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Title: ^{129}Xe-MRI ventilation and acinar abnormalities highlight the significance of spirometric dysanapsis: Findings from the NOVELTY ADPro UK sub study

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ABSTRACT

Rationale: Airways dysanapsis is defined by CT or spirometry as a mismatch between the size of the airways and lung volume and is associated with increased risk of developing COPD. Lung disease in participants with dysanapsis and a label of asthma and/or COPD remains poorly understood.

Methods: In participants with asthma and/or COPD, we used ^{129}Xe-MRI to assess ventilation, acinar dimensions and gas exchange, and pulmonary function tests, and compared people with spirometric dysanapsis (FEV1/FVC <-1.64z and FEV1 >-1.64z) to those with normal spirometry (FEV1, FVC and FEV1/FVC >-1.64z).

Results: From 165 participants assessed in the NOVELTY ADPro study with a physician-assigned diagnosis of asthma and/or COPD, 43 had spirometric dysanapsis and were age-matched to 43 participants with normal spirometry. Participants with dysanapsis had significantly increased ventilation defects (median difference (md) (95% CI) = 4.0% (1.42,5.38),p<0.001), ventilation heterogeneity (md (95% CI) = 2.56% (1.31,3.56),p<0.001) and measures of acinar dimensions (md (95% CI) = 0.004cm^2.s^{-1} (0.0009,0.007),p=0.009) from ^{129}Xe-MRI, than those with normal spirometry. At 1-year follow up, only participants with dysanapsis had a significant increase in ventilation defects (md (95% CI)=0.45% (0.09,2.1),p=0.016). Lower FEV1/FVC in the dysanapsis cohort was associated with increased ventilation defects (r=-0.64,R^2=0.41,p<0.001) and increased acinar dimensions (r=-0.52,R^2=0.38,p<0.001), with the highest values seen in those with an FVC above the upper limit of normal.

Conclusions: Participants with asthma and/or COPD, presenting to primary care with spirometric dysanapsis, exhibited increased lung abnormalities on ^{129}Xe-MRI, when compared to those with normal spirometry. Spirometric dysanapsis in asthma and/or COPD is therefore associated with significant lung disease and the FEV1/FVC is related to the degree of airways abnormality on 129Xe-MRI.

What is already known on this topic?

Airways dysanapsis describes a mismatch between the size of the lung volume and the size of the airway tree and may be a lung phenotype at risk for developing COPD. Dysanapsis can be defined by CT imaging and by spirometry, however the clinical significance of the spirometric pattern is unknown.

What this study adds?

Clinically stable participants from primary care in the UK, with a physician assigned label of asthma and/or COPD, with spirometric dysanapsis have significantly increased ^{129}Xe-MRI ventilation abnormalities and greater acinar dimensions (indicative of emphysema) when compared to participants matched for age but with normal spirometry. Having a smoking history and dysanapsis is associated with more severe lung damage as measured by ^{129}Xe-MRI. The severity of ^{129}Xe-MRI abnormalities is related to the severity of the FEV1/FVC, not the FEV1 alone.

How this study might affect research, practice or policy?

Participants with suspected airways disease, presenting to clinical practice in primary care with symptoms and the spirometric pattern of airways dysanapsis, likely have significant lung function abnormalities, both in terms of increased ventilation heterogeneity and greater acinar dimensions.

INTRODUCTION

The relationship between the size of the airway tree and the lung volume is variable between individuals [1]. In addition, evidence suggests that there are differences in airway calibre, despite comparable lung volumes, between women and men and between men and boys[2]. For some individuals, the growth of the airways in comparison to the lung volume appears to be mismatched whereby lung volume is relatively large in comparison to the volume of the airway tree. This phenomenon of dysanapsis between airway and lung size is thought to occur during childhood development, and there is evidence to suggest that dysanapsis puts the individual at greater risk of developing COPD [3].

Dysanapsis has been previously quantitatively assessed by both computed tomography (CT) [3 4] and spirometry [1 5 6]. CT image-based dysanapsis is quantified from measuring the airway geometry in relation to the lung volume, whereas from spirometry it reflects a pattern of low FEV1/FVC with an FEV1 within the normal range[7]. Spirometric dysanapsis was originally described to help explain the variation in expiratory flow seen in healthy subjects [1] and was recently described as a normal variant for some asymptomatic individuals, when compared to people with mild airways disease, particularly in young males with a large FVC[8]. More recently, CT based dysanapsis has been associated with reduced FEV1 and FEV1/FVC in both people with COPD [3] and in healthy controls [4].

The clinical significance of spirometric dysanapsis has been recently questioned as to whether it is associated with clinical pathology [7]. In children, spirometric dysanapsis is associated with obesity and with increased morbidity in those with obesity and asthma [5 9 10], whilst in children born pre-term, dysanapsis is common at school-age and is phenotypically distinct to other spirometric patterns of lung disease [6].

There is little physiological evidence as to whether this pattern of spirometric dysanapsis in adults with a physician assigned diagnosis of airways disease is significant and how the lung physiology of those with dysanapsis compares to those with a normal spirometry pattern. The advanced diagnostic profiling (ADPro) study is a sub study of NOVELTY [www.clinicaltrials.gov, NCT02760329 [11]] and has the aim of physiologically phenotyping people with a physician assigned diagnosis of asthma and/or COPD in primary care, using ^{129}Xe MRI and advanced lung function tests. ^{129}Xe MRI is an imaging technique with which three important aspects of lung function and structure; lung ventilation, alveolar microstructure and gas exchange of the lung, can be visually assessed and quantified [12]. ^{129}Xe ventilation MRI is highly sensitive to detect early obstructive lung disease in conditions such as asthma

[13] and cystic fibrosis [14], whilst ^{129}Xe MRI assessment of the alveolar microstructure with diffusion weighted imaging, is sensitive to early emphysema in smokers [15]. With unique sensitivity to detect different aspects of lung pathophysiology, ^{129}Xe MRI may provide insight into whether people with a physician assigned diagnosis of asthma and/or COPD and with spirometric dysanapsis have significant lung pathology in comparison to people with a physician assigned diagnosis of asthma and/or COPD and with a normal spirometry pattern.

METHODS

A detailed description of the ADPro study methodology was published previously [16]. In brief, people with asthma and/or COPD, participating in the NOVELTY study who were recruited from two primary care centres in York UK, aged >16 years, were eligible. Consented participants were invited to attend the University of Sheffield MRI unit, Sheffield, UK, for assessment. At attendance, participants had to be free from exacerbation for 6 weeks prior. In total 165 participants attended a first visit (July 2020 - June 2021), and 143 of these attended a second visit approximately one year later (August 2021 - June 2022).

At visit one, all ^{129}Xe MRI testing was performed post-bronchodilator in the following order: (i)^{129}Xe-ventilation [17], (ii) ^{129}Xe-diffusion [18] to assess alveolar microstructure and (iii) ^{129}Xe-gas exchange [19]. ^{129}Xe-ventilation MRI was performed twice, first at end-inspiratory tidal volume (EIVt) and secondly at total lung capacity as previously detailed [20]. From ^{129}Xe-ventilation MRI, the ventilation defect percent (VDP) and the ventilation heterogeneity index (VHI) were calculated to assess the proportion of the lung without any ventilation and the degree of ventilation heterogeneity in ventilated lung regions [20]. From ^{129}Xe-diffusion weighted MRI, the apparent diffusion coefficient (ADC) and the mean diffusive length scale (Lm_D) were calculated to assess the size of the acinar airspaces [18] and the red blood cell to membrane ratio (RBC/M) was calculated from^{129}Xe gas-exchange MRI, as a marker of gas exchange [19].

Participants then performed detailed lung function tests: (i) N_2 multiple breath washout to calculate lung clearance index (LCI), (ii) airwave oscillometry to calculate the resistance at 5Hz (R5), R5-20 and the area under the reactance curve (AX), (iii) gas transfer for carbon monoxide, (iv) body plethysmography and finally, (v) spirometry to measure FEV1, FVC and the FEV1/FVC ratio. All lung function testing was performed in accordance with international guidelines [21-25] and metrics were converted into z-scores (z) using recommended reference equations [26 27]. At visit two, testing was

performed both pre and post bronchodilator in the order depicted in supplemental figure 1, using the same methods.

For the analyses in this manuscript, all 165 people assessed in the ADPro study at visit 1 were reviewed for those that had either 'normal' spirometry or spirometric dysanapsis to form the two sub-cohorts to be assessed here (see supplementary figure 2 for a CONSORT diagram). Spirometric dysanapsis was defined as an FEV1/FVC < lower limit of normal (<-1.64z-score) and an FEV1 >-1.64z. Normal spirometry was defined as having an FEV1, FVC and an FEV1/FVC >-1.64z. In order to reduce the impact of age and natural lung function ageing on ^{129}Xe MRI group comparisons, an age-matched control cohort of those from ADPro with normal spirometry was derived using an equal number of participants from each age decile as the dysanapsis cohort. A comparison of ^{129}Xe-MRI and lung function metrics between the dysanaptic group and all participants with normal spirometry (i.e. not matched for age) can be found in the supplementary material.

Metrics were assessed for a normal distribution using the Shapiro-Wilks test and either parametric or non-parametric analysis methods were used accordingly. Unpaired t-tests or Mann-Whitney tests were performed to determine whether the dysanaptic cohort were significantly different to the normal cohort. Paired t-tests or Wilcoxon signed rank tests were performed to assess longitudinal change and response to bronchodilator. Pearson or Spearman correlations were used to assess the relationship between FEV1/FVC and the different lung function metrics, a p-value of <0.0025 was deemed significant to account for the number of comparisons made (n=20). Simple linear regression was performed within group to determine which ^{129}Xe-MRI and lung function metrics related to the most variance seen in FEV1/FVC. A significant longitudinal change in VDP (%) was classed as >2, (the smallest detectable difference in asthma [28 29]). Post bronchodilator, a significant change in FEV1 was classed as >8% of predicted [30]. Statistical analysis was performed in GraphPad Prism (V9).

RESULTS

165 participants were assessed in the ADPro study. The majority of these participants had mild disease, with 77% of participants having an FEV1 within the normal range. From the 126 participants with a normal FEV1, 43 had an abnormal FEV1/FVC and therefore had the spirometric dysanapsis pattern, meaning that 83 participants had spirometry values within the normal range. When compared to the dysanapsis cohort, these 83 participants were on average slightly younger at a median of 57.2 years vs 62.4 years (p=0.04). Therefore, to reduce the impact of age on ^{129}Xe-MRI, an

age-matched cohort of 43 participants from those with normal spirometry was derived. The resulting participant demographics and lung function metrics are presented in Table 1 for these two cohorts.

Table 1: Subject demographics, lung function and ^{129}Xe-MRI metrics for participants with spirometry-based airways dysanapsis and those with normal spirometry. Data are displayed from the baseline visit. The p-value, mean or median difference and 95% confidence interval (CI) columns denote the outcome of either an unpaired t-test or a Wilcoxon test (depending on whether the data were normally distributed) for continuous variables or a Chi-square test for categorical variables between the participants with dysanapsis versus those with normal spirometry. Data are described as either mean (SD), or median (25%, 75% percentile). For the ease of interpretation, if any of the data in an individual row were non-normally distributed, then all data were described as median (25%, 75% percentile).

	Spirometric dysanapsis	Normal spirometry	p-value	Mean or median difference	95% CI
Number of participants	43	43			
Age (years)	62.4 (55.3, 72.0)	63.8 (55.1, 72.7)	0.94	1.4	-4.9, 5.1
Male/Female	26/17	26/17	0.99		
Height (cm)	171.0 [10.5]	171.7 [9.1]	0.73	-0.7	-4.9, 3.5
Weight (kg)	80.5 [18.3]	84.1 [14.8]	0.32	-3.6	-10.7, 3.6
BMI	25.9 (23.2, 30.4)	27.3 (24.3, 32.2)	0.20	-1.4	-3.3, 0.7
Diagnosis; N of asthma, asthma and COPD or COPD	14/21/8	31/10/2	0.0009		
Smoking history Never/Former / Current	9/17/17	20/20/3	0.0008		
FEV1 (z)	-0.9 (-1.3, -0.6)	-0.2 (-0.6, 0.6)	<0.0001	-0.8	-1.0, -0.4
FVC (z)	0.85 (0.21, 1.30)	0.3 (-0.2, 0.9)	0.005	0.5	0.1, 0.9
FEV1/FVC (z)	-2.17 (-2.64, -1.89)	-0.90 (-1.28, -0.46)	<0.0001	-1.3	-1.7, -1.2

TLco (z)	-0.24 (-1.2, 0.55)	0.22 (-0.53, 0.93)	0.15	-0.5	-1.0, 0.1
RV/TLC (z)	0.58 [0.77]	0.56 [0.65]	0.90	0.02	-0.3, 0.3
LCI	10.5 (9.1, 12.5)	9.8 (8.4, 11.2)	0.19	0.7	-0.3, 1.5
R5 (z)	1.48 [1.11]	0.71 [1.18]	0.004	0.8	0.2, 1.3
R5-R20 (z)	1.07 (0.34, 2.36)	0.32 (-0.15, 1.40)	0.019	0.8	0.1, 1.4
AX (z)	1.5 (0.7, 2.3)	1.2 (0.5, 1.7)	0.018	0.5	0.1, 1.0
X5 (z)	-1.13 (-1.95, -0.11)	-0.65 (-1.73, 0.06)	0.12	-0.5	-1.1, 0.1
VDP (%)	6.5 (3.1, 12.6)	2.5 (1.3, 5.1)	0.0002	4.0	1.4, 5.4
VHI (%)	12.4 (10.3, 14.0)	9.8 (8.2, 11.1)	<0.0001	2.6	1.3, 3.6
VDP @ TLC (%)	4.7 (2.7, 7.1)	2.6 (1.5, 3.8)	0.0005	2.1	0.7, 2.9
ADC $cm^2.s^{-1}$	0.040 (0.035, 0.047)	0.037 (0.033, 0.041)	0.009	0.004	0.001, 0.007
Lm_D µm	311.2 (285.6, 337.0)	295.2 (272.4, 311.4)	0.01	16.0	4.4, 33.2
RBC/M	0.33 [0.1]	0.32 [0.09]	0.86	-0.004	-0.05, 0.04

In the spirometric dysanapsis and age-matched normal spirometry cohorts, respectively, 32.6% and 72.1% had a physician-assigned diagnosis of asthma, 48.8% and 23.3% had asthma and COPD and 18.6% and 4.7% had COPD. In the 3 years prior to assessment, the dysanapsis cohort had a mean of 0.84 exacerbations/year compared to 1.26 in the control cohort.

Comparison of lung function tests

Despite all participants having an FEV1 within the normal range, participants with spirometric dysanapsis had significantly lower FEV1z (median difference (md) (95% CI) = -0.77z (-0.42, -0.96), p<0.001) and higher FVCz (md (95% CI) = 0.53z (0.13, 0.85), p=0.005) than the control group, although there was large overlap between the two groups. There were no differences between the two groups for TLco, RV/TLC and LCI. Participants with spirometric dysanapsis had significantly higher R5z (md (95% CI) = 0.76z (0.25, 1.28), p=0.004), R5-R20z (md (95% CI) = 0.75z (0.1, 1.3), p=0.02) and AXz (md (95% CI) = 0.55z (0.1, 0.99), p=0.02) than the control group, but there was no difference for X5 (Figure 1).

^{129}Xe-MRI to assess ventilation, acinar dimensions and gas exchange

Participants in both cohorts had abnormal VDP (>2%); 86% of participants with spirometric dysanapsis compared to 70% of participants with normal spirometry. Using a more conservative threshold, 61% of participants with dysanapsis when compared to 23% with normal spirometry had VDP >5%. On average, those with dysanapsis had significantly higher VDP than the age-matched cohort (median VDP = 6.5 (3.1, 12.6)% and 2.5 (1.3, 5.1)% respectively, md (95% CI) = 4.0 (1.42, 5.38), p<0.001 – figure 1). In addition, those with dysanapsis had a greater degree of ventilation heterogeneity than the controls (median (IQR) VHI = 12.4 (10.3, 17.3)% and 9.8 (8.2, 11.1)% respectively, md (95% CI) = 2.56% (1.31, 3.56), p<0.001). Figure 2 shows example ^{129}Xe-ventilation images for participants with spirometric dysanapsis and those with normal spirometry, where examples show that irrespective of age and when approximately matched for FEV1, those with dysanapsis have significantly worse ventilation abnormalities than those with normal spirometry. When ^{129}Xe-ventilation MRI was performed at TLC (in addition to the standard lung volume EIVt), VDP remained significantly higher in the dysanapsis group, when compared to controls (md (95% CI) = 2.05% (0.71, 2.88), p<0.001), who had a median reduction in VDP of 2.2% at TLC when compared to EIVt. In comparison, those with normal spirometry had a static VDP at TLC when compared to EIVt, with a median reduction of 0.1%.

The dysanapsis group had significantly larger acinar dimensions than those with normal spirometry when calculated with both quantitative acinar metrics: (i) apparent diffusion coefficient (median (IQR) ADC = 0.040cm^2.s^{-1} (0.035, 0.047) and 0.037cm^2.s^{-1} (0.033, 0.041) respectively, md (95% CI) = 0.004cm^2.s^{-1} (0.0009, 0.007), p=0.009, figure 1) and (ii) the mean diffusive length scale (median (IQR) Lm_D = 311.2µm (285.6, 337.0) and 295.2µm (272.4, 311.4) respectively, md (95% CI) = 16 µm (4.4, 33.2), p=0.01). Figure 3 highlights three example ADC maps, demonstrating the difference between dysanapsis and normal spirometry. Despite the increased acinar dimensions of the dysanapsis group, there were no significant differences between the dysanapsis and normal spirometry cohorts for ^{129}Xe gas-exchange (RBC/M).

From the dysanapsis and normal spirometry groups 20.9% and 46.5%, respectively, were never smokers, 39.5% and 46.5% were former smokers and 39.5% and 7.0% were current smokers. Within each spirometry group there was no significant difference in VDP between never, former and current smokers using Kruskal-Wallis analyses. There was no difference in ADC between smoking status in the normal spirometry group, however ADC in the dysanapsis group was higher in former smokers compared to never smokers (p=0.02). Between the spirometry groups, there was no difference in VDP for never smokers, however in those with a smoking history (former and current combined), both VDP (md (95% CI) = 4.89% (1.5, 7.3), p<0.001) and ADC (md (95% CI) = 0.005cm^2.s^{-1} (0.002, 0.009), p=0.004)

were significantly higher in the dysanapsis group when compared to the normal spirometry group as shown in figure 4. For AOS metrics or LCI, there was no significant difference between spirometry groups for never smokers or for those with a smoking history.

Associations with FEV1/FVC and impact of a large FVC

In the normal spirometry group, FEV1/FVC was not correlated with any of the ^{129}Xe-MRI or lung function metrics. In the dysanapsis group, FEV1/FVC was correlated with VDP (at EIVt and TLC), VHI, ADC, LmD, and FVC (a correlation matrix is included in the supplementary material (S-Figure 3)). VDP (at EIVt), ADC and Lm_D accounted for the highest proportions of the variation in FEV1/FVC; VDP R^2=0.41, p<0.001, ADC R^2=0.39, p<0.001 and Lm_D R^2=0.38 (p<0.001) using simple linear regression (Figure 5). The other metrics with a significant association with FEV1/FVC had a weaker relationship; VDP at TLC R^2=0.24 (p=0.001), VHI R^2=0.23 (p=0.001) and BMI R^2=0.13 (p=0.02).

In the dysanapsis cohort, there were eight participants with FVC >ULN. Figure 6 shows the relationships of VDP and ADC with FVC in the dysanapsis cohort, and highlights that these eight had significantly higher VDP (md (95% CI) = 6.29% (0.04, 10.17), p=0.046) and ADC (md (95% CI) = 0.012$cm^2.s^{-1}$ (0.006, 0.02), p=0.001) than those with FVC in the normal range.

Comparison of longitudinal change and bronchodilator response

Longitudinal data at 1 year were available for 35 participants with spirometric dysanapsis and 38 of the normal spirometry group and are detailed in Table 2. At 1 year, 21 (60%) participants retained the definition of spirometric dysanapsis, whilst 6 (17%) participants had abnormal FEV1 and the remaining 8 (23%) had normal spirometry. 5/6 participants with abnormal FEV1 at visit 2 were current smokers and 4 had a diagnosis of asthma and COPD and 2 COPD only. All 6 participants who went on to have abnormal FEV1 at visit 2 had substantial ventilation defects, ventilation heterogeneity and increased acinar dimensions at baseline, with VDP (median = 12.7%, range = 7.4, 19.8%), VHI (median = 14.0%, range = 12.9, 15.9%) and ADC (median = 0.047$cm^2.s^{-1}$, range = 0.041, 0.075$cm^2.s^{-1}$) measurements larger than the median for the whole dysanaptic cohort (see Table 1). In contrast, 8 participants (6 with asthma and 2 with asthma and COPD) were dysanaptic at baseline and went on to have a normal spirometry pattern at visit 2. These participants mostly had MRI values at the lower end of the distribution of the whole dysanaptic cohort at baseline (median (range) VDP = 3.1% (0.5, 6.1%), VHI = 10.2% (7.1, 12.7%) and ADC = 0.034$cm^2.s^{-1}$ (0.032, 0.044)). 35 participants (92%) with normal spirometry at baseline retained this pattern at 1 year, 2 participants developed spirometric dysanapsis and 1 participant had reduced FEV1/FVC and FEV1 at visit 2. A Sanky-plot can be found in the

supplementary material to summarise the longitudinal evolution of classification of both groups of participants (S-Figure 4).

Table 2: Subject demographics, lung function and ^{129}Xe-MRI metrics for participants with spirometry-based airways dysanapsis and those with normal spirometry one year post baseline visit. The p-value, mean or median difference and 95% confidence interval (CI) columns, denote the outcome of either an unpaired t-test or a Wilcoxon test (depending on whether the data were normally distributed) between the participants with spirometric dysanapsis versus those with normal spirometry when compared to the baseline data in Table 1. Data are described as either mean (SD), or median (25%, 75% percentile). For ease of interpretation, if any of the data in an individual row were non-normally distributed, then all data were described as median (25%, 75% percentile).

Visit 2 - 1 year follow up					
	Spirometric Dysanapsis	Normal spirometry	Statistical comparison with baseline data		
			p-value	Mean or median difference	95% CI
Number of participants	35	38			
BMI	26.8 (23.4, 30.9)	27.0 (25.0, 32.9)	0.94	0.64	-2.32, 2.55
FEV1 (z)	-0.78 (-1.56, -0.35)	-0.1 (-0.9, 0.5)	0.93	0.05	-0.29, 0.22
FVC (z)	0.94 (0.43, 1.34)	0.3 (-0.2, 0.9)	0.33	-0.06	-0.29, 0.13
FEV1/FVC (z)	-2.2 (-2.9, 0.4)	-0.79 (-1.02, -0.49)	0.47	0.02	-0.20, 0.25
TLco (z)	-0.8 (-1.3, 0.4)	0.31 (-0.79, 0.87)	0.24	-0.31	-0.64, 0.36
RV/TLC (z)	0.55 [0.73]	0.67 [0.69]	0.67	-0.02	-0.69, 0.53
R5 (z)	0.80 [0.87]	0.77 [1.09]	0.003	-0.58	-0.9, -0.33
R5-R20 (z)	0.87 (0.09, 1.59)	0.3 (-0.3, 1.5)	0.35	-0.54	-0.93, 0.23
AX (z)	1.2 (0.7, 2.0)	1.00 (0.22, 1.67)	0.15	-0.47	-0.8, 0.19
X5 (z)	-0.62 (-1.36, -0.10)	-0.44 (-1.36, 0.34)	0.09	0.57	-0.006, 1.12
VDP (%)	6.5 (3.3, 15.6)	3.0 (1.6, 4.9)	0.016	0.45	0.09, 2.1
VHI (%)	12.3 (10.6, 15.2)	9.9 (8.3, 11.0)	0.38	0.26	-0.28, 0.72
ADC $cm^2.s^{-1}$	0.04 (0.036, 0.047)	0.038 (0.033, 0.041)	0.98	0	-0.001, 0.001

Lm_D µm	311.4 (288.1, 334.6)	294.9 (276.2, 314.5)	0.25	-2.8	-7.3, 2.2
RBC/M	0.30 [0.1]	0.30 [0.08]	0.002	-0.03	-0.05, -0.01

For participants with dysanapsis, longitudinally there was a significant improvement in R5 (md (95% CI)= -0.5z (-0.9, -0.3), p=0.003) and a worsening in both ^{129}Xe-MRI VDP (md (95% CI)= 0.45% (0.09, 2.1), p=0.016, Figure 7) and RBC/M (md (95% CI)= -0.03 (-0.05, -0.01), p=0.002), despite no change in FEV1, or any other 129Xe-MRI or lung function metrics (p>0.05). In total, 49% of participants with dysanapsis had a change in VDP >2% (the smallest detectable difference in asthma [28 29]), including 34% with a longitudinal worsening of VDP and 14% with an improvement in VDP. When considering the change in FEV1/FVC between the two visits, the change in VDP was the only metric to significantly correlate (r=-0.46, p=0.006). For the participants with normal spirometry, on average there were no significant changes over time for lung function and ^{129}Xe-MRI metrics. 29% of participants with normal spirometry had a change in VDP >2%, including 16% with a worsening of VDP and 13% with an improvement in VDP.

40% of participants with spirometric dysanapsis and 37% of participants with normal spirometry had a significant FEV1 bronchodilator response of >8% of predicted. There were however no significant differences between the two groups for the magnitude of change of any of the metrics (supplemental table 1).

DISCUSSION

From the analyses in the NOVELTY ADPro study, which we believe to be the largest ^{129}Xe-MRI study conducted to date, we have demonstrated that people with a physician-assigned diagnosis of asthma and/or COPD and spirometric dysanapsis, have significant ^{129}Xe-MRI ventilation defects, enlarged acinar airspaces and increased airways resistance, when compared to people with asthma and/or COPD and a normal spirometric pattern (figures 1, 2 and 3). We have also demonstrated that people with spirometric dysanapsis are more likely to have increased ventilation abnormalities when followed up at 1-year (figure 7). Our results highlight the importance of effectively managing participants with spirometric dysanapsis and a large FVC who appear to have highly abnormal ^{129}Xe-MRI measures of lung ventilation and microstructure. We therefore propose that the spirometric dysanapsis pattern is not a normal physiological variant in people with a physician assigned diagnosis of asthma and/or COPD.

Despite having an FEV1 within the normal range, participants with an abnormal FEV1/FVC have evidence of significant airways disease on ^{129}Xe-MRI. ^{129}Xe-MRI has high sensitivity in detecting early lung disease in people with obstructive lung diseases. Here we demonstrate that in those with spirometric dysanapsis, there exist significant ventilation defects distributed across the lungs which are heterogeneous in size and location, and that ventilation is significantly greater and more homogeneous in those with a normal FEV1/FVC (Figure 2). In addition, ventilation defects worsen longitudinally on ^{129}Xe MRI in spirometric dysanapsis, despite having relatively stable FEV1, which was not the case in normal spirometry. Those with spirometric dysanapsis also have a degree of volume-reversible ventilation defects as judged by the reduction in VDP seen at TLC when compared to EIVt that is not present in those with normal spirometry, a finding previously documented in people with CF [20]. Similarly, people with spirometric dysanapsis have significantly greater acinar dimensions when compared to those with normal FEV1/FVC. In those with dysanapsis and a history of smoking, increased ventilation defects and acinar dimensions possibly reflect the link between the presence of dysanapsis and the risk of COPD in smokers. When assessing smoking history using AOS metrics or LCI, there were however no differences between smoking status demonstrating the added sensitivity of ^{129}Xe-MRI in the assessment of smoking related lung disease. Figure 3 demonstrates ADC maps from three participants. The enlarged airspaces in the participant with dysanapsis are most likely the signs of emphysema, which enlarges the acinar space through destruction of the acinar architecture. These findings are complemented by the increased airways resistance in the dysanapsis cohort for R5 and R5-R20, which has previously been described in children with asthma and dysanapsis [10].

It is evident from our results that people presenting to primary care with spirometric dysanapsis are likely to have significant airways disease, with our data suggesting that the severity of FEV1/FVC as calculated by the z-score is a more indicative marker of the severity of obstructive lung disease on ^{129}Xe-MRI than the FEV1 alone. Worse values for FEV1/FVC in the dysanaptic cohort were significantly correlated to both increasing VDP and ADC, and these two metrics explained roughly the same amount of variance in FEV1/FVC severity (Figure 5). The data we present here also highlight that those with the largest lung size relative to their peers, described by an FVC z-score >ULN, have some of the most severe abnormalities of ventilation and acinar dimensions. In participants with a large FVC, the FEV1/FVC z-score should be examined carefully. For example, one subject has an FVC of 2.77z (144% predicted) an FEV1 of -0.36z (94% predicted) and FEV1/FVC of -3.0z with a VDP of 13% and an ADC of 0.07 cm^2/s. This person therefore has significantly enlarged airspaces and large ventilation defects,

consistent with extensive obstructive lung disease, yet their FEV1 is just below the healthy average for their demographics (participant (i) in figure 3). In this case the FEV1/FVC gives a greater insight into the severity of the obstructive lung disease, especially considering that if this person's FEV1 were to fall below the LLN in the future, without a change in FVC, the FEV1/FVC would be approximately -4.0z.

There is increasing evidence that airways dysanapsis, when quantified from CT by the ratio of airway size to lung volume, is associated with an increased future risk of COPD and mortality [3]. Up until recently, the question remained as to whether this pattern was of clinical interest and there are still no longitudinal studies investigating whether asymptomatic people with this pattern of airways dysanapsis go on to develop COPD. Whilst the question remains as to whether asymptomatic people with dysanapsis have abnormal lung physiology, here we have approached the same question in clinically stable people, managed in primary care, with a physician-assigned diagnosis of asthma and/or COPD. The diagnosis here is not one based on a strict set of quantitative criteria and is based on the physician's clinical judgement using the tools available to them, of which spirometry is often one. Therefore, diagnosis of asthma and/or COPD may often be based on the spirometry-based pattern of dysanapsis measured. In addition, these people are clinically very stable, with only 18% reporting an exacerbation in the previous three years leading into the study visit.

Airways dysanapsis has evolved from being orginally a spirometry described phenotype towards a CT derived phenotype assessed by the measurement of airway diameter and lung volumes [3 4 31]. Therefore, it is relevant to question whether these two methods are describing the same phenomena, as one is derived from physiological assessment and the other from anatomical imaging. Nevertheless, there is evidence that shows a correlation exists when comparing the two [3 4]. A limitation of our study is that we were unable to compare our spirometry data to CT imaging, which was not performed during this MRI study, morevover ^{1}H anatomical MRI has insufficient resolution for assessing the required number of airway generations [32]. A further limitation is that we do not have a group with spirometric dysanapsis without a diagnostic label against which to compare, and therefore we do not know if asymptomatic individuals have ^{129}Xe-MRI abnormalities. Finally, we acknowledge that diagnosis of asthma and/or COPD is based on the physician's judgement and not a strict set of objective criteria and there may be some participants who should have an alternative diagnosis. Irrespective, spirometry remains the most accessible point-of-care test available clinically, and we therefore suggest that understanding this dysanaptic spirometry pattern remains highly relevant. Here, we have shown the clinical relevance of spirometric dysanapsis in comparison to people matched for age and sex and with a clinical label of asthma and/or COPD.

CONCLUSIONS

We have demonstrated that clinically stable people, managed in primary care and with a physician-assigned diagnosis of asthma and/or COPD with spirometric dysanapsis – exhibit significantly more ventilation abnormalities, enlarged acinar airspaces and increased airways resistance when compared to an age-matched cohort with normal spirometry and a similar diagnostic label. ^{129}Xe-MRI confirms that spirometric dysanapsis is not a normal physiological variant in people with a diagnostic label, and instead is a pattern associated with increased lung damage.

Contributorship: JMW and RH designed the study. LJS proposed the research question for this manuscript. LH recruited participants, recorded participant reported outcomes, administered bronchodilator, and provided clinical care to participants during study visits. LA co-ordinated study visits. DC, JB, GJC, and H-FC acquired the MRI scans. RM, OR, JEB, GN, GJC, and JMW polarised ^{129}Xe, and maintained the polariser and regulatory manufacturing licensing. OR, JMW, and MR maintained the radiofrequency coils. DC, JB, HMa, and PJCH administered gas for MRI scans. LJS and D-JJ performed pulmonary function tests. MLB managed data transfer and storage. AMB managed the ventilation analysis workflow. AMB, HMa, JRA, and RM performed ventilation MRI analysis. H-FC performed diffusion MRI analysis. GJC performed IDEAL MRI analysis. AJS radiologically reviewed the MR images. MLB, HMa, and LJS collated the MRI and PFT metrics. LJS performed the statistical analysis. LJS, HMa, NDW, JMW performed the initial data interpretation. LJS prepared the outline of the paper. Writing – original draft preparation: all authors. Writing – reviewing and editing: all authors. JMW is the guarantor of this work.

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Competing Interests: LJS, HM, AB, GJC, HFC, PJCH, MLB, JA, RM, SR, AJS, DC, JBr, JBa, OR, DJJ, IS, BAT, MR, GN, NDW, LA, and JMW are employees of POLARIS, University of Sheffield, which received institutional grants from AstraZeneca to perform the ADPro study. Outside of the submitted work; HM

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Figure Legends:

Figure 1: A comparison of ^{129}Xe-MRI metrics between those with a dysanapsis (N=43) and normal spirometry (N=43) pattern. Box and whisker plots are shown where the box indicates the 25th and 75th centiles and the horizontal line is the median, whilst the whiskers depict the minimum and maximum values. Mann-Whitney comparisons were performed to compare the two groups and the resulting p value is displayed on each graph. Abbreviations: ^{129}Xe = xenon; MRI = magnetic resonance image; VDP = ventilation defect percent; VHI = ventilation heterogeneity index; ADC = apparent diffusion coefficient

Figure 2: Single slice ^{129}Xe ventilation image examples from participants with (left) dysanapsis and (right) normal spirometry patterns. Each image is from a different subject. Each row of paired images represents an age decile from the study population. With the exception of row 1, paired images are also approximately matched for FEV1 in addition to age. Subjects 1a and 1b respectively; age = 38 years and 38 years; VDP = 1.8% and 1.1%; FEV1 = -0.95z and 1.29z. Subjects 2a and 2b; age = 44 years and 48 years; VDP = 8.0% and 2.1%; FEV1 = -1.5z and -1.31z. Subjects 3a and 3b; age = 58 years and 55 years; VDP = 10.8% and 2.2%; FEV1 = -1.35z and -1.14z. Subjects 4a and 4b; age = 60 years and 63 years; VDP = 25.9% and 1.3%; FEV1 = -0.66z and -0.59z. Subjects 5a and 5b; age = 72 years and 75 years; VDP = 10.4% and 0.8%; FEV1 = 0.84z and 1.11z. Abbreviations: ^{129}Xe = xenon; VDP = ventilation defect percent; FEV1 = forced expiratory volume in 1 second.

Figure 3: ^{29}Xe-MRI ADC (apparent diffusion coefficient - cm^2/s) image examples from three participants (viewing from posterior to anterior, left to right) with accompanying slice by slice ADC values. Participant i) has spirometric dysanapsis: FEV1 = -0.36z, FVC = 2.77z, FEV1/FVC = -3.0z, aged 71 years and a physician assigned diagnosis of COPD. This participant has raised ADC values especially in the upper lobes, consistent with emphysema. Participant ii) has normal spirometry with a large FVC: FEV1 = 1.45z, FVC = 2.16z, FEV1/FVC = -0.83z, aged 73 years and a physician assigned diagnosis of COPD. The mean ADC is lower than participant i) with a homogeneous distribution and therefore this participant does not have the level of disease seen in participant i). Participant iii) has normal spirometry: FEV1 = -0.53z, FVC = -0.11z, FEV1/FVC = -0.73z, aged 74 years and a physician assigned diagnosis of asthma and COPD. The mean ADC is the lowest of the three participants and without evidence of any significant areas of enlarged acinar dimensions.

Figure 4: The effect of smoking on ^{129}Xe-MRI measured VDP and ADC between the dysanapsis and normal spirometry groups. Box and whisker plots are shown where the box indicates the 25th and 75th centiles and the horizontal line is the median, whilst the whiskers depict the minimum and maximum values. Mann-Whitney comparisons were performed to compare the two groups and the resulting p

value is displayed on each graph. Plot A compares VDP between groups for never smokers. Plot B compares VDP between groups for people with any smoking history. Plot C compares ADC between groups for never smokers. Plot D compares ADC between groups for those with any smoking history.

Figure 5: Scatter plots depicting the relationship between FEV1/FVC and VDP or ADC in participants with the dysanapsis spirometry pattern (closed circles) and with a normal spirometry pattern (open diamonds). The solid black line represents the linear regression line of best fit and the dashed lines represent the 95% confidence intervals for each of the two groups independently. For the dysanapsis group the relationship between ADC and FEV1/FVC = $R2=0.38$, $r=-0.52$, $p<0.001$ and for the normal spirometry group = $R2=0.05$, $r=0.11$, $p=0.48$. For the dysanapsis group the relationship between VDP and FEV1/FVC = $R2=0.41$, $r=-0.64$, $p<0.001$ and for normal spirometry = $R2=0.04$, $r=-0.18$, $p=0.25$. Abbreviations: VDP = ventilation defect percent; ADC = apparent diffusion coefficient; FEV1/FVC = forced expiratory volume in 1 second divided by the forced vital capacity.

Figure 6: Scatter plots depicting the relationships of VDP and ADC with FVC in participants with the dysanapsis spirometry pattern. The vertical dotted line is placed at the upper limit of normal (ULN) for FVC. The eight people with an FVC above the ULN on average had significantly higher VDP and ADC than the people with dysanapsis and an FVC <ULN, highlighting more advanced lung function abnormalities in those with the largest FVC values. VDP = ventilation defect percent; ADC = apparent diffusion coefficient; FVC = forced vital capacity.

Figure 7: Plots A and B demonstrate the individual change between visits 1 and 2 for VDP and FEV1/FVC in participants with the dysanapsis spirometry pattern. Plot C demonstrates the relationship between the change (Δ) in FEV1/FVC compared to the change in VDP between the two visits.