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Cystic fibrosis is associated with adverse neonatal outcomes in Washington State, 1996-2013

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Abstract

Objective—To determine whether cystic fibrosis (CF) is associated with adverse neonatal outcomes in a recent birth cohort in the United States.

Study design—A retrospective matched cohort study of infants born in Washington State from 1996-2013 was identified through birth certificate data and linked to statewide hospital discharge data. Infants with CF were identified by hospitalization (through age 5 years) in which a CF-specific ICD-9 code was recorded. “Unexposed” infants lacked CF-related ICD-9 codes and were randomly selected among births, frequency-matched to “exposed” infants on birth year. Associations of CF with adverse neonatal outcomes (low birth weight, small for gestational age, pre-term birth and infant mortality) were estimated through Poisson regression. We performed extreme value imputation to address possible ascertainment bias.

Results—We identified 170 infants with CF and 3,400 unexposed infants. CF was associated with increased relative risk (95% confidence interval) of 3.5 (2.5-4.9), 1.6 (1.1-2.4), 3.0 (2.2-4.0), and 6.8 (1.7-26.5) for low birth weight, small for gestational age, pre-term birth, and infant death, respectively. The estimated relative risks were similar among infants born from 2006-2013, except small for gestational age was no longer associated with CF diagnosis. Results were robust to extreme value imputation and exclusion of infants with meconium ileus.

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The authors declare no conflicts of interest.

Conclusions—Observed associations of CF with low birth weight, pre-term birth and infant death are unlikely to be due to ascertainment bias. Further work is needed to determine how to prevent these adverse neonatal outcomes.

Keywords

low birth weight; prematurity; pre-term birth; small for gestational age; infant mortality

Cystic fibrosis (CF) is the most common early lethal genetic disease in Caucasians, occurring in approximately 1 in every 3500 live births (1). CF is caused by autosomal recessive inheritance of a defect in the cystic fibrosis transmembrane regulator (CFTR) gene. This mutation results in reduced chloride transport across membranes and accumulation of thick, abnormal mucus in the lungs, pancreas, liver, intestine and reproductive tract (2). CFTR mutations can lead to pancreatic insufficiency and recurrent respiratory infections, among other complications. There is evidence that the CFTR gene also has physiologic importance in fetal development due to its activity in the fetal pituitary gland (3), the placenta (4-8), and the fetal pancreas (7).

Late in development, typically developing fetuses grow rapidly, in part through absorption of nutrients transported by the placenta into amniotic fluid (7, 9-11). Impaired pancreatic exocrine function has been associated with intrauterine growth retardation in babies born small-for-gestational age (SGA)(12). It is plausible that the CFTR would be particularly important in the final stages of fetal development, when fetal pancreatic insufficiency or disruption of the transplacental nutrient transport system could constrain growth (7). This hypothesis has been supported by several studies in which CF was associated with lower mean birth weight (4, 7, 13, 14), SGA (14) and with pre-term delivery (14). These studies were small, several suffered methodologic limitations, and two were conducted in the 1950s. It is yet unknown whether CF increases neonatal mortality.

Thus, we sought to determine whether there were associations of CF with low birth weight (LBW), SGA, pre-term birth and infant mortality in a recent cohort in the United States. Until 2006, CF was not diagnosed in Washington State until patients displayed clinical symptoms, often between birth and the age of 14.5 months (15). Since 2006, newborn screening for CF has been mandated in Washington State, and nearly all infants with CF are diagnosed within weeks of delivery. Poor neonatal outcomes could be a harbinger of more severe disease in infants with CF, and when infants are diagnosed through screening, these adverse neonatal outcomes may identify infants that need earlier and more aggressive nutritional interventions (16, 17) or targeted CF therapies (18, 19).

Methods

We conducted a retrospective matched cohort study of infants born in Washington State between 1996 and 2013, with a focused analysis of the cohort born since newborn screening for CF began, from 2006-2013. We used birth certificate data from Washington State, linking the records to hospital discharge data from the Comprehensive Hospital Abstract Reporting System (CHARS) for the mother and child birth hospitalization, infant hospitalizations through the first 5 years of life, and birth and death certificate data (20). The

exposed cohort, infants with CF, was identified by the first hospitalization (through age 5 years) in which a CF-specific diagnosis code was recorded (ICD-9 codes 277.00, 277.01, 277.02, 277.03, 277.09). A CF-related complication need not have been the primary indication for hospitalization, rather, any hospitalization for which a CF-specific ICD-9 code was listed would have led to inclusion in the study. For comparison, an unexposed group of infants without CF (i.e. without these ICD-9 codes) were randomly selected from among birth certificates over the same time period and frequency-matched to the exposed infants on year of birth at a ratio of 20:1.

All variables used to ascertain neonatal outcomes were derived from birth certificate data, with the exception of mortality, which was taken from infant death certificates (20). The primary outcome of interest was LBW, birth weight <2500 grams. Secondary outcomes were: birth weight; SGA, defined as birth weight below the 10^{th} percentile for gestational age and sex; pre-term birth, defined as gestational age <37 weeks; and infant death during the first year of life. For SGA, the gestational age was a clinical estimate noted by the birth certificate certifier. For pre-term birth, this “clinical” estimate was used if available, and, if not, a “calculated” estimate from maternal report of last menstrual period was substituted.

We identified potential confounders *a priori* by fitting directed acyclic graphs (21); only maternal diagnosis of CF and maternal and paternal race met the standard definition of a confounder, which must be associated with risk of CF and the adverse neonatal outcome and not be in the causal pathway between them. Due to the high proportion of infant records lacking paternal race, and due to a small number of mothers with a diagnosis of CF (n=2; one in each exposure group), these covariates were not included in the adjusted analysis. We estimated the association of CF with outcomes by fitting unadjusted regression models and models adjusted for maternal race (white or non-white): linear regression for birthweight and Poisson regression for LBW, SGA, pre-term birth, and infant death. When an outcome is binary, the exponentiated coefficient from Poisson regression yields a risk ratio (RR) instead of an incident rate ratio (22). We used the sandwich estimator to obtain robust estimates of standard errors to estimate 95% confidence intervals (CI)(23). It is possible t he CFTR mutation might influence birth weight by leading to prematurity. We performed secondary analyses to estimate the association of CF with LBW independent of prematurity by 1) additionally adjusting for gestational age as a continuous covariate, or 2) limiting the analysis to term infants.

Not all children with CF are hospitalized during their first six years of life (24). Thus, ascertaining the exposed cohort through hospitalization records raises the possibility of selection bias for the cohort. To address this limitation, we performed a sensitivity analysis using information provided by the Washington State Department of Health CF newborn screening program, which should identify almost every infant with CF within weeks of birth.

There were 137 infants born with CF in Washington state during the newborn screening period (2006-2013); nine of these infants had normal newborn screening results and were diagnosed with CF after clinical symptoms occurred (25). The overall birth prevalence of CF in Washington State can be calculated based on vital statistics data; between 2006 and 2013, there were 702,670 live births in Washington State (17), giving an estimated birth prevalence

of CF of 1 per 5,128 live births. The birth prevalence in the overall period, 1996-2013, should not have differed substantially from the prevalence in the sub-cohort. Applying the prevalence 1 per 5,128 live births to the 1,502,273 live births in 1996-2013 (17) gives an expected 293 infants with CF. We used this information to estimate the under-ascertainment of CF and performed extreme value imputation for the missing exposed infants. In imputing the missing outcome information, we conservatively assumed outcomes among missed infants with CF occurred in the same proportion as in infants without CF.

Imputation of extreme values

For the 1996-2013 cohort, we expected 293 infants with cystic fibrosis (CF) but ascertained only 170. Therefore, we assumed there were 123 “missed cases” during this time, infants born in the cohort who had CF but for whom CF was not noted in the records used for ascertainment.

We conservatively assumed that missed cases would have the same adverse neonatal outcome prevalence (LBW, SGA, pre-term birth, and infant death) as in infants without CF (5.9%, 8.4%, 8.5%, and 0.3%, respectively). We then calculated the additional number of cases of the adverse outcomes (LBW, SGA, pre-term birth, and infant death) expected in the 123 missing infants with CF (missed cases: 7, 10, 10, and 0, respectively) to derive the total number of expected infants with CF who experienced each adverse outcome (totals: 39 LBW infants, 33 SGA infants, 51 pre-term infants, and 3 neonatal deaths).

For the 2006-2013 sub-cohort, the infants identified after the initiation of mandatory newborn screening for CF, we expected 137 infants with CF but ascertained only 68. Therefore, there were 69 “missed cases” of CF during this time. We made the same assumption as for the overall cohort, that missed cases would have the same ad verse neonatal outcome prevalence (LBW, SGA, pre-term birth, and infant death) as in infants without CF (6.8%, 8.0%, 10.3%, and 0.4%, respectively).

We then calculated the additional number of cases of the adverse outcomes (LBW, SGA, pre-term birth, and infant death) expected in the 69 missing infants with CF (missed cases: 5, 6, 7, and 0, respectively), giving a total expected of (22 LBW infants, 11 SGA infants, 26 pre-term infants, and 3 neonatal deaths).

For each cohort we calculated the imputed unadjusted RR and 95% CI for each adverse outcome. (ref?) After imputation we re-estimated RRs.

Although male infant sex and maternal cigarette smoking during pregnancy should not influence the incidence of CF, they may influence the early emergence of clinical signs of CF, and they are also associated with birth weight. Thus, in sensitivity analyses we further adjusted for infant sex and maternal cigarette smoking (yes or no).

We also assessed whether observed associations of adverse neonatal outcomes in infants with CF could be attributed to presentation with meconium ileus, assumed to be related to hospitalization, neonatal mortality, and/or prematurity in some infants with CF. After exclusion of infants with meconium ileus, we estimated the association of CF with adverse neonatal outcomes using Poisson regression, adjusted for maternal race. We used the

sandwich estimator to obtain robust estimates of standard errors to estimate 95% confidence intervals (CI) (23).

Both to describe the early disease course in CF and to explore possible biases induced by ascertaining CF through hospitalization records, we summarized information from the hospitalization data, stratified by LBW: age at index hospitalization, number of hospital readmissions through age 5 years, and other hospital diagnoses recorded during the index hospitalization. We grouped hospital diagnoses as respiratory illnesses, gastrointestinal problems, failure to thrive or poor weight gain, infection, and meconium ileus (Table x; available at www.jpeds.com).

Statistical analyses

All statistical analyses were performed using Stata 13 (Stata Corp, College Station, TX). We did not perform dichotomous significance testing but estimated two-tailed p-values with a level of 0.05 (26). Institutional review board (IRB) approval was obtained through the University of Washington. This project is considered exempt from review by the Washington State Department of Health IRB because no personally identifying information was provided.

Results

In the years 1996-2013, 170 children were identified with CF-specific ICD-9 codes during a hospitalization through the first 5 years of life. Compared with parents of infants without CF, parents of infants with CF were more often White (mothers 91.2% versus 69.5%, and fathers 75.9% versus 62.5%, respectively; Table I). There were no notable differences in maternal age, maternal education, marital status, parity category, maternal smoking status, Medicaid insurance status, paternal education, or infant sex between the two exposure groups. A substantial proportion of records were missing data on paternal characteristics (12% and 19% missing paternal race or education, respectively). After imputing extreme values for missing data, the estimated unadjusted associations of CF with adverse neonatal outcomes were weakened but still indicative of increased risk (Table IV).

Over the whole period, LBW, SGA, pre-term birth and infant death were more common in infants with CF than in unexposed infants (Table II); among the sub-cohort born in 2006-2013, SGA was no longer associated with CF. Mean birth weights were 3031 (standard deviation (SD) 759 grams) and 3387 grams (SD 581 grams) for infants with and without CF, respectively. CF was associated with increases in risk of approximately 3.5, 1.5, 3, and 7 for LBW, SGA, pre- term birth, and infant death, respectively (Table III), adjusted for maternal race (white/non-white). The adjusted mean difference in birth weights was 373 grams (95% CI 284-462 grams, $p< 0.0001$). Other than for SGA, the estimated RRs were similar or greater in the sub-cohort born from 2006-2013.

Adjusting for gestational age greatly weakened the association of CF with LBW (RR 1.1, 95% CI 0.7-1.8, p=0.723). Restricting the analysis to term infants weakened but did not remove the association of CF with LBW (RR 2.6, 95% CI 1.1-6.0, p=0.030) in the overall cohort and in the 2006-2013 sub-cohort (RR 3.1, 95% CI 0.9-11.0, p=0.076). In sensitivity

analyses to address possible ascertainment bias, the results were robust to extreme value imputation, i.e., point estimates weakened, but the interpretation was unchanged (Table IV). Further adjustment for maternal smoking and male sex left estimated RRs nearly unchanged (data not shown). In sensitivity analyses performed by excluding infants born with meconium ileus, point estimates changed only minimally and, for some outcomes, increased relative to the original analyses (Table V; available at www.jpeds.com).

Among the infants with CF hospitalized within 6 years of birth (through age 5), infants with LBW were more often male than infants not born with LBW (75.0% vs 52.2%) (Table VI; available at www.jpeds.com). Among the LBW infants, 81 % were premature compared with 11% of non-LBW infants. The LBW infants tended to have more respiratory disease during their first hospitalization for which a CF diagnosis was recorded, as well as lower Apgar scores at birth. Compared with non-LBW infants, a higher proportion of LBW infants were diagnosed with CF during their birth hospitalization (44% vs 18%). Most children with CF in this cohort (n= 137, 81%) were hospitalized between 1 and 5 times through their first 5 years of life. Children with CF and LBW did not appear to be hospitalized more frequently than children with CF without LBW (range 0-12 vs 0-21 admissions, respectively, through the first 5 years of life; Table VI).

Discussion

We observed strong associations of CF with adverse neonatal outcomes, including LBW, pre-term birth, and infant death, among a Washington State cohort of children identified through hospitalization records between birth and 5 years of age. The results appear robust to a range of sensitivity analyses undertaken to address the study limitations, in particular the ascertainment method.

Most patients with CF are not hospitalized for CF-related complications before age 6 (24). Thus, the cohort identified in this study may be biased towards the sickest CF patients, those whose clinical signs of disease emerge the earliest, which may limit generalizability of the results to the entire population of patients with CF. Additionally, infants who are premature or have LBW are at higher risk for complications that may result in multiple hospitalizations and more opportunities to have a CF-specific ICD-9 code. Infants born with CF in Washington State who moved out of state prior to hospitalization would also be missed with our ascertainment method, which is more likely to occur in healthy infants. These potential sources of bias could have led to an over-estimation of the association of CF with adverse outcomes. Using data from the Washington State Department of Health Newborn Screening starting in 2006, we inferred that the study ascertainment methods captured 50% of patients with CF born in 2006-2013 and almost 60% of patients with CF born in 1996-2013. In imputation analyses, we assumed conservatively that the missed infants with CF were no likelier to experience adverse neonatal outcomes than the general population, and we performed an additional sensitivity analysis that excluded patients with meconium ileus. The persistently strong associations cannot be ascribed to ascertainment bias alone.

The risk of infant death is based on only 3 deaths (1.76%) among infants with CF and 11 deaths (0.32%) among infants without CF during the 1996-2013 cohort; all of the deaths

among children with CF occurred during 2006-2013. It is known that meconium ileus is associated with increased morbidity and mortality among the 15-20% of infants with CF who exhibit this condition (27, 28), and 1 of the 3 deaths in the CF group was in an infant with meconium ileus. There is statistical instability in the risk estimate for infant death due to the small number of events, which lends caution to the interpretation of this result. Yet lack of statistical significance should not be confused with lack of an association (26); the estimated increase in risk is large and should raise sufficient concern to be explored in other cohorts, particularly in light of the associations with other adverse neonatal outcomes.

In total, there have been four previous evaluations of neonatal outcomes for infants with CF (4, 7, 13, 14), with sample size ranging from 70 to 173 infants with CF. The two prior US studies were conducted in the 1950s and had strong limitations, lacking appropriate comparison groups of infants without CF and little data on possible confounders or biasing factors (4, 13). A more recent German study had a stronger study design but was restricted to infants born at term (7). In all four studies, CF was associated with LBW or lower mean birth weight (4, 7, 13, 14). None of the four studies included neonatal mortality as an outcome.

Only one of the previous studies addressed the association of CF with neonatal outcomes other than LBW (14). In that cohort study of 70 Italian infants with CF identified through newborn screening, the RR for LBW was 2.7, for SGA was 1.7 and for pre-term birth was 2.6 (14). In addition, in the Italian study all SGA children with CF were infants born at term and all pre-term infants with CF had adequate birth weight for their gestational age (14), suggesting that fetal growth abnormalities in infants with CF may arise late in gestation in infants born at-term. CFTR is expressed in the human placenta (5) and is specifically located in apical membrane vesicles that facilitate transport of nutrients into the amniotic fluid (6), supporting biologic plausibility for this theory. In contrast to the Italian study, we did not observe a stronger association of CF with LBW in term (versus pre-term) infants. And, the association of CF with LBW remained, though was attenuated, after adjusting for gestational age. Taken together, the lower average birth weight associated with CF may be in part due to an association with prematurity but does not appear to be solely due to prematurity.

In both the primary analyses and in the imputation analyses, the associations of CF with LBW, pre-term birth, and neonatal mortality persisted after 2006, when newborn screening for CF began. Importantly, advances in the care of children with CF have led to vastly improved outcomes in patients with CF during the past 15 years (29). The observed increased risk of adverse neonatal outcomes in the recent cohort likely reflects the lack of prenatal identification of CF diagnosis and the limited treatment options available prenatally. This raises questions about the utility of universal prenatal diagnosis of CF, which could potentially trigger increased prenatal monitoring and perhaps use of targeted CF therapies by the mother in an attempt to protect the unborn child from these adverse neonatal outcomes. For example, newborn screening has been associated with prevention of malnutrition through early comprehensive nutritional therapy (30), and prenatal diagnosis could allow pregnant women to have targeted nutritional interventions, which could be studied as a means of preventing LBW among infants with CF.

Our study explore s the early life history of infants with CF and adverse neonatal outcomes. LBW, SGA and preterm birth are well established risk factors for morbidity and mortality in the general population and also, presumably, in infants with CF. Different CFTR mutations confer variability in disease severity, spectrum of symptoms, and timing of clinical presentation, with the most common CFTR mutation (F508del) exhibiting a severe phenotype. (31, 32) It is plausible that adverse neonatal outcomes may serve as early markers of the CF disease course, in that LBW or prematurity may signal early emergence or more severe clinical disease. It did not appear that infants with CF and LBW were hospitalized more frequently than infants with CF without LBW, yet this secondary, exploratory analysis can be improved upon with a dataset more suited to the purpose.

In conclusion, this study provides evidence that CF is associated with increased risk of LBW, pre-term birth, and possibly infant death. Although it is plausible that LBW might predict a more severe disease course in CF, this hypothesis has yet to be established. Nevertheless, identification of associations with adverse neonatal outcomes could affect counselling and decision-making regarding prenatal testing for CF, because there may be a role for studies of nutritional or pharmacologic interventions for pregnant women with the prenatal diagnosis of an infant with CF.

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Abbreviations

CF	Cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
SGA	small-for-gestational age
LBW	low birth weight
US	United States
RR	risk ratio
CI	confidence intervals
SD	standard deviation

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Table 1

Maternal, paternal and infant characteristics in a cohort of children with cystic fibrosis (CF present) and birth-year matched children without CF (CF absent) in Washington State from 1996-2013[1]

	CF Present (N= 170)		CF Absent (N= 3,400)	
Maternal Characteristics				
Age (years), mean (SD)	27.7	(6.5)	27.9	(6.1)
White race, n (%)	155	(91.2)	2,363	(69.5)
Education completed, n (%)				
Grade School	3	(1.8)	147	(4.3)
High School	62	(36.5)	1,285	(37.8)
College	102	(53.3)	1,812	(53.3)
Cigarette smoking (during pregnancy), n (%)	27	(15.9)	389	(11.4)
Married, n (%)	112	(65.9)	2,363	(69.5)
Parity, n (%)				
Nulliparous	79	(46.5)	1,414	(41.6)
Primiparous	47	(27.7)	1,050	(30.9)
Multiparous	39	(22.9)	857	(25.2)
Medicaid Insurance, n (%) [2]	68	(40.0)	1,450	(42.7)
Paternal Characteristics				
White race, n (%) [3]	129	(75.9)	2,124	(62.5)
Education completed, n (%) [4]				
Grade School	3	(1.8)	130	(3.8)
High School	59	(34.7)	1,038	(30.5)
College	73	(42.9)	1,594	(46.9)
Infant Characteristics				
Male Sex	96	(56.5)	1,716	(50.5)
APGAR score at 5 minutes <7	12	(7.1)	62	(1.8)

CF=cystic fibrosis, SD=standard deviation

[1] <5% missing data unless otherwise noted

[2] "Medicaid Insurance" includes Medicaid, Medicare and Charity as a payment source for the birth hospitalization. Comparison group includes all other payment sources.

[3] Paternal race was missing for 15.9% of children with CF present, and for 12.2% of children with CF absent

[4] Paternal education was missing for 20.6% of children with CF present, and for 18.8% of children with CF absent

Table 2

Description of neonatal adverse outcomes for a cohort of children with cystic fibrosis (CF present) compared to birth-year matched children without CF (CF absent) in Washington State from 1996- 2013 and 2006-2013[1]

	1996-2013				2006-2013			
	CF Present (N=170)		CF Absent (N=3400)		CF Present (N=68)		CF Absent (N=1360)	
Low Birth Weight (<2500 grams), n (%)	32	(18.8)	201	(5.9)	17	(25.0)	92	(6.8)
Small for Gestational Age[2] (<10th percentile), n (%)	23	(13.5)	286	(8.4)	5	(7.4)	109	(8.0)
Pre-term Birth (<37 weeks), n (%)	41	(24.1)	288	(8.5)	19	(27.9)	140	(10.3)
Infant Death[3] (Death <1 year), n (%)	3	(1.8)	11	(0.3)	3	(4.4)	5	(0.4)

CF=cystic fibrosis, SGA=small for gestational age

[1] <1% missing data unless otherwise noted

[2] SGA missing for 1.2% of children with CF present (1996-2013), and for 3.8% of children with CF absent (1996-2013); SGA missing for 2.9% of children with CF present (2006-2013), and for 2.9% of children with CF absent (2006-2013)

[3] Infant death among infants with CF present occurred in 2 infants without meconium ileus and 1 infant with meconium ileus

Table 3

Adjusted associations of cystic fibrosis with neonatal adverse outcomes for a cohort of children with cystic fibrosis (CF present) compared to birth-year matched children without CF (CF absent) in Washington State from 1996- 2013 and 2006-2013

	1996-2013			2006-2013		
	RR[1]	**(95% CI)**	**p-value**	**RR[1]**	**(95% CI)**	**p-value**
Low Birth Weight (<2500 grams)	3.5	(2.5-4.9)	<0.001	4.0	(2.5-6.3)	<0.001
Small for Gestational Age (<10th percentile)	1.6	(1.1-2.4)	0.025	1.0	(0.4-2.4)	0.985
Pre-term Birth (<37 weeks)	3.0	(2.2-4.0)	<0.001	2.8	(1.9-4.3)	<0.001
Infant Death (Death <1 year)	6.8	(1.7-26.5)	0.006	12.1	(2.5-57.3)	0.002

CF=cystic fibrosis, RR=risk ratio, CI=confidence interval

[1] Poisson regression analyses adjusted for maternal race (white/non-white)

Table 4

Results of extreme value imputation for assessing associations of adverse neonatal outcomes with cystic fibrosis in a cohort of infants born in Washington State in the years 1996-2013.

	1996-2013		2006-2013	
	RR* (95% CI)	**Imputed RR* (95% CI)[1]**	**RR* (95% CI)**	**Imputed RR* (95% CI)[2]**
LBW	3.2 (2.3-4.5)	2.3 (1.6-3.1)	3.7 (2.3-5.8)	2.4 (1.5-3.7)
SGA	1.6 (1.1-2.3)	1.3 (1.0-1.9)	0.9 (0.4-2.2)	1.0 (0.6-1.8)
Pre-term Birth	2.8 (2.1-3.8)	2.1 (1.6-2.7)	2.7 (1.8-4.1)	1.8 (1.3-2.7)
Infant Death	5.5 (1.5-19.4)	3.2 (0.9-11.3)	12.0 (2.9-49.2)	6.0 (1.4-24.7)

RR=risk ratio, LBW=low birth weight, SGA=small for gestational age, CF=cystic fibrosis

*RR (relative risk) presented are unadjusted for confounding by maternal race yet are similar to the adjusted estimates shown in Table 3.

[1]The prevalence of LBW, SGA, pre-term birth, and infant death in infants without CF, born in 1996-2013, was 5.9%, 8.4%, 8.5%, and 0.3%, respectively. We applied these prevalence estimates to the 123 infants with CF expected to have been missed through the study's ascertainment method in the 1996-2013 birth cohort.

[2]The prevalence of LBW, SGA, pre-term birth, and infant death in infants without CF born in 2006-2013, was 6.8%, 8.0%, 10.3%, and 0.4%, respectively). We applied these prevalence estimates to the 69 infants with CF expected to have been missed through the study's ascertainment method in the 2006-2013 cohort.

Table 5 online

Adjusted associations of cystic fibrosis with neonatal adverse outcomes for a cohort of children with cystic fibrosis (CF present) without meconium ileus compared to birth-year matched children without CF (CF absent) in Washington State from 1996- 2013 and 2006-2013

	1996-2013			2006-2013		
	RR[1]	**(95% CI)**	**p-value**	**RR[1]**	**(95% CI)**	**p-value**
Low Birth Weight (<2500 grams)	3.3	(2.3-4.9)	<0.001	4.2	(2.6-6.6)	<0.001
Small for Gestational Age (<10th percentile)	1.5	(1.0-2.4)	0.062	1.1	(0.5-2.7)	0.782
Pre-term Birth (<37 weeks)	2.9	(2.1-4.0)	<0.001	2.9	(1.8-4.4)	<0.001
Infant Death (Death <1 year)	5.4	(1.1-27.3)	0.042	9.3	(1.5-57.4)	0.016

CF=cystic fibrosis, RR=risk ratio, CI=confidence interval

[1] Poisson regression analyses adjusted for maternal race (white/non-white)

Table 6 online

Characteristics of a cohort of children with cystic fibrosis (CF) identified by hospitalization through the first 5 years of life with a CF-specific ICD-9 code in Washington State from 1996-2013

	LBW (n= 32)		Non-LBW (n=138)		All infants with CF (n= 170)	
	n	(%)	n	(%)	n	(%)
Males	24	(75.0)	72	(52.2)	96	(56.5)
Pre-term birth (<37 weeks)	26	(81.3)	15	(10.9)	41	(24.1)
Timing of index hospitalization[1]						
Birth	14	(43.8)	25	(18.1)	39	(22.9)
By 14.5 months	21	(65.6)	96	(69.8)	117	(68.8)
Apgar score at 5 minutes <7[2]	7	(21.9)	5	(3.6)	12	(7.1)
Hospital diagnoses[3]						
Respiratory	16	(50.0)	8	(5.8)	24	(14.1)
Gastrointestinal	6	(18.8)	17	(12.3)	23	(13.5)
Failure to thrive	1	(3.1)	7	(5.1)	8	(4.7)
Fever/ Infection	5	(15.6)	10	(7.2)	15	(8.8)
Meconium ileus	6	(18.8)	19	(13.8)	25	(14.7)
# of hospital admissions[4]						
0	6	(18.8)	12	(8.7)	18	(10.6)
1-5	20	(62.5)	99	(71.7)	119	(70.0)
>5	6	(18.8)	27	(19.6)	33	(19.4)

CF=cystic fibrosis, LBW=low birth weight

[1] Age at hospitalization when ICD-9 code first indicated CF

[2] Apgar score at 5 minutes was missing for one child with LBW

[3] Other medical diagnoses during index hospitalization, identified by ICD9 codes (Table x)

[4] Number of hospital admissions through age 5 years; “0” refers to ICD-9 code present during birth hospitalization with no subsequent hospitalizations

Table x

ICD-9 codes used to identify a cohort of infants with cystic fibrosis (CF) and other hospital diagnoses from Washington State hospital discharge data linked to birth certificates 1996-2013.

CF-specific	277.00, 277.01, 277.02, 277.03, 277.09
Hospital Diagnoses	
Respiratory	493,417, 466.0, 490, 491, 480 – 488, 518.81, 518.1, 770, 769, 997.31
Gastrointestinal	251.8, 251.9, 577.9, 557.8, 579.8, 579.9, 560, 777.1, 008, 564, 009.2, 009.3, 787.91, 779.32, 779.33
Failure to thrive	783.21, 779.34, 783.41, 779.31
Fever/ Infection	780.6, 780.61, 078.2, 771, 136.9
Meconium ileus	277.01, 777.1