Dutch Cystic Fibrosis Registry

Annual report for 2017
Foreword

This tenth report by the Dutch CF Registry has been made possible with the cooperation of almost all the people with Cystic Fibrosis (CF) themselves and the efforts of many of the staff at the seven CF centres. This report includes the data of 1578 of the estimated 1600 people with CF and CF-related disease in the Netherlands. This report encompasses 98% of the Dutch patients with CF.

CF is a complex disease, and there are many factors that influence the progress of the disease. The treatment followed is such a factor. To be able to compare and interpret the information on the treatment in different centres, the possible related factors have to be taken into account, such as age, sex, type of mutation and the severity of the symptoms.

Since 2014, the CF centres are no longer displayed anonymously. We do this to promote transparency. Since 2014, data about the so-called indicators have also been added: figures which say something about aspects of the quality of care offered at the CF centres. But I would like to stress that the interpretation of the tables and diagrams must be done with great care. The quality of care in a CF centre is influenced by many factors and is hard to capture in one number or diagram. This means that a centre where, for example, the average pulmonary function is high, not automatically also offers the best care.

This online report contains more analyses and information than previous years and has been redesigned to make the data more accessible. An interactive version with the key information can also be consulted by a wider audience via [www.ncfs.nl/over-cystic-fibrosis.cf-registry-2017](http://www.ncfs.nl/over-cystic-fibrosis.cf-registry-2017).

This report presents the data for each centre separately and also at a national level. The CF centres have each received an overview of their own data in relation to the national averages. Each year, the Dutch Cystic Fibrosis Foundation ([Nederlandse Cystic Fibrosis Stichting](https://ncfs.nl), NCFS) organises meetings with the centres’ paediatric pulmonologists, chest physicians, paediatric gastroenterologists and paediatric nutritionists. At these meetings, the treatment, results and differences between the centres are discussed in an open and positive atmosphere. If relative differences show up, these are analysed and where possible translated into guidelines, such as the current development of a new guideline and standard of care, covering all aspects of the diagnosis, treatment and support of patients with CF. The Registry also provides important information for this purpose.

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

September 2018

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Summary

On www.ncfs.nl/over-cystic-fibrosis/cf-registry-2017 an interactive summary with infographics can be consulted by a wider audience.
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1. Introduction

The Dutch Cystic Fibrosis Foundation (Nederlandse Cystic Fibrosis Stichting, NCFS) has coordinated, managed and financed the Dutch CF Registry since 2007, and publishes an annual report on the situation in the Netherlands. The Registry steering group determines the Registry policy and is composed of representatives from all the CF centres and the NCFS.

All information from the national Registry is pseudonymised. This means that the only person who can deduce the data to an individual patient is the patient’s own doctor at the CF centre.

Each CF centre enters data of people with CF in their care and keeps track of the course of the disease over the years. The quality of the data is being systematically monitored by the Registry coordinator at the NCFS, with automated checks in the software, and by the statisticians of the European Registry. Strict procedures are followed out to ensure that patient data are not traceable by others. The Dutch and European laws and regulations are applicable.

The Dutch CF Registry has been registered with the Dutch Data Protection Authority (Autoriteit Persoonsgegevens), which ensures that the privacy legislation is complied with. Patients with CF are informed about the Registry and have given their consent in writing for the entry of their (pseudonymised) data in the Registry. A small number of patients (4; 0.3%) refused to participate in the Registry. Data from 20 patients from Rotterdam who underwent a lung transplant are missing from the 2017 Registry.

The Dutch CF Registry provides data to the European CF Registry (www.ecfs.eu/projects/ecfs-patient-registry/intro). Registries with data from people with CF are already maintained in 31 European countries. These data are used to support scientific research and improve the care and treatment of patients with CF.

The Dutch CF Registry has adopted the definitions of the European CF Registry (www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). The use of data from the Dutch or European Registry requires the approval of the Dutch steering group or the European review board. These consist of Dutch and European CF specialists, respectively. Requests for information from the Dutch or European Registry can be submitted via application forms which are available on the websites www.ncfs.nl/over-cystic-fibrosis/cf-registratie-2017 and www.ecfs.eu/ecfspr. The Registry does not provide individual patient data.

A report is prepared each year, including an interactive summary for a wider audience. This is also available in English on the NCFS website www.ncfs.nl/over-cystic-fibrosis/cf-registry-2017. If you have questions or comments, you can contact the NCFS Research and Quality of Care department via info@ncfs.nl.
2. Methods

The Dutch CF Registry records the medical and social information of patients with CF. The steering group of the Dutch Registry has determined which parameters (variables) with related definitions are to be recorded, and mainly bases this choice on the parameters used in the European Registry. This results in a database with the data of approximately 45,000 European patients with CF. The definitions applied per parameter are almost identical to the definitions of the American CF Registry; this contains the data of a further 28,000 patients with CF.

For the purposes of the report over 2017, the seven Dutch CF centres have entered the data of approximately 160 variables into an Excel file. These data were collected during the year. For the pulmonary function, the highest value recorded in that year is recorded, in line with the European definitions. As regards the pulmonary function, the same reference values are used for all centres, namely the international reference values according to the Global Lung Initiative (GLI 2012; http://erj.ersjournals.com/content/early/2012/06/27/09031936.00080312.abstract?papetoc).

For the calculation of Z-scores for the growth in children (weight-for-height and BMI), the Growth Analyzer application by the Stichting Kind en Groei in Rotterdam was used. The reference values of the Dutch population from 2010 (Talma) are used.

Percentages and averages or medians are determined per centre for the various items. Important outcome parameters, such as the pulmonary function value FEV1 and Body Mass Index for the nutritional condition are displayed as an uncorrected value, only for patients with a confirmed diagnosis of CF and whom have not had a lung transplant.

For each chapter, the criteria used for inclusion or exclusion during the analysis are indicated. For most analyses, only patients with a confirmed diagnosis of CF without a history of lung transplant were included. When we refer to adults, we mean people aged 18 and over, and when we refer to children, we mean the category of newborns up to children aged 17 years.

Output parameters and confounder analysis

Outcome parameters such as FEV1, BMI and weight-for-height say something about the quality of care patients receive. However, there are many factors that influence the FEV1, BMI and weight-for-height. Some of them can be influenced by the centre (for example the treatment), but others cannot. These are also referred to as confounders. The steering group has identified the following possible confounders: sex, age, age at diagnosis, ethnic background, severity of the mutation class, meconium ileus, pancreatic insufficiency and historical lung transplant. Other factors such as socio-economic status, active or passive smoking and compliance may also be confounders, but no data are included in the Registry.

In consultation with the department of clinical epidemiology at the Julius Centre in Utrecht, the differences per centre in FEV1, BMI, BMI Standard Deviation Score (SDS) and weight-for-height SDS are corrected for most confounders (sex, age, pancreatic sufficiency, meconium ileus and ethnic background). The analyses were done for children and for adults separately. Patients who underwent a lung transplant were not included in the analysis, because this would distort the picture. The variable “age of diagnosis” is not included in the analysis, because insufficient data were available in a number of centres. The median age at which the patients were diagnosed hardly differs from the centres for which data are available.

We looked at the differences between the centres with a multi-variable linear regression model, both for children and adults. The possible influence of confounders was examined by adding them to the model. Differences between centres do not change significantly after correction (adjustment) for possible confounders. This is in line with the conclusions from the analysis of the American and UK CF Registry.
Concepts
In this report, various mathematical concepts are used.

Z-score:
The Standard Deviation Score (SDS), also called Z-score. A Z-score with a value of 0 is average. The scores of 97% of healthy Dutch children are between -2 and +2.

Median:
The median value indicates 50% of the patients has a value which is lower than that value and 50% has a value that is higher. Especially when the values are not normally distributed, it is better to use median scores than averages.
3. Demographic data

This chapter describes the demographic data of people with CF who were included in the Dutch CF Registry in 2017.

In the ‘Guideline on diagnosis and treatment of CF’ (2007) and in the report ‘Centre Care’ (NCFS 2003), it is recommended that patients with CF visit a CF centre at least once a year.

Seven CF centres in the Netherlands are treating patients with CF or CF-related disease. In 2017, 1578 people with CF or CF-related disease were included in the Registry, of whom 639 were children (<18 years) and 939 were adults (≥18 years). Four people did not give their consent and the data of 20 people with a lung transplant are missing. In total, there were approximately 1600 people with CF or CF-related disease in the Netherlands in 2017 and approximately 98.5% is included in the Dutch CF Registry.

For the analyses in this chapter, all registered patients are included.

**Characteristics**

The number of registered people increases slightly each year, in 2017 this is 1578 (Fig. 1). The increase is caused by the increasing number of adults; the number of children remains more or less the same over the years. The distribution of men and women in the Registry is also stable, with slightly more than half being male (Fig. 2). In 2017, 843 men and boys were registered.

*Figure 1. Number of people in the Dutch CF Registry. The total number of registered people per year, broken down by children (<18 years) and adults (≥18 years).*
The age of people with CF and CF-related disease is slowly going up, both the mean and the median values (Fig. 3). In 2017, the mean age was 23.7 and the median age 22.1.

Figure 2. Men/women distribution in the period 2009-2017.

Figure 3. The median and mean age of people with CF and CF-related disease.
In recent years, 10-20 people with CF die each year (Fig. 4). In the past four years, less than 15 people have died each year. In addition, over the whole period, the median age of death goes up.

Figure 4. Number of deceased patients and median age of death.

Figure 5 shows the number of people per age year according to 2017 data. The cumulative percentage can also be seen, from which can be deduced, among other things, that in 2017 half of the people were younger than 22.

Figure 5. The number of people per age year and the cumulative percentage.
**CF centres**

The number of children and adults receiving treatment at each CF centre is shown in Table 1 and Figure 6. The distribution between the various centres has remained fairly stable over the years (Table 1).

*Table 1. Distribution per centre from 2014, broken down by the children’s centre and the adult centre.*

<table>
<thead>
<tr>
<th>Centre</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UMC Utrecht</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>206</td>
<td>196</td>
<td>190</td>
<td>191</td>
</tr>
<tr>
<td>Adults</td>
<td>231</td>
<td>245</td>
<td>260</td>
<td>281</td>
</tr>
<tr>
<td><strong>Erasmus MC Nijmegen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>149</td>
<td>143</td>
<td>140</td>
<td>149</td>
</tr>
<tr>
<td>Adults</td>
<td>121</td>
<td>120</td>
<td>139</td>
<td>138</td>
</tr>
<tr>
<td><strong>HagaZiekenhuis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>55</td>
<td>63</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Adults</td>
<td>210</td>
<td>210</td>
<td>217</td>
<td>215</td>
</tr>
<tr>
<td><strong>Amsterdam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>102</td>
<td>105</td>
<td>104</td>
<td>100</td>
</tr>
<tr>
<td>Adults</td>
<td>100</td>
<td>106</td>
<td>109</td>
<td>116</td>
</tr>
<tr>
<td><strong>UMC Groningen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>69</td>
<td>73</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Adults</td>
<td>88</td>
<td>84</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td><strong>Radboud UMC Nijmegen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>47</td>
<td>49</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>Adults</td>
<td>50</td>
<td>57</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td><strong>Maastricht UMC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>34</td>
<td>28</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Adults</td>
<td>37</td>
<td>42</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>1,499</td>
<td>1,521</td>
<td>1,549</td>
<td>1,578</td>
</tr>
</tbody>
</table>
Figure 6. The number of people per CF centre in 2017.
4. Diagnosis

The Dutch CF Registry registers people who have CF or a CF-related disease. For the analyses in this chapter, only those people who have a confirmed diagnosis are included. A person is diagnosed with CF if a physician confirms that he/she has two CFTR mutations, and/or a sweat chloride value higher than 60 mmol/L, and/or clinical symptoms. Since 2011, newborns in the Netherlands are screened for CF via the heel prick. CF can also be detected in older children and adults, if they were born before 2011, or because the child was missed in the screening (false negative), or because the test was not carried out (for example in the case of immigration).

Screening and symptoms

Figure 7 shows how many children with CF (year of birth 2012-2017) were diagnosed via the heel prick, or if they were false negatively or did not have a heel prick. The number of children with a false negative heel prick has been very low since 2015. The total number of children diagnosed with CF in 2012-2017 is higher, as 26 children in the Registry were born before 2012 but were only diagnosed in 2012-2017. In addition, since this year we also register who has CFSPID (CF Screen Positive, Inconclusive Diagnosis). These are children for whom a clear diagnosis of CF was not possible after screening, but who could possibly develop symptoms of CF in the future. Currently, this refers to 24 children. The number of children diagnosed with CF in 2017 may have been underestimated, with children born at the end of 2017 being diagnosed with CF a few weeks later. This difference will be corrected in the report for 2018.

The number of children (<18 years) in 2017 in the Dutch CF Registry is 639. Of those, 590 have a confirmed diagnosis, 187 children via newborn screening and 403 in a different way. Of the 939 registered adults, 886 have a confirmed CF diagnosis. 12.5% of adults were diagnosed with CF after they reached the age of 18 years.

The symptoms, as visible around the time of diagnosis, are also recorded in the Registry (Fig. 8). Meconium ileus (MI) is shown separately from the other symptoms, which are broken down in the second half of the graph. Of the children not diagnosed through newborn screening, 80% had symptoms around the time of diagnosis, particularly respiratory and nutritional problems. Of the
children diagnosed via newborn screening, only 40% had clinical symptoms. Family history plays a role in both groups: for 17.6% and 7.8% of the children not screened and screened, respectively.

Mutations

CF is caused by mutations in the CFTR gene that lead to a disruption in the performance of the chloride channel (the CFTR protein). Of the 1,578 people registered, 1,476 people were diagnosed with CF, of whom 590 were children and 886 adults. In about 98% of the people the genotype is known in 2017 (Fig. 9), and more than half of the people with CF has two F508del mutations. Of the remaining 1.9%, it was not possible to determine which two mutations were present (unknown) for 0.8%. For the other 1.1% no mutation analysis was carried out; these are all adults.

It is important to know the genotype of someone with CF, because the current and upcoming drugs, CFTR modulators that improve the performance of the CFTR protein, are suitable for specific (types of) mutations.
The CFTR mutation F508del is most common (Fig. 9). The other mutations are much less common, which is also visible in Table 2, showing the fifteen most common CFTR mutations. After F508del, A455E is the most common mutation. A455E is relatively common in the Netherlands, compared to other countries.

CFTR mutations can be divided into 5 classes, with almost no functional CFTR being created in classes 1, 2 and 3, and some in classes 4 and 5, but much less compared to healthy persons. In the cell, the CFTR gene is turned into a protein strand that is folded into a chloride channel.

- Class 1 mutations: no full protein strand is created, so no chlorine channel can be folded;
- Class 2 mutations: the protein strand is not folded up properly, so that it almost does not end up in the cell wall as a chloride channel;
- Class 3 mutations: chloride channels are created that sit in the cell wall, but they hardly open to let chloride pass;
- Class 4 mutations: with these versions of CF, there is some chloride transport, because CFTR as a chloride channel opens occasionally, but not often enough;
- Class 5 mutations: too few chloride channels are created, and/or they won’t stay put in the cell wall that well.

Figure 10 shows how often the various classes occur in the Netherlands according to the 2017 data. The percentage of classes that are unknown is higher than the percentage of CFTR mutations that are unknown (Fig. 9). This is because in a number of people the genotype is known, but not the class of the mutation(s).
Table 2. Most common CFTR mutations and corresponding mutation class.

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Frequency (%)</th>
<th>Mutation class</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>72.6</td>
<td>2</td>
</tr>
<tr>
<td>A455E</td>
<td>4.1</td>
<td>5</td>
</tr>
<tr>
<td>G542X</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>1717-1G-&gt;A</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>3272-26A-&gt;G</td>
<td>1.2</td>
<td>5</td>
</tr>
<tr>
<td>R1162X</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>S1251N</td>
<td>1.2</td>
<td>3</td>
</tr>
<tr>
<td>N1303K</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>R117H</td>
<td>1.0</td>
<td>4</td>
</tr>
<tr>
<td>R553X</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>2789+5G-&gt;A</td>
<td>0.7</td>
<td>5</td>
</tr>
<tr>
<td>3849+10kbC-&gt;T</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>711+1G-&gt;T</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>E60X</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>W1282X</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9</td>
<td>N.A.</td>
</tr>
<tr>
<td>Not done</td>
<td>1.1</td>
<td>N.A.</td>
</tr>
<tr>
<td>Other known mutations</td>
<td>8.3</td>
<td>N.A.</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0</strong></td>
<td><strong>N.A.</strong></td>
</tr>
</tbody>
</table>

Figure 10. Distribution of classes of CFTR mutations, assuming the mildest mutation per person. Unknown means that after genetic testing, the mutations have remained unknown or that the mutation class is not known. Not done means that no mutation analysis was carried out (or that the results were lost).
5. Pulmonary function

CF is mainly manifested in the airways (and the digestive system). Because of the sticky mucus, bacteria and fungi get stuck in the airways, where they can cause infections and inflammation. This causes the lung function to decrease progressively. Therefore, to follow the course of CF, the lung function is often measured. The most commonly used measure is the FEV1 (forced expiratory volume in 1 second), as a percentage of the predicted value relative to healthy peers of the same age, sex and height.

For the analyses in this chapter, people with a confirmed CF diagnosis were included, excluding the patients with a lung transplant, which amounts to 1375 people (588 children (<18 years) and 787 adults (≥18 years)). When data are displayed by centre, the same order is always used with the following abbreviations: Ams, Amsterdam; DeHa, The Hague; Gron, Groningen; Maas, Maastricht; Nijm, Nijmegen; Rott, Rotterdam; Utr, Utrecht.

The FEV1% may vary per centre. Figure 11 and 12 show the median FEV1% for the past three years per centre and in total, for children (Fig. 11) and adults (Fig. 12). Overall, both children and adults have shown an increase in FEV1% in 2016 and 2017, compared to 2015.

Figure 11. Lung function of children with CF. Median FEV1% in 2015, 2016 in 2017.
The lung function of people with CF decreases with age. Figure 13 shows the lung function in 2017 per age category, with the number of people listed for each category. As the age increases, the lung function decreases to around 60% in people aged 27-30.
Another way to look at the differences in lung function is to calculate the z-score. A score of 0 means an average lung function calculated on the basis of the healthy reference population. With the data of 2017, the Z-score is calculated per centre; for children and adults (Fig. 14). The median Z-scores for the children’s centres are at or just below 0, while the median Z-score for adults is around -2.5.

From 2015-2017, the largest group of children has a lung function above 90%, and the largest group of adults has a lung function between 40% and 70% (Fig. 15). On average, the lung function of adults and children appears to increase over the years, as the percentage of children in the first three categories and the percentage of adults in the first two categories goes down over the years. The lung function hardly differs between men and women (not shown).

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![Figure 14. Lung function of children and adults with CF. Z-score of median FEV1% predicted in children and adults, by centre in 2017. List of abbreviations: C, Children; A, Adults.](#)

![Figure 15. Categories of lung function in 2015-2017 for children (<18 years) and adults (≥18 years). Per category, the percentage of the group of children or adults is calculated.](#)
A pulmonary function test performed four times a year by CF centres on people with CF is a measure of the quality of care provided. Figure 16 shows the data for 2017. On average, the pulmonary function has been measured at least four times in 70-75% of people, but the differences between centres are large.

Figure 16. Percentage of people with CF whose lung function was measured at least four times this year. Indicator for quality of care for Zorginstituut Nederland. Broken down per centre and for children and adults. Children under 6 years are not included in the calculations.
6. Microorganisms

The condition of the airways is influenced by the presence of microorganisms, such as bacteria and fungi. This section uses the data of people with a confirmed diagnosis of CF and without previous lung transplants.

The occurrence (prevalence) of nine microorganisms in 2017 is shown per age group in Figure 17. The trends in the years 2013-2017 are shown in Figure 18. *Pseudomonas aeruginosa* becomes more common with age, as is *Aspergillus fumigatus*. These are also the most common microorganisms, along with *Staphylococcus aureus*. The colonisation with *Haemophilus influenzae* decreases with age (Fig. 17). The prevalence of all nine microorganisms appears to have been reasonably stable over the years, apart from the increase in *Aspergillus fumigatus* (Fig. 18).

![Figure 17. Prevalence of microorganisms in 2017 by age group (every six years).](image)
The colonisation with *Pseudomonas aeruginosa* is an important predictor of severity of the disease and prognosis of CF. The Dutch CF Registry records whether someone is chronically infected with this bacterium (Fig. 19). In principle, such a chronic infection is treated with inhalation antibiotics, which is also recorded in the Registry. In 2017, 447 people had a chronic *Pseudomonas aeruginosa* infection. Data on inhalation antibiotics were known for 433 people, of whom 89.4% were prescribed this medication. Figure 19 shows the treatment percentage for each centre.

**Figure 18.** Prevalence of microorganisms in 2013-2017.

**Figure 19.** Prevalence and treatment of *Pseudomonas aeruginosa* per centre in 2017, broken down by children (<18 years) and adults (≥18 years).
An indicator of the quality of care is that sputum cultures are taken four times a year, to monitor the presence of micro-organisms in the respiratory tract. Figure 20 shows the percentage of people who had at least four sputum cultures in 2017. This does not include people for whom it was not possible to take a sputum culture.

![Sputum samples chart](image)

**Figure 20.** Percentage of people with CF who had at least four sputum cultures taken in 2017. Indicator for quality of care. Broken down per centre and for children and adults.
7. Nutritional condition

Besides pulmonary function problems, people with CF often have digestive issues. For people with CF, it is important that they keep a stable weight and that children with CF thrive. To assess the nutritional condition of children, the Z-score, the value in relation to healthy children of the same age, ethnicity and sex, is used. One measure for the nutritional condition is the measure weight-for-height, shown per centre for the past three years (Fig. 21). Compared to previous years, almost all centres show a decrease. The Z-score drops just below zero again in 2017 (Fig. 21).

**Children**

Another measure to assess the nutritional condition is the Body Mass Index (BMI), where height plays a greater role (the formula is kg/m²). For the children, the median Z-score is also calculated here, and the figures of the past few years are shown here per centre (Fig. 22) or as a total (Fig. 23). Just like the measure weight-for-height, the BMI also dropped in the past two years, and the median Z-score fell below 0, with the exception of a few centres.

*Figure 21. Weight-for-height of children (<18 years) from 2015-2017, broken down by centre.*
Yet another way to look at the nutritional condition is to determine the weight or height in relation to peers of the same sex. The data of the children in 2017 are therefore broken down by weight-for-age (Fig. 24) and height-for-age (Fig. 25). The weight does not always lag behind and differs between boys and girls around puberty and early adulthood (Fig. 24). The heights are lower than average in all age groups from 3 years (Fig. 25) and appear to partly recover when reaching adulthood. This could be an indication of delayed puberty, which is regularly seen in children with CF.
Adults
The BMI is the most informative measure for the nutritional condition of adults. Over the past three years, the median BMI of the entire adult group has remained virtually the same. Figure 26 shows a breakdown of the BMI by age group in 2017. It can be seen that as the age increases, the median BMI increases slightly. Compared to the past three years, the BMI remains fairly stable, although some centres are showing a clear increase (Fig. 27).
Figure 26. Median BMI of adults (≥18 years), by age group in 2017.

Figure 27. BMI of adults (≥18 years) per centre, from 2015-2017.
8. Comorbidity

People with CF often show other conditions, due to CF, which is called comorbidity. Figure 28 shows the percentage of children and adults with a condition for ten disorders. Most conditions are more common in adults than in children. The prevalence of ABPA (allergic bronchopulmonary aspergillosis) is similar in children and adults. The percentage of CFRD (CF-related diabetes) is higher in adults than in children (32.6% vs. 14.3%, Fig. 28), and also appears, seen for the whole population, to be more common in 2017 than in previous years (Fig. 29).

Figure 28. Comorbidity in 2017, broken down by children (<18 years) and adults (≥18 years). Percentages of people that had or did not have this comorbidity in 2017, or for which no data were available. List of abbreviations: C, Children; A, Adults; ABPA, Allergic bronchopulmonary Aspergillosis; CFRD, CF-related diabetes; DIOS, Distal Intestinal Obstruction Syndrome; GERD, Gastro-Oesophageal Reflux Disease.

Figure 29. Prevalence CF-related diabetes (CFRD) 2013-2017. Percentage of the total population.
In order to discover CFRD in time, it is important that people with CF, who have pancreatic insufficiency and are older than 10 years of age, undergo an annual glucose tolerance test (GTT). This is also an indicator of the quality of care. Figure 30 shows that on average 50% of adults and about 75% of children had a GTT in 2017. This is comparable with the details for 2016.

Figure 30. Percentage of people with CF (over 10 years of age and with pancreatic insufficiency) who passed a glucose tolerance test in 2017. Indicator for quality of care. Broken down per centre and for children and adults. People who already have CF-related diabetes are not included.
9. Treatment

The treatment of people with CF focuses on both the basic defect and the symptoms. In this section we focus on the treatment of the respiratory tract, the digestive system and the use of CFTR modulators. A section is about hospital admissions and outpatients’ visits. People with a confirmed diagnosis of CF and without previous lung transplant are included. The chapter concludes with an overview of transplants.

Treatment

Figure 31 shows the percentage of children and adults treated for respiratory problems in 2017. Proportionally, adults are more often prescribed corticosteroids for inhalation, bronchodilators, oxygen, antibiotics via inhalation and macrolides. Figure 32 shows the percentages of people treated with inhaled antibiotics. It shows that use is often more than twice as high in adults compared to children.

![Respiratory treatment chart]

*Figure 31. Treatment of the respiratory tract in 2017, broken down by children (<18 years) and adults (≥18 years). Percentages within the group of children or adults.*
Figure 32. Treatment with maintenance inhaled antibiotics in 2015-2017 for children (<18 years) and adults (≥18 years). Percentages of treatment within the group of children or adults.

Figure 33 describes the percentages of children and adults being treated for digestive problems. About 80% uses pancreatic enzymes. Proton pump inhibitors and supplemental feeding are also often prescribed.

Figure 33. Treatment of digestive system in 2017, broken down by children (<18 years) and adults (≥18 years). Percentages within the group of children or adults.
With the development of CFTR modulators, there is also an increase in prescriptions. In the Netherlands, Kalydeco is used since 2014, from 2015 people started using Orkambi and a few have been using Symkevi since 2017, after participating in the clinical trial (Fig. 34A, B and C, respectively). Of the people with a gating mutation who qualify for Kalydeco, 94.7% actually had it prescribed in 2017, 5.6% of them stopped later. Of the people with a R117H mutation who qualify for Kalydeco, 9.1% actually had it prescribed in 2017, 33.3% of them stopped again (1 person). In addition, Kalydeco is prescribed off label to 17 people with a genotype, other than the ones for which Kalydeco has been registered.

For Orkambi, the percentage of people who were prescribed the drug is 76.9%, and 3.9% of these people also stopped. Another 20 people are prescribed Orkambi off-label (for another genotype, or an age younger than 12 years).

**Figure 34. Treatment of children (<18 years) and adults (≥18 years) with CFTR modulators. Number of people since 2014 (A, Kalydeco), since 2015 (B, Orkambi) or in 2017(C, Symkevi).**

**Intravenous treatments and visits to outpatients’ clinics**

Intravenous (IV) treatments are prescribed if pills or inhalation medication do not work adequately to control a bacterial or fungal infection, in the event of exacerbations. In 2017, for the first time, the Registry records the number of days someone was treated intravenously (IV), at home or in the hospital (Fig. 35). The total number of days of IV treatment increases with age. The percentage of people receiving IV treatment, at home or in hospital, varies over the years (Fig. 36).
To monitor someone with CF properly, it is recommended that they visit the outpatients’ clinic at least four times a year. How many people per centre actually do so, is an indicator of good care. Figure 37 shows that on average more than 75% of people visit the hospital outpatients’ clinic at least four times a year.
Transplants

Lung, liver or kidney transplants may be a last-resort treatment option. The first two are recorded in the Dutch CF Registry, specifying which persons have received a transplant and when. The numbers are calculated in the population with a confirmed CF diagnosis.

In 2017, one person had a liver transplant.

At the end of 2017, 15 people with CF were on the waiting list for a lung transplant (Table 3). Two adults died while on the waiting list. Six lung transplants were carried out in 2017. The data of lung transplants from Rotterdam are not included in the Dutch CF Registry in 2017, but verification with the Dutch Transplantation Foundation showed that a total of six lung transplants were performed nationally in people with CF.

Table 3. Lung transplants in 2014-2017, broken down by children (<18 years) and adults (≥18 years).

<table>
<thead>
<tr>
<th>Lung transplant</th>
<th>2014</th>
<th>2015</th>
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</tr>
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<tbody>
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<td>0</td>
</tr>
<tr>
<td>Adults</td>
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<td>9</td>
<td>12</td>
<td>6</td>
</tr>
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<table>
<thead>
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<td>Children</td>
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<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Adults</td>
<td>23</td>
<td>20</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

Figure 37. Percentage of people who visited the outpatients’ clinic at least four times in 2017. Indicator for quality of care. Broken down per centre and for children and adults.
10. Social situation

This section presents the societal and social situation of people aged 18 or over with a confirmed CF diagnosis and without previous lung transplant.

Having CF sometimes means that working and/or studying is not possible. Figure 38 shows that of the 787 adults, approximately 65% work or study. Figure 39 shows the marital/relationship status for the same group of people.

This year, 16 women were pregnant, and all 16 were pregnant before and/or already had children. In total, 78 women with CF have been pregnant in previous years.
11. 50+ and CF

More and more people with CF grow older than 50 years. The Registry includes 100 over-50s, 86 of whom have a confirmed diagnosis. In this section the following data of these 86 people are included: 50 years or older, with a confirmed diagnosis of CF, and independent of any lung transplant. Half of the people are between 50 and 55 years old (Fig. 40) and the oldest patient is 75 years old.

![Age distribution 50+](image)

*Figure 40. Age distribution of people with CF over 50. The number of people per age or age category, including the cumulative percentage.*

Other characteristics of this group are: slightly more men than women (Fig. 41) and slightly more than half has a F508del mutation in combination with another mutation (heterozygous) (Fig. 42).

![Distribution men/women age 50+](image)

*Figure 41. Men/women distribution of people with CF over 50.*
Via this link, more information about people with CF over 50 years of age can be found: www.ncfs.nl/over-cystic-fibrosis/cf-registry-2017/50-plus.