Real-world effectiveness of airway clearance techniques in children with cystic fibrosis

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Airway clearance techniques are beneficial when performed as recommended, but most people spend time and energy using methods that do not improve lung function. Work is needed to increase the proportion of people doing effective airway clearance at home. https://bit.ly/43yDVMV

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Abstract

Background Cystic fibrosis (CF) is commonly characterised by thick respiratory mucus. From diagnosis, people with CF are prescribed daily physiotherapy, including airway clearance techniques (ACTs). ACTs consume a large proportion of treatment time, yet the efficacy and effectiveness of ACTs are poorly understood. This study aimed to evaluate associations between the quality and quantity of ACTs and lung function in children and young people with CF.

Methods Project Fizzyo, a longitudinal observational cohort study in the UK, used remote monitoring with electronic pressure sensors attached to four different commercial ACT devices to record real-time, breath-by-breath pressure data during usual ACTs undertaken at home over 16 months in 145 children. ACTs were categorised either as conformant or not with current ACT recommendations based on breath pressure and length measurements, or as missed treatments if not recorded. Daily, weekly and monthly associations between ACT category and lung function were investigated using linear mixed effects regression models adjusting for clinical confounders.

Results After exclusions, 45 224 ACT treatments (135 individuals) and 21 069 days without treatments (141 individuals) were analysed. The mean±SD age of participants was 10.2±2.9 years. Conformant ACTs (21%) had significantly higher forced expiratory volume in 1 s (FEV_1) (mean effect size 0.23 (95% CI 0.19–0.27) FEV_1 % pred per treatment) than non-conformant (79%) or missed treatments. There was no benefit from non-conformant or missed treatments and no significant difference in FEV_1 between them (mean effect size 0.02 (95% CI −0.01–0.05) FEV_1 % pred per treatment).

Conclusions ACTs are beneficial when performed as recommended, but most people use techniques that do not improve lung function. Work is needed to monitor and improve ACT quality and to increase the proportion of people doing effective airway clearance at home.

Introduction

Cystic fibrosis (CF) is an inherited condition most commonly characterised by thick respiratory mucus [1]. To improve mucus clearance, children and young people with CF (CYPwCF) are taught airway clearance techniques (ACTs) from an early age, which are believed to help reduce infection and improve lung function [2]. However, clear evidence for the clinical benefits of ACT treatments has been difficult to demonstrate [3–9]. Inability to conceal allocation of treatments from participants during randomisation and

personal preference for different types of ACTs have been important confounders limiting clinical trials [10]. There have also been challenges with measuring the frequency of ACT treatments undertaken at home, and importantly, the quality of these treatments.

ACTs are one of the most burdensome therapies in CF [11]. Desire to replace ACTs with exercise was evidenced in the original James Lind Alliance research questions for CF [12]. Moreover, as CYPwCF become healthier with the introduction of CF transmembrane conductance regulator (CFTR) modulator therapies, the CF community has placed more emphasis on reducing treatment burden, with clinical trials underway investigating the effects of discontinuing nebulised therapies [13, 14]. This further raises the question of whether ACTs can be safely stopped entirely and for whom [15]. To inform these therapeutic decisions, the clinical benefit of the quantity and/or quality of ACTs needs to be established.

Project Fizzyo, a longitudinal observational cohort study in the UK, used remote monitoring with electronic pressure sensors attached to four different commercially available ACT devices to record real-time, breath-by-breath pressure data during usual treatments undertaken at home over 16 months [16]. An analysis of baseline data in the first 2 months of the study, comprising 742 084 breaths from 9081 ACT treatments, demonstrated that the number of treatments undertaken and the number of treatments that met recommendations varied within and between CYPwCF over time [17].

The primary aim of this study was to present an analysis of the full 16-month Project Fizzyo dataset to evaluate associations between characteristics of ACT quality and quantity and lung function. In the first instance, quality and quantity were defined using current ACT recommendations for breath pressure and length, which have been determined as best practice from physiological principles and expert opinion. Second, we used a data-driven approach to identify whether any other specific combinations of breath pressure and length were associated with improved lung function.

Methods

Setting and participants

The protocol for Project Fizzyo has been published [16]. In summary, 145 eligible children with a confirmed diagnosis of CF aged 6–16 years were recruited between 2018 and 2019 from three London paediatric CF centres (Great Ormond Street Hospital, Royal London Hospital and Royal Brompton Hospital) and followed for 16 months. Ethical approval was granted by London – Brighton and Sussex Research Ethics Committee (18/LO/1038).

Sample size was not estimated for this study as there were no prior data available for the proportion of people who undertook ACTs as recommended or treatment effects that would be expected.

Exposure: ACT

A bespoke Fizzyo sensor captured real-time breath pressure data from habitual ACT treatments in children using four different commercially available ACT devices in common use (supplementary figure S1; also see figure 3 in Raywood *et al*. [16]). The devices incorporated positive expiratory pressure (PEP) (Astra PEP and Pari PEP) and oscillating PEP (OPEP) (Acapella and Aerobika) mechanisms [16, 17]. Data were synced to a secure Azure cloud for access by the research team. Raw data were pre-processed through the removal of blank, duplicate and non-physiological values, and non-linear baseline drift was corrected [17]; ACT data synced outside the study window or on the day of study recruitment were excluded.

Pre-processed ACT data were summarised into treatments, detailing the number of breaths, mean mid-expiratory breath pressure (cmH_2O) (termed "pressure" throughout) and mean breath length (s) (termed "length" throughout). Breath length is related to lung size during growth and development, so it was further standardised against an age-specific threshold [17]. Per treatment, the difference in mean expired breath length from the individualised threshold was calculated as a percentage. A tolerance window allowing all expired breaths "a bit shorter than normal" (−10%) up until "longer than normal but not maximal" (+40%) was considered to comply with ACT advice normally given in clinic.

Each ACT treatment was categorised as "conformant" or "non-conformant". Conformant treatments were in accordance with accepted ACT recommendations, defined as: pressure between 5 and 25 cmH_2O and length between −10% and +40% of age-specific breath length threshold (*i.e.* sustained breath duration but not maximal) [4, 18]. Non-conformant treatments were defined as: pressure outside 5–25 cmH_2O or length outside −10% and +40% of age-specific breath length threshold.

A day was assumed to have no treatment if no ACT data existed but it had been prescribed (*i.e.* missing data were inferred as no treatments rather than excluded). For CYPwCF who did not complete an end of study visit but who did not formally terminate the study early, the study end date was considered as 30 days after the last synced treatment to avoid overestimating the number of no treatment days.

The data were also summarised weekly and monthly; for every week/month in the study the number of total treatments, conformant and non-conformant treatments, and no treatment days were tallied. A cap of 18 treatments per week and 70 treatments per month was incorporated, as numbers higher than this likely resulted from errors with syncing.

Outcome: lung function

Forced expiratory volume in 1 s (FEV_1) was the primary outcome. FEV_1 data were measured at recruitment and all available FEV_1 measures across all clinical records were also extracted from electronic health records originating from 1) the lung function laboratory at each participating hospital, where FEV_1 was measured during routine clinical encounters (typically quarterly) as well as hospitalisations, and 2) participant data from the UK CF Registry at each hospital. The two clinical data sources were merged, duplicates were removed and FEV_1 was converted to percentage predicted using the Global Lung Function Initiative (GLI) reference equations [19] (R package rspiro [20]).

To align the daily/weekly/monthly ACT data to the approximately quarterly FEV_1 data, flexible polynomials were fitted to all observed FEV_1 data for a participant and extrapolated as daily/weekly/monthly (see supplementary material for details) [21]. Clinical data associated with the end of each timescale were extrapolated as the value for that week/month.

Confounders

Demographics data (age, sex and ethnicity for GLI calculations) and CF genotype (number of F508del copies) were collected at recruitment. Potential clinical confounders were identified from clinical records (including *via* the UK CF Registry). Intravenous antibiotic therapy was described daily as a continuous measure indicating the number of intravenous antibiotic courses (both at home and in hospital) in the previous 12 months. CFTR modulator therapy was recorded as binary, indicating whether or not the individual was prescribed any modulator therapy.

Statistical methods

To evaluate the association between treatment type (categorical variable: conformant ACT, non-conformant ACT or no treatment day) and daily (extrapolated) FEV_1, a linear mixed effect regression (LMER) model was used (R package lme4 [22]). The model included a random slope and intercept for each individual to account for repeated measures. Age, disease severity (baseline FEV_1), number of intravenous antibiotic courses in the previous 12 months, CFTR modulator therapy and hospital centre were included as fixed effects. Since many participants were prescribed two treatments per day, a sensitivity analysis was carried out using one randomly selected treatment per day.

Further analyses investigated the association between quantity of each treatment type and FEV_1, based on the number of weekly or monthly 1) ACT treatments, 2) conformant ACT treatments, 3) non-conformant ACT treatments and 4) no treatment days.

An exploratory analysis was conducted using the same LMER models to determine if any ACT breath pressure–length treatment patterns, other than those normally recommended, were associated with improvements in FEV_1. We iteratively compared the weekly effect on FEV_1 of all possible combinations of pressure and % breath length difference against no treatment.

Results

Participant data

There were 145 CYPwCF recruited to the study aged 6.0–16.7 years (mean 10.2 years), with comparable numbers of males and females. After exclusions, 141 participants contributed data (figure 1). At baseline, mean FEV_1 was 88.2% predicted (supplementary table S1: all baseline characteristics). There were eight (5.5%) CYPwCF who were already prescribed CFTR modulators at enrolment and an additional 24 started on modulators when they became available in the UK towards the end of the study. The median (range) follow-up time was 480 (30–550) days. All available data from the 141 participants were used in the analyses regardless of length of time in the study (figure 2). Those who completed the study were, on average, younger with a higher FEV_1 than those who terminated the study early (supplementary table S2).

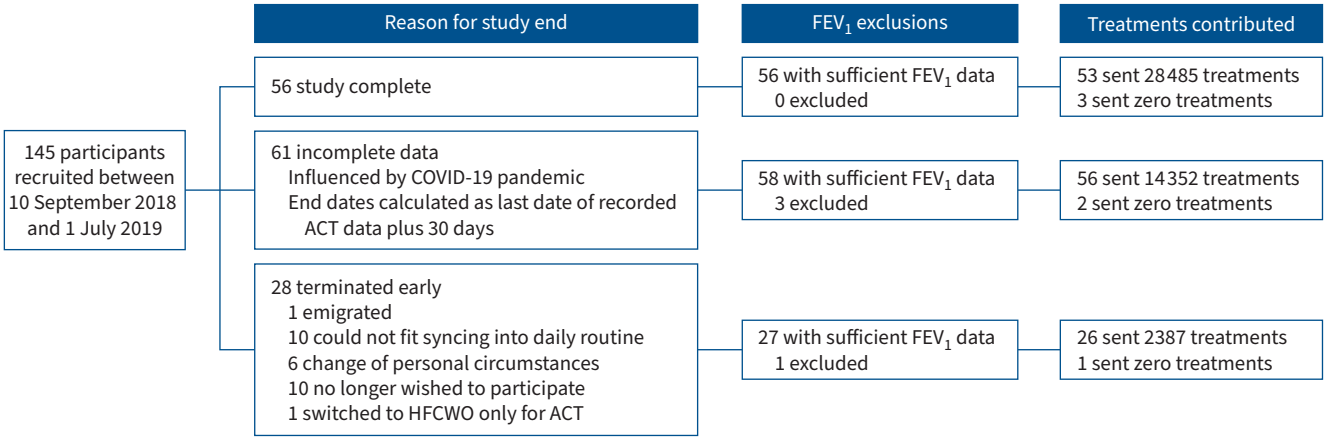

FIGURE 1 Flow of participants and data through the study. Participant stratification for reasons relating to end of study. FEV_1: forced expiratory volume in 1 s; COVID-19: coronavirus disease 2019; ACT: airway clearance technique; HFCWO: high-frequency chest wall oscillation.

ACT treatment data

After exclusions, 45 224 treatments comprising 4 065 498 breaths from 135 individuals were analysed (figure 1 and table 1; see supplementary figure S3 for data exclusions). Quantity and patterns of treatments varied considerably across participants (figure 2), but were generally habitual and consistent within an individual. There was a median (range) of 224 (0–1027) treatments per person; six individuals did not record any treatments.

Of 48 151 total study days captured, there were 21 069 days with no treatments from 141 individuals. The range per person of no treatment days was large (2–463 days), indicating that some individuals rarely missed a treatment while others rarely did any ACTs using their Fizzyo sensor-compatible devices (table 1 and figure 2).

Of the total 45 224 treatments, 9359 (20.7%) were conformant with the prescribed guidelines for treatment quality (table 1). Device type influenced treatment profile; within devices there was a higher percentage of conformant treatments with PEP devices (24.0%) than within OPEP devices (9.2%) (figure 3). However, within both device types most treatments were non-conformant (OPEP 55.5% *versus* PEP 50.2%) or were missed treatment days (OPEP 35.3% *versus* PEP 25.8%).

ACT treatment quality

FEV_1 (extrapolated daily) was highest for treatments that were conformant with recommended ACT techniques in both unadjusted and adjusted models (0.23 (95% CI 0.19–0.27) FEV_1 % pred per treatment) (supplementary table S3). There was no significant difference in FEV_1 (extrapolated daily) between non-conformant treatments and missed treatment days (0.02 (95% CI −0.01–0.05) FEV_1 % pred per treatment). Similar results were observed in the sensitivity analyses of single treatments per day (supplementary table S3).

ACT treatment quality and quantity

Higher numbers of conformant ACTs were significantly associated with improved FEV_1 (figure 4a and b, and supplementary table S4). A weekly adjusted linear effect of 0.056 FEV_1 % pred was observed, such that every additional conformant ACT completed in a week was associated with an improvement of 0.056 FEV_1 % pred. Importantly, a minimum of five conformant treatments per week and similarly 20 conformant treatments per month were associated with an effect size greater than the effect of non-conformant ACTs.

Conversely, there was no association between the total number of ACT treatments completed in a week or a month on FEV_1, either unadjusted or adjusted (figure 4a and b, and supplementary table S4). Higher numbers of missed treatment days were associated with significantly lower FEV_1 than lower numbers of missed treatment days (figure 4c and d, and supplementary table S4). Similarly, on a weekly level, higher numbers of non-conformant ACTs were associated with significantly lower FEV_1 than lower numbers of

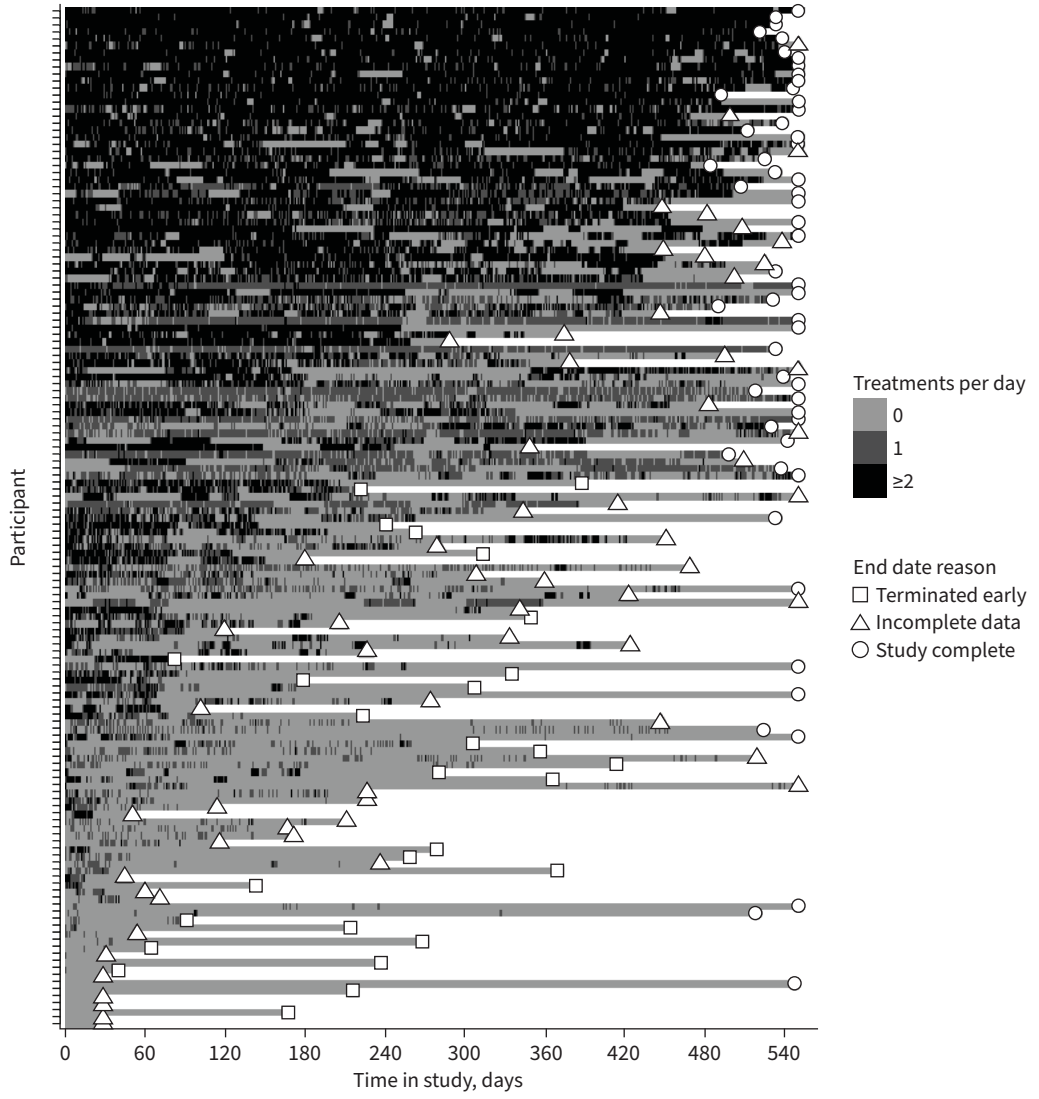

FIGURE 2 Quantity of airway clearance technique (ACT) treatments across the study for each participant. Participants (*y*-axis) are arranged in ascending order of number of ACT treatments completed in the whole study. Reasons relating to end of study indicated as symbols at the end of each participant row.

non-conformant ACTs, although no association was observed at the monthly level (figure 4a and b, and supplementary table S4).

Alternative breath patterns

A data-driven approach was carried out to identify if any alternative ACT breath patterns (combinations of pressure and % breath length difference), to those normally recommended, might also provide clinical benefit (figure 5a). The weekly LMER effect size of 0.056 FEV_1 % pred observed with conformant ACTs was used as a minimum benchmark to identify potentially useful alternative ACT patterns.

In addition to current clinical ACT recommendations (low pressure and medium breath length; n=9359), weeks with ACT breath patterns comprising 1) high pressure (around 40–65 cmH_2O) and short length (around −50– −25%) (n=1126) or 2) low pressure (around 10–15 cmH_2O) and long length (around 70–85%) (n=606) were also positively associated with higher FEV_1 (figure 5a). The high-pressure, short-length technique was almost solely carried out by young children (mean age 9.5 years) using OPEP devices and the low-pressure, long-length technique was almost solely carried out by older children (mean age 11.3 years) using PEP devices (figure 5b). The weekly effect size of the three profiles combined (n=11 085 (32% of treatments)) was enhanced to 0.060 FEV_1 % pred. However, most treatments (68%)

TABLE 1 Description of treatment parameters and clinical characteristics for different types of airway clearance technique (ACT) data

	ACT treatments			No ACT treatment days
	All treatments	Conformant treatments	Non-conformant treatments	
Treatment parameters				
Participants, n	135	110	135	141
Treatment count				
n (%)	45 224 (100)	9359 (20.7)	35 865 (79.3)	21 069
n per person	224 (0–1027)	10 (0–632)	178 (0–988)	129 (2–463)
Breath count, n	4 065 498	883 583	3 181 915	
Pressure, cmH_2O	20.4±11.0	14.5±4.4	22.0±11.6	
Length, s	1.7±0.9	2.1±0.3	1.6±1.0	
Breath length threshold for age per person, s	1.9±0.1	1.9±0.2	1.9±0.1	
Breath length difference, %	−11.2±45.9	11.3±14.3	−17±49.3	
Clinical				
Measured FEV_1				
Days, n	622	137	485	494
% pred	84.2±16.0	86.8±15.7	84.8±16.1	82.9±15.8
Extrapolated FEV_1				
Days, n	27 082	5364	21 718	21 069
% pred	89.1±13.2	90.8±13.6	88.7±13.1	86.7±14.0
Intravenous antibiotic courses in prior 12 months, n	1.0±1.5	0.8±1.2	1.0±1.5	1.2±1.5
Days on CFTR modulators, n (%)	3088 (11)	729 (14)	2359 (11)	2250 (11)
Treatment count, n per centre (%)				
Centre A	22 659 (50)	3432 (37)	19 227 (54)	11 523 (55)
Centre B	10 575 (23)	2378 (25)	8197 (23)	5499 (26)
Centre C	11 990 (27)	3549 (38)	8441 (24)	4047 (19)
Weekly dataset (n=6900 weeks)				
Treatment count, n per person per week	6 (0–18)	0 (0–16)	4 (0–18)	2 (0–7)
Monthly dataset (n=1674 months)				
Treatment count, n per person per month	25 (0–67)	0 (0–60)	18 (0–65)	10 (0–30)

Continuous variables are reported as mean±SD; variables describing n per person are reported as median (range). FEV_1: forced expiratory volume in 1 s; CFTR: cystic fibrosis transmembrane conductance regulator.

were carried out using combined parameters of breath pressure and length that were not associated with improved FEV_1 (figure 5a).

Discussion

Results suggest that commonly prescribed breath pressure and length recommendations for ACTs using PEP/OPEP devices are justified, and in this study were associated with improved FEV_1 compared with non-conformant treatments and no treatment days. In addition, evidence of cumulative benefit or harm on FEV_1 was observed; more conformant treatments per week or month resulted in better FEV_1, while more non-conformant or missed treatments resulted in lower FEV_1. These are important findings as 49% of all adults and 76% of CYPwCF use PEP/OPEP devices for their airway clearance treatments [23]. However, there was wide variability in ACT breath pressure–length treatment profiles between individuals and the majority of participants were not performing ACTs in a way that conferred benefit.

Remote monitoring using a sensor was low burden for participants and provided detailed data on habitual patterns of ACTs in the home that could be evaluated against clinical outcomes. ACT devices currently provide little, if any, user feedback during ACTs. Some include a rudimentary pressure gauge but none provide feedback on breath length. Most of the CYPwCF in this study spent many hours completing their ACTs without real-time knowledge of treatment performance to inform quality and apparently deriving no clinical benefit.

Given the positive associations observed with conformant ACTs, much can now be done to support and increase the proportions of people doing regular high-quality treatments, including 1) measuring breath pressure–length treatment profiles during ACT assessments in the clinic to recognise and retrain suboptimal ACTs, 2) embedding guided breath pressure and length feedback mechanisms into ACT devices or paired

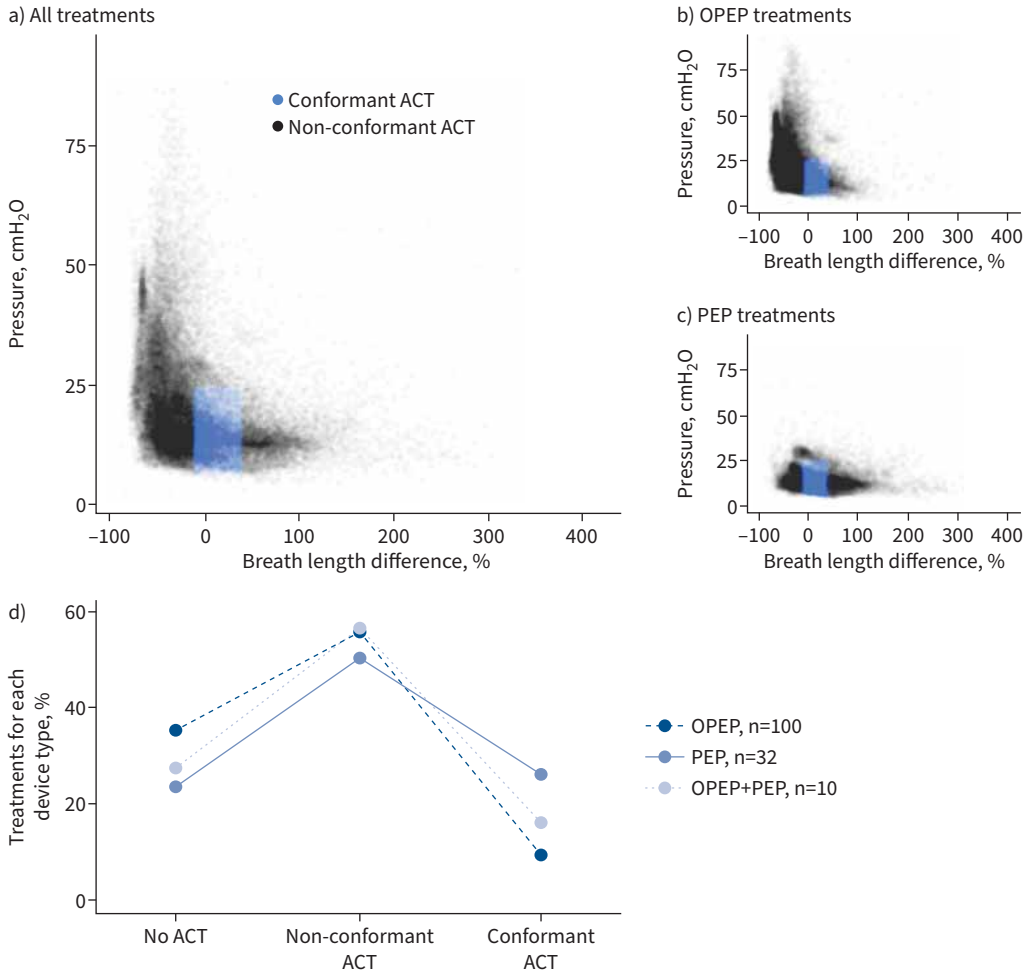

FIGURE 3 Airway clearance technique (ACT) treatment quality. a–c) Scatter plots of pressure *versus* % breath length difference for each treatment. Each point represents the mean value for one ACT treatment (around 100 breaths). Transparency indicates density of treatments. Individual panels show a) all treatments, b) only treatments using an oscillatory positive expiratory pressure (OPEP) device and c) only treatments using a positive expiratory pressure (PEP) device. d) Within each device type, the percentage of ACT treatments stratified across different types of ACT. n: number of people using each device type; OPEP+PEP: individual uses both types of devices and the specific device attached to the treatment is unknown.

apps to facilitate good quality ACTs at home, and 3) providing CYPwCF information about the magnitude of effect for high-quality ACTs to allow individuals to make informed choices about managing their condition.

Worryingly, future studies that ignore the quality of unsupervised ACTs at home, *e.g.* those investigating whether ACTs can be ceased or replaced by exercise, will potentially be vulnerable to bias since benefits may be masked when the majority of treatments are poorly executed. Measures of ACT quality should be a standard in research studies and clinical assessments moving forwards.

Furthermore, the current "one-size-fits-all" advice for different ACT device types may not be helpful. Our data demonstrated that specific devices tended to facilitate distinctive breath pressure profiles, an observation confirmed by another study using electronic sensors to record 110 supervised and unsupervised ACTs in 18 adults with CF [24]. The potential benefit of high-pressure, short-length expired breaths observed in this study is interesting. This technique resembles "high-pressure PEP therapy", a modification of the original PEP therapy developed in Austria during the 1980s involving more forceful expiration and generating pressures of 40–100 cmH_2O [8, 25]. These findings require further confirmatory research, but imply that different ACT advice may be beneficial and necessary for different devices.

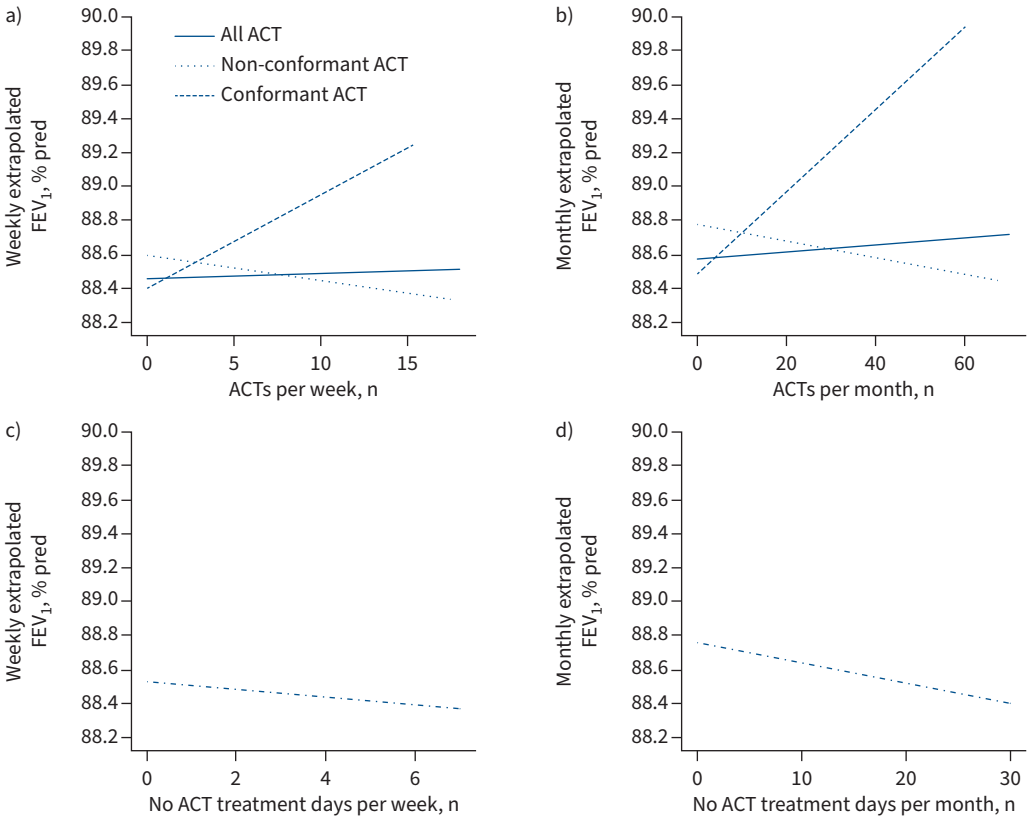

FIGURE 4 a, c) Weekly and b, d) monthly effect of the quantity and quality of airway clearance techniques (ACTs) on forced expiratory volume in 1 s (FEV_1). a, b) Number of total ACTs associated with FEV_1 and the effect of ACTs when categorised as conformant or non-conformant. c, d) Effect of total number of days without an ACT treatment on FEV_1. Each line is the result from individual linear mixed effect regression models adjusted for age, intravenous antibiotic courses in the previous 12 months, baseline FEV_1, cystic fibrosis transmembrane conductance regulator modulators and hospital centre. Estimates and confidence intervals are displayed in supplementary table S4.

The results of the study are limited by the small subgroup of individuals consistently completing high numbers of conformant ACTs. These few individuals had improved baseline clinical parameters compared with those individuals completing consistently non-conformant or no ACTs. Thus, it is not clear whether the association between ACT quality and FEV_1 is a causal relationship, reflecting habitually conformant ACTs in the years preceding this study, or if the association is related to factors not captured, *e.g.* socioeconomic status, parental involvement, *etc.* It is also possible that the subgroup of individuals who were highly adherent to ACTs were also more generally competent, diligent and adherent with other CF therapies. Positive associations between conformant ACTs and FEV_1 may have reflected, to some extent, individual mastery of other components of the complex multidimensional CF healthcare package. It would only be possible to unpick the relative benefits of individual CF therapies if adherence to and competence with all therapies were measured simultaneously in future. The study results were also limited by differences in data contribution, where those who completed the study were younger with higher baseline FEV_1 than those who terminated early. However, age and FEV_1 were accounted for in the models, reducing some of the bias introduced from these individuals.

Project Fizzyo is the largest study of this kind in the world to date; even the small subgroup of conformant ACTs (883 583 breaths, 9359 treatments) is the largest dataset ever accumulated. Although associations in observational studies do not imply causation, the significant positive and negative signals involving conformant and non-conformant ACTs, no treatments and FEV_1 were strong and persistent at the daily, weekly and monthly levels. These findings provide a clear basis for confirmation *via* a randomised controlled trial to investigate what the relative benefits of conformant ACTs might be in the era of CFTR modulators and indeed whether these treatments can ever safely be stopped.

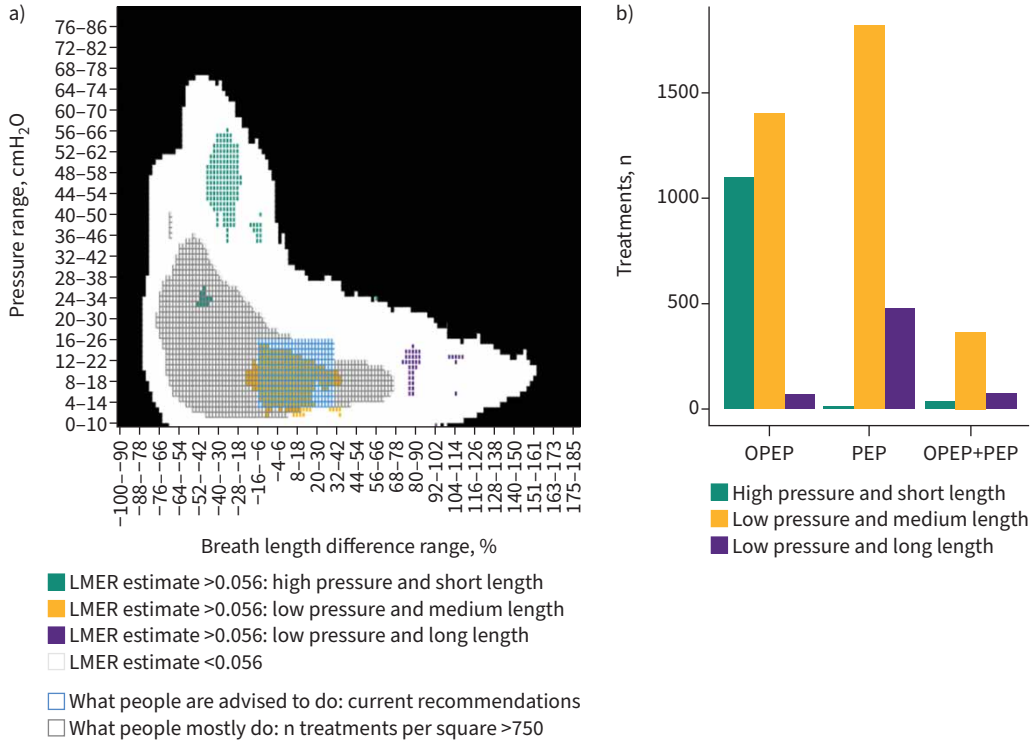

FIGURE 5 Data-driven approach to identify optimal airway clearance techniques (ACTs). a) Heatmap displaying the effect size of 10 201 weekly adjusted linear mixed effect regression (LMER) models investigating the effect on forced expiratory volume in 1 s (FEV_1) of each combination of a small range of pressure and a small range of % breath length difference compared with days with no treatments. The squares outlined in blue indicate current ACT recommendations and the squares outlined in grey indicate where the majority of treatments were completed. Black filled squares indicate that <0.1% of treatments comprised the ACT profile and thus the LMER models were unstable and excluded. White filled squares indicate ACT profiles with a weekly effect size less than the 0.056 FEV_1 % pred that was observed with conformant treatments. Squares filled with colours indicate a weekly effect size of the LMER models greater than 0.056 FEV_1 % pred. The colours green, yellow and purple were categorised from the observed clustering of pressure and % breath length difference into distinct profiles. b) Bar chart showing the number of treatments completed by each type of device across the different categorisations of ACT profiles derived from a). OPEP: oscillatory positive expiratory pressure device; PEP: positive expiratory pressure device; OPEP+PEP: individual uses both types of devices and the specific device attached to the treatment is unknown.

The real-world magnitude of effect of conformant ACTs is difficult to estimate since few people completed the conformant treatments consistently for the whole 16-month study. This is highlighted in the contrast between the weekly and monthly models. In addition, the days of no treatments were assumed from missing data; however, it is not clear what proportions were from a missed treatment compared with the missed use of the sensor. Future work should actively capture when a treatment is missed, *e.g.* by incorporating sensors that cannot be detached from the devices. Furthermore, FEV_1 was not measured daily and it is difficult to attribute improvements directly using these data alone. The scarcity of FEV_1 data was also a limitation for the alignment with ACT data; however, the flexible polynomials worked well to capture the overall daily/weekly/monthly trajectories of FEV_1 [21]. The extrapolation of a single measure artificially reduces the true biological variability of lung function measures and uncertainty in the extrapolated measure was not incorporated into the final LMER model. Future work should incorporate the use of home-based spirometers to robustly capture more frequent outcomes.

With new CFTR modulator therapies the CF community is eager to know whether regular ACT treatments should remain a core component of the management of CF. A relatively small number of participants were on CFTR modulators during the study and none were on new highly effective elexacaftor/tezacaftor/ivacaftor. In the future it will be possible to evaluate relative benefits of ACTs for CYPwCF on

elexacaftor/tezacaftor/ivacaftor using a similar research design to that employed here. Despite the availability of these new therapies, there is still a large proportion of individuals who have existing bronchiectasis lung damage or who are not eligible for, or have access to, CFTR modulators, or have drug intolerability or interactions. The estimated ACT effect sizes in this study, having accounted for other clinical confounders, suggest potential clinical importance. This does not support the notion of dropping or substituting ACTs with confidence. Future studies that investigate the impact of good quality ACT treatments in different subgroups of individuals will help to inform who will still benefit from sustained, good quality ACTs and who may benefit from stopping altogether. Furthermore, people living with other chronic respiratory disorders involving excessive mucus (*e.g.* non-CF bronchiectasis and primary ciliary dyskinesia) may benefit from these advances to better understand how and when ACTs will be useful.

Conclusions

Some, but not all ACT breathing patterns are associated with clinical benefit in CYPwCF. There is an opportunity to optimise therapy and reduce the burden for people with CF by facilitating effective ACTs.

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Data sharing agreement: The study protocol is published open access [16]. De-identified participant data are hosted in a secure DRE through GOSH DRIVE (www.goshdrive.com). Access to the data, data dictionary and informed consent forms through the DRE is available with permission from the corresponding author.

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Conflicts of interest: G. Davies reports personal UKRI fellowship, UKRI and NIHR grants, speaker honoraria from Chiesi Ltd, and speaker honoraria, consulting fees and participation on a board from Vertex Pharmaceuticals, outside the submitted work. S. Stanojevic reports consulting fees from Chiesi Ltd, speaker fees from Vyaire Medical, participation on a board for Ndd technologies, and leadership role from the European Respiratory Society and the American Thoracic Society, outside the submitted work. The remaining authors have no potential competing interests to disclose.

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