The Belgian Cystic Fibrosis Registry

sciensano

Facts and highlights

2021 BCFR

Objectives

The aims of the CF registry are to : 1) study disease epidemiology among people with CF in Belgium, 2) provide a tool for the assessment of disease management and quality of care for patients with CF, 3) provide a database for scientific research to CF researchers and 4) to participate in international CF related studies and projects.

Demographics

There were 1379 People With Cystic Fibrosis (PwCF) included in the CF registry.

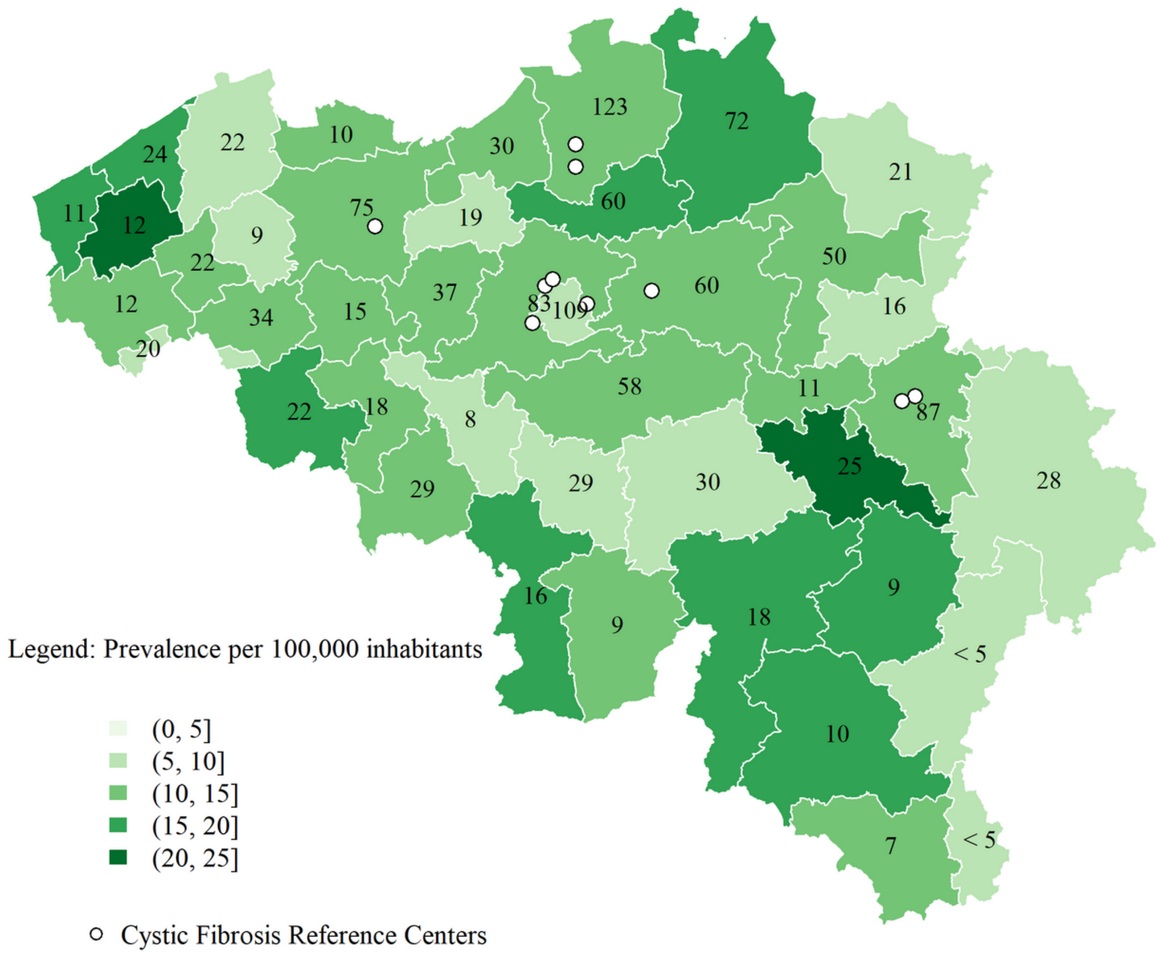
52.6% are male, 47.4% are female.

There are 7 accredited CF reference centers distributed across the country in 10 clinics, most of them are University Hospitals.

Mucoviscidose referentiecentrum UZ Brussel
Muco-Referentiecentrum Antwerpen
(St Vincentiusziekenhuis & UZ Antwerpen)
Referentiecentrum voor Mucoviscidose UZ Gent
Muco-Referentiecentrum Gasthuisberg Leuven
Centre de référence de la Mucovicidose UCL
Centre Liégeois de rééducation fonctionnelle pour la Mucoviscidose
(CHR La Citadelle & C MontLegia)
Institut de Mucoviscidose HUB
(Hôpital Universitaire des Enfants Reine Fabiola & Hôpital Erasme)

Each CF reference center has a pediatric and adult clinic.

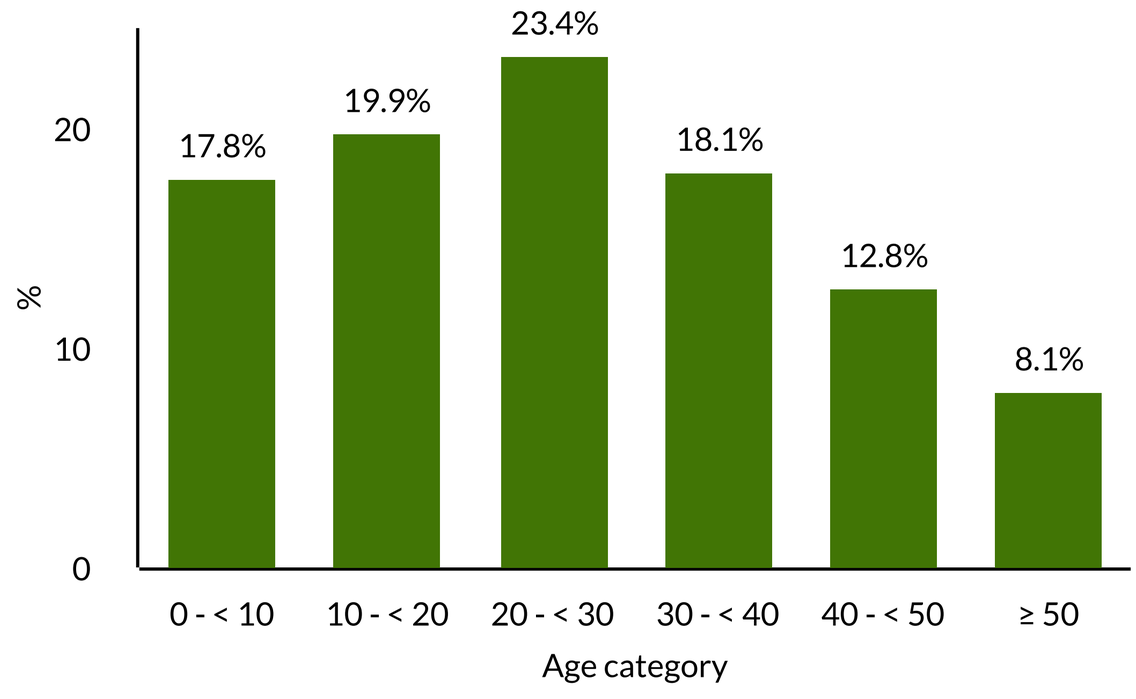
The registry covers about 90 - 95% of CF patients living in Belgium.



In the figure above, the text presents the number resident PwCF while the colour is the prevalence per district; the highest being Diksmuide (23.2) and Hoei (21.9). About 12 patients resided outside the country in 2021.

The proportion of adults has increased from 38.4% in 2000 to 65.8% in 2021.

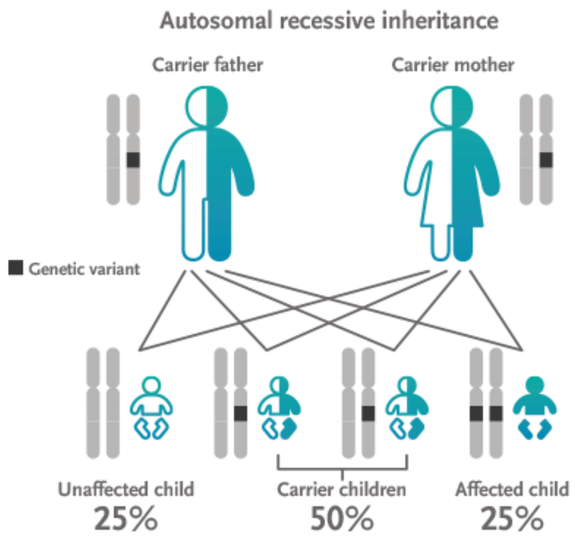
Age distribution in 2021



The median age is 24.5 years, (24.1 for the male and 25.4 for the female).

Diagnosis information

A person is born with Cystic Fibrosis (CF) by inheriting a defective copy of the CFTR (CF transmembrane conductance regulator) gene from each parent.



https://www.invitae.com/en/patients/reproductive-health/

The median age at diagnosis is 4.3 months for male and 4.5 months for the female. There were 33 newly diagnosed PwCF in 2021. Four of the newly diagnosed were adults aged 18 years or above. By age 5 years, 80.9% of all people with CF in the registry had been diagnosed.

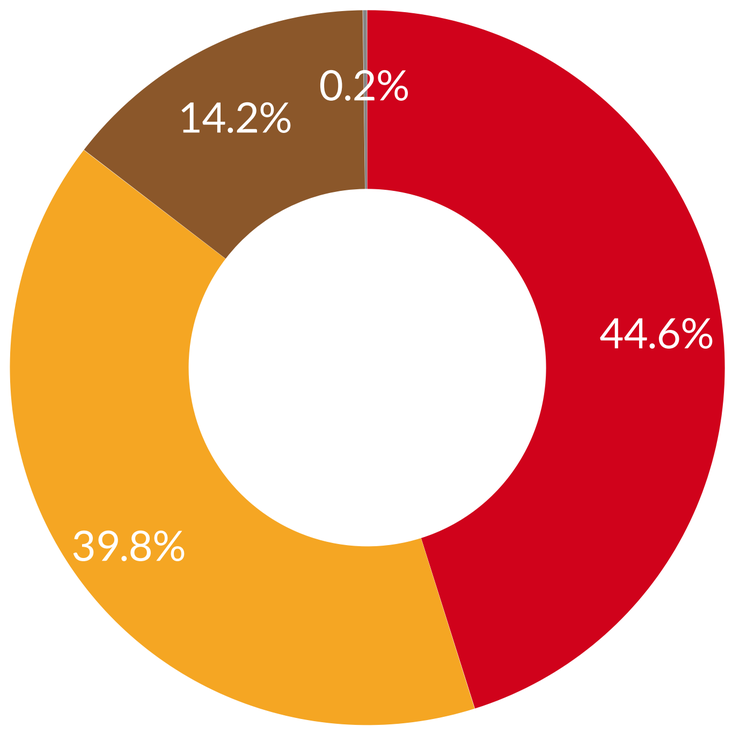
median age at diagnosis
4.4 Months

The most prevalent mutations are F508del (86.4%), G542X (4.8%), N1303K (4.8%), 3272-26A->G (4.2%) and S1251N (2.8%)

More than 2000 mutations in the CFTR gene have been identified to date. A majority of these are extremely rare. While not all CFTR mutations lead to CF, and about 719 have been confirmed as disease causing. About 88.0% of those seen in 2021 have both mutations in this recent list.

https://www.cftrscience.com/cftr-mutations https://www.cftr2.org/ *CFTR2_29April2023*

Proportion by genotype

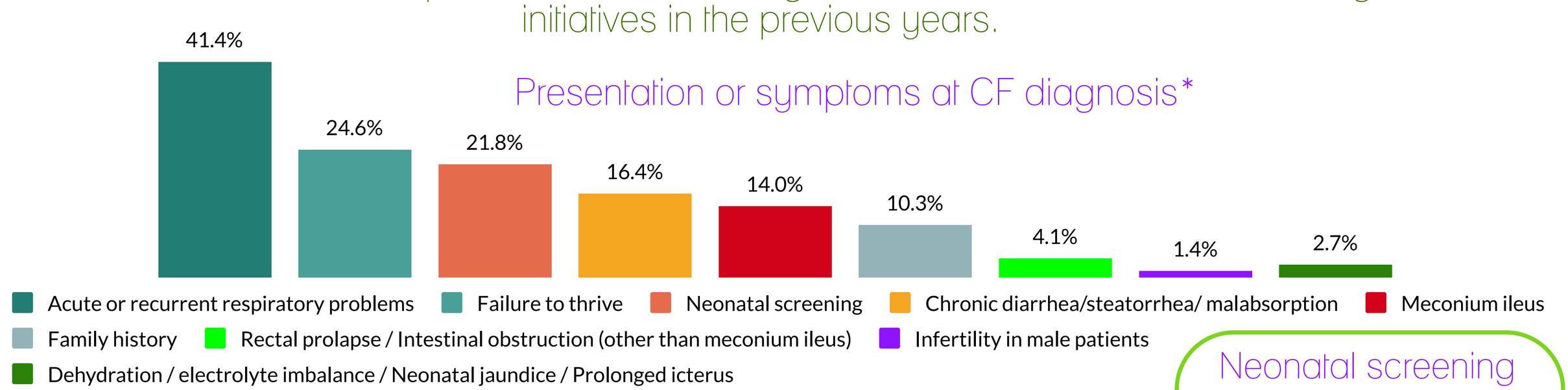


Almost half (44.6%) of the people in the Belgian CF registry are F508del homozygous, 39.8% are heterozygous, 14.2% have other mutations while for 0.2% the mutations were not identified.

Homozygous - having two identical alleles of a particular gene
Heterozygous - having two different alleles of a particular gene

Most PwCF (41.4%) present with acute or recurrent respiratory symptoms. A newborn (neonatal) screening program, coordinated regionally, was introduced in 2019 in Flanders and in 2020 in Walloonia. A few patients have been diagnosed after local neonatal screening initiatives in the previous years.

Presentation or symptoms at CF diagnosis*



*The reasons above are not mutually exclusive. Since the introduction of new born screening programs covering all the regions, about 80.0% of new CF cases are diagnosed after neonatal screening.

Neonatal screening among new cases
78.8%

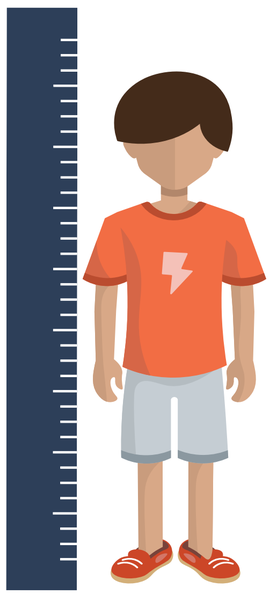
Definitions :

- The Cystic Fibrosis Transmembrane conductance Regulator (CFTR) is an epithelial ion channel protein that regulates the transport of water and of chloride ions in and out of cells. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning / defective, these ions cannot flow freely in and out of the cell. This occurs in Cystic Fibrosis, and is characterized by the build-up of a thick, sticky mucus.
- A mutation is a permanent alteration in the DNA sequence that makes up a gene, either due to mistakes when the DNA is copied or as the result of environmental factors, such that the sequence differs from what is found in most people.
- Newborn (neonatal) screening is the practice of testing all babies in their first days of life for certain rare disorders and conditions that can hinder their normal development. Early treatment can improve their health and prevent severe disability or even death.

Growth and nutrition

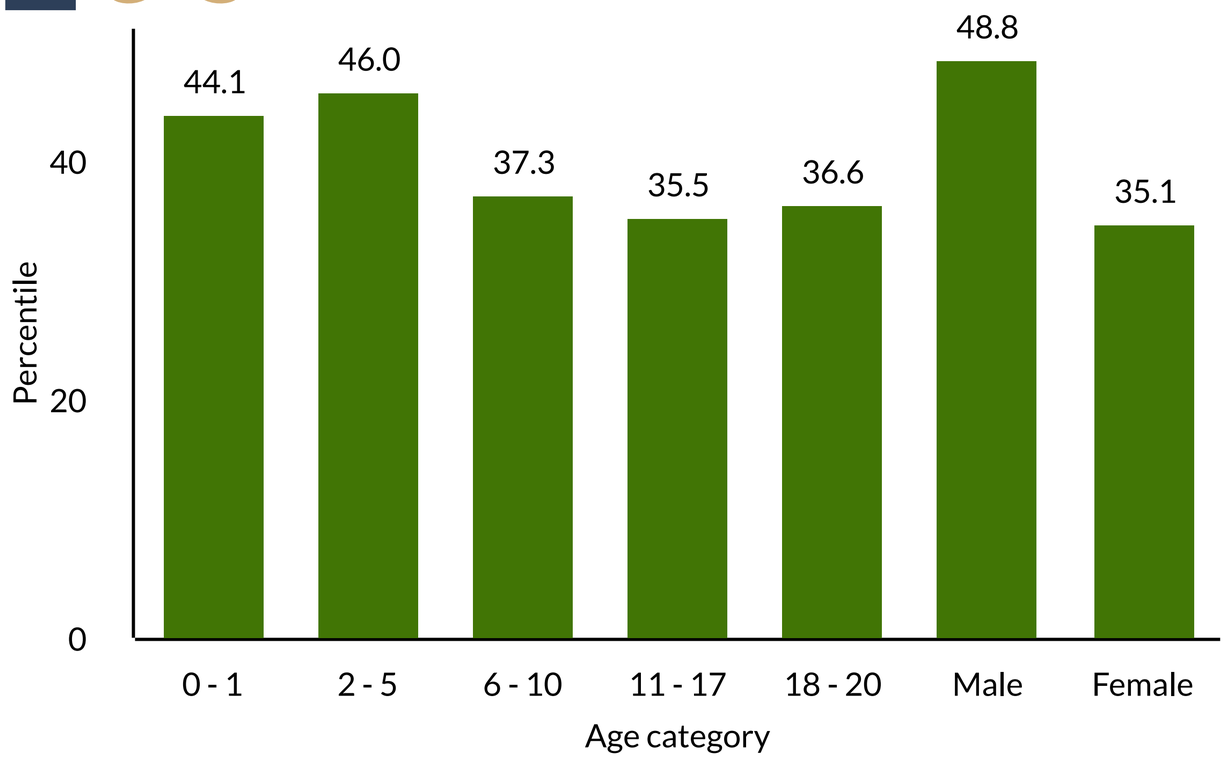
The nutritional status (BMI) of PwCF in Belgium has improved in the last 2 decades, most importantly in adolescents and young adults.The goal of a good nutritional status is to have a median percentile of 50 or above for the BMI, height and weight.

Children with CF may have stunted growth and may not grow tall as quickly as peers of the same age and gender.



Median Height percentile in patients 0 - 20 years

38.5

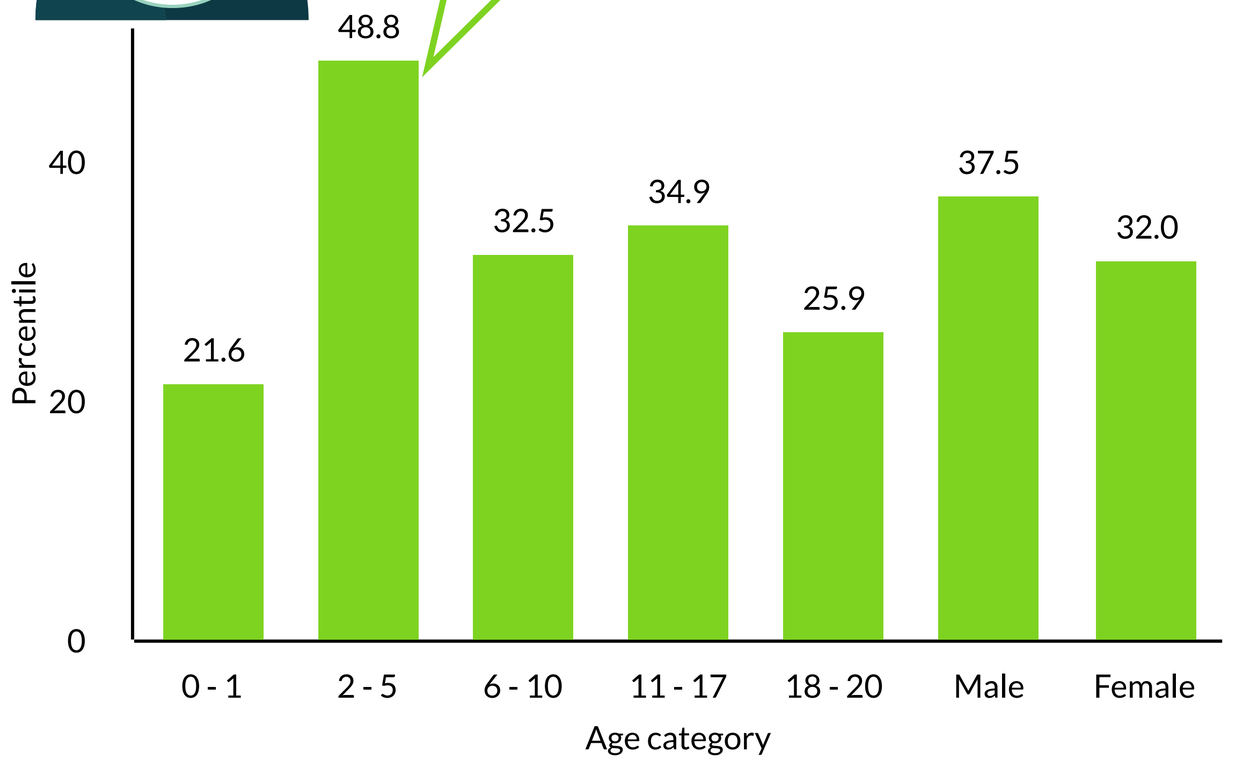


Weight gain has been a challenge in CF. A well balanced high calorie, high protein and high fat diet as well as the intake of pancreatic enzymes were crucial to achieving a good nutritional status. CFTR modulator therapy, however, has shown to have significant effect on long-term weight gain.

Mouzaki M. et al. 2023

Median Weight percentile in patients 0 - 20 years

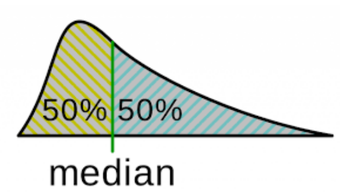
34.8



Nutritional care is of great importance for people with CF. Because of thick mucus, the pancreas is unable to produce and/or carry digestive enzymes to the gut. This leads to poor absorption of proteins, fats and fat soluble vitamins resulting in poor weight gain and growth. Maintaining or achieving a better nutritional status has a positive impact on lung function.

Adults with BMI between 18.5kg/m^2 and 25kg/m^2

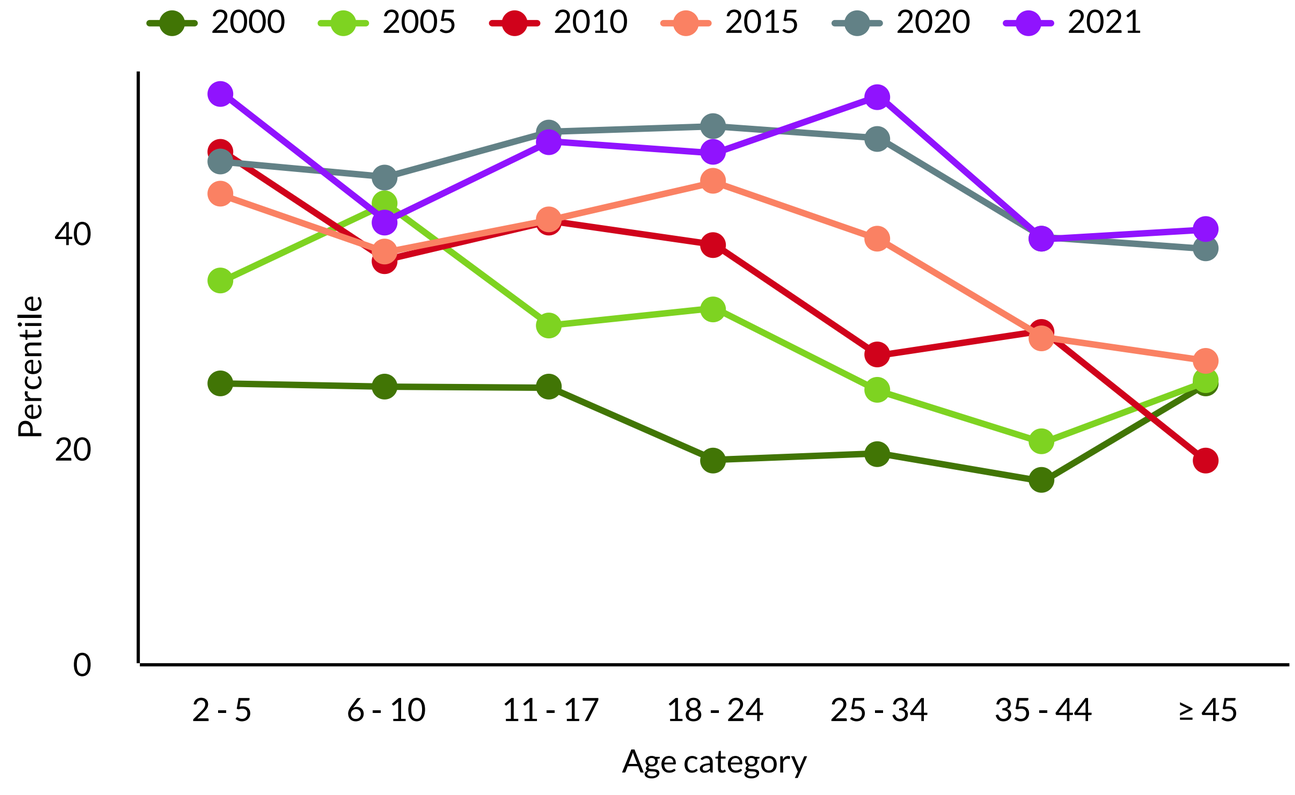
70.5%



Median BMI percentile in patients 2 - 20 years

40.5

Median BMI percentile



Definitions :

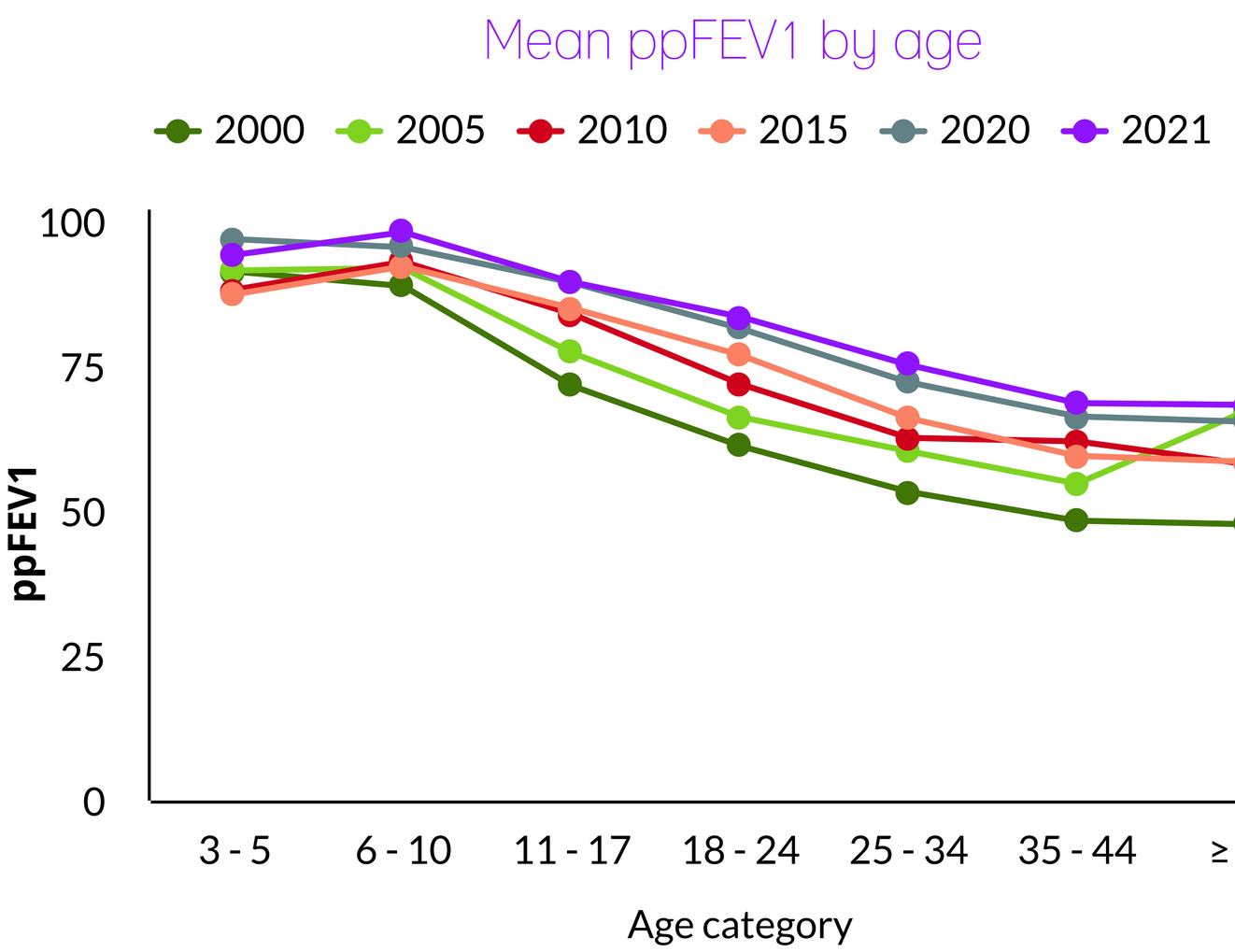
- A median is a point that divides the data into two numerically equal groups based on their ordered values. Median age implies that half the people are younger than this age and half are older.
- A percentile is each of the 100 equal portions into which a group of values can be divided according to the distribution of these values. The median is also the 50th percentile (P50) and is the value at which half of the observations are larger and the other half smaller. The "mean", also called the "average", is the sum of all the elements in a group then divide this sum by the number of elements used.
- BMI is the ratio between a person's weight (in kg) and the height (expressed in m^2).

Pulmonary function

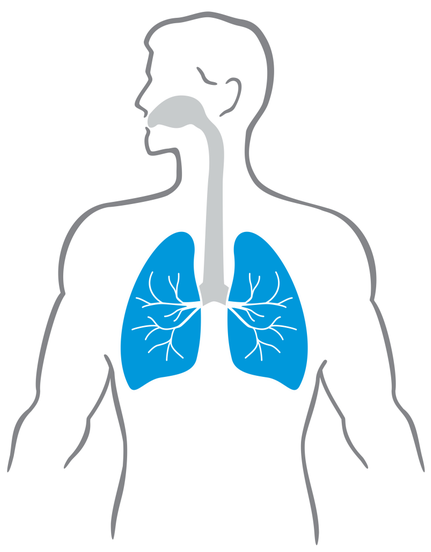
In the last 2 decades, there have been advancements in CF care and therapy, including the highly effective CFTR modulators. We will continue to see improvements in pulmonary function across the age categories.

The percentage of predicted forced expiratory volume in one second (ppFEV1) is a clinical parameter used to monitor lung function impairment.
Because most people with CF develop progressive pulmonary disease, measures of pulmonary involvement, in particular ppFEV1, are used to follow up the lung disease.
The ppFEV1 partly determines the prognosis. However, considerable heterogeneity exists in prognosis and disease severity, even among people with the same mutations.

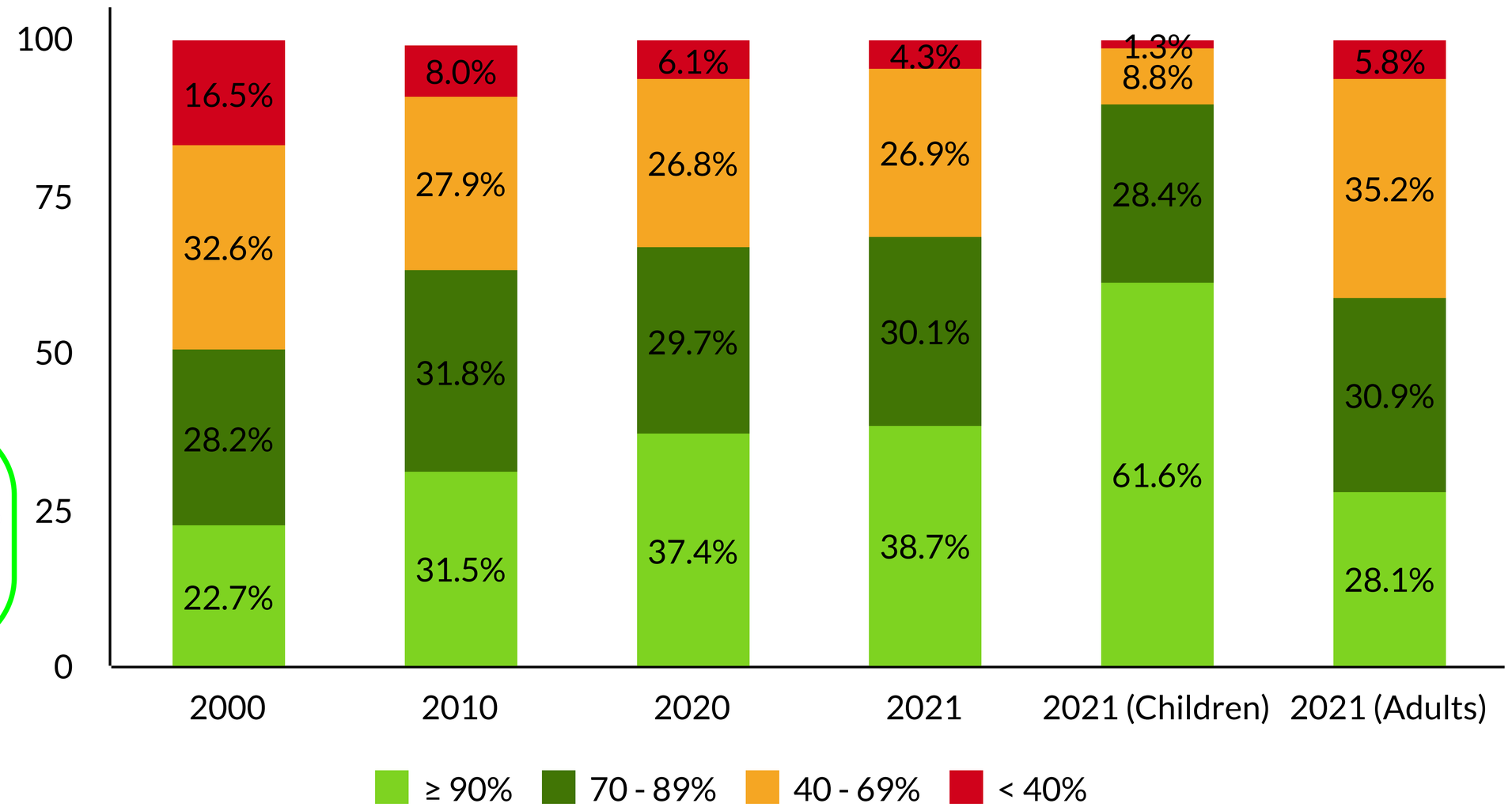
Schluchter MD, 2006, McKone E, 2003



FEV1% predicted values (ppFEV1) were divided in four classes corresponding to different degrees of lung function impairment: near normal (≥ 90%), mild impairment (70 - 89%), moderate impairment (40 - 69%) and severe impairment (< 40%).



The mean ppFEV1 in 2021 was 81.3% (93.3% in children and 75.2% in adults)



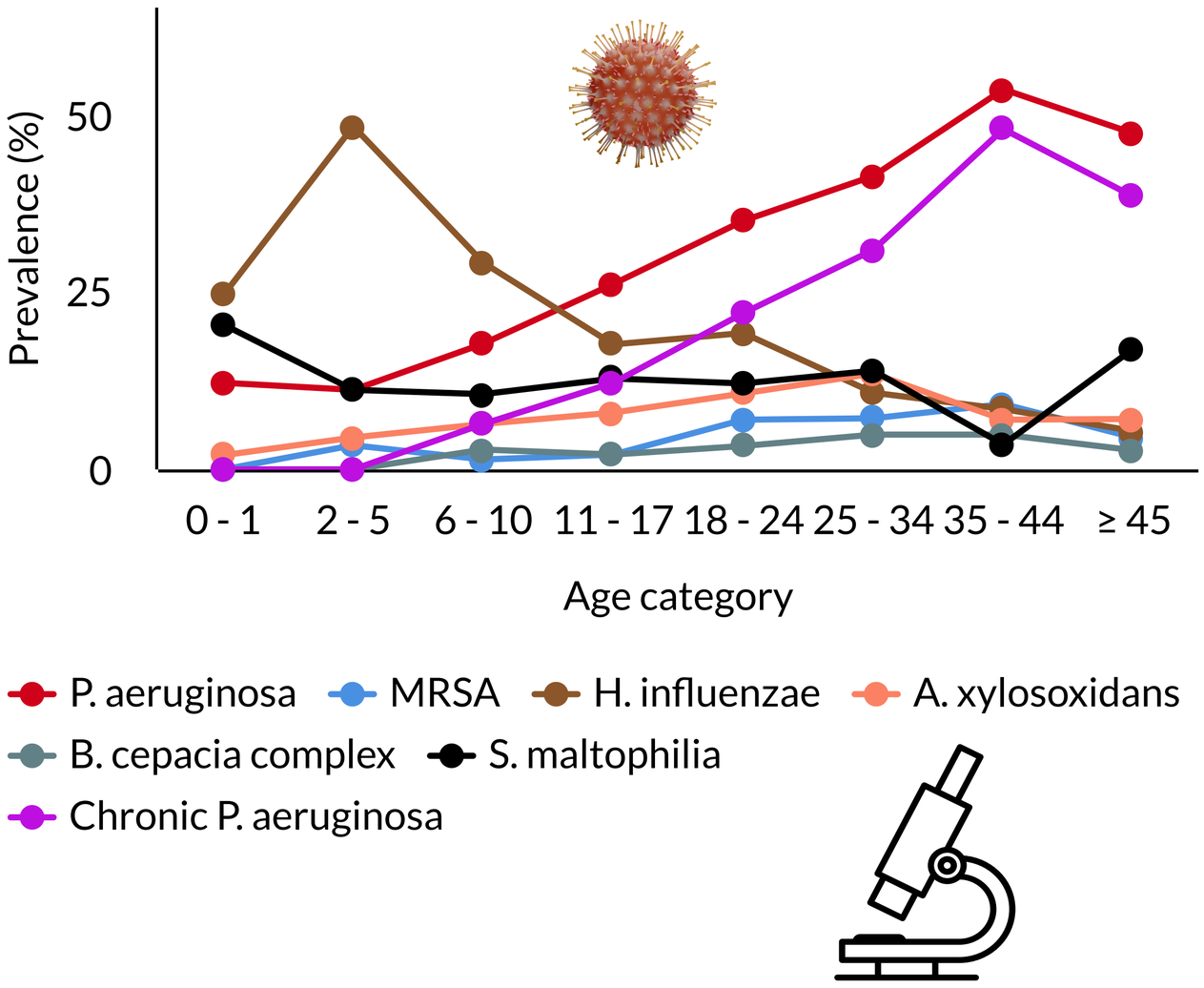
Definitions :

- The forced expiratory volume in one second (FEV1) is the amount of air that a person is able to exhale forcefully in one second, following full inspiration. It is expressed as a percentage of the predicted value (ppFEV1) for a reference population with same age, gender, height and ethnic background.
- Prevalence is the proportion of a population that is affected or that has a given attribute at a given time.
- Chronic Pseudomonas aeruginosa infection is defined as having more the 50% of the sputum samples positive taken in a 12 months period with at least 4 sputum samples taken during that period.

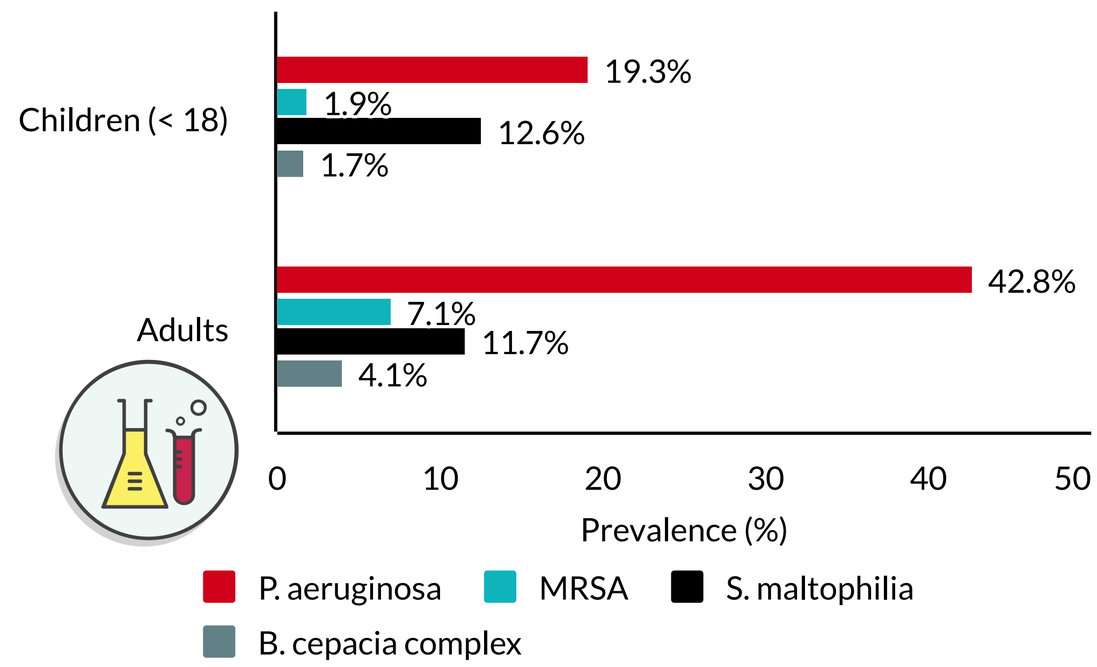
Microbiology

One of the main goals of CF care is to prevent or postpone infections and to reduce the risk of chronic infections (or colonization), which increases respiratory morbidity and treatment burden. Sputum samples, throat swabs and bronchoalveolar lavage cultures are taken to monitor the presence of pathogens.

Age related prevalence of microbes in 2021



Prevalence of infections in 2021



MRSA - Methicillin Resistant Staphylococcus aureus

Bacterial infection may occur very early in life. In children common bacteria such as Staphylococcus aureus and Haemophilus influenzae may infect the lungs.

Infection by Pseudomonas aeruginosa and sometimes Burkholderia cepacia complex and other gram-negative pathogens occur at a later age. The airways of people with CF may also be chronically infected by fungi like Aspergillus fumigatus.

Hart CA 2002, de Vrankrijker AM, 2011

At least 98.9% of the PwCF had 4 or more cultures taken in the year 2021. The figure above (left) shows a high prevalence of H. influenzae at a very young age, with its reduction with age replaced by the progressive increase of the other bacteria especially P. aeruginosa.

Complications

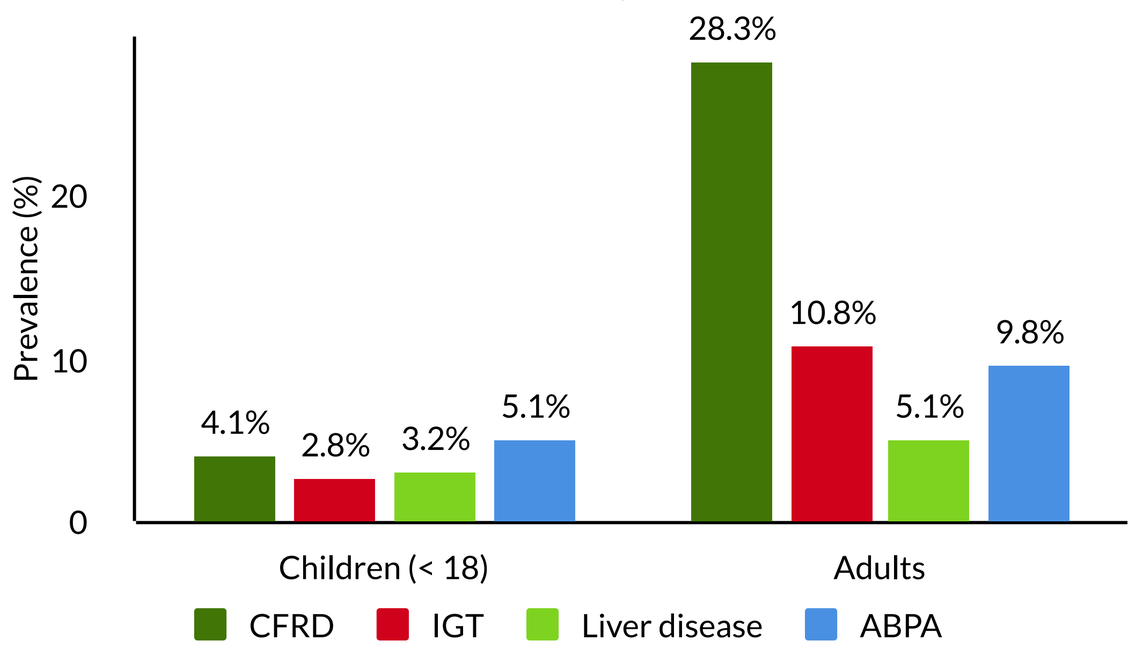
Cystic Fibrosis affects the respiratory, digestive, and reproductive systems with variable degrees of severity. Most of the PwCF, 85.9% of the children and 77.4% of the adults, are pancreatic insufficient.

The defective chloride channel in CF causes a range of disturbances within the human body, disrupting the transport through the cell wall of chloride, other ions and water.

Complications in CF are mainly found in organs where mucus linings are needed (airways, intestines) and in glands which need fluid to excrete their substances (pancreas, testicles…).

Flume PA 2009, Sinaasappel M 2002, Goodin B 2005, McCallum TJ 2000, Lyon A 2002

Prevalence of complications in 2021



CFRD - Cystic Fibrosis Related Diabetes
IGT - Impaired Glucose Tolerance
ABPA - Allergic Bronchopulmonary Aspergillosis

The lower prevalence of Pancreatic Insufficiency in adults is due to a higher number of patients with mild genotype and Pancreatic Sufficiency in the adult patients. The most important other complication is CFRD, especially among adults.

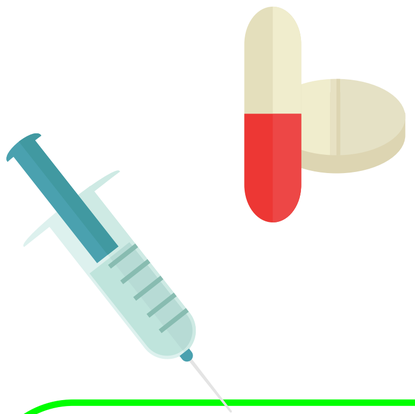
Among non-transplant PWCF with a CT scan during the year, about 74.9% had Bronchiectasis (49.1% children and 88.9% adults)

Definitions :

- Exocrine pancreatic insufficiency (PI) is the inability of the pancreas to produce and transport enough pancreatic enzymes to the duodenum to digest fat and proteins resulting in malabsorption with steatorhea (fatty stools), malnutrition and a deficiency in fat-soluble vitamins.
- Bronchiectasis is a long-term condition where the airways of the lungs become widened, leading to a build-up of excess mucus that can make the lungs more vulnerable to infection.

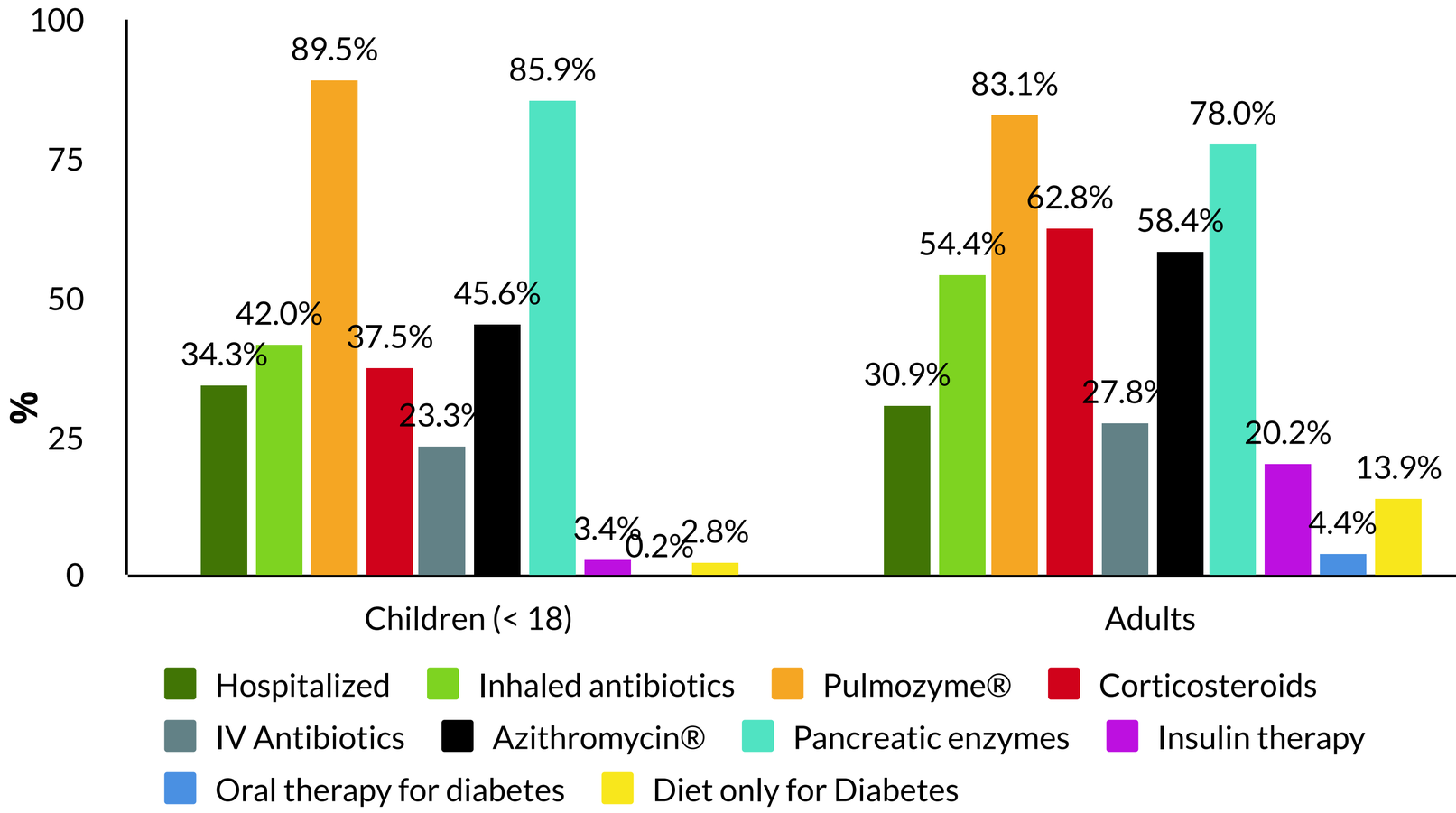
Treatment burden

Treatment of CF was mostly based on preventing or reducing symptoms in order to avoid complications or to stabilize the patient. The introduction of modulator therapy has drastically changed Cystic Fibrosis disease management.



Most PwCF did regular chest physiotherapy (99.9%). The most used therapies were mucolytics (rhDNase, 85.7% and Hypertonic saline 67.4%) and Bronchodilators 75.3%. During the year 2021, 90.1% of the PwCF made at least 4 required visits to the clinic.

Therapy, medication and hospitalization in 2021

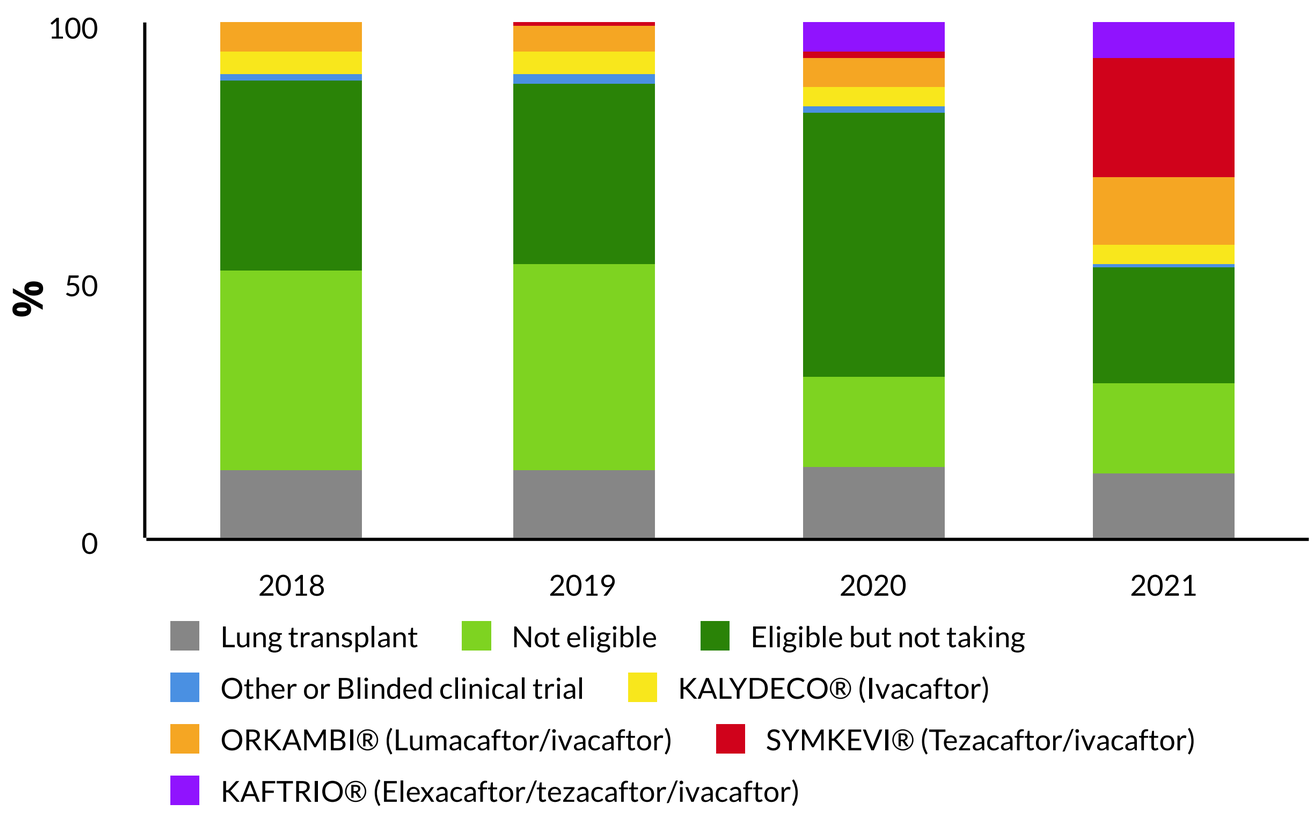


CFTR modulator therapy

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators are a class of drugs that act by improving production, intracellular processing, and/or function of the defective CFTR protein. These drugs are an extraordinary advance in management of cystic fibrosis (CF) because they target the production or function of the mutant CFTR protein rather than its downstream consequences. *Middleton PG, Taylor-Cousar JL, 2021*

CFTR modulator use and access 2018 - 2021

With the expansion of the labels to younger patients and more gene variants, and the medication costs reimbursement agreements by the National Institute for Health and Disability Insurance (NIHDI, RIZIV), more people with CF living in Belgium continue to have access to modulator therapy.



This figure represents the proportion of PwCF by CFTR modulator therapy status. It is based on the modulator being taken by the last consultation of the year. About 46.2% of the PwCF (41.8% children and 48.4% adults) in 2021 took one of the available modulators.

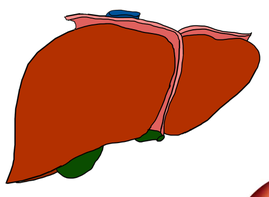
Definitions :

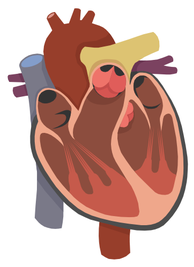
- ABPA is an allergic reaction to Aspergillus fumigatus a fungus that colonizes the airways of some people with CF.
- CFRD / IGT - The malfunctioning of the endocrine part of the pancreas by fibrosis leads to an insufficient secretion of insulin leading to IGT or diabetes.
- Liver disease - Due to a defective CFTR protein some patients have problems in their biliary tract, where bile is thick and sticky and has difficulty getting out of the liver, causing irritation and inflammation in the bile ducts and leading to scarring (cirrhosis).

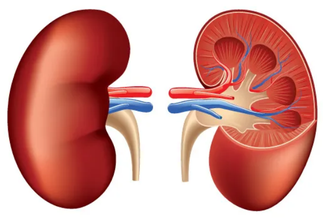
Transplantation and Cystic Fibrosis

When a person with CF develops severe and progressive lung disease, lung transplantation may become an option. A lung transplant is indicated only for patients who have a severe disease, who have exhausted all other forms of conventional medical treatment and whose short term survival is compromised.

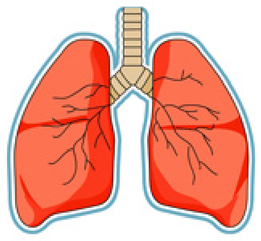
The most frequent organ transplant done to people with Cystic Fibrosis in Belgium is the lung transplant. A few people will need other types of organ transplants such as a liver, kidney, pancreas, heart or a combination.







Type of transplant	n
Lung	275
Kidney	22
Liver	21
Lung-Heart	15
Lung-Liver	11
Lung-Kidney	3
Liver-Kidney	2
Heart	1
Lung-Liver-Kidney	1

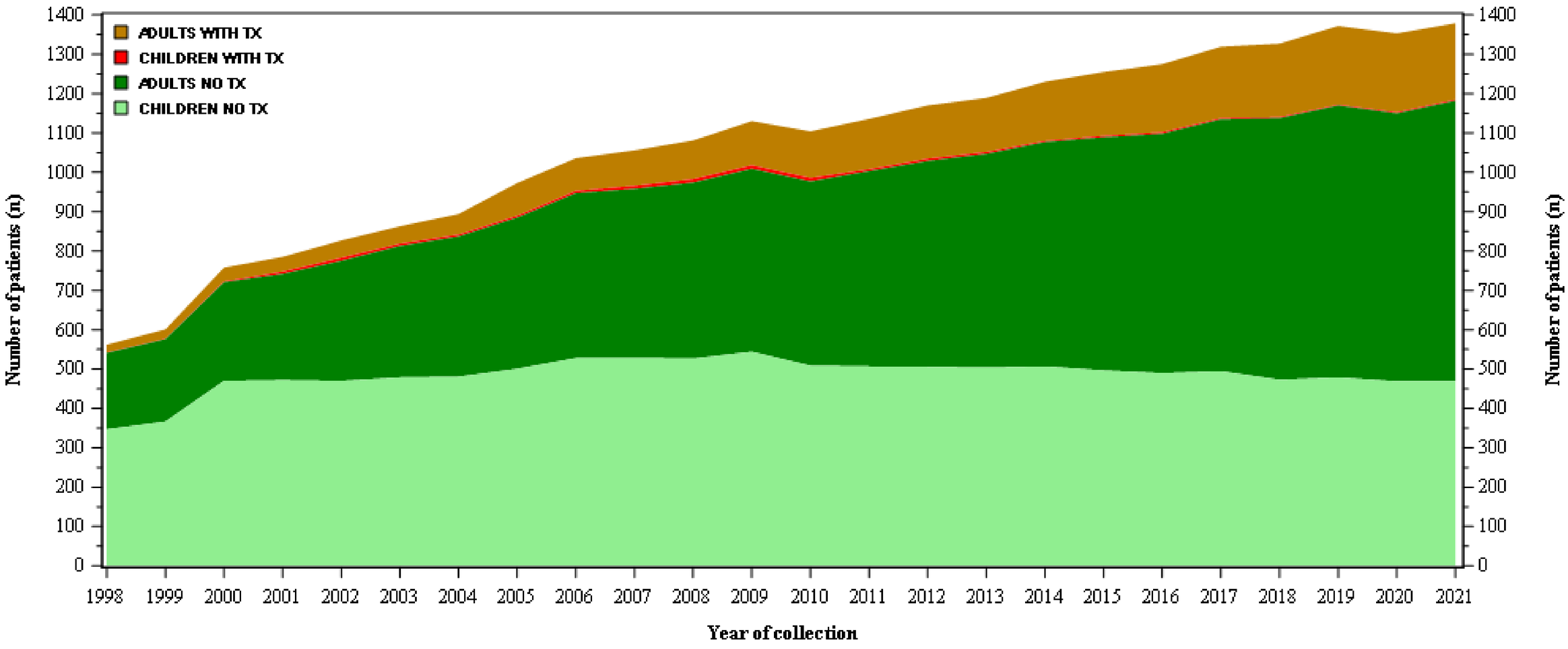


In 2021, there were 216 people with CF alive (102 male, 114 female) who had received a transplanted organ in the past.

Their median age (range) at the last consultation was 39.4 (2.6 – 69.1) years. 97.7% of those with a transplant were adults.

The registry records show that since its inception in 1999, at least 307 people with CF, 146 male and 161 female have benefited from transplantation. While most were in adult patients, at least 31 were children.

Number of people with CF by transplant status



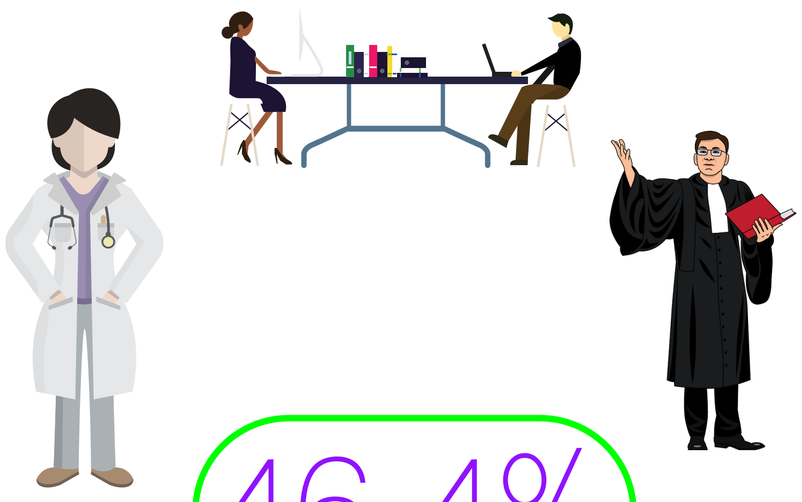
©BCFR Generated on 08/11/2023

In 2021 at least one in every five adults with CF (20.8%) was a transplant patient.

Life statistics

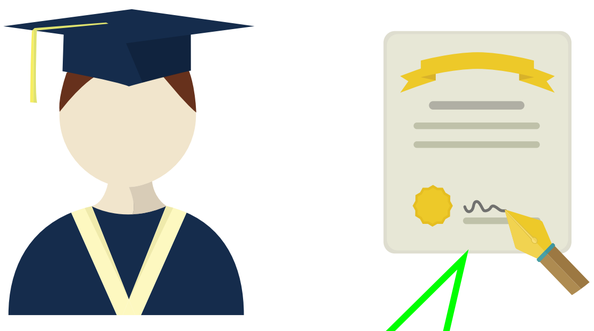
People with CF are living longer. And with the new life changing modulator therapies and reduced therapy burden, this is introducing new challenges and expectations alike. The proportion graduating and taking up a career either part-time or full-time are important indicators of social integration.

In 2021 almost half of the adults with CF aged 18 years and above had a full-time or part-time job.



46.4%

More than three quarters of adults had either a high school diploma or college qualification / degree



78.7%

**Employment and education level excludes adults attending school.*

At least 391 children (biological or adopted) have been reported from 239 parents with CF since the start of the registry.
In 2021, there were 18 children reported (including nine pregnancies) by a parent with CF in 2021.

391

Kaplan E 1968, Barreto C 1991, Dreyfus DH 1996, Sawyer SM 2005,Janice E Whitty 2010, Jelin AC 2017

Due to advancements in CF care and treatments including the highly effective CFTR modulators, people with CF continue to have improved life expectancy with better quality of life.

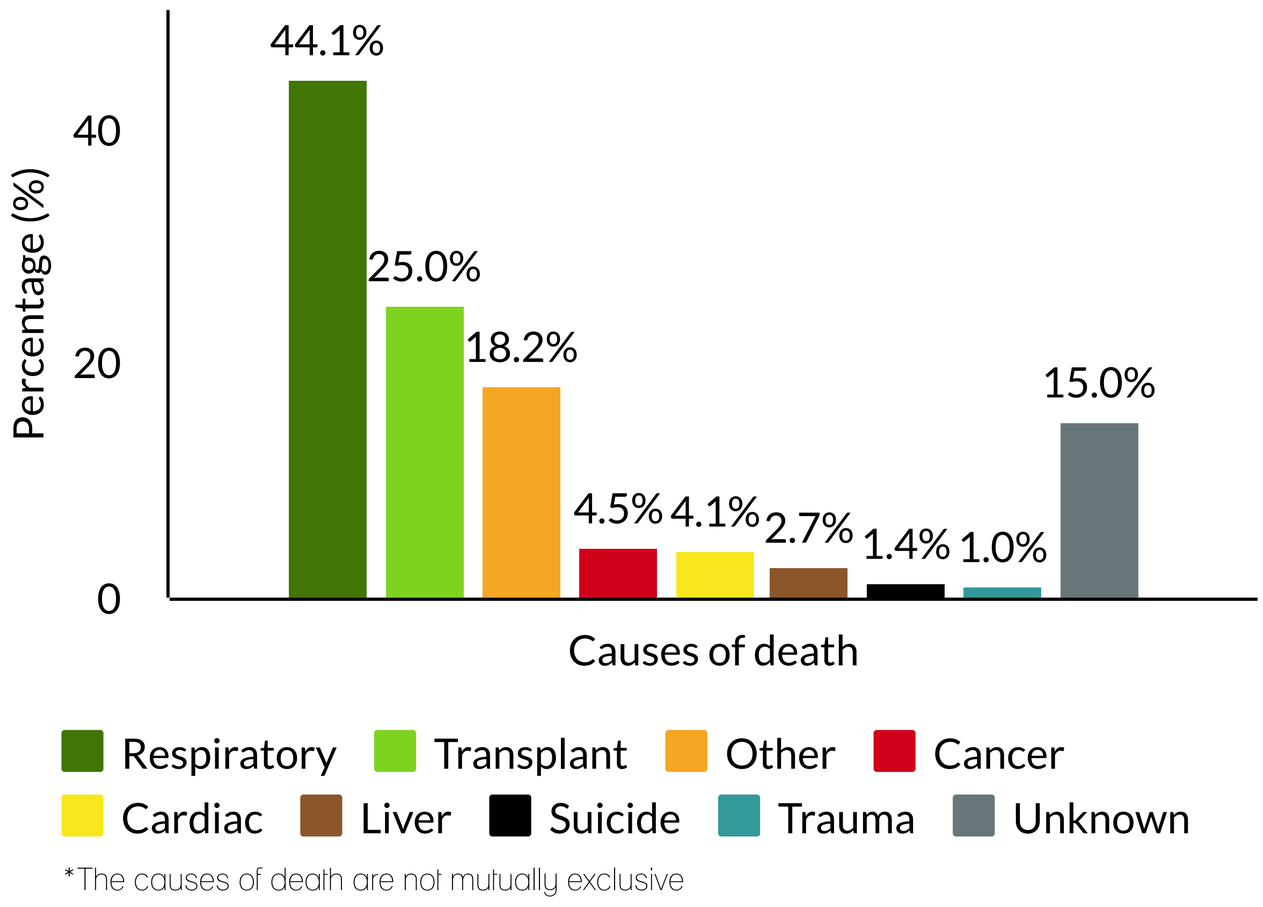
Since inception of the registry, there have been 220 reported deaths, mostly from respiratory causes. About 9.1% of the reported deaths were in children below 18 years.

While survival estimates for people with CF in Belgium are currently not available, the median predicted survival for children born with CF between 2017 and 2021 according to the CF foundation (USA) is about 53.1 years.

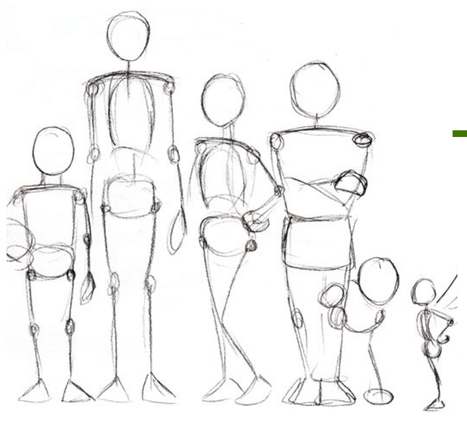
This means that assuming no further improvements in mortality rate or clinical care and ignoring the potential impact of CFTR modulators in younger PWCF, at least half of children born with CF from 2017 to 2021 are predicted to live beyond 53.1 years of age.

Cystic Fibrosis Foundation 2021

Main causes of death*



*The causes of death are not mutually exclusive



Suggested reference: The Belgian Cystic Fibrosis Registry highlights 2021, Brussels, Belgium.
Source : Annual report Belgian Cystic Fibrosis Registry (BCFR) 2021.