Article:
Marshall, H. orcid.org/0000-0002-7425-1449, Smith, L.J. orcid.org/0000-0002-5769-423X, Biancardi, A.M. orcid.org/0009-0000-2765-0773 et al. (24 more authors) (2025) Phenotyping asthma and/or COPD using 129Xe MRI and comprehensive physiologic testing. American Journal of Respiratory and Critical Care Medicine. rccm.202501-0288OC. ISSN: 1073-449X

https://doi.org/10.1164/rccm.202501-0288oc

Phenotyping Asthma and/or COPD Using ^{129}Xe MRI and Comprehensive Physiologic Testing

Helen Marshall[1,2], Laurie J. Smith[1], Alberto M Biancardi[1,2], Guilhem J. Collier[1], Ho-Fung Chan[1], Paul J.C. Hughes[1], Martin L. Brook[1,2], Joshua R. Astley[1], Ryan Munro[1], Smitha Rajaram[1], Andrew J. Swift[1,2], David Capener[1], Jody Bray[1], James E. Ball[1], Oliver Rodgers[1], Demi-Jade Jakymelen[1], Bilal A. Tahir[1,2], Madhwesha Rao[1], Graham Norquay[1], Nicholas D. Weatherley[1], Leanne Armstrong[1], Latife Hardaker[3], Alberto Papi[4], Helen K. Reddel[5], Hana Müllerová[6], Rod Hughes[7], Jim M. Wild[1,2] for the NOVELTY Scientific Community and NOVELTY study investigators

[1]POLARIS, Section of Medical Imaging and Technologies, Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK; [2]Insigneo Institute, University of Sheffield, Sheffield, UK; [3]Priory Medical Group, York, UK; [4]University of Ferrara, Ferrara, Italy; [5]The Woolcock Institute of Medical Research, Macquarie Medical School; Faculty of Medicine, Health and Human Sciences, Macquarie University; Sydney Local Health District; and the University of Sydney, Sydney, NSW, Australia; [6]Respiratory and Immunology, Medical and Payer Evidence Strategy, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [7]Early Respiratory & Immunology Clinical Development, AstraZeneca, Cambridge, UK

Correspondence to: Helen Marshall, POLARIS, Division of Clinical Medicine University of Sheffield, 18 Claremont Crescent, Sheffield, S10 2TA. Email: h.marshall@sheffield.ac.uk. Phone: +44 (0)114 2159145.

Word count: 3678 (max 3,500)

Running title: Phenotyping asthma and/or COPD using ^{129}Xe MRI (46/50 characters including spaces)

Descriptor: 8.17 Imaging: Physiologic Correlates

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

At a Glance Commentary

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 chronic obstructive pulmonary disease (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 second 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.

Author Contributions

Conceptualization: J.M.W. and R.H. designed the study.

Methodology: L.H. recruited patients, recorded patient reported outcomes, administered bronchodilator, and provided clinical care to patients during study visits. L.A. coordinated study visits. D.C., J.B., G.J.C., and H.-F.C. acquired the MRI scans. R.M., O.R., J.E.B., G.N., G.J.C., and J.M.W. polarized ^{129}Xe, and maintained the polarizer and regulatory manufacturing licensing. O.R., J.M.W., and M.R. maintained the radiofrequency coils. D.C., J.B., H.Ma., and P.J.C.H. administered gas for MRI scans. L.J.S. and D.-J.J. performed pulmonary function tests. M.L.B. managed data transfer and storage.

Formal analysis: A.M.B. managed the ventilation analysis workflow. A.M.B., H.Ma., J.R.A., and R.M. performed ventilation MRI analysis. H.-F.C. performed diffusion MRI analysis. G.J.C. performed IDEAL MRI analysis. P.J.C.H. performed T_1 MRI analysis. S.R. radiologically scored the ^{1}H MR images. A.J.S. radiologically reviewed the MR images. M.L.B., H.Ma., and L.J.S. collated the MRI and PFT metrics. H.Ma. performed the statistical analysis. H.Ma., L.J.S., G.J.C., H.-F.C., N.D.W., J.M.W., A.M.B., and P.J.C.H. performed the initial data interpretation. H.R. suggested the sex differences and exacerbations analyses. H.Ma. prepared the outline of the paper.

Writing – original draft preparation: all authors.

Writing – reviewing and editing: all authors.

Support: 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).

Abstract (250/250 words)

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 second 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.

Key words: asthma, COPD, xenon-129 MRI, pulmonary function tests.

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: (i) 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 (ii) whether ^{129}Xe MRI could differentiate diagnostic groups when forced expiratory volume in 1 second (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 two 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 minutes 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 1.5T 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.

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 (ANOVA) tests with Tukey's correction (normal data) in GraphPad Prism. 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: (i) differences in ^{129}Xe MRI VDP, VH_I, and Lm_D were assessed in patients with normal FEV_1 (z-score >−1.64); (ii) differences in ^{129}Xe MRI RBC/gas, RBC/M, and Lm_D were assessed in

patients with normal TLco (z-score >−1.64); and (iii) ^{129}Xe MRI, PFT, and clinical metrics were assessed in age-matched patients.

Methods details and additional exploratory analyses are presented in the supplement.

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 supplementary Table E1).

^{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 *($P < 0$*.001) and asthma+COPD versus asthma ($P < 0.05$) (Figure 3 and Table 2). VDP, Lm_D, RBC/gas, M/gas, and LCI were also different between COPD versus asthma+COPD ($P < 0.01$ or $P < 0.05$). 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 supplementary Table E2 and the numbers of patients with each measurement are summarized in supplementary Table E3. 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%) (supplementary Table E4). Post-bronchodilator air trapping was present in three (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, supplementary Table E5) 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 *(*$P < 0.0001$). Acinar dimensions were also smaller (closer to age-matched normal) in asthma+COPD than in COPD *(*$P < 0.05$). 16.0% of patients had abnormally large acinar dimensions (Lm_D >1.64 z-scores) (Table E5). 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: $P < 0.001$; RBC/M: $P < 0.05$) (Figure 5) and 14.6% of patients had enlarged acinar dimensions.

^{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 (supplementary Table E6; supplementary Figure E1). Differences

with a statistical significance of $P < 0.0001$ 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 (supplementary Figure E2). 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. VDP and VH_I 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_I, 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 (supplementary Figure E3A) and TLco z-score, RBC/gas, and Lm_D (supplementary Figure E3B) show reasonable separation, and some overlap, between populations of patients with asthma alone (red dots) and COPD alone (blue dots). Supplementary Figure E3B 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

283 increased ventilation heterogeneity, airways resistance and lung compliance. Metrics
284 were more similar in asthma+COPD and COPD, although significant differences in
285 some metrics (VDP, $Lm_{D,}$ RBC/gas, M/gas, and LCI) were observed. Substantial
286 heterogeneity was also seen within diagnostic groups. Of significance, patients with
287 asthma+COPD or COPD but with a normal FEV_1, had significantly worse ^{129}Xe-
288 ventilation and acinar-dimension metrics than those with asthma. Similarly, among
289 patients with normal TLco, ^{129}Xe MRI gas-transfer and acinar-dimension metrics
290 were worse in those with COPD versus those with asthma. These findings, alongside
291 the substantial heterogeneity within diagnostic groups with normal FEV_1 or TLco,
292 highlight the powerful capability of ^{129}Xe MRI to phenotype patients with minimal
293 global and regional airways disease.

294 The differences between the diagnostic groups suggest that there are fundamental
295 structural and functional differences that can be detected using advanced imaging
296 alongside PFTs. Higher VDP, indicating that ^{129}Xe cannot access a greater
297 proportion of the lung (15, 32), indicates increased airway obstruction, possibly due
298 to mucus plugging and destruction of the small airways (33). The median VDP for
299 patients with asthma in this study was low relative to the upper limit of normal for a
300 healthy population (31), indicating that patients with asthma had, on average, more
301 preserved lung function with limited ventilation obstruction; despite this, VDP values
302 of up to 17.4% were observed, which is similar to the findings of others (34-36).
303 Median VDP was higher, indicative of less preserved lung function, among patients
304 with asthma+COPD and COPD versus asthma, and to a lesser extent, in those with
305 COPD versus asthma+COPD. ^{129}Xe diffusion MRI demonstrated that acinar
306 dimensions (measured by Lm_D) were larger in patients with COPD and
307 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 ^{1}H MRI (two patients in total) is a limitation of ^{1}H 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 ^{1}H 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 subanalysis 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 one or two 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 two 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.

Author Disclosures

HMa, LJS, AMB, GJC, H-FC, PJCH, MLB, JRA, RM, SR, AJS, DC, JB, JEB, OR, D-JJ, IS, BAT, MR, GN, NDW, LA, and JMW are employees of the University of Sheffield, which received institutional grants from AstraZeneca to perform the ADPro study. Outside of the submitted work, HMa has received research grants from GSK and the Engineering and Physical Sciences Research Council; JMW has received research grants from GSK, MRC, NIHR, and the Engineering and Physical Sciences Research Council; PJCH was supported by a research grant from Yorkshire Cancer Research; AJS has received research grants and payment or honoraria for lectures/presentations/speakers bureaus from Janssen Pharmaceuticals; BAT has received personal fees from Yorkshire Cancer Research for his senior fellowship; NDW has received support from Boehringer Ingelheim for attending meetings and has received fees for advisory board membership; and HMa, JMW, and LJS have received support from AstraZeneca for attending meetings. HMü and RH are employees of AstraZeneca. Outside of the submitted work, RH has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, and Novartis.

Data Sharing

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.

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 supplementary Tables E10 and E11. 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 (Link).

References (max 50)

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2023 Report. 2023 January 20, [cited 2025 Jan 17]. Available from: https://goldcopd.org/2023-gold-report-2/.

2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2025 update). 2025 May 2025 [cited 2025 11 June]. Available from: www.ginaasthma.org.

3. Reddel HK, Vestbo J, Agusti A, Anderson GP, Bansal AT, Beasley R, Bel EH, Janson C, Make B, Pavord ID, Price D, Rapsomaniki E, Karlsson N, Finch DK, Nuevo J, de Giorgio-Miller A, Alacqua M, Hughes R, Mullerova H, Gerhardsson de Verdier M, Novelty study investigators. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J* 2021; 58: 2003927.

4. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med* 2005; 99: 11–19.

5. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. *PLoS One* 2015; 10: e0136065.

6. Gershon AS, Campitelli MA, Croxford R, Stanbrook MB, To T, Upshur R, Stephenson AL, Stukel TA. Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA* 2014; 312: 1114–1121.

7. Stewart NJ, Smith LJ, Chan HF, Eaden JA, Rajaram S, Swift AJ, Weatherley ND, Biancardi A, Collier GJ, Hughes D, Klafkowski G, Johns CS, West N, Ugonna K, Bianchi SM, Lawson R, Sabroe I, Marshall H, Wild JM. Lung MRI with hyperpolarised gases: current & future clinical perspectives. *Br J Radiol* 2022; 95: 20210207.

8. Coxson HO, Leipsic J, Parraga G, Sin DD. Using pulmonary imaging to move chronic obstructive pulmonary disease beyond FEV1. *Am J Respir Crit Care Med* 2014; 190: 135-144.

9. Svenningsen S, Kirby M, Starr D, Leary D, Wheatley A, Maksym GN, McCormack DG, Parraga G. Hyperpolarized (3) He and (129) Xe MRI: differences in asthma before bronchodilation. *J Magn Reson Imaging* 2013; 38: 1521–1530.

10. Kirby M, Svenningsen S, Owrangi A, Wheatley A, Farag A, Ouriadov A, Santyr GE, Etemad-Rezai R, Coxson HO, McCormack DG, Parraga G. Hyperpolarized 3He and 129Xe MR imaging in healthy volunteers and

519 patients with chronic obstructive pulmonary disease. *Radiology* 2012; 265:
520 600–610.

521 11. Kaushik SS, Cleveland ZI, Cofer GP, Metz G, Beaver D, Nouls J, Kraft M,
522 Auffermann W, Wolber J, McAdams HP, Driehuys B. Diffusion-weighted
523 hyperpolarized 129Xe MRI in healthy volunteers and subjects with chronic
524 obstructive pulmonary disease. *Magn Reson Med* 2011; 65: 1154–1165.

525 12. Qing K, Ruppert K, Jiang Y, Mata JF, Miller GW, Shim YM, Wang C, Ruset IC,
526 Hersman FW, Altes TA, Mugler JP, 3rd. Regional mapping of gas uptake by
527 blood and tissue in the human lung using hyperpolarized xenon-129 MRI. *J*
528 *Magn Reson Imaging* 2014; 39: 346–359.

529 13. Kuo CR, Jabbal S, Lipworth B. I Say IOS You Say AOS: Comparative Bias in
530 Respiratory Impedance Measurements. *Lung* 2019; 197: 473–481.

531 14. Chukowry PS, Spittle DA, Turner AM. Small Airways Disease, Biomarkers and
532 COPD: Where are We? *Int J Chron Obstruct Pulmon Dis* 2021; 16: 351–365.

533 15. Marshall H, Wild JM, Smith LJ, Hardaker L, Fihn-Wikander T, Mullerova H,
534 Hughes R. Functional imaging in asthma and COPD: design of the NOVELTY
535 ADPro substudy. *ERJ Open Res* 2023; 9: 00344–02022.

536 16. Marshall H, Smith L, Biancardi A, Collier G, Chan H-F, Hughes P, Astley J,
537 Munro R, Rajaram S, Capener D, Bray J, Smith I, Armstrong L, Hardaker L,
538 Fihn-Wikander T, Hughes R, Wild J. A comparison of 129Xe MRI and
539 advanced lung function testing in patients with asthma and /or COPD: The
540 NOVELTY ADPro substudy. *Eur Respir J* 2021; 58: PA1872.

541 17. Marshall H, Smith LJ, Biancardi A, Collier GJ, Chan HF, Hughes PJC, Brook ML,
542 Astley J, Munro R, Rajaram S, Swift AJ, Capener D, Bray J, Ball J, Rodgers
543 O, Jakymelen D, Smith I, Tahir BA, Rao M, Norquay G, Weatherley ND,
544 Armstrong L, Hardaker L, Fihn-Wikander T, Hughes R, Wild JM. Physiological
545 Phenotypes of Patients with Asthma and/or COPD Using 129Xe MRI. *Am J*
546 *Respir Crit Care Med* 2022; 205: A2175.

547 18. Smith L, Marshall H, Jakymelen D, Biancardi A, Collier G, Chan H, Hughes P,
548 Brook M, Astley J, Munro R, Rajaram S, Swift A, Capener D, Bray J, Ball J,
549 Rodgers O, Smith I, Tahir B, Rao M, Norquay G, Weatherley N, Armstrong L,
550 Hardaker L, Fihn-Wikander T, Hughes R, Wild J. 129Xe-MRI and lung
551 function to phenotype ventilation heterogeneity in asthma and/or COPD. *Eur*
552 *Respir J* 2022; 60: 2865.

553 19. Tomaszewski EL, Atkinson MJ, Janson C, Karlsson N, Make B, Price D, Reddel
554 HK, Vogelmeier CF, Mullerova H, Jones PW, Community NS, investigators
555 Ns. Chronic Airways Assessment Test: psychometric properties in patients
556 with asthma and/or COPD. *Respir Res* 2023; 24: 106.

557 20. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory
558 Questionnaire. *Respir Med* 1991; 85 Suppl B: 25–31;discussion 33–37.

21. Karlsson N, Atkinson MJ, Mullerova H, Alacqua M, Keen C, Hughes R, Janson C, Make B, Price D, Reddel HK. Validation of a diagnosis-agnostic symptom questionnaire for asthma and/or COPD. *ERJ Open Res* 2021; 7: 00828–02020.

22. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, Thamrin C, Arets HG, Aurora P, Fuchs SI, King GG, Lum S, Macleod K, Paiva M, Pillow JJ, Ranganathan S, Ratjen F, Singer F, Sonnappa S, Stocks J, Subbarao P, Thompson BR, Gustafsson PM. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J* 2013; 41: 507–522.

23. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522.

24. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, MacIntyre NR, Thompson BR, Wanger J. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017; 49: 1600016.

25. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellaca RL, Farre R, Hall GL, Ioan I, Irvin CG, Kaczka DW, Kaminsky DA, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oppenheimer BW, Simpson SJ, Thamrin C, van den Berge M, Oostveen E. Technical standards for respiratory oscillometry. *Eur Respir J* 2020; 55: 1900753.

26. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019; 200: e70-e88.

27. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.

28. Hall GL, Filipow N, Ruppel G, Okitika T, Thompson B, Kirkby J, Steenbruggen I, Cooper BG, Stanojevic S, contributing GLINm. Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J* 2021; 57: 2000289.

29. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, Hall GL, Global Lung Function Initiative Twg, Global Lung Function Initiative T. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017; 50: 1700010.

30. Oostveen E, Boda K, van der Grinten CP, James AL, Young S, Nieland H, Hantos Z. Respiratory impedance in healthy subjects: baseline values and bronchodilator response. *Eur Respir J* 2013; 42: 1513-1523.

31. Collier G, Biancardi A, Chan H-F, Marshall H, L. S, Saunders L, Stewart N, Norquay G, Hughes P, Wild J. Dependence of diffusion and ventilation metrics on hyperpolarized 129Xe lung MRI with demographics in healthy volunteers [abstract]. International Society for Magnetic Resonance in Medicine Annual Meeting. Honolulu, Hawai'i, USA; 2025. p. 0917.

32. Ebner L, He M, Virgincar RS, Heacock T, Kaushik SS, Freemann MS, McAdams HP, Kraft M, Driehuys B. Hyperpolarized 129Xenon Magnetic Resonance Imaging to Quantify Regional Ventilation Differences in Mild to Moderate Asthma: A Prospective Comparison Between Semiautomated Ventilation Defect Percentage Calculation and Pulmonary Function Tests. *Invest Radiol* 2017; 52: 120–127.

33. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, Wright AC, Gefter WB, Litzky L, Coxson HO, Paré PD, Sin DD, Pierce RA, Woods JC, McWilliams AM, Mayo JR, Lam SC, Cooper JD, Hogg JC. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2011; 365: 1567–1575.

34. Marshall H, Kenworthy JC, Horn FC, Thomas S, Swift AJ, Siddiqui S, Brightling CE, Wild JM. Peripheral and proximal lung ventilation in asthma: Short-term variation and response to bronchodilator inhalation. *J Allergy Clin Immunol* 2021; 147: 2154-2161.e2156.

35. Mussell GT, Marshall H, Smith LJ, Biancardi AM, Hughes PJC, Capener DJ, Bray J, Swift AJ, Rajaram S, Condliffe AM, Collier GJ, Johns CS, Weatherley ND, Wild JM, Sabroe I. Xenon ventilation MRI in difficult asthma: initial experience in a clinical setting. *ERJ Open Res* 2021; 7: 00785–02020.

36. Svenningsen S, Kjarsgaard M, Haider E, Venegas C, Konyer N, Friedlander Y, Nasir N, Boylan C, Kirby M, Nair P. Effects of Dupilumab on Mucus Plugging and Ventilation Defects in Patients with Moderate-to-Severe Asthma: A Randomized, Double-Blind, Placebo-Controlled Trial. *Am J Respir Crit Care Med* 2023; 208: 995-997.

37. Petersson-Sjögren M, Chan HF, Collier GJ, Norquay G, Olsson LE, Wollmer P, Londahl J, Wild JM. Airspace Dimension Assessment (AiDA) by inhaled nanoparticles: benchmarking with hyperpolarised ^{129}Xe diffusion-weighted lung MRI. *Sci Rep* 2021; 11: 4721.

38. Myc L, Qing K, He M, Tustison N, Lin Z, Manichaikul AW, Patrie J, Cassani J, Nunoo-Asare RN, Huang Y, Obaida Z, Tafti S, Ropp AM, Miller GW, Mata J, Altes T, Mugler J, Shim YM. Characterisation of gas exchange in COPD with dissolved-phase hyperpolarised xenon-129 MRI. *Thorax* 2021; 76: 178–181.

39. Marshall H, Horsley A, Taylor CJ, Smith L, Hughes D, Horn FC, Swift AJ, Parra-Robles J, Hughes PJ, Norquay G, Stewart NJ, Collier GJ, Teare D,

643 Cunningham S, Aldag I, Wild JM. Detection of early subclinical lung disease in
644 children with cystic fibrosis by lung ventilation imaging with hyperpolarised
645 gas MRI. *Thorax* 2017; 72: 760–762.

646 40. Swift AJ, Wild JM, Fichele S, Woodhouse N, Fleming S, Waterhouse J, Lawson
647 RA, Paley MNJ, Van Beek EJR. Emphysematous changes and normal
648 variation in smokers and COPD patients using diffusion 3He MRI. *Eur J*
649 *Radiol* 2005; 54: 352-358.

650 41. Beasley R, Hughes R, Agusti A, Calverley P, Chipps B, Del Olmo R, Papi A,
651 Price D, Reddel H, Müllerová H, Rapsomaniki E. Prevalence, Diagnostic
652 Utility and Associated Characteristics of Bronchodilator Responsiveness. *Am*
653 *J Respir Crit Care Med* 2024; 209: 390–401.

654 42. Collier GJ, Smith LJ, Saunders LC, Swift AJ, Marshall H, Stewart NJ, Norquay G,
655 Hughes PJC, Thomspson AAR, Wild JM. Age, sex, and lung volume
656 dependence of dissolved xenon-129 MRI gas exchange metrics. *Magn Reson*
657 *Med* 2024; 92: 1471–1483.

658 43. Matin TN, Rahman N, Nickol AH, Chen M, Xu X, Stewart NJ, Doel T, Grau V,
659 Wild JM, Gleeson FV. Chronic Obstructive Pulmonary Disease: Lobar
660 Analysis with Hyperpolarized ^{129}Xe MR Imaging. *Radiology* 2017; 282: 857–
661 868.

662 44. Eddy RL, Westcott A, Maksym GN, Parraga G, Dandurand RJ. Oscillometry and
663 pulmonary magnetic resonance imaging in asthma and COPD. *Physiol Rep*
664 2019; 7: e13955.

665 45. Shah SA, Quint JK, Sheikh A. Impact of COVID-19 pandemic on asthma
666 exacerbations: Retrospective cohort study of over 500,000 patients in a
667 national English primary care database. *Lancet Reg Health Eur* 2022; 19:
668 100428.

669

Tables and Figures

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, 31.3); 0.19	−17.4% (−40.1, 5.4); 0.17	−30.4% (−54.7, −6.1); **0.02**
Age, years	60.3 (21.4)	52.8 (21.8)	61.9 (14.5)	69.9 (13.2)	−9.1 (−14.0, −4.2); **0.0004**	−13.3 (−19.5, −7.1); **< 0.0001**	−4.2 (−10.8, 2.4); 0.35
BMI, kg/m^2	27.3 (8.0)	27.7 (8.9)	27.6 (8.5)	26.7 (7.4)	1.8 (−0.5, 4.2); 0.45	3.4 (0.4, 6.4); **0.045**	1.5 (−1.7, 4.7); 0.66
Ethnicity							

Asian	1 (0.6%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (−2.4, 4.8); > 0.99	1.2% (−2.4, 4.8); > 0.99	0 (0, 0); NA
Other	1 (0.6%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (−2.4, 4.8); > 0.99	1.2% (−2.4, 4.8); > 0.99	0 (0, 0); NA
White	163 (98.8)	81 (97.6)	55 (100%)	27 (100%)	−2.4% (−7.2, 2.4); 0.67	−2.4% (−8.1, 3.3); > 0.99	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, 23.8); 0.35	−10.5% (−33.5, 12.5); 0.42	−18.9% (−42.5, 4.8); 0.11
Moderate	76 (46.1%)	43 (51.8%)	21 (38.2%)	12 (44.4%)	13.6% (−4.6, 31.9); 0.16	7.4% (−16.7, 31.4); 0.66	−6.3% (−31.7, 19.2); 0.76
Severe	47 (28.5%)	18 (21.7%)	24 (43.6%)	5 (18.5%)	−21.9% (−39.3, −4.6); **0.01**	3.2% (−16.4, 22.8); 0.94	25.1% (2.7, 47.5); **0.047**
Smoking status							

Never	51 (30.9%)	44 (53.0%)	7 (12.7%)	0 (0.0%)	40.3% (24.9, 55.7); **< 0.0001**	53.0% (39.8, 66.2); **< 0.0001**	12.7% (1.2, 24.3); 0.13
Former	70 (42.4%)	26 (31.3%)	30 (54.5%)	14 (51.9%)	−23.2% (−41.3, −5.2); **0.01**	−20.5% (−44.3, 3.3); 0.09	2.7% (−23.0, 28.4); 0.99
Current	44 (26.7%)	13 (15.7%)	18 (32.7%)	13 (48.1%)	−17.1% (−33.2, −0.9); **0.03**	−32.5% (−55.3, −9.6); **< 0.0001**	−15.4% (−40.7, 9.9); 0.27
Pack years							
All patients	9.2 (36.7)	0.0 (9.0)	25.0 (41.4)	42.0 (42.8)	−23.0 (−31.8, −14.3); **< 0.0001**	−35.3 (−46.5, −24.2); **< 0.0001**	−12.3 (−24.1, −0.5); 0.18
Ever smokers	24.0 (37.0)	9.2 (19.5)	34.4 (32.7)	42.0 (42.8)	−19.7 (−31.8, −7.6); **< 0.001**	−27.6 (−41.6, −13.6); **< 0.0001**	−7.9 (−21.4, 5.5); 0.70
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, 0.2); > 0.99	−0.4 (−1.0, 0.3); > 0.99	−0.0 (−0.7, 0.6); > 0.99
CAAT score	11.0 (13.0)	10.0 (12.5)	14.0 (16.0)	13.0 (12.0)	−3.8 (−7.4, −0.1); **0.037**	−3.4 (−8.1, 1.2); 0.20	0.3 (−4.6, 5.2); > 0.99

SGRQ score	24.5 (32.9)	15.4 (29.4)	31.4 (32.6)	26.7 (33.3)	−10.8 (−20.3, −1.4); **0.017**	−9.5 (−21.6, 2.5); 0.19	1.3 (−11.2, 13.8); > 0.99
RSQ score	3.0 (5.0)	2.0 (4.5)	4.0 (4.0)	4.0 (9.0)	−2.3 (−3.9, −0.7); **0.0022**	−2.3 (−4.3, −0.3); 0.06	−0.0 (−2.2, 2.1); > 0.99
% with FPC	30.0%	21.7%	39.6%	33.3%	−17.9% (−37.1, −1.3); 0.07	−11.7% (−37.6, 14.2); 0.44	6.3% (−21.6, 34.1); 0.82
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, 0.13); > 0.99	−0.08 (−0.21, 0.05); > 0.99	−0.11 (−0.25, 0.02); 0.47
Baseline neutrophils, ×10^3 µL^{-1}	4.2 (1.8)	3.7 (1.6)	4.4 (1.8)	5.0 (1.7)	−0.5 (−1.3, 0.2); 0.18	−1.1 (−2.2, −0.0); **0.034**	−0.6 (−1.7, 0.5); 0.40
Hemoglobin, gL^{-1}	143.0 (18.0)	142.0 (15.5)	144.5 (19.0)	139.5 (14.7)	−1.8 (−9.0, 5.5); > 0.99	3.0 (−7.5, 13.6); > 0.99	4.8 (−6.0, 15.6); 0.39
GINA (2016/2017)†							
1	34 (25%)	14 (17%)	19 (35%)	0 (NA)	−19.5% (−36.1, −2.9); **0.02**	NA	NA

2	4 (2.9%)	2 (2.4%)	2 (3.7%)	0 (NA)	−1.2% (−8.4, 6.0); > 0.99	NA	NA
3	30 (22%)	25 (30%)	5 (9.3%)	0 (NA)	21% (7.1, 35.0); **0.01**	NA	NA
4	40 (29%)	23 (28%)	17 (31%)	0 (N/A)	−3.2% (−20.3, 13.9); 0.83	NA	NA
5	30 (22%)	19 (23%)	11 (20%)	0 (N/A)	2.9% (−12.5, 18.3); 0.85	NA	NA
GOLD (2019)†							
1	42 (55%)	0 (NA)	31 (60%)	11 (44%)	NA	NA	19.3% (−6.1, 44.6); 0.16
2	25 (32%)	0 (NA)	18 (35%)	7 (28%)	NA	NA	4.9% (−19.2, 29.0); 0.85
3	8 (10%)	0 (NA)	2 (3.8%)	6 (24%)	NA	NA	−22.3% (−42.3, −2.3); **0.01**

4	2 (2.6%)	0 (NA)	1 (1.9%)	1 (4.0%)	NA	NA	−1.9% (−11.7, 8.0); > 0.99
Medications[†]							
LAMA	50 (30%)	11 (13%)	27 (49%)	12 (44%)	−35.8% (−52.4, −19.2); **< 0.0001**	−31.2% (−53.7, −8.6); **< 0.0001**	4.6% (−21.1, 30.3); 0.87
LABA	3 (1.8%)	2 (2.4%)	1 (1.8%)	0 (0%)	0.6% (−4.8, 6.0); > 0.99	2.4% (−3.3, 8.1); > 0.99	1.8% (−3.5, 7.2); > 0.99
ICS	111 (69%)	67 (81%)	37 (69%)	7 (28%)	11.6% (−4.8, 28.0); 0.17	51.1% (29.4, 72.8); **< 0.0001**	39.5% (15.6, 63.3); **< 0.0001**
Triple therapy	64 (39%)	11 (13%)	38 (69%)	15 (56%)	−55.8% (−71.6, −40.1); **< 0.0001**	−42.3% (−64.9, −19.7); **< 0.0001**	13.5% (−11.6, 38.7); 0.34
Biologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0, 0); NA	0 (0, 0); NA	0 (0, 0); NA

Definition of abbreviations: ^{129}Xe = xenon-129; BMI = body mass index; CAAT = Chronic Airways Assessment Test; CI, confidence interval; 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).

*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 supplementary Table E3).

680 **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, −4.4); **< 0.0001**	−15.5 (−18.8, −12.2); **< 0.0001**	−8.5 (−12.0, −4.9); **0.022**
VH_I	11.0 (5.1)	9.1 (2.6)	16.5 (5.7)*	20.2 (7.3)*	−8.0 (−9.3, −6.7); **< 0.0001**	−11.3 (−13.0, −9.7); **< 0.0001**	−3.4 (−5.2, −1.6); 0.29
Lm_D, µm	301.5 (55.0)	284.3 (28.5)	327.1 (53.4)*,†	342.9 (72.8)*	−41.05 (−55.31, −26.80); **< 0.0001**	−69.04 (−87.07, −51.00); **< 0.0001**	−27.98 (−47.11, −8.86); **0.002**
RBC/gas	0.0028 (0.0015)	0.0031 (0.0016)	0.0025 (0.0011)*,†	0.0018 (0.0010)*	0.00085 (0.00042, 0.00129); **0.0001**	0.00146 (0.00092, 0.00200); **< 0.0001**	0.00060 (0.00003, 0.00118); **0.02**

M/gas	0.0091 (0.0030)	0.0096 (0.0030)	0.0089 (0.0029)*,†	0.0077 (0.0029)*	0.00099 (0.00006, 0.00191); **0.033**	0.00259 (0.00113, 0.00339); **< 0.0001**	0.00127 (0.00007, 0.00248); **0.036**
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); **< 0.0001**	27.5 (17.6, 37.5); **< 0.0001**	9.4 (−1.2, 20.0); 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); **< 0.0001**	1.70 (1.04, 2.35); **< 0.0001**	0.53 (−0.17, 1.23); 0.89
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); **< 0.0001**	2.01 (1.39, 2.63); **< 0.0001**	0.68 (0.01, 1.34); 0.18

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); **< 0.0001**	12.1 (15.4, 26.9); **< 0.0001**	7.5 (1.4, 13.6); 0.16
$FEF_{25–75\%}$ z-score	−1.49 (1.65)	−0.78 (1.54)	−1.93 (1.46)*	−2.49 (1.36)*	1.25 (0.79, 1.70); **< 0.0001**	1.77 (1.19, 2.35); **< 0.0001**	0.52 (–0.10, 1.14); 0.12
FVC z-score	0.32 (1.19)	0.48 (1.21)	0.04 (1.10)	0.23 (1.49)	0.17 (–0.24, 0.59); 0.38	0.29 (–0.24, 0.82); 0.72	0.12 (0.45, 0.68); > 0.99
LCI	8.8 (2.6)	8.0 (1.7)	9.8 (2.9)*,†	11.0 (4.0)*	−2.0 (−2.8, −1.2); **< 0.0001**	−3.6 (−4.7, −2.6); **< 0.0001**	−1.6 (−2.7, −0.5); **0.0025**
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); **< 0.0001**	2.25 (1.49, 3.00); **< 0.0001**	1.26 (0.46, 2.06); 0.20
RV/TLC z-score	0.67 (1.11)	0.44 (0.90)	0.83 (1.29)*	1.19 (2.03)*	−0.62 (−1.05, −0.20); **0.0021**	−0.92 (−1.46, −0.38); **< 0.001**	−0.30 (−0.84, 0.28); > 0.99
R5–R20 z-score	0.96 (2.47)	0.54 (1.84)	1.40 (2.63)*	2.60 (4.49)*	−0.77 (−1.77, 0.23); **0.037**	−2.53 (−3.83, −1.24); **< 0.001**	−1.76 (−3.12, −0.40); 0.22

AX z-score	1.40 (1.69)	1.10 (1.59)	1.82 (1.55)*	2.58 (2.38)*	−0.75 (−0.26, −0.24); **0.0017**	−1.34 (−1.99, −0.68); **< 0.0001**	−0.59 (−1.27, 0.10); 0.11

Definition of abbreviations: ^{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 second; 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 Hz 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 < 0.05 are emboldened. *Difference compared with the asthma group (*P* < 0.05). †Difference compared with the COPD group (*P* < 0.05). ‡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 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_I = ventilation heterogeneity index.

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 second; 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.

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, towards 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.

Figure 5. Patients with normal FEV_1 (*A–C*) or normal TLco (*D–F*): ^{129}Xe MRI metrics for patients with physician-assigned diagnoses of asthma, asthma+COPD, and COPD.

Whiskers denote minimum and maximum values. ^{129}Xe MRI metrics for physician-assigned diagnosis groups of asthma, asthma+COPD, and COPD. Top row: patients with normal FEV_1; (*A*) VDP, (*B*) VH_I, 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)%; < 0.0001, VDP_{asthma} vs. VDP_{COPD} = −7.2 (−10.2, −4.3)%; < 0.0001; (*B*) $VH_{Iasthma}$ vs. $VH_{Iasthma+COPD}$ = −2.6 (−3.6, −1.7); < 0.0001, $VH_{Iasthma}$ vs. VH_{ICOPD} = −4.3 (−5.8, −2.8); < 0.0001; (*C*) $Lm_{Dasthma}$ vs. $Lm_{Dasthma+COPD}$ = −29.8 (−43.9, −15.7) µm; < 0.0001, $Lm_{Dasthma}$ vs. Lm_{DCOPD} = −60.4 (−82.1, −38.7) µm; < 0.0001, $Lm_{Dasthma+COPD}$ vs. Lm_{DCOPD} = −30.7 (−54.0, −7.3)µm; 0.0064; (*D*) RBC/gas_{asthma} vs. $RBC/gas_{asthma+COPD}$ = 0.00066 (0.00016, 0.00116); 0.0118, RBC/gas_{asthma} vs. RBC/gas_{COPD} = 0.0012 (0.00042, 0.00198); 0.0004; (*E*) RBC/M_{asthma} vs. RBC/M_{COPD} = 0.070 (0.004, 0.137); 0.0357; (*F*) $Lm_{Dasthma}$ vs. $Lm_{Dasthma+COPD}$ = −31.4 (−42.3, −20.5)µm; < 0.0001, $Lm_{Dasthma}$ vs. Lm_{DCOPD} = −29.3 (−46.8, −11.8)µm; 0.0003.

^{129}Xe = xenon-129; CI, confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; 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_I = ventilation heterogeneity index.