



Structure and function imaging in primary ciliary dyskinesia: cross-sectional study with ^{129}Xe ventilation/ ^1H anatomical magnetic resonance imaging

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Most clinically stable children with PCD had visible ventilation abnormalities when assessed with ^{129}Xe MRI. ^{129}Xe -derived VDP was abnormal in 75% of children who had normal FEV₁.

<https://bit.ly/3LJ4pZ3>

Cite this article as: Schofield L, Smith L, Marshall H, *et al.* Structure and function imaging in primary ciliary dyskinesia: cross-sectional study with ^{129}Xe ventilation/ ^1H anatomical magnetic resonance imaging. *ERJ Open Res* 2026; 12: 00984-2025 [DOI: 10.1183/23120541.00984-2025].

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This article has an editorial commentary:
<https://doi.org/10.1183/23120541.00113-2026>

Received: 28 July 2025
Accepted: 24 Dec 2025

Abstract

Background In primary ciliary dyskinesia (PCD), impaired mucociliary clearance leads to respiratory infections. Whilst forced expiratory volume in 1 s (FEV₁) is commonly used to evaluate lung function in PCD its sensitivity to detect abnormalities in mild disease is limited. This study explores the utility of ^{129}Xe ventilation and ^1H anatomical magnetic resonance imaging (MRI) to assess lung health in children with PCD.

Methods This prospective cohort study assessed clinically stable children with PCD (aged 5–18 years) using ^{129}Xe MRI, ^1H MRI and spirometry during one session. Ventilation defect percentage (VDP) was the primary metric calculated from ^{129}Xe MRI.

Results 35 children were assessed (mean±SD age 12.3±3.3 years, FEV₁ z-score −1.5±1.7). Most children had visible ventilation abnormalities and 82.8% had an abnormal ^{129}Xe VDP (median (interquartile range) ^{129}Xe VDP 6.3% (1.3–16.1%)). 16 participants had a normal FEV₁ (z-score > −1.6); however, 12 of these individuals had abnormal ^{129}Xe VDP. ^1H MRI found 55.9% participants had a region of collapse, 61.3% had bronchiectasis and 50.0% had evidence of air trapping.

Conclusions ^{129}Xe MRI can identify early lung function abnormalities in children with PCD and demonstrates that the extent of ventilation distribution abnormalities in PCD varies between individuals. ^1H MRI provides complementary diagnostic information on structural abnormalities.

Introduction

Primary ciliary dyskinesia (PCD) is an inherited condition in which structural and/or functional ciliary abnormalities impair mucociliary clearance. People with PCD experience chronic infections with exacerbations of the upper and lower respiratory tract, fuelling inflammation and the development of bronchiectasis [1]. Whilst forced expiratory volume in 1 s (FEV₁) from spirometry is the most widely used clinical outcome measure in PCD, large variability in FEV₁ is seen during periods of disease stability [2]. Additionally, FEV₁ can be insensitive to detect abnormalities; 73% of people with PCD with structural lung abnormalities on computed tomography (CT) scan have FEV₁ within the normal range [3]. Whilst lung clearance index (LCI) from multiple-breath washout is more sensitive to detect lung abnormalities



than FEV₁ [4], the correlation of LCI with other outcomes remains unclear [5]. As such, more sensitive outcome measures are needed to accurately assess lung abnormalities in PCD.

Hyperpolarised gas ventilation magnetic resonance imaging (MRI) using helium-3 (³He) or xenon-129 (¹²⁹Xe) [6] permits the visualisation and quantitative assessment of the distribution of ventilation within the lung in three dimensions. ¹²⁹Xe, which is more readily available than ³He, is now commonly used in hyperpolarised gas MRI research [6] and offers potential clinical application [7]. Ventilation abnormalities, visible as areas without gas signal, are known as ventilation defects. Ventilation defect percentage (VDP), the proportion of the thoracic cavity with no gas signal, is the most commonly used metric. Hyperpolarised gas ventilation MRI has shown promise in evaluating lung ventilation defects in other chronic suppurative lung diseases (CSLDs) [8], but its application in PCD to date has been limited. VDP is a sensitive marker of lung health in cystic fibrosis (CF) [8–10] and other obstructive lung diseases [6]. In a small study of children with PCD, ³He VDP was found to be more sensitive to detect abnormalities than LCI and FEV₁ [11]; however, there are no published data using ¹²⁹Xe MRI to assess people with PCD. Recognising that it is a safe, ionising radiation-free and well-tolerated technique [6], children with PCD and parent representatives were supportive of research to explore the utility of ¹²⁹Xe MRI.

¹H MRI of the lungs can identify structural abnormalities without ionising radiation and does not require access to hyperpolarised gas technology. Findings from ¹H ultrashort echo time (UTE) MRI sequences are increasingly comparable with CT imaging findings and offer longitudinal assessment capability in CSLDs [12]. In some centres ¹H MRI is used for routine clinical assessment of people with CF [13]. In PCD, ¹H MRI can identify collapse, consolidation, mucus plugging and bronchiectasis [14], and agreement has been seen between abnormalities identified on ¹H MRI and high-resolution CT (HRCT) [15]. Functional abnormalities have been identified in people with PCD previously using the matrix pencil ¹H MRI (MP-MRI) method, but this had lower spatial resolution and was less sensitive than UTE structural MRI to detect abnormalities [3].

This study aimed to assess lung physiology and structure in children and young people with PCD using ¹²⁹Xe ventilation and ¹H anatomical MRI. This work is part of a larger study (ASPECT-PCD [16]) which assessed lung health with ¹²⁹Xe MRI on the same day before and after airway clearance; this article summarises the cross-sectional data from the study population.

Methods

This prospective study recruited children (aged 5–18 years) with PCD from four centres in the North of England between April 2022 and August 2023. For inclusion, participants needed to: have a confirmed PCD diagnosis according to European Respiratory Society guidelines [17], be clinically stable at the time of assessment (not on treatment antibiotics for a chest exacerbation), have resting oxygen saturation ≥90% on air and not have any contraindications to MRI scanning. All eligible participants, or their parents/guardians if <16 years old, were approached to take part by members of their direct clinical care team and provided written informed consent. The study was approved by the Oxford B Research Ethics Committee (21/SC/0197).

Lung imaging

Hyperpolarised ¹²⁹Xe MRI scanning was performed at a single site (University of Sheffield, Sheffield, UK) on either a 1.5-T GE HDxt or 1.5-T GE Artist MRI scanner (GE, Milwaukee, WI, USA) using a ¹²⁹Xe transmit–receive vest coil (Clinical MR Solutions, Brookfield, WI, USA). ¹²⁹Xe MR images were acquired using a three-dimensional (3D) steady-state free precession (SSFP) sequence [18]. The ¹²⁹Xe gas was polarised using an in-house polariser under regulatory licence (MS-18739) [19]. Images were acquired during breath-hold at end-inspiratory tidal volume (EITV), following inhalation of a titrated mixture of ¹²⁹Xe and medical-grade nitrogen, administered *via* a Tedlar plastic bag from residual volume. Total volume of inhaled gas was calculated based on participant's height and ranged between 0.4 and 1.0 L [20]. To estimate the thoracic cavity for image analysis, ¹H 3D spoiled gradient echo (SPGR) MR images were acquired pre and post the ¹²⁹Xe images during separate matched breath-holds at EITV. ¹²⁹Xe images were segmented using a semi-automated method to calculate ¹²⁹Xe VDP [21], and the ventilation heterogeneity index (VHI) was also assessed [22].

¹H imaging sequences included: 3D SPGR acquired at two lung inflation levels (functional residual capacity plus inhaled bag volume (*i.e.* EITV) and residual volume), radial 3D UTE during free breathing [23], 2D SSFP at expiratory breath-hold and 2D T2-weighted half-Fourier acquisition single-shot turbo spin echo (HASTE) imaging at expiratory breath-hold.

These were performed using an 8-channel or 16+-channel anterior array plus a spine ^1H array (HDxt and Artist MRI scanner, respectively) to provide high-resolution anatomical images. A consultant paediatric radiologist reviewed all images to assess for typical PCD features, including bronchiectasis, collapse, consolidation and air trapping. Participants were imaged at three times on the same day (see the supplementary material for study schedule). Baseline ^1H imaging was primarily used to assess for abnormalities; however, where baseline images were not readable, ^1H MR images from later time-points were used.

Further details on sequence details, image acquisition, processing and calculation of ^{129}Xe MRI metrics are provided in the supplementary material.

Acquisition of non-imaging data

Clinical and diagnostic information were obtained prior to the study visit from medical notes and the clinical team. Spirometry was performed immediately prior to the first MRI scan with a MasterScreen PFT Pro (Vyaire, Basingstoke, UK) in accordance with technical standards [24]. All spirometry metrics were assessed using a z-score, with -1.64 used as the lower limit of normal [25]. Quality of life was assessed on the same day using the age-appropriate version of the paediatric health-related quality of life instrument for PCD (QOL-PCD) online questionnaire: adolescent version for those aged 13–17 years and child and parent-proxy versions for those aged <13 years [26].

Statistical analysis

Statistical analysis was performed using Prism version 9.5.1 (GraphPad, Boston, MA, USA). Normal distribution was assessed using the Shapiro–Wilk test. Data are presented as mean with standard deviation if they are normally distributed or median with interquartile range (IQR) otherwise. Group comparisons were completed using the unpaired t-test, Mann–Whitney U-test (not normal distribution), parametric ANOVA test or Kruskal–Wallis ANOVA test, depending on data distribution and number of groups. Correlation was assessed using Spearman’s rank-based correlation. Statistical significance was defined as $p < 0.05$. ^{129}Xe VDP of 1.2% and VHI of 9.5% were used as the upper limits of normal from a population of children without history of lung disease [27].

Results

93 individuals were assessed for eligibility; 16 did not meet inclusion criteria and 77 were approached. 36 individuals consented to participate, of which 35 young people were assessed with ^{129}Xe and ^1H MRI and one individual withdrew due to intolerance of the scanner sounds. 35 participants were assessed with QOL-PCD in total: adolescent version ($n=16$), both child and parent-proxy versions ($n=14$), child version ($n=3$) and parent-proxy version ($n=2$). Full details of screening and recruitment are provided in figure 1. Baseline clinical demographics are provided in table 1 and QOL-PCD data are provided in the supplementary material.

Spirometry

34 individuals performed technically acceptable spirometry [28] (table 2); one dataset was not technically acceptable and was excluded. 55.8% ($n=19$) had no evidence of airway obstruction ($\text{FEV}_1/\text{forced vital capacity (FVC)}$ z-score > -1.64). No correlation was seen between FEV_1 and age, age at diagnosis, number of antibiotic courses or lower respiratory symptoms/physical functioning QOL-PCD domains. No significant differences in FEV_1 were seen between ultrastructural defect groups or in those who had/had not recently grown *Pseudomonas aeruginosa*.

^{129}Xe MRI

A summary of ^{129}Xe -derived metrics is provided in table 2 and an image from each of the participants is provided in figure 2. Most children had visible ventilation abnormalities and 82.8% ($n=29$) had an abnormal VDP. Six children had very minimal ventilation abnormalities and were comparable to healthy children.

No difference in ^{129}Xe VDP was seen according to sex or situs abnormalities. No correlation was seen between ^{129}Xe VDP and age or age at diagnosis. ^{129}Xe VDP was highest in the inner dynein arm (IDA) defect or microtubular disorganisation (MTD) group, with a median (IQR) of 12.8% (1.5–19.3%). The median (IQR) values for the other groups were outer dynein arm defect (ODA), 5.8% (1.8–7.1%); combined ODA and IDA defects, 9.2% (5.0–19.6%); and normal ultrastructure with a genetic diagnosis of PCD, 0.4% (0.3–2.5%). There was no statistically significant difference in ^{129}Xe VDP between the groups.

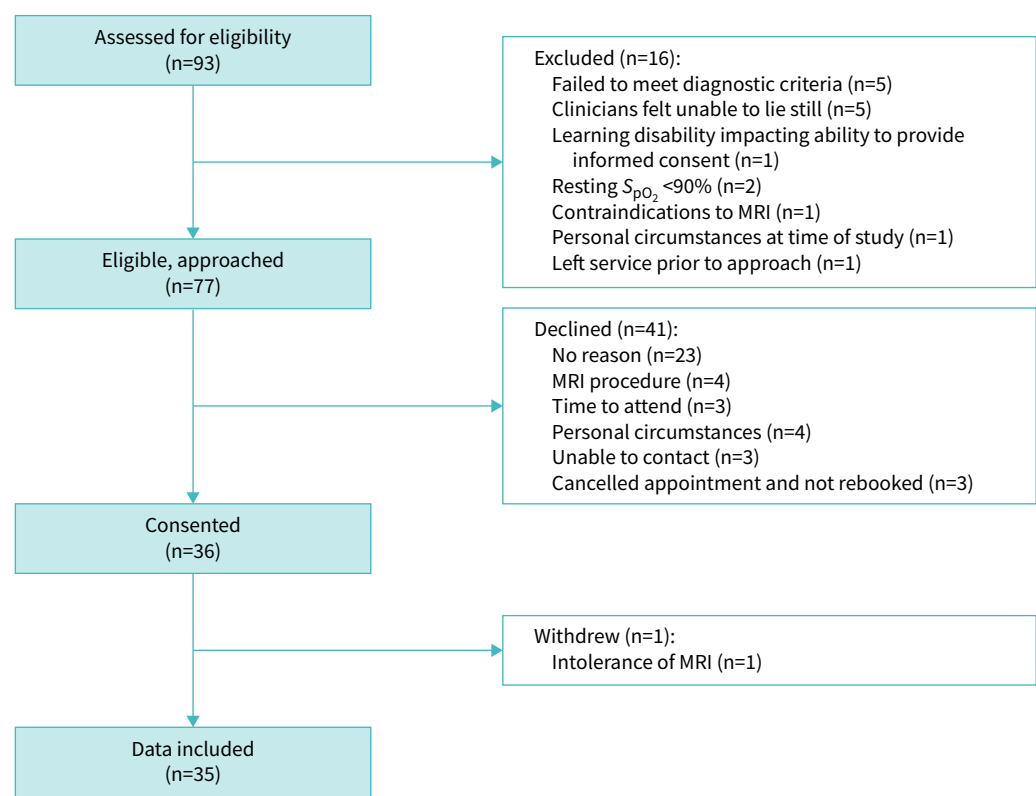


FIGURE 1 Flow diagram summarising the number of potential participants who were screened and their reasons for exclusion or declining the procedure. S_{pO_2} : peripheral oxygen saturation; MRI: magnetic resonance imaging.

^{129}Xe VDP correlated moderately with FEV_1 ($r = -0.54$, $p = 0.001$), FVC ($r = -0.42$, $p = 0.01$) and FEV_1/FVC ($r = -0.57$, $p < 0.001$) (figure 3a–c). The number of individuals with abnormal ventilation was greater as assessed by ^{129}Xe VDP when compared to FEV_1 ; 16 participants had FEV_1 within the normal range ($z\text{-score} > -1.64$), yet 12 of these individuals (75%) had raised VDP when compared to healthy children (^{129}Xe VDP $> 1.2\%$). Two children had normal VDP ($< 2.0\%$) with abnormal spirometry: one with an obstructive pattern (FEV_1/FVC $z\text{-score} < -1.64$ and $\text{FEV}_1 < -1.64$) and one with a mixed pattern (FEV_1/FVC $z\text{-score} < -1.64$ and $\text{FVC} < -1.64$). Three children had no evidence of obstruction (FEV_1/FVC $z\text{-score} > -1.64$) but had a restrictive pattern on spirometry (FEV_1 and FVC $z\text{-score} < -1.64$). All of these children had abnormal VDP (11.0%, 11.3% and 27.7%).

TABLE 1 Participant demographics, including ultrastructural defects (n=35)	
Male	19 (54)
Age (years)	12.3±3.3
Age at diagnosis (years)	3 (0–6)
Ultrastructural defect	
IDA or MTD only	9 (25.7)
ODA only	8 (22.9)
IDA and ODA	12 (34.3)
No defect [#]	6 (17.1)
Situs inversus	14 (40.0)
Antibiotic courses in last 12 months [¶] (n)	2.5 (1–4)
<i>Pseudomonas aeruginosa</i> (cultured in last 12 months)	5 (14.3)
Data are presented as n (%), mean±SD or median (interquartile range). IDA: inner dynein arm; MTD: microtubular disarrangement; ODA: outer dynein arm. [#] : primary ciliary dyskinesia diagnosis confirmed by genetics; [¶] : oral or intravenous, planned or unplanned.	

TABLE 2 Spirometry and ¹²⁹ Xe magnetic resonance imaging (MRI) metrics	
Spirometry (n=34)	
FEV ₁	
z-score	−1.5±1.7
% pred	81.3±20.6
FVC	
z-score	−0.7±1.5
% pred	90.1±21.6
FEV ₁ /FVC	
z-score	−1.5±1.3
% pred	87.2±11.7
¹²⁹Xe MRI (n=35)	
VDP (%)	6.3 (1.3–16.1)
VHI (%)	11.3±3.2
Data are presented as mean±SD or median (interquartile range). FEV ₁ : forced expiratory volume in 1 s; FVC: forced vital capacity; VDP: ventilation defect percentage; VHI: ventilation heterogeneity index.	

Examples of cases in which only one of the two lung health measures were abnormal (either FEV₁ or ¹²⁹Xe VDP) are shown in figure 4.

There was no correlation between ¹²⁹Xe VDP and the number of antibiotics administered in the last 12 months. Whilst ¹²⁹Xe VDP was higher in individuals who had cultured *P. aeruginosa* in the previous 12 months (11.0%) than those who had not (5.4%), this was not statistically significant (p=0.15). Across the three versions of the QOL-PCD, only the social function domain (adolescent version) showed a moderate correlation with ¹²⁹Xe VDP (r= −0.57, p=0.02).

25 participants (71.4%) had abnormally high ¹²⁹Xe VHI. ¹²⁹Xe VHI correlated moderately with spirometry: FEV₁ z-score (r= −0.52, p=0.002), FVC z-score (r= −0.38, p=0.03) and FEV₁/FVC z-score (r= −0.58, p<0.001) (figure 3d–f). No correlation was seen between ¹²⁹Xe VHI and age, age at diagnosis, number of antibiotic courses and lower respiratory/physical functioning QOL-PCD domains. No significant differences in ¹²⁹Xe VHI were seen between ultrastructural defect groups or those who had/had not recently grown *P. aeruginosa*.

¹H MRI assessment of lung structure

Baseline UTE scans were deemed readable for 24 out of 34 (70.1%) participants; a further five participants (14.7%) had unreadable baseline UTE images, but scans from later time-points within the day were readable. In the remaining five cases image acquisition issues permitted assessment for collapse but not bronchiectasis (n=3). Of those with readable images: 19 out of 31 (61.3%) had bronchiectasis, 19 out of 34 (55.9%) had a region of collapse and 17 out of 34 (50.0%) had evidence of air trapping. All 19 with collapse identified had a region of collapse in their middle lobe (right middle lobe in situs solitus and left middle lobe in situs inversus). ¹²⁹Xe imaging was more sensitive to detect abnormalities than ¹H MRI; four out of six (66.7%) of those with no structural abnormalities had both abnormal VDP and VHI (figure 5). Figure 6 provides an example visual comparison of abnormalities identified on ¹H and ¹²⁹Xe MRI.

Discussion

This cross-sectional study found that ¹²⁹Xe MRI detects ventilation abnormalities in most children with PCD. 82.8% of the study population had abnormal ventilation assessed by ¹²⁹Xe VDP; 75% of individuals with no evidence of obstructive airways disease using spirometry had abnormal ventilation (VDP >1.2%). Whilst ventilation abnormalities were common, a small number of individuals with PCD did not have ventilation abnormalities. ¹H MRI also identified structural abnormalities: 55.9% of children with PCD had areas of collapse and 61.3% had bronchiectasis.

Our findings are consistent with the previous small study by SMITH *et al.* [11] which found VDP (using ³He MRI) to be abnormal in children with PCD who had normal FEV₁. With the finding that ¹²⁹Xe VDP is often abnormal in individuals with normal FEV₁, our results align with previous hyperpolarised gas MRI literature in CSLDs [9, 11, 20, 29–32]. For the first time, this study found a small number of children with PCD with abnormal FEV₁, including one without restrictive lung disease but normal ventilation on ¹²⁹Xe MRI [27]. Whilst this study found a moderate correlation of ¹²⁹Xe VDP with FEV₁ in children with PCD, other studies have reported no corelation between ¹²⁹Xe VDP and FEV₁ [29], and a stronger

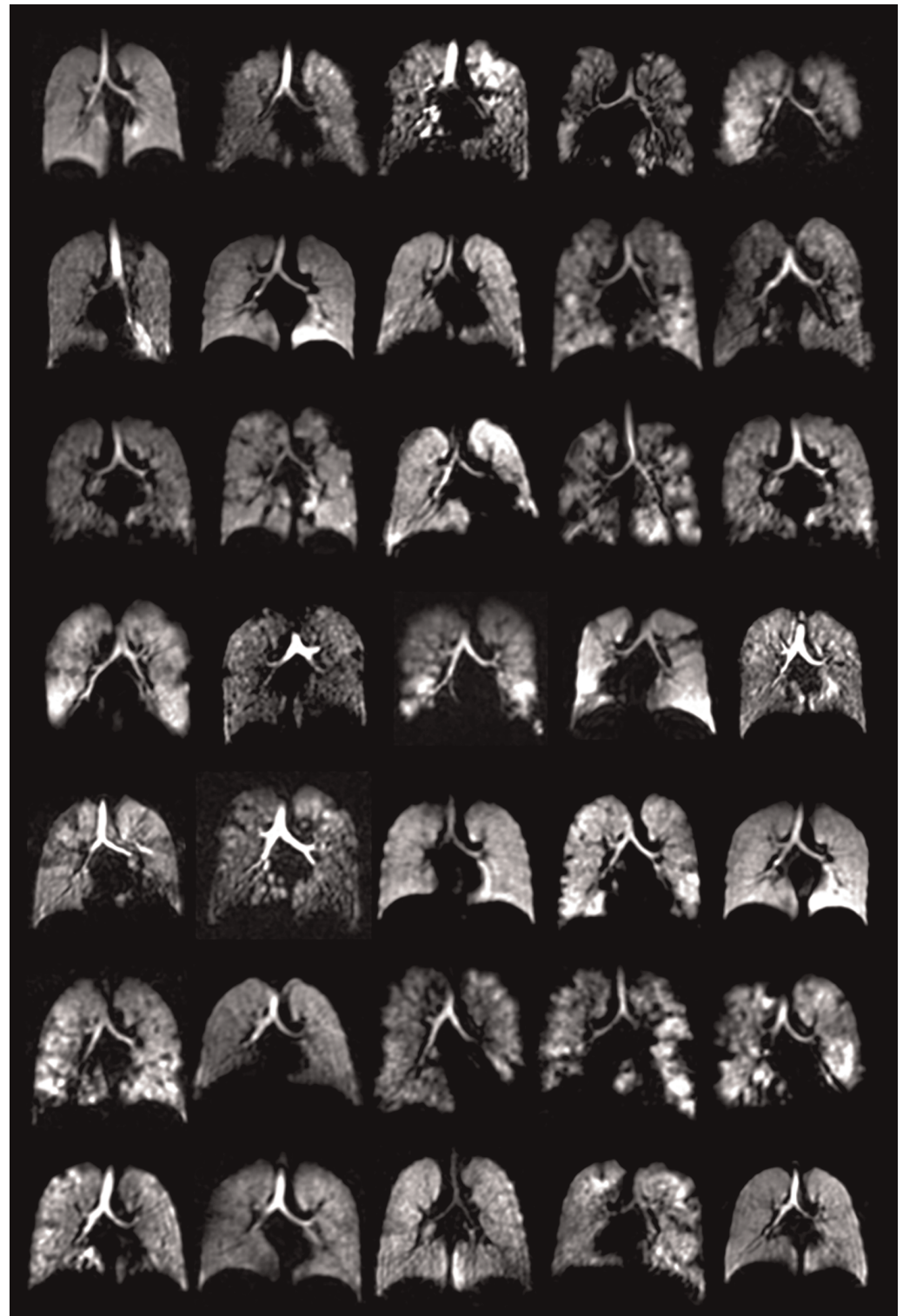


FIGURE 2 ^{129}Xe ventilation magnetic resonance images for all participants in the study ($n=35$). Each image depicts a different participant, showing a central slice.

correlation between ^3He VDP and FEV_1/FVC [11]. In paediatric CF, the relationship between ^{129}Xe VDP and FEV_1 is also variable [30, 33, 34]. This variability in correlation between VDP and FEV_1 may arise from the differing study populations or image acquisition methods. These findings illustrate that reliance

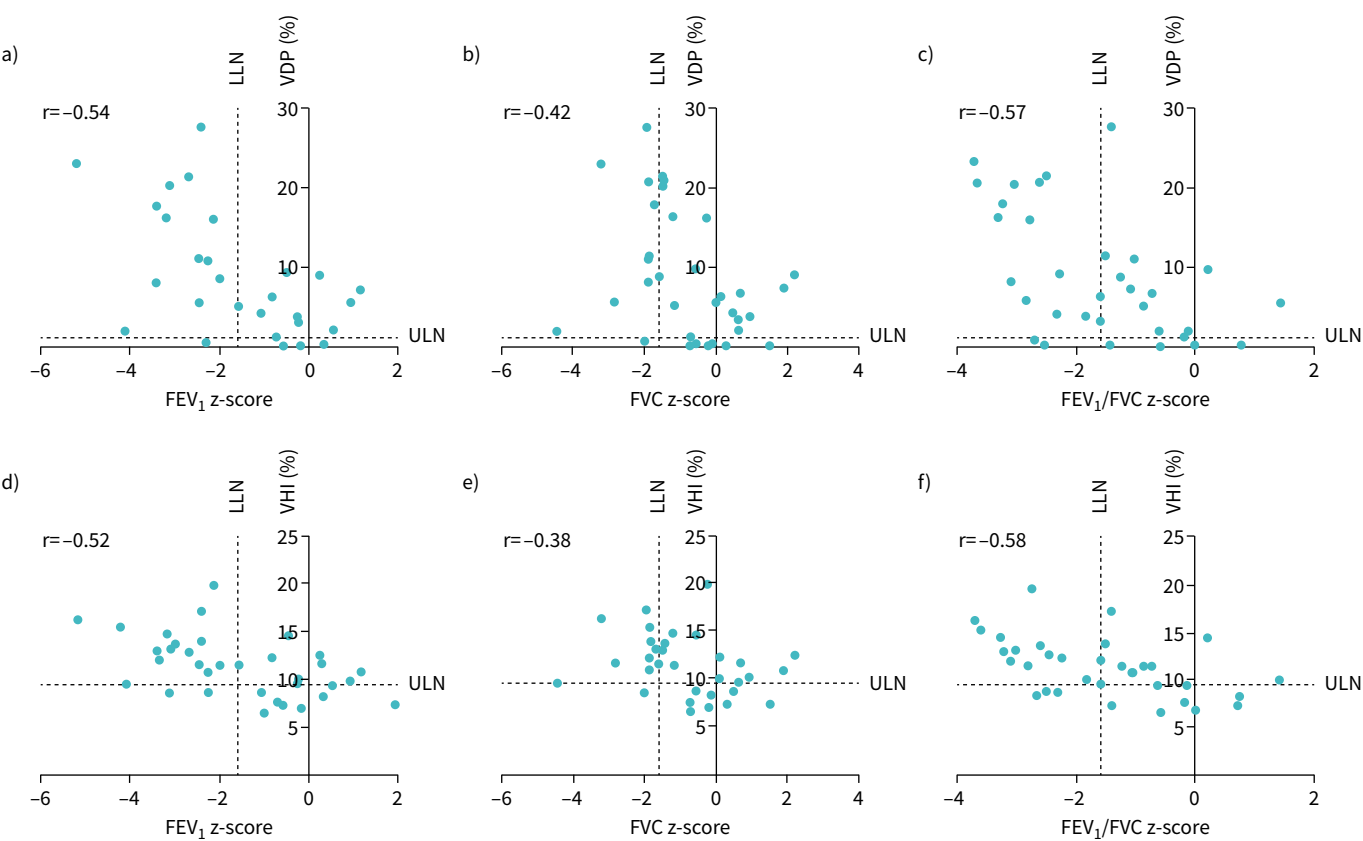


FIGURE 3 Spearman's rank correlations of ¹²⁹Xe a–c) ventilation defect percentage (VDP) and d–e) ventilation heterogeneity index (VHI) with spirometry metrics: a, d) forced expiratory volume in 1 s (FEV₁), b, e) forced vital capacity (FVC) and c, f) FEV₁/FVC. Vertical dashed lines indicate FEV₁, FVC and FEV₁/FVC lower limit of normal (LLN; −1.64); horizontal dashed lines indicate VDP and VHI upper limit of normal (ULN; 1.2% and 9.5%, respectively).

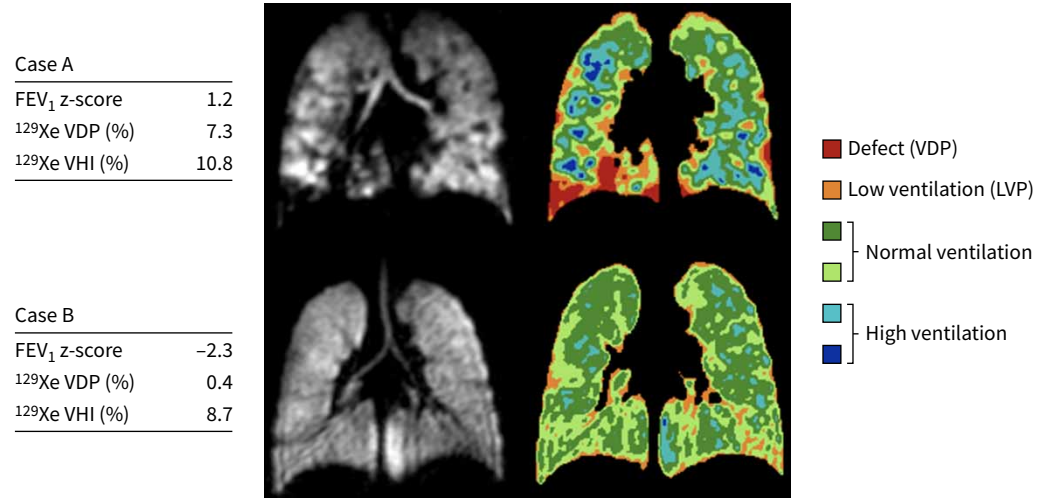


FIGURE 4 ¹²⁹Xe imaging data from example cases with discordant spirometry and ¹²⁹Xe ventilation defect percentage (VDP) findings. Case A: normal forced expiratory volume in 1 s (FEV₁) but both abnormal VDP and ventilation heterogeneity index (VHI). Case B: abnormal FEV₁ (moderate obstruction) but normal VDP and VHI. LVP: low ventilation percentage.

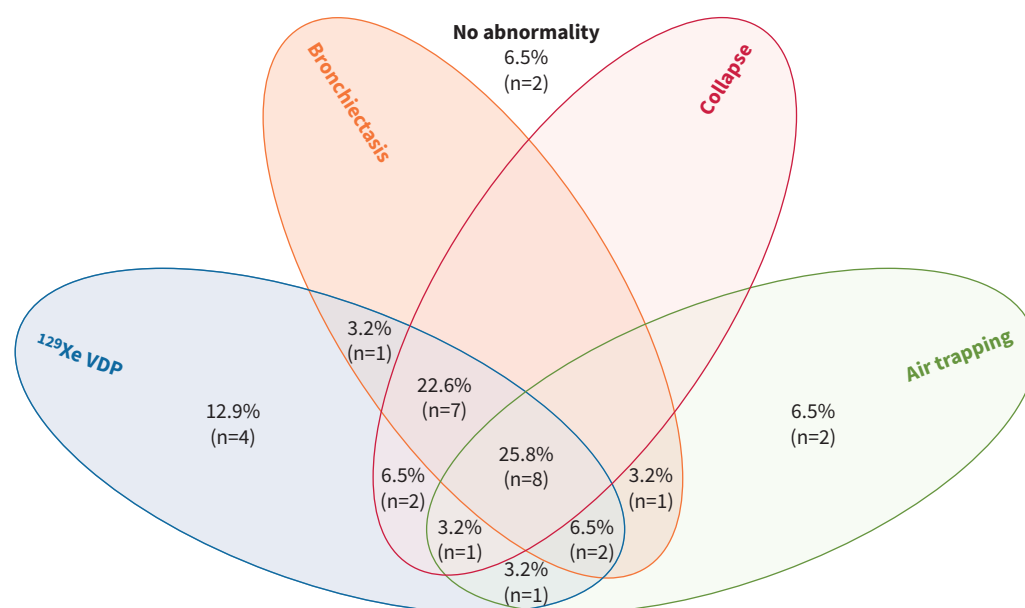


FIGURE 5 Venn diagram illustrating the frequencies of abnormal ^{129}Xe ventilation defect percentage (VDP), bronchiectasis, collapse and air trapping in the study cohort. Diagram only includes participants with readable ultrashort echo time images (n=31).

on spirometry alone for the clinical assessment of lung health in CSLDs may lead to instances of false assurance of normal lung health. These studies show the importance of using a range of tools to assess different components of lung function in CSLDs.

The clinical picture in PCD is complex; neither spirometry nor ^{129}Xe metrics (VDP and VHI) correlated with age, age at diagnosis or number of antibiotic courses in the last 12 months, and limited correlation was seen with quality of life assessed by the QOL-PCD. VDP was higher and FEV_1 was lower in those with IDA and ODA defects than those with normal ciliary ultrastructure. Previous research reported that individuals with IDA and MTD ciliary defects have the highest CT scan disease scores [35], and this study provides further evidence that ciliary ultrastructural defects may influence disease severity.

Bronchiectasis, bronchial wall thickening, mucus plugging and atelectasis are common CT findings in people with PCD [36, 37]. The frequency of abnormalities identified in children with PCD using ^1H MRI in this study is lower than previously reported: 100% structural abnormalities, 97% and 94% bronchiectasis or wall thickening [3, 14]. It is unclear if the lower frequency seen may arise from differences in diagnostic inclusion criteria, image acquisition or a true variance. Finding the anatomical middle lobe, whether located on the left or right side of the body, to be a common area of collapse in PCD, this study adds further evidence to the CT scan findings of middle lobe collapse reported by JAIN *et al.* [38] and highlights the importance of monitoring this area in children with PCD. These data also highlight the potential of ^1H MRI to reduce the number of CT scans of the lungs and provide a viable longitudinal lung imaging assessment method.

This is the largest cohort of children with PCD assessed by ^{129}Xe MRI to date, employing a prospective study design with standardised imaging and spirometry methods, an age-appropriate, validated QOL-PCD instrument and clinical data. This study used ^{129}Xe ventilation MRI, a highly sensitive technique, to provide quantitative and qualitative information on the range of functional abnormalities seen in PCD, and ^1H anatomical MRI to detect structural abnormalities. Although two children struggled with the MRI scanner noise, one of whom withdrew from the study, the scans were well tolerated by the vast majority of individuals, including those as young as 6 years old. As MRI is ionising radiation-free, it is well placed for assessing children and young people, especially longitudinally. The cross-sectional design precluded assessment of longitudinal changes or inferring causality. Future long-term follow-up studies to determine whether baseline ^{129}Xe VDP predicts key clinical outcomes including exacerbation frequency and lung function decline are needed. Further evaluation of healthy children with ^{129}Xe MRI will provide more robust paediatric reference values, enabling multicentre research and clinical implementation of the findings.

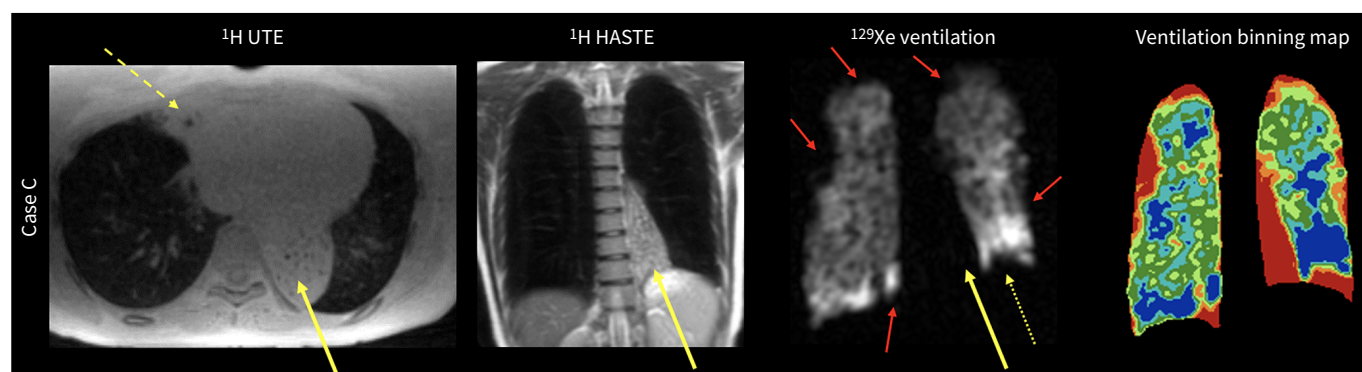


FIGURE 6 Case C: example to illustrate comparison of ^1H anatomical magnetic resonance imaging (MRI) (ultrashort echo time (UTE) and half-Fourier acquisition single-shot turbo spin echo (HASTE) images) and ^{129}Xe MRI (ventilation image and binning map) findings. Arrows indicate areas where collapse corresponds to ^{129}Xe ventilation defect (yellow) and areas of ^{129}Xe defect with no evidence of abnormality on ^1H (red). Solid arrows indicate where comparison has been made on the slice depicted, the dashed arrow indicates where comparison was made with a more anterior ventilation image slice and the dotted arrow indicates where comparison was made with a more inferior UTE slice. Ventilation binning maps shows areas of ventilation defect (red), low ventilation (red/orange), normal ventilation (dark green/light green) and high ventilation (turquoise/blue).

Whilst HRCT scans were not included to ensure an ionising radiation-free protocol, studies permitting direct comparison of HRCT and ^1H MRI in children with CSLDs are warranted. As LCI is widely available, inclusion of LCI in the study protocol would have provided a valuable comparison of ^{129}Xe MRI with LCI. Future work from the ASPECT-PCD study [16] will evaluate the effects of airway clearance techniques using ^{129}Xe MRI.

Conclusions

^{129}Xe ventilation MRI can detect ventilation abnormalities in children with PCD; we also demonstrate that the extent of ventilation distribution abnormalities in PCD varies between individuals. Ventilation abnormalities are identifiable using ^{129}Xe ventilation MRI in children with PCD who have normal FEV_1 . ^1H MRI provides complementary diagnostic information on structural abnormalities. ^{129}Xe ventilation MRI offers a sensitive, safe and well-tolerated imaging technique that is well placed for future longitudinal studies in children with PCD.

Provenance: Submitted article, peer reviewed.

Ethics statement: All eligible participants, or their parents/guardians if <16 years old, were approached to take part by members of their direct clinical care team and provided written informed consent. The study was approved by the Oxford B Research Ethics Committee (21/SC/0197).

Conflict of interest: L. Schofield reports support for the present study from the National Institute for Health and Care Research (NIHR), Leeds Hospitals Charity and Child Health Outcome Research at Leeds (CHORAL); consultancy fees from Aparito; payment or honoraria for lectures, presentations, manuscript writing or educational events from the Association of Chartered Physiotherapists in Cystic Fibrosis; and a leadership role with the PCD Registry. L.J. Smith reports grants from the Cystic Fibrosis Trust, Vertex Pharmaceuticals and Sheffield Children's Hospital Charity; payment or honoraria for lectures, presentations, manuscript writing or educational events from the Association of Chartered Physiotherapists in Cystic Fibrosis; and support for attending meetings from AstraZeneca. H. Marshall reports grants from GSK and EPSRC, and support for attending meetings from the ERS and ERS/ESPR. D. Hughes, A. Biancadi, J. Bray, D. Capener, G. Collier, S. Fazal, E. Moya, R. Munro, G. Norquay, E. Robson, O. Rodgers, A. Shawcross, S.J. Singh, N. West and A. Zalewska report no disclosures. S. Shanks reports support for the present study from the ASPECT-PCD study/NIHR. N. Stewart reports grants from UKRI Future Leaders Fellowship, EPSRC Prosperity Partnership, Rosetrees Trust Seedcorn and AMS Springboard. D. Hind reports grants from the NIHR, participation on a data safety monitoring board or advisory board with Implementing Mobile Mental health Recording Strategy for Europe (IMMERSE project), and is the Trial Steering Committee Chair for the DOORSTEP and PANDA-S trials. J.M. Wild reports grants from the MRC, payment or honoraria for lectures, presentations, manuscript writing or educational events from Vertex, and a UK patent issued for a xenon polarisation system.

Support statement: This study was funded by the National Institute of Health and Care Research (NIHR301558) and the Medical Research Council (MR/M008894/1). This research was supported by Child Health Outcomes Research at Leeds (CHORAL) (www.choralresearch.org.uk). CHORAL is funded by Leeds Hospitals Charity, the University of Leeds and Leeds Teaching Hospitals NHS Trust. Funding information for this article has been deposited with the Open Funder Registry.

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