Title

Reversible Airflow Obstruction Predicts Future Chronic Obstructive Pulmonary Disease Development in the SPIROMICS Cohort: An Observational Cohort Study.

Journal

American Journal of Respiratory and Critical Care Medicine, 206(5)

Authors

Han, MeiLan
Hansel, Nadia
Krishnan, Jerry
et al.

Publication Date

2022-09-01

DOI

10.1164/rccm.202201-0094OC

Peer reviewed

ORIGINAL ARTICLE

Reversible Airflow Obstruction Predicts Future Chronic Obstructive Pulmonary Disease Development in the SPIROMICS Cohort

An Observational Cohort Study

Russell G. Buhr[1,2], Igor Z. Barjaktarevic[1], P. Miguel Quibrera[3], Lori A. Bateman[3], Eugene R. Bleecker[4], David J. Couper[3], Jeffrey L. Curtis[5,6], Brett A. Dolezal[1], MeiLan K. Han[5], Nadia N. Hansel[7], Jerry A. Krishnan[8], Fernando J. Martinez[9], William McKleroy[10], Robert Paine III[11,12], Stephen I. Rennard[13], Donald P. Tashkin[1], Prescott G. Woodruff[10], Richard E. Kanner[11*], and Christopher B. Cooper[1,14*]; for the SPIROMICS Investigators

[1]Division of Pulmonary and Critical Care Medicine, and [14]Department of Physiology, David Geffen School of Medicine, University of California, Los Angeles, California; [2]Center for the Study of Healthcare Innovation, Implementation, and Policy, Health Services Research and Development, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California; [3]Collaborative Studies Coordinating Center, Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina; [4]Division of Genetics, Genomics, and Precision Medicine, University of Arizona, Tucson, Arizona; [5]Division of Pulmonary and Critical Care Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan; [6]Medical Service, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan; [7]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [8]Breathe Chicago Center, Division of Pulmonary and Critical Care Medicine, University of Illinois at Chicago College of Medicine, Chicago, Illinois; [9]Division of Pulmonary and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York; [10]Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, California; [11]Division of Respiratory, Critical Care, and Occupational Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [12]Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, Utah; and [13]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska

ORCID IDs: 0000-0001-6159-7435 (R.G.B.); 0000-0002-8096-0858 (I.Z.B.); 0000-0002-4767-3494 (E.R.B.); 0000-0002-4313-9235 (D.J.C.); 0000-0001-5191-4847 (J.L.C.); 0000-0003-0405-608X (B.A.D.); 0000-0002-9095-4419 (M.L.K.H.); 0000-0002-8740-9751 (N.N.H.); 0000-0001-5525-4778 (J.A.K.); 0000-0002-2412-3182 (F.J.M.); 0000-0002-3184-9256 (W.M.); 0000-0002-4511-4437 (R.P.); 0000-0001-7909-0253 (S.I.R.); 0000-0002-5607-4872 (D.P.T.); 0000-0003-3176-0603 (P.G.W.); 0000-0001-6915-599X (R.E.K.); 0000-0002-6314-0903 (C.B.C.).

Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) is defined by fixed spirometric ratio, $FEV_1/FVC < 0.70$ after inhaled bronchodilators. However, the implications of variable obstruction (VO), in which the prebronchodilator FEV_1/FVC ratio is less than 0.70 but increases to 0.70 or more after inhaled bronchodilators, have not been determined.

Objectives: We explored differences in physiology, exacerbations, and health status in participants with VO compared with reference participants without obstruction.

Methods: Data from the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) cohort were obtained. Participants with VO were compared with reference participants without obstruction.

Measurements and Main Results: We assessed differences in baseline radiographic emphysema and small airway disease at study entry, baseline, and change in lung function by spirometry, functional capacity by 6-minute walk, health status using standard questionnaires, exacerbation rates, and progression to COPD between the two groups. All models were adjusted for participant characteristics, asthma history, and tobacco exposure. We assessed 175 participants with VO and 603 reference participants without obstruction. Participants with VO had 6.2 times the hazard of future development of COPD controlling for other factors (95% confidence interval, 4.6–8.3; $P < 0.001$). Compared with reference participants, the VO group had significantly lower baseline pre- and post-bronchodilator (BD) FEV_1, and greater decline over time in post-BD FEV_1, and pre- and post-BD FVC. There were no significant differences in exacerbations between groups.

Conclusions: Significant risk for future COPD development exists for those with pre- but not post-BD airflow obstruction. These findings support consideration of expanding spirometric criteria defining COPD to include pre-BD obstruction.

Clinical trial registered with www.clinicaltrials.gov (NCT 01969344).

Keywords: spirometry; COPD; pulmonary physiology; survival analysis; multilevel modeling

(Received in original form January 14, 2022; accepted in final form May 10, 2022)

Am J Respir Crit Care Med Vol 206, Iss 5, pp 554–562, Sep 1, 2022

Originally Published in Press as DOI: 10.1164/rccm.202201-0094OC May 12, 2022
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Currently, chronic obstructive pulmonary disease (COPD) is defined by a postbronchodilator $FEV_1/FVC < 0.70$. There are concerns that this results in misspecification of patients who still experience respiratory symptoms, exacerbations, and decline of lung function.

What This Study Adds to the Field: This study highlights the finding that those with prebronchodilator $FEV_1/FVC < 0.70$ that corrects to ≥ 0.70 with bronchodilator administration have a high prevalence of respiratory symptoms and greater radiographic emphysema and airway disease and progress to COPD and lung function loss at greater rates than those without.

The Global Initiative on Obstructive Lung Disease (GOLD) stipulates that a diagnosis of chronic obstructive pulmonary disease (COPD) must be predicated on demonstrating airflow obstruction defined as having a postbronchodilator (BD) ratio of $FEV_1/FVC < 0.70$ (1). This has raised issues and concerns that have been debated in the literature.

First, it has been recognized that the use of a fixed ratio of $FEV_1/FVC < 0.70$, as opposed to the lower limit of normal (LLN) calculated from reference values for FEV_1 and FVC, leads to underdiagnosis of COPD in younger individuals and overdiagnosis in older individuals (2). Yet older individuals with FEV_1/FVC of less than 0.70 but more than the LLN still appear to have worse health status (3). Second, reliance on post-BD FEV_1/FVC raises concern that some individuals might have evidence of airflow obstruction on pre-BD testing that "corrects" following administration of bronchodilators. We have called this variable obstruction (VO) and chose this terminology to delineate differences in physiology and avoid conflation with "bronchodilator responsiveness" (4, 5). This category probably includes many symptomatic people with current or former tobacco exposure with so-called "preserved spirometry" who have been shown to have COPD symptoms and exacerbations (6).

One obvious question is whether individuals with VO actually have pre-COPD with early airway pathophysiologic changes (7, 8), and whether these changes eventually progress to fixed obstruction, with post-BD $FEV_1/FVC < 0.70$. We sought to investigate individuals with variable obstruction using the SPIROMICS (Sub-Populations and Intermediate Outcomes in COPD Study) cohort of extensively characterized patients with COPD of varying severity as well as people with current or former tobacco exposure with preserved spirometry and nonsmoking controls (9). Our hypothesis is that individuals with VO may have numerous features of COPD, evidenced by radiographic abnormalities on computed tomography (CT) of the chest, and that they progress to fixed obstruction over time.

The SPIROMICS parent study was approved by the institutional review boards of each individual site before the enrollment of participants. All participants provided informed consent.

Methods

Cohort Specification

Participants were recruited into SPIROMICS as previously reported and followed longitudinally, with planned annual visits for up to 3 years after enrollment (9), and via SPIROMICS II, a fifth visit that took place ~3 years after visit 4. They were included for this substudy if they had ≥20 pack-years of cumulative tobacco exposure and did not have COPD by GOLD criteria at time of entry to the study, defined as a post-BD FEV_1-to-FVC ratio of 0.70. Participants were excluded from longitudinal analyses if they did not complete at least two visits in the study with both pre- and post-BD spirometry in each of these visits.
A consolidated standards of reporting trials diagram illustrating flow of eligible participants into the analysis is found in Figure 1.

Variable and Outcome Definitions

Participants were classified as having "no obstruction" if their pre- and post-BD spirometry both had $FEV_1/FVC \geq 0.70$, whereas those who had a pre-BD spirometry with $FEV_1/FVC < 0.70$ and a post-BD $FEV_1/FVC \geq 0.70$ were classified as having "variable obstruction". Those with post-BD $FEV_1/FVC < 0.7$ were classified as having "fixed obstruction", meeting the definition

*Co–senior authors.

A complete list of SPIROMICS Investigators may be found before the beginning of the References.

Supported by the NIH NHLBI (contracts HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, and HHSN268200900020C and grants U01HL137880, U24HL141762, and L30HL134025 [to R.G.B.]) and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals, Inc.; Chiesi Farmaceutici S.p.A.; Forest Research Institute, Inc.; GlaxoSmithKline; Grifols Therapeutics, Inc.; Ikaria, Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals, Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan. R.G.B. additionally received support from NIH National Center for Advanced Translational Sciences grant KL2TR001882. The findings and opinions in this manuscript do not necessarily represent those of the Department of Veterans Affairs.

Author Contributions: R.G.B., I.Z.B., L.A.B., E.R.B., J.L.C., B.A.D., M.K.H., N.N.H., J.A.K., F.J.M., W.M., R.P., S.I.R., D.P.T., P.G.W., R.E.K., and C.B.C. enrolled participants and collected data. R.G.B., I.Z.B., R.E.K., and C.B.C. conceived the design of the analysis. R.G.B., P.M.Q., and D.J.C. analyzed the data. R.G.B. and C.B.C. drafted the manuscript with critical editing from I.Z.B., D.J.C., B.A.D., N.N.H., J.A.K., R.P., D.P.T., and R.E.K. All authors reviewed and approved the final version of the manuscript for publication.

Correspondence and requests for reprints should be addressed to Russell G. Buhr, M.D., Ph.D., Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California at Los Angeles, 1100 Glendon Avenue, Suite 850-820, Los Angeles, CA 90024. E-mail: rbuhr@mednet.ucla.edu.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

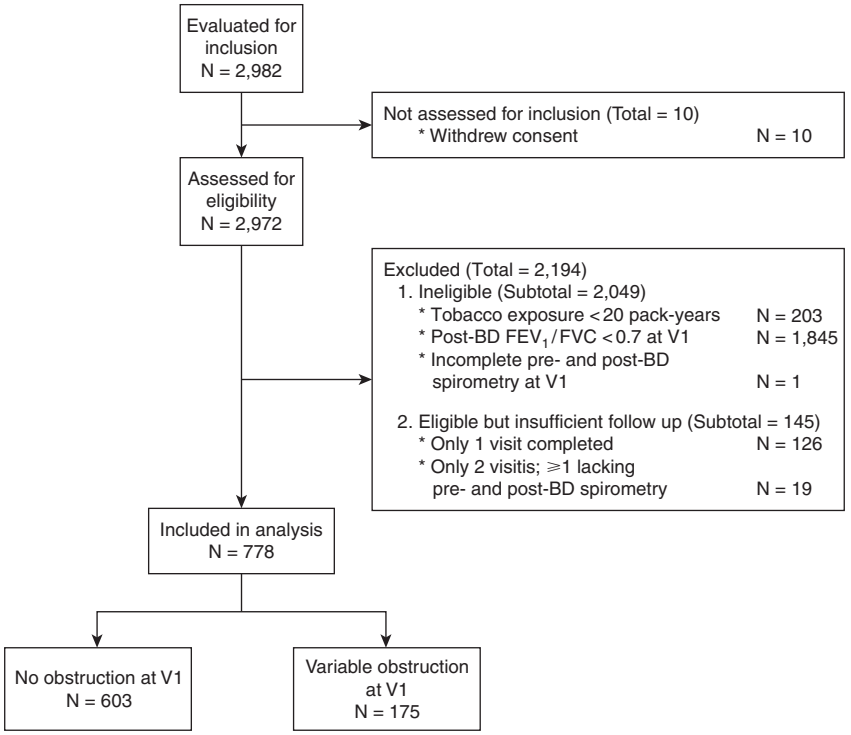

Figure 1. Consolidated standards of reporting trials flow diagram for study inclusion and exclusion. BD = bronchodilator; V = visit.

for COPD under GOLD criteria (1). Participants were excluded from analysis if fixed obstruction was present at baseline. For modeling, we stratified VO versus no obstruction using baseline spirometry at study entry.

Progression to COPD was defined by those who developed fixed obstruction during the study, defined as post-BD FEV_1/FVC < 0.70. Information about exacerbations was collected by participant self-report using questionnaires at quarterly intervals and summed by year of participation, classified by total number, and further defined as "healthcare utilization" if the exacerbation necessitated intervention with systemic corticosteroids and/or antibiotics, and as "severe" if the participant had an emergency department visit or hospitalization.

Statistical Analysis

The no-obstruction and VO subgroups were compared using Student's *t* test for continuous and chi-square tests for categorical variables. A Sankey diagram was plotted to illustrate transitions between outcome states using SankeyMatic. All analyses were conducted in SAS version 9.4.

Covariate Selection

A prespecified set of covariates was chosen based on prior literature for items with known association with our outcomes of interest. Physiologic, radiographic and outcome models were adjusted for age, self-reported sex, race (recategorized to binary as White versus non-White owing to low numbers for other racial identities), body mass index at the time of study entry, self-reported current tobacco use, cumulative tobacco exposure in pack-years, and history of diagnosis of asthma. Longitudinal models included an interaction term between VO and years of follow up. Exacerbation models included post-BD FEV_1 percent predicted at study entry owing to known association of FEV_1 with exacerbation risk (10).

Model Development

Emphysema and functional small airway disease were quantified by parametric response mapping (PRM) (11, 12) on chest CT, which were available only at the baseline visit at the time of this analysis. A linear regression model was fit to determine and quantify the effect size of VO on the degree of radiographic emphysema (PRM^{emph}) and small airways disease (PRM^{fsad}) at the time of study entry, controlling for other factors felt to potentially affect these radiographic outcomes (e.g., tobacco exposure and history of asthma).

In longitudinal analyses, mixed effects models were used with observations nested within participants, with random intercepts and slopes at the participant level to account for repeated measures. Change in physiologic and functional measurements (i.e., spirometry and 6-minute-walk distance) as well as change in COPD Assessment Test (CAT) (13) and St. George's Respiratory Questionnaire (SGRQ) (14) were fit using mixed-effects generalized linear models. Change in dyspnea over time by modified Medical Research Council (mMRC) questionnaire (15) was dichotomized to mMRC < 2 and $\geqslant 2$ and modeled using generalized estimating equations for odds of moving to the higher degree of dyspnea over time. Covariates were modeled as time invariant at baseline value.

Time to Event Analysis for Progression to COPD

Hazard for development of COPD was estimated using an interval censored nonparametric time-to-event model (16, 17), akin to the Cox proportional hazards model, but with discrete events rather than continuous time, with event-free curves compared using the log rank test of equality. This model was used in order to reduce SEs of parameter estimates due to the unknown time the participant's physiology changed relative to when it was measured, given that participants had prespecified intervals between visits where spirometry was conducted (18).

Sensitivity Analysis

An *a priori* designated sensitivity analysis was performed comparing those diagnosed with asthma in childhood versus those diagnosed with asthma at any point in their lives. The model fit between the original and sensitivity models was compared using Akaike information criteria (19, 20).

Results

Characteristics of the Cohort

Of the 2,982 participants in SPIROMICS, we identified an analytic cohort of 778 participants eligible for analysis, of whom 603 had normal FEV_1/FVC both before and after BD administration and 175 of whom had VO on baseline visit spirometry

(Figure 1). Participants with variable obstruction were 2.5 years older on average and more commonly male, both statistically significant. Those with variable obstruction reported significantly more childhood asthma and a non–statistically significant trend toward ever being diagnosed with asthma, with cohort prevalence similar to population estimates (21). There was not a significant difference in the prevalence of chronic bronchitis between the two groups (Table 1). No significant racial or ethnic difference in distribution of VO was observed, nor was there a significant difference in active tobacco use with a trend toward more cumulative tobacco exposure in the VO group. Those with VO exhibited significantly lower mean pre-BD FEV_1 at the time of enrollment, but mean post-BD values did not differ significantly. They also exhibited significantly higher pre- and post-BD FVC and lower pre- and post-BD FEV_1/FVC values.

Significantly more radiographic structural changes were observed among those with VO, with nearly twice the emphysema and 1.5 times more small airway disease, and nearly 5 times as frequent BD responsiveness by American Thoracic Society/European Respiratory Society criteria (22). In addition, the average magnitude of change in FEV_1 after bronchodilator administration was significantly higher (1.8 times absolute volume and 1.7 times by percent predicted) among those with VO, whereas that for FVC demonstrated no significant differences.

Transitions from Variable to Fixed Obstruction

We evaluated transitions between states, represented graphically in a Sankey diagram

Table 1. Baseline Characteristics of Cohort at Entry to Study

Variable	Never Obstructed (*N* = 603)	Variable Obstruction (*N* = 175)	*P* Value*
Age, mean ± SD	60.7 ± 9.7	63.2 ± 9.4	0.003
Male sex, *n* (%)	264 (44%)	98 (56%)	0.005
Body mass index, mean ± SD, kg/m^2	29.2 ± 5.0	28.5 ± 5.1	0.125
Hispanic/Latinx ethnicity, *n* (%)	37 (6%)	7 (4%)	0.354
Racial identity, *n* (%)			
White	417 (69%)	124 (71%)	0.992
Black	153 (25%)	41 (23%)	
Other/mixed race	29 (5%)	9 (5%)	
Not reported	4 (0.7%)	1 (0.6%)	
Reported history of childhood asthma, *n* (%)	33 (6%)	18 (11%)	0.026
Reported history of any diagnosis of asthma, *n* (%)	85 (15%)	32 (19%)	0.185
Reported history of diagnosis of chronic bronchitis, *n* (%)	76 (13%)	23 (14%)	0.897
Current combusted tobacco use, *n* (%)	291 (49%)	74 (43%)	0.195
Tobacco exposure, mean ± SD, pack-years	43 ± 27	46 ± 21	0.056
Spirometric values, mean ± SD			
Baseline FEV_1 (pre-BD), L	2.65 ± 0.68	2.47 ± 0.64	0.001
Baseline FEV_1 (pre-BD), % predicted	94 ± 14	84 ± 12	<0.001
Baseline FVC (pre-BD) L	3.49 ± 0.89	3.66 ± 0.94	0.032
Baseline FVC (pre-BD), % predicted	95 ± 13	95 ± 13	0.814
Baseline FEV_1/FVC (pre-BD)	0.76 ± 0.04	0.68 ± 0.02	<0.001
Baseline FEV_1 (post-BD), L	2.78 ± 0.70	2.7 ± 0.67	0.201
Baseline FEV_1 (post-BD), % predicted	98 ± 13	92 ± 11	<0.001
Baseline FVC (post-BD), L	3.54 ± 0.89	3.72 ± 0.92	0.020
Baseline FVC (post-BD), % predicted	96 ± 13	97 ± 13	0.546
Baseline FEV_1/FVC (post-BD)	0.79 ± 0.05	0.73 ± 0.02	<.001
Bronchodilator response			
BD responsive by ATS/ERS criteria, *n* (%)	40 (7%)	55 (31%)	<0.001
Δ FEV_1 pre-/post-BD, mean ± SD, ml	129 ± 130	238 ± 151	<0.001
Δ FVC pre-/post-BD, mean ± SD, ml	48 ± 168	60 ± 189	0.460
Δ FEV_1 pre-/post-BD, mean ± SD	4.6 ± 4.5%	8.2 ± 5.2%	<0.001
Δ FVC pre/post-BD, mean ± SD, % predicted	1.3 ± 4.7%	1.7 ± 5.2%	0.352
Radiographic % PRM^{emphysema}, mean ± SD	0.42 ± 1.12%	0.82 ± 1.47%	0.002
Radiographic % PRM^{fsad}, mean ± SD	7.61 ± 9.25%	11.07 ± 9.82%	<0.001
Baseline CAT Score†, mean ± SD	11.3 ± 8.5	10.7 ± 7.7	0.439
Baseline SGRQ total score‡, mean ± SD	23.7 ± 19.6	24.3 ± 19.0	0.705
Baseline mMRC ⩾ 2, *n* (%)	85 (14%)	18 (10%)	0.207
Medications in use at enrollment, *n* (%)			
Inhaled bronchodilators	130 (21%)	48 (28%)	0.126
Nebulized bronchodilators	29 (5%)	10 (6%)	0.694
Inhaled corticosteroids	65 (11%)	28 (16%)	0.085
Years of follow-up, mean ± SD	7.0 ± 2.4	7.0 ± 2.3	0.927

Definition of abbreviations: ATS/ERS = American Thoracic Society/European Respiratory Society; BD = bronchodilator; CAT = chronic obstructive pulmonary disease assessment test; fsad = functional small airway disease; mMRC = modified Medical Research Council dyspnea scale; PRM = parametric response mapping; SGRQ = St. George's respiratory questionnaire.

*t test for continuous, Fisher exact for racial identity, and chi-square test for other categorical variables.

†N = 722.

‡N = 684.

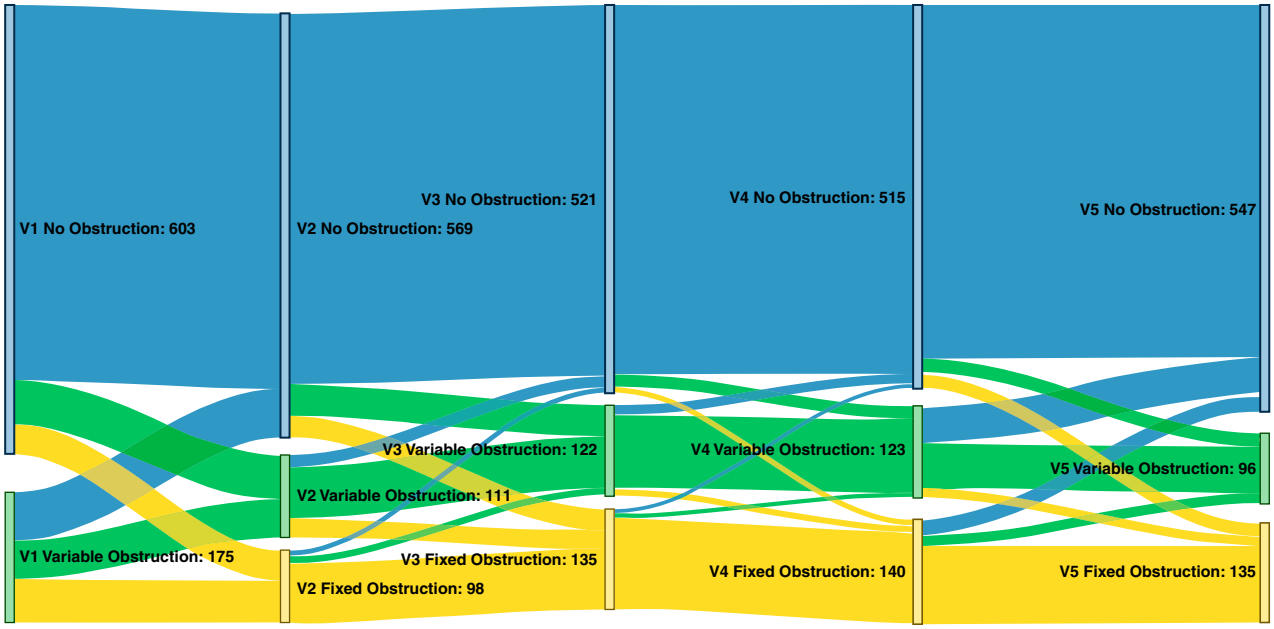

Figure 2. Sankey diagram illustrating transition states over time. Flows are shown color coded as the subsequent state, such that flows that are blue have no obstruction at next visit, flows that are green have variable obstruction at the next visit, and flows that are gold have fixed obstruction at the next visit. The nodes demonstrate the number in each state at each visit. Given unknown time of transition between visits, for missing (no spirometry performed or visit missed) or incomplete data (lacking both pre- and postbronchodilator results to be able to derive type of obstruction), last observation is carried forward until a new spirometry is available. V = visit.

(Figure 2). As in clinical practice, we carried forward previous observations until a new observation was made in cases where a complete pre- and post-BD spirometry test was not available for analysis, as without both phases of the spirometry test, it would be impossible to determine if VO were present. Among those with VO at baseline, 37% reverted to no obstruction at the subsequent visit, whereas 30% continued to have VO, and 33% progressed to fixed obstruction (COPD) at visit 2. Conversely, of those with no obstruction at baseline, 84% remained with no obstruction at visit 2 with very small proportions converting to VO (10%) or fixed obstruction (9%).

Interestingly, a small proportion who developed fixed obstruction at visit 2 reverted to VO (10%) or no obstruction (7%) by visit 3. Similar patterns were observed in the transitions between visits 3 and 5. A version of the Sankey diagram without last observation carried forward is found in Figure E1 in the online supplement to illustrate transitions inclusive of incomplete spirometry tests or missed visits. It should be noted that there were more missed visits for visits 3 and 4. This is in part owing to rolling recruitment in two time-limited phases of the study. As such, some participants did not have visit 1 until after others had completed visit 2 or even visit 3, and some participants did not complete all four visits before the end of the study time period for SPIROMICS I. Because visit 5 was conducted under a new funding mechanism (SPIROMICS II), participation again increased for visit 5, which influenced the temporal distribution of data.

Time to Progression to COPD

Presence of variable obstruction at study entry portended an adjusted 6.2-fold hazard of developing COPD, defined by fixed obstruction noted on spirometry after BD administration (Table 2). The magnitude of difference in COPD hazard is more than 5.6 times greater than that observed for every 10 pack-years of tobacco exposure (Table E1). This corresponded to progression to COPD during the study that was significantly higher among those with VO than those without VO at study entry (61% vs. 14%, $P < 0.001$).

An interval censored time-to-event curve (Figure 3) further demonstrated the rapidity of development of COPD among those with VO. The median time to COPD development for those with VO was 1.95 years, whereas 75.3% of those without VO at study entry had not developed COPD by the end of follow-up (log rank $P < 0.001$).

Radiographic Disease Patterns

Participants with VO at study entry had 0.3% more emphysema by PRM than those without obstruction at baseline (Table 2) even after adjusting for other factors. To put this effect into context, every 10 pack-years of cumulative tobacco exposure conferred only 0.04% more emphysema when controlling for other factors (Table E2). A parallel pattern was observed for small airway disease, where participants with VO had 2.17% greater PRM^{fsad} than those without (Table 2), an effect size 20 times greater than that per 10 pack-years of tobacco exposure (Table E3).

Difference in Physiologic Lung Function

Variable obstruction present at study entry was associated with 9.6% lower baseline pre-BD FEV_1 (Table 3), corresponding to 225 ml less airflow ($P < 0.001$). Rate of decline of pre-BD FEV_1, however, was not significantly different between these groups (Table 3). In post-BD models, the adjusted baseline difference in FEV_1 was significantly lower for

Table 2. Model Summary for Outcomes of Interest with Estimate of Effect Size for Presence of Variable Obstruction

Outcome	Unadjusted			Multivariable		
	N	Effect Estimate for VO (95% CI)	*P*	*N*	Effect estimate for VO (95% CI)	*P*
Progression to COPD*†	778	6.26 (4.70 to 8.35)	<0.001	670	6.17 (4.57 to 8.32)	<0.001
Exacerbation outcomes‡						
Exacerbation in next 365 days§	589	1.05 (0.59 to 1.87)	0.877	579	1.08 (0.58 to 2.01)	0.820
Total exacerbations‖	772	0.93 (0.69 to 1.29)	0.671	737	1.00 (0.72 to 1.38)	0.975
Exacerbations requiring health care‖	772	1.01 (0.73 to 1.41)	0.960	737	1.067 (0.77 to 1.50)	0.704
Exacerbations requiring ED/ hospitalization‖	772	1.21 (0.73 to 2.02)	0.469	737	1.23 (0.74 to 2.09)	0.432
Radiographic outcomes*						
Baseline PRM Emphysema	692	0.40% (0.19% to 0.62%)	<0.001	661	0.30% (0.09% to 0.51%)	0.006
Baseline PRM Functional Small Airways Disease	692	3.47% (1.79% to 5.15%)	<0.001	661	2.17% (0.56% to 3.78%)	0.008
HRQoL and functional outcomes*						
Baseline effect for CAT score	778	1.00 (0.88 to 1.14)	0.953	743	1.02 (0.91 to 1.20)	0.716
Δ CAT score per year	778	1.03 (1.01 to 1.05)	<0.001	743	1.04 (1.02 to 1.06)	<0.001
Baseline effect for mMRC < 2 vs. ⩾2§	778	1.00 (0.92 to 1.10)	0.948	743	1.05 (0.94 to 1.17)	0.354
Δ mMRC (odds of ⩾2) per year§	778	0.86 (0.57 to 1.31)	0.477	743	0.97 (0.61 to 1.53)	0.891
Baseline effect for SGRQ score	773	1.07 (0.92 to 1.25)	0.369	736	1.10 (0.96 to 1.23)	0.176
Δ SGRQ per year	773	1.00 (0.98 to 1.02)	0.889	736	1.01 (0.99 to 1.03)	0.305
Baseline effect for 6MWD, m	778	−3.3 (−18.4 to 11.9)	0.671	743	−3.0 (−17.4 to 11.4)	0.683
Δ 6MWD per year, m	778	0.9 (−2.0 to 3.9)	0.534	743	0.3 (−2.5 to 3.1)	0.845

Definition of abbreviations: 6MWD = 6-minute-walk distance; CAT = COPD assessment test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ED = emergency department; HRQoL = health-related quality of life; mMRC = modified Medical Research Council Dyspnea Scale; PRM = parametric response mapping; SGRQ = St. George's respiratory questionnaire; VO = variable obstruction.
Estimates as β coefficient unless otherwise noted.
*Adjusted for age, self-reported sex, self-reported race, tobacco exposure status and cumulative tobacco history, body mass index, and self-reported history of ever having asthma.
†Hazard ratio.
‡Adjusted for age, self-reported sex, self-reported race, tobacco exposure status and cumulative tobacco history, postbronchodilator % predicted FEV_1 and self-reported history of ever having asthma. *N* reflects complete case analysis
§Odds ratio.
‖Incidence rate ratio.

those with VO by 6.6%, with 0.6% more annual decline. This corresponded to a significantly lower baseline value of 135 ml with 17 ml greater annual decline.

When we evaluated FVC using the same models, we found that participants with VO did not have significantly different baseline pre-BD FVC (70 ml greater; $P = 0.166$), but they did experience a greater rate of pre-BD FVC decline (−28 ml/yr; $P < 0.001$) than those never obstructed at baseline. In post-BD assessments, those with VO had a 100.9-ml significantly lower baseline post-BD FVC with 16 ml more loss of post-BD FVC per year than those without VO ($P = 0.017$). The relative magnitude of differences in FEV_1 and FVC among those with VO, where post-BD FEV_1 fell more over time relative to FVC, likely explains the conversion from variable to fixed obstruction observed. These differences are also shown graphically in Figure E2.

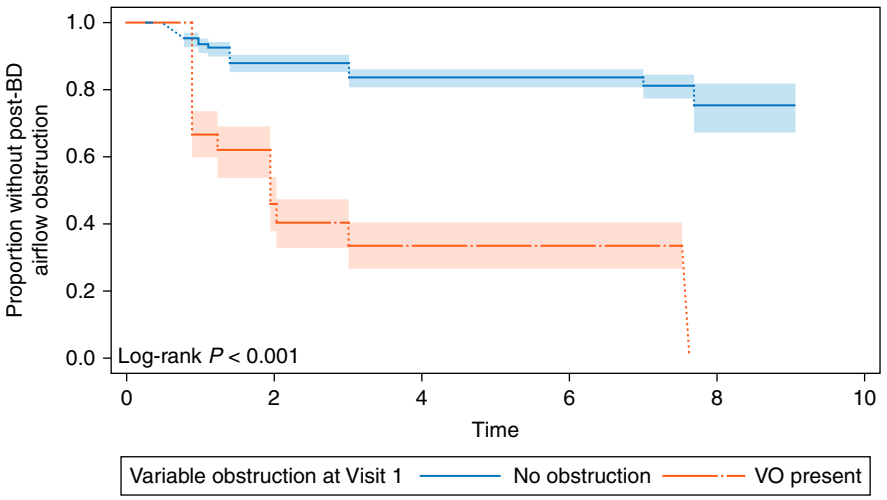

Figure 3. Interval-censored time-to-event model for progression to chronic obstructive pulmonary disease by presence of variable obstruction, where the blue line is those without variable obstruction (data as observed), and the red line is those with variable obstruction at study entry. Data shown with 95% confidence intervals. BD = bronchodilator; VO = variable obstruction.

Functional capacity by 6-minute-walk distance was not significantly different between those with and without VO (Table 2). The mean adjusted effect of VO was 3 m lower average walk distance with 0.3 m less decline in distance per year for those with VO.

Symptoms and Health Status

Participants with variable obstruction were observed to have an adjusted CAT score that

Table 3. Summary of Physiologic Outcome Models

Model Type Outcome	Unadjusted *N* = 778		Multivariable *N* = 743	
	Effect Estimate for VO (95% CI)	*P* Value	Effect Estimate for VO (95% CI)	*P* Value
Baseline effect pre-BD FEV_1 % predicted	−8.79% (−10.97% to −6.61%)	<0.001	−9.61% (−11.79% to −7.43%)	<0.001
Annualized Δ pre-BD FEV_1 % predicted	−0.05% (−0.004% to 0.003%)	0.785	−0.13% (−0.51% to 0.25%)	0.489
Baseline effect post-BD FEV_1 % predicted	−5.91% (−8.02% to −3.79%)	<0.001	−6.60% (−8.73% to −4.48%)	<0.001
Annualized Δ post-BD FEV_1 % predicted	−0.53% (−0.90% to −0.15%)	0.006	−0.61% (−0.99% to −0.23%)	0.002
Baseline effect pre-BD FEV_1, ml	−162.70 (−274.34 to −51.06)	0.004	−225.00 (−298.99 to −0.15)	<0.001
Annualized Δ pre-BD FEV_1, ml	−1.64 (−11.52 to 8.24)	0.745	−3.86 (−13.44 to 5.72)	0.430
Baseline effect post-BD FEV_1, mL	−75.08 (−190.19 to 40.03)	0.201	−135.30 (−208.80 to −61.80)	<0.001
Annualized Δ post-BD FEV_1, ml	−14.11 (−23.68 to −4.54)	0.004	−16.89 (−26.35 to −7.43)	0.001
Baseline effect pre-BD FVC % predicted	0.21% (−2.03% to 3.38%)	0.857	−0.11% (−2.33% to 2.12%)	0.925
Annualized Δ pre-BD FVC % predicted	−0.54% (−0.92% to 0.58%)	0.006	−0.65% (−2.33% to −0.27%)	0.001
Baseline effect post-BD FVC % predicted	1.05% (−1.09% to 3.19%)	0.337	0.74% (−0.14% to 2.88%)	0.497
Annualized Δ post-BD FVC % predicted	−0.30% (−0.69% to 0.09%)	0.131	−0.36% (−0.75% to 0.04%)	0.080
Baseline effect pre-BD FVC, ml	164.60 (13.29 to 315.91)	0.033	69.83 (−29.01 to 168.67)	0.166
Annualized Δ pre-BD FVC, ml	−24.05 (−37.62 to 0.01)	0.001	−27.91 (−41.26 to −14.56)	<0.001
Baseline effect post-BD FVC, ml	196.20 (46.08 to 346.32)	0.011	100.90 (5.27 to 196.53)	0.039
Annualized Δ post-BD FVC, ml	−13.69 (−27.02 to −0.36)	0.045	−16.22 (−29.57 to −2.87)	0.017

Definition of abbreviations: BD = bronchodilator; CI = confidence interval; VO = variable obstruction.
Estimate reflects difference for VO compared to no obstruction. Adjusted for age, self-reported sex, body mass index, self-reported history of asthma, current tobacco smoking, and cumulative tobacco exposure. *N* reflects complete case analysis.

was 1.02 points higher on average than those without VO, a value that was not statistically significant (Table 2). Those with VO, however, accrued an average of 1.04 more points per year ($P < 0.001$), which would meet the minimum clinically important difference threshold of 2 points for the test after 1 year of follow-up (23). Similarly, those with VO at study entry had a 1.1-point higher SGRQ score at baseline and an increase of 1.01 points per year higher than those with nonobstructed baseline spirometry, which, while not statistically significant, would meet the established MCID of 4 points for the battery after 3 years of follow-up (24). Lastly, there was no significant difference in increase of dyspnea by mMRC over the study between the two groups.

Exacerbations

We operationalized exacerbations after study entry in two ways. We first compared the odds of having an exacerbation within 1 year of study entry on the basis of variable obstruction status, adjusting for the factors noted above. Among those with VO, the odds of an exacerbation within 1 year of study entry were 7.5% higher than those with no obstruction (Table 2), but this was not significant. We also compared incidence rate ratios for subsequent exacerbations after study entry using a zero-inflated negative binomial model. Although adjusted models demonstrated lower rates of annual exacerbations among those with VO, none of these differences were statistically significant.

Sensitivity Analysis

When we specified models using history of childhood asthma rather than any personal history of asthma, we found very minor variations in effect sizes for variable obstruction on lung function outcomes after this change of covariate with no sign changes nor any variables that changed degree of significance (Tables E4 and E5). Those with childhood asthma did not have greater worsening of CAT score over time, whereas those with any diagnosis of asthma did. There was no difference in model fit by Akaike information criteria with this change, defined *a priori* as a change in AIC by 25 points or more.

Discussion

In this analysis of participants with current or former tobacco exposure but without COPD at study entry, we found that presence of VO, defined by pre-BD $FEV_1/FVC < 0.70$ with post-BD $FEV_1/FVC \geq 0.70$, portended a significant hazard for future development of COPD. We also saw more emphysema and more functional small airway disease among those with VO and significantly more annual decline in FEV_1. These findings raise a question as to whether this represents a unique phenotype of lung disease, another point on the asthma–COPD overlap (ACO) continuum, or a proverbial stop along the way to development of progressive, irreversible lung obstruction.

Pre-COPD Hypothesis

The designation of COPD as an entity is principally made by aggregated phenotypic characteristics, hallmarked by chronic cough or wheezing, progressive dyspnea, airflow obstruction, and emphysema. However, there is increasing interest in describing endotypes using biomarkers that could be deployed in a precision medicine approach to diagnosis and treatment of the underlying pathology (25, 26). Our findings indicate that current spirometric definition for COPD is inadequate and probably identifies patients too late in the course of their disease (8, 27).

Because the hazard of future fixed airflow obstruction among those with VO is high, we may be detecting respiratory changes compatible with a pre-COPD state. This is further supported by findings in other published work from this cohort that BD responsiveness by FEV_1 was very common in earlier stages of COPD (5). This is an interesting contrast to the Lung Health Study 1, where a large proportion of participants had only mild COPD (i.e., $FEV_1 \geq 80\%$ of predicted), and only a small proportion had bronchodilator responsiveness by ATS/ERS criteria (28), and to the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, where the

majority of BD responsiveness was observed among those with moderate airflow obstruction (29). This raises the question as to whether VO's relationship with BD responsiveness may represent a signal that future progression to fixed obstruction is coming in at-risk patients, and whether early interventions could change the trajectory of disease.

Support for Revision of Spirometric Criteria for COPD

Our findings also bring into question the requirement for post-BD FEV_1/FVC < 0.70 for the diagnosis of COPD as recommended by GOLD (1) and raise questions about the appropriateness of this criterion and the potential delay in the diagnosis of COPD. Most patients with respiratory complaints consistent with COPD are assessed in primary care offices (30, 31). This is coupled with the fact that access to pulmonary function testing creates a potential barrier to the diagnosis of COPD (32–34). Use of pre-BD spirometry alone in the assessment of COPD could potentially improve diagnosis by office spirometry, which could be more easily deployed in a primary care setting than laboratory-based pulmonary function tests as part of routine evaluation of respiratory complaints in at-risk patients. Furthermore, VO as a marker could be used in addition to other spirometric indices to enhance earlier COPD diagnosis (35–37).

ACO Overlap Hypothesis

We observed an increased hazard of future fixed obstruction among participants with a clinical diagnosis of asthma. This raises questions as to whether the reversibility of obstruction described by this analysis represents a phenotype of hyperreactive airway disease. ACO is associated with increased respiratory symptoms, poorer health status, as well as exacerbations (38, 39) and emphysema (40). The clinical guidance on management of ACO as a separate entity from COPD or asthma is lacking, at least in part owing to inconsistent definitions for diagnosis. The VO phenotype may represent some point on the continuum of ACO and may provide a venue for further study in the harmonization of asthma and COPD treatments, which could differ from either diagnosis alone (41, 42).

Limitations

Because we only document lung function at and following entry to the study, participants may have had variable or fixed obstruction before study entry, as would also be the case in clinical practice where previous records are not available. We account for this in our evaluation of transition states by carrying the last known observation forward until a new one occurs. The study design did not allow for us to make additional adjustments for early-life risk factors for COPD, such as low birth weight or home environment in childhood. In addition, data on death were incomplete at the time of our analyses, and our analyses are therefore agnostic to vital status.

Some participants were known to be taking respiratory medications, but there were no significant differences between the VO and nonobstructed groups (Table 1), and as such, we did not adjust for treatments in our models, which would have been more complex owing to time-varying use of medications and questions of validity given unknown treatment adherence. However, if some participants did not withhold their medication for a sufficient duration before spirometry, this may have skewed results somewhat, particularly among those without fully reversible obstruction (4, 5). In addition, the study protocol uses four metered dose inhalations each of albuterol and ipratropium, which represents a dose higher than in standard clinical practice, affecting generalizability. However, this goal of achieving "maximal bronchodilation" in SPIROMICS could have revealed a larger subpopulation of subjects whose airflow obstruction was still potential reversible. This would identify more patients likely to respond to novel treatments targeting airway inflammation and dilation.

Conclusions

This analysis demonstrates that among a well-phenotyped cohort of clinical research participants, airflow obstruction that corrects with inhaled BD is associated with a significantly increased hazard of the development of COPD, as well as higher burdens of emphysema and small airway disease. Were we to accept pre-BD obstruction as a diagnostic criterion for COPD, we could potentially diagnose more patients and intervene earlier using interventions like smoking cessation and novel therapies that target early airway inflammation (43). Data on early pharmacotherapy to reduce progression of obstructive lung disease offer conflicting results (28, 44, 45). Using presence of VO and/or respiratory symptoms as criteria to consider initiation of COPD-specific therapies in these patients who we know experience exacerbations and limitations in their health status (6) may offer benefit and should undergo further investigation. Prospective studies to assess the long-term changes in disease trajectory by early intervention with COPD therapies and smoking cessation assistance among those with this phenotype, as well as the health status and economic tradeoffs thereof, are needed to understand the utility of changes to clinical practice. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the SPIROMICS participants and participating physicians, investigators, and staff for making this research possible. More information about the study and how to access SPIROMICS data is at www.spiromics.org. The project officers from the Lung Division of the NHLBI were Lisa Postow, Ph.D., and Lisa Viviano, B.S.N.

SPIROMICS Investigators: Neil E. Alexis; Wayne H. Anderson; Mehrdad Arjomandi; Igor Barjaktarevic; R. Graham Barr; Lori A. Bateman; Surya P. Bhatt; Eugene R. Bleecker; Richard C. Boucher; Russell P. Bowler; Stephanie A. Christenson; Alejandro P. Comellas; Christopher B. Cooper; David J. Couper; Gerard J. Criner; Ronald G. Crystal; Jeffrey L. Curtis; Claire M. Doerschuk; Mark T. Dransfield; Brad Drummond; Christine M. Freeman; Craig Galban; MeiLan K. Han; Nadia N. Hansel; Annette T. Hastie; Eric A. Hoffman; Yvonne Huang; Robert J. Kaner; Richard E. Kanner; Eric C. Kleerup; Jerry A. Krishnan; Lisa M. LaVange; Stephen C. Lazarus; Fernando J. Martinez; Deborah A. Meyers; Wendy C. Moore; John D. Newell, Jr.; Robert Paine III; Laura Paulin; Stephen P. Peters; Cheryl Pirozzi; Nirupama Putcha; Elizabeth C. Oelsner; Wanda K. O'Neal; Victor E. Ortega; Sanjeev Raman; Stephen I. Rennard; Donald P. Tashkin; J. Michael Wells; Robert A. Wise; and Prescott G. Woodruff.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Prevention, Diagnosis, and management of COPD. 2021 [accessed 2021 Dec. 14]. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf.
2. van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *COPD* 2014;11:113–120.
3. García-Rio F, Soriano JB, Miravitlles M, Muñoz L, Duran-Tauleria E, Sánchez G, *et al.* Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest* 2011;139:1072–1080.
4. Barjaktarevic I, Kaner R, Buhr RG, Cooper CB. Bronchodilator responsiveness or reversibility in asthma and COPD - a need for clarity. *Int J Chron Obstruct Pulmon Dis* 2018;13:3511–3513.
5. Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, *et al.*; NHLBI SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS). Clinical significance of bronchodilator responsiveness evaluated by forced vital capacity in COPD: SPIROMICS Cohort analysis. *Int J Chron Obstruct Pulmon Dis* 2019;14:2927–2938.
6. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, *et al.*; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811–1821.
7. Martinez FJ, Agusti A, Celli BR, Han MK, Allinson J, Bhatt SP, *et al.* Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med* 2022;205:275–287.
8. Han MK, Agusti A, Celli BR, Criner GJ, Halpin DMG, Roche N, *et al.* From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med* 2021;203:414–423.
9. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, *et al.*; SPIROMICS Research Group. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014;69:491–494.
10. Zider AD, Wang X, Buhr RG, Sirichana W, Barjaktarevic IZ, Cooper CB. Reduced COPD exacerbation risk correlates with improved FEV_1: a meta-regression analysis. *Chest* 2017;152:494–501.
11. Boes JL, Hoff BA, Bule M, Johnson TD, Rehemtulla A, Chamberlain R, *et al.* Parametric response mapping monitors temporal changes on lung CT scans in the subpopulations and intermediate outcome measures in COPD Study (SPIROMICS). *Acad Radiol* 2015;22:186–194.
12. Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, *et al.* Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012;18:1711–1715.
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648–654.
14. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. Respir Med 1991;85 Suppl B:25–31; discussion 33–27.
15. Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58:226–227.
16. Finkelstein DM. A proportional hazards model for interval-censored failure time data. *Biometrics* 1986;42:845–854.
17. Zhang Z, Sun J. Interval censoring. *Stat Methods Med Res* 2010;19:53–70.
18. Lindsey JC, Ryan LM. Tutorial in biostatistics methods for interval-censored data. *Stat Med* 1998;17:219–238.
19. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): the general theory and its analytical extensions. *Psychometrika* 1987;52:345–370.
20. Vrieze SI. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). *Psychol Methods* 2012;17:228–243.
21. Global Initiative for Asthma. Global strategy for asthma management and prevention 2021 [updated 2021] [accessed 2021 Dec. 15]. Available from: www.ginasthma.org.
22. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–968.
23. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, *et al.* Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med* 2014;2:195–203.
24. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002;19:398–404.
25. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med* 2019;381:1248–1256.
26. Martinez FJ, Han MK, Allinson JP, Barr RG, Boucher RC, Calverley PMA, *et al.* At the root: defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;197:1540–1551.
27. Celli BR, Agustí A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018;4:00132-02017.
28. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;272:1497–1505.
29. Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, *et al.* Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;31:742–750.
30. van Schayck CP, Chavannes NH. Detection of asthma and chronic obstructive pulmonary disease in primary care. *Eur Respir J Suppl* 2003;39:16s–22s.
31. Han MK, Steenrod AW, Bacci ED, Leidy NK, Mannino DM, Thomashow BM, *et al.* identifying patients with undiagnosed COPD in primary care settings: insight from screening tools and epidemiologic studies. *Chronic Obstr Pulm Dis (Miami)* 2015;2:103–121.
32. Ragaišienė G, Kibarskytė R, Gauronskaitė R, Giedraitytė M, Dapšauskaitė A, Kasiulevičius V, *et al.* Diagnosing COPD in primary care: what has real life practice got to do with guidelines? *Multidiscip Respir Med* 2019;14:28.
33. Perez X, Wisnivesky JP, Lurslurchachai L, Kleinman LC, Kronish IM. Barriers to adherence to COPD guidelines among primary care providers. *Respir Med* 2012;106:374–381.
34. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, *et al.*; BOLD Collaborative Research Group, the EPI-SCAN Team, the PLATINO Team, and the PREPOCOL Study Group. Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015;148:971–985.
35. Fortis S, Comellas AP, Bhatt SP, Hoffman EA, Han MK, Bhakta NR, *et al.* Ratio of FEV_1/slow vital capacity of < 0.7 is associated with clinical, functional, and radiologic features of obstructive lung disease in smokers with preserved lung function. *Chest* 2021;160:94–103.
36. Hoesterey D, Das N, Janssens W, Buhr RG, Martinez FJ, Cooper CB, *et al.* Spirometric indices of early airflow impairment in individuals at risk of developing COPD: spirometry beyond FEV_1/FVC. *Respir Med* 2019;156:58–68.
37. Yee N, Markovic D, Buhr RG, Fortis S, Arjomandi M, Couper D, *et al.* Significance of FEV_3/FEV_6 in recognition of early airway disease in smokers at risk of development of COPD: analysis of the SPIROMICS cohort. *Chest* 2022;161:949–959.
38. Leung JM, Sin DD. Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. *BMJ* 2017;358:j3772.
39. Postma DS, Rabe KF. The Asthma-COPD overlap syndrome. *N Engl J Med* 2015;373:1241–1249.
40. Kurashima K, Takaku Y, Ohta C, Takayanagi N, Yanagisawa T, Kanauchi T, *et al.* Smoking history and emphysema in asthma-COPD overlap. *Int J Chron Obstruct Pulmon Dis* 2017;12:3523–3532.
41. Maselli DJ, Hardin M, Christenson SA, Hanania NA, Hersh CP, Adams SG, *et al.* Clinical approach to the therapy of asthma-COPD overlap. *Chest* 2019;155:168–177.
42. Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, *et al.* Effect of triple therapy in patients with asthma-COPD overlap. *Int J Clin Pharmacol Ther* 2019;57:384–392.
43. Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BG Jr. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;146:1345–1348.
44. Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819–1823.
45. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297–1303.