Early Disease Progression and Methods to Detect and Monitor Early Lung Disease in Cystic Fibrosis

Introduction

CF, cystic fibrosis.

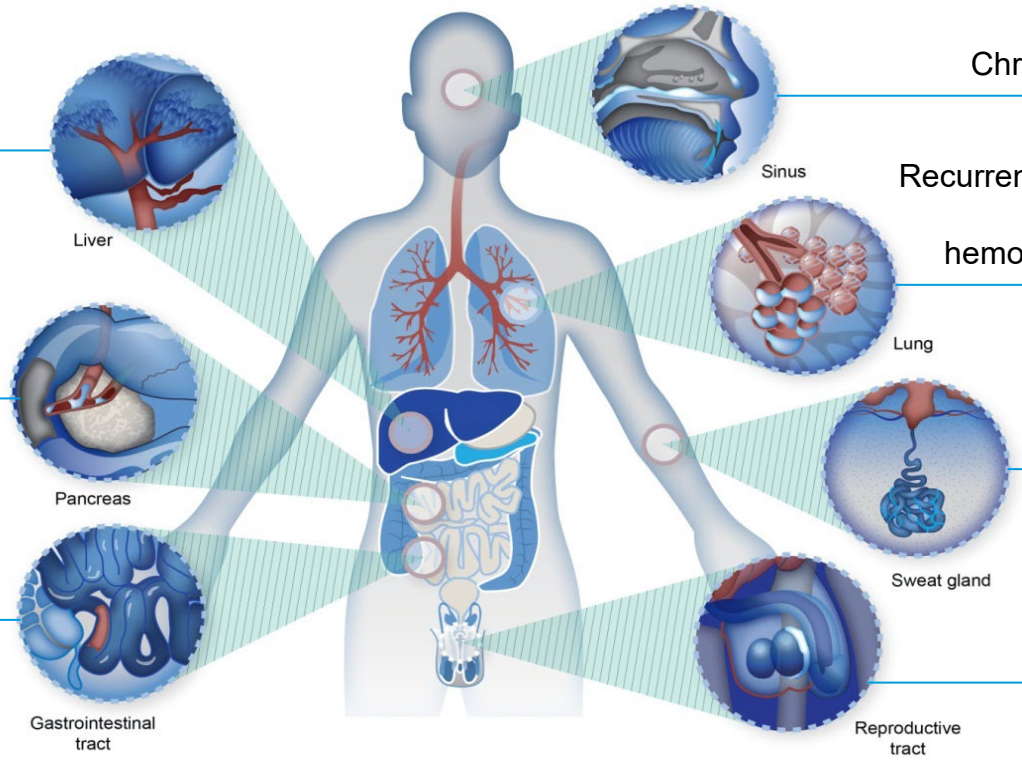
Cystic Fibrosis Is a Rare, Life-Shortening, Genetic Disease

- Approximately 4,338 people with CF in Canada[1]
- Manifests clinically throughout the body

Neonatal jaundice, liver disease, fatty liver, cirrhosis, and biliary calculi[2]

Exocrine pancreatic insufficiency, pancreatitis, and cystic fibrosis-related diabetes[2]

Meconium ileus, malabsorption, and distal intestinal obstruction syndrome[2]



Chronic sinusitis and nasal polyps[2]

Recurrent bacterial and fungal infection, bronchiectasis, pneumothorax, hemoptysis, and respiratory failure[2,*]

Abnormally high excretion of sodium and chloride (salt) in sweat, and dehydration[2]

Infertility, congenital bilateral absence of the vas deferens in men. Cervical mucus abnormality in women[2]

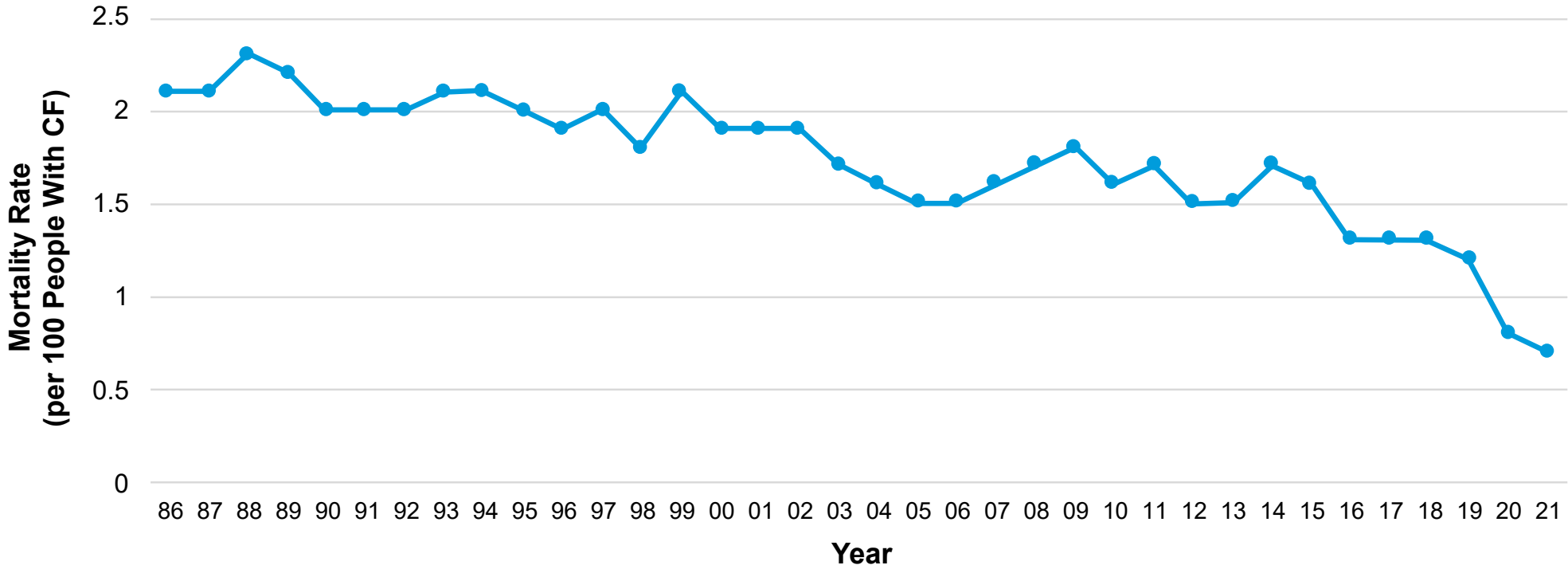
Information in figure is from Shteinberg et al (2021).[2] *Lung disease is the main cause of morbidity and mortality in cystic fibrosis.[3]

CF, cystic fibrosis.

1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023
2. Shteinberg M, et al. *Lancet*. 2021;397(10290):2195–2211. 3. Turcios NL. *Respir Care*. 2020;65(2):233–251.

CF Mortality Rates Have Declined Over Time

Annual Mortality Rate (per 100 People With CF) in the US, 1986–2021[1]



In 2021, based on the US Cystic Fibrosis Patient Registry, mortality rate was 0.7 deaths per 100 individuals with CF; median age at death was 33.9 years[1]

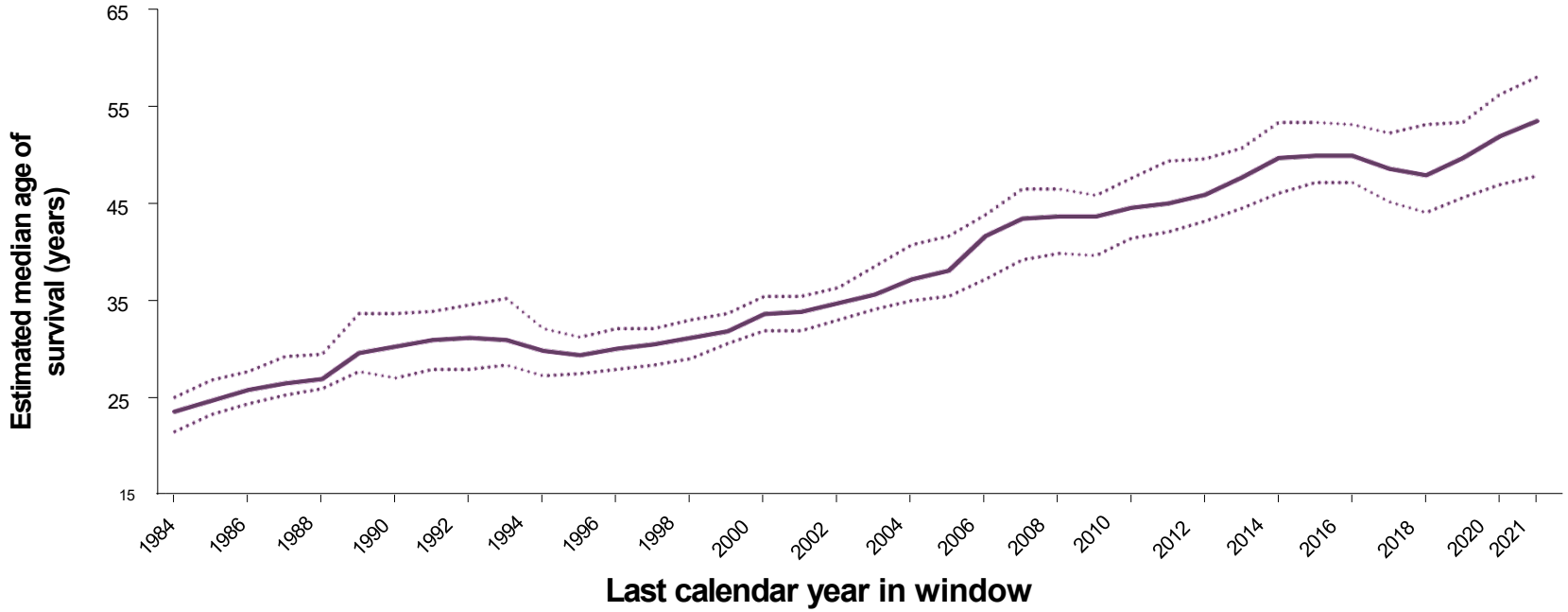
In 2021, based on the Canadian Cystic Fibrosis Patient Registry, median age at death was 38.7 years[2]

Figure permission: Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report. Bethesda, Maryland. ©2022, Cystic Fibrosis Foundation. CF, cystic fibrosis.

1. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 2. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Median Predicted Survival Has Improved Over Time

Canadian Estimated median age of survival for a moving 5-year window with 95% confidence intervals, 1984 to 2021[1]



In 2021, the median age of survival in Canada was estimated to be 57.3 years, compared to less than 36 years in 2001[1]

CF, cystic fibrosis.

1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Substantial Progress Has Been Made in Enhancing the Standard of Care and Improving CF Survival Rates

- Early recognition of CF resulted in survival benefits in pwCF as early as the 1950s, at a time when limited therapeutic options were available[1]
- Survival rates in pwCF have continued to improve over time, increasing from approximately 6 months in 1938[2] before the first pathologic description of CF[1] was made to current (2017–2021) median predicted survival of 57.3 years in Canada[3].

Median Survival Age of People With Cystic Fibrosis[3–4]

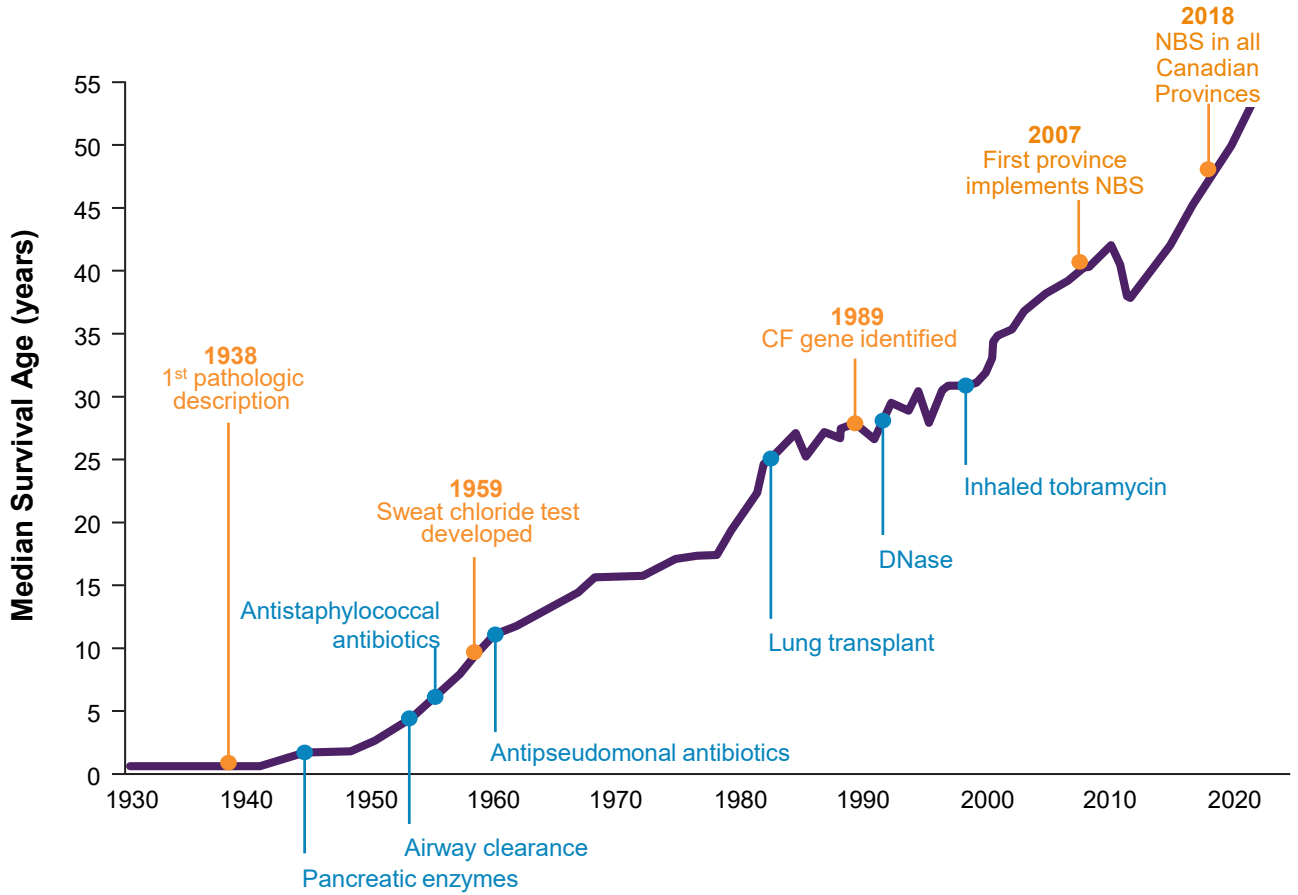


Image adapted from https://www.cysticfibrosis.org.uk. Accessed March 2023.
Permission granted by Cystic Fibrosis Trust.

CF, cystic fibrosis; DNase, deoxyribonuclease; NBS, newborn screening; pwCF, people with cystic fibrosis.

1.Shwachman H, Kulczycki LL. *Am J Dis Child.* 1958;96:7–15. 2. Davis PB. *Am J Respir Crit Care Med.* 2006;173(5):475–482. 3. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023 4. Cystic Fibrosis Trust. https://www.cysticfibrosis.org.uk. Accessed March 2023.

Despite Improvements, Life Expectancy May Still Be Shortened in People With CF

- Structural and functional lung defects can have ‘clinically silent’ progression early in life without symptoms or abnormalities on X-ray and spirometry (FEV_1)[1]
- Other manifestations can similarly have clinically silent progression[2]

Since disease is established at an early age, study authors suggest that further improvement of long-term survival will likely be achieved through early disease detection and early disease progression prevention[1]

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second.

1. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265. 2. Woolridge JL, et al. *J Cyst Fibros*. 2015;14(6):792–797.

Early Progression of CF

Gastrointestinal disease

Respiratory disease

CF, cystic fibrosis.

Signs and Symptoms of CF Are Present at Birth and Continue to Progress Across the Lifespan*

Pre-Natal/Infancy

- Meconium ileus/other intestinal obstruction (~11%)[1]
- Pancreatic insufficiency (may reach 85% in adulthood)[2]
- Lung infection (*P. aeruginosa* ~18%)[1]

Childhood/Adolescence

- Lung infection (*P. aeruginosa* ~17%)[1]
- Nasal polyps (up to 86%)[3]**
- CFRD (~5%)[1]†
- CF liver disease: cirrhosis, non-cirrhosis, and/or other (1.8%, 3.4%, 1.4%, respectively)[1,2]
- Depression (~10%)[1]

Adulthood

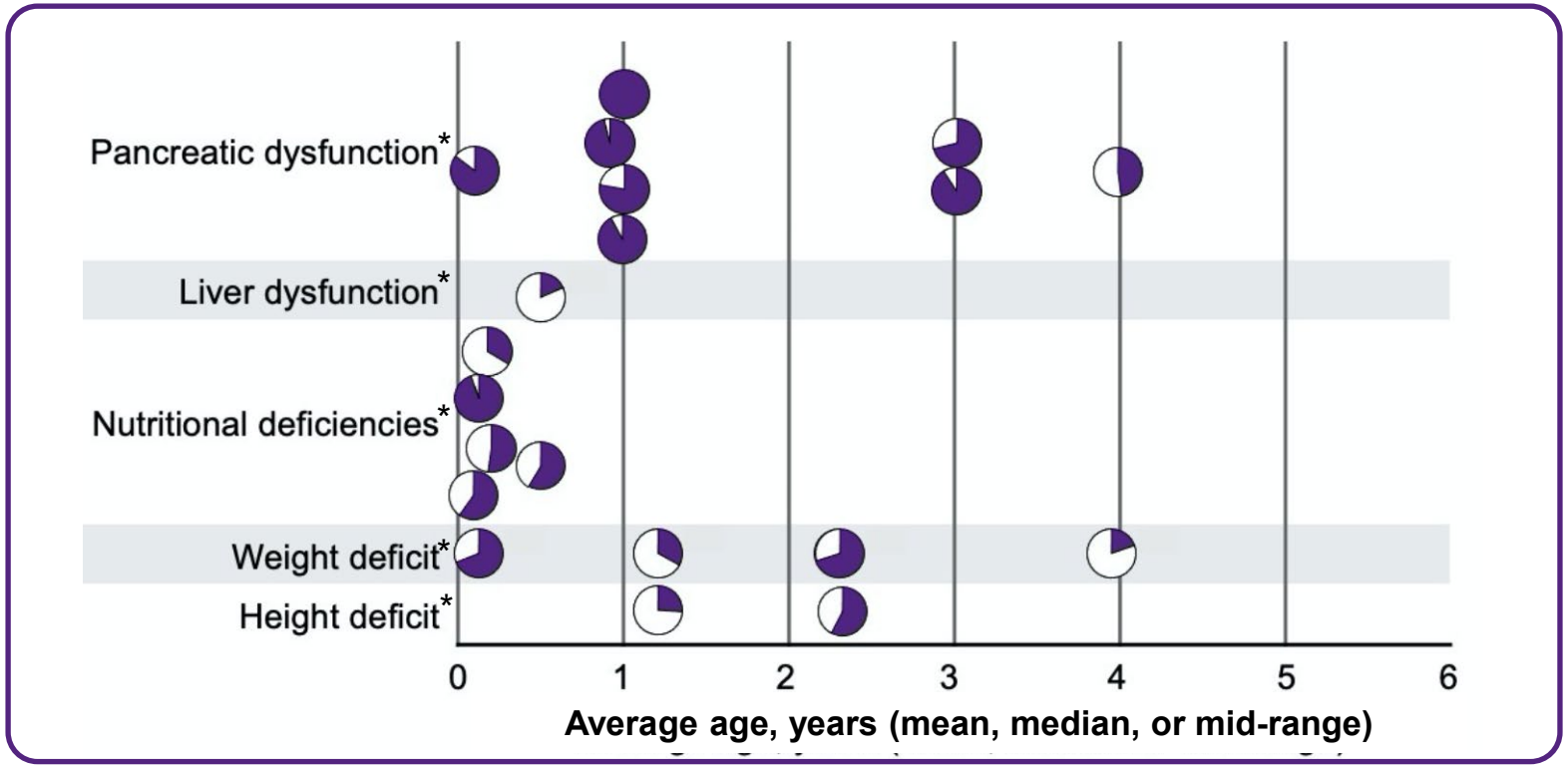
- Lung infection (*P. aeruginosa* ~20–50%)[1]
- Distal intestinal obstructive syndrome (~2%)[1]
- Severe lung disease (~5–25% with FEV_1 <40%)[1]
- CFRD (~29%)[1]†
- Bone disease (~20–60%)[1]
- CF liver disease: cirrhosis, non-cirrhosis, and/or other (4.1%, 3.2%, 1.7%, respectively)[1]
- Infertility (97–98% of men)[4]
- Depression (~30%)[1]

CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FEV_1, forced expiratory volume in 1 second.
*Information from US sources referenced below
**Up to 86% in children of all ages. Prevalence in children <6 years of age is only 6%, and prevalence is dependent on type of mutation.[2]
†The majority of individuals diagnosed with CFRD are noted in the Registry as being treated with insulin, as recommended by clinical guidelines.[1]

1. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 2. Wilschanski M, Durie PR. *Gut*. 2007;56(8):1153–1163. 3. Mohd Slim MA, et al. *BMJ Case Rep*. 2016;2016:bcr2016214467. 4. Hull SC, Kass NE. *J Androl*. 2000;21(6):809–813.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Manifestations of CF in the Digestive System Occur Early in Life



Pancreatic and liver dysfunction can be observed within the first year of life and contribute to nutritional and growth deficiencies

*Each circle represents 1 study. The shaded proportion of a circle represents the percentage of people with CF in that study who had that abnormality at that timepoint. Figure adapted from the *Journal of Cystic Fibrosis*, 15(2), VanDevanter DR, et al. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment, 147–157, ©2016, with permission from Elsevier.

CF, cystic fibrosis; y, years.

VanDevanter DR, et al. *J Cyst Fibros*. 2016;15(2):147–157.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Meconium Ileus Is a Common Symptom Reported at Diagnosis in Infants

Symptoms Reported at CF Diagnosis

	All Individuals (%)	Diagnosed in 2021 (%)	Diagnosed in 2021 Age <1 y (%)	Diagnosed in 2021 Age ≥1 y (%)
Number of individuals (n)	**32,100**	**779**	**563**	**216**
Acute or persistent respiratory abnormalities	34.0	16.3	1.8	50.2
CBAVD or infertility/GU abnormalities	0.8	2.8	0.2	9.0
Digital clubbing	0.5	0.8	0.0	2.6
Edema	0.5	0.0	0.0	0.0
Electrolyte imbalance	2.8	0.1	0.0	0.4
Failure to thrive/malnutrition	25.6	3.9	2.6	6.9
Liver problems	1.0	0.8	0.4	1.7
Meconium ileus/other intestinal obstruction	16.5	8.2	11.2	N/A
Nasal polyps/sinus disease	3.8	4.8	0.2	15.5
Rectal prolapse	2.5	0.1	0.0	0.4
Steatorrhea/abnormal stools/malabsorption	20.0	4.1	2.6	7.7
Other	5.2	8.1	2.8	20.6

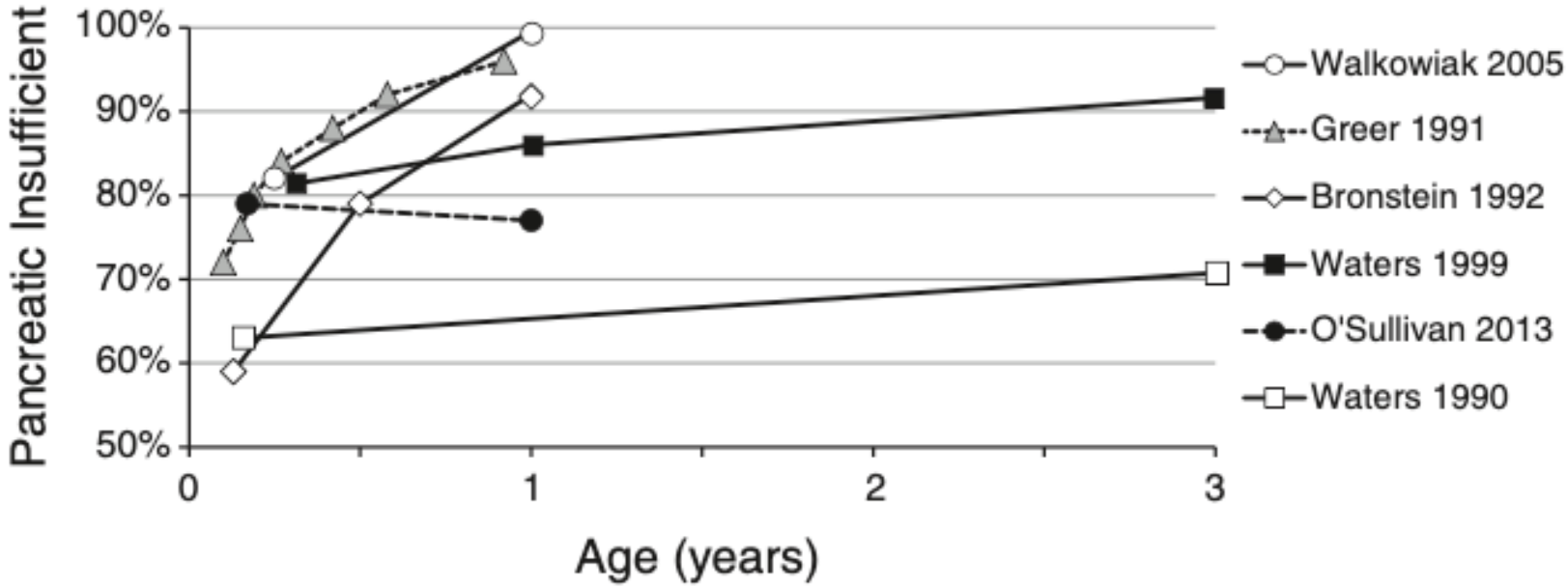
In 2021 in the US, 11.2% of infants diagnosed with CF before age 1 year presented with meconium ileus (or other intestinal obstruction), and 24.6% of those had bowel perforation

Figure permission: Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report. Bethesda, Maryland. ©2022, Cystic Fibrosis Foundation.
CBAVD, congenital bilateral absence of the vas deferens; CF, cystic fibrosis; GU, genitourinary; N/A, not applicable; y, years.

Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Pancreatic Insufficiency Is a Common Early Manifestation of CF in Infants

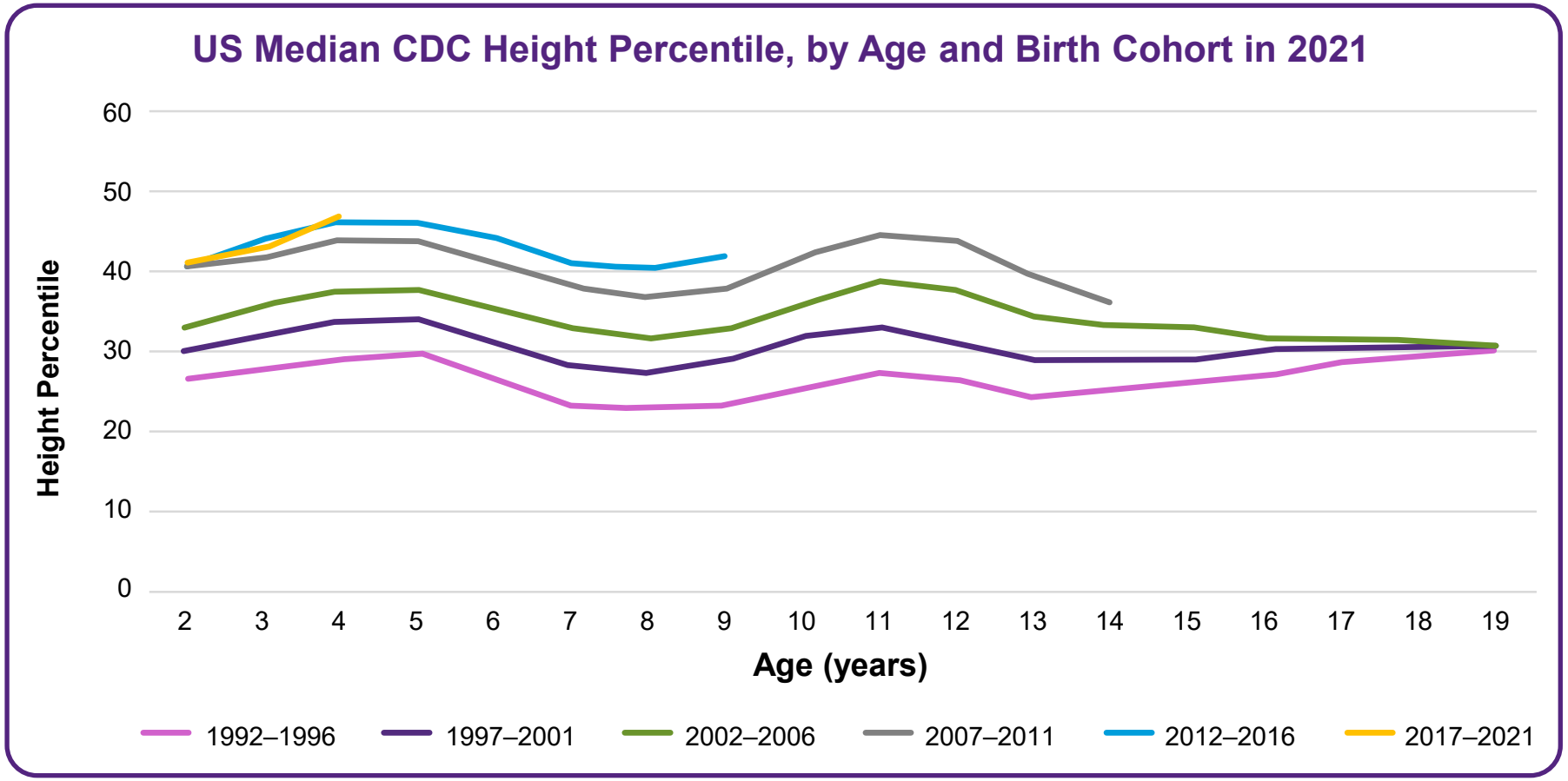


59% to 71% of infants with CF are pancreatic insufficient at birth, with an additional 16% to 20% becoming pancreatic insufficient by 6 months of age

Image reprinted from the *Journal of Cystic Fibrosis*, 15(2), VanDevanter DR, et al. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment, 147–157, ©2016, with permission from Elsevier.
CF, cystic fibrosis; y, years.

VanDevanter DR, et al. *J Cyst Fibros*. 2016;15(2):147–157.

Nutritional and Growth Deficiencies Are Seen in Children With CF



- Early intervention due to NBS has potentially led to improvements in nutritional deficiencies
- In 2021, the height percentiles of children with CF remained well below that of the general US population, with deficiencies seen throughout childhood

Figure permission: Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report. Bethesda, Maryland. ©2022, Cystic Fibrosis Foundation.
CDC, Centers for Disease Control and Prevention; CF, cystic fibrosis; NBS, newborn screening; US, United States; y, years.

Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Early GI Disease Progression Leads to Worse Outcomes Later in Life

- Meconium ileus at birth is a risk factor for bronchiectasis by 3 months of age[1]
- Meconium ileus at birth is associated with worse spirometric lung function by 11 years of age[2]
- Infants with pancreatic insufficiency acquire *P. aeruginosa* airway infection at twice the rate of infants with CF without pancreatic insufficiency[3]
- Low weight for age in 3-year-olds predicts poor lung function at 6 years of age[4]

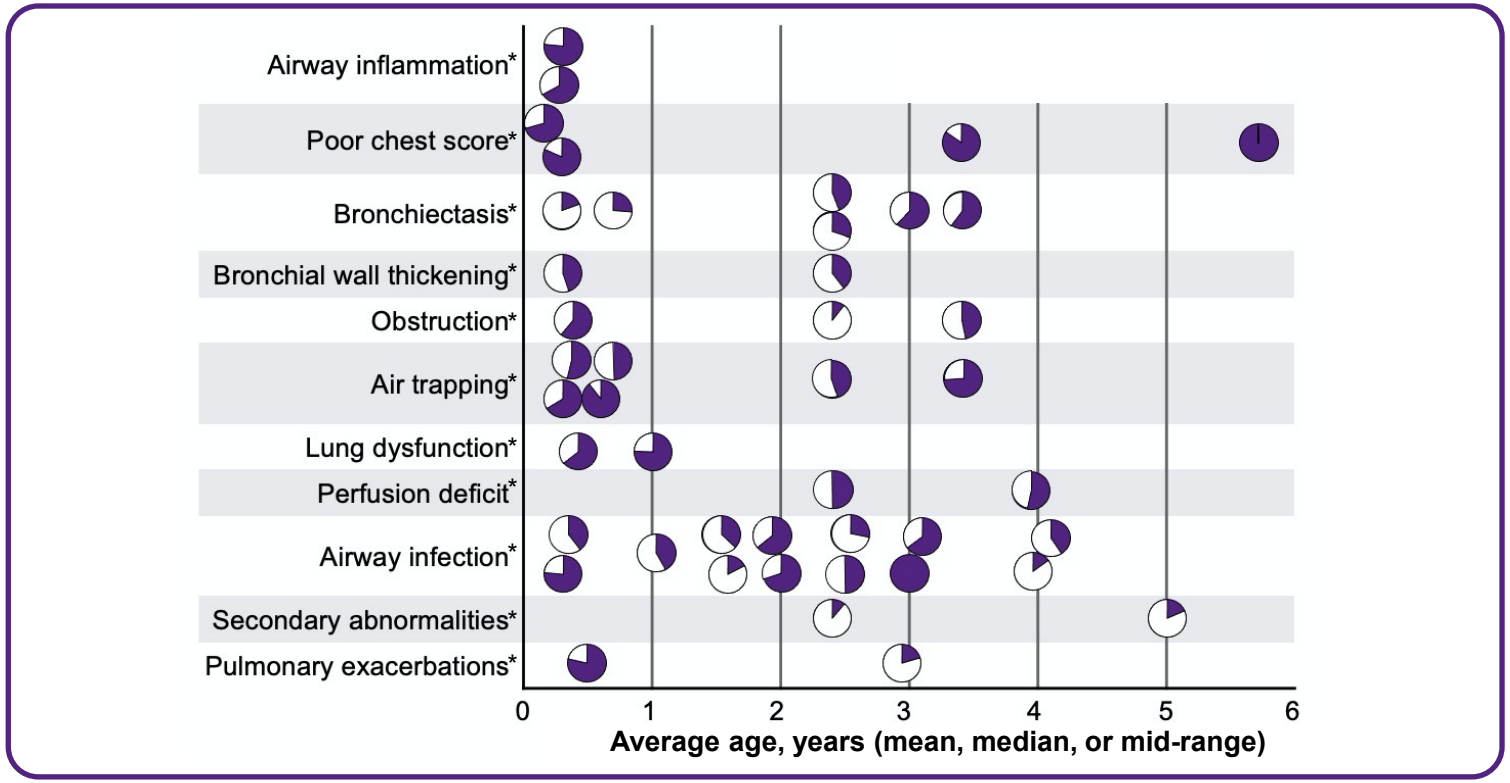
Early GI disease progression is associated with subsequent poor respiratory outcomes[5]

CF, cystic fibrosis; GI, gastrointestinal; y, years.

1. Sly PD, et al. *N Engl J Med*. 2013;368:1963–1970. 2. Farrell PM, et al. *Pediatr Pulmonol.* 2003;36(3):230–240. 3. Baussano I, et al. *Pediatrics.* 2006; 118(3):888–895. 4. Konstan MW. et al. *J Pediatr.* 2003;142(6):624–630.
5. VanDevanter DR, et al. *J Cyst Fibros*. 2016;15(2):147–157.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Respiratory System Disease Progression Occurs Early in Life



Respiratory abnormalities can be observed within the first year of life and contribute to pulmonary exacerbations and later complications

*Each circle represents 1 study. The shaded proportion of a circle represents the percentage of children with CF in that study who had that abnormality at that timepoint. Figure adapted from the *Journal of Cystic Fibrosis*, 15(2), VanDevanter DR, et al. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment, 147–157, ©2016, with permission from Elsevier.

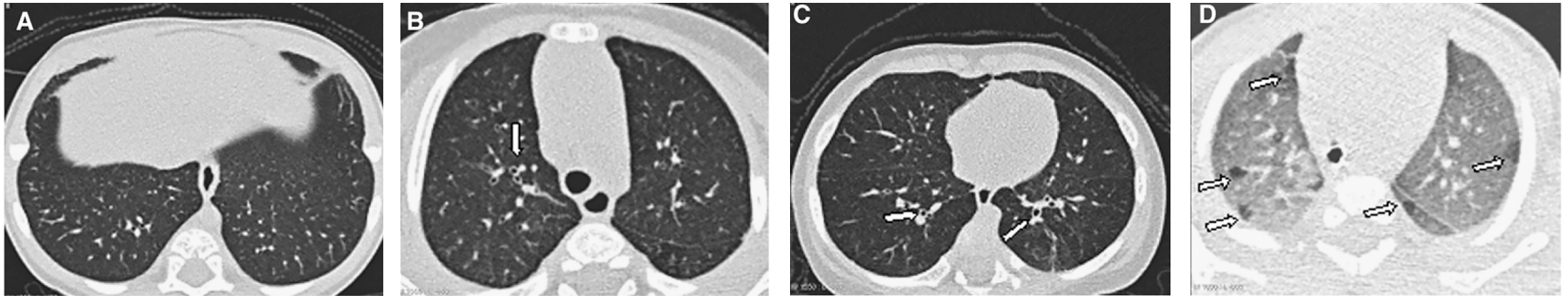
CF, cystic fibrosis; y, years.

VanDevanter DR, et al. *J Cyst Fibros*. 2016;15(2):147–157.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Structural Lung Abnormalities Can Be Detected in the First Year of Life

Computed Tomography Scans of Infants (median age 3.6 months, N=57)



Healthy Lung

Bronchial Dilatation
Observed in 18.6%

Bronchial Wall Thickening
Observed in 45.0%

Gas Trapping
Observed in 66.7%

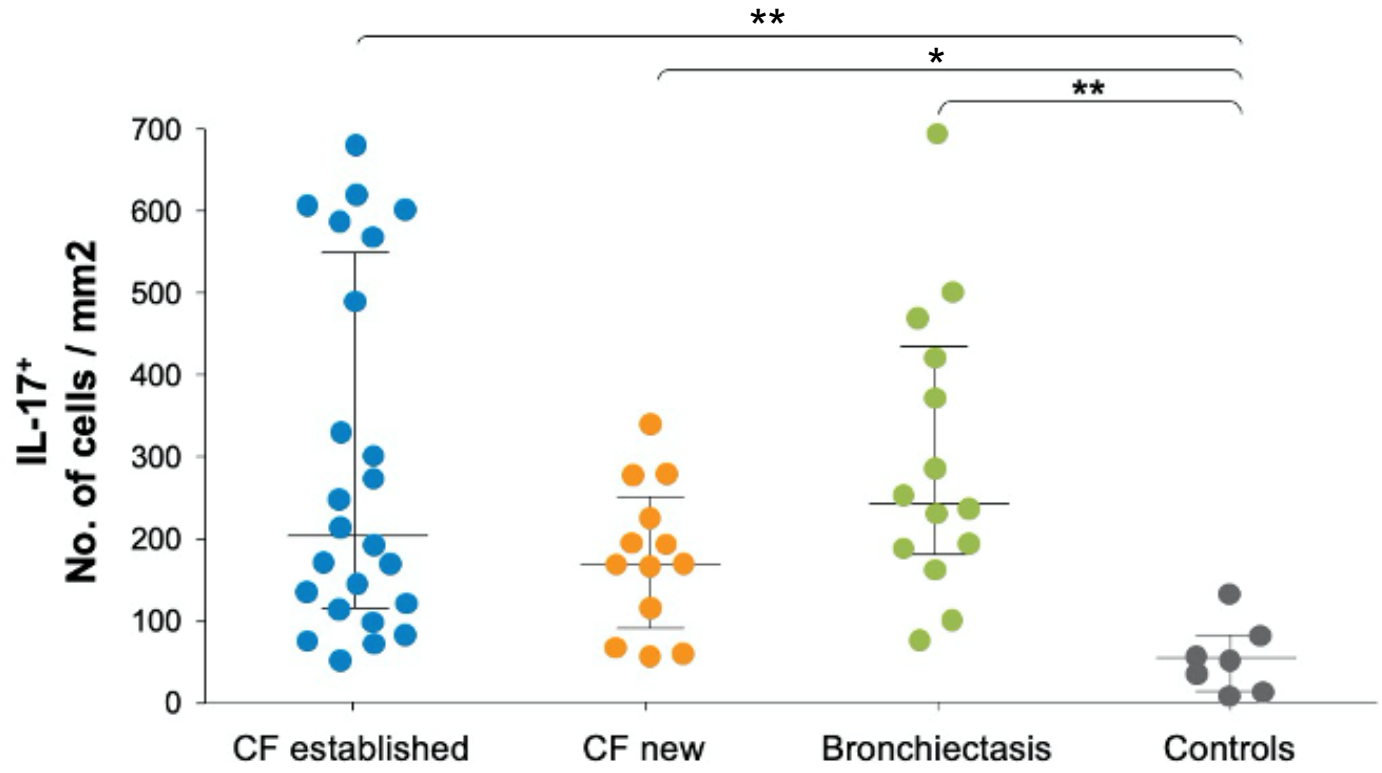
80.7% of infants had an abnormal chest CT

Majority of infants with abnormal scans had no respiratory symptoms at time of CT

Sly PD, et al. *Am J Respir Crit Care Med*. 2009;180(2):146–152.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Inflammatory Components Are Present in the Lung at an Early Age



- IL-17, a mediator of many pro-inflammatory signaling cascades, was measured in people with CF and controls (age 0.4–12.4 years)[a]
- Bronchoalveolar lavage fluid showed early onset of increased inflammatory markers

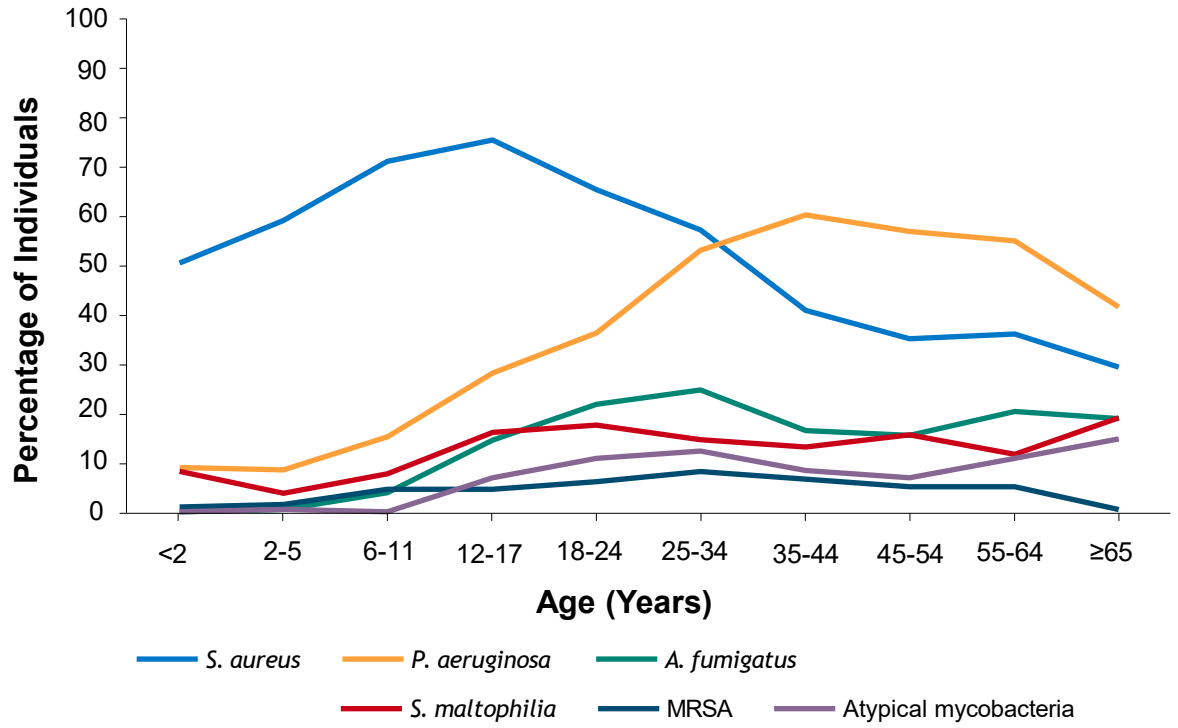
*P<0.05, **P<0.01. [a]Median age (years) for each group: CF established, 9.3; CF new, 1.7; Bronchiectasis (non-CF), 8.9; Controls, 7.5.

CF, cystic fibrosis; IL-17, interleukin 17; y, years.

Tan H, et al. *Am J Respir Crit Care Med*. 2011;184(2):252–258.

Respiratory Colonization Is Common in Children With CF From an Early Age

Prevalence of Respiratory Microorganisms by Age Cohort, 2021

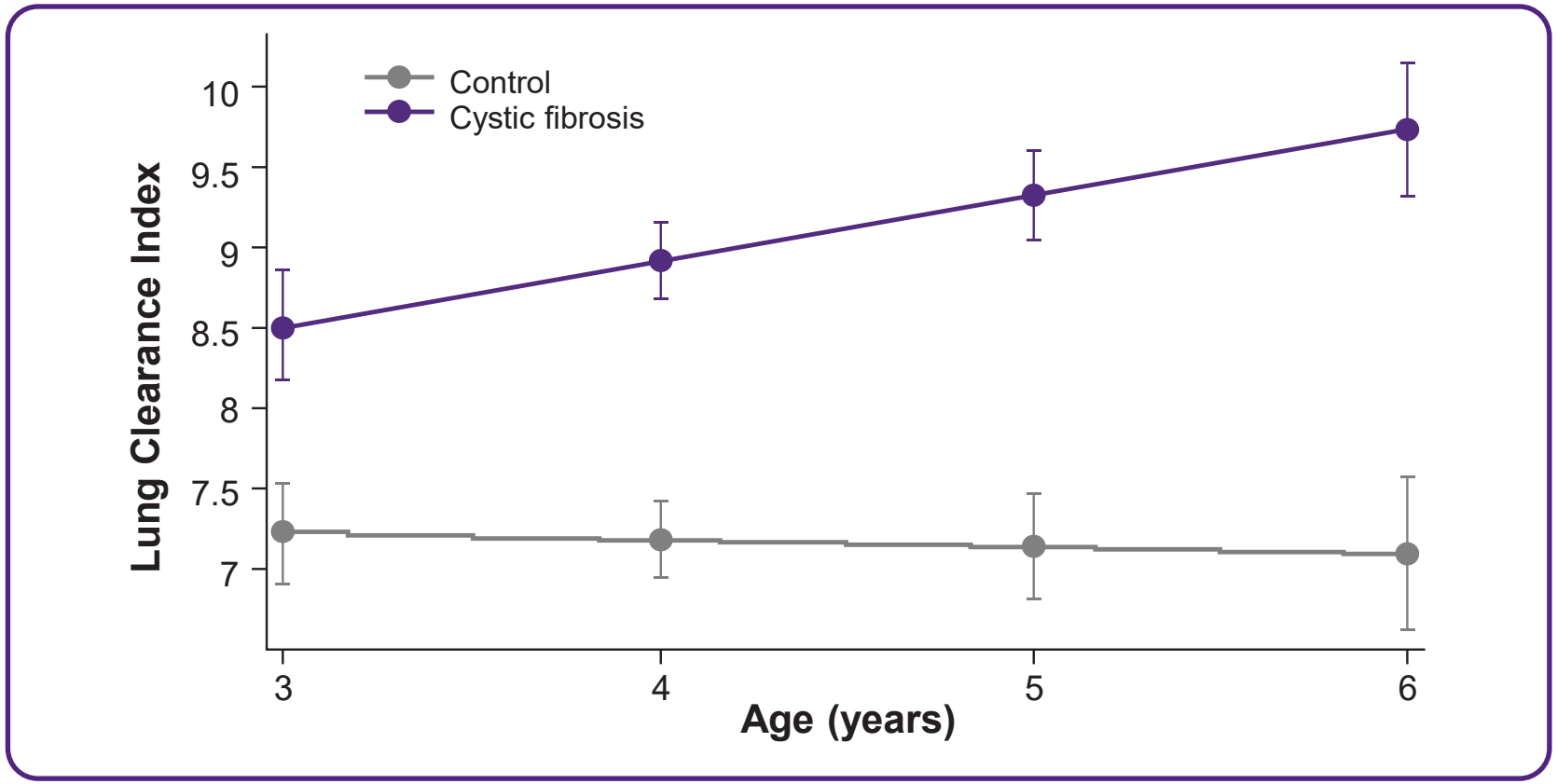


In 2021, many young people with CF were colonized with respiratory pathogens

Figure permission: Canadian Cystic Fibrosis Patient Registry 2021 Annual Data Report.
CF, cystic fibrosis; MRSA, methicillin-resistant *S. aureus*; y, years.

Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Worsening Lung Function in Preschool-Aged Children with CF



LCI (but not spirometry) identified significant deterioration of lung function over time in preschool-aged children with CF

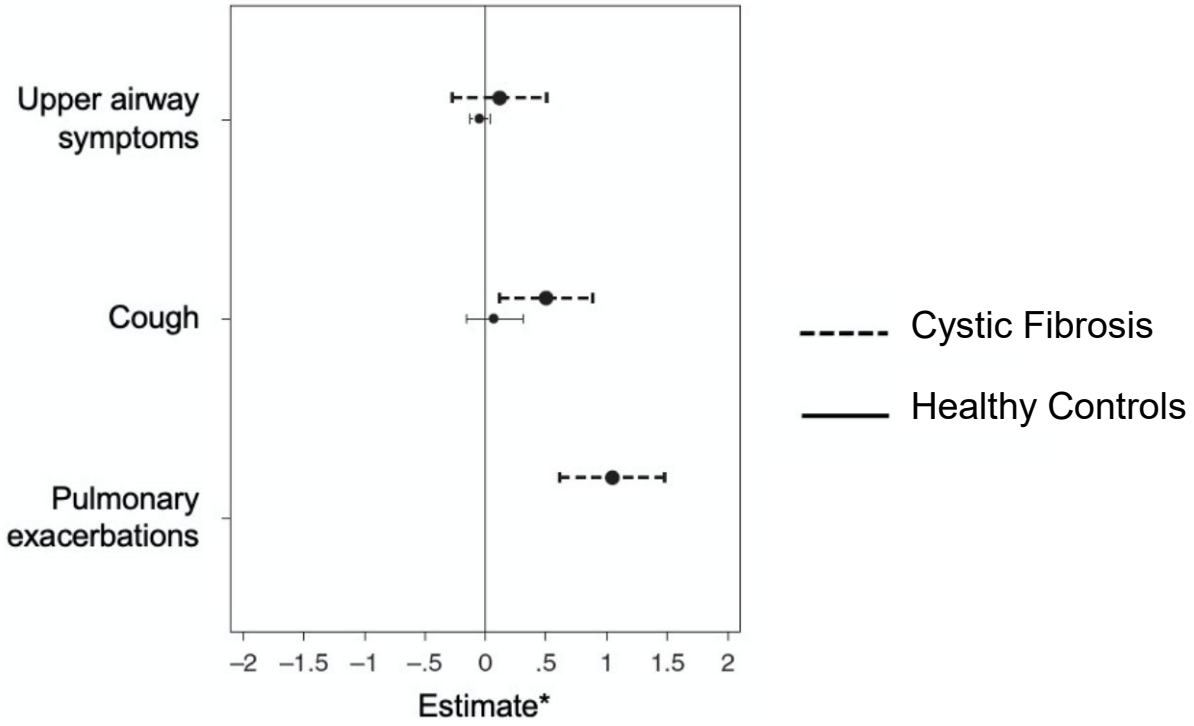
- In a study of preschool-aged children with CF and age-matched controls (n=156, age 2.5–6 years), 800 LCI measurements were taken over 12 months

CF, cystic fibrosis; LCI, lung clearance index; y, years.

Stanojevic S, et al. *Am J Respir Crit Care Med.* 2017;195:1216–1225.

Pulmonary Exacerbations Are a Main Driver of Worsening Lung Function in Preschool-Aged Children With CF

Association Between Pulmonary Symptoms and LCI



- In a study of preschool-aged children with CF and age-matched controls (n=156, age 2.5–6 years), LCI worsened during cough episodes and pulmonary exacerbations in children with CF
- Neither upper airway symptoms nor cough were associated with higher LCI values in healthy participants

*Absolute LCI during symptomatic visits, derived from a mixed-effects model of LCI, adjusted for age; symptoms were treated as time-varying covariates. Adapted with permission from the American Thoracic Society. ©2022, American Thoracic Society. All rights reserved. Stanojevic S, et al. 2017. Progression of lung disease in preschool patients with cystic fibrosis. *Am J Respir Crit Care Med*. 195(9):1216–1225. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://www.atsjournals.org/doi/10.1164/rccm.201610-2158OC. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

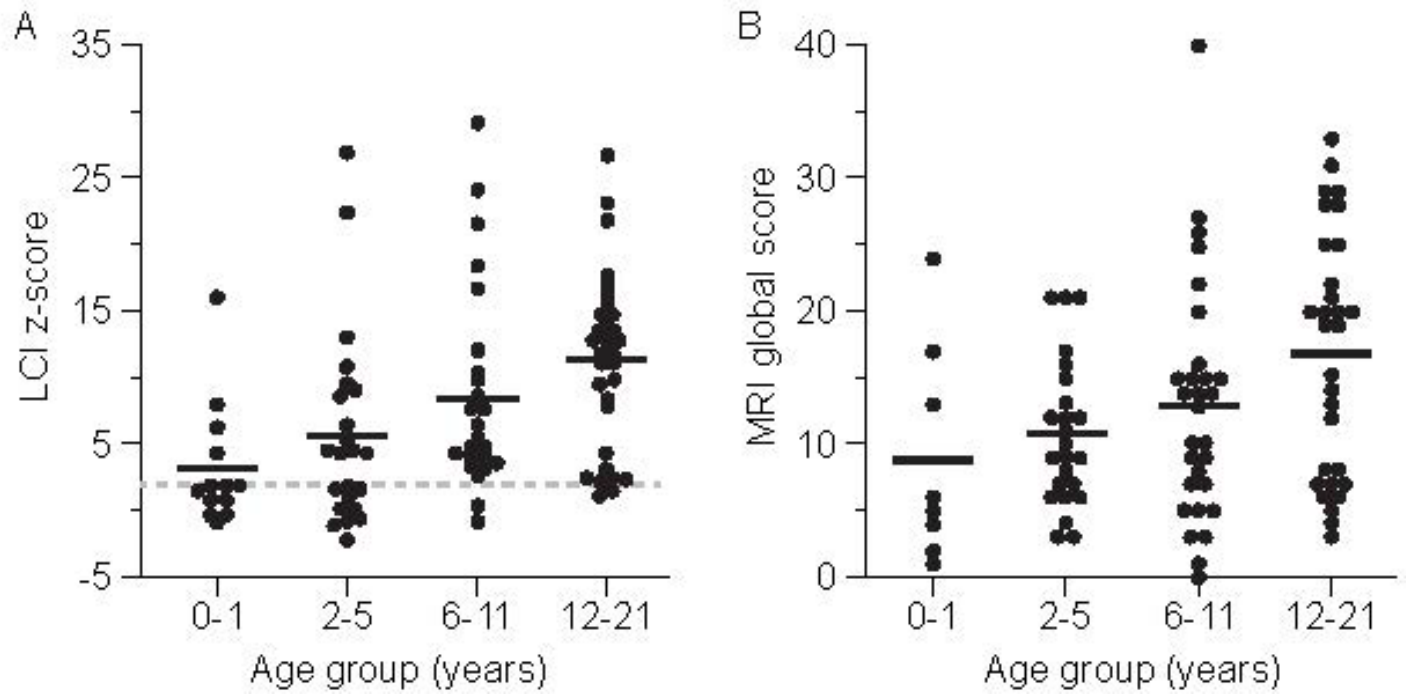
CF, cystic fibrosis; LCI, lung clearance index; y, years.

Stanojevic S, et al. *Am J Respir Crit Care Med*. 2017;195:1216–1225.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

Variability in Severity of Early Lung Disease

Variability of Lung Disease in Children With CF Using Various Methods



- Among individuals with similar genotypes, several factors can affect CF disease severity
- These may include modifier genes, epigenetic modifications, age and mode of diagnosis, and environmental factors

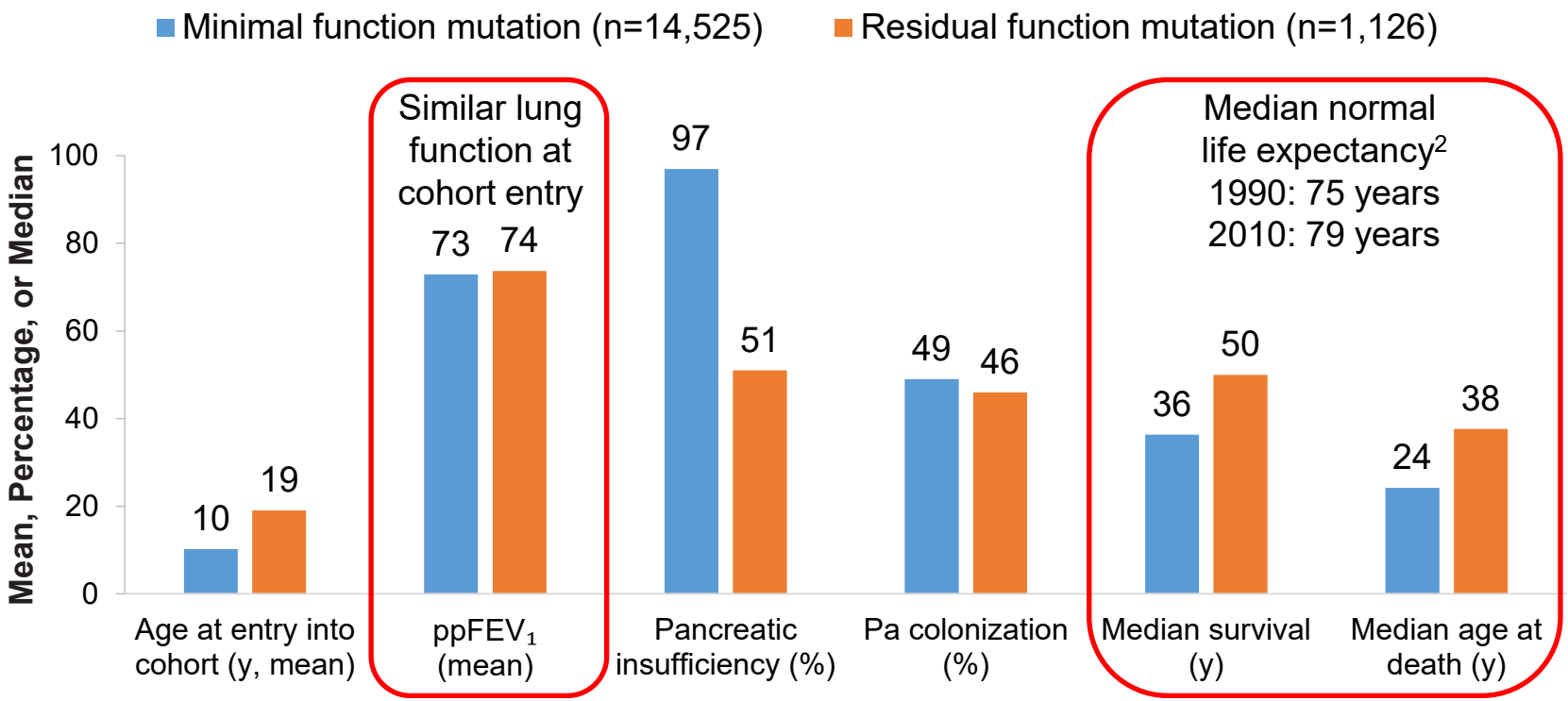
CF, cystic fibrosis; LCI, lung clearance index; MRI, magnetic resonance imaging; y, years.

Stahl M, et al. *Genes (Basel)*. 2021;12(6):803.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

People With CF With Residual Function and Minimal Function Mutations Have Similar Outcomes

Characteristics of pwCF With Residual Function and Minimal Function Mutations*[1]



- CF has a considerable BOI, from infancy through childhood, and across genotypes[3]

Even pwCF with residual function mutations have considerable BOI and reduced life expectancy[1,3]

*Clinical characteristics assessed during the year of cohort entry, and followed between 1993 and 2002.[1]
Minimal function mutations: Both alleles: *G542X, R553X, W1282X, R1162X, 621–1G>T, 1717–1G>A, 1078delT, 3659delC, F508del, I507del, N1303K, S549N, G85E, G551D,* and *R560T.*
Residual function mutations: At least 1 allele: *R117H, R334W, R347P, 3849+10KbC>T, 2789+5G>A,* and *A455E.*

BOI, burden of illness; CF, cystic fibrosis; Pa, *Pseudomonas aeruginosa*; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; pwCF, people with CF; y, years

1. McKone EF, et al. *Chest*. 2006;130(5):1441–1447. 2. CDC. Life expectancy at birth. https://www.cdc.gov/nchs/data/hus/2011/022.pdf. Accessed March 2023. 3. Bresnick K, et al. *BMJ Open Respir Res*. 2021;8(1):e000998.

Infant (<2y) | Toddler (2-3y) | Preschool (3-5y) | Middle-Childhood (6-12y) | Teenager (13-19y)

By School Age, 60–80% of Children With CF Have Abnormalities That Persist Into Later Life*[1–4]

Prevalence of CT Abnormalities as a Function of Age[2]

Age	1st Year of Life	2nd Year of Life	3rd Year of Life	4th Year of Life	5th Year of Life	6th Year of Life
Number of children with CF by age group	47	13	7	11	11	7
Bronchiectasis, n (%)	4 (8.5)	1 (7.7)	2 (28.6)	4 (36.4)	7 (63.6)	3 (42.9)
Air trapping, n (%)	29 (61.7)	6 (46.2)	4 (57.1)	7 (63.6)	6 (54.5)	4 (57.1)
Bronchial wall thickening, n (%)	17 (36.2)	6 (46.2)	5 (71.4)	7 (63.6)	5 (45.5)	5 (71.4)

Data indicate the number (percent) of children in each age group with the presence of structural abnormality identified by CT. An individual child may have more than one structural abnormality detected.

Structural observations suggest that lung disease is established by early school age, and to improve long-term survival in the newborn screening era, interventions must focus on preventing lung disease progression and target early lung disease[1]

*Bronchiectasis and/or gas trapping/hypoperfusion and lung function abnormalities (eg, LCI).
Table reprinted from the *Journal of Pediatrics*, 155(5), Stick SM, et al Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening, 623–628, ©2009, with permission from Elsevier.
CF, cystic fibrosis; CT, computed tomography; LCI, lung clearance index; y, years.

1. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265. 2. Stick SM, et al. *J Pediatr*. 2009;155(5):623–628.e1. 3. Wainwright CE, et al. *JAMA*. 2011;306(2):163–171. 4. Owens CM, et al. *Thorax*. 2011;66(6):481–488.

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Early Progression of CF Predicts Later Consequences

Structural Predictors of FEV_1 Z-score Decline

CF-CT Extent Score at Age 5–6 Years	Unadjusted		Adjusted[a]	
	Mean Change (95% CI)	*P*-Value	Mean Change (95% CI)	*P*-Value
People with CF, n	**697**		**663**	
Mucus plugging	**–0.19 (–0.29 to –0.09)**	***P*<0.001**	**–0.17 (–0.26 to –0.09)**	***P*<0.001**
Trapped air	**–0.11 (–0.16 to –0.05)**	***P*<0.001**	**–0.09 (–0.14 to –0.04)**	***P*<0.001**
Bronchiectasis	**–0.05 (–0.09 to –0.01)**	***P*=0.021**	–0.04 (–0.08 to 0.00)	*P*=0.051
Bronchial wall thickening	–0.02 (–0.07 to 0.03)	*P*=0.450	–0.01 (–0.05 to 0.04)	*P*=0.734
Total score	**–0.03 (–0.05 to –0.01)**	***P*=0.001**	**–0.02 (–0.04 to –0.01)**	***P*=0.006**

Data presented for 167 children that had a CT scan available at age 5–6 years and a total of 697 annual spirometry measurements in the following 10 years.
[a]Models were adjusted for intrinsic disease severity (homozygous D508 mutation, pancreatic sufficiency, and sex), test center, and age at spirometry.
Bold data signifies *P*<0.05, mean change in CF-CT score of different structural components.

Table adapted with permission from the European Respiratory Society. ©2022, ERS. *European Respiratory Journal* May 2020, 55 (5) 1900748; DOI: 10.1183/13993003.00748-2019.

CF, cystic fibrosis; CI, confidence interval; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; y, years.

- Mucus plugging and gas trapping at age 5–6 years on CT predicts subsequent lung function trajectory for up to 10 years and is more predictive than early spirometry[1]
- Early atelectasis on CT predicts later bronchiectasis[2]

1. Turkovic L, et al. *Eur Respir J*. 2020;55(5):1900748. 2. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265.

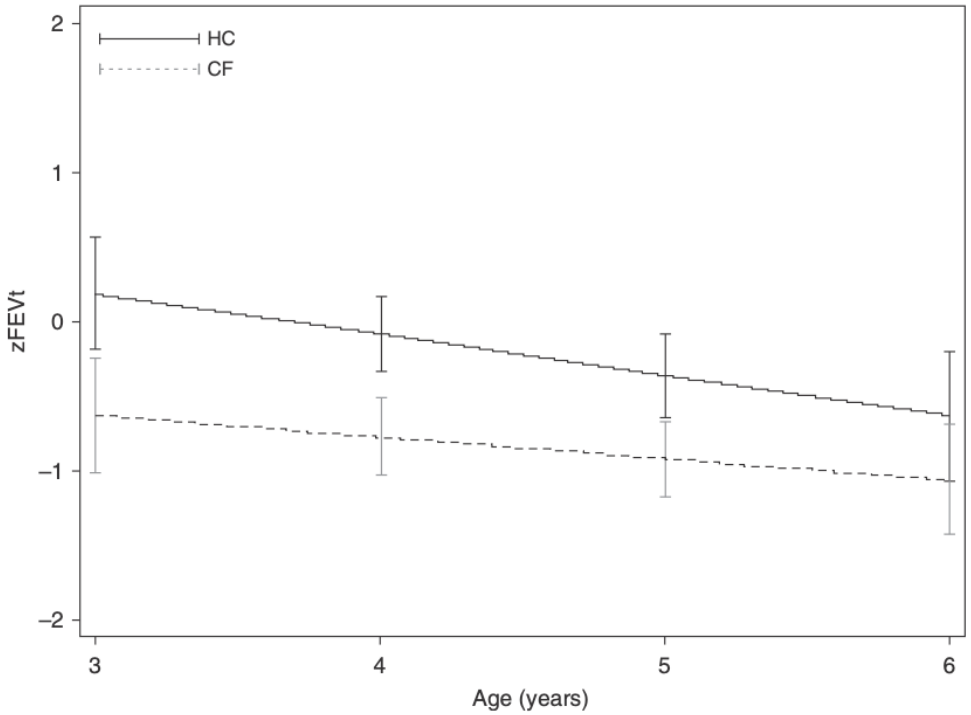
Methods to Detect and Monitor Early Lung Disease in CF

- Spirometry
- Multiple breath washout
- Chest X-ray
- CT
- MRI

CF, cystic fibrosis; CT, computed tomography; MRI, magnetic resonance imaging.

Spirometry-Based Classifications of "Normal" and "Mild Lung Disease" May Be Inaccurate in Children With CF Under 6 Years of Age

No difference in the rate of change in FEV_t z-scores between healthy preschoolers and those with CF[1]



- Spirometry is commonly used in the diagnosis and monitoring of lung function in pwCF 6 years or older[2]
- Spirometry is rarely performed in children <6 years of age and is not a sensitive measure of early lung disease[3–5]
- Although FEV_1 is typically preserved in young children, it can mask evidence that CF disease begins earlier[6,7]

Spirometry fails to detect significant early structural or functional abnormalities[4]

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; FEV_t, forced expiratory volume in t second, where t is either 0.75 or 1; HC, healthy controls; pwCF, people with cystic fibrosis.

1. Stanojevic S, et al. *Am J Respir Crit Care Med*. 2017;195(9):1216–1225. 2. Jat KR. *Prim Care Respir J*. 2013;22(2):221–229. 3. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 4. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265. 5. Konstan MW. *J Pediatr.* 2007;151(2):134–139. 6. Tiddens HA. *Pediatr Pulmonol. 2002;*34(3):228–231. 7. VanDevanter DR, et al. *J Cyst Fibros*. 2016;15(2):147–157.

Multiple Breath Washout Is a Sensitive and Validated Functional Measurement

Published Preschool MBW Feasibility to Date Using Commercial MBW Systems

Author Year	Subjects	Age Tested (range, y)	MBW-Naïve (%)	Interface	No. of Acceptable Tests Required	No. of Subjects Attempted	Subjects Successful (%)
Jensen 2014 (65)*	**CF**	2.9–5.0	0	Facemask	≥2 tests	30	83
Benseler 2015 (59)*	**Healthy**	2.8–5.9		Facemask	3 tests (successful on both equipment systems)	24	83
	CF	3.3–5.9				27	70
Robinson (64)*	**CF, wheeze**	2.0–6.9	77	Facemask	3 tests 2 tests	46 46	85 91
			77	Mouthpiece	3 tests 2 tests	46 46	50 63
Foong 2015 (66)	**Healthy**	3.0–6.6	100 0	Mouthpiece	≥2 tests (first visit) ≥2 tests (subsequent visit)	60 19	72 86
	CF	2.6–6.6	100 0	Mouthpiece	≥2 tests (first visit) ≥2 tests (subsequent visit)	78 59	67 82
Vilmann 2016 (63)*	**Healthy, asthmatic**	3–6	100	Mouthpiece	≥2 tests 3 tests	66 66	89 67
Downing 2016 (11)*	**Healthy, PCD, CF, wheeze**	2.1–5.9	100	Mouthpiece	≥2 tests within 30 minutes	116	73
Yammine 2016 (12)†	**Asthmatic**	3.1–6.7	100	Mouthpiece	3 tests within 20 minutes 2 tests within 20 minutes	62 62	24 60
Stanojevic 2017 (17)*	**Healthy, CF**	2.5–5.9	100	Facemask	≥2 tests (first visit) ≥2 tests (subsequent visits)	150 150	66 89

- MBW is a non-invasive lung function test, which detects unevenness of gas mixing, most commonly reported as LCI[1] and can be used in preschool-aged children[2]

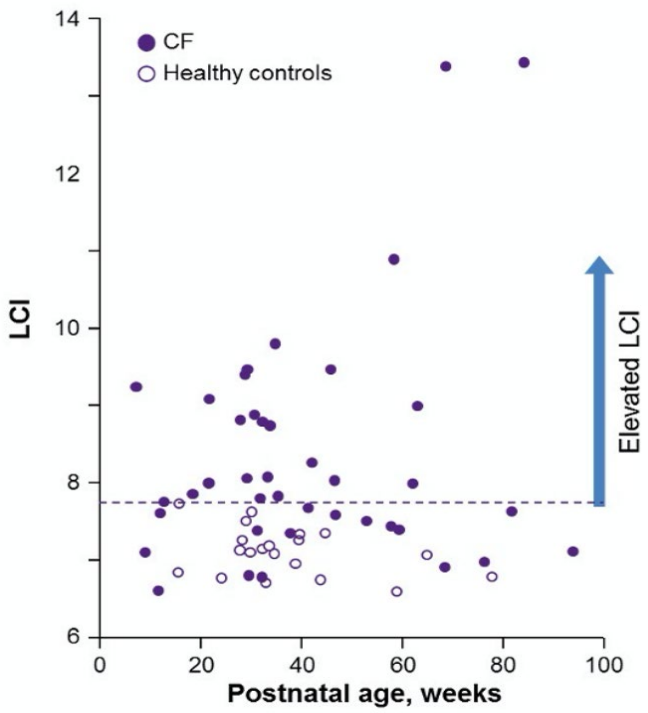
MBW can detect early lung disease in CF[2]

*Modified from off-the-shelf equipment in an attempt to improve suitability for preschool testing. †Additional time restriction criteria of 20 minutes specified for total test session duration.

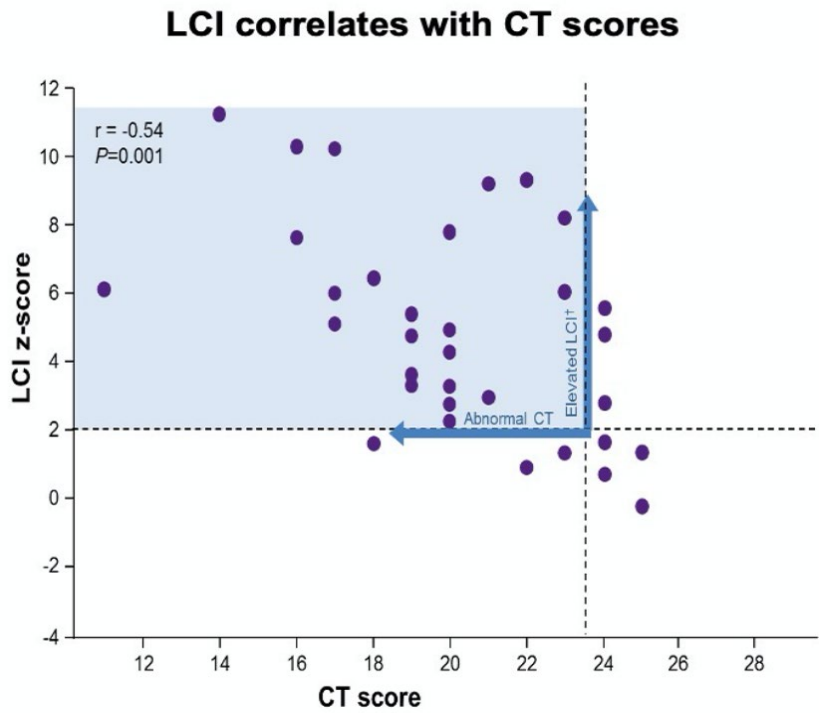
CF, cystic fibrosis; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; LCI, lung clearance index; MBW, multiple breath washout; PCD, primary ciliary dyskinesia; y, years.

1. Robinson PD, et al. *Respiration*. 2009;78(3):339–355. 2. Robinson PD, et al. *Am J Respir Crit Care Med*. 2018;197(5):e1–e19.

LCI Detects Abnormal Lung Function Early in CF and Correlates With Findings From CT



7.8 was set as the ULN LCI based on the mean (SD) LCI in healthy controls of 7.2 (0.3)



LLN for CT score=>23
ULN for LCI z-score=2

- Infants and young children with CF had elevated LCI compared with controls[1]
- LCI is sensitive to the presence and extent of structural lung disease as measured by CT in preschool- and school-aged children with CF[2]
- In a study of 34 pwCF (ages 6–26 years) with early lung disease and normal FEV_1 (>80% of predicted normal value), LCI was abnormal in 76.5% of pwCF and correlated significantly with structural changes measured by chest CT in 82.3%[3]

LCI/MBW is complementary to chest CT[4]

Left-hand figure adapted from Lum et al (2007).[1] Right-hand figure adapted from *Respiratory Medicine*, 104, Ellemunter H, et al. Sensitivity of lung clearance index and chest computed tomography in early CF lung disease, 1834–1842, ©2010, with permission from Elsevier.

CF, cystic fibrosis; CT, computed tomography; FEV1, forced expiratory volume in 1 second; LCI, lung clearance index; LLN, lower limit of normal; MBW, multiple-breath washout; pwCF, people with CF; SD, standard deviation; ULN, upper limit of normal.

1. Lum S et al. *Thorax*. 2007;62(4):341–347. 2. Ramsey KA, et al. *Am J Respir Crit Care Med*. 2016;193(1):60–67. 3. Ellemunter H, et al. *Respir Med*. 2010;104(12):1834–1842. 4. Owens CM, et al. *Thorax*. 2011;66(6):481–488.

Oscillometry Is Easily Administered in Young Children But Has Limitations

- Oscillometry is another tidal breathing technique measuring airway impedance of the respiratory system, which is administered relatively quickly in children[1]
- In children with respiratory disease including CF (n=84) aged between 2 and 8 years, resonance frequency, a forced oscillation technique, was significantly impaired compared with controls (n=200) (P<0.01)[2]
- Resonance frequency could be used to identify children with CF, albeit with low diagnostic ability[2]
- There may be additional limitations, as oscillometry did not correlate with neutrophil elastase activity, pathogenic infection, or structural lung abnormalities[3]

CF, cystic fibrosis.

1. Frey U. *Paediatr Respir Rev*. 2005;6(4):246–254. 2. Evans DJ, et al. *Pediatr Pulmonol*. 2019;54(6):751–758. 3. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265.

Chest X-rays Are Insensitive to Detect Early Structural Lung Damage

Percentage and Number of Abnormal Chest X-ray and LCI Measurements in Children With CF Between 1 and 6 Years of Age (N=48)*

	Age (years)						
	0	1	2	3	4	5	6
Chest X-ray n=296 measurements, Percentage (n/n)	29.4 (5/17)	40.7 (11/27)	37.1 (13/35)	52.3 (23/44)	61.1 (33/54)	58.5 (31/53)	63.6 (42/66)
LCI n=271 measurements, Percentage (n/n)	69.2 (9/13)	47.6 (10/21)	73.5 (25/34)	67.5 (27/40)	68.6 (35/51)	74.1 (43/58)	63.0 (34/54)

- Table summarizes mean proportions of abnormal LCI and chest X-ray (as indicated by Northern Score ≥1) in children with CF
- The proportions of cases with abnormal LCI values were significantly higher than the proportions of cases with abnormal chest X-ray until 4 years of age (P<0.05)

Chest X-rays are less sensitive than MBW examinations in detecting early lung disease (before age 4 years) in CF

*Pathological Northern Score was defined as Northern Score ≥1. Pathological LCI was defined as LCI_{adj} >7.0, where age-adjusted LCI values were calculated as LCI_{adj} = LCI - 0.12 * max(6 - age, 0), based on estimates from a reference population of 140 healthy children.

Table from Svedberg et al (2022).

CF, cystic fibrosis; LCI, lung clearance index; MBW, multiple-breath washout.

Svedberg M, et al. *Acta Paediatr*. 2022;111(6):1253–1260.

CT Is a Sensitive Imaging Modality for the Detection and Monitoring of Early Lung Disease

Association Between MBW Outcomes and Extent of Structural Disease Based on CT Using PRAGMA-CF Scores

	LCI	M1/M0	M2/M0
Infants			
Disease, %	0.03 (–0.14 to 0.20)	0.00 (–0.01 to 0.01)	0.02 (0.04 to 0.16)
Bronchiectasis, %	–0.33 (–0.82 to 0.16)	0.01 (–0.02 to 0.04)	**0.31 (0.18 to 0.45)***
Air trapping, %	0.04 (–0.04 to 0.12)	0.00 (–0.00 to –0.01)	**0.05 (0.03 to 0.08)***
Preschool			
Disease, %	**0.10 (0.02 to 0.19)†**	**0.02 (0.00 to 0.04)†**	**0.17 (0.03 to 0.31)†**
Bronchiectasis, %	0.11 (0.00 to 0.22)	**0.02 (0.00 to 0.05)†**	**0.20 (0.01 to 0.39)†**
Air trapping, %	0.02 (–0.01 to 0.05)	0.00 (0.00 to 0.01)	0.02 (–0.03 to 0.07)
School age			
Disease, %	**0.18 (0.10 to 0.27)***	0.03 (–0.02 to 0.08)	**0.36 (0.19 to 0.53)***
Bronchiectasis, %	**0.29 (0.14 to 0.43)***	0.04 (–0.05 to 0.13)	**0.55 (0.28 to 0.83)***
Air trapping, %	**0.06 (0.04 to 0.07)***	0.01 (–0.01 to 0.02)	**0.10 (0.06 to 0.14)***

- CT is the gold standard for demonstrating CF-related structural disease[1]
- CT scan abnormalities including bronchiectasis and air trapping correlate with markers of lung inflammation,[2,3] infection,[4] and with LCI[5,6]

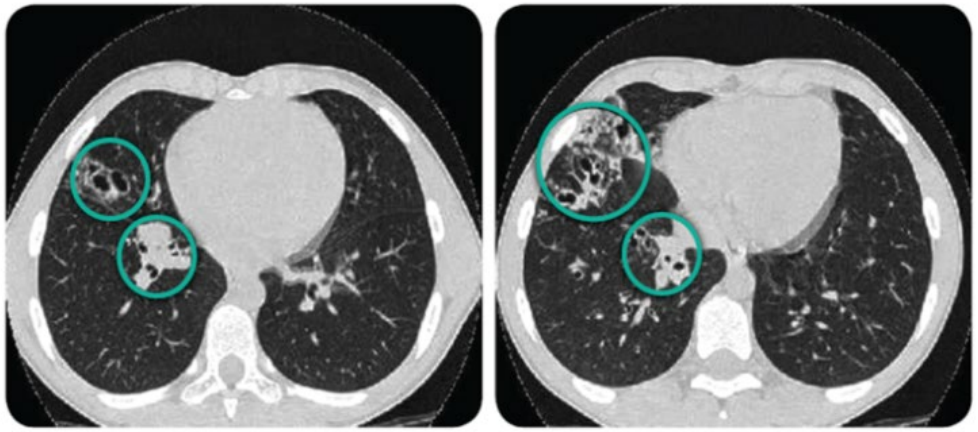
CT has high sensitivity to detect early lung impairment[5,7]

Values in parentheses are 95% confidence intervals. Coefficients indicate the increase in MBW outcomes for each unit increase in CT outcomes. Bold values are statistically significant. *P<0.001. †P<0.05.

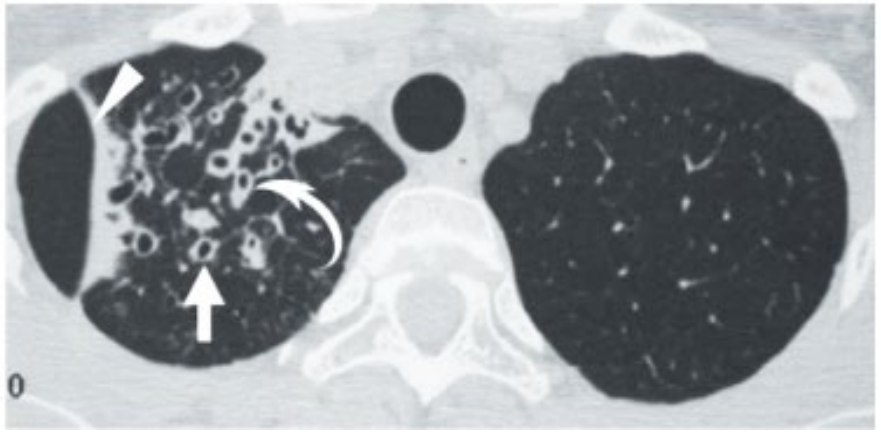
CF, cystic fibrosis; CT, computed tomography; LCI, lung clearance index; M1/M0, first moment ratio; M2/M0, second moment ratio (MBW ventilation distribution outcomes); MBW, multiple breath washout; PRAGMA-CF, Perth-Rotterdam Annotated Grid Morphometric Analysis for Cystic Fibrosis.

1. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265. 2. Sly PD, et al. *N Engl J Med*. 2013;368:1963–1970. 3. Wijker NE, et al. *Eur Respir J*. 2020;55:1901694. 4. Mott LS, et al. *Thorax*. 2012;67:509–516. 5. Ramsey KA, et al. *Am J Respir Crit Care Med*. 2016;193:60–77. 6. Gustafsson PM, et al. *Thorax*. 2008;63:129–134. 7. Owens CM, et al. *Thorax*. 2011;66:481–488.

People With CF Can Have Structural Lung Damage Despite Normal FEV_1



CT of peripheral and focal end-stage lesions in right middle and lower lobes in a 13-year-old CF person with FEV_1 99% predicted[1]



CT scans of a 30-year-old CF person with moderate bronchiectasis and bronchial wall thickening with FEV_1 94% predicted[2]

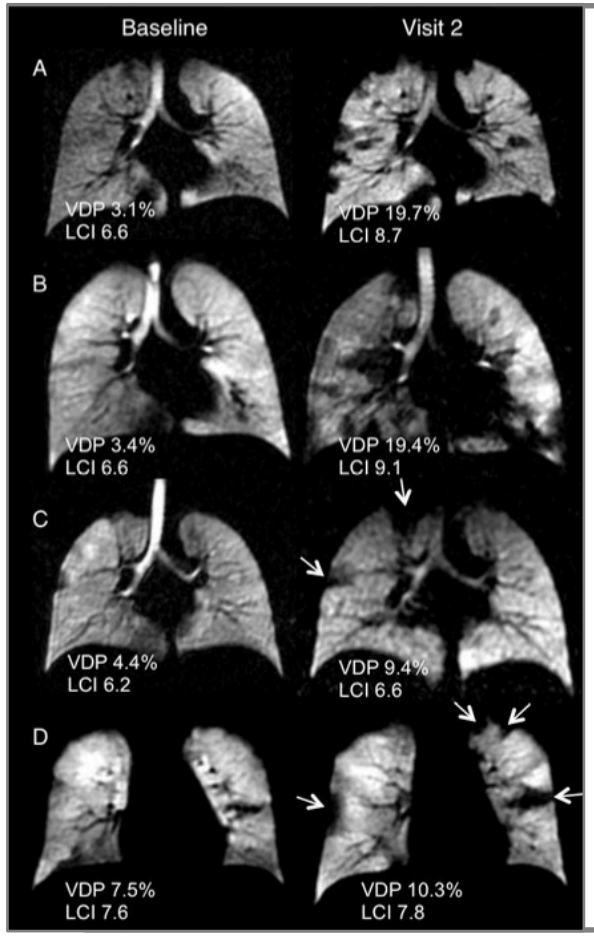
Left-hand figure reprinted with permission from de Jong PA, et al. *Radiology* 2004;231:434–439. Copyright The Radiological Society of North America (RSNA®). Right-hand figure reprinted with permission from *Chest*, 130(5), Judge EP, et al. Pulmonary abnormalities on high-resolution CT demonstrate more rapid decline than FEV_1 in adults with cystic fibrosis, 1424–1432, ©2006, with permission from Elsevier.

CF, cystic fibrosis; CT, computed tomography; FEV_1, forced expiratory volume in 1 second.

1. de Jong PA, et al. *Radiology*. 2004;231(2):434–439. 2. Judge EP, et al. *Chest*. 2006;130(5):1424–1232.

MRI Can Detect Early Lung Disease and Can Provide Both Structural and Functional Information

- MRI can detect early structural lung disease[1,2]
- Hyperpolarized gas MRI allows for measurement of regional ventilation/perfusion homogeneity (morphofunctional MRI)[1]
- Specific CF-MRI scoring systems have been developed[3]
- VDP appears to be the most promising functional MRI index[4]



MRI from 4 different children with CF tested at two timepoints (1.3–2.0 years apart), showing localized ventilatory defects (white arrows).

Increases in VDP were associated with increases in LCI for children A and B, but for not C and D[1,5]

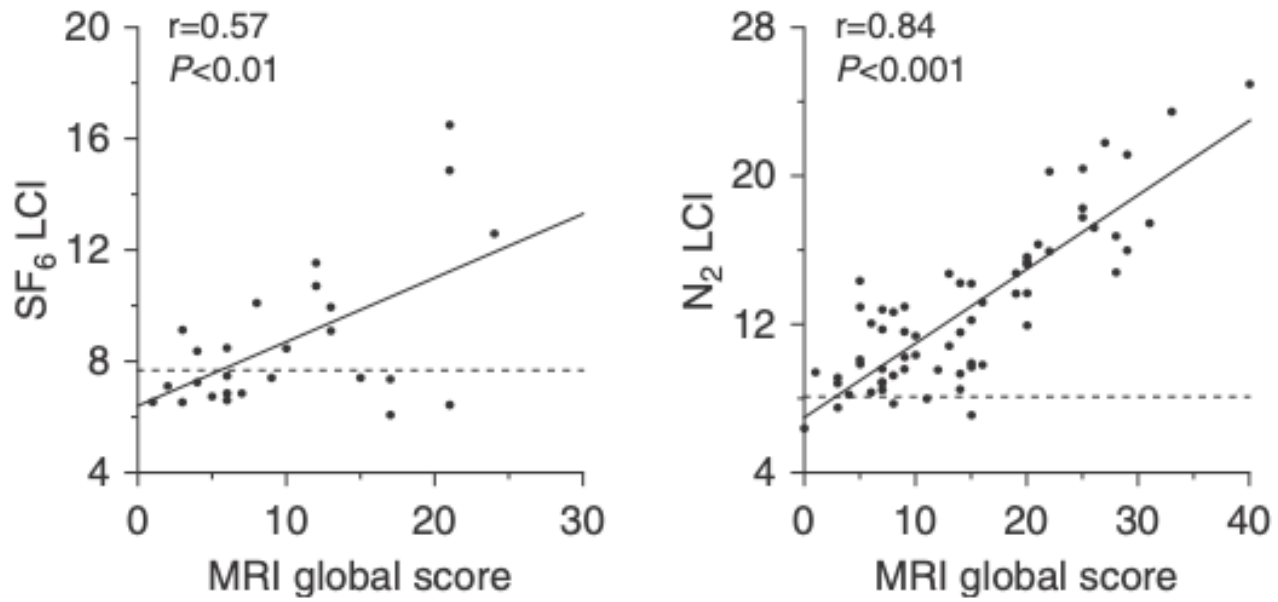
MRI detected changes in pwCF who were clinically stable and had normal spirometry values[1,5]

Figure reproduced from *Thorax*, Bayfield KJ, et al, 76,1255–1265, 2021. With permission from BMJ Publishing Group Ltd.

CF, cystic fibrosis; LCI, lung clearance index; MRI, magnetic resonance imaging; pwCF, people with cystic fibrosis; VDP, ventilation defect percentage

1. Smith L, et al. *Am J Respir Crit Care Med* 2018;197:397–400. 2. Wielpütz MO, *Am J Respir Crit Care Med*. 2014;189(8):956–965. 3. Eichinger M, et al. *Eur J Radiol* 2012;81:1321–1329. 4. Rayment JH, et al. *Eur Respir J* 2019;53. 5. Bayfield KJ, et al. *Thorax* 2021;76:1255–1265.

MRI Structural Abnormalities Correlate With MBW Measurements



Correlation between LCI, determined with sulfur hexafluoride (SF_6) MBW (left) or nitrogen (N_2) MBW (right) and abnormal lung structure and perfusion detected by MRI global score in children with CF. The dashed line indicates the upper limit of normal for the LCI (SF_6, 7.68; N_2, 8.08).

- Both LCI and MRI are sensitive to detect differences in disease severity and response to antibiotic therapy for pulmonary exacerbations in children with CF across the entire pediatric age range (0.2–21.1 years)
- LCI and MRI may be useful as complementary sensitive and non-invasive outcome measures for early detection and monitoring and as endpoints in early intervention trials in children with CF

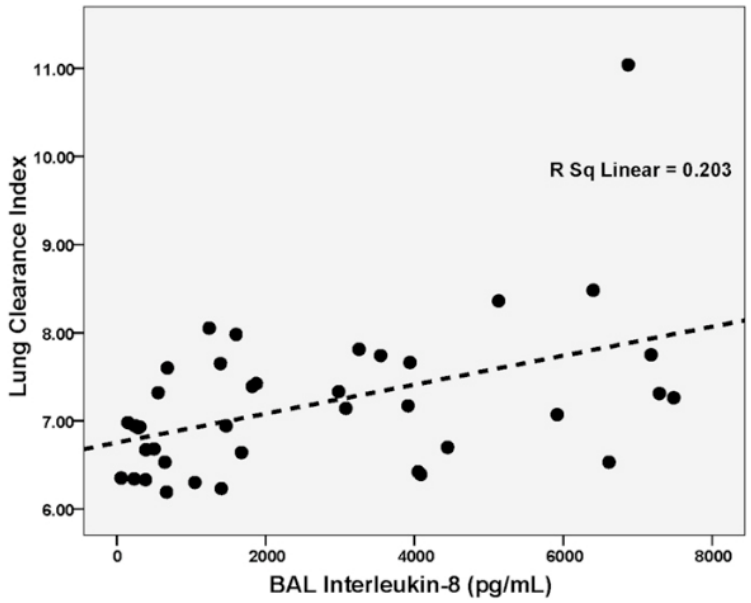
MBW and MRI are sensitive in detecting early disease and are complementary

CF, cystic fibrosis; LCI, lung clearance index; MBW, multiple-breath washout; MRI, magnetic resonance imaging.

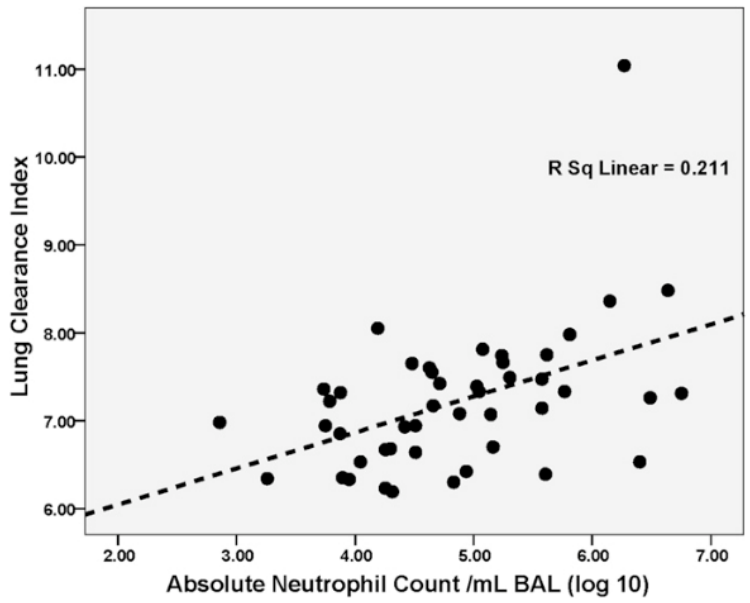
Stahl M, et al. *Am J Respir Crit Care Med*. 2017;195(3):349–359.

LCI Correlates With Bronchoalveolar Lavage Measures in Young Age

IL-8



Absolute Neutrophil Count



Association between LCI and BAL IL-8 (left) and absolute neutrophil count (right) in children (0–3 years old) with CF. There was a significant relationship between LCI and IL-8 in young children with CF (R^2=0.20, P=0.004). There was a significant relationship between LCI and absolute neutrophil count in infants and young children with CF (R^2=0.21, P=0.001)[1]

- Bronchoalveolar lavage (BAL) is the present standard for diagnosing lower airway infection and inflammation in young children[1]
- However, BAL is invasive and limited sampling may underestimate infection or inflammation because of regional variability. In addition, few centers perform surveillance BAL in young children with CF[1]

BAL is the only way to properly investigate colonization of the lower airways and to measure inflammatory markers[2]

BAL, bronchoalveolar lavage; CF, cystic fibrosis; IL-8 interleukin-8; LCI, lung clearance index; MBW, multiple-breath washout; MRI, magnetic resonance imaging.

1. Belessis Y, et al. *Am J Respir Crit Care Med*. 2012;185(8):862–873. 2. Stahl M, et al. *Genes (Basel)*. 2021;12(6):803.

Comparison of Methods to Detect and Monitor Early Lung Disease in CF

Technique	Investigated Aspect of CF Lung Disease	Applicable Age Range	Advantages	Disadvantages
Spirometry	Lung function	≥3 years	Good availability	Necessitates cooperation Insensitive for mild changes
MBW	Lung function	From infancy on (requiring sedation in some young pwCF)	Performed in tidal breathing with minimal cooperation detects early ventilation inhomogeneities	Only available at specialized centers Harmonization between devices, tracer gases and protocols pending
CT	Lung structure	From infancy on (requiring sedation in some young pwCF)	Good availability Short duration of performance High resolution images detecting early morphological changes	Ionizing radiation (limiting repeatability) No information on lung function
MRI	Lung structure Lung function	From infancy on (requiring sedation in some young pwCF)	Sensitive to early CF lung disease Can be repeated in short time (no radiation)	Performed at specialized centers Investigation takes longer than CT Lower resolution than CT
BAL	Infection Inflammation	From infancy on (requiring anesthesia in some young pwCF)	Only way to properly investigate colonization of the lower airways and to measure inflammatory markers	Invasive BAL-directed therapy has shown no advantage over standard therapy

MBW, CT, MRI, and BAL can all be used from infancy and can be complementary

BAL, bronchoalveolar lavage; CF, cystic fibrosis; CT, computed tomography; MBW, multiple-breath washout; MRI, magnetic resonance imaging; pwCF, people with cystic fibrosis.

Stahl M, et al. *Genes (Basel)*. 2021;12(6):803.

Summary

Summary

- Early in life, people with CF may have structural and functional abnormalities across organ systems, despite reports of lung function in the normal range[1–6]
- Early disease manifestations can predict later disease progression[2,3]
- Newer imaging and functional testing modalities that are more sensitive in detecting disease may be helpful to establish early organ involvement[7,8]
- While newborn screening and earlier management of CF have led to improvements in life expectancy, life expectancy remains reduced versus the general population[7,9,10]

CF, cystic fibrosis.

1. VanDevanter DR et al. *J Cyst Fibros*. 2016. 2. Bayfield KJ, et al. *Thorax*. 2021;76(12):1255–1265. 3. Turkovic L, et al. *Eur Respir J*. 2020;55(5):1900748. 4. Wijker NE, et al. *Eur Respir J*. 2020;55:1901694. 5. Sawicki GS et al. ATS, 2017. Poster A4847. 6. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf.. Accessed March 2023.7. Ellemunter H, et al. *Respir Med*. 2010;104(12):1834–1842. 8. Robinson PD, et al. *Am J Respir Crit Care Med*. 2018;197(5):e1–e19. 9. Ramsey KA, et al. *Am J Respir Crit Care Med*. 2016;193:60–77. 10. Smith L, et al. *Am J Respir Crit Care Med* 2018;197:397–400.