Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis

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Study aim: The aim of this study was to characterise adherence in an adult population with CF and to investigate if variation in lung function was a predictor of adherence to treatment.

Patients and methods: Patients aged ≥ 16 years from an adult CF centre undertook adherence measures by medication possession ratio (MPR) and self-report and were assigned to one of three adherence categories (<50%, 50-<80%, 80% and above) by their composite score (MPR). Ordinal regression was used to identify predictors of adherence including coefficient variation measures for forced expiratory volume in 1 second (FEV_1), weight and C-reactive protein, measured up to 6 and 12 months.

Results: MPR data for 106 of 249 patients [mean age 29.8 (±9.2) years] was retrieved, indicating a mean adherence of 63%. Coefficient of variation FEV_1 was inversely related to adherence and was a univariate predictor of adherence (6 months: 0.92 [0.87-0.98] p= 0.005 and 12 months: 0.94 [0.93-0.99], p=0.03]) and remained significant in the final models. The coefficient variation of weight and C-reactive protein were not predictive of adherence.

Conclusions: Coefficient of variation FEV_1 was identified as an objective predictor of adherence. Further evaluation of this potential marker of adherence is now required.

Introduction

Advances in early diagnosis and treatment of cystic fibrosis (CF) have resulted in significant improvements in survival with many patients living into adulthood and middle age.[1,2] This success has been achieved through specialised multidisciplinary care in combination with intense treatment regimens which are time consuming and negatively impact on daily life. Poor adherence to treatment remains a significant problem, being as low as 40 to 50%.[3-7] Adherence problems can negatively influence health outcomes such as pulmonary exacerbations,[8] health related quality of life,[3] and healthcare costs;[6-9] trends that are also apparent across other respiratory diseases.[10-12]

Consensus regarding the accurate measurement of adherence is lacking and has proved difficult in day-to-day practice. The use of subjective self-report, supported by objective measures including pharmacy collection, medication possession ratio and chipped hardware such as the i-neb,[4] are frequently used as part of good practice in reporting study findings. While all of these have inherent limitations,[7] objective physiological measures that might define adherence more accurately are lacking.

Studies in other chronic diseases have recently highlighted the association between variation in physiological measures such as blood pressure [13-15] and immunosuppressive therapy [16] and adherence to medication. These provide objective measures, which may help to characterise poor adherence and trigger interventions to support better outcomes. Attention has focused on the variability of lung function as an improved predictor of lung decline in CF, above that of FEV_1 alone; the hypothesis being that it is a more sensitive marker that may reflect exacerbations, individual pulmonary variation, and adherence.[17]

In CF there is evidence that low rates of medication adherence are associated with increased pulmonary exacerbations.[8,18] Given the maintenance effect of medications such as nebuliser therapies on respiratory function, it is therefore plausible that poor adherence might be associated with greater variation in lung function. A variability measure that accounts for natural changes, exacerbations and individual variation over time might also provide greater predictive accuracy than studies that have shown an association between adherence and the single measure of baseline FEV_1.[8]

In the day to day management of patients with CF we have recognised apparent differences in the fluctuation of lung function, weight and infection markers in patients known to have poor adherence. Patterns in diseases such as these have only become apparent following implementation of a disease-specific electronic patient record containing rich clinical ‘real time’ diagnostic, biochemical, anthropometric, pulmonary function and pathology data.[19] This

detailed longitudinal data which is routinely displayed graphically has provided a basis for testing whether variation indices might predict adherence within a population with CF.

The aim of this study was to characterise adherence in a large adult population with cystic fibrosis and to test the hypothesis that increased variation in lung function was an indicator of poor adherence to treatment.

Methodology

Participants: Patients attending a large regional adult cystic fibrosis unit were recruited from December 2012 to August 2013. Participants were identified from an electronic register of 400 patients, of 16 years and over, who had a diagnosis of CF as defined by the presence of a positive clinical phenotype with either two CF-causing mutations and/or two positive sweat tests. Participants were consecutively invited to participate in the study as they attended a routine out-patient visit at a time of clinical stability. Patients attended every 2-3 months, in line with local policy. Exclusion criteria included pregnancy, neurological disease, malignancy and renal disease to avoid potential influences on adherence patterns.

Measures:
Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) for the preceding 12 months were recorded. Each was measured using a calibrated, compact spirometer (Vitalograph, UK) undertaken by an experienced physiotherapist, and using the best value from a series of at least three attempts in accordance with guidelines.[20] In addition, age, gender, genotype, baseline weight (kg), height (m), BMI (kg/m^2), Vitamins A, D, E, C-reactive protein (CRP), number intravenous antibiotic treatment days within the last year were recorded.

Coefficient of variation (CoV) for FEV_1 was calculated by extracting all consecutive highest then lowest values for FEV_1 for 6 and 12 months prior to baseline from the electronic health record. These time scales were chosen to align with pharmacy retrieval data CoV FEV_1 (6 months) and to examine the impact of longer term patterns of variation on adherence CoV FEV_1 (12 months). The total, mean and standard deviation of all values for FEV_1 for each participant was calculated. The equation for coefficient of variation for FEV_1 was then calculated according to standard deviation FEV_1/mean FEV_1. Coefficient of variation for weight and CRP were similarly examined.

Adherence measures

Pharmacy collection: Individual medications and prescribed days of treatment were retrieved from the EHR for the time period ≤ 6 months prior to the baseline index date; a time scale chosen

to enable greater comparability with the level of self-reported adherence reported by the DMI-CF disease specific questionnaire.[7] Community pharmacy details were abstracted from the EHR and participants gave contact details for all other community pharmacies used within this time period. A letter of request was sent to all pharmacies together with a copy of the patient's signed consent form requesting amount medication prescribed for ≤ 6 months prior to the baseline index date. Up to 2 repeat requests were made by phone to maximise prescription data return. Similarly for patients using the i-neb, the prescribed number of doses was also retrieved from the EHR and medication uptake then downloaded from the ineb ≤ 6 months prior to the baseline index date. Patient MPR was then adjusted for all medications prescribed during inpatient admission and any out-patient prescriptions issued from the ward. The MPR was calculated from at least two prescription collections for each individual medication and then averaged to obtain a composite MPR. Medication possession ratio (MPR) was calculated using the equation, medication dispensed divided by the number days medication prescribed, multiplied by 100.

Adherence self-report: For each participant, a record of all routinely prescribed medications was generated at baseline from the electronic health record. All subjects completed a Disease Management Interview-CF (DMI-CF) self-report adherence questionnaire at baseline.[7] Percentage adherence to each prescribed medication was then calculated by dividing the reported dose by the prescribed dose for the each of the following medications and treatments; airway clearance, recombinant DNase, bronchodilators, inhaled steroids, pancreatic enzyme replacement therapy, nutrition, oral nutritional supplements or nasogastric/gastrostomy feed, vitamins, oral antibiotics, inhaled antibiotics and insulin.

A composite adherence measure was calculated, omitting airway clearance, nutrition and insulin fpr self-report to enable a composite measure comparable to adherence by MPR. Composite adherence was calculated as the sum of all medications patients prescribed on the electronic record, divided by the total number of self-reported medications taken.

Statistical analysis: Patient characteristics across medication and treatment adherence adherence (MPR), were compared using the Pearson chi–squared test (categorical variables) and the ANOVA (continuous variables). The Wilcoxon sign rank test was used to compare adherence by self-report with pharmacy.

Patients were assigned to one of three categories according to adherence reported by MPR, [< 50% adherence, 50 < 80% adherence and 80% and above]; a classification used in previous research in CF.[8] Ordinal regression was used to identify univariate predictors of adherence for testing in a multivariate model, using coefficient variation measures 6 and 12 months preceding baseline respectively. Genotype was defined as 3 categories (Delta F508 homozygous, Delta F508 heterozygous and 'other'). Only univariate variables with a p value of <0.1 were used in the

multivariate model. A forwards and backwards stepwise fashion process was used to construct a final model.

Model evaluation: A chi^2 score test was used to evaluate the proportional odds assumption and whether this was violated. Other methods used to check the assumption were the calculation of single score tests for each covariate and included the parallel lines assumption. Multi-collinearity was checked through calculation of the variance inflation factor (VIF) for each predictor. The likelihood ratio, score and Wald Tests were examined to determine the improvement of the MLR model over the intercept model.

All analysis was implemented using SPSS 22 (University Chicago, Illinois). P values <0.05 were considered significant

Ethical approval: The study received ethical approval from London City and East ethics committee [Ref: 12/LO/1776] and met all applicable institutional regulations at Leeds Teaching Hospitals NHS Trust, UK.

Results

Participant characteristics: Of 267 patients invited to participate in the study, 250 subjects were enrolled, 17 declined to participate (15 citing that they did not want to participate in this specific study and 2 citing that they did not wish to participate in studies in general). A further participant withdrew prior to analysis (n=249). Of this number, pharmacy refill data were obtained for 106 patients.

With the exception of presence of diabetes, no differences were observed in characteristics between those with pharmacy refill data and those without (Table 1) Adherence by MPR was subsequently used in further analysis.

Table 1. Participant characteristics for those with and without MPR refill data

Characteristic	MPR data available (n=106)	No MPR data available (n=143)	P value
Age (years)	29.8 (±8.2)	29.5 (±9.8)	0.8
Gender [n=male (%)]	46 (43.4%)	57 (39.9%)	0.6
Genotype [n (%)] F508/F508 F508/heterozygous Other	 72 (68.0%) 31 (29.2%) 3 (2.8%)	 81 (56.7%) 51 (35.6%) 11 (7.7%)	 0.1
Cystic fibrosis related diabetes [n=diabetic (%)	17 (16%)	11 (7.7%)	0.04
Microbiological status (n, %) Non-pseudomonas Pseudomonas Cepacia Mycobacterium abcessus	 23 (21.7%) 75 (70.8%) 5 (4.7%) 3 (2.8%)	 32 (22.4%) 88 (61.5%) 12 (8.4%) 11 (7.7%)	 0.2
Weight (Kg)	64.0(±13.6)	64.3 (±13.7)	0.9
BMI (Kg/m^2)	22.4 (±3.6)	22.6 (±4.0)	0.6
FEV_1 (%)	60.2 (±24.5)	62.4 (±25.9)	0.5
FVC (%)	78.7 (±22.1)	80.2 (±24.0)	0.6
HbA_1C (mmol/mol)	45.2 (±13.8)	44.5 (±12.1)	0.7
Intravenous antibiotic treatment days (preceding 1 year period)	29.1 (±40.0)	28.0 (±39.4)	0.8
Number medications (n)	13.8 (±4.5)	13.1 (±4.7)	0.3

Mean ±SD and 2 sample t-test for normally distributed variables: Pearson Chi^2 for categorical variables

Baseline characteristics are shown in Table 2. Participants were predominantly homozygous for the delta F508 mutation and had good nutritional status. Clinical and demographic characteristics were similar between adherence categories (MPR) (Table 2), but were significantly different for age, number medications, weight, BMI, Vitamin A, Vitamin D, Vitamin E.

Table 2. Participant characteristics according to adherence measured by MPR

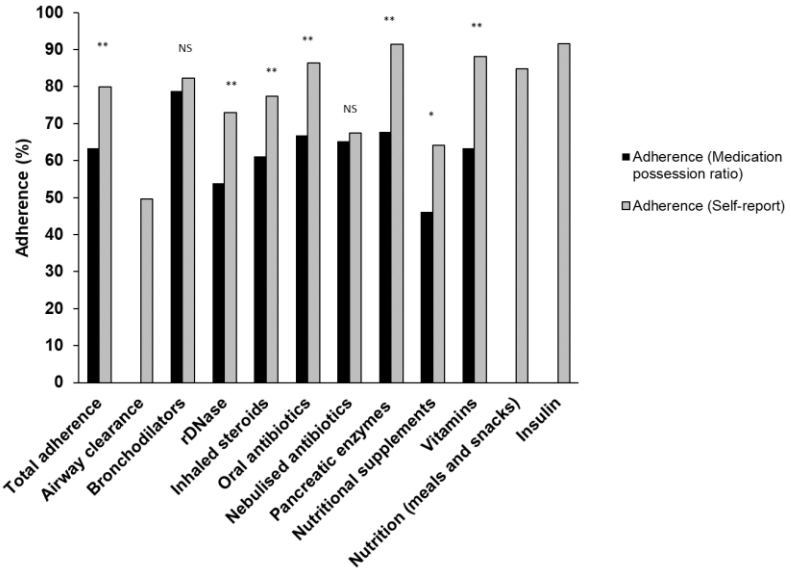
Characteristic.	Adherence	Adherence Categories			
	Mean (SD or %) Total study population	Poor adherence <50%	Moderate adherence 50 <80%	Good adherence >80%	Difference across category
					p-value
Number [n (%)]	106	34 (32.1%)	38 (35.8%)	34 (32.1%)	0.86
Age (Years)	29.8 (±8.2)	27.3(±6.8)	30.3 (±8.4)	31.8 (±8.7)	0.07
Gender [(M/F) %]	60M (56.6%)	17M/17F	23/15	20/14	0.63
Genotype [n (%)]					0.60
F508/F508	72 (67.9%)	24 (22.6%)	23 (21.7%)	25 (23.5%)	
F508/heterozygous	31 (29.2%)	9 (8.5%)	13 (12.4%)	9 (8.5%)	
Other	3 (2.8%)	1 (0.9%)	2 (1.9%)	0	
Cystic fibrosis related diabetes	17 (16%)	2 (1.9%)	10 (9.4%)	5 (4.7%)	0.06
Microbiological status					0.3
Non-pseudomonas	23 (21.7%)	7 (6.6%)	9 (8.5%)	7 (6.6%)	
Pseudomonas	75 (70.8%)	25 (23.6%)	24 (22.6%)	26 (24.5%)	
Cepacia	5 (4.7%)	0 (	4 (3.8%)	1 (0.9%)	
Mycobacterium abcessus	3 (2.8%)	2 (1.9%)	1 (0.9%)	0 (	
Medications (n)	13.8 (±4.5)	11.8 (±4.1)	14.7 (±4.4)	14.7 (±4.4)	0.005
Intravenous antibiotic treatment days (preceding 1 year period))	29.0 (±40.1)	22.4 (±25.9)	35.0 (±51.4)	28.7 (±37.0)	0.44
Weight (Kg)	64.6 (±13.6)	59.3 (±11.8)	66.5 (±13.2)	67.5 (±14.7)	0.02
BMI (Kg/m^2)	22.4 (±3.6)	20.8 (±2.8)	22.9 (±3.1)	23.4 (±4.3)	0.005
FEV_1 (%)	60.1 (±24.6)	62.7 (±24.2)	58.0 (±25.8)	60.3 (±24.0)	0.71
FVC (%)	78.6 (±22.2)	79.3 (±23.1)	75.8 (±21.9)	81.5 (±21.7)	0.55
HbA_1C (mmol/mol)	45.2 (±13.8)	41.7 (±10.7)	49.1 (±18.3)	44.3 (±8.9)	0.07
Vitamin A (µmol/l)	1.7 (±0.8)	1.4 (±0.60)	1.9 (±1.0)	1.8 (±0.53)	0.02
Vitamin D (mmol/l)	66.6 (±26.0)	51.8 (±23.3)	72.9 (±26.3)	74.0 (±22.7)	0.001
Vitamin E (mg/l)	28.2(±10.7)	22.4 (±10.1)	29.9 (±9.6)	31.7 (±10.6)	<0.001

* Mean ±SD and ANOVA for normally distributed variables: Pearson Chi^2 for categorical variables

Adherence measures: Pharmacy refill collection was retrieved for 106 of the 249 participants and 249 completed the DMI-CF self-report adherence questionnaire. Comparison of the two adherence measures revealed significant differences for rDNase, inhaled steroids, oral antibiotics, pancreatic enzyme supplementation, nutritional supplements and vitamins. MPR reported adherence was consistently below that of self-reported adherence for all medications and treatments (Fig.1). For three aspects of adherence an accurate MPR could not be

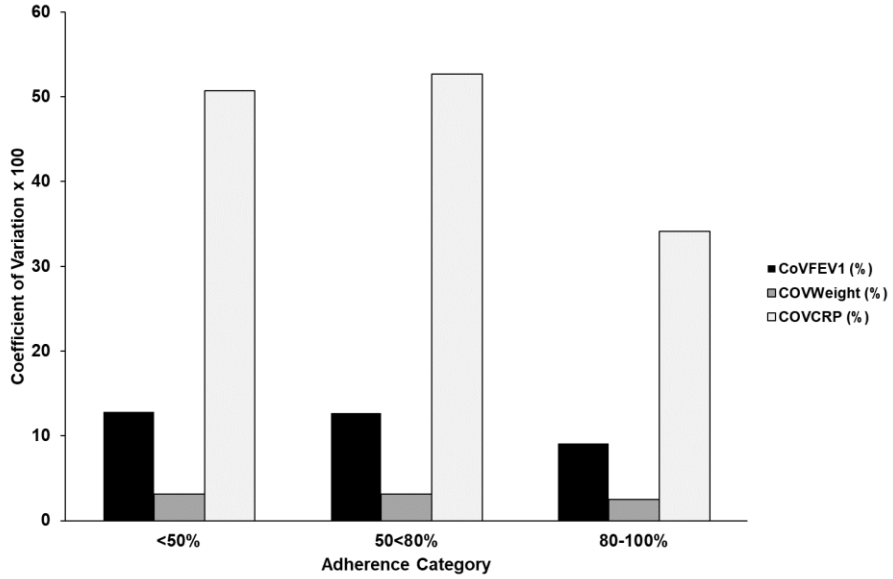
calculated, either due to lack of verifiable data (nutrition and airway clearance) or highly variable dosage (insulin). The composite score for adherence (MPR) was 63.4% (±25.3) and for self-report 79.9% (±19.7) respectively (Fig. 1), with only 32.1% of subjects lying within the highest category adherence (Table 2). For 3 patients a score of zero was recorded for MPR. For one patient this a comparable score of 3% was obtained for self-report. The remaining 2 patients had no further adjustment to MPR, after checking for in-patient admission and prescriptions issued at end of in-patient stay.

FIGURE 1 Adherence measured by medication possession ratio (MPR) and self-report. Composite self-reported adherence calculated only from medications and treatments with a corresponding MPR value



Variation measures : Mean coefficient of variation for FEV_1 ,calculated from the preceding 6 month period, was 11.4% (±7.4%) and CoV weight and CRP were 2.1 % (±1.4%) and 35.8% (±41.0%) respectively. These patients had on average 4.67% higher CoV FEV_1 and 7.3% higher CoV CRP compared to those with good adherence. CoV for weight remained stable across MPR adherence categories. (Fig. 2).Values were similar using CoV FEV_1 (12 month preceding period), [CoV FEV1 11.4% (±7.2%), CoV weight 2.9 % (±2.1%), and CoV CRP 46.7% (±46.4%)]. In total, 38/106 (35.8% participants with MPR data) had stable CRP of < 10mg/L throughout the period of the study and zero fluctuation.

FIGURE 2 Relationship between coefficient variation measures and adherence, measured by medication possession ratio. CoV: coefficient of variation; FEV1: forced expiratory volume in 1 s; CRP: C-reactive protein.



Univariate and multivariate analysis: In an unadjusted ordinal model, predictors of adherence (MPR) were age, number of medications prescribed, body mass index, CoV FEV_1 (6 months preceding), Vitamin D and E (Table 3). Following a stepwise regression, CoV FEV_1, number of medications, and BMI remained significant (Fig 3). The odds of being in a higher adherence category increased with every unit of BMI, each 1% reduction in CoV FEV_1, and each additional medication [Fig. 3]. This was replicated using CoV FEV_1 (12 months preceding).

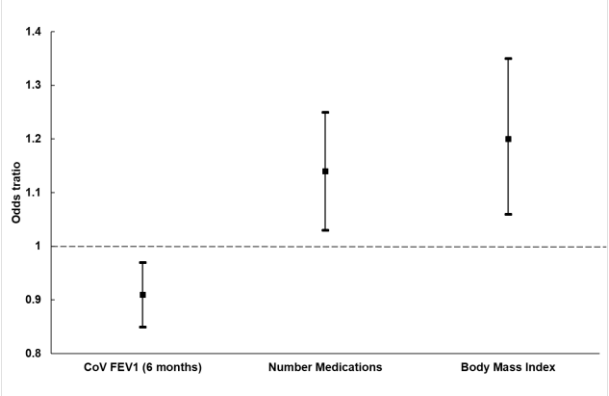
Table 3. Univariate analysis of predictors of adherence measured by MPR

	Adherence (MPR)	
Characteristic	**p-value**	**Odds ratio [CI]**
Age (years)	0.03	1.05 [1.01-1.11]
Gender	0.46	1.31 [0.64-2.65]
Genotype		
Delta F508 homozygous	0.55	1.93 [0.22-16.81]
Delta F508 heterozygous	0.58	1.87 [0.20-17.87]
Other	.	(Reference)
Number medications (n)	0.008	1.12 [1.03-1.22]
Intravenous antibiotics in preceding year (no. days)	0.61	1.00 [0.99-1.01]
Body mass index (kg/m^2)	0.004	1.18 [1.05-1.32]
Baseline FEV_1 (%)	0.68	1.0 [0.98-1.01]
$HbA1_C$	0.55	1.01 [0.98-1.03]
6 month preceding		
CoV FEV_1	0.005	0.92 [0.87-0.98]
CoV Weight	0.60	0.94 [0.73-1.20]
CoV CRP	0.80	1.00 [0.99-1.01]
12 month preceding		
CoV FEV_1	0.02	0.94 [0.89-0.99]
CoV Weight	0.29	0.92 [0.79-1.07]
CoV CRP	0.14	1.00 [0.99-1.00]
Vitamin A	0.09	1.57 [0.93-2.65]
Vitamin D	0.001	1.02 [1.01-1.04]
Vitamin E	<0.001	1.07 [1.03-1.11]
FEV_1 decline (%)	0.91	1.00 [0.98-1.03]
Diagnosis of CFRD	0.40	0.65 [0.25-1.70]
		(Reference)
Microbiological status		
Non pseudomonas	0.22	4.9 [0.38-62.5]
Pseudomonas	0.20	5.1 [0.43-59.7]
Cepacia	0.19	6.9 [0.37-129.5]
Mycobacterium abcessus		(Reference)

*Test of parallel lines non-significant for all variables (MPR)

FIGURE 3 Final models of inverse and positive predictors of adherence by medication possession ratio (MPR) using the coefficient of variation of the forced expiratory volume in 1 s (CoV FEV1). a) Final model using data from preceding 6 months. Score test for the proportional odds assumption: Chi-squared=13.6, p=0.06. Goodness of fit test of overall model (likelihood ratio): Chi-squared(7)=28.6, p<0.0001. Pseudo R2 (Nagelkerke) =27.4. b) Final model using data from preceding 12 months. Score test for the proportional odds assumption: Chi-squared=10.2, p=0.18. Goodness of fit test of overall model (likelihood ratio): Chi-squared(7)=25.1, p<0.0001. Pseudo R2 (Nagelkerke)=27.1. Both models were adjusted for the presence of cystic fibrosis-related diabetes and microbiological status.

a)



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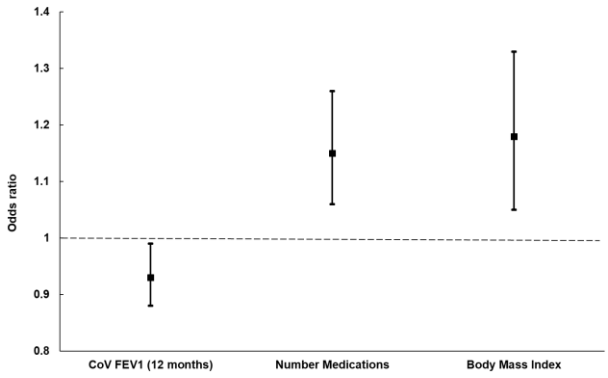

Discussion

This is the first study to demonstrate a significant inverse relationship between coefficient of variation FEV_1 (CoV FEV_1) and adherence to treatment in adults with cystic fibrosis. This was true of values based on lung function measures taken up to 6 months and 12 months preceding baseline. Similar inverse relationships in physiological parameters have recently been reported in other chronic diseases. For example the coefficient of variation of blood pressure, renal function and peak flow increased with reduced adherence to antihypertensive, immunosuppressant and asthma therapy respectively.[13-16, 21] These observations suggest that variability in physiological parameters may be an important marker of adherence to treatment in chronic disease more generally.

The underlying mechanism for the predictive value of CoV FEV_1 was not addressed in the current study but may reflect poor disease control, reduced adherence to physiotherapy and nebulised therapy. Delays in patients seeking medical intervention at times of exacerbation may also be

important, as it is not infrequent for patients with poor adherence to dramatically improve their lung function during hospital admission, resulting in larger variation in lung function than is seen in those who enter treatment at an earlier stage.

It can be argued that in patients with asthma, where lung function is routinely used as an objective measure of airways obstruction, the disease is also characterised by a high degree of variability demonstrated by peak flow (PF) and FEV_1 falling abruptly on treatment withdrawal. In contrast, CF is associated with endobronchial infection, mucus retention and to a lesser extent airway hypersensitivity. The withdrawal of inhaled corticosteroids in patients with CF without asthma appears to have no impact on change in lung function, antibiotic usage and rescue bronchodilator. [22] It suggests that the variation in lung function in this study is not explained by the diurnal variation or hyper responsiveness reported in asthma.

Weight loss may occur as a result of reduced adherence to pancreatic and oral supplements and increased energy expenditure during episodes of pulmonary infection. Surprisingly, the coefficient variation of weight was consistent in all groups, with high levels of reported adherence to nutritional recommendations and pancreatic enzyme replacement therapy in patients with a stable BMI in mid-normal range (22.5-22.8kg/m^2). These findings, and the inclusion of BMI as a positive predictor of adherence in the final model, may reflect better patient engagement with nutritional recommendations. Similarly the inflammatory marker, CRP was not a predictor of adherence, and may in part have been due to normal CRPs in many of the patients and routine early antibiotic intervention prior to elevation in CRP.

Age was a significant positive predictor of MPR adherence in the univariate but not final model. It confirms the complexity of adherence measurement and the difficulties in defining a single marker alone. While reduced adherence is well documented during the transition from childhood into adolescence and young adulthood,[5,9,23] the impact of age as adulthood progresses is less clear. Quittner et al examined medication possession ratio in 3,827 patients and showed a decline in adherence that stabilised in the fourth decade of life; a trend replicated by others.[9] Conversely studies of smaller sample sizes have indicated a positive impact of age [24] whilst acknowledging the wide variation between individuals. Our own results indicate that adherence improves with age and suggests that interventions to improve adherence should be targeted towards those in early adulthood.

A significant predictor of adherence in the overall models were number of medications prescribed. This relationship was replicated when adherence was measured according to self-report [Supplementary Table 1]. As adherence category improved, patient medications rose from 10 to 14 medications daily. This positive association contrasts with previous reports that

associate treatment burden with barriers to adherence,[25,26] but agrees with findings by Quittner et al who reported a positive association between medication regimen complexity and adherence.[9] However their proposal that a more complex regimen may be a proxy for disease severity and a greater willingness to undertake prescribed medication, was not borne out in our own study. Whilst an upward trend in disease severity was observed, this was not significant, nor was there a difference in intravenous antibiotic treatment days different across adherence categories. Others have also shown that high treatment burden is independent of disease severity.[27] Why increased medication may be associated with improved adherence in our study is therefore unclear. We hypothesise that increase treatment burden may reflect improved clinical control especially as it is our practice to stop or change medications in partnership with patients in response to poor treatment uptake. It is not infrequent that the team stop all treatment in patents with very poor adherence in order to start again, adjusting therapy accordingly. Another possibility is that some individuals are “resilient” and have developed specific coping strategies that enable them to perform this complex regimen on a regular basis.

Adherence measured by MPR was consistently below that measured by self-report with a mean discrepancy of 14% for the composite scores. Similar trends are consistent in the literature, although there is little consensus as to how it might best be addressed in reporting data. Quittner et al. have advocated triangulation of data with at least 2 measures employed, integrated through regression analysis into a single index.[7] We chose to report adherence by MPR and self-report measures, noting that neither provide a definitive measure of adherence. The discrepancies observed agree with previous reports in adult cohorts; physiotherapy being the least frequently adhered to treatment (49%), and pancreatic enzyme replacement therapy the best (91%).[28] In general adherence to respiratory treatments was poorer than to nutritional therapies suggesting that challenges in improving treatment uptake have changed little in 20 years.

Adherence (MPR) was a composite measure assimilated from core medications that were present on an established questionnaire, the DMI-CF.[7] It.is probable that each medication or treatment has a different weighting of importance both within and between patients. In turn this highlights the complexity of developing a valid adherence index measure for wider use. It is also likely that the composite measure used within this study might be reduced to contain fewer medications, although consensus is lacking as to what this might be.

The study has several limitations inherent to all studies examining adherence through cross-sectional design and reliant on current methods of adherence measure. Firstly, adherence is known to be a fluid measure, changing over time and by treatment component.[29,30]

Measurement is complex and although MPR is considered a more accurate measure of adherence than self-report, it has inherent limitations associated with changes in prescription and medication carryover. The former was partially accounted for within the study by accurate prescription data documented within the EHR system against which prescription collection could be aligned. For treatments such as pancreatic enzyme replacement therapy where patients self-titrate against differing snack and meal content, this is less useful and whilst average daily intake of PERT was obtained and documented, error is likely. MEMS data, considered the 'gold standard' can provide greater accuracy,[31] but has inherent costs and its own bias if doses are removed but not consumed. It has led to a recognition that measurement technique and that studies should incorporate more than one measure.[7] Our own results demonstrate concordance between both measures of adherence and enabled patterns of objective measures of adherence to emerge that can inform future adherence interventions and predictive variables that can be further explored to aid evaluation.

The measure of lung function itself is also prone to error. We sought to minimise this through a standardised approach to measurement of pulmonary function within the clinic setting, where trained physiotherapists undertook all measures in line with current guidance.[20] In healthier subjects FEV_1 is also known to lack sensitivity in detecting early change, when in fact lung damage is present.[32] The threshold for variation to occur may therefore be different in early compared to moderate and late disease despite similar levels of poor adherence and this requires further study. In future research the more sensitive lung function clearance index may add further value and accuracy in determining smaller changes in lung function measurement.[33]

The study also has a number of strengths. Electronic clinical records that contain data captured in 'real time' enabled accurate extraction of all FEV_1 data points for calculation of CoV FEV_1. [17] As a measure CoV FEV_1 provides an average of lung function dispersion values over time, making use of longitudinal data that can be incorporated into a single index. This is considered important in future studies, in a move away from 'snapshot' values that may contribute to bias. Importantly the final model was robust meeting the validity criteria for ordinal regression and achieving a model of good fit.

Conclusion: Coefficient of variation FEV_1 is a significant predictor of adherence. This novel marker of adherence requires further evaluation across treatment regimens and duration of treatment.

Contributors: HW was involved in the conception, design, data analysis, interpretation, drafting/critical revision of the work and final approval.

NS, SD, KP, SW were involved in data acquisition, critical revision and final approval.

DP was involved in the conception, design, data interpretation, critical revision and final approval

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Supplementary Table 1 Univariate predictors of self-reported adherence

Adherence (self-report)		
Characteristic	**p-value**	**Odds ratio [CI]**
Age (years)	0.002	1.05 [1.02-1.08]
Gender	0.88	1.04 [0.63-1.72] Reference = female
Genotype **Delta F508 homozygous** **Delta F508 heterozygous** **Other**	 0.43 0.30 	 1.53 [0.53-4.37] 1.78 [0.60-5.31] (reference)
Number medications (n)	<0.001	1.15 [1.09-1.23]
Intravenous antibiotics in preceding year (no. days)	0.61	1.00 [1.0-1.01]
Body mass index (kg/m^2)	0.58	1.02 [0.95-1.09]
Baseline FEV$_1$ (%)	0.82	1.00 [0.99-1.01]
HbA1$_C$	0.01	1.03 [1.01-1.05]
6 month preceding		
CoV FEV$_1$	0.09	0.95 [0.89-1.00]
CoV Weight	0.10	0.79 [0.61-1.04]
CoV CRP	0.90	1.00 [0.99-1.00]
12 month preceding		
CoV FEV$_1$	0.03	0.96 [0.93-0.99]
CoV Weight	0.44	0.96 [0.85-1.07]
CoV CRP	0.33	1.00 [1.00-1.01]
Vitamin A	0.16	1.30 [0.90-1.88
Vitamin D	<0.001	1.03 [1.02-1.04]
Vitamin E	0.03	1.03 [1.00-1.05]
FEV$_1$ decline (%)	0.91	1.00 [0.98-1.01]
Diagnosis of CFRD	0.76	0.89 [0.40-1.96] (Reference)
Microbiological status **Non pseudomonas** **Pseudomonas** **Cepacia** **Mycobacterium abcessus**	 0.72 0.97 0.60 	 1.2 [0.39 -3.97] 1.02 [0.35-3.00] 1.47 [0.35-6.20] (Reference)