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Non-Cystic Fibrosis Bronchiectasis in Childhood: Longitudinal Growth and Lung Function

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ABSTRACT

Background: Non-Cystic Fibrosis (non-CF) bronchiectasis often starts in childhood with significant impact on adult morbidity. Little is known about disease progression through childhood and the effect on growth and spirometry. This study reviews longitudinal lung function and growth in children with non-CF bronchiectasis.
Methods: The case notes of patients with non-CF bronchiectasis were reviewed retrospectively. Patients were included if at least three calendar years of lung function data were available. Anthropometric measurements and annual spirometry were analysed over both two and four consecutive years. Changes over time were assessed using Generalized Estimating Equations.
Results: Fifty-nine patients (31 males) were identified. At baseline, the median age was 8.2y (range 4.8-15.8y), the mean ± (SD) for height, weight and body mass index (BMI) for-ages z-scores were -0.68±1.31, -0.19±1.34 and 0.19±1.38, respectively. At baseline mean z-score for FEV_1 was -2.61±1.82 (SD). Over 2-years (n=59) mean FEV_1 and FVC improved by 0.17 (p=0.039, 95% CI 0.01 to 0.34) and 0.21 (p=0.016, 95% CI 0.04 to 0.39) z-scores per annum, respectively. Over 4-years, there was improvement in height-for-age z-scores (slope 0.05, p=0.01, 95% CI 0.01 to 0.095) but no improvement in other anthropometric variables. There was no change in spirometry [FEV_1 slope 0.00, p=0.999, 95% CI -0.09 to 0.09 and forced vital capacity (FVC) slope 0.09, p=0.859, 95% CI -0.09 to 0.1].
Conclusions: Children with non-CF bronchiectasis show an adequate growth over time; lung function stabilised but did not normalise with treatment, underscoring the need for early detection and institution of appropriate therapy.

Introduction

Bronchiectasis is conventionally used as a descriptive term for an irreversible pathologic state, characterised by chronic suppurative airway disease manifested clinically by chronic productive cough and radiologically by bronchial dilation and often, thick walled bronchi. The incidence of non-cystic fibrosis (non-CF) bronchiectasis has fallen since the late 19th century, particularly in developed countries[1] and the adult mortality rate associated with it has decreased from over 30% in 1940 to 13% in 1981.[2] In children, the disease is reported to have an estimated prevalence of 1 in 5800 in North East England and 1 in 1700 in New Zealand.[1, 3] In recent years, diagnosis has become easier with the widespread use of high-resolution computerised tomography (HRCT). Eastham *et al* recently described a 10-fold increase in the rate of HRCT diagnosed non-CF bronchiectasis referred to a UK paediatric tertiary hospital .[1] The widespread prevalence and increasing diagnosis of this condition in childhood will have a potential impact on adult health services.

In another study, 80% of adults with newly diagnosed bronchiectasis, reported chronic respiratory symptoms in childhood suggesting that the disease process often starts early on.[2] Unlike in adults where bronchiectasis is most commonly reported as idiopathic[4], aetiological factors are identified in more than 70% of some paediatric populations.[5] Identifying the underlying aetiology is important as it allows individualised treatment of a potentially irreversible disease process where early interventions are believed to minimise long-term morbidity and mortality. Recent evidence suggesting that radiological changes described in bronchiectasis may remain static, show improvement or even completely resolve over prolonged periods of time could be due to the beneficial effects of early aggressive treatment.[1, 6] However, the impact of modern treatment regimens on the course of childhood bronchiectasis has not been well established on long-term follow-up in a developed world context.

In many chronic suppurative lung diseases in childhood, there is poor growth and progressive lung function decline. Although many studies of children with CF have documented the decline in lung function and nutritional issues, far less is known about the course of non-CF bronchiectasis in the developed world. We hypothesised that children with non-CF bronchiectasis could be stabilised with standard aggressive medical treatment. The aim of the study was therefore to evaluate in children with non-CF bronchiectasis: 1) the clinical course of the disease, reflected by change in lung function measurements over a two and a four-year period and 2) their growth in the same periods.

Methods

Subjects

The study population consisted of patients attending the paediatric respiratory clinics at the Royal Brompton Hospital (RBH) and Great Ormond Street Hospital for Children (GOSH) (London, UK) between 1986 and 2002.[5] Inclusion criteria were a definitive diagnosis of non-CF bronchiectasis made by HRCT, reported independently by paediatric radiologists, ability to perform reliable spirometry and availability of annual anthropometric and spirometry [forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)] data for at least two-calendar year follow-up period. CF was excluded by sweat testing and CF genotype; and by measurement of transepithelial potential difference in equivocal cases. Full details of the diagnostic workup have been reported before.[5]

Patients were reviewed by paediatric respiratory specialists every 3 months in both centres. The treatment protocols did not change during the study and children were prescribed standard aggressive treatment of non-CF bronchiectasis, including airway clearance techniques; and oral, nebulised or intravenous antibiotics depending on the nature and frequency of bacterial isolates. Prophylactic antibiotics were not routinely prescribed and depended on the clinical context. In the absence of any generally agreed protocols, and with no evidence base, the decision to start prophylactic antibiotics was made on an individual basis, after discussion with the family. The decision was arbitrary, and based on a clinical assessment of the severity, frequency and duration of exacerbations. Bronchodilators and steroids were prescribed if clinically indicated, and continued if a response was observed. Specific treatment was also given for any underlying cause (intravenous immunoglobulins (IVIG) for underlying immunodeficiency).[5]

Study design

A retrospective review of the computerised database previously described was used to identify children eligible for inclusion. Aetiology of bronchiectasis, age, gender, spirometric parameters (FEV_1 and FVC), height and weight for each year were recorded. Body Mass Index (BMI) was calculated as: BMI (kg/m^2) = weight in kilograms / (height in meters)^2. Z-scores were calculated for all anthropometric measures.[7] We analysed children who had 2 years follow-up data to maximise the sample size, and 4 years to maximise duration of follow-up, albeit at the cost of reducing patient numbers.

Pulmonary Function

Spirometry was performed according to the American Thoracic Society guidelines [8] with either a *Jaeger* spirometer at GOSH (*Viasys Healthcare*, Germany) or *Compact Vitallograph* at RBH (Vitallograph, UK) by fully trained paediatric respiratory technicians. At least three technically acceptable manoeuvres were performed each time spirometry was done, and the highest value of FEV_1 and its corresponding FVC were recorded. The flows were reported from the 'best' manoeuvre, identified as that with the highest sum of FEV_1 and FVC. Data collected were the ''best annual" (individual's best spirometric result for each calendar year) FEV_1 and its corresponding FVC. Values were expressed as percent predicted and z-scores for the patient's age, sex and height.[9] The lung function tests were carried out during routine clinic visits when patients were clinically stable, as far as could be determined. Baseline data were collected during the first patient visit following referral from the local hospital. Children, who did not have data of at least one spirometry per year during a period of clinical stability for three consecutive years, were excluded.

Approval was obtained from the local ethics committees of the two hospitals to carry out this retrospective review.

Statistical methods

Study size was opportunistic as there were insufficient data to inform a power calculation. Mean and standard deviations were calculated for baseline anthropometric and lung

function measurements. Independent samples T-test were used (or the non-parametric equivalent - Mann-Whitney) to compare data between subgroups of different aetiology, FEV_1 categories and patient inclusion vs. exclusion in 4-year analysis. General Estimating Equations (GEE) were used to describe changes over time; these extend the linear regression model while adjusting for the correlated nature of serial lung measurements.

Results

A presumptive underlying aetiology was identified in 61% of the patients, based on identification or exclusion of a cause using specific investigations (Table 1). The baseline mean z-scores for anthropometric measurements were within the normal range (between -2 and +2) but the mean FVC and FEV_1 z-scores were reduced: -2.61±1.82 (SD) and -2.66±1.68 (SD) respectively, confirming obstructive airways disease

Table 1. Study group characteristics at baseline

	Patients studied (n=59)
Sex M:F	31:28
Aetiology	
Idiopathic	23
Congenital malformation	4
Post-infectious	4
Primary Immunodeficiency	25
Aspiration	3
Age[•] (years)	8.2 [4.8 to 15.8]
Growth[#]	
Height (cm) / Height–for-age z-scores	123.8±13.1 / -0.68±1.31
Weight (Kg) / Weight–for-age z-scores	25.5±6.8 / -0.19±1.34
BMI / BMI–for-age z-scores	16.4±1.9 / 0.19±1.38
Lung Function[#]	
FVC (% Pred)/ FVC z-score	76.2±19.7 / -2.61±1.82
FEV_1 (%/Pred) / FEV_1 z-score	68.3±21.0 / -2.66±1.68

Legend - [•]Median [range]; [#]mean±SD.

Differences in mean FEV_1 and FVC z-scores were noted between various causes of disease (Table 2). Children with idiopathic aetiology did not show any difference in spirometric parameters compared to those with primary immunodeficiency; but height-for-age was significantly higher in the idiopathic group (p = 0.003, mean difference 1.06, 95% CI 0.37 to 1.76). The numbers were too small to draw conclusions in the other aetiological groups.

Table 2. Baseline characteristics of study group, according to aetiology

	Idiopathic (n=23)	Primary Immunodeficiency (n=25)	Congenital malformations (n=4)	Post-infectious (n=4)	Aspiration (n=3)	p–value
Age•♣ (years)	9.3 [4.8 to15.8]	8.0 [5.1 to 15.3]	8.0 [6.2 to 12.3]	8.5 [7.4 to 12.3]	8.4 [6.6 to 8.7]	0.91
Growth#						
Height♦	-0.15±1.0	-1.21±1.34	0.25±2.20	-0.95±0.61	-1.14±0.74	**0.003**
Weight♦	-0.08±1.20	-0.46±1.54	1.27 ±1.66	1.28±0.30	-0.86±1.44	0.36
BMI♦	-0.11±1.43	0.32±1.5	1.07±1.05	0.86±0.38	0.30±0.70	0.4
Lung Function#						
FVC♦	-2.43±1.76	-2.5±1.92	-1.38±0.64	- 4.65±1.25	-3.55±1.03	0.90
FEV_1♦	-2.6±1.35	-2.44±1.92	-1.70±0.21	- 4.88±1.37	- 3.33±1.12	0.76

Legend: •Median [range]; #mean z-scores ±SD. The last column shows comparison between Idiopathic and Primary Immunodeficiency only (analysis: ♣Mann-Whitney test; ♦Independent Samples T-test).

Males had higher baseline spirometry but the observed differences were not statistically significant [Females: FVC z-score -2.2±2.02 (SD), FEV_1 z-score -2.28±1.82 (SD), Males: FVC z-score was -3.0±1.55, FEV_1 z-score was -3.01±1.45 (SD)]. There were also no differences in anthropometric z-scores between the two sexes at baseline.

Patients with $FEV_1 < -2$ z-scores at first visit (n=37) were mainly males (n=23) and were significantly older [median age 9.3y (5.8y to 15, p=0.03)]. There were more cases with underlying idiopathic aetiology in this group (43%) compared to those with normal FEV_1 (31%), at baseline. They had a significant lower mean BMI z-score compared with children with $FEV_1 \geq -2$ z-scores (p=0.02) (Table 3).

Table 3. Comparison of patients according to whether FEV_1 z-score was abnormal at baseline or not.

	Patients FEV1 < -2 Z-score at baseline (n=37)	Patients FEV1 ≥ - 2 z-score at baseline (n=22)	
Sex M:F	23:14	8:14	
Aetiology			
Idiopathic	16	7	
Congenital malformations	0	4	
Post-infectious	4	0	
Immunodeficiency	14	11	
Aspiration	3	0	
			p-value
Age[•] [♣] (years)	9.3 [5.8 to15.8]	7.5 [4.8 to 12.3]	**0.03**
Growth[#] [♦]			
Height-for-age z-scores	-0.73±1.3	-0.6±1.4	0.7
Weight-for-age z-scores	-0.44±1.3	0.23±1.3	0.07
BMI-for-age z-scores	-0.15±1.5	0.67±1.0	**0.02**

Legend - [•]Median [range]; [#]mean z-scores ±SD. Analysis: [♣]Mann-Whitney test; [♦]Independent Samples T-test.

The follow-up data are presented at 2-years and 4-years. Fifty-nine children (31 males) with non-CF bronchiectasis had lung function data over two follow-up years and 31 (17 males) children had 4-year follow-up data (Table 4).

Table 4. Anthropometric and lung function data during follow-up period.

	Baseline (n=59)	Year 2 (n=59)	Year 4 (n=31)
Growth			
Height (cm) / Height–for-age z-scores	123.8±13.1 / -0.68±1.31	134.2±13.7 / -0.50±1.2	145.4 ±13.5 / -0.35±1.2
Weight (Kg) / Weight–for-age z-scores	25.5±6.8 / -0.19±1.34	31.9±8.7 / -0.13±1.14	39.0±11.0 / -0.16±1.0 [a]
BMI / BMI–for-age z-scores	16.4±1.9 / 0.19±1.38	17.3±2.2 / 0.15±1.17	18.2±2.8 / 0.04±1.1 [a]
Lung Function			
FVC (% Pred) / FVC z-score	76.2±19.7 / -2.61±1.82	72.4±20.6 / -2.39±1.8	70.5±17.8 / -2.68±1.62
FEV_1 (%/Pred) / FEV_1 z-score	68.3±21.0 / -2.66±1.68	71.6±20.5 / -2.34±1.7	69.2±17.7 / -2.62±1.52

Legend - Mean±SD; [a] n=30

During the follow-up period, organisms were isolated in cough swabs or sputum in 36 patients. The two commonest organisms isolated were: *H. influenzae* (n=20) and *S. pneumoniae* (n=9), followed by Moraxella catarrhalis (n=6), Staphylococcus aureus (n=3), Klebsiella pneumoniae (n=1) and Streptococcus group A (n=1). Two or more organisms were isolated in 12 children. The commonest organisms isolated together were *H. influenzae* and *S. pneumoniae*. During the follow-up, only one female had grown P. *aeruginosa*. It was not possible to determine whether these organisms were isolated during infective exacerbations and therefore no further analysis was performed.

Lung Function and growth

1. Three consecutive annual measurements

Serial measurements in 59 patients over a 2-year follow-up from baseline, showed an improvement (Fig 1) in z-score of FEV_1 (slope 0.17 p=0.039, 95% CI 0.01 to 0.34) and FVC (slope 0.21 p=0.016, 95% CI 0.04 to 0.39) per annum. (For example: If a patient started with a baseline FEV_1 of 0.8 z-scores, at 2-year follow-up their expected FEV_1 z-score would be 1.14) Anthropometric measurements did not change over the 2-year follow-up (Fig 2) [Height z-scores: slope 0.03, p=0.274, 95% CI (-0.03 to 0.1); Weight z-scores: slope 0.07, p=0.098, 95% CI -0.01 to 0.16 and BMI z-scores: slope 0.05, p=0.335, 95% CI -0-06 to 0.16)].

Females had higher BMI, FEV_1 and FVC z-scores with a slope of 0.11 (p= 0.750; 95% CI -0.58 to 0.89); 0.34 (p= 0.401; 95% CI -0.45 to 1.13) and 0.42 (p= 0.325; 95% CI -0.41 to 1.24), respectively, but these were not statistically different. The average height-for-age z-score was lower in females than males by 0.33 z-scores (p=0.303; 95% CI -0.98 to 0.31) over 2 year period of follow-up.

Those with reduced FEV_1 at baseline (< -2 z-scores), also had reduced weight (slope -0.26; p= 0.017 95% CI -0.47 to -0.05) and BMI z-scores (slope -0.27; p= 0.049 95% CI -0.53 to -0.001) at 2-years compared to those with normal FEV_1 at presentation. Furthermore, the rate of change in spirometry was greater in those with reduced spirometry at baseline [(FEV_1 slope: -1.84 (p< 0.0005; 95% CI -2.14 to -1.54) and FVC slope: -1.8 (p<0.0005; 95% CI -2.12 to -1.47)].

2. Five consecutive annual measurements

Thirty-one patients were included. The patients excluded were more likely to be older (p=0.023), have primary immunodeficiency (64%) and less likely to be idiopathic (25%). At baseline, there was no difference in mean z-scores for anthropometric or spirometric measurements (Table 5).

Table 5. Differences at baseline in children included and excluded from 4 years follow-up analysis

	Patients studied (n=31)	**Patients excluded** (n=28)	
Sex M:F	17:14	14:14	
Aetiology			
Idiopathic	16	7	
Congenital malformation	3	1	
Post-infectious	3	1	
Primary Immunodeficiency	7	18	
Aspiration	2	1	
			P value
Age[•] (years)	7.6 [4.8 to 12.5]	10.1 [5.1 to 15.8]	**0.023[♣]**
Growth [#]			
Height	-0.57±1.26	-0.79±1.38	0.529[♦]
Weight	-0.21±1.18	-0.17±1.53	0.914[♦]
BMI	0.08±1.22	0.31±1.56	0.543[♦]
Lung Function[#]			
FVC	-2.16±1.67	-2.34±1.96	0.710[♦]
FEV_1	-2.72±1.57	-2.58±1.81	0.742[♦]

Legend - [•]Median [range]; [#]mean z-scores ±SD. Analysis: [♣]Mann-Whitney test; [♦]Independent Samples T-test.

Examination of five consecutive annual measurements (Fig 3) in 31 patients, demonstrated an improvement in height-for-age z-score (slope 0.054, p=0.01, 95% CI 0.013 to 0.095). There were no significant trends for weight-for-age or BMI z-scores. There was also no evidence of change in FVC and FEV_1 z-scores (Fig 4) (slope 0.009, p=0.859, 95% CI -0.09 to 0.107 and slope 0.000, p=0.999, 95% CI -0.09 to 0.09 respectively (For example: If a patient started with a baseline FEV_1 of 0.8 z-scores, at 4-year follow-up their expected FEV_1 would 0.84). The group was too small for further subgroup analysis.

Discussion

The main finding of this study is that children with non-CF bronchiectasis receiving treatment in specialist centres have stable lung function z-scores as determined by spirometry, associated with steady growth (Figs.1 - 4). Children with abnormal lung function at referral were older and had poorer nutritional state. Although the majority of patients were infected at some time point, we could not characterise their infection status in detail due to lack of data, which is a weakness of this study. Serial examination of the first three consecutive years after initial referral and treatment showed a small improvement in spirometric parameters. In a subgroup in which five consecutive annual data were available, although, the mean baseline FEV_1 z-score was low, there was no significant deterioration in spirometry or nutrition over the study period. The reasons for the differences in evolution in spirometry over three and five annual measurements are unclear, but inspection of the raw data (Figs 1 and 3) suggests that

there is no real clinically significant change at any time point, and that spirometry remained stable after referral.

The main limitation of our study is that we have not considered other criteria to assess disease severity such as change in HRCT[10, 11], presence of chronic infection, co-morbidity or number of exacerbations, which have been shown to be associated with fall in FEV_1 (1.4 to 3% per year) in adults.[12, 13] The interval between onset of symptoms and diagnosis was not quantified. The follow-up described in our series is limited to the first two and 4-years after referral to a tertiary hospital, not after diagnosis. These children were generally referred with an undiagnosed respiratory problem rather than for tertiary management after diagnosis. Other factors known to play a role in growth and lung function evolution are environmental and social issues, which were not studied. It is not routine to repeat HRCT scans on follow-up in children with bronchiectasis at our two centres; hence the lack of HRCT criteria. We cannot exclude the possibility that some children may have shown regression of changes. However, the scans were reviewed by experienced clinicians and radiologists, and, as far as is possible, 'pre-bronchiectasis' patients were removed from the study. The ideal study, with individual diagnoses studied separately, is not feasible given the low numbers, and heterogeneity of paediatric disease. This would require a multicentre study, which would introduce more treatment variability. Nevertheless, the study group reflects a cohort of non-CF bronchiectasis patients in two tertiary respiratory centres. However, it should be noted that this retrospective data with differing aetiologies and overall evolution might not be representative of all patients with non-CF bronchiectasis.

The obstructive lung disease seen in our study is as expected, but conflicting results have been reported regarding its progression in childhood. *Twiss et al* described deteriorating FEV_1 in a group of 6 to 15 year-old children with non-CF bronchiectasis over a 4.5-year period[14], which was consistent with lung function decline in adults with bronchiectasis.[15, 16] Ethnicity, social and genetic factors may contribute to these differences as the prevalence of paediatric bronchiectasis in New Zealand is one of the highest reported. Additionally, the bronchiectasis described in this population was extensive and severe.[10, 17] However, *Twiss et al* also reported a wide variability in individual disease severity and progression, with some children not showing deterioration in their lung function. In contrast a study from Turkey, showed an improvement in FEV_1 of 11% per year in school age children.[18] Their cohort, compared to the New-Zealand cohort had less severe disease and different management. Our study cannot be directly compared with other similar studies as the clinical context is different, outcome measures are not the same and our spirometry results are presented as z-scores. The use of z-scores is an advantage as they take into account the age-related between subject variability[9], such that results over time are more comparable. The extent to which lung function changes over time within the same individual is difficult to assess without knowledge of how much change can be expected in health over the same period.

In the present study, underlying aetiology for bronchiectasis was known in more than half of the patients (61%). Investigation for a cause of bronchiectasis may allow early implementation of disease specific therapy (IVIG) which may have contributed to a good outcome.[5] Another possible contributor might be the aggressive use of airway clearance and treatments for infection, but this is conjectural. Antibiotic use was not protocol driven, which was a weakness of the study, but there is no evidence base or generally agreed consensus on

which to base a protocol. There is a clear need for evidence-based guidelines on this point, and the lack of such guidelines makes comparisons between the results of different series difficult.

Twiss et al study described a consistent trend for those with primary immunodeficiency to have a more rapid decline in lung function.[14] This was not so in our study which includes a relatively large group with primary immunodeficiency (n=25). Although subgroup analysis is not reliable due to small numbers, the underlying aetiology may influence disease severity. Three patients with post-infectious bronchiectasis had poorer lung function compared to other groups, with marked airflow obstruction already present at baseline [(mean FEV_1 z-score -4.88±1.37(SD)], which is similar to other studies.[14] Although post-infectious aetiology is rare in the developed world it is still a significant cause in developing countries.[18] However, it would not be prudent to extrapolate our findings to developing countries, given the very different circumstances, both in terms of aetiology of bronchiectasis and delivery of health care, and the very small numbers of post-infective bronchiectasis in our series.

In contrast to some CF studies[19-21] the majority of our patients did not show poor anthropometric parameters at baseline making it impossible to assess if improvement in weight improved lung function. Nevertheless, during 2-years follow-up, patients with worse FEV_1 showed a significant lower weight and BMI z-scores and tended to keep lung function lower. These patients were older at referral and hence likely to have received treatment later, which might have contributed to the severity of disease. Overall 2-year mean height z-scores for female patients was lower than males, but this was not statistically significant (slope -0.33, p=0.303). Our study demonstrates that females with non-CF bronchiectasis have equally good lung function and growth as their male counterparts, similar to recent findings in CF patients.[22]

In conclusion, children with non-CF bronchiectasis show an adequate growth in time and lung function stabilises but does not normalise with treatment, underscoring the need for early detection and institution of appropriate therapy. Children diagnosed with non-CF bronchiectasis can be stabilized in terms of lung function by modern, aggressive treatment, but may nonetheless have considerable respiratory morbidity. We cannot prove from this study that early detection of bronchiectasis and initiation of treatment is beneficial, although this seems likely. Further studies are needed to determine the best, evidence based management of these patients.

Competing Interests: None

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Figure Legends

Fig 1. Evolution of FEV_1 and FVC z-scores with time (n=59, 2 years)
Fig 2. Evolution of height and BMI-for-age z-scores with time (n=59, 2 years)
Fig 3. Evolution of height and BMI-for-age z-scores with time (n=31, 4 years)
Fig 4. Evolution of FEV_1 and FVC z-scores with time (n=31, 4 years)

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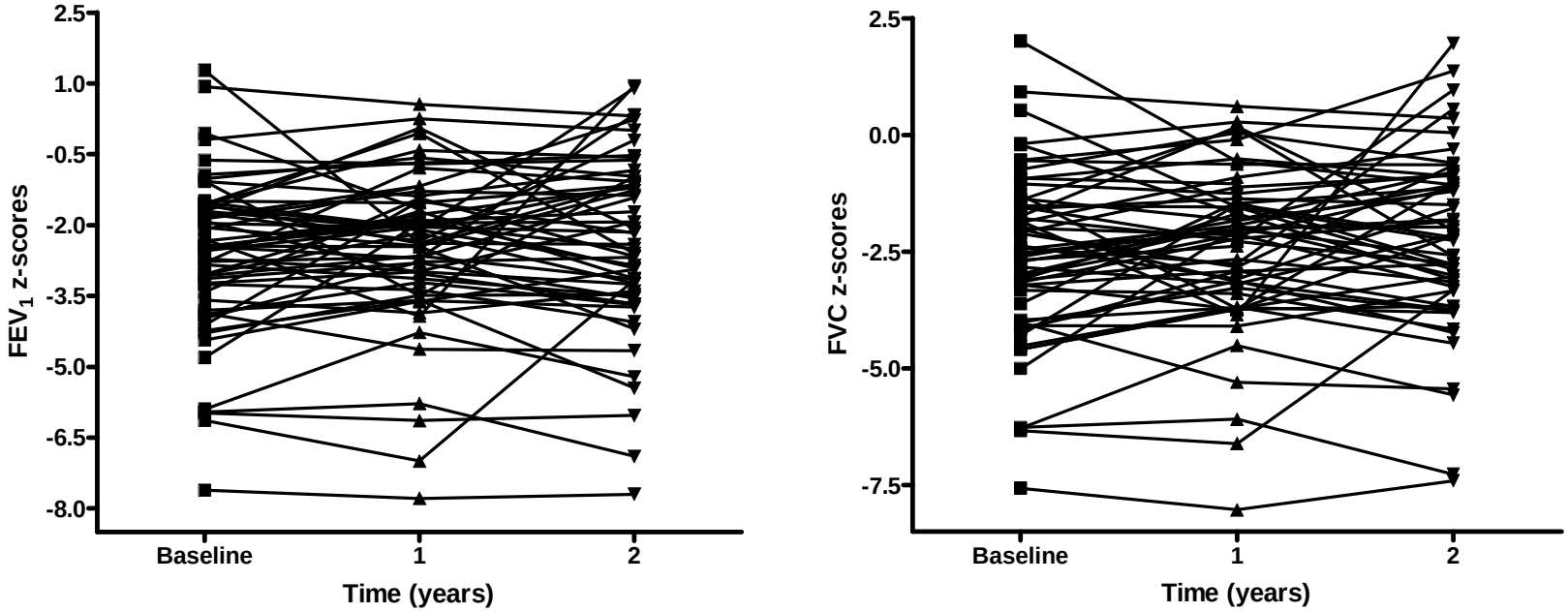

Fig 1. Evolution of FEV_1 and FVC z-scores with time (n=59, 2 years)

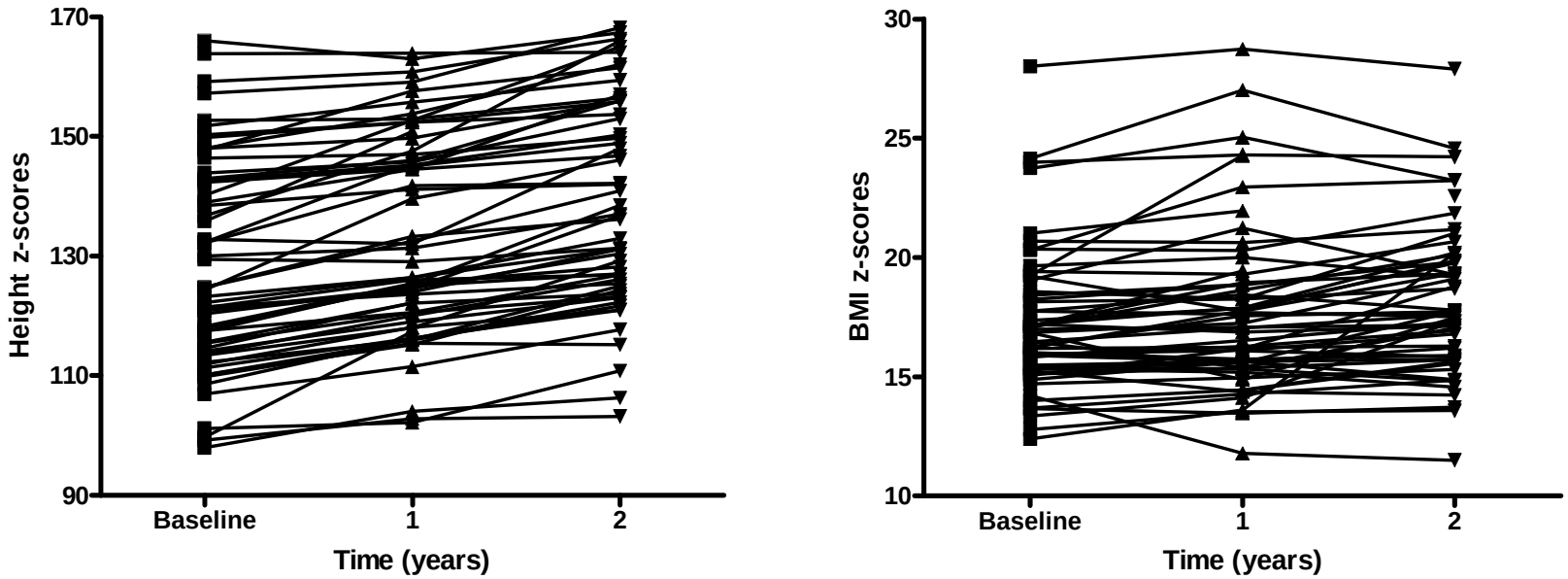

Fig 2. Evolution of height and BMI-for-age z-scores with time (n=59, 2 years)

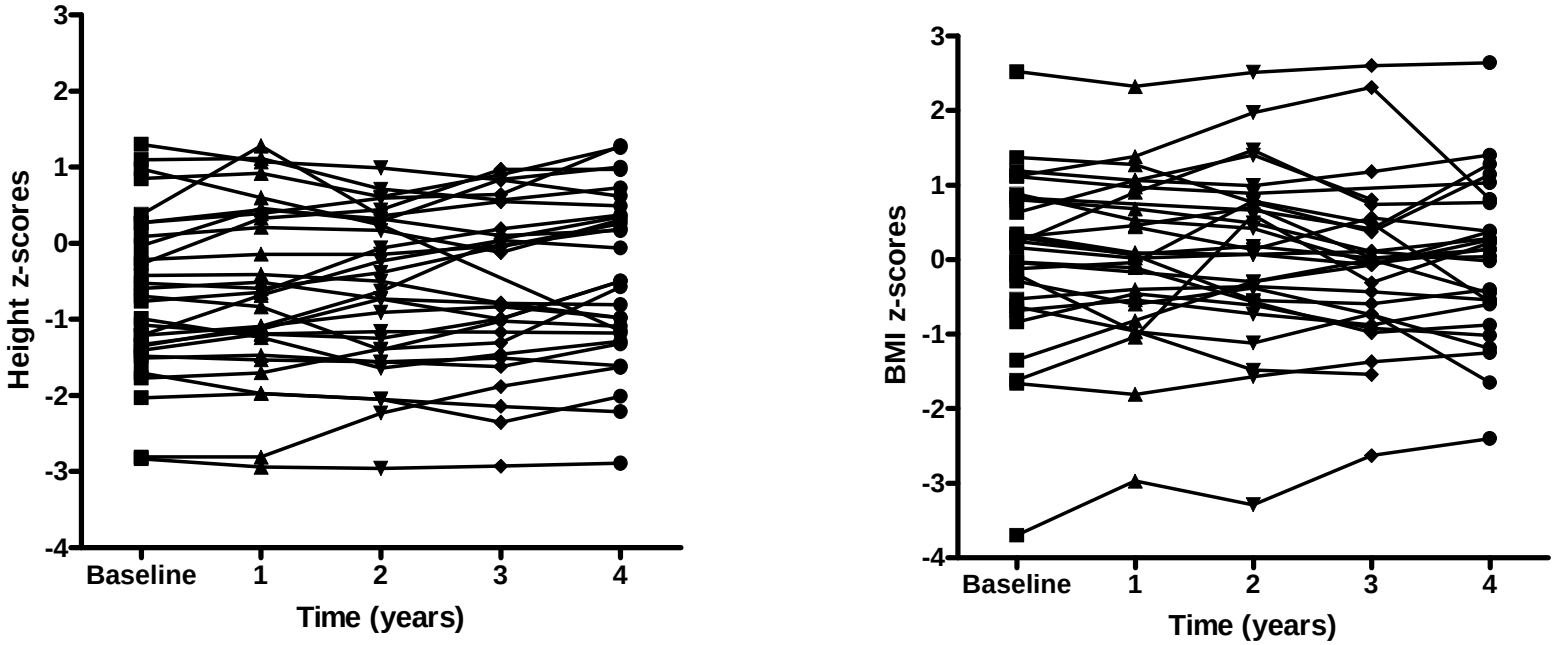

Fig 3. Evolution of height and BMI-for-age z-scores with time (n=31, 4 years)

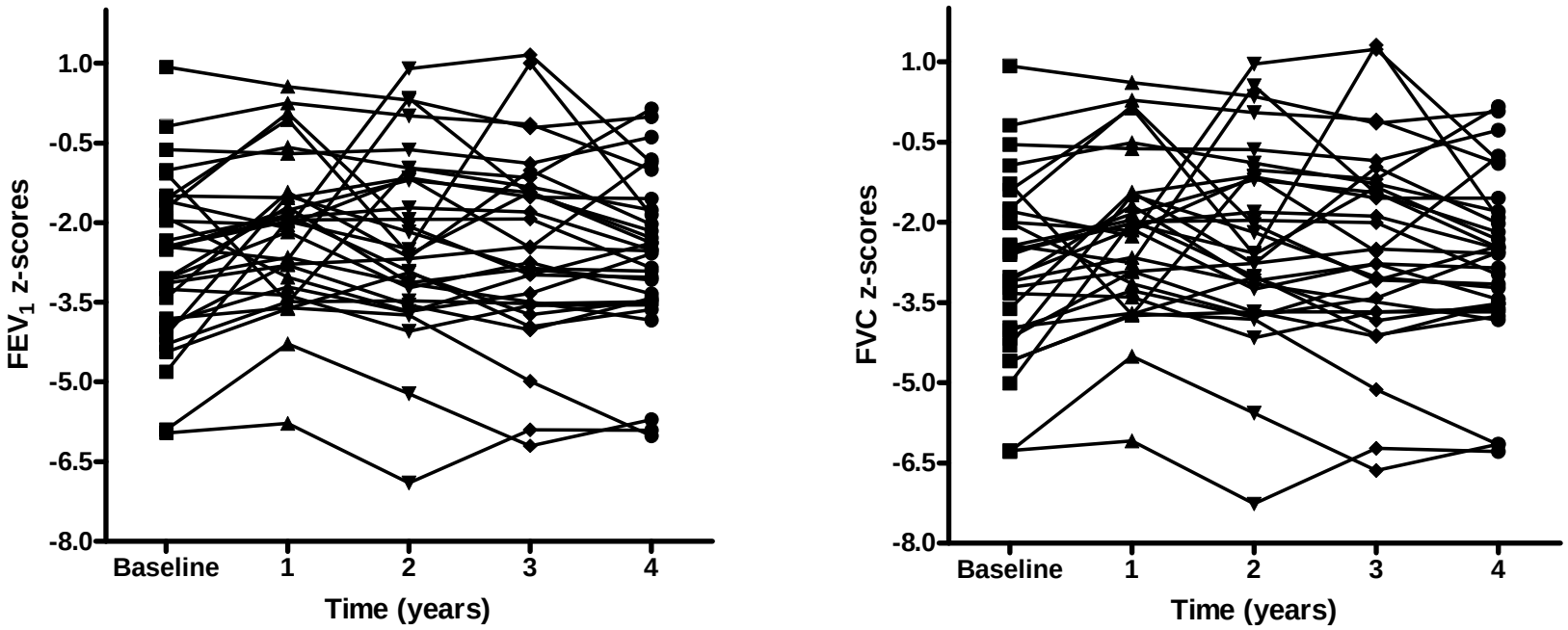

Fig 4. Evolution of FEV_1 and FVC z-scores with time (n=31, 4 years)