The Belgian Cystic Fibrosis Registry

sciensano

Facts and highlights

2016

Objectives

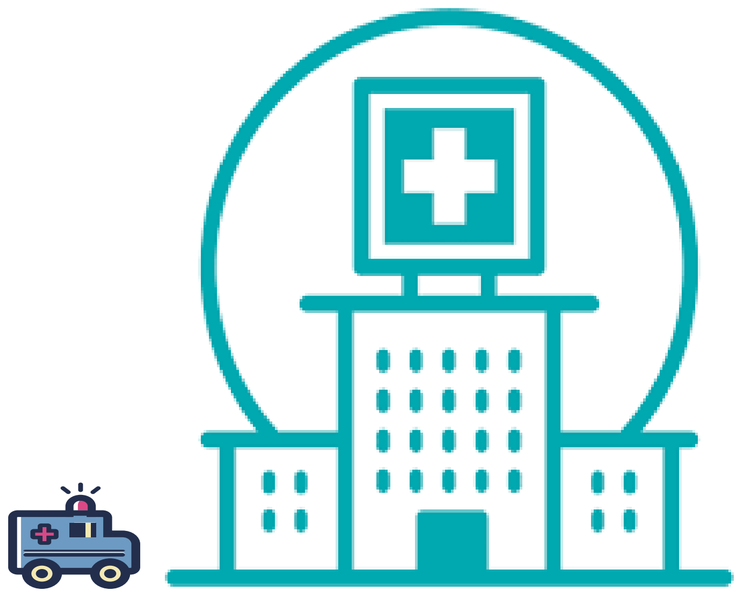
The aims of the CF registry are to : 1) study disease epidemiology among people with CF in Belgium, 2) provide a tool for the assessment of disease management and quality of care for patients with CF, 3) provide a database for scientific research to CF researchers and 4) to participate in international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

Demographics

There were 1275 People With Cystic Fibrosis (CF) included in the CF registry.

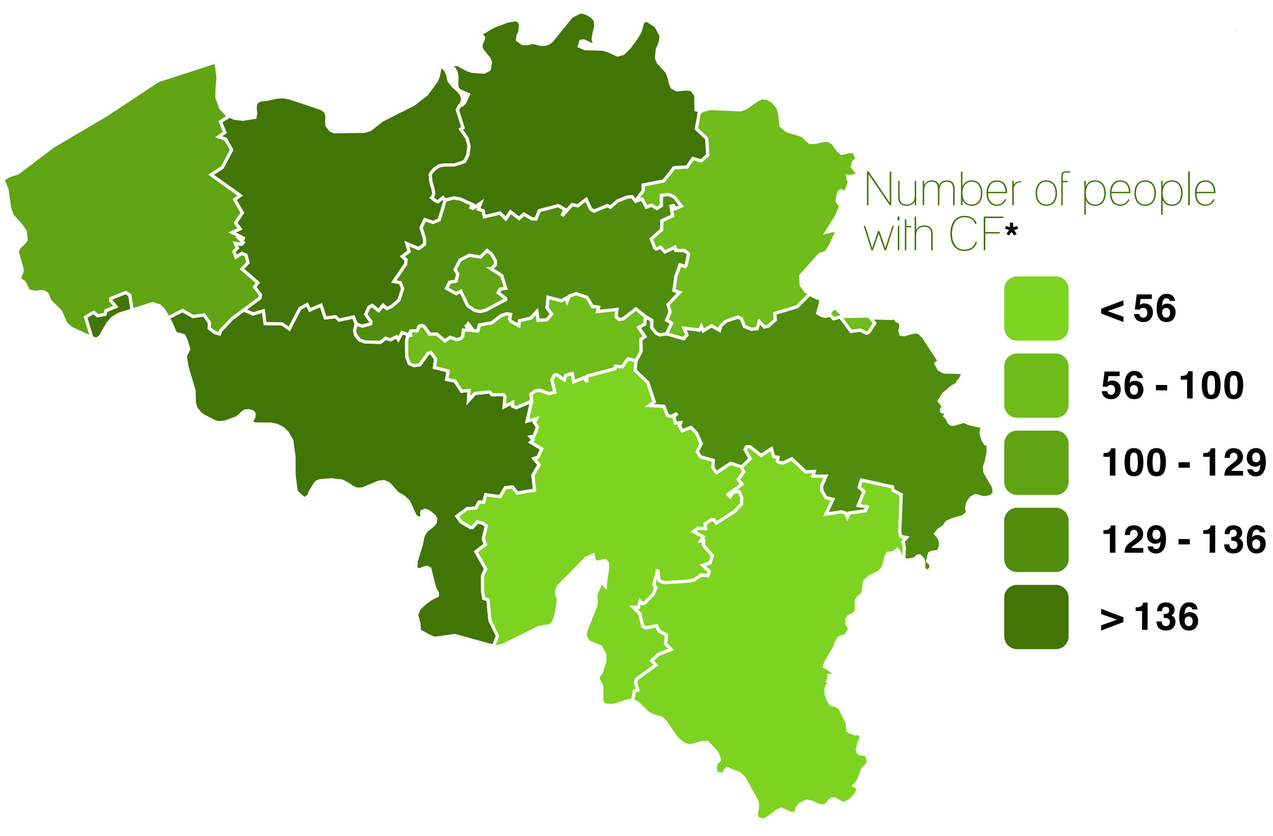
52.0% of the patients are male, 48.0% are female.

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



Each CF reference center has a pediatric and adult clinic.

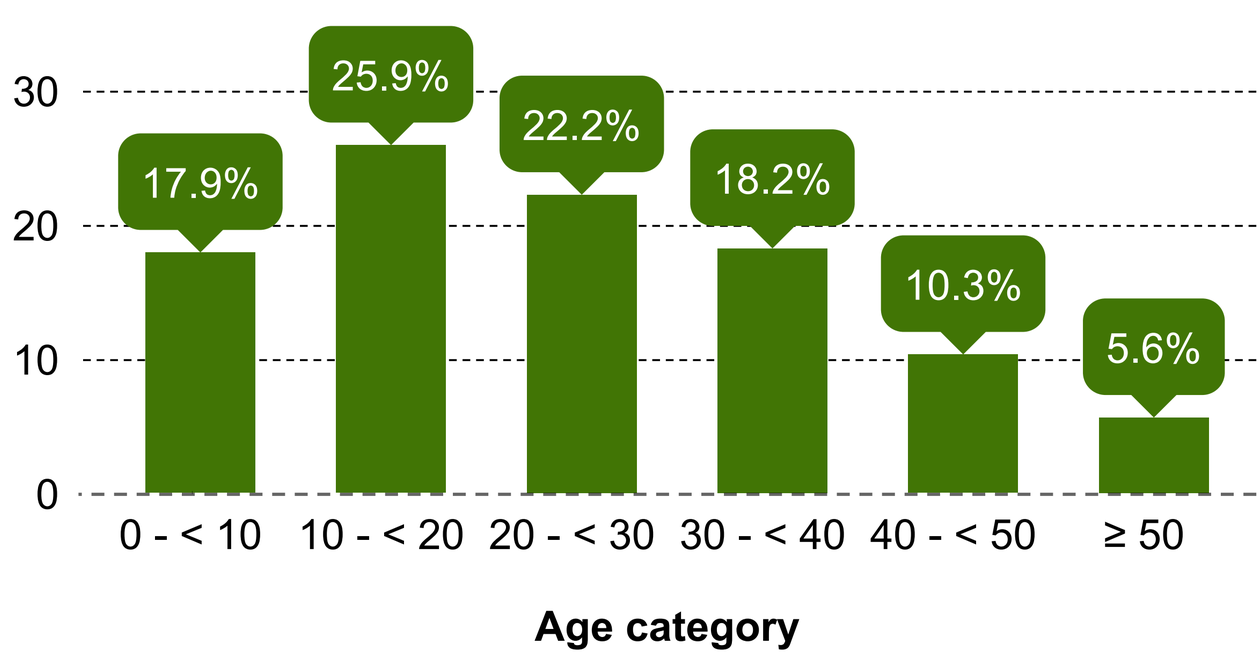
The registry covers about 90 - 95% of CF patients living in Belgium.



* About 13 patients resided outside the country in 2016

The proportion of adults has increased from 38.4% in 2000 to 61.2% in 2016.

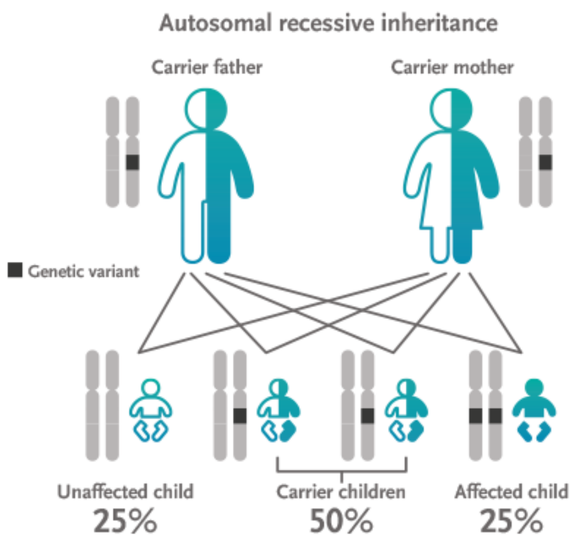
Age distribution



The median patient age is 22.5 years, (22.5 for male and 22.6 for female patients).

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/

There were 23 newly diagnosed CF patients in 2016. Three of the newly diagnosed patients were adults aged 18 years or above.

The median age at diagnosis is 6.0 months in male and 5.2 months in female patients.

median age at diagnosis

5.7

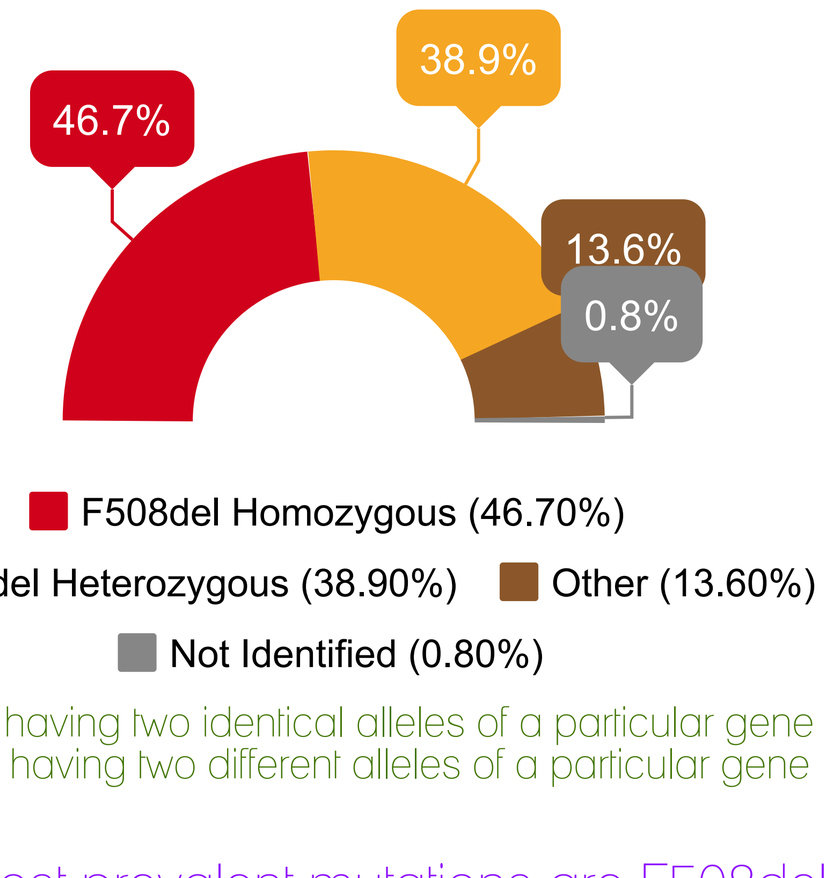
Months

By age 18 years, 95% of all patients had been diagnosed

More than 2000 mutations in the CFTR gene have been identified to date. A majority of these are extremely rare. Not all CFTR mutations lead to CF, and only 336 have been confirmed as disease causing.

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

Almost half of the patients in the Belgian CF registry are F508del homozygous.

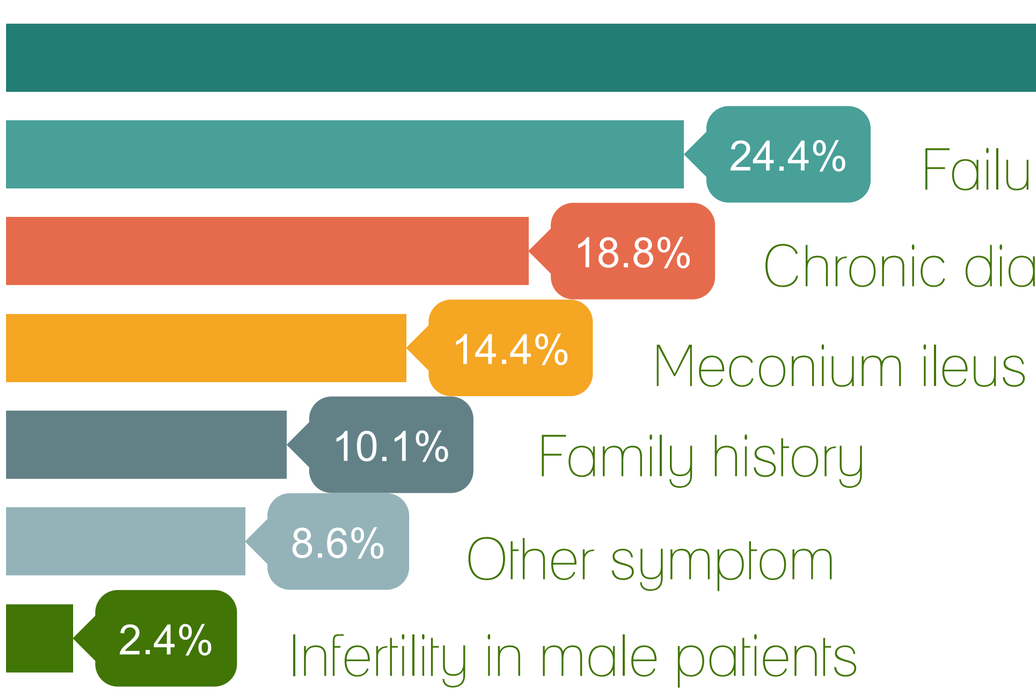


Homozygous - having two identical alleles of a particular gene
Heterozygous - having two different alleles of a particular gene

The most prevalent mutations are F508del (85.6%), G542X (5.2%), N1303K (4.5%), 3272-26A->G (3.5%) and 1717-1G->A (2.9%)

Most patients present with acute or recurrent respiratory symptoms. A national neonatal screening program will be introduced in 2019.

Reasons or symptoms at CF diagnosis*



*Not mutually exclusive

Neonatal screening

17.6%

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.
- A carrier, in this case, is an individual who has by inheritance one defective copy of the CFTR gene and one normal copy. They have no CF, no outward, visible expression of the inheritable disease, but they can transmit it to their offspring.

Growth and nutrition

There have been improvements in BMI across most age categories over the years.
The goal is to have a median percentile of 50 or above.

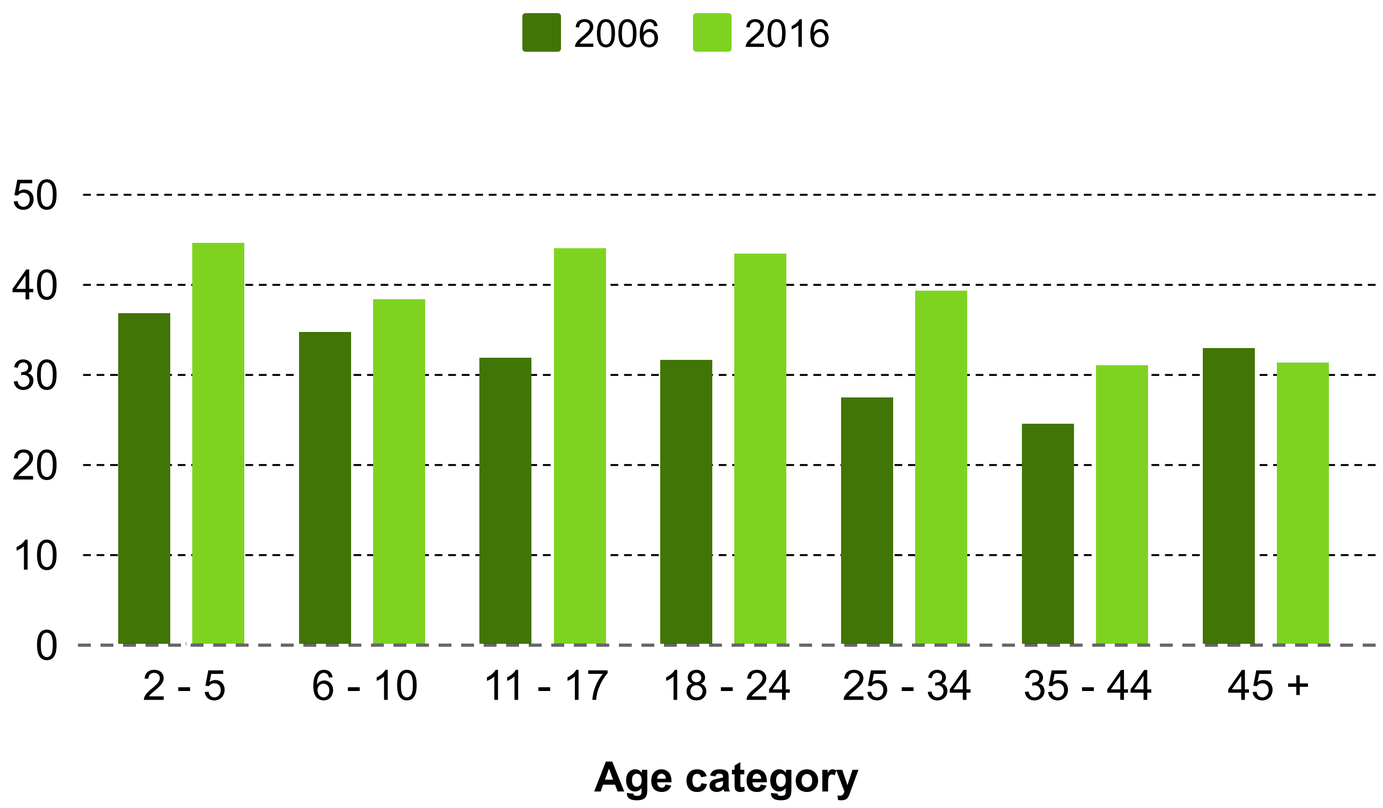
Nutritional care is of great importance for patients with CF. Because of thick mucus, the pancreas is unable to produce and/or carry digestive enzymes to the gut. This leads to poor absorption of proteins, fats and fat soluble vitamins resulting in poor weight gain and growth. Maintaining or achieving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

Adult patients with BMI between 18.5kg/m^2 and 25kg/m^2

73.2%

Median BMI percentile in patients 2 - 20 years

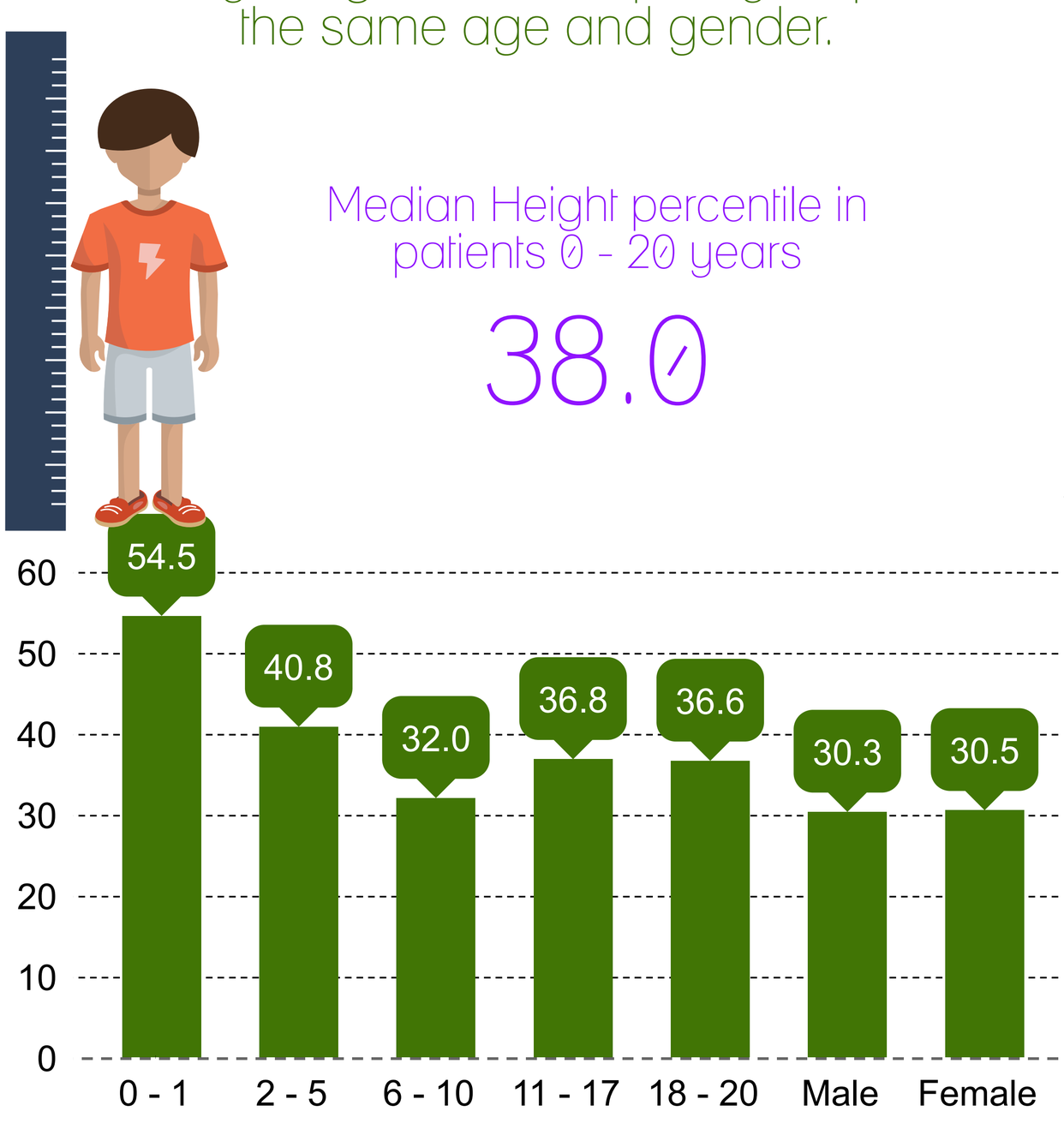
34.9



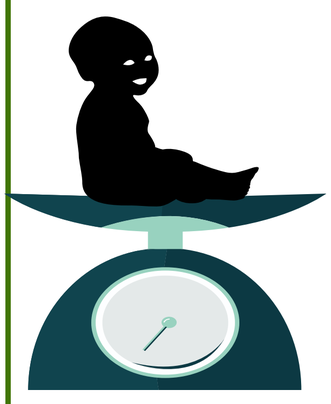
With CF, patients may have stunted growth and may not grow tall as quickly as peers of the same age and gender.

Median Height percentile in patients 0 - 20 years

38.0

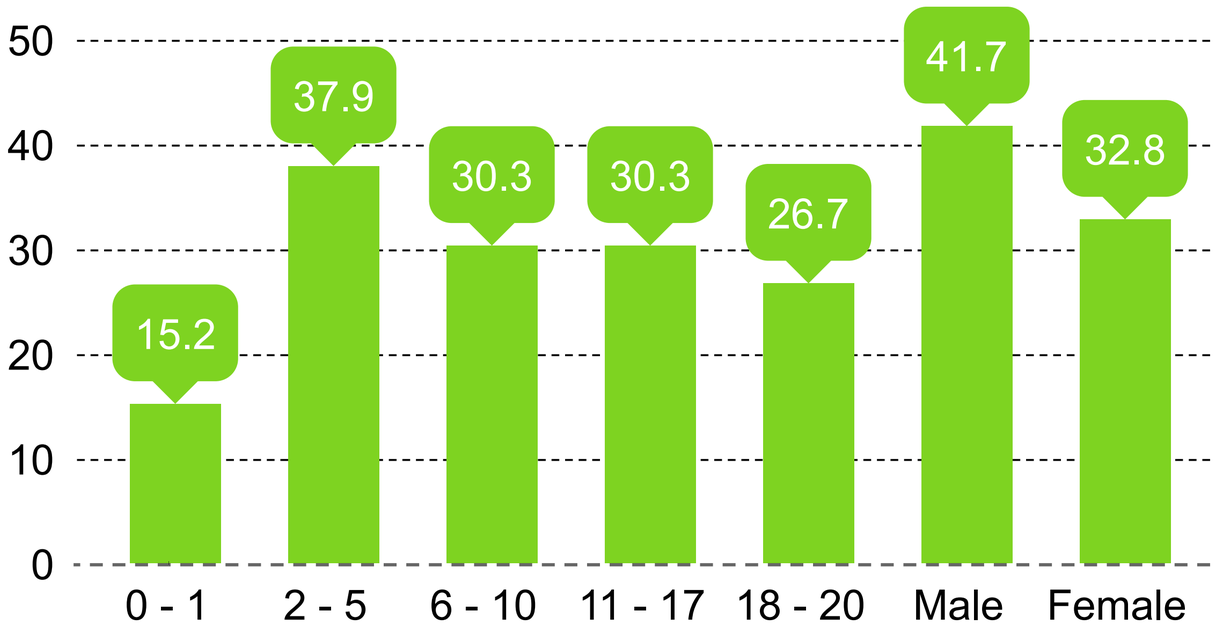


Weight gain is always a challenge in CF. A well balanced high calorie, high protein and high fat diet as well as the intake of pancreatic enzymes are crucial to achieving a good nutritional status.

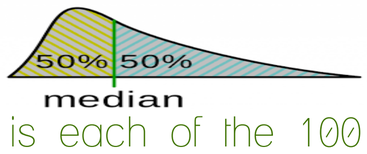


Median Weight percentile in patients 0 - 20 years

31.6



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).

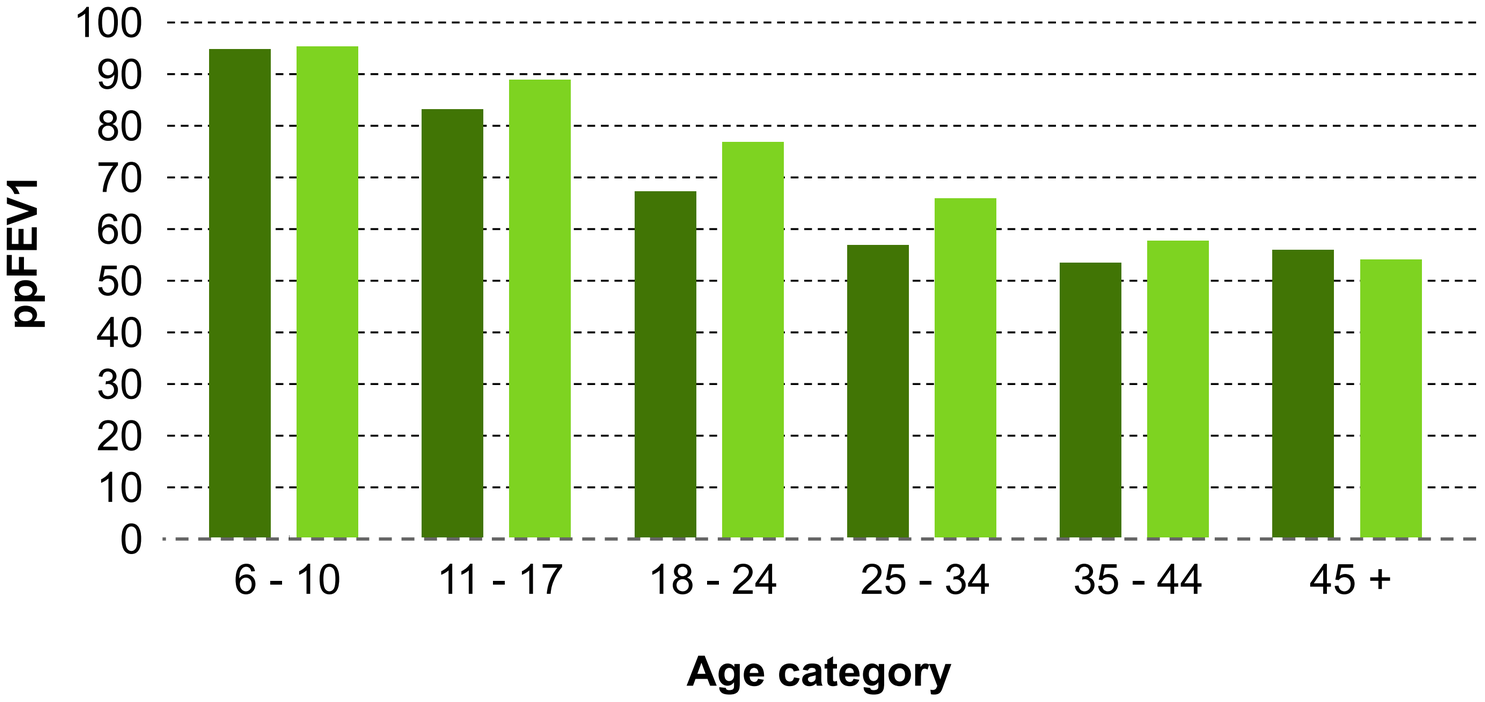
Lung function

In the last ten years, there have been improvements in lung function across most 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 patients 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 patients with the same mutations.

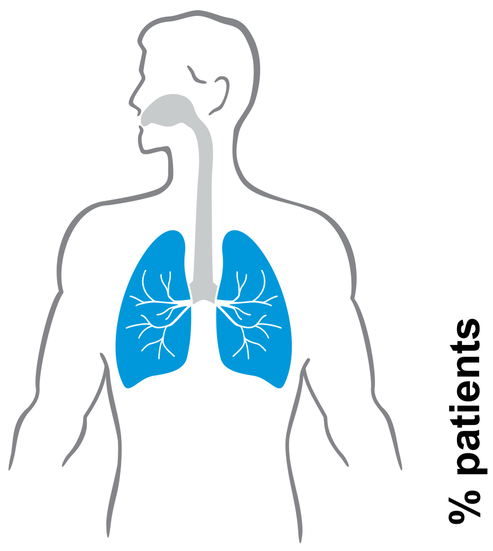
Schluchter MD, 2006, McKone E, 2003

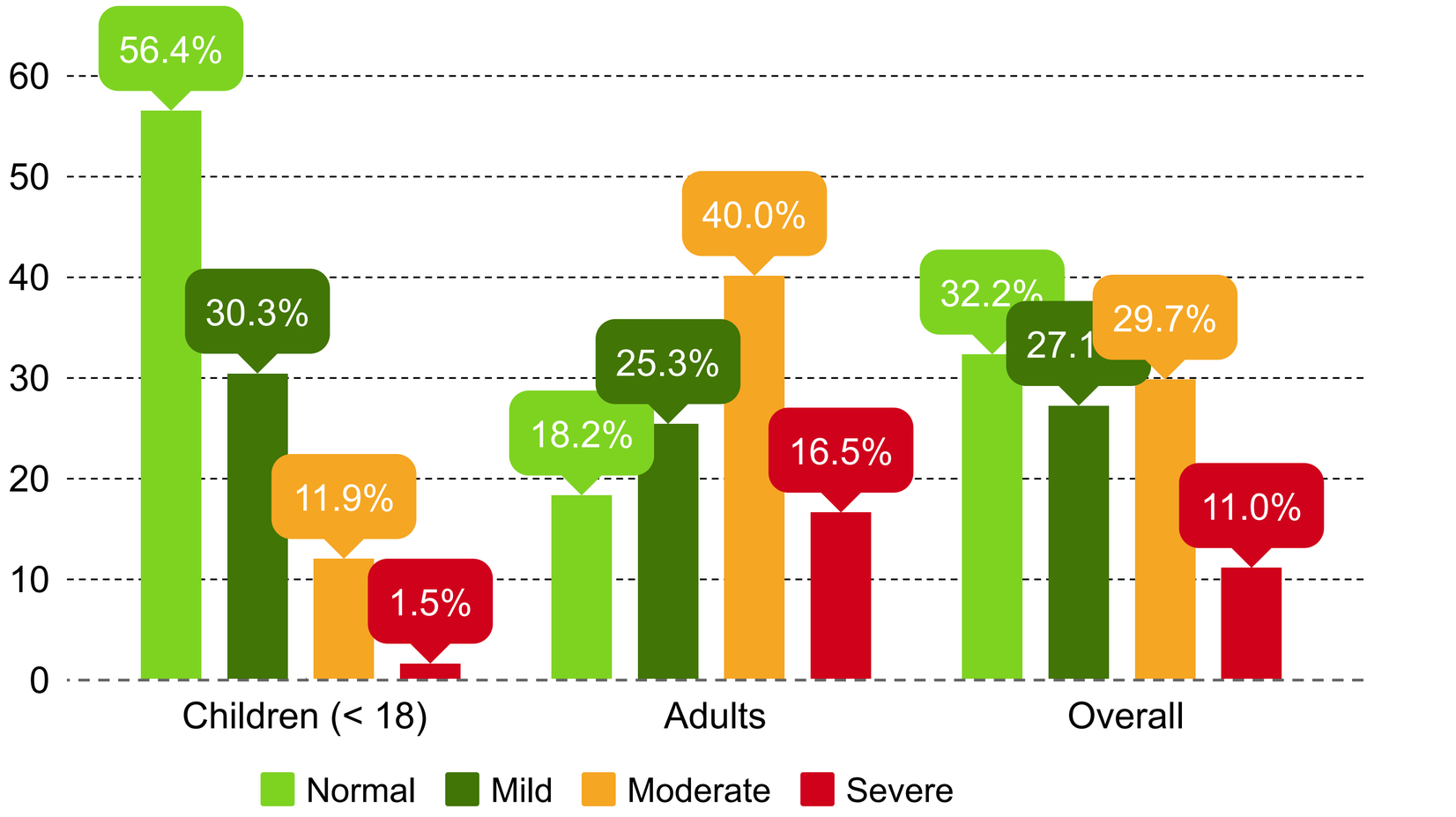
Mean ppFEV1 by age

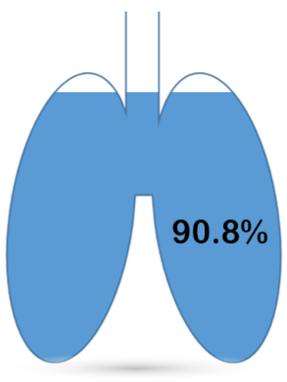


FEV1% predicted values are divided in four classes corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) impairment.

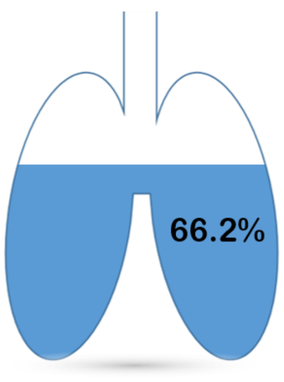
Lung function severity classification



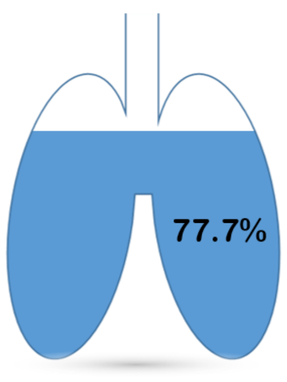




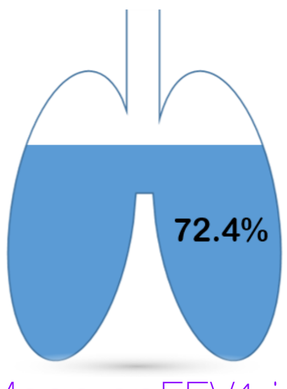
Mean ppFEV1 in children



Mean ppFEV1 in adults



Mean ppFEV1 in males

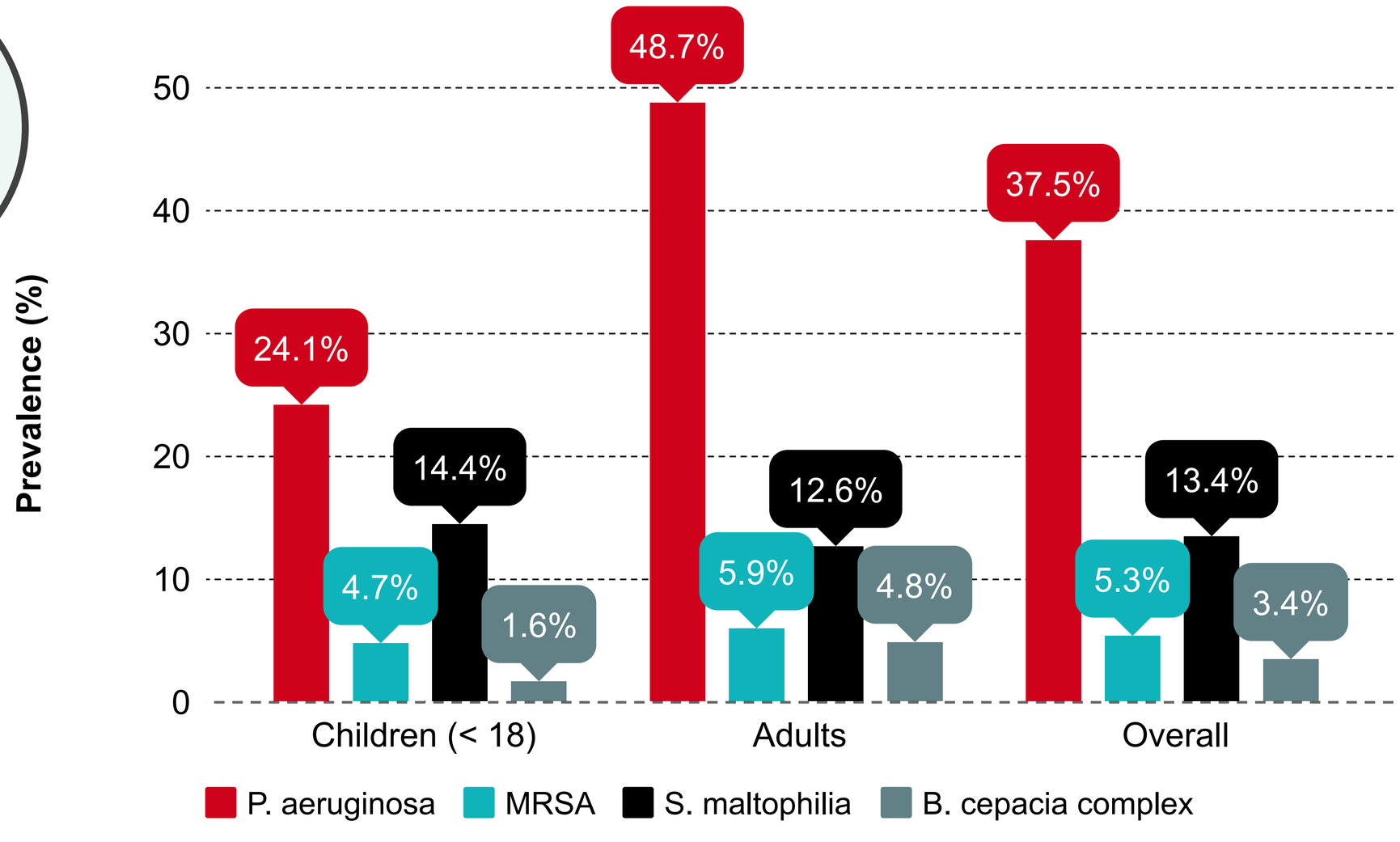


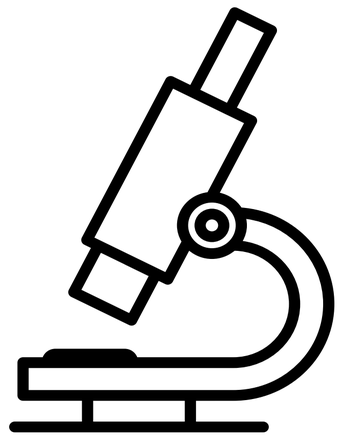
Mean ppFEV1 in females

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.

Prevalence of infections in 2016





MRSA - Methicillin Resistant Staphylococcus aureus

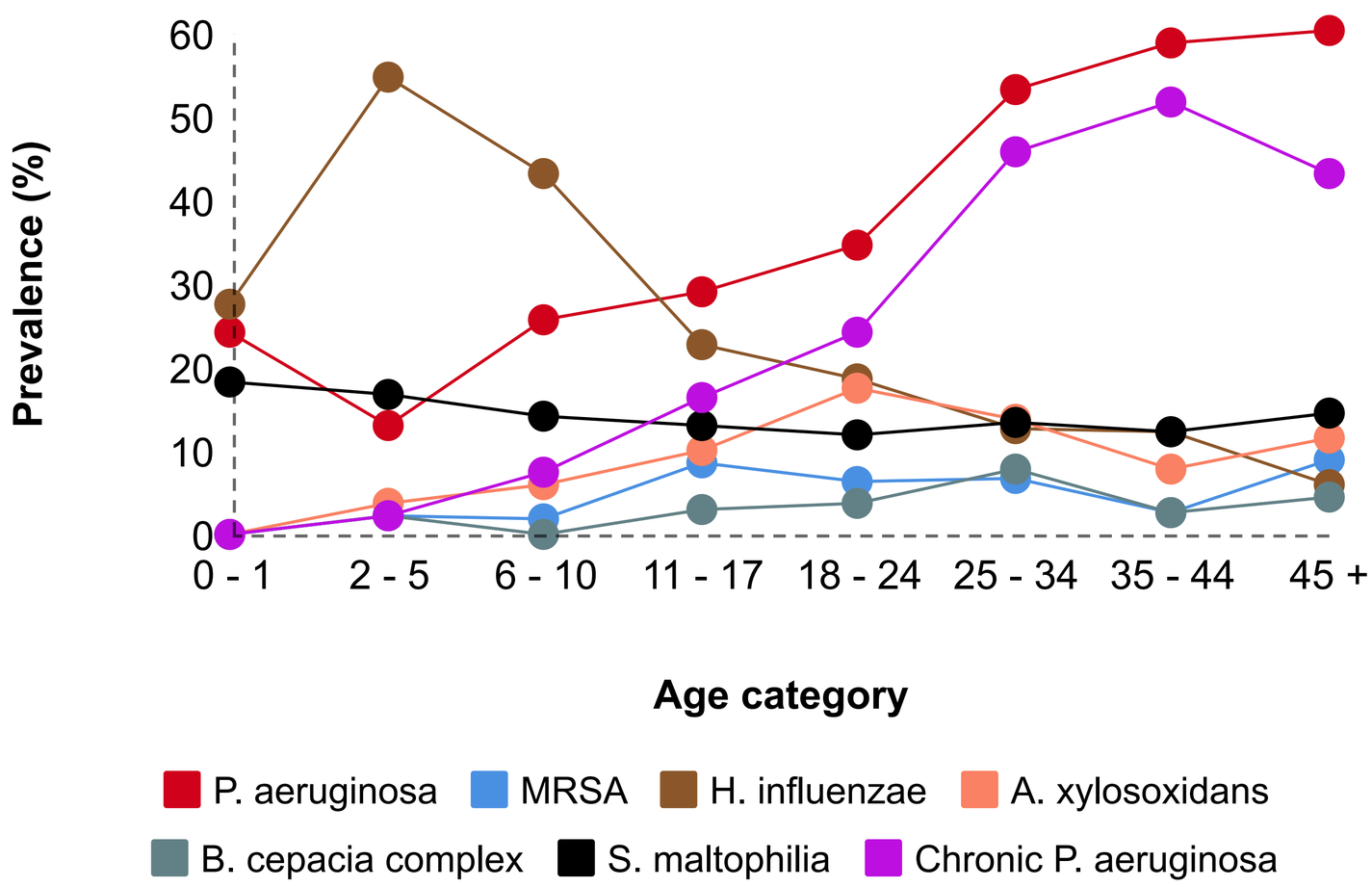
Sputum samples, throat swabs and bronchoalveolar lavage cultures are taken to monitor the presence of pathogens. At least 82.1% of the patients had 4 or more cultures taken during the year 2016.

Bacterial infection may occur very early in the natural history of the disease. 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 patients with CF may also be chronically colonized by fungi like Aspergillus fumigatus.

Hart CA 2002, de Vrankrijker AM, 2011

Age related prevalence of infections



Definitions :

- The forced expiratory volume in one second (FEV1) is the amount of air that a person is able to expire 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.

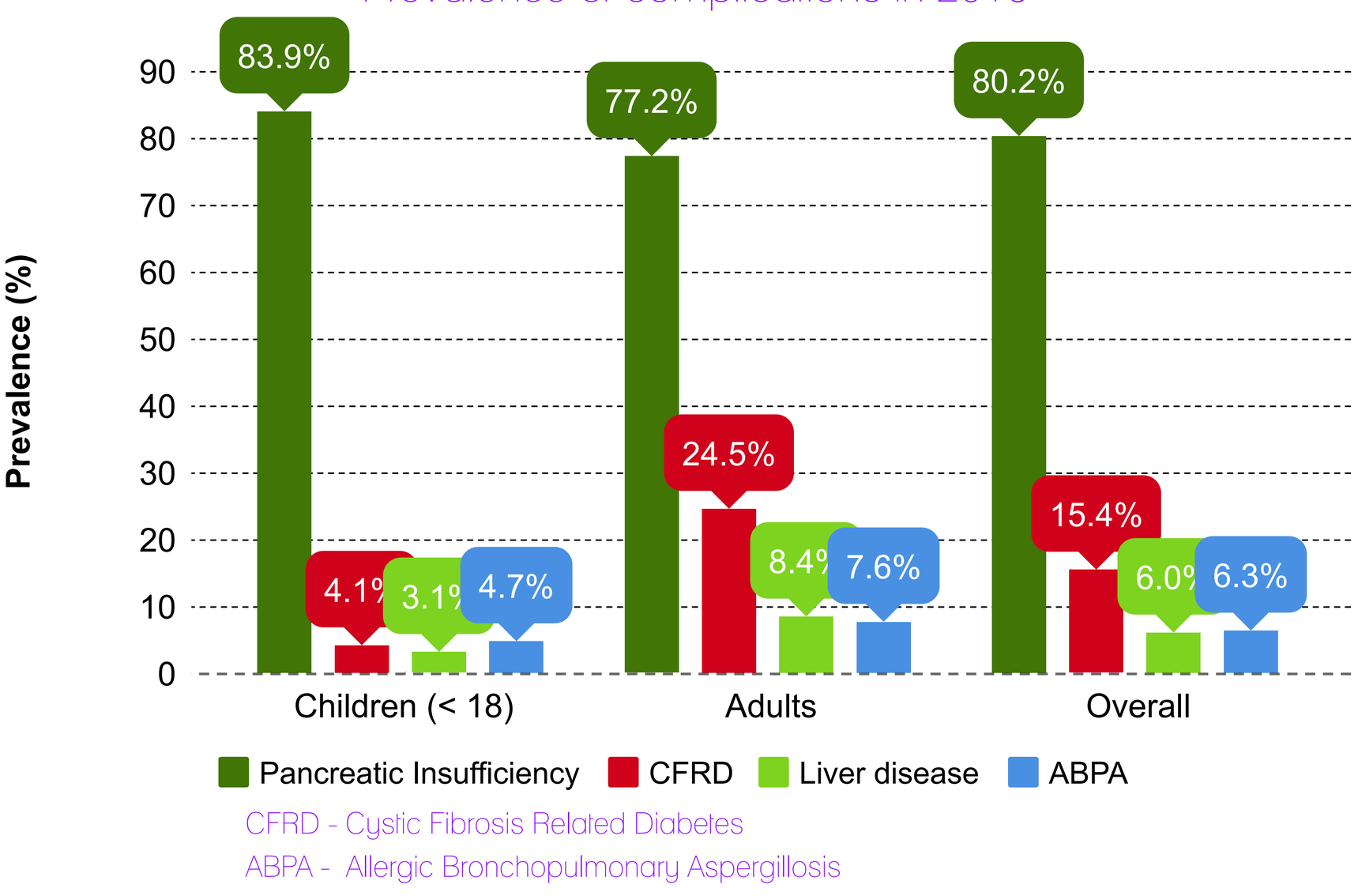
Complications

Cystic Fibrosis affects the respiratory, digestive, and reproductive systems with variable degrees of severity.

The defective chloride channel in CF causes a range of disturbances within the human body. In CF, the transport through the cell wall of chloride, other ions and water are disturbed. 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 2016



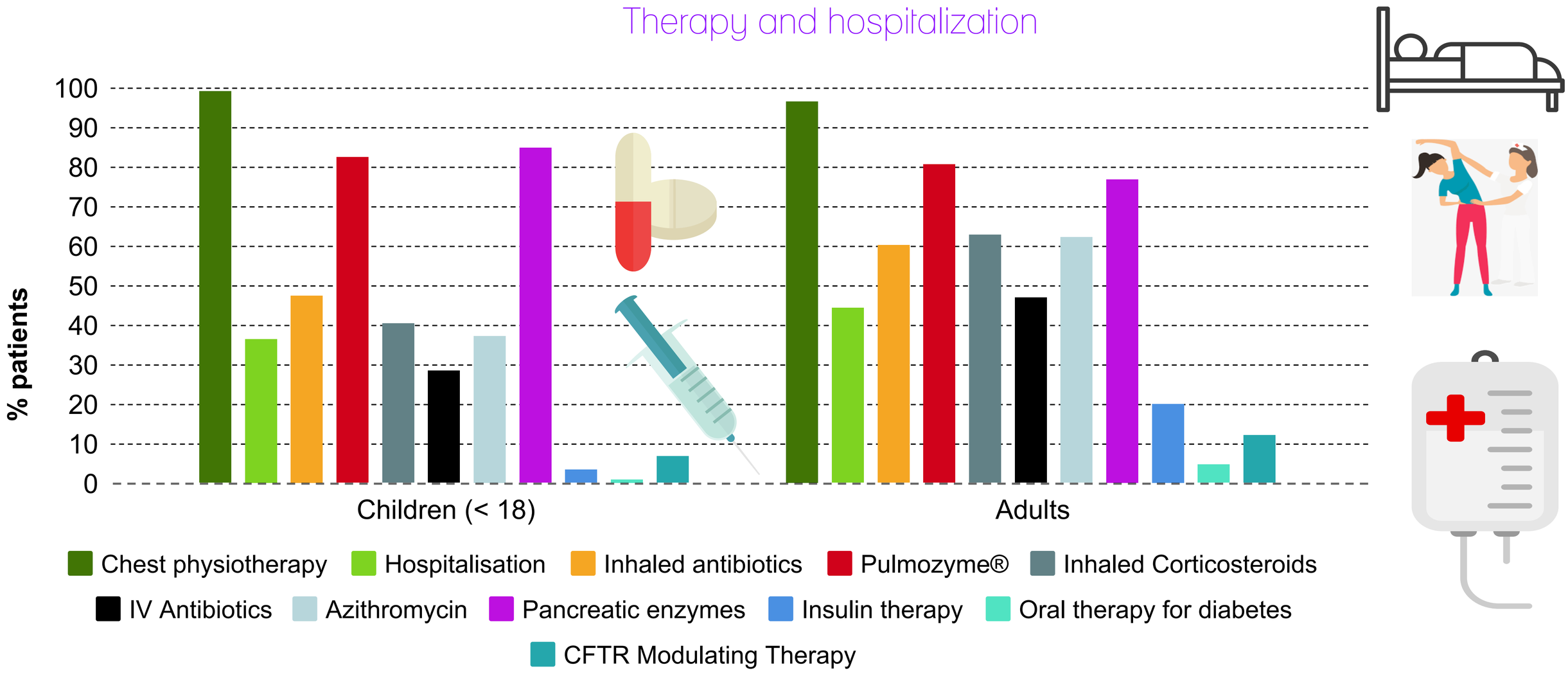
CFRD - Cystic Fibrosis Related Diabetes

ABPA - Allergic Bronchopulmonary Aspergillosis

Therapy and hospitalisation

Till today no definitive cure for CF exists. Treatment of CF remains mostly based on preventing or reducing symptoms in order to avoid complications or to stabilize them. There are now new therapies in the pipeline that target the basic defect. During the year 2016, 85.4% of the patients had at least 4 required visits to the clinic.

Therapy and hospitalization



Definitions :

- ABPA is an allergic reaction to Aspergillus fumigatus a fungus that colonizes the airways of some people with CF.
- CFRD - The malfunctioning of the endocrine part of the pancreas by fibrosis leads to an insufficient secretion of insulin leading to diabetes.
- Exocrine pancreatic insufficiency 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.
- 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).

Transplants and Cystic Fibrosis

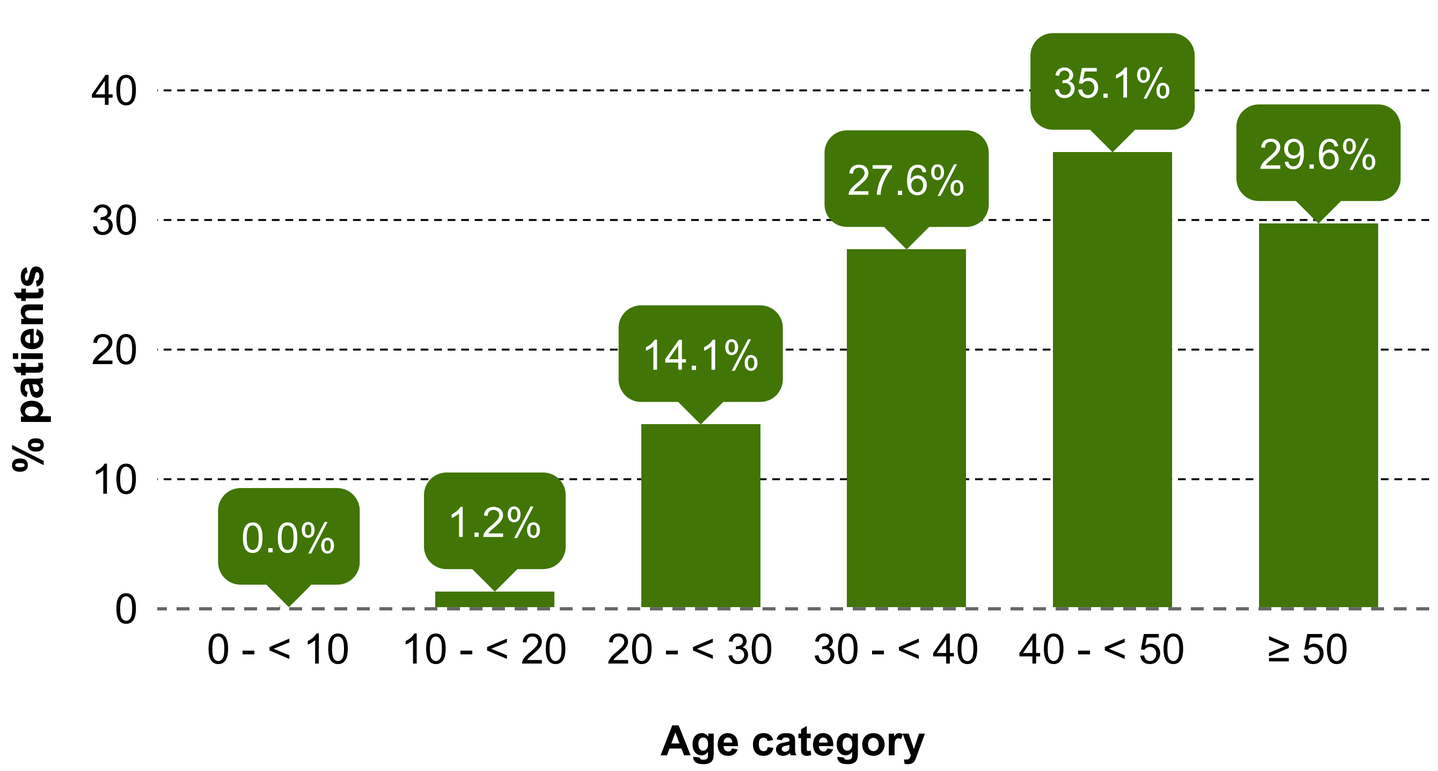
When a patient with CF develops severe and progressive lung disease, lung transplantation may become an option. A lung transplant is indicated only for patients who have a severe disease, who have exhausted all other forms of conventional medical treatment and whose short term survival is compromised.

The registry records show that since its inception in 1998, at least 248 patients, 117 male and 131 female, have benefited from transplantation; either single or multiple.

In 2016, there were 175 patients (82 male, 93 female) who had received a transplant.

The median age (range) at the last consultation was 36.3 (12.6 – 67.7) years. 97.7% of these transplant patients were adults.

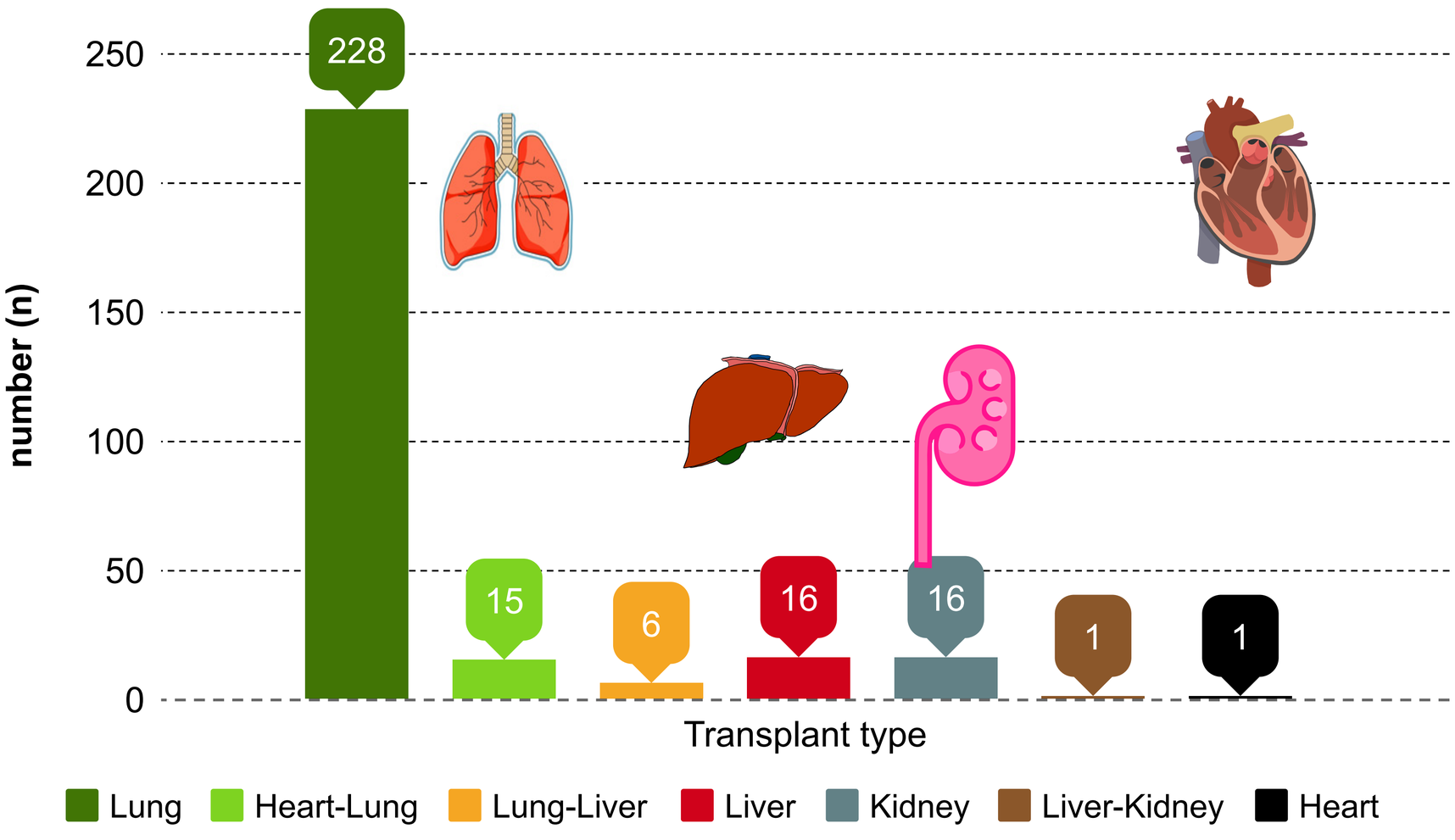
Proportion of transplanted in each age category



In 2016 at least one in every five adult patients was a transplant patient.

The most frequent organ transplant done to Cystic Fibrosis patients in Belgium is the lung transplant. A few patients will need other types of organ transplants such as a liver or kidney. About 283 transplants have been reported since the inception of the registry.

Type of transplant



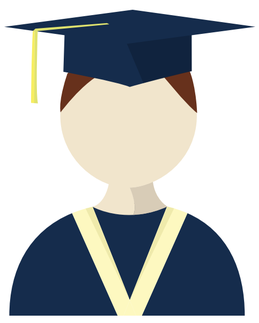
Life statistics

People with CF are living longer. This introduces new challenges and expectations alike. Despite their therapy burden, they are now studying, graduating and taking up a career either part-time or even full-time and some are raising a family. They are thus taking up roles in society that were previously less attainable by cohorts decades back.

In 2016, almost half of the adult patients, 18 years and above had a full-time or part-time job.

49.1%

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



76.9%

There have been at least 278 biological children reported from 170 patients since the start of the registry. In 2016, 148 of these patients were alive and there were 17 children born of a CF parent.

278

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 novel treatments, including the CFTR treatments that are in the pipeline, people with CF continue to have better survival and life expectancy and with better quality of life.

There have been 170 reported deaths to the registry, with the youngest at 0.6 years and the oldest case at 76.9 years.

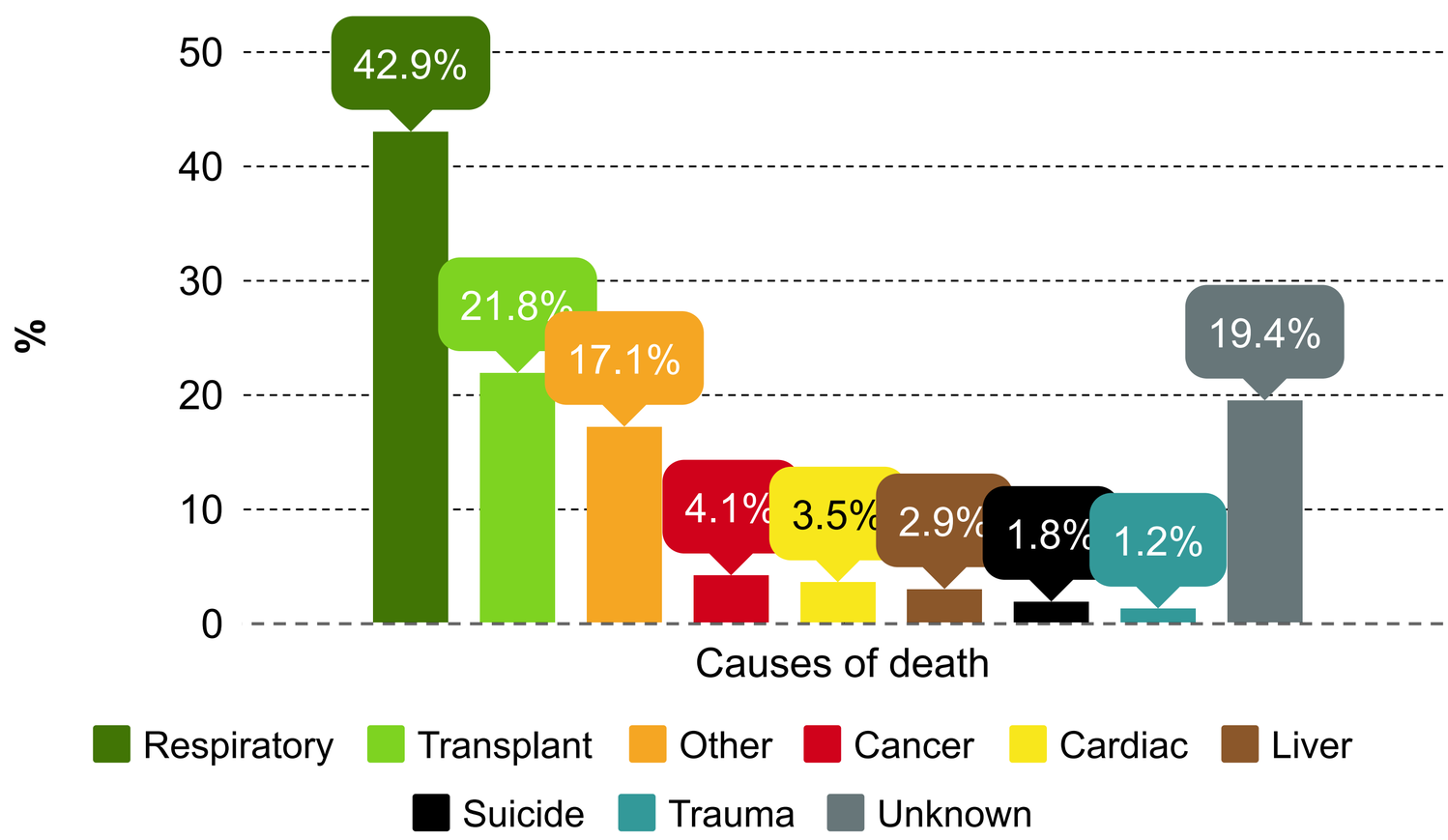
Eighteen (10.6%) of the deaths were in children below 18 years while 8 (4.7%) of the deaths were in children younger than ten years.

The median predicted survival for children born with CF in 2016 is about 47.7 years.

This means that at least 50% of children born with CF in 2016 will live to be 47.7 years or older.

Cystic Fibrosis Foundation 2016

Main causes of death*



*The causes of death are not mutually exclusive

Suggested reference: The Belgian Cystic Fibrosis Registry highlights 2016, Brussels, Belgium.

Source : Annual report Belgian Cystic Fibrosis Registry (BCFR) 2016.