

Sleep-disordered breathing in cystic fibrosis pediatric subjects

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ABSTRACT

Objectives: To describe the frequency of sleep-disordered breathing (SDB) in pediatric cystic fibrosis (CF) and to study associations between polysomnographic respiratory parameters and available clinical information. **Methods:** This was a retrospective, cross-sectional study. The sample data were obtained from information recorded on patient charts in 2015 and 2016. The study included all individuals with CF aged from 2 to 20 years for whom records were available for polysomnography performed within the previous two years. **Results:** Sixteen individuals with CF (mean age 11 ± 5.6 years old) were included. Polysomnographic respiratory parameter abnormalities were defined as an apnea-hypopnea index (AHI) exceeding one event per hour of sleep or an oxyhemoglobin saturation (SpO_2) nadir below 90%; observed in 10 subjects (62.5%). Forced expiratory volume in first second (FEV_1) was correlated ($r=0.602$, $p=0.023$) with mean sleep SpO_2 . FEV_1 was also negatively correlated with sleep peak end-tidal carbon dioxide (EtpCO_2) ($r=-0.645$, $p=0.024$). Additionally, chronic airway colonization by *Pseudomonas aeruginosa* was associated with mean EtpCO_2 in non-REM sleep ($p=0.024$). **Discussion:** SDB was frequently observed in this sample of children with CF. There was an association between CF respiratory disease progression markers and sleep breathing parameters in children. Sleep studies appear to be an important tool for assessment of the respiratory status of these individuals with CF, although further studies are needed, especially with carbon dioxide sleep analysis.

Keywords: Cystic Fibrosis; Pediatrics; Polysomnograph; Sleep Apnea Syndromes.

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INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that compromises the normal physiology of several different organs. The main cause of morbidity and mortality in these patients is respiratory system involvement¹. As with other chronic respiratory disorders, ventilation impairment begins during sleep, especially during the rapid eye movement (REM) stage^{2,3}. In children, the REM stage of sleep is of longer duration than in adults. Although overnight polysomnography is costly and access is limited, it is considered the gold standard test for evaluation of respiratory abnormalities during sleep^{4,5}.

Cystic fibrosis patients exhibit decreases in sleep oxyhemoglobin saturation (SpO₂) that are associated with reduced intercostal muscle activity, irregular breathing patterns, and hypoventilation caused by reduced tidal volume and minute ventilation². Hypoxemia and hypercapnia during sleep are common findings in patients with advanced lung disease, but they are also described in some individuals with mild or moderate disease⁶⁻⁸. Even in the absence of frank hypoxemia, nocturnal SpO₂ is lower in the CF pediatric population than in healthy controls^{5,7,9,10}. For nocturnal carbon dioxide (CO₂) estimation, a study comparing CF children with healthy controls found an association between peak CO₂ and CF¹¹. Polysomnography (PSG) findings are conflicting with regard to the greater frequency of obstructive sleep apnea in CF children compared to controls^{5,7,9,11,12}.

There are also previous studies that have investigated associations between sleep-disordered breathing (SDB) and waking clinical and functional variables (such as spirometry data). These studies have reported different and even conflicting results^{7,13-15}. Furthermore, there are studies that have described improvements in CF disease after treatment of obstructive sleep apnea-hypopnea syndrome (OSAHS)¹⁶⁻¹⁸.

Although relevant, studies of SDB in CF pediatric populations have reported discrepant findings and are subject to limitations¹⁹. Therefore, the objectives of this study were to describe SDB frequency and to study associations between changes in polysomnography respiratory indexes and available clinical data.

MATERIAL AND METHODS

This was a cross-sectional study performed by review of medical records for 2015 and 2016 from a CF center. The project was approved by the Institutional Ethics Committee (number 1.294.834). Participants were recruited from among patients in follow-up at the multidisciplinary CF outpatient clinic at a tertiary hospital in Porto Alegre (Southern Brazil). Subjects included were aged from 2 to 20 years and had undergone nocturnal PSG during the previous two years. Exclusion criteria were use of nocturnal ventilatory support, prior lung transplantation, unavailability of medical records and irregular follow-up.

Subjects had been referred to the outpatient clinic for CF investigation, either because of symptoms of CF (such as recurrent respiratory infections, low weight gain, and fatty stools)¹ or because of an abnormal newborn CF screening test. Sweat testing and/or CFTR genotyping was used to confirm CF.

The following information was extracted from medical records and used for patients' clinical, functional and sleep evaluation:

1. Date of birth, sex, age of diagnosis;
2. Anthropometric data (weight and height) and indicators of nutritional status (weight for age, height for age and body mass index - BMI), which were classified by percentiles and Z scores, according to National Center for Health Statistics charts²⁰;
3. Comorbidities, treatment, number of exacerbations per year, Shwachman score^{15,21} and bacterial airway colonization (chronic colonization by *Pseudomonas aeruginosa* [PA] was defined as PA present in at least 50% of cultures over one year)^{22,23};
4. Lung function data, such as forced expiratory volume in first second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio and forced expiratory flow from 25% to 75% of FVC (FEF₂₅₋₇₅). The Global Lung Function Initiative international equation was used as the reference for percentiles and for Z scores for age, height, and sex²⁴. Examinations were performed using Koko equipment (PDS Instrumentation, Inc., Louisville, CO, USA) and all procedures were conducted in accordance with American Thoracic Society criteria²⁵;
5. Polysomnography data included: sleep efficiency, sleep latency for sleep and REM sleep onset, apnea-hypopnea index per hour of sleep (AHI), obstructive AHI index per hour of sleep (OAHI, where central apneas were discounted in the numerator calculation), baseline and minimal oxyhemoglobin saturation, desaturation index (which was defined as at least a 3% reduction from baseline SpO₂), mean values of exhaled CO₂ (EtpCO₂) in REM and NREM sleep and when awake, total time and percentage of total sleep time (TST) with measured value of high carbon dioxide, and highest (peak) sleep EtpCO₂ value. Examination data were recorded using Alice 5[®] (Philips Respironics) equipment, with the exception of one examination (which was performed with Bio-Logic[®]). In all subjects, the test was conducted at night with spontaneous breathing and the study was performed according to international American Academy of Sleep Medicine recommendations.

For statistical analysis, categorical variables were described as absolute and relative frequencies, and continuous variables as mean and standard deviation. Continuous variables outcomes were compared using the t-test. The Fisher's exact test or chi-square test were used for associations between categorical variables. Spearman and Pearson tests were used for correlation analysis, as appropriate for distribution of variables. A 0.05 significance (*p*) cutoff was used.

RESULTS

Ninety-one subjects are followed at the PUCRS CF Center and 16 cases had undergone PSG. Among these individuals with PSG records, 75% were male and mean age was 11 ± 5.6 years. Thirteen subjects had identified genotypes (> 80% had at least one allele for F508del). All subjects had pancreatic insufficiency and were on enzyme replacement therapy.

The mean AHI for the sample was 1.4 ± 1.8 events per hour of sleep and after exclusion of central apneas (OAHI), the mean value was 1.2 ± 1.7 events per hour of sleep. Subjects' mean sleep SpO₂ was 95.7 ± .3%, with a minimum of 89.5 ± 3.9%. Fifteen subjects (93%) had zero percent of their TST with

SpO₂ below 90%. Of fourteen individuals for whom information about EtpCO₂ measurements was available, just one individual had a CO₂ peak higher than 50mmHg and remained 0.1% of TTS (approximately 0.4 minutes) with this range. Mean EtpCO₂ values during NREM and REM sleep were 34.3 ± 3.1 mmHg and 35.1 ± 2.6 mmHg respectively and the whole-sample peak value was 42.1 ± 3.5 mmHg. When the parameters for normality were defined as AHI less than or equal to one hourly sleep event and an SpO₂ nadir greater than or equal to 90%, only six subjects (37.5% of the total, mean age of 11.7 years and BMI Z score of -0.18) met these criteria for normality. Table 1 lists additional characterization data and results broken down by respiratory findings (defined as normal for patients with AHI less than or equal to one event per hour of sleep and an SpO₂ nadir greater than or equal to 90%).

Tables 2 and 3 show associations between clinical variables (lung function and chronic PA airway colonization) and PSG findings. FEV₁ was associated with mean nocturnal SpO₂ (96.87 ± 1.12% when FEV₁ ≥ 90% and 94.16 ± 2.78% when FEV₁ < 90%; *p*=0.027). Chronic PA colonization was associated with mean EtpCO₂ value during NREM sleep (33 ± 2.77 mmHg in those free from PA and 37 ± 1.41 mmHg in individuals with chronic PA; *p*=0.024). Except for significant associations between Z scores for BMI and Z scores for lung function variables (FEV₁ and FEF₂₅₋₇₅) and PA colonization, other clinical data (Shwachman score, number of exacerbations) were not significantly associated with FEV₁ or PA.

Correlations were observed between variables associated with CF lung diseases and PSG respiratory variables. There was a correlation between FEV₁ Z score and peak CO₂ level

Table 1. Clinical and functional characteristics of study participants.

Information	All patients	Normal	Abnormal	<i>p</i>
Age; mean ± SD	11.0 ± 5.6	11.7 ± 6.4	10.6 ± 5.4	0.738
Boys; n (%)	12/16 (75%)	3/6 (50%)	9/10 (90%)	0.118
BMI Z score; mean ± SD	0.13 ± 0.61	-0.18 ± 0.58	0.32 ± 0.57	0.125
≥ one DF508 allele; n (%)	11/13 (84.6%)	3/5 (60%)	8/8 (100%)	0.128
Chronic PA airway colonization; n (%)	7/16 (43.7%)	4/6 (66.6%)	3/10 (30%)	0.302
Respiratory exacerbations/year; mean ± SD	3.1 ± 2.0	2.0 ± 1.3	4.0 ± 2.2	0.067
FVC %predict; mean ± SD [†]	92.22 ± 23.22	91.54 ± 27.74	92.60 ± 22.16	0.944
FVC Z score; mean ± SD [†]	-0.67 ± 1.99	-0.74 ± 2.39	-0.64 ± 1.89	0.937
FEV ₁ %predict; mean ± SD [†]	87.95 ± 26.21	91.04 ± 27.03	86.23 ± 27.24	0.758
FEV ₁ Z score; mean ± SD [†]	-0.99 ± 2.19	-0.76 ± 2.34	-1.12 ± 2.24	0.789
FEV ₁ /FVC Z score; mean ± SD [†]	-0.68 ± 1.30	-0.04 ± 0.65	-1.04 ± 1.47	0.106
FEF ₂₅₋₇₅ Z score; mean ± SD [†]	-1.03 ± 1.92	-0.30 ± 1.31	-1.43 ± 2.15	0.247
Snoring; n (%) [‡]	5/15 (33.3%)	0/5 (0%)	5/10 (50%)	0.101
AHI; mean ± SD	1.4 ± 1.8	0.2 ± 0.3	2.1 ± 2.0	0.036
OAHI; mean ± SD	1.2 ± 1.7	0.2 ± 0.3	1.7 ± 1.9	0.078
Mean SpO ₂ ; mean ± SD [‡]	95.7 ± 2.3	96.2 ± 0.4	95.5 ± 2.8	0.458
SpO ₂ nadir; mean ± SD	89.5 ± 3.9	92.7 ± 1.6	87.6 ± 3.7	0.002
Mean NREM EtpCO ₂ ; mean ± SD [§]	34.3 ± 3.1	34.4 ± 3.4	34.3 ± 3.1	0.954
Mean REM EtpCO ₂ ; mean ± SD [§]	35.1 ± 2.6	34.6 ± 3.0	35.4 ± 3.5	0.625
Peak sleep EtpCO ₂ ; mean ± SD [†]	42.1 ± 3.5	42.2 ± 2.9	42.1 ± 4.2	0.983
Change CO ₂ REM-NREM; n (%) [§]	6/12 (50%)	2/5 (40%)	4/7 (57.1%)	1.00

*n=13; †n=14; ‡n=15; §n=12.

Table 2. Comparison between patients with FEV₁ ≥ 90% and < 90% of predicted.

Information	FEV ₁ ≥ 90% (n=8)	FEV ₁ < 90% (n=6)	<i>p</i>
	mean ± SD	mean ± SD	
Age	11.75 ± 4.74	11.83 ± 5.6	0.976
BMI Z score	0.16 ± 0.57	0.11 ± 0.59	0.897
Shwachman score [†]	93.71 ± 5.02	85.5 ± 12.12	0.273
AHI	1 ± 1.85	1.5 ± 1.87	0.628
OAHI	0.75 ± 1.48	1.16 ± 1.94	0.656
Mean SpO ₂	96.87 ± 1.12	94.16 ± 2.78	0.027*
SpO ₂ nadir	89 ± 3.77	89 ± 4.42	1.00
Mean NREM EtpCO ₂ [‡]	33.86 ± 3.48	35.75 ± 2.21	0.358
Mean REM EtpCO ₂ [‡]	34.85 ± 3.02	36.25 ± 1.25	0.410
Peak sleep EtpCO ₂ [‡]	41.14 ± 2.41	43.4 ± 5.31	0.340

*Significance cutoff (*p*) < 0.05; †n=7 for FEV₁ ≥ 90% and n=4 for FEV₁ < 90% of predicted; ‡n=7 for FEV₁ ≥ 90% and n=5 for FEV₁ < 90% of predicted.

FEV₁=forced expiratory volume in one second SD=standard deviation; BMI=body mass index; AHI=apnea-hypopnea index; OIAH=obstructive AHI index - without central apneas; SpO₂=oxyhemoglobin saturation; EtpCO₂=end-tidal carbon dioxide; NREM=non rapid eye movement (REM) stage.

Table 3. Comparison between patients with and without chronic *Pseudomonas aeruginosa* (PA) airway colonization.

Information	With PA (n=9)	Without PA (n=7)	P
	mean ± SD	mean ± SD	
Age	9.44 ± 5.05	12.14 ± 6.22	0.354
BMI Z score	0.40 ± 0.55	-0.22 ± 0.49	0.034*
Shwachman score [†]	95.71 ± 3.54	87 ± 10.17	0.093
FEV ₁ Z score [‡]	0.21 ± 1.38	-2.59 ± 2.09	0.011*
FEV ₁ /FVC Z score [‡]	-0.18 ± 1.1	-1.34 ± 1.34	0.102
FEF ₂₅₋₇₅ Z score [‡]	0 ± 1.34	-2.4 ± 1.74	0.013*
AHI	1.33 ± 1.73	1 ± 1.82	0.715
OAHI	0.77 ± 1.39	1 ± 1.82	0.786
Mean SpO ₂ [§]	96.77 ± 1.09	94.16 ± 2.78	0.071
SpO ₂ nadir	88.88 ± 3.33	90.28 ± 4.78	0.502
Mean NREM EtpCO ₂	33 ± 2.77	37 ± 1.41	0.024*
Mean REM EtpCO ₂	34.12 ± 2.64	37 ± 1.15	0.068
Peak sleep EtpCO ₂ [‡]	41 ± 2.44	43.66 ± 4.41	0.173

*Significance cutoff (p)<0.05; [†]n=7 without and 6 with chronic airway colonization by *Pseudomonas aeruginosa* (PA); [‡]n=8 without and 6 with PA; [§]n=6 with PA; ||n=8 without and 4 with PA.

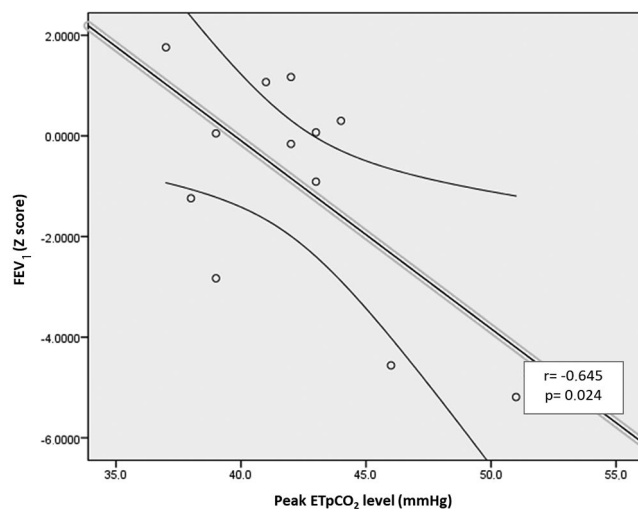
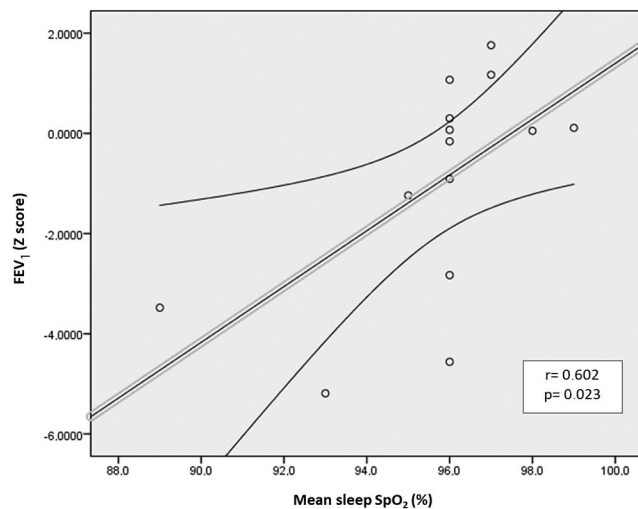
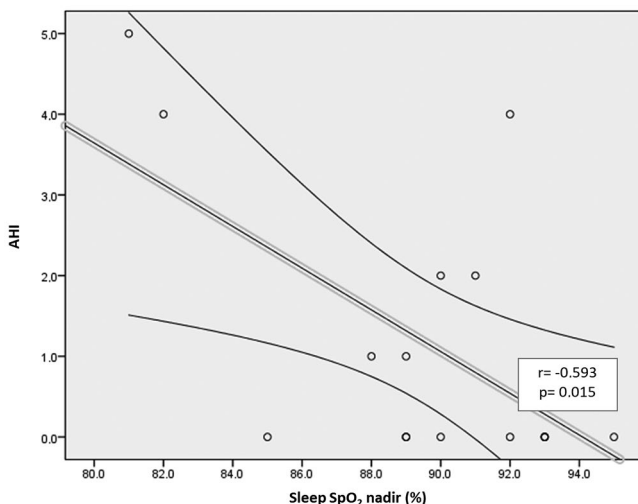
SD=standard deviation; BMI=body mass index; FVC=forced vital capacity; FEV₁=forced expiratory volume in one second; FEF₂₅₋₇₅=forced expiratory flow from 25% to 75% of FVC; AHI=apnea-hypopnea index; OIAH=obstructive AHI index - without central apneas; SpO₂=oxyhemoglobin saturation; EtpCO₂=end-tidal carbon dioxide; NREM=non rapid eye movement (REM) stage.

(Figure 1A). Moreover, FEV₁ Z score was correlated with mean sleep SpO₂ (Figure 1B). Additionally, a correlation was observed between AHI and SpO₂ nadir (Figure 1C). None of the other correlations were statistically significant.

DISCUSSION

We observed that FEV₁ was correlated ($r=0.602$, $p = 0.023$) with mean sleep SpO₂. Furthermore, FEV₁ was negatively correlated with peak EtpCO₂ at night in our pediatric CF population sample. Interestingly, we found that the presence of airway PA colonization exhibited an association with mean EtpCO₂ during NREM sleep (33 ± 2.77 mmHg *vs.* 37 ± 1.41 mmHg, $p=0.024$). We also found that chronic PA airway colonization exhibited associations with BMI and with lung function parameters, as previously described²⁶. Finally, AHI was negatively correlated with SpO₂ nadir.

Although recommended in pediatric PSG²⁷, capnography is not always performed for patients with CF. Also, results can be described in different forms: peak and average in sleep (REM and NREM)^{10,11}; during wakefulness⁵; percent of sleep time with CO₂ above a cutoff¹⁹; and, more recently, by comparing CO₂ increase in REM sleep in relation to the NREM value (change CO₂)¹⁵. Unlike Waters et al.¹⁵, in our study the change CO₂ ranged from -1 to +3 (CO₂ in REM sleep increased in relation to NREM in half of the 12 subjects for whom these data were available and remained the same or reduced in the other six subjects) and was not associated

**Figure 1A.** Correlation between FEV₁ (Z score) and the EtpCO₂ peak.**Figure 1B.** Correlation between FEV₁ (Z score) and mean sleep SpO₂.**Figure 1C.** Correlation between AHI and sleep SpO₂ nadir.

with any clinical or functional variables. In our study, FEV₁ Z score correlated with peak EtpCO₂ and chronic PA infection was associated with mean CO₂ in NREM sleep; findings that have not been described previously. When using exhaled CO₂ measurements, values may be underestimated (compared with transcutaneous CO₂) in patients with respiratory disease^{5,11,16}. Therefore, we can speculate that if we had used transcutaneous measurement and a larger sample size, we could have found even more consistent findings.

We also observed a correlation between AHI and sleep SpO₂ nadir, which is expected when evaluating associated respiratory disorders (CF and OSAHS). Most studies seem to agree with our finding^{6,9}, even those employing different definitions for OSAHS. One example is a study Ramos et al.²⁸ conducted with 67 CF patients aged from 2 to 14 years, in which they observed a relationship between an apnea index (number of obstructive and mixed apneas by TST) and lower SpO₂ values.

It is known that pulmonary function assessment is an essential tool in CF follow-up²⁹, and it has been evaluated in other studies of sleep in CF subjects. Comparing our results to Uyan et al.¹⁴, we observed different findings. They did not find a correlation between mean SpO₂ and FEV₁ in 24 children with CF (mean age 9.5 years and FEV₁ > 40%), but did describe an association between SpO₂ nadir and FEV₁. In a more recent publication, Spicuzza et al.⁹ also found no correlation between mean SpO₂ and FEV₁ ($r^2=0.03$, $p=0.14$). On the other hand, de Castro-Silva et al.⁷ observed a similar result to ours (correlation between FEV₁ and mean SpO₂; $p < 0.001$). Moreover, Waters et al.¹⁵ detected a correlation with baseline SpO₂, but not with its nadir. They did not report the sleep mean SpO₂ in their sample of 42 CF patients aged 8 to 12 years¹⁵. The reasons for this lack of uniformity may be due to different methodologies used by the studies: 1) regarding the SpO₂ parameter (mean, nadir, baseline, time and percentage of TST with SpO₂ below a certain value)³⁰, as in the case of Waters et al.¹⁵; 2) regarding the pulmonary function predictive equation used, such as Knudson et al.³¹ in Uyan and Polgar³² in Waters et al.¹⁵ and Spicuzza et al.⁹; and 3) differences between subjects' severity profiles in the studies.

One potential implication of our study is the possible inclusion of PSG as part of a routine annual check-up at CF centers. Although there is no consensus on performing PSG in individuals with mild and/or stable disease, there are recent studies suggesting early SDB investigation and PSG may be useful in CF patients^{5,6,9}. In our sample of 16 subjects, only six subjects (37.5%) were classified as normal considering AHI less than or equal to one event per hour of sleep and SpO₂ nadir greater than or equal to 90% as criteria for normality. Thus, in addition to other results, our impression is that SBD evaluation by PSG has a potential positive impact in CF patients and this benefit may be even greater when considering some subgroups, such as those colonized by PA and those with persistent reductions in pulmonary function parameters, especially FEV₁.

For instance, it is difficult to describe the immediate clinical relevance of differences observed in our study. Both values were within the normal range, even in subjects colonized

by PA. However, we believe these findings may serve as markers for CF respiratory disease progression, rather than revealing a respiratory disturbance.

Small sample size was the most relevant limitation of our study. However, it is known that PSG is not readily available, especially for the pediatric population^{33,34}. Even in countries with greater PSG availability, CF pediatric population studies rarely include more than 40 subjects. Interestingly, Brazilian studies by Ramos et al. have the largest number of individuals (more than 60)^{6,28,35}, but they did not conduct sleep CO₂ assessment. Nevertheless, we believe our sample size may have been restricted by both the study methodology adopted (a retrospective study) and the PSG access difficulties faced by patients. Ultimately, there are few sleep centers that conduct PSG on children available. Although our study is restricted in quantity, our subjects' ages and clinical manifestations are comprehensive. This raises two observations: 1) our sample encompasses subjects with different severities; 2) whether it is possible to predict disease progression using PSG.

Finally, we agree with a previous study⁵ that suggested sleep analysis could serve as an early indicator for CF pulmonary disease progression, although further multicenter studies are necessary to assess PSG findings including nocturnal capnography. The potential positive impact of PSG for pediatric CF patients may be even greater within some subgroups, such as those colonized by PA and those with persistent reductions in pulmonary function parameters, especially FEV₁.

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