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EARLY LIFE GROWTH PATTERNS PERSIST FOR 12 YEARS AND IMPACT PULMONARY OUTCOMES IN CYSTIC FIBROSIS

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Abstract

Background—In children with cystic fibrosis (CF), recovery from growth faltering within 2 years of diagnosis (*Responders*) is associated with better growth and less lung disease at age 6 years. This study examined whether these benefits are sustained through 12 years of age.

Methods—Longitudinal growth from 76 children with CF enrolled in the Wisconsin CF Neonatal Screening Project was examined and categorized into 5 groups: R_{12}, R_6, and R_2, representing Responders who maintained growth improvement to age 12, 6, and 2 years, respectively, and I_6 and N_6, representing Non-responders whose growth did and did not improve during ages 2–6 years, respectively. Lung disease was evaluated by % predicted forced expiratory volume in one second (FEV_1) and chest radiograph (CXR) scores.

Results—Sixty-two percent were Responders. Within this group, 47% were R_{12}, 28% were R_6, and 25% were R_2. Among Non-responders, 76% were N_6. CF children with meconium ileus (MI) had worse lung function and CXR scores compared to other CF children. Among 53 children with

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pancreatic insufficiency without MI, R_{12} had significantly better FEV_1 (97–99% predicted) and CXR scores during ages 6–12 years than N_6 (89–93% predicted). Both R_6 and R_2 experienced a decline in FEV_1 by ages 10–12 years.

Conclusions—Early growth recovery in CF is critical, as malnutrition during infancy tends to persist and catch-up growth after age 2 years is difficult. The longer adequate growth was maintained after early growth recovery, the better the pulmonary outcomes at age 12 years.

Keywords

growth; growth faltering; catch-up growth; pulmonary function; quantitative chest radiography; lung disease

INTRODUCTION

The associations between nutrition and pulmonary status in patients with cystic fibrosis (CF) have been reported.[1–9] The positive association between better nutritional status in early life and better lung function in later years has led to the development of CF clinical practice guidelines for comprehensive nutrition management,[10] in hopes of delaying progression of lung disease. The introduction of widespread newborn screening (NBS) for CF offers an opportunity to treat and prevent malnutrition.[11–13] However, almost half of U.S. infants still demonstrate some degree of malnutrition in the first months of life.[14]

The present study represents the third of a series of Responder studies we conducted over the past decade. Responder I utilized an innovative concept of early weight recovery to define treatment responders within 2 years of diagnosis in infants with CF and identified factors associated with the likelihood of being Responders.[15] Responder II examined whether Responders achieved better pulmonary status at 6 years of age when reliable pulmonary function data can be obtained in the majority of children with CF. We demonstrated that Responders had fewer cough symptoms, better lung function, and better chest radiograph scores at age 6 years compared to Non-responders.[8]

It is unknown if pulmonary benefits associated with early growth recovery experienced by the Responders are sustained beyond age 6 years. The present study, Responder III, was designed to fill in this gap of knowledge. Specifically, we examined: 1) whether Responders who maintained adequate growth during ages 2–6 years continued to do so through age 12 years, 2) whether Non-responders continue to follow their respective growth trajectories during ages 6–12 years, and 3) the impact of growth during ages 6–12 years on pulmonary status at age 12 years in Responders and Non-responders.

MATERIALS AND METHODS

Study Population

The study population included 76 children with CF who were enrolled in the Wisconsin Randomized Clinical Trial of CF Neonatal Screening Project (WI-RCT) and had complete growth data and valid pulmonary function data through 12 years of age. The WI RCT is a prospective longitudinal investigation initiated in 1985 to assess the benefits and risks of

NBS for CF.[13,16] Briefly, randomization of newborns occurred from 4/15/85 until 6/30/94; for half of the randomly assigned newborns, early diagnosis of CF was established through NBS, while the diagnosis of CF in newborns randomized to the control arm was generally established through signs and symptoms of CF. Longitudinal follow-up of the WI RCT cohort continued through 2011 until the youngest patient reached 17 years of age. The WI RCT was approved by the human subjects committee at the University of Wisconsin and the Research and Publications Committee/Human Rights Board at Children's Hospital of Wisconsin.

A total of 138 children were enrolled in the WI RCT.[12] The Responder I study included 100 children who had complete data on growth, plasma fatty acid and dietary data in the first 2 years of life with analyses focused on the subgroup of 80 subjects who had pancreatic insufficiency (PI) but no meconium ileus (MI).[15] The Responder II study included 91 children (9 children lost to follow up during 2–6 years of age)[8] and the present study (Responder III) included 76 children (15 children lost to follow up during 6–12 years of age).

Growth assessment and definition of responders

Weight, recumbent length before age 2 years and standing height after age 2 years were measured every 3 months.[11,12] Age- and sex-specific z-scores for weight (WTz), length/height (HTz) and body mass index (BMIz) were computed by using the 2000 CDC growth charts,[17] which were used in our Responder I and II studies and the recommended growth references for all ages before the CDC and the American Academy of Pediatrics recommended WHO growth charts for age 0–2 years in 2010 and 2012.[18, 19] In addition, by using the CDC charts in the present Responder III study, we avoided the discrepancies that would have been encountered when switching between growth charts at age 24 months, which we recently described.[20]

Responders were defined by recovery from malnutrition and growth faltering resulting from untreated CF as indicated by catch-up weight gain to the level comparable to their birth weight z-score within 2 years of diagnosis.[15] The rationale for this approach is based on findings that birth weights in infants with CF were similar[21, 22] or only slightly lower[22, 23] than those of healthy infants, but a large percentage of CF children fall below the 5th percentile by the time of diagnosis.[21, 22, 24] In addition, physical growth of infants and young children varies greatly due to intrauterine, genetic and nutritional influences. Therefore, recovery of weight to a level comparable to one's birth weight z-score represents a more individualized indicator of treatment responsiveness than using a common reference level (such as weight > 5th or 10th percentile) for all children with CF.

Classification of growth patterns during 2–6 and 6–12 years of age

Growth pattern during age 2–6 years was evaluated using HTz and BMIz.[8] WTz was not used to define growth pattern because WTz is influenced by both age and height. For example, a child may have a low WTz because he or she is short for age and not because of a low weight for height. On the other hand, BMIz is an independent indicator of weight for height proportion, thus provides a complimentary measure to HTz.

The cumulative changes in HTz and BMIz during age 2–6 years (i.e., ΔHTz and ΔBMIz) were estimated using linear regression for each subject (i.e., slope multiplied by the 4-year interval). Thereafter, ΔHTz and ΔBMIz were evaluated relative to a one-channel difference (equivalent to approximately 0.67 Z-score) on the respective CDC growth charts.[8] As illustrated in Figure 1, Responders whose ΔHTz and/or ΔBMIz increased or remained stable during ages 2–6 years were classified as "maintained" while Responders whose ΔHTz and/or ΔBMIz declined were classified as "not maintained". On the other hand, Non-responders whose ΔHTz and/or ΔBMIz increased during ages 2–6 years were classified as "improved", while Non-responders whose ΔHTz and ΔBMIz remained stable or declined during age 2–6 years were classified as "not improved."

The above process was repeated for ages 6–12 years, resulting in 8 possible subgroups (Figure 1). However, 3 subgroups had fewer than 5 patients. Therefore, we categorized growth patterns through age 12 years into 5 groups: 3 Responder groups (R_{12}, R_6, and R_2, representing Responders who maintained growth improvement to age 12, 6, and 2 years, respectively) and 2 Non-responder groups (I_6: Non-responders whose growth improved during 2–6 years of age and N_6: Non-responders whose growth did not improve during 2–6 years of age).

Pulmonary outcome measures at ages 6–12 years

Pulmonary function tests (PFT) were performed every 6 months beginning at age 4 years for the purpose of familiarizing and training young children with CF on this test, as described in detail previously.[25] Only data validated with the Pediatric Alternate Spirometry System and/or ATS criteria were included,[25] and the percentage of PFT measurements in children younger than 5.5 years did not differ significantly between Responders (6.2%) and Non-Responders (7.0%). Percent predicted forced expiratory volume in one second (FEV_1) were calculated using equations from Wang et al.[26] Chest radiographs obtained at diagnosis, 2 and 4 years of age, and annually thereafter were scored using the Brasfield system[24] and the Wisconsin system[25, 28, 29] by two raters (a pediatric pulmonologist and a thoracic radiologist). A total of 580 FEV_1 measurements (7.6 ± 3.3 per patient) and 521 chest radiographs (6.9 ± 1.4 per patient) were analyzed.

Statistical Analysis

Analysis of variance was used to compare means when the data were normally distributed, and nonparametric analysis of variance was used when the data were skewed. Chi-square and Fisher's exact test were used to compare categorical variables as appropriate. For longitudinal analyses, mixed effects models were used to evaluate the associations between growth and pulmonary outcomes with Responder status while adjusting for sex, diagnosis by NBS and birth weight z-scores. SAS 9.4 (SAS Institute, Inc, Cary, NC) and R (www.rproject.org) were used for data processing and statistical analyses. P-values < 0.05 were considered statistically significant.

In consistent with Responder I and II studies,[8,15] all analyses that compared growth and pulmonary outcomes were stratified or conducted separately by gastrointestinal phenotype, on the basis of the following rationale: 1) PS patients are at lower risk of malnutrition and

are able to achieve normal growth (i.e., mean weight- and length-for-age at approximately the 50th percentile) with energy intake at 99% of their recommended requirement,[12] and 2) MI patients have been shown to experience poorer growth despite a higher energy intake than patients without MI with a similar age at diagnosis and treatment protocol.[30]

RESULTS

Characteristics of the study population

Table 1 compares the characteristics of the study populations across the three Responder studies. The 76 children with CF included in Responder III is a subset of children who completed follow-up to 12 years of age and had valid PFT measurements. Consistent with the Responder I and Responder II studies,[8,15] Responders had significantly lower birth weights but higher height z-scores and BMI z-scores at 2 years of age compared to Non-responders. None of the characteristics shown in Table 1 differ significantly across the 3 Responder studies.

Growth patterns during 6–12 years of age in relation to prior growth and Responder status

Figure 1 shows that 62% (47 out of 76 CF children) were Responders. About three-quarters of the Responders (35 out of 47) followed their growth trajectories and maintained their growth improvement during 2–6 years; about two-thirds of the latter (22 out of 35) sustained the improvement to 12 years of age (R_{12}), while the other one-third (13 out of 35) only maintained growth improvement to 6 years of age (R_6). About a quarter of Responders (12 out of 47) did not maintain their growth improvement beyond 2 years of age (R_2). Among Non-responders, about three-quarters (22 out of 29) followed their growth trajectories and did not improve during 2–6 years (N_6); moreover, 90% of N_6 (20 out of 22) had no further improvement during 6–12 years. Only a quarter of Non-responders (7 out of 29) had improved growth during 2–6 years (I_6), and none of them maintained the improvement through 12 years of age. These data demonstrate that growth patterns established early in life tend to persist and determine subsequent growth trajectories. Overall, of the 76 children with CF included in this study, 29% were R_{12}, 17% R_6, 16% R_2, 9% I_6 and 29% N_6.

Growth and pulmonary status during 6–12 years of age by gastrointestinal phenotype

As shown in Figure 2, the MI subgroup had significantly lower height z-scores than the PI (p=0.014) and PS (p=0.005) groups, and significantly lower BMI scores than the PS group (p=0.003). Compared to the PS group, the PI group did not differ significantly in height z-scores (p=0.13), but their BMI z-scores were lower (p=0.028).

Differences in height and BMI were also reflected in different Responder rates across the three phenotypes. The percentage of R_{12} was lowest in MI (12%), followed by PI (32%) and highest in PS (50%), while the percentage of N_6 was higher in MI (47%) compared to PI (23%) and PS (33%). However, these differences did not reach statistical significance, most likely due to the small sample size of the PS group (n=6).

Regarding pulmonary outcomes, Figure 3 shows that FEV_1 was significantly lower and declined at a faster rate during age 6–12 years in MI compared to PI (p=0.008) and PS

(p=0.024). Wisconsin CXR scores were also worst in MI, but the differences were only significant compared with PI.

These results provide evidence to support our previous approach in Responder I and II studies[8,15] that delineating growth-pulmonary relationships in CF is best conducted by separate analysis for each phenotype, because differences in growth and pulmonary outcomes are not uniform across phenotypes, making it difficult to satisfactorily adjust the confounding by phenotype. Due to small sample sizes for the MI and PS groups and to provide comparison with Responder I and II studies,[8,15] we conducted the remaining analyses below within the PI group only.

Growth and pulmonary status during 6–12 years of age in the PI group

Figure 4 shows that the three Responder groups (R_{12}, R_6 and R_2) had significantly higher height z-scores than the two Non-responder groups (N_6 and I_6), $p < 0.01$ for all pairwise comparisons. Smaller differences in BMI z-scores were observed, but significant differences were observed in R_{12} and R_6 compared to N_6 and R_2, $p < 0.05$ for all pairwise comparisons. The major difference between I_6 and N_6 is that the I_6 group was very short (mean height z-score <10th percentile) with normal BMI (~60th percentile), while the N_6 group was taller (~20th percentile) but had lower BMI (~35th percentile). The I_6 group is the shortest among the 5 groups, and their temporary improvement in growth during ages 2–6 years was due to increase in BMI and not in height status.

Figure 5 shows that all five groups had mean FEV_1 >89%. R_{12} maintained the highest FEV_1 (97–99%) during ages 6–12 years that was consistently higher than N_6 (89–93%), p=0.037. Both R_6 and R_2 had very good FEV_1 at 6–8 years but their FEV_1 declined around 10–12 years of age. Wisconsin CXR scores revealed increasing severity of lung disease from 6 to 12 years of age in all five groups (Figure 5). This finding supports our previous observation[22] that the Wisconsin CXR score is more consistent and sensitive than FEV_1 in detecting mild lung disease in young children with CF. R_{12} had the lowest (i.e., best) CXR scores throughout 6–12 years of age. The CXR scores for R_{12} were significantly better compared to N_6 (p=0.016), I_6 (p=0.034) and R_6 (p=0.033).

Growth and pulmonary status at 12 years of age in the PI group

Figure 6 shows the associations between growth and pulmonary outcomes at age 12 years. FEV_1 and Wisconsin CXR scores mirrored height z-scores, with the three Responder groups (R_{12}, R_6 and R_2) better than the 2 Non-responder groups (N_6 and I_6). Overall, R_{12} had normal height and near normal BMI z-scores and the best FEV_1 and Wisconsin CXR scores at age 12 years. This finding suggests that the longer adequate growth is maintained, the better the pulmonary outcomes at age 12 years.

DISCUSSION

Long-term outcome studies after NBS are rare but very much needed and valuable in the CF population. The present study examined growth and pulmonary outcomes more than a decade following diagnosis of CF through NBS in a prospectively followed cohort.[12,13] Results from the present study and our previous work[8,15] advance our knowledge in

understanding growth patterns and their impact on lung disease progression in children with CF and PI from infancy through 12 years of age. Specifically, we demonstrated that growth patterns established early in life tend to persist and determine subsequent growth trajectories. That is, infants with CF and PI who recovered birth weight z-scores by 2 years of age (Responders) are more likely to maintain better height and BMI z-scores through 12 years of age, while Non-responders are more likely to continue sub-optimal growth. Most noteworthy is that in our study cohort, none of the Non-responders achieved further catch-up growth consistently during 2–12 years. Temporary improvements in BMI were achieved for a minority of patients (n=7 during age 2–6 but not 6–12 years, and n=2 during age 6–12 but not 2–6 years), although height z-scores remained low. This illustrates how difficult it is to attain catch-up growth after the first 2 years of life, when growth rate is the highest during the life span. Our results are consistent with a recent report by Heltshe et al who showed that weight for age as early as 4 months of life appears to predict growth at 2 years of age.[14]

The most important clinical implication resulting from our findings is that, in children with CF and PI, early response (recovery of birth weight z-scores within 2 years of diagnosis) is not only essential in setting the foundation for future growth trajectory but also critical in increasing the likelihood of achieving better structural and functional lung disease at age 6 years.[8] However, in the present Responder III study, we found that the pulmonary benefit experienced by Responders at age 6 years were lessened at 12 years of age. That is, achieving Responder status at age 2 years alone is not sufficient to sustain normal lung function through 12 years of age: maintaining growth improvement through age 12 years is also needed. For example, our data in Figures 5 and 6 showed that both R_2 and R_6 had good FEV_1 and CXR scores at 6 years, yet only R_{12} sustained normal measurements of FEV_1 (and had the smallest worsening in CXR scores) from 6 to 12 years. Temporary growth improvement in BMI but not height status, as was observed in the I_6 group, was accompanied by transient increases in FEV_1 that were not sustained at age 12 years and worsening CXR scores during 6–12 years of age.

An unanswered question is whether one can predict which infants would be Non-Responders (approximately one out of three infants) and which Non-Responders would continue growth faltering through 6 years of age (approximately three out of four Non-Responders), as well as which Responders will not maintain growth improvement beyond 2 years of age (approximately one out of four Responders), in order to intervene early with more aggressive nutrition therapy. Definitive answers to this question would be extremely difficult to obtain, as randomized clinical trials with multiple arms to test each potential determinant over 12 years are not feasible. In our Responder I study,[15] early diagnosis through NBS with less severe malnutrition and pulmonary disease at the time of diagnosis, in conjunction with high dietary intakes of calories (at >120% of estimated requirement) and higher plasma levels of linoleic acid (the principle essential fatty acid) were found to increase the likelihood of being Responders. We concluded that frequent monitoring of plasma linoleic acid through assessment of plasma essential fatty acid profile is necessary and should be implemented in routine clinical care.[15] However, current practice guidelines from the US Cystic Fibrosis Foundation[10, 31, 32] still conclude that no sufficient evidence is present to recommend for or against essential fatty acid supplementation and that more research is needed. In our Responder II study,[8] we found that Responders maintained adequate growth

through age 6 years despite lower caloric intake than Non-responders. This is likely due to the fact that poor growth in Non-responders prompted increase in caloric supplementation in order to promote catch-up growth, while Responders only needed to ingest sufficient calories to maintain current growth. *Pseudomonas aeruginosa* infection reduced the likelihood of being a Responder,[15] but was not significantly associated with subsequent growth patterns during 2–6 years[8] or 6–12 years of age (data not shown). By age 12 years, 43 of 47 Non-Responders and 25 of 29 Responders had at least one recorded culture positive for *Pseudomonas*. We did not observe significant differences in *Pseudomonas* infections between Responders and Non-Responders. This may be due, at least partially, that very few subjects were never positive for *Pseudomonas* by 12 years of age.

Our study has two limitations. First, the sample size is relatively small, which limits our ability to perform subgroup comparisons or to adjust for potential confounders. Studies with large sample size are needed to validate our findings, especially for Non-responders with growth improvement at ages 2–6 years (the I_6 group) and to investigate more in-depth in MI and PS patients. Second, our studies are observational, therefore, our findings on the impact of growth on pulmonary outcomes do not imply causality. Instead, it's likely that associations are bidirectional, i.e., better growth leads to better pulmonary outcomes and vice versa.

CONCLUSIONS

Results from this long-term outcome study provide clear evidence that in infants with CF, early nutritional response (recovery of birth weight z-scores within 2 years of diagnosis) determines subsequent growth trajectories and increases the likelihood of achieving better growth, better lung function and less severe chest radiographic abnormalities through 12 years of age. Further studies are needed to identify optimal CF interventions that can maximize the chance for achieving early growth recovery, as catch-up growth after infancy is difficult to attain.

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Abbreviations

BMIz	Age- and sex-specific z-scores for body mass index

CF	Cystic fibrosis
CXR	Chest radiograph
FEV_1	Forced expiratory volume in 1 second
HTz	Age- and sex-specific z-scores for length (< 2 years) or height (≥ 2 years)
I_6	Non-responders whose growth improved during 2–6 years of age
MI	Meconium ileus
N_6	Non-responders whose growth did not improve during 2–6 years of age
NBS	Newborn screening
PFT	Pulmonary function tests
PI	Pancreatic insufficiency
PS	Pancreatic sufficiency
R_6	Responders who maintained their growth through 6 years of age
R_{12}	Responders who maintained their growth through 12 years of age
WI RCT	Wisconsin Randomized Clinical Trial of CF Newborn Screening
WTz	Age- and sex-specific z-scores for weight

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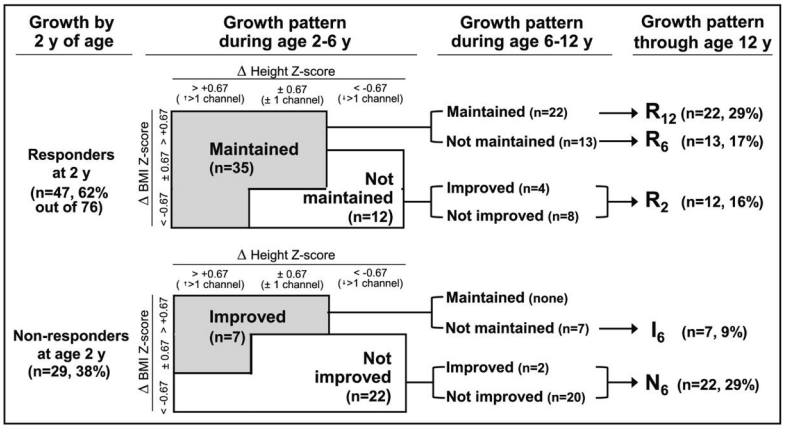

Figure 1.

Classification of growth patterns through 12 years of age. Responders recovered birth weight z-scores within 2 years of diagnosis while Non-responders did not. R_{12}, R_6, and R_2 maintained growth improvement to age 12, 6 and 2 years, respectively. I_6 had growth improvement during age 2–6 years while N_6 did not. (50)

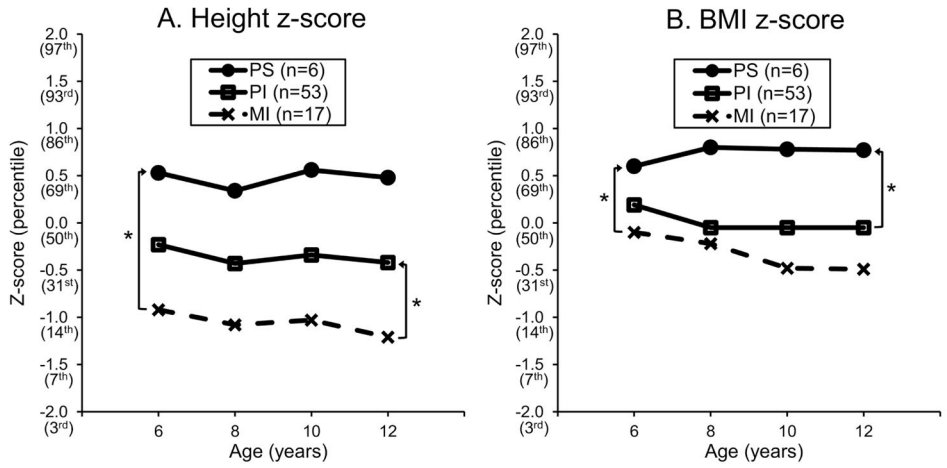

Figure 2.

Comparison of growth during ages 6–12 years by gastrointestinal phenotype. MI: meconium ileus; PI: pancreatic insufficiency without MI; PS: pancreatic sufficiency. Differences among 3 phenotypes were assessed by mixed effects models adjusting for sex, birth weight z-score and diagnosis by NBS; arrows with * indicate pairwise comparisons with $p<0.05$. (49)

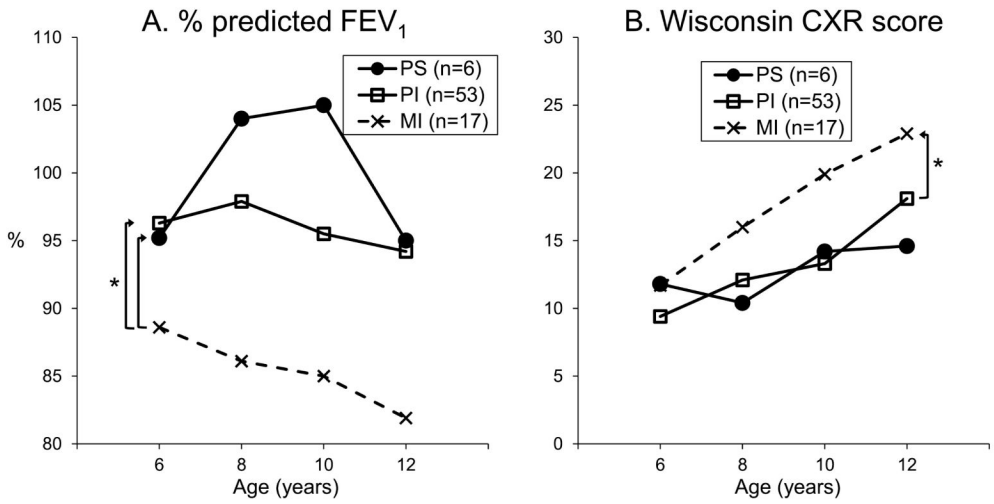

Figure 3.

Comparison of pulmonary status during ages 6–12 years by gastrointestinal phenotype (see Figure 1 legend for abbreviations). Differences among 3 phenotypes were assessed by mixed effects models adjusting for sex, birth weight z-score and diagnosis by NBS; arrows with * indicate pairwise comparisons with $p<0.05$. (47)

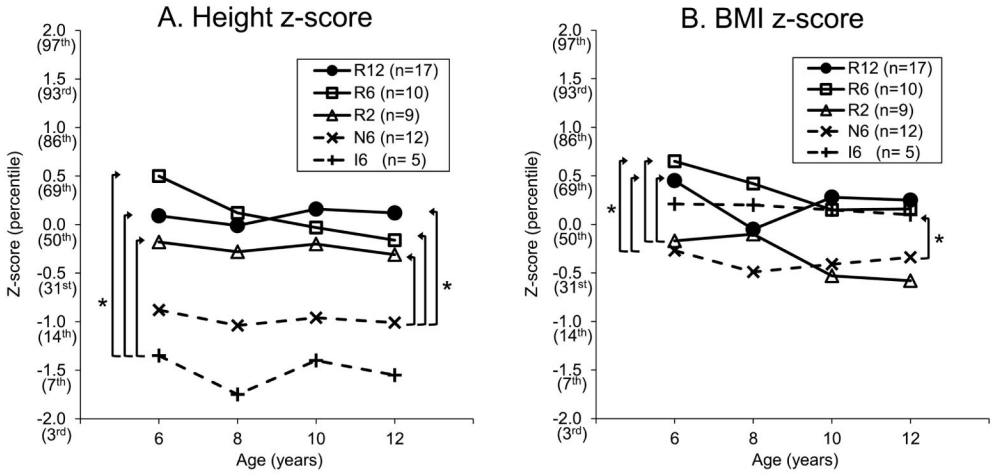

Figure 4.

Comparison of growth during ages 6–12 years in PI patients among R_{12}, R_6, R_2, N_6 and I_6 (see Figure 1 legend for abbreviations). Differences were assessed by mixed effects models adjusting for sex, birth weight z-score and diagnosis by NBS; arrows with * indicate pairwise comparisons with $p<0.05$. (50)

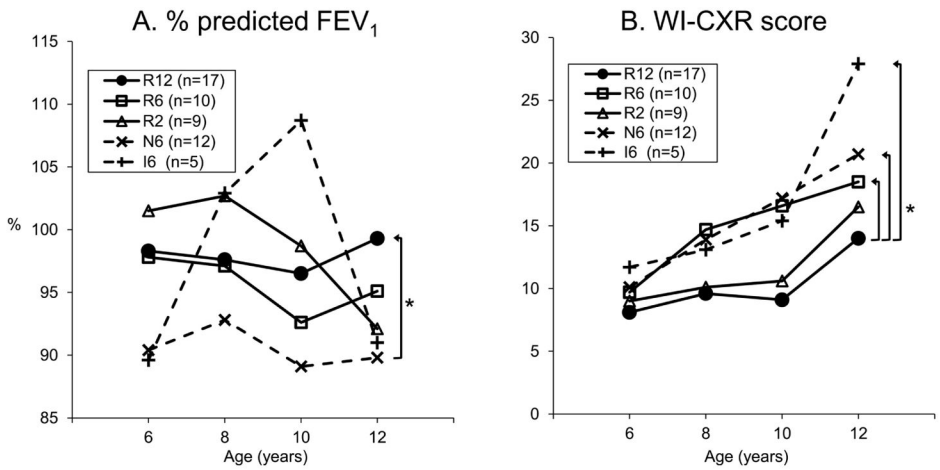

Figure 5.

Comparison of pulmonary status during ages 6–12 years in PI patients among R_{12}, R_6, R_2, N_6 and I_6 (see Figure 1 legend for abbreviations). Differences were assessed by mixed effects models adjusting for sex, birth weight z-score and diagnosis by NBS; arrows with * indicate pairwise comparisons with $p<0.05$. (51).

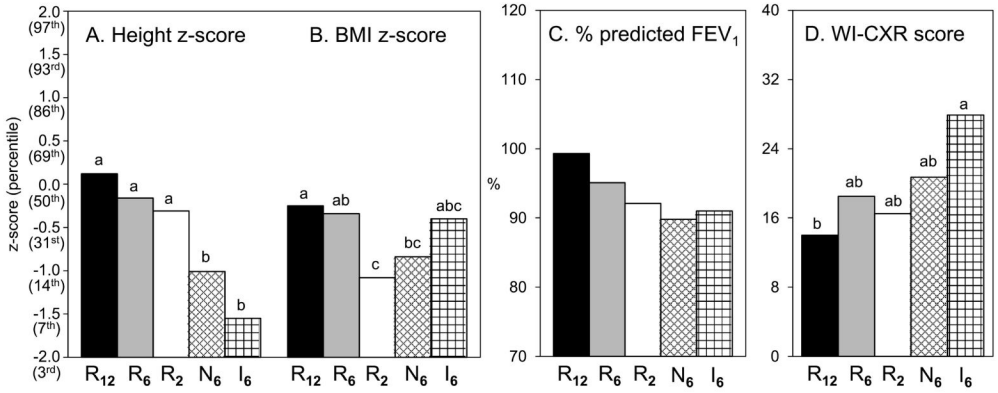

Figure 6.

Comparison of growth and pulmonary status at age 12 years in PI patients among R_{12}, R_6, R_2, N_6 and I_6 (see Figure 1 legend for abbreviations). Differences were assessed by linear regression adjusting for sex, birth weight z-score and diagnosis by NBS. Pairwise comparisons of all 5 groups were performed, and bars with different alphabet letters are statistically different at $p<0.05$. (50)

Table 1

Baseline characteristics of responders and non-responders

	Responder I (N=100, ref 15)		Responder II (N=91, ref 8)		Responder III (N=76, this study)	
	Responder	**Non-Responder**	**Responder**	**Non-Responder**	**Responder**	**Non-Responder**
Number of subjects	61	39	56	35	47	29
Male, n (%)	33 (54%)	24 (62%)	30 (54%)	22 (63%)	25 (53%)	16 (55%)
Age at diagnosis in months						
mean ± SD	3.4 ± 5.4	2.2 ± 2.7	3.6 ± 5.6	2.0 ± 2.7	4.0 ± 6.0	2.1 ± 2.9
median	1.8	1.6	1.8	1.6	1.9	1.6
Diagnosed by newborn screening, n (%)	42 (69%)	20 (51%)	37 (66%)	19 (54%)	29 (62%)	15 (52%)
CFTR genotype, n (%)						
F508del/F508del	38 (62%)	22 (56%)	34 (61%)	22 (63%)	28 (60%)	17 (59%)
F508del/Other	20 (33%)	15 (38%)	19 (34%)	12 (34%)	17 (36%)	11 (38%)
Other/Other	3 (5%)	2 (5%)	3 (5%)	1 (3%)	2 (4%)	1 (3%)
Gastrointestinal phenotype, n (%)						
Meconium ileus (MI)	12 (20%)	11 (28%)	11 (20%)	11 (31%)	7 (15%)	10 (34%)
No MI but Pancreatic Insufficient (PI)	45 (74%)	26 (67%)	41 (73%)	22 (63%)	36 (77%)	17 (59%)
Pancreatic Sufficient (PS)	4 (6%)	2 (5%)	4 (7%)	2 (6%)	4 (8%)	2 (7%)
Birth weight, mean ± SD						
kg	3.22 ± 0.36	3.46 ± 0.45 *	3.21 ± 0.36	3.49 ± 0.45 *	3.21 ± 0.37	3.49 ± 0.47
z-score	−0.46 ± 0.65	0.0 ± 0.86 *	−0.48 ± 0.65	0.07 ± 0.87 *	−0.47 ± 0.37	0.08 ± 0.91
Growth at age 2 years, mean ± SD						
Height z-score	−0.06 ± 0.95	−0.90 ± 0.83 *	−0.03 ± 0.92	−0.87 ± 0.83 *	0.07 ± 0.91	−0.88 ± 0.85 *
BMI z-score	0.40 ± 0.93	−0.36 ± 0.76 *	0.36 ± 0.95	−0.36 ± 0.77 *	0.44 ± 0.93	−0.33 ± 0.84 *

* $p<0.05$ compared to responders within each study. No significant differences were found across the 3 responder studies.