WETENSCHAPPELIJK INSTITUUT
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BMR | RBM

THE BELGIAN CYSTIC FIBROSIS REGISTRY

SUMMARY REPORT 2009

BMR Belgisch Mucoviscidose Register
RBM Registre Belge de la Mucoviscidose

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http://www.wiv-isp.be/epidemio/epien/index20.htm

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What is Cystic Fibrosis?

Cystic Fibrosis (CF) is a hereditary disease with autosomal recessive transmission: only subjects who have inherited two disease causing mutations – one from each parent - are affected. It has a prevalence of 1 in 2850 live births in Belgium (1).

The disease is caused by the alteration (mutation) of the *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) gene which is located on the long arm of chromosome 7. More than 1500 mutations have been identified in the *CFTR* gene since its discovery in 1989. The *CFTR* gene codes for the CFTR protein. This is an ion channel involved in the regulation of chloride ion transport across the cell membrane. It is mainly found in the cell membranes of the respiratory and digestive tract, the sweat glands and the reproductive tract. The dysfunction of the CFTR protein leads to the production of sweat with a high salt content and mucus secretions with an abnormal viscosity causing dysfunction of many organs such as the lungs, pancreas and liver.

In the respiratory tract, thick mucus production results in persistent cough caused by chronic infection and inflammation leading to severe bronchial obstruction and finally lung destruction.

In the pancreas, the sticky exocrine pancreatic secretions lead to obstruction and blocking of the ducts with secondary damage to the secretory gland tissue. Diminished secretion of pancreatic enzymes leads to fat and protein malabsorption causing steatorrhea (fatty stools) and failure to thrive. Fat malabsorption also causes deficiency of fat soluble vitamins (A, D, E and K).

Most of the children with CF have a history of recurrent chest infections, steatorrhea and failure to thrive.

Newborns with CF can be affected by meconium ileus: intestinal obstruction with vomiting, abdominal distension and delay in passing the first meconium stools. The spectrum of presenting features is very wide and can vary with the age at time of clinical presentation. The diagnosis is usually made in early childhood but in some patients with late or milder symptoms it can occur later into adulthood.

Although there is no neonatal CF screening program in Belgium yet, infants with CF can be identified in the first weeks of life by assessing their blood immunoreactive trypsin (IRT) combined with the most frequent *CFTR* mutations.

The sweat test remains the gold standard for the diagnosis of CF. In the majority of patients with typical features, the sweat test is diagnostic. It reveals an excessive quantity of chloride (salt) (> 60 mEq/L). In atypical forms, the sweat test chloride levels can fall into the intermediate range (30-60 mEq/L).

It is advised to perform genotyping in all patients with CF, to identify the CF causing mutations. The most common mutation in Belgium is F508del.

Today there is no causal cure for CF, treatment is symptomatic and is essentially based on respiratory (e.g. physiotherapy, inhalation therapy, antibiotics), digestive and nutritional management (e.g. pancreatic enzymes and hypercaloric diet).

Due to medical progress and intensification of the care for patients with CF, the quality of life and the life expectancy have increased. Promising therapies aiming to correct the basic defect are being evaluated.

CF Patient care in Belgium

Since 1999, 7 CF reference centres have been accredited by the National Institute for Health and Disability Insurance (INAMI - RIZIV[1]) and receive financial support. An annual care and revalidation agreement (CF convention) for patients with CF is signed between each of the 7 CF reference centres and the RIZIV-INAMI (2,3). Each centre has specific expertise in CF care and ensures multidisciplinary follow-up of the patients in order to provide optimal medical, paramedical, psychological and social care to the patient and their relatives.

Most of the persons with CF in Belgium are followed in one of the 7 national CF reference centres and are recorded in the national CF Registry.

The Belgian Cystic Fibrosis Registry (BMR-RBM)

The intent of a CF Registry is to include, in a single database, the entire population of patients with CF, within a defined geographical area. In 2009, 1129 persons with CF attending a Belgian CF reference centre were registered in the BMR-RBM.

The BMR-RBM was started in 1999 as a scientific project initiated by the Medical Committee of the CF-patient organisation (BVSM-ABLM) and the 7 CF-reference centres in Belgium collecting data of 1998. It was coordinated by the Vrije Universiteit Brussel (VUB). The main sponsor was the CF-Patient organisation, the cosponsor was the Fund Alfonse and Jean Forton of the King Baudouin Foundation. The VUB sponsored the overheads. After 5 years the scientific project came to an end and new sponsors were contacted.

In 2006, the RIZIV-INAMI became the principal sponsor and the Registry was transferred to the section of Public Health and Surveillance of the Scientific Institute of Public Health (IPH). Since then, the IPH ensures the collection and the management of the data under the supervision of the board of the BMR-RBM and the guidance of a scientific steering group. The board consists of a physician from each CF centre and the scientific collaborators of the IPH. The scientific steering group holds all stakeholders (representatives of the INAMI-RIZIV, patient association, CF Centers and scientific collaborators of the IPH).

The Belgian CF Registry lies since 2006 within the framework of the CF convention described above. Participation in collection of data for the CF Registry is one of the obligatory tasks of the CF reference centres.

The objectives of the Registry are :

1 | to study epidemiological aspects of CF in Belgium

2 | to provide an evaluation tool for the assessment of the management and quality of care for patients with CF

3 | to provide a database for scientific research to CF researchers

4 | to participate to the European CF Patients Registry (ECFS-PR) (4) and other international projects.

[1] BVSM-ABLM : Belgische Vereniging voor Strijd tegen Mucoviscidose
Association belge de Lutte contre la Mucoviscidose

Prior to the registration, the physicians provide each patient and their parents (or legal representative) information about the objectives of the Registry.

The patients are only included in the Registry after signing an informed consent. They are identified by a unique code. Their names are never transferred to the Registry.

The clinical data is collected by the treating physician from medical records and consists of more than 200 variables.

These are divided into 2 sections:

1 | The core data contains demographic data, age of CF diagnosis and initial symptoms, genotype, sweat test and nasal transepithelial potential difference results. This data is collected when the patient enters the Registry and is updated if necessary during follow-up years.

2 | Yearly follow-up sheets collect clinical data (height, weight), lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow 25-75% (FEF 25-75)), complications that occurred or still active during the registration year, microbiology, treatments as well as social data.

SUMMARY OF REPORT 2009

The data presented in this report relates to the population observed in 2009 and also shows cumulative data since the start of the data registration in 1998 for some selected attributes. The data from the previous years of the Registry is updated each year and we always present the most recent information.

1 | DEMOGRAPHIC DATA

Table 1 | Demographic data since the start of the Registry

	Number of patients	New diagnoses	Median age (years)	Age range (years)	Males (%)	Adults ≥ 18 yrs (%)	Number of lung (-heart) transplants	Deaths reported
1998	566	37	14.9	0.0 - 55.6	50.4	38.5	8	5
1999	604	26	15.2	0.2 - 56.2	52.5	39.1	4	12
2000	761	35	14.8	0.1 - 57.3	51.8	37.7	10	9
2001	785	28	14.5	0.0 - 58.6	52.9	38.9	12	9
2002	825	31	15.3	0.3 - 58.9	52.8	42.3	11	10
2003	855	32	15.8	0.0 - 55.0	54.3	43.4	9	14
2004	887	35	16.6	0.1 - 55.9	53.9	45.6	12	8
2005	945	47	17.5	0.3 - 56.8	52.1	48.1	10	3
2006	1026	52	17.4	0.2 - 60.9	51.4	48.6	14	7
2007	1057	32	17.4	0.0 - 62.0	51.4	49.3	16	8
2008	1087	25	18.1	0.1 - 67.4	51.7	50.3	16	5
2009	1129	39	18.5	0.1 - 68.2	52.0	51.1	10	10

Table 1 shows that 1129 patients were followed by the multidisciplinary teams of the reference centres in 2009. The number of patients enrolled in the Registry has doubled since 1998. In 2009, the median age was 18.5 years with an age range from 0.1 to 68.2 years and the proportion of males was 52.0%. The percentage of adults has risen steadily since the start of the Registry and now represent 51.1% of the total number of patients. In 2009, 10 patients received a lung transplant and one a liver transplant. There were 39 new diagnoses and 10 deaths reported.

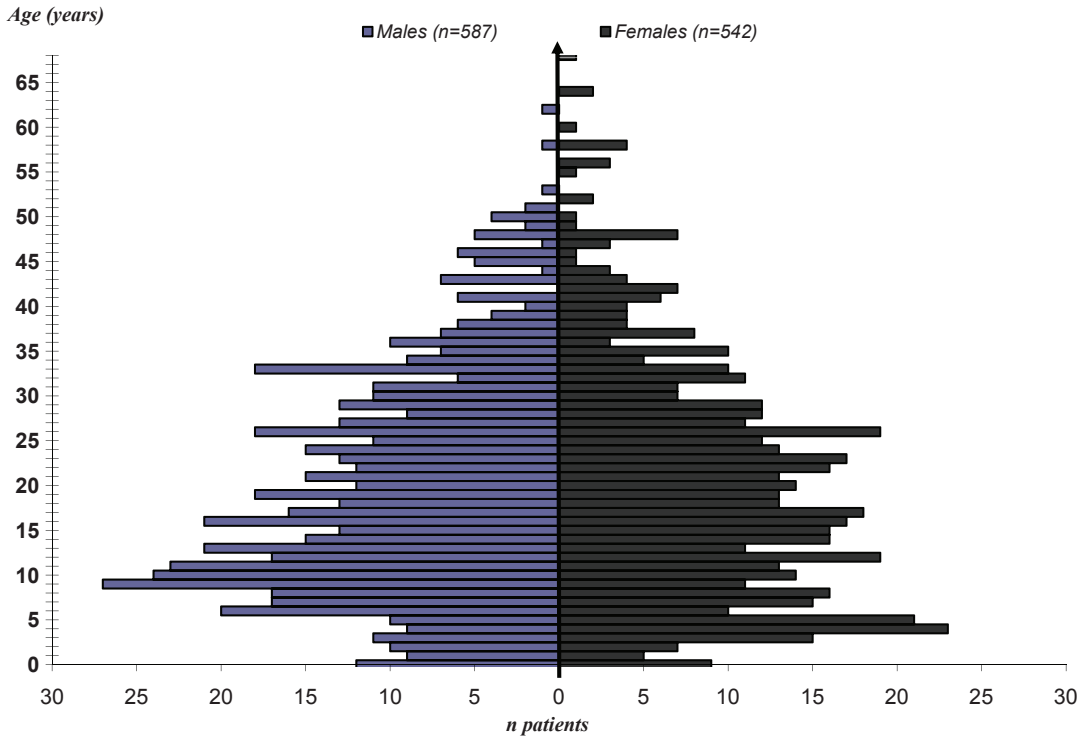

Figure 1 | Age distribution related to gender for patients with CF on December 31, 2009

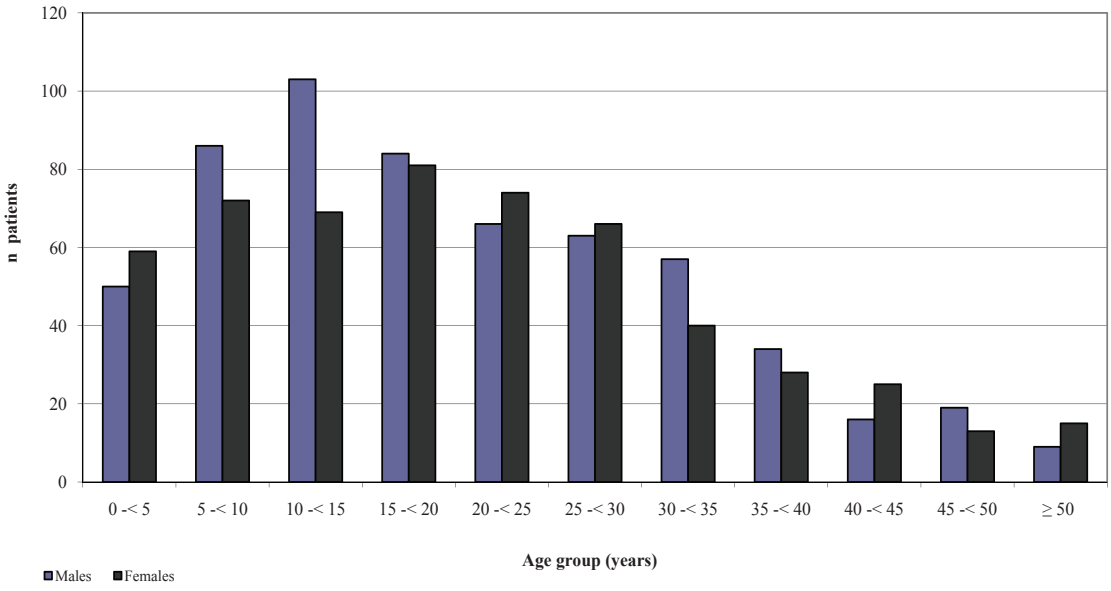

Figure 2| Gender distribution of patients with CF by 5 year age groups

Figures 1 & 2 show the age distribution of the patients with CF at December 31, 2009 by gender. The age distribution over the years is shown in figure 3. It shows an increase in the total number of patients and also in the proportion of patients aged 40 years and above. Whereas 7 (1.2%) patients were older than 40 years in 1998, this number reached 96 (8.5 %) in 2009. In 2009 more than half of the registered patients were adults (figure 4)

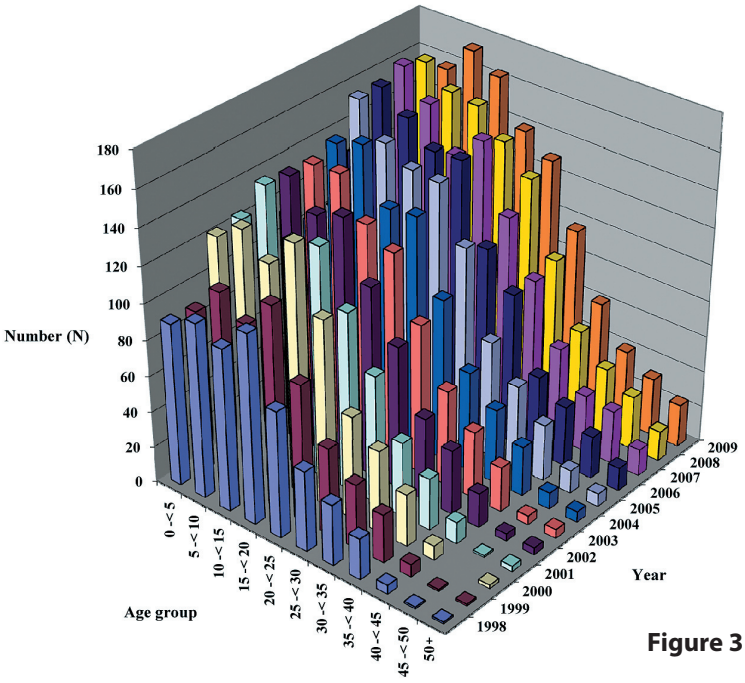

Figure 3 | Number of patients by age categories and by registration year

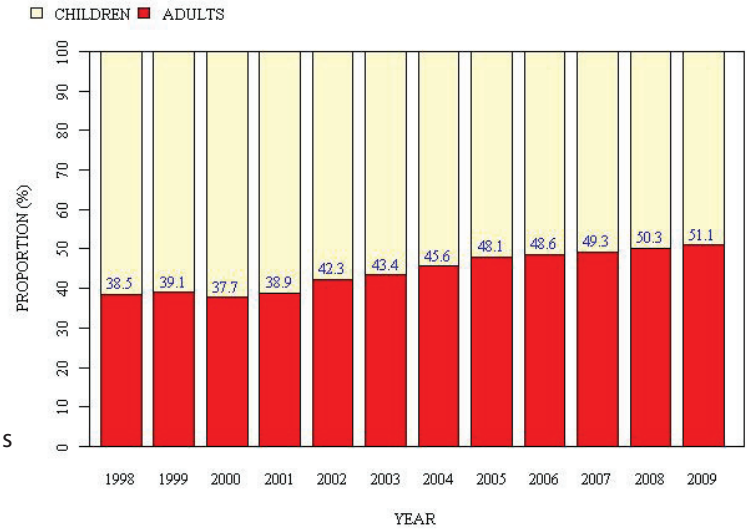

Figure 4 | Proportion of children and adults over the years

2 | DIAGNOSIS

2.1 | Diagnostic signs

In a patient with suggestive symptoms, a family history of cystic fibrosis or a positive neonatal screening test, the diagnosis of CF is confirmed by an abnormal sweat test and/or the identification of two mutations in the *CFTR* gene. Although no national neonatal screening program was implemented in Belgium, some children were screened for CF. Most patients present with a combination of respiratory and/or gastrointestinal symptoms. Chronic cough, recurrent chest infections, chronic sinusitis are the most common respiratory signs at presentation. Common gastrointestinal symptoms include meconium ileus (obstruction of the bowel with sticky secretions in the newborn infant), chronic diarrhea and failure to thrive due to malabsorption.

Less frequently, salt loss, jaundice or a rectal prolapse are the first diagnostic signs. In some cases, the diagnosis of cystic fibrosis is delayed until adulthood. Most of these patients are expected to have had a milder clinical course.

The diagnostic signs or clinical presentation are illustrated in table 2. In the Registry, It is possible to report more than one diagnosis sign or symptom for the same patient. Over the years, the commonest clinical presentation of CF remains acute or recurrent respiratory problems. Other common features at presentation were failure to thrive, chronic diarrhea/steatorrhea and meconium ileus. About 17.0% of the patients were diagnosed via neonatal screening test.

Table 2 | Reasons for CF diagnosis

	1998	2003	2009
Acute or recurrent respiratory problems	43.2	43.4	43.7
Failure to thrive	23.5	22.9	25.0
Chronic diarrhea/steatorrhea/malabsorption	27.5	24.0	22.1
Neonatal screening test	15.3	15.5	16.6
Meconium ileus	15.9	14.3	13.6
Family history	8.7	7.8	9.5
Nasal polyposis / chronic sinusitis	2.5	3.4	4.2
Rectal prolapse	3.8	2.7	2.9
Intestinal obstruction (other than meconium ileus)	3.0	3.0	2.7
Prenatal diagnosis	0.8	1.8	2.1
Dehydration / electrolyte imbalance	1.5	1.5	1.7
Neonatal jaundice	0.6	0.5	0.1
Infertility	0.4	0.9	0.8
Diagnosis other		6.3	8.0

The reasons for diagnosis are not mutually exclusive.

2.2 | Age at diagnosis

In figure 5, the bars represent the number of patients diagnosed in each age group. The curve shows the cumulative percentage. From data 2009, the median age at diagnosis was 6.8 months with 65.3 % of the patients diagnosed before their first birthday. In 8.0 % of the patients, diagnosis was delayed until adulthood (18 years or older).

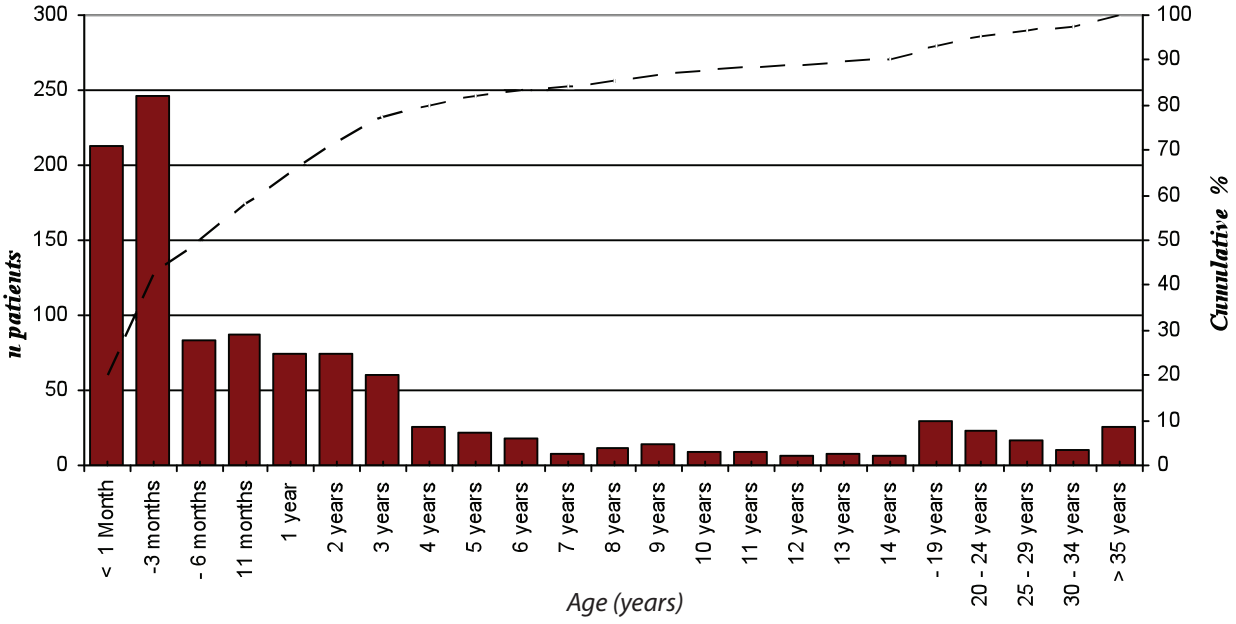

Figure 5 | Age at diagnosis of CF

2.3 | Genotyping

About 98.0% of the patients registered in 2009 have undergone a genetic analysis. Almost half (45.9%) were homozygote for F508del and 38.5% were heterozygote for this mutation (table 3). The proportion of patients in which only one or no mutation was identified was 10.6%.

Table 4 shows that the most common genetic mutation, F508del, was identified in 66.4% of the alleles while the N1303K and G542X were identified in 2.9% and 2.8% respectively. The group labeled 'other mutations' are those mutations which were present in less than 0.2% of the alleles. Respectively 953 (84.4%), 57 (5.0%) and 56 (5.0%) of the patients were carriers of either the F508del, N1303K or G542X mutation on at least one allele.

Table 3 | Genotype: mutation pairs (chromosomes)

	n	%
F508del- F508del	518	45.9
F508del-Other	369	32.7
F508del-NI	66	5.8
Other-Other	100	8.9
Other-NI	25	2.2
NI-NI	29	2.6
Subtotal	1107	
Missing	22	1.9
Total	1129	

NI = not identified

Table 4 | Most frequent mutations (alleles) and number of patients carrying those mutations

	patients		alleles	
Mutation	n	%	n	%
F508del	953	84.4	1471	66.4
N1303K	57	5.0	63	2.9
G542X	56	5.0	61	2.8
1717-1G->A	34	3.0	34	1.5
3272-26A->G	28	2.5	28	1.3
S1251N	27	2.4	27	1.2
R117H	26	2.3	26	1.2
A455E	21	1.9	21	1.0
2789+5G->A	19	1.7	19	0.9
R553X	19	1.7	19	0.9
W1282X	16	1.4	16	0.7
2183AA->G	13	1.2	13	0.6
3849+10kbC->T	12	1.1	12	0.5
L927P	12	1.1	12	0.5
R1162X	10	0.9	12	0.5
3659delC	8	0.7	8	0.4
394delTT	7	0.6	8	0.4
I507del	8	0.7	8	0.4
E60X	7	0.6	7	0.3
W401X	6	0.5	6	0.3
Y1092X	6	0.5	6	0.3
306insA	5	0.4	5	0.2
3905insT	5	0.4	5	0.2
D1152H	5	0.4	5	0.2
G85E	5	0.4	5	0.2
G970R	5	0.4	5	0.2
L165S	5	0.4	5	0.2
R334W	5	0.4	5	0.2
Others	141	12.8	153	7.2
Not identified	120	10.6	149	6.7
Subtotal			2214	
Missing	22	1.9	44	
Total			2258	

3 | ANTHROPOMETRY (HEIGHT, WEIGHT AND BMI)

In this section data from 117 patients who have received (a) transplant(s) have been excluded.

Persons with CF are known to be prone to nutritional deficiencies. Because of thick mucus, the pancreas is unable to produce and/or carry digestive enzymes to the intestines. This leads to poor absorption of proteins, fats and fat soluble vitamins resulting in poor weight gain and growth. Nutritional care is of great importance for patients with CF. Maintaining or achieving a better nutritional status has a positive impact on lung function. For this reason, close follow-up of height, weight and BMI is standard practice in all CF centers.

3.1 | Height

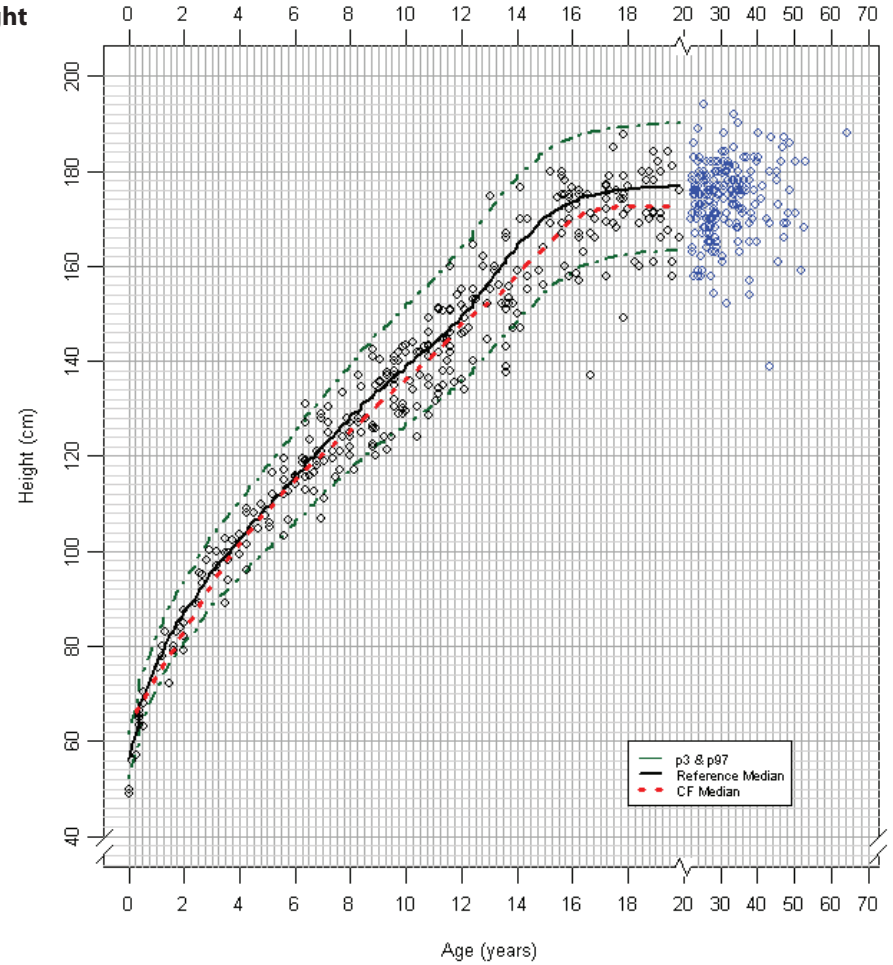

Figure 6 | Height in males.

Figures 6 & 7 show the height of 580 children with CF (307 males and 273 females) aged between 0 and 20 years (using the CDC reference curves (5)). Most male and female CF children had a height within the normal range, between the 3rd and 97th percentile (green lines). The median height of children with CF (dotted red line) was below the median height of the reference population (black line), meaning that patients with CF are shorter than their healthy peers. 9.5% of the patients were considered to be too short, with a height below the 3rd percentile. The heights of the 402 adults (age ≥ 20 years) (208 males and 194 females) are represented by the blue scatters plots.

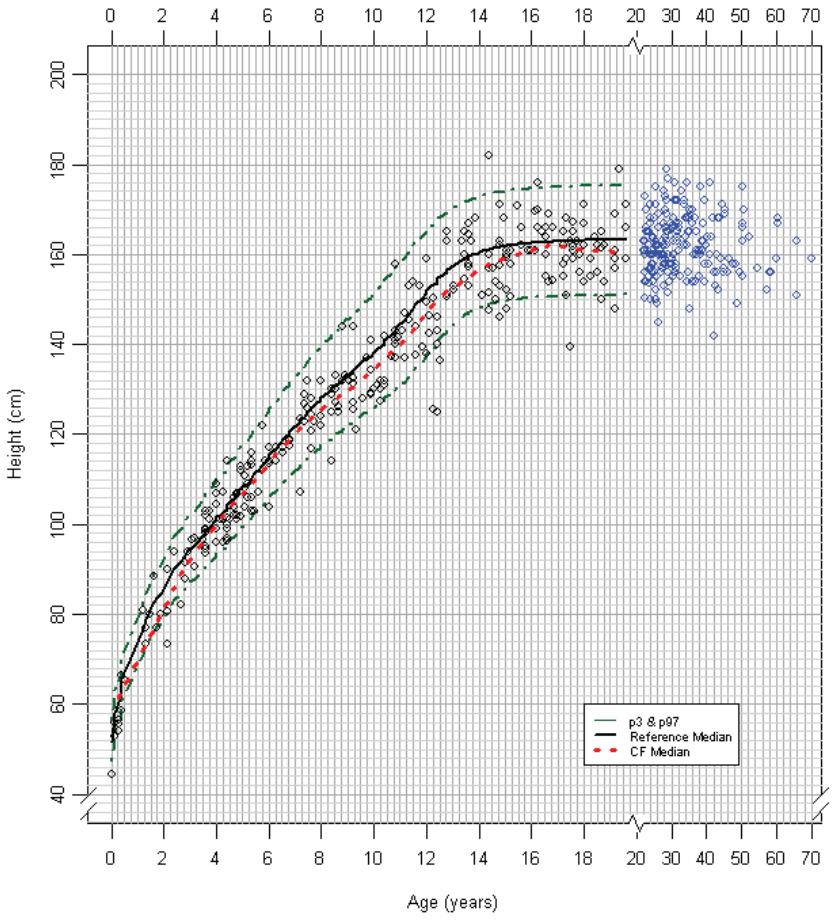

Figure 7 | Height in females.

3.2 | Weight

Figures 8 & 9 show the scatter plots of weight of 594 children with CF (320 males and 274 females). The weight of most of the patients was between the 3rd and 97th percentile with a higher proportion below the 50th percentile. 13.7% of the patients (13.5% of the males and 13.9% of the females) were underweighted (weight below the 3rd percentile. The median weight for the patients with CF (dotted red line) was below the median weight for the reference population (black line). The blue dots represent the weight of 402 adults (older than 20 years); 208 males and 194 females.

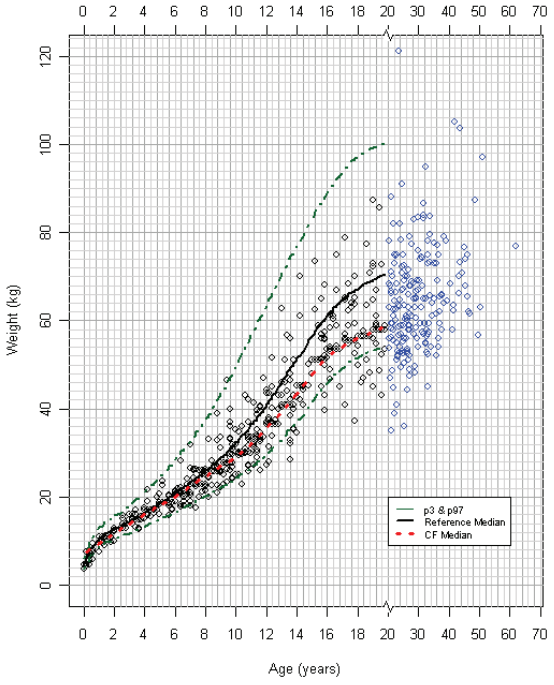

Figure 8 | Weight in males.

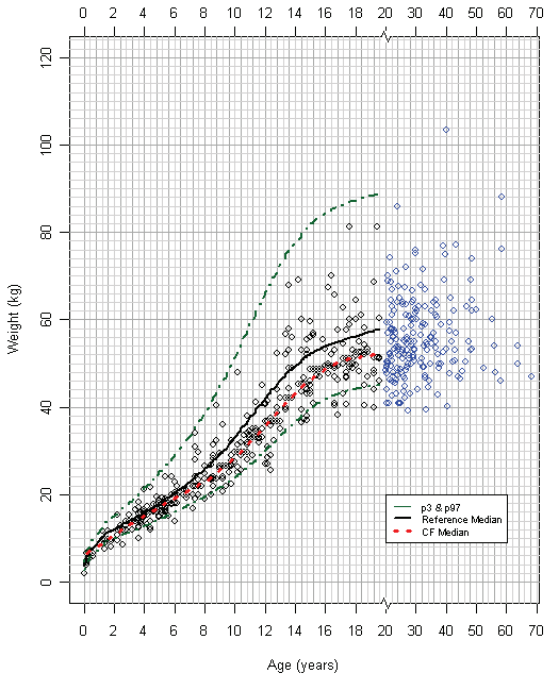

Figure 9 | Weight in females.

3.3 | BMI

The body mass index (BMI) is obtained by dividing the weight (in kg) by the square of the height (in m). BMI is a 'rough' measure of nutritional status, a higher BMI reflecting better nutrition. Figures 10 and 11 show a decreasing median BMI percentile with age in the Belgian children with CF aged 2 years and above. Ideally, children with CF should have a median BMI close to that of the non-CF population (black line).

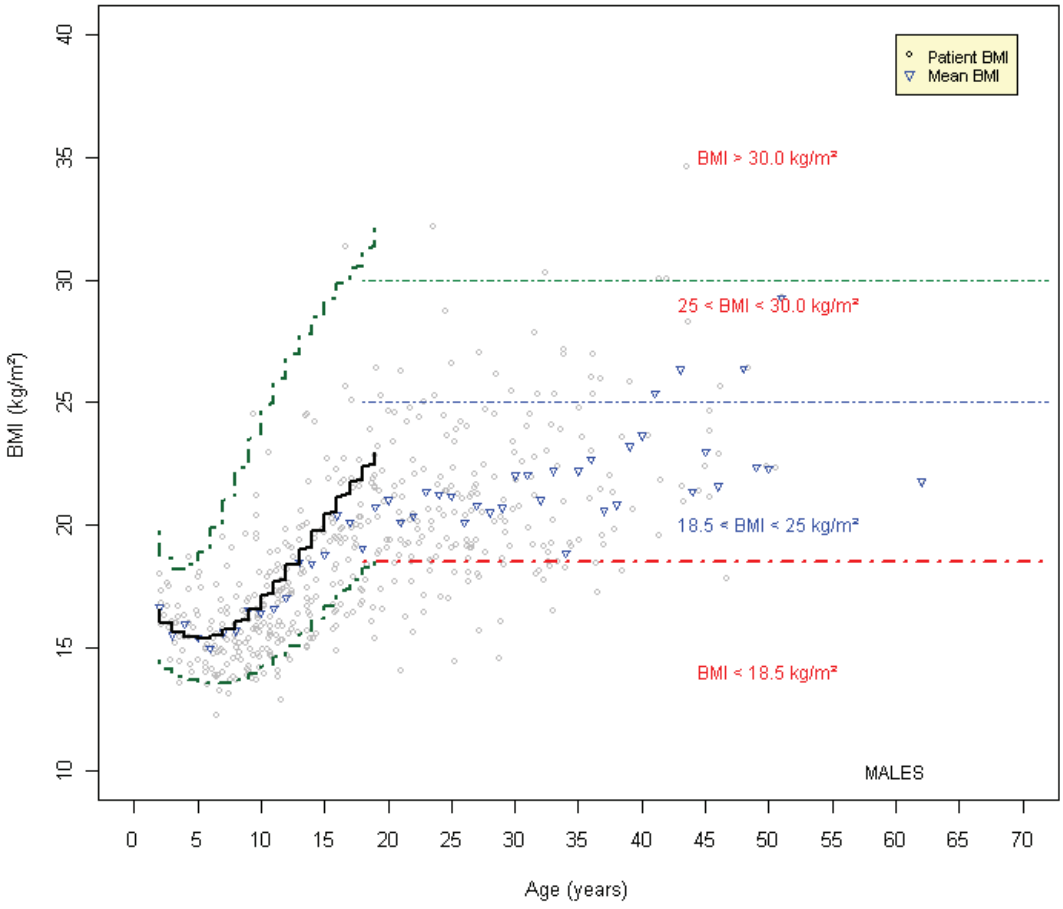

Figure 10 | BMI in males

In adults, the patients are classified as underweight (< 18.5 kg/m^2), in the normal range (18.5-25 kg/m^2) or as overweight (> 25 kg/m^2). In 2009, the BMI was in the normal ranges (18.5-25 kg/m^2) in 70.6% of the adult patients (69.8% of the males and 71.4 % of the females). The proportion of underweight adult patients was 17.6 % (16.8 % and 18.4 % in males and females respectively).

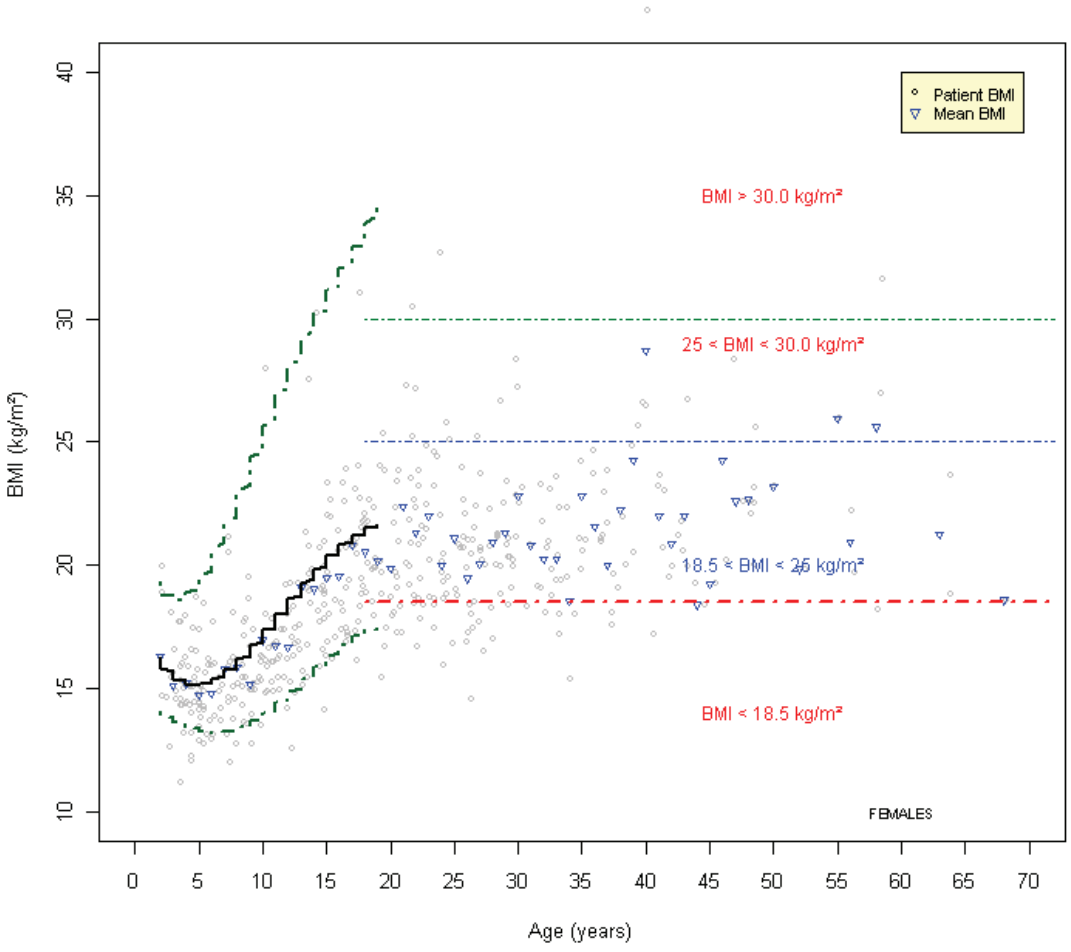

Figure 11 | BMI in females

Figures 12 and 13 show the evolution of the BMI over the last 12 years of analysis in the Belgian children and adults with CF. Only patients with the most frequent genetic mutation (F508del homozygote) were included in this analysis, to compare a similar population over the years. In the reference population, by definition, 10% of the children have a BMI below the 10th percentile

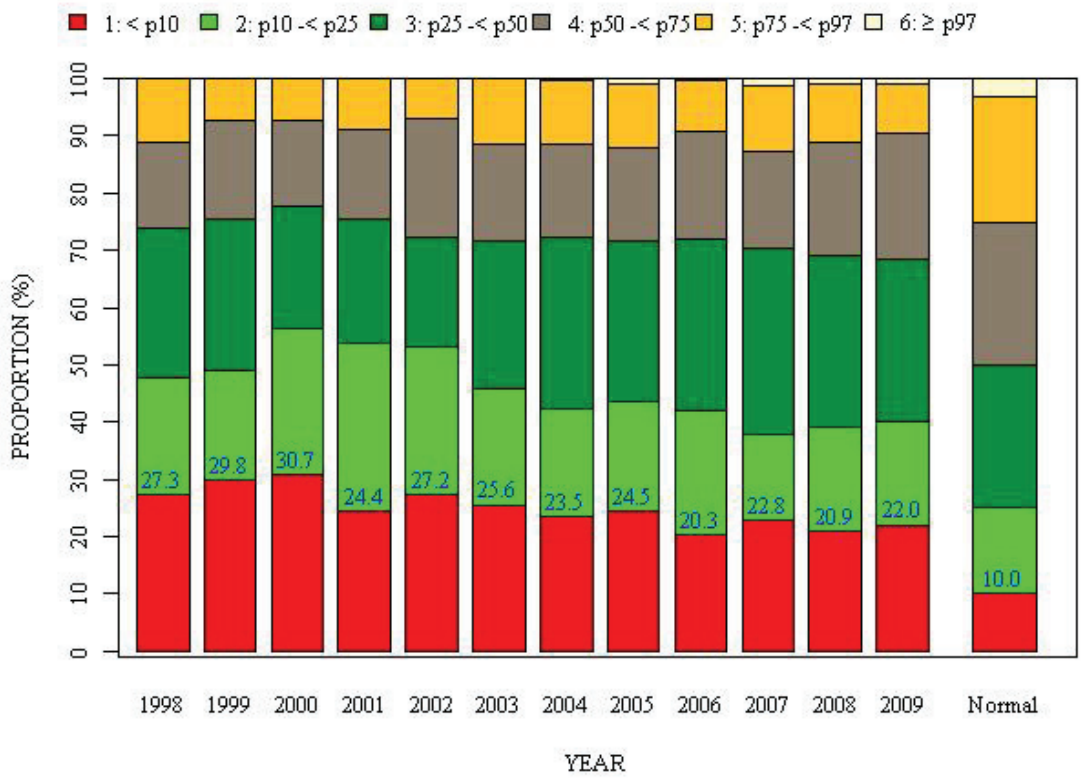

Figure 12 | CDC BMI percentiles of children aged 2-20 years

(see last bar of figure 12, red part). In the children with CF, over the last 12 years, the proportion of patients with a low BMI (below the 10th percentile) has steadily declined from 27.3 in 1998 to 22.0% in 2009. Among the adults, the proportion of underweight individuals decreased from 37.8% to 22.8% over the same period.

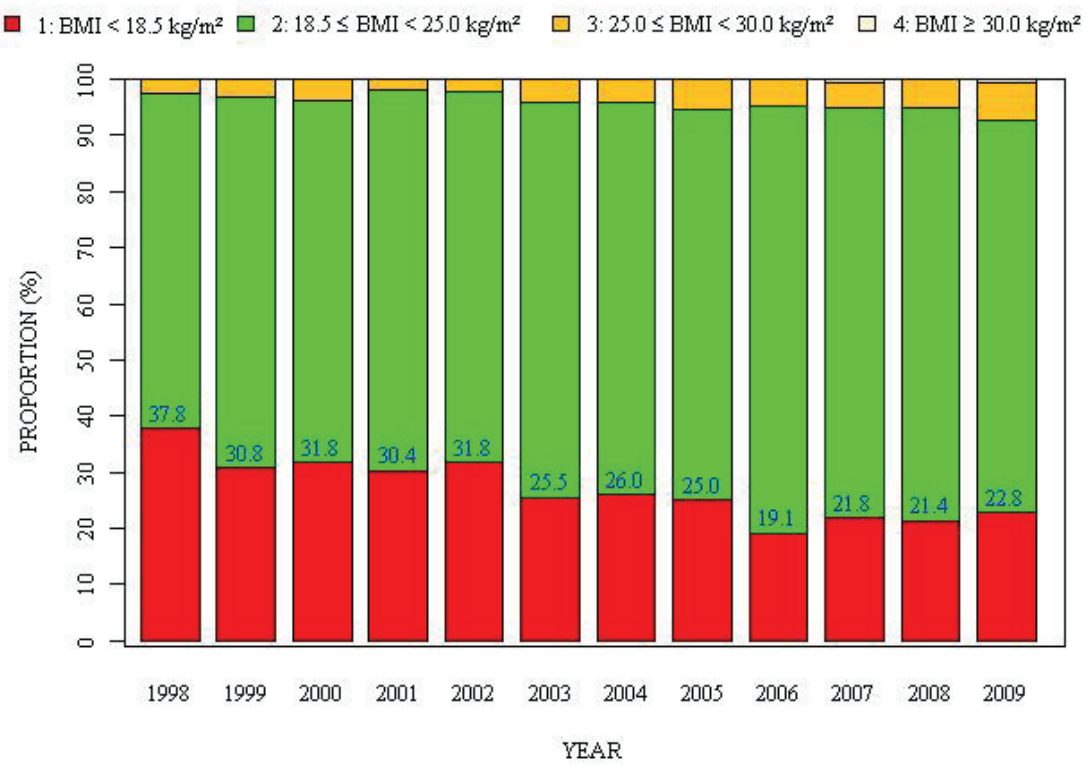

Figure 13 | Proportions of adult patients in each BMI group

4| Lung function

Because most patients with CF develop progressive pulmonary disease, measures of pulmonary involvement, in particular FEV_1, have been used as markers of disease severity and to predict survival. However, considerable heterogeneity exists in prognosis and severity, even among patients of the same genotype.

The forced expiratory volume in 1 second (FEV_1) is the amount of air that a person is able to expire forcefully in one second, following full inspiration. The percent predicted FEV_1 is a clinical parameter to monitor lung function impairment and is expressed as a percentage of the predicted value for a reference population with same age, gender and height[2].

The FEV_1% predicted values are divided in four classes for the CF population corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) impairment.

The data presented excludes patients who have benefited from a lung transplant. Below the age of 6 years lung function measurements are not always reliable and are thus not reported here.

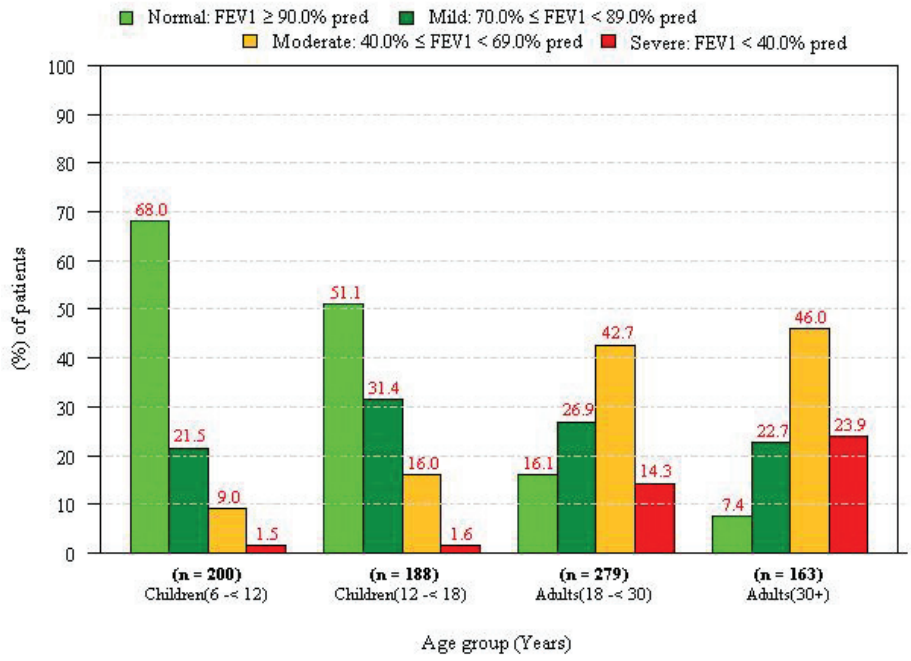

Figure 14| Classification of patients by lung function severity category and age group

[2]Wang's reference equations (6) were used for males, 6 – 17 years and females 6 – 15 years, while Hankinson's (7) were used for predictions for the males 18 years and above and females from 16 years onwards.

In 2009, the lung function taken at the last outpatient clinic of the year was reported in the Registry and was available for 98.9% of the patients aged 6 years and above.

The majority of children below 12 years (89.5%) had normal lung function or a mild lung function impairment (≥ 70%) whereas in the adult population aged 30 years and above this was only 30.1%. 3 children (1.5%) less than 12 years had severe lung function impairment while this was the case in 39 (23.9 %) of the adults aged 30 years and above (figure 14).

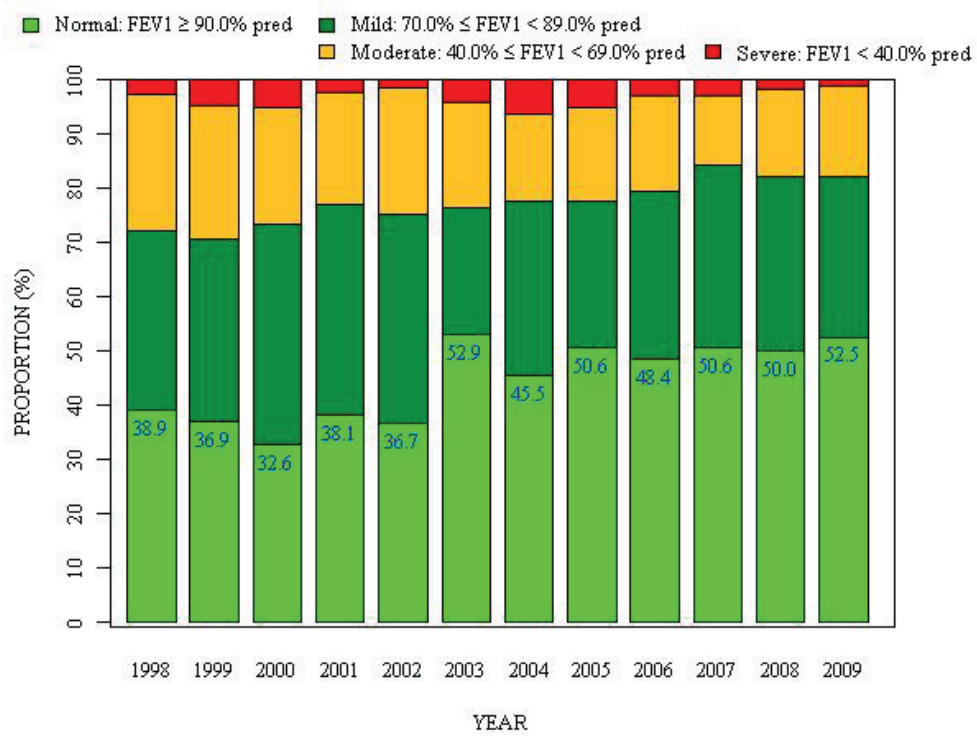

Figure 15 | Classification of F508del homozygous children by lung function severity category over the years

Figures 15 and 16 show the proportion of children and adults in the different classes of lung function over the years. Only patients with the most frequent genetic mutation (F508del homozygote) were included in this analysis, to compare a similar population over the years.
The proportion of children with % of predicted FEV_1 higher than 90% (light green) has increased over the years from 38.9% in 1998 to 52.5% in 2009.
Amongst the adults (figure 16), over the years, there is a decline in the proportion of patients with severe lung function impairment (values less than 40.0% of the predicted, in red on the graph) from about 31.2% in 1998 to 17.7% in 2009.

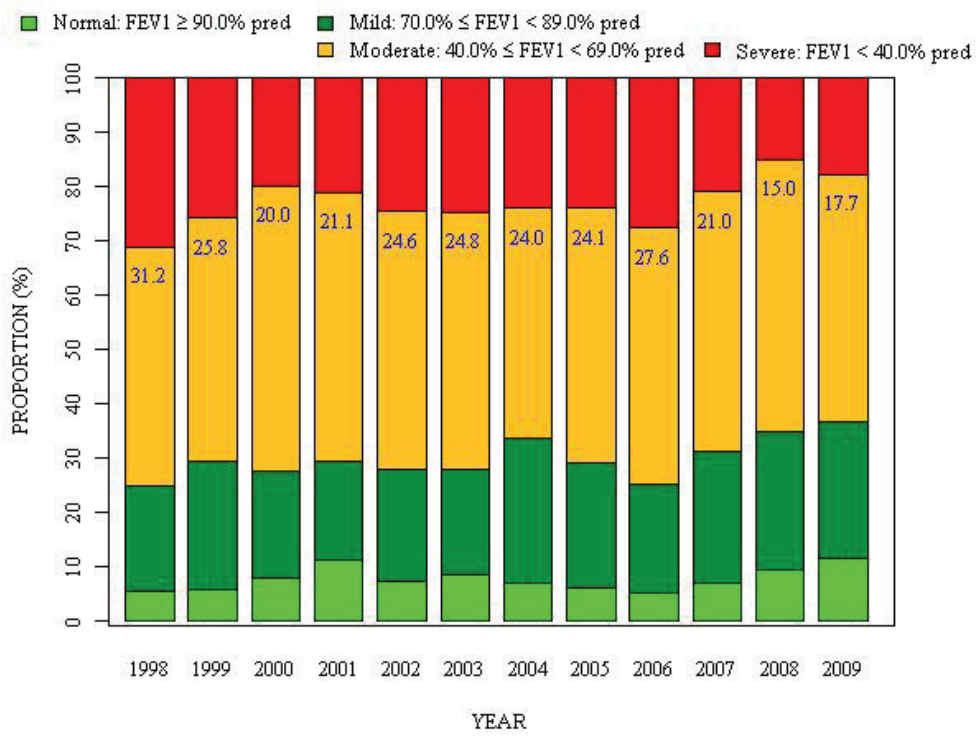

Figure 16| Classification of F508del homozygous adults by lung function severity category over the years

The production of thick mucus in the lung increases the likelihood of bacterial infections and decreases the ability to protect against infection. Over time, inflammation and infection are responsible for lung damage. Bacterial colonisation occurs very early in the natural history of the disease. In the initial stage, common bacteria such as *Staphylococcus aureus* and *Haemophilus influenzae* infect the lungs. They precede from a few months to several years the colonization by *Pseudomonas aeruginosa* and sometimes *Burkholderia cepacia*. The airways of patients with CF may also be chronically colonized by fungi like *Aspergillus fumigatus.*

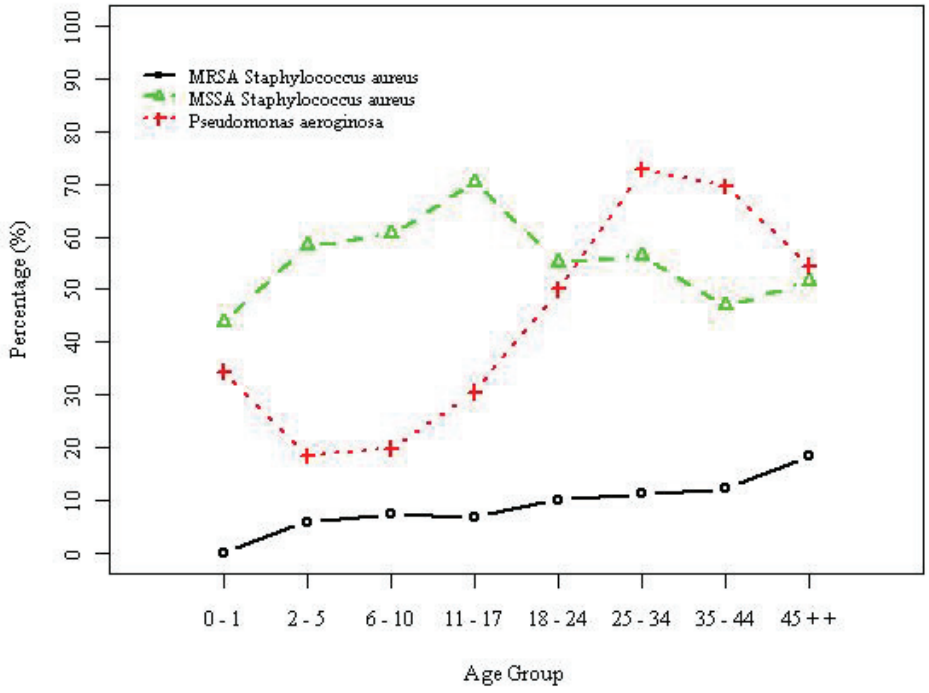

Figure 17| Annual prevalence of *Pseudomonas aeruginosa*, *Methicillin-sensitive Staphylococcus aureus* (MSSA), *Methicilin-resistant Staphylococcus aureus* (MRSA) related to age groups in the Belgian CF-population

One of the main goals of CF care is to postpone by all possible means infections with pathogens such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* and to reduce the risk of chronic colonization which increases respiratory morbidity and treatment burden.

In this section, a selection of pathogens are presented, based on their prevalence in the patient population. Data from transplant patients are not included in this chapter.

In 2009, 96% of the patients had at least one culture during the year. 42.0% of the patients tested positive to *Pseudomonas aeruginosa*; while *Methicillin-resistant Staphylococcus aureus* (MRSA) was detected in 8.6%. Only 2.7% tested positive for *Burkholderia cepacia*.

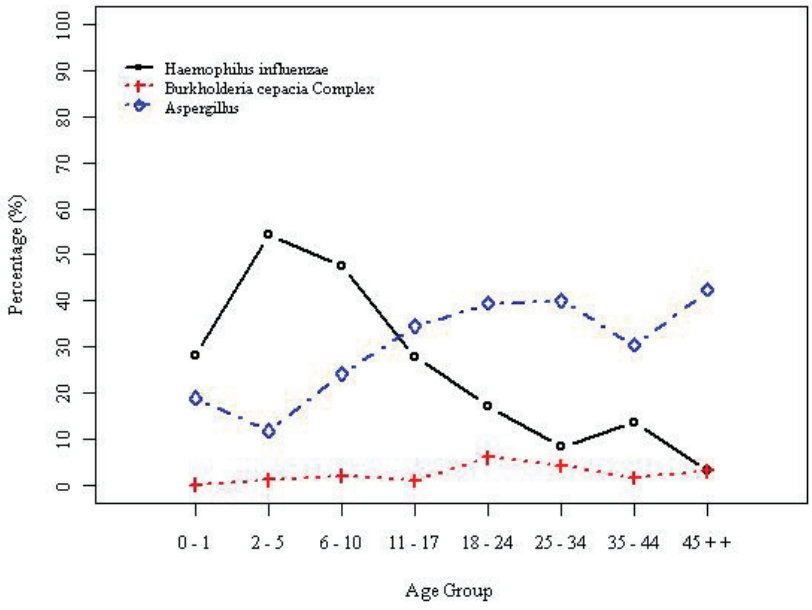

Figure 18 | Annual prevalence of *Haemophilus influenzae*, *Burkholderia cepacia* complex and *Aspergillus* related to age groups in the Belgian population with CF

Annual prevalence related to age of typical CF-pathogens found in the airway cultures done during the whole year 2009 is illustrated in figures 17 & 18.

In the Belgian CF population, *Pseudomonas aeruginosa* was found in about 25% of the patients in the first decade of life. This percentage rose in the second decade and reached 70% in the adult life (figure 17). The proportion of patients with chronic infection with *Pseudomonas aeruginosa* also increases with age (figure 19).

Methicillin-sensitive Staphyloccoccus aureus (MSSA) was present in about 45% of the patients below the age of one year and this percentage increased progressively over the consecutive age groups reaching the highest percentage in the age range of 11-17 years (figure 17).

The prevalence of *Methicillin-resistant Staphylococcus aureus* (MRSA) was low with higher levels found in the older age groups (figure 17). *Burkholderia cepacia* complex was not frequently found in our country (figures 18 and 19).

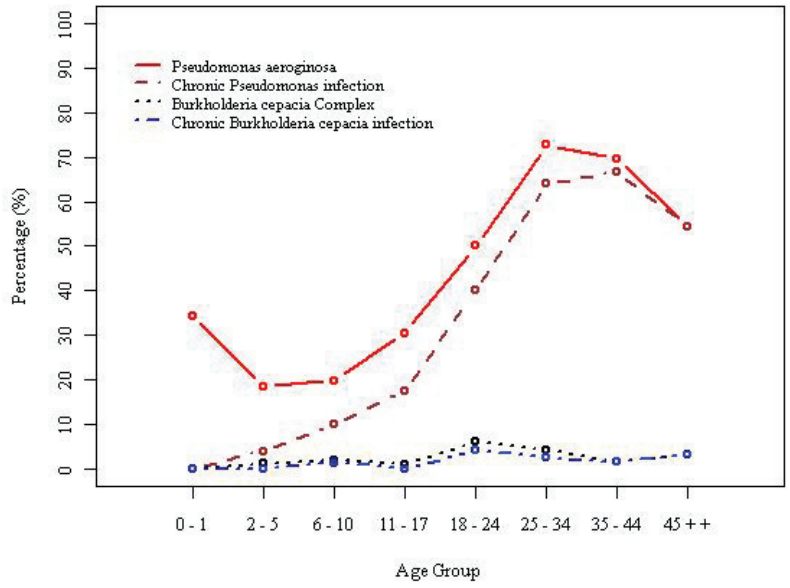

Figure 19| Annual prevalence of isolation and of chronic infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia* related to age groups in the Belgian population with CF

6 | COMMON COMPLICATIONS

The defective chloride channel in CF causes a range of disturbances within the human body. Chloride channels are needed to regulate fluids exchanges at the surface of epithelial cells. Complications in CF are mainly found in organs where mucofilms are needed (airways, intestines) and glands which need fluid to excrete their substances (pancreas, testis...). The most frequent complications are detailed below.

6.1 | Respiratory system complications

Allergic bronchial pulmonary aspergillosis (ABPA)
ABPA is an allergic reaction to *Aspergillus fumigatus* a fungus that colonizes the airway of some people with CF. Diagnosis is not always obvious as many symptoms of ABPA (cough, wheezing, shortness of breath, decline in lung function) are common symptoms of CF lung disease. Diagnosis relies on a combination of the clinical picture, blood tests and chest radiography or CT. If not treated, ABPA can cause bronchiectasies (which are chronic dilatation of the bronchi or bronchioles).

Nasal polyps
In patients with CF, chronic infections of the upper airways (chronic sinusitis) may cause the formation of nasal polyps which are mucosal overgrowths. They are responsible for nasal obstruction.

Haemoptysis
When the damage within the bronchi reaches a blood vessel the patient with CF is coughing blood. Haemoptysis is mild in most cases, but sometimes the bleeding is so severe that embolisation of the bleeding vessel is needed.

A pneumothorax occurs when air reaches the vacuum of the pleural space, mainly caused by destruction of the alveoli causing the leakage of air. This complication is more common in adults who have more advanced lung disease.

6.2 | Gastro-Intestinal complications

Pancreatic enzymes are needed to digest fat and proteins. **Pancreatic insufficiency** is the inability of the pancreas to produce and excrete enough enzymes to digest fat and proteins resulting in malabsorption with steatorhea (fatty stools), malnutrition and a deficiency in fat-soluble vitamins (A, D, E and K).

Gastro-oesopahgeal reflux is a condition in which contents of the stomach or small intestine repeatedly move back up into the esophagus. When repeated it causes oesophagitis and may worsen the respiratory function.

Distal intestinal Obstruction syndrome (DIOS)
The intestinal cells with defective chloride channels produce thick intestinal mucus which in combination with stools can cause obstruction of the bowels. DIOS causes acute abdominal pain and if not treated can progress to intestinal obstruction. DIOS usually responds to medical treatment but in a few cases surgery is required.

Liver disease
Only a subgroup of persons with CF develop liver disease leading to cirrhosis (replacement of the liver tissue by fibrosis). Sometimes cirrhosis evolves to portal hypertension and in advanced cases a liver transplant can be proposed.

6.3 | Endocrine complications

CF related Diabetes
Insulin is a hormone which maintains the balance of sugar in blood. Dysfunction of the endocrine part of the pancreas leads to insufficient secretion of insulin and to diabetes. Insulin is the treatment of diabetes.

CFRD prevalence increases with age. In 2009 in the Belgian CF Registry, no children under 12 years had CFRD. Eleven (5.7%) of the 12 – 17 yr old, 65 (22.4%) of the 18 - 29 yr old and 37 (21.8%) of patients aged 30 and above were reported to have CF related diabetes (figure 20).

Since patients with CF are living longer, they are at increasing risk of developing CFRD. In the Belgian CF population, the proportion of patients with CFRD has increased over the years from 27 (6.0%) in 1998 to (113) 11.2% in 2009.

6.4 | Reproductive system complications

Most men with cystic fibrosis are infertile because of congenital bilateral absence of the vas deferens (which allows the transport of the spermatozoids). However, as the production of spermatozoids is preserved, techniques of assisted procreation are available.

Although women with cystic fibrosis may be less fertile, it is possible for them to have successful pregnancies. Those pregnancies require close surveillance.

6.5 | Other complications

Oseopenia and osteoporosis
Osteopenia and osteoporosis are the result of a progressive loss of the bone mass. They are more frequent and earlier in cystic fibrosis due to various risk factors like malabsorption of vitamins D, use of glucocorticoids, chronic inflammation, sedentarity…

CF related arthritis/arthropathy
Patients with advanced lung disease sometimes develop painful inflammation of joints. The exact cause is not known and regression of joint symptoms is usually seen when respiratory disease improves.

Psychiatric disease
Difficult to define and quantify, the psychological repercussions of CF are frequent and often involve a poor adherence to the treatment.

In this section we consider the most common complications recorded in non transplanted patients. The percentage of patients presenting these complications in 2009 are reported in table 5.

Table 5 | Complications

	Complications*	n patients	% of patients
Respiratory	Allergic bronchopulmonary aspergillosis	74	7.4
	Nasal polyps	117	11.6
	Massive haemoptysis	27	2.7
	Pneumothorax	3	0.3
Gastro-intestinal	Pancreatic insufficiency	850	84.6
	Gastro-oesophageal reflux	189	18.8
	Intestinal obstruction (no surgery)	91	9.1
	Intestinal obstruction (requiring surgery)	10	1.0
	Cirrhosis with portal hypertension	24	2.4
Endocrine	CF related diabetes (CFRD)	113	11.2
Other	Osteopenia / osteoporosis	133	13.2
	CF related arthritis / athropathy	26	2.6
	Psychiatric disease	14	1.4

*Complications are not mutually exclusive. Percentages are based on 1005 non transplanted patients

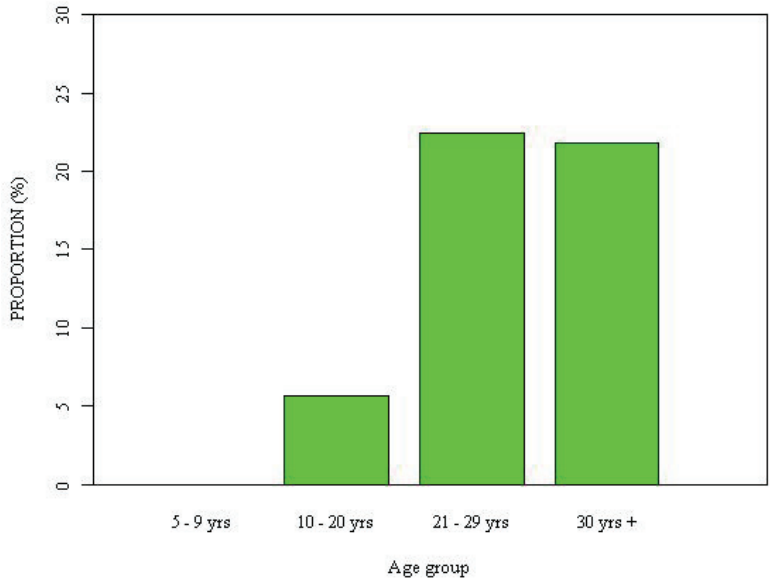

Figure 20 | Proportion of patients with CF related diabetes over the years

7 | TREATMENTS, VISITS AND HOSPITALISATIONS

Till today no cure for CF exists. Treatment of the disease is therefore based on preventing or reducing symptoms and complications.

1 | Prevent and tightly control respiratory infections

Because mucus is stuck within the bronchi, improving mucus clearance is one the most important interventions. A patient with CF has regular chest physiotherapy sessions.

Different kinds of inhaled medications are used to treat CF symptoms. They include mucolytics that thin the sticky airway secretions such as RhDNase or hypertonic saline. Bronchodilators are given to dilate the bronchi. Inhaled antibiotics are used to treat infection and to prevent or postpone colonization. In advanced lung disease oxygen is needed.

Every year, half of the patients with CF are hospitalized, mostly for the treatment of pulmonary exacerbations caused by an infection requiring intravenous antibiotics.

Inflammation caused by repeated infections plays an important role in the progression of lung injury. This explains the interest in the use of anti-inflammatory drugs such as azithromycine or inhaled corticosteroids as complementary treatment.

2 | Optimizing the nutritional status

Because the nutritional status of a patient correlates with disease severity, every person with CF should take a well balanced high-caloric and high-fat diet. Most individuals with CF are pancreatic insufficient and must take pancreatic enzymes at every meal to digest food correctly. Also supplements of vitamins A, D, E and K are administered routinely. Some people with CF benefit from supplemental feedings given overnight by a tube placed into the stomach (enteral feeding) or even intravenous nutrition (parenteral feeding).

3 | Monitoring the onset of other complications followed by appropriate therapeutic interventions

Complications of the disease are regularly monitored.

When clinical, biological or imaging findings point towards liver disease, ursodeoxycholic acid is started. It is a hydrophilic bile acid normally present in human bile which stimulates the biliary secretion and protect the hepatic cells.

Depending on complications, other medications are prescribed such as insulin for CF related diabetes, biphosphonates for osteoporosis, proton-pump inhibitors for gastro-esophageal reflux or maldigestion…

The treatment burden for CF patients is high. Most CF patients spend a lot of time every day performing therapies. This imposes also a substantial burden on their family.

In this section, we will present data on treatments given to patients as recorded in 2009.

Table 6 | Main therapies

Treatment	% of patients receiving the treatment
Respiratory therapies	
Regular chest physiotherapy	92.6
Inhalation therapy (antibiotics excluded)	
RhDNase	58.4
Other mucolytics	50.2
Hypertonic saline	30.2
Bronchodilators	70.5
Corticosteroids	52.0
Oral anti-inflammatories drugs	
Azithromycin	41.2
Systemic corticosteroids	6.4
NSAID	4.6
Oxygen therapy	2.4
Antibiotics	
Oral or IV antibiotics	98.4
Inhaled antibiotics	55.3
Tobramycin	15.0
Digestive and nutritional therapies	
Pancreatic enzymes	86.0
Fat soluble vitamins (A,D,E, and K)	84.2
Proton pump inhibitor + H2 receptor blocker	38.1
Ursodeoxycholic acid	28.1
Enteral feeding	2.2
Parenteral feeding	2.4
Other treatments	
Insulin therapy	10.7
Oral therapy for diabetes	2.4

7.1 | Respiratory therapies

About 93 % of the patients were reported to follow regular chest physiotherapy.
Ninety one percent of the patients took on a daily basis at least one mucolytic (RhDNase, hypertonic saline or another mucolytic). Inhaled bronchodilators were the most frequent additional drugs (70.5%). Among anti-inflammatory drugs, azithromycin was given to 41% of the patients while systemic corticosteroids and non steroidal anti-inflammatory drugs (NSAID's) were given to only a small proportion of the patients.

7.2 | Antibiotics

The proportion of patients using inhaled antibiotics was about 55 %. Over 98.4 % of the patients received oral or intravenous antibiotics. Half of the patients received oral antibiotics. The need for intravenous antibiotics increases with age. About 30% of the children and half of the adults received at least one treatment with intravenous antibiotics during the year 2009 (figure 21). Adolescents and adults received more days of intravenous antibiotics than children. The children had a median (Inter Quartile Range (IQR)) of 15.0 (12.0 – 28.0) days of IV antibiotics while adults had a median of 21.5 (14.0 - 43.0) days.

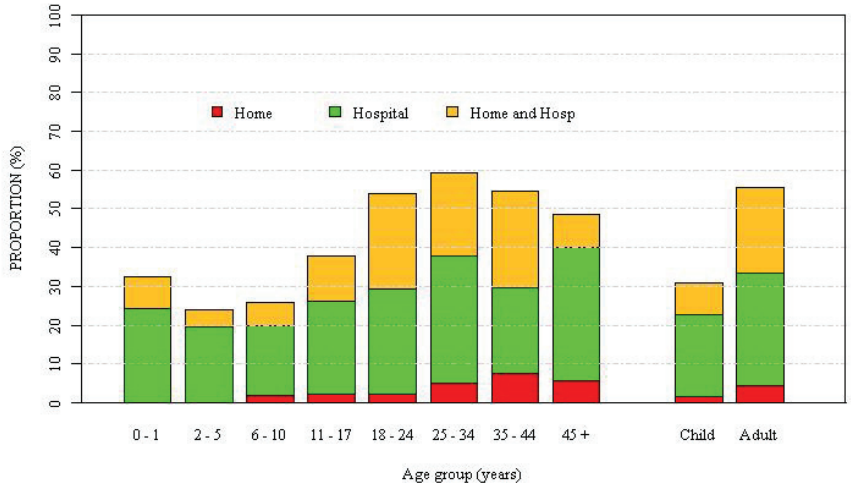

Figure 21 | Proportion of patients using IV antibiotics by age

7.3 | Digestive and nutritional therapies

Pancreatic enzymes replacement therapy were taken by 86.0 % of the patients; a supplement of fat-soluble vitamins A, D, E and K by 84.2 % of them. Ursodeoxycholic acid was given in a quarter of the patients.

7.4 | Other therapies

10.7 % of all patients, i.e. 2.4 % of the children and 20.6 % of the adults, were treated with insulin.

7.5 | Outpatient visits and hospitalizations

The median (IQR) number of outpatients visits of the patients with CF was 5 (4 - 7). 47.7 % of the patients (38.4% of the children and 58.6% of the adults) were hospitalized in 2009 with a median (IQR) number of 12 (4 – 23) days.

8 | LUNG AND OTHER TRANSPLANTATIONS

When a patient with CF develops severe and progressive lung disease, lung transplantation may become an option.
However, like other major surgeries, lung transplantation involves significant risks. A lung transplant is indicated only for patients who have a severe disease and who have exhausted all other forms of conventional medical treatment. For these patients, lung transplantation may offer prolonged survival and an improved quality of life; in some cases even a 'new' life.
The success rate of lung transplantation for CF patients is steadily improving. At present the actuarial survival rate is > 60 % at 3 years and > 40 % at 10 years after surgery (8).

The longest surviving patients had their transplant operations now more than 20 years ago.

The first (heart-)lung transplant in a Belgian patient with CF was performed in 1988. Since this time more than 170 patients with CF (9) (134 reported in the CF Registry) have received a (heart-)lung transplant in Belgium and approximately 10 lung transplants per year are now performed for CF. Some patients with CF will need other types of transplantations such as liver transplantation for end-stage CF-related liver cirrhosis or renal transplantation for end-stage renal disease because of diabetes, antibiotic toxicity or the toxicity of immunosuppressive drugs required after lung transplantation.

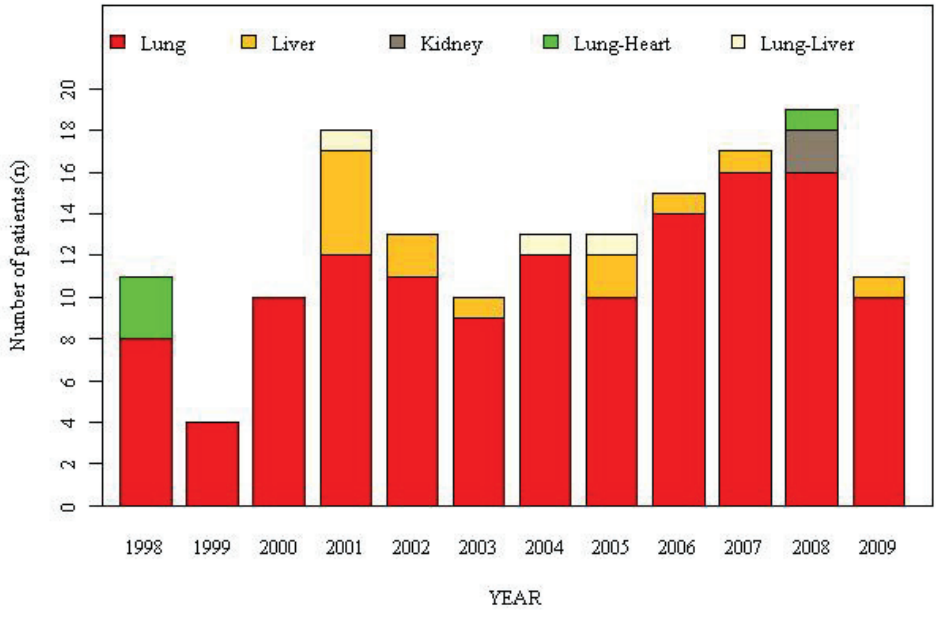

Figure 22 | Number of transplants by year reported in the BMR-RBM

9| Conclusions

This edition of the public report of the Belgian CF Registry (BMR-RBM) includes data that compares to previous years for a selection of parameters of interest. It is the hope that the provision of this information will continue to enlighten the public in general and people with interest in CF about this life threatening hereditary chronic disease.

Continuous efforts have been made throughout the past years by everyone involved in the Belgian CF Registry (physicians, nurses and staff from the CF reference centres, database managers, scientific collaborators…) to improve the quality of the data and provide a useful database for monitoring the natural evolution of the disease and for use as a research instrument in generating and addressing various research hypotheses.

The number of patients enrolled in the Registry has continued to rise and has doubled since 1998. CF is now no longer only a disease of childhood, as the number of patients aged 18 years and above has steadily risen from 39% to about 51% in 2009.

Based on the data collected each year, a national scientific report dedicated to the CF centres is published annually. Since 2006, centre reports are also provided to the centres. From 2008 onwards, a feedback report is being provided with analyses that compare the results from each centre with data from the other centres in order to improve the quality of care provided to the patients with CF in their respective centres through benchmarking.

Physicians from the centres and researchers have continued to submit research questions to the BMR-RBM, and currently a number of research questions are being analyzed. Several abstracts have been presented at international conferences (10).

Finally, we are greatly indebted to the patients and their families or care-givers who agreed to contribute data to this Registry and have made the various research issues including this report possible.

10| References

1. Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008; 7:450-453.

2. http://www.inami.be/care/fr/revalidatie/convention/mucoviscidose/pdf/agreement.pdf
http://www.inami.be/care/nl/revalidatie/convention/mucoviscidose/pdf/agreement.pdf

3. http://www.inami.be/care/fr/revalidatie/convention/mucoviscidose/pdf/avenant.pdf
http://www.inami.be/care/nl/revalidatie/convention/mucoviscidose/pdf/avenant.pdf

4. http://www.ecfs.eu/projects/ecfs-patient-registry/information-about-ecfspr-cf-patients

5. Kuczmarski RJ, Ogden CL Guo SS et all. 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics, Vital Health Stat 2002; 11(246): 1 – 190.

6. Wang X., Dockery D W Wypij. D., Fay. M. E., and Ferris. B. G. 1993. Pulmonary function between 6 and 18 years of age. Paediatr. Pulmonol. 15:75–88.

7. Hankinson J. L., Odencrantz J. R., and Fedan. K. B. 1999. Spirometric reference values from a sample of the general U.S. population. Am. J. Respir. Crit. Care. Med. 159:179–187.

8. Christie JD, Edwards LB, Kucheryavaya AY, Aurora P, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report--2010. J Heart Lung Transplant. 2010 29:1104-18.

9. Van Raemdonck D, on behalf of the Thoracic Committee of the Belgian Transplantation Society. (Heart-)Lung transplantation in Belgium. Annual report 2009. Personal communication.

10. Thomas M, Vermeulen F, De Baets F, Desager K, De Wachter E, Knoop C, Lebecque P., Sacré JP, Cuppens H., De Boeck K., on behalf of the members of the BMR-RBM.
Who should be analyzed in a cystic fibrosis Registry ? Data from the Belgian CF Registry (BMR-RBM). J Cyst Fibros 2011; 10 (Suppl1): 41.

NOTES

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