American Journal of Respiratory and Critical Care Medicine, 2026, 212, 72–85
https://doi.org/10.1164/rccm.202501-0288OC
Published: 10 October 2025
Original Research | Chronic Obstructive Pulmonary Disease

Phenotyping asthma and/or chronic obstructive pulmonary disease using ^{129}Xe MRI and comprehensive physiologic testing

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Abstract

Rationale: **Asthma and chronic obstructive pulmonary disease (COPD) significantly overlap by conventional diagnostic criteria, yet important treatment differences remain, and people with both asthma and COPD (asthma + COPD) have worse clinical outcomes than people with a single diagnosis. Hyperpolarized xenon-129 magnetic resonance imaging (^{129}Xe MRI) and pulmonary function tests (PFTs) are sensitive to lung function and structure.**

Objective: **To determine whether ^{129}Xe MRI alongside PFTs can aid phenotyping of real-world patients with asthma and/or COPD.**

Methods: **Patients ≥16 years with physician-assigned asthma and/or COPD were recruited from primary care. ^{129}Xe and proton MRI, multiple-breath nitrogen washout, airwave oscillometry, transfer factor of the lung for carbon monoxide (TLco), body plethysmography, and spirometry were assessed post-bronchodilator. Differences between diagnostic groups were assessed.**

Results: **The study assessed 165 patients. ^{129}Xe MRI and PFT metrics differed significantly between diagnostic groups. On ^{129}Xe MRI, patients with COPD had significantly reduced and more heterogeneous ventilation, greater acinar dimensions, and lower gas transfer, in addition to lower spirometry, greater airways resistance and reactance, and more air trapping than patients with asthma. Similarly, ^{129}Xe MRI metrics demonstrated greater abnormalities in COPD than asthma when comparing only those with normal forced expiratory volume in 1 s or TLco. Lung function and structure were worse in asthma + COPD than asthma and better than COPD.**

Conclusions: **^{129}Xe MRI alongside PFTs provide phenotypically distinct airway disease signatures to aid diagnosis of asthma and/or COPD. ^{129}Xe MRI is highly sensitive to minimal lung disease and identifies functional/structural phenotypes that may help to guide treatment decisions.**

Keywords asthma, COPD, xenon-129 MRI, pulmonary function tests

Received: January 29, 2025; **Accepted:** September 3, 2025

At a Glance Commentary

Current Scientific Knowledge on the Subject: Asthma and chronic obstructive pulmonary disease (COPD) significantly overlap by conventional diagnostic criteria, yet important treatment differences remain. People with both asthma and COPD have worse clinical outcomes than people with a single diagnosis. Hyperpolarized xenon-129 magnetic resonance imaging (^{129}Xe MRI) and pulmonary function tests (PFTs) are sensitive to lung function and structure.

What This Study Adds to the Field: This research shows the utility of xenon-129 magnetic resonance imaging (^{129}Xe MRI) in the phenotyping of patients with asthma and/or COPD to obtain diagnostic information (and therefore guide appropriate treatment) including when conventional lung function tests are normal. In this real-world population of primary care patients with asthma and/or COPD, lung function was lower and structure more abnormal in asthma + COPD than in asthma, but better than in COPD. Among people with normal forced expiratory volume in 1 s or transfer factor of the lung for carbon monoxide, patients with COPD had reduced and more heterogeneous ventilation, greater acinar dimensions, and lower gas exchange on ^{129}Xe MRI than patients with asthma.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous obstructive lung diseases, and some patients have characteristics of both.[1,2] The NOVEL observational longiTudinal studY (NOVELTY, NCT02760329) has previously demonstrated that disease characteristics overlap between patients with asthma, asthma + COPD, and COPD, and that conventional criteria poorly differentiate between these diagnostic groups.[3] Despite this, there are important differences in treatment recommendations; for example, long-acting bronchodilators alone are recommended for patients with COPD but are contraindicated for patients with asthma.[2]

Randomized controlled trials that inform treatment guidelines generally require patients to satisfy stringent inclusion criteria; the resulting highly selective patient sample restricts the validity of results to fewer than 10% of real-world patients.[1,2,4] Studies often exclude patients who have features of both diseases, the prevalence of which is between 15% and 32% of patients who have diagnoses of asthma or COPD.[2] These patients exhibit worse quality of life, and more hospitalizations and exacerbations when compared with those with a single diagnosis.[5] Furthermore, patients with asthma + COPD are more likely to die or be hospitalized if treated with bronchodilators alone, rather than bronchodilators in combination with inhaled corticosteroids.[6] Improved characterization of the lung function and structure of patients with asthma + COPD in order to determine if they have more asthma-like or more COPD-like disease could help guide management and treatment.

More extensive multimodal investigation of lung structure and function that goes beyond diagnostic labels and spirometry may reveal the presence of phenotypes that will inform our understanding of underlying mechanisms and point to potential treatment strategies. Hyperpolarized xenon-129 magnetic resonance imaging (^{129}Xe MRI) is new to clinical practice, highly sensitive to regional lung function abnormalities in patients with obstructive lung disease,[7] and can provide novel insights for phenotyping obstructive lung disease, such as alveolar microstructure and gas exchange.[8] Studies utilizing ^{129}Xe MRI have observed increased ventilation heterogeneity in asthma[9] and in COPD,[10] and elevated acinar dimensions[11] and reduced gas exchange[12] in COPD compared with the lungs of healthy volunteers. Pulmonary function tests (PFTs) such as multiple-breath nitrogen washout (MBNW) and airwave oscillometry (AOS) have increasing clinical potential and can provide complementary information about global small airways obstruction, ventilation heterogeneity, airways resistance, and lung compliance.[13,14]

The Advanced Diagnostic Profiling (ADPro) substudy of NOVELTY is using ^{129}Xe MRI and comprehensive PFT assessments to phenotype lung disease.[15] In this work, we aimed to determine: (1) whether ^{129}Xe MRI and comprehensive PFTs, including MBNW and AOS, can aid in the phenotyping of a real-world population of patients with physician-assigned asthma and/or COPD; and (2) whether ^{129}Xe MRI could differentiate diagnostic groups when forced expiratory volume in 1 s (FEV_1) or transfer factor of the lung for carbon monoxide (TLco) were within the normal ranges. Some of the results of this study have previously been reported in congress abstracts.[16-18]

Methods

Patients ≥16 years old with a physician-assigned or suspected diagnosis of asthma and/or COPD participating in NOVELTY,[15] were recruited from 2 primary care centers in York, UK. Patients were assessed at the University of Sheffield, Sheffield, UK, during a single visit between July 2020 and June 2021. The following order of assessments was performed ≥20 min after the administration of inhaled salbutamol 400 µg: ^{129}Xe MRI, proton (^{1}H) MRI, MBNW, AOS, TLco, body plethysmography, and spirometry (~90 min after salbutamol administration).

Demographics and clinical metrics

Demographic data, Chronic Airways Assessment Test (CAAT),[19] St George's Respiratory Questionnaire (SGRQ),[20] and Respiratory Symptom Questionnaire (RSQ) scores,[21] physician-reported exacerbations over the previous year, hemoglobin level, and neutrophil and eosinophil count were taken from the NOVELTY database at the timepoint closest to the ADPro visit.

MRI and PFTs

^{1}H (structural proton) and ^{129}Xe MRI were acquired supine using a 1.5 T whole-body MRI system. The following MRI metrics were calculated: ventilation defect percent (VDP; percentage of unventilated lung), ventilation heterogeneity index (VH_i; the interquartile range of the coefficient of variation of signal intensity within

ventilated regions), mean diffusive length scale (Lm_D; a measure of acinar dimension), ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces (RBC/gas), ratio of ^{129}Xe dissolved in the alveolar membrane to ^{129}Xe in the airspaces (M/gas), and ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the alveolar membrane (RBC/M; measures of alveolar gas exchange).[15] Figure 1 depicts the application of ^{129}Xe MRI in assessing lung ventilation, acinar microstructure, and gas exchange.

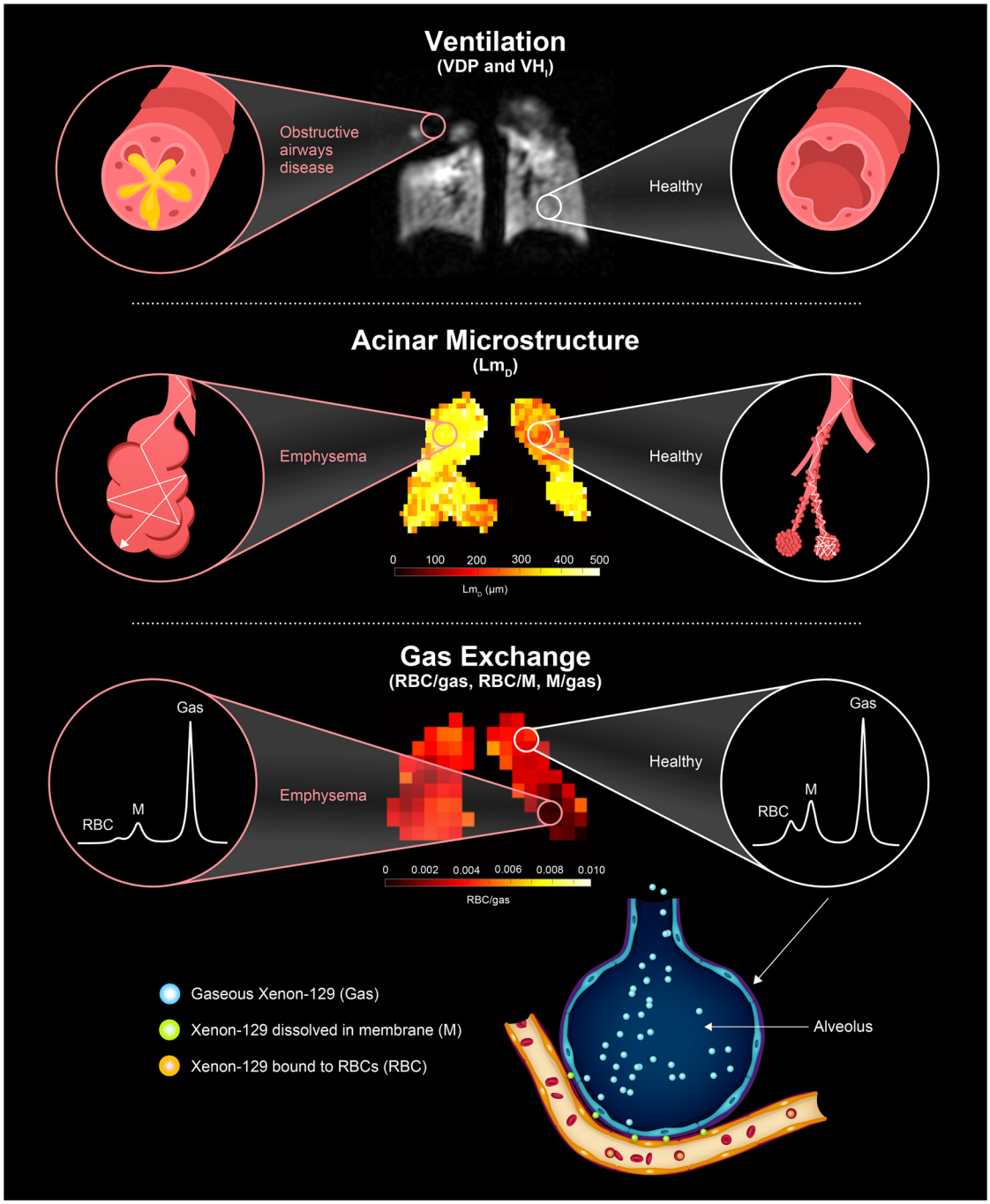

Figure 1 Application of ^{129}Xe MRI to assess functionality of lung ventilation, acinar microstructure, and gas exchange. The patient inhales ^{129}Xe and holds it within their lungs during a short breath-hold. Top: in a ^{129}Xe ventilation image, the signal is proportional to the density of gas, with black depicting unventilated regions, which could be caused by obstruction of the airways. Middle: in an ^{129}Xe map of acinar dimensions, lighter colors depict enlarged alveolar spaces which may indicate an emphysema phenotype. In healthy acini, ^{129}Xe bounces off the alveolar, duct, and bronchiole boundaries, diffusing a shorter distance during imaging than in emphysematous acini where airspaces are enlarged and boundaries destroyed. Bottom: in a ^{129}Xe map of gas exchange, darker colors depict areas of reduced gas transfer which may indicate an emphysema phenotype with reduced xenon dissolved in M and reduced ^{129}Xe bound to the RBCs. A small proportion of inhaled gaseous ^{129}Xe (blue) dissolves into the M (green) and transfers to the RBCs (orange) allowing measurement of gas exchange. Lm_D = mean diffusive length scale; M = membrane; M/gas = ratio of ^{129}Xe dissolved in the alveolar membrane to ^{129}Xe in the airspaces; RBC = red blood cell; RBC/gas = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces; RBC/M = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the alveolar membrane; VDP = ventilation defect percent; VH_l = ventilation heterogeneity index.

All PFTs were performed after MRI and according to international guidelines.[22-26] The lung clearance index (LCI) was calculated from MBNW; AOS was used to measure the resistance and reactance at 5 Hz, the difference between the resistance at 5 and 20 Hz (R5-R20), and the area under the reactance curve (AX); and total lung capacity (TLC), residual volume (RV), and RV/TLC were measured using body plethysmography. TLco was calculated from gas transfer. Spirometry, including FEV_1, forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow at 25-75% of the FVC ($FEF_{25-75\%}$) was performed. Measurements were converted to *z*-scores (lower limit of normal −1.64).[27-30]

Statistical analysis

Differences between physician-assigned diagnoses (asthma, asthma + COPD, and COPD) were assessed using Kruskal-Wallis tests with Dunn's correction (non-normal data) or analysis of variance tests with Tukey's correction (normal data) in GraphPad Prism. Diagnosis signatures were created to compare differences in key metrics between diagnosis groups. Spearman's correlations between key metrics were performed with Holm-Sidak correction for multiple comparisons ($\alpha = 0.05$).

Sub-analyses were performed to investigate specific subgroups: (1) differences in ^{129}Xe MRI VDP, VH_1, and Lm_D were assessed in patients with normal FEV_1 (*z*-score > −1.64); (2) differences in ^{129}Xe MRI RBC/gas, RBC/M, and Lm_D were assessed in patients with normal TLco (*z*-score > −1.64); and (3) ^{129}Xe MRI, PFT, and clinical metrics were assessed in age-matched patients.

Methods details and additional exploratory analyses are presented in the Supplementary Material.

Results

Patient demographics and clinical characteristics by physician-assigned diagnosis

Patient demographics and clinical characteristics are summarized in Table 1. Overall, 165 patients (aged 27-82 years) were assessed; 83 patients (50.3%) had a physician-assigned diagnosis of asthma, 55 (33.3%) had a physician-assigned diagnosis of asthma + COPD, and 27 (16.4%) had a physician-assigned diagnosis of COPD. When compared with patients with COPD, patients with asthma were younger (median: 52.8 vs 69.9 years) and were less likely to be current smokers (15.7% vs 48.1%). Similarly, compared with patients with asthma + COPD, patients with asthma were younger (median: 52.8 vs 61.9 years), less likely to be current smokers (15.7% vs 32.7%), and had lower CAAT scores (median: 10.0 vs 14.0), SGRQ scores (median: 15.4 vs 31.4), and RSQ scores (median: 2.0 vs 4.0), indicating better health status and fewer symptoms. There was a lower proportion of female patients in the asthma + COPD group (40.0%) compared with the COPD group (70.4%), and a higher percentage of patients with physician-assigned severe disease in the asthma + COPD group (43.6%) compared with the asthma (21.7%) or COPD (18.5%) groups. As expected, there were medication differences between physician-assigned diagnosis groups (Table 1 and Table S1).

^{129}Xe MRI and PFT results by physician-assigned diagnosis

Figure 2 shows example ^{129}Xe MR images from a patient from each diagnostic group with normal FEV_1 and normal TLco.

Among all patients, many MRI and PFT metrics were different between patients with COPD versus asthma ($P < .001$) and asthma + COPD versus asthma ($P < .05$) (Figure 3 and Table 2). VDP, Lm_D, RBC/gas, M/gas, and LCI were also different between COPD versus asthma + COPD ($P < .01$ or $P < .05$). Patients with COPD had worse spirometry (FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$), lower gas transfer, more gas trapping, more heterogeneous ventilation, greater acinar dimensions, higher airways reactance, and higher peripheral airways resistance than patients with asthma. VDP was abnormal (>2.16%)[31] in 47% of patients with asthma, 87% of patients with asthma + COPD, and 100% of patients with COPD. Acinar dimensions (Lm_D) were abnormally large (>1.64 *z*-scores)[31] in 55.6% of patients with COPD, 46.3% of patients with asthma + COPD, and 6.2% of patients with asthma. Considerable heterogeneity was also observed in some variables within diagnostic groups as seen in the wide range of data observed, for example, for VDP in COPD and AX in asthma + COPD. Additional metrics are presented in Table S2 and the numbers of patients with each measurement are summarized in Table S3. The diagnostic signatures of patients with asthma, asthma + COPD, and COPD are shown in Figure 4.

Abnormalities on anatomical ^{1}H MRI were observed in 19.0% of patients, of which atelectasis was the most common (asthma: 9.6%; asthma + COPD: 14.8%; COPD: 11.1%) (Table S4). Post-bronchodilator air trapping was present in 3 (3.7%) patients with asthma, but not in patients with asthma + COPD or COPD. Emphysema was observed on anatomical ^{1}H MRI in one patient with asthma + COPD and one with COPD.

^{129}Xe MRI metrics in patients with normal FEV_1 or normal TLco

In patients with spirometry data, post-bronchodilator FEV_1 was normal (*z*-score > −1.64) in 95.1%, 67.9%, and 46.2% of patients with asthma, asthma + COPD, and COPD, respectively. In 126 patients with normal post-bronchodilator FEV_1, ventilation defects were prevalent (Figure 5, Table S5) and 61.1% had abnormal VDP. In this group of patients, ^{129}Xe MRI metrics of ventilation abnormality and acinar dimensions were smaller (closer to age-matched normal) in asthma than in COPD or asthma + COPD groups ($P < .0001$). Acinar dimensions were also smaller (closer to age-matched normal) in asthma + COPD than in COPD ($P < .05$). 16.0% of patients had abnormally large acinar dimensions (Lm_D >1.64 *z*-scores) (Table S5). In patients with gas transfer data, post-bronchodilator TLco was normal (*z*-score > −1.64) in 95.1%, 77.4%, and 46.2% of patients with asthma, asthma + COPD, and COPD, respectively. In 131 patients with normal TLco, ^{129}Xe MRI metrics of gas transfer and acinar dimensions were worse in COPD than in asthma groups (RBC/gas, Lm_D: $P < .001$; RBC/M: $P < .05$) (Figure 5) and 14.6% of patients had enlarged acinar dimensions.

Table 1 Patient demographics and clinical characteristics.

					Statistical comparison (MD [95% CI]; *P*-value)		
	All patients (*n* = 165)	Asthma (*n* = 83)	Asthma + COPD (*n* = 55)	COPD (*n* = 27)	Asthma vs asthma + COPD	Asthma vs COPD	Asthma + COPD vs COPD
Female	86 (52.1%)	44 (53.0%)	22 (40.0%)	19 (70.4%)	13.0% (−5.3 to 31.3); .19	−17.4% (−40.1 to 5.4); .17	−30.4% (−54.7 to −6.1); **.02**
Age, years	60.3 (21.4)	52.8 (21.8)	61.9 (14.5)	69.9 (13.2)	−9.1 (−14.0 to −4.2); **.0004**	−13.3 (−19.5 to −7.1); **<.0001**	−4.2 (−10.8 to 2.4); .35
BMI, kg/m^2	27.3 (8.0)	27.7 (8.9)	27.6 (8.5)	26.7 (7.4)	1.8 (−0.5 to 4.2); .45	3.4 (0.4 to 6.4); **.045**	1.5 (−1.7 to 4.7); .66
Ethnicity							
Asian	1 (0.6%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (−2.4 to 4.8); >.99	1.2% (−2.4 to 4.8); >.99	0 (0-0); NA
Other	1 (0.6%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (−2.4 to 4.8); >.99	1.2% (−2.4 to 4.8); >.99	0 (0-0); NA
White	163 (98.8)	81 (97.6)	55 (100%)	27 (100%)	−2.4% (−7.2 to 2.4); .67	−2.4% (−8.1 to 3.3); >.99	0 (0-0); NA
Physician-assessed disease severity							
Mild	42 (25.5%)	22 (26.5%)	10 (18.2%)	10 (37.0%)	8.3% (−7.1 to 23.8); .35	−10.5% (−33.5 to 12.5); .42	−18.9% (−42.5 to 4.8); .11
Moderate	76 (46.1%)	43 (51.8%)	21 (38.2%)	12 (44.4%)	13.6% (−4.6 to 31.9); .16	7.4% (−16.7 to 31.4); .66	−6.3% (−31.7 to 19.2); .76
Severe	47 (28.5%)	18 (21.7%)	24 (43.6%)	5 (18.5%)	−21.9% (−39.3 to −4.6); **.01**	3.2% (−16.4 to 22.8); .94	25.1% (2.7-47.5); **.047**
Smoking status							
Never	51 (30.9%)	44 (53.0%)	7 (12.7%)	0 (0.0%)	40.3% (24.9-55.7); **<.0001**	53.0% (39.8-66.2); **<.0001**	12.7% (1.2-24.3); .13
Former	70 (42.4%)	26 (31.3%)	30 (54.5%)	14 (51.9%)	−23.2% (−41.3 to −5.2); **.01**	−20.5% (−44.3 to 3.3); .09	2.7% (−23.0 to 28.4); .99
Current	44 (26.7%)	13 (15.7%)	18 (32.7%)	13 (48.1%)	−17.1% (−33.2 to −0.9); **.03**	−32.5% (−55.3 to −9.6); **<.0001**	−15.4% (−40.7 to 9.9); .27
Pack years							
All patients	9.2 (36.7)	0.0 (9.0)	25.0 (41.4)	42.0 (42.8)	−23.0 (−31.8 to −14.3); **<.0001**	−35.3 (−46.5 to −24.2); **<.0001**	−12.3 (−24.1 to −0.5); .18
Ever smokers	24.0 (37.0)	9.2 (19.5)	34.4 (32.7)	42.0 (42.8)	−19.7 (−31.8 to −7.6); **<.001**	−27.6 (−41.6 to −13.6); **<.0001**	−7.9 (−21.4 to 5.5); .70
Exacerbations over previous year*	0.8 (0.0, 8.0)	0.6 (0.0, 2.0)	0.9 (0.0, 7.0)	1.0 (0.0, 8.0)	−0.3 (−0.9 to 0.2); >.99	−0.4 (−1.0 to 0.3); >.99	−0.0 (−0.7 to 0.6); >.99
CAAT score	11.0 (13.0)	10.0 (12.5)	14.0 (16.0)	13.0 (12.0)	−3.8 (−7.4 to −0.1); **.037**	−3.4 (−8.1 to 1.2); .20	0.3 (−4.6 to 5.2); >.99
SGRQ score	24.5 (32.9)	15.4 (29.4)	31.4 (32.6)	26.7 (33.3)	−10.8 (−20.3 to −1.4); **.017**	−9.5 (−21.6 to 2.5); .19	1.3 (−11.2 to 13.8); >.99
RSQ score	3.0 (5.0)	2.0 (4.5)	4.0 (4.0)	4.0 (9.0)	−2.3 (−3.9 to −0.7); **.0022**	−2.3 (−4.3 to −0.3); .06	−0.0 (−2.2 to 2.1); >.99
% with FPC	30.0%	21.7%	39.6%	33.3%	−17.9% (−37.1 to −1.3); .07	−11.7% (−37.6 to 14.2); .44	6.3% (−21.6 to 34.1); .82
Baseline eosinophils, ×10^3 μL^{-1}	0.2 (0.1)	0.2 (0.2)	0.2 (0.1)	0.2 (0.3)	0.04 (−0.05 to 0.13); >.99	−0.08 (−0.21 to 0.05); >.99	−0.11 (−0.25 to 0.02); .47

(Continued)

Table 1 Continued.

					Statistical comparison (MD [95% CI]; *P*-value)		
	All patients (*n* = 165)	**Asthma (*n* = 83)**	**Asthma + COPD (*n* = 55)**	**COPD (*n* = 27)**	**Asthma vs asthma + COPD**	**Asthma vs COPD**	**Asthma + COPD vs COPD**
Baseline neutrophils, ×10³ µL⁻¹	4.2 (1.8)	3.7 (1.6)	4.4 (1.8)	5.0 (1.7)	−0.5 (−1.3 to 0.2); .18	−1.1 (−2.2 to −0.0); **.034**	−0.6 (−1.7 to 0.5); .40
Hemoglobin, gL⁻¹	143.0 (18.0)	142.0 (15.5)	144.5 (19.0)	139.5 (14.7)	−1.8 (−9.0 to 5.5); >.99	3.0 (−7.5 to 13.6); >.99	4.8 (−6.0 to 15.6); .39
GINA (2016/2017)†							
1	34 (25%)	14 (17%)	19 (35%)	0 (NA)	−19.5% (−36.1 to −2.9); **.02**	NA	NA
2	4 (2.9%)	2 (2.4%)	2 (3.7%)	0 (NA)	−1.2% (−8.4 to 6.0); >.99	NA	NA
3	30 (22%)	25 (30%)	5 (9.3%)	0 (NA)	21% (7.1-35.0); **.01**	NA	NA
4	40 (29%)	23 (28%)	17 (31%)	0 (N/A)	−3.2% (−20.3 to 13.9); .83	NA	NA
5	30 (22%)	19 (23%)	11 (20%)	0 (N/A)	2.9% (−12.5 to 18.3); .85	NA	NA
GOLD (2019)†							
1	42 (55%)	0 (NA)	31 (60%)	11 (44%)	NA	NA	19.3% (−6.1 to 44.6); .16
2	25 (32%)	0 (NA)	18 (35%)	7 (28%)	NA	NA	4.9% (−19.2 to 29.0); .85
3	8 (10%)	0 (NA)	2 (3.8%)	6 (24%)	NA	NA	−22.3% (−42.3 to −2.3); **.01**
4	2 (2.6%)	0 (NA)	1 (1.9%)	1 (4.0%)	NA	NA	−1.9% (−11.7 to 8.0); >.99
Medications†							
LAMA	50 (30%)	11 (13%)	27 (49%)	12 (44%)	−35.8% (−52.4 to −19.2); **<.0001**	−31.2% (−53.7 to −8.6); **<.0001**	4.6% (−21.1 to 30.3); .87
LABA	3 (1.8%)	2 (2.4%)	1 (1.8%)	0 (0%)	0.6% (−4.8 to 6.0); >.99	2.4% (−3.3 to 8.1); >.99	1.8% (−3.5 to 7.2); >.99
ICS	111 (69%)	67 (81%)	37 (69%)	7 (28%)	11.6% (−4.8 to 28.0); .17	51.1% (29.4-72.8); **<.0001**	39.5% (15.6-63.3); **<.0001**
Triple therapy	64 (39%)	11 (13%)	38 (69%)	15 (56%)	−55.8% (−71.6 to −40.1); **<.0001**	−42.3% (−64.9 to −19.7); **<.0001**	13.5% (−11.6 to 38.7); .34
Biologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0-0); NA	0 (0-0); NA	0 (0-0); NA

[129]Xe = xenon-129; BMI = body mass index; CAAT = Chronic Airways Assessment Test; COPD = chronic obstructive pulmonary disease; FPC = frequent productive cough; GINA = Global Initiative for Asthma score; GOLD = Global Initiative for Chronic Obstructive Lung Disease stage; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MD, mean difference; NA, not applicable; RSQ = Respiratory Symptom Questionnaire; SGRQ = St George's Respiratory Questionnaire.
Data are presented as *n* (%) or median (IQR), except exacerbation data which are presented as mean (min, max). Significant *P*-values of <.05 are emboldened.
*Physicians were asked to record exacerbations as "During the past 12 months, on how many occasions has your patient experienced an exacerbation of their asthma or COPD beyond the patient's usual day-to-day variance?".
†Percentages were calculated using the number of patients with information available (see Table S3).

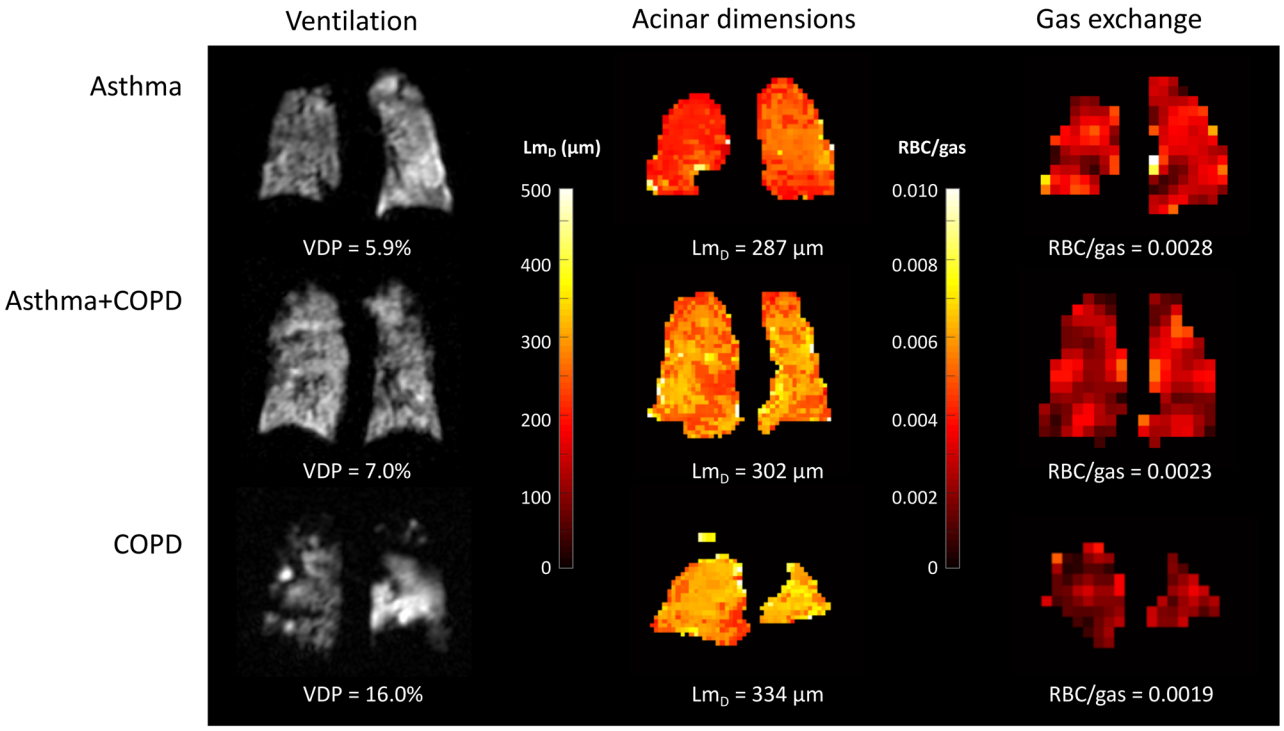

Figure 2 Example ^{129}Xe MR images from patients with normal FEV$_1$ and TLco; (top) a patient with asthma, (middle) a patient with asthma + COPD, and (bottom) a patient with COPD. Whole lung values are presented. ^{129}Xe = xenon-129; COPD = chronic obstructive pulmonary disease; Lm$_D$ = mean diffusive length scale (acinar dimensions); MR = magnetic resonance; RBC/gas = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces; VDP = ventilation defect percent.

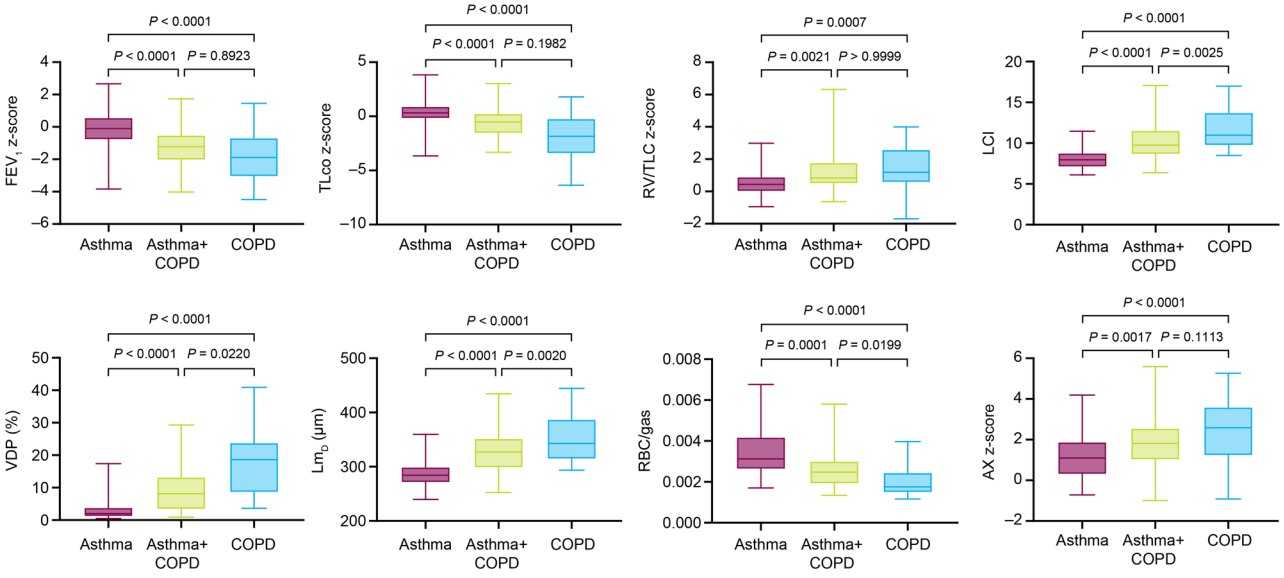

Figure 3 Key ^{129}Xe MRI and PFT metrics grouped according to physician-assigned diagnosis. Whiskers denote minimum and maximum values. PFTs: (*A*) FEV$_1$ *z*-score, (*B*) TLco *z*-score, (*C*) RV/TLC *z*-score, (*D*) LCI, and (*H*) AX *z*-score. ^{129}Xe MRI: (*E*) VDP, (*F*) Lm$_D$ (acinar dimensions), and (*G*) RBC/gas (gas transfer). ^{129}Xe = xenon-129; AX = area under the reactance curve; COPD = chronic obstructive pulmonary disease; FEV$_1$ = forced expiratory volume in 1 s; LCI = lung clearance index; Lm$_D$ = mean diffusive length scale; MRI = magnetic resonance imaging; ns = not significant; TLco = transfer factor of the lung for carbon monoxide; PFT = pulmonary function test; RBC/gas = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces; RV = residual volume; TLC = total lung capacity; VDP = ventilation defect percent.

Table 2 ^{129}Xe MRI and PFT metrics.

					Statistical comparison (MD [95% CI]; *P*-value)		
	All patients (*n* = 165)	Asthma (*n* = 83)	Asthma + COPD (*n* = 55)	COPD (*n* = 27)	Asthma vs asthma+ COPD	Asthma vs COPD	Asthma+ COPD vs COPD
^{129}Xe MRI metrics							
VDP, %	4.2 (9.4)	2.0 (2.7)	8.2 (9.9)*,†	18.6 (15.3)*	−7.0 (−9.7 to −4.4); **<.0001**	−15.5 (−18.8 to −12.2); **<.0001**	−8.5 (−12.0 to −4.9); **.022**
VH_I	11.0 (5.1)	9.1 (2.6)	16.5 (5.7)*	20.2 (7.3)*	−8.0 (−9.3 to −6.7); **<.0001**	−11.3 (−13.0 to −9.7); **<.0001**	−3.4 (−5.2 to −1.6); .29
Lm_D, µm	301.5 (55.0)	284.3 (28.5)	327.1 (53.4)*,†	342.9 (72.8)*	−41.05 (−55.31 to −26.80); **<.0001**	−69.04 (−87.07 to −51.00); **<.0001**	−27.98 (−47.11 to −8.86); **.002**
RBC/gas	0.0028 (0.0015)	0.0031 (0.0016)	0.0025 (0.0011)*,†	0.0018 (0.0010)*	0.00085 (0.00042-0.00129); **.0001**	0.00146 (0.00092-0.00200); **<.0001**	0.00060 (0.00003-0.00118); **.02**
M/gas	0.0091 (0.0030)	0.0096 (0.0030)	0.0089 (0.0029)*,†	0.0077 (0.0029)*	0.00099 (0.00006-0.00191); **.033**	0.00259 (0.00113-0.00339); **<.0001**	0.00127 (0.00007-0.00248); **.036**
Spirometry, MBNW, TLco, body plethysmography, and airwave oscillometry metrics							
FEV_1 % predicted	90.8 (24.9)	98.5 (18.7)	81.6 (21.1)*	70.7 (41.4)*	18.2 (10.4-26.0); **< .0001**	27.5 (17.6-37.5); **<.0001**	9.4 (−1.2 to 20.0); .81
FEV_1*z*-score	−0.63 (1.57)	−0.11 (1.35)	−1.22 (1.54)*	−1.89 (2.38)*	1.17 (0.65-1.68); **< .0001**	1.70 (1.04-2.35); **<.0001**	0.53 (−0.17 to 1.23); .89
FEV_1*z*-score <−1.64‡	35 (21.7)	4 (4.9)	17 (32.1)	14 (53.8)	-	-	-
FEV_1/FVC *z*-score	−1.51 (1.9)	−1.03 (1.41)	−2.11 (1.94)*	−3.01 (1.59)*	1.33 (0.84-1.82); **< .0001**	2.01 (1.39-2.63); **<.0001**	0.68 (0.01-1.34); .18
FEV_1/FVC	66.8 (18.8)	72.9 (11.9)	59.4 (16.4)*	50.1 (18.1)*	13.6 (9.1-18.1); **<.0001**	12.1 (15.4-26.9); **<.0001**	7.5 (1.4-13.6); .16
$FEF_{25-75\%}$*z*-score	−1.49 (1.65)	−0.78 (1.54)	−1.93 (1.46)*	−2.49 (1.36)*	1.25 (0.79-1.70); **<.0001**	1.77 (1.19-2.35); **<.0001**	0.52 (−0.10 to 1.14); .12
FVC *z*-score	0.32 (1.19)	0.48 (1.21)	0.04 (1.10)	0.23 (1.49)	0.17 (−0.24 to 0.59); .38	0.29 (−0.24 to 0.82); .72	0.12 (0.45-0.68); >.99
LCI	8.8 (2.6)	8.0 (1.7)	9.8 (2.9)*,†	11.0 (4.0)*	−2.0 (−2.8 to −1.2); **<.0001**	−3.6 (−4.7 to −2.6); **<.0001**	−1.6 (−2.7 to −0.5); **.0025**
TLco *z*-score	−0.05 (1.69)	0.32 (1.10)	−0.52 (1.81)*	−1.84 (3.21)*	0.98 (0.39-1.57); **<.0001**	2.25 (1.49-3.00); **<.0001**	1.26 (0.46-2.06); .20
RV/TLC *z*-score	0.67 (1.11)	0.44 (0.90)	0.83 (1.29)*	1.19 (2.03)*	−0.62 (−1.05 to −0.20); **.0021**	−0.92 (−1.46 to −0.38); **<.001**	−0.30 (−0.84 to 0.28); >.99
R5-R20 *z*-score	0.96 (2.47)	0.54 (1.84)	1.40 (2.63)*	2.60 (4.49)*	−0.77 (−1.77 to 0.23); **.037**	−2.53 (−3.83 to −1.24); **<.001**	−1.76 (−3.12 to −0.40); .22
AX *z*-score	1.40 (1.69)	1.10 (1.59)	1.82 (1.55)*	2.58 (2.38)*	−0.75 (−0.26 to −0.24); **.0017**	−1.34 (−1.99 to −0.68); **<.0001**	−0.59 (−1.27 to 0.10); .11

^{129}Xe = xenon-129; AX = area under the reactance curve; COPD = chronic obstructive pulmonary disease; $FEF_{25-75\%}$ = forced expiratory flow at 25% and 75% of the pulmonary volume; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; LCI = lung clearance index; Lm_D = mean diffusive length scale (acinar dimensions); MBNW = multiple-breath nitrogen washout; MD = mean difference; M/gas = ratio of ^{129}Xe dissolved in the alveolar membrane to ^{129}Xe in the airspaces; MRI = magnetic resonance imaging; R5-R20 = difference between resistance at 5 and 20 Hz; RBC/gas = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces; RV = residual volume; TLC = total lung capacity; TLco = transfer factor of the lung for carbon monoxide; VDP = ventilation defect percent; VH_I = ventilation heterogeneity index. Data are presented as median (interquartile range). Significant *P*-values of <.05 are emboldened.

*Difference compared with the asthma group (*P* <.05).

†Difference compared with the COPD group (*P* <.05).

‡The percentage was calculated using the number of patients who completed spirometry (161, 82, 53, and 26 for all patients, and patients with asthma, asthma + COPD, and COPD, respectively).

Figure 4 Diagnosis ^{129}Xe MRI/PFT signatures in patients with physician-assigned (*A*) asthma, (*B*) asthma + COPD, (*C*) COPD, and (*D*) in all patients. The center is at −1.1. Radar plots have been generated from the median values of each metric in each diagnostic group; however, values have been transformed for the purpose of visual comparison between groups (see the Supplementary Materials for the methodology). Higher scores, toward the outer edge of the plot, indicate that a higher degree of lung abnormalities has been identified by ^{129}Xe MRI and PFTs. ^{129}Xe = xenon-129; AX = airway reactance; COPD = chronic obstructive pulmonary disease; LCI = lung clearance index; Lm_D = mean diffusive length scale; MRI = magnetic resonance imaging; PFT = pulmonary function test; RBC/gas = ratio of ^{129}Xe in the red blood cells to ^{129}Xe in the airspaces; TLco = transfer factor of the lung for carbon monoxide.

^{129}Xe MRI and PFT metrics in age-matched patients

The trends observed in the whole dataset remained in the subset of age-matched patients, albeit with reduced statistical significance due to the smaller number of patients included (Table S6; Figure S1). Differences with a statistical significance of $P < .0001$ between patients with physician-assigned asthma and COPD remained for VDP, Lm_D, LCI, FEV_1 *z*-score, and TLco *z*-score.

Correlations between metrics

There were moderate-strong correlations between ^{129}Xe MRI and PFT metrics (Figure S2). Strong negative correlations were observed between VDP and FEV_1/FVC *z*-score, VH_l and FEV_1/FVC *z*-score, and Lm_D and TLco *z*-score. VDP and VH_l showed moderate positive correlations with Lm_D and LCI. CAAT, SGRQ, and exacerbations in the previous year had the weakest correlations with MRI and PFT metrics. Smoking pack-years showed moderate correlation with VDP, VH_l, Lm_D, RBC/gas, FEV_1 *z*-score, TLco *z*-score, and LCI.

Three-dimensional plots of the relationships between FEV_1 *z*-score, VDP, and LCI (Figure S3A) and TLco *z*-score, RBC/gas, and Lm_D (Figure S3B) show reasonable separation, and some overlap, between populations of patients with asthma alone (red dots) and COPD alone (blue dots). Figure S3B shows the direct influence of lung microstructure on gas exchange; in patients with increased acinar dimensions (Lm_D), the reduction in gas exchange surface area was associated with impaired transport of ^{129}Xe into the blood (RBC/gas) and reduced TLco.

Discussion

Among patients with physician-assigned diagnoses of asthma and/or COPD, ^{129}Xe MRI and PFT metrics provided phenotypically distinct signatures of airways disease. Patients with COPD had increased ventilation defects and acinar dimensions and reduced gas exchange on ^{129}Xe MRI when compared to those with asthma, and increased ventilation heterogeneity, airways resistance, and lung compliance. Metrics were more similar in asthma + COPD and COPD, although significant differences in some metrics (VDP, Lm_D, RBC/gas, M/gas, and LCI) were observed. Substantial heter-

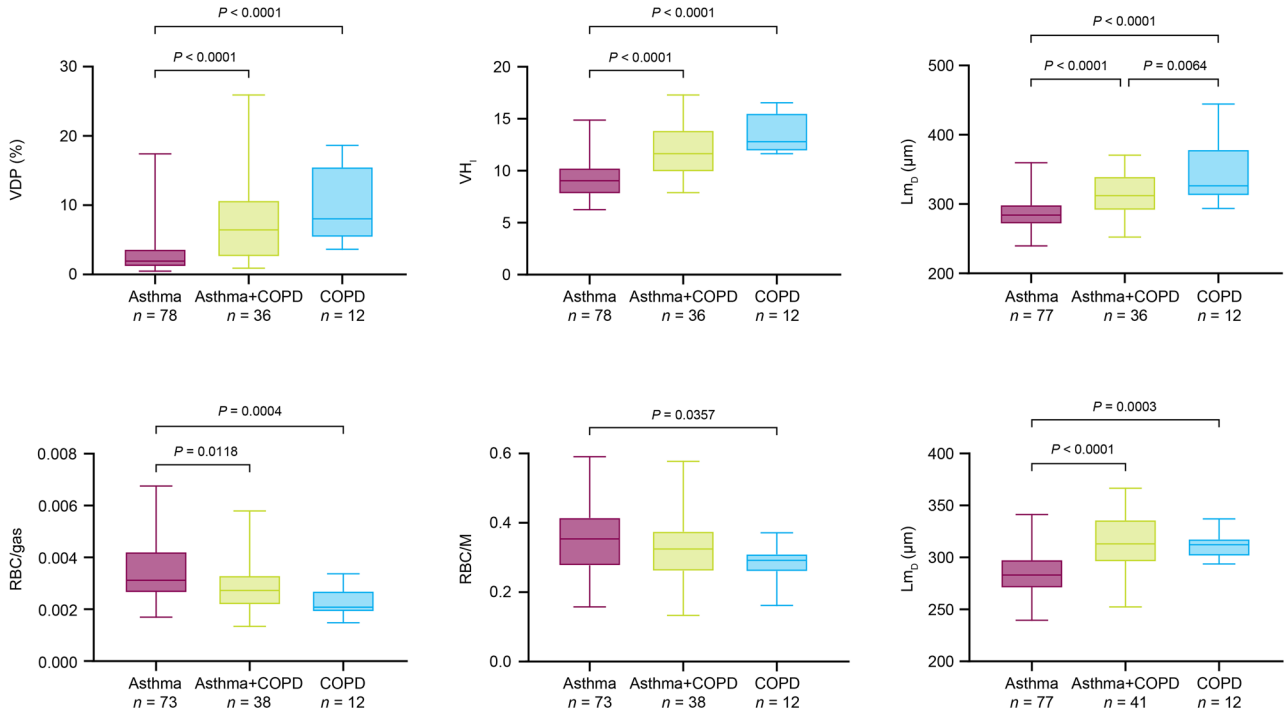

Figure 5 Patients with normal FEV_1 (top row) or normal TLco (bottom row): ^{129}Xe MRI metrics for patients with physician-assigned diagnoses of asthma, asthma + COPD, and COPD. Whiskers denote minimum and maximum values. Top row: patients with normal FEV_1; (*A*) VDP, (*B*) VH_l, and (*C*) Lm_D (acinar dimensions). Bottom row: patients with normal TLco; (*D*) RBC/gas (gas transfer), (*E*) RBC/M, and (*F*) Lm_D (acinar dimensions). Differences between physician-assigned diagnosis groups, presented as MD (CI); *P*-value: (*A*) VDP_{asthma} vs $VDP_{asthma+COPD}$ = −4.9 (−6.8, −3.0)%; <.0001, VDP_{asthma} vs VDP_{COPD} = −7.2 (−10.2, −4.3)%; <.0001; (*B*) $VH_{lasthma}$ vs $VH_{lasthma+COPD}$ = −2.6 (−3.6, −1.7); <.0001, $VH_{lasthma}$ vs VH_{lCOPD} = −4.3 (−5.8, −2.8); <.0001; (*C*) $Lm_{Dasthma}$ vs $Lm_{Dasthma+COPD}$ = −29.8 (−43.9, −15.7) μm; <.0001, $Lm_{Dasthma}$ vs Lm_{DCOPD} = −60.4 (−82.1, −38.7) μm; <.0001, $Lm_{Dasthma+COPD}$ vs Lm_{DCOPD} = −30.7 (−54.0, −7.3)μm; .0064; (*D*) RBC/gas_{asthma} vs $RBC/gas_{asthma+COPD}$ = 0.00066 (0.00016, 0.00116); .0118, RBC/gas_{asthma} vs RBC/gas_{COPD} = 0.0012 (0.00042, 0.00198); .0004; (*E*) RBC/M_{asthma} vs RBC/M_{COPD} = 0.070 (0.004, 0.137); .0357; (*F*) $Lm_{Dasthma}$ vs $Lm_{Dasthma+COPD}$ = −31.4 (−42.3, −20.5)μm; <.0001, $Lm_{Dasthma}$ vs Lm_{DCOPD} = −29.3 (−46.8, −11.8)μm; .0003. ^{129}Xe = xenon-129; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; Lm_D = mean diffusive length scale; MD, mean difference; MRI = magnetic resonance imaging; RBC/gas = ratio of ^{129}Xe dissolved in the red blood cells to ^{129}Xe in the airspaces; RBC/M = red blood cell/membrane; TLco = transfer factor of the lung for carbon monoxide; VDP = ventilation defect percent; VH_l = ventilation heterogeneity index.

ogeneity was also seen within diagnostic groups. Of significance, patients with asthma + COPD or COPD but with a normal FEV_1, had significantly worse ^{129}Xe-ventilation and acinar-dimension metrics than those with asthma. Similarly, among patients with normal TLco, ^{129}Xe MRI gas-transfer and acinar-dimension metrics were worse in those with COPD versus those with asthma. These findings, alongside the substantial heterogeneity within diagnostic groups with normal FEV_1 or TLco, highlight the powerful capability of ^{129}Xe MRI to phenotype patients with minimal global and regional airways disease.

The differences between the diagnostic groups suggest that there are fundamental structural and functional differences that can be detected using advanced imaging alongside PFTs. Higher VDP, indicating that ^{129}Xe cannot access a greater proportion of the lung,[15,32] indicates increased airway obstruction, possibly due to mucus plugging and destruction of the small airways.[33] The median VDP for patients with asthma in this study was low relative to the upper limit of normal for a healthy population,[31] indicating that patients with asthma had, on average, more preserved lung function with limited ventilation obstruction; despite this, VDP values of up to 17.4% were observed, which is similar to the findings of others.[34-36] Median VDP was higher, indicative of less preserved lung function, among patients with asthma + COPD and COPD versus asthma, and to a lesser extent, in those with COPD versus asthma + COPD. ^{129}Xe diffusion MRI demonstrated that acinar dimensions (measured by Lm_D) were larger in patients with COPD and asthma + COPD than those with asthma, and that more than half of patients with COPD and approaching half of patients with asthma + COPD had abnormally large acinar dimensions, indicative of emphysema.[15,37] This suggests that the low rate of emphysema detected on anatomical ^1H MRI (2 patients in total) is a limitation of ^1H MRI methods used in detecting subtle changes in parenchymal tissue density rather than a genuine reflection of the amount of emphysema in the study population and that ^{129}Xe diffusion MRI is sensitive to early emphysematous changes that are not evident on ^1H MRI. Furthermore, RBC/gas, a marker of gas transfer efficiency between the alveoli and the blood, and M/gas, an indicator of pulmonary tissue density,[38] were lower in patients with COPD compared with those with asthma and asthma + COPD consistent with the presence of emphysema. Overall, these ^{129}Xe MRI findings indicate a phenotype of reduced and more heterogeneous ventilation (possibly due to a greater extent of small airways disease and/or mucus plugging) and reduced gas exchange (likely because of emphysema) in COPD, and to a lesser extent in asthma + COPD, compared with asthma.

LCI mirrored the ^{129}Xe ventilation MRI results of increased ventilation heterogeneity in COPD compared to asthma + COPD, and in asthma + COPD compared to asthma. Similarly, TLco matched ^{129}Xe MRI results showing greater gas transfer in asthma compared to asthma + COPD and COPD. Patients with asthma had less air trapping than patients with COPD or asthma + COPD. AOS found greater airways resistance and increased lung compliance in COPD than asthma, highlighting differences in underlying lung mechanics between the diagnoses.

^{129}Xe MRI metrics detected abnormalities in patients with normal FEV_1 or TLco, demonstrating the exquisite sensitivity of functional MRI to identify and phenotype subclinical disease. Hyperpolarized gas (^{129}Xe or Helium-3) ventilation MRI is known to be highly sensitive to early-stage obstructive lung disease, for example detecting ventilation abnormalities in children with cystic fibrosis with normal spirometry, LCI, and computed tomography (CT).[39] Hyperpolarized gas MRI measurements of acinar dimensions have shown sensitivity to emphysematous changes in asymptomatic smokers,[40] while gas transfer (RBC/M and RBC/gas) measurements have not previously been assessed in clinical populations with normal conventional lung function.[40] Here we highlight that ^{129}Xe MRI metrics are often abnormal and phenotypically different between diagnostic groups in patients where the FEV_1 or TLco are normal, thus highlighting the power and sensitivity of ^{129}Xe MRI to be used to diagnose and phenotype patients with mild and/or early-stage airways disease.

^{129}Xe MRI and PFT metrics reflect the severity and extent of different lung disease pathophysiology in an individual allowing personalized assessment and management. For example, assessment of a patient with asthma + COPD in the clinic with ^{129}Xe MRI and PFTs would provide a picture of whether the lung pathophysiology was more asthma-like or COPD-like and their treatment could be tailored accordingly. Similarly, ^{129}Xe MRI provides novel lung physiology signatures allowing greater confidence in the diagnosis of airways disease. For example, even in a patient with normal FEV_1 and TLco, enlarged acinar dimensions (Lm_D), reduced gas transfer (RBC/gas, RBC/M), and reduced pulmonary tissue density (M/gas) on ^{129}Xe MRI are indicative of emphysema and COPD. Distinguishing asthma with persistent airflow limitation from COPD is important due to differences in the treatment options for asthma and COPD. ^{129}Xe MRI and advanced PFTs can aid in this; a patient with asthma and persistent airflow limitation could have ventilation defects, increased LCI, and airways resistance but with normal acinar dimensions, gas exchange, and reactance. Whereas a patient with COPD could have ventilation defects, increased LCI, and airways resistance but also enlarged acinar dimensions, reduced gas exchange, and increased reactance.

For all ^{129}Xe and PFT metrics, the extent of lung function or structure impairments in patients with asthma + COPD was greater than in patients with asthma and less than in patients with COPD. Given the poorer clinical outcomes of patients with asthma + COPD when compared to patients with a single diagnosis previously reported,[5] the results of the comparison between asthma + COPD and COPD are somewhat counterintuitive. The dissonance could be due to the differences in patient populations studied; however, in this cohort recruited from primary care, it suggests that any poorer clinical outcomes experienced by the asthma + COPD patient group would not be caused by having fundamentally worse lung function or structure than the COPD patient group.

The assessment of patients post-bronchodilator minimized the contribution of airflow obstruction due to smooth muscle contraction, and bronchodilator responsiveness has been found not to discriminate between asthma and COPD in the wider NOVELTY study.[41] Bronchodilator responsiveness data were not acquired in this cohort at this timepoint, so differential bronchodilator responsiveness effects between diagnosis groups cannot be ruled out. In addition to differences in lung physiology between diagnoses, as expected, there were differences in clinical variables between diagnosis groups, such as medications, symptom scores, and smoking status. However, these clinical variables are intrinsic to the diagnoses and will have had an unquantifiable contribution to the differences in lung physiology that were observed.

Earlier studies have shown that ^{129}Xe MRI metrics are age dependent: acinar dimensions increase with age[37] and gas transfer reduces with age.[42] The age-matched sub-analysis supports the finding that the differences observed between diagnosis groups in the whole population were not due to older age in the COPD versus asthma groups.

There have been limited studies to date investigating the use of ^{129}Xe MRI in diagnosing patients with obstructive lung disease. Existing studies tend to be small, use only 1 or 2 MRI metrics, are limited to a single patient population, or lack comparison between diagnostic groups.[10-12,32,35,43,44] A previous study reported relationships between hyperpolarized gas MRI VDP and AOS metrics in patients with asthma and patients with COPD.[44] Correlations have been reported between ^{129}Xe MRI metrics and PFTs in some small studies, including: VDP and spirometry in patients with asthma and COPD,[10,32,35] VDP and RV/TLC, and VH_I and spirometry in patients with asthma,[32,35] apparent diffusion coefficient (ADC) and spirometry in patients with COPD,[11] and ADC and TLco and TLco/alveolar volume in patients with COPD.[10,11,43] In this study, we found moderate-strong correlations between ^{129}Xe MRI and PFT metrics; in particular, strong negative correlations were observed between VDP and FEV_1/FVC *z*-score, VH_I and FEV_1/FVC *z*-score, and Lm_D and TLco *z*-score.

To the best of our knowledge, this study is the first study to investigate ^{129}Xe MRI and PFT characteristics in a population of patients with a physician-assigned diagnosis of asthma + COPD and the largest ^{129}Xe MRI study conducted to date. NOVELTY enrolls a broad patient population by including patients according to their physician-assigned diagnosis from both primary and secondary care and by avoiding stringent inclusion criteria. Therefore, findings from the NOVELTY dataset are generalizable to the heterogenous population of patients who present in clinical practice.

Limitations include the uneven sample sizes of the diagnostic groups, particularly the small size of the group of patients with COPD, and uneven proportions of male and female patients within each diagnostic group. The higher proportion of patients with physician-assigned disease severity in the asthma + COPD group may have contributed to the overlap of lung physiology metrics between the asthma + COPD and COPD groups. Additionally, during the assessment period, those with asthma or COPD were advised to "shield" themselves from COVID-19 and 2 national lockdowns took place in the UK (November 2020 and January-March 2021); asthma exacerbations were substantially lower than usual over the 18 months following March 2020 than prior to COVID-19.[45] Clinical variables such as symptom scores and exacerbation history were

acquired on average 7-12 months before the MRI and PFTs were performed, which may have reduced the correlations between clinical and physiological variables. Although MRI and PFT data from healthy volunteers are available in the literature, there was no control group assessed as part of this study. CT is clinically established for the detection of emphysema and structural abnormalities in the lung, and whilst ^{1}H MRI shows promise its clinical use and evidence base is limited. CT images were not acquired due to the associated radiation dose, resulting in a lack of gold-standard structural imaging data. Finally, the attending physician determined the patient's diagnostic label and disease severity according to their expertise and judgment, which may not have been in accordance with guideline recommendations.

^{129}Xe MRI and PFTs provide novel signatures of lung physiology which are phenotypically different in COPD compared to asthma. Importantly, ^{129}Xe MRI metrics were sensitive to lung function abnormalities and were able to differentiate people with COPD from those with asthma when conventional lung function tests were normal. Patients with physician-diagnosed COPD on ^{129}Xe MRI had worse ventilation, greater acinar dimensions, and lower gas transfer than patients with asthma, in addition to worse spirometric limitation, greater airways resistance and lung compliance, and greater air trapping. Lung function and structure were worse in asthma + COPD than in asthma, and better in asthma + COPD than in COPD. These data demonstrate the power and sensitivity of ^{129}Xe MRI and PFTs in identifying phenotypes of airways disease to potentially guide clinical management, including in patients with otherwise minimal evidence of disease.

Acknowledgments

The authors would like to thank the patients who participated in this study, the NOVELTY Scientific Community, and the NOVELTY study investigators who are listed in full in Tables S10 and S11. This is independent research carried out at the National Institute of Health and Care Research (NIHR) Sheffield Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of AstraZeneca, the NIHR, or the Department of Health and Social Care. AstraZeneca was granted a courtesy review. Medical writing support, including assisting authors with development of the outline and initial draft and incorporation of comments, was provided by Katie Webster, BSc, and Matt Brownsword, PhD, and editorial support, including referencing, figure preparation, formatting, proofreading, and submission was provided by Jess Fawcett, BSc, all of Core (a division of Prime, London, UK), supported by AstraZeneca, according to Good Publication Practice Guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460).

Author contributions

Conceptualization: Jim M. Wild and Rod Hughes designed the study. Methodology: Latife Hardaker recruited patients, recorded patient reported outcomes, administered bronchodilator, and provided clinical care to patients during study visits. Leanne Armstrong coordinated study visits. David Capener, Jody Bray, Guilhem J. Collier, and Ho-Fung Chan acquired the MRI scans. Ryan Munro, Oliver Rodgers, James E. Ball, Graham Norquay, Guilhem J. Collier, and Jim M. Wild polarized ^{129}Xe, and maintained the polarizer and regulatory manufacturing licensing. Oliver Rodgers, Jim M. Wild, and Madhwesha Rao maintained the radiofrequency coils. David Capener, Jody Bray, Helen Marshall, and Paul J.C. Hughes administered gas for MRI scans. Laurie J. Smith and Demi-Jade Jakymelen performed pulmonary function tests. Martin L. Brook managed data transfer and storage. Formal analysis: Alberto M. Biancardi managed the ventilation analysis workflow. Alberto M. Biancardi, Helen Marshall, Joshua R. Astley, and Ryan Munro performed ventilation MRI analysis. Ho-Fung Chan performed diffusion MRI analysis. Guilhem J. Collier performed IDEAL MRI analysis. Paul J.C. Hughes performed T_1 MRI analysis. Smitha Rajaram radiologically scored the ^{1}H MR images. Andrew J. Swift radiologically reviewed the MR images. Martin L. Brook, Helen Marshall, and Laurie J. Smith collated the MRI and PFT metrics. Helen Marshall performed the statistical analysis. Helen Marshall, Laurie J. Smith, Guilhem J. Collier, Ho-Fung Chan, Nicholas D. Weatherley, Jim M. Wild, Alberto M. Biancardi, and Paul J.C. Hughes performed the initial data interpretation. Helen K. Reddel suggested the sex differences and exacerbations analyses. Helen Marshall prepared the outline of the paper. Writing—original draft preparation: all authors. Writing—reviewing and editing: all authors.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. H.Ma., L.J.S., A.M.B., G.J.C., H.-F.C., P.J.C.H., M.L.B., J.R.A., R.M., S.R., A.J.S., D.C., J.B., J.E.B., O.R., D.-J.J., B.A.T., M.R., G.N., N.D.W., L.A., and J.M.W. are employees of the University of Sheffield, which received institutional grants from AstraZeneca to perform the ADPro study. Outside of the submitted work, H.Ma. has received research grants from GSK and the Engineering and Physical Sciences Research Council; J.M.W. has received research grants from GSK, MRC, NIHR, and the Engineering and Physical Sciences Research Council; P.J.C.H. was supported by a research grant from Yorkshire Cancer Research; A.J.S. has received research grants and payment or honoraria for lectures/presentations/speakers bureaus from Janssen Pharmaceuticals; B.A.T. has received personal fees from Yorkshire Cancer Research for his senior fellowship; N.D.W. has received support from Boehringer Ingelheim for attending meetings and has received fees for advisory board membership; and H.Ma., J.M.W., and L.J.S. have received support from AstraZeneca for attending meetings. H.Mü. and R.H. are employees of AstraZeneca. Outside of the submitted work, R.H. has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, and Novartis.

Funding

The NOVELTY study is funded by AstraZeneca. Lung imaging and lung function assessments were performed at the POLARIS Lung Imaging Centre (University of Sheffield, Sheffield, UK), which

received research grant funding from the Medical Research Council (MR/M008894/1).

Data availability

De-identified participant data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at https://vivli.org/. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/. The NOVELTY protocol is available at https://astrazenecagrouptrials.pharmacm.com. This article has an online data supplement, which is accessible at the Supplements tab.

Artificial intelligence disclaimer

No artificial intelligence tools were used in writing this manuscript.

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 American Journal of Respiratory and Critical Care Medicine 2026 212(1) 72–85
https://doi.org/10.1164/rccm.202501-0288OC
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