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ORIGINAL RESEARCH

Defining Resilience to Smoking-related Lung Disease
A Modified Delphi Approach from SPIROMICS

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Abstract

Rationale: Diagnosis of chronic obstructive pulmonary disease (COPD) relies on abnormal spirometry. However, spirometry may underestimate the effects of smoking, missing smokers with respiratory disease who have minimal or no airflow obstruction.

Objectives: To develop a multidimensional definition of a lung-related "resilient smoker" that is useful in research studies and then identify a resilient smoker subgroup in the SPIROMICS (SubPopulations and InteRmediate Outcome Measures In COPD Study) cohort using this definition.

Methods: We performed a three-round modified Delphi survey among a panel of COPD experts to identify and reach a consensus on clinical and radiographic domains to be included in a lung-related resilient smoker definition. Consensus on domains of resilience was defined as ⩾80% of experts voting "agree" or "strongly agree" on a 5-point Likert scale. The Delphi-derived definition of resilience was applied to SPIROMICS to identify resilient smokers, whom we then characterized using known biomarkers of COPD.

Results: Consensus was achieved on 6 of 12 diagnostic items, which include cough and sputum production, dyspnea, radiographic measures of emphysema and small airways disease, exacerbations, and decline in forced expiratory volume in 1 second. Although 892 SPIROMICS participants were classified as smokers with preserved lung function by spirometry, only 149 participants (16.7%) qualified as resilient smokers by our definition. Blood biomarker expression of CRP (C-reactive protein) and sTNFRSF1A (soluble tumor necrosis receptor factor1A) was lower in resilient than nonresilient smokers ($P = 0.02$ and $P = 0.03$).

Conclusions: A Delphi-derived consensus definition of resilient smoker identified 83.3% of smokers with preserved spirometry as "nonresilient" based on the presence of adverse effects of smoking on the lung. Resilient smokers were biologically distinct from nonresilient smokers based on CRP measurements.

Clinical trial registered with ClinicalTrials.gov (NCT01969344).

Keywords: chronic obstructive pulmonary disease; smoking; spirometry; consensus development; biomarkers

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A complete list of SPIROMICS Smoking Resilience Group members may be found before the beginning of the References.

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Tobacco smoke is the most common environmental risk factor for chronic obstructive pulmonary disease (COPD) (1). Despite this strong association, it is estimated that only 15–25% of smokers will develop COPD using spirometric criteria for the diagnosis (2, 3). Most clinical and translational studies of smoking in COPD focus on risk factors for the development and progression of disease. Relatively few studies examine factors that characterize those who display "resilience" to smoking and maintain ideal respiratory health in the face of this noxious exposure (4). Yet, factors associated with resilience may represent protective pathways required for preservation of lung health. Harnessing these protective mechanisms could provide an opportunity for therapeutic advances in patients with COPD and for maintenance of population lung health more generally.

Recent literature suggests that COPD prevalence may be vastly underestimated (5, 6). The current diagnosis is confirmed by the presence of airflow limitation on spirometry (post-bronchodilator ratio of forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <0.7) (3). However, we and others have shown that a substantial proportion of smokers who do not meet spirometric criteria for COPD still have respiratory symptoms (7, 8), exacerbations (9), and radiographic abnormalities (10). Furthermore, COPD is clinically heterogeneous, and spirometry does not capture all aspects of COPD-related pathology. For example, radiographic domains of COPD, including emphysema, expiratory air trapping, and airway wall thickening, correlate poorly with severity of airflow obstruction measured by spirometry (11). Yet, multiple clinical and radiographic domains of smoking-related lung disease may be associated with clinical outcomes, indicating they are capturing relevant pathology (7, 12, 13). Together these data suggest that abnormal spirometry alone lacks sensitivity for detecting the adverse effects of tobacco smoke exposure on lung health.

One undesirable consequence of relying on spirometry alone to diagnose COPD and smoking-related lung disease is that it may overestimate the prevalence of "resilient smokers." This misclassification may confound the identification and examination of factors associated with resilience. Our goal was to develop a multidimensional definition of resilience to the pulmonary effects of smoking that is suitable for use in clinical and translational research studies. We performed a modified Delphi survey among a group of obstructive airway disease experts to identify and reach consensus on a multidomain framework for defining resilient smokers. The Delphi method is a well-established approach to consensus development when standard evidence is not available (14). The Delphi method has been used in developing diagnostic criteria for chronic hypersensitivity pneumonitis (15), early management of COPD (16), a framework for asthma treatment goals (17), and definition, diagnosis, and treatment of acute exacerbations of idiopathic pulmonary fibrosis (18). We applied our newly derived resilience definition to SPIROMICS (the SubPopulations and InteRmediate Outcome Measures In COPD Study), a longitudinal prospective cohort of smokers (19), to identify a resilient smoker subpopulation. Finally, we determined whether this resilient subpopulation displays an altered biomarker profile when compared with all other smokers. We assert that defining the resilient smoker is the first research step toward identifying the protective clinical and biologic features contributing to resilience that could be exploited for the development of new COPD therapies.

Methods

Modified Delphi Process

We used a modified Delphi method to develop consensus on a definition of a resilient smoker that accounts for criteria beyond normal spirometry. Through an anonymous one-person, one-vote system, all experts had equal influence in decision-making. A survey approach allows for statistical analyses (20–22). SPIROMICS investigators ($n = 72$), considered experts in smoking-related lung disease, were invited by e-mail to participate in a web-based Delphi survey (Provo UT; Qualtrics). Experts voted by Likert scale between 1 and 5 (strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree) on domains and symptoms of impairment that should be considered in the consensus definition. They were also asked to list other domains not included in the initial survey via open-answer responses. Following the first round of voting, variables that received discordant votes were discussed via teleconference and a provisional definition of lung-related resilience was created. A second round of the Delphi was conducted in which individual experts were asked to *1*) vote "agree"/"disagree" on the provisional definition, *2*) vote on additional domains that were submitted from round one, and *3*) vote

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on cutoff values of "normal" for the domains for which there are not established reference values. We defined consensus as greater than 80% of experts rating a domain as ⩾4 (agree or strongly agree) on a 5-point Likert scale. Consensus was achieved on all survey items in round 2. A brief third-round Delphi was conducted to further refine which measurement tool and cutoff value to use for the symptoms of cough and sputum production, and to vote on values of normal rate of FEV_1 decline. The results of this iterative Delphi method were analyzed anonymously and led to the development of a multidimensional definition of a lung-related resilient smoker.

Application of Delphi-derived Resilient Smoker Definition to SPIROMICS

We applied our Delphi method–derived consensus definition and reference ranges of lung-related resilience to smokers with preserved spirometry in the SPIROMICS cohort to derive a subgroup of resilient smokers. Each variable of the consensus definition was evaluated for efficacy in excluding smokers with preserved spirometry. A group of "nonresilient smokers" was also derived and defined as smokers with normal spirometry and an abnormality in any one of the domains of the lung-related resilience definition. Characteristics of these subgroups were compared using *t* tests and chi-squared tests.

Correlation of Resilient Smoker Definition with Biological Markers of COPD

The Delphi-derived consensus definition of a resilient smoker was correlated with known biomarkers of COPD: airway concentration of soluble mucins (23), plasma fibrinogen (24), CRP (C-reactive protein) (25), and soluble TNF (tumor necrosis factor) receptors sTNFRSF1A (also known as sTNF-R55) and sTNFRSF1B (also known as sTNF-R75) (26–29). Additional detail on the method for making these measurements is provided in the online supplement. These biomarkers do not follow a normal distribution and were natural log transformed before analysis.

Biomarker levels in nonsmoking control subjects and nonresilient smokers and those in COPD Global Initiative for Chronic Obstructive Lung Disease stages 1, 2, and 3/4 (combined) were compared with the resilient smoker population using *t* tests, linear regression, and multivariate models adjusted for relevant covariates including age, sex, race, smoking-pack year, and smoking status. False discovery rate–adjusted *P* values were calculated using the Benjamini-Hochberg procedure (30).

Results

Of the 72 SPIROMICS investigators invited to participate in the Delphi survey, 21 completed the first round, 13 participated in the teleconference, 27 completed the second round, and 16 participated in the third round. The majority of participants worked at academic institutions and were involved in COPD clinical care and/or research. Two participants worked in the pharmaceutical industry in roles that included COPD research.

Domains of Resilience

In round 1 of the Delphi survey, nine domains were rated by participants for their relevance to a lung-related smoking resilience definition. Five of the nine initial domains reached 80% consensus (Figure 1). In a teleconference conducted after round 1, 13 of the invited experts verbally agreed on the domains that did and did not reach consensus for inclusion into a resilient smoker definition.

In the first-round survey, Delphi members suggested four other domains to be considered for inclusion into the definition, three of which were included in the round 2 survey for voting. The domain that was excluded from further voting was fatigue, as it was thought that this symptom was too nonspecific for inclusion.

In the round 2 survey, we sought endorsement of this provisional multidimensional definition of resilience through a "yes/no" vote and received 88.5% approval.

After two rounds of Delphi surveys, 6 out of 12 domains reached consensus for inclusion into our definition of lung-related smoking resilience. These include symptoms related to dyspnea and cough/sputum production, exacerbation history, radiographic measures of emphysema and small airways disease, and rate of FEV_1 decline (Figure 1).

Determination of Cutoff Values

We chose previously validated instruments to identify a range of respiratory symptoms important to smoking-related lung disease, including dyspnea, cough, and sputum production. The Modified Medical Research Council (mMRC) questionnaire was chosen to quantify dyspnea (31). Scores range from 0 to 4, with higher scores indicating more severe dyspnea. An mMRC score cutoff of ⩾2 has been used to separate patients with "less breathlessness" from "more breathlessness" (3, 32). In the Delphi survey round 3, experts who participated in this survey were divided between using sputum and cough questions from St. George's Respiratory Questionnaire (SGRQ) and sputum and cough questions from the COPD Assessment Test (CAT). Neither measurement achieved 80% agreement to achieve consensus. We proposed that if either SGRG or CAT measurement was positive in relationship to cough and sputum–related questions, the smoker would not be resilient. Within SPIROMICS, we had more missing data for SGRG; therefore, we chose to use the CAT score to assess for cough and sputum production. The CAT is an eight-question instrument that includes questions that are important in a resilient smoker such as cough, sputum production, dyspnea, and impacts on health status. Scores for each question range from 0 to 5, with higher scores indicating greater severity of symptoms (33). Responses to the first two questions of the CAT assess the frequency and severity of cough (question 1) and phlegm (question 2) (33). A score ⩾2 for the CAT question of cough and ⩾2 for phlegm production has also been identified as a valid method for classifying chronic cough and sputum production with agreement with the SGRQ and other validated measurements tools of these symptoms (34, 35). Values below these same cutoffs (<2) were used when defining resilience.

Delphi members voted that a resilient smoker would have no history of COPD exacerbations, defined as events that required healthcare use (office visits, emergency department visits, or hospitalization) and the use of antibiotics, systemic corticosteroids, or both. Because individual exacerbation rates can vary from year to year (36), the Delphi also reached consensus in defining the exacerbation-free period as 12 months before enrollment into SPIROMICS (no retrospective exacerbations) and in the 3-year SPIROMICS study follow-up period (no prospective exacerbations).

Emphysema, as measured as percentage of total lung volume, and functional small airways disease (air trapping), measured by parametric response mapping (PRM^{fSAD}) as a lung density of less than −857 Hounsfield units at residual volume, were the radiographic features chosen for inclusion (37). To determine the normal cutoff value for percentage of emphysema, the Delphi panel endorsed use of the reference equations and

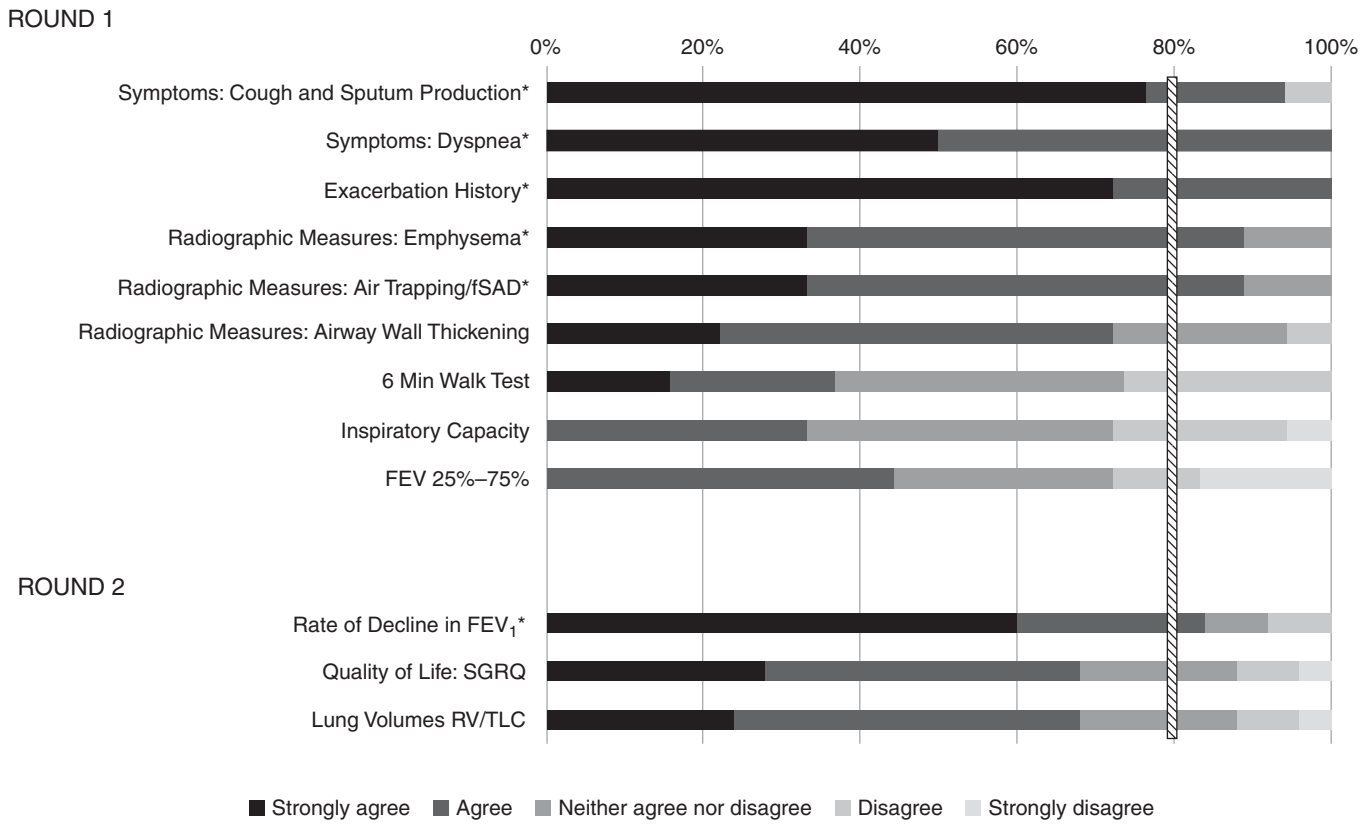

Figure 1. Results of Delphi rounds 1 and 2. *Indicates domain achieved consensus (⩾80% panel members with vote of "strongly agree" or "agree"). The vertical hashed bar represents 80% cutoff. FEV 25–75% = forced expiratory volume at 25–75% of pulmonary volume; FEV_1 = forced expiratory volume in 1 second; fSAD = functional small airway disease; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity.

Table 1. Final domains and measurement cutoffs for a "resilient smoker" defined by Delphi survey

Domain	Cutoff Value for "Normal"
Symptoms	
Cough/sputum production	Cough and phlegm CAT questions <2
Dyspnea	mMRC score of 0–1
Exacerbation history	
Retrospective	None in past 12 mo at SPIROMICS baseline visit
Prospective	None in SPIROMICS 3-yr follow-up period
Radiographic features	
Emphysema (%)	LLN calculated from the MESA lung study (Reference 38)
Air trapping/PRM^{fSAD}	LLN calculated from age-adjusted healthy never-smokers
Lung function	
Annual rate of decline in FEV_1	95% upper limit confidence interval from the Framingham offspring cohort (Reference 42)

Definition of abbreviations: CAT = COPD Assessment Test; FEV_1 = forced expiratory volume in 1 second; LLN = lower limit of normal; mMRC = Modified Medical Research Council Dyspnea Scale; PRM^{fSAD} = functional small airway disease measured by parametric response mapping.

lower limit of normal from the MESA (Multi-Ethnic Study of Atherosclerosis) Lung Study (38). PRM^{fSAD} does not have established normal cutoff values. The Delphi panel thus endorsed the development of age-adjusted lower limits of normal for $PRMf^{SAD}$ using published data (39). Age-adjusted PRM^{fSAD} values were derived in the SPIROMICS cohort using linear regression from healthy never-smoking control subjects, using the upper limit of the 95% confidence interval (CI) as the cutoff below which a participant was considered normal. In a "yes/no" voting process, these proposed cutoffs received >95% approval in Delphi round 2.

There are no well-established cutoff values for longitudinal abnormal rate of FEV_1 decline in former and current smokers (40, 41). We proposed to use FEV_1 decline in normal subjects as a metric of comparison to define a resilient smoker. In the round 3 Delphi survey, 87.5% of participants voted to use the reference values from the Framingham offspring cohort from healthy never-smoking males and females (42). The mean annualized rate of decline for healthy never-smoking males was 19.6 ml/yr (95% CI, 17.1–22.1 ml/yr), and that for females was 17.6 ml/yr (95% CI, 13.8–21.4 ml/yr). We used the upper limit of the 95% CI as the cutoff value of "normal" rate.

The final domains included in the definition and, if applicable, their associated normal cutoff values are presented in Table 1.

Application of the Consensus Definition of "Resilient Smoker" to the SPIROMICS Cohort

The integrated, multidimensional definition of resilience was applied to the 2,973 SPIROMICS participants (Figure 2). Never-smokers ($n = 202$) and smokers with abnormal spirometry (post-bronchodilator $FEV_1/FVC < 0.7$, $n = 1,847$) were excluded first. Those participants with normal FEV_1/FVC ratio but FVC less than the lower limit of normal were also excluded as it was unclear if this abnormality represented restriction, either intrathoracic (i.e., lung) disease misclassified as COPD or extrathoracic abnormality (e.g., obesity, pleural disease, or chest wall disease) that could confound analyses (7). After these exclusions, 892 participants had preserved spirometry. After application of additional Delphi-derived resilience domains, 743 of these participants were excluded (83.3%), resulting in 149 (16.7%) resilient smokers. We found that 449 smokers with preserved spirometry had an abnormality in at least one of the Delphi-derived domains of resilience, which created our "nonresilient" subpopulation.

The smokers with preserved lung function who were considered nonresilient most commonly had symptoms of cough and sputum production measured by the CAT (65.9% of smokers) and radiographic evidence of small airways disease measured by PRM^{fSAD} greater than the lower limit of normal (30.4% of smokers) (Figure 3).

Demographic and Clinical Differences

The demographics and clinical characteristics of the participants at baseline are shown in Table 2, comparing never-smokers, resilient smokers, and nonresilient smokers.

Statistically, there was no significant difference in smoking pack-years ($P = 0.22$), the average number of cigarettes smoked per day ($P = 0.13$), and the mean age at which they stopped smoking ($P = 0.13$) between the resilient and nonresilient population. However, resilient smokers were distinguished from nonresilient smokers by less current smoking (38.9% vs. 51.0%, $P = 0.01$). A total of 4.8% of resilient smokers were told they were diagnosed with COPD by a health professional in comparison to 32.5% of the nonresilient smokers ($P < 0.001$). There was no statistically significant difference in smoking-related comorbidities between these groups except for history of cardiovascular condition, which was higher in the nonresilient smoking population ($P = 0.03$).

Asthma diagnosis was less prevalent in resilient than nonresilient smokers ($P < 0.001$). Additionally, nonresilient smokers were more likely to have used inhaled bronchodilators and inhaled corticosteroids before study enrollment ($P < 0.001$). When adjusting for asthma diagnosis, the difference in inhaled bronchodilator and corticosteroid use between resilient and nonresilient smokers remained statistically significant ($P < 0.001$) (Table E1 in the online supplement).

Biomarkers of COPD in Resilient versus Nonresilient Participants

To increase our confidence that the definition of resilient smoker from SPIROMICS identified a biologically distinct subpopulation, we determined whether known biomarkers of COPD were expressed differently between resilient and nonresilient smokers without spirometric airflow obstruction. We studied total mucin concentrations in sputum, serum fibrinogen, serum CRP, and soluble TNF receptors (sTNFRSF1A and sTNFRSF1B).

We observed that CRP levels in resilient smokers were similar to healthy nonsmoking control subjects and lower in comparison to nonresilient smokers (unobstructive smoker having ≥ 1 abnormal clinical domain). In unadjusted analysis, nonresilient smokers have CRP levels that are 56.6% higher in comparison to resilient smokers ($P = 0.003$). When adjusting for age, sex, race, pack-years of smoking, current smoking status, and asthma, nonresilient smokers have CRP levels that are 41.6% higher ($P = 0.023$) (Table 3). P values adjusted for the number of biomarkers studied using the Benjamini-Hochberg procedure were <0.05 in the univariate linear model for CRP. sTNFRSF1A levels were also lower in resilient smokers in comparison to nonresilient smokers. This statistically significant difference was seen only in the multivariate adjusted model ($P = 0.03$).

Discussion

Widely accepted definitions of resilience to smoking-related obstructive lung disease do not exist, yet understanding the mechanisms that underlie resilience could be crucial for advancing COPD research and therapeutic approaches. In this study, we developed a comprehensive definition of resilience to respiratory consequences of smoking that is multidimensional and incorporates clinical and physiologic domains in addition to preserved spirometry. We identified six clinical and physiologic domains via the Delphi method and established cutoff values of normal for each of these domains. The Delphi process additionally established covariates and exposures for adjustment in our resilient smoker model. Of the 2,771 SPIROMICS participants with at least 20 pack-years of smoking, 892 smokers (32.2%) had preserved spirometry. We found that application of the clinical, radiographic, and physiologic domains of resilience to these smokers with preserved spirometry resulted in exclusion of 83.3% of these smokers with preserved spirometry from our resilient group. The remaining 16.7% ($n = 149$) resilient smokers differed objectively and biologically from those defined as nonresilient.

Investigating lung-related resilience to cigarette smoke exposure is essential to understanding the mechanisms and pathways related to preservation of lung health. Examining resilience in biologic studies could provide insight into endogenous pathways that may serve as protective factors against COPD development. These pathways could subsequently be leveraged for therapeutic advancements and even prevention of COPD. Identifying these pathways is in alignment with the U.S. National Heart, Lung, and Blood Institute strategic goals and objectives for COPD research and should enable a better understanding of the transition from healthy lungs to COPD.

We developed a comprehensive definition of smoking-related resilience to COPD using a modified Delphi survey. The concept of resilience is widely discussed; however, there are no broadly accepted definitions of resilience. In particular, resilience in the context of smoking-related lung disease has not yet been defined or explored. In this three-round modified Delphi survey, COPD experts identified and established 80% consensus on six clinical, physiologic, and radiographic domains to develop a comprehensive definition of smoking-related resilience to airway disease in smokers. The results of this Delphi survey indicate that experts thought that the absence of respiratory symptoms as measured by CAT and mMRC scores, and no retrospective or prospective incidence of COPD exacerbations, classified a participant as a resilient smoker. Additionally, the absence of significant computed tomography (CT) radiographic findings measured by percentage of emphysema and air trapping by PRM^{fSAD} and annual rate of decline in FEV_1 within normal

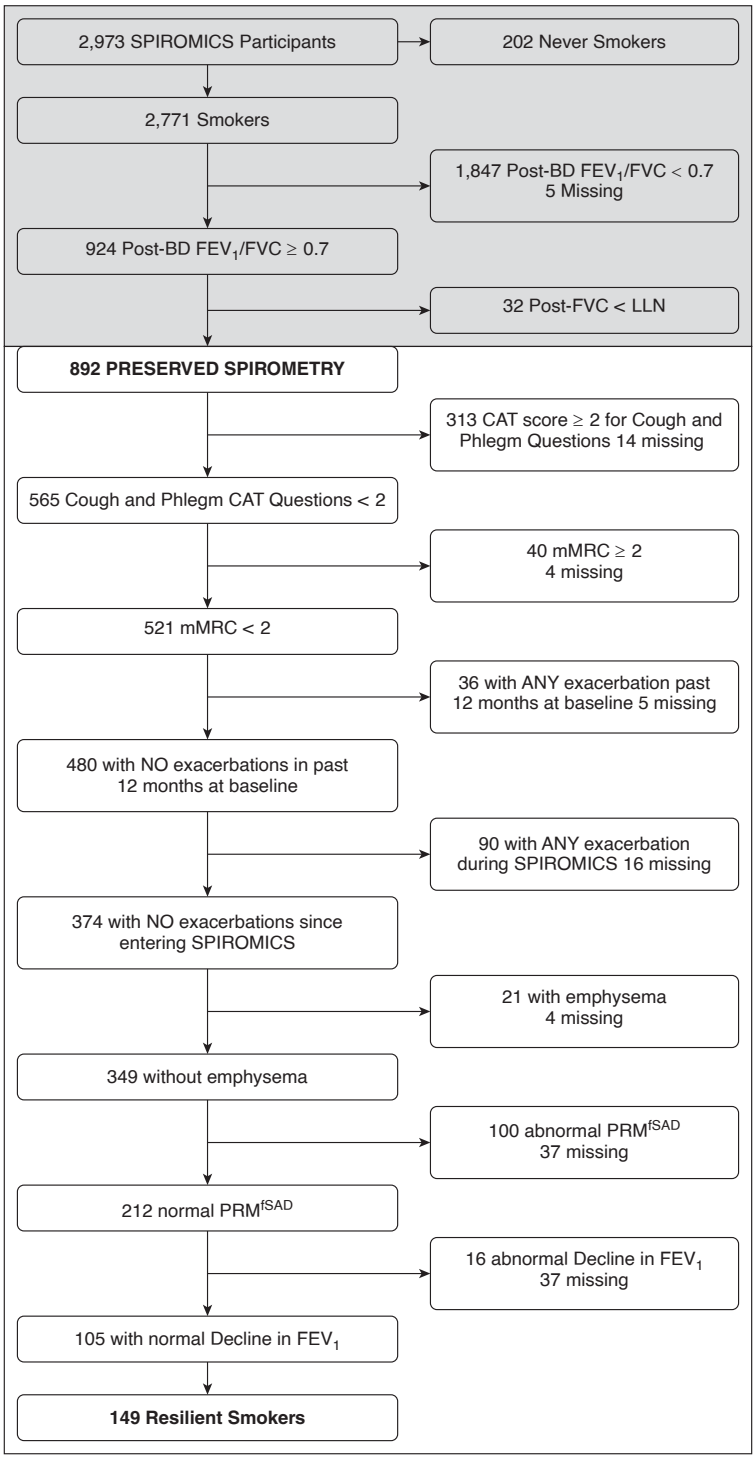

Figure 2. Application of the Delphi definition to SPIROMICS to identify resilient smokers. Out of the 2,973 participants, 892 smokers had preserved spirometry. In an iterative fashion, those with symptoms measured by CAT and mMRC scores were excluded. Next, those with COPD exacerbations, followed by those with abnormal computed tomography radiographic findings, and then abnormal rate of FEV_1 decline, were removed. This resulted in 149 resilient smokers. CAT = COPD Assessment Test; FVC = forced vital capacity; LLN = lower limit of normal; mMRC = Modified Medical Research Council Dyspnea Scale; Post-BD FEV_1 = post-bronchodilator forced expiratory volume in 1 second; PRM^{fSAD} = functional small airway disease measured by parametric response mapping.

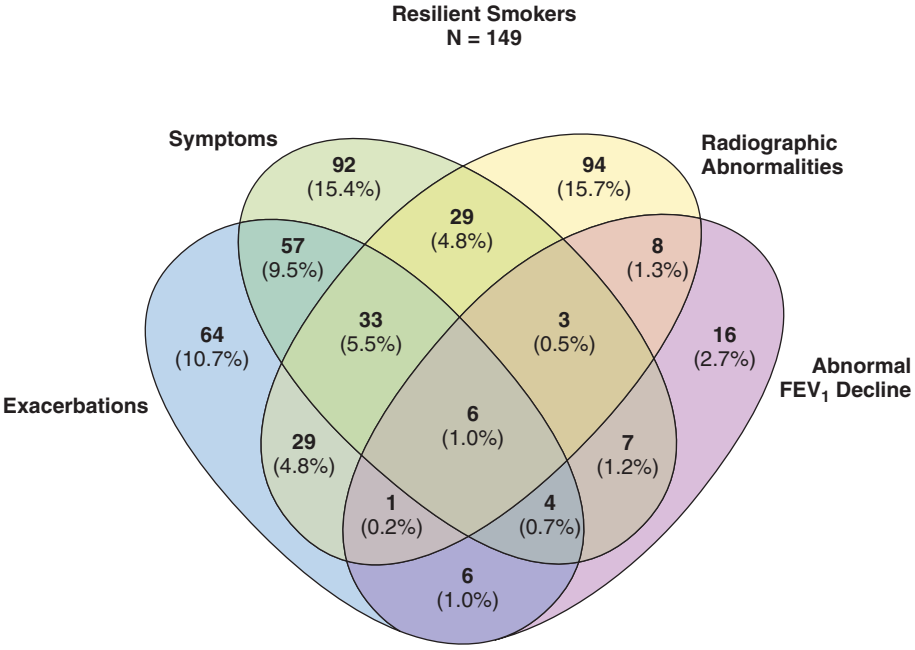

Figure 3. In the 892 smokers with preserved spirometry, representation and overlap of those subjects with symptoms, exacerbations, radiographic abnormalities, and abnormal FEV_1 decline, which we defined as nonresilient smokers. *N* = 294 participants were excluded because of missing data. Symptoms, measured by abnormal COPD Assessment Test or Modified Medical Research Council Dyspnea scale, are represented by the green circle. Exacerbations, both retrospective and prospective, are represented by the blue circle. Radiographic abnormalities measured by emphysema or functional small airway disease measured by parametric response mapping are represented by the yellow circle. Abnormal FEV_1 decline is represented by the pink circle. The white background indicates those who did not have abnormalities in any of the above domains and are classified as resilient smokers. FEV_1 = forced expiratory volume in 1 second.

limits in comparison to healthy never-smokers was deemed necessary for classification as resilient. The iterative nature of this two-round Delphi survey–facilitated discussion provided a rigorous approach to definition development.

The results of this study confirm that spirometry underestimates the deleterious effect of smoke exposure. In the SPIROMICS cohort, 30.4% of smokers with normal spirometry had abnormal CT radiographic findings measured by PRM^{fSAD}, and 8.0% had imaging findings consistent with emphysema. Symptoms of cough and sputum were present in 65.9% as measured by CAT symptom-related question score ⩾2, and dyspnea in 12.7% measured by mMRC ⩾2. A total of 14.5% of participants had a history of COPD exacerbation within the past year at the time of SPIROMICS study enrollment, and 28.1% experienced one or more exacerbations during the 3-year SPIROMICS follow-up period. Abnormal annual rate of FEV_1 decline was present in 8.5% of participants. Our work extends previous findings that a substantial proportion of smokers who do not meet criteria for COPD by spirometry nonetheless do have respiratory symptoms, exacerbations, and radiographic abnormalities that suggest they are experiencing adverse effects from tobacco exposure (7, 9, 12, 43).

We sought to provide biological validation that our resilient and nonresilient smokers with preserved spirometry differed in an objective and relevant way. We analyzed known biologic markers of COPD and found that resilient smokers had lower CRP compared with nonresilient smokers, as well as lower sTNFRSF1A levels in adjusted models. We did not find differences in several other COPD-relevant biomarkers, which could indicate that, as with COPD, the deleterious effects of smoking in "nonresilient" smokers are heterogeneous. Thus, biomarkers relevant to specific biologic pathways and associated with specific clinical outcomes (e.g., exacerbations or symptoms) may not be relevant to the entire nonresilient smoker population (26, 29). CRP elevation in the nonresilient group may suggest that systemic inflammation may be associated with worsening lung health over time (44).

The use of the resilient smoker criteria is meant primarily as a research tool and may not be feasible to apply to the general population or in a clinical setting. The CT radiographic measurements of percent emphysema and PRM^{fSAD} are used in research studies and are not routinely measured for clinical use. Biomarker analysis with removal of these radiographic research measurements was repeated. This resulted in an increase in the number of resilient smokers, but the differences in CRP and sTNFRSF1A levels between resilient and nonresilient smokers remained. However, COPD providers can apply respiratory symptom questionnaires, including the CAT and mMRC instruments, in a clinical setting. Additionally, this definition of lung-related resilience was developed specifically in relationship to obstructive lung disease and is not meant to include resilience to other diseases related to tobacco exposure.

Our study has several limitations. The Delphi method is useful in helping to develop definitions and address answers to questions that lack research-based evidence. However, the development of this multidimensional definition of a resilient smoker through the Delphi process reflects the opinion of a select sample of COPD experts who do not represent all health professionals involved in COPD. Expert selection bias is a generally understood

Table 2. Characteristics of SPIROMICS participants by never-smokers, resilient smokers, and nonresilient smokers

	Never-Smoker (*n* = 202)	Resilient Smoker (*n* = 149)	Nonresilient Smoker (*n* = 449)
Age, yr	56.5 ± 10.12	62.20 ± 10.13	60.49 ± 9.46
Male sex	78 (38.6)	73 (49.0)	206 (45.9)
Female sex	124 (61.4)	76 (51.0)	243 (54.1)
White race*	140 (69.3)	122 (81.9)	298 (66.4)
Black race*	46 (22.8)	19 (12.8)	128 (28.5)
Non-Hispanic	174 (86.1)	141 (94.6)	421 (94.0)
Current smoker†	0 (0.0)	58 (38.9)	229 (51.0)
Smoking pack-years	0.00 ± 0.07	41.68 ± 28.67	44.83 ± 26.90
Average number of cigarettes/d	5.5 ± 6.36	23.07 ± 8.57	24.58 ± 10.91
Age stopped smoking, yr	17.0 ± 3.27	50.88 ± 10.62	51.91 ± 9.48
History of asthma as child	4 (2.0)	5 (3.4)	36 (8.1)
History of asthma (ever)*	12 (6.0)	9 (6.0)	92 (20.5)
COPD diagnosis*	0 (0.0)	7 (4.8)	140 (32.5)
Cardiovascular condition†	93 (46.7)	77 (52.4)	280 (62.8)
High blood pressure	64 (32.2)	57 (38.8)	206 (46.2)
CAD	7 (3.5)	5 (3.4)	26 (5.8)
CHF	1 (0.5)	0 (0.0)	9 (2.0)
Claudication	8 (4.0)	6 (4.1)	30 (6.7)
Angina	12 (6.0)	7 (4.8)	37 (8.3)
Diabetes	19 (9.6)	14 (9.5)	65 (14.6)
Inhaled bronchodilators (past 3 mo)*	9 (4.5)	9 (6.1)	123 (27.6)
Inhaled steroids (past 3 mo)*	5 (2.5)	2 (1.4)	71 (15.9)
Ever smoked pipe	1 (0.5)	14 (9.4)	28 (6.3)
Average number of pipes/wk	0.50 ± 1.90	2.11 ± 5.55	1.92 ± 5.20
Ever smoked cigar	0 (0.0)	10 (6.7)	27 (6.0)
Regularly smoked marijuana	15 (40.5)	48 (57.8)	170 (66.1)
Average number of joints/wk	2.13 ± 4.47	4.87 ± 7.23	6.67 ± 11.30
Years smoking marijuana	5.90 ± 10.26	13.63 ± 14.09	12.05 ± 11.76
Exposure to VGDF	40 (19.9)	48 (32.4)	178 (39.7)
Years exposed to VGDF	3.2 1 ± 8.64	8.50 ± 14.83	7.47 ± 12.22
Post-BD FEV_1, % predicted*	101.82 ± 11.56	99.86 ± 13.73	96.60 ± 11.65
Post-BD FEV_1/FVC, % predicted*	102.75 ± 5.97	101.99 ± 5.90	99.34 ± 6.15

Definition of abbreviations: CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; FVC = forced vital capacity; Post-BD FEV_1 = post-bronchodilator forced expiratory volume in 1 second; VGDF = vapors, gas, dust, and fumes. Resilient and nonresilient groups were compared using a *t* test for continuous variables and chi-square test for categorical variables. Data are reported as mean ± standard deviation or *n* (%).
*Indicates statistically significant difference with $P < 0.01$.
†Indicates statistically significant difference with $P < 0.05$.

limitation of the Delphi process (45). We missed potentially helpful contributions from general pulmonologists, other disciplines, and international experts. The inclusion of these groups of individuals may have potentially resulted in different domains that may have been included or excluded in our definition of resilience. The cutoff values of "normal" for some of the domains of resilience were established based on limited evidence and then voted on during the Delphi process. Specifically, the cutoff for normal values of PRM^{fSAD} was derived from an age-adjusted linear regression from healthy never-smokers (39). Additionally, the SPIROMICS cohort on which this Delphi-based definition was applied is not a random sample and cannot estimate the prevalence or clinical and biologic features of all smokers with preserved lung function. There may be inherent bias in the SPIROMICS study as many of the participants may have volunteered because of symptoms suggestive of COPD despite having preserved spirometry.

Future investigation of this resilient smoker population will focus on additional factors that convey resilience to cigarette smoke exposure. Mechanisms to be examined include mucociliary function, purification of toxins in the lung, maintenance of a healthy lung microbiome, preservation of the pulmonary vasculature, and prevention of cellular senescence. With the application of the resilient smoker definition, new biologic factors that are underrecognized as contributors to COPD may be identified as well.

In conclusion, spirometry substantially underestimates the effects of cigarette smoke on the lung. Using a modified Delphi method, we developed a consensus-based definition of resilient smokers that extends beyond normal spirometry to include pertinent clinical and radiographic criteria. Application of this resilient smoker definition to SPIROMICS excluded 88.2% of smokers who would have otherwise been classified as resilient smokers based on spirometry alone. The development of a definition of lung-related smoking resilience is a vital first step and research tool in investigating resilience in this population and provides insight into protective factors of COPD to leverage for prevention and treatment. ■

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Table 3. Univariate and multivariate models of biomarkers in nonresilient smokers and never-smokers

		Unadjusted					Adjusted				
	Group	Coefficient	SE	95% CI		*P* Value	Coefficient	SE	95% CI		*P* Value
Sputum mucin (in mg/ml)	Resilient			Reference					Reference		
n = 806	Nonresilient	0.02	0.15	−0.28	0.32	0.90	−0.04	0.15	−0.34	0.26	0.80
	Never-smoker	−0.26	0.17	−0.60	0.08	0.13	−0.08	0.18	−0.44	0.27	0.65
CRP (in μg/ml)	Resilient			Reference					Reference		
n = 1,539	**Nonresilient**	**0.45**	**0.15**	**0.15**	**0.75**	**0.003***	**0.35**	**0.15**	**0.05**	**0.65**	**0.02**†
	Never-smoker	0.09	0.17	−0.24	0.41	0.59	0.14	0.18	−0.21	0.49	0.42
Fibrinogen (in mg/ml)	Resilient			Reference					Reference		
n = 1,539	Nonresilient	0.01	0.05	−0.08	0.1	0.85	−0.01	0.05	−0.10	0.08	0.79
	Never-smoker	−0.08	0.05	−0.17	0.02	0.11	−0.06	0.05	−0.17	0.04	0.23
sTNFRSF1A (in pg/ml)	Resilient			Reference					Reference		
n = 1,539	Nonresilient	0.08	0.05	−0.02	0.18	0.12	**0.11**	**0.05**	**0.01**	**0.20**	**0.03**†
	Never-smoker	−0.03	0.05	−0.14	0.08	0.56	0.07	0.06	−0.04	0.18	0.23
sTNFRSF1B (in ng/ml)				Reference					Reference		
n = 1,539	Nonresilient	0.06	0.04	−0.03	0.14	0.20	0.07	0.04	−0.02	0.16	0.11
	Never-smoker	−0.07	0.05	−0.17	0.02	0.14	0.03	0.05	−0.07	0.13	0.52

Definition of abbreviations: CI = confidence interval; CRP = C-reactive protein; SE = standard error; sTNFRSF1A = soluble tumor necrosis factor receptor 1A; sTNFRSF1B = soluble tumor necrosis factor receptor 1B.
Reference group = Resilient smokers. Multivariate models adjusted for age, sex, race, cigarette pack-years, current smoking status, and asthma diagnosis. $P < 0.05$ shown in bold typeface. All biomarkers were natural log transformed.
*False discovery rate < 0.05.
†False discovery rate < 0.1.

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