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PREDICTIVE EFFECTS OF LOW BIRTH WEIGHT AND SMALL FOR GESTATIONAL AGE STATUS ON RESPIRATORY AND NUTRITIONAL OUTCOMES IN CYSTIC FIBROSIS

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Abstract

INTRODUCTION: Prior literature shows that neonates with cystic fibrosis (CF) are more likely to be born low birth weight (LBW, <2500 grams) and/or small for gestational age (SGA, <10th percentile for weight) than non-CF counterparts. There is limited literature exploring the predictive effects of birth parameters on long-term outcomes.

METHODS: The study population (CF Twin and Sibling Study) was recruited between 2000–2013 (n=1677). Relationships between FEV₁ percent predicted at 6, 12, or 18 years or BMI z-score at 2, 6, 12, or 18 years, and predictor variables (LBW or SGA status) were assessed using adjusted linear regressions.

RESULTS: Mean birth weight was 3.3±0.7 kg (Females: 3.2±0.7kg; males: 3.4±0.7kg) and mean gestational age was 38.4±2.6 weeks, with 10.2% of participants classified as SGA. Predictors of LBW included female sex, pancreatic insufficiency, and prematurity. Predictors of SGA included female sex. After adjustment, LBW was associated with lower BMI at ages 2–12 years and SGA was associated with lower BMI at age 2 years. LBW was associated with lower FEV₁ percent predicted only at age 6 years. SGA was not associated with FEV₁.

CONCLUSIONS: We did not observe higher rates of LBW or SGA in full term infants compared to the general population. We observed associations particularly between LBW and BMI or FEV₁, but these associations decreased with age, suggesting that alternate factors contribute to outcomes over time. In lieu of the ability to target growth during gestation, efforts could be considered to optimize infant nutritional status, which may improve later life outcomes.

Keywords

Cystic fibrosis; FEV₁; birth weight; gestational age; BMI; neonate

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, life threatening genetic disorder caused by deleterious variants in the CF transmembrane conductance regulator (*CFTR*) gene. These variants cause defective chloride ion transport across cell membranes, leading to viscous secretions and ultimately causing respiratory, gastrointestinal, pancreatic and genitourinary disease.

The effect of CF on nutritional status through childhood and adolescence has been well established. Growth deficiencies in CF have been attributed to malabsorption, higher energy expenditure and increased caloric needs. Birth weight has been observed to be lower for infants with CF compared to their peers in some studies. One population-based study found the average birth weight of Danish infants with CF to be approximately 200 grams lighter than national means.¹ Another Cleveland-based study reported that both male and female infants with CF had lower birth weights than U.S. national averages.² Similarly, amongst infants with CF in Washington State born between 1996–2013, the average birth weight was 373 grams lighter than the state mean, and infants with CF were also more likely to be born small for gestational age (SGA).³ In contrast, the U.S. Cystic Fibrosis Foundation Patient Registry reported in 2017 that birth weights were similar between term infants with and without CF (<https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf>). Multiple hypotheses have been proposed for differences that exist in birth weights between infants with and without CF, including an association between decreased levels of insulin-like growth factor 1 (IGF-1) and the *CFTR* genotype, absence of placental *CFTR*, and decreased in utero pancreatic function, though further research is required to elucidate the primary cause.^{4,5}

While the earliest manifestations of CF are gastrointestinal, including low birth weight, meconium ileus or failure to thrive, pulmonary disease accounts for a significant proportion of CF-related morbidity and mortality. Routine pulmonary function testing (PFTs) is initiated by 6 years of age, and the percent predicted forced expiratory volume in one second (%FEV₁) is the primary measure used to assess lung function in CF. An association between nutritional and pulmonary outcomes has also been well documented. Konstan *et al.* demonstrated significant correlation between suboptimal growth indices (as measured by weight for age (WFA), height for age (HFA) and percent ideal body weight (%IBW)) at age 3 years and pulmonary function age 6 years.⁶ Similarly, Lai *et al.* demonstrated that the recovery of birth weight z-score within two years of CF diagnosis was associated with decreased frequency of self-reported respiratory symptoms, higher %FEV₁ and higher Brasfield and Wisconsin chest radiographic scores.⁷ Furthermore, another prospective observational study using data from the U.S. CF Foundation Patient Registry showed that those with WFA <10th percentile at age 4 years had lower %FEV₁ throughout childhood and adolescence, and that those with the highest WFA percentiles at 4 years of age had fewer pulmonary exacerbations, decreased hospital stay and increased survival at 18 years of age.⁸

While the predictive effect of birth weight on later life pulmonary function in the non-CF population has been explored,^{9,10} there is minimal existing literature on the effects of birth weight on pulmonary function in patients with CF, with the exception of one study which

found that low birth weight correlated with %FEV₁ at ages 6 and 10 years, with a BW increase of 100 grams correlating with a 1% increase in %FEV₁ (n=79).² To further elucidate these relationships, we conducted a retrospective cohort study examining the predictive effects of birth weight and SGA status on the primary outcomes of body mass index (BMI) z-scores and %FEV₁ and a post hoc outcome of height z-score at selected time points during childhood and adolescence.

METHODS

Study Population:

The study population (CF Twin and Sibling Study; P.I.: G.R. Cutting) were recruited from CF centers between 10/27/2000 and 3/31/2013 based on having a twin or sibling also with CF (n=2086 in 1018 families; n=1677 with birth weight data).¹¹ Longitudinal data with multiple assessment time points were collected through chart review and questionnaires with data supplementation from the U.S. CF Foundation Patient Registry through 12/31/16.¹² Written informed consent was obtained from participants (or their parents/legal guardians) enrolled in the CF Twin-Sibling Study. This study, including the CF Foundation Patient Registry data downloads, was approved by the Johns Hopkins University Institutional Review Board (#NA_00035659).

Clinical Data:

Birth weight and gestational age were obtained from chart review when available, and parental recall when not. Low birth weight was classified as <2500 grams and small for gestational age status (<10th percentile for weight) for each subject was derived using U.S. norms.¹³ The primary measure of lung function was the maximum FEV₁ percent predicted (Global Lung Function Initiative reference equations) obtained between 6–7yo, 12–13yo, and 18–19yo.¹⁴ Similarly, the primary nutritional measure was the maximum BMI percentile based on CDC norms obtained between 2–3yo, 6–7yo, 12–13yo, and 18–19yo. The mean %FEV₁ and BMI percentile values obtained during those same time periods were used in sensitivity analyses. For regression analyses involving BMI, BMI z-score was used instead of BMI percentile as it was more normally distributed. Lung function and BMI data were excluded if a subject had undergone lung transplantation or was known to be on CFTR modulator therapy. *P. aeruginosa* status was considered positive for a given time period (2–3yo, 6–7yo, 12–13yo, and 18–19yo) if a subject had any positive cultures for *P. aeruginosa* within that time period. Exocrine pancreatic status was able to be determined for 1676 individuals (by genotype for 1580 individuals [www.cfftr.org], fecal elastase for 17, fecal fat for 3, and any reported enzyme use for 76).

Statistical Analysis:

All analyses were performed using STATA/IC 15.1 (StataCorp, College Station, TX). A two-sided *P* value of <0.05 was considered statistically significant for assessment of potentially confounding demographic factors, while the significance *p* value for this study is 0.0125 for tests involving BMI (Bonferroni correction: 0.05/4) and is 0.0167 for FEV₁ (Bonferroni correction: 0.05/3) given the assessment at multiple time points; all *p* values reported in the text and tables are exact *p* values. Student *T* tests, chi squared tests, and adjusted clustered

linear/logistic regression were used to explore correlation between birth weight and small for gestational age status with factors that could be associated with birth weight at outcomes based on published CF and non-CF literature including sex, race/ethnicity, *CFTR* genotype, presence of meconium ileus, gestational age, exocrine pancreatic status, zygosity, and birth year. Final predictors of birth weight and SGA status were generated by selecting predictors that were significant in univariate regressions and dropping non-significant predictors in a multivariable model in stepwise fashion. Linear regressions were used to explore relationships between the dependent outcome variable (%FEV₁ or BMI z-score) with independent predictor variable (birth weight or SGA status), adjusting for possible confounders. All regressions were clustered by family to account for relatedness.¹⁵

RESULTS

Demographics:

Table 1 outlines population demographics (n=1677). Approximately half of the study population was female (47.5%). Additionally, approximately half were homozygous for the *F508del* variant in *CFTR* (48.5%). The majority of participants were singleton gestation siblings (88.1%). Dizygous and monozygous twin gestations accounted for 8.6% and 3.3% of the participants, respectively. A minority of the population was non-white (7.9%). Mean birth weight was 3.3 ± 0.7 kg, and for full term singleton infants, the mean birth weights for males and females were 3.6kg (n=598) and 3.4kg (n=556), respectively. The mean gestational age was 38.4 ± 2.6 weeks, with 10.2% of participants classified as small for gestational age (SGA: weight <10th percentile) at birth. Of the 1347 singleton gestation infants, 8.1% were SGA, and 14.3% were born prematurely (<37 weeks gestation). The majority of participants were pancreatic insufficient (86.3%).

Both low birth weight (LBW: <2500 grams) and SGA infants were more likely to be female ($p=0.048$ and 0.012 , respectively) and to be of twin gestation ($p<0.001$ and $p<0.001$, respectively). LBW infants were also more likely to be non-white (15.7%; $p<0.001$), born at an earlier gestational age (mean 33.9 weeks or be premature; $p<0.001$), have meconium ileus (32.7%; $p<0.001$), have an earlier age of diagnosis ($p=0.014$) and be pancreatic insufficient (91.9%; $p=0.026$) than non-LBW infants. These associations were not demonstrated with SGA infants. No statistically significant differences were observed in either by birth weight or proportion of SGA infants amongst birth year cohorts (prior to 1970, 1970–1979, 1980–1989, 1990–1999, 2000 or later) or by *CFTR* genotype (% *F508del* homozygous).

Factors associated with birth weight and small for gestational age status:

To assess the role of possible determinants of birth weight and SGA status, we performed univariate and multivariable regression (Table 2). Analysis was restricted to singleton gestations to eliminate the effects of multiple gestation on birth weight. Female sex was associated with a 190 gram lower birth weight ($p<0.001$) and pancreatic insufficiency was associated with a 220 gram lower birth weight ($p<0.001$). Increasing gestational age was associated with a 120 gram greater birth weight per additional week of gestation ($p<0.001$). Neither race/ethnicity, birth year, the presence of meconium ileus, nor *CFTR* genotype were associated with birth weight. Predictors of SGA status included female sex. Females were

twice as likely to be SGA ($p=0.002$) than males. Race/ethnicity, *CFTR* genotype, presence of meconium ileus and pancreatic insufficiency were not associated with SGA status.

Respiratory and nutritional outcomes associated with birth weight and SGA status:

Table 3 outlines respiratory and nutritional outcomes for the study population based on LBW and SGA status. Without adjustment for potential determinants of birth weight or SGA status, LBW was associated with lower maximum BMI percentiles attained at 2yo ($p<0.001$), 6yo ($p<0.001$), and 12yo ($p<0.001$), but not 18yo ($p=0.013$; significance threshold 0.0125) (Figure 1A). SGA status was also associated with lower maximum BMI percentiles at 2yo ($p<0.001$), 6yo ($p=0.004$) and 12yo ($p=0.012$), although not at 18yo ($p=0.59$) (Figure 1B).

We next evaluated respiratory outcomes using measures of maximum %FEV₁ at 6yo, 12yo, and 18yo, as well as respiratory culture positivity for *Pseudomonas aeruginosa* (PA) at 2yo, 6yo, 12yo, and 18yo. There was no association between LBW or SGA status and maximum %FEV₁ at any time point (Figures 1C and 1D). There was no association between LBW or SGA status and PA positivity after adjustment for testing at multiple time points.

To account for potential confounders, we performed adjusted regression to assess the relationship between birth weight, SGA status, and long-term respiratory and nutritional outcomes (Table 4). Nutritional outcomes: Birth weight was associated with BMI z-score at 2yo ($p<0.001$), 6yo ($p<0.001$), and 12yo ($p<0.001$), but not at 18yo ($p=0.016$; significance threshold 0.0125), when adjusted for sex, race/ethnicity, twin gestation, gestational age at birth, meconium ileus, age at diagnosis, and pancreatic insufficiency. On linear regression using SGA status as a dichotomous independent variable, SGA status predicted BMI z-score at 2yo ($p=0.001$), however not at 6, 12 or 18yo, when adjusted for sex, twin gestation, meconium ileus, and pancreatic insufficiency. We also performed several sensitivity analyses to assess the robustness of our results. Similar results were also demonstrated using mean BMI z-score, a population restricted to *F508del* singleton gestation only, and maximum BMI percentiles (Supplemental Tables 1, 2, and 3, respectively).

Given that birth weight was predictor of BMI z-score at ages 2, 6, 12, and 18yo, we also wished to determine whether it was actual birth weight or birth weight serving as a proxy for prematurity that was associated with BMI z-score. In regressions adjusted for sex, race/ethnicity, twin gestation, meconium ileus, age at diagnosis, and pancreatic insufficiency, gestational age at birth (weeks) was associated with BMI z-score at age 6yo ($p=0.011$), but not 2, 12, or 18yo (Supplemental Table 4).

Although all regressions in this study were adjusted for pancreatic insufficiency, we also performed regressions to assess the effect of pancreatic insufficiency independent of birth weight and/or SGA status. In linear regressions adjusted for sex, race/ethnicity, twin gestation, meconium ileus, and age at diagnosis, pancreatic insufficiency was associated with lower BMI z-scores at ages 6yo, 12yo, and 18yo (Supplemental Table 5). Of note the effect size seen with pancreatic insufficiency (decreased BMI z-scores of -0.19 to -0.42 at ages 6–18yo for pancreatic insufficient subjects) is similar to that seen with birth weight

(decreased BMI z-scores of -12 to -0.36 at ages 2–18yo for each 1 kg decrease in birth weight; Table 4).

Although we used BMI z-scores for regressions due to the non-normal distribution of BMI percentiles amongst the study population, we also wished to provide an estimate of the association with percentiles, which are more commonly used in clinical practice. The regressions using maximum BMI percentile suggested that every kilogram greater birth weight is associated with a 12.8%ile greater BMI percentile at age 2 years, but only a 5.0%ile greater BMI percentile at age 18 years (Supplemental Table 3). Likewise, SGA is associated with a 9.9% lower BMI percentile at 2 years of age, but this difference is not significant at later time points.

Every additional 1 kilogram of birth weight was associated with a 2.9% increase in maximum %FEV₁ at 6yo ($p=0.013$), although not at 12yo or 18yo, when adjusted for sex, race, meconium ileus status, gestational age at birth, twin gestation, pancreatic insufficiency and PA positivity. These results were also demonstrated when using mean %FEV₁ (Supplemental Table 1), but not in *F508del* singleton gestation (Supplemental Table 2). No associations were found between SGA status and %FEV₁ at any time point. Likewise, prematurity was not a predictor of later lung function as gestational age in weeks was not associated with %FEV₁ at any time point (Supplemental Table 4). Pancreatic insufficiency was only associated with %FEV₁ at 12yo, but not at 6yo or 18yo ($p=0.011$; Supplemental Table 5).

Linear Growth: Given the association of LBW and SGA status with BMI z-scores, we undertook a post hoc analysis of height z-scores as a measure of linear growth (Supplemental Table 6). We found that lower birth weights were associated with lower height z-scores at all ages assessed (2yo, 6yo, 12yo, and 18yo; all p values <0.001). Similarly, being born for small for gestational age was also associated with lower height z-scores at all ages assessed (2yo, 6yo, 12yo, and 18yo; all p values <0.001).

Sex-specific analyses: Interaction terms for sex were not significant for tests between LBW and SGA status for the outcomes of BMI z-scores and %FEV₁ at any time points (Supplemental Table 7).

DISCUSSION

Our study demonstrated a correlation between birth weight and pulmonary function outcomes as measured by percent predicted FEV₁ at 6 years old, which is typically the earliest age at which children are adequately able to complete standard pulmonary function testing. This is consistent with previous research published by Darrah *et al.*, although their study demonstrated associations between birth weight and pulmonary function at both 6 and 10 years of age.² The relationship between birth weight and pulmonary function did not extend into adolescence in either our study or Darrah *et al.* The loss of predictive effect of birth weight at later time points suggests an increasing contribution to variability in lung function from alternative factors, which could potentially include later life BMI,

environmental factors such as tobacco smoke exposure, and the frequency and severity of respiratory exacerbations.

While there are numerous studies which have identified close associations between early life nutritional indices such as BMI z-score and weight for age and later lung function in children with CF, there is limited data on the contribution of birth weight. Our findings outline the potential benefits of early nutritional intervention for LBW neonates with cystic fibrosis, who may be at higher risk for poorer respiratory outcomes at earlier ages than their counterparts. SGA status was not found to be predictive of later lung function, even at 6 years of age, and on our review of the literature there did not appear to be studies looking at potential differences in SGA status and low birth weight effects in prior CF studies. It should be noted that our definitions of LBW and SGA capture 2 largely non-overlapping groups; specifically, full term infants comprise 84.0% of the 156 SGA infants in our study population, whereas preterm infants comprise 82.2% of the 157 LBW infants in our study where gestational age is known.

We also demonstrated significant relationships between birth weight and BMI z-score at 2, 6, and 12 years old, although by 18 years old the strength of the relationship was not significant. This is likely due to multiple other factors having increasing contribution to nutritional outcomes as time progresses, including frequent respiratory infections, increasing energy requirements, malnutrition and compliance with nutritional supplementation. Interestingly, a difference was again demonstrated between the predictive effects of birth weight and SGA status, with SGA status only being predictive of nutritional outcomes at 2 years old. It should also be noted that actual birth weight appeared to be more closely associated with later nutritional outcomes than prematurity. Nevertheless, while it appears that the association between LBW/SGA status and BMI z-score lessens with time, our post hoc analysis demonstrated that linear growth (as measured by height z-scores) remains diminished into adulthood with low birth weights and/or being SGA. This may suggest that nutritional interventions by CF care centers may improve BMI z-scores for LBW and/or SGA individuals, but may not necessarily affect linear growth.

It should be noted that while several previous single center or state studies have shown that neonates with CF have reduced birth weight compared to the general population,^{2,3,16,17} we saw this as well in the entire study sample, but did not observe this when we looked only at full term infants, which may be a function of higher rates of prematurity in CF. In our study population 14.3% of singleton births were premature compared to ~10% in the general U.S. population, and for full term singleton infants in our study population, the mean birth weights for males and females were 3618 grams (n=598) and 3433 grams (n=556), respectively, with similar published 50th percentile birth weights for the general population (3580 and 3441 grams for males and females, respectively).¹³ Factors contributing to the increased incidence of preterm birth among infants with CF are unknown, but it has been speculated that CFTR, expressed on the placenta, may affect gestational duration.^{3,16} Despite the increase in preterm births that we observed, the rates of SGA (10.2%) and LBW (4.9%) in singleton infants our study were on par with the general population (SGA: 10%; LBW: 6.6%),^{13,18} similar to what has been reported by the U.S. CF Foundation Data

Registry. Both low birth weight and SGA infants were more likely to be of twin gestation, which is also consistent with general population characteristics.¹⁸

While our study does not demonstrate higher than average rates of low birth weight or SGA, it does demonstrate a positive correlation between both birth weight and early childhood lung function as well as childhood and adolescent BMI. Optimizing birth weight in infants with CF would therefore be beneficial to respiratory outcomes both via improved childhood pulmonary function, as well as improved childhood and adolescent BMI, which in turn also influence pulmonary function. Unfortunately, there are minimal available interventions to address possible intrauterine growth restriction in CF, and even if there were, the majority of diagnoses occur postnatally. In mothers with a known risk of carrying a neonate with CF, it would be beneficial to address co-existing factors which may also affect intra-uterine growth, such as maternal smoking, hypertension, alcohol use and maternal medical conditions, creating as optimal an environment as possible for fetal growth and development.

While we did not assess the effects of catch-up growth for LBW and/or SGA infants within the first 2 years of life, efforts could be considered to optimize nutritional status in the neonatal and infantile period, in lieu of the ability to target growth during the fetal period. With the introduction of newborn screening, neonatal CF diagnoses are being established in many cases even prior to the demonstration of sub-optimal growth. This allows time to intervene both with increasing caloric intake as well as the early initiation of pancreatic enzyme replacement therapy, with the hope that nutritional optimization and period of catch up growth may occur. Studies have shown an association between introduction of CF newborn screening and improved nutritional outcomes, likely due to earlier optimization of feeds and treatment of malabsorption.^{19–21}

Limitations of our study included the use of parental-reported birth weight which introduces chance of recall bias; however, a published meta-analysis suggests that parental recall is adequate for epidemiological studies in high income countries.²² Also, the use of cross-sectional regression models may be less informative than longitudinal mixed models, which our data availability for all individuals did not permit. Additionally, in general, the Twin-Sibling Study population has higher lung function than the general CF population owing to the original recruitment of having at least 2 living twins or siblings with CF. Only 27.2% of the study population was born after 2000, suggesting a lower rate of initial diagnosis by neonatal screening (universal screening in the United States was achieved in 2010), which may limit the generalizability in an era of universal screening. Lastly, this study was conducted using data from before CFTR modulator medications were available, and the early use of such medications will likely affect childhood outcomes. The primary strength of this study was its sample size of over 1600 subjects.

In summary, while our research did not show an increased prevalence of low birth weight or SGA status in full term infants with CF as compared to the general population, we did show an association between lower birth weights and both pulmonary and nutritional outcomes for children with CF, which again emphasizes the need for early nutritional intervention in these patients. Closer monitoring of growth parameters of fetuses at risk of being born with CF should also be considered. Future research should address whether a true association exists

between CF and LBW/SGA status in an era of newborn screening and CFTR modulator therapies, and potential mechanisms of such a relationship elucidated, so as to identify potential future therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Full term infants with cystic fibrosis have similar birth weights to those without.
- Prematurity rates may be higher in CF compared to general population.
- Low birth weights in CF are associated with lower BMIs in later life.
- Low birth weights in CF are associated with lower FEV1 at 6yo.

FIGURE 1: Nutritional (body mass index [BMI] percentiles) and pulmonary outcomes (forced expiratory volumes in 1 second [FEV₁] % predicted) by birth weight (panels A and C) and small for gestational age (SGA)(panels B and D). Asterisks indicate *p* values <0.05 for *t* tests between the adjacent bars.

TABLE 1.

Demographics

	Mean $\pm$ S.D. [Range]	Study Population (n=1677)	Birth Weight <2500 grams (n=172)	Birth Weight 2500 grams (n=1505)	P value	Small for Gestational Age (n=156)	Appropriate for Gestational Age (n=1372)	P value
Demographics	Sex (% female)	47.5%	54.7%	46.7%	0.048	57.1%	46.4%	0.012
	Race/Ethnicity (% non-white)	7.9%	15.7%	7.0%	<0.001	9.6%	7.2%	0.28
	Gestational Age (weeks)	38.4 $\pm$ 2.6 [24, 43] (n=1528)	33.9 $\pm$ 3.1 [24.5, 42] (n=157)	38.9 $\pm$ 2.0 [30, 43] (n=1371)	<0.001	38.7 $\pm$ 2.2 [30, 42]	38.3 $\pm$ 2.6 [24.5, 43]	0.13
	Preterm Birth [<37 weeks] (%)	20.0% (n=1528)	82.2% (n=157)	12.9% (n=1371)	<0.001	16.0%	20.5%	0.18
Birth History	Zygosity (%):							
	Dizygous	3.3%	18.6%	1.5%	<0.001	6.4%	2.8%	<0.001
	Monozygous	8.6%	39.5%	5.1%		23.7%	6.9%	
	Sibling	88.1%	41.9%	93.4%		69.9%	90.2%	
	Birth Year (%):							
	<1970	2.4%	1.7%	2.5%	0.93	4.5%	2.0%	0.10
	1970–1979	6.1%	7.0%	6.1%		5.8%	5.5%	
	1980–1989	20.0%	20.4%	19.9%		19.2%	19.7%	
	1990–1999	44.3%	42.4%	44.5%		49.4%	44.2%	
	>2000	27.2%	28.5%	27.0%		21.2%	28.7%	
Birth History	Meconium Ileus (% yes)	20.9% (n=1663)	32.7% (n=171)	19.5% (n=1492)	<0.001	26.5% (n=155)	20.2% (n=1361)	0.07
	Age of Diagnosis (years)	2.0 $\pm$ 4.7 [0, 50.5]	1.2 $\pm$ 3.5 [0, 40.5]	2.1 $\pm$ 4.8 [0, 50.5]	0.014	1.8 $\pm$ 4.9 [0, 40.5]	2.0 $\pm$ 4.3 [0, 50.5]	0.53
	CFTR Genotype (% <i>F508del</i> homozygotes)	48.5%	52.9%	48.0%	0.22	49.4%	48.0%	0.75
Cystic Fibrosis Characteristics	Pancreatic Insufficiency (% yes)	86.3% (n=1676)	91.9%	85.7% (n=1504)	0.026	91.0%	85.6% (n=1371)	0.06

Table 2.

Determinants of Birth Weight and SGA Status (Final Models for Singletons Only)

Coefficient ± S.E. [95% C.I.]*	Birth Weight (kg) (n = 1346)	P value	SGA Status (0=no, 1=yes) (n = 1347)	P value
Sex (male=0; female=1)	-0.19 ± 0.03 [-0.25, -0.14]	<0.001	1.97 ± 0.43 [1.28, 3.03]	0.002
Race/Ethnicity (white=0; non-white=1)	<i>Not significant in univariate model</i>	-	<i>Not significant in univariate model</i>	-
Gestational Age (weeks)	0.12 ± 0.01 [0.11, 0.14]	<0.001	<i>Not included as accounted for in determining SGA status</i>	-
Birth Year (year)	<i>Not significant in univariate model</i>	-	<i>Not significant in univariate model</i>	-
Meconium Ileus (no=0; yes=1)	<i>Not significant in multivariable model</i>	-	<i>Not significant in univariate model</i>	-
CFTR Genotype (other genotype=0; F508del homozygote=1)	<i>Not significant in univariate model</i>	-	<i>Not significant in univariate model</i>	-
Pancreatic Insufficiency (no=0; yes=1)	-0.22 ± 0.05 [-0.33, -0.12]	<0.001	<i>Not significant in univariate model</i>	-

* Linear regressions with birth weight as a continuous dependent variable and logistic regressions with small-for-gestational-age as a dichotomous dependent variable. Models were generated by selecting predictors that were significant in univariate regression and then dropping non-significant predictors in the multivariable model in a stepwise fashion. Age of diagnosis was not included in models as it was felt not to potentially impact birth weight. No twins were included. All regressions were clustered by family.

TABLE 3.

Respiratory and Nutritional Outcomes

Mean $\pm$ S.D. [Range]	Study Population (n=1677)	Birth Weight <2500 grams (n=172)	Birth Weight 2500 grams (n=1505)	<i>P</i> value [*]	Small for Gestational Age (n=156)	Appropriate for Gestational Age (n=1372)	<i>P</i> value [*]
Maximum BMI Percentile at 2yo	63.0 $\pm$ 26.7 [0, 100] (n=1208)	54.4 $\pm$ 30.0 [0, 100] (n=132)	64.0 $\pm$ 26.1 [0, 100] (n=1076)	<0.001†	54.3 $\pm$ 28.0 [0, 100] (n=114)	64.4 $\pm$ 26.0 [0, 100] (n=986)	<0.001†
Maximum BMI Percentile at 6yo	61.0 $\pm$ 24.4 [0, 100] (n=1380)	51.7 $\pm$ 27.5 [0, 100] (n=151)	62.1 $\pm$ 23.8 [0, 100] (n=1229)	<0.001†	55.8 $\pm$ 27.7 [0, 100] (n=126)	62.4 $\pm$ 23.7 [0, 100] (n=1131)	0.004†
Maximum BMI Percentile at 12yo	48.7 $\pm$ 27.2 [0, 100] (n=1292)	38.6 $\pm$ 27.6 [0, 100] (n=139)	49.9 $\pm$ 26.9 [0, 100] (n=1153)	<0.001†	43.5 $\pm$ 28.5 [0, 100] (n=119)	50.1 $\pm$ 26.8 [0, 100] (n=1045)	0.012†
Maximum BMI Percentile at 18yo	45.9 $\pm$ 27.8 [0, 100] (n=879)	39.0 $\pm$ 27.5 [0, 100] (n=88)	46.7 $\pm$ 27.8 [0, 100] (n=791)	0.013	45.2 $\pm$ 28.6 [0, 100] (n=81)	46.9 $\pm$ 27.7 [0, 100] (n=703)	0.59
Maximum FEV₁ Percent Predicted at 6yo	99.9 $\pm$ 17.4 [29, 171] (n=1255)	100.8 $\pm$ 19.2 [33, 171] (n=127)	99.8 $\pm$ 17.2 [29, 152] (n=1128)	0.56	101.1 $\pm$ 17.8 [34, 171] (n=112)	100.3 $\pm$ 17.1 [32, 152] (n=1038)	0.60
Maximum FEV₁ Percent Predicted at 12yo	91.6 $\pm$ 18.0 [14, 143] (n=1269)	89.0 $\pm$ 20.7 [19, 142] (n=139)	92.0 $\pm$ 17.7 [14, 143] (n=1130)	0.07	90.0 $\pm$ 19.1 [22, 128] (n=113)	92.1 $\pm$ 17.9 [14, 143] (n=1033)	0.24
Maximum FEV₁ Percent Predicted at 18yo	83.3 $\pm$ 22.2 [17, 131] (n=884)	82.7 $\pm$ 23.1 [22, 126] (n=92)	83.4 $\pm$ 22.1 [17, 131] (n=792)	0.78	83.4 $\pm$ 22.5 [31, 126] (n=85)	84.1 $\pm$ 22.0 [17, 131] (n=705)	0.80
P. aeruginosa at 2yo (% yes)	49.3% (n=1040)	40.4% (n=114)	50.4% (n=926)	0.042	52.0% (n=100)	49.5% (n=848)	0.64
P. aeruginosa at 6yo (% yes)	60.0% (n=1291)	54.3% (n=140)	60.6% (n=1151)	0.15	65.5% (n=116)	59.3% (n=1061)	0.19
P. aeruginosa at 12yo (% yes)	74.7% (n=1364)	72.6% (n=146)	75.0% (n=1218)	0.54	82.5% (n=126)	73.5% (n=1109)	0.027
P. aeruginosa at 18yo (% yes)	86.3% (n=1222)	89.0% (n=1222)	86.1% (n=1222)	0.38	90.8% (n=120)	85.0% (n=985)	0.08

* Exact *p* values are reported in this table. However, the significance *p* value for this study is 0.0125 for tests involving BMI and *Pseudomonas* (0.05/4) and is 0.0167 for FEV₁ (0.05/3) given the assessment at multiple time points; significant values after Bonferroni correction are noted by a cross (†).

Table 4.

Models of Birth Weight and SGA status and Outcomes

Coefficient $\pm$ S.E. [95% C.I.]	Birth Weight (kg) *	P value ***	SGA Status (0=no, 1=yes) **	P value ***
Maximum BMI Z-score at 2yo	0.43 $\pm$ 0.06 [0.31, 0.55] (n=1097)	<0.001†	-0.33 $\pm$ 0.10 [-0.53, -0.13] (n=1097)	0.001†
Maximum BMI Z-score at 6yo	0.31 $\pm$ 0.05 [0.21, 0.42] (n=1253)	<0.001†	-0.16 $\pm$ 0.09 [-0.35, 0.02] (n=1253)	0.086
Maximum BMI Z-score at 12yo	0.25 $\pm$ 0.06 [0.13, 0.37] (n=1158)	<0.001†	-0.17 $\pm$ 0.12 [-0.40, 0.06] (n=1158)	0.148
Maximum BMI Z-score at 18yo	0.18 $\pm$ 0.08 [0.03, 0.33] (n=782)	0.016	-0.01 $\pm$ 0.14 [-0.29, 0.27] (n=782)	0.931
Maximum FEV₁ Percent Predicted at 6yo	2.9 $\pm$ 1.2% [0.6, 5.3] (n=1057)	0.013†	1.5 $\pm$ 2.0% [-2.5, 5.4] (n=1057)	0.469
Maximum FEV₁ Percent Predicted at 12yo	1.7 $\pm$ 1.3% [-0.8, 4.2] (n=1114)	0.191	-0.9 $\pm$ 2.0% [-4.9, 3.1] (n=1114)	0.667
Maximum FEV₁ Percent Predicted at 18yo	-1.1 $\pm$ 1.7% [-1.8, 4.8] (n=776)	0.363	0.5 $\pm$ 2.9% [-5.1, 6.2] (n=776)	0.849

* Linear regressions with nutritional or respiratory outcome as the dependent variable and birth weight as a continuous independent variable, and adjusted for sex, race/ethnicity, twin gestation, gestational age at birth (weeks), meconium ileus, age at diagnosis, and pancreatic insufficiency. BMI Z-score was used instead of BMI percentile owing to the non-normal distribution of BMI percentiles. Regressions for lung function were also adjusted for *P. aeruginosa*. All regressions were clustered by family.

** Linear regressions with nutritional or respiratory outcome as the dependent variable and small-for-gestational-age status as a dichotomous independent variable, and adjusted for sex, twin gestation, meconium ileus, and pancreatic insufficiency. BMI Z-score was used instead of BMI percentile owing to the non-normal distribution of BMI percentiles. Regressions for lung function were also adjusted for *P. aeruginosa*. All regressions were clustered by family.

*** Exact *p* values are reported in this table. However, the significance *p* value for this study is 0.0125 for tests involving BMI (0.05/4) and is 0.0167 for FEV₁ (0.05/3) given the assessment at multiple time points; significant values after Bonferroni correction are noted by a cross (†).