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Original Article

Factors in childhood associated with lung function decline to adolescence in cystic fibrosis

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ABSTRACT

Background: Despite improvements in general health and life expectancy in people with cystic fibrosis (CF), lung function decline continues unabated during adolescence and early adult life.
Methods: We examined factors present at age 5-years that predicted lung function decline from childhood to adolescence in a longitudinal study of Australasian children with CF followed from 1999 to 2017.
Results: Lung function trajectories were calculated for 119 children with CF from childhood (median 5.0 [25%-75%=5.0–5.1]) years) to early adolescence (median 12.5 [25%-75%=11.4–13.8] years). Lung function fell progressively, with mean (standard deviation) annual change -0.105 (0.049) for forced vital capacity (FVC) Z-score ($p<0.001$), -0.135 (0.048) for forced expiratory volume in 1-second (FEV_1) Z-score ($p<0.001$), -1.277 (0.221) for FEV_1/FVC% ($p<0.001$), and -0.136 (0.052) for forced expiratory flow between 25% and 75% of FVC Z-score ($p<0.001$). Factors present in childhood predicting lung function decline to adolescence, in multivariable analyses, were hospitalisation for respiratory exacerbations in the first 5-years of life (FEV_1/FVC $p = 0.001$, FEF_{25-75} $p = 0.01$) and bronchoalveolar lavage neutrophil elastase activity (FEV_1/FVC% $p = 0.001$, FEV_1 $p = 0.05$, FEF_{25-75} $p = 0.02$). No examined factor predicted a decline in the FVC Z-score.
Conclusions: Action in the first 5-years of life to prevent and/or treat respiratory exacerbations and counteract neutrophilic inflammation in the lower airways may reduce lung function decline in children with CF, and these should be targets of future research.

1. Introduction

Survival in cystic fibrosis (CF) has increased progressively in recent decades to the extent that in many countries there are now more adults than children with CF. In Australia in 2020, the mean age of patients with CF was 22.6-years, with 55.7% being adults (≥18-years old) [1]. However, patients with CF still die from progressive lung disease. Lung function, as represented by the forced expiratory volume in 1-second (FEV_1) percent predicted, has improved in each successive 5-year cohort across all age groups from 6 to >30-years of age from 2008 to 2020 [1]. The full impact of therapies that improve cystic fibrosis transmembrane conductance regulator (CFTR) function are not yet apparent but are not expected to reverse existing structural damage. Meanwhile, lung function

Abbreviations: ACFBAL, Australasian cystic fibrosis bronchoalveolar lavage; CF-FAB, longitudinal observational follow-up study of the ACFBAL cohort.

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continues to deteriorate. At the end of 2020, 3.7% of Australian children with CF aged 6 to 11-years had FEV_1 values <70% and would be considered to have moderate to severe lung function impairment. This increased to 8.2% at 12–17 years of age, 34.5% at 18–29 years, 49.8% at 30–39 years and 56.0% for those aged 40+ years [1]. A very similar pattern is seen in the United States [2].

If the progressive loss of lung function that begins to accelerate during late adolescence is to be prevented, a better understanding of factors associated with, or initiating, this decline is required [3]. Multiple factors have been implicated in progressive lung disease in CF including poor nutrition [3,4]; inflammation in the lower airways [3,5-7] and infection [8], including with specific organisms such as *Pseudomonas aeruginosa* [3,7], *Staphylococcus aureus* [9], *Aspergillus* [10,11], total bacterial load [12]; and acute respiratory exacerbations, especially those not treated aggressively [13]. A shift from a reactive treatment strategy to one that advocates preventing loss of lung function has been proposed [3]. Such treatment needs to commence before lung function loss becomes inevitable. Australian data show that 50–70% of children have radiographic evidence of mild bronchiectasis around the age they start school [14,15] and that the likelihood of developing persistent bronchiectasis can be predicted as early as 3-months of age [6,7]. Thus, an understanding of modifiable early life factors associated with lung function loss from childhood to adolescence would aid a preventative treatment strategy [3].

The present study is part of the CF-FAB project (ACTRN12613000778785), a follow-up of the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study (see online data supplement). ACFBAL was a randomised clinical trial conducted in Australia and New Zealand between 1999 and 2009 to determine the safety and utility of bronchoalveolar lavage (BAL)-directed treatment of an acute pulmonary exacerbation during the first 5-years of life, with the aim of reducing *P. aeruginosa* infection and preventing bronchiectasis in young children with CF (ACTRN01260500006656635) [15]. The present analyses aim to determine factors present in childhood associated with loss of lung function between 5-years of age and early adolescence in this study cohort.

2. Methods

2.1. Study population

The study population consists of children who finished the ACFBAL study and enroled in the CF-FAB study. Details of the ACFBAL study have been published previously [15,16]. CF-FAB was conducted between 2013 and 2017 involving seven sites from four Australian states (New South Wales, Queensland, South Australia, and Victoria) and one New Zealand site (Auckland). More details of CF-FAB methodology are shown in the online supplement. Ethics committees at each site approved the study and parents/guardians provided written, informed consent for their children's participation.

2.2. ACFBAL study

Variables obtained from the ACFBAL study during the first 5-years of life and explored as candidate explanatory variables in these analyses included sex, genotype, pancreatic sufficiency status, weight, height, lung function, presence of bronchiectasis as measured using the PRAGMA scoring system, respiratory exacerbations, hospitalisation for exacerbations, BAL fluid inflammatory indices (neutrophil elastase [NE] activity, interleukin [IL]−8), and bacterial cultures. These variables have been described in ACFBAL publications [11,15-17]

Data on annual best lung function and hospitalisations between the end of the ACFBAL study and CF-FAB first visit were obtained from the Australian CF data registry and the Auckland CF clinic.

2.3. CF-FAB study

At the first study visit clinical data were recorded including current symptoms, physical examination, weight, height, concomitant medications, spirometry and specimen collection. This report contains the measurement of lung function obtained at study entry.

2.4. Spirometry

Spirometry was measured at each site according to American Thoracic Society standards. Outcome variables reported included FEV_1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) reported as Z-scores, calculated using Global Lung Function Initiative Caucasian equations [18] and the ratio of FEV_1/FVC (%). Pre-bronchodilator lung function obtained at the end of the ACFBAL study was used in analyses as this provided a more complete data set.

2.5. Inflammation biomarkers

An aliquot of BAL obtained from the ACFBAL end-of-study bronchoscopy at age 5-years was used to measure NE activity and IL-8 (see online supplement for details).

2.6. Microbiology

BAL fluid was processed for culture as described previously [11,15] and in five of the eight centres this included employing Sabouraud dextrose agar with gentamicin routinely as selective media for detecting fungal species. For the present study BAL samples were categorised by the organisms grown as follows: (i) no BAL evidence of infection (bacterial growth $<10^3$ colony-forming units (CFU)/mL); (ii) recognised CF respiratory bacterial pathogens $\geq 10^3$ CFU/mL (*P. aeruginosa, S. aureus, Haemophilus influenzae*); (iii) any growth of *Aspergillus*; and (iv) other microorganisms $\geq 10^3$ CFU/mL. Individual children could be represented in more than one category. Analyses were undertaken by comparing the presence and absence of a particular organism, e.g., *Aspergillus* versus no *Aspergillus.*

2.7. Statistical analysis

Continuous variables are summarised as mean (standard deviation; SD) or median (25th−75th percentile) as appropriate. Categorical variables are summarised as frequency (percentage). Lung function trajectories were calculated using data collected from the Australian CF data registry or Auckland clinic. Spirometry results (FVC, FEV_1 and FEF_{25-75} Z-scores and FEV_1/FVC%) from the end of the ACFBAL study (childhood) to the first CF-FAB study were analysed. The annual best lung function was selected based on FEV_1. For children in the 4-to-6-year age group only the highest lung function value was analysed, due to low numbers and the physiological limitations on the interpretation of FEV_1 [19]. Lung function trajectories were calculated using a mixed-effects linear regression model with age (years) included as a fixed effect, subject included as a random intercept and age as a random slope. This model allows the change in lung function over time to be calculated for each child individually. The deviation of each individual's change in lung function from the population average change was then used as the outcome variable in subsequent analyses.

Univariable associations between individual characteristics and lung function trajectory were assessed using linear regression models. Candidate variables for the best multivariable model were defined as those univariably significant at the $p<0.20$ level. The

Table 1
Demographic and clinical characteristics of the children who participated in ACFBAL (childhood) and entered the CF-FAB study (adolescence). Lung function in childhood come from reporting the highest value for each child measured at 4,5, or 6y.

Characteristics	*Childhood* $n = 119$	Adolescence $n = 119$
Age (year): median (25%–75%)	5.0 (5.0–5.1)	12.5 (11.4–13.8)
Males: n (%)	61 (51.3)	
Height (cm): mean (SD)	108.3 (3.7)	151.4 (9.3)
Height Z-score: mean (SD)	−0.1 (0.8)	−0.3 (0.8)
Pancreatic insufficiency: n (%)	114 (95.8)	
Genotype: copies of p.Phe508del		
2 copies: n (%)	80 (67.2)	
1 copy: n (%)	36 (30.3)	
0 copies: n (%)	3 (2.5)	
Lung function: mean (SD)		
FVC Z-score	0.2 (1.1)	−0.5 (1.3)
FEV_1 Z-score	−0.1 (1.1)	−1.2 (1.4)
FEV_1/FVC%	90.8 (7.1)	79.1 (7.5)
FEF_{25-75} Z-score	−0.5 (1.0)	−1.6 (1.3)
Respiratory exacerbations prior to final ACFBAL visit: mean (SD)		
Total exacerbations	13.0 (5.1)	
Early life exacerbation (age ≤2-years)	4.3 (2.6)	
Hospital admission for respiratory exacerbation	2.6 (2.6)	
NE activity: n (%)	**BAL $n = 92$**	
Present	36 (39.1)	
IL-8 (pg/mL)	**BAL $n = 113$**	
Median (25%–75%)	2656 (566–12,830)	
Microorganisms: n (%)*	**BAL $n = 119$**	
No evidence of infection†	9 (7.6)	
Pseudomonas aeruginosa	23 (19.3)	
Haemophilus influenzae	61 (51.3)	
Staphylococcus aureus	62 (52.1)	
Aspergillus species	20 (16.8)	
Other organisms‡	67 (56.3)	

Abbreviations: ACFBAL, Australasian Cystic Fibrosis Bronchoalveolar Lavage; BAL, Bronchoalveolar Lavage; CF-FAB, Cystic Fibrosis-Follow-up of the ACFBAL study; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1-second; FVC, forced vital capacity; IL-8, interleukin-8; NE, neutrophil elastase activity; SD, standard deviation.

* Bacteria/Fungi grouped by organism (children can be in more than one category).

† No evidence of infection: in BAL samples this was $<10^3$ colony-forming units/mL, while in sputum it refers to only upper airway commensals being cultured, such as α-haemolytic streptococci, *Neisseria* species, *Haemophilus* (non-*influenzae*) species, diphtheroids and/or Coagulase-negative *Staphylococci*.

‡ *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia, Streptococcus pneumoniae, Moraxella catarrhalis, Achromobacter xylosoxidans, Enterobacter cloacae, Klebsiella pneumoniae, Candida* species and other (non-*Aspergillus*) fungi.

multi-collinearity of candidate variables was examined using pairwise correlations. When correlations were ≥0.8, individual-level variable selection was undertaken to determine which variables should be considered for models. The best multivariable model for each lung function outcome was identified using the Bayesian information criterion (BIC). The BIC identifies the model with the most explanatory power relative to its complexity [20]. In particular, the BIC prevents overfitting in multivariable regression (when compared to, for example, the r^2 statistic) by adding penalty terms for the number of predictors in the model and the sample size. The model with the smallest BIC statistic was selected as the final multivariable model following the procedure detailed in Table S1 [21]. Each lung function outcome was modelled separately. All analyses were conducted using Stata/SE version 17.0 (StataCorp LLC, College Station, TX, USA).

3. Results

Eight-hundred and sixty-four measurements of lung function were available from 119 children who participated in the ACFBAL and CF-FAB studies. In all, 157 children finished ACFBAL but 38 withdrew or did not have lung function data available. Characteristics of children who completed ACFBAL and were included in the present study were similar to those not proceeding to CF-FAB, except children continuing to CF-FAB were more likely to grow specific pathogens in their BAL cultures at age 5-years (Table S2). Table 1 shows demographic and clinical characteristics of the children in the present study. The presence of NE was identified in the BAL fluid of 40% of participants at the end of ACFBAL (Tables S2, S3). Childhood risk factors significantly associated with lower lung function at the end of the ACFBAL study in the subset of children included in the present study were presence of bronchiectasis ($p<0.001$), hospitalisations for respiratory exacerbations ($p<0.001$) and NE activity in BAL ($p<0.001$) (Table S3).

Study participants were in early childhood at the end of ACFBAL [median 5.0 (25%–75%=5.0–5.1) years] and in late childhood to early adolescence at the beginning of CF-FAB [median 12.5 (25%–75%=11.4–13.8) years]. The association between age and lung function is displayed in the online supplement (Figure S1). Mean lung function showed a progressive fall from the end of ACFBAL to the beginning of CF-FAB for FVC, FEV_1, FEV_1/FVC% and FEF_{25-75}, with the slope of each trajectory negative and significantly different from zero (all $p<0.001$) (Fig. 1, Table S4, Figure S2).

3.1. Factors present at 5-years of age predicting lung function decline to adolescence

Univariable associations between candidate ACFBAL variables and lung function trajectory slopes are shown in Table S5. Factors predicting lung function decline were similar for FEV_1/FVC

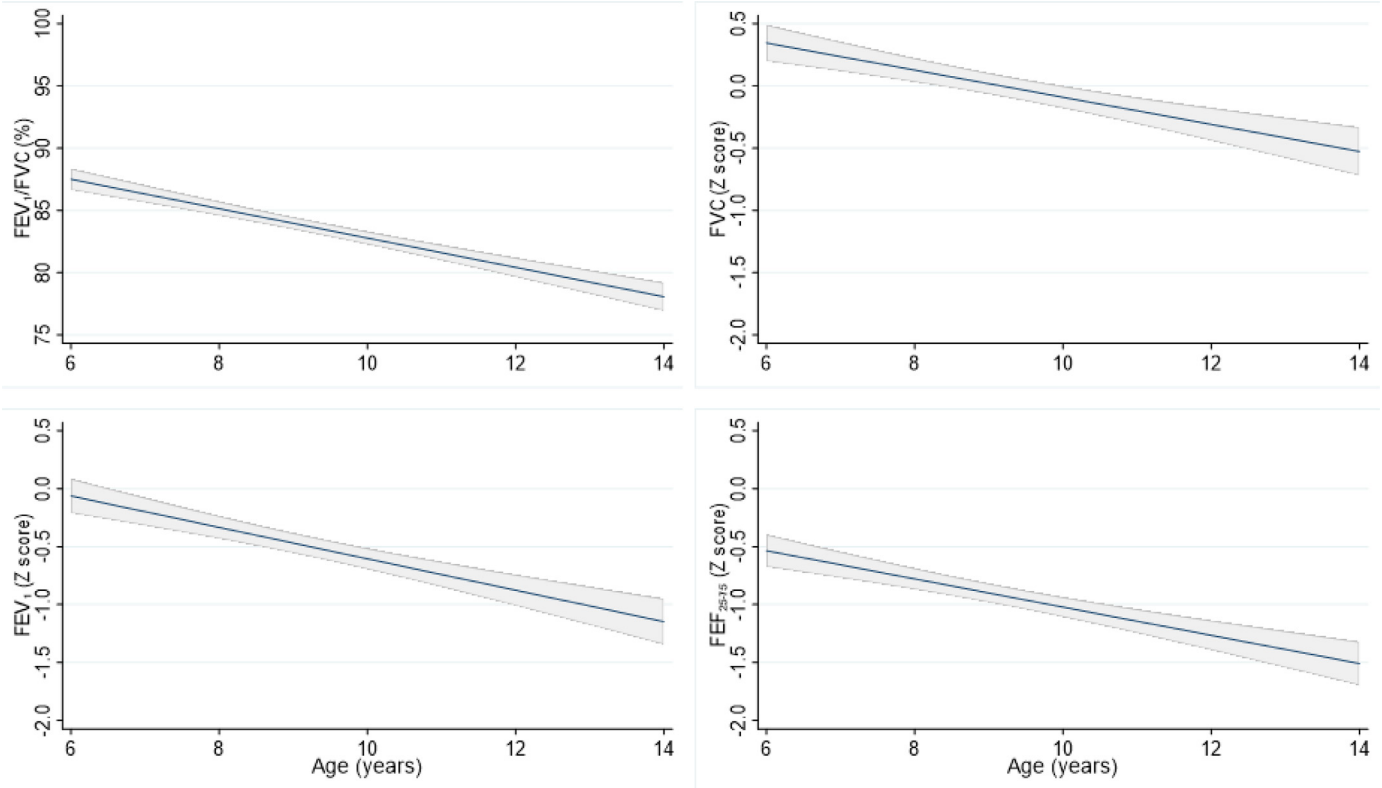

Fig. 1. Mean (95%CI) slope of the lung function parameters FEV_1/FVC%, FVC Z-score, FEV_1 Z-score and FEF_{25-75} Z-score for participants in the ACFBAL and CF-FAB studies on age. **(records = 864, subjects = 119).**

Table 2
Best multivariable models from analyses examining the ability of variables available at the end of the ACFBAL study at age 5-years to predict change in lung function (FEV_1/FVC%, FEV_1 Z-score and $FEF_{25-75\%}$ Z-score). Best multivariable model selected using the Bayesian information criterion. For binary variables, the coefficient represents the additional mean annual decline in outcome if that variable is present.

ACFBAL explanatory variable	Univariable model			Multivariable adjusted model		
	n	Coefficient (95%CI)	p	n	Coefficient (95%CI)	p
FEV_1/FVC (%)						
Hospitalisations for respiratory exacerbations	115	−0.03 (−0.04, −0.01)	**0.001**	89	−0.03 (−0.04, −0.01)	**0.001**
NE activity in BAL	89			89		
Present	34	−0.16 (−0.25, −0.07)	**0.001**	34	−0.14 (−0.23, −0.06)	**0.001**
FEV_1 Z-score						
NE activity in BAL	90			90		
Present	34	−0.02166 (−0.04329, −0.00002)	**0.05**	34	−0.02166 (−0.04329, −0.00002)	**0.05**
FEF_{25-75} Z-score						
Hospitalisations for respiratory exacerbations	115	−0.005 (−0.009, −0.002)	**0.005**	89	−0.005 (−0.010, −0.002)	**0.01**
NE activity in BAL	89			89		
Present	34	−0.03 (−0.05, −0.01)	**0.01**	34	−0.026 (−0.048, −0.004)	**0.02**

Abbreviations: ACFBAL, Australasian Cystic Fibrosis Bronchoalveolar Lavage; BAL, Bronchoalveolar Lavage; CI, confidence intervals; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1-second; FVC forced vital capacity; NE, neutrophil elastase activity.

(%), FEV_1 (Z-score) and FEF_{25-75} (Z-score), while none of the factors examined predicted decline in FVC (Z-score). Factors predicting lung decline were respiratory exacerbations requiring hospitalisation (FEV_1/FVC, FEV_1, FEF_{25-75}), presence of bronchiectasis (FEV_1/FVC, FEV_1, FEF_{25-75}), NE activity in BAL (FEV_1/FVC, FEV_1, FEF_{25-75}), high IL-8 in BAL (FEV_1/FVC), and growth of *Aspergillus* in BAL (FEV_1/FVC, FEF_{25-75}). The best multivariable models to predict FEV_1/FVC% trajectory, FEV_1 trajectory, and FEF_{25-75} trajectory (Table S6) included data from 89, 90, and 89 children, respectively. The models for FEV_1/FVC% and FEF_{25-75} contained the same two ACFBAL variables: NE activity in BAL, and hospitalisations for respiratory exacerbations in the first 5-years of life, while the model for FEV_1 contained NE activity only (Table 2). As NE activity in BAL could not be measured in 27/119 (24.3%) children finishing the ACFBAL study, the analyses presented in Table S5 and Table 2 have a reduced sample size. To examine available variables in the full data set ($n = 119$), analyses were re-run with NE activity excluded (Table S7). Under these circumstances, hospitalisation for respiratory exacerbations in the first 5-years of life remained the most significant factor associated with increased lung function decline (FEV_1/FVC $p = 0.001$, FEF_{25-75} $p = 0.005$) (Table 3).

4. Discussion

The present study shows that hospitalisation for respiratory exacerbations in the first 5-years of life, early life respiratory exacerbations, and markers of lower airway neutrophilic inflammation and infection, especially with *Aspergillus*, were factors predicting the rate of decline of lung function from childhood to adolescence in children with CF born in the first decade of the 21st century.

Table 3
Associations between the most explanatory ACFBAL variables and lung function trajectory when neutrophil elastase activity was excluded from the analyses due to missing data ($N = 27$). Individual changes were calculated using mixed-effects regression models. The best multivariable models, as selected using the Bayesian information criterion, contained only one variable, consequently only the univariable model is presented. The coefficient represents the additional mean annual decline in outcome if that variable is present.

ACFBAL explanatory variable	Univariable model		
	n	Coefficient (95%CI)	p
FEV_1/FVC (%)			
Hospitalisations for respiratory exacerbations	115	−0.03 (−0.04, −0.01)	**0.001**
FEF_{25-75} Z-score			
Hospitalisations for respiratory exacerbations	115	−0.005 (−0.009, −0.002)	**0.005**

Abbreviations: ACFBAL, Australasian Cystic Fibrosis Bronchoalveolar Lavage; BAL, Bronchoalveolar Lavage; CI, confidence intervals; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1-second; FVC forced vital capacity; IL-8, interleukin-8.

These factors are amenable to treatment, however, progressive falls in lung function continue to occur with current treatment strategies.

Respiratory exacerbations in early life, especially those requiring hospitalisation were associated with an accelerated loss of lung function from childhood to adolescence in the present study. Respiratory exacerbations in the ACFBAL cohort have been reported previously [16]. Overall, 168 children had 2080 exacerbations in the first 5-years of life, with 80.1% managed in the community. Exacerbations occurring in the first 2-years of life were associated with lower lung function (FEV_1 Z-score) and those requiring hospitalisation were associated with an increased odds of bronchiectasis at 5-years of age (odds ratio 2.67 [95% confidence interval 1.13–6.31]) [16]. In the children who participated in both studies, the number of hospitalisations in the first 5-years of life was a strong predictor of both lower lung function at 5-years and accelerated lung function decline. Together, these data suggest a continuing effect of early-life respiratory exacerbations that is not simply explained by an effect on lung function in childhood. Previous studies have demonstrated an association between respiratory exacerbations and loss of lung function during childhood and adolescence [22,23]. Indeed, patients not receiving aggressive therapy for acute respiratory exacerbations, especially with intravenous antibiotics, were less likely to show lung function recovery [23]. Almost paradoxically, those with the best lung function, and thus potentially the most to lose, were less likely to be hospitalised and receive intravenous antibiotics [24]. Although the present observational study is unable to establish causality, treating acute respiratory exacerbations of CF promptly and aggressively may reduce lung function decline, and are important targets for future interventional studies. Further research is needed to allow impending exacerbations to be predicted and then ideally prevented.

A significant factor predicting spirometry decline from childhood through adolescence was neutrophilic inflammation. In the present study we used free NE activity and IL-8 levels in BAL fluid at age 5-years. Markers of neutrophilic inflammation were significantly associated with decreased spirometry to adolescence in all analyses, except FVC. We have reported previously that markers of neutrophilic inflammation, especially free NE activity in BAL, were associated with an increased risk of persistent bronchiectasis in CF [6,25,26]. These findings are consistent with an earlier study that showed that the initial level of NE activity in a three-year longitudinal study in 35 children with CF was the best predictor of accelerated loss of lung function [27]. The present study provides further support to adopting treatment regimens designed to preserve lung function from a young age [3]. This might include both the early introduction of CFTR modulators [28] and strategies that detect and treat neutrophilic inflammation [29].

Perhaps one of the more surprising results of the present study was finding that *Aspergillus* in the BAL fluid of 5-year-olds predicted greater decline in spirometry to adolescence when considered univariably. *Aspergillus* is frequently detected in BAL or sputum cultures and, in the absence of features characteristic of allergic bronchopulmonary aspergillosis, is frequently ignored [30]. Recent longitudinal studies have demonstrated that culturing *Aspergillus* in respiratory samples is associated with increased air trapping on computed-tomography scans [10,11], although the effect on lung function has been less clear [11,30]. In the full ACFBAL study and also the sub-group participating in the present study, *Aspergillus* in BAL fluid at 5-years of age was not associated with lower lung function at 5-years of age. Data from the ACFBAL study demonstrated that acquiring *P. aeruginosa* and especially having undergone a subsequent eradication program increased the risk of growing *Aspergillus* at 5-years of age [17]. We have reported previously increased inflammation in the presence of *Aspergillus* alone, without bacteria being present, in the lower airways of young children with CF [5]. Further research into the long-term effects of *Aspergillus* in the lungs is warranted, including whether it is a marker or cause of lung function deterioration. Similarly, eradication protocols used following detection of *P. aeruginosa* should be investigated.

We do need to acknowledge several limitations and technical issues with the present study. Around 30% of those completing the ACFBAL study did not participate in the present study. Loss to follow-up is a major challenge for longitudinal studies that can introduce bias and affect the generalisability of the results. The major difference between those completing both studies and participants completing only the ACFBAL study was that they were more likely to have evidence of infection in their end of ACFBAL study BAL cultures. However, no differences in hospitalisation, respiratory exacerbations, spirometry, neutrophilic inflammation, or growth of *Aspergillus* were seen. In addition, the early life risk factors associated with lower lung function at age 5-years were similar in the children participating in the present follow-up study to the total ACFBAL population. In the absence of data defining lower airway fungal infections, we accepted any growth of *Aspergillus* in BAL cultures as significant, which may have led to misclassifying transient lower airway colonisation or upper airway contamination as infection. Also, three centres did not routinely use selective fungal media routinely for CF respiratory specimens, although no site bias was identified for culturing *Aspergillus*. When considering variables for inclusion in our models we were restricted to data collected as part of the ACFBAL and CF-FAB studies, and consequently could not include factors such as environmental tobacco smoke or socioeconomic status, which previous studies have shown to be associated with lung function. Clinicians are more familiar with lung function being reported in percent predicted values, while we used instead Z-scores to report lung function data. Z-scores allow direct comparisons of lung function from children of different heights. In the present study, where lung function was measured over a 10-year period, considerable growth-associated increases in lung function, expressed in absolute units, occurred. As lung function during childhood grows along trajectories [31], children's Z-scores should remain approximately the same. This allows identifying factors associated with a change in Z-score.

In summary, the results of the present study demonstrate that low lung function, neutrophilic inflammation, and *Aspergillus* in the lower airways at age 5-years predict lower lung function in adolescence. The value of specific therapeutic interventions aimed at these factors in early life should be a focus of future intervention studies.

The following investigators constitute the ACFBAL study investigators group

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Credit author statement

Begum: statistical analysis, drafting manuscript
Byrnes: conception, data collection, manuscript revision
Cheney: data collection, manuscript revision
Cooper: conception, data collection, manuscript revision
Fantino: laboratory aspects, manuscript revision
Gailer: data management, manuscript revision
Grimwood: conception, manuscript revision
Guitierrez Cardenas: laboratory aspects, manuscript revision
Massie: conception, data collection, manuscript revision
Robertson: conception, data collection, manuscript revision
Sly: conception, drafting manuscript, overall supervision
Tiddens: conception, data collection, manuscript revision
Wainwright: conception, data collection, manuscript revision
Ware: statistical analysis, manuscript revision, overall supervision

Supplementary material

This manuscript has an online data supplement. lung function trajectories in CF online supplement R1.docx

Declaration of Competing Interest

None of the authors have any conflict to declare with regard to the work presented in this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.03.008.

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