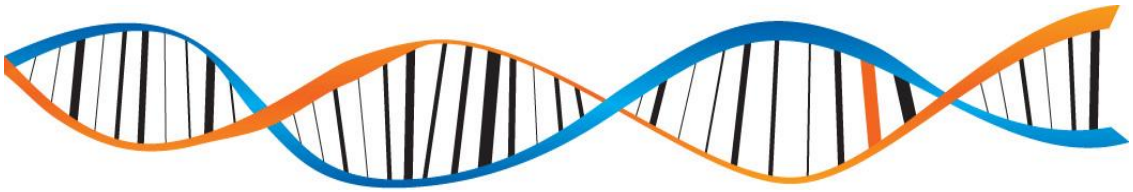
# Dutch Cystic Fibrosis Registy



## Report 2016

NCFS • October 2017



NEDERLANDSE CYSTIC FIBROSIS STICHTING

# Foreword

This ninth Dutch CF Registry report was drafted thanks to the cooperation of nearly all people who suffer from Cystic Fibrosis (CF) and thanks to the efforts of so many people who work at the seven CF centres. It contains the details of 1,549 of the approximately 1,575 people who suffer from CF and CF-related illnesses in the Netherlands. This report, therefore, is about 98% of Dutch patients with CF. CF is a complex syndrome and there are many factors that influence the development of symptoms. Treatment is one such factor. In order to be able to compare and interpret data about the treatment given at various centres, it is necessary to scrutinise potentially connected factors such as age, gender, type of mutation and the gravity of the symptoms.

Since 2014, the CF centres are no longer shown in an anonymous form as this increases transparency. Since 2014, details about the so-called indicators have also been added. Indicators are figures that say something about aspects of the quality of the care provided by CF centres. I wish to emphasise that tables and diagrams must be interpreted with due care. The quality of the care provided by a CF centre is determined by many factors and cannot be summarised in a single figure or diagram. This does not automatically mean that a centre that shows the highest average lung function, for instance, provides the best care. That would be a wrong conclusion to draw.

This report presents the data on a centre-by-centre basis but also on a national level. Each of the CF centres received an overview of their own data compared to the national averages. Each year, the Dutch Cystic Fibrosis Foundation [Nederlandse Cystic Fibrosis Stichting (NCFS)] organises meetings with paediatric pulmonologists, chest physicians, paediatric gastroenterologists and paediatric dieticians of the centres. During such meetings, the parties discuss the treatment, results and differences between the centres in an open and positive atmosphere. Any relevant differences are analysed and worked out into guidelines, if possible. October 2016 saw the start of the development of a new guideline and care standard that includes all aspect of diagnostics, treatment and support in the case of CF. This registry provides important information in that respect.

The shared ambition of the CF centres and the NCFS remains unchanged: better care that results in a better and longer life for people with CF.

October 2017

Jacquelien Noordhoek, chairperson of the Dutch CF Registry Steering Group.

**Composition of the Dutch CF Registry Steering Group**
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# Contents

# Summary

Important findings of the Dutch CF Registry in 2016:

In the Netherlands, there are approximately **1,575 people with CF** or a CF-related illness*.
Nearly 60% of them is older than 17. The oldest patient with CF in the Netherlands is 74.
The number of people with CF aged over 50 is 81 (2015: 70).

For half of the children, the **diagnosis** was made before the age of one month. In 2010, it was four months. In 8% of patients, the diagnosis was made after the age of 18.

In the Netherlands, there are **more men** (53.1%) than women (46.9%) with CF.

88% of people with CF have at least one **F508del mutation**.

In 2016, 14 people with CF had a **lung transplant**. There are 125 People with CF who have had a lung transplant and who are still alive in 2016.
At the end of 2016, there were 15 People with CF on the **waiting list** for a lung transplant, considerably less than at the end of 2015 (24).

In 2016, 12 adults and two children with CF **died**. Half of them was younger than 37.

Half of the children have a **lung function (FEV1)** of more than 95% of the predicted value.
Half of the adults have a lung function (FEV1) of more than 70% of the predicted value.
The lung function of children and adults with CF has gradually improved during the past few years.

The average **nutritional status** (the length/weight proportion) of children with CF is comparable to that of healthy peers.
On average, children with CF are smaller than healthy peers.
The average nutritional status of children and adults with CF has gradually improved during the past few years.
The differences between centres have reduced.

56% of children and 38% of adults with CF use **food supplements**.

One-third of all patients suffer from a chronic **Pseudomonas aeruginosa** infection. This is 52% in adults and 10% in children. This percentage is clearly dropping among children. In 2012, it was as high as 25%.

19% of People with CF have a **CF-related liver disease**.

**CF-related diabetes** occurs in 10% of children and 31% of adults.

In 2016, one in six children and one in four adults were given an **intravenous antibiotics course** in hospital. One in ten children had an intravenous course through home care. In adults, this figure is one in five.

59% of adults are in **employment** or follow a study programme. 1% are retired.

***** For the benefit of Registry, the CF diagnosis is persisted when two mutations are known and which are known to cause CF (according to the CFTR mutation database ( **https://www.cftr2.org/** ) ; and/or when the chloride concentration during the sweat test is 60 mmol or higher. In 1,452 (93.7%) of the 1,549 registered patients, the CF diagnosis was confirmed on the basis of those criteria.

# 1. Introduction

The Dutch Cystic Fibrosis Foundation (NCFS) has been coordinating, managing and financing the Dutch CF Registry since 2007 and publishes a report on the situation in the Netherlands each year. The Registry Steering Group consists of representatives from all CF centres and the NCFS. The Steering Group stipulates the Registry policy.

All information obtained from the national Registry is anonymised. Only the practitioner of a patient's own CF centre is able to trace data back to an individual patient.
Every CF centre enters and updates data of its patients in order to see how the illness progresses over time. The quality of the data is systematically checked by the Registry coordinator at the NCFS by means of automated software checks, and by statisticians of the European Registry. Strict checks are carried out in order to ensure that patient data cannot be traced by others. This is subject to Dutch and European legislation.
The Dutch CF Registry has been reported to the Dutch Data Protection Authority [College Bescherming Persoonsgegevens] which monitors compliance with privacy legislation. People with CF have been informed about the Registry and have given their written consent for their (anonymised) details to be included in the Registry. A small number of patients (4; 0.3%) refused to take part in the Registry. The details from 20 lung transplantees from Rotterdam are missing from the Registry for 2016.

CF Registries that contain medical information about People with CF are being kept in as many as 35 countries. This facilitates scientific research and it improves the care and treatment of CF patients. The Dutch CF Registry supplies data to the European CF Registry. (http://www.ecfs.eu/projects/ecfs-patient-registry/intro). The NCFS is very actively involved in the European CF Registry.

The Dutch CF Registry has adopted the definitions of European CF Registry. (http://www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions).
The use of data from the Dutch or the European Registry requires the consent of the Netherlands Steering Group or the European review committee. They consist of Dutch and European CF specialists respectively as well as experts in the field of the legal and ethical aspects of the use of personal details. Requests for data from the Dutch or European Registries can be submitted by means of request forms on the websites https://www.ncfs.nl/over-cystic-fibrosis/cf-registratie and https://www.ecfs.eu/ecfspr.

Appendix 1 lists the requests made in 2016 for data from the Dutch CF Registry.

A report is drawn up every year. This report, including an English translation thereof, is available on the website of the NCFS https://www.ncfs.nl/over-cystic-fibrosis/cf-registratie. Here, you can also consult an interactive map of the Netherlands with information about the centres https://www.ncfs.nl/over-cystic-fibrosis/centra.
If you have any questions or comments, please contact the Research and Quality of care Manager of the NCFS on info@ncfs.nl

# 2. Methods

The Dutch CF Registry reports lists medical and social data of People with CF. The Steering Group of the Dutch Registry has determined which parameters and associated definitions are recorded and based its decision mainly on the parameters (variables) used in the European Registry. This creates a database with data from approximately 42,000 European People with CF . The definitions applied for each parameter are virtually the same as those used for the American CF Registry; that includes the data of another 28,000 People with CF.

For the 2016 report, the seven Dutch CF centres had entered the data of about 150 variables in an Excel file. The data was collected throughout the year. In the case of the lung function, the highest value of that year is used for the Registry, which is in line with the European definitions.
All centres have used the same reference values for the lung function, namely
the international reference values in accordance with the Global Lung Initiative (GLI 2012; http://erj.ersjournals.com/content/early/2012/06/27/09031936.00080312.abstract?papetoc)
The Growth Analyser of the Stichting Kind en Groei in Rotterdam (a knowledge centre for the growth and development of children) was used to calculate the Z-scores for growth in children (weight according to length and BMI). The reference values of the Dutch population from 2010 (Talma) are used.

For various items, percentages and averages or medians per centre have been determined. Important outcome parameters such as the FEV1 lung function value and the Body Mass Index for the nutritional status are presented as uncorrected values, only from patients with a confirmed CF diagnosis and who have not had a lung transplant. FEV1 and Body Mass Index are also presented per age group.

**Outcome parameters and confounder analysis**

Outcome parameters such as FEV1, BMI and weight according to length say something about the quality of care received by patients. There are, however, many factors that determine FEV1, BMI and weight according to length. Some of those can be influenced by the centre (such as treatment, for instance) but others cannot. They are also referred to as confounders. The Steering Group has defined gender, age, age during diagnosis, ethnic background, the seriousness of the mutation category, meconium ileus, pancreatic insufficiency and lung transplants in the past as potential confounders. The socio-economic status can be a confounder but the Registry does not contain any details of this.

In consultation with the clinical epidemiology department of the Julius Centre in Utrecht, centre differences in FEV1, BMI, BMI Standard Deviation Score (DVS) and weight according to length SDS are corrected for most confounders (gender, age, pancreatic sufficiency, meconium ileus and ethnic background). Separate analyses are carried out for children and adults. Patients who had a lung transplant are not included in the analyses as this would distort the picture.
The “age of diagnosis” variable is not included in the analysis as a number of centres did not have enough data available. The median age at which the diagnosis is made does, for that matter, hardly differ from the centres that do have such data available.
We looked at the differences between the centres with a multi-variable linear regression model, both for children and adults. The potential influence of confounders was tested by adding them to the model.

Differences between centres do not change significantly after a correction (adjustment) for possible confounders. This is in accordance with the conclusions from the analyses of the American and the UK CF Registries.

# 3. Demographic data

The Dutch 'CF Diagnostics and Treatment Guideline' (2007) and the 'Centre Care report' (NCFS, 2003) recommend that People with CF visit a CF centre at least once a year.
In 2016, the seven Dutch CF centres treated approximately 1,575 people with CF and CF-related diseases. More than half (59%) of these people are older than 17. The number of adults is steadily rising while the number of children has remained fairly constant during the past five years. The data of 1,549 (98.4%) patients with CF (93.7%) and CF-related diseases (6.3%) is included in the Registry for 2016. In analyses of diagnostics, treatment and complications, only the data of people with a confirmed CF diagnosis is included.
Four people (0.3%) have refused to give their consent to have their details included. The details from 20 lung transplantees are missing from the Registry for 2016. When we use the word 'adults', we consistently refer to people of 18 or older.

For the presentation of the following overviews, the details of all registered patients are used.

| | **2009** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** |
|---|---|---|---|---|---|---|---|---|
| **Number of patients in the Registry** | 1299 | 1346 | 1374 | 1452 | 1476 | 1499 | 1521 | 1549 |
| Number of adults (≥ 18) | 649 | 714 | 745 | 804 | 821 | 846 | 869 | 907 |
| Number of children (< 18) | 650 | 632 | 629 | 648 | 655 | 653 | 652 | 642 |
| | | | | | | | | |
| Percentage of men | 53.6 | 53.6 | 53.5 | 53.4 | 54.1 | 54.2 | 52.9 | 53.1 |
| Percentage of women | 46.4 | 46.4 | 46.5 | 46.6 | 45.9 | 45.8 | 47.1 | 46.9 |
| | | | | | | | | |
| **Number of patients who died** | | | | | | | | |
| Children | 2 | 2 | 1 | 1 | 4 | 2 | 1 | 2 |
| Adults | 8 | 15 | 11 | 16 | 15 | 11 | 12 | 12 |
| | | | | | | | | |
| **Median* age upon death** | 30 | 37 | 34 | 38 | 31 | 37 | 42 | 37 |
| | | | | | | | | |
| **Median* age in years** | | | | | | | | |
| Children | 9.8 | 10.0 | 9.9 | 9.8 | 10.1 | 9.2 | 9.4 | 9.7 |
| Adults | 29.7 | 29.1 | 28.9 | 29.8 | 27.9 | 30.3 | 29.8 | 28.8 |
| Total | 18.0 | 18.8 | 19.2 | 20.0 | 18.2 | 21.0 | 21.0 | 21.3 |
| | | | | | | | | |
| **Average age in years** | 20.6 | 21.0 | 21.2 | 21.8 | 20.3 | 22.5 | 22.7 | 23.2 |
| Standard deviation | 13.6 | 13.7 | 13.9 | 14.3 | 13.7 | 13.9 | 14.6 | 14.7 |

** The median value indicates that half of the people have a value that is higher than the median and the other half have a lower value.*

**Number of patients in the Registry per centre**

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|---|---|---|
| **CF centre UMC Utrecht** | | | | | | | | |
| Children | 225 | 221 | 221 | 220 | 221 | 206 | 196 | 190 |
| Adults | 135 | 166 | 165 | 204 | 202 | 231 | 245 | 260 |
| **CF centre Erasmus MC** | | | | | | | | |
| Children | 132 | 126 | 137 | 147 | 151 | 149 | 143 | 140 |
| Adults | 112 | 121 | 131 | 133 | 124 | 121 | 120 | 139 |
| **CF centre HagaZiekenhuis** | | | | | | | | |
| Children | 47 | 50 | 49 | 56 | 56 | 55 | 63 | 59 |
| Adults | 187 | 197 | 203 | 210 | 213 | 210 | 210 | 217 |
| **CF centre Amsterdam** | | | | | | | | |
| Children | 113 | 99 | 90 | 95 | 100 | 102 | 105 | 104 |
| Adults | 72 | 80 | 83 | 89 | 95 | 100 | 106 | 109 |
| **CF centre UMC Groningen** | | | | | | | | |
| Children | 71 | 70 | 63 | 63 | 65 | 69 | 73 | 74 |
| Adults | 74 | 75 | 80 | 81 | 85 | 88 | 84 | 83 |
| **CF centre Radboud UMC Nijmegen** | | | | | | | | |
| Children | 29 | 32 | 41 | 39 | 42 | 47 | 49 | 52 |
| Adults | 37 | 42 | 47 | 48 | 52 | 50 | 57 | 56 |
| **CF centre Maastricht UMC** | | | | | | | | |
| Children | 33 | 30 | 28 | 33 | 36 | 34 | 28 | 26 |
| Adults | 32 | 37 | 36 | 34 | 34 | 37 | 42 | 40 |
| **Total** | 1,299 | 1,346 | 1,374 | 1,452 | 1,476 | 1,499 | 1,521 | 1,549 |

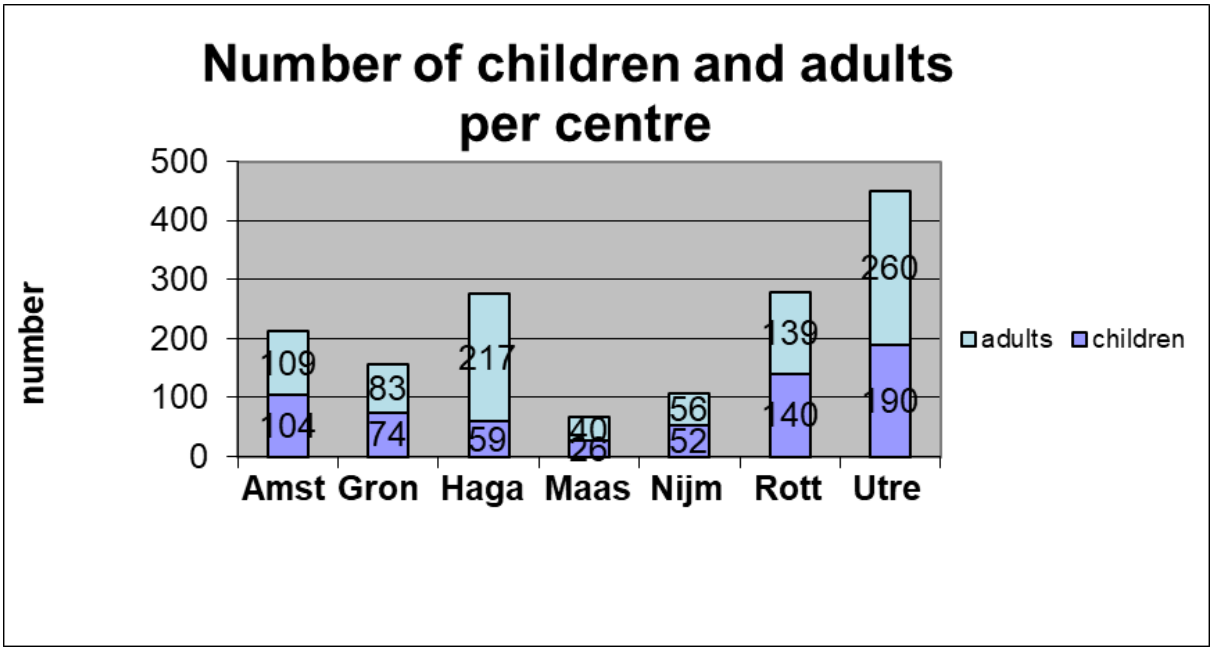



**Figure 1. Number of children and adults per centre**

# 4. Diagnosis

The CF Diagnosis is often made at a young age but increasingly so also at an adult age. In 50% of the group of children, the CF diagnosis was made before the age of one month. However, in 15% of adults and 8% of all patients, the diagnosis was made after the age of 18.

### Screening

In 28.8% of children, the CF diagnosis was made after newborn screening for CF. Since 2008, newborns in a number of provinces were screened for CF by means of the heelprick in a trial.
Since 1 May 2011, this type of screening (IRT/PAP/DNA) has been conducted among all newborns in the Netherlands.
Figure 2 shows the number of children per year who were diagnosed with CF, both for the group with newborn screening and the group of children who were diagnosed mostly at a slightly later age. It is known that in a small number of children, the CF diagnosis is not made immediately after the newborn screening test but at a later age. It is, therefore, important to remain alert to symptoms that may point to CF.
It is highly likely that a number of children who were born at the end of 2016 and who were diagnosed with CF a couple of weeks later are not yet included in the Registry for 2016. This data will be included in the Registry for 2017.

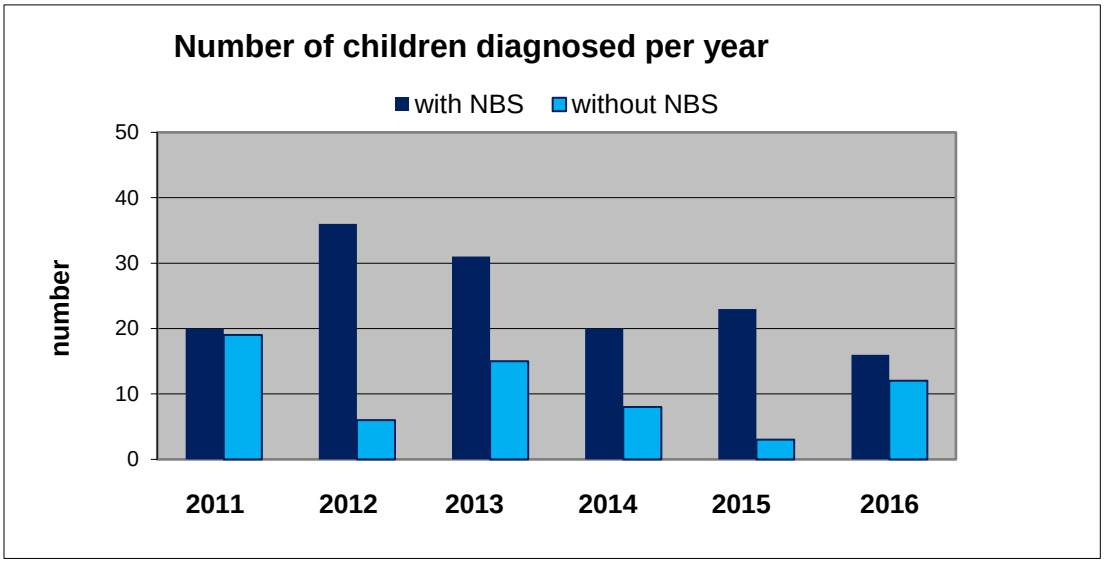
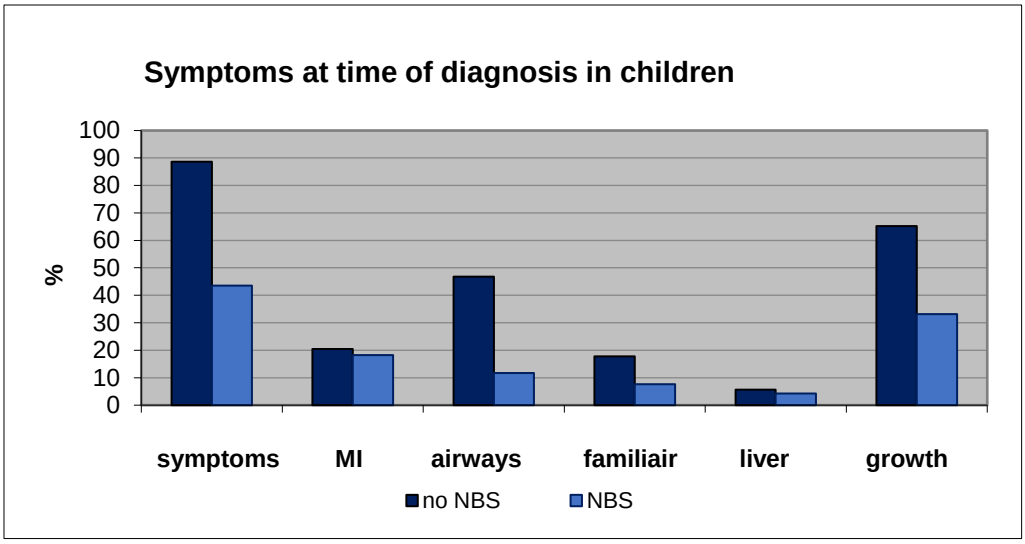



**Figure 2. Number of children diagnosed per year, both after newborn screening (NBS) and at a later age, virtually always without newborn screening (NBS).**

### Symptoms upon diagnosis

Symptoms that lead to the CF diagnosis vary. The CF diagnosis can be made quickly in children who were born with an obstructed intestine (meconium ileus, MI; 19.9% of children). Poor growth or a poor nutritional status leads to a CF diagnosis in 55% of the cases. In 36% of children, the diagnosis was made on the basis of respiratory problems, 5% suffer from problems with the liver and in 15% of children, the diagnosis was made on the basis of a family history of CF. Other symptoms and combinations also occur. After the introduction of newborn screening, the percentage of children with symptoms at the time of the diagnosis dropped (figure 3).




MI: Meconium Ileus

**Figure 3. Symptoms at the time of diagnosis in children with CF before and after the introduction of newborn screening (NBS).**

**Mutations**

In 97.3% of patients, the result of a genetic examination is known. In children, this figure is as high as 99.9%.
The percentage of patients with a F508del mutation on both chromosomes (homozygotic) is 51.7%. In children, this is 55%, in adults, it is 49.5%.

The percentage of patients with a F508del mutation on a single chromosome and a different mutation on the other chromosome (heterozygotic) is 36.1%, both in children and adults.
The percentage of patients with a non-F508del mutation on both chromosomes is 9.9%. In children, this is 8.8%, in adults, it is 10.1%.

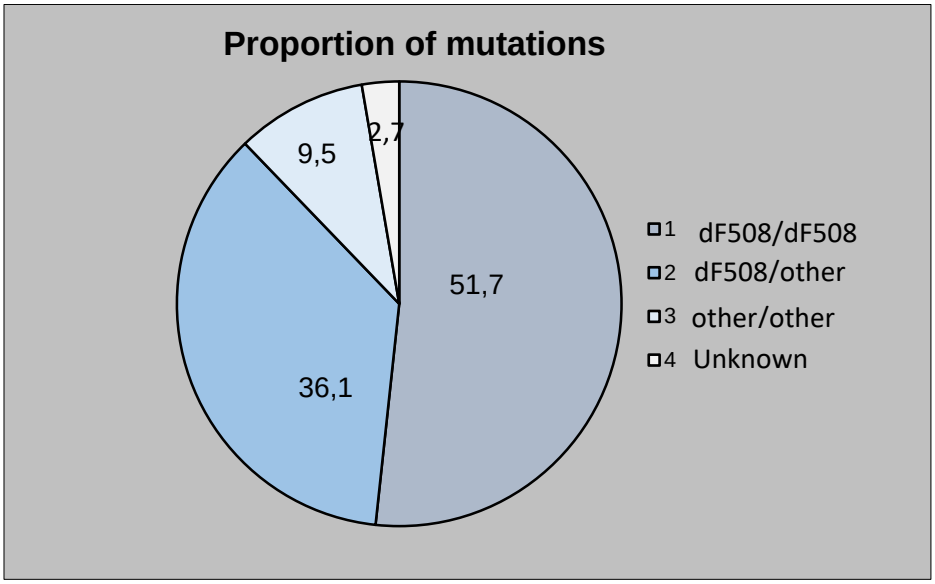



**Figure 4. Distribution of mutations in children and adults combined**

The distribution of the percentage of patients with a homozygotic F508del mutation various per CF centre for children (50 to 71%) and adults (41 to 57%).

In 87.8% of patients, the F508del mutation occurs on at least one chromosome.
The other mutations are much rarer.
Table 1 provides an overview of the most common mutations (when occurring more than 0.5%) in patients who have undergone DNA testing. Both “arms” (alleles) of the pair of chromosomes are included in the percentage calculation.

| **Mutation** | **Frequency (%)** | **Mutation category** |
|---|---|---|
| F508del | 71.5 | 2 |
| A455E | 4.0 | 5 |
| R117H | 2.7 | 4 |
| G542X | 1.8 | 1 |
| 1717-1G>A | 1.5 | 1 |
| S1251N | 1.2 | 3 |
| 3272-26A>G | 1.2 | 5 |
| R1162X | 1.2 | 1 |
| N1303K | 1.0 | 1 |
| R553X | 1.0 | 1 |
| 2789+5G>A | 0.7 | 5 |
| 711+1G>T | 0.6 | 1 |
| 3849+10kbC->T | 0.6 | 5 |
| E60X | 0.6 | 1 |
| W1282X | 0.5 | 1 |
| Unknown mutation | 1.6 | |
| Other known mutations | 8.3 | |
| **Total** | **100** | |

**Table 1. Overview of the most common mutations.**
The total percentage (100) concerns 1,515 patients for whom an analysis of the mutations was conducted.
For 34 patients, no mutation examination was carried out or the results are not known.

Globally, currently more than 2,000 mutations are known that lead to CF or a so-called CF-related disease. Mutations can be grouped into categories. The nature of the disorder differs for each category due to differences in the cells, caused by the mutations.
In the case of category-1 mutations, no CFTR protein is formed, which means no chloride channels are generated in the cell wall.
The most common F508del mutation is a category-2 mutation. This results in a distorted transport of the CFTR protein to the cell surface, which means chloride channels do not develop.
In the case of category-3 mutations, chloride channels are formed but they are not activated, so they do not function.
In the case of category-4 and 5 mutations, chloride channels are in place but their numbers are limited or they function less well. As a group, these mutations are regarded as the “milder mutations”. However, no predictions about the prognosis for individual patients with CF should be derived from this.

A large number of rare mutations cannot be categorically grouped into a category. Also, a number of people have mutations of which it is not sure if they will lead to “true CF symptoms”. This is referred to as a “CF-related disease” *. Among other things, this often applies to people with an R117H mutation, which is relatively common (2.7%, see table 1) and which, so far, has been found a couple of times a year in children after newborn screening. Some people with this mutation, however, also show clear

symptoms of CF. Since 01/07/2016, children with an R117H mutation discovered after newborn screening are no longer referred to a CF centre as a standard.

* For the Registry, the CF diagnosis is confirmed when two mutations are known and which are known to cause CF (according to the CFTR2 mutation database); and/or when the chloride concentration during the sweat test is 60 mmol or higher. In 1,452 (93.7%) of the 1,549 registered patients, the CF diagnosis was confirmed on the basis of those criteria.

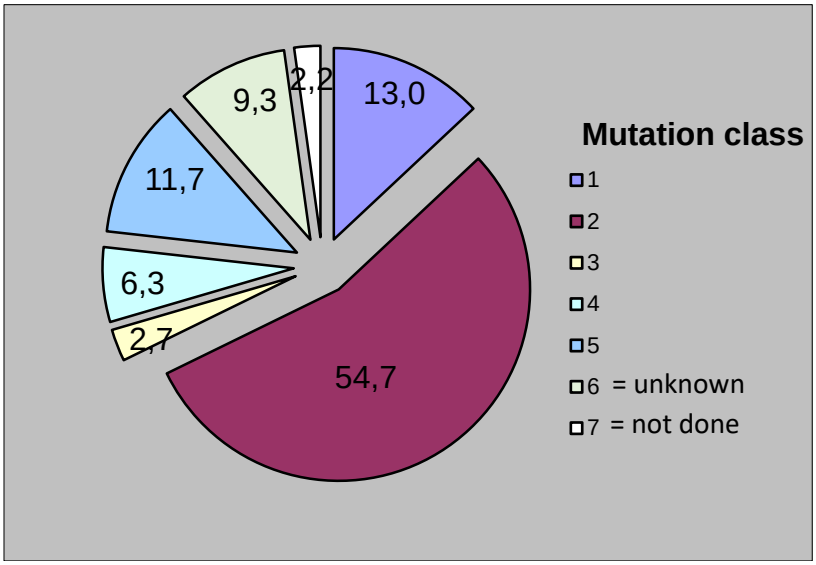



**Figure 5. Sub-division into mutation category (percentage) of all patients**
During the categorisation, the “mildest” category, if applicable, was assumed.
In 2.2% of patients, no mutation examination was carried out or the results are not known (“not done”).
In 9.3% of patients, a mutation was found but the exact category was not established (“unknown”).

# 5. Overview children (younger than 18)

For the overviews in this paragraph, the details of 596 children with a confirmed CF diagnosis were used. The diagnosis was confirmed on the basis of CF mutations and/or a positive sweattest. In 46 children, this was not (yet) the case.

The following diagrams show the centres in the same order each time. The red bars on the right show the totals for all centres.

For all diagrams, the alphabetic order is as follows, using the associated abbreviations:

Amst : CF centre Amsterdam (AMC and VUMC)
Gron : CF centre UMC Groningen
Haga : CF centre HagaZiekenhuis The Hague
Maas : CF centre Maastricht UMC
Nijm : CF centre Radboud UMC Nijmegen
Rott : CF centre Erasmus MC Rotterdam
Utre : CF centre UMC Utrecht

## 5.1 Lung function

*The FEV1 value is the maximum amount of air that can be breathed out in one second and it is an important indicator of the lung function. The FEV1 value is shown as a percentage of the predicted value (the reference value, compared to healthy peers).*
*The median value in children aged 6 to 8 is 94.3%. This means that 50% of children have a value that is lower than 94.3%, and that 50% have a value that is higher.*

The median FEV1 value in children aged 6 to 18 varies from 88 to 99% per centre and amounts to 94.3% for all paediatric centres combined (2015: 95.5%).

Figure 5 shows the FEV1 values per centre for the years 2014, 2015 and 2016.

*The interquartile range for all centres combined is 21.7% and varies from 16 to 25% per centre. Each classification is divided into four quartiles. The first quartile is the value below which 25% of FEV1 values lie when all measured values are placed in order of size, the second quartile below which 50% of FEV1 values lie, etc. The interquartile range is a measure of dispersion and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).*

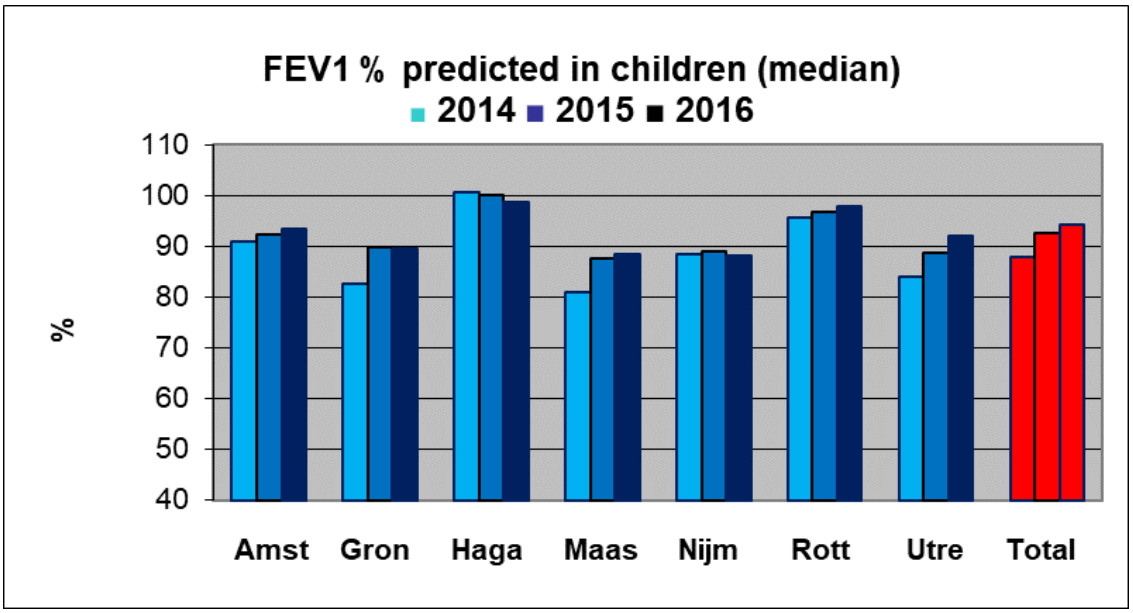



**Figure 6. Median FEV1 percentage compared to reference values in healthy children per centre and total**

Figure 7 shows the median FEV1% values per age group (6 to 12 and 12 to 18). Up to the age of 12, the median FEV1% at all centres is about 100% of the predicted value and it is exactly 100% for all centres combined.

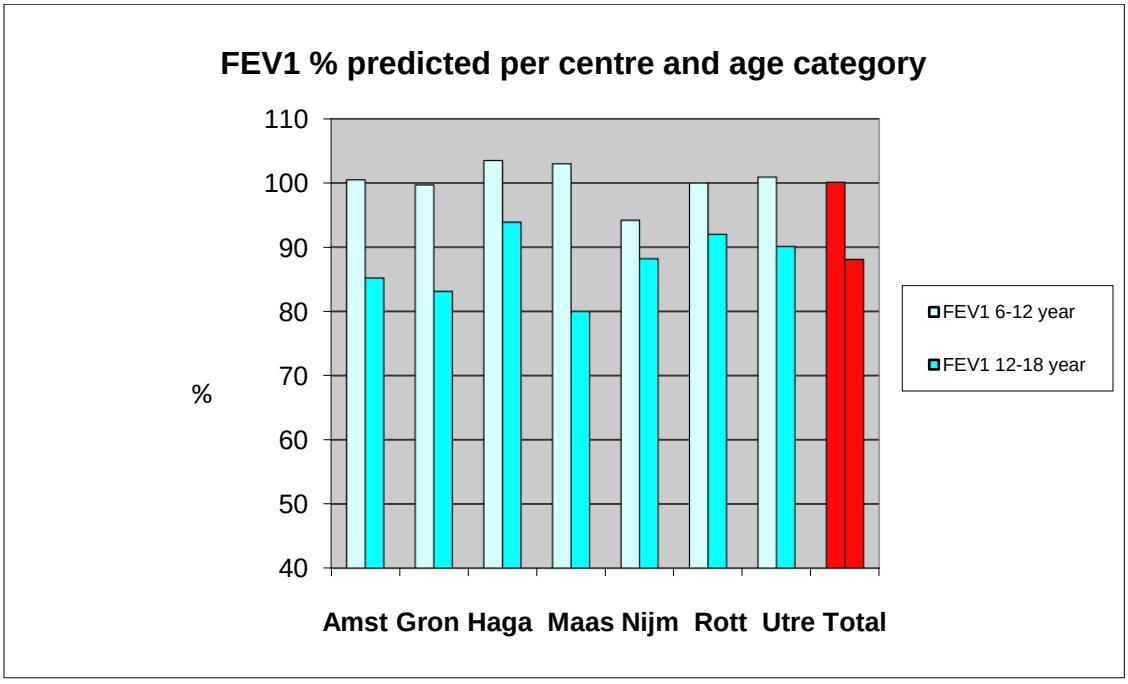



**Figure 7. Median FEV1 percentage compared to reference values in healthy children per age category and per centre**

Figure 8 shows the percentage of children per lung function category (with a FEV1 of less than 40%, between 40 and 70%, between 70 and 90% and more than 90%). This classification was chosen because other countries also use it, facilitating international comparisons.
The figure tells us that 60% of children up to the age of 18 have a lung function of more than 90% and that the percentage of children with a poorer lung function is falling.

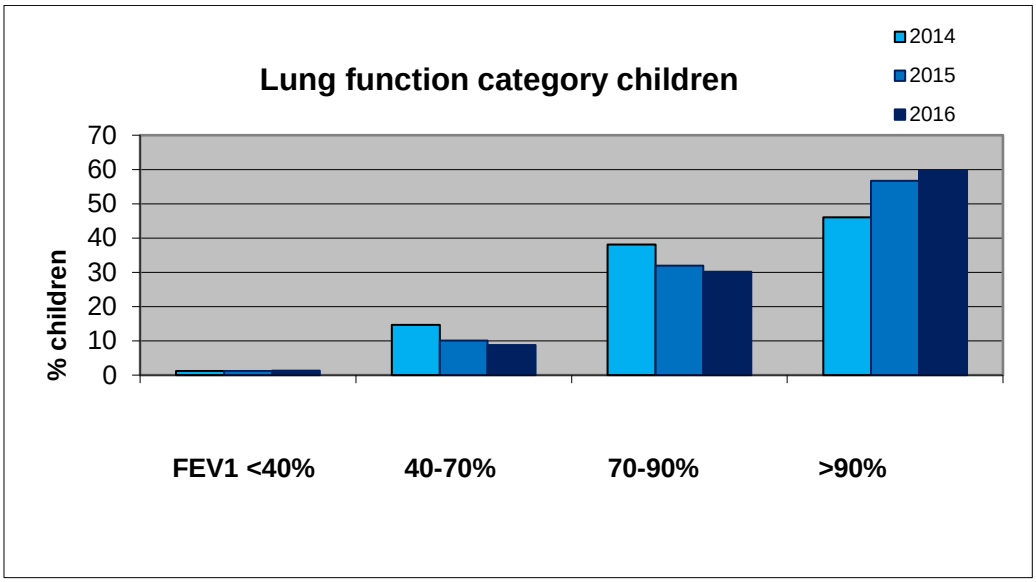



**Figure 8. Percentage of children per lung function category**

## 5.2 Micro-organisms

The airways of people with CF harbour varying quantities of micro-organisms (bacteria and fungi) that cause infections.
The occurrence of a number of important micro-organisms in children is shown in figure 9 below.
The definitions of the European CF Registry were used. This means that a chronic infection with Pseudomonas aeruginosa (PA) is regarded as being present if more than 50% of at least four sputum cultures were positive in the past year and/or if it concerns a significant rise in anti-pseudomonas antibodies (modified Leeds criteria). Also, when there are not enough cultures, the practitioner may decide there is no reason to review the previously diagnosed chronic PA infection.

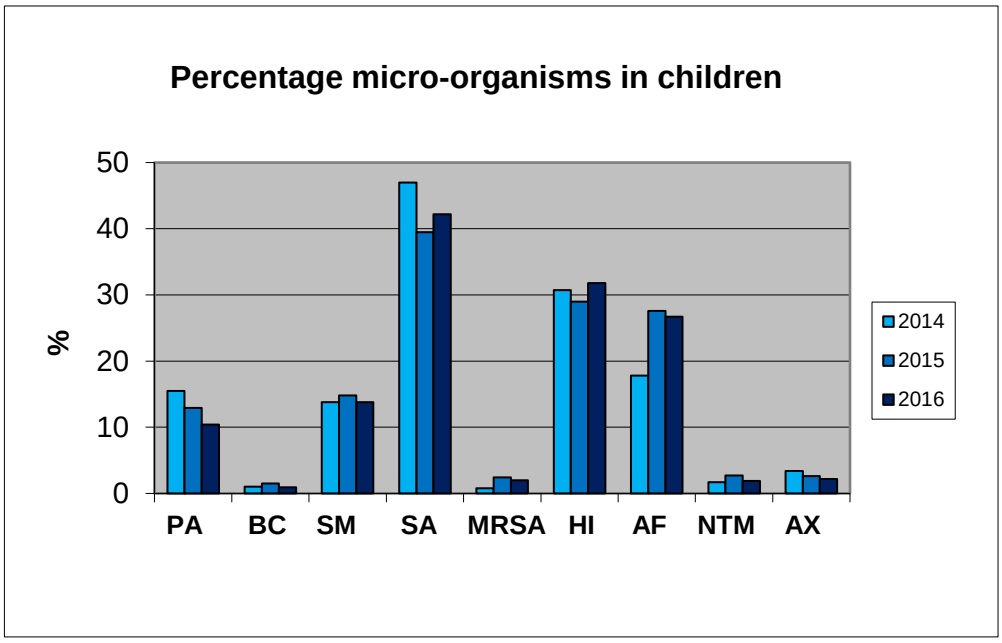



**Figure 9. Percentage of micro-organisms in children**

**PA** Pseudomonas aeruginosa
**BC** Burkholderia cepacia
**SM** Stenotrophomonas maltophilia
**SA** Staphylococcus aureus
**MRSA** Methicillin-resistant Staphylococcus aureus
**HI** Haemophilus influenzae
**AF** Aspergillus fumigatus
**NTM** Nontuberculous mycobacteria
**AX** Achromobacter xylosoxidans

Pseudomonas aeruginosa (PA) in particular influences the treatment and prognosis for many children with CF. Figure 10 shows the percentage of children with a chronic PA infection per centre. This varies per centre from 2 to 18%. In practice, the definition of chronic PA infection appears to be difficult at times, which may affect the registration thereof. Out of the total group of children, the percentage of patients with a chronic PA infection is 10.4%. In 2013, it was as high as 21.4%.

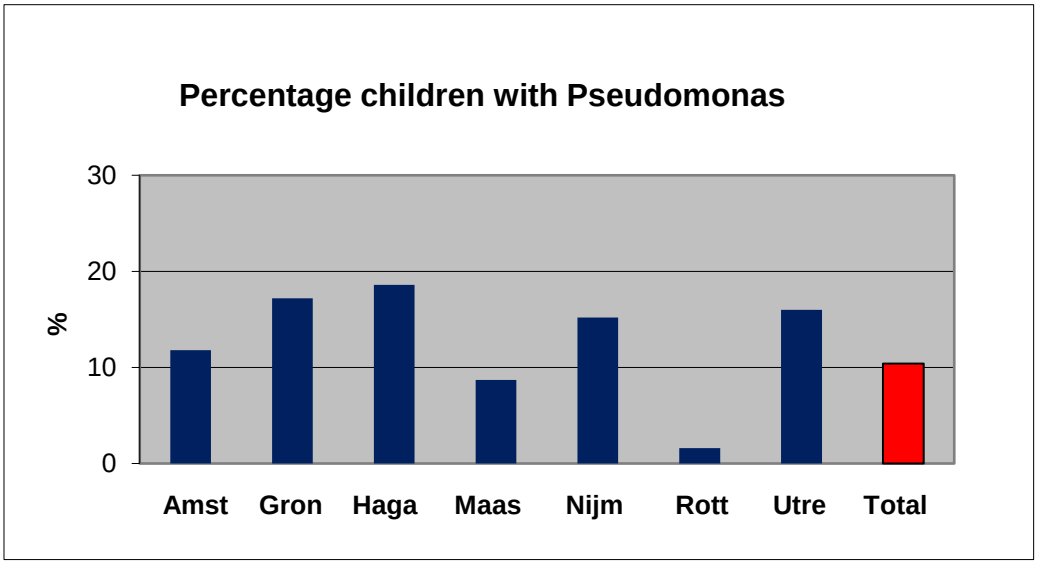



**Figure 10. Percentage of chronic PA infection in children, per centre**

The percentage of children aged 6 and over with a chronic PA infection that is treated with inhaled antibiotics is 79%.

Figure 10.A shows this percentage per centre.

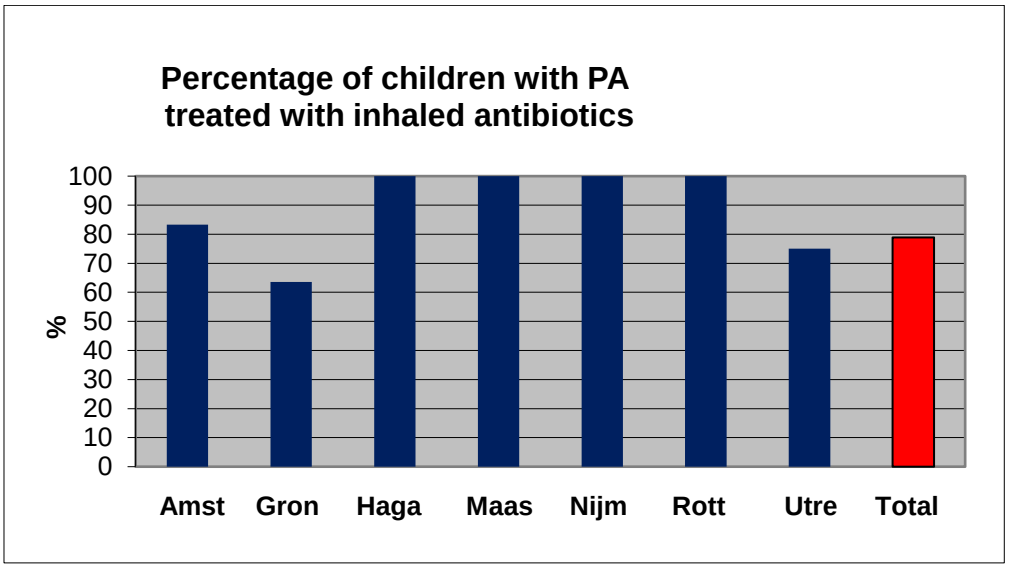



**Figure 10.A. Percentage of children older than 6 with a chronic PA infection that is treated with inhaled antibiotics, per centre**

## 5.3 Nutritional status

The optimisation of growth and weight is important for children with CF. Body weight in proportion to body height is one measure of the nutritional status, the Body Mass Index (BMI) is another. This index is calculated by dividing the weight (in kilos) by the square of the body height (in metres).
The height and weight for age are both also shown.

*All these measurements can be expressed as a standard score, also referred to as the Z-score. A Z-score with a value of 0 is average. 97% of healthy Dutch children have a score between the values -2 to +2.*

The Registry contains measures for height and weight that were taken during the lung function examination with the highest FEV1 value. For children who did not undergo a lung function examination, the measures at the time of the annual comprehensive examination were used.

**Weight according to length**
The median Z-scores for weight according to height (figure 11) vary per centre from -0.17 to +0.39. The median value for all centres combined is +0.07 (2015: +0.07).
*This means that 50% of children have a value that is lower than +0.07 and that 50% have a value that is higher.*

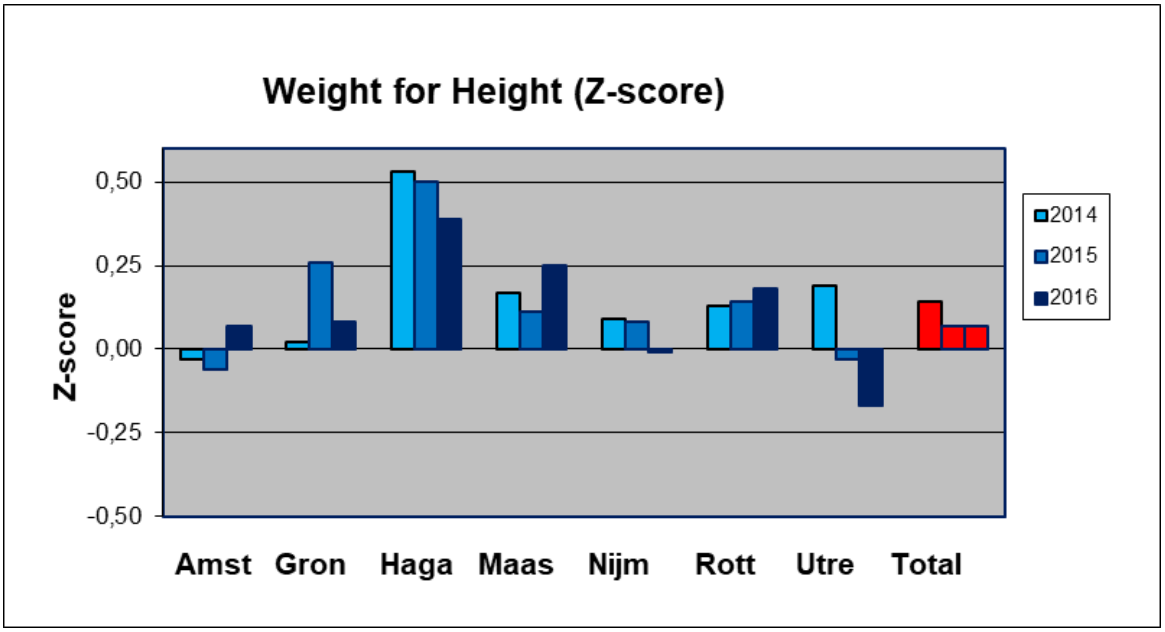



**Figure 11. Median Z-scores for weight according to height per centre from 2014 to 2016**

Figure 12 shows the change to the median Z-score for weight according to height in all children in the 2008-2016 period.

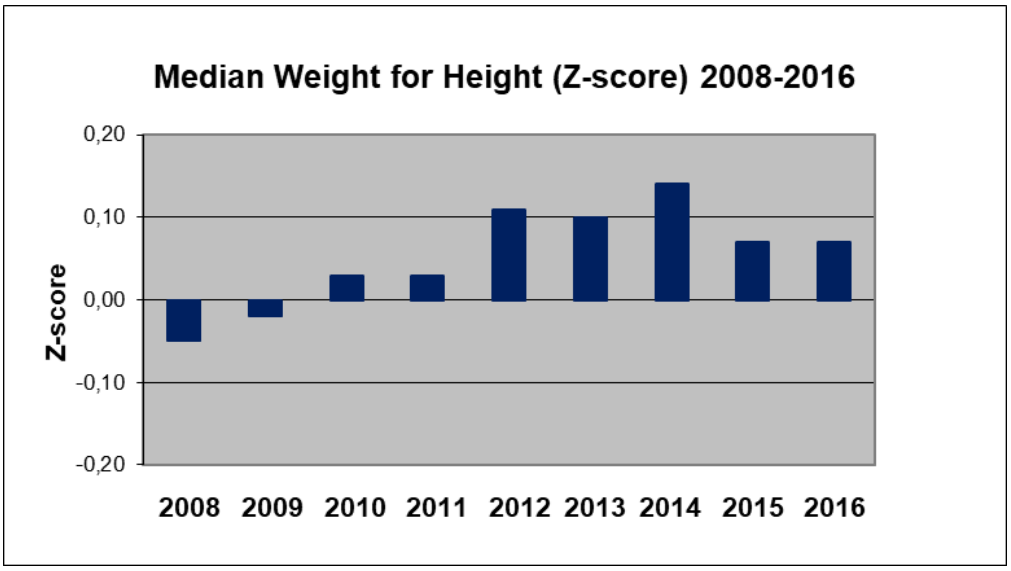



**Figure 12. Median Z-scores for weight according to height from 2008 to 2016**

Broken down into age cohort (0 to 6, 6 to 12 and 12 to 18), the median Z-scores for weight according to length are -0.09, 0.18 and 0.08 respectively.

**BMI**

The median Z-scores for BMI (figure 13) vary per centre from -0.16 to +0.45. The median value for all centres combined is +0.02.
Broken down into age cohort (0 to 6, 6 to 12 and 12 to 18), the median Z-scores for BMI are -0.06, 0.20 and -0.22 respectively.

That means that the average nutritional status of children with CF is slightly better than that of their healthy peers and that the nutritional status of children with CF has improved considerably until 2015 (figure 14). The lower score in 2016 will be studied in more detail.

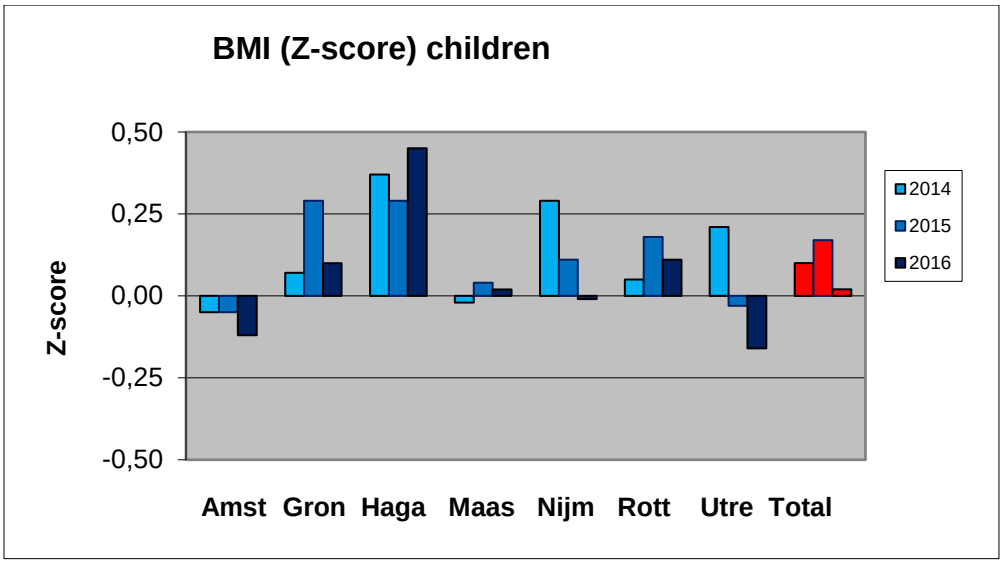



**Figure 13. Median Z-scores for BMI per centre from 2014 to 2016**

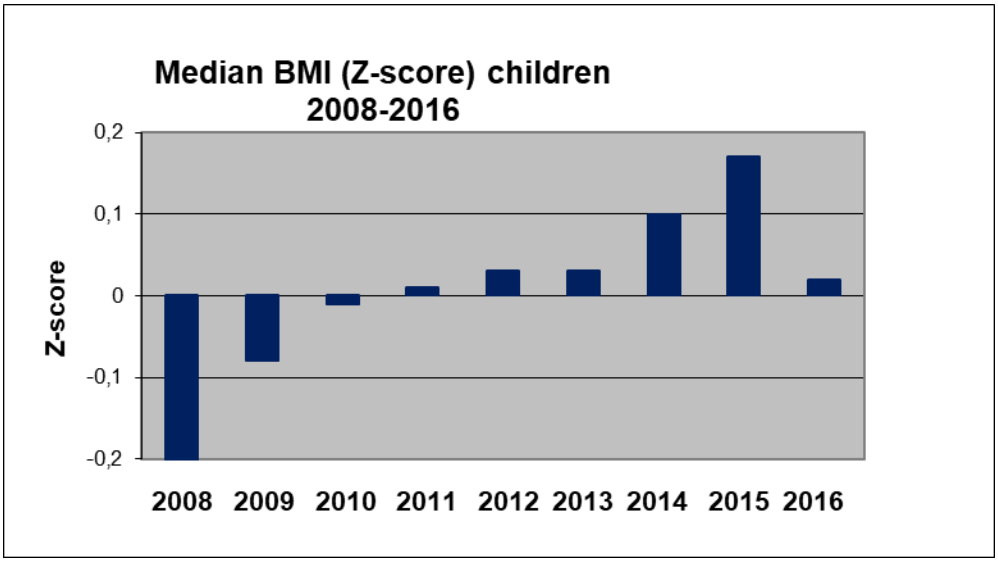



**Figure 14. Median Z-scores for BMI from 2008 to 2016**

**Weight and height according to age**

Figures 15 and 16 show the Z-scores for weight and height according to age per centre and total. This shows that the average body length in particular of children with CF is less compared to healthy peers.

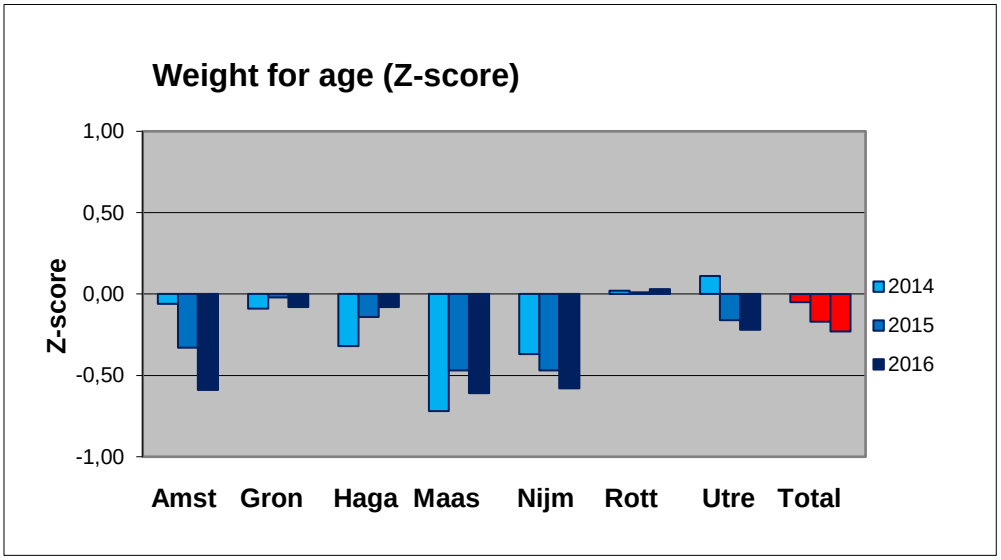



**Figure 15. Median Z-scores for weight according to age per centre from 2014 to 2016**

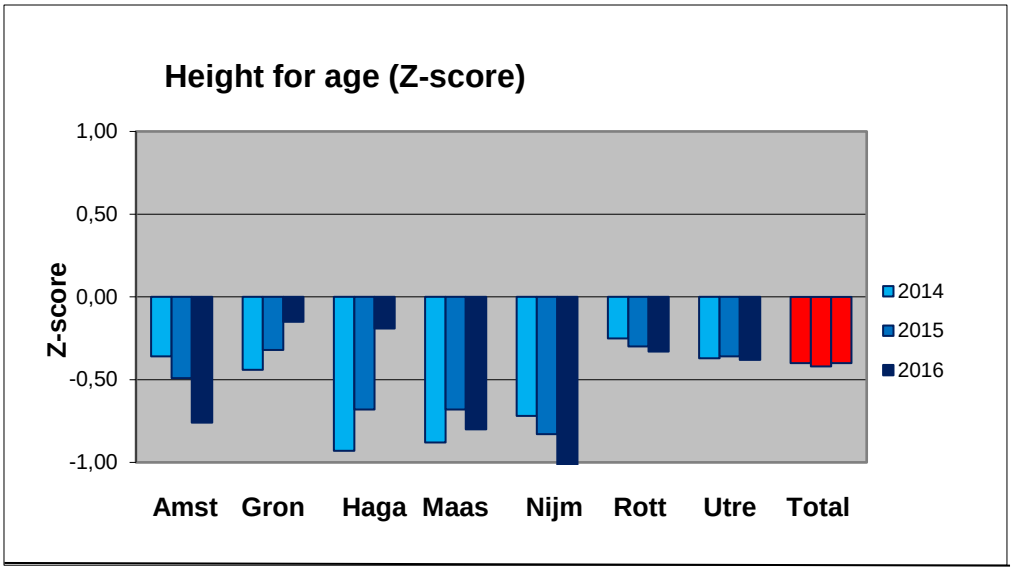



**Figure 16. Median Z-scores for height according to age per centre from 2014 to 2016**

## 5.4 Comorbidity

A number of children with CF suffer from so-called comorbidity. Examples include:
ABPA: Allergic bronchopulmonary aspergillosis is an allergic reaction to the Aspergillus fungus.
CFRD: CF-related diabetes. A number of patients develop a specific type of diabetes that is related to CF. In order to discover CFRD fast, the 'CF Diagnostics and Treatment Guideline' (2007) recommends conducting an Oral Glucose Tolerance Test (OGTT) for children aged 10 and up who do not suffer from diabetes. An OGTT was conducted in 78% of children who qualified for it (2013: 60%).
DIOS: Distal intestinal obstruction syndrome is a serious obstruction of the distal part of the small intestines and it is a common occurrence in people with CF .
Liver disease: Liver function disorders/transaminase disorders gradually develop in some people with CF and they can lead to a seriously disrupted liver function.
In the CF Registry, liver disease is defined as the existence of steatosis (fatty degeneration) and/or cirrhosis (atrophy).

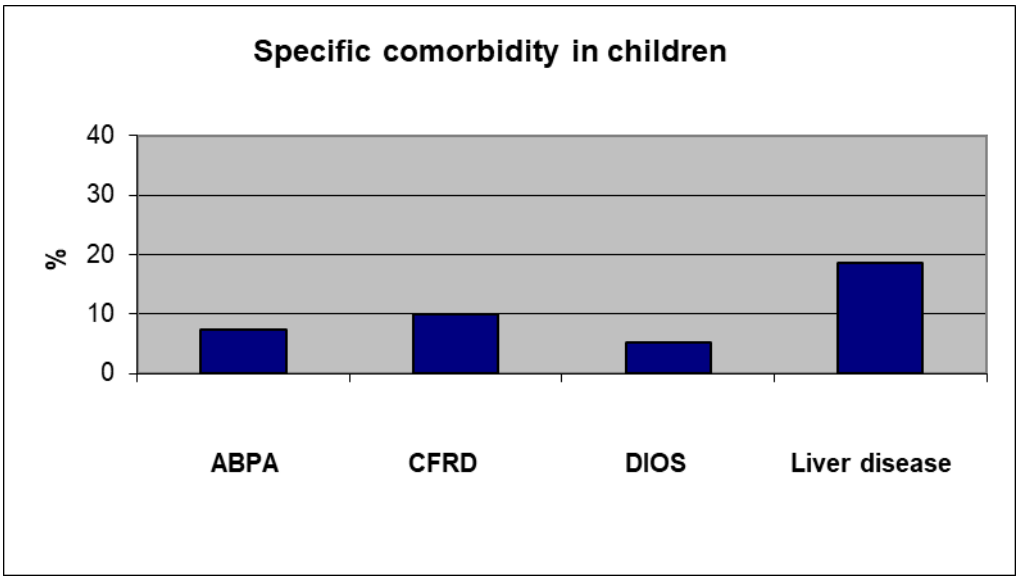



**Figure 17. Percentage specific comorbidity in children**

The percentage of children with ABPA varies per centre from 3 to 13%.
The percentage of children with CFRD varies per centre from 0 to 19%.
The percentage of children with DIOS varies per centre from 0 to 11%.
The percentage of children with liver disease varies per centre from 4 to 33%.

## 5.5 Treatment

The table below shows the percentages of various aspects of the treatment of children with a confirmed CF diagnosis (n=610).

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|---|---|---|
| **Use of pancreatic enzymes** | 89.3 | 89.5 | 85.8 | 92.1 | 89.8 | 91.2 | 88.7 | 89.5 |
| **Use of protonpump inhibitors** | 36.1 | 37.7 | 37.6 | 45.4 | 42.7 | 42.3 | 37.2 | 38.0 |
| **Use of food supplements** | 51.9 | 52.8 | 59.9 | 50.6 | 48.2 | 61.6 | 49.1 | 56.4 |
| Energy-rich liquid food | 50.7 | 47.6 | 52.4 | 43.7 | 43.3 | 55.4 | 37.2 | 55.6 |
| Food via a tube or gastrostomy | 12.2 | 11.3 | 12.3 | 16.7 | 13.0 | 11.5 | 11.9 | 12.3 |
| **Use of ursodeoxycholic acid** | 26.7 | 26.8 | 27.5 | 28.6 | 26.8 | 27.4 | 25.1 | 26.1 |
| **Nebulising with mucus thinners** | | | | | | | | |
| RhDNase | 62.2 | 64.0 | 63.9 | 73.1 | 68.3 | 60.8 | 72.7 | 68.3 |
| Acetylcystein | 2.6 | 0.8 | 0.3 | 0.3 | 0.6 | 0.2 | 0 | 0 |
| Hypertonic saline | 20.2 | 20.9 | 23.5 | 24.7 | 20.8 | 28.8 | 28.5 | 26.5 |
| **Intravenous antibiotics** | | | | | | | | |
| In hospital | - | - | 24 | 22 | 20.6 | 24.2 | 17.3 | 16.9 |
| Home treatment | - | - | 11 | 7 | 6.0 | 13.4 | 8.6 | 10.4 |
| **Maintenance antibiotics** | | | | | | | | |
| Tobramycin nebuliser solution | | | | 19.6 | 14.3 | 19.8 | 7.8 | 8.9 |
| Colistin inhalation | | | | 13.0 | 12.4 | 17.9 | 7.4 | 8.2 |
| Dry powder antibiotics | | | | 3.9 | 5.9 | 3.8 | 1.9 | 1.6 |
| Aztreonam lysine inhalation | | | | 1.2 | 1.7 | 2.6 | 0.7 | 1.4 |
| Inhaled antibiotics total | 27.7 | 26.0 | 25.9 | 24.8 | 25.7 | 37.0 | 26.5 | 20.4 |
| Macrolides | 24.1 | 25.0 | 24.1 | 23.7 | 21.5 | 25.8 | 19.5 | 15.3 |
| **Corticosteroids** | | | | | | | | |
| Oral | 9.1 | 8.7 | 7.1 | 8.1 | 8.4 | 12.8 | 9.2 | 8.7 |
| Inhaled medication | 19.7 | 19.4 | 14.4 | 20.4 | 25.2 | 28.3 | 33.7 | 36.3 |
| **Bronchodilators** | | | | | | | | |
| Inhaled medication | 28.0 | 27.0 | 29.0 | 34.0 | 29.6 | 29.5 | 28.5 | 35.9 |
| **Use of extra oxygen** | 2.6 | 2.4 | 1.5 | 2.3 | 2.6 | 2.1 | 1.9 | 1.2 |
| **Non-invasive ventilation** | 0.3 | 0.3 | 0.6 | 1.1 | 0.7 | 0.3 | 0.5 | 0.2 |
| **Kalydeco** (no. of users**)** | | | | | | 5 | 14 | 17 |
| **Orkambi** (no. of users) | | | | | | | 3 | 9 |

## 5.6 Transplants in children

The table below shows the number of children that have been involved in a transplant process.

| | |
|---|---|
| Liver transplant before 2016 | 0 |
| Liver transplant on the waiting list as at 31/12/2016 | 0 |
| Liver transplant in 2016 | 0 |
| | |
| Lung transplant before 2016 | 4 |
| Lung transplant on the waiting list as at 31/12/2016 | 2 |
| Lung transplant in 2016 | 1 |

### 5.7 Patients who died

In 2016, two children with CF died.

# 6. Adults (18 and older)

This paragraph provides the details of 758 adults without a lung transplant (n=98) and with a confirmed CF diagnosis. The diagnosis was confirmed on the basis of CF mutations and/or a positive sweat test. In 57 adults, this was not (yet) the case. In 15% of adults with CF, the diagnosis was made after the age of 18.

The following diagrams show the centres in a fixed order each time. The red bars on the right show the totals for all centres.

For all diagrams, the order is as follows, using the associated abbreviations:

Amst : CF centre Amsterdam (AMC)
Gron : CF centre UMC Groningen
Haga : CF centre HagaZiekenhuis The Hague
Maas : CF centre Maastricht UMC
Nijm : CF centre Radboud UMC Nijmegen
Rott : CF centre Erasmus MC Rotterdam
Utre : CF centre UMC Utrecht

## 6.1 Lung function

The FEV1 value is the maximum amount of air that can be breathed out in one second and it is an important indicator of the lung function. The FEV1 value is shown as a percentage of the predicted value (the reference value, compared to healthy peers).
The median value is 70.2% *This means that 50% of adults have a value that is lower than 70.2% of the predicted value and that 50% have a value that is higher. In 2015, this median value was 66.3%.*

The median FEV1 value of adults varies from 62 to 73% per centre (in 2015, this varied from 64 to 72% per centre).

Figure 18 shows the FEV1 values per centre for the years 2014 to 2016.

*The interquartile range for all centres combined is 35% and varies from 26 to 42% per centre. Each classification is divided into four quartiles. The first quartile is the value below which 25% of FEV1 values lie when all measured values are placed in order of size, the second quartile below which 50% of FEV1 values lie, etc. The interquartile range is a measure of dispersion and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).*

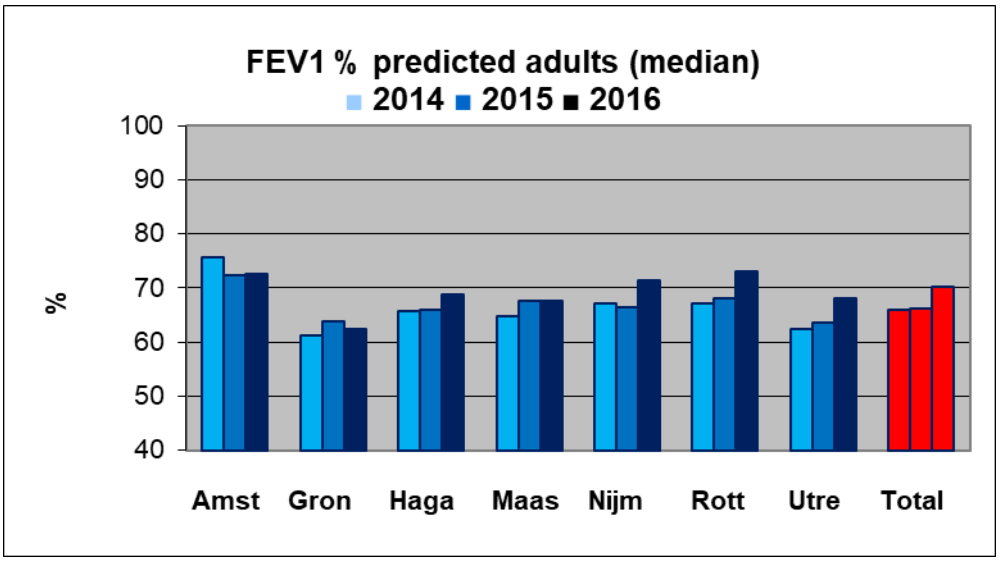



**Figure 18. Median FEV1 percentage compared to reference values in healthy adults per centre**

Figure 19 shows the percentage of adults per lung function category (FEV1 of less than 40%; between 40 and 70%; between 70 and 90% and higher than 90%). This classification was chosen because other countries also use it, facilitating international comparisons.
The fact that the number of groups with a FEV1 < 70% is gradually falling and that the number of groups with a higher FEV1 is gradually rising is a positive development. The percentage of patients with a FEV1 < 40% varies from 8 to 18% per centre.

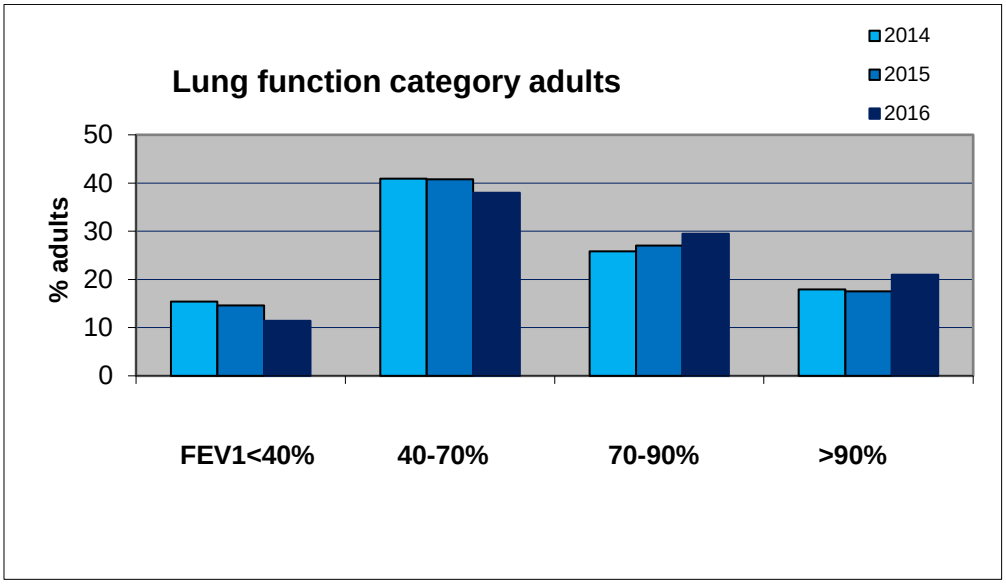



**Figure 19. Percentage of adults per lung function category**

## 6.2 Micro-organisms

The airways of people with CF harbour varying quantities of micro-organisms (bacteria and fungi) that cause infections that get progressively worse.
The occurrence of a number of important micro-organisms in adults is shown in the figure below.
Since 2010, the definitions of the European CF Registry are used. This means that a chronic infection with Pseudomonas aeruginosa is regarded as being present if more than 50% of the sputum cultures were positive in the past year and/or if it concerns a significant rise in anti-pseudomonas antibodies (modified Leeds criteria). Also, when there are not enough cultures, the practitioner may decide there is no reason to review the previously diagnosed chronic PA infection.

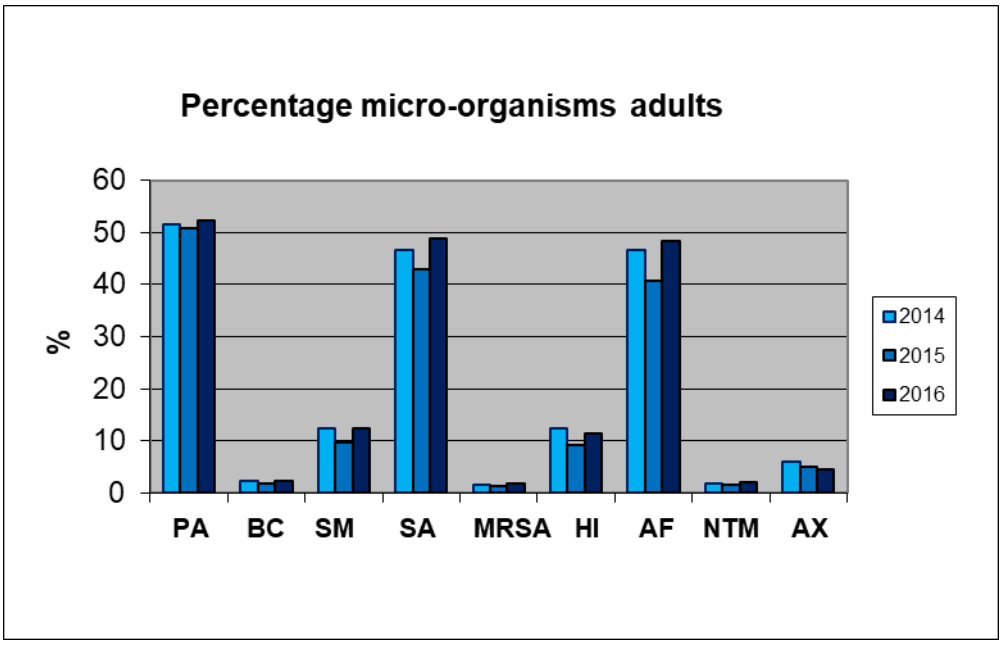



**Figure 20. Percentage of micro-organisms in adults**

**PA** Pseudomonas aeruginosa
**BC** Burkholderia cepacia
**SM** Stenotrophomonas maltophilia
**SA** Staphylococcus aureus
**MRSA** Methicillin-resistant Staphylococcus aureus
**HI** Haemophilus influenzae
**AF** Aspergillus fumigatus
**NTM** Nontuberculous mycobacteria
**AX** Achromobacter xylosoxidans

The percentage of adults with a chronic Pseudomonas infection remains unchanged at about 50%.
The percentage of adults in whom a Burkholderia, MRSA or Mycobacteria is generated remains low.

Pseudomonas aeruginosa (PA) in particular has an impact on the treatment and prognosis for many adults with CF. Figure 21 shows the percentage of adults with a chronic PA infection per centre. This percentage is 52% for the total group of adults.

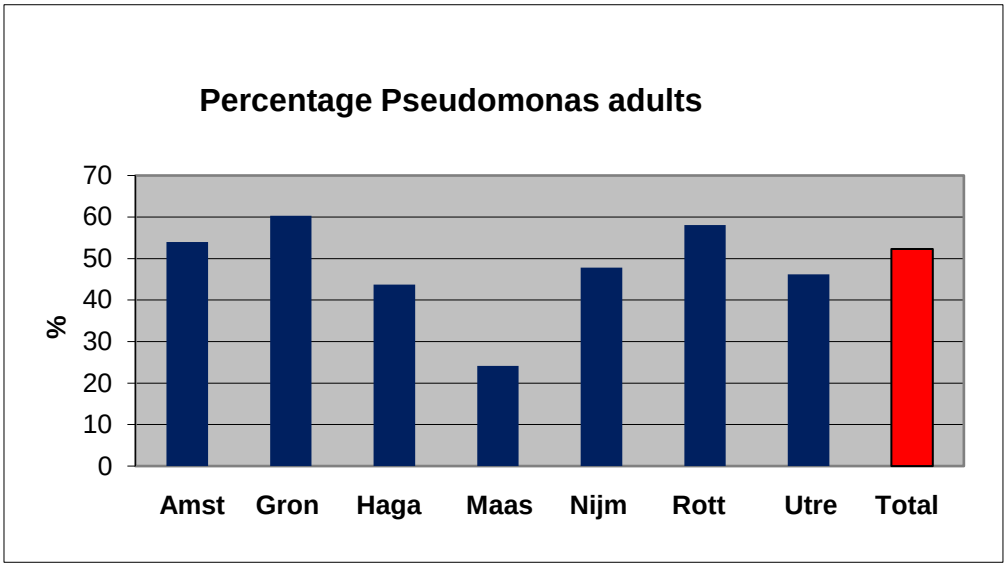



**Figure 21. Percentage chronic PA infection in adults per centre**

The percentage of adults with a chronic PA infection that is treated with inhaled antibiotics is 85%.

Figure 21.A shows this percentage per centre.

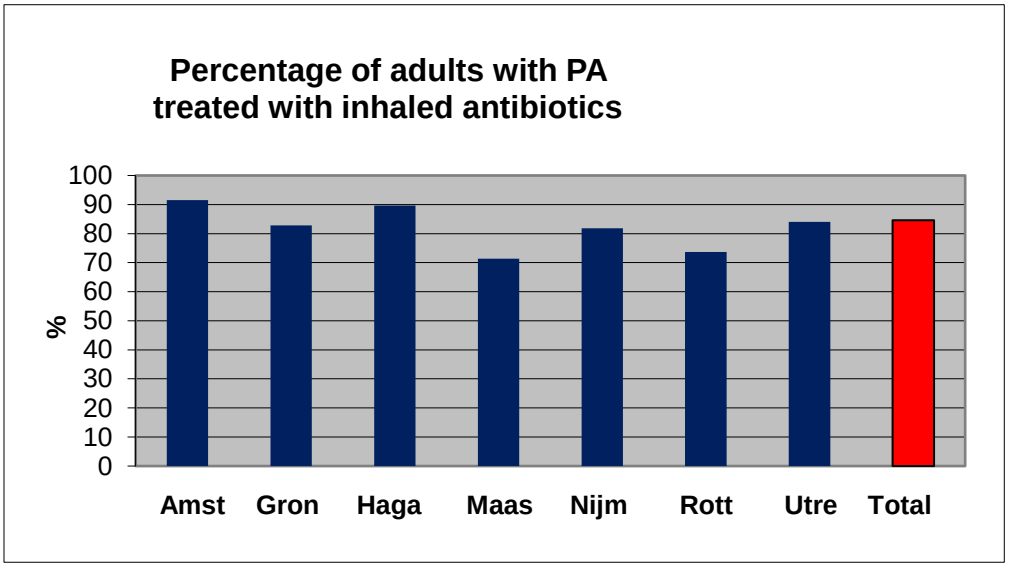



**Figure 21.A. Percentage of adults with a chronic PA infection that is treated with inhaled antibiotics, per centre**

## 6.3 Nutritional status

Maintaining a good nutritional status or improving it is important for adults with CF.
*The nutritional status of adults is indicated by the Body Mass Index (BMI). The BMI is calculated by dividing the body weight (in kilos) by the square of the body height (in metres).*
The median BMI values for adults vary from centre to centre (figure 22) from 21.1 to 22.6 (2015: 21.1 to 22.4). The total of all centres combined is 21.8 (in previous years, this was 21.6 (figure 23)). This means that 50% of adults have a value that is lower than 21.8. BMI values between 18.5 and 25 are regarded as normal but for people with CF, the aim is to achieve a higher than average value.

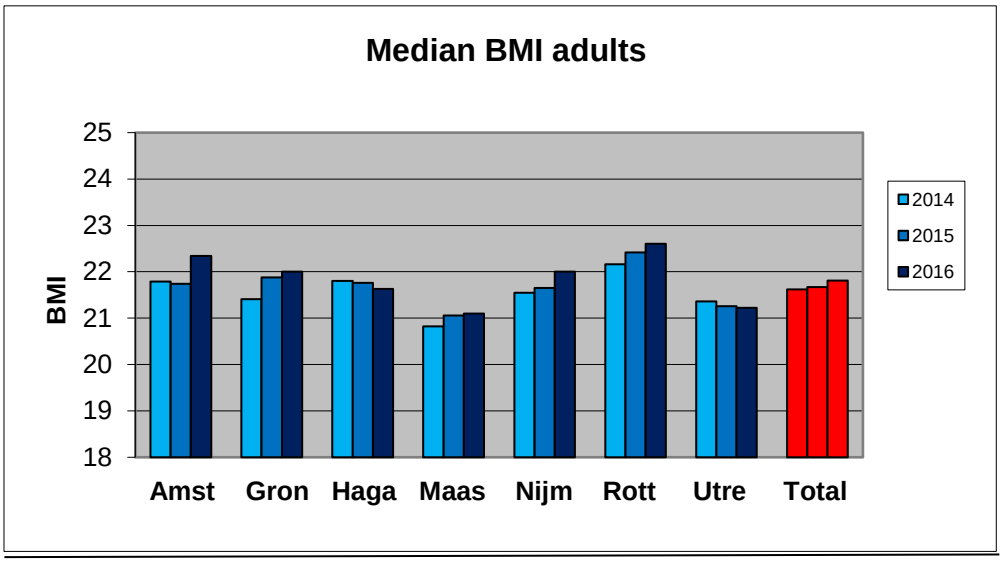



**Figure 22. Median BMI values for adults per centre from 2014 to 2016**

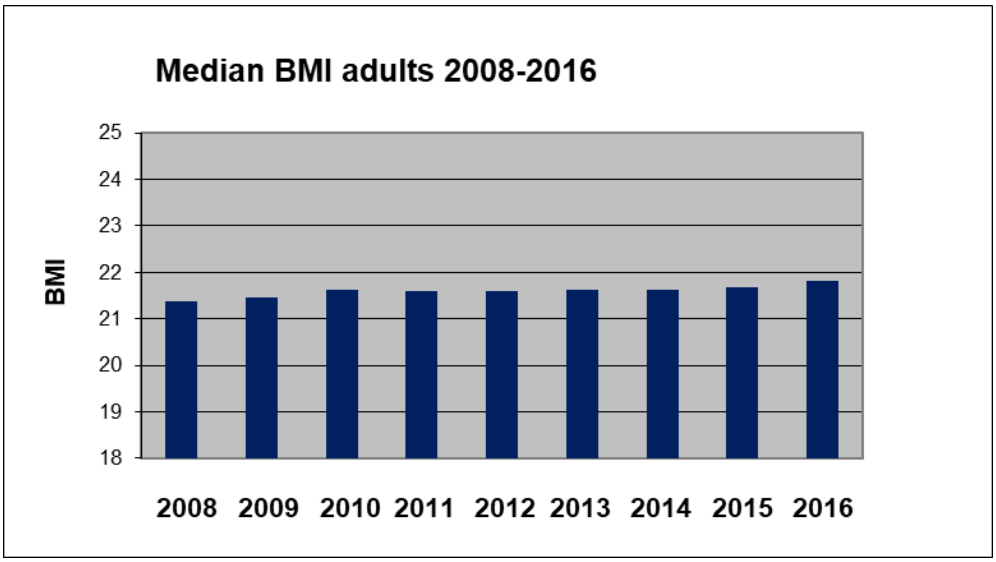



**Figure 23. Median BMI values for adults from 2008 to 2016**

## 6.4 Comorbidity

A number of adults with CF suffer from so-called comorbidity. Examples include:
ABPA: Allergic bronchopulmonary aspergillosis is an allergic reaction to the Aspergillus fungus.
CFRD: CF-related diabetes. Adults, in particular, can develop a special form of CF-related diabetes. In order to discover CFRD fast, the 'CF Diagnostics and Treatment Guideline' (2007) recommends conducting an Oral Glucose Tolerance Test (OGTT) for adults who do not suffer from diabetes. An OGTT was conducted in 52% of adults who qualified for one. In 2015, this figure was 59%, in 2014 60%, in 2013 50% and in 2012 37%.
DIOS: Distal intestinal obstruction syndrome is a serious obstruction of the distal part of the small intestines and it is a common occurrence in people with CF .
Liver diseases: Liver function disorders and transaminase disorders gradually develop in some people with CF and they can lead to a seriously disrupted liver function.
In the CF Registry, liver disease is defined as the existence of steatosis (fatty degeneration) and/or cirrhosis (atrophy).

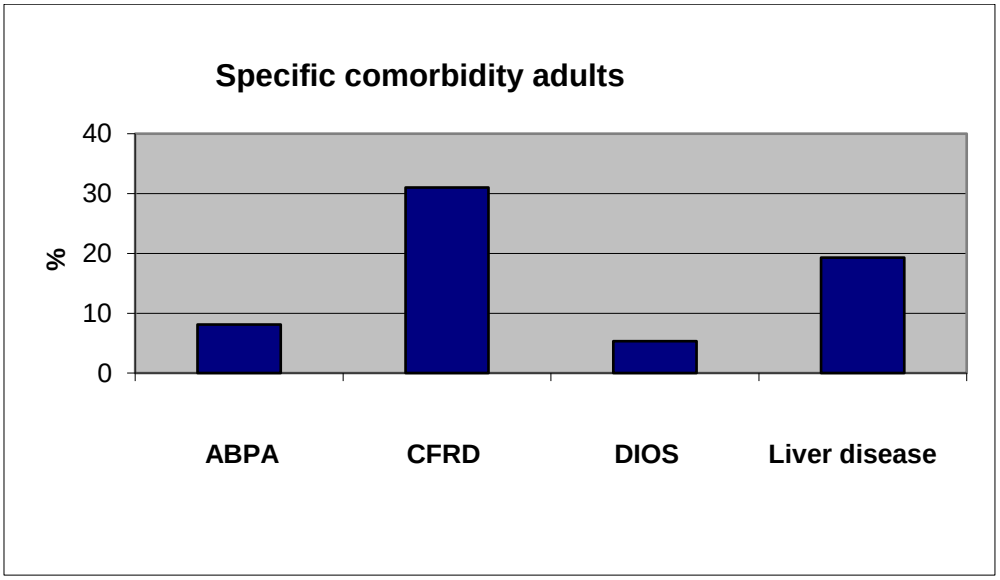



**Figure 24. Percentage specific comorbidity in adults**

The percentage of adults with ABPA varies per centre from 0 to 16%.
The percentage of adults with CFRD varies per centre from 22 to 45%.
The percentage of adults with DIOS varies per centre from 0 to 11%.
The percentage of adults with liver disease varies per centre from 9 to 40%.

## 6.5 Treatment

The table below shows the percentages of various aspects of the treatment of adults with CF.

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|---|---|---|
| **Use of pancreatic enzymes** | 82.6 | 80.5 | 76.8 | 80.3 | 76.7 | 79.0 | 75.7 | 77.4 |
| **Use of protonpump inhibitors** | 47.1 | 48.8 | 46.5 | 48.8 | 53.0 | 53.8 | 49.8 | 45.1 |
| **Use of food supplements** | 42.5 | 41.2 | 40.3 | 47.7 | 38.2 | 40.8 | 43.5 | 38.3 |
| Energy-rich liquid food | 41.5 | 39.7 | 38.4 | 45.0 | 35.4 | 39.0 | 35.1 | 36.6 |
| Food via a tube or gastrostomy | 12.3 | 9.2 | 7.5 | 7.8 | 7.3 | 5.4 | 4.4 | 5.2 |
| **Use of ursodeoxycholic acid** | 29.6 | 29.1 | 29.3 | 29.2 | 29.3 | 28.7 | 24.6 | 26.5 |
| **Nebulising with mucus thinner** | | | | | | | | |
| RhDNase | 54.6 | 60.3 | 60.7 | 63.8 | 63.0 | 64.4 | 62.9 | 66.5 |
| Acetylcystein | 9.6 | 6.5 | 5.3 | 3.8 | 3.9 | 2.9 | 3.0 | 4.2 |
| Hypertonic saline | 17.6 | 26.5 | 27.5 | 26.7 | 28.9 | 27.5 | 26.5 | 30.7 |
| **Intravenous antibiotics** | | | | | | | | |
| In hospital | - | - | 24 | 22.4 | 22.5 | 23.4 | 32.2 | 24.1 |
| Home treatment | - | - | 25 | 22.4 | 22.7 | 21.8 | 26.9 | 20.7 |
| **Maintenance antibiotics** | | | | | | | | |
| Tobramycin nebuliser solution | - | - | - | 10.2 | 12.4 | 15.0 | 23.2 | 21.0 |
| Colistin | - | - | - | 31.3 | 29.8 | 26.4 | 27.8 | 25.2 |
| Dry powder antibiotics | - | - | - | 28.1 | 28.3 | 21.6 | 9.9 | 20.5 |
| Aztreonam lysine inhalation | - | - | - | 10.9 | 18.3 | 16.3 | 16.4 | 21.8 |
| Inhaled antibiotics total | 54.4 | 52.8 | 56.1 | 58.8 | 58.7 | 59.7 | 58.5 | 56.4 |
| Macrolides | 63.8 | 64.4 | 63.7 | 69.3 | 64.1 | 67.9 | 62.4 | 60.8 |
| **The use of corticosteroids** | | | | | | | | |
| Oral | 17.2 | 14.8 | 16.4 | 2.3 | 19.4 | 12.6 | 9.2 | 12.3 |
| Inhaled medication | 44.8 | 49.4 | 45.9 | 44.4 | 51.7 | 56.0 | 53.5 | 48.7 |
| **The use of bronchodilators** | | | | | | | | |
| Inhaled medication | 59.4 | 63.6 | 65.5 | 65.4 | 56.3 | 60.2 | 60.4 | 64.0 |
| **Use of extra oxygen** | 8.2 | 8.1 | 7.2 | 5.3 | 5.1 | 5.4 | 5.8 | 5.9 |
| **Non-invasive respiration** | 3.1 | 1.6 | 1.2 | 0.3 | 1.2 | 0.4 | 0.4 | 0.9 |
| **Kalydeco** (no. of users**)** | | | | | | 8 | 18 | 31 |
| **Orkambi** (no. of users) | | | | | | | 10 | 74 |

## 6.6 Transplants in adults

The table below shows the number of adults that have been involved in a transplant process.

| | |
|---|---|
| Liver transplant before 2016 | 5 |
| Liver transplant on the waiting list as at 31/12/2016 | 0 |
| Liver transplant in 2016 | 1 |
| Lung transplant before 2016 | 98 (exclusive of 20 non-registered patients in 2016) |
| Lung transplant on the waiting list as at 31/12/2016 | 15 |
| Lung transplant in 2016 | 14 |

## 6.7 Patients who died

In 2016, two adults with CF died.

## 6.8. Social situation

The table below shows the work/study percentages for 596 adults.

| Work/study | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|
| Unemployed | 10.8 | 14.9 | 10.4 | 12.3 | 10.7 |
| In fulltime employment | 17.6 | 14.9 | 15.3 | 16.9 | 17.8 |
| In part-time employment | 21.5 | 22.2 | 26.7 | 26.2 | 26.5 |
| Fulltime house husband/wife | 1.7 | 1.0 | 1.4 | 1.6 | 1.4 |
| Student | 27.3 | 24.5 | 20.1 | 17.8 | 15.0 |
| Retired | 0.5 | 1.4 | 1.4 | 1.0 | 0.6 |
| Unable to work | 13.2 | 10.7 | 12.8 | 12.5 | 15.2 |
| Not known | 7.4 | 10.,4 | 11.9 | 11.7 | 12.8 |

**Marital status**

The table below shows the marital status percentages for 820 adults.

| | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|
| Single/never married | 55.8 | 53.0 | 43.0 | 40.0 | 46.1 |
| Married/cohabiting | 36.2 | 34.0 | 41.4 | 50.2 | 49.1 |
| Divorced | 1.1 | 1.4 | 1.6 | 2.0 | 3.5 |
| Widow/widower | 0.1 | 0.3 | 0.2 | 0.1 | 0.2 |
| Not known | 6.8 | 11.3 | 13.8 | 7.7 | 1.1 |

**Pregnancy**

The Registry contains details of a total of 409 adult women with CF.

Seven women were pregnant in 2016 (data of 349 women known).

Eighty-six women gave birth before 2016 (data of 275 women known).

## 6.9 Over 50s with CF

In 2016, there were 81 people (2015: 70) over the age of 50 with a confirmed CF diagnosis. Out of those people, 11 persons had a lung transplant and 3 are on the waiting list for a lung transplant.

Twenty people are older than 60. The oldest patient with CF in the Netherlands is 74.5.

53% are male and 47% are female.

The percentage of patients with a F508del mutation on both chromosomes (homozygotic) is 19.8%.
The percentage of patients with a F508del mutation on a single chromosome and a different mutation on the other chromosome (heterozygotic) is 59.3%.
The percentage of patients with a non-F508del mutation on both chromosomes is 13.6%.
In 7.4% of people, the mutation is not known.
Half of the over 50s have at least one category 4 or 5 mutation.
In 65%, the diagnosis was made after the age of 18.

The median lung function is 71%.
The median BMI is 22.8.

- 42% use pancreatic enzymes
- 23% use extra food supplements
- 57% suffer from a chronic Pseudomonas infection
- 46% use inhaled antibiotics
- 5 people use Kalydeco and 5 people use Orkambi

- 33% have CF-related diabetes (CFRD)
- 3% have CF-related liver disease (CFLD)
- 16% suffer from a loss of hearing
- 39% suffer from decreased bone strength (early-stage osteoporosis) and 18% suffer from strongly decreased bone strength (osteoporosis)

- 83% live with a partner
- 52% have a job or used to have a job and are now retired
- 36% of women have at least one child

## 7. Lung function in children and adults, men and women

Figure 25 shows the median FEV1 (percentage of predicted value) per age group from 6 to 74 years for 2014 to 2016. The decline of lung function is to a lesser extent in nearly all age groups than it used to be. The median FEV1 for all age groups combined is 79.7%. In 2015, this was 77.0%.

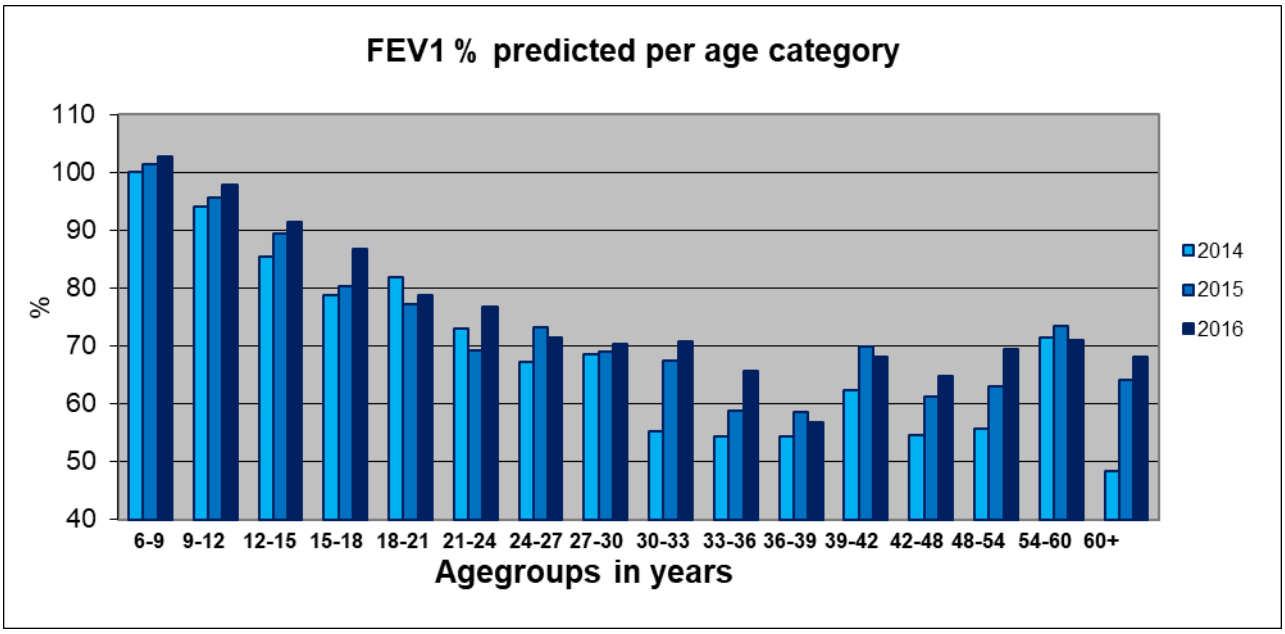



**Figure 25. Lung function (median FEV1% of the predicted value) per age category**

Figure 26 shows the median FEV1 (percentage of the predicted value) per age group from 6 to 74 for men and women. Up to the age of 27, the FEV1 tends to be higher in boys, after that, there are many differences.

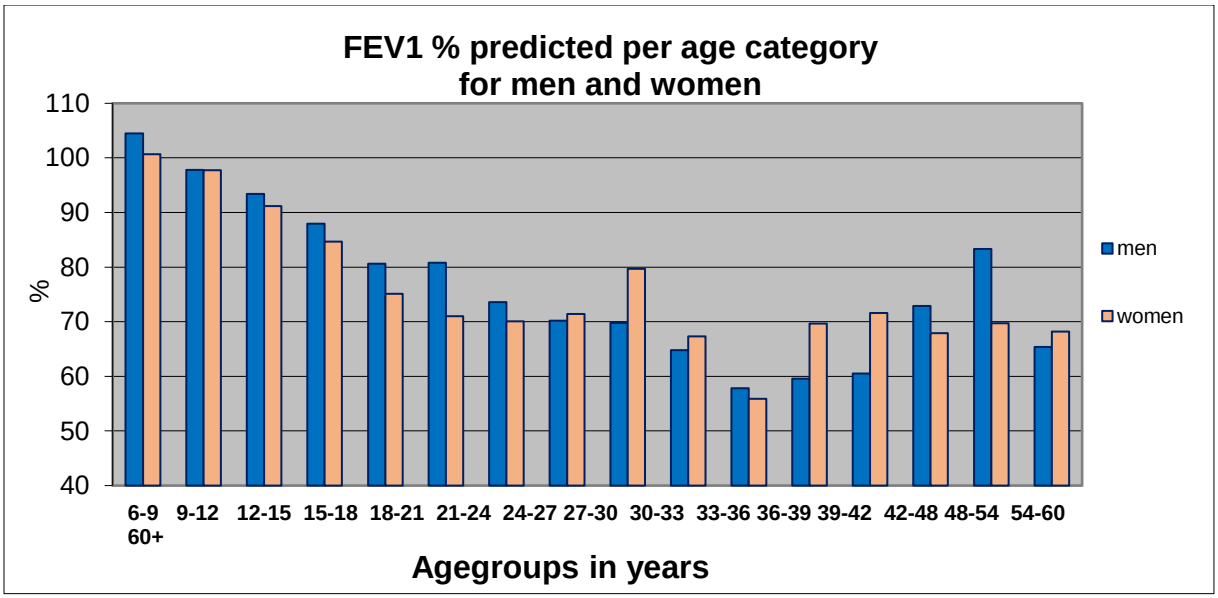



**Figure 26. Lung function (median FEV1% of predicted value) per age category for men and women.**

# 8. Indicators

**Introduction**

European and Dutch guidelines served as a basis for the development of a number of tools that provide an insight into the quality of care received by people with CF .
The NCFS quality mark serves to assess the quality of care, specifically from the perspective of people with CF .
It is important to know if the implementation of a directive will have the desired effect on the quality of care. Indicators are used to measure this.
Indicators are measurable elements of the care provision, giving an indication of the quality of the care provided. An indicator serves as an alert; it is not an immediate quality standard but it highlights a certain aspect of the performance and it may be a reason to investigate matters further. It is the core of the quality care: the actual measurement of the quality of care and the possible implementation of improvements on the basis of that measurement with the aim of improving the quality of care.
The CF Registry is used to measure a number of indicators each year. Until 2014, hospitals were obliged to disclose this information to the “Zichtbare Zorg (ZiZo)” organisation (a National healthcare transparency programme). However, much of that information was also collected within the framework of the Dutch CF Registry.

In order to prevent double Registration and to make information more accessible to a wider public, it has been agreed to include all information about CF-related indicators in the annual report of the Dutch CF Registry of the NCFS with effect from 2014.

Indicators give care providers an insight into the results of their own care process and they facilitate the internal management and improvement thereof. Indicators used for this purpose are referred to as internal indicators. Indicators can also be used to compare (benchmark) the performances of CF centres with each other. Continuous process improvements are facilitated by structural feedback on the outcome of the care and the introduction of benchmarking.
Indicators can serve yet another purpose. The government, the Netherlands Healthcare Inspectorate [Inspectie voor de Gezondheidszorg (IGZ)] and patients/consumers want to assess if care providers offer sufficient quality and they are, therefore, looking for suitable indicators. Indicators used for this purpose are referred to as external indicators. External indicators can also be used during DBC negotiations. In the case of CF, the developed external indicators are already being used by the Association of Dutch Health Insurers [Zorgverzekeraars Nederland (ZN)] for healthcare procurement purposes.

The CF care indicators listed below were developed on the basis of recommendations in the Dutch (2007) and European (2014) guidelines. The set of indicators will be evaluated and re-adopted in the course of 2018.

The following diagrams show the centres in a fixed order each time. The red bars on the right show the totals for all centres.

For all diagrams, the alphabetic order is as follows, using the associated abbreviations:

Amst : CF centre Amsterdam (AMC and VUMC)
Gron : CF centre UMC Groningen
Haga : CF centre HagaZiekenhuis The Hague
Maas : CF centre Maastricht UMC
Nijm : CF centre Radboud UMC Nijmegen
Rott : CF centre Erasmus MC Rotterdam
Utre : CF centre UMC Utrecht

**Outcome indicators**

1. Lung function

The lung function is an important indicator of the seriousness and the prognosis for people with Cystic Fibrosis. The percentage of predicted FEV1 *(*forced expiratory volume in 1 second) is a good and popular indicator for this.

The European Standards of Care guideline states that the lung function is an important indicator in the assessment of morbidity and mortality of CF. FEV1 percentage of predicted is the strongest clinical predictor of mortality and is used as a primary parameter in many clinical trials (Kerem, 1992; Ramsey, 1994; Grasemann, 1995; Flume, 2007, Smith 2014).

Figure 6 (page 13) shows the median highest FEV1 value for children per centre and the total for all centres. Figure 18 (page 25) shows these values for adults.

**2. Nutritional status**

About 80% of all People with CF suffer from an exocrine pancreas disorder. They also have a high need for calories, at times up to 150% of what a healthy person needs. That is why pancreatic enzyme supplements and a well-balanced high-calory diet with vitamin supplements are so important. Like lung function, the nutritional status is an important indicator of the prognosis.

The optimisation of growth and weight is important for children with CF. Body weight in proportion to body height is one measure of the nutritional status, the Body Mass Index (BMI) is another. This index is calculated by dividing the weight (in kilos) by the square of the body height.
These measurements can be expressed as a standard score, also referred to as the Z-score. A Z-score with a value of 0 is average. 97% of healthy Dutch children have a score between the values -2 to +2.
The Registry contains measures for height and weight that were taken during the lung function examination with the highest FEV1 value. For children who did not undergo a lung function examination, the data at the time of the annual comprehensive examination was used.
Figure 11 (page 17) shows the median Z-score for weight according to height per centre.

Maintaining a good nutritional status or improving it is also important for adults with CF. Figure 22 (page 28) shows the median BMI value for adults per centre.

**3. Infrastructure indicator**

In order to be able to gain enough experience and expertise, members of a multidisciplinary care team have to be involved in the care and treatment of People with CF on a daily basis. One condition for each centre, therefore, is to have a minimum of 50 children or adults with CF undergoing treatment and who are offered continuous/chronic care (Kerem, 2005; Conway, 2014). The complexity of the illness requires specialist CF teams at the centres.
A CF centre can only offer added value if it offers more expertise and facilities than can be found outside the centre. A centre needs to have a minimum number of sub-specialist members of staff. All sub-specialists should be in regular contact with patients and they should be able to demonstrate that

they attend extra training and refresher courses on an annual basis. The centre's expertise has to be accessible to People with CF. Furthermore, the care offered by the centre has to be of a verifiable high quality. Diagnostics and treatment protocols are in place and the implementation of this care has to be verifiable. The European Cystic Fibrosis Society (ECFS) provides guidelines which a centre has to comply with (Kerem 2005; Conway 2014). During the NCFS quality mark procedure, the conditions for a good infrastructure of a CF centre are verified.
The number of people with CF per centre are registered on an annual basis. Figure 30 shows the number of children and adults per centre.

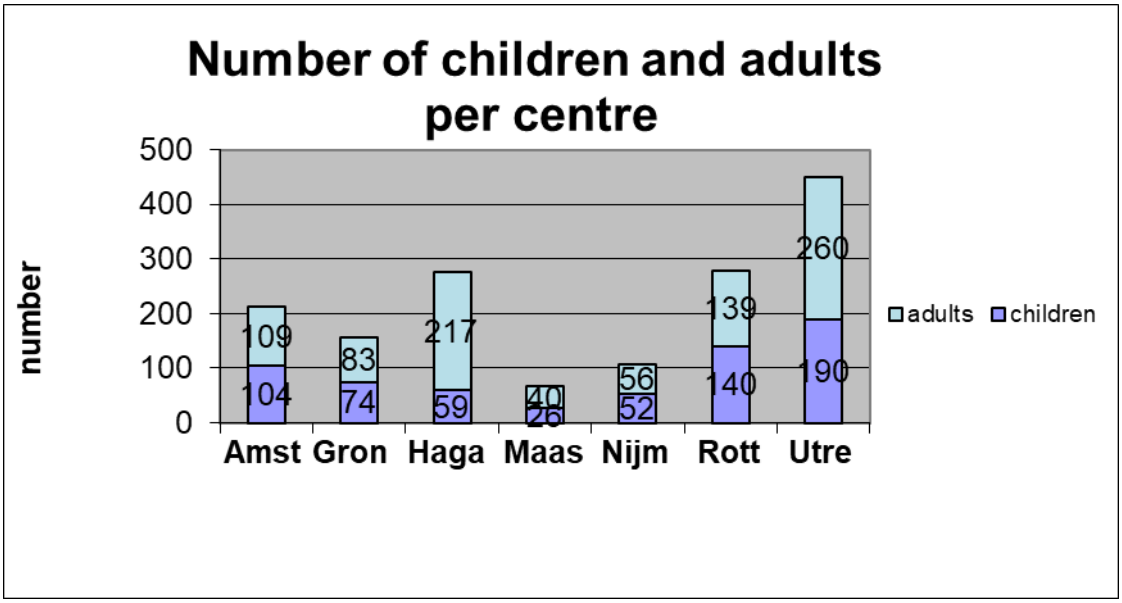



**Figure 27. Number of children and adults per centre**

### 4. Process indicators

A regular outpatient clinic measurement of various parameters helps to detect infections, disorders in the nutritional status, etc. early. This makes it possible to provide more effective care, ultimately resulting in an improved prognosis. According to the guidelines, an outpatients check must be conducted at least four times a year. During these checks, apart from anamnesis and a physical examination, sputum samples are taken, while a lung function examination is carried out from the age of six.
Figure 28 shows the percentage of children per centre who have visited the outpatient's department at least four times a year.

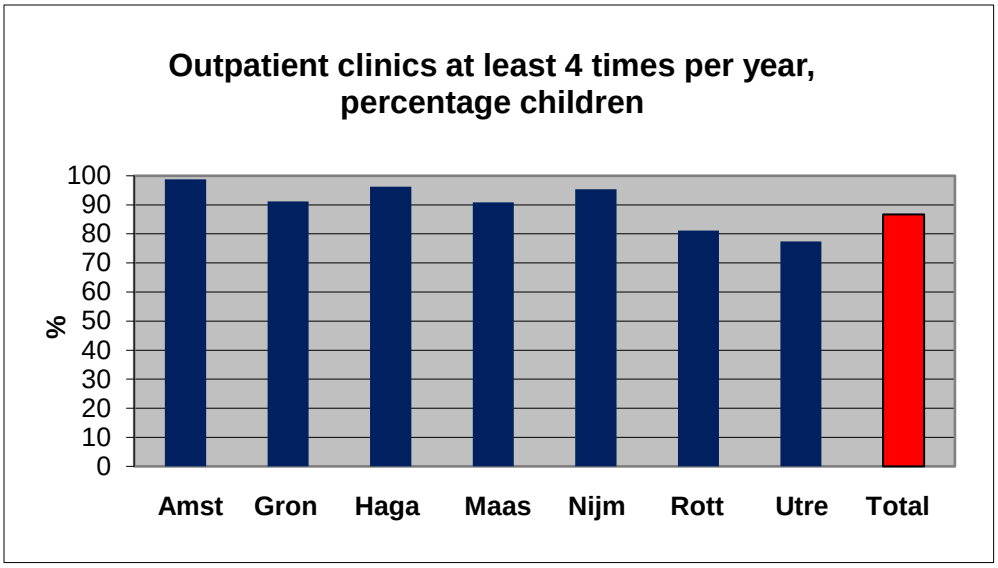



**Figure 28. Percentage of children per centre who have visited the outpatient's department at least four times a year**

Figure 29 shows the percentage of adults per centre who have visited the outpatient's department at least four times a year.

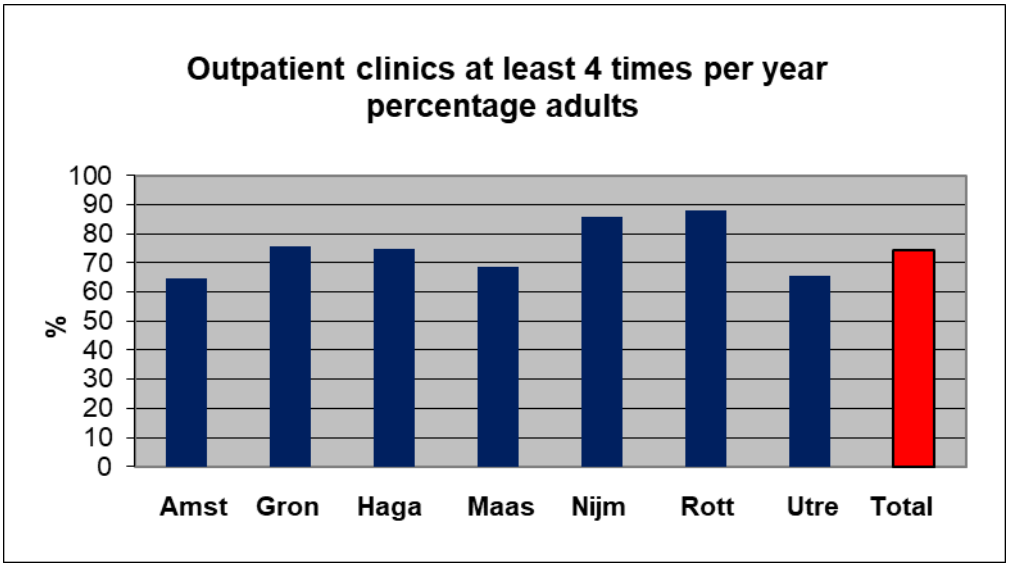



**Figure 29. Percentage of adults per centre who have visited the outpatient's department at least four times a year**

Figure 30 shows the percentage of children per centre from whom a sputum sample was taken at least four times a year.

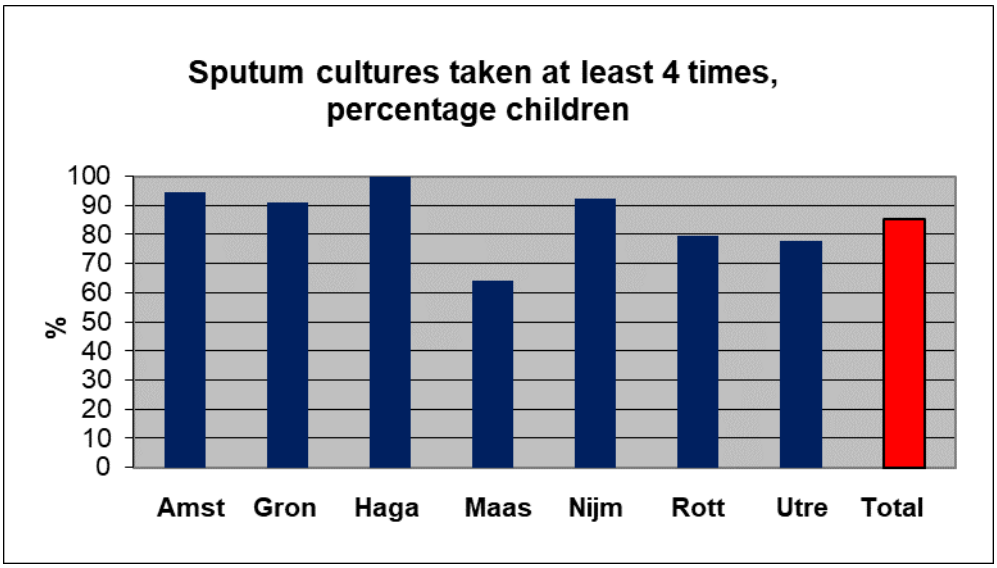



**Figure 30. Percentage of children per centre from whom a sputum sample was taken at least four times a year.**

Figure 31 shows the percentage of adults per centre from whom a sputum/phlegm sample was taken at least four times a year.

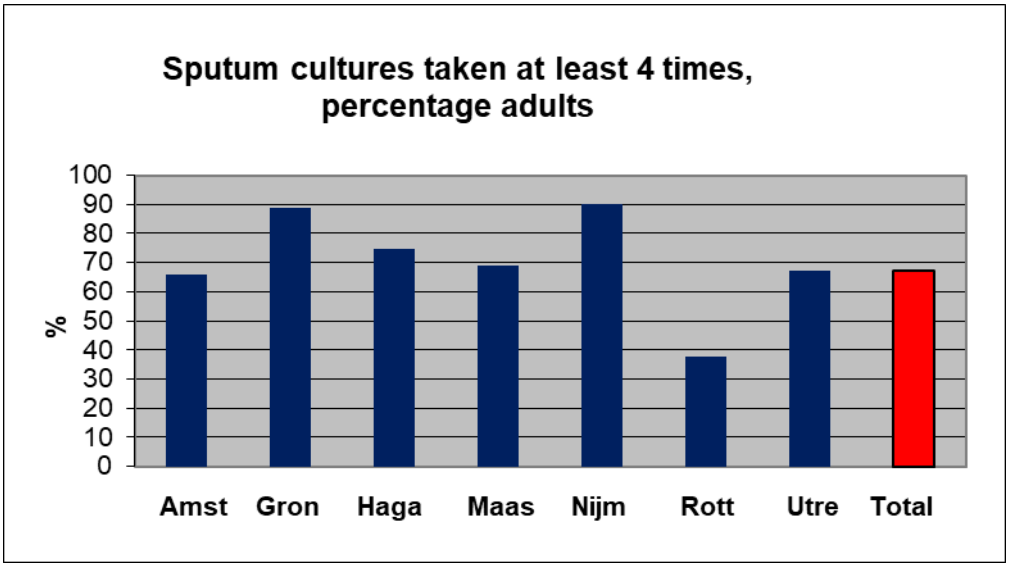



**Figure 31. Percentage of adults per centre from whom a sputum/phlegm sample was taken at least four times a year.**

Figure 32 shows the percentage of children per centre whose lung function was measured at least four times a year.

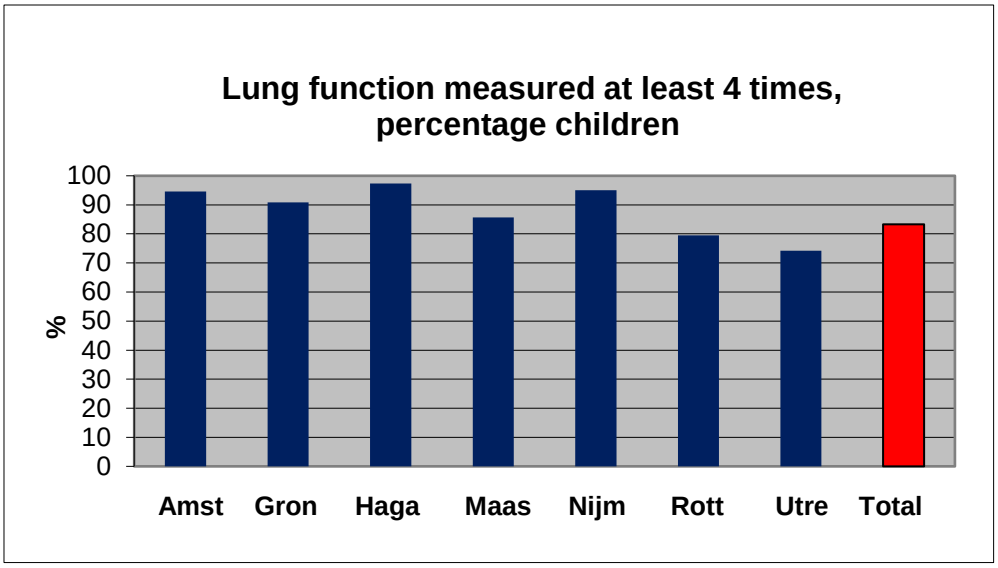



**Figure 32. Percentage of children per centre whose lung function was measured at least four times a year**

Figure 33 shows the percentage of adults per centre whose lung function was measured at least four times a year.

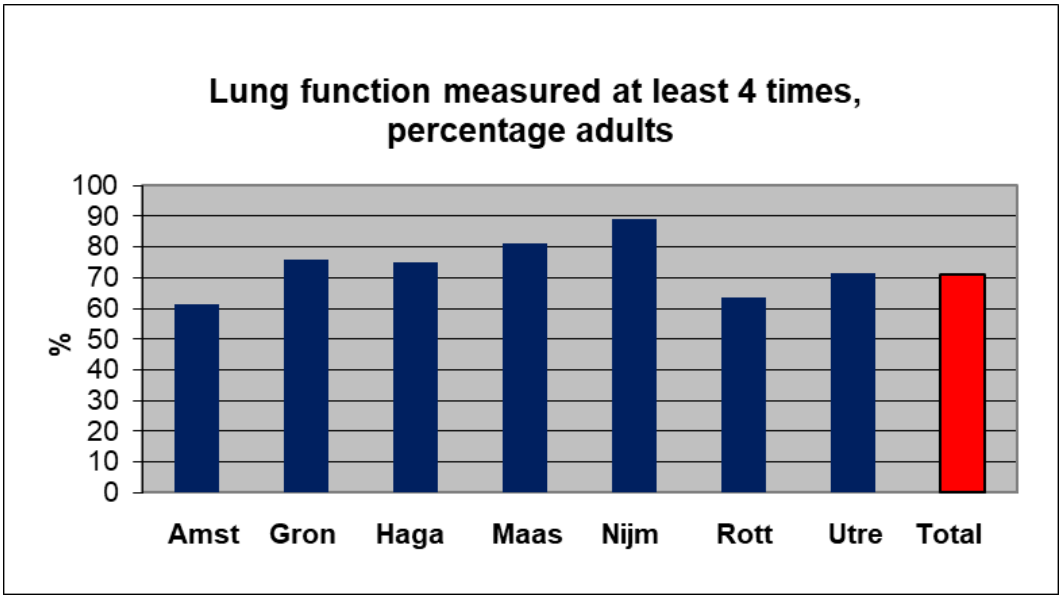



**Figure 33. Percentage of adults per centre whose lung function was measured at least four times a year**

Children, and adults in particular may develop a specific form of CF-related diabetes (CFRD). The 'CF Diagnostics and Treatment Guideline' (2007) recommends subjecting children older than 10 and adults without diabetes to an annual Glucose Tolerance Test (GTT) in order to detect CFRD at the earliest possible stages. Figure 34 shows the percentage of children per centre who had a GTT in 2016. The percentage is calculated over children older than 10, without CFRD and with a pancreatic insufficiency.

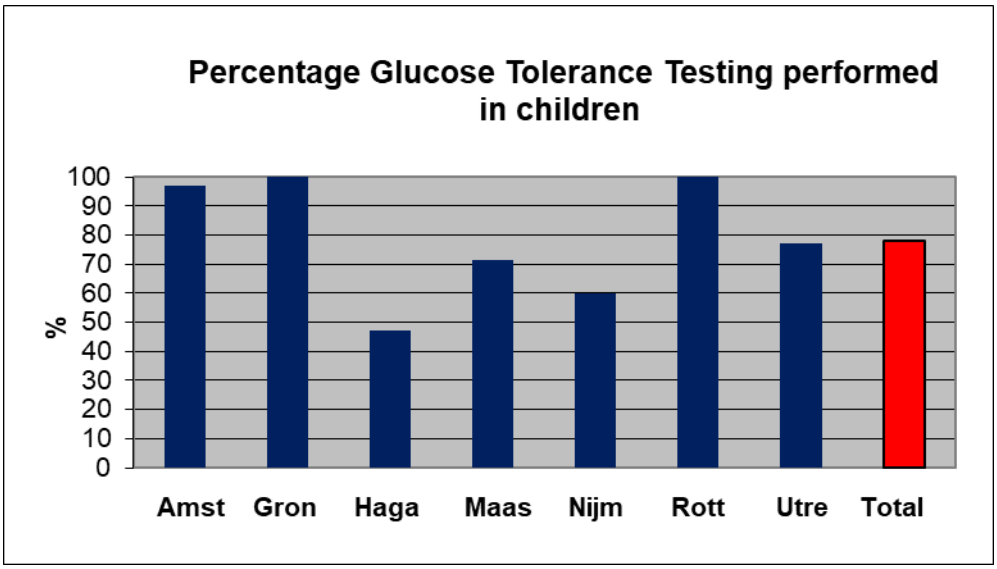



**Figure 34. Percentage of children per centre who had a GTT in 2016**

Figure 35 shows the percentage of adults per centre who had a GTT in 2016. The percentage is calculated over adults, without CFRD and with a pancreatic insufficiency.

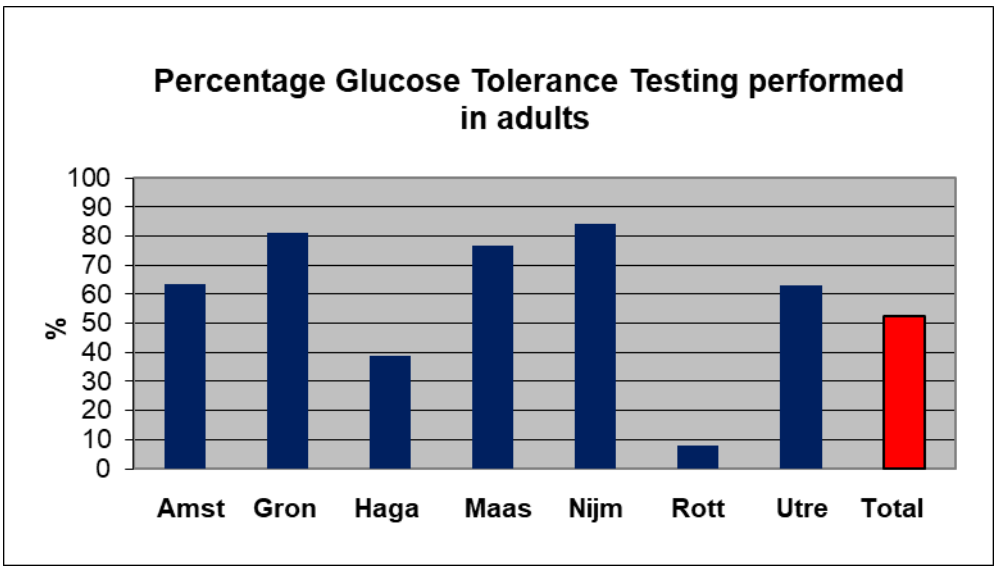



**Figure 35. Percentage of adults per centre who had a GTT in 2016**

**Appendix 1: Publications and honoured requests in 2016 of data from the Dutch CF Registry**

## Publications

**Height Assessment in the Dutch-Origin Paediatric Cystic Fibrosis Population.**
Woestenenk JW, Gulmans VA, van der Ent CK, Houwen RH.
Nutr Clin Pract. 2017 Feb; 32(1):130-132. doi: 10.1177/0884533616639109. Epub 2016 Jul 10.

## Data requests

**Request Radboud UMC**
Additional data in order to be able to carry out a longitudinal study among patients of the relationship between patient characteristics and fungus cultures.
Status: data provided. In analysis process.

**Request MUMC**
Data for a study into GE complications in adults who suffer from CF.
Status: data provided. In analysis process.

**Request CFTR2 mutation database**
Update mutations Dutch patients with CF.
Status: processed in database: **http://www.cftr2.org**

**Request Vertex**
Overview of mutations in the Netherlands for the Tezacaftor reimbursement submission file.
Status: currently in application procedure EMA.

**Request Neonatal Newborn screening Advisory Group NVK/ RIVM**
Cross-check of data from newborn screening Registry (NEORAH) and the Dutch CF Registry.
Status: conducted by CF Registry coordinator and data from both databases updated. This cross-check will be carried out on an annual basis.

For a Dutch contribution to data requests from the European CF Registry, visit
https://www.ecfs.eu/projects/ecfs-patient-registry/overview-data-applications