups compared with never smokers, although the never smokers had significant comorbid disease, reflecting the age distribution of the group. Detailed information by race is provided in eTable 2 and eTable 3 in the Supplement.

NHANES Cohort

Individuals selected from the 2007 to 2010 NHANES for comparison with the COPDGene cohort are described in eTable 4 in the Supplement. There were 1176 never smokers and 748 GOLD 0 group members in the NHANES cohort. Age distributions were similar to those of the COPDGene cohort, and there were slightly more men (41.1% [483 of 1176]) in the never smokers and more non-Hispanic African Americans (29.4% [346 of 1176]). Current smoking was higher in the COPDGene cohort vs NHANES (59.7% [2619 of 4388] vs 48.8% [352 of 721]), and pack-years in COPDGene (37.2 vs 34.2) were also slightly higher than NHANES. The never smokers in the NHANES had significant comorbid disease (44.5% [522 of 1174] with obesity, 13.1% [154 of 1176] with cancer, and 5.7% [67 of 1174] with coronary artery disease) as did the never smokers group in COPDGene consistent with age distribution.

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Radiologic Findings

There was a significant increase in airway wall area percentage at the segmental and subsegmental levels in the GOLD 0 group compared with never smokers (**Table 2**). The mean values for emphysema (percentage low attenuation area, −950 Hounsfield units) and gas trapping (percentage low attenuation area, −856 Hounsfield units) were similar. After combining the individuals who had emphysema exceeding 5% or gas trapping exceeding 20% on CT analysis, 26.0% (964 of 3708) of the GOLD 0 group had quantitative radiologic evidence of lung disease. Evidence of bronchial airway disease was seen with increased segmental airway wall area percent (mean [SD], 60.1 [2.9] of the GOLD 0 group vs 58.4 [2.1] of never smokers; $P < .001$) in the GOLD 0 group, and 32.2% (1325 of 4118) of them had values above the median airway wall area percent of 61.2. There was a steady increase in the proportion of individuals with emphysema or gas trapping disease in each decade of advancing age among the current and former smokers ($P < .001$, Cochran-Armitage test for trend).

Visual scoring on the 300 randomly selected CT scans demonstrated significant increases in emphysema and airway thickening in the GOLD 0 group (24.0% [72 of 300] and 30.7% [92 of 300], respectively) compared with never smokers (3.0% [3 of 100] and 9.0% [9 of 100], respectively). Overall, 42.3% (127 of 300) of CT scans in the GOLD 0 group showed emphysema or airway thickening, and 84.7% (61 of 72) of those who visually scored positive for emphysema had less than 5% quantitative emphysema, suggesting that visual scoring is more sensitive in identifying emphysema. Representative CT examples are shown in eFigure 2 in the Supplement of GOLD 0 group members who had definite emphysema or definite airway thickening. In both individuals whose CT scans are depicted in eFigure 2 in the Supplement, there were significant imaging abnormalities, despite preserved airflow.

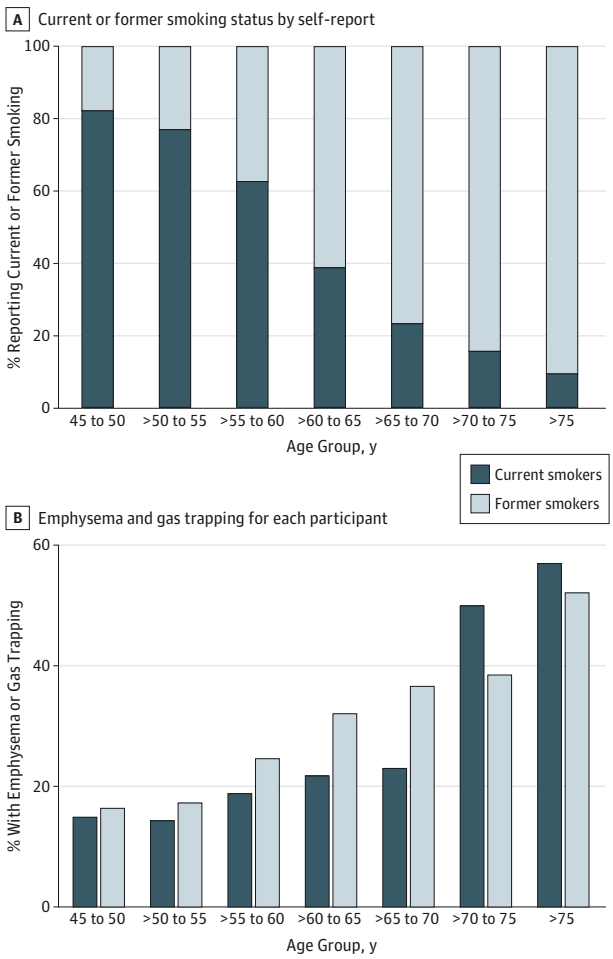
Respiratory Symptoms

Significant dyspnea (modified Medical Research Council dyspnea score, ≥2) was reported in 23.5% (1029 of 4387) of the GOLD 0 group vs only 3.7% (4 of 108) of never smokers and 22.7% (175 of 794) of the GOLD 1 group. Episodes of severe respiratory exacerbations over the previous year were reported in the GOLD 0 group at a rate similar to that in the GOLD 1 group (4.3% [190 of 4388] and 4.9% [39 of 794], respectively). Chronic bronchitis was present in 12.6% (552 of 4388) of the GOLD 0 group, although the 15.7% (125 of 794) reported in the GOLD 1 group was significantly higher ($P = .02$). Never smokers had no reports of severe respiratory exacerbations or chronic bronchitis.

Comparison of Current vs Former Smokers

Current smokers showed striking differences compared with former smokers (eTable 1 in the Supplement). In the GOLD 0 group, current smokers were younger and had a lower educational level, fewer comorbid diseases, and greater pack-years of smoking. They had a lower 6-minute walk distance, worse SGRQ total scores, and more dyspnea, chronic bronchitis, and exacerbations. However, they also had less emphysema and gas trapping but higher airway wall area percentage, suggesting greater active airway inflammation. The pattern of more symptoms but less emphysema and gas trapping with more airway thickening among current smokers persisted in the GOLD 1 group and in the GOLD 2 through 4 groups. Individuals in all groups were likely to stop smoking with advancing age, especially in those older than 60 years (**Figure 1** and eFigure 3 in the Supplement), although no data were collected regarding their reasons for smoking cessation.

Figure 1. With Advancing Age, Current Smoking Decreases, and Emphysema and Gas Trapping Increase in the Global Initiative for Obstructive Lung Disease (GOLD) 0 Group



A, Current or former smoking status was assessed in the GOLD 0 group by self-report. The percentage of individuals reporting current or former smoking in each age category is shown and demonstrates steady declines in current smoking with advancing age. Individuals were not surveyed about their reasons for smoking cessation. B, The presence of emphysema and gas trapping was determined for each participant. Individuals with emphysema (>5%) or gas trapping (>20%) were identified by age group. Overall, 20.1% (744 of 3708) of the GOLD 0 group had abnormal emphysema or gas trapping. After age 75 years, 65.3% (382 of 585) of current and former smokers had radiologic evidence of disease. The increase in emphysema or gas trapping by advancing age group ($P < .001$ for both, Cochran-Armitage test for trend) supports the hypothesis that imaging changes are later manifestations of smoking-related lung disease. The age-related pattern is present in current and former smokers ($P < .001$ for both, Cochran-Armitage test for trend).

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Table 3. Smokers With Symptoms or Impairments, Including Individuals With Self-reported Asthma

Variable	No. (%)		
	Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)
Individual Scores			
Chronic bronchitis, by criteria	0	552 (12.6)	125 (15.7)
History of ≥1 severe exacerbation	0	190 (4.3)	39 (4.9)
St George's Respiratory Questionnaire total score >25	4 (3.7)	1143 (26.0)	226 (28.5)
Six-minute walk distance <350 m	4 (3.7)	674 (15.4)	109 (13.7)
Modified Medical Research Council dyspnea score ≥2	4 (3.7)	1029 (23.5)	175 (22.0)
Emphysema >5%	9 (8.3)	428 (9.8)	273 (34.4)
Gas trapping >20%	11 (10.2)	536 (12.2)	319 (40.2)
Sums			
Any impairment	26 (24.1)	2375 (54.1)	585 (73.7)
6 Impairments	0	8 (0.2)	6 (0.8)
5 Impairments	0	32 (0.7)	17 (2.1)
4 Impairments	0	156 (3.6)	65 (8.2)
3 Impairments	1 (0.9)	414 (9.4)	92 (11.6)
2 Impairments	4 (3.7)	690 (15.7)	204 (25.7)
1 Impairment	21 (19.4)	1089 (24.8)	201 (25.3)
No impairment	82 (75.9)	1990 (45.4)	209 (26.3)

Table 4. Respiratory Medications

Medication Use by Individuals With Symptoms or Impairments, No. (%)	Never Smokers (n = 26)	GOLD 0 (n = 2375)	GOLD 1 (n = 585)	GOLD 2-4 (n = 3690)
Any respiratory medications	0	475 (20.0)	170 (29.1)	2768 (75.0)
Inhaled long- and short-acting β-agonists	0	411 (17.3)	146 (25.0)	2616 (70.9)
Single-drug or combination inhaled corticosteroids	0	183 (7.7)	91 (15.6)	1886 (51.1)
Inhaled anticholinergics[a]	0	157 (6.6)	88 (15.0)	2033 (55.1)
Chronic oral corticosteroids	0	18 (0.7)	5 (0.9)	218 (5.9)
Medication Use by Individuals Without Symptoms or Impairments, No. (%)	**Never Smokers (n = 82)**	**GOLD 0 (n = 1990)**	**GOLD 1 (n = 209)**	**Gold 2-4 (n = 193)**
Any respiratory medications	2 (2.7)	99 (5.0)	24 (11.6)	39 (1.5)
Inhaled long- and short-acting β-agonists	1 (1.4)	84 (4.2)	21 (10.1)	33 (1.4)[b]
Single-drug or combination inhaled corticosteroids	0	36 (1.8)	7 (3.2)	18 (1.0)[b]
Inhaled anticholinergics[a]	0	12 (0.6)	7 (3.2)	15 (0.8)[b]
Chronic oral corticosteroids	0	2 (0.1)	1 (0.5)	1 (0.5)[b]

[a] Tiotropium bromide, ipratropium bromide, or combination with albuterol.

[b] n = 187.

Impairments and Use of Medications

Impairments were common among the GOLD 0 group: 54.1% (2375 of 4388) of these current and former smokers had 1 or more impairments compared with 73.7% (585 of 794) of the GOLD 1 group and 24.1% (26 of 108) of the never smokers. The GOLD 0 group had worse quality of life (mean [SD] SGRQ total score, 17.0 [18.0] vs 3.8 [6.8] for the never smokers; $P < .001$). Analysis of the relative frequency of each impairment and of the cumulative frequency of impairments showed that the GOLD 0 group was more similar to the GOLD 1 group than to the never smokers (**Table 3**). A modest effect of participant-reported asthma on reports of impairments is shown in eTable 5 in the Supplement.

Medication use also suggests clinically significant respiratory disease in the GOLD 0 group. Among individuals with respiratory impairments or symptoms (n = 2375), 20.0% (475 of 2375) were using some respiratory medication compared with 29.1% (170 of 585) of the symptomatic individuals in the GOLD 1 group (**Table 4** and **Table 5**). By contrast, only 5.96% (108 of 1812) of the GOLD 0 group members without impairments or symptoms used respiratory medications. Individuals who had been prescribed medications were more likely to be female and reported worse dyspnea, greater exacerbations, and more chronic bronchitis, with much worse quality of life and more airway disease (but not greater emphysema or gas trapping).

Functional Exercise Tolerance and Quality of Life

The GOLD 0 group had a significantly worse 6-minute walk distance than never smokers (mean [SD], 447 [103] vs 493 [102] m; $P < .001$). All 4 scales of the SGRQ were significantly higher (worse) in the GOLD 0 group compared with never smokers,

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Table 5. GOLD 0 Individuals Who Use Respiratory Medications

Individuals Who Use Respiratory Medications	Use (n = 611)	No Use (n = 3760)	*P* Value
Age, mean (SD), y	56.3 (8.4)	56.7 (8.4)	.56
Female sex, No./total No. (%)	420/657 (63.9)	1634/3710 (44.0)	<.001
Non-Hispanic African American race, No./total No. (%)	318/657 (48.4)	1479/3710 (39.9)	<.001
Current smoking, No./total No. (%)	398/657 (60.6)	2141/3710 (57.7)	.16
Pack-years, mean (SD)	40.8 (23.7)	36.6 (19.5)	.01
Six-minute walk distance, mean (SD), m	404 (106)	463 (104)	<.001
Severe exacerbation, No./total No. (%)	133/657 (20.2)	62/3710 (1.7)	<.001
Chronic bronchitis, No./total No. (%)	164/657 (25.0)	369/3710 (10.0)	<.001
Modified Medical Research Council dyspnea score ≥2, No./total No. (%)	354/657 (53.9)	667/3710 (18.0)	<.001
St George's Respiratory Questionnaire total score, mean (SD)	36.3 (21.2)	13.8 (15.2)	<.001
% LAA at −950 Hounsfield units inspiratory, mean (SD)	1.95 (2.96)	1.99 (2.40)	.32
Emphysema >5%, No./total No. (%)	60/657 (9.3)	368/3710 (9.9)	.23
% LAA at −856 Hounsfield units expiratory, mean (SD)	10.8 (9.7)	11.0 (9.7)	.79
Gas trapping >20%, No./total No. (%)	82/555 (14.8)	451/3137 (14.4)	.71
Airway wall area percentage, mean (SD) (n = 3969)	60.8 (2.9)	59.9 (2.9)	<.001
No. (%) with segmental airway wall area percentage >61.2[a]	53	47	<.001

Abbreviation: LAA, low attenuation area.

[a] The 61.2 is the median value for the whole cohort, including those with chronic obstructive pulmonary disease, selected as the reference value for airway wall thickening.

suggesting that smoking affects this group broadly. We also compared the 36-Item Short Form Health Survey version 2 physical and mental component scores and found that the GOLD 0 group had significantly worse quality-of-life scores on both components than never smokers ($P < .001$) (Table 1).

Factors That Predicted Worse Quality of Life Among the GOLD 0 Group

Using the SGRQ total score as the outcome variable in a multiple regression model, we tested the following variables as predictors: age, sex, race, body mass index, current smoking status, pack-years, chronic bronchitis, severe exacerbations, any flare of respiratory trouble, bronchodilator responsiveness, FEV_1 percentage predicted, coronary artery disease, gastroesophageal reflux disease, and modified Medical Research Council dyspnea score. Except for race, sex, bronchodilator responsiveness, and FEV_1 percentage predicted, all other variables were significant predictors of quality of life in the GOLD 0 group (eTable 6 in the Supplement).

NHANES Comparison and Occult Airflow Obstruction

The distribution of prebronchodilator FEV_1 percentage predicted values among the 3 groups (never smokers, GOLD 0, and GOLD 1) of the COPDGene cohort is similar to that of the 3 groups in the NHANES (**Figure 2**). The results incorporating a large group of never smokers and still sizable numbers of GOLD 0 and GOLD 1 individuals suggest that these groups in the COPDGene cohort are similar to a truly population-based cohort and that the decrease in the mean FEV_1 between never smokers and the GOLD 0 group is less likely to be due to skewed recruitment of participants. Rates of coronary artery disease in the GOLD 0 group were 7.5% (329 of 4388) for the COPDGene cohort and 10.3% (74 of 719) for the NHANES cohort, and obesity prevalences in the GOLD 0 group were 36.8% (1615 of 4388) for the COPDGene cohort and 41.7% (300 of 719) for the NHANES cohort.

Discussion

This study demonstrates that many current and former smokers who did not meet the spirometric criteria for COPD had significant respiratory disease. There was clinical disease with dyspnea, chronic bronchitis, lower 6-minute walk distances, and worse quality of life, and more than half of the individuals had emphysema or evidence of airway disease on CT scan, demonstrating physiological changes from smoking. It appears that smoking progressively takes its toll with advancing age, even when spirometry remains within the population norms. Current smokers had more ongoing respiratory symptoms. However, with advancing age, the numbers of former smokers increased, and they had more smoking-related symptoms and CT-identified lung disease.

Quantitative analysis of airway wall area percentage showed increased airway thickness in 32.2% (1325 of 4118) of the GOLD 0 group, and 42.3% (127 of 300) of our visually scored CT scans in the GOLD 0 group manifested significant emphysema or airway thickening, demonstrating how imaging complements spirometry to define smoking-induced lung damage. Visual scoring was more sensitive in identifying early emphysema than quantitative analysis of lung density and identified a high frequency of airway wall thickening in this group.[25] Computed tomography scans have previously identified early emphysema and airway disease in smokers without spirometric disease,[8,26] and this structural lung damage was associated with greater decline in lung function.[10] In our large group of GOLD 0 members, we found lung damage among a sizable proportion, and the proportion increased with age.

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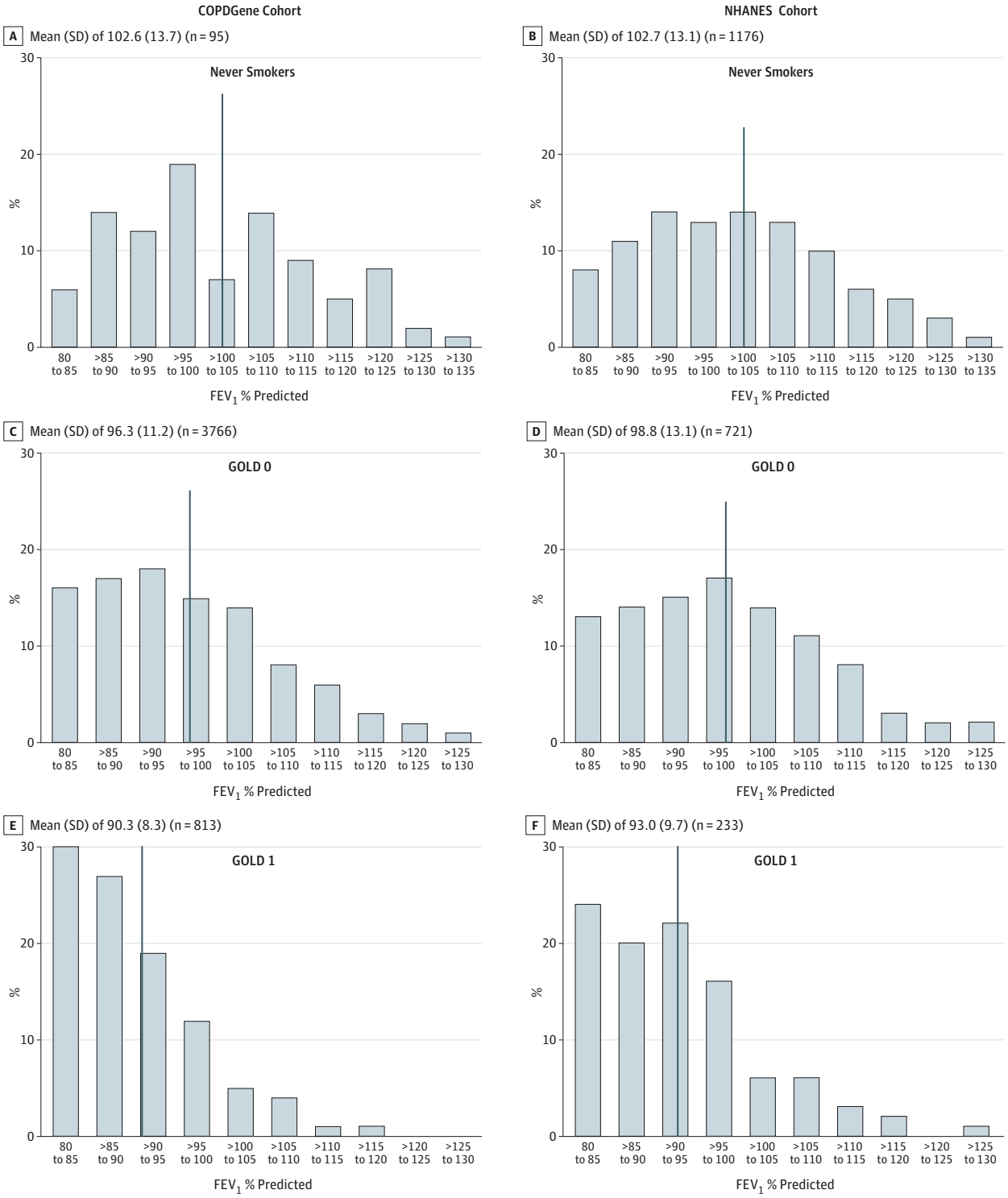
Figure 2. Evidence of Occult Obstructive Disease in the Global Initiative for Obstructive Lung Disease (GOLD) 0 Group



Histograms of prebronchodilator forced expiratory volume in the first second of expiration (FEV_1) percent predicted values in the Genetic Epidemiology of COPD (COPDGene) cohort and the 2007 to 2010 National Health and Nutrition Examination Survey (NHANES) cohort, segregated by never smokers, GOLD 0 smokers, and GOLD 1 smokers. The black bar in each graph demarcates the mean for that group. For visual clarity, graphs were minimally truncated above 135% of the FEV_1 percentage predicted. Individual panels represent the distributions of prebronchodilator FEV_1 percent predicted in the 6 groups. COPD indicates chronic obstructive pulmonary disease.

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We used a conservative cutoff for emphysema (>5% lung attenuation area at −950 Hounsfield units, representing the 95th percentile for never smokers). In the GOLD 0 group, we found that 10.4% (428 of 4110) of the individuals had emphysema exceeding that level. A recent study by Mohamed Hoesein et al[27] using CT scans from the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) instead selected the 75th percentile (1.2% for current smokers and 1.7% for former smokers). Using those criteria, we would have identified more CT emphysema and matched our visual scoring of emphysema more closely.

A significant proportion of the GOLD 0 group (54.1% [2375 of 4388]) had 1 or more respiratory-related impairments related to smoking. The impairments that we quantified are commonly identified in individuals with known COPD, supporting the association of these characteristics with effects of smoking on lung and general health. Comparison with the GOLD 1 group, defined as having mild COPD, demonstrates similar proportions of individuals with these impairments, but they are distinguished primarily by greater levels of radiologic findings. In general, the GOLD 0 group had significantly worse quality of life, more respiratory exacerbations, and reduced physical function compared with the somewhat older never smokers. For individuals who ostensibly did not have obstructive lung disease, adjusted models showed that current smoking, pack-years, respiratory symptoms and exacerbations, and dyspnea accounted for a large proportion of the variance in their quality of life.

The GOLD 0 group was younger and had fewer pack-years of smoking exposure than the GOLD 1 group in both the COPDGene and NHANES cohorts, suggesting that some portion of the GOLD 0 group may be in an earlier phase of lung disease, with the potential to progress. The GOLD 0 group had evidence of airflow obstruction compared with never smokers of similar age despite falling within the population norms for FEV_1. We postulate that some of these smokers may have attained a lower maximal lung function earlier in life given that the smoking habit began before age 19 years in 74.1% (3253 of 4388) of the GOLD 0 group or sustained a significant loss of airflow. Burrows[16] described both of these proposed mechanisms in his description of obstructive lung disease, and he and Fletcher and Peto[11] demonstrated the effect of smoking on the natural history of chronic airflow obstruction. More recent work has confirmed reductions in maximal lifetime FEV_1 in smokers, and the presence of respiratory symptoms (eg, chronic bronchitis) increases the rate of FEV_1 decline.[28] Therefore, we believe that a single measurement of FEV_1 can be used to identify obstruction when it is below a population-defined lower limit of normal, but it may not be able to define loss of function when it remains above a population norm but has declined significantly for an individual.

Although current guidelines[29] for treating COPD do not include treating smokers with normal spirometry, practicing physicians appear to recognize the role of medications to relieve symptoms. Respiratory medications were being taken by 20.0% (475 of 2375) of the subset of the GOLD 0 group with 1 or more impairments. Despite the use of medication by these individuals, they reported more symptoms and had more evidence of airway disease. Further research is needed to delineate effective treatments for the GOLD 0 group of patients.

The study has several limitations. Recruitment of smokers without COPD was community based and focused on a smoking history rather than known COPD. Although we have shown that the study groups align well with the NHANES cohort, our study was not rigorously population based, and it is possible that the recruitment strategy we used resulted in a group with greater symptoms or imaging abnormalities than would be found in another study. However, rates of coronary artery disease and obesity in our GOLD 0 group were slightly lower than those in the NHANES cohort, suggesting that we have not recruited a sicker group of individuals. Findings may differ in other racial groups.

Conclusions

Overall, our findings point to limitations in the current diagnostic criteria for COPD and suggest that smokers with clinical and physiological disease are not identified by spirometry. Some authors have identified difficulties in defining a disease in which there are alternative definitions.[30,31] Chronic obstructive pulmonary disease has a spirometric definition but also pathologic and structural changes (emphysema and large and small airway inflammation with thickening), in addition to symptoms of dyspnea, exercise limitations, and chronic bronchitis. We found that more than half of the smokers with normal spirometry have significant disease. We believe that our results highlight the importance of smoking prevention and cessation as a primary strategy to prevent lung disease and other long-term effects of smoking. In the US population of more than 76 million people 55 years or older, there are an estimated 35 million who are current or former smokers, many of whom may remain undiagnosed when identification of COPD is based solely on spirometry.[2,32] Unfortunately, stopping smoking does not appear to eliminate lung disease, and these individuals may require the attention of health care systems.[33] Strategies to prevent the development and progression of COPD are needed for this large segment of the US population.

ARTICLE INFORMATION

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Author Affiliations: National Jewish Health, Denver, Colorado (Regan, Lynch, Curran-Everett, Bowler, Tanner, Make, Crapo); Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Anschutz Medical Campus, Aurora (Regan, Hokanson); Section of Pulmonary and Critical Care Medicine, Medical Service, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan (Curtis); Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Health System, Ann Arbor (Curtis, Han); Department of Radiology, Columbia University Medical Center, New York, New York (Austin); Department of Diagnostic Radiology, Hôpital Pitié-Salpêtrière, Assistance Publique–Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France (Grenier); Department of Diagnostic and Interventional Radiology, University of Heidelberg, Heidelberg, Germany (Kauczor); Translational Lung Research Center Heidelberg, German Center of Lung Research, University of Alabama, Birmingham

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(Bailey); Pulmonary and Critical Care, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (DeMeo, Washko, Silverman); Division of Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute, Harbor–University of California, Los Angeles, Medical Center, Torrance (Casaburi); Department of Radiology, University of California, San Diego (Friedman); Department of Radiology, University of Edinburgh, Edinburgh, Scotland (Van Beek); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Beaty); Section of Pulmonary and Critical Care Medicine, Department of Medicine, Temple University, Philadelphia, Pennsylvania (V. Kim); Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea (S. S. Kim); Department of Radiology, St Marianna University School of Medicine, Sugao, Miyamaeku, Kawasaki, Kanagawa, Japan (Yagihashi); Department of Radiology, Duke University Medical Center, Durham, North Carolina (Washington); Pulmonary Medicine, HealthPartners, Minneapolis–St Paul, Minnesota (McEvoy); Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Preventive Medicine and Environmental Health, College of Public Health, University of Kentucky, Lexington (Mannino).

Author Contributions: Dr Regan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Regan, Lynch, Curran-Everett, Curtis, Bailey, DeMeo, Casaburi, Friedman, Van Beek, Hokanson, Bowler, Beaty, Washko, Han, V. Kim, McEvoy, Tanner, Mannino, Make, Silverman.
Acquisition, analysis, or interpretation of data: Regan, Lynch, Curran-Everett, Austin, Grenier, Kauczor, Bailey, Casaburi, Bowler, Washko, S. S. Kim, Yagihashi, Washington, Crapo.
Drafting of the manuscript: All authors.

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Group Information: The Genetic Epidemiology of COPD (COPDGene) Investigators are as follows:
COPDGene® Investigators—Core Units.
Administrative Core: James Crapo, MD (PI), Edwin Silverman, MD, PhD (PI), Barry Make, MD, Elizabeth Regan, MD, PhD. *Genetic Analysis Core*: Terri Beaty, PhD, Nan Laird, PhD, Christoph Lange, PhD, Michael Cho, MD, Stephanie Santorico, PhD, John Hokanson, MPH, PhD, Dawn DeMeo, MD, MPH, Nadia Hansel, MD, MPH, Craig Hersh, MD, MPH, Peter Castaldi, MD, MSc, Merry-Lynn McDonald, PhD, Emily Wan, MD, Megan Hardin, MD, Jacqueline Hetmanski, MS, Margaret Parker, MS, Marilyn Foreman, MD, Brian Hobbs, MD, Robert Busch, MD, Adel El-Bouiez, MD, Peter Castaldi, MD, Megan Hardin, MD, Dandi Qiao, PhD, Elizabeth Regan, MD, Eitan Halper-Stromberg, Ferdouse Begum, Sungho Won, Brittney Fredericksen, Sharon Lutz, PhD. *Imaging Core*: David A Lynch, MB, Harvey O Coxson, PhD, MeiLan K Han, MD, MS, MD, Eric A Hoffman, PhD, Stephen Humphries MS, Francine L Jacobson, MD, Philip F Judy, PhD, Ella A Kazerooni, MD, John D Newell, Jr., MD, Elizabeth Regan, MD, James C Ross, PhD, Raul San Jose Estepar, PhD, Berend C Stoel, PhD, Juerg Tschirren, PhD, Eva van Rikxoort, PhD, Bram van Ginneken, PhD, George Washko, MD, Carla G Wilson, MS, Mustafa Al Qaisi, MD, Teresa Gray, Alex Kluiber, Tanya Mann, Jered Sieren, Douglas Stinson, Joyce Schroeder, MD, Edwin Van Beek, MD, PhD. *PFT QA Core, Salt Lake City, UT*: Robert Jensen, PhD. *Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO*: Douglas Everett, PhD, Anna Faino, MS, Matt Strand, PhD, Carla Wilson, MS. *Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO*: John E. Hokanson, MPH, PhD, Jennifer Black-Shinn, MPH, PhD, Gregory Kinney, MPH, PhD, Sharon Lutz, PhD, Katherine Pratte, MSPH.

COPDGene® Investigators—Clinical Centers. *Ann Arbor VA:* Jeffrey Curtis, MD, Carlos Martinez, MD, MPH, Perry G. Pernicano, MD. *Baylor College of Medicine, Houston, TX*: Nicola Hanania, MD, MS, Philip Alapat, MD, Venkata Bandi, MD, Mustafa Atik, MD, Aladin Boriek, PhD, Kalpatha Guntupalli, MD, Elizabeth Guy, MD, Amit Parulekar, MD, Arun Nachiappan, MD. *Brigham and Women's Hospital, Boston, MA*: Dawn DeMeo, MD, MPH, Craig Hersh, MD, MPH, George Washko, MD, Francine Jacobson, MD, MPH. *Columbia University, New York, NY*: R. Graham Barr, MD, DrPH, Byron Thomashow, MD, John Austin, MD, Belinda D'Souza, MD, Gregory D.N. Pearson, MD, Anna Rozenshtein, MD, MPH, FACR. *Duke University Medical Center, Durham, NC*: Neil MacIntyre, Jr., MD, Lacey Washington, MD, H. Page McAdams, MD. *Health Partners Research Foundation, Minneapolis, MN*: Charlene McEvoy, MD, MPH, Joseph Tashjian, MD. *Johns Hopkins University, Baltimore, MD*: Robert Wise, MD, Nadia Hansel, MD, MPH, Robert Brown, MD, Karen Horton, MD, Nirupama Putcha, MD, MHS. *Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA*: Richard Casaburi, MD, Alessandra Adami, PhD, Janos Porszasz, MD, PhD, Hans Fischer, MD, PhD, Matthew Budoff, MD, Dan Cannon, PhD, Harry Rossiter, PhD. *Michael E. DeBakey VAMC, Houston*, TX: Amir Sharafkhaneh, MD, PhD, Charlie Lan, DO. *Minneapolis VA:* Christine Wendt, MD, Brian Bell, MD. *Morehouse School of Medicine, Atlanta, GA*: Marilyn Foreman, MD, MS, Gloria Westney, MD, MS, Eugene Berkowitz, MD, PhD. *National Jewish Health, Denver, CO*: Russell Bowler, MD, PhD, David Lynch, MD. *Reliant Medical Group, Worcester, MA*: Richard Rosiello, MD, David Pace, MD. *Temple University, Philadelphia, PA*: Gerard Criner, MD, David Ciccolella, MD, Francis Cordova, MD, Chandra Dass, MD, Robert D'Alonzo, DO, Parag Desai, MD, Michael Jacobs, PharmD, Steven Kelsen, MD, PhD, Victor Kim, MD, A. James Mamary, MD, Nathaniel Marchetti, DO, Aditti Satti, MD, Kartik Shenoy, MD, Robert M. Steiner, MD, Alex Swift, MD, Irene Swift, MD, Gloria Vega-Sanchez, MD. *University of Alabama, Birmingham, AL:* Mark Dransfield, MD, William Bailey, MD, J. Michael Wells, MD, Surya Bhatt, MD, Hrudaya Nath, MD. *University of California, San Diego, CA*: Joe Ramsdell, MD, Paul Friedman, MD, Xavier Soler, MD, PhD, Andrew Yen, MD. *University of Iowa, Iowa City, IA*: Alejandro Cornellas, MD, John Newell, Jr., MD, Brad Thompson, MD. *University of Michigan, Ann Arbor, MI*: MeiLan Han, MD, Ella Kazerooni, MD, Fernando Martinez, MD. *University of Minnesota, Minneapolis, MN*: Joanne Billings, MD, Tadashi Allen, MD. *University of Pittsburgh, Pittsburgh, PA*: Frank Sciurba, MD, Divay Chandra, MD, MSc, Joel Weissfeld, MD, MPH, Carl Fuhrman, MD, Jessica Bon, MD. *University of Texas Health Science Center at San Antonio, San Antonio, TX*: Antonio Anzueto, MD, Sandra Adams, MD, Diego Maselli-Caceres, MD, Mario E. Ruiz, MD.

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