FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

THE BURDEN OF CYSTIC FIBROSIS IN BELGIUM: A REGISTRY-BASED STUDY

Steff De Smet

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A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE IN HEALTHCARE MANAGEMENT AND POLICY

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THE BURDEN OF CYSTIC FIBROSIS IN BELGIUM: A REGISTRY-BASED STUDY

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Name student: Steff De Smet

Signature

Preface

Dear reader,

This master's dissertation is a contiguous part of different aspects of my life. As such, I would like to share some thoughts and experiences. In addition, I am convinced that some expression of gratitude is in its place.

While I am writing this preface, the ten years I have studied at Ghent University are reaching their end. This period has largely made me who I am today, and I would not dare to dream about a life without intellectual challenges. Furthermore, during those times, I have learned about many different aspects of life. Most importantly, I have found that perseverance, gratitude and patience are crucial elements in all of them. Although professional and personal lives are sometimes exhausting, the little things that arise through this attitude, I have found, are an incredible source of energy and happiness.

I want to thank one person in particular, and that is my mother. She deserves all the respect and happiness in the world, as she does everything to make sure her children may experience the same. I also want to thank my brother and two best friends Tom and Dimitri, for their belief in me, their support and their awe-inspiring personalities. I hope these persons will continue to be a part of the rest of my life.

In addition, I would like to thank my promotor prof. dr. D. De Smedt for her introduction on this dissertation's topic, and my co-promotor prof. dr. B. Devleesschauwer for his inspiring suggestions. I hope they continue their efforts on improving public health and I wish them the best.

Sincerely,

Steff De Smet

3/30/2018

Abstract

Background: Cystic fibrosis is the most common life-limiting autosomal recessive disease among people of European heritage. This rare disease is known to cause substantial distress on patient level. However, the specific impact on individual health as well as the national impact on public health remains to be elucidated. The aim of this dissertation is to quantify and elaborate the disease burden of cystic fibrosis in Belgium.

Methodology: The Belgian Cystic Fibrosis Registry provides data concerning cystic fibrosis patients in Belgium. These data are used as the primary input to calculate the burden of cystic fibrosis in 2014 in Belgium. Disability-adjusted life years (DALYs), the sum of years of life lost (YLLs) and years lived with disability (YLDs), are calculated using a prevalence approach (hybrid model) in a multi-aspect disease model.

Results: In 2014, patients with cystic fibrosis in Belgium are accountable for 484.8 YLLs and 437.6 YLDs, corresponding with 922.4 DALYs in total (0.75 DALYs per patient). The YLD component consists of primary lung dysfunction (242.7 YLDs), non-transplantation-related complications (143.2 YLDs) and transplantation-related complications (51.6 YLDs). Non-transplantation-related complications are further divided into respiratory complications (11.1 YLDs), digestive/endocrine complications (79.5 YLDs) and other complications (52.6 YLDs). On population level, each complication category is largely explainable by one type of complication, respectively nasal polyps (10.5 YLDs), pancreatic dysfunction (44.2 YLDs) and psychological/psychiatric diseases (25.2 YLDs). The latter complication is found to have the biggest burden on the level of the patient.

Conclusions: Cystic fibrosis is the paragon of rare diseases. As a separate entity, its impact on public health is unpretentious. Nonetheless, this burden of disease study strongly suggests that cystic fibrosis should receive sufficient public health support in order to decrease the disease burden. Public health policies should emphasize certain disease-related topics because of their impact on public health and/or individual health.

Samenvatting

Achtergrond: Mucoviscidose is de meest frequente levensverkortende erfelijke ziekte bij personen met Europese origine. Het is bekend dat deze zeldzame ziekte een belangrijke weerslag heeft op het leven van de individuele patient. De specifieke impact op deze individuele patient, alsook de ziektelast op nationaal niveau, is echter nog niet opgehelderd. Het doel van deze masterproef is de ziektelast van mucoviscidose bij Belgische patiënten te kwantificeren en verduidelijken.

Methodologie: Het Belgische Mucoviscidose Register verzamelt data betreffende patiënten met mucoviscidose in België. Deze data worden gebruikt als primaire informatiebron om de ziektelast te berekenen voor het jaar 2014. Levensjaren gecorrigeerd voor premature mortaliteit en beperkingen (DALYs) worden berekend aan de hand van een prevalentiebenadering

Resultaten: In 2014 worden 922.4 DALYs toegeschreven aan mucoviscidose patiënten (0.75 DALYs per patiënt), overeenkomstig 484.8 verloren levensjaren door premature mortaliteit (YLLs) en 437.6 verloren levensjaren door beperkingen (YLDs). De YLD component bestaat uit primaire long dysfunctie (242.7 YLDs), complicaties gerelateerd aan transplantatie (51.6 YLDs) en complicaties niet gerelateerd aan transplantatie (143.2 YLDs). Complicaties niet gerelateerd aan transplantatie worden verder onderverdeeld in respiratoire complicaties (11.1 YLDs), digestieve/endocriene complicaties (79.5 YLDs) en andere complicaties (52.6 YLDs). Op nationaal niveau wordt de ziektelast van elke complicatie categorie sterk bepaald door één bepaald type complicatie, respectievelijk nasale poliepen (10.5 YLDs), pancreas dysfunctie (44.2 YLDs) en psychologische/psychiatrische aandoeningen (25.2 YLDs). Deze laatste complicatie heeft bovendien de grootste weerslag op de individuele patient.

Conclusie: De impact van mucoviscidose als aparte entiteit blijft op populatieniveau beperkt. Desalniettemin ondersteunt deze studie de stelling dat voor mucoviscidose voldoende publieke ondersteuning is vereist, zodat de ziektelast kan worden ingeperkt. De bevoegde beleidsinstanties worden aanbevolen om bepaalde ziekte-gerelateerde topics te benadrukken wegens hun effect op de publieke en/of individuele gezondheid.

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List of abbreviations

ABPA: Allergic bronchopulmonary aspergillosis

BCFR: Belgian Cystic Fibrosis Registry

CF: Cystic fibrosis

CFTR: Cystic Fibrosis Transmembrane Conductance Regulator

CFRD: Cystic fibrosis-related diabetes

COPD: Chronic obstructive pulmonary disease

DALYs: Disability-adjusted life years

DIOS: Distal intestinal obstruction syndrome

DW: Disability weight

FEV_1: Forced expiratory volume in one second

FEV_1 % predicted: Forced expiratory volume in one second as a percentage of the predicted value in healthy subjects

GBD: Global burden of disease

GER: Gastro-esophageal reflux

IGT: Impaired glucose tolerance

LE: Life expectancy

NIHDI: National Institute for Health and Disability Insurance

WIV-ISP: Scientific Institute of Public Health (Wetenschappelijk Instituut Volksgezondheid – Institut Scientifique de Santé Publique)

QALYs: Quality-adjusted life years

HRQoL: Health-related quality of life

YLLs: Years of life lost

YLDs: Years lived with disability

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Preamble

Rare diseases occur infrequently and therefore have a small health impact at population level. However, the clinical impact of these diseases is often significant, leading to an important health impact at patient level. To allow for comparison across heterogeneous groups of disorders, disease burden measurement requires a “common currency”. The Disability-Adjusted Life Year (DALY) has emerged as the key summary measure of population health for quantifying burden of disease. DALYs reflect the healthy life years lost due to illness and death. As such, they combine mortality and morbidity, the latter incorporating disease occurrence as well as severity. They allow for comparable estimates of both the population and patient level impact of diseases, and are therefore the preferred metric for quantifying the health impact of rare diseases. This dissertation elaborates on the disease burden of cystic fibrosis (CF).

Introduction

General aspects of cystic fibrosis

Cystic fibrosis is a progressively deteriorating hereditary disease with autosomal recessive transmission. This means that only subjects who have inherited two disease-causing mutations – one allele from each parent - are affected. Carrier rates of CF-causing mutations in Europe fluctuate around one in 25 persons (Wenstrom, Wilkins-Haug, & Barss, 2018). If both parents carry a mutation associated with CF, each pregnancy will bear a one in four chance of having a child with CF. Prevalence of the disease is highest in populations of Caucasian descent, such as those of Europe, North America and Australasia (Estivill, Bancells, & Ramos, 1997). However, prevalence differs from country to country and is 1/2,850 live births in Belgium (Farell, 2008). The earliest medical descriptions of CF find their origin in the 1930s (Quinton, 1999). The disease obviously existed prior to these dates even though it remained largely unrecognized and so went undiagnosed. In the centuries before, it was even thought of to be caused by witchcraft (Littlewood, 2016).

The Cystic Fibrosis Transmembrane Conductance Regulator gene

The disease is caused by a mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which is located on the long arm of chromosome 7. Since it was discovered in 1989, more than 2,000 (Cystic Fibrosis Mutation Database, 2011) mutations have been identified in the CFTR gene, of which the majority is extremely rare. Note that not all these mutations are associated with classical CF and many may cause atypical clinical pictures (Rodman, et al., 2005). The CFTR gene codes for a similar named protein, which is an ion channel involved in the regulation of chloride ion transport across the cell membrane (Talwalker, Koff, Lee, Britto, & Mulenos, 2017). It is mainly found in the cell membranes of the respiratory and digestive tract, the sweat glands and the reproductive tract. The 2,000 known mutations are grouped in six

classes according to their functional defect: Class I (defect of protein synthesis), Class II (default of protein folding with premature degradation, which interferes with the protein trafficking to the cell surface), Class III (gating mutations responsible of deficient channel opening), Class IV (decrease of CFTR conductance channel), Class V (decreased amount of CFTR protein synthesis) and Class VI (decreased stability of CFTR protein at the cell membrane). Some CFTR mutations have characteristics of more than one mutation class (Veit, Avramescu, Chiang, Houch, & Cai, 2016) and for many mutations it is not known what the dominating functional defect is.

Cystic Fibrosis Transmembrane Conductance Regulator protein dysfunction

The abnormal or absent functioning of the CFTR protein leads to the production of sweat with high salt concentrations and mucus secretions with an abnormal viscosity causing dysfunction of many organs, most notably the lungs and the pancreas (Talwalker, Koff, Lee, Britto, & Mulenos, 2017). In the respiratory tract, thick mucus production results in problems of airway clearing. This in turn, leads to persistent cough caused by chronic infection and inflammation, and later to severe bronchial obstruction and ultimately destruction of the lungs. In the pancreas, the sticky exocrine pancreatic secretions lead to obstruction and blocking of the pancreatic ducts with secondary damage to the secretory gland tissue (Wilschanski & Novak, 2013). The diminished secretion of pancreatic enzymes leads to fat and protein malabsorption causing steatorrhea and failure to thrive. Fat malabsorption also causes deficiencies of fat soluble vitamins (A, D, E and K).

Diagnosis of cystic fibrosis

Most children with CF present with recurrent chest infections, steatorrhea and failure to thrive. Additionally, newborns with CF can be affected by meconium ileus i.e. an intestinal obstruction with vomiting, abdominal distension and delay in passing the first meconium stools. However, the spectrum of presenting features is very wide (Appendix 1: symptoms and clinical reasons for CF diagnosis), especially in case of atypical mutations. Furthermore, given the hereditary nature

of the disease, family history can provide an important clue when considering CF. The diagnosis is usually made in early infancy (Table 1), but in some patients with atypical clinical presentations this can be later in life (Rodman, et al., 2005). Although currently there is no national neonatal CF screening program in Belgium (for more information see Appendix 2: prevention of cystic fibrosis), there are some local initiatives where patients are screened (Proesmans, et al., 2010). Infants with CF can be identified in the first weeks of life by assessing their blood immunoreactive trypsin combined with screening for the most frequent CFTR mutations (Castellani, et al., 2009). Nonetheless, the sweat test remains the gold standard for the diagnosis of CF and should always be done in case of suspected CF. In the majority of patients with typical features, the sweat test is diagnostic by revealing an excessive quantity of chloride (> 60 mmol/L). In atypical forms, the sweat test chloride levels can fall into the intermediate range (30-60 mmol/L) (Pagaduan, et al., 2018). Additionally, it is advised to perform genotyping in all patients with CF to identify the CF causing mutations. The F508del is the most common mutation, not just in the Belgian CF population but also worldwide (Appendix 3: atypical mutations).

Treatment of cystic fibrosis

Currently, there is no definitive treatment option for CF. As such, treatments try to impede disease progression and delay symptomatic deterioration. Mostly, they are based on respiratory management (e.g. physiotherapy, inhalation therapy, antibiotics and anti-inflammatories) and nutritional management (e.g. pancreatic enzymes and hypercaloric diet) (Appendix 4: treatments in patients with cystic fibrosis). Nonetheless, due to medical progress and intensification of the care for patients with CF, the quality of life and the life expectancy have increased with most of the patients surviving into early adulthood. Consequently, the landscape of CF care has changed markedly, with currently more adult patients than children in many countries (Table 1).

However, to further improve the life expectancy and quality of life, new and more effective treatments are needed. Recently, research and development activities in molecular medicine have yielded promising small-molecule pharmacological agents. They target the molecular defect that is at the base of the disease. Thus, while they still do not correct the fault (mutation) in the stars (genetic make-up), they act on the upstream end of the symptomatic cascade of events. In other words, these small-molecules correct the function of the dysfunctional CFTR protein. They are specific for the type of functional distortion, and thus effective only in patients carrying specific mutations. Currently two of those small molecules are approved in Europe for clinical use: ivacaftor (Kalydeco®) (Borowitz, Lubarsky, Wilschanski, Munck, & Gelfond, 2016) (Quittner, Suthoff, Rendas-Baum, Bavliss, & Sermet-Gaudelus, 2015) (Sawicki, McKone, & Pasta, 2015) for patients carrying certain class III (gating) mutations and those carrying the R117H mutation and lumacaftor in association with ivacaftor (Orkambi®) (Wainwright, Elborn, & Ramsey, 2015) (Bulloch, Hanna, & Giovane, 2017) for patients homozygous for the F508del mutation. Other CFTR modulating therapies are currently in development and are being evaluated in several ongoing clinical trials (Quon & Rowe, 2016) (De Boeck & Amaral, 2016).

Notwithstanding their beneficial effects, these small molecules still do not correct the faulty genetic sequence. The pipeline of truly corrective strategies under clinical investigation, ever more approaching the basic defect, is increasing continuously and the number of pharmaceutical companies that are entering the field is rising (Cystic Fibrosis Foundation, 2018). Amongst those are mutation-specific premature stop codon-read through drugs and antisense oligonucleotides that correct the basic defect at the mRNA level (Zomer-van Ommen, et al., 2016). Restoring the defective gene by gene editing can already be achieved in CF cell lines (Sanz, Hollywood, Scallan, & Harrison, 2017). Mutation agnostic treatments, which try to stabilize CFTR expression at the cell membrane, are explored as well (Laselva, Molinski, Casavola, & Bear, 2016). Combinations of these therapies can be anticipated (Fajac & De Boeck, 2017).

Though some patients qualify to receive a lung transplantation, or other transplantations for that matter, this does not correct the underlying defect. Indeed, almost all published studies have reported a ten-year survival of less than 60% (Vos, Verleden, & Dupont, 2016) or five-year mortality rates of approximately 50% (Lynch, Sayah, Belperio, & Weigt, 2015). Thus, transplantations cannot be considered as a definitive cure, but rather as a drastic intervention in patients with advanced disease. Additionally, timely listing for lung transplantation is critical, because up to 25-41% of CF patients die while awaiting a lung transplant (Lynch, Sayah, Belperio, & Weigt, 2015). A lung transplantation is indicated only for patients who have severe disease and who have exhausted all other forms of conventional medical treatment (Adde, Campos, de Oliveira Braga Teixeira, & Rodrigues, 2018). For these patients, lung transplantation may offer prolonged survival and improved quality of life (Whitehead, et al., 1995).

Care of patients with cystic fibrosis in Belgium

Since 1999, seven CF reference centers have been accredited by the National Institute for Health and Disability Insurance (NIHDI) and receive financial support. An annual care and revalidation agreement (CF convention) for patients with CF is signed between each reference center and the NIHDI (Mucoviscidose: tegemoetkoming in de kosten, 2014). Each center has specific expertise in CF care and ensures multidisciplinary follow-up of patients in order to provide optimal medical, paramedical, psychological and social care for the patients and their relatives. The majority of CF patients in Belgium are followed by one of the national CF reference centers and are registered in the Belgian CF Registry (The Belgian Cystic Fibrosis Registry (BMR-RBM), 2018).

Disability-adjusted life years

Disability-adjusted life years (DALYs) are used to estimate the burden of diseases and risk factors on public health (Murray & Acharya, 1997). DALYs have been the key measure in different Global Burden of Disease (GBD) studies, each presenting a comprehensive assessment of the worldwide health impact of disease, injury and risk factors (Murray & Lopez, 1996) (World Health Organization, 2008) (Murray, et al., 2012) (Murray & GBD 2015 Collaborators, 2016). The corresponding Medical Subject Heading (MeSH term) is “Global Burden of Disease”. It is defined as “a measure of the burden of disease using the disability-adjusted life year (DALY). This time-based measure combines years of life lost due to premature mortality and years of life lost due to time lived in states of less-than-full health. The metric was developed to assess the burden of disease consistently across diseases, risk factors and regions.” The burden of disease is divided into two components i.e. morbidity and mortality (Devleesschauwer, et al., 2014). Morbidity is quantified in terms of years lived with disability (YLDs) and corresponds with the loss of healthy life years due to a less-than-perfect health state. This means that years lived with a particular disease are adjusted according to a disease-specific disability weight. Mortality is quantified as years of life lost (YLLs) and accounts for the loss of life years due to premature mortality. As such, the higher the total number of DALYs incurred by a specific disease, the more relevant it is for public health. Although rare diseases have a relatively small impact on this population level, it is still an interesting measure because it allows for comparison between multiple rare diseases. In

addition, DALYs can provide relevant information on the level of the patient as well. Specifically, it is possible to differentiate the disease burden on patient level in a multi-aspect model, where different disease stages and characteristics can be quantified in terms of DALYs. If only one disability weight is available for a given disease, it is still possible to compare it with other diseases to see which disease has the most significant disease burden on patient level. In addition, one of the main goals of disease burden studies is to substantiate the allocation of resources.

Study aim

The aim of this study is to quantify and elaborate the burden of CF in Belgium, on patient as well as on population level.

Methodology

The Belgian Cystic Fibrosis Registry

The intent of the Belgian CF registry (BCFR) is to centralize data concerning the Belgian CF population. Since 2006, the NIHDI is the principal sponsor while coordination of the registry is performed by the department of Public Health and Surveillance of the Scientific Institute of Public Health (WIV-ISP). As such, the WIV-ISP ensures the data collection and management under the supervision of the board of the BCFR and the guidance of a scientific steering group. Since 2006, the BCFR lies within the framework of the CF convention described above. Participation in data collection for the BCFR is one of the obligatory tasks of each CF reference center. Data has been collected since 1998. As from 2004, a new data collection tool was integrated in the HealthData.be platform (www.HealthData.be, 2018), which has improved the data collection and validation procedures. It has also facilitated communication between the researchers and the data providers. This shows that the BCFR should not be seen as a static merely administrative undertaking, but as a continuingly innovating project to enhance CF patient's care.

Relationship between the BCFR and cystic fibrosis health care

Each one of the seven reference centers receive a copy of the national annual report. Furthermore, they receive a report concerning the data from patients within the individual center. In addition, a benchmarking report is provided with analyses that compare the results of each center with those from other centers. As such, the quality of care in a particular center can be improved by optimizing dimensions of care on which they score less than average. These scores are corrected for some known factors such as patient age and gender with further corrections planned as more confounding data are collected by the registry, including socioeconomic data. Physicians from the centers and researchers can submit research questions to the BCFR, and currently a number of research questions are being analyzed. For these reasons, the establishment of the registry has a direct impact on CF patient care, and in extension, public

health. In general, the development of more disease-related registries is desired (Lacaze, et al., 2017) (for more information see Appendix 5: registries of rare diseases).

Objectives of the registry

The aims of the BCFR are to study epidemiological aspects of CF in Belgium and to provide a tool for the assessment of the management and quality of care for patients with CF. It also provides a database for scientific research to CF researchers both at the WIV-ISP and the CF reference centers. As such, epidemiological data extracted from the BCFR reports are used as the primary input for this dissertation (Wanyama, Thomas, & Malfroot, 2014). The registry also participates in activities related to the European CF Society Patient Registry (ECFSPR) (ECFS Mission Statement, 2018) (European Cystic Fibrosis Society Patient Registry, 2017) and other international projects (CFTR2 Project, 2018).

Study population

The registry targets patients with CF that receive care in Belgium. In 2014, there were 1,230 patients included in the registry (Table 1). Approximately 1,300 patients are registered as members of the CF patient association (Muco Vereniging, 2018). Thus, the BCFR coverage of CF patients is estimated to be more than 90%. The small discrepancy between both is probably caused by the use of less stringent criteria to become a member of the patient association compared to the criteria to receive follow-up by a CF reference center.

Data collection

Once a year, the clinical and demographic data are collected for all patients by the treating physician. The data are extracted from medical records and consist of more than 200 recorded items. These data are divided into two categories. Firstly, the core data are collected when the patient enters the registry, which are updated if necessary during follow-up years. It contains demographic data, age of diagnosis and initial symptoms, genotype (mutations), sweat test and information on neonatal screening. Information about mortality in CF patients is also available. Secondly, data collected on a yearly base include clinical data (height, weight), lung function

(forced expiratory volume in one second [FEV_1]), complication occurrence, microbiology results, treatments and socio-economic data. An extended summary of the items collected by the BCFR can be found in the yearly BCFR reports (Wanyama, Thomas, & Malfroot, 2014).

Table 1

Summary of data reports 2011 – 2014*		
	2011	**2014**
Number of CF patients	1171	1230
Number of CF patients with complete records	1161	1230
Number of CF patients without observation	10	0
Number of CF patients with a transplant	134	151
Number of CF patients who were not seen	9	23
New CF diagnoses	36	36
Number of patients without a confirmed diagnosis	20	7
Number of patients with a revoked diagnosis		2
Median patient age in years (range)	19.7 (0.0 - 70.4)	21.3 (0.1 - 76.7)
Median patient age male (range)	19.6 (0.2 - 64.2)	21.2 (0.2 - 67.3)
Median patient age female (range)	19.8 (0.0 - 70.4)	21.5 (0.1 – 76.7)
Males (%)	51.8	52.0
Adults ≥ 18 years (%)	54.7	58.4
Median age at diagnosis (months) (range in years)	6.5 (0.0 - 65.0)	5.7 (-0.2 - 74.2)
Median age at diagnosis, male (months) (range in years)	6.5 (0.0 - 49.2)	5.9 (-0.2 - 59.5)
Median age at diagnosis, female (months) (range in years)	6.7 (0.0 - 65.0)	5.6 (-0.1 - 74.2)
Median age at diagnosis new cases in months (range in years)	3.4 (0.0 - 49.2)	2.5 (0.0 - 60.0)
Total number of deaths reported	8	10
Median age at death in years	27.7 (9.3 - 45.8)	37.4 (11.5 - 76.9)
Number of transplants performed	16	6
Number of deaths among transplant patients	2	4
Overall mean FEV_1 % predicted	77.8	76.0
In male	80.9	78.4
In female	74.5	73.3

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Calculation of disability-adjusted life years

General concepts

To measure the burden of disease in a particular period (e.g. the year 2014), DALYs can be calculated in different ways. The most commonly used approach is called the incidence approach. This approach is particularly suited to estimate future disease burden, and as such can be very helpful to substantiate the allocation of resources in order to anticipate possible trends in disease burden. However, in this dissertation, a hybrid perspective (often called a prevalence approach) is applied for reasons of convenience (based on data availability). Furthermore, this method is most suited to measure population health at a particular time (the year 2014 in this dissertation), and to evaluate the performance of a health care system (Schroeder, 2012). This hybrid approach is the core methodology in this dissertation. Although, a pre-emptive incidence approach will also be considered at the end. The important thing to keep in mind is that both methods measure different things.

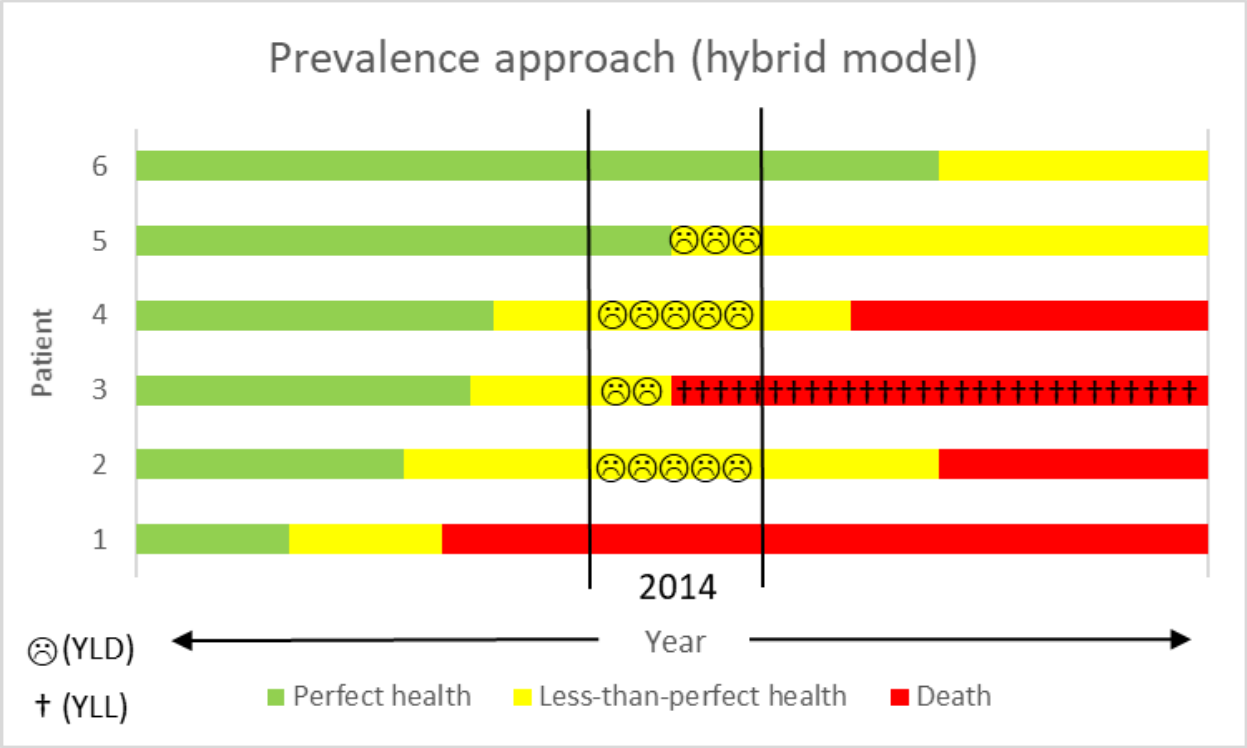
The conceptual difference between those two approaches is clarified in the section below. In extension of these two methods, a theoretical concept called the pure prevalence approach is also considered, which may further clarify the important distinction between prevalence and incidence approaches.

As already described, the burden of disease, quantified as DALYs, contains the two components YLLs and YLDs. This is applicable to all approaches. Consequently, the general formula can be written as:

$$DALYs = YLLs + YLDs$$

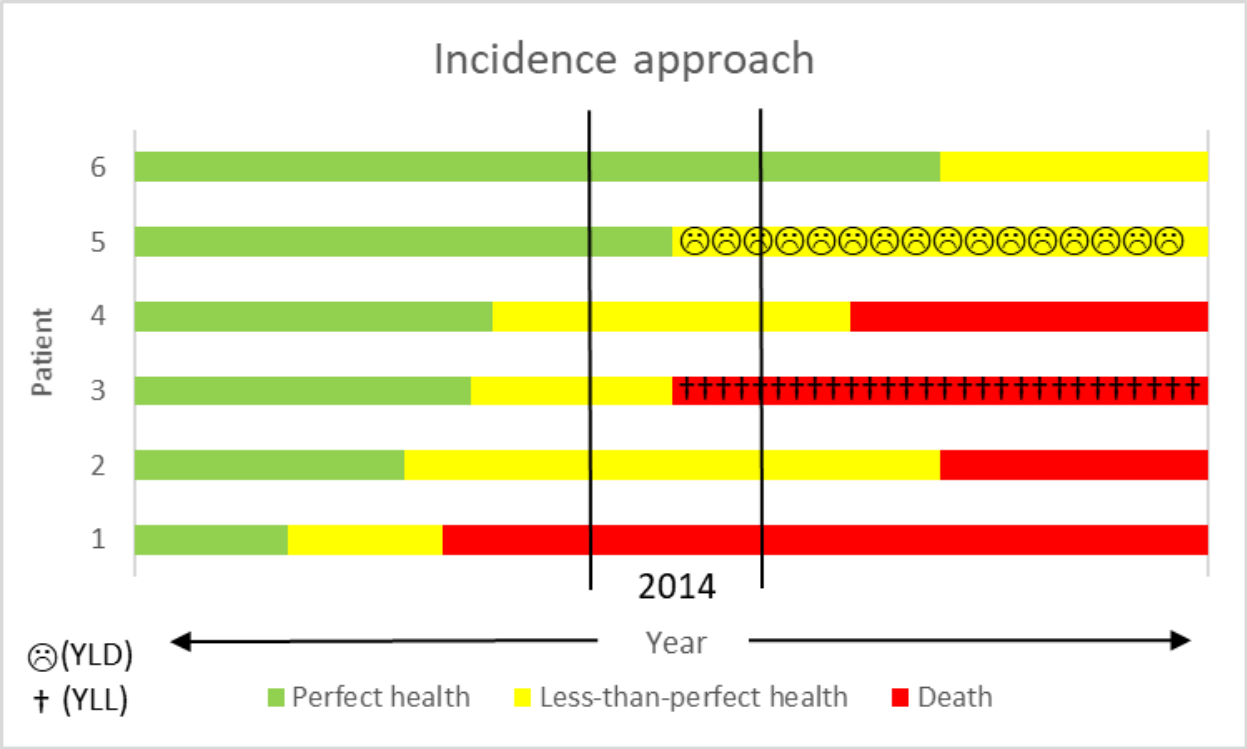
The prevalence approach (hybrid model) (Figure 1) can best be summarized as the current and future years of life lost due to premature mortality due to deaths in a particular year, plus the amount of disability experienced in that year. The hybrid approach is usually described in the literature as the prevalence perspective. However, the YLLs are also considering health loss in the future that would not have occurred if patients had not died in that particular period. In the meantime, YLDs are only considering the loss of health due to the disease in that particular period. As such, this approach only considers health states in a particular period and does not account for future YLDs. Thus, calling this a hybrid approach may be more suited than calling it the prevalence approach (Schroeder, 2012).

Figure 1



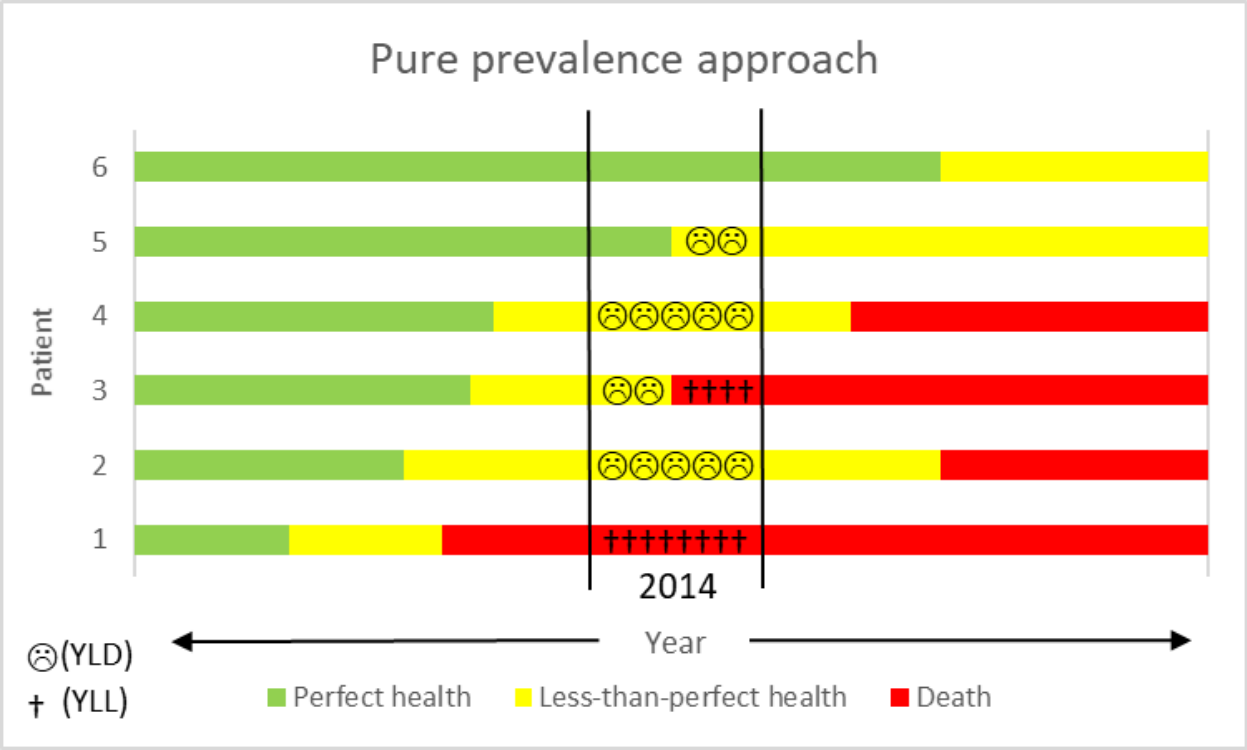
The incidence approach (Figure 2) can best be summarized as the stream of lost health due to new health-related events (deaths and disease incidence) occurring in a particular period, because it also takes future YLDs into account. Nonetheless, the events had to take place in the particular year to be included in the calculations (cfr. incidence).

Figure 2



The pure prevalence approach is a theoretical concept, which has never been applied in burden of disease studies. It is clear why this is called the pure prevalence approach, as it includes DALYs due to all deaths and disease-related events that affect the year 2014 (Figure 3). Roughly, DALYs measured by this approach indicate the amount of additional health that would have been experienced in a particular time frame, if the disease had not occurred in the particular year or in the years before.

Figure 3



Calculation of years of life lost

Years of life lost, which account for the mortality component, are calculated as follows:

$$YLLs = number\ of\ deaths\ x\ life\ expectancy\ at\ the\ age\ of\ death$$

To this end, standard life expectancies as reported by the World Health Organization are used (World Health Organization, 2017). This will ensure comparability with other burden of disease studies and is recommended as the standard for reporting results. These reference life expectancies are constructed based on the lowest estimated age-specific mortality rates from all locations with populations over 5 million, and are characterized by above average ages at death. For example, the life expectancy at birth is set at 91.6 years. No distinction is made for males and females. While this may still not represent the ultimate achievable human life spans, it does represent a set of life spans which are thought likely to be achieved by a substantial number of people who are alive today.

A yearly average of mortality is calculated by considering BCFR mortality data of the last ten years (2005-2014) (Table 2). When only considering 2014, some age categories are not represented and it would be inaccurate to generalize results based on only one year. If considering more than ten years, a different distribution would be included in the calculations. For example, before 2005 almost no deaths occurred after the age of 40 years, while deaths at this age will occur more and more. This would be less relevant because CF patients become older as scientific discoveries are continuingly under development. As such, accurateness of the numbers is improved while also taking the trend of increasing ages at death into account. The average age of death per age category is defined as the median of the upper and lower boundary of each age category. To calculate this average mortality, the number of deaths in each age category in the last ten years was divided by the total number of deaths in the last ten years, and then multiplied with the average yearly number of deaths during those ten years. The proportion of deaths in male and female patients is based on all reported deaths, as this is the only known element that relates gender and death. More specifically, it is known that during the last ten years, 76 CF patients deceased, of which 41 (54%) were male and 35 46%) female. This makes it possible to stratify the above mentioned average distribution according to gender. To this end, the numbers of deaths

in the average distribution are multiplied with 54% and 46%, for males and females respectively. The years of life lost are calculated by multiplying the number of deaths for each age category by the standard life expectancy (LE) for each age category.

Table 2

Numbers of deaths by age category and year*																			
Age at death	**0 - 4**	**5 - 9**	**10 - 14**	**15 - 29**	**20 - 24**	**25 - 29**	**30 - 34**	**35 - 39**	**40 - 44**	**45 - 49**	**50 - 54**	**55 - 59**	**60 - 64**	**65 - 69**	**70 - 74**	**75 - 79**	**Total**	**Male (54%)**	**Female (46%)**
1998	1	.	.	2	.	1	1	.	.	.	.	.	.	.	.	.	5		
1999	.	.	.	5	2	4	.	1	.	.	.	.	.	.	.	.	12		
2000	.	.	.	1	2	1	3	2	.	.	.	.	.	.	.	.	9		
2001	.	2	.	1	3	2	.	2	.	.	.	.	.	.	.	.	10		
2002	.	.	.	.	1	3	4	2	.	.	.	1	.	.	.	.	11		
2003	.	1	1	3	4	3	1	1	.	1	.	.	.	.	.	.	15		
2004	.	.	.	2	2	3	1	.	1	.	.	.	.	.	.	.	9		
2005	1	.	.	.	1	1	.	.	.	.	.	.	.	.	.	.	3		
2006	1	.	.	2	.	.	.	2	1	.	.	.	.	.	.	.	6		
2007	.	1	1	1	.	2	.	1	1	1	.	.	.	.	.	.	8		
2008	.	.	.	2	.	3	.	.	.	1	.	.	.	.	.	.	6		
2009	.	.	1	1	2	2	2	.	1	1	.	.	.	.	.	.	10		
2010	.	.	.	.	3	.	2	.	.	.	1	1	.	.	.	.	7		
2011	.	1	.	.	2	3	1	.	1	1	.	.	.	.	.	.	9		
2012	.	1	.	1	1	2	2	2		.	1	.	.	.	.	.	10		
2013	.	.	.	1	2	3	.	.	.	.	.	.	.	.	.	.	6		
2014	.	.	1	.	.	3	1	4	.	.	.	.	.	1	.	1	11		
1998-2014 (all reported deaths)	3	6	4	22	25	36	18	17	5	5	2	2	0	1	0	1	147	79	68
2005-2014 (10 years)	2	3	4	8	11	19	8	9	4	4	2	1	0	1	0	1	76	41	35
average distribution (1 year)	0.20	0.30	0.40	0.80	1.10	1.90	0.80	0.90	0.40	0.40	0.20	0.10	0.00	0.10	0.00	0.10	7.60	4.1	3.5
average distribution (males)	0.11	0.16	0.22	0.43	0.59	1.03	0.43	0.49	0.22	0.22	0.11	0.05	0.00	0.05	0.00	0.05	4.10		
average distribution (females)	0.09	0.14	0.18	0.37	0.51	0.87	0.37	0.41	0.18	0.18	0.09	0.05	0.00	0.05	0.00	0.05	3.50		

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Calculation of years lived with disability

Years lived with disability, reflecting the morbidity component, are calculated as follows:

$$YLDs = prevalence\ of\ the\ disease\ x\ its\ respective\ disability\ weight$$

Note that for the primary purpose of this dissertation, a prevalence approach is considered, as incidence numbers are not available for the different aspects that compose CF. Indeed, the disease model (see section: the cystic fibrosis disease model) used in this thesis, implies that CF can be considered as a multi-component disease. By using disability weights and prevalences for all these different components (and subcomponents), the YLDs for all these different aspects can be calculated. As such, the burden of CF is calculated using a bottom-up approach. This is a necessary step, because no disability weight for CF is yet reported. Other studies used proxy values based on chronic obstructive pulmonary disease (Bell, et al., 2011). So, although the overall incidence of CF is known, the incidences of the different aspects (such as severity categories and complications) of which it exists, are not. Nonetheless, by calculating the total YLDs in the prevalence approach, and subsequently dividing it by the number of CF patients, a composite CF disability weight can be inferred. This will be used to pre-emptively estimate incidence-based DALYs.

Disability weights have a central position in the calculation of the YLLs and YLDs. The rationale behind disability weights is that life years need to be corrected for the suffering of patients during those years. In case of YLLs the disability weight is non-arbitrarily set at one: the life year completely dissolves. When considering YLDs, the disability weights are set between zero (perfect health) and one (death), corresponding with personal preferences among health states as revealed by large population surveys. The particular disability weights used to account for non-fatal health outcomes are derived through the application of paired comparison questions and person trade-off (World Health Organization, 2017). The disability weights used in this dissertation are, if possible, directly extracted from the WHO report, which provides the most widely used and updated estimates of deaths and DALYs by cause, age, and sex for years 2000-2015 as part of its update of Global Health Estimates 2015 (World Health Organization, 2017). Lay descriptions of the corresponding health states are also provided in order to better grasp the

implications for the patient. These are the descriptions on which the general population applied its preferences. However, no disability weights are available for all (sub)components considered. Consequently, in those cases, approximate values are used, based on extrapolation and careful judgement of disability weights that are known. The specific way in which these disability weights are excogitated, is reported in the result section, as this will allow for a more comfortable read-through. In a minority of instances, the used disability weight are extracted from another source (Stouthard, Essink-Bot, Bonsel, Barendregt, & Kramers, 1997).

The cystic fibrosis disease model

As the section above already touched upon, CF can divided in different components. In order to fully exploit the data collected by the BCFR, separate calculations are made for CF as a primary disease (i.e. the primary disease component) and CF as a cause of complications (i.e. the complication component), including transplantation-related complications.

The primary disease component corresponds with the basic lung dysfunction that typifies CF. In this context, patients are stratified according to the severity of the primary disease, which is quantified by the forced expiratory volume in one second as a percentage of the predicted value in healthy subjects (FEV_1 % predicted). The FEV_1 % predicted is the volume of air that patients can exhale in one second, compared to a healthy person with similar gender, age and height (Kim, Corey, Stephenson, & Strug, 2018). As such, four categories are defined: normal lung function (FEV_1 % predicted ≥ 90%), mild lung dysfunction (FEV_1 % predicted between 70% and 89%), moderate lung dysfunction (FEV_1 % predicted between 40% and 69%) and severe lung dysfunction (FEV_1 % predicted < 40%).

The complication component is further divided according to the clinical systems involved. Three broad categories of complications can be distinguished: respiratory complications, digestive/endocrine complications and other complications. In order to keep the flow of this dissertation logical and comfortable to read, further elaboration on the different complication categories and subcomponents is provided in the result section. In short, the calculation of YLDs due to complications requires the determination of an appropriate disability weight and the assessment of the duration for each complication (in case of complications that resolve in less than one year i.e. are not chronic). Additionally, patients that have received transplantation are considered to suffer from post-transplantation complications.

General remarks

All calculations are performed in a deterministic way in Microsoft Excel worksheets. All tables (see section: Results) and figures (see section: Discussion) are generated by Microsoft Excel and modified in Word if appropriate.

DALYs are also calculated with respect to the general population in Belgium. The Belgian population according to age group and gender is extracted from the federal department Statistics Belgium (StatBel, 2014).

The core data and calculations can be combined to gain additional insights. The way this is done is always elaborated in the respective sections.

Results

Years of life lost due to cystic fibrosis

Years of life lost for each age category and both genders are calculated (Table 3). In an average year of the last ten years, nearly eight CF patients died. For all age categories, 261.8 and 223.0 YLLs are found for males and females respectively. Adding both numbers together leads to 484.8 YLLs for the total CF population in Belgium. On average, each death causes 63.0 YLLs. The YLLs are calculated per 100,000 Belgians. From this aggregate number it can be calculated that for every 100,000 Belgians, approximately 4.3 years of life are lost each year due to premature mortality in CF patients.

Table 3

Years of life lost due to premature mortality, 2014						
	Deaths (average)*	**Standard LE****	**YLLs*** **		**Population*****	**YLLs per 100,000**
			total	per death		
Males						
0-4	0.11	91.6	9.9	91.6	330,251	3.0
5-9	0.16	84.5	13.7	84.5	327,067	4.2
10-14	0.22	79.5	17.2	79.5	311,286	5.5
15-19	0.43	74.5	32.2	74.5	320,418	10.0
20-24	0.59	69.6	41.3	69.5	351,002	11.8
25-29	1.03	64.6	66.3	64.6	350,576	18.9
30-34	0.43	59.6	25.8	59.6	366,824	7.0
35-39	0.49	54.7	26.6	54.7	362,120	7.3
40-44	0.22	49.7	10.7	49.7	391,762	2.7
45-49	0.22	44.8	9.7	44.8	409,720	2.4
50-54	0.11	39.9	4.3	39.9	405,659	1.1
55-59	0.05	35.1	1.9	35.1	367,397	0.5
60-64	0.00	30.3	0.0	/	322,803	0.0
65-69	0.05	25.5	1.4	25.5	278,696	0.5
70-74	0.00	20.8	0.0	/	195,259	0.0
75-79	0.05	16.4	0.9	16.4	172,543	0.5
80-84	0.00	12.5	0.0	/	125,595	0.0
85+	0.00	7.6	0.0	/	85,331	0.0
Total	4.16		261.8	63.0	5,474,309	4.8
Females						
0-4	0.09	91.6	8.4	91.6	315,598	2.7
5-9	0.14	84.5	11.7	84.5	311,987	3.7
10-14	0.18	79.5	14.6	79.5	298,247	4.9
15-19	0.37	74.5	27.4	74.5	306,896	8.9
20-24	0.51	69.6	35.2	69.6	346,735	10.2
25-29	0.87	64.6	56.5	64.6	353,408	16.0
30-34	0.37	59.6	21.9	59.6	364,854	6.0
35-39	0.41	54.7	22.6	54.7	356,443	6.3
40-44	0.18	49.7	9.2	49.7	382,080	2.4
45-49	0.18	44.8	8.2	44.8	398,562	2.1
50-54	0.09	39.9	3.7	39.9	401,675	0.9
55-59	0.05	35.1	1.6	35.1	371,463	0.4
60-64	0.00	30.3	0.0	/	331,845	0.0
65-69	0.05	25.5	1.2	25.5	299,299	0.4
70-74	0.00	20.8	0.0	/	226,858	0.0
75-79	0.05	16.4	0.8	16.4	223,294	0.3
80-84	0.00	12.5	0.0	/	195,150	0.0
85+	0.00	7.6	0.0	/	191,813	0.0
Total	3.54		223.0	63.0	5,676,207	3.9
Males + females	7.70		484.4	63.0	11,150,516	4.3

*Average mortality distribution (Table 2), based on mortality data as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Standard life expectancies as reported by the World Health Organization are used (World Health Organization, 2017)

***$YLLs = number\ of\ deaths\ x\ life\ expectancy\ at\ the\ age\ of\ death$

**** Belgian population according to age group and gender is extracted from the federal department Statistics Belgium (StatBel, 2014).

The primary disease component of cystic fibrosis

FEV_1 categories

The primary disease component of CF entails the basic decline in lung function that characterizes CF patients. This means that lung function, measured as a decline in FEV_1 % predicted, acts as the central attribute of CF patients. As such, the BCFR categorizes CF patients according to the severity of their lung dysfunction (Table 4).

Table 4

FEV1 categories by age group*						
FEV_1 category	**Age group**					
	Children (6-17 years)		**Adults (≥ 18 years)**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Normal: ≥ 90% predicted	222	60.7%	87	15.3%	309	33.1%
Mild: 70% - 89% predicted	84	23.0%	151	26.6%	235	25.2%
Moderate: 40% - 69% predicted	41	11.2%	195	34.3%	236	25.3%
Severe: < 40% predicted	8	2.2%	103	18.1%	111	11.9%
Missing	11	3.0%	32	5.6%	43	4.6%
Subtotal	366		568		934	
Transplants	1		150		151	
< 6 years	145		-		145	
Total	**512**		**718**		**1230**	

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Disability weights

Health states related to CF are able to deliver insights in this primary disease component. In this context, calculations are performed with disability weights for chronic obstructive pulmonary disease (COPD) and asthma (World Health Organization, 2017).

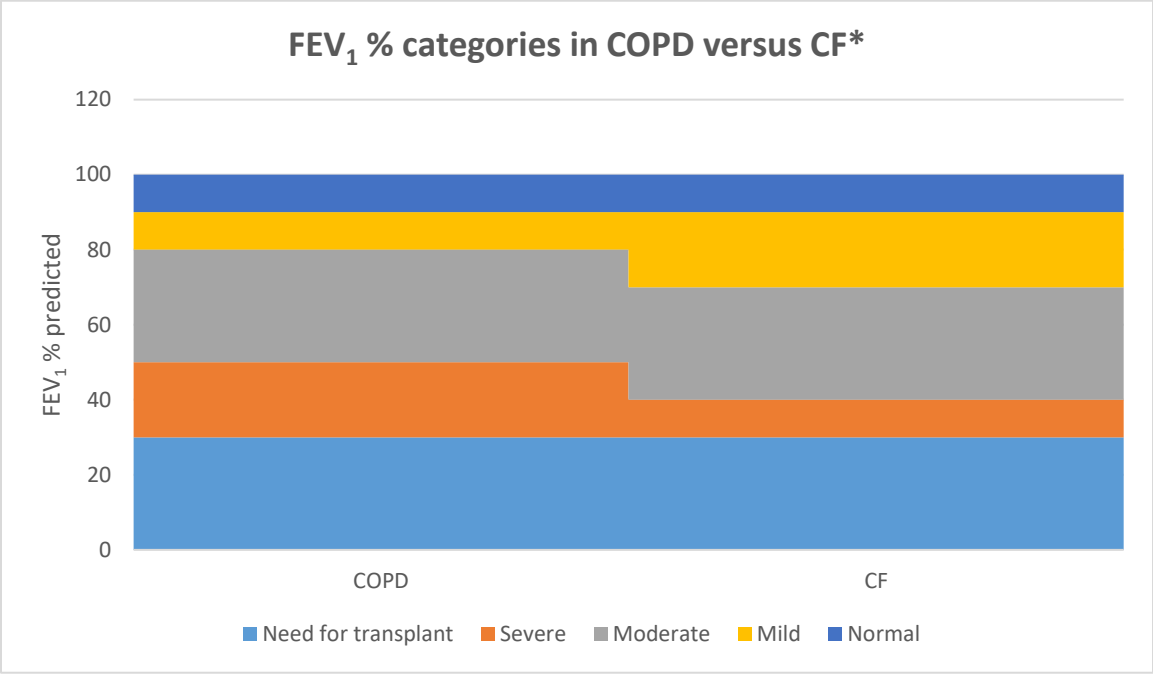
Normal lung function

Although categorized under normal lung function (i.e. FEV_1 % predicted > 90%), it is indeed so that even these patients suffer some abnormalities in their lung function (Accurso, et al., 2011). However, these abnormalities are not persistent and as such not measurable between episodes. This is also the case in patients suffering from asthma: between asthmatic episodes the FEV_1 tends to normalize (Menzies, Jackson, Mistry, Housten, & Lipworth, 2008). Due to these similarities, it seems reasonable to use the disability weights related to asthma interchangeably with CF patients that have "normal" lung function. As such, the average of the disability weights for (partially) controlled and uncontrolled asthma is used as the disability weight for CF patients with normal lung function (Table 6).

Abnormal lung function

In order to assign disability weights to the other three categories (i.e. mild, moderate and severe impairment of lung function), extrapolation of disability weights that are associated with COPD is performed (Table 6). This is necessary because the classification of CF and COPD according to FEV_1 % predicted uses different boundaries (Figure 4). It would be indeed incorrect to use the disability weight for moderate COPD as disability weight for moderate CF, because the upper and lower boundaries for the FEV_1 % predicted category are 10% lower for the latter. Assuming a linear relationship between FEV_1 % predicted and its effects on disability, the COPD disability weights were adjusted for use in a CF context. To this end, a linear regression method was used, as provided by the forecast function in MS Excel. This function predicts the CF disability weights based on known variables, i. e. the FEV_1 % predicted category midpoints and COPD disability weights (Table 5). In this disease model it is assumed that it is not possible to live (for a substantial time) when the FEV_1 % predicted is lower than 30%. In that case, transplantation is needed, so that patients end up in another category. Indeed, the case fatality rate of patients with a FEV_1 % predicted less than 30% is very high (Egan, et al., 2002). Patients should be referred to lung transplantation centers when the FEV_1 % predicted has fallen to 30% or less (Adde, Campos, de Oliveira Braga Teixeira, & Rodrigues, 2018). Transplantation will later be considered a complication, rather than a primary health state.

Figure 4



*FEV_1 categories are according to the GOLD classification for COPD (Hernandez, Garcia, Falco, Garcia, & Martin, 2018), and according to the BCFR report for CF (Wanyama, Thomas, & Malfroot, 2014)

Table 5

Linear regression method to calculate cystic fibrosis disability weights according to FEV_1 % predicted*					
COPD			CF		
Range FEV_1 % predicted	Range FEV_1 % predicted midpoint	DW	Range FEV_1 % predicted	Range FEV_1 % predicted midpoint	DW (forecast)
80%-90%	0.85	0.019	70%-90%	0.80	0.071
50%-80%	0.65	0.225	40%-70%	0.55	0.298
30%-50%	0.40	0.408	30%-40%	0.20	0.704
<30%	/	1	<30%	/	/

*Performed in MS Excel

Table 6

Disability weights used in the primary disease component of cystic fibrosis					
WHO health state**	**FEV_1 category of asthma and COPD***	**Lay description****	**DW****	**FEV_1 category of CF**	**Adjusted DW*****
Asthma: controlled	FEV_1 % predicted ≥ 90%	Has wheezing and cough once a month, which does not cause difficulty with daily activities.	0.015		
Asthma: partially controlled	Episodic but tends to normalize	Has wheezing and cough once a week, which causes some difficulty with daily activities.	0.036		
Asthma: uncontrolled	Episodic but tends to normalize	Has wheezing, cough and shortness of breath more than twice a week, which causes difficulty with daily activities and sometimes wakes the person at night.	0.133		
Asthma: mean of (partially) controlled and uncontrolled	FEV_1 % predicted ≥ 90% in general	Combination of the three descriptions above.	0.061	Normal : FEV_1 % predicted ≥ 90%	0.061
COPD and other chronic respiratory problems, mild	FEV_1 % predicted ≥ 80%	Has cough and shortness of breath after heavy physical activity, but is able to walk long distances and climb stairs.	0.019	Mild : 70% ≤ FEV_1 % predicted ≤ 89%	0.071
COPD and other chronic respiratory problems, moderate	50% ≤ FEV_1 % predicted ≤ 80%	Has cough, wheezing and shortness of breath, even after light physical activity. The person feels tired and can walk only short distances or climb only a few stairs.	0.225	Moderate : 40% ≤ FEV_1 % predicted ≤ 69%	0.298
COPD and other chronic respiratory problems, severe	30% ≤ FEV_1 % predicted ≤ 50%	Has cough, wheezing and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.	0.408	Severe : FEV_1 % predicted < 40%	0.704
COPD and other chronic respiratory problems, very severe	FEV_1 % predicted < 30% or respiratory failure	NA	NA	NA	NA

*For COPD the GOLD classification system is used for the WHO disability weights (Hernandez, Garcia, Falco, Garcia, & Martin, 2018)

** Health states, disability weights and lay descriptions are extracted from the most recent GBD study (World Health Organization, WHO methods and data sources for global burden of disease estimates 2000-2015, 2017)

***Adjusted disability weights are calculated according to methods described in the text

NA: not available

The distribution of CF patients according to FEV_1 severity category (Table 4) for Belgian children and adults with CF is used, in combination with the calculated adjusted disability weights (Table 6), to calculate two general disability weights: one for children and one for adults. Indeed, it seems necessary to make a distinction between both groups, as the distribution varies significantly, with children generally having a milder impairment of lung function.

In short, the distribution of CF patients according to FEV_1 category is multiplied with the adjusted disability weights, which relate to the different FEV_1 categories. As a result, disability weights for children and adults are calculated (Table 7). Note the relatively big difference in the disability weights for both groups, which is assumed to be caused by the progressively deteriorating nature of the disease (Theodore, Elkin, Pasta, Jacobs, & Konstan, 2014). Additionally a third disability weight is calculated as the average of the two, which has relevance towards the adolescent CF population. It is important to recognize this group, as they suffer the fastest decline in lung function (Theodore, Elkin, Pasta, Jacobs, & Konstan, 2014) (see also sections below).

Table 7

General disability weights for the primary disease	
Group	**General DW**
Children (6-17 years)	0.102
Adults (> 17 years)	0.258
Adolescents (transition: 15 - 19 years)	0.180

In order to generate the YLDs due to the primary disease component, the number of children and adults with CF in Belgium is needed, which is provided by the BCFR as an age and gender distribution of CF patients (Table 8).

Table 8

Age distribution of cystic patients by gender, 2014*									
Age	**Males**			**Females**			**All Patients**		
	n	**cum n**	**cum %**	**n**	**cum n**	**cum %**	**n**	**cum n**	**cum %**
0 -< 5	56	56	8.8%	54	54	9.2%	110	110	8.9%
5 -< 10	56	112	17.5%	74	128	21.7%	130	240	19.5%
10 -< 15	82	194	30.3%	72	200	33.9%	154	394	32.0%
15 -< 20	104	298	46.6%	65	265	44.9%	169	563	45.8%
20 -< 25	81	379	59.2%	72	337	57.1%	153	716	58.2%
25 -< 30	58	437	68.3%	70	407	69.0%	128	844	68.6%
30 -< 35	65	502	78.4%	66	473	80.2%	131	975	79.3%
35 -< 40	56	558	87.2%	39	512	86.8%	95	1070	87.0%
40 -< 45	39	597	93.3%	26	538	91.2%	65	1135	92.3%
45 -< 50	17	614	95.9%	21	559	94.7%	38	1173	95.4%
≥ 50	26	640	100.0%	31	590	100.0%	57	1230	100.0%
TOTAL	**640**			**590**			**1230**		

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Years lived with disability due the primary disease component

Subsequently, the YLDs due to the primary disease component are calculated, for each age category and both genders (Table 9). This results in 126.8 YLDs for male patients and 116.0 YLDs for female patients, corresponding with a total of 242.7 YLDs due to the primary disease. Per patient, on average 0.20 YLDs are experienced in the year 2014 due to this primary lung dysfunction.

Table 9

Years lived with disability due to the primary disease, 2014							
	Prevalence*		DW	YLDs			
	males	females		males	females	total	per patient
≤ 4 years	56	54	0.102	5.7	5.5	11.3	0.10
5 - 9 years	56	74	0.102	5.7	7.6	13.3	0.10
10 - 14 years	82	72	0.102	8.4	7.4	15.8	0.10
15 - 19 years	104	65	0.180	18.7	11.7	30.4	0.18
20 - 24 years	81	72	0.258	20.9	18.6	39.5	0.26
25 - 29 years	58	70	0.258	15.0	18.0	33.0	0.26
30 - 34 years	65	66	0.258	16.8	17.0	33.8	0.26
35 - 39 years	56	39	0.258	14.4	10.1	24.5	0.26
40 - 44 years	39	26	0.258	10.1	6.7	16.8	0.26
45 - 49 years	17	21	0.258	4.4	5.4	9.8	0.26
≥ 50 years	26	31	0.258	6.7	8.0	14.7	0.26
Total	640	590		126.8	116.0	242.7	0.20

*Prevalences as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

The complication component of cystic fibrosis

In addition to CF as a primary disease entity, patients also suffer from CF-related complications. Three categories of complications can be distinguished, which relate to the clinical systems that are often involved in the disease progression. The categories are: respiratory complications, digestive/endocrine complications and other complications. In the section below, the specific complications which constitute those categories are discussed regarding their prevalence as reported by the BCFR opposed to the prevalences reported in the published studies. In addition, the degree of causality between CF and the respective complication, as well as the duration of the complication and used disability weight, are assessed if appropriate. In general, prevalences of complications as reported by the BCFR are lower than those reported by scientific publications. Nonetheless, the BCFR reported prevalences are similar to those in other registries, such as the Australian Cystic Fibrosis Data Registry (Bell, et al., 2011). Generally, most complications are thought to be caused by CF. Furthermore, for each complication a clinical description is provided, because a decent understanding of the complication is necessary in order to assign specific disability weights. Post-transplantation complications are considered a separate category and the corresponding YLDs are also calculated. For each complication category a table is presented at the end of the respective section (Table 10, Table 11, Table 12 and Table 13). A summary of the YLDs due to all complications, which also shows the impact on the level of the patient, is compiled and shown at the end of the section (Table 15).

Respiratory complications

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder that often occurs in patients with CF and is characterized by a hypersensitivity response to the allergens of the fungus *Aspergillus fumigatus*, which results in airway inflammation, bronchospasm, and bronchiectasis. In most published studies, the prevalence of ABPA is about 8.9% in patients with CF (Janahi, Rehman, & Al-Naimi, 2017), which is slightly higher than the prevalence reported by the BCFR (6.7%). Since the clinical features of this condition overlap significantly with those of CF, ABPA is challenging to diagnose and remains undiagnosed in many patients. In addition, there may be a long delay (of up to ten years) between the first occurrence of symptoms and subsequent diagnosis (Mou, Ye, Yang, & Jin, 2014). Diagnosis relies on a combination of the clinical picture, blood tests, lung function and imaging. In patients with CF, development of ABPA has been associated with a progressive decline in pulmonary function (Paty, et al., 1991). In case of ABPA in its burnt-out stage with permanent fibrotic damage of the lung, this decline has already been captured by the primary disease component. However, CF-ABPA patients also suffer from acute episodes which exacerbate pulmonary dysfunction. These episodes often burden the patients heavily in their daily activities. For this reason, the disability weight for a severe acute, infectious health state is used. On average, each affected patient goes through one acute episode of approximately two weeks each year (Nepomuceno, Esrig, & Moss, 1999). As such, acute episodes of ABPA lead to 0.37 YLDs.

Pneumothorax

A pneumothorax is a feared complication and occurs when air reaches the vacuum of the pleural space. It is mainly caused by destruction of the alveoli leading to the leakage of air. This complication is more common in adults who have more advanced lung disease (Kioumis, Zaroqoulidis, Huang, Li, & Dryllis, 2014). Consequently, with improved survival into adult life, the incidence of pneumothorax is expected to increase. According to the literature, one in 167 CF patients experience this complication, which is double the prevalence of 0.3% as reported by the BCFR (Flume, Strange, Ye, Ebeling, & Hulsey, 2005). Next to considerable morbidity, there is an attributable mortality to the complication (Flume, Strange, Ye, Ebeling, & Hulsey, 2005). Pneumothorax occurs almost exclusively in patients who already have severe lung impairment, as this is the main predisposing factor (Kioumis, Zaroqoulidis, Huang, Li, & Dryllis, 2014). This severe lung impairment is already categorized under the primary disease component as described above. However, the acute onset and troubling nature of the complication need to be taken into consideration. The course of this complication has resemblance to the one caused by acute myocardial infarction, as patients experience comparable symptoms, and need to go through similar diagnostic procedures (Reamy, Williams, & Odom, 2017). The median length of hospital stay is 13 days according to one study (MacDuff, Tweedie, McIntosh, & Innes, 2010) so that it seems reasonable to apply a complication duration of two weeks. The other part of the year is characterized by general worry, which has a corresponding disability weight, because patients may fear recurrence. As such, pneumothorax causes 0.16 YLDs.

Nasal polyps

Nasal polyps are mucosal overgrowths caused by chronic infections of the upper airways (e.g. rhinosinusitis) (Steinke, et al., 2012). They are responsible for nasal obstruction, mouth breathing, epistaxis, anosmia and rhinorrhea. The prevalence of nasal polyps as reported in the literature is remarkably higher (37%) than as reported by the BCFR (19%) (Hadfield, Rowe-Jones, & Mackay, 2000). Exceptions aside, it is no severe disease but it can be quite a nuisance, in which case the overgrowths need to be removed surgically (Weber & Ferrari, 2008). The disability weight used for nasal polyps is that of a generic uncomplicated disease. It is calculated that nasal polyps cause 10.05 YLDs.

Hemoptysis

Hemoptysis is a common complication in CF, occurring in approximately 9% of the population (Hurt & Simmonds, 2012). The BCFR only reports massive hemoptysis (> 240 cc/24h or long lasting), a more severe variant which is associated with older patients and carries a high case fatality rate. Patients with massive hemoptysis who do not respond to initial medical treatments should undergo bronchial artery embolization (25% of cases in the BCFR). This will control the bleeding in the majority of cases but recurrence rates are high and there are little data to support long-term improved outcomes (Lee, Kim, Yong, Shin, & Kim, 2015). Surgery is a last resort in patients with CF. The majority (approximately 60% patients) has a FEV_1 < 40% predicted at the time of first episode of massive hemoptysis. However, it still occurs in patients with mild disease and the remainder of patients have a less impaired lung function. Most patients will experience severe deterioration of lung function (Hurt & Simmonds, 2012). It is necessary to account for this acute deterioration of lung function, as this is not yet captured by the primary disease component. Disability weights for FEV_1 categories are reported above (Table 5). An adjusted disability weight is calculated by taking the proportion of severe versus non-severe impairment of lung function into account. Patients who go through an episode of hemoptysis also experience the symptoms of severe anemia (Ittrich, Bockhorn, Klose, & Simon, 2017), for which a disability weight is available. For this reason, the disability weight is further modified according to a multiplicative model in which both health states proportionally contribute to the combined disability weight (Hilderink, Plasmans, Snijders, Boshuizen, & Poos, 2016):

$$1 - \left(1 - DW_{weighted\ FEV1}\right) * (1 - \ DW_{anaemia}) = DW_{hemoptysis}$$

It is hard to define a standard duration of an episode of hemoptysis. For this reason, an arbitrary duration of two weeks is applied. Initial therapy does often not prevent recurrent episodes (Lee, Kim, Yong, Shin, & Kim, 2015). Consequently, the other part of the year is subjected to general worry. It is calculated that hemoptysis accounts for 1.43 YLDs.

Table 10

Years lived with disability due to respiratory complications, 2014									
Complication*	**N**	**%**	**Health state****	**Lay description****	**DW****	**Adjusted DW*****	**Duration (days)******	**YLDs *******	**Total YLDs**
Allergic bronchopulmonary aspergillosis (ABPA)	72	6.7%	Infectious disease, acute episode, severe	Has a high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0.133		14	0.37	0.37
Pneumothorax	3	0.3%	Acute myocardial infarction: days 1-2	Has severe chest pain that becomes worse with any physical activity. The person feels nauseous, short of breath, and very anxious.	0.432		2	0.01	0.16
			Acute myocardial infarction: days 3-28	Gets short of breath after heavy physical activity, and tires easily, but has no problems when at rest. The person has to take medication every day and has some anxiety.	0.074		12	0.01	
			Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049		353	0.14	
Nasal polyps	205	19.0%	Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049		365	10.05	10.05
Massive hemoptysis	20	1.9%	40% of cases: 40% ≤ FEV_1 predicted ≤ 70%	Has cough, wheezing and shortness of breath, even after light physical activity. The person feels tired and can walk only short distances or climb only a few stairs.	0.566			0.48	1.43
			60% of cases: FEV_1 % predicted < 40%	Has cough, wheezing and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.		0.631	14		
			Anemia: severe	Feels very weak, tired and short of breath, and has problems with activities that require physical effort or deep concentration.	0.149				
			Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049		353	0.95	
Total	300							11.05	11.05

*Respiratory complications as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Health states, disability weights and lay descriptions are extracted from the most recent GBD study (World Health Organization, WHO methods and data sources for global burden of disease estimates 2000-2015, 2017)

***If appropriate, an adjusted disability weight is calculated according to methods described in the text

****Durations as estimated in the literature (see text for references); chronic complications have a duration of 365 days

*****$YLDs = N\ x\ (adjusted)DW\ x\ \frac{duration}{365}$

Digestive and endocrine complications

Exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency is the most prevalent complication of CF in all complication categories (in 2014 > 80% of patients in Belgium are affected). Pancreatic insufficiency is the inability of the pancreas to produce digestive enzymes and/or transport these enzymes to the duodenum. Subsequently, fat and protein digestion and absorption is impaired. (Gibson-Corley, Meyerholz, & Engelhardt, 2016). As such, it is a malabsorption syndrome, resembling kwashiorkor. The most characteristic symptom is steatorrhea while other common signs and symptoms include unexplained weight loss and deficiencies of fat-soluble vitamins (A, D, E and K) and other micronutrients. Pancreatic enzyme replacement therapy can relieve symptoms and long-term sequelae (Durie, Baillargeon, Bouchard, Donnellan, & Zepeda-Gomez, 2018). The disability weight for kwashiorkor is applied to calculate the YLDs. According to the calculations, exocrine pancreatic insufficiency causes 44.2 YLDs.

Acute pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas and a rather unusual complication in CF patients. The prevalence as reported by the BCFR is similar to the one in the general population (approximately 1%) (Turner, 2003). Consequently, the causality between CF and acute pancreatitis is doubtful. Nonetheless, some degree of causality can be assumed, because CF has significant impact on the overall pancreatic function. Abdominal pain is the cardinal symptom. About 90% of patients have nausea and vomiting, which can be severe and unremitting, and fever (Mitchell & Cappell, 2008). In some cases, death is unavoidable. Altogether, the health state of severe abdominopelvic problems is the best proxy for this complication. The hyper-acute stage of pancreatitis lasts from a few days to more than a week. However, fully recovery can take multiple weeks or even longer (Hochman, Louie, & Bailey, 2006). For this reason, a duration of two weeks is applied. Again, the remaining part of the year is subjected to general uneasiness. It is calculated that acute pancreatitis accounts for 0.8 YLDs.

Cystic fibrosis-related diabetes

The rise of cystic fibrosis-related diabetes (CFRD) is the paragon of how increased survival of CF patients will increase the complication-related burden of CF. It is estimated that nearly 50% of adult CF patients will eventually develop CF-related diabetes (Habib, et al., 2015). The malfunctioning of the endocrine part of the pancreas by fibrosis and/or autolysis leads to an insufficient secretion of insulin, which is normally responsible for glucose homeostasis (Kayani, Mohammed, & Mohiaddin, 2018). This results in an impaired glucose tolerance (IGT) and eventually diabetes. The BCFR reports a prevalence of 16.3%, which is in agreement with a relatively dated source of CFRD prevalence (Lannq, Thorsteinsson, Lund-Andersen, Nerup, & Schiotz, 1994). A more recent cross-sectional study points towards a significantly higher prevalence of up to 33% (Moran, Dunitz, Nathan, Saeed, & Holme, 2009). Be aware of the fact that environmental and life style effects complicate the causality between CF and diabetes and hence, CFRD prevalence. The disability weight for diabetic neuropathy is used, although approximately only one third of diabetes patients have a diagnosis of diabetic peripheral neuropathy (Schwarzenberg, et al., 2007). For this reason, the disability weight is adjusted proportionally by combining it with the disability weight for uncomplicated diabetes, retrieved from another source (Stouthard, Essink-Bot, Bonsel, Barendregt, & Kramers, 1997). The (unadjusted) disability weight for uncomplicated diabetes is also used for the calculation of YLDs due to IGT. Together, CFRD and IGT are found to be responsible for 21.4 YLDs. Another way to obtain a disability weight for diabetes would be to divide the total YLDs due to diabetes by its prevalence, as those data are reported in the context of the last Global Burden of Disease Study (Vos & GBD 2015 Collaborators, 2016). This disability weights corresponds well with the adjusted disability weight calculated above (0.077 versus 0.091 respectively). Nonetheless, the higher of the two is used in the calculations, because CF patients are on multiple occasions found to have more peripheral nerve dysfunction (although not always directly related to diabetes) compared to a model diabetes patient (El-Salem, Aburahma, & Rawashdeh, 2010) (Chakrabarty, et al., 2013).

Gastro-esophageal reflux

Gastro-esophageal reflux (GER) is a condition in which gastric and/or intestinal contents repeatedly move back up into the esophagus, mostly because of an inappropriate relaxation of the lower esophageal sphincter (Hauser, De Schepper, Malfroot, De Wachter E, & De Schutter, 2016). This complication is a major problem in the early life of CF patients, and, in contrast to most other CF-related pathologies, it improves with age (Malfroot & Dab, 1991). The symptoms most commonly observed are pyrosis and regurgitation (Eusebi, Ratnakumaran, Yuan, Solaymani-Dodaran, & Bazzoli, 2018). Mostly, the symptoms cause intermittently annoying episodes on a daily basis. For this reason, the disability weight for a mild abdominopelvic problem is used. However, when persistent, it can cause esophagitis and malnutrition. It can also lead to respiratory infections which may worsen the respiratory function. In rare cases, a Barrett's esophagus develops, which may transform into esophageal carcinoma (Lowe & Hsu, 2017). It is calculated that GER leads to 2.9 YLDs.

Liver cirrhosis

Liver cirrhosis represents an irreversible scarring process and is found to affect 16.6% of the CF population (older than 2 years) (Fustik, 2013). Of these patients, only 20% find themselves in a decompensated cirrhosis stage, which is characterized by portal hypertension. Symptoms are variable and include fatigue, itchiness, jaundice, ascites, anorexia, nausea, and weight loss. Cirrhosis often has no signs or symptoms until the hepatic deterioration is substantial, hence decompensated (Berzigotti, 2017). The BCFR reports only patients in this advanced stage, which accounts for 4% of the Belgian CF patients. As such, the disability weight for decompensated cirrhosis of the liver is applied. In the situation of advanced disease with hepatic insufficiency, a liver transplant may be required. The pathogenic process of CF-related liver disease is known and implies a causal relationship (Fustik, 2013). As such, decompensated cirrhosis of the liver is found to cause 7.7 YLDs.

Gallstones

Gallstones are relatively common in young adults with CF. Note that patients with liver cirrhosis have a higher chance of developing gallstones (Acalovschi, 2014) (see also section: Discussion). Gallstones are often asymptomatic and consequently remain undiagnosed (Behari & Kapoor, 2012). The prevalence reported by the BCFR is assumed to concern symptomatic gallstones, which usually require surgery (Mayo Clinic, 2012). The cardinal symptoms are mid upper abdominal pain, colic and dyspepsia (Thijs & Knipschild, 1998), which are acute and are relieved by cholecystectomy. This procedure usually resolves the most impactful symptoms of the complication within a few days. As such, an arbitrary duration of three days is put in place. The health state that best resembles this complication is the one regarding a severe abdominopelvic problem. After removal of the gallbladder, patients do not experience prolonged distress as the formation of new stones is excluded. It is calculated that gallstones lead to 0.1 YLDs.

Intestinal obstruction

Meconium ileus at birth, distal intestinal obstruction syndrome (DIOS), and constipation are an interrelated group of intestinal obstruction syndromes with a variable severity of obstruction that occur in CF patients. Due to abnormally viscid mucofecal material in the terminal ileum and caecum, this leads to a partial or complete bowel obstruction (Subhi, Ooi, Finlayson, Kotsimbos, & Wilson, 2013). These complications, DIOS in particular, can cause acute abdominal pain and, if left untreated, it can progress to a complete bowel obstruction with severe vomiting. The complication usually responds to medical treatment, but surgical intervention may be required in some cases (Colombo, et al., 2011). It predominantly occurs after the age 18 years, and half of the patients experience relapse. Studies on the prevalence of DIOS are difficult to compare with the BCFR (3.6%) because only lifetime prevalence are published in the literature (7–8% in children, 14-16% in adults) (Van der Doef, Kokke, Van der Ent, & Houwen, 2011). Other studies report even higher prevalences (Perez-Aguillar, Ferrer-Calvete, Nicolas, Berenguer, & Ponce, 1999) (Dray, Bienvenu, Desmazes-dufeu, Dusser, & Marteau, 2004). With the increasing life expectancy of CF patients, the prevalence of DIOS needs to be regularly reassessed. More than 90% of cases are resolved with medical management within 2–3 day (Subhi, Ooi, Finlayson, Kotsimbos, & Wilson, 2013). Only a small proportion, 2 of 39 patients in accordance to the BCFR

report 2014, needs surgical relief. Note the hyper-acute character of the disease, which distinguishes it from milder forms of obstruction such as constipation. As such, the short but impactful nature of the complication justifies the use of the disability weight for severe abdominopelvic problems. The remaining part of the year is subjected to general distress, which has a corresponding disability weight. It is found that intestinal obstruction syndromes (which presumably represent cases of DIOS) cause 2.0 YLDs.

Gastroparesis

Gastroparesis is a motility disorder that leads to a delayed gastric emptying, which can result in symptoms of nausea, vomiting, postprandial fullness, epigastric pain and regurgitation (Triadafilopoulos, Nguyen, & Clarke, 2017). It is a chronic condition for which symptomatic therapy and life style recommendations exist. The BCFR reports only two CF patients with gastroparesis, which is only 0.2% of the CF population. However, a meta-analysis reports a prevalence as high as 38% (Corral, Dye, Mascarenhas, Barkin, & Salathe, 2016). The use of different diagnostic modalities is assumed to cause this big gap in prevalence. For this reason, these two patients probably suffer a relatively severe variant of the complication. Although mostly it is a relatively mild disorder, this consideration justifies to align the complication with the disability weight of a moderate abdominopelvic problem. Interestingly, none of the standard textbooks have mentioned gastroparesis as a gastrointestinal manifestation of CF (Mandaliya, Hadjiliadis, & Cohen, 2016). This, in addition to the gap in prevalence between the BCFR and the recent meta-analysis, suggests the need for more awareness of this complication by the CF reference centers. Gastroparesis is responsible for 0.2 YLDs.

Clostridium difficile

Clostridium difficile is a spore forming Gram-positive organism responsible for antibiotic-associated colitis (Leeds, 2016). Indeed, patients with CF receive large amounts of (broad-spectrum) antibiotics which destroy the normal gastro-intestinal flora so that *C. difficile* can flourish. Despite high carrier rates of up to 46%, CF patients have low rates of active disease (Dunwoody, Steel, Landy, & Simmonds, 2018). Because of this, the small share of patients that is reported by the BCFR to have this infection (1.4%) is presumed to have the active disease variant. Symptoms of active disease include moderate to severe abdominal pain, severe diarrhea, other gastro-intestinal symptoms and infectious disease symptoms. In CF patients it is often associated with a respiratory and nutritional failure, which makes it a potentially life-threatening condition (Piccolo, Tai, Ee, Mulrennan, & Bell, 2017). For this reason, disability weights for severe diarrhea, a severe abdominopelvic problem and severe impairment of lung function are combined in the same multiplicative manner as described for hemoptysis. In general, the diarrhea and other associated symptoms tend to resolve after approximately seven days (Ingle, Deshmukh, Desai, Abraham, & Joshi, 2011). As such, *C. Difficile* is found to be responsible for 0.2 YLDs.

$$1 - (1 - DW_{severe\ diarrhea}) * (1 - \ DW_{FEV1}) * (1 - DW_{abdominal\ problem}) = DW_{C.Difficile}$$

Table 11

Years lived with disability due to digestive and endocrine complications, 2014									
Complication*	**N**	**%**	**Health state****	**Lay description****	**DW****	**Adjusted DW*****	**Duration (days) ******	**YLDs *******	**Total YLDs**
Exocrine pancreatic insufficiency	867	80.4%	Kwashiorkor	Is very tired and irritable and has diarrhea.	0.051		365	44.2	44.2
Acute pancreatitis	14	1.3%	Abdominopelvic problem: severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324		14	0.2	0.8
			Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049		351	0.7	
CF-related diabetes (CFRD)	176	16.3%	33%: diabetic neuropathy	Has pain, tingling and numbness in the arms, legs, hands and feet. The person sometimes gets cramps and muscle weakness.	0.133				16.0
						0.091	365	16.0	
			67%: uncomplicated diabetes mellitus	No or few problems with walking, washing, dressing, cognitive function, performing usual activities. No pain or dis-comfort, not anxious or depressed	0.070				
Impaired glucose tolerance (IGT)	77	7.1%	Uncomplicated diabetes mellitus	No or few problems with walking, washing, dressing, cognitive function, performing usual activities. No pain or dis-comfort, not anxious or depressed	0.070		365	5.4	5.4
Gastro-esophageal reflux (GER)	265	24.6%	Abdominopelvic problem: mild	Has some pain in the belly that causes nausea but does not interfere with daily activities.	0.011		365	2.9	2.9
Cirrhosis with portal hypertension	43	4.0%	Decompensated cirrhosis of the liver	Has a swollen belly and swollen legs. The person feels weakness, fatigue and loss of appetite.	0.178		365	7.7	7.7

Gallstones	36	3.3%	Abdominopelvic problem: severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324	3	0.1	0.1
Intestinal obstruction	39	3.6%	Abdominopelvic problem: severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324	3	0.1	2.0
			Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049	362	1.9	
Gastroparesis	2	0.2%	Abdominopelvic problem: moderate	Has pain in the belly and feels nauseous. The person has difficulties with daily activities.	0.114	365	0.2	0.2
Clostridium infection (treatment needed)	15	1.4%	Diarrhea, severe	Has diarrhea three or more times a day with severe belly cramps. The person is very thirsty and feels nauseous and tired.	0.247			0.2
			Abdominopelvic problem: severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324 0.826	7	0.2	
			Severe : < 40% predicted	Has cough, wheezing and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.	0.658			
Total	1534						79.5	79.5

*Digestive and endocrine complications as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Health states, disability weights and lay descriptions are extracted from the most recent GBD study (World Health Organization, WHO methods and data sources for global burden of disease estimates 2000-2015, 2017)

***If appropriate, an adjusted disability weight is calculated according to methods described in the text

****Durations as estimated in the literature (see text for references); chronic complications have a duration of 365 days

*****$YLDs = N\ x\ (adjusted)DW\ x\ \frac{duration}{365}$

Other complications

Cystic fibrosis-related arthritis

Cystic fibrosis-related arthritis is a relatively infrequent chronic complication in which patients, often with advanced lung disease, develop painful inflammation of the joints (Doyen, et al., 2005). The exact pathogenic mechanism is not known, but regression of symptoms is usually seen when respiratory function is stabilized (Thornton & Rangaraj, 2016), which suggests a causal relationship. No disability weight for arthritis is available in the default source, but a Dutch study brings solace (Stouthard, Essink-Bot, Bonsel, Barendregt, & Kramers, 1997). It is calculated that CF-related arthritis leads to 4.8 YLDs.

Cancer

The overall burden of cancer in CF patients remains low. The BCFR reports only four CF patients to have (non-specified) malignant disease in 2014. However, according to the literature, patients have an increased risk of digestive tract cancer, particularly following transplantation (Maisonneuve, Marshall, Knapp, & Lowenfels, 2013). They also have a slightly increased risk of lymphoid leukemia and testicular cancer, and a decreased risk of melanoma. Cancer-related disability weights are available, and the mean of primary and metastatic disease is applied. Although the YLDs due to cancer are calculated, the causality between CF and malignant disease remains unclear and doubtful (Johannesson, Askling, Montgomery, Ekbom, & Bahmanyar, 2009), especially when considering non-specified malignant disease. Cancer is calculated to be responsible for 1.5 YLDs.

Psychiatric disease

Psychiatric diseases and psychological symptoms are a major issue in patients with CF. It should be noted that the prevalence of psychiatric symptoms in CF patients is significantly higher than the one found in the general population. The prevalence of major depression is estimated to be approximately 3.0 to 6.4% in healthy adults (Mollica, 1989) and 2% in healthy children (Petti, 1983). In contrast, using behavioral indices, symptoms in the range of clinical depression may occur in as much as 42.4% of adult patients and 14.8% of young patients (Pearson, Pumariega, & Seilheimer, 1991). Similarly, the prevalence of anxiety disorders in the general population is thought to be approximately 7.3% in adults (Regier & Burke, 1989) and less than 2% in children (Adams, 1989), but the rate of clinically significant symptoms of anxiety seems to be much higher in CF patients: 22.2% in adult patients and 6.9% in young patients (Pearson, Pumariega, & Seilheimer, 1991). It is hypothesized that younger patients may express psychological distress through less direct means than older patients, hence the lower prevalences in young patients (Pearson, Pumariega, & Seilheimer, 1991). Altogether, these findings emphasize the tendency for CF patients to develop emotional disturbances. Furthermore, awareness of the fact that anxiety and depression, and global emotional difficulties for that matter, are mental states that are strongly intercorrelated, is important (Pfeffer, Pfeffer, & Hodson, 2003). In the BCFR 2014 report, patient registry is based on patients who were treated by a specialist (psychiatrist or neurologist). Because the prevalence of psychiatric disorders (as one group), as reported by the BCFR, is relatively low (3.8%), and the patients are known to receive specialized treatment, it is concluded that it concerns severe forms of this respective complication. Thus, the weighted average of the disability weights for severe depression and severe anxiety is used. For the sake of simplicity, it is assumed that affected patients experience symptoms during the whole year. However, depressive and anxiety disorders tend to have complex, often episodic, disease courses (Angst, Gamma, Rössler, Ajdacic, & Klein, 2009). It is calculated that psychiatric and psychological issues account for 25.2 YLDs.

Osteoporosis and osteopenia

Osteoporosis and osteopenia, which is associated but less advanced, are systemic skeletal disorders characterized by low bone mass and alterations of bone quality, with a consequent increase in bone fragility and fractures (Raisz, 2005). They are frequent complications of CF due to various risk factors such as the malabsorption of vitamin D, the use of glucocorticoids and chronic inflammation. It is indeed found to be highly prevalent in CF patients: a meta-analysis calculated prevalences of 23.5% and 38%, for osteoporosis and osteopenia respectively (Paccou, Zeboulon, Combescure, Gossec, & Cortet, 2010). The BCFR found prevalences to be substantially lower, 1.9% and 10.5% respectively. Possibly, CF patients are only screened for these conditions if they show signs or symptoms. As such, asymptomatic patients are presumably excluded from the BCFR reports. The most important reasons for diagnosis are severe back pain, a stooped posture and bone fractures that result from minor injuries. Fractures are supposed to be the main symptom that leads to diagnosis (Kanis, 2002). The most common fractures are located in the hip, wrist and vertebra and all can lead to substantial short term and long term disability. The different types of fractures tend to show an equal distribution, at least in more advanced stages of osteoporosis (Center, 2017). Thus, CF patients are assumed to have similar rates of these three different types of fractures. Disability weights are available for those three types of fractures, for short term as well as long term. The duration of the fractures is, assuming a general course of a model fracture, arbitrarily set on 4 weeks for the acute phase. Hereafter, all patients are assumed to suffer from long term fracture-associated limitations. Patients with osteopenia are assumed not to have fractures but merely a limited skeletal problem, so that the disability weight for a mild low back pain can be used. Together, osteopenia and osteoporosis account for 3.9 YLDs.

Infertility

The majority of males with CF is characterized by a congenital bilateral absence of the ductus deferens leading to infertility (Jarzabek, Zbucka, Pepinski, Szamatowicz, & Domitrz, 2004) (99% as reported by the BCFR). This anatomic structure is normally responsible for the transport of spermatozoids. Thus, as the spermatozoids are preserved, techniques of assisted reproduction are possible (Hubert, et al., 2006). Females with CF are found to be less fertile than normal healthy women (Hodges, Palmert, & Drumm, 2008). This is because the thickened cervical mucus may act as a barrier to the penetration of spermatozoids. Nonetheless, it is possible for them to conceive and have successful pregnancies. However, pre-gestational diabetes, preterm delivery, caesarian deliveries and other complications occur more frequently in CF patients compared to healthy females (Jelin, Sharshiner, & Caughey, 2017). In addition, pulmonary function can worsen during pregnancy (Whitty, 2010). Consequently, patients with CF who wish to have children, need supplementary assistance and surveillance. The continuingly increasing life expectancy stresses the importance of attention for infertility. To calculate the YLDs associated with infertility, the desire for children is supposed to be similar to the one in the general population, in which parenthood is still the norm. Mostly, women get pregnant between the ages of 20 and 40 and in extension of this, only patients in these age categories are presumed to suffer from this complication. Furthermore, it is assumed that male and female patients all experience a similar effect of this complication. In other words, the need for reproductive techniques in the case of male patients is assumed to have a similar effect as the difficulties in pregnancy and delivery experienced by female patients. The disability weight for a generic disease with minimal interference in daily life that leads to anxiety and uncertainty about diagnosis (pregnancy), is used. As such, it is calculated that infertility leads to 6.1 YLDs. Note that (slightly higher) disability weights for primary and secondary infertility are also available. However, when reviewing the corresponding lay descriptions, these do not seem appropriate for use in CF patients. The reason for this is that they both imply an impossibility to conceive, whereas in CF patients assisted reproduction techniques are almost always a possibility.

Other complications and surgery/anesthesia

In addition to the complications already described, the BCFR reports 15.8% of the CF patients to suffer from other (non-specified) complications. Obviously, it is impossible to assess the causal relationship between CF and these complications, nor to assign accurate disability weights to these complications. Nonetheless, it is attempted to take them into account by assuming they are generic, uncomplicated diseases characterized by general distress, daily medication and anxiety. As such, they are estimated to cause 10.3 YLDs.

Furthermore, approximately 10% of CF patients are reported to undergo some sort of surgery and general anesthesia. Note that transplant surgery is not included in this prevalence, as complications are reported only for non-transplanted patients. Although the type of surgery is not elaborated, it is presumed to concern procedures to correct the eligible complications described above. These include sinus surgery (polypectomy), gastro-intestinal surgery and lung surgery (such as lobectomy) (Cuenca & Beierle, 2008). Nasal polyp-related procedures constitute by far the largest share of surgery. Unfortunately, no disability weights are available for general surgical procedures. Although, disability weights for diseases requiring hospitalization and often invasive procedures are available (such as acute myocardial infarction), in addition to disability weights for diseases which impair daily activities (such as fractures). By taking these into consideration, an arbitrary disability weight of 0.35 is applied. On average, recovery of sinus surgery takes approximately ten days (Kemppainen, Tuomilehto, Kokki, Seppä, & Nuutinen, 2007). Altogether, surgery and general anesthesia is estimated to cause 0.9 YLDs.

Table 12

Years lived with disability due to other complications, 2014									
Complication*	**N**	**%**	**Health state****	**Lay description****	**DW****	**Adjusted DW*****	**Duration (days)********	**YLDs *********	**Total YLDs**
CF-related arthritis	23	2.1%	Rheumatoid arthritis: mild	Some problems with walking, washing, dressing, performing usual activities. Some pain and discomfort	0.210		365	4.8	4.8
Cancer	4	0.4%	Cancer: diagnosis and primary therapy	Has pain, nausea, fatigue, weight loss and high anxiety.	0.288				1.5
						0.370	365	1.5	
			Cancer: metastatic	Has severe pain, extreme fatigue, weight loss and high anxiety.	0.451				
Psychiatric disease	41	3.8%	33%: anxiety disorders, severe	Constantly feels very anxious and worried, which makes it difficult to concentrate, remember things and sleep. The person has lost pleasure in life and thinks about suicide.	0.523				25.2
						0.613	365	25.2	
			67%: major depressive disorder, severe episode	Has overwhelming, constant sadness and cannot function in daily life. The person sometimes loses touch with reality and wants to harm or kill himself (or herself).	0.658				
Osteopenia	113	10.5%	Low back pain, mild	Has mild back pain, which causes some difficulty dressing, standing, and lifting things.	0.020		365	2.3	2.3
Osteoporosis	21 (7 for each type of fracture)	1.9%	Fracture of neck of femur: short term, with or without treatment	Has broken a hip and is in pain. The person cannot stand or walk, and needs help washing, dressing, and going to the toilet.	0.258		28	0.1	1.6
			Fracture of neck of femur: long term, with treatment	Had a broken hip in the past, which was fixed with treatment. The person can only walk short distances, has discomfort when moving around, and has some difficulty in daily activities.	0.058		337	0.4	

			Fracture of vertebral column: short or long term, with or without treatment	Has broken back bones and is in pain, but still has full use of arms and legs.	0.111	365	0.8	
			Fracture of radius or ulna: short term, with or without treatment	Has a broken forearm, which causes severe pain, swelling, and limited movement.	0.028	28	0.02	
			Fracture of radius or ulna: long term, without treatment	Had a broken forearm in the past that did not heal properly, causing some pain and limited movement in the elbow and wrist. The person has difficulty with daily activities such as dressing.	0.043	337	0.3	
Infertility	507	41.2%	Generic uncomplicated disease: anxiety about diagnosis	Has a disease diagnosis that causes some worry but minimal interference with daily activities.	0.012	365	6.1	6.1
Surgery (general anesthesia)	97 (109)	9% (10.1%)	Acute myocardial infarction: days 1-2	Has severe chest pain that becomes worse with any physical activity. The person feels nauseous, short of breath, and very anxious.	0.432			0.9
					0.356	10	0.9	
			Fracture of pelvis: short term	Has a broken pelvis bone, with swelling and bruising. The person has severe pain, and cannot walk or do daily activities.	0.279			
Others	170	15.8%	Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049			10.3
					0.060	365	10.3	
			Generic uncomplicated disease: anxiety about diagnosis	Has a disease diagnosis that causes some worry but minimal interference with daily activities.	0.012			
Total	976						52.6	52.6

*Other complications as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Health states, disability weights and lay descriptions are extracted from the most recent GBD study (World Health Organization, WHO methods and data sources for global burden of disease estimates 2000-2015, 2017)

***If appropriate, an adjusted disability weight is calculated according to methods described in the text

****Durations as estimated in the literature (see text for references); chronic complications have a duration of 365 days

*****$YLDs = N\ x\ (adjusted)DW\ x\ \frac{duration}{365}$

Transplantation-related complications

Progressive respiratory insufficiency remains the major cause of mortality in CF patients (Appendix 6: primary causes of death for reported cases). When a patient with CF develops severe and progressive lung disease, lung transplantation is eventually required. However, like other major surgeries, lung transplantation involves significant risks. In 2014, of the ten reported deaths, four concerned transplantation patients. Six patients benefitted from a lung transplant in 2014 (Table 1).

Some patients with CF will need other types of transplantations, such as liver transplantation for end-stage CF-related liver cirrhosis (Lamireau, Martin, Lallier, Marcotte, & Alvarez, 2006), or renal transplantation (Schindler, Radke, Paul, & Frei, 2001) for end-stage renal disease due to diabetes or pharmacological toxicity. Sometimes, the lung transplantation is combined with a heart transplantation (Thomas, 2005). Some patients have received a transplant on more than one occasion. As such, the BCFR reports 236 transplants on 208 patients during its history of data collection.

Of all the patients living with CF in Belgium, 151 (12.3%) is known to have at least one transplant organ (Table 13). Female patients have received slightly more transplantations than males (80 females versus 71 males). The mean and median age of the transplant patients in the year of the first transplant was 29.2 and 28.3 years respectively. In 2014, only one transplantation patient with CF under the age of 18 is alive.

Table 13

Type of transplant by year*									
	Lung	Lung-heart	Lung-liver	Liver	Kidney	Liver-kidney	Heart	Transplants performed	Transplants alive
1991	.	2	.	.	.	.	.	2	1
1992	.	.	.	.	.	.	.	-	-
1993	.	2	.	.	.	.	.	2	1
1994	.	3	.	.	.	.	.	3	1
1995	2	3	.	1	.	.	.	6	1
1996	.	1	.	.	.	.	.	1	-
1997	1	3	.	.	.	.	.	4	4
1998	9	1	.	.	.	.	.	10	3
1999	5	.	.	.	.	.	.	5	2
2000	10	.	.	.	.	.	.	10	5
2001	13	.	1	4	.	.	.	18	13
2002	10	.	.	2	.	.	.	12	8
2003	9	.	.	1	.	.	.	10	8
2004	12	.	.	.	.	.	.	12	9
2005	10	.	1	3	.	.	.	14	8
2006	14	.	.	1	1	.	1	17	10
2007	14	.	.	1	1	.	.	16	9
2008	15	.	.	.	3	.	.	18	12
2009	10	.	.	1	.	1	.	12	9
2010	12	.	2	1	.	.	.	15	12
2011	15	.	.	.	2	.	.	17	12
2012	12	.	.	.	.	.	.	12	11
2013	11	.	.	.	3	.	.	14	8
2014	5	.	.	.	1	.	.	6	4
Total	**189**	**15**	**4**	**15**	**11**	**1**	**1**	**236**	**-**
Alive	132	6	4	8	1	-	-	-	151

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

A transplantation-related disability weight and methodological considerations

The general disability weights calculated for children, adolescents and adults (Table 7) did not take transplantation patients into account. Nonetheless, when considering CF as a primary disease entity, transplantation patients were divided into the different age categories and as such, have already one of those disability weights assigned. In addition, transplantation patients are not included in the prevalences of the earlier reported complication categories (this might explain some of the differences in the prevalences reported by the BCFR compared to prevalences reported by other scientific publications). Nonetheless, according to the literature, transplantation patients experience specific complications, in addition to a higher prevalence of the complications already described (Lynch, Sayah, Belperio, & Weigt, 2015). In this section, transplantation is regarded to be a complication of CF, from which other complications arise.

The lung function of CF patients improves significantly (Algar, et al., 2008) after transplantation so that they end up in one of the other FEV_1 categories. This is the reason why the primary disease component has already accounted for transplantation patients. Indeed, as previously mentioned, no patients with a FEV_1 % predicted less than 30% are supposed to be alive in the disease model.

However, including transplantation patients in the primary disease component does not cover the overall burden these patients experience. Considering the general nature of the post-transplantation health state, combined with the high frequency of complications, it is reasonable to use the disability weight for a terminal disease (0.540). However, as already mentioned, calculations concerning the primary disease component already contain a part of transplantation-related YLDs. Because all transplant patients are adults (except for one), the general disability weight for adults was thus implicitly used in the previous calculations. As such, a correction of the disability weight for terminal diseases is made, so that it only corresponds with the complications that occur in the CF patients after transplantation. So again, a multiplicative model is applied, which delivers the disability weight for transplantation-related complications in an average transplanted patient.

$$DW_{terminal\ disease} = 1 - \left(1 - DW_{complications\ post-transplant}\right) * \left(1 - DW_{primary\ disease\ in\ adults}\right)$$

Rewriting this formula gives:

$$DW_{complications\ post-transplant} = 1 - \frac{1 - DW_{terminal\ disease}}{1 - DW_{primary\ disease\ in\ adults}}$$

Multiplying the adjusted disability weight with the number of transplantation patients leads to 51.6 YLDs due to transplantation-related complications (Table 14).

Table 14

Years lived with disability due to transplantation-related complications, 2014						
Complication*	**N**	**%**	**Health state**	**Lay description**	**DW****	**YLDs**
						total per patient
Transplantation	151	12.3%	Post-transplant CF	This state attempts to capture all complications in CF patients that have received transplantation	0.342	51.6 0.042

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**An adjusted disability weight is calculated according to methods described in the text

Table 15

Total years lived with disability due to complications, 2014				
Complication category	**N***	**YLDs**		
	patients with complication	**total**	**per CF patient****	**per complication**
Respiratory complications				
Nasal polyps	205	10.0	0.00817	0.0490
Massive hemoptysis	20	1.4	0.00116	0.0716
Allergic bronchopulmonary aspergillosis (ABPA)	72	0.4	0.00030	0.0051
Pneumothorax	3	0.2	0.00013	0.0522
Subtotal***	300	11.1	0.00899	0.0368
Digestive & endocrine complications				
Exocrine pancreatic insufficiency	867	44.2	0.03595	0.0510
CF-related diabetes (CFRD)	176	16.0	0.01299	0.0908
Cirrhosis with portal hypertension	43	7.7	0.00622	0.0178
Impaired glucose tolerance (IGT)	77	5.4	0.00438	0.0700
Gastro-esophageal reflux	265	2.9	0.00237	0.0110
Intestinal obstruction	39	2.0	0.00163	0.0513
Acute pancreatitis	14	0.8	0.00068	0.0595
Clostridium infection (treatment needed)	15	0.2	0.00019	0.0158
Gastroparesis	2	0.2	0.00019	0.1140
Gallstones	36	0.1	0.00008	0.0027
Subtotal***	1534	79.5	0.06467	0.0519
Other complications				
Psychiatric disease	41	25.2	0.02045	0.6135
Infertility	507	6.1	0.00495	0.0120
CF-related arthritis	23	4.8	0.00393	0.2100
Osteopenia	113	2.3	0.00184	0.0200
Osteoporosis	21	1.6	0.00129	0.0754
Cancer	4	1.5	0.00120	0.3695
Surgery (general anesthesia)	97	0.9	0.00077	0.0097
Others	170	10.3	0.00835	0.0604
Subtotal***	879	52.6	0.04277	0.0598
Transplantation-related complications	151	51.6	0.04179	0.3404
All complications**(incl transplantation)**	2713 (2864)	143 (194.6)	0.13276	0.0528

*Prevalence as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Based on 1,230 CF patients as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

***Subtotal: the column "YLDs per complication" represents the number of YLDs per general categorical complication (no information on multimorbidity available)

****All complications: the column "YLDs per complication represents" the number of YLDs due to a general complication (includes all non-transplanted patients who suffer from one or more than one complication). Dividing 2713 complications by 1079 multiplied by the disease weight of a general complication (0.0528) leads to the number of YLDs due to complications for an average CF patient: 0.133 YLDs.

The total burden of cystic fibrosis in Belgium

By combining the YLLs, the YLDs due to the primary disease component and the YLDs due to the different categories of complications including transplantation, the total burden of CF in Belgium can be calculated (Table 15). In order to continue the stratification by age, it is assumed that the occurrence of all non-transplant-related complications correlate with the prevalence of CF in each age category. Transplant-related complications are divided between adult patients (older than 20), while also taking the relative number of transplants in males and females into consideration. This results in a disease burden of 922.4 DALYs for all age categories and both genders. This corresponds with 8.3 DALYs per 100,000 Belgians in the general population. Approximately half of this burden is caused by YLLs (484.8 DALYs), the other half by YLDs (437.6 DALYs). The YLD component is divided into YLDs due to the primary disease (242.7 DALYs), YLDs due to complications (143.2 DALYs) and YLDs due to transplantation (51.6 DALYs). The number of DALYs per CF patient (both males and females) is found to be 0.75 for the year 2014.

Table 16

Total burden of cystic fibrosis in Belgium, 2014*									
	N	**YLLs**	**YLDs**			**DALYs**		**Population**	**DALYs per 100,000**
			primary disease	complications	post-transplant	total	per CF patient		
Males									
0-4	56	9.9	5.7	6.8	0	22.4	0.40	330,251	6.8
5-9	56	13.7	5.7	6.8	0	26.2	0.47	327,067	8.0
10-14	82	17.2	8.4	9.9	0	35.5	0.43	311,286	11.4
15-19	104	32.2	18.7	12.6	0	63.5	0.61	320,418	19.8
20-24	81	41.3	20.9	9.8	5.8	77.7	0.96	351,002	22.1
25-29	58	66.3	15.0	7.0	4.1	92.4	1.59	350,576	26.4
30-34	65	25.8	16.8	7.9	4.6	55.0	0.85	366,824	15.0
35-39	56	26.6	14.4	6.8	4.0	51.8	0.92	362,120	14.3
40-44	39	10.7	10.1	4.7	2.8	28.2	0.72	391,762	7.2
45-49	17	9.7	4.4	2.1	1.2	17.3	1.02	409,720	4.2
≥ 50	26	8.5	6.7	3.1	1.8	20.2	0.78	1,953,283	1.0
Total	640	261.8	126.8	77.3	24.3	490.2	0.77	5,474,309	9.0
Females									
0-4	54	8.4	5.5	6.0	0	20.0	0.37	315,598	6.3
5-9	74	11.7	7.6	8.3	0	27.5	0.37	311,987	8.8
10-14	72	14.6	7.4	8.0	0	30.0	0.42	298,247	10.1
15-19	65	27.4	11.7	7.3	0	46.4	0.71	306,896	15.1
20-24	72	35.2	18.6	8.0	6.1	67.9	0.94	346,735	19.6
25-29	70	56.5	18.0	7.8	5.9	88.3	1.26	353,408	25.0
30-34	66	21.9	17.0	7.4	5.6	51.8	0.79	364,854	14.2
35-39	39	22.6	10.1	4.4	3.3	40.3	1.03	356,443	11.3
40-44	26	9.2	6.7	2.9	2.2	21.0	0.81	382,080	5.5
45-49	21	8.2	5.4	2.3	1.8	17.7	0.84	398,562	4.4
≥ 50	31	7.3	8.0	3.5	2.6	21.4	0.69	2,241,397	1.0
Total	590	223	116.0	65.9	27.4	432.2	0.73	5,676,207	7.6
Males + females	*1230*	484.8	242.7	143.2	51.6	922.4	0.75	11,150,516	8.3

*Based on tables in the sections above

Composite disability weights for cystic fibrosis in Belgium

As the number of CF patients in Belgium is known, and the number of YLDs is calculated, it is possible to infer a composite disability weight for a model CF patient (Table 17). By doing so, a composite disability weight of 0.356 is established. Furthermore, composite disability weights for all each categories and both genders are calculated.

Table 17

Calculation of composite disability weights for cystic fibrosis						
	N*	YLDs				DW**
		primary disease	complications	post-transplant	total	
Males						
0-4	56	5.7	6.8	0.0	12.5	0.223
5-9	56	5.7	6.8	0.0	12.5	0.223
10-14	82	8.4	9.9	0.0	18.3	0.223
15-19	104	18.7	12.6	0.0	31.3	0.301
20-24	81	20.9	9.8	5.8	36.4	0.450
25-29	58	15.0	7.0	4.1	26.1	0.450
30-34	65	16.8	7.9	4.6	29.2	0.450
35-39	56	14.4	6.8	4.0	25.2	0.450
40-44	39	10.1	4.7	2.8	17.5	0.450
45-49	17	4.4	2.1	1.2	7.6	0.450
≥ 50	26	6.7	3.1	1.8	11.7	0.450
Total	640	126.8	77.3	24.3	228.4	0.357
Females						
0-4	54	5.5	6.0	0.0	11.6	0.214
5-9	74	7.6	8.3	0.0	15.8	0.214
10-14	72	7.4	8.0	0.0	15.4	0.214
15-19	65	11.7	7.3	0.0	19.0	0.292
20-24	72	18.6	8.0	6.1	32.7	0.454
25-29	70	18.0	7.8	5.9	31.8	0.454
30-34	66	17.0	7.4	5.6	29.9	0.454
35-39	39	10.1	4.4	3.3	17.7	0.454
40-44	26	6.7	2.9	2.2	11.8	0.454
45-49	21	5.4	2.3	1.8	9.5	0.454
≥ 50	31	8.0	3.5	2.6	14.1	0.454
Total	590	116.0	65.9	27.4	209.2	0.355
Males + females	1230	242.7	143.2	51.6	437.6	0.356

*Prevalences as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Composite disability weights are calculated as described in the text

Discussion

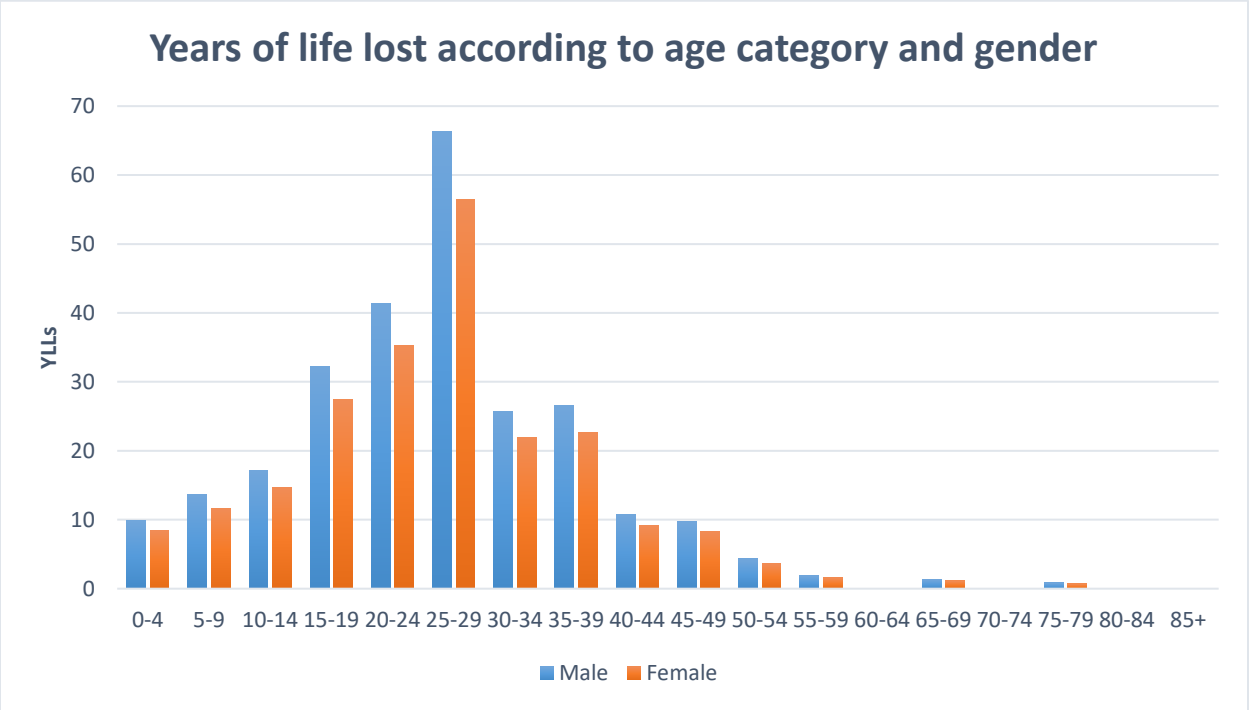
The burden of cystic fibrosis

Impact of demographic factors on the burden of cystic fibrosis

The role of age in years of life lost

The category 25-29 years of age is responsible for the highest YLLs (Figure 5). The reason is that most deaths occur in this age category. Note that this is based on the death reports from the last ten years, which means that the patients taken into consideration were born more than two or three decades ago. As previously mentioned, scientific research and commercial development of new therapies has provided substantial improvements in CF patient care and will continue to do so. As a result, the age category in which most deaths occur will probably further undergo a shift towards older age categories. This will also lead to an overall decline in YLLs due to premature mortality, because the standard life expectancy is lower at higher ages. However, this will probably result in more YLDs as CF patients will live longer with CF and its associated complications (see also section: Incidence perspective). Note that today, already half of the burden of CF is related to morbidity.

Figure 5

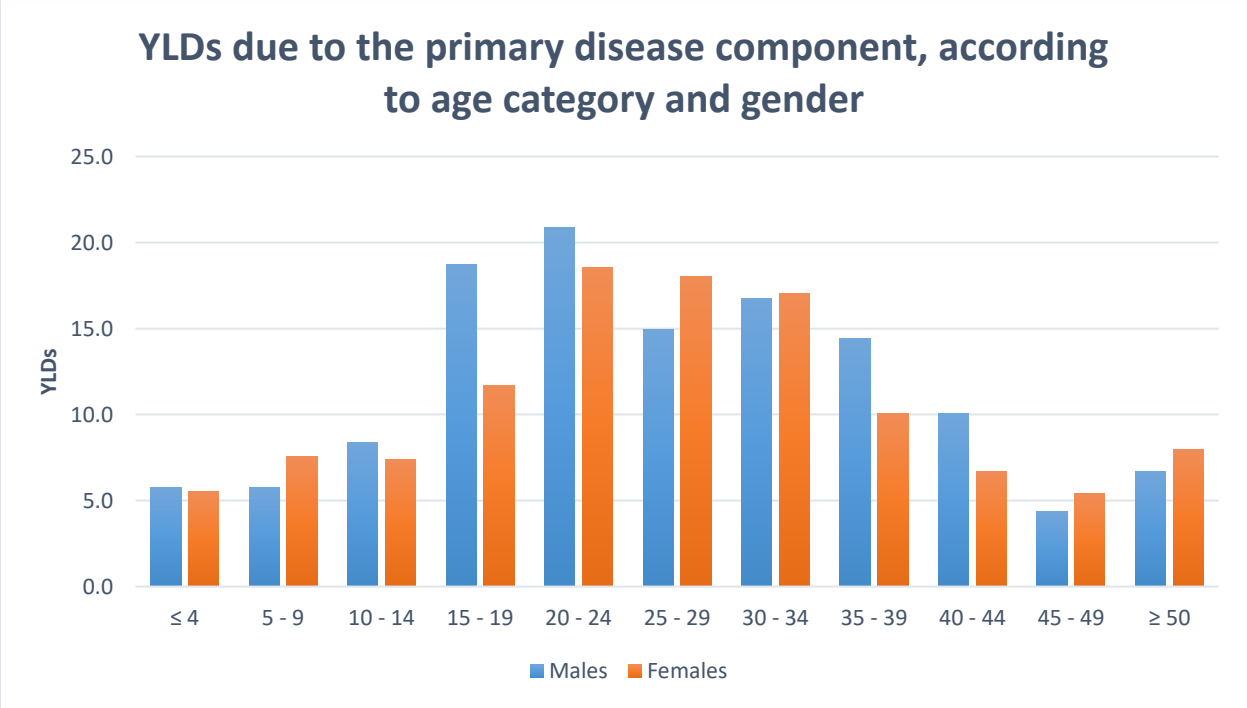

Years of life lost according to age category and gender
YLLs
70
60
50
40
30
20
10
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Male
Female

The role of age in years lived with disability due to the primary disease component

Years lived with disability due to the primary disease component are most prominently present between the ages of 15 and 40 (Figure 6). Although disease prevalence again plays an important role, the used disability weights and hence estimated severity of the primary disease contributes to a large extent to this finding. Indeed, disability weights are higher for adults and adolescents compared to children, hence reflecting the natural course of the disease.

In some cases, dysfunction of individual organs due to the dysfunction of the CFTR protein, is compounded by the effects of systemic inflammation (Elborn, 2007). This systemic inflammation is a reaction to the chronic respiratory infections and particularly contributes to CF-related bone disease, CF-related diabetes and CF-related arthritis. Consequently, aggressive treatment of the pulmonary disease in conjunction with holistic management plans to treat specific organ diseases is an important strategy in improving morbidity and reducing mortality of CF patients. As such, this finding emphasizes the importance of the burden of CF due to the primary disease component.

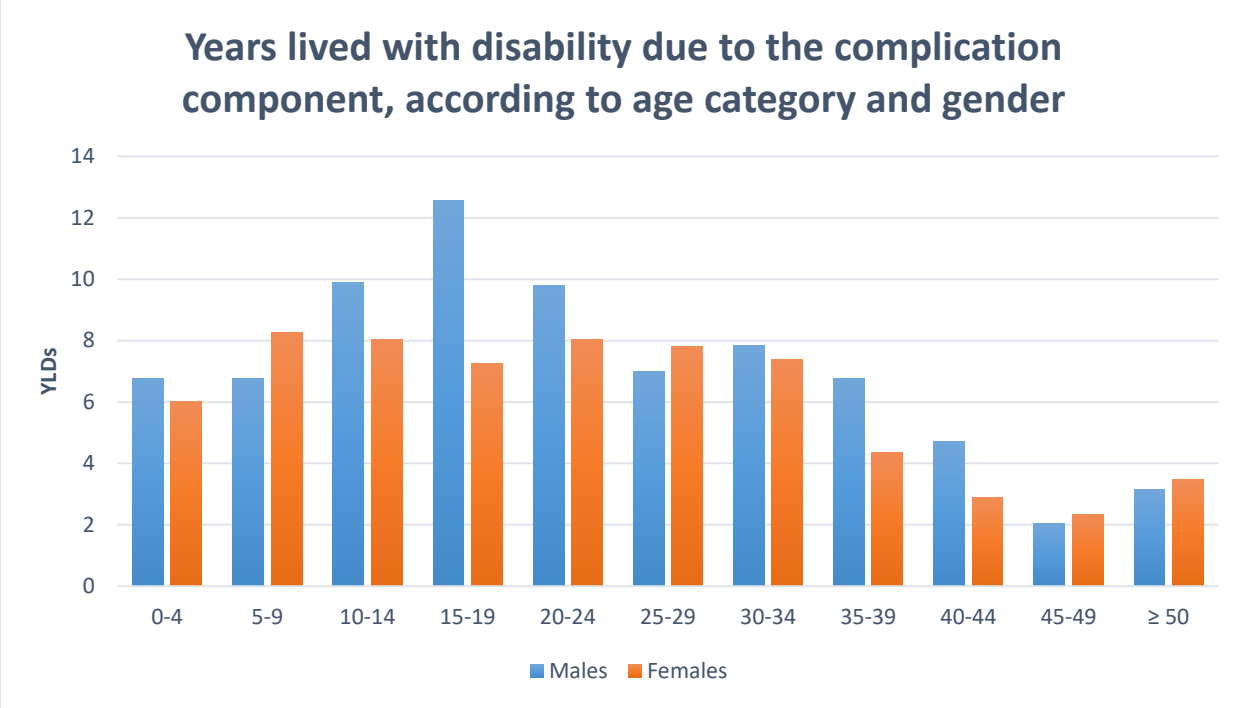
Figure 6



The role of age in years lived with disability due complications

In order to continue the stratification by age, it is assumed that the occurrence of all complications correlate with the prevalence of CF in each age category. Thus, the probability of each complication is regarded similar at all ages. While this is more or less correct in some cases, other complications predominantly occur in specific age ranges (Cystic Fibrosis Foundation Patient Registry, 2015). In extension, it should be emphasized that most complications are related to disease progression and general deterioration of the patient. Consequently, YLDs that arise from complications are in reality characterized by a skewed distribution, and older patients experience a disproportionate share of them. Although this skewness is not shown in the figure below (Figure 7), it is important to be aware of this. To stratify according to gender, the same male/female ratio as previously calculated is used. In this model, YLDs due to complications peak at the age category between 15 and 19 years of age.

Figure 7

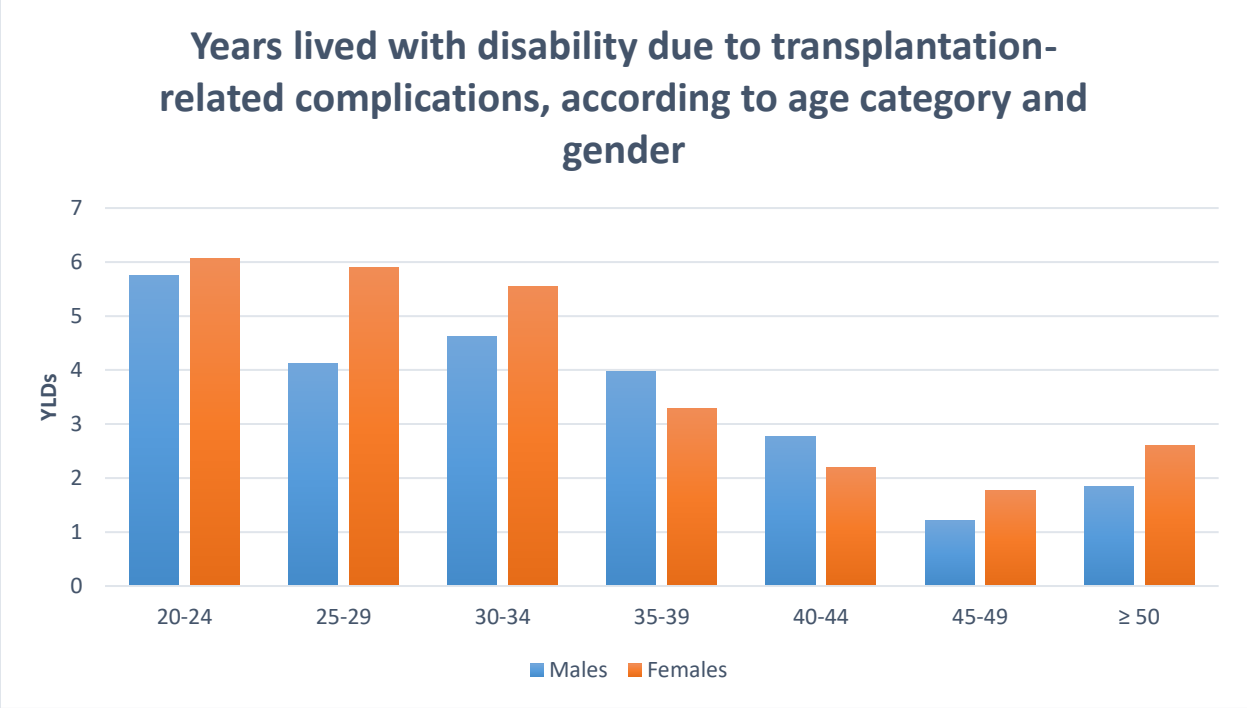


It is important to understand that not all complications caused by CF are included in the calculations. Firstly, the complications included are the only complications on which data is collected by the BCFR. Secondly, although these respiratory (Ng, Flight, & Smith, 2014), digestive/endocrine (Borowitz & Gelfond, 2013) and other (Cystic Fibrosis Trust, 2018) complication categories include the most prevalent and impactful (Cystic Fibrosis Canada, 2018) (MayoClinic, 2018), others may occur in the context of CF. Furthermore, the degree of causality between CF and these omitted complications remains irresolute. Fortunately, most of these complications are so rare and only reported in disparate case studies (Pekcan, et al., 2009) (Wiebicke, Artlich, & Gerling, 1993) that it would be superfluous to include them in the calculations. In addition, some complications may result in new (un)related complications and these sequela are also not accounted for in the DALY calculation.

The role of age in years lived with disability due to transplantation-related complications

In order to stratify YLDs due to transplantation-related complications according to age and gender, the transplantation distribution by gender and the CF prevalence by age category and gender is combined. Due to the slightly higher prevalence of transplantations in females, and hence the associated complications, the total YLDs of this component is higher in female patients. However, the age distribution (Figure 8), is exclusively determined by the prevalence of CF in the age categories (older than 20). Altogether, most YLDs due to transplantation-related complications occur in young adults.

Figure 8



The general role of gender

As already explained, the proportion of deaths in male and female CF patients is estimated using mortality data from the last ten years, and this is applied to an average age and sex distribution of mortality. Due to reasons described above, this is an accurate estimate, which leads to a similar burden in male patients compared to female patients (Figure 5). However, it is clear that male patients lead to a few more YLLs in each age category, and this can be explained by the use of the gender ratio. Note that this gender ratio (54% males) is not only applicable in Belgium, as trans-national registers find similar percentages (approximately 52% males) (Cystic Fibrosis Foundation Patient Registry, 2015) (European Cystic Fibrosis Society Patient Registry, 2017).

The effect of gender in YLDs is somewhat less proportionally divided (Figure 6 and Figure 7). This is clear especially in the age between 15 and 19, where male patients almost account for twice as much YLDs. The only reason for this is that prevalence in this age category is also almost double for males compared to females. Indeed, the used disability weights are the same in both sexes, so this has no effect on the YLD distribution according to gender. Note that this may be a proxy approach, as female patients are reported to have somewhat lower FEV1 % predicted values (Table 1). Similarly, YLDs in the other age categories reflect the prevalence of CF in those age categories, as stratified by gender. Analogous reflections can be made for YLDs due to transplantation-related complications (Figure 8).

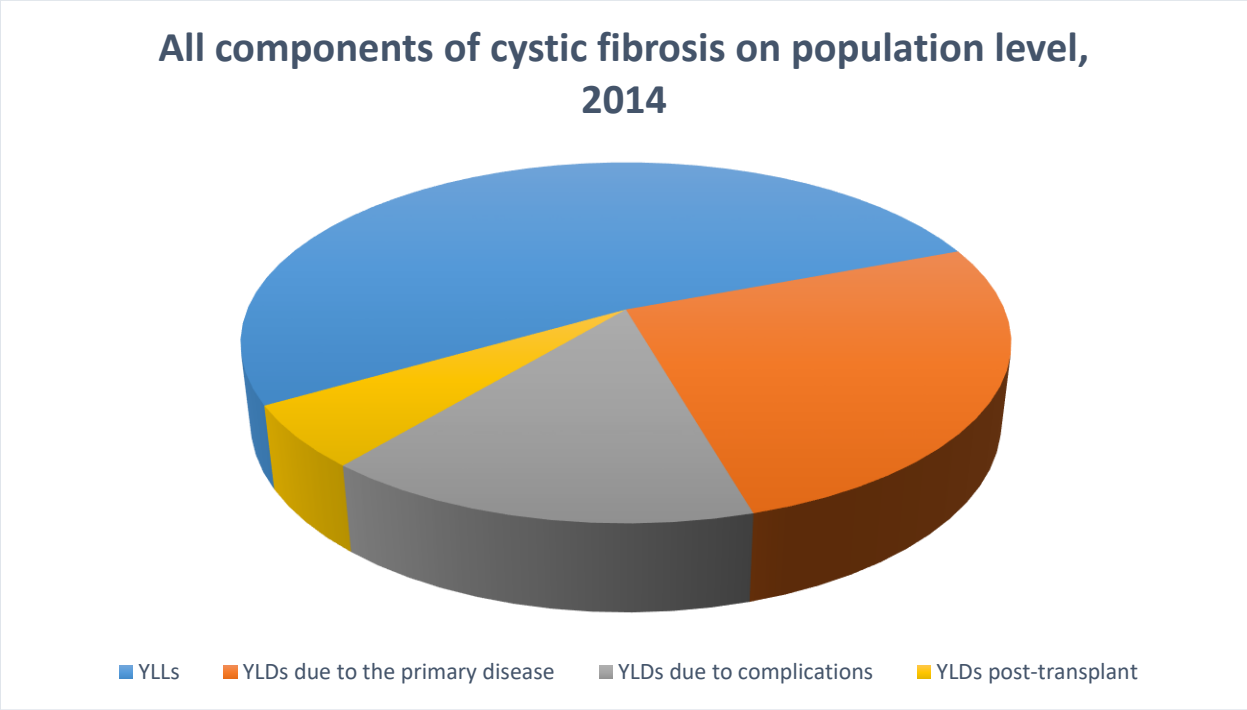
In summary, male and female CF patients account for similar amounts of YLLs as well as YLDs. This is because the occurrence of mortality is almost the same (41 male deaths versus 35 female deaths) and the number of male CF patients is not so different from the number of female CF patients (640 males versus 590 females).

Impact of the different components on the burden of cystic fibrosis

Impact of all components

On population level, mortality causes as much DALYs as all other components combined (Figure 9). The primary disease on its turn, causes more YLDs than all complications combined (including transplantation-related complications).

Figure 9

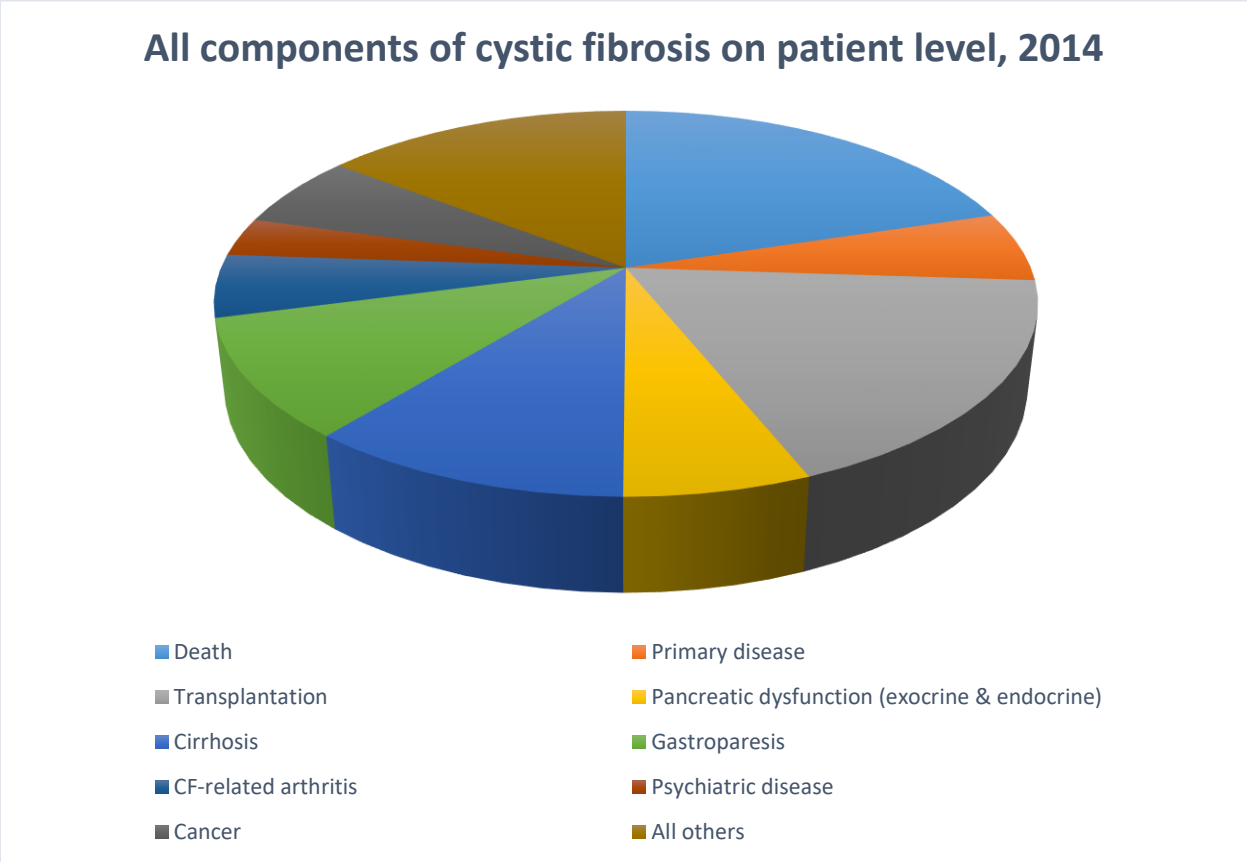


It can be misguiding to compare all life years lost in the present ánd the future due to premature mortality, with all years lived with disability in the present. Indeed, premature mortality causes an average of 63.0 YLLs per death (note that when considering a normal life expectancy of 91.6 years, this corresponds with a mean life duration of 28.6 years, which is indeed the mean age at death as reported by the BCFR report in 2014 (Wanyama, Thomas, & Malfroot, 2014)), whereas the other components are responsible for much less DALYs. As such, comparison of the numbers should be interpreted in relation to the specific definitions of YLLs and YLDs in this DALY model. Furthermore, it would be superfluous to compare the number of YLLs with the number of YLDs

caused by a “general” complication, as different complications have a highly variably impact on individual health.

Nonetheless, some measure can be compiled to compare the impact of death with the impact of certain other CF-related problems (more specifically the primary disease component, highly impactful complications and transplantation status) while using this hybrid approach (Figure 10). To this end, it is possible to proportionally assign a part of the YLLs to the year 2014, taking the normal life expectancy into account. As such, something like a disability weight for future death is assumed. By dividing the number of YLLs per death by the standard life expectancy, 0.69 YLLs could be assigned to the year 2014 (note that all patients are affected by this). Although this is an arbitrary way of comparison, no other meaningful way is possible to relate these different overarching components to each other on a patient level. More meaningful comparisons of individual health disturbances may be better assessed by comparing all the elements which constitute each component (see section: Impact of complications).

Figure 10

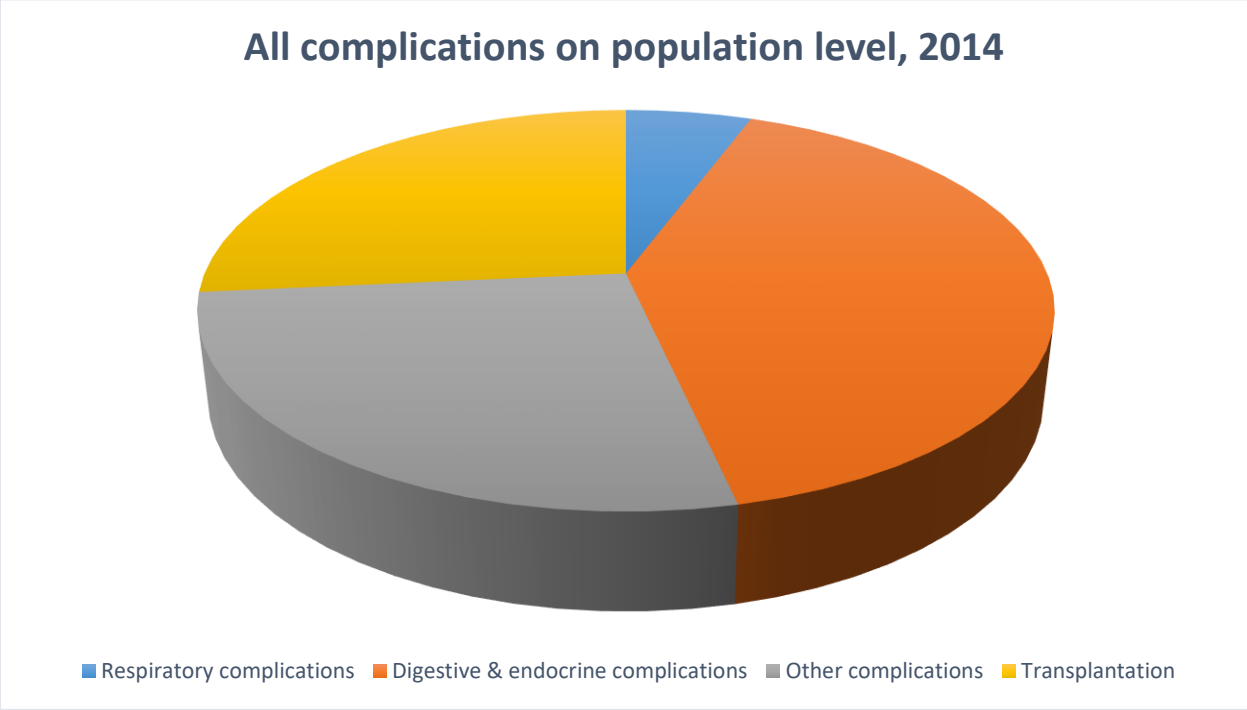


Impact of complications

Years lived with disability due to all complications

A pie chart visualizes the proportion of DALYs that each complication category causes on the level of the population (Figure 11). Digestive and endocrine complications have the biggest impact on public health (79.5 YLDs). Transplantation-related complications and other complications lead to a similar amount of YLDs (51.6 and 52.6 respectively). Respiratory complications are a significantly less important cause of YLDs (11.1 YLDs). This is because a large part of the respiratory component of the disease is included in the primary disease component.

Figure 11



Years lived with disability due to respiratory complications

In total, respiratory complications compose 11.05 DALYs, of which the vast majority is caused by nasal polyps (Figure 12) (Table 10). The high prevalence of this complication, in addition to its chronic nature, explains this finding. It seems that optimal management for nasal polyps can have substantial influence on the burden of CF. However, other respiratory complications such as hemoptysis and pneumothorax are much more devastating and impactful on patient level (Figure 13). Because of their relatively low prevalence and temporary character this is not obvious at the level of public health.

Figure 12

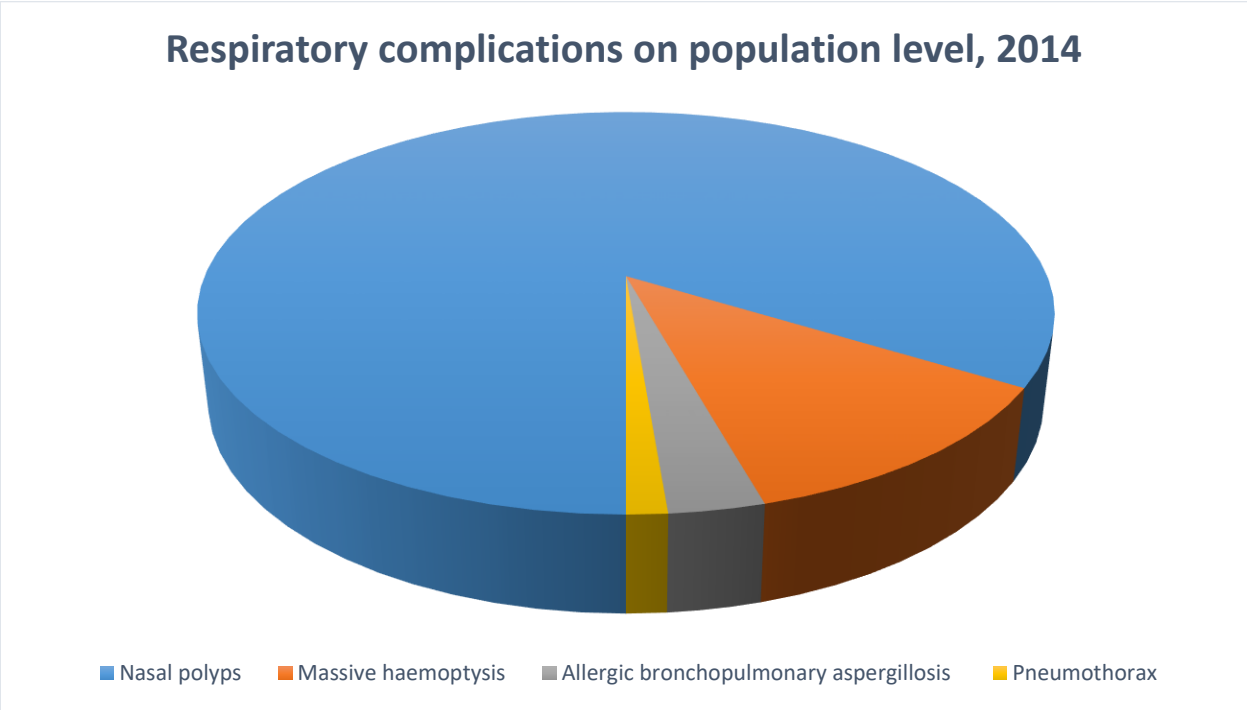
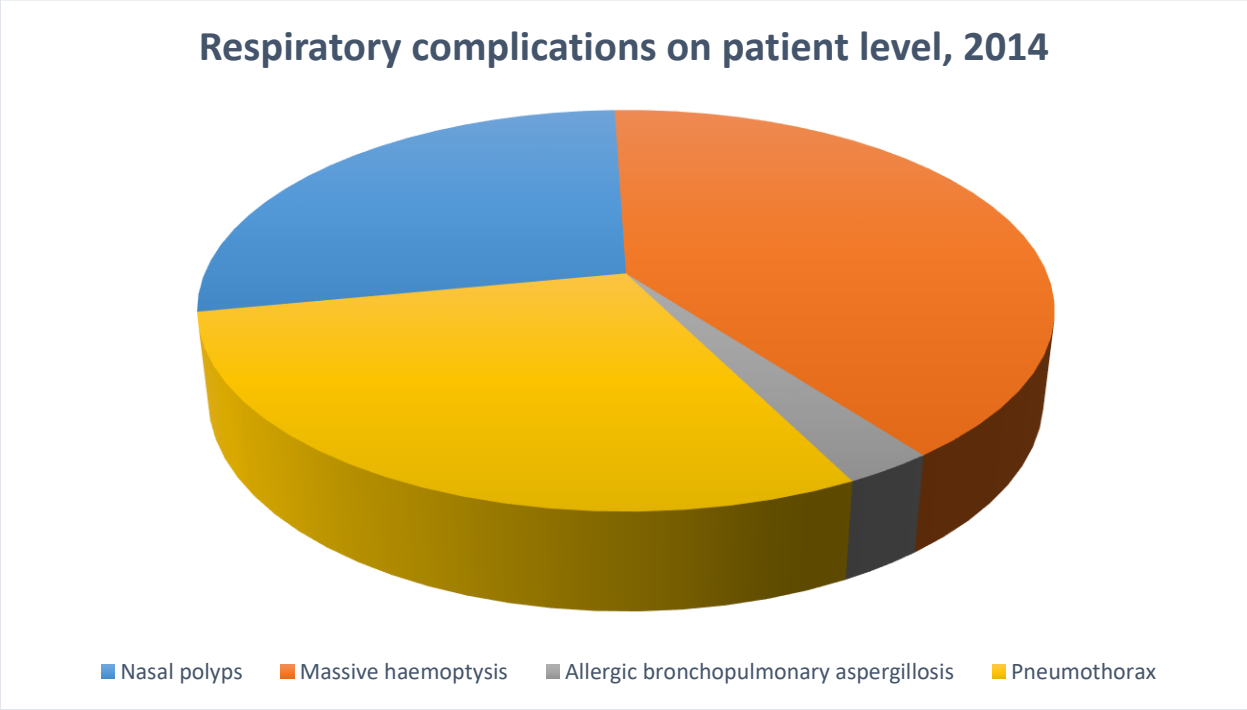


Figure 13



Years lived with disability due to digestive/endocrine complications

In total, digestive/endocrine complications compose 79.5 DALYs, of which the majority is caused by exocrine pancreatic insufficiency (Figure 14) (Table 11). When also taking the endocrine pancreatic dysfunction into consideration, it is obvious that overall, pancreatic functioning is the main cause of YLDs in this complication category. Again, the high prevalence of these complications, in addition to their chronic nature, explain this finding. However, the other digestive/endocrine complications such as cirrhosis of the liver with portal hypertension and gastroparesis have more impact on patient level (Figure 15). Because of their relatively low prevalence and temporary character however, this is only clear on patient level. The impact of pancreatic dysfunction on individual health is still noteworthy (especially when considering the exocrine and endocrine function combined). Consequently, it seems that optimal management for exocrine and endocrine pancreatic functioning can have substantial influence on CF patient care, as well as public health.

Figure 14

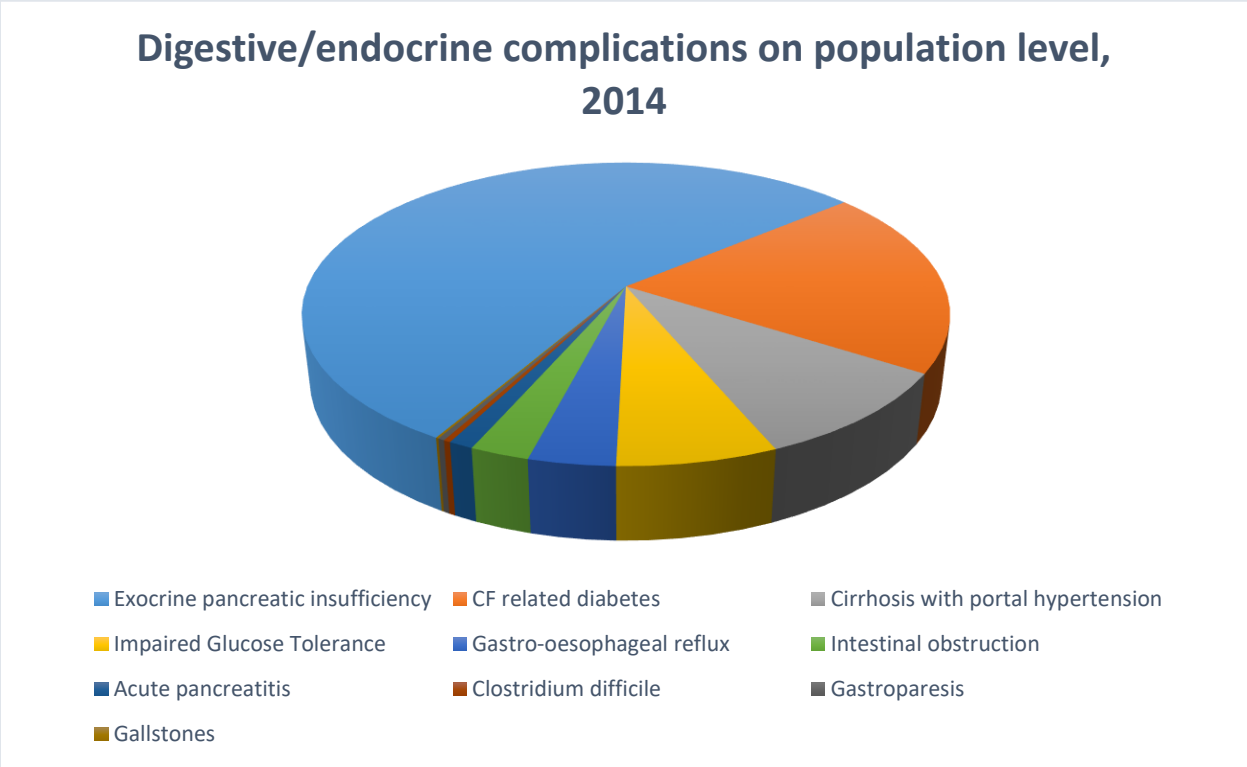
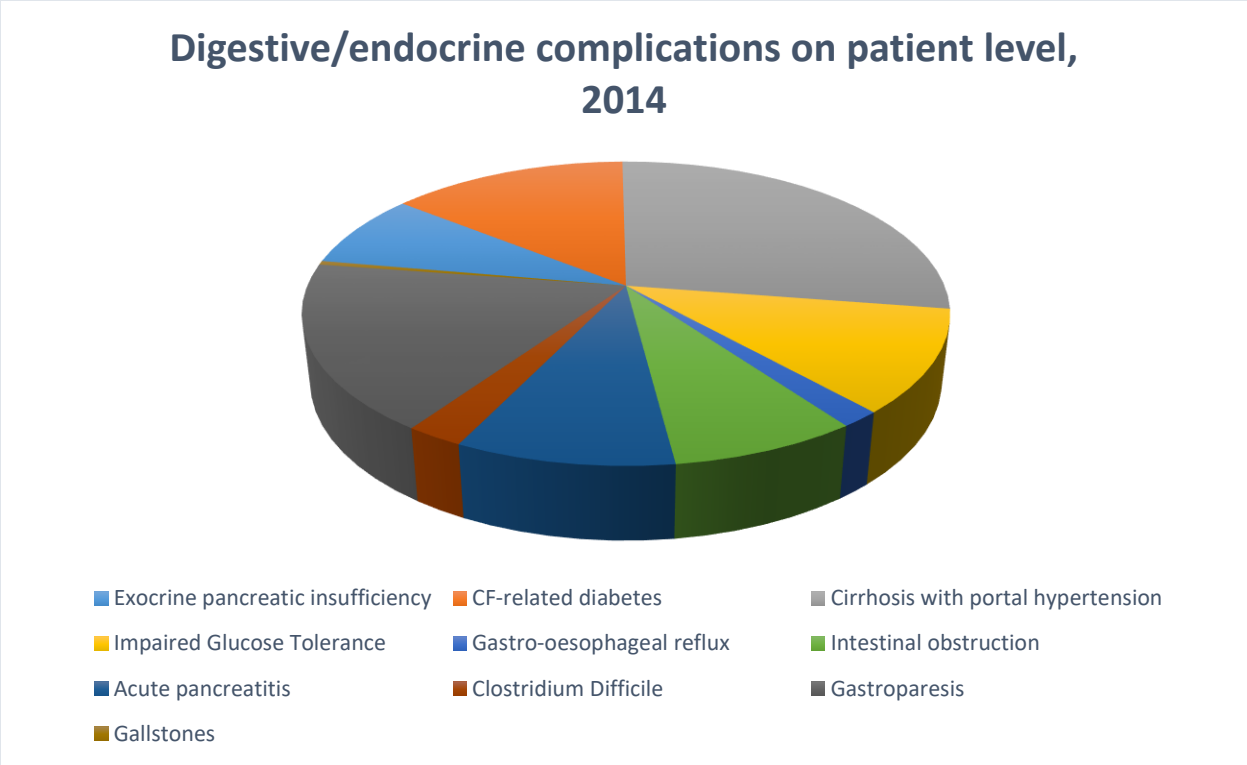


Figure 15



Years lived with disability due to other complications

On population level, other complications cause 52.6 YLDs. Similar to the other complication categories, this category is on population level largely defined by one type of complication (Figure 16) (Table 12). The high prevalence and chronicity of psychiatric diseases and psychological symptoms explain why they account for the biggest proportion of YLDs. In addition, these conditions appear to have significant impact on the level of the patient (Figure 18). They even appear to have a bigger impact on individual health than cancer and transplantation status. Consequently, psychological assessment and follow-up of CF patients are crucial, as well for the individual patients, as for the public health. In addition, post-transplantation complications cause a significant burden on public health, as it causes as many YLDs as the group of other complications combined (Figure 17). Not surprisingly, transplantation status has also a significant effect on individual health.

Figure 16

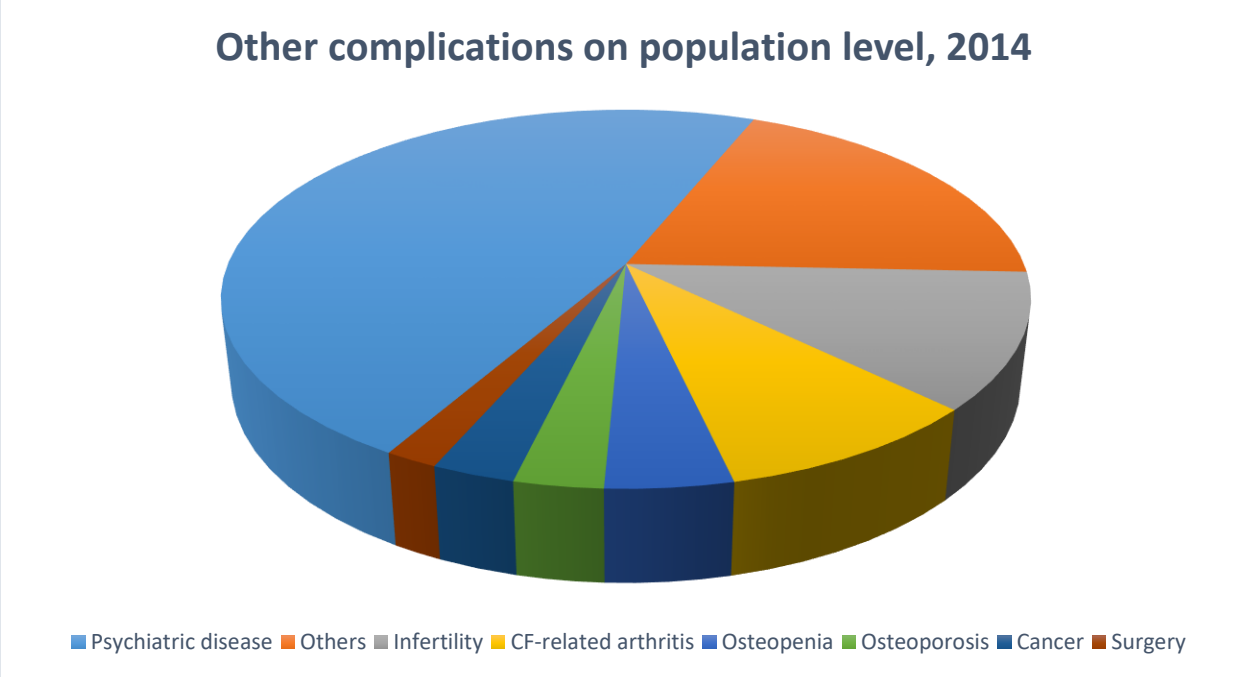


Figure 17

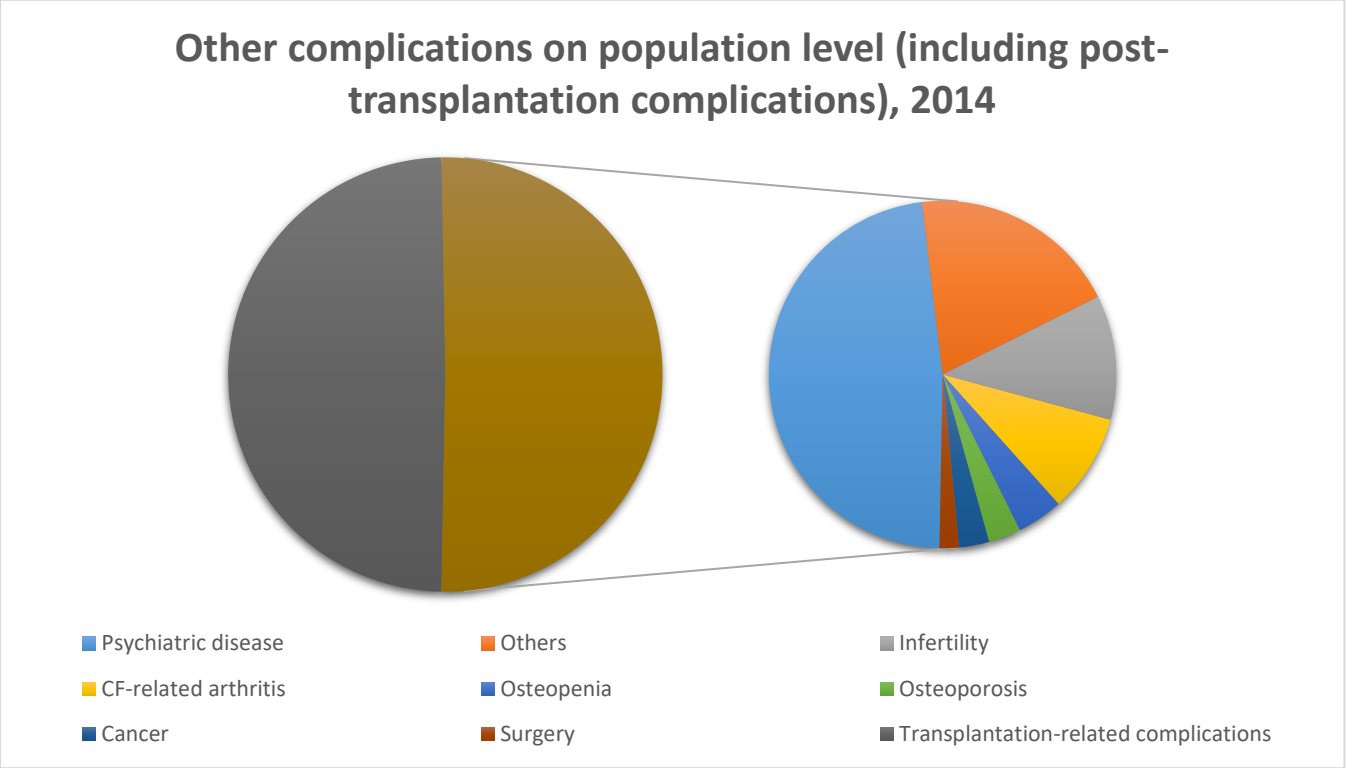
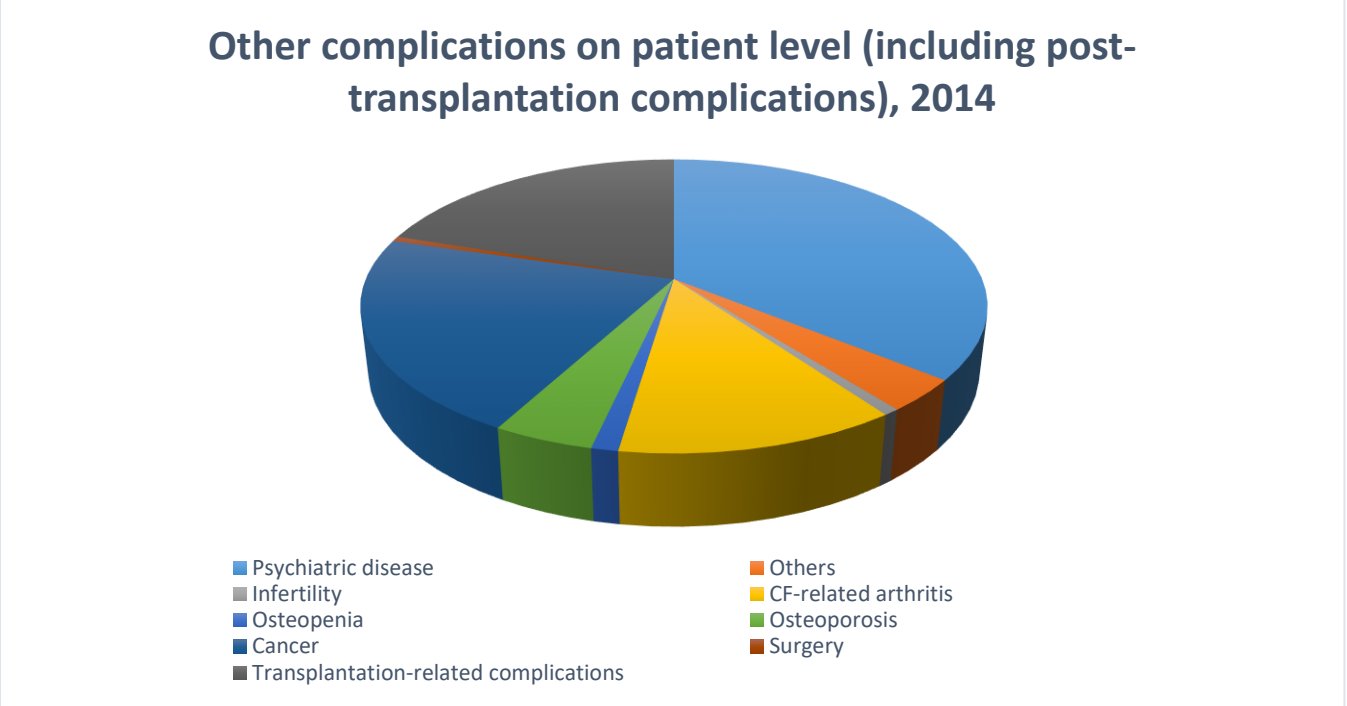


Figure 18



Summary of the effects of complications on the burden of cystic fibrosis

It is clear that on the level of the population, each complication category is largely defined by one or two complications. In the group of respiratory complications, nasal polyps account for 90% of the YLDs. Exocrine pancreatic insufficiency accounts for 55% of the digestive/endocrine complications, while CF-related diabetes and impaired glucose tolerance together adds another 27% of the YLDs. The residual category is characterized by a high burden of psychiatric disease, which constitutes 48% of the DALYs. On the level of the patient, nasal polyps have little influence on health, pancreatic dysfunction has moderate effects on it, and psychiatric diseases appear to have the biggest impact on individual health. Other diseases that leave a big footprint on patients do not cause a significant burden on public health. In contrast, some conditions that barely alter individual health (e.g. nasal polyps and infertility), are so prevalent and characterized by a chronic disease course, that they lead to a considerable burden on public health.

Multimorbidity

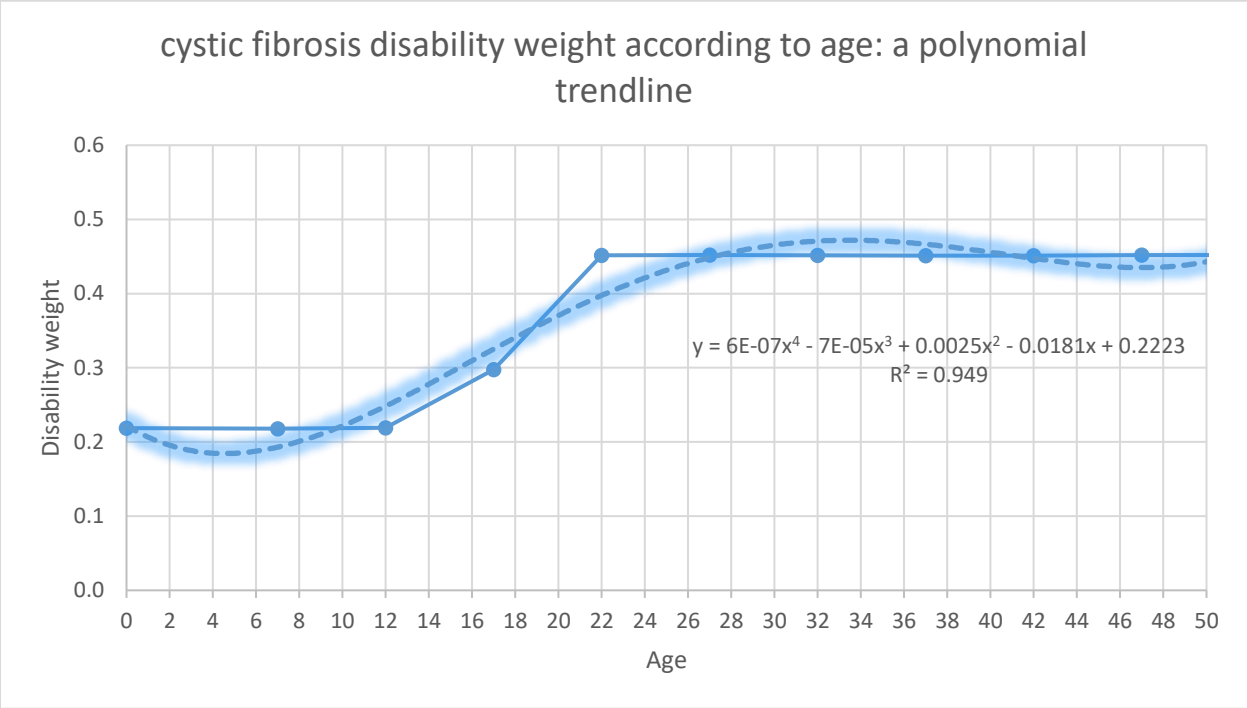
For each separate complication, adjusted disability weights are established using a multiplicative model when opportune. Thus, one complication can be composed out of different health states. Nonetheless, possible relationships between the different complications are not taken into account. Again, the reason for this is twofold. Firstly, no data are available in the BCFR reports that enables to find correlations between different complications. Secondly, published evidence on this topic is scarce. However, some studies have established possible relationships between certain complications. Most notably, a relationship between exocrine pancreatic insufficiency and CF-related diabetes (endocrine pancreatic insufficiency) is suggested (Gibson-Corley, Meyerholz, & Engelhardt, 2016), and the risk of developing CF-related diabetes later in life can already be estimated short after birth (Soave, et al., 2014). Similarly, an association between liver cirrhosis and gallstones is reported (Acalovschi, 2014). The effect of this associative element on the burden of disease is important to consider. The reason for this is that CF patients who simultaneously suffer from multiple complications, in general experience less disability than the sum of the disabilities should those complications occur in different patients. As such, the YLDs due to complications may be overestimated because multimorbidity is not accounted for.

Disability weights specific for cystic fibrosis

A composite disability weight of 0.356 is proposed for the general CF population in Belgium (Table 17). Disability weights are almost equal when stratifying according to gender. In contrast, age has a profound impact on disease burden, with disability weights of 0.223 and 0.454 for young patients and adult patients respectively. This corresponds with the disease's progressively deteriorating nature (Theodore, Elkin, Pasta, Jacobs, & Konstan, 2014). Calculation of composite disability weights for CF according to age (both genders combined, not shown) is performed, and made visual in a graph (Figure 19). By computing a polynomial trendline, it is possible to smooth out the brusque transition in disability weights for different ages (due to the use of only three general disability weights in the primary disease component. This is particularly relevant in the CF population between the ages of ten and thirty, and it is assumed to better represent the incremental disease progression in adolescents and young adults.

Indeed, while the disease is progressing rapidly, and despite the substantial burden of CF and its associated treatment demands, most adults with CF work or study and many establish relationships and families (Bell, et al., 2011). As it is estimated that more than 90% of children with CF will reach adulthood, caring for adolescents requires a focus that allows for minimal interruption of schooling while allowing people with CF to achieve their potential. The CF care team needs to consider flexible access to care for the individual who continues to study, work and develop lifelong relationships. Data concerning education, employment and other socioeconomic parameters can be consulted in appendix (Appendix 7: education level and Appendix 8: social allowances or benefits and employment).

Figure 19



It is interesting to see how the calculated general composite disability weight for CF relates to other disability weights reported by the WHO. All disability weights reported by the WHO that are 0.054 points higher or lower than the CF disability weight of 0.356 (this represents a deviation of 15.0%) are shown in ascending order (Table 18) (World Health Organization, 2017). Health states which concern impairment of lung function, the cardinal symptom of CF, are highlighted in blue. The first notable finding is that CF should be regarded as a disease with a high disease burden on patient level, as it is comparable with some very impactful diseases. This is made clear by the lay descriptions of the corresponding health states. Indeed, many of the diseases are characterized by substantial physical and psychological symptoms, with considerable effect on activities of daily life. In extension, a lay description of CF that tends to describe the health state of a general CF patient, is proposed. Secondly, it seems that the disability weight of severe COPD is a good proxy for the disability weight of CF (0.408 and 0.356 respectively). Indeed, some researchers have applied the severe COPD disability weight in the context of burden of CF studies (Begg, et al., 2007). Comparison of this COPD disability weight with the disability weight for CF calculated in this dissertation supports the validity of the results of these studies.

Table 18

WHO disability weights between 0.302 and 0.410*		
Health state	**Lay description**	**DW**
Neck pain, most severe	Has constant neck pain and arm pain, and difficulty turning the head, holding arms up, and lifting things. The person gets headaches, sleeps poorly, and feels tired and worried.	0.304
Burns of ≥20% total surface area: short term, with or without treatment	Has a painful burn over a large part of the body. Parts of the burned area have lost feeling, and the person feels anxious and unwell.	0.314
Stroke: long-term consequences, moderate plus cognition problems	Has some difficulty in moving around, in using the hands for lifting and holding things, dressing and grooming, and in speaking. The person is often forgetful and confused.	0.316
Musculoskeletal problems, generalized, moderate	Has pain and deformity in most joints, causing difficulty moving around, getting up and down, and using the hands for lifting and carrying. The person often feels fatigue.	0.317
Abdominopelvic problem: severe	Has severe pain in the belly and feels nauseous. The person is anxious and unable to carry out daily activities.	0.324
Gastric bleeding	Vomits blood and feels nauseous.	0.325
Back pain, severe, with leg pain	Has severe back and leg pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly and feels worried.	0.325
Hearing loss: complete, with ringing	Cannot hear at all in any situation, including even the loudest sounds, and cannot communicate verbally or use a phone, and has very annoying ringing in the ears for more than half of the day. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.327
Tuberculosis, not HIV infected	Has a persistent cough and fever, is short of breath, feels weak, and has lost a lot of weight.	0.333
Heroin and other opioid dependence, mild	Uses heroin (or methadone) daily and has difficulty controlling the habit. When not using, the person functions normally.	0.335
Distance vision blindness	Is completely blind, which causes great difficulty in some daily activities, worry and anxiety, and great difficulty going outside the home without assistance.	0.338
Vesicovaginal fistula	Has an abnormal opening between the bladder and the vagina, which makes her unable to control urinating. The woman is anxious and depressed.	0.342
Cystic fibrosis**	Variable though substantial and progressive impairment of lung function, combined with a high burden due to digestive problems. Psychological problems are often present and become worse as the disease progresses. The serious symptoms in combination with the need for extensive treatment procedures (which often take multiple hours a day), have a profound impact on activities of daily life. Other complications may arise and significantly aggravate the disease. Eventually, lung transplantation is required.	0.356
Severe chest injury: short term, with or without treatment	Has a serious chest injury, which causes severe pain, shortness of breath and anxiety.	0.369

Back pain, most severe, without leg pain	Has severe back pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly and feels worried.	0.372
Alcohol use disorder: moderate	Drinks a lot, gets drunk almost every week and has great difficulty controlling the urge to drink. Drinking and recovering cause great difficulty in daily activities, sleep loss, and fatigue.	0.373
Lower airway burns: with or without treatment	Has a burn in the throat and lungs, which causes great difficulty breathing and a lot of anxiety.	0.376
Amputation of both arms: long term, without treatment	Has lost part of both arms, leaving pain and tingling in the stumps and flashbacks from the injury. The person needs help with basic daily activities such as eating and using the toilet.	0.383
Intellectual disability / mental retardation, severe	Has very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.	0.383
Back pain, most severe, with leg pain	Has severe back and leg pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly and feels worried.	0.384
Dementia: moderate	Has memory problems and confusion, feels disoriented, at times hears voices that are not real, and needs help with some daily activities.	0.388
Major depressive disorder: moderate episode	Has constant sadness and has lost interest in usual activities. The person has some difficulty in daily life, sleeps badly, has trouble concentrating, and sometimes thinks about harming himself (or herself).	0.396
Fracture of neck of femur: long term, without treatment	Had a broken hip bone in the past, which was never treated and did not heal properly. The person cannot get out of bed and needs help washing and going to the toilet.	0.402
Motor impairment: severe	Is unable to move around without help, and is not able to lift or hold objects, get dressed or sit upright.	0.402
Disfigurement: level 3	Has an obvious physical deformity that makes others uncomfortable, which causes the person to avoid social contact, feel worried, sleep poorly, and think about suicide.	0.405
Tuberculosis, HIV infected	Has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss.	0.408
COPD and other chronic respiratory problems, severe	Has cough, wheezing and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.	0.408

*Health states, disability weights and lay descriptions are extracted from the most recent GBD study (World Health Organization, WHO methods and data sources for global burden of disease estimates 2000-2015, 2017)

**Suggested disability weight and lay description, based on calculations and findings in this dissertation

Incidence perspective

Estimation of the burden of cystic fibrosis in the near future

The calculation of DALYs using an incidence approach, measures the future stream of healthy years of life lost due to each incident case of disease or injury (see also section: General concepts). As such, it is possible to assess the burden of CF in future years (Table 19). To this end, some assumptions are made. Firstly, the mean incidence rate of the recent period 2011-2014 is used. In Belgium, the incidence of CF is approximately 32 new diagnoses per year for recent years. Secondly, the standard life expectancy of 91.9 years is applied for all those patients. Thirdly, a large scale survival modelling study estimated the age at death for patients that are born in the year 2010 to be approximately 38.5 years. Fourthly, the composite disability weight for CF as calculated above is used. Note that this implies that patients born in recent years, are assumed to resemble the characteristics of the BCFR population of 1,230 patients in 2014. Altogether, the burden of CF in a year in the near future is estimated to be 67.0 DALYs per patient, which corresponds with 2168.6 DALYs for all patients together. Despite the lower number of YLLs per patient (63.0 versus 53.3 YLLs), the total burden in this incidence approach is higher than the burden of CF using a hybrid approach (2128.2 versus 922.4). The most important reason is that 32 persons are diagnosed with CF each year, and the deaths of all these patients is accounted for. In contrast, the hybrid approach considered an average yearly number of deaths of 7.7 CF patients. Furthermore, it also considers the lifelong disability of those patients (in addition to the assumptions described).

Table 19

Estimation of burden of cystic fibrosis in a year in the near future: incidence approach								
Incidence*	LE**	Age at death***	Age at diagnosis****	DW*****	YLDs	YLLs	DALYs	
					Per patient	Per patient	Per patient	All patients
31.8	91.9	38.62	0	0.356	13.7	53.3	67.0	2128.2

*Incidence based on mean incidence in the years 2011-2012-2013-2014 as reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

**Standard life expectancy at birth according to the World Health Organization (World Health Organization, 2017)

***Age at diagnosis is zero because from 2019 onwards, a national neonatal screening program will be implemented ((Van den Brandt, Croo, Van Malderen, Franssen, & Saeys, 2016)

****Age at death is set according to predictions of the age at death in CF patients born in the year 2010 (MacKenzie, et al., 2014)

*****Disability weight for CF patients as calculated above

Estimation of the burden of cystic fibrosis in the recent past

Similarly, it is possible to estimate the burden of CF in an average year of the last 16 years (1998-2014) (Table 20). The incidence of CF used in these calculations is based on the mean incidence of that period and is slightly higher than if only considering the last four years (approximately 35 versus 32 new diagnoses respectively). The standard life expectancy is not changed as it represents the possible life span of people in a general population. The mean age at death is used (28.6 years). The median age at diagnosis is extracted from an older BCFR report, which spans the years 1998-2007, and is found to be 7 months. The same composite disability weight as calculated above is used. Note that this indeed implies that patients in any of those years had the same characteristics of the patients in 2014. Altogether, the burden of CF in a recent year is estimated to have been 73.3 DALYs per patient, which corresponds with 2576.3 DALYs for all patients together.

Table 20

Estimation of burden of cystic fibrosis in a year in the recent past: incidence approach								
Incidence*	LE**	Age at death***	Age at diagnosis****	DW*****	YLDs	YLLs	DALYs	
					Per patient	Per patient	Per patient	All patients
35.2	91.9	28.6	0.58	0.356	10.0	63.3	73.3	2576.3

*Mean incidence in the years 1998-2014, based on BCFR reports 2007 and 2014 (Peeters, 2007) (Wanyama, Thomas, & Malfroot, 2014)

**Standard life expectancy at birth according to the World Health Organization (World Health Organization, 2017)

***Median age at diagnosis is seven months in the years 1998-2007, extracted from the BCFR report 2007 (Peeters, 2007)

****Mean age at death in the years 1998-2014, extracted from the BCFR report 2007 (Wanyama, Thomas, & Malfroot, 2014)

*****Disability weight for CF patients as calculated above

Trends of the burden of cystic fibrosis in Belgium

Comparison of a year in the near future with a year in the recent past leads to the conclusion that the burden of CF is declining. This is the case for individual (74.2 versus 68.3 DALYs) as well as public health (2608.8 versus 2168.6 DALYs). The reason for this is the foreseen decrease in premature mortality. Thus, the number of YLLs per patient will be less in the future (53.3 versus 63.3 YLLs). In contrast, the number of YLDs per patient will increase (15.0 versus 10.9 YLDs) because, assuming a constant disability weight, the number of years lived with disability will grow. Nonetheless, the estimated decline in YLLs is more than double compared to the estimated incline in YLDs (10 years of life won versus 3.7 years of life lost).

In addition, these numbers can be compared with the DALYs for an average CF patient, as derived from the hybrid approach used in this dissertation: 63.0 YLLs, 0.20 YLDs due to the primary disease, 0.13 YLDs due to complications and 0.04 YLDs due to transplantation-related complications. This leads to a total of 63.4 DALYs for an average CF patient for the year 2014. This is lower than the incidence estimates, because future YLDs are not taken into account.

Disability- and quality adjusted life years

Next to disability-adjusted life years (DALYs), another summary measure of health is widely applied, namely quality-adjusted life years (QALYs). Both take a different perspective when considering health, with DALYs stressing the importance of health loss due to disability and mortality (Murray & Acharya, 1997), and QALYs focusing on health gain based on quality of life (Weinstein, Torrance, & McGuire, 2009). As a consequence, disability weights (DALY philosophy) and utility scores (QALY philosophy) are characterized by an inverse relationship, and DALYs are to be avoided and QALYs to be accumulated. Where DALYs are intended to calculate the burden of disease by considering both years of life lost (YLLs) and years lived with disability (YLDs), QALYs are intended to combine the duration of the disease and a person's health-related quality of life (HRQoL). QALYs are mainly used in cost-effectiveness and treatment-efficacy analyses and are often used to give information on the individual burden (Rios-Diaz, et al., 2016). In contrast, DALYs are predominantly used as a summary measure of disease burden that can track changes in population health over time. There is no conclusive evidence of one summary measure being superior to the other. Both provide a quantitative model, neither without flaws (Sassi, 2006).

It has been argued that the impact of interventions on disease burdens may be more adequately captured QALYs. Some authors suggest that the use of QALYs enables researchers to account for the fact that disability is not always a hallmark of a high-priority health state, and that health states may be better accounted for in terms of the value added by their treatment (Weinstein, Torrance, & McGuire, 2009). Indeed, (cost-) effectiveness studies often use the QALY approach. As such, QALY research can provide additional insights that should be considered when making decisions concerning national public health.

In the context of this dissertation, an article was written on the clinical and sociodemographic factors that influence HRQoL in CF patients, using the QALY approach (Appendix 10: factors influencing quality of life in patients with cystic fibrosis: a systematic review). This article's objective was to conduct a systematic review of the literature concerning the relationships between clinical and sociodemographic factors and HRQoL in patients with CF. The most important findings of this systematic review are described in the section:

Relationships between cystic fibrosis and quality of life).

Disability weights and utility scores

The disability weights that are used in this dissertation, are estimated through a large-scale empirical investigation with a major emphasis on surveying respondents from the general population, in which judgments about health losses associated with many causes of disease and injury were elicited through a standardized approach (World Health Organization, 2017). To this end, a trade-off method was applied, involving comparisons of health for pairs of health states described by lay descriptions consisting of a brief summary of the health state of an average or modal case. In contrast, utility measures in QALY investigations are often derived by means of (general or disease-specific) questionnaires, such as the cystic fibrosis questionnaire (CFQ) (Abbott & Hart, 2005). In theory, disability weights and utility weights are each other's inverse and both can be developed using the same tools.

Measurement of health-related quality of life in cystic fibrosis

The CFQ, which has versions for children (≥ 8 years old), teens (≥ 14 years old) and adults (for which a revised version is available: CFQ-R), and the similar Cystic Fibrosis Quality of life questionnaire (CFQoL) are the primary used measurement instruments that have undergone validation and have shown clinical sensitivity for use in a CF context (Quittner, et al., 2009). CFQ-R datasets can be mapped into EQ-5D utility values, which may be interesting in future research (Acaster, Pinder, Mukuria, & Copans, 2014).

Health-related quality of life measurements are a way of including the patients' perspective in clinical practice and research. As a multidimensional construct, which includes physical, psychological and social well-being and functioning, it provides crucial patient information neglected by other outcome measures (Abbott, et al., 2011) and reflects the whole spectrum of a patient's daily life (Abbott, Webb, & Dodd, 1997) (Table 21).

Table 21

Domains of quality of life assessed in the CFQ(-R) questionnaire	
Physical functioning	Weight
Respiratory symptoms	Body image
Social functioning	Eating disturbances
Emotional functioning	Digestion
Role functioning	Vitality
Treatment burden	Health perceptions

Relationships between cystic fibrosis and quality of life

General relationships between cystic fibrosis and quality of life

It is important to be aware of the fact that, somewhat surprisingly, CF patients often report very high HRQoL scores. A phenomenon called “response shift” may be responsible for this finding: a re-evaluation of the meaning of life with subsequent adaptation to changing conditions (Abbott, 2009). This means that ceiling effects occur and it can potentially be difficult to demonstrate HRQoL improvements, after installing a new therapy for example. In extension, an important note is that improved symptoms not necessarily correlate with improved HRQoL (Abbott, 2009). This contrasts the finding that CF patients, according to the general population, experience a high number of YLDs due to the relatively high disability weights used in the calculations.

Further support of these findings comes from a longitudinal study that performed HRQoL measurements at baseline and one year later (Debska & Mazurek, 2015). It is found that, despite important disease progression, this one year period could not reveal significant changes in HRQoL. Interestingly, the authors suggest that HRQoL should be considered as a trait, rather than a health state. This personal trait may have a bigger impact on HRQoL than any clinical or other variable.

However, these results contrasted with the findings of another study (Van Horck, et al., 2017). The authors measured HRQoL at baseline and one year later and found significant improvements in CFQ-R total scores as well as most domain scores. The authors speculate that merely participating in an intensive study improved HRQoL because of the extra attention that patients

experience, e.g. the extra contacts with the nurses and physicians of the CF team. Better treatment adherence during the study might strengthen this observed improvement. However, as the baseline age increases, HRQoL improvement weakens in this study and becomes negative in children older than twelve. The drop in HRQoL in these children may be the consequence of the increasing disease severity and treatment intensity, as reflected by the scores of the treatment burden domain and the respiratory symptom domain. In addition, the number of pulmonary exacerbations was found to have an impact on treatment burden score. This makes sense, as they require additional therapies. An alternative explanation for these findings may be a better coping style during childhood, in contrast with the problems related to CF in adolescents (Mc Hugh, Mc Feeters, Boyda, & O'Neill, 2016). Either way, things get worse in adolescence and this is also apparent in the burden of disease calculations in this dissertation.

Specific relationships of sociodemographic factors and quality of life in patients with cystic fibrosis

Progressing age is repeatedly found to be substantially and negatively correlated with HRQoL (Abbott, 2009) (Habib, et al., 2015). This, in combination with the calculated burden of disease in different age categories, indicates that increasing life expectancy is indeed important to anticipate for, as well on the level of the patient as on the level of public health. In addition, age at diagnosis is found to affect HRQoL in CF patients, which further stresses the importance of a neonatal screening program (for more information see Appendix 2: prevention of cystic fibrosis).

Another finding is that female CF patients consistently report poorer HRQoL than male patients, and this for all ages and almost all dimensions (Abbott, 2009) (Abbott, Morton, Hurley, & Conway, 2015). Interestingly, female patients seem to have a more accurate perception of their objective clinical status than men. This is not evident from the DALY calculations and might be hard to act upon, as ethical consideration would discourage dual care programs for males and females.

As already mentioned, new challenges arise in CF patients, as more and more go to school, get a job, and start families. In this context, it is found that school attending (young) patients and employed (adult) patients consistently report higher scores of HRQoL, particularly when it is a source of a meaningful life and not a source of too much stress (Knudsen, et al., 2016).

Furthermore, a lower level of education is predictive of psychological symptoms, and warrants extra attention (Olveira, et al., 2016). Although, full-time schedules are negatively associated with HRQoL, possibly due to the fact that CF treatments are very time consuming and thus incompatible with very demanding professional lives (Olveira, et al., 2016). The DALY calculations revealed an important burden of disease in adolescents and young adults, in which these processes of personal development are paramount. Young adults are likely still transitioning to adult roles, including starting a career and family, which may be characterized by disorientation, distress, irritability, anxiety and depression (Chick & Meleis, 1986). These findings combined, lead to the conclusion that CF patient care should focus at these age categories.

Specific relationships of clinical factors and quality of life in patients with cystic fibrosis

The most important findings in the last decade of the previous century are consistent correlations between lung function parameters and the functional and physical aspects of HRQoL (Moço, et al., 2015). A review of the literature showed that FEV_1 % predicted and pulmonary exacerbations have the most significant impact on HRQoL (Habib, et al., 2015) (Forte, et al., 2015). This corresponds with the high amount of YLDs due to the primary disease component, as calculated in this burden of disease study.

Nonetheless, differences in pulmonary function can only explain so much of the variability in HRQoL, which means that other factors need to be considered. As such, were previous research focused mainly on factors concerning the primary disease, more recent research also includes complication-related factors, such as psychiatric disease and psychological factors. These factors seem to be important as they have profound effects on CF patients' HRQoL.

It is demonstrated that young adults with CF show frequent symptoms of depression (Knudsen, et al., 2016) and anxiety (Olveira, et al., 2016). Furthermore, symptoms of depression or anxiety and reduced HRQoL, are significantly correlated and clinically relevant. Importantly, depression and anxiety affect almost all HRQoL domains. As calculated above, psychiatric diseases and psychological symptoms account for a substantial number of YLDs in CF patients. In addition to the classic clinical follow-up of patients with CF, emphasis should now be on psychological support in a continuously growing multidisciplinary setting, in order to enhance the HRQoL of CF

patients. This is primarily important on the level of the patient. Nonetheless, the calculation of YLDs recognizes its importance on population level as well.

A large number of other complication-related factors and their specific relationships with HRQoL in CF patients have been investigated. For example, a significant association is found between chronic rhinosinusitis (promoting the development of nasal polyps) and the respiratory functioning domain of the CFQ-R questionnaire (Habib, et al., 2015). This is rather easy to understand, as many questions of this domain are related to symptoms of rhinosinusitis. Despite the high prevalence of chronic rhinosinusitis in CF patients, evidence based guidelines for its management in CF patients are yet to be established.

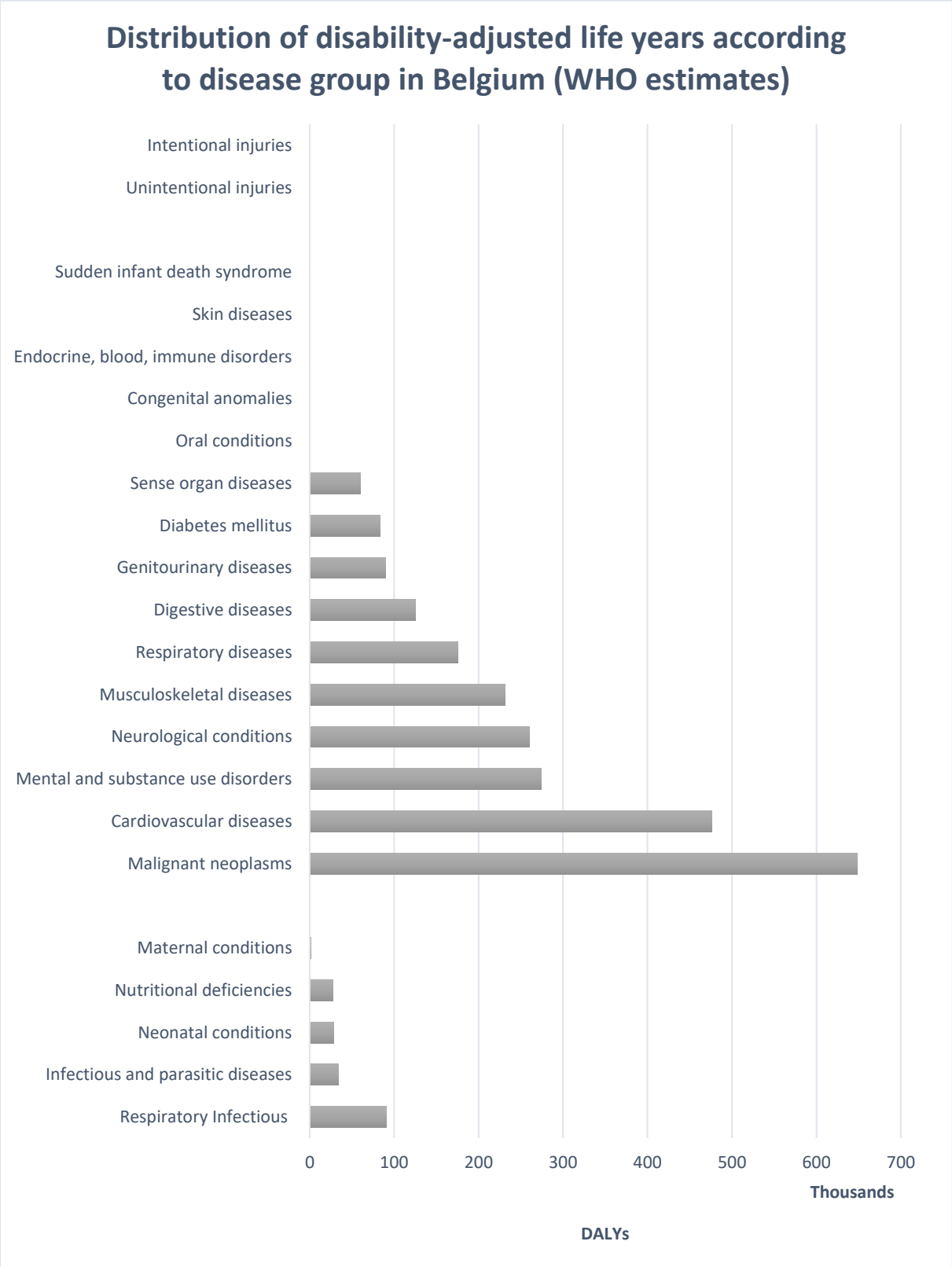
Interestingly, the effects of exocrine pancreatic insufficiency on HRQoL have not yet been investigated in a CF setting. Although, a low body mass index, which is a direct consequence of exocrine pancreatic insufficiency, is on multiple occasions found to have significant effects on HRQoL in CF patients (Bodnar, et al., 2014) (Abbott, Morton, Hurley, & Conway, 2015). A detailed and up-to-date elucidation of other factors that affect HRQoL in CF patients can be found in the article attached in the appendix section (Appendix 10: factors influencing quality of life in patients with cystic fibrosis: a systematic review). Most notably, CF-related diabetes and transplantation status have important effects on HRQoL. Indeed, this strengthens the relevance of the YLDs due to these complications.

Other burden of disease studies

Profile of disease burden in Belgium

The WHO provides DALY estimates by country and disease group (World Health Organization DALY estimates, 2000-2015 by country, 2018). The total number of DALYs in Belgium is estimated to be approximately 3.1 million. The distribution of DALYs according to disease group shows that malignant diseases have the highest impact on public health, accounting for roughly 650,000 DALYs (21%). Cardiovascular diseases are responsible for another 475,000 DALYs (15.3%) (Figure 20). This dissertation found CF to cause 922.4 DALYs (0.03%). However, when considering rare diseases as a group, it becomes clear that they may not be overlooked. When the estimate that one in seventeen persons (approximately 650,000 Belgians) indeed suffer from a rare disease is more or less correct, and assuming a disability weight of 0.356 (i.e. the disability weight for CF) for rare diseases as a group, a disease burden of 231,400 DALYs can be calculated. This would correspond with 7.5% of the total disease burden in Belgium. However, bearing in mind the scarcity of resources, priorities must be set. In this context, it is indicated to compare the burden of patients with the burden of other rare diseases.

Figure 20


Distribution of disability-adjusted life years according to disease group in Belgium (WHO estimates)
Intentional injuries
Unintentional injuries
Sudden infant death syndrome
Skin diseases
Endocrine, blood, immune disorders
Congenital anomalies
Oral conditions
Sense organ diseases
Diabetes mellitus
Genitourinary diseases
Digestive diseases
Respiratory diseases
Musculoskeletal diseases
Neurological conditions
Mental and substance use disorders
Cardiovascular diseases
Malignant neoplasms
Maternal conditions
Nutritional deficiencies
Neonatal conditions
Infectious and parasitic diseases
Respiratory Infectious
0
100
200
300
400
500
600
700
Thousands
DALYs

Hemophilia and melanoma

The burden of hemophilia (incidence approximately 1/5,000) in Belgium has been investigated (Henrard, et al., 2014). However, the study applied an incidence approach, which can induce some difficulties in comparing the results with the main findings from this dissertation (Schroeder, 2012) (Wagner, et al., 2015). However, a preemptive incidence approach is also considered in this dissertation, and this only strengthens the considerations that follow. In Belgium, hemophilia resulted in 145 undiscounted and unweighted DALYs in total. It is mentionable that patients who suffer from hemophilia generally have a normal life expectancy (26 YLLs, corresponding with only 18% of the total number of DALYs). Indeed, an important ethical and personal issue arises, namely the relative importance of a long life versus a healthy life (Rappange, Brouwer, & van Exel, 2016). This study on CF patients found 484.8 YLLs and 437.6 YLDs, which makes that the burden of CF is equally caused by premature mortality and years lived with disability. Although hemophilia also has a minor impact on the overall disease burden, repercussions on the level of the patient remain substantial. Nonetheless, the repercussions of CF on individual patients is even more significant. Either way, the total burden of CF as well as the burden due to living in an impaired health state in individual CF patients is larger compared to hemophilia patients. So, regardless of the perspective, of those two diseases CF should receive priority support. However, resources are scarce and both diseases have different economic costs. As such, it would be interesting to estimate the economic costs associated with CF, and compare them with the costs of hemophilia (i.e. a cost of illness study assessing both direct and indirect costs for society). Consequently, it will be possible to assess the economic return of prioritizing one disease above the other, while taking public as well as individual health into account. Note that estimates concerning the socio-economic cost of CF, composed of direct and indirect costs for society, already exist. It is found that CF-related costs are high compared to costs of other rare diseases such as hemophilia (Angelis, Tordrup, & Kanavos, 2015). With the increase in life expectancy and expensive treatment modalities, this cost (especially the direct cost) will presumably continue to grow. Similar considerations are applicable to the burden of disease of melanoma in Belgium, which is estimated to accumulate approximately 10,125 DALYs for the Belgian public health (Tromme, et al., 2016). The age standardized incidence is estimated to be

12.1/100,000 (Belgian Cancer Registry, 2015) and 15,921 persons (0.14% of the total Belgian population) are alive (on 01/01/2014) after being diagnosed with malignant melanoma between 2004 and 2013. Whether melanoma, and especially other less frequent types of cancer, are to be considered rare is open for debate. However, the burden of cancer as a disease group is an encompassing term for less frequent diseases, which often need distinguished public investments. As such, the burden of those diseases can or should also be compared with the burden of rare diseases. Furthermore, malignant diseases remain one of the most significant causes for impaired health on the level of the patient.

Knowledge gaps, limitations, future research and implications for health policy makers

The BCFR does not collect data regarding incidences of different CF-related complications. It is recommended that the BCFR includes this information in its set of collected data, so that in the future, the burden of CF can be estimated using a more refined incidence approach. This will provide additional information, especially because of the changing demographic characteristics of the CF population. Data regarding multimorbidity could also generate additional insights in the burden of cystic fibrosis. In this regard, further development of data collection methodologies such as integrated online platforms could prove to be beneficial.

In this study it was often necessary to allocate disability weights to particular CF-related health states for which they were not primarily meant. Although this was done with caution and careful judgement, this may be a limitation of the study. The true prevalence of certain complications and their causal relationship with CF remains doubtful. In the case of acute complications, it was necessary to estimate a general duration, which can be seen as arbitrary. In order to account for a transition period from childhood to adulthood, the mean of the disability weights of the primary disease component for children and adults was used. In calculative terms this may be open for debate, however, a correction is strongly suggested by the literature so that the natural course of the disease if reflected.

In general, initiatives to reduce the burden of CF should be encouraged and given full support. Collaboration between the many different stakeholders, such as the CF patient association, scientific community, CF reference centers and public health policy makers should be further developed. Recent efforts have already led to a neonatal screening program, which will be implemented in the near future.

The way in which care is delivered should be adjusted to the sociodemographic changes in the CF population. In extension, existing guidelines and treatment protocols should continuingly be refined. In particular, CF caregivers should closely monitor psychological and psychiatric disturbances in CF patients. Similarly, complications that occur more in older patients such as CF-related diabetes should receive appropriate attention. Aggressive treatment of the primary lung

dysfunction remains important. In addition, adolescents and young adults should be the primary target for health policy makers.

Fundamental research and commercial development of next-generation therapies should receive adequate funding. The ultimate goal of those efforts should be to develop a definitive cure for CF. Nonetheless, in the meantime premature mortality is characterized by an incremental decline, which corresponds with a rise in years lived with disability. As such, efforts to support the quality of life of CF patients should also receive be embraced.

The burden of other rare diseases should be investigated and should take both the perspective of the patient as the perspective of the population into account. These could be compared so that priorities can be set. In addition, quality of life studies can lead to the recognition of otherwise overlooked issues. Furthermore, cost of illness studies could provide additional insights by assessing the economic burden of rare diseases. Altogether, multiple perspectives will provide a more comprehensive measure to underpin the action plans of health policy makers on national as well as international level.

Conclusion

Cystic fibrosis is a severe and progressive condition with considerable premature mortality. In 2014, the burden of the disease is approximately equally caused by morbidity and premature mortality. Nonetheless, sociodemographic changes in the CF population may change this finding in future decades. The burden of cystic fibrosis is found to be significant on the level of the patient. In addition, in comparison with other rare diseases, the burden on public health also appears to be substantial. Nonetheless, a declining trend of disease burden due to CF is reckoned.

Several ways to further reduce the burden of cystic fibrosis are possible and should receive full support. These include efforts in research and development of advanced therapies, promoting collaboration between the many stakeholders, improvements in data collection and optimization of CF care standards.

In order to reduce the overall burden of diseases in Belgium, insights from other (types of) studies can lead to the economically rational allocation of resources, while taking both patient health as well as public health into account.

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Appendices

Appendix 1: symptoms and clinical reasons for CF diagnosis

Symptoms and clinical reasons for CF diagnosis*						
Symptom or sign	**All patients**		**Newly diagnosed****			
	1988-2014		**2013**		**2014**	
	N	**%**	**N**	**%**	**N**	**%**
Acute or recurrent respiratory problems	509	42.7%	12	46.2%	12	33.3%
Failure to thrive	289	24.2%	7	26.9%	6	16.7%
Chronic diarrhea/steatorrhea/ malabsorption	240	20.1%	5	19.2%	3	8.3%
Neonatal screening test	201	16.8%	6	23.1%	10	27.8%
Meconium ileus	171	14.3%	3	11.5%	5	13.9%
Family history	125	10.5%	3	11.5%	5	13.9%
Nasal polyposis / chronic sinusitis	53	4.4%	3	11.5%	1	2.8%
Rectal prolapse	32	2.7%	0	0.0%	0	0.0%
Intestinal obstruction (other than meconium ileus)	26	2.2%	0	0.0%	1	2.8%
Prenatal diagnosis	36	3.0%	1	3.8%	2	5.6%
Dehydration / electrolyte imbalance	19	1.6%	1	3.8%	1	2.8%
Neonatal jaundice / prolonged icterus	2	0.2%	1	3.8%	0	0.0%
Infertility	12	1.0%	0	0.0%	0	0.0%
Diagnosis other	96	8.0%	1	3.8%	6	16.7%
no diagnosis reasons given***	37	3.1%	2		0	

**There were 28 newly diagnosed in 2013, percentages are based on 26 patients. There were 36 newly diagnosed in 2014, percentages are based on 36 patients.

***The overall percentages are based on 1193, 37 patients did not have information on any of the above reasons given in the 2014 data and were excluded from the calculations.

Note: reasons for diagnosis are not mutually exclusive.

As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Prevention of cystic fibrosis

Neonatal and carrier screening

In the United States of America, screening for a CTFR mutation panel is recommended for everyone who plans to conceive (American College of Obstetricians and Gynecologists Committee on Genetics, 2011). In case both partners are carrying a CF mutation, prenatal diagnostic tests are performed in the first trimester of the pregnancy in order to investigate the CFTR locus of the fetus. These procedures may include chorionic villus sampling and amniocentesis. When the fetus is found to be affected by a bi-allelic CFTR mutation, two options are to be considered. Firstly, couples can continue the pregnancy and prepare for a child with CF. Couples can use this time to learn as much as possible about the disease, current treatment options, and the experiences of other families who have a child with CF. Secondly, another option is to end the pregnancy. It is needless to say that these considerations are intermingled with ethical principles and personal preferences.

In Belgium, preconceptional carrier screening, is also possible. However, health-economic considerations have led to a negative advice for its routine application (Belgian Health Care Knowledge Center, 2010). Nonetheless, progress in secondary and tertiary prevention of CF is being made, as the Flemish Parliament reached an agreement in principle to systematically perform neonatal screening for CF, which will take effect in 2019 (Van den Brandt, Croo, Van Malderen, Franssen, & Saeys, 2016). Although in this case it is not possible for parents to choose between the two above mentioned options, this should lead to an even more early diagnosis of CF (Appendix 9: neonatale screening: “Levensbelangrijke doorbraak voor mensen met muco”). Consequently, early disease progression can be avoided and ultimately, this will lead to a lesser burden for CF patients, and in extension for the public health.

Next-generation preventive methods

When taking a more revolutionary point of view, it would be possible to screen all future parents for all known disease-causing genetic sequences. Since the advent of the Human Genome Project, opening doors to an era of genomic medicine, genetic sequencing has become a relevant and critical tool in individualized disease prevention (Anderson & Schrijver, 2010). Genomics has recently celebrated reaching the $1,000 genome milestone, making affordable DNA sequencing a reality (Erlich, 2015). As such, it would be possible to assess the genetic make-up of future parents, and in case both parents are carrying a CFTR mutation, appropriate steps can follow. The advantage of sequencing the whole genome, instead of only examining the CFTR gene, is that at the same time thousands of other disease-related mutations (e.g. leading to Duchenne disease which occurs every 3,300 pregnancies) can be traced. Although this type of screening and prevention is still a project for the future, a highly

active biotechnology subsector of genomics firms has already emerged in parallel to the publicly funded Human Genome Project (Wiechers, Perin, & Cook-Deegan, 2013). In this context, it will be interesting to see how the relationship between private and public initiatives will develop. For example, currently, such extensive screening programs remain for the happy few. Because of this, the Superior Health Council of Belgium, still separated from the Belgian Health Care Knowledge Center, wants to establish pilot projects that investigate the feasibility of such extensive screening procedures in the setting of public health care (Superior Health Council of Belgium, 2017). It should be noted however, that the wealth of genetic information generated by these methods, will inevitably have ethical and juridical consequences. When taking an even more visionary stance, the combination of such extensive screening protocols with the previously described advanced treatments, could eventually lead to in utero gene therapies.

Current state of affairs

In the meantime, family history and abnormal findings during the follow-up of pregnancy remain the most important reasons for genetic counseling and CFTR mutation screening. An example of the latter is the finding of hyperechogenic fetal bowel, prenatally detected by ultrasound during the second trimester of pregnancy in 0.1-1.8% of fetuses (Muller, et al., 2002). It has been described as a normal variant but has often been associated with severe diseases, notably CF, which is present in 17% of the cases (Muller, et al., 2002). As such, fetal bowel anomalies indicate a risk of severe CF and justify careful CFTR molecular analysis.

Atypical mutations

The most frequent mutation is F508del, which is a deletion of three nucleotides resulting in the deletion of phenylalanine on position 508 of the CFTR protein. It is responsible for approximately 70% of the CF alleles (European Working Group on CF Genetics, 1990). The protein-disrupting nature of this mutation explains why it was never found in a normal individual in a homozygous state.

Mutation pairs*			
Mutation pair	**N**	**%**	**Cumulative %**
F508del homozygous	559	45.40%	45.40%
F508del heterozygous	460	37.40%	82.80%
F508del - NI	31	2.50%	85.40%
Other - other	158	12.80%	98.20%
Other - NI	6	0.50%	98.70%
NI - NI	16	1.30%	100.00%
Total	**1230**		
NI = not identified			

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Almost half of the patients affected by CF are homozygous for the mutation F508del. F508del homozygotes present a classical form of the disease with an increase in electrolytes in sweat, pancreatic insufficiency and obstructive lung pathology (Tomaiuolo, Sangiuolo, Bombieri, Bonizzato, & Cardillo, 2008). Comparing the clinical presentation of patients homozygous for F508del with patients that have other genotypes makes the phenotypic consequences of the type of mutation clear.

Indeed, the age of onset and the severity of the disease are, at least in part, related to the particular genotype (Marson, Bertuzzo, & Ribeiro, 2017). In general, genetic configurations other than two F508del alleles give rise to more atypical and often milder forms of CF (Jeffrey & Dungan, 2010) (Brunson, Bridges, Graves, Schwann, & Anderson, 2009). Thus, F508del alleles account for the majority of DALYs and this is not only because of their prevalence, but also because of their effect on disease severity. As a consequence, it seems opportune to continuingly focus on developing targeted therapies for the classical form of CF, caused by a bi-allelic F508del mutation.

Appendix 4: treatments in patients with cystic fibrosis

Treatments in patients with cystic fibrosis*						
Physiotherapy, inhalation therapy, oral anti-inflammatory and antibiotics						
Treatment	**Children**		**Adults**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Regular chest physiotherapy	504	98.6%	542	95.4%	1046	96.9%
Antibiotics	450	88.1%	496	87.3%	946	87.7%
Oral only	282	55.2%	196	34.5%	478	44.3%
IV only	3	0.6%	10	1.8%	13	1.2%
Oral and IV	147	28.8%	255	44.9%	402	37.3%
Inhaled antibiotics	256	50.1%	353	62.1%	609	56.4%
Inhalation therapy (excluding antibiotics)	484	94.7%	519	91.4%	1003	93.0%
RhDnase	378	74.0%	430	75.7%	808	74.9%
Other mucolytics	103	20.2%	112	19.7%	215	19.9%
Hypertonic saline	296	57.9%	336	59.2%	632	58.6%
Bronchodilators	399	78.1%	421	74.1%	820	76.0%
Corticosteroids	203	39.7%	344	60.6%	547	50.7%
Intranasal steroids	251	49.1%	286	50.4%	537	49.8%
Oral anti-inflammatories	184	36.0%	348	61.3%	532	49.3%
Azithromycin	171	33.5%	327	57.6%	498	46.2%
Systemic corticosteroids	26	5.1%	32	5.6%	58	5.4%
NSAID	6	1.2%	57	10.0%	63	5.8%
Oxygen therapy	8	1.6%	28	4.9%	36	3.3%
Digestive and nutritional therapies						
Pancreatic enzymes	433	84.7%	440	77.5%	873	80.9%
Fat soluble vitamins (A, D, E and K)	446	87.3%	430	75.7%	876	81.2%
Proton pump inhibitor and/or H2 receptor blocker	227	44.4%	288	50.7%	515	47.7%
Ursodeoxycholic acid	136	26.6%	122	21.5%	258	23.9%
Enteral feeding	21	4.1%	4	0.7%	25	2.3%
Parenteral feeding	9	1.8%	15	2.6%	24	2.2%
Gastrostomy tube	27	5.3%	12	2.1%	39	3.6%
Prokinetics	14	2.7%	25	4.4%	39	3.6%
Other treatments						
Insulin therapy	15	2.9%	111	19.5%	126	11.7%
Oral therapy for diabetes	2	0.4%	26	4.6%	28	2.6%
Bisphosphonates	0	0.0%	11	1.9%	11	1.0%
Anti-conceptive therapy (females aged 12 and over)	14	18.9%	117	57.1%	131	47.0%
Use of psychopharmaca	11	2.2%	54	9.5%	65	6.0%
CFTR modulating therapy	19	3.7%	33	5.8%	52	4.8%

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Registries of rare diseases

A rare disease is, according to the European definition, a life-threatening or chronically debilitating condition from which not more than one person per two thousand citizens in the European Community suffer. Rare diseases are a complex and heterogeneous mosaic of more than 6,000 conditions, most of them caused by genetic aberrations (EURORDIS, 2018). In Belgium, approximately 1,230-1,300 persons have CF, which corresponds with a prevalence slightly higher than one person per then thousand citizens. Note that there is no widely endorsed incidence-related definition.

It is roughly estimated that one person out of seventeen is affected by a rare disease, which corresponds with approximately 400 million people worldwide (Genetic Alliance, 2016). Patients with rare diseases such as CF (estimated worldwide prevalence of at least 70,000), are scattered across countries. Hence, knowledge about such diseases is fragmented, and access to research material (e.g. biological samples) is often limited. This means that it is critical that investments in fundamental research are aligned with investments in dedicated infrastructure and international networks (e.g. registries).

An extensive overview of disease registries in Europe can be found online (Orphanet, 2018). In Europe, more and more registries are now available through various initiatives by hospitals, patient organizations and pharmaceutical companies, or as a combined effort (Eucerd/EMA Workshop report, 2011). Many countries have established CF registries. The coverage of these registries reveals that registries exist at regional, national and international level. Unfortunately, registries are not always compatible with each other and may not use the same coding system. Consequently, this hampers the collection of reliable epidemiological data on rare diseases across registries. In recent years, the impact and burden of disease is beginning to receive more attention from investigators in public health, and initiatives are better funded at national and European level (van Weely & Leufkens, 2013). As such, efforts are undertaken to combine various (national) databases into larger overarching international disease registries (Forrest, Bartek, Rubinstein, & Groft, 2011). An example in this respect is the European Cystic Fibrosis Society patient registry (ECFS), which not only combines many national CF registries into one international database, but also oversees the sharing of relevant information to its stakeholders. Indeed, the integration of data registries allows comparison of outcomes between CF centers within and between countries. In this way, practices that will enhance health care can be identified. For example, the finding that children with CF from Australia had better survival than patients from the United Kingdom, was attributed to the model of coordinated specialized center care in Australia and led to the development of specialized CF

care centers worldwide (Bell, et al., 2011). Approximately 42,000 CF patients are included in this European trans-national registry (European Cystic Fibrosis Society Patient Registry, 2017). Additionally, data concerning approximately 30,000 CF patients are found in the American trans-national registry (Cystic Fibrosis Foundation Patient Registry, 2015). It would be interesting to apply the methodology used in this dissertation on this overarching level. As such, the burden of CF could be calculated for all the registered patients worldwide.

Appendix 6: primary causes of death for reported cases

Primary causes of death for reported cases*		
Cause of death	**N**	**%**
Respiratory	62	*42.2*
Transplant	36	*24.5*
Other	30	*20.4*
Cancer	6	*4.1*
Cardiac	5	*3.4*
Liver	5	*3.4*
Suicide	3	*0.2*
Trauma	2	*1.4*
Unknown + missing	20	*13.6*

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Appendix 7: education level

Education level*						
Education level	**Children**		**Adults**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
No school	44	8.7%	61	9.4%	105	9.1%
Regular school / education attendance	454	90.1%	126	19.5%	580	50.4%
Has finished school/education	4	0.8%	455	70.4%	459	39.9%
Unknown	2	0.4%	4	0.6%	6	0.5%
Subtotal	**494**	0.0%	**646**	0.0%	**1150**	0.0%
Missing	8		72		80	
Total	**512**	0.0%	**718**	0.0%	**1230**	0.0%

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Appendix 8: social allowances or benefits and employment

Social allowances or benefits and employment*				
Description	**Children**		**Adults**	
	N	**%**	**N**	**%**
Additional child allowance	480	93.8%	87	12.1%
Income support (in adults)	.	.	158	22.0%
Disability allowance	1	0.2%	92	12.8%
Preferential tariff (in adults)	.	.	426	59.3%
Pension allowance (in adults)	.	.	11	1.5%
Integration support (in adults)	.	.	239	33.3%
Employment*	.	.	204	34.5%
*Amongst the 204 patients who said they were employed, 108 (52.9%) worked full time, 86 (42.2%) part-time while for 10 patients, this was unknown.				

*As reported by the BCFR report 2014 (Wanyama, Thomas, & Malfroot, 2014)

Appendix 9: neonatale screening: "Levensbelangrijke doorbraak voor mensen met muco"

Neonatale screening: "Levensbelangrijke doorbraak voor mensen met muco"

News article from www.muco.be (donderdag, december 21, 2017)

De Mucovereniging reageert verheugd op het nieuws dat er een principepsakkoord is bereikt met betrekking tot de invoering van neonatale screening op mucoviscidose in ons land. Deze screening zal ten laatste begin 2019 ingevoerd worden. Eindelijk! Door de invoering van een systematisch opsporingsbeleid zal mucoviscidose binnenkort bij de geboorte kunnen opgespoord worden.

Ulrike Pypops, Verantwoordelijke Dienst Families & Volwassenen met muco, reageert bijzonder tevreden op het nieuws: Als Mucovereniging hebben we meer dan 7 jaar actie gevoerd om ervoor te zorgen dat neonatale screening op muco ook eindelijk in ons land zou ingevoerd worden. Binnenkort is het eindelijk zover. Deze doorbraak is van levensbelang voor elke pasgeborene met muco in ons land. Daardoor zullen zij optimaal kunnen genieten van nieuwe medicijnen die in de toekomst beschikbaar zullen worden."

Mucoviscidose is de meest voorkomende erfelijke levensbedreigende ziekte in België. De invoering van een systematisch opsporingsbeleid of neonatale screening is een basisvoorwaarde om kinderen met muco zo snel mogelijk te laten genieten van de gespecialiseerde zorg die ons land aanbiedt. Door hen tijdig de nodige zorg te verlenen, kan groeiachterstand, ondervoeding en onherstelbare longschade vermeden worden. Voor deze kinderen is het dus van levensbelang dat zij zo vroeg mogelijk doorverwezen worden naar een gespecialiseerd ziekenhuis.
De voordelen van neonatale screening zijn duidelijk, aldus Ulrike Pypops, Verantwoordelijke Dienst Families & Volwassenen met muco: "Kinderen die na de leeftijd van twee maanden op basis van symptomen gediagnosticeerd worden (en dus niet via neonatale screening) kennen een slechter klinisch verloop, ondanks het feit dat ze meer chronische therapieën krijgen gedurende de eerste 10 levensjaren. In 2010 concludeerde het Federaal Kenniscentrum voor de gezondheidszorg dat dankzij neonatale screening voor mucoviscidose de mediane diagnoseleeftijd van ongeveer 10 maanden zou kunnen dalen naar minder dan twee maand. Het nut van een opsporingsprogramma voor pasgeborenen kan dus niet onderschat worden!"

Ondanks deze feiten bleef het dossier van neonatale screening de voorbije jaren aanmodderen. Om het dossier uit het slop te krijgen, lanceerde de Mucovereniging zowel in 2011 als in 2016 een petitieactie die in totaal door meer dan 75.000 mensen ondertekend werd. Ook achter de schermen bleef de Mucovereniging volop ijveren voor een doorbraak. De Mucovereniging is dan ook verheugd dat pasgeborenen mede dankzij deze inspanningen in 2019 eindelijk gescreend zullen worden op mucoviscidose.

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Appendix 10: factors influencing quality of life in patients with cystic fibrosis: a systematic review

FACTORS INFLUENCING QUALITY OF LIFE IN PATIENTS WITH CYSTIC FIBROSIS: A SYSTEMATIC REVIEW

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Words: 5350

Keywords: Quality of life, factors, clinical, sociodemographic, cystic fibrosis, Cystic Fibrosis Questionnaire, management implications

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Table of contents

Abstract

Objective: to conduct a systematic review of the literature concerning the relationships between clinical and sociodemographic factors and quality of life in patients with cystic fibrosis.

Background: clinical research and practice has significantly prolonged life expectancy of patients with cystic fibrosis, and continues to do so. Emphasis in the management of patients with cystic fibrosis should therefore now increasingly be on improving quality of life.

Methods: a systematic review of studies using validated disease specific measurement instruments was performed.

Findings: previous research focused mainly on factors concerning the primary disease, whereas recent research also includes more remote factors, such as psychological factors and other interdisciplinary factors. These factors seem to be important in patients with cystic fibrosis as they have profound effects on their quality of life.

Relevance: in addition to the classic clinical follow-up of patients with cystic fibrosis, emphasis should now be on psychological support in a continuously growing multidisciplinary setting, in order to enhance their quality of life.

Introduction

Quality of life (QoL) measurements are a way of including the patients' perspective in clinical practice and research. As a multidimensional construct, which includes physical, psychological and social well-being and functioning, it provides crucial patient information neglected by other outcome measures (Abbott, Hart, Havermans et al., 2011) and reflects the whole spectrum of a patient's daily life (Abbott, Webb and Dodd, 1997). Research through the past decades shows an increasing trend of providing data on certain life domains that contribute to QoL. Important to recognize is the fact that QoL outcomes are not necessarily in line with the more traditional outcome measures, such as clinical variables. Nonetheless, one can put forward that QoL represents the true endpoint to be achieved. This is because it is intended to evaluate the impact of the disease, and everything that comes with it, on the wider aspects of the patient's life.

Clinical research and practice has significantly prolonged life expectancy of patients with cystic fibrosis, and continues to do so. Emphasis in the management of patients with cystic fibrosis should therefore now increasingly be on improving quality of life.

Theoretical framework

What is cystic fibrosis?

Cystic fibrosis (CF) is an autosomal recessive and life-shortening disorder caused by defects in the CFTR gene on chromosome 7 (Royce and Carl, 2011). This gene codes for a transmembrane regulator (CFTR), a protein that acts as a chloride channel, and malfunctions in case of genetic alterations that effect the CFTR gene. The result is an increased production of thickened secretions in the internal organs. Lung and pancreatic secretions cause the biggest problems with respectively lung damage and maldigestion/malabsorption as their consequences.

How to assess QoL?

Assessing QoL is something different than asking "how are you doing". Appropriate instruments are needed so that a standardized, valid and reliable way of collecting patient information is achieved. In the past, QoL information has been randomly collected and subsequently, results are not always scientifically valid or comparable. It is fortunate to see that substantial efforts have been made to validate and optimize

QoL measuring instruments so that reliable claims can be made (Abbott and Hart, 2005; Toucheque and Etienne, 2014).

Reaching consensus about conceptual and operational measurements of QoL has proven to be an obstacle. It is indeed so that different instruments provide different information, even regarding similarly named life domains. This limitation can explain, in some degree, some inconsistent findings regarding the relationships between CF and QoL.

Patient's perceptions are crucial

Also, be aware that when using a particular measurement instrument, the implication is that for example physical and social functioning are major aspects of QoL. This erroneously implies that the frail or disabled must have a lower QoL than younger, active people. Bear in mind that QoL is much more than this and how important these aspects are is dependent on the patient's perception of what augments or diminishes their QoL. In this regard, it is inappropriate for clinicians and researchers to impose their perceptions concerning QoL on their patients. The domains and items that contribute to a QoL measurement instrument should come directly from the patients themselves. A comprehensive definition that represents those aspects that are perceived as important to the patient is essential. It is important to accept the fact that perceptions and beliefs about QoL are extremely complex and individually determined. Note that it can be tricky to establish standardized QoL measurement instruments while still capturing an individual emphasis on QoL.

Measuring QoL reveals additional information

An important note and a general rule is that improved symptoms not necessarily correlate with improved QoL (Abbott, 2009). Furthermore, the identification of how symptoms impact on QoL is crucial. Think about weight issues for example: a therapy that increases BMI might be seen as successful if a patient gains weight, but this may not be perceived in the same way by the patient who wants to maintain a slim appearance. Also, be aware of the fact that, somewhat surprisingly, CF patients often report very high QoL scores. A phenomenon called "response shift" may be responsible for this finding: a re-evaluation of the meaning of life with subsequent adaptation to changing conditions (Abbott, 2009). This means that ceiling effects occur

and it can potentially be difficult to demonstrate QoL improvements, after installing a new therapy for example.

Categories of QoL measurement instruments

Three categories of measurement instruments exist (Abbott et al., 1997). First, generic measures are developed for general use in a variety of diseases. Therefore they are restricted in their usefulness for a detailed examination of specific diseases such as CF. These instruments contain unnecessary items for CF patients, yet they do not include some relevant aspects of CF. This has lead, (un)fortunately, to researchers developing their own, non-validated measurement instruments. Obviously, methodological problems arise, especially with regard to the comparability across studies. The SF-36 is a widely used example, although its sensitivity to changes in cystic fibrosis has not been validated. Secondly, utility measures such as the Quality of Well-Being Scale, exist. These quantify QoL by a single numerical value and allow cost-utility analysis. Reducing QoL to a single number however is arbitrary. It does not allow for examination of the different dimensions of QoL, and their sensitivity to detect changes in CF treatments is also not supported by evidence. Thirdly, disease-specific measurements are developed with a greater responsiveness to changes in QoL in particular diseases, such as CF. Also note that even specific airway measures are not specific for a multisystem disease like CF. Rather than trying to make existing measures “CF friendly” it is advisable to use instruments specifically designed for CF. In this manner, irrelevant aspects can be discarded and sensitivity for relevant aspects can be improved. The Cystic Fibrosis Questionnaire (CFQ), which has versions for children (≥8 years old), teens (≥14 years old) and adults (for which a revised version is available: CFQ-R), and the similar Cystic Fibrosis Quality of life questionnaire (CFQoL) are the only measurement instruments that have undergone validation and have shown clinical sensitivity for use in a CF context (Figure 1: CFQ(-R) domains). Note that individualized profiles are also possible to measure QoL. These instruments have the advantage of being specific to the individual, but are more complex to administer, interpret, and compare.

Figure 1: CFQ(-R) domains

Important life domains according to CFQ(-R)	
Physical Functioning	Body Image
Vitality	Treatment Burden
Emotional Functioning	Health Perceptions
Social Functioning	Respiratory Symptoms
Role Functioning	Digestion
Eating Disturbances	Weight

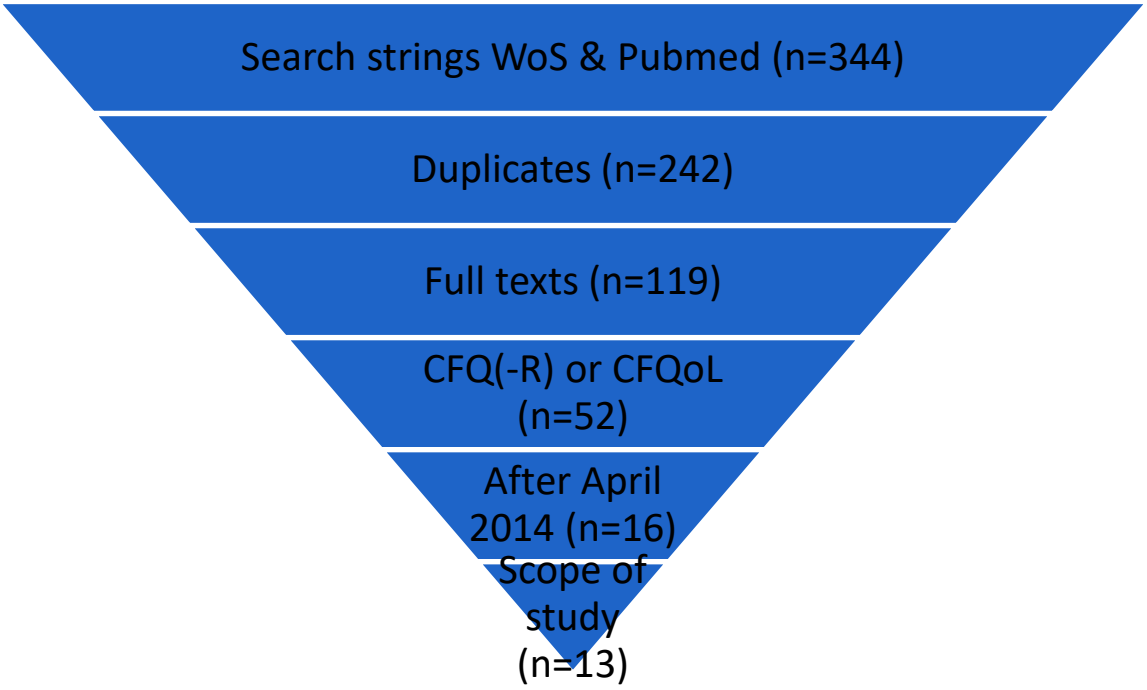
Methodology

Search strategy

A systematic review of studies concerning the relationships between clinical and sociodemographic factors in CF patients and QoL was conducted (Figure 2: Search strategy). In essence, this review summarizes the current state of affairs regarding those factors and QoL in CF, building further on the most important findings of previously conducted reviews.

Web of Science and Pubmed were searched to allocate all papers written in English. The search string for Pubmed was (Appendix 1: Printscreen of Pubmed search): ((quality of life[Title] OR health-related quality of life[Title] OR health related quality of life[Title] OR life quality[Title]) AND (cystic fibrosis[Title] OR mucoviscidosis[Title])) NOT non-cystic fibrosis Filter: English. This lead to 137 results. The search string for WoS was (Appendix 2: Printscreen of WoS search): TI= (quality of life OR health-related quality of life OR health related quality of life OR life quality) AND TI= (cystic fibrosis OR mucoviscidosis) AND LANGUAGE: (English). This lead to 206 results. Endnote was able to find duplicates in both databases and this resulted in 242 unique articles, of which 15 had characteristics of a review. Further, the availability of a full text version was necessary. 119 articles, of which 10 reviews, were assessed based on their abstract. Only articles using the CFQ(-R) or slightly different CFQoL measurement instrument were included, as to avoid conclusions based on non-validated methods (52 articles). As previous reviews exist, which will be summarized here, this review focusses on articles published between April 2014 and October 2017 (16 articles). Full reading resulted in the exclusion of some articles due to methodological issues or non-compatible scope of the study. Only studies investigating the influence of sociodemographic and clinical factors on QoL were included in this review (13 articles).

Figure 2: Search strategy



Quality assessment

Considerable concern about the reliability of QoL studies exist. Poorly designed studies are likely to produce biased results and hence misinformed decision-making. Inadequate reporting means that readers are not able to assess the validity and usefulness of the conclusions. Both an appropriate QoL measurement instrument and sound methodology are necessary for valid inferences about QoL related issues. Therefore, all studies were subjected to the STROBE guidelines (von Elm, Altman, Egger et al., 2014) (Appendix 3: STROBE guidelines applied, for a detailed example of the quality assessment used).

Reporting of results

A summary MS Excel sheet was used to record the following: Author, aim of the study, population size and age range, measurement instrument, found correlations and conclusions (Table 1: Summary of studies). An overview of the correlations between QoL domain scores and clinical and sociodemographic factors was also constructed using MS Excel (Table 2: Overview of correlations between QoL and clinical and sociodemographic factors).

Results from previous reviews

Lung function as the first factor to influence QoL

In the past, research focused on more functional and/or physical domains of QoL, which was always measured by general (in-house) measurement instruments and in small patient populations (Abbott et al., 1997). This was however the first step in the area of QoL measurement of CF. The most important findings in the last decade of the 20th century were consistently significant correlations between lung function parameters and the functional and/ or physical aspects of. Nonetheless, differences in pulmonary function could only explain about 10% of the variability of QoL, which means that other factors were yet to be discovered. Then already it was also stated that this functional status predicted survival time. Consequently, it can be used as an overall measure of health. Significant benefits on different domains of QoL scores were also shown after heart-lung transplantation in three out of for studies. Another finding is that gender affected some QoL domain scores, with female patients getting the short end of the stick.

The way of treatment administration has its consequences

The next review confirmed positive correlations between lung function and QoL (Abbott & Gee, 2003). Nonetheless, once again were the conclusions drawn from inadequately powered or inaccurately designed studies. Another study tested the effect of home versus hospital administered intravenously antibiotic therapy on QoL in 17 patients. Overall, QoL improved when therapy is administered at home and the simpler the treatment administration (e.g. prepared by the pharmacist versus self-preparation), the higher the QoL improvement. Two studies strongly suggest a positive correlation between physical exercise and QoL (Abbott & Hart, 2005).

Psychological and other factors find their way into the research domain

Another review of Abbott (2009) reported relationships between age and QoL. Increasing age was associated with poorer physical and social functioning, but somewhat surprisingly a better QoL regarding concerns for the future. Another finding is that female CF patients consistently reported poorer QoL than male patients, and this for all ages and almost all domains, which confirms previous research. Interestingly, female patients seemed to have a more accurate perception of their objective clinical status than men. A higher QoL in employed patients in contrast to

non-employed patients with similar age and disease severity was also reported. Although, full-time work was negatively associated with QoL, possibly due to the fact that CF treatments very time consuming and thus incompatible with busy schedules. Cross-cultural differences in the perception of CF and its relationships with QoL have been reported. Forced expiratory volume (FEV1) percentage of predicted is the most important indicator of disease status and those with higher values tend to report a better QoL, again stressing the importance of lung function. Further factors with a negative impact on QoL include: urinary incontinence, enteral tube feeding, pain, diabetes, having an intravenous access device and being on the transplantation waiting list. The way of coping (e.g. rumination versus seeking social support or optimism versus pessimism) also seems to play a substantial role in how patients perceive their QoL, and interventions can be deduced from this finding. Other psychosocial factors, such as anxiety and depression, have been found to affect QoL, so that screening for and treating those illnesses may improve QoL. When investigating the effect of time, the most important finding is the stability of QoL, with oscillation of scores around a personal average, by the way often independent from the course of FEV1. Lung transplantation, as the most radical intervention in terms of clinical improvement, resulted in much higher QoL. Some domains, most notably the physically oriented domains, seem to be predictive for survival time. This is important, because this means that CF patients seem to be aware of something important that is not identified by traditional risk factors. Furthermore, this potentially means that cognitive and behavioral interventions can prolong survival time.

New factors are still being discovered

The most recent review (Habib, Manji, Wilcox et al., 2015), which used the most stringent exclusion criteria, showed that FEV1 % predicted and pulmonary exacerbations have the broadest impact on QoL. Male subjects tended to report higher physical functioning and lower body image scores compared to female subjects. This can be explained by the gender related preferences of weight: men want to be more muscular, women want to be skinny. Age was negatively correlated with physical functioning and treatment burden. Employed patients reported higher scores of QoL, particularly when it is a source of a meaningful life and not a source of too much stress. Depressive symptoms are associated with worse QoL. Lower BMI was associated with

worse body image and less vitality. Borderline significant associations were found between P. Aeruginosa infection and QoL.

The most important remark on the reviews conducted in the past is that the heterogeneous use of non-validated measurement instruments affects the validity of conclusions. Therefore, this review will only address those studies with a sound methodology in which properly validated measurement instruments are used. Indeed, it may be more ethical not to include inappropriately designed studies at all, so that misleading results can be avoided.

Results from this review

A summary of studies conducted after April 2014, as well as an overview of the reported associations, can be consulted below and should be accompanying the reader during the next section (Table 1: Summary of studies and Table 2: Overview of correlations between QoL and clinical and sociodemographic factors).

Things get worse in adolescence

Van Horck, Winkens, Wesseling et al. (2017) measured QoL at baseline and one year later and found significant improvements in CFQ-R total scores as well as most domain scores. The authors speculate that merely participating in an intensive study improved QoL because of the extra attention that patients get, e.g. the extra contacts with the nurses and physicians of the CF team. Better treatment adherence during the study might strengthen this observed improvement. However, as the baseline age increases, QoL improvement weakens and becomes negative in children older than 12. An explanation for these findings may be a better coping style during childhood, in contrast with the problems related to CF in adolescents. An alternative explanation for the drop in QoL in children of 12 years and over may be the consequence of the increasing disease severity and treatment intensity, as reflected by the scores of the treatment burden domain and the respiratory symptom domain. In addition, the number of pulmonary exacerbations was found to have an impact on treatment burden score. This makes sense, as they require additional therapies.

Depression is common and may lead to low therapy compliance

Knudsen, Mortensen, Jarden et al. (2016) demonstrated that young adults with CF have difficulties with adherence to their treatments, show frequent symptoms of depression, and have an impaired QoL. Furthermore, symptoms of depression and reduced QoL were significantly correlated. These results support the hypothesis that CF patients may fail to perform their prescribed treatments due to mental health problems, such as depression. Interestingly, being depressed affects all QoL domains, but treatment burden. Thus, the findings suggest that alertness for and treatment of depression is an important issue. In addition, dubious perceptions of treatment burden and poor adherence should be addressed using systematic, behavioral interventions. Similar results are reported for work or educational disability. This study recommends annual screening for depression and other mental illnesses in those with CF aged 12 and older. Young adults are likely still transitioning to adult roles, including starting a career and family, which according to Chick and Meleis (1986) may be characterized by disorientation, distress, irritability, anxiety and depression.

What about sexual satisfaction?

Aguiar, Marson, Gomez et al. (2017) report that sexual satisfaction is now more important than ever, as survival time has increased and more CF patients become sexually active. Sexual satisfaction is related with higher QoL scores on all life domains but treatment burden and weight, and should therefore be a topic in psychological consults. Male patients scored better on physical, emotional and sexual aspects compared to women. The effects of exercise tolerance on QoL were of similar nature.

Sleep quality is important

Forte, Barni, Perin et al. (2015) used a battery of tests to show associations between several CFQ domain scores and demographic variables (sex, age at diagnosis, current age), clinical scores (pulmonary function, BMI, 6MWD, pulmonary arterial systolic pressure) and sleep quality (apnea-hypopnea index, arousal index). The correlation between sleep quality and the physical, vitality and health perception domains of QoL seems substantial and should therefore be addressed by appropriate attention. Special attention should go to the effects of nocturnal feeding.

Longitudinal study designs can have added value

Abbott, Morton, Hurley et al. (2015) were able to identify a great number of demographic and clinical variables impacting QoL over time. This longitudinal work confirms the cross-sectional findings that advancing age, sex, BMI, lung function and transplantation are important predictors of outcome across many domains of QoL. Variables which did not consistently emerge as important in cross-sectional regression models have also now been shown to be independent predictors of QoL longitudinally. These include BMI, having a TIVAD, CF-related diabetes and B. Cepacia complex.

Hospitalization negatively impacts quality of life

Bodnar, Kadnar, Holics et al. (2014) showed that malnutrition, hospitalization and current PA infection have a significant and negative impact on QoL in CF patients. Passive smoking, parental educational level and chronic diseases of parents did not affect the QoL of CF patients, although reporting of these items may have been biased.

Additional information may come from rather unexpected corners

Kilcoyne, Lavelle, McCarthy et al. (2016) found that chest abnormalities, assessed by radiologists on CT scans, are independent predictors of QoL scores. The most important radiological abnormality was lung consolidation, with effects on the physical, vitality and respiratory QoL domains. This is the first study to investigate radiological associations with QoL in CF patients. The results show that (QoL in) CF can and should be managed in an ever-growing multidisciplinary approach. However, although teens and adults are included, the authors state to be careful when extrapolating these findings to a pediatric population.

Coping styles affect emotional and social quality of life

Mc Hugh, Mc Feeters, Boyda et al. (2016) showed that coping is important when considering QoL, as it influences social and emotional functioning domains. The so-called positive coping styles improved these life domains, in contrast with negative coping approaches. This is still a rather unmet psychological need and its management should be included in the follow-up of CF patients.

Mental illnesses other than depression also impact quality of life

Olveira, Sole, Girón et al. (2016) found that symptoms of depression and anxiety are increased in CF patients. These symptoms are correlated with worse QoL scores. Interestingly, all QoL domain scores were affected except the vitality domain. A possible explanation is that atypical depressions are more common in CF patients compared to other patients with mental illness. It seems appropriate to screen for depression, anxiety, and possibly other mental disorders in order to improve CF patient's QoL. A lower level of education was predictive of psychological symptoms, and warrants extra attention.

Once again the importance of pulmonary function is confirmed

Moco, Lopes, Vigário et al. (2015) conducted a cross-sectional study with limited sample size and found that different parameters for pulmonary function are associated with QoL in CF patients. These correlations were found for different CFQ-R domains, even some of them were not directly related to pulmonary function. Interestingly, the forced vital capacity parameter was negatively associated with treatment burden and weight symptoms. Further research of the relationships between pulmonary tests and QoL is desired. Nonetheless, this study confirms the complexity of the disease and suggests that pulmonary function may reflect the overall status of a patient's disease severity. It is possible, for example, that patients with disabling respiratory symptoms become socially isolated.

Cross-cultural differences exist

Borawska-Kowalczyk, Bodnar, Meszaros et al. (2015) found different QoL scores between Polish and Hungarian children with CF. Although both are Eastern European countries, differences on multiple aspects exist between the two. Cultural differences might lead to different interpretations of the CFQ-R questions. Second, CF care trajectories in both countries are different. Thirdly, a different health insurance system, which affects financial burden might be an important factor. A major limitation of the study was the fact that Hungarian patients' mean age was significantly lower than that of the Polish children. Further, this study found that regular school attendance significantly improves multiple QoL domains. So, it is important that the decision for home education is not taken lightly.

Chronic rhinosinusitis is a prevalent comorbidity

Habib, Buxton, Singer et al. (2015) found a significant association between chronic rhinosinusitis and the respiratory functioning domain of the CFQ-R questionnaire. This is rather easy to understand, as many questions of this domain are related with symptoms of rhinosinusitis. Despite the high prevalence of chronic rhinosinusitis in CF patients, evidence based guidelines for its management are yet to be established.

Quality of life as a personal trait

Debska and Mazurek (2015) performed a longitudinal study with QoL measurements at baseline and one year later. They found that, despite important disease progression, this one year period could not reveal significant changes in QoL. These results contrasted with the findings of a previously mentioned study (Van Horck et al., 2017). Interestingly, the authors suggest that QoL should be considered as a trait, rather than a condition or state. This personal trait may have a bigger impact on QoL than any clinical variable. Nonetheless, they found interrelationships between some variables and individual QoL change, of which the most important was that worse lung function at baseline predicted several QoL domain scores. Physical activity and pulmonary exacerbations also had an effect on QoL. Again, this emphasizes the need for the optimization of lung functionality. Place of residence, which can be seen as a micro-cultural environment, was also found to be associated with QoL, with rural areas showing worse scores.

Table 1: Summary of studies

Authors (year)	Aim of the study is to...	Population size (age range)	Correlations	Conclusions	Measurement instruments
Van Horck et al. (2017)	Investigate the longitudinal (1 year) effect of treatment and clinical variables on QoL.	49 (6-18)	The treatment burden domain correlated with the exacerbation rate. All scores improved significantly during the year except digestive symptoms. The mean total CFQ-R score was 68.6 at T = 0 and 76.6 at T = 12. Almost all domain scores also improved significantly, from 3.3 points (respiratory symptoms domain) to 31.7 points (physical functioning domain). Only age at baseline had a strong longitudinal association with change of CFQ-R total score in 1 year	In the group as a whole, QoL improved significantly over time. However, changes over time were significantly influenced by age: below 12 years of age, QoL improved in most patients whereas a deterioration was observed in most children >12 years. Strategies how to preserve or ideally to improve QoL in adolescence should be developed.	CFQ-R
Knudsen et al. (2016)	To examine the relationships among treatment adherence, symptoms of depression and QoL in a population of young adults with CF.	67 (18-30)	MMAS-8 was completed by 66 participants. 74.2 % scored in the low adherence range, 18.2 % had medium adherence, and 7.6 % reported high adherence. The MDI was completed by all participants. MDI scores indicated symptoms of depression in 32.8 %, of which 19.4 % expressed symptoms of moderate or severe depression. MDI and MMAS-8 scores were negatively associated, indicating that symptoms of depression were associated with worse adherence, $r = -0.412$, $p < 0.001$. Symptoms of depression were associated with low QoL scores ($p < 0.01$) on all QoL domains except for the domain treatment burden. No associations were found between the MMAS-8 scores and the CFQ-R.	Despite improved physical health, many patients with CF report poor adherence, as well as impaired mental wellbeing and QoL. Thus, more attention to mental health issues is needed.	Morisky Medication Adherence Scale (MMAS-8), Major Depression Inventory (MDI), CFQ-R
Aguiar et al. (2017)	To investigate QoL, sexual satisfaction (SS) and physical performance in CF patients	52 (≥ 18)	There was a positive correlation between CFQ domains and SSQ questions. The CFQ showed a positive correlation with peripheral oxygen saturation of hemoglobin (SpO2) and the distance walked in the 6MWD. The SSQ showed positive correlation with the distance walked. Male patients showed better scores in the emotional CFQ domain, better performance in SSQ and physical performance.	There was a correlation between CFQ, SSQ and 6MWT in CF. QoL surveys should therefore assess the domain ‘‘sexuality’’, as it influences patients' lives.	CFQ, Sexual Satisfaction Questionnaire (SSQ), 6 Minute Walk Distance (6MWD)
Forte et al. (2015)	To evaluate the association between clinical parameters, lung function, sleep quality and polysomnographic variables and CFQ.	51 (≥ 16)	For QoL scores, age at diagnosis, clinical score, and sleep quality index were associated with the physical functioning domain; the percent-of-predicted 6MWD and pulmonary arterial systolic pressure were associated with the role domain; sex and sleep quality index were associated with the vitality domain; the apnea-hypopnea index was associated with the emotional functioning domain; sex and body mass index (BMI) were associated with the body image domain; the percent-of-predicted 6MWD and sleep quality index were associated with the health perception domain; age, sex, BMI, and arousal index were associated with the weight domain; age, sex, percent-of-predicted FEV1, percent-of-predicted 6MWD, and pulmonary arterial systolic pressure were associated with the respiratory symptom domain; and the clinical score was associated with the digestive symptom domain.	Age at diagnosis, clinical score, sleep quality score, 6MWD, sex, apnea-hypopnea index, BMI, current age, arousal index, FEV1, and pulmonary arterial systolic pressure were predictors of QoL scores.	CFQ, Pulmonary function, Clinical evaluation, Echocardiography, 6MWD, Sleep questionnaires, Polysomnography (and WHOQOL-BREF)

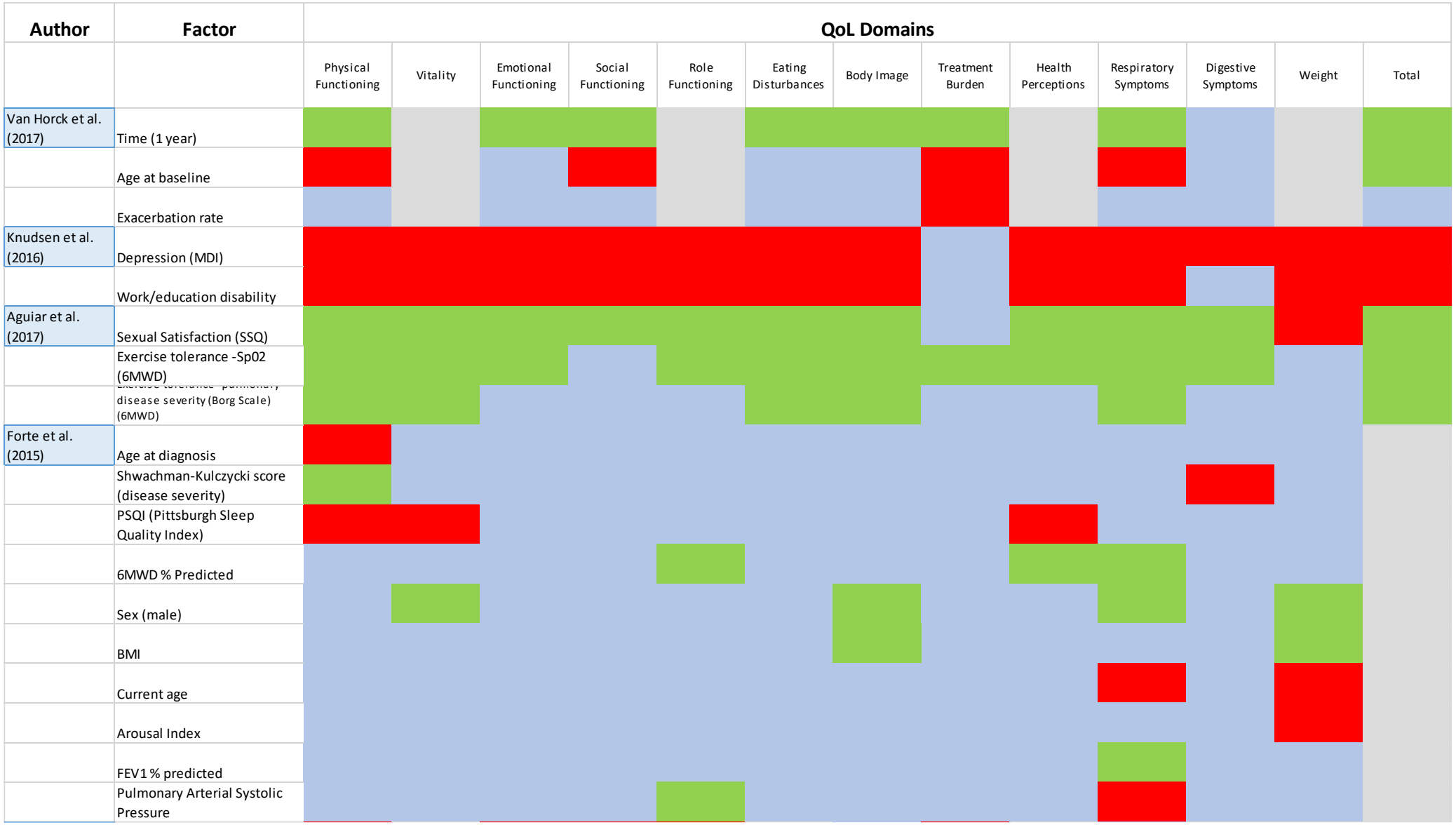
Table 1: Summary of studies (continued)

Authors (year)	Aim of the study is to...	Population size (age range)	Correlations	Conclusions	Measurement instruments
Abbott et al. (2015)	To investigate the association between QoL and demographic (age, gender) and clinical measures (FEV1 % predicted, BMI, CF-related diabetes, B. Cepacia complex, totally implantable vascular access device, nutritional and transplant status) in an observational longitudinal setting (12 year follow-up).	234 (14-48)	Demographic and clinical variables were identified as being significant for QoL over time. In addition to lung function, transplant status, age, having a totally implantable vascular access device, CF-related diabetes, BMI and B. Cepacia complex impacted on many QoL domains longitudinally. Gender was important for the domain of body image.	Demographic and changes in clinical variables were independently associated with a change in QoL over time. Compared with these longitudinal data, cross-sectional data are inadequate when evaluating the relationships between QoL domains and key demographic and clinical variables, as they fail to recognise the full impact of the CF disease trajectory and its treatments on QoL.	CFQoL, Pulmonary function, Clinical evaluation
Bodnar et al. (2014)	To evaluate factors affecting CF patients' QoL and to assess the level of agreement on QoI between children and their parents.	59 (8-30)	Lower CFQ-R scores were detected in hospitalised patients than in non-hospitalised patients in their Physical functioning domain. PA-infected patients had QoL scores that were significantly worse in the Body image ($p < 0.01$) and Respiratory symptoms ($p < 0.05$) domains than the PA culture-negative patients. Patients with a low BMI (<25th BMI pc) had significantly lower scores in the Eating, Body image and Treatment burden domains, than the adequate-weight patients (>25th BMI pc) ($p < 0.01$). A strong child–parent agreement was found in the Physical functioning domain ($r = 0.77$, $p < 0.01$). Passive smoking, parental educational level and chronic diseases of parents do not affect the QoL of CF patients.	Passive smoking, parental educational level and chronic diseases of parents do not affect the QoL of CF patients. In contrast, hospitalisation, PA infection and malnutrition have a significant and negative impact on patients' QoL and the clinical severity of the disease. Parents and children were consistent in their scoring of symptoms and behaviours that were observable.	CFQ-R, Lung funtion, Shwachman-Kulczycki (disease severity), BMI, extra questionnaire
Kilcoyne et al. (2016)	To evaluate the relationship between lung parenchymal abnormalities on chest CT and QoL in adult CF patients	101 (15-48)	There were 18 inpatients and 83 outpatients. For the cohort of inpatients, CT abnormalities were significantly ($P<0.005$ for all) associated with Respiratory Symptoms (Air Trapping), and also with Social Functioning (Consolidation) and Role Functioning (Consolidation). For outpatients, CT abnormalities were significantly ($P<0.005$ for all) associated with Respiratory Symptoms (Consolidation) and also with Physical Functioning (Consolidation), Vitality (Consolidation, Severity of Bronchiectasis), Eating Problems (airway wall thickening), Treatment Burden (Total CT Score), Body Image (Severity of Bronchiectasis) and Role Functioning (Tree-in-bud nodules). Consolidation was the commonest independent CT predictor for both inpatients (predictor for 2 domains) and outpatients (predictor in 3 domains).	Chest CT abnormalities are significantly associated with QoL measures in adult CF, independent of clinical or spirometric measurements.	CFQ-R, Bhalla score (CT abnormalities)
Mc Hugh et al. (2015)	To examine which specific coping styles were positively or negatively associated with social and emotional QoL in CF patients.	122 (≥ 18)	Higher substance abuse and disengagement was associated with lower emotional QoL whereas greater use of religion, instrumental coping and acceptance was positively associated with emotional QOL. Active coping was linked to better social QoL and a negative association was reported between distraction coping with both emotional and social domains.	Ascertaining which coping factors enhance or diminish emotion and social well-being is an important component of QoL research.	CFQ-R

Table 1: Summary of studies (continued)

Authors (year)	Aim of the study is to...	Population size (age range)	Correlations	Conclusions	Measurement instruments
Olveira et al. (2016)	To investigate the relationship of self-reported symptoms of depression and anxiety with QoL.	336 (≥ 18)	12.2% had elevated depression-related scores, 29.7% had elevated anxiety-related scores (HADS≥8). After adjusting for confounders, only less education, intravenous antibiotics, psychiatric medications and psychotherapy were significantly associated with elevated psychological symptoms. Specifically, regardless of lung function, patients who were depressed or anxious reported worse QoL.	Patients with depressive and/or anxiety symptoms had significantly lower scores for most scales of the CFQ-R (except vitality and weight for depression and vitality for anxiety).	CFQ-R, HADS (Hospital Anxiety and Depression Scale)
Moço et al. (2015)	To evaluate the association between respiratory function, functional capacity and QoL.	21 (≥ 18)	The following associations were found between pulmonary function and CFQ-R domains: - Forced vital capacity (FVC (%)) and treatment burden and digestive symptoms ($r = -0.433$, $p < 0.05$; $r = -0.443$, $p < 0.05$, respectively). - FVC ratio (FEV1/FVC (%)) and physical functioning, social and respiratory symptoms ($r = 0.5$, $p < 0.05$; $r = 0.58$, $p < 0.01$; $r = 0.45$, $p < 0.05$, respectively). - Residual volume (%) and physical functioning ($r = 0.49$, $p < 0.05$). - Airways' resistance and physical functioning and emotional functioning ($r = -0.44$, $p < 0.05$; $r = -0,46$, $p < 0.05$, respectively). - Carbon monoxide diffusing capacity (%pred) and physical functioning ($r = -0,51$; $p < 0.05$).	Adults with CF have reduced QoL, which in part is explained by the severity of the pulmonary disease.	CFQ-R, 6MWD, pulmonary function tests
Borawska-Kowalczyk et al. (2015)	To compare QoL in CF patients from two Eastern European countries (Poland & Hungary).	141 patients (6-18) 102 parents	In the patient group, a significant difference between the two countries was found only in Treatment burden, whereas in the parent group, there were significant differences in Treatment burden, Emotional functioning, Eating and Digestive symptoms. School attendance was revealed as an important factor influencing QoL.	Observed differences in the evaluation of QoL may be caused by different healthcare charachteristics between countries, supplemented by cultural influences.	CFQ-R
Habib et al. (2015)	To determine the prevalence of chronic rhinosinusitis among adults with CF and to evaluate the impact of chronic rhinosinusitis on QoL.	113 (≥ 19)	Following adjustment for sex and lung function, individuals with chronic rhinosinusitis reported significantly worse scores on the respiratory symptoms domains compared with their counterparts without chronic rhinosinusitis (regression coefficient, 23.93; 95% CI, 28.02 to 0.15).	The majority of adults with CF have evidence of concomitant chronic rhinosinusitis, which is independently associated with worse respiratory functioning. Chronic rhinosinusitis should be diagnosed and managed to optimize the QoL of adults with CF.	CFQ-R, Clinical evaluation
Debska et al. (2015)	To determine the effects of clinical factors, physical activity, and sociodemographic variables on 1-year changes in QoL in Polish adolescents and adults with CF.	67 (14-37)	The highest scores in both QoL examinations came from the domains of physical and social functioning, and the lowest from future concerns, body image, and career concerns. No significant changes of QoL scores were documented over a period of 1 year. Patients with better baseline spirometry results more frequently reported an improvement in the treatment issues (subjects with FEV1 50% of predicted, P=0.020) and in the career concerns (patients with FVC 50% of predicted, P=0.039). The improvement in the career concerns also depended upon daily physical activity (P=0.024), which was shown to modulate future concerns (P=0.032), along with place of residence and living conditions (P=0.003). Moreover, the time elapsed from the last pulmonary exacerbation was related to the change in social functioning (P=0.026).	When planning treatment, attention should be paid to interventions which may improve QoL. Systematic chronic therapy improves lung function, related to treatment issues and career concerns. Maintaining good physical condition and activity may positively influence future and career concerns. Special attention must be devoted to patients living in rural areas and enduring difficult living conditions, as they are especially vulnerable to deterioration in future concerns.	CFQoL, Pulmonary function

Table 2: Overview of correlations between QoL and clinical and sociodemographic factors



Author	Factor	QoL Domains												
		Physical Functioning	Vitality	Emotional Functioning	Social Functioning	Role Functioning	Eating Disturbances	Body Image	Treatment Burden	Health Perceptions	Respiratory Symptoms	Digestive Symptoms	Weight	Total
Van Horck et al. (2017)	Time (1 year)													
	Age at baseline													
	Exacerbation rate													
Knudsen et al. (2016)	Depression (MDI)													
	Work/education disability													
Aguiar et al. (2017)	Sexual Satisfaction (SSQ)													
	Exercise tolerance -Sp02 (6MWD)													
	disease severity (Borg Scale) (6MWD)													
Forte et al. (2015)	Age at diagnosis													
	Shwachman-Kulczycki score (disease severity)													
	PSQI (Pittsburgh Sleep Quality Index)													
	6MWD % Predicted													
	Sex (male)													
	BMI													
	Current age													
	Arousal Index													
	FEV1 % predicted													
	Pulmonary Arterial Systolic Pressure													

Table 2: Overview of correlations between QoL and clinical and sociodemographic factors (continued)

Author	Factor	QoL Domains												
		Physical Functioning	Vitality	Emotional Functioning	Social Functioning	Role Functioning	Eating Disturbances	Body Image	Treatment Burden	Health Perceptions	Respiratory Symptoms	Digestive Symptoms	Weight	Total
Abbott et al. (2015)	Age (5 year increase)													
	BMI (1 unit decrease)													
	TIVAD													
	B. Cepacia complex													
	FEV1 % predicted (10% decrease)													
	Listed for transplant													
	Received transplant													
	CFRD (CF-related diabetes)													
	Sex (female)													
Bodnar et al. (2014)	Age													
	Shwachman-Kulczycki score (disease severity)													
	BMI													
	FEV1 % Predicted													
	Pseudomonas Aeruginosa infection													
	Hospitalisation													
Kilcoyne et al. (2016)	Sex (male) (out-patients)													
	BMI (out-patients)													
	Age (out-patients)													
	Consolidation (out-patients)													
	Airway wall thickening (out-patients)													
	Severity of bronchiectasis (out-patients)													

Table 2: Overview of correlations between QoL and clinical and sociodemographic factors (continued)

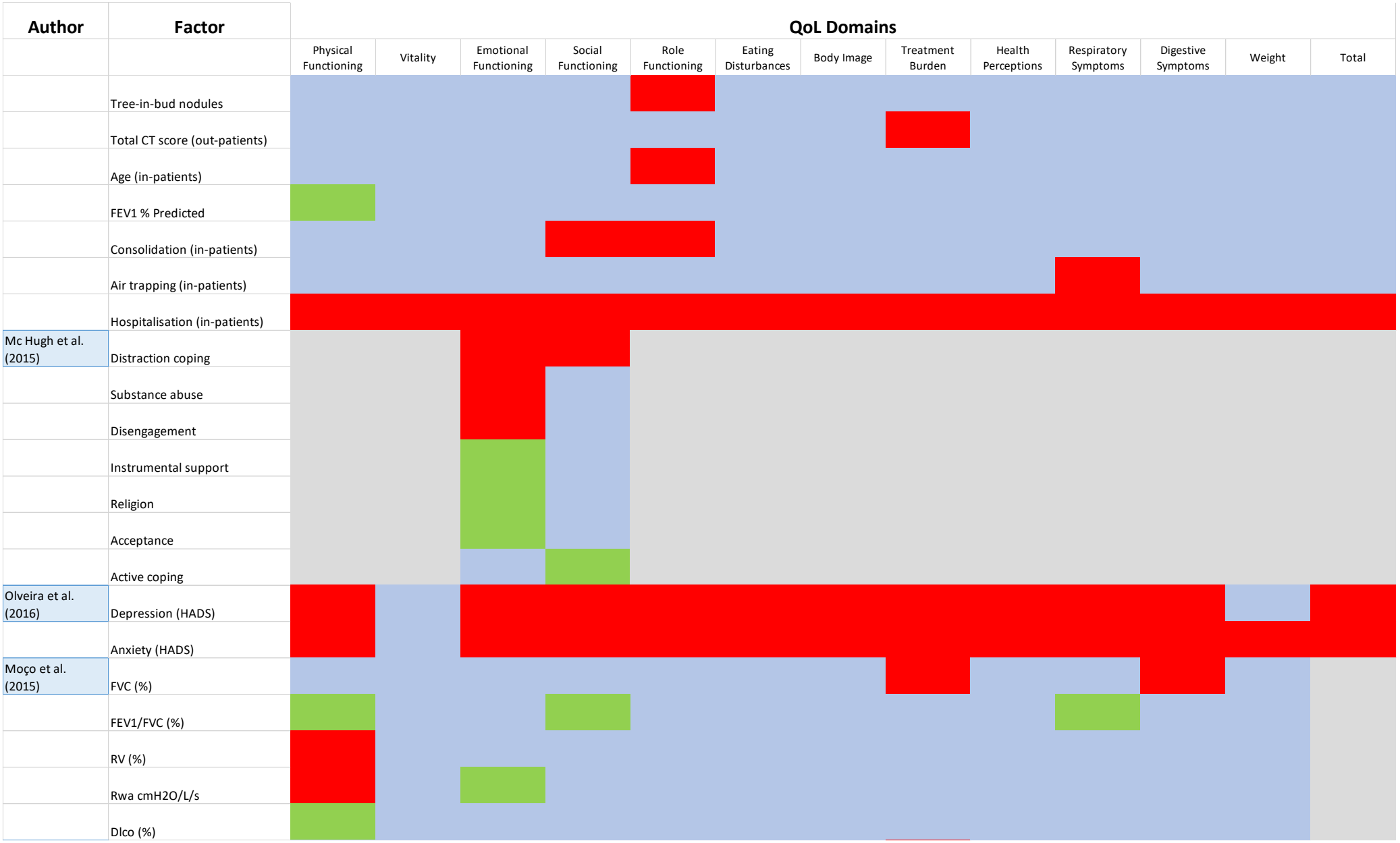


Table 2: Overview of correlations between QoL and clinical and sociodemographic factors (continued)

Author	Factor	QoL Domains												
		Physical Functioning	Vitality	Emotional Functioning	Social Functioning	Role Functioning	Eating Disturbances	Body Image	Treatment Burden	Health Perceptions	Respiratory Symptoms	Digestive Symptoms	Weight	Total
Borawska-Kowalczyk et al. (2015)	Origin (Poland vs Hungary) (patient perspective)													
	Origin (Poland vs Hungary) (parent perspective)													
	School attendance													
Habib et al. (2015)	Chronic rhinosinusitis													
Debska et al. (2015)	FEV1 > 50% Predicted (baseline)													
	Time since last exacerbation													
	Place of residence (city)													
	Physical activity													
	Time (1 year)													

Legend		
	Positive correlation	Level of significance: P<0,05 (Multivariate analysis)
	Negative correlation	
	No correlation	
	No information	

Discussion

Several sociodemographic and clinical factors are confirmed and discovered

On the one hand, studies included in this review appear to confirm previous results reported in older reviews. On the other hand, this review points out that new relationships between clinical and sociodemographic factors and QoL are still being discovered. Sociodemographic factors that are confirmed and further explored include: current age, gender and cultural influences. Age at diagnosis and place of residence appear as new sociodemographic factors. Clinical factors that are confirmed and further explored include lung function, exacerbation rate, disease severity, transplantation status, BMI, physical activity, work or educational disability P. Aeruginosa infection, hospitalization status , depression, and coping styles. Newly found relationships between clinical factors and QoL include: anxiety, sexual satisfaction, exercise tolerance, sleep quality, totally implanted vascular access device, B. Cepacia complex, CF-related diabetes, chronic rhinosinusitis, and radiological abnormalities.

Why is measuring QoL important?

Three major reasons exist to include QoL measures in clinical research (Abbott et al., 1997). These have led to the exponential rise of QoL research. First, it describes how a patients thinks, feels and acts, and is thus a meaningful outcome for patients as well as health professionals. Secondly, QoL measures are complementary to traditional clinical measures. Indeed, it is a fact that patients with similar levels of clinical disease severity, demonstrate a wide variability in their daily functioning and QoL. Therefore, QoL can provide added value as it can supply information not captured by other outcomes (Abbott, 2009). Thirdly, QoL measurement offers great opportunities to determine if and how patients benefit from therapies. If the patients decide the therapy is ineffective, they might stop it, regardless of clinical evidence: adverse effects for example can impact on their daily life. The same reasoning can be applied in the other direction.

Survival time and quality of life

An important note is that many diseases, such as CF, tend to evolve over time. Advances in the management and care of patients with CF have indeed increased

survival time. This has lead, for example, to new career opportunities, and consequently new challenges in the care of CF patients.

Median survival in 2008 is 37,4 years and still increasing, with over half of children born in the 1990s expected to survive into their fifth decade (Royce and Carl, 2011). In Belgium the median survival time for children born after 2000 is reaching the age of 50 (Rapport Belgisch Mucoviscidose Register, not yes published). Note that survival time, as an isolated parameter, is debatable, and the importance of adequately measuring the QoL in CF patients needs to be emphasized.

Cystic fibrosis remains incurable

Unfortunately, CF remains a progressively deteriorating and ultimately fatal multi-system disease. Numerous advances in the clinical care of CF have led to improved survival, although definitive correction of the dysfunctional CFTR protein remains elusive (Nakano and Tluczek, 2014). In order to maintain acceptable QoL scores, different treatment regimens exist. These are primarily directed towards the correction of malfunctioning organs and the relief of symptoms. To this end different therapies can be administered such as antibiotics, mucolytics, bronchodilators and corticosteroids. Physiotherapy and exercises are complementary therapies to aid in clearing respiratory secretions. Patients who suffer from pancreatic malfunctioning can receive oral pancreatic enzymes, vitamins and feed supplements in order to reduce the effects of gastrointestinal malabsorption. In some cases there is need for nocturnal enteral feeding in order to maintain a high-energy diet and to preserve body weight. In this context, it is imperative that treatment policies are organized to reach a crucial goal, i.e. improving QoL.

New challenges arise

Due to the increase of survival in combination with pancreatic malfunctioning, the incidence of diabetes rises in CF populations (Abbott & Gee, 2003), for which supplementary treatments will be required. Estimated is that nearly 50% of the adults with CF develop CF related diabetes (Habib et al., 2015). This impact, and that of other increasingly prevalent chronic comorbidities, remains to be further elucidated.

Limitations

Most studies have a cross-sectional design that makes it impossible to draw conclusions regarding cause and effect. Therefore, it could be interesting if, based on our current knowledge, longitudinal studies are performed.

Limited sample sizes may have influenced the validity of the results in some smaller studies. International collaboration is a feasible approach, as it will provide larger patient samples in combination with more homogenous measurement instruments.

As already explained, studies which did not use the CFQ(-R) or CFQoL measurement instrument were not included in the current review. Consequently, some potential relationships between other factors and QoL are not acknowledged. Future studies should only use measurement instruments, which are validated in a CF context.

Future research

As the disease evolves, more CF patients suffer from comorbidities such as CF-related diabetes, rhinosinusitis and many others. It would be interesting to measure the effects of these diseases on QoL.

Different other factors require further examination. These might include clinical and sociodemographic factors, psychological factors and intervention-related factors.

The effect of CF on the QoL of caregivers may also be an interesting topic to explore so that a more complete burden of disease could be assessed.

Cost-utility analyses that assess the price to be paid per QALY can aid in choosing particular management policies above others.

It would be very interesting to be able to convert disease specific measurement scores to generic scores. In this way, it would be possible to directly compare the impact of different diseases on QoL, and resources could be allocated accordingly.

Research in the field of disability adjusted life years (DALYs) would be interesting to aid governments in priority setting. In this way we can determine which (rare) disease has the highest impact on public health. This will be the focus of a master's dissertation in the near future.

Management implications

On average, CF patients spend two hours a day to administer seven different treatments (Habib et al., 2015). Therefore, CF management should focus on prioritizing and optimizing the management of factors that have the biggest impact on QoL.

Factors relating to the primary disease, such as lung function, stay at the center of CF patient care. In particular, efforts to optimize the respiratory component of the disease remain necessary.

In addition, this review highlights the importance of psychological factors, which stresses the need for psychological follow-up of CF patients. This could be done in CF reference centers during routine follow-up, or psychological screening consultations could be organized, for example every year. In this manner, cognitive and behavioral interventions can help CF patients which are depressed, anxious, have a bad sleep quality and sexual satisfaction,

Decisions around hospitalization and whether or not to work or study should not be taken lightly, as they have profound effects on QoL.

A multidisciplinary approach in managing QoL in CF patients is mandatory. Even some rather unexpected specialists, such as radiologists, can give direct information about QoL in CF patients. Furthermore, the growing prevalence of comorbidities will require such an approach.

Conclusion

This systematic review highlighted the importance of measuring methods and the importance of QoL measurement in CF patients. Furthermore, it showed that many clinical and sociodemographic factors influence QoL, and that a good understanding of how those factors manifest themselves may improve management and care of patients with CF.

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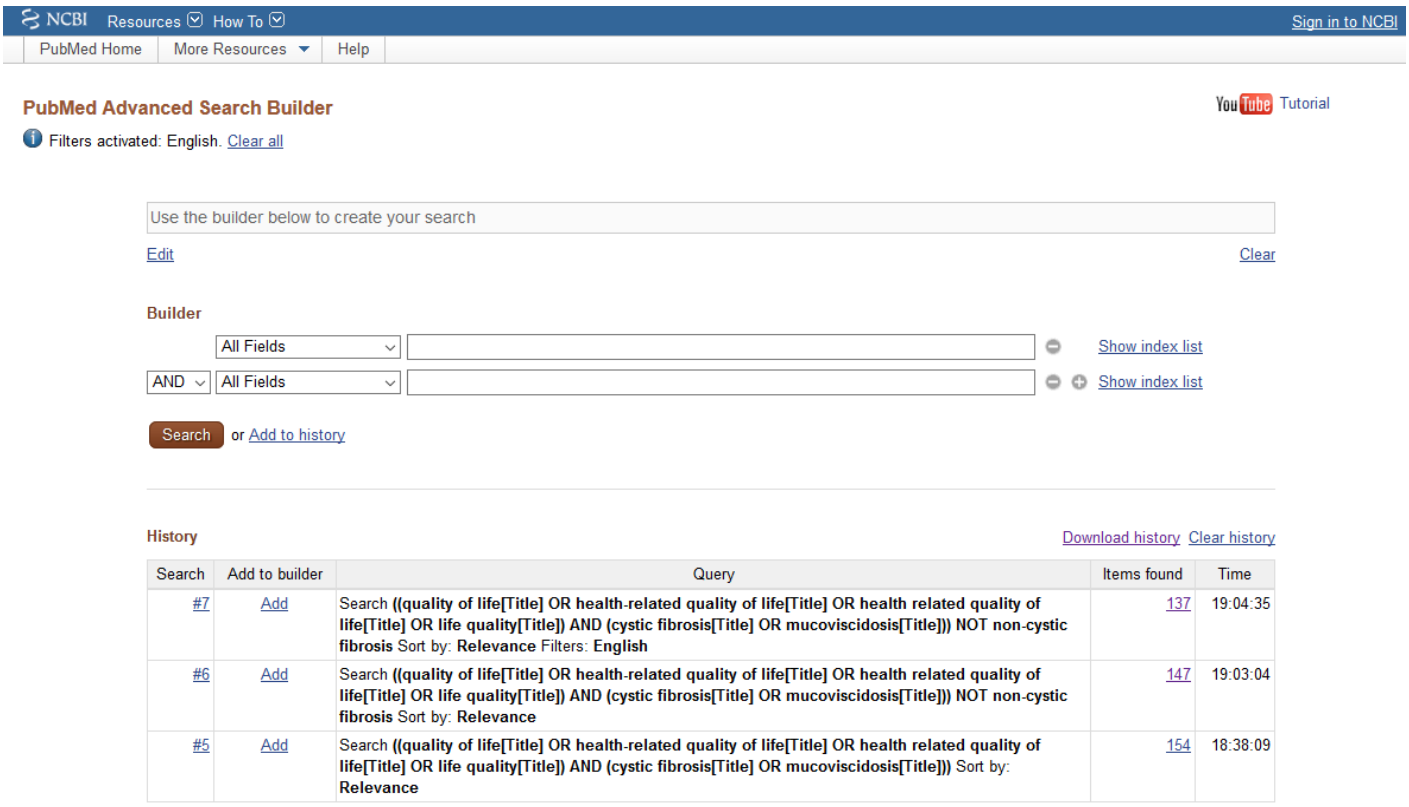
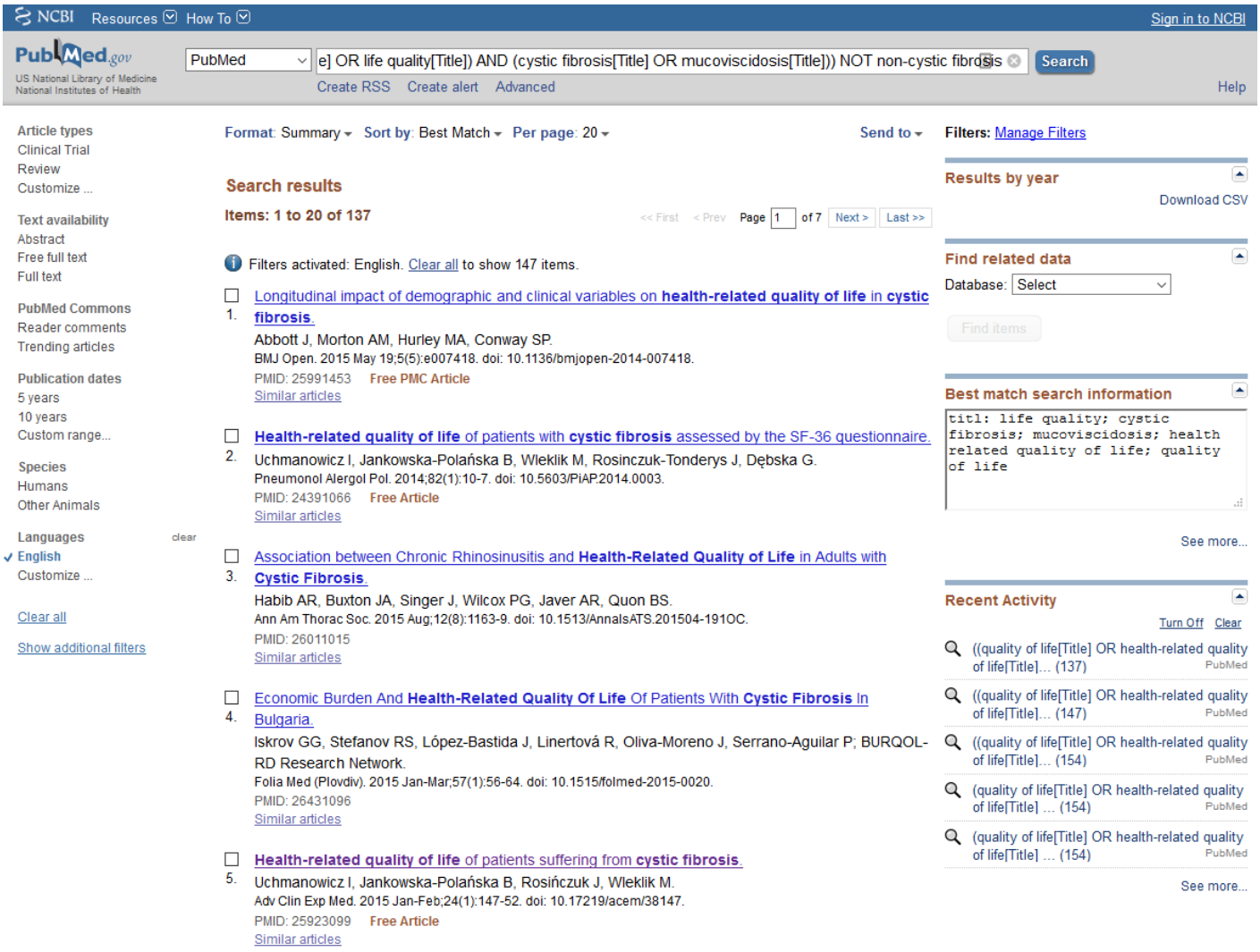
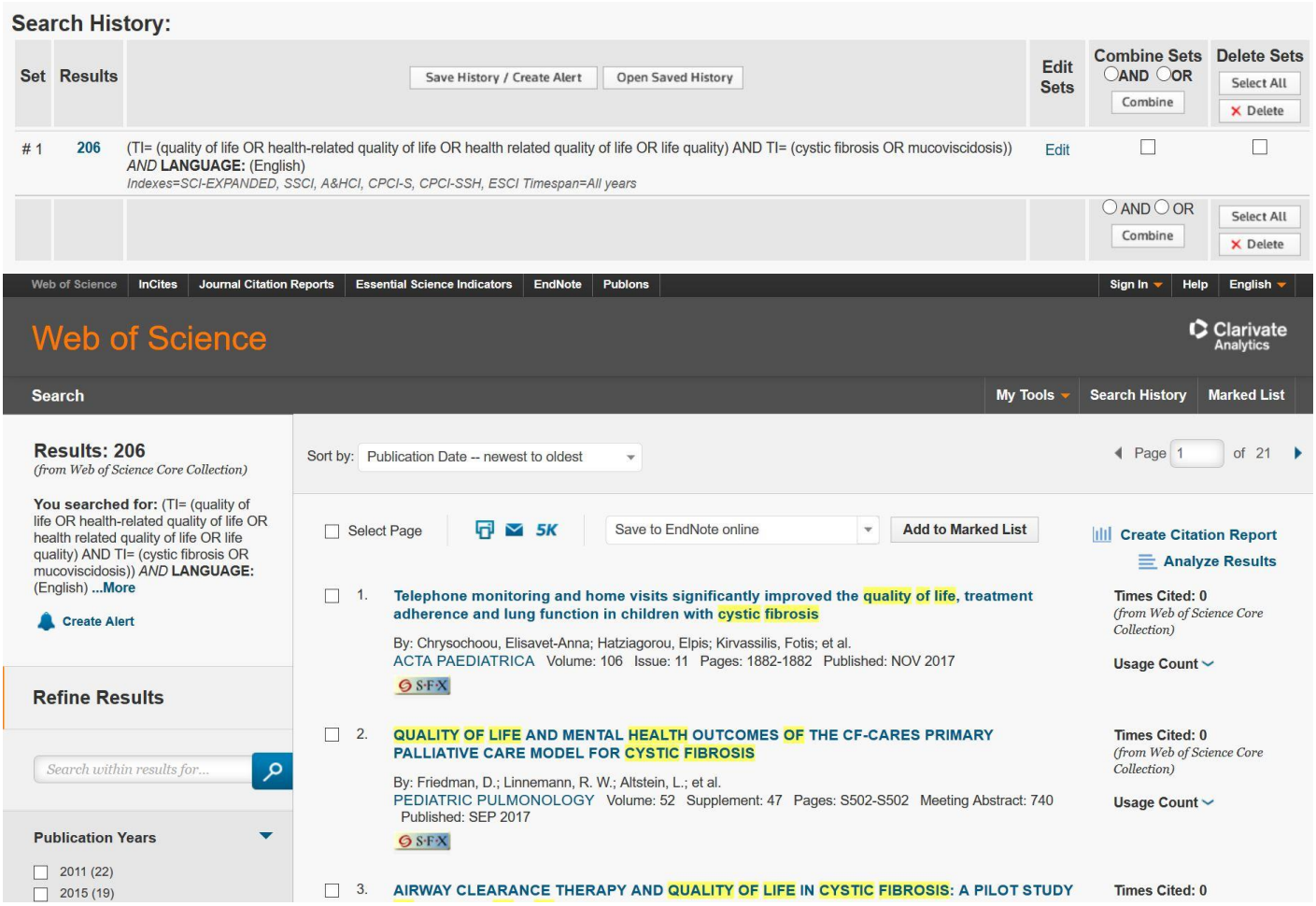
Appendices

Appendix 1: Printscreen of Pubmed search





Appendix 2: Printscreen of WoS search



Search History:

Set	Results		Edit Sets	Combine Sets	Delete Sets
		Save History / Create Alert · Open Saved History		AND OR · Combine	Select All · Delete
# 1	206	(TI= (quality of life OR health-related quality of life OR health related quality of life OR life quality) AND TI= (cystic fibrosis OR mucoviscidosis)) *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
				AND OR · Combine	Select All · Delete

Web of Science · InCites · Journal Citation Reports · Essential Science Indicators · EndNote · Publons · Sign In · Help · English

Web of Science — Clarivate Analytics

Search · My Tools · Search History · Marked List

Results: 206
(from Web of Science Core Collection)

You searched for: (TI= (quality of life OR health-related quality of life OR health related quality of life OR life quality) AND TI= (cystic fibrosis OR mucoviscidosis)) *AND* **LANGUAGE:** (English) **...More**

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Page 1 of 21

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Publication Years

2011 (22)
2015 (19)

1. **Telephone monitoring and home visits significantly improved the quality of life, treatment adherence and lung function in children with cystic fibrosis**
By: Chrysochoou, Elisavet-Anna; Hatziagorou, Elpis; Kirvassilis, Fotis; et al.
ACTA PAEDIATRICA Volume: 106 Issue: 11 Pages: 1882-1882 Published: NOV 2017
Times Cited: 0 *(from Web of Science Core Collection)*
Usage Count

2. **QUALITY OF LIFE AND MENTAL HEALTH OUTCOMES OF THE CF-CARES PRIMARY PALLIATIVE CARE MODEL FOR CYSTIC FIBROSIS**
By: Friedman, D.; Linnemann, R. W.; Altstein, L.; et al.
PEDIATRIC PULMONOLOGY Volume: 52 Supplement: 47 Pages: S502-S502 Meeting Abstract: 740 Published: SEP 2017
Times Cited: 0 *(from Web of Science Core Collection)*
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3. **AIRWAY CLEARANCE THERAPY AND QUALITY OF LIFE IN CYSTIC FIBROSIS: A PILOT STUDY**
Times Cited: 0

Appendix 3: STROBE guidelines applied

STROBE guidelines applied to: Abbott, J., Morton, A. M., Hurley, M. A., & Conway, S. P. (2015). Longitudinal impact of demographic and clinical variables on health-related quality of life in cystic fibrosis. BMJ Open, 5(5).				
Item		**Recommendation**	**Status**	**Explanation**
Title and abstract				
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Longitudinally.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		The abstract was a complete summary of the entire article.
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported		QoL is more important than ever, now that CF research has already highly improved survival rates for CF patients.
Objectives	3	State specific objectives, including any prespecified hypotheses		Understanding the determinants for sustaining a good QoL with advancing CF disease may assist in the development of interventions to improve it.
Methods				
Study design	4	Present key elements of study design early in the paper		The key element of study design is that a longitudinal setting was used, in contrast to other studies that investigate the same topic in a cross-sectional manner.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		Every 2 years, CF patients from large UK CF centres were send the CFQ questionnaire. This was done 7 times so that a follow-up period of 12 years was established.
Participants	6	*Cohort study* ?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up		All above described CF patients were eligible for the study. Follow-up measurements at each time point included: demographic, clinical and CFQ variables. All these variables are explained in sufficient detail.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		Variables: age, gender, FEV1 % predicted, BMI, CFRD, B. Cepacia complex, TIVAD, nutritional status, lung transplant status, CFQ domain scores.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Most of the variables mentioned earlier are easy to measure (e.g. yes/no). The QoL was measured by the CFQ questionnaire for which psychometric properties were good and internal reliability, validity, sensitivity and test-retest reliability were found to be robust. All questionnaires were mailed to the patients themselves before their clinic visit, so that they presumably filled them in by themselves and asked for the physician's help for things they didn't understand completely.
Bias	9	Describe any efforts to address potential sources of bias		No potential sources of bias were reported.
Study size	10	Explain how the study size was arrived at		All CF patients who agreed to participate in the study were enrolled, rather than defining how many patients were needed so that the study was adequately powered.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		Means, variances and covariances of the random coefficients for the quantitative covariates FEV1 % predicted, BMI and the model intercept were estimated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding		The longitudinal relationships between the nine domains of CFQ and the 11 variables recording patient characteristics were modelled using binomial regression models with fixed and random coefficients.
		(*b*) Describe any methods used to examine subgroups and interactions		Multivariate regression analysis with many variables was used.
		(*c*) Explain how missing data were addressed		Some patients enrolled at later time points (not T1), but their data were still included in the analyses.
		(*d*) *Cohort study* ?If applicable, explain how loss to follow-up was addressed		Some patients dropped out or died during the 12 years, but their available data were still included in the analyses. Hence, the analyses were not based only on survivors.
		(*e*) Describe any sensitivity analyses		No sensitivity analysis was performed.

Results				
Participants	13	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		A table presents the number of patients who participated for each total number of study time points (T1–T7) and the consequent number of patient assessments which the clinic visits contributed to the longitudinal data. A total of 770 completed patient assessments were obtained for 234 patients.
		(*b*) Give reasons for non-participation at each stage		The intention was to follow individuals every 2 years but, on occasion, some patients failed to attend annual review or to participate in the study, or had died.
		(*c*) Consider use of a flow diagram		No flow diagram was used.
Descriptive data	14	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		The demographic, clinical characteristics and HRQoL measures recorded at all the assessments combined are shown in a table.
		(*b*) Indicate number of participants with missing data for each variable of interest		Missing data was not reported at this level of detail.
		(*c*) *Cohort study* ?Summarise follow-up time (eg average and total amount)		The intention was to follow individuals every 2 years, the median number of completed patient assessments was three with a range of 2–5 assessments.
Outcome data	15	*Cohort study* ?Report numbers of outcome events or summary measures over time		Measures over time were provided only indirectly by means of a correlation coefficient. Outcomes were not reported for each time point.
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		A table presents the number of patients who participated for each total number of study time points (T1–T7) and the consequent number of patient assessments which the clinic visits contributed to the longitudinal data. A total of 770 completed patient assessments were obtained for 234 patients.
		(*b*) Give reasons for non-participation at each stage		The intention was to follow individuals every 2 years but, on occasion, some patients failed to attend annual review or to participate in the study, or had died.
		(*c*) Consider use of a flow diagram		No flow diagram was used.
Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses		No other analysis were done.
Discussion				
Key results	18	Summarise key results with reference to study objectives		For age (5 year increase), BMI (1 unit decrease), FEV1% predicted (10% decrease), oral supplements and enteral tube feeds, small changes, generally less than 5% were predicted. Having CFRD, TIVAD, B. cepacia complex and being listed for lung transplant predicted greater decrements across HRQoL domains. The largest changes in QoL were associated with having received a lung transplant; large increases in QoL occurred for Treatment issues, Chest symptoms, Concerns for the future and Emotional responses. Conversely, receiving a transplant predicted large decreases in Social functioning, Career concerns and Body image.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		Major limitations are that this was a single-centre study and several important variables were not evaluated, including the frequency of pulmonary exacerbations and microbiological status. A limitation of the analysis itself was that it did not estimate QoL in relation to the time since the change occurred.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		This is a longitudinal observational study and, as such, it has the advantage over a cross-sectional study of being able to determine temporality. For this reason, it is justifiable to interpret demographic and clinical changes as having impact on QoL. Hence, this work has demonstrated that the demands created by the CF disease trajectory and its treatments profoundly impact all aspects of a person's quality of life. The modelling approach taken has provided fundamental insight into the way in which changes in these measures impact on QoL.

Generalisability	21	Discuss the generalisability (external validity) of the study results		Demographic and changes in clinical variables were independently associated with a change in QoL over time. Compared with these longitudinal data, cross-sectional data are inadequate when evaluating the relationships between HRQoL domains and key demographic and clinical variables, as they fail to recognise the full impact of the CF disease trajectory and its treatments on quality of life. This longitudinal work confirms the cross-sectional findings that advancing age, lung function and transplantation are important predictors of outcome across many domains of life quality. Variables which did not consistently emerge as important in cross-sectional regression models have also now been shown to be independent predictors of HRQoL longitudinally. So, the longitudinal study design does not only confirms previous study results, it is also superior to cross-sectional studies as it makes it possible to identify other predictive variables.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		No competing interest declared.
Color codes				
Status		Recommendation was followed		
		Recommendation was not followed (with sufficient detail)		
		Recommendation was not necessary or relevant		