Review

Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment

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Donald R. VanDevanter [a,*], Jennifer S. Kahle [b], Amy K. O'Sullivan [c], Slaven Sikirica [c], Paul S. Hodgkins [c]

[a] Case Western Reserve University School of Medicine, Cleveland, OH, USA
[b] BPS International, San Diego, CA, USA
[c] Vertex Pharmaceuticals Incorporated, Boston, MA, USA

Abstract

Background: Studies have described illness associated with cystic fibrosis (CF) early in life, but there is no comprehensive accounting of the prevalence and ages of disease manifestation and progression described in individual studies.
Methods: We searched for peer-reviewed English-language studies of the health of children ≤6 years old with CF (published 1990–2014). Structural abnormalities and dysfunction of the digestive and respiratory systems were summarized across relevant studies by system and age group.
Results: Primary studies (125 total) from 22 countries described abnormalities, dysfunction, and disease progression in infancy and early childhood. Improved health was consistently observed in association with diagnosis via newborn screening compared with cohorts diagnosed later by symptomatic presentation.
Conclusions: The peer-reviewed literature is remarkably consistent: CF-associated growth impairment and airway abnormalities are reported at birth, and disease progression is reported in infancy and throughout childhood. Earlier access to routine CF management is associated with improved subsequent health status.
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Keywords: Child; Disease progression; Comprehensive survey; Data collection; Infant; Preschool; Health status

Contents

* Corresponding author at: 12520 33rd Street Ct E, Edgewood, WA 98372 USA. Tel.: +1 253 370 5859.
 E-mail address: drv15@case.edu (D.R. VanDevanter).

1. Introduction

Cystic fibrosis (CF) is a life-shortening, multisystem genetic disease. Since the 1930s, the development and use of an arsenal of symptomatic treatments and extensive prophylactic daily treatment regimens have extended the CF median predicted survival from just a few months following diagnosis to 38 years of age for the cohort in the US CF Foundation Patient Registry in the years 2008 to 2012 [1], and 34 to 44 years of age for the cohort in the United Kingdom (UK) CF Registry in the years 2009 to 2013 [2]. Despite this dramatic improvement, CF continues to be characterized by digestive and respiratory dysfunction contributing to growth deficits, chronic respiratory infection, progressive lung tissue damage, and premature death [1]. The median age of death among individuals with CF followed in the US and UK patient registries was 27 to 28 years in 2012 [1,2].

The discovery of the mutated CF gene (cystic fibrosis transmembrane conductance regulator; *CFTR*) in 1989 [3,4] and the function of wild-type CFTR protein in 1992 [5] established the underlying pathophysiology present in CF epithelial tissues, including that of the sweat gland, the pancreas, the airway, and the intestine. It is now recognized that interventions targeting the underlying *CFTR* defect across body systems have the potential to improve outcomes throughout life for persons with CF. Because CF is a progressive, multiorgan disease, initiation of symptomatic and prophylactic treatments early in life with the help of newborn screening has been shown to improve outcomes compared with later initiation of treatment secondary to later diagnosis [6]. Similarly, it is likely that the initiation of interventions that target the underlying *CFTR* defect before significant disease progression has great potential to avoid accumulation of tissue damage, allowing for better health maintenance and more normal function for persons with CF. The optimal time for initiation of treatments is dependent on when complications and cumulative damage begin to occur in persons with CF.

It has long been appreciated that newborns with CF can have serious pancreatic insufficiency and gastrointestinal complications related to their disease, as discussed in two recent reviews [7,8]. In contrast, only fairly recently reviews [9–11] and critical analyses [12,13] have begun to suggest that abnormalities of the respiratory system consistent with early disease progression can be observed early in life in children with CF. To date, a comprehensive review of the ages of earliest disease manifestation and progression across organ systems is lacking, which represents a knowledge gap. Although it is understood that disease progression will be unique to each individual, it is important to establish the ages at which CF signs and symptoms manifest and disease progression have been observed on a large scale. Thus, we undertook a comprehensive review of published primary studies of health, disease, and disease progression in the respiratory and digestive systems reported for young children with CF worldwide. We focused on the respiratory and digestive systems because the major symptoms and causes of death are associated with these two body systems [1].

The three research questions were: (1) At what ages have CF-related dysfunction and structural differences been demonstrated in young children with CF (≤ 6 years of age)? (2) At what ages has disease progression been reported in young children with CF? (3) At what ages are there improved outcomes with early versus late treatment initiation in young children with CF?

2. Methods

2.1. Search details and dates

Three large literature databases (MEDLINE, CENTRAL, and EMBASE) were searched between June and August 2014 for peer-reviewed, English-language, primary studies of the health of young children (≤ 6 years of age) with CF. The search strategy (Supplementary Material 1) was designed to capture a broad range of study types to provide a comprehensive summary of available results. Studies of treated and/or untreated children with CF (all genotypes) published between January 1, 1990 and August 6, 2014 were included. Studies including a wider age range were included only if outcomes for children aged 6 years or younger were analyzed separately from outcomes for older groups. Reviews, systematic reviews, meta-analyses, animal studies, studies of older persons only, non–peer-reviewed publications, case studies, and treatment or diagnosis guidelines were excluded.

Duplicate citations and articles of inappropriate types, publication dates, and language were removed in a primary sort. A secondary sorting of titles and abstracts eliminated inappropriate study populations (non-CF, adults, older children, parents) and in vitro studies. A single researcher conducted the first two sorting phases. A final sorting of titles and abstracts restricted the articles included to relevant studies of the digestive and/or respiratory systems in young children (study sample ages ≤ 6 years were determined from the title or abstract of each study). Two researchers performed the final sort independently and agreed on inclusion of each study, with discrepancies resolved upon reading the full text. Two researchers extracted data from each study independently from each other.

In included studies, outcomes for children with CF were compared with outcomes for control populations without CF, population norms (e.g., standard growth charts), baseline values for study participants or between treatment groups (i.e., earlier versus later treatment initiation). The purpose of this review was to include a broad range of studies and study outcomes were synthesized here in a non-statistical manner, due to the heterogeneity of the study designs, outcome measures, and study populations. Outcomes were summarized as *worse* or *improved* if statistically significant differences were reported; outcomes that did not reach statistical significance were summarized as *not different*.

3. Results

3.1. Search results

In all, 271 studies describing the health or illness of young children with CF were drawn from an initial pool of 14,071 citations (including 3,310 duplicates). Of these, 125 were identified as relevant studies of the CF digestive and/or respiratory systems (Supplementary Fig. 1). A wide variety of study designs, study sample sizes, and countries of origin were represented in the included studies (Supplementary Table 1). Study populations were from 22 countries in 8 major world regions (North America; South America; Oceania; Western Asia; and Western, Eastern, Northern, and Southern Europe) [14].

3.2. Summary of results

Literature exists for outcomes in children ≤ 6 years of age relating to all three of the research questions for both the CF digestive and respiratory systems. For Research Question 1 (At what ages have CF-related dysfunction and structural differences been demonstrated in young children with CF [≤ 6 years of age]?), there was a substantial evidence base for tissue abnormalities and organ dysfunction in children prenatally, from birth, and throughout early childhood to 6 years of age. Abnormalities were observed at the molecular, cellular, tissue, and organ levels, and manifested as large-scale physical signs and symptoms. With respect to Research Question 2 (At what ages has disease progression been reported in young children with CF?), progression of disease in both the respiratory and digestive systems was demonstrated in infants as young as 6 months of age, with significant respiratory structural and functional decline occurring with each year of age in children aged ≤ 6 years. Moreover, development of complications and accumulation of damage were observed in young children, including an increased risk of *P. aeruginosa* airway infection in infancy (defined as up to 1 year of age in this review) and potentially irreversible lung damage by 2 years of age. Finally, for Research Question 3 (At what ages are there improved outcomes with early versus late treatment initiation in young children with CF?), a large evidence base demonstrated better outcomes with earlier initiation of standard-of-care treatment as a result of earlier diagnosis compared with later treatment initiation due to later diagnosis. A difference in CF diagnosis and associated treatment initiation of 4 to 13 months during infancy had a significant impact on outcomes throughout childhood. Initiation of treatment and medical management within 2 months from birth was associated with improved outcomes in both the respiratory and digestive systems in children ≤ 6 years of age.

3.3. CFTR expression and morbidity observed throughout early childhood

In all, 5 articles studied *CFTR* expression and function early in life. Substantial prenatal *CFTR* mRNA expression was observed in the pancreas, liver, gall bladder, and intestine, with somewhat lower levels of expression in the trachea [15] and airways [16]. CFTR protein expression was also observed in prenatal epithelium and glands of the intestine, as well as in the ciliated cells, collecting ducts, and glands of airways. Immediately before birth, CFTR protein expression was observed in the periphery of acini of the airways [17], and *CFTR* mRNA was observed in airway mucus-producing glands in infants and 2-year-olds [16]. Direct evidence of reduced CFTR function in young children with CF included dysfunction of the cellular lining in the distal bowel of 3-year-olds [18] and airways of 2-year-olds [19].

Structural abnormalities and dysfunction in the digestive and respiratory systems were observed prenatally, in infants, and throughout childhood among children with CF, including bowel, pancreatic, and liver abnormalities, nutritional deficiencies, growth deficits, airway anomalies, inflammation, pulmonary dysfunction, infection, and pulmonary exacerbations. A total of 99 studies reported various abnormalities and morbidities in children ≤ 6 years of age. These studies were organized by similarities in reported outcomes and study population ages, and the citations are listed in Table 1. A total of 3 studies reported outcomes that were not different from those in non-CF controls. The results of these studies are described in the footnotes to Table 1.

Although the 99 studies listed in Table 1 identified significant morbidity in the CF study populations, only a subset of these (41 total) also reported the proportion of the CF study population in whom abnormalities and illness was observed. These proportions of the study samples suffering morbidity are shown as individual pie charts for these 41 studies in Fig. 1, organized by outcome and age. Morbidity was observed in 50% or more of the study sample for a majority of respiratory system outcomes (24/44 total). There are more total outcomes than the number of articles because more than one outcome was presented in some articles. Likewise, morbidity was observed in 50% or more of the study sample for a majority of digestive system outcomes (14/20 total). Many types of abnormalities were observed in high proportions of children with CF from infancy throughout early childhood. Specific measures of morbidity varied among studies.

3.4. Progression of disease

The studies that document disease progression at the youngest ages are summarized here and in Figs. 2 and 3. Evidence of disease progression in both digestive and respiratory systems of children with CF was observed by

Table 1
Types of abnormalities and morbidity observed in the respiratory and digestive systems of children ≤ 6 years of age with CF.

	Prenatal (no. of studies)	Infants [a] (no. of studies)	Toddlers [b] (no. of studies)	Preschoolers [c] (no. of studies)
Respiratory system				
Airway lining and walls/mucus coating abnormalities	2 [16,20]	6 [16,19–23]	5 [16,19,22–24]	2 [19,23]
Inflammation/immune response	1 [25]	7 [26–32]	5 [27,29,32–34] [d]	3 [29,32,33]
Poor chest-imaging scores [e]	—	3 [30,35,36]	3 [35,37,38]	3 [35,37,38]
Bronchiectasis	—	5 [30,39–42]	5 [37,38,40–42]	4 [37,38,40,41]
Airway wall thickening/smaller luminal area	—	5 [22,30,40,43,44]	5 [22,38,40,43,44]	3 [38,40,43]
High airway resistance/mucus plugging/obstruction	—	3 [40,45,46]	7 [37,38,40,45,47–49]	6 [37,38,40,47–49]
Air-trapping/hyperinflation	—	8 [30,39,41,44,45,50–52]	7 [37,41,44,45,51–53]	2 [37,41]
Lung dysfunction [f]	—	12 [44,50,52,54–62]	15 [44,47,52,54–56,58–60,62–67]	10 [47,55,56,62–65,67–69]
Perfusion deficits	—	1 [40]	3 [38,40,70]	3 [38,40,70]
Infection [g]/colonization	—	8 [30,56,71–76]	12 [34,36,47,56,70,72–78]	6 [47,56,70,72,74,75]
Abnormalities secondary to infection [h]	—	3 [40,74,79] [i]	4 [40,74,78,79] [i]	4 [40,74,79,80]
Pulmonary exacerbations	—	3 [81–83]	3 [81–83]	3 [81–83]
Digestive system				
Intestinal lining and walls/mucus coating abnormalities	4 [20,84–86]	2 [20,86]	2 [18,87]	2 [18,87]
Inflammation	—	—	1 [87]	1 [87]
Pancreatic dysfunction	—	9 [72,88–95]	7 [72,88,91–95]	1 [72]
Liver dysfunction	—	2 [96,97]	—	—
Nutritional deficiencies [j]	—	9 [88,90,96,98–103]	1 [98]	—
Weight deficit [k]	—	14 [50,51,58,59,61,88–90,95,104–108]	15 [51,58,59,63,64,70,95, 104,106,108–113]	9 [63,64,70,104,106,108, 110,112,113]
Height deficit	—	12 [50,54,59,61,90,95, 104–106,108,114,115] [l]	15 [54,59,63,64,95,104, 106,108–115] [l]	9 [63,64,95,104,106,110, 112–114]

[a] Infants: age range from 0 to <1 year old.
[b] Toddlers: age range from 1 to 3 years old.
[c] Preschoolers: age range from >3 to 6 years old.
[d] One study reported that exhaled nitric oxide (one type of immune response indicator) was not lower in 1-year-olds with CF than non-CF controls [116].
[e] Chest imaging methods include: X-ray, computed tomography, and magnetic resonance imaging.
[f] Lung function measures include: forced expiratory volume, forced expiratory flow, forced vital capacity, lung clearance index, maximal flow at functional residual capacity, respiratory rate, and respiratory symptoms (cough and crackles).
[g] Includes both CF-related opportunistic bacterial infection and increased incidence of seasonal viral infection.
[h] Airway structural changes proposed by the individual study authors to be secondary to infection include: nasal polyps, bronchial surfactant composition alteration and lung collapse, and reduced pulmonary tissue elasticity.
[i] The elastic properties of lung tissue (respiratory compliance) were reported to be normal at 41 to 97 weeks of age [117].
[j] Nutritional deficiencies included: Vitamins A, D, and E; essential fatty acids, protein, sodium, potassium, and zinc.
[k] Weight deficits included low body mass index.
[l] One study reported that height z-scores measured in children with CF between 0.12 and 2.5 years old were not different from those in non-CF controls [58].

6 months of age. Worsening of lung function as measured by spirometry was observed in infants 6 months to 1 year of age [58] (Fig. 2). While 59% to 71% of infants with CF were determined to be pancreatic insufficient at birth, pancreatic function declined in a subset of those determined to be pancreatic sufficient at birth, such that an additional 16% to 20% were insufficient by 6 months of age (Fig. 3) [88,90,95]. In addition, airway viral and bacterial infection/colonization was observed in children as young as 2 to 6 months of age [30,71] (Table 1), including *P. aeruginosa*, a complication of CF.

Progression of disease continued throughout childhood, including worsening of airway resistance [45], airway inflammation [78], air trapping [45,124], lung structure [35,40,43,123–126], lung function (Fig. 2) [58,61,63,66,112,123], and nutrient deficiencies [127,128]. Accumulation of lung damage was evident by 1 year of age [36,123,124], and lung structure and function worsened significantly each year of life in young children aged 0

to 6 years [35,43,58,123,124]. One study, however, reported that although 4 spirometric measures of lung function all worsened between ages 0 to 5 years and 6 to 16 years, they worsened by a significant amount from measures recorded in younger age groups only at ages older than 16 years [40]. Another study reported a worsening in lung clearance index in 33% of children between ages 3 to 5 years and 6 to 10 years, and improvement in 15% of children over this same period [110], although there is a question as to whether improvement in lung clearance index with age may be an artifact of the changing ratio of lung volume to equipment dead space volume with the growth of the lungs as the children aged [129]. Respiratory structural abnormalities proposed by the individual study authors to be secondary to infection including nasal polyps [80], lung collapse [40,79], and reduced pulmonary tissue elasticity [74] were evident within a few years of life (Table 1), and "potentially irreversible" lung damage was evident by 2 years of age [35]. One study reported that the pulmonary
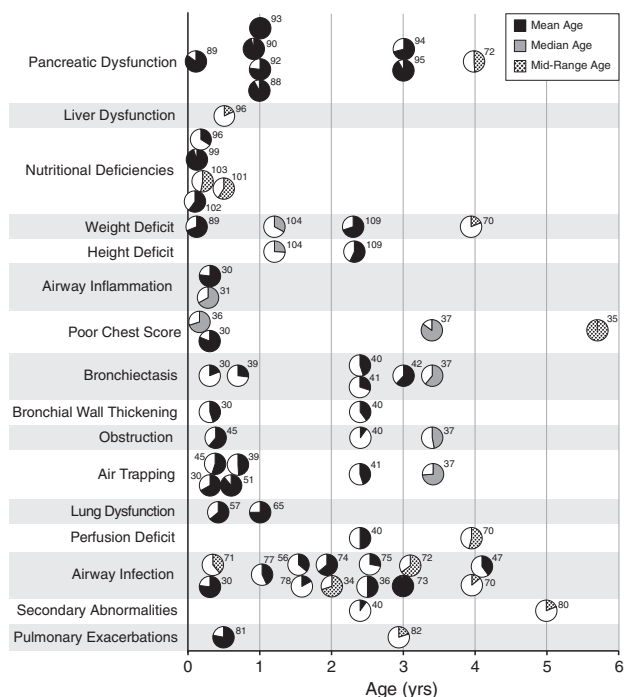
Fig. 1. Percentage of study samples with morbidity. The shaded portion of each pie chart corresponds to the percentage of the study sample with CF that was reported to have specific morbidities or abnormalities. The sizes of the study samples with CF ranged from 11 to 9895 (see Supplemental Table 1 for additional information on study sample sizes). Numbers next to each pie chart are the study citation. Mid-range age was calculated by subtracting the youngest age from the oldest age, dividing by two, and adding the result to the youngest age.

exacerbation rate increased by an average of 9% per year of age in young children (with 0 to 1 year old as the reference age); hospitalizations for pulmonary exacerbations increased from 64 total admissions among 168 infants aged 0 to 1 years to 86 hospital admissions among 158 children aged 4 to 5 years [130]. In another study, early respiratory symptoms (coughing, wheezing, rapid
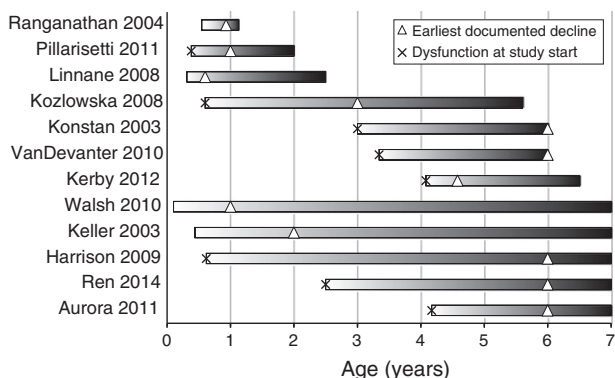

Fig. 2. Worsening of lung function in young children with CF. Twelve studies documented within-patient longitudinal measures of lung function and all 12 reported decline [58,61,63,66,110,112,118–123]. Bars represent the age (mean, median, or mid-range) at which lung function was first measured (study start) to oldest age of follow-up (presented results truncated at 7 years). White triangles represent the youngest documentation of within-patient worsening. Note: For each study, lung function decline was observed at the youngest age of follow-up. Black ×s represent lung dysfunction (signs and symptoms, obstruction, or low spirometry measures) compared with non-CF controls at study start.

breathing) at 5 months of age were associated with greater numbers of hospitalizations for respiratory illness by 17 months of age [131].

Early signs of digestive system morbidity were associated with subsequent poor respiratory outcomes and vice versa. Meconium ileus at birth was a risk factor for bronchiectasis by 3 months of age [42]. Low or high weight for age and height for age in 3-year-olds predicted low or high spirometric lung function outcomes, respectively, at 6 years of age [119,122]. In one study, pancreatic insufficiency was associated with an increased hazard ratio for *P. aeruginosa* airway infection starting at 2 months of age, with 62% of children reported to have airway infection by 8 years of age [72]. Pancreatic insufficiency was also associated with worse chest X-ray scores and meconium ileus was associated with worse spirometric lung function outcomes by 11 years of age [35]. Conversely, any occurrence of more serious hospital-managed pulmonary exacerbation versus less serious home-managed pulmonary exacerbation between ages 0 and 5 years was associated with significantly lower weight at 5 years of age [130]. A *P. aeruginosa*–positive culture at 4 years of age predicted lower weight population norm percentile at 12 years of age [132]. One study, however, reported that better growth was observed by age 18 months, specifically in infants with hyperinflation at diagnosis, not those without hyperinflation or with pulmonary obstruction [45].

3.5. Effects of early diagnosis and onset of treatment

In all, 12 studies compared health outcomes among children diagnosed with CF with the help of newborn screening with outcomes among those diagnosed as a result of symptom presentation. The latter populations ranged from 4 to 24 months of age before diagnosis, and were likely not systematically treated with routine CF care until after diagnosis. In this context, routine CF care included a variety of treatments and interventions recommended for children with CF at the time and place of care, including prophylactic and symptomatic nutritional and vitamin supplements, high-calorie diets, pancreatic enzyme supplements, chest physiotherapy, mucus thinners, anti-inflammatories, and antibiotics. Most studies compared health outcomes associated with initiation of routine CF care 12 to 14 months earlier among cohorts diagnosed by screening at about 1 month of age with outcomes in cohorts diagnosed by symptom presentation at about 14 months of age.

In general, children with access to earlier routine CF care secondary to earlier diagnosis had better outcomes compared with those children whose access was later as a result of later diagnosis. Benefits of earlier diagnosis included reduced airway inflammation [133], improved lung structure [134], improved lung function [95,133,135], delayed chronic airway infection [134], lower incidence of mucoid *P. aeruginosa* colonization [104], improved growth (Fig. 4) [95,104,106,111,133–138], reduced hospitalizations [104,138], and improved survival [133,136,139,140]. Of importance, these differences could not be accounted for simply by greater inclusion of children with less severe forms of CF in newborn screening cohorts, as they were observed among children with identical *CFTR* genotypes,
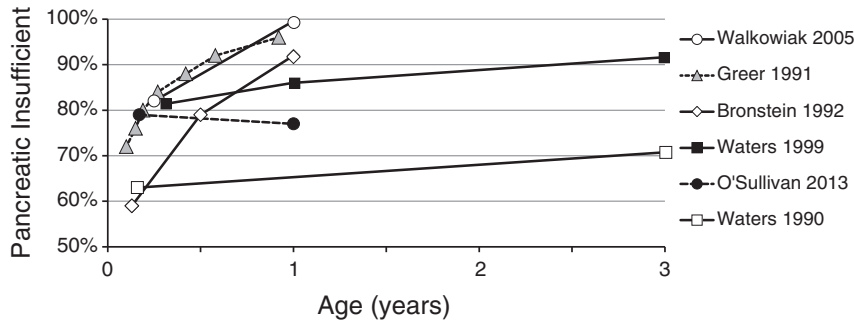
Fig. 3. Pancreatic function variability. Six studies reported results indicating varying pancreatic status early in life; the results of these 6 studies are presented here [88,90,92–95]. Data points represent the percentage of the study sample that were pancreatic insufficient at that age. Circles represent measurement of pancreatic function using fecal elastase, squares represent measurement of pancreatic function using pancreatic isoamylase, fecal fat, pancreas stimulation, and/or symptoms, and other symbols represent measurement of fecal fat. Note that the *y*-axis begins at 50%. Walkowiak (2005) was the single study of this group with a study sample restricted to severe *CFTR* mutations [93]; other studies included a representative sample of genotypes. O'Sullivan 2013 reported that a subgroup of infants with CF tested as pancreatic sufficient after having tested as pancreatic insufficient and vice versa. By 1 year old, 23% (3/13) of children were determined to be pancreatic insufficient who were previously sufficient, and 8% (4/48) of children were determined to be pancreatic sufficient who were previously insufficient [92]. Pancreas sufficiency or insufficiency was a result of the natural course of CF. The youngest measurement for Waters (1999) was the mid-range age of two group median diagnosis ages and the oldest age was estimated from information given in the text.

percentage pancreatic insufficiency, and history of meconium ileus (Supplementary Table 2, study and study sample characteristics for Fig. 4).

Two studies compared cohorts of patients with mean ages of diagnosis that were earlier by only 4 months (2 versus 6 months of age). Chest X-ray scores at 5 years of age were not found to differ between the groups [95], but lung function was improved for the early diagnosis group between 5 and 10 years of age [95,135] and weight and height were greater until age 5 years [95]. In a third study, a 5 to 8 months earlier diagnosis (1 versus 6 to 9 months of age) was associated with a higher survival rate (98% versus 88%) up to 16 years of age [136].

4. Discussion

During the first decades after CF was initially characterized, infant mortality was dramatically reduced with the introduction of pancreatic enzyme supplementation and greater attention to early nutrition, as well as the coincident expansion of the availability of antimicrobials to treat acute airway infection. Over recent decades, the development and use of chronic and acute therapies targeted at downstream CF symptoms and pathologies have provided valuable reduction of symptoms for individuals with demonstrable disease. Clinical trial outcomes characterizing the clinical efficacy of pulmonary therapies, such as sustained increases in pulmonary function or reduced risk of treatment with intravenous antibiotics, have not translated well to very young children with CF, however, primarily because spirometry measures were not developed for and are not sensitive in early CF disease [141]. As the use of these therapies has become more common at younger ages, along with the introduction of several prophylactic pulmonary treatments, a natural interest in earlier, preventive intervention has led to the questions: (1) How early does disease manifest and begin to progress for newborns with CF, and (2) would earlier management of CF pathology translate to improved health outcomes for persons with CF?

With regard to the question of the prevalence of *CFTR* dysfunction in infants and children with CF, the peer-reviewed
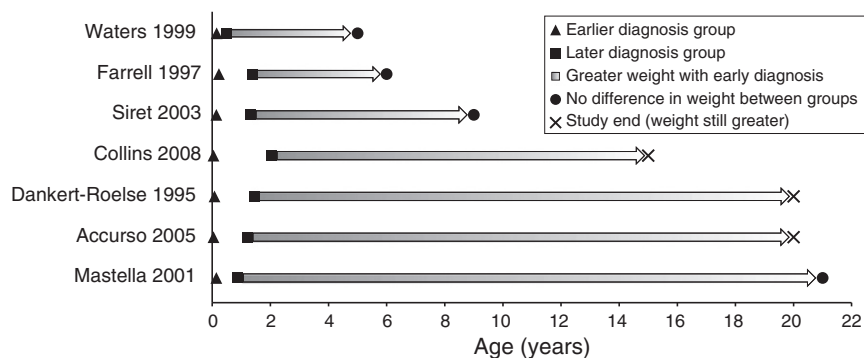

Fig. 4. Improved weight with earlier versus later diagnosis and treatment initiation. Children diagnosed and treated earlier (triangles) gained more weight over 5–20 years than did children diagnosed and treated later (squares). Arrows indicate the ages in each study at which the children diagnosed earlier weighed significantly more than the children diagnosed later. Circles denote the age at which weights between the two groups were no longer significantly different, due to "catch-up growth" of the late-diagnosis group of children. For 3 studies, weight was still significantly different between the two groups at the end of the study (black ×). Note: these comparisons were between groups of children with CF, and while these data represent improved weight, weight was not always improved to population norms with early diagnosis and treatment initiation [95,104,106,111,133,136,138]. The details of each study and study sample characteristics are provided in Supplementary Table 2.

literature is unequivocal: CFTR protein dysfunction contributes to growth deficits and airway pathologies *from birth*, is associated with CF pathologies detectable *in infancy*, and results in significant progression of respiratory disease with each year of life in young children with CF. This conclusion should hardly be surprising, as the pathologic ramifications of *CFTR* dysfunction in the digestive system of infants with CF have been recognized for more than half a century; the disease was named for pancreatic autopsy findings in this population [142]. That pathologies related to *CFTR* dysfunction are present at birth is irrefutable: elevated concentrations of circulating immunoreactive trypsinogen secondary to *CFTR* dysfunction in the neonatal exocrine pancreas are exploited for CF newborn screening, elevated sweat chloride concentrations secondary to *CFTR* dysfunction in the newborn sweat gland are diagnostic, and >10% of newborns diagnosed with CF today present with meconium ileus and bowel obstruction [1]. Further, the literature is remarkably consistent with regard to observations of CF-associated growth impairment and cumulative anatomical and functional airway abnormalities beginning in infancy and progressing through childhood.

The implementation of CF newborn screening has provided a means of examining whether or not earlier and more comprehensive intervention in infants and young children with CF improves health outcomes. Multiple studies have demonstrated growth advantages in cohorts of children with CF identified with the help of newborn screening when compared with cohorts diagnosed from months to years later by symptom presentation. With the exception of randomized controlled study designs, these comparisons are hampered by an obvious problem: children diagnosed on the basis of symptom presentation are by definition symptomatic, while a majority of infants diagnosed with the help of newborn screening are not; thus, these groups are not necessarily comparable with respect to the severity of underlying CFTR dysfunction. Comparisons of contemporary cohorts of children with identical *CFTR* genotypes, however, have demonstrated a clear advantage with respect to height-for-age *z*-scores and pulmonary function *z*-scores for children identified with the help of newborn screening [143]. Given that earlier diagnosis translates to earlier access to routine care provided by multidisciplinary CF care teams, it follows that earlier intervention in infants is most likely responsible for better health outcomes at an older age. Earlier access to today's rigorous multidisciplinary CF care, however, is not sufficient to prevent cumulative anatomical and functional changes observed in the airways of infants and young children with CF and shortened lifespan. Our review confirms that underlying CFTR dysfunction in infants and young children remains associated with increased risk of mucus plugging, inhomogeneous ventilation, reduced airflow, opportunistic bacterial infection, gas trapping, bronchial wall thickening, pancreas and liver dysfunction, nutritional deficiencies, growth deficits, and increases in concentration of cytokines and other inflammatory markers.

4.1. Limitations and possible biases

The purpose of this review was to include a wide range of study types from researchers worldwide. The inclusion of studies with many different study designs, sample populations, genotypes, diagnostic methods, outcome measures, and regions of origin is a possible limitation, however. In consideration of this limitation, the conclusions were maintained at a conservative level, and results were not subjected to meta-analysis.

An additional limitation is the possibility of Type II statistical errors in studies of small sample size, due to the relatively small number of children with CF. The large number of studies reporting statistically significant differences despite small sample sizes suggests that this limitation was negligible. The large magnitude of the differences measured in children with CF may account for the statistical significance reached despite small study sample sizes.

As with any review based on published articles, there may be publication bias in the studies available for review. For instance, investigators may have a greater interest in publishing (as well as an ability to publish) data demonstrating morbidity in CF as opposed to data showing no difference between affected and unaffected children, which could introduce bias. In the same way, studies of interventions demonstrating resolution of symptoms may be published at a greater rate than those showing no effect, introducing bias.

Accepting these possible limitations, this literature survey has identified a strikingly large number of studies describing consistent structural and functional effects of reduced *CFTR* expression in newborns, with progressive and cumulative CF-related morbidity observed as children with CF age. Access to today's routine care from multidisciplinary teams, even shortly after birth, appears insufficient to prevent inexorable disease progression, suggesting that there is an opportunity for improved health outcomes. Consistent observations of CFTR dysfunction and CF disease progression in infancy and early childhood suggest that careful evaluation of the potential benefits of pharmacotherapies is warranted in these young patients.

In conclusion, the peer-reviewed literature is remarkably consistent regarding all three of our research questions. (1) At what ages have CF-related dysfunction and structural differences been demonstrated in young children with CF (≤ 6 years of age)? CF-associated growth impairment and airway abnormalities are reported at birth and the underlying pathology of CF directly related to reduced CFTR protein function was demonstrated in young children with CF. Abnormalities and dysfunction of the digestive and respiratory systems were reported throughout early childhood in CF. (2) At what ages has disease progression been reported in young children with CF? Disease progression is reported in infancy and throughout childhood. The youngest age at which disease progression was reported was by the age of 6 months in both digestive (pancreatic sufficiency decline) and respiratory systems (lung function decline). Accumulation of lung damage was reported by 1 year of age, and lung structure and function worsened significantly each year of life in young children, with potentially irreversible lung damage reported by the age of 2 years. (3) At what ages are there improved outcomes with early versus late treatment initiation in young children with CF? Earlier access to routine CF management improved subsequent health status. Earlier diagnosis (by 4–14 months) and standard-of-care treatment initiation in infancy compared

with later diagnosis and subsequent treatment initiation improved long-term outcomes, including survival.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2015.09.008.

Conflicts of interest

Author roles

DV participated in the design of the project, study inclusion, interpretation of the data, writing and critical revision of the manuscript, and approved the final version for submission. JK participated in the design of the project, literature search and sort, study inclusion, data extraction and compilation, interpretation of the data, and writing and critical revision of the manuscript, and approved the final version for submission. AOS, SS, and PH participated in the design of the project, critical review and revision of the manuscript, and interpretation of the data, and approved the final version for submission.

Disclosures and acknowledgments

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