Health Related Quality of Life and Gastrointestinal Symptoms in Patients with Pancreas Insufficient Cystic Fibrosis

A cross-sectional study

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May 2020

2020

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Acknowledgements

By delivering this master´s thesis, my five years master-degree have come to an end. Writing this thesis have been educational, giving and fun, but in the same time hard and intense. The time has now come, and I am ready to start a new chapter in my life as a Clinical Nutritionist.

I want to show my special gratitude to my supervisors Sedegheh Gharagozlian and Hilde Kristin Brekke, further also to Inger Elisabeth Moen who have helped me along the way. I would like to especially mention Sedegheh who have helped me a lot, been available for answering my questions, big or small, and helped me through bumps in the way of finishing this thesis. Thank you for always finding the time for me when I have needed help. Hilde- thank you for all the help on the finish line for this thesis and thank you for reminding me of ´´the red thread´´. Further I would like to thank all the clinical nutritionists at Medical Clinic, Ullevål for taking me in with open arms, being including and supportive along the way.

I would like to show my appreciation to the staff at the Department of Pulmonary Medicine, who have helped me when needed. I would especially mention Audun Os, as he has shared his experiences with what might affect the patients' health related quality of life. I would also like to thank Lars Nordsletten, Department of Orthopedics, for teaching me how to interpret DXA results, and answering my questions. Furthermore, I would like to thank all the participants in this study for sharing their experiences.

I would also like the thank Niherthana Sripalan for collecting the data used in my thesis and handing them over to me. Thank you for the incredible work you have done in the data collection. Further I would like to thank all my fellow students for five incredible years. Without you these five years would not have been the same.

At last but not least I would like to thank my family, especially my parents. Thank you for always being there for me and giving me the chance to follow my dreams. Thank you for all the support, by words, with laugh, advices at all times, and financially at hard times. I will never be able to thank you enough. Brother and sister, those words are to you as well (and thanks for all the FPL tips, bro). I would also like to thank my aunts, uncles and nephews for taking care of me when moving across the country. Thank you for looking after me, including me and being there. These five years would never have been the same without you.

Abstract

Background: Cystic fibrosis (CF) is an autosomal recessive disorder, caused by a mutation in the CFTR-gene. One complication with CF is pancreas insufficiency (PI) as a result of mucus blockade of the small tubes in the pancreas. Patients with CF are in previous studies shown to have reduced health related quality of life (HRQoL) and are believed to have increased gastrointestinal (GI) symptoms. However, studies on this topic have not been conducted in Norwegian patients with pancreas insufficient cystic fibrosis (PI-CF).

Objectives: To assess HRQoL and GI-symptoms in Norwegian patients with PI-CF and evaluate their possible associations with nutritional status, including sarcopenia and lung function.

Methods: This study was a cross-sectional pilot study, including adult Norwegian patients with PI-CF at Oslo University Hospital, Ullevål in the period of August to December 2018. HRQoL and GI-symptoms were investigated using the Cystic Fibrosis Questionnaire Revised (CFQ-R) and The Gastrointestinal Symptom Rating Scale (GSRS). Nutritional status was assessed by body mass index (BMI), body composition using dual X-ray absorptiometry and handgrip strength. Dietary intake was assessed by repeated 24-h dietary recalls. Lung function was assessed by forced expiratory volume in the first second.

Results: 33 subjects were included in the study. In mean the participants had reduced HRQoL in seven of 12 domains. GI-symptoms were significantly increased ($p<0.05$) for all GSRS domains except reflux symptoms compared to the healthy population. BMI classified 54.4% as malnourished according to the European Society for Clinical Nutrition and Metabolism recommendations for patients with CF. Less than 50% of the study population had an energy intake covering >75% of estimated total energy expenditure. Further, more than 30% of the participants were overweight or obese using the World Health Organization definitions. Both malnutrition and overweight were found to be related with reduced HRQoL and increased GI-symptoms in the study population. 27.3% of the study population were diagnosed with sarcopenia. Participants with sarcopenia had significantly reduced HRQoL compared to non-sarcopenic participants ($p<0.05$).

Conclusion: Impaired HRQoL, increased GI-symptoms and a high prevalence of malnutrition and sarcopenia was observed among patients with PI-CF. Prevalence of overweight and obesity was also high. Both malnutrition and overnutrition was associated with more GI-symptoms and reduced HRQoL. Further studies with larger number of participants are needed to verify our findings.

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Abbreviations

ASM: Appendicular skeletal muscle mass

ASMI: Appendicular skeletal muscle mass index

BMD: Bone mineral density

BMI: Body mass index

BMR: Basal Metabolic Rate

CF: Cystic Fibrosis

CFRD: Cystic Fibrosis related Diabetes

CFTR: Cystic fibrosis transmembrane conductance regulator

CFQ-R: The Cystic Fibrosis Questionnaire Revised

DIOS: Distal intestinal obstruction syndrome

DXA: Dual- Energy X-ray Absorptiometry

E%: Energy percent

ECFSPR: European Cystic Fibrosis Society Patient Registry

ESPEN-ESPGHAN-ECFC guidelines: European Society of Clinical Nutrition and Metabolism- European Society for Pediatric Gastroenterology, Hepatology and Nutrition- European Cystic Fibrosis Society

ESPEN: European Society for Clinical Nutrition and Metabolism

EWGSOP: The European Working Group on Sarcopenia in older people

FEV_1: Forced expiratory volume in the first second

FFM: Fat free mass

FFMI: Fat free mass index

GI: Gastrointestinal

GSRS: The Gastrointestinal Symptoms Rating Scale

HbA1c: Glycated hemoglobin

HGS: Hand grip strength

HRQoL: Health related quality of life

IRT: Immunoreactive trypsinogen

LF: Lung factor

MDT: Multidisciplinary team

MJ: Megajoule

n: Number

OUH: Oslo University Hospital

PAL: Physical Activity Level

PEP: Positive expiratory pressure

PERT: Pancreatic enzyme replacement therapy

PI: Pancreatic Insufficiency

PI-CF: Pancreas insufficient Cystic Fibrosis

PS: Pancreatic sufficiency

PS-CF: Pancreas sufficient Cystic Fibrosis

QOL: Quality of life

SD: Standard deviation

TEE: Total Energy Expenditure

WHO: World Health Organization

1 Introduction

1.1 Cystic fibrosis

1.1.1 Definition and epidemiology

Cystic fibrosis (CF) is an autosomal recessive disorder that affects lungs, pancreas, liver, intestine, sweat glands and reproductive organs. The most severe complication in CF is the progressing lung disease, which is the major cause of morbidity and mortality (1). According to the Cystic Fibrosis Foundation more than 70 000 people are affected of CF worldwide, of these more than 30 000 in the United States (2). The prevalence of the disease is highest in Europe, with a total of more than 48 000 people with CF from 35 participating countries including Norway, of these more than 10 500 people with CF in the United Kingdom (3-5). The incidence of the disease is highest in white Caucasians, occurring in about one of 2 000 births, compared to one in 17 000 in African American (6). **Figure 1** illustrates how the incidence of CF varies in the different parts of the world. In 2018 there were about 370 people with CF in Norway, and every year 8-10 newborns are diagnosed with CF (7). The Norwegian CF register includes 258 patients (8).

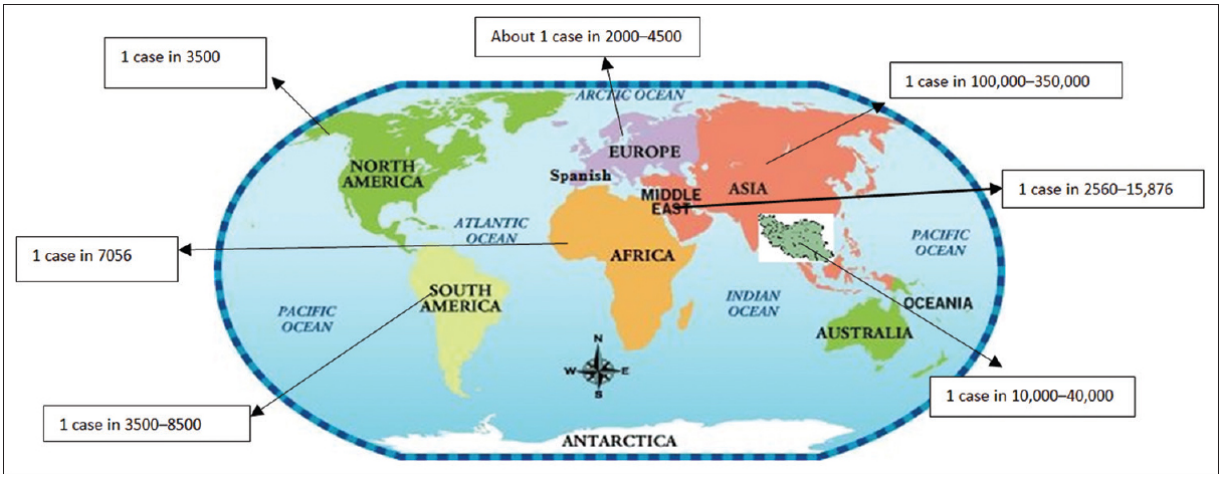


Figure 1 Incidence of Cystic Fibrosis in different parts of the world (9).

1.1.2 Etiology

CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, on chromosome 7 (1). It is a recessive disease, and requires disease causing mutations in both copies of the gene. Today we know of more than 2 000 different mutations that causes various severity of the disease. Of these 2 000 different mutations, there are tests

available for identifying 70 (10). The most common mutation is F508del (also known as Phe508del), and more than 280 of the Norwegian patients with CF have this mutation (1, 8). A normal CFTR gene regulates chlorine transportation through mucus producing cells, water further follows which allows the mucus to become thin. A mutation in this gene leads to abnormality in chloride channels in mucus- and sweat producing cells, resulting in thick and sticky mucus, which further affects multiple organs, including lungs and gastrointestinal (GI) tract (11). Further the CFTR gene regulates bicarbonate release especially in the pancreas, ileum, duodenum and lung, which reduce pH of the secretions (12). Bicarbonate secretion dysfunction is believed to be the major cause of CF pathology in these organs (13). The CFTR mutation results in severe lung infections and obstruction in the canaliculi of pancreas and gall blather duct, which prevents bile- and enzymes flow.

The mutations causing CF are branched into different groups, depending on type of mutation (11). Normally group 1 mutations leads to most severe complications, as they affects protein production, and group 6 mutations are less severe complications, as they regulate the amount of functional CFTR (1, 11). The different classes of CF mutations described above are illustrated in **figure 2**. However, knowledge of the mutations are useful to guide initial therapy, but should not be used to make assumptions about the severity of the disease. Clinical observations are needed for this.

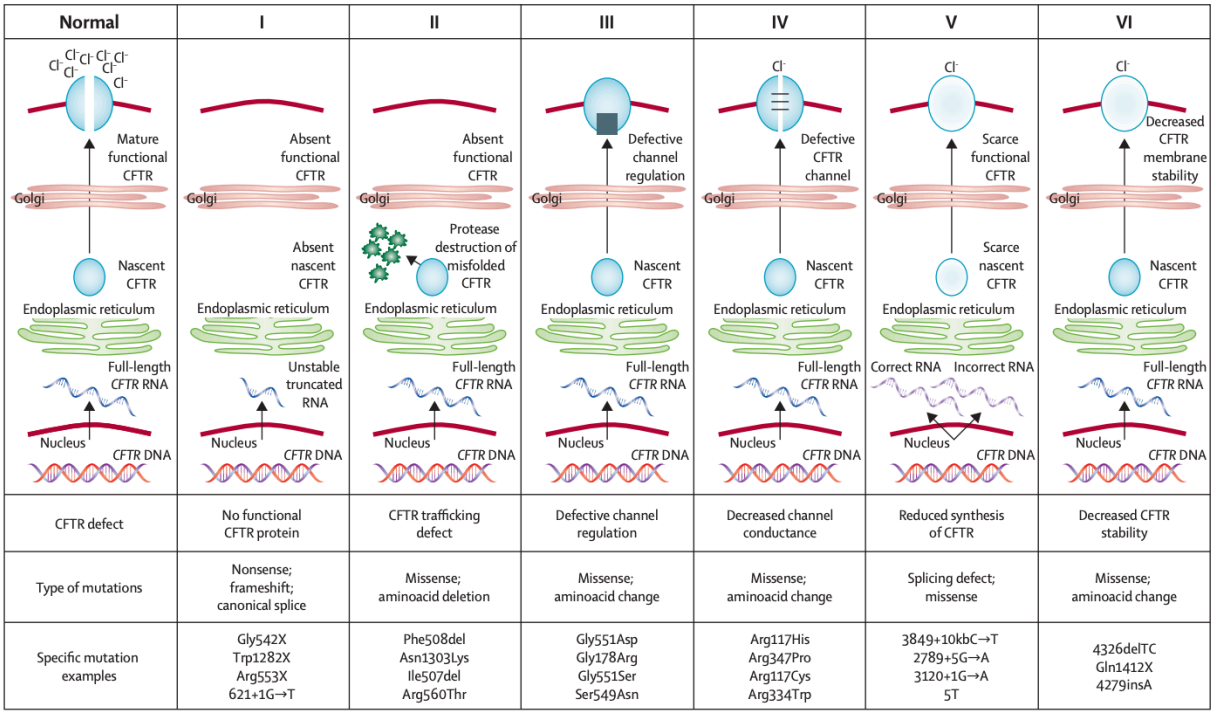


Figure 2 Different groups of Cystic Fibrosis causing mutations (14).

1.1.3 Pathogenesis

Patients with CF can experience several different symptoms, as the disease affects different parts of the body. Further the severity of the symptoms can vary within the patients group, as each patient experience different challenges (15). As a result of increased life expectancy, previous rare or unknown complications have come to light (10). Together with pulmonary disease, GI-symptoms, pancreatic disease and hepatic manifestation should have consideration as all patients with CF will experience at least one of these symptoms due to their condition (16).

Pulmonary function

More than 90% of all patients with CF have respiratory problems (17). These problems often revile during the first months after birth, resulting in cough, repeated episodes of bronchiolitis or obstructive bronchitis. The abnormalities in the patient's secretion results in chronic infection with particularly Pseudonomas species. Patients with CF have much thicker mucus, than people with healthy lungs (18). Therefore the mucus in patients with CF clogs the lungs, which creates the perfect environment for bacterial growth, compared to healthy people where the thin layer of mucus help the body remove dirt and bacteria out of the lungs (18). Further the thick mucus production will increase, as the lung disease progress, and chronic airway infection is established. Due to the increased infection rate, people with CF are not recommended meeting each other, as they can have different types of bacteria, that can spread to another. It is further recommended to test pulmonary function, using Forced expiratory volume in the first second (FEV_1) at least every three months (19).

Cystic fibrosis and pancreatic insufficiency (PI)

Apart from the lungs, pancreas is the most affected organ in CF (20). The damage of the pancreas begins in utero, at 17 weeks gestation (21). Pancreatic insufficiency (PI) is a common complication of CF, and approximately 85-90% of the patients will be affected at some point in their life (19, 22). PI is defined as postprandial enzyme output $\leq$10% of normal, and is diagnosed when measured fecal pancreatic elastase-1 <100 μg/g stool (19). The major consequence of PI is fat malabsorption due to reduced production and transport of pancreatic enzymes. The digestion enzymes produced in the pancreas are transported in the small tubes to the digestive system. Due to the thick mucus, the small tubes from pancreas become blocked, and therefore the enzymes build up in the pancreas, creating an inflammation. This

leads to PI, and patients with pancreas insufficient cystic fibrosis (PI-CF) are reliant on digestion enzyme supplementation with their meals (23). Due to fat malabsorption, patients with PI-CF are at risk for steatorrhea, malnutrition and deficiencies of fat-soluble vitamins. Patients with class 1-3 mutations usually develop PI during their first months of life. Not treated PI can cause excretion of up to 80% of fat, due to lipase deficiency, and is therefore a major reason for failure to thrive in infants (19). Further, patients with PI-CF have increased risk for developing CF-related diabetes (CFRD). Patients with pancreas sufficient cystic fibrosis (PS-CF) should conduct an annual fecal elastase test, to evaluate pancreatic enzyme levels, as PS-CF can convert to PI-CF (16).

Cystic fibrosis related diabetes

Problems with the pancreas can lead to CFRD, which affects around a third of all patients with CF (23). The prevalence of CFRD increases with age, for comparison 1.5% of all 10 years old with CF have CFRD, and 50% of all 30 years old with CF have CFRD (24). CFRD is a combination of insulin resistance and reduced insulin production (25). Due to PI and inflammation in the pancreas, the production of insulin is inhibited (26). CFRD adversely affects pulmonary function and increases risk of mortality, as a result of higher blood glucose levels which stimulates bacterial colonization in the lungs (19). It is recommended to perform an annual glucose tolerance test on patients with CF >10 years (19). For patients with diabetes mellitus type 1 and 2, HbA1c is used for diagnostics. As patients with CFRD only experience postprandial hyperglycemia, and rarely experience fasting hyperglycemia, HbA1c and fasting blood glucose can be false low (10). Therefore, for detecting CFRD HbA1c has a sensitivity of only 50% compared to an oral glucose tolerance test, which is the preferred diagnosis method. Most patients with CFRD are treated with insulin. Patients with CFRD do not only have impaired insulin secretion, but also impaired glucagon production, as the CFTR gene also have a role in glucagon suppression (27, 28). CFRD is most common in patients with PI-CF, however CFRD can also occur in patients with PS-CF.

Nutritional status and recommendations

Malnutrition is a well-known complication in CF (29). Malnutrition is defined as body mass index (BMI) <18.5 kg/m^2 according to WHO (30), or according to the European Society for Clinical Nutrition and Metabolism (ESPEN), as fat free mass index (FFMI) <17 kg/m^2 in men and <15kg/m^2 in women (31). However, according to ESPEN the goal for patients with CF is to achieve BMI >22 kg/m^2 for women and >23 kg/m^2 for men (19). Patients with CF have

increased energy needs, higher energy losses and decreased nutritional intake and absorption (32-34). The primary cause of energy loss is malabsorption due to PI. Further, CFRD and insulin deficiency or insulin resistance will lead to increased energy losses before treatment (35, 36). As poor nutritional status in children results in stunted growth and delayed physical- and mentally development, it is important to focus on nutritional status from young age (37). There is good evidence that optimal nutritional status is important for survival and pulmonary function for this patient group. However, in later years the incidence of overweight have increased (38). ESPEN further recommends that patients with CF have an energy intake of 120-200% of a heathy person with the same sex, age and size. When estimating energy needs for patients with CF, it is important to take FEV_1 into account. It is thought that patients with CF may have a higher protein need compared to non-CF individuals, and it is recommended to be ≥20% of the total energy intake. Further ESPEN recommend 35-40% of their caloric intake from fat and 40-45% of their caloric intake from carbohydrates (37, 39, 40).

Sarcopenia

Sarcopenia is characterized by progressive loss of skeletal muscle mass and muscle strength. Patients with CF are shown to have decreased fat free mass (FFM) and bone mineral density (BMD) compared to the healthy population, which is associated with decreased muscle strength (41). This is believed to increase risk for sarcopenia and osteoporosis. However, no cut-off values are at this point developed specific for sarcopenia in patients with CF.

According to the newest recommendations from The European Working Group on Sarcopenia in Older People (>60 years) (EWGSOP), appendicular skeletal muscle mass (ASM) and appendicular skeletal muscle mass index (ASMI) are used for sarcopenia definition, while hand grip strength (HGS) is used for suspecting sarcopenia (42). ASM is defined as the sum of muscle mass of the four limbs (43). Exact sarcopenia cut-off values are found in **table 1.**

Table 1 Sarcopenia Cut-off values (42).

Test	Cut-off for men	Cut-off for women
HGS*	<27 kg	<16 kg
ASM	<20 kg	<15 kg
ASMI	<7.0 kg/m^2	<5.5 kg/m^2

*HGS alone can only be used for suspecting sarcopenia, and not for diagnosis.
Abbreviations: HGS; hand grip strength, ASM; appendicular skeletal muscle mass, ASMI; appendicular skeletal muscle mass index

1.1.4 Diagnosis and treatment

Cystic fibrosis diagnosis

The diagnosis is confirmed using DNA-based diagnostic and newborn screening. Today CF is implemented in the newborn screening program in countries with a high prevalence of the disease (14, 44). In Norway CF screening was included in the newborn screening program in 2012. The screening program involves immunoreactive trypsinogen (IRT) followed by testing for a panel of common CF mutations (14, 45). It is recommended that a newly diagnosed infant should be seen by a CF specialist team within 35 days, and no longer than 58 days after birth (46). Before CF was implemented in the newborn screening program, CF was diagnosed when the patients experienced symptoms of their disease, and therefore consulted health care professionals. Due to newborn screening we have the ability to diagnose patients before outbreak of symptoms, and further implement treatment for preventing symptoms of the disease, and learn parents how to keep their child with CF as healthy as possible (47). This gives us the ability to reduce disease severity, burden- and costs of care (14).

If newborn screening shows suspicion of CF, a sweat test is conducted. A sweat test measures the concentration of sweat chlorine, and is considered as the gold standard for CF diagnosis (48). Patients with CF have an increased concentration of chlorine in their sweat, and CF is suspected if chloride levels are between 30-60 mmol/l. Further levels above 60 mmol/l are definitely considered abnormal, and CF is likely to be diagnosed (14, 25, 47). If the sweat test gives reason to suspect CF further genetic analyzes are required, searching for CFTR mutations on the long arm of chromosome 7 (25, 49). Due to frequent airway infections, respiratory tract culture for pathogenesis is performed. Further spirometry and chest X-ray are routinely used to investigate and monitor lung function (46).

Medical treatment

The intention of treatment in CF is that the patients can achieve normal growth, physical- and mental development, maintain optimal nutritional status, delay progression of lung disease and further increase quality of life (QOL) and life expectancy (50). The treatment is individualized and requires a team of different health professionals. Lung treatment is important to prevent lung changes and infections. Patients with CF are treated with different antibiotics, and treatment is increased with sign of impaired lung function, or sign of infection. Further Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are used to control

airway inflammation. β-agonists with humidified oxygen are inhaled to remove thick and sticky mucus from the lungs, dilating the airways and reduce viscoelasticity (11). Further physiotherapy and exercise including a high frequency chest wall oscillation device and positive expiratory pressure (PEP) are recommended (51). Intestinal blockages are treated with oral rehydration and osmotic laxatives, or hyperosmolar contrast enemas, depending on if the blockage is incomplete or complete (11). Oral polyethylene glycol can be used regularly to prevent recurrence. Patients with PI-CF are dependent on enzyme supplementation (lipases, proteases and amylases) with each meal (52).

In 1989 the CFTR gene was discovered, giving hope for future therapy of CF (25). In 2012 the first mutation-specific treatment was approved. This treatment was based on correcting structural and functional abnormalities in the CFTR gene, and is shown to increase pulmonary function, body weight, QOL, and further decrease infection rate (25). However, this treatment is mutation-specific, and therefore different treatments are needed for different mutations causing CF (25).

Pancreatic enzyme replacement therapy (PERT)

PI cause deficiency of digestive enzymes. Patients with PI-CF are therefore reliant on pancreatic enzyme replacement therapy (PERT) to maintain adequate nutritional status (19). PERT includes oral administration of pancreatic enzymes, especially protease and lipase. These enzymes are essential for digestion of proteins and fat. The enzymes are consumed as enteric-coated tablets or - microspheres, to prevent inactivation from gastric acid. The enzyme dosage is individualized, as the need of enzymes depends on weight, age and the meals´ fat content (19, 50). At this point there is no evidence or guidelines for optimizing the enzyme dosage, regarding on different severity of PI. Therefore, it is important to monitor growth and nutritional status to determine the treatment (19). For children (>4 years) and adults the recommended dosage is 2000-4000 U lipase/gram fat (19).

Prognosis

CF was identified in 1938 by Dorothy Andersen (14). In the 1950s, life expectancy for these patients were a few months. Since then life expectancy for the patients have increased dramatically, and today median age of survival is more than 40 years in developed countries (14). During the six last decades the therapeutic targets of the disease is better understood, and the importance of treating infections, airway clearance and correcting nutrition deficits

have been important for the increase in life expectancy. Progressive lung disease followed by respiratory failure is now the most common cause of death for patients who do not receive lung transplantation. All patients who develop respiratory failure should be offered lung transplantation when FEV_1 is <30% of predicted, and have frequent exacerbations or are on trajectory of declining lung function (14).

Follow up

To provide specialized and comprehensive CF care, a multidisciplinary team (MDT) is included in the treatment (53, 54). This team should include physiotherapist, microbiologist, clinical nurse specialist, clinical psychologist, clinical nutritionist, pharmacist and clinical geneticist. This team is responsible for giving the patient and the patients family sufficient care and guidance, for the best possible treatment and follow up, resulting in good QOL (55). It is recommended with follow up twice a year, never less than once a year with the MDT (56). Further it is recommended that the follow up takes place at a national CF-center, however due to long distances that requires travelling, a local CF-team can benefit. A yearly consultation is important for preventing and declare complications regarding the disease. Further it is recommended routinely policlinic care, every 4-12 weeks, depending on the patient´s clinical picture (55).

1.2 Health related quality of life

The importance of patient-reported outcomes have had greater focus the last years, and it is important to optimize health related quality of life (HRQoL) as life expectancy have increased dramatically, and further comorbidities continues to rise (57, 58). For patients with CF the balance between maintaining nutritional status and lung function, and at the same time prevent or reduce other disease- or age specific symptoms is important.

HRQoL is important for both primary and secondary outcomes in studies, and for patient follow up. This gives us the ability to investigate the progression of the disease, and to describe how the patients are handling the disease. When it comes to CF specific, the importance of patient reported respiratory symptoms have come to light. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is the most widely accepted method for measuring HRQoL in patients with CF. This is a valid questionnaire, measuring multiple dimensions, and the form is now translated to more than 36 languages, and there are specific forms for children,

caretakers/parents, adolescent and adult (59). The forms´ respiratory domain have been approved as an endpoint in clinical trials by the US food and drug administration (60). Previous studies have found that FEV_1 have the broadest impact on HRQoL, and has been associated with 11 of 12 domains (58). The most studied factors for evaluating HRQoL are FEV_1, sex, BMI, age and pulmonary exacerbations (58).

1.3 Gastrointestinal symptoms

Patients with CF often experience digestive symptoms like constipation, nausea, swollen abdomen, greasy and bulky stools, frequent and/or difficult bowel movements and loss of appetite (23). For reducing these symptoms, patients can use different medication. For optimizing digestion, it is important that patients with PI-CF use and optimize their dose of digestion enzymes. Apart from the symptoms mentioned above, patients with CF can have additional diagnoses, affecting the GI tract. One example of this is Distal intestinal obstruction syndrome (DIOS), which is a condition unique to patients with CF, that usually occurs between 5-15 years of age (23). The CFTR mutation causes thickened secretion that causes GI complications. Further impaired bile flow and pancreatic secretion causes malabsorption and maldigestion. Due to thickened secretion and maldigestion, patients with CF are exposed to intestinal obstruction (1). DIOS is characterized by accumulation of inspissated fecal material in the distal ileum and proximal colon, and is suspected when the patients experience acute colicky abdominal pain and vomiting (61, 62). About 10-15% of the CF population are diagnosed with DIOS, and it is mainly seen in patients with PI-CF (63, 64). However the exact estimation is difficult to determine, as DIOS symptoms overlap with constipation (65). The disease is treated with stool softening laxatives combined with rehydration. For reducing risk of further episodes, it is important to avoid dehydration and optimize pancreatic enzyme dosage.

Apart from what is mentioned above, it is important to remember that CF patients can have all other conditions that also appears in the general population, like Inflammatory Bowel Disease, appendicitis, and further CF patients have increased risk for digestive cancers (66), and debut of colorectal cancer at younger age than the rest of the population. In patients with CF colorectal cancer has been reported in patients under the age of 25 (67). Further children with CF have 6-8 times higher prevalence of gastroesophageal reflux (68).

Other GI complications patients with CF can experience are meconium ileus, rectal prolapse and fibrosis colonopathy (69). Meconium ileus occurs exclusively in children with CF due to inspissated meconium. About 15% of children with CF symptoms are diagnosed with meconium ileus during the first day or two in life. The disease develops when thick secretions occlude the hallow GI lumen, normally in the terminal ileum (70). The disease is potentially deadly without surgical treatment (71, 72). Meconium ileus and the other GI-symptoms occur in this patient group due to thick mucus and lack of normal pancreatic enzymes (73, 74).

2 Objectives and aims

Objectives

CF has a strong association with impaired HRQoL. There are several factors that are believed or showed to affects HRQoL, including pulmonary function, GI-symptoms, pancreatic function and nutritional status. At this points few studies have investigated nutritional status and pulmonary function in the Norwegian CF population, and to the authors knowledge no studies have seen the mentioned parameters in relation with HRQoL and GI-symptoms in patients with PI-CF separately. The aim of this study is to assess HRQoL and GI-symptoms in the Norwegian PI-CF population, and further investigate the relation between nutritional status and lung function and HRQoL and GI-symptoms in patients with PI-CF. We hypothesize that malnourished patients with PI-CF have impaired HRQoL, and experience more severe GI-symptoms.

Aims

Evaluate health related quality of life

- Evaluate HRQoL in patients with PI-CF compared to a healthy population using the CFQ-R.

Evaluate gastrointestinal symptoms

- Evaluate the presence and severity of GI-symptoms in patients with PI-CF compared to a reference group using the GSRS.

Assess malnutrition

- Evaluate malnutrition with nutritional intake and requirements compared to individual requirements.
- Evaluate presence of malnutrition by BMI, fat free mass index and sarcopenia, and compare the results with the general population and ESPEN guidelines.

Evaluate health related quality of life and gastrointestinal symptoms in relation to malnutrition and lung function

- Compare CFQ-R and GSRS scores for subjects with and without malnutrition and sarcopenia.
- Compare CFQ-R and GSRS scores for subjects with and without impaired lung function.

3 Subjects and methods

3.1 Subjects and recruitment

3.1.1 Study design

This master thesis is a part of a pilot, cross-sectional study that investigates HRQoL, GI-symptoms, dietary intake and nutritional status in patients with PI-CF. The present work was conducted at Division of Medicine, Oslo University Hospital (OUH), Ullevål in collaboration with the University of Oslo. The project was planned by Sedegheh Gharagozlian and colleagues. The participants were recruited from Department of Pulmonary Medicine, OUH, Ullevål. The data collection was conducted between August 2018 and December 2018. The study is divided into two theses, where the first thesis focused on nutritional status (including vitamin- and mineral status, and dietary intake) in Norwegian patients with PI-CF. In the present master thesis HRQoL and GI-symptoms in patients with PI-CF will be described. Further, HRQoL and GI-symptoms will be seen in relation with nutritional status, including sarcopenia and lung function. The analysis used in this study were performed from January 2020.

3.1.2 Study population and recruitment

Patients with PI-CF were invited to participate in the study. Patients who met the inclusion criteria were recruited when they attended their routine appointment with the CF-team at Department of Pulmonary Medicine, OUH, Ullevål in August 2018 to December 2018. The patients received information and an invitation to the study (**Appendix 1)** when they attained their consultation. Further they went through the written consent form (**Appendix 2**). A former master´s student conducted this part, and the patients signed the written consent form if they wanted to participate in the study, and received a copy of this form.

3.1.3 Inclusion and exclusion criteria

Patients diagnosed with PI-CF >18 years who came to control at OUH, Ullevål in the period August 18 - December 18 were invited to join the study. Patients who were pregnant, unable to correspond in Norwegian or English, or had CF related liver disease were excluded. Further participants who had not filled out the GSRS and CFQ-R were excluded from the data analysis.

3.2 Data collection

The data were collected at OUH, Ullevål, Department of Pulmonary medicine. To investigate HRQoL, the participants completed The Cystic Fibrosis Questionnaire Revised (CFQ-R) (**Appendix 3**). GI-symptoms were investigated using the Gastrointestinal Symptom Ratings Scale (GSRS) (**Appendix 6**). Height, weight and BMI were measured to investigate nutritional status. Further handgrip strength (HGS) tests were performed to measure muscle strength.

Hight, weight and lung function were measured during the patients breathing examination before their consultation. A former master´s student was allowed to stay in the room during the examination to report the results. Lung function results for all participants were achieved from medical journals. The participants fulfilled the CFQ-R and GSRS while they were waiting for their consultation. Further the participants were signed up for an appointment for Dual Energy X-Ray Absorptiometry (DXA) to measure body composition.

3.2.1 Health related quality of life

The participants HRQoL was evaluated using the CFQ-R (**Appendix 3**). The form consists of 50 questions regarding 12 different domains. Five of these domains measures physical HRQoL (Physical Functioning, Earing Disturbances, Digestive Symptoms, Respiratory Symptoms and Weight), while seven domains measure psychosocial HRQoL (Body Image, Health Perceptions, Vitality, Treatment Burden, Emotional Functioning, Social Functioning and Role). **Appendix 4** gives an overview of which items that are included in the different domains. All these domains are considered to affect QOL. Further a CFQ-R total score was calculated as a mean of all domains, and a measurement for all over HRQoL. Each item has 4-point Likert response rates, where the participants can rate symptoms from (1) always to (4) never, (1) a lot of difficulties to (4) no difficulty and (1) very true to (4) very false. The form is designed for self-administration, and the participants completed the form on their own. A former master student was present to answer questions and helping the participants if necessary. When helping the participants the master's student was aware to not influence the participants answers. Further the individual scores were calculated using a Microsoft Excel file, where the present masters student manually punched the participants answers, and double checked for errors. Calculations were completed to investigate if the participating men and women had reduced QOL for each domain compared to a healthy population, giving each

participant a score from 0-100 for each subscale, where the higher score reflects better QOL. **Appendix 5** illustrates how the participants were divided into reduced HRQoL or not compared to the healthy population, depending on sex. If participants had more than 50% missing items in one domain, they were excluded from further analysis. Also, if participants had not answered an item, or had two answers for an item, further calculations were performed excluding those items. Clinically significant difference for the CFQ-R is not established.

3.2.2 Gastrointestinal symptoms

To determine the participants GI-symptoms, the GSRS was used (**Appendix 6**). The form consists of 15 questions regarding abdominal pain, diarrhea, constipation, indigestion and reflux. **Appendix 7** gives av overview of which items that are included in the different domains. Each item has a 7-points Likert response rate, where the participants rate their symptoms from 1=no symptoms to 7= very severe symptoms. For this form higher response rates indicate more severe symptoms. This form is also designed for self-administration and was completed in the same manner as described above for the CFQ-R. Further the present master student manually punched the GSRS answers and double checked for errors. The individual scores were calculated by summation of the item responses for each group of questions and dividing by the number of items in each domain. In this way an individual GSRS score for each domain were calculated, and further an individual GSRS total score was calculated, as a mean of all domains. These calculations were completed using Microsoft Excel. If participants had more than 50% missing items in one domain, they were excluded from further analysis. Also, if participants had not answered an item, or had two answers for an item, further calculations were performed excluding those items. The results of the study population were compared to normative data collected in the Swedish population among a group of 60-69 years. Comparisons are only made for the total study population, and not for female and male separately, as separate reference data are not available. Clinically significant difference is set to 0.5 points for the GSRS (75).

It is important to notice that the symptom-scale for the CFQ-R and the GSRS are in different direction (a higher score in the CFQ-R indicate better HRQoL, while a higher score in the GSRS indicate more severe symptoms). Therefore, reduced scores for all CFQ-R domains indicates increased symptoms and increased scores for all CFQ-R domains indicates reduced

symptoms, while reduced scores for all GSRS domains indicate reduced symptoms and increased scores for all GSRS domains indicated increased symptoms. Additionally, when investigating correlation, the results will be opposite. A positive correlation between domains in the CFQ-R and factors will illustrate less symptoms, while a positive correlation between the domains in the GSRS and factors will illustrate increased symptoms. Further a negative correlation between the domains in the CFQ-R and parameters will illustrate increased symptoms, while a negative correlation between the domains in the GSRS and parameters will illustrate less symptoms.

3.2.3 Anthropometry and spirometry

Weight

Weight was measured using the Sea Medical Body Composition Analyzer 704 (Seca GmbH & Co. KG, Hamburg, Germany). Weight was measured without heavy clothes, shoes and outwear. Clothing adjustment is shown to be useful if it is 0.8 kg for women, and 1.2 kg for men, as men have a significantly greater clothing weight than women (76). Bodyweight was in this study adjusted for clothing by subtracting 1-1.5 kg, regarding of what the participants were wearing. A nurse at the Department of Pulmonary disease performed all measurements regarding anthropometry and lung function.

Height

Height was measured using the Seca 704 digital wireless stadiometer (Seca GmbH & Co. KG, Hamburg, Germany). Height was measured without shoes, and the participants was asked to stand in an upright position, with a straight back, looking straight forward. The device measured height to the nearest 0.1 centimeter.

Body mass index and nutritional status

BMI were calculated by using measured weight and height, by dividing weight (kg) with height in squared meters for each participant. The calculated BMI were compared with cut-off values for adults from World Health Organization (WHO) (**table 2**) (77). Further the BMI were compared with the ESPEN BMI recommendations for patients with CF, shown in **table 3** (19).

Table 2 WHO´s cut off values for BMI for white, Hispanic and Black individuals (30).

BMI (kg/m^2)	Nutritional Status
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight/pre obesity
30.0-34.9	Obesity class 1
35.0-39.9	Obesity class 2
>40.0	Obesity class 3

Table 3 ESPEN guidelines BMI recommendations for patients with CF.

Sex	Recommended BMI (kg/m^2)
Male	> 23
Female	> 22

Lung function

FEV_1 was used to assess lung function for the participants. This is a measurement of the amount volume of air expired within the first second after forced expiration. In this study we use the % of predicted FEV_1 compared to a reference group for each participant, dependent on sex, age and height. How FEV_1 is used to classify lung function is shown in **table 4**.

Table 4 Classification of lung function according to FEV_1

FEV1 % of predicted	Classification
> 80 %	Normal
80 – 60 %	Mild impairment
59 – 40 %	Moderate impairment
< 40 %	Severe impairment

3.2.4 Body composition analysis

Body composition was analyzed using the Dual Energy X-ray Absorptiometry (DXA), in this study using a Lunar Prodigy Advance Dual Energy X-ray Absorption, DF+ 14685, Prodigy 4 model (GE healthcare Norge AS, Oslo, Norway). The software program used by this machine was enCORE, version 16 sp2. The devise measures body composition using a low dose of radiation that measures and separates the different body compositions (soft tissue, bone composition, bone-mineral density, lean- and fat-tissue mass and percentage of fat). Before the analysis, the participants name, sex, age and ethnicity were plotted. A nurse at the Department of Orthopedics at OUH, Ullevål performed the measurements, and instructed the

participant to wear light clothes and remove shoes and outwear, further any materials with metal etc. belts, buttons and zips. When conducting the analysis, the participants had to lay calm. We conducted a full body scan, however, in the present study we are going to use the measurements FFM and muscle mass in the four different limbs from the scan. FFMI (FFM/height^2), AMS and AMSI (AMS/height^2) were calculated for each participant. ASM and ASMI were used to define sarcopenia in the study population (**table 1**). According to ESPEN, malnutrition is defined by low FFMI <17 kg/m^2 in men and <15kg/m^2 in women (31). In this study the ESPEN FFMI cut-off values and the ESPEN BMI recommendations for patients with CF will be used to determine malnutrition.

3.2.5 Physical test

HGS was measured using KERN WOC17006539, MAP 80K1 (KERN & Sohn GmbH, Ziegelei 1, 72336 Balingen, Germany) handgrip dynamometer. Guidelines by the American Society of Hand Therapist were used to standardize the HGS measurements (78). For the analysis the dominant arm was used for each participant. For the measurement the participants were seated upright against the back of a chair without armrests, with feet placed on the floor. The forearm was in a neutral position with wrist slightly extended, elbow was flexed, and the shoulder was adducted and neutrally rotated. The test was repeated three times within a minute, and the mean value for each participant was used for further calculations. **Table 5** shows the reference values for HGS from the healthy population, used for comparison with the study population (79).

Table 5 Cut-off values for hand grip strength for healthy men and women

Age (y)	**Male**		**Female**	
	Mean (±SD)	Min-max	Mean (±SD)	Min-max
20-29	53 (±8)	(36-70)	32 (±5)	(19-44)
30-39	54 (±10)	(36-83)	33 (±5)	(21-49)
40-49	54 (±7)	(34-70)	32 (±6)	(19-46)
50-59	51 (±9)	(29-79)	28 (±5)	(14-39)
60-69	45 (±7)	(32-63)	26 (±5)	(10-40)
70-79	38 (±9)	(17-51)	21 (±4)	(12-29)
80-95	31 (±8)	(16-44)	16 (±4)	(10-27)

3.2.6 Dietary intake and nutritional needs

A previous master´s student conducted three 24 hours diet recalls. Two weekdays and one weekend day were selected. In each recall the student asked the participants to recall all foods and beverages they had consumed the day before. The recall was conducted as an interview. Further brand names, portion size and method used for preparation were asked. Intake of snacks, alcohol and nutritional supplements (both energy providing nutrients and vitamin/mineral supplementation). In this study these results are used to calculate each participant´s mean energy intake and intake of energy giving nutrients (carbohydrates, protein and fat). Mean dietary intake was analyzed using a software program called Dietist Net, version 19.02.25 (Kost och Näringsdata AB, Bromma, Sweden). This program contains food items from Norway, Sweden and other countries. The program estimates intake of energy, macro- and micronutrients. Further each participant´s total energy intake and intake of energy giving nutrients were compared with each participant´s calculated energy needs, and recommended intake of energy providing nutrients for patients with CF. Recommended intake of different energy providing nutrients for patients with CF (ESPEN) and for the healthy population (NNR) are illustrated in **table 6** (19, 80).

Table 6 Recommended intake of energy giving nutrients for patients with CF and for the general population.

Nutrient	ESPEN	NNR 2012
Carbohydrate, E%	40-45	45-60
Protein, E%	≥ 20	10-20
Fat, E%	35-40	35-40

Recommended daily energy intake for each participant in this study is calculated by estimating each participant´s total energy expenditure (TEE). TEE is estimated using the Harries Benedict formula which estimates basal metabolic rate (BMR) in kcal (**table 7**), physical activity level (PAL) 1.6, and lung factor (LF) depending on FEV_1 values (**table 8**). The LF-factor table are made together with Inger Elisabeth Moen, as a more detailed table than what is given by Ramesy et. al (81).

Table 7 The Harris-Benedict equation used in this study for calculating the participants BMR (in kcal).

Sex	Harris-Benedict equation
Men	W x 13.75 + H x 5 – Y x 6.8 + 66
Women	W x 9.6 + H x 1.8 – Y x 4.7 + 655

Abbreviations: W; weight in kg, H; height in cm, Y; years, BMR; basal metabolic rate.

Table 8 Illustrates which LF are used for different FEV_1 values.

FEV_1 % of predicted	LF
> 80%	0.0
40-80 %	0.2
< 40 %	0.3-0.5
30-39 %	0.3
20-29 %	0.4
10-19 %	0.5

Abbreviations: FEV_1; forced expiratory volume in the first second, LF; lung factor

3.3 Statistical analysis

The statistical analysis was performed using the software program SPSS statistics, version 25 (IBM SPSS Statistics 25). For statistically significant level p-values <0.05 was used. To determine if the data was normally- or non-normally distributed histograms, normality plots (Q-Q Plot) and tests of normality were used. Missing values were excluded from analysis, and number of participants included in each analysis are described in table. Continuous normally distributed variables are presented in mean and standard deviation (SD). Independent samples t-test was used to compare means between groups for normally distributed data for continuous variables. For comparing a study population´s mean to a known normative mean the One-Sample-t-test was used. To present categorical data frequencies (n) and percentages (%) were used. To compare two categorical variables, Pearson Chi-Square test was performed. Fisher test was used if the cells had expected frequency of five or less. Pearson´s correlation coefficient was used to examine association between specific variables.

3.4 Ethical considerations

This project was ethically approved by Regional Committees for Medical and Health Research Ethics (case nr. 2018/ 1035) in REK south-east (25.06.2018) (**Appendix 8**). Participants were informed about the project, the aims, the benefits and disadvantages of this project before they signed a written consent (**Appendix 2**). The participants further received a

copy of the written consent. All the participants were ensured that participation in the study was voluntary, and that they could withdraw from the study at any point. All sensitive information collected in this study were handled in a safe way. Sensitive information in paper was locked in a sideboard at OUH, Ullevål. Electronic sensitive information was saved in an electronic folder for sensitive data in the research server at OUH. Identifiable information like the participants names were replaced with unidentifiable codes. Information about the participants will be deleted within five years after end of the project. There was no health risk associated with this study for the participants, and they were further ensured according to the law of the patients' damage (Pasientsikkerhets loven). The participants were informed that if the blood samples or DXA analysis showed any abnormalities, the participants´ general practitioner would get information upon patient´s consent.

4 Results

4.1 Study sample

4.1.1 Study population

In this study 33 participants, 20 men and 13 women were included, out of 49 eligible (67.3%). **Figure 3** shows an overview of the recruitment process.

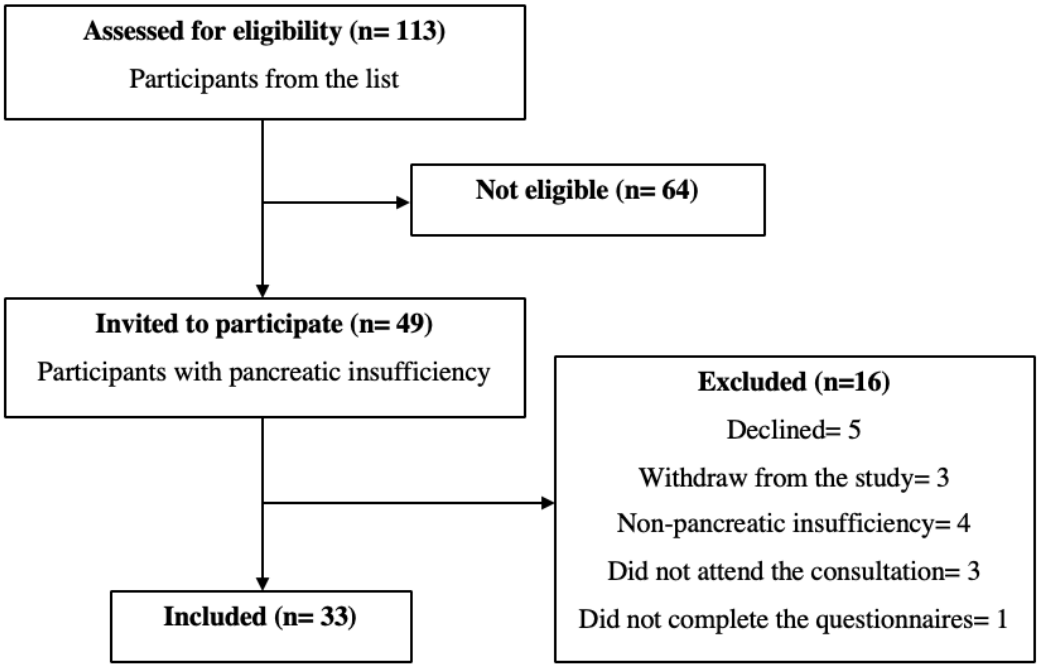


Figure 3 Flow chart of the recruitment process of the participants.

4.1.2 Characteristics of the study population

Table 9 shows characteristics of the study population, including anthropometric- and lung function measures. The majority of the participants in this study were men (60.6%). The mean age for all participants were 35.5 (14.8) years, ranging from 18 years to 75 years. Men were significantly taller and heavier than women ($p<0.05$). All participants were Caucasian. Further six participants (18.2%) were diagnosed with diabetes.

Table 9 Background characteristics for the study population (n=33)

	Female (n=13)**	**Male (n=20)****	**P-value**
Age, Mean (SD)	35.6 (17.9)	35.4 (12.9)	0.961
Anthropometric Measures			
Weight[a] Mean (SD)	61.0 (12.8)	80.1 (17.9)	0.002*
Min-max	45.9-83.0	53.9-125	
Height Mean (SD)	163.2 (7.4)	179.3 (4.6)	0.000*
Min-max	154-174	171-188	
BMI Mean (SD)	22.8 (3.7)	24.9 (5.1)	0.213
Min-max	18.9-29.6	17.4-37.7	
Lung function			
FEV_1 Mean (SD)	66.2 (27.1)	62.2 (25.8)	0.672
Min-max	32-102	27-96	
Diabetes Status			
Diabetes type 1, n (%)	1 (7.7)	1 (5.0)	1.000***
Diabetes type 2, n (%)	1 (7.7)	1 (5.0)	1.000***
CFRD, n (%)	0 (0.0)	2 (10.0)	0.508***
Ethnicity			
Caucasian/white race, n (%)	13 (100)	20 (100)	

Continuous variables are considered normally distributed.
*Independent-samples T-test showed p <0.05
**Chi-Square test showed p>0.05in sex
***Fisher´s Exact test showed p>0.05 in diabetes status
[a]Body weight were adjusted for clothing weight by subtracting 1-1.5 kg for men and women.
Abbreviations: Age; age in years, weight; weight in kg, height; height in cm, BMI; body mass index (kg/m^2), n; number, SD; standard deviation, min; minimum, max; maximum, FEV_1; forced expiratory volume in the first second (% of predicted), CFRD; Cystic fibrosis related diabetes.

4.2 Evaluate health related quality of life

All 33 participants fulfilled the CFQ-R, with a total of 2.5% missing items, a median of 0%, ranging from 0% to 34% missing items. **Figure 4** shows the variation within the study populations CFQ-R results. A higher score indicates increased HRQoL for the different domains. The lowest score was observed for vitality. An overview of how many women and men that had reduced HRQoL compared to the healthy population is shown in **table 10**. Only one participant had not reduced HRQoL in any domains compared to the healthy population. Most participants had reduced HRQoL for Health Perceptions (87.5%), while fewest participants had reduced HRQoL for Body Image (35.5%). All together the participants had in mean reduced HRQoL in seven of 12 domains, ranging from 0-12. Men had in mean reduced HRQoL in seven domains, ranging from 2 to 12, while women in mean had reduced HRQoL in seven domains, ranging from 0-11. There were significantly more men than women with reduced HRQoL within the role-domain (p=0.011).

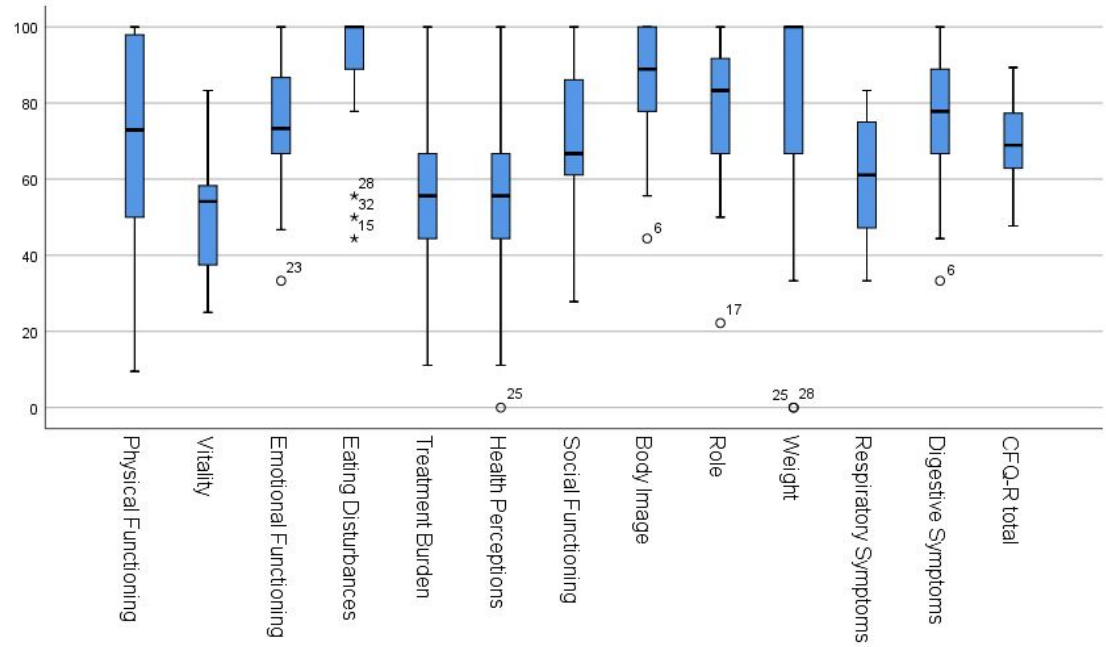


Figure 4 CFQ-R scales for the study population (n=33). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.

Table 10 Overview of participants with reduced HRQoL compared with the healthy population.

	Female (n=13) n (%)	**Male (n=20) n (%)**	**Total (n=33) n (%)**
Physical functioning	7 (58.3)[1]	10 (50)	17 (53.1)[1]
Vitality	9 (75)[1]	17 (85)	26 (81.3)[1]
Emotional functioning	9 (75)[1]	10 (50)	19 (59.4)[1]
Eating disturbances	8 (61.5)	7 (35)	15 (45.5)
Treatment Burden	9 (69.2)	13 (65)	22 (66.7)
Health Perception	10 (76.9)	18 (90)	28 (87.5)
Social functioning	9 (69.2)	13 (65)	22 (66.7)
Body Image	2 (18.2)[2]	9 (45)	11 (35.5)[2]
Role	4 (40)[3]	17 (85)	21 (70)[3]
Weight	5 (38.5)	8 (42.1)[1]	13 (40.6)[1]
Respiratory symptoms	10 (76.9)	13 (65)	23 (69.7)
Digestive symptoms	10 (76.9)	12 (60)	22 (66.7)

[1]One subject has insufficient data, and is therefore excluded from this calculation
[2]Two subjects have insufficient data, and are therefore excluded from this calculation
[3]Three subjects have insufficient data, and are therefore excluded from this calculation
Abbreviations: n; number

4.3 Evaluate gastrointestinal symptoms

The GSRS questionnaire was completed by all 33 participants, with a total of 1.6% missing items, a median of 0%, ranging from 0% to 46.7% missing items. **Figure 5** shows the variations in symptoms within the study population. There were large variations in GI-

symptoms within the study population. As shown in the figure most of the participants in this study experience their symptoms as mild to moderate. The highest score in the study population was reported for the domain indigestion. When looking into each question for each domain two participants (6.1%) experience their indigestion symptoms as moderate to moderately severe, three participants (9.1%) experience their constipation symptoms as moderate to moderately severe and severe. Apart from this, all participants had symptoms classified as no-mild/moderate symptoms. Results compared to reference group is showed in **table 11**. The study population had significantly more diarrhea, indigestion, constipation, abdominal pain and GSRS total symptoms ($p<0.05$). There were no clinical or statistical significantly differences between sex for any of the symptoms within the study population.

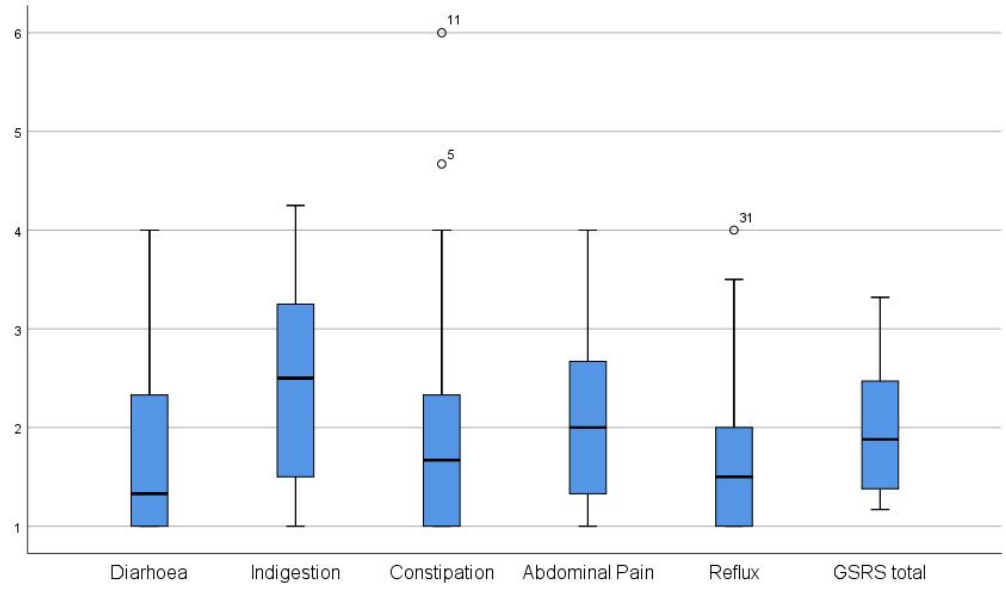


Figure 5 GSRS scales for the study population (n=33). Y-axis shows GSRS domain mean score, 1-7 where 7 indicates most GI-symptoms. Boxes represent interquartile range, whiskers represent lowest and highest reported score. The box line shows the group median.

Table 11 Overview of the participants GSRS results compared to a reference group (n=33)

Symptom	**Study sample** Mean (95% CI)	**Reference group** Mean (95% CI)	**p-value**
Diarrhea	1.7 (1.4-2.0)	1.3 (1.2-1.4)	0.006*
Indigestion	2.4 (2.0-2.7)	1.8 (1.7-1.9)	0.002*
Constipation	2.1 (1.6-2.5)	1.5 (1.4-1.7)	0.012*
Abdominal pain	2.1 (1.8-2.3)	1.5 (1.4-1.6)	0.001*
Reflux	1.7 (1.4-2.0)	1.4 (1.3-1.5)	0.055
GSRS Total	2.0 (1.8-2.2)	1.5 (1.4-1.6)	0.000*

*One-Sample t-test showed $p<0.05$
Abbreviations: CI; confidence interval, GSRS; gastrointestinal rating scale

4.4 Assess nutritional status

4.4.1 Evaluate nutritional status with nutritional intake and requirements

All the participants completed three days of dietary recalls. An overview of total energy intake, energy needs and intake of macronutrients are presented in **table 12**. For the entire study population, the participants mean energy intake covered 78.1 (24) % of TEE, ranging from 46.1% to 144.6%. Three participants (9.1%) had an energy intake <50% of TEE, 15 participants (45.5%) had an energy intake covering 50-75% of TEE, nine participants (27.3%) had an energy intake covering 75-100% of TEE and six participants (18.2%) had a total energy intake that covered >100% of TEE. For the entire study population protein accounted for 17.7 (3.8) E%, ranging from 12.7 E% to 25.7 E%, carbohydrates for 48.1 (9.4) E%, ranging from 19.0 E% to 62.3 E%, fat for 31.7 (8.8) E%, ranging from 20.0 E% to 63.9 E%. Nine participants (27.3%) were within the ESPEN recommendation for protein intake, 24 participants (72.7%) had a lower protein intake then recommended, for carbohydrates four participants (12.1%) were within the recommendations, six participants (18.2%) had a lower intake than recommended, and 23 participants (69.7%) had a higher intake than recommended, for fat eight participants (24.2%) were within the recommendations, 23 participants (69.7%) had a lower intake than recommended and two participants (6.1%) had ha higher intake then recommended. Apart from energy intake and TEE there were no significantly differences between men and women ($p<0.05$).

Table 12 Overview of total energy intake, energy needs and intake of macronutrients (n=33)

	Female (n=13)		**Male (n=20)**		**p-value**
	Mean (SD)	Min-max	Mean (SD)	Min-max	
Energy intake, MJ/d	8.6 (2.2)	5.6-12.2	11.0 (3.2)	7.9-21.0	0.025*
TEE	10.8 (1.0)	9.3-12.3	14.6 (1.8)	11.2-18.4	0.000*
% of TEE	80.4 (23.1)	49.0-131.1	76.7 (25.0)	46.1-144,6	0.666
Protein, E%	17.7 (4.6)	12.9-25.3	17.7 (3.3)	12.7-25.7	0.975
Carbohydrates, E%	48.3 (10.2)	28.2-62.3	48.0 (9.2)	19.0-60.1	0.943
Fat, E%	31.1 (7.4)	22.4-49.9	32.1 (9.1)	20.0-63.9	0.760

*Independent-samples T-test showed $p > 0.05$
Abbreviations: MJ; mega joule, TEE; total energy expenditure, E%; energy percent, IE; international units.

4.4.2 Evaluate nutritional status with BMI

BMI results are showed in **table 9.** Mean BMI were 24 (4.7) kg/m^2, ranging from 17.4 kg/m^2 to 37.7 kg/m^2. According to the WHO guidelines one participant (3%) were underweight, 21 participants (63.6%) were normal weight, eight participants (24.2%) were overweight, two participants (6.1%) had obesity class 1 and one participant (3%) had obesity class 2. Further according to the ESPEN recommendation 18 participants (54.5%), eight women and ten men did not achieve the BMI goal for patients with CF.

4.4.3 Evaluate nutritional status with sarcopenia

Body Composition

Of the 33 participants, 26 were able to perform DXA measurements. Results from the DXA scan is shown in **table 13**. Men had significantly higher FFM, ASM and ASMI than women ($p<0.05$). Mean FFMI for the total study population was 18.6 (8.7) kg/m^2, ranging from 12.7 kg/m^2 to 60.3 kg/m^2. When using the ESPEN FFMI for cut off, four women and three men (25.9%) were classified as malnourished. According to the EWGSOP sarcopenia definition, eight participants had ASM below the sarcopenia cut-off value (<20 kg for men and <15 kg for women) and six participants had ASMI below the sarcopenia cut-off value (<7.0 kg/m^2 for men and <5.5 kg/m^2 for women). Five participants had both ASM and ASMI below the sarcopenia cut-off value. In total 27.3% participants were diagnosed with sarcopenia. Further we found a significant positive correlation between BMI and FFMI for participants with BMI ≤25 kg/m^2 ($p<0.05$), and no significant relation between BMI and FFMI for participants with BMI >25 kg/m^2. The same findings were found when investigating the relation between BMI and ASM, and BMI and ASMI **(Appendix 9)**.

Table 13 DXA results for the study population (n=26).

	Female (n=13)		**Male (n=13)**		**p-value**
	Mean (SD)	Min-max	Mean (SD)	Min-max	
FFM, kg	41.5 (5.6)	32.9-49.1	58.6 (8.5)	44.7-76.1	<0.001*
FFMI, kg/m^2	15.6 (1.6)	12.7-18.0	21.4 (11.4)	13.8-60.3	0.078
ASM, kg	16.2 (3.3)	11.6-22.1	25.2 (5.5)	13.9-37.0	<0.001*
ASMI, kg/m^2	6.0 (1.0)	4.3-7.6	7.9 (1.5)	4.3-10.6	0.001*
HGS, kg	22.8 (6.6)	9.8-34.1	42.4 (9.9)	23.0-60.6	<0.001*

Continuous variables are considered normally distributed.
*Independent-samples T-test showed $p<0.05$
Abbreviations: SD; standard deviation, min; minimum, max; maximum, FFM; fat free mass, FFMI; fat free mass index, HGS; hand grip strength, ASM; appendicular skeletal muscle mass, ASMI; appendicular skeletal muscle mass index

HGS

HGS results are presented in **table 13**. Men had significantly higher HGS than women ($p<0.05$). According to sarcopenia guidelines three participants had HGS below the cut-off value, suspecting sarcopenia. Further 19 participants (61.3%), ten women (76.9%) and nine men (50%) had lower HGS than the reference value. However, compared to reference values, the HGS results in this study population were significantly reduced, regardless of age for all participants ($p<0.05$).

4.5 Assess lung function

Lung function results are showed in **table 9.** Mean FEV_1 for all participants were 63.7 (26) % of predicted, ranging from 27% to 102%. Further, 13 participants (39.4%) were classified with normal FEV_1, four participants (12.1%) were classified as mild impaired, eight participants (24.2%) were classified as moderate impaired and eight participants (24.2%) were classified with severe impaired lung function. We found a positive correlation between FEV_1 and BMI ($p<0.05$) (**Appendix 9**).

4.6 Compare HRQoL among subjects with and without malnutrition

4.6.1 Nutritional status evaluated by BMI

When using the ESPEN BMI cut-off values 18 participants (eight women and ten men) were defined as malnourished. **Figure 6** illustrates how the CFQ-R scale results are in nourished and malnourished participants when using the ESPEN BMI cut-off values. Malnourished participants had significantly reduced HRQoL, i.e. increased symptoms for the domains eating disturbances ($p=0.04$) and weight ($p=0.01$).

When investigating BMI in relation with HRQoL there was a significantly positive correlation between BMI, eating disturbance and the weight domain ($p<0.05$) (**Appendix 9**). When dividing the participants into two groups with BMI $\leq$25 kg/m^2 and BMI >25 kg/m^2, there was a significantly positive correlation between participants with BMI $\leq$25 kg/m^2 and the weight domain ($p<0.05$), and no correlations between the weight domain and BMI for participants with BMI >25 kg/m^2 (**Appendix 9**). Further there were a significantly negative correlation between body image and BMI for participants with BMI >25 kg/m^2 ($p<0.05$) (**Appendix 9**).

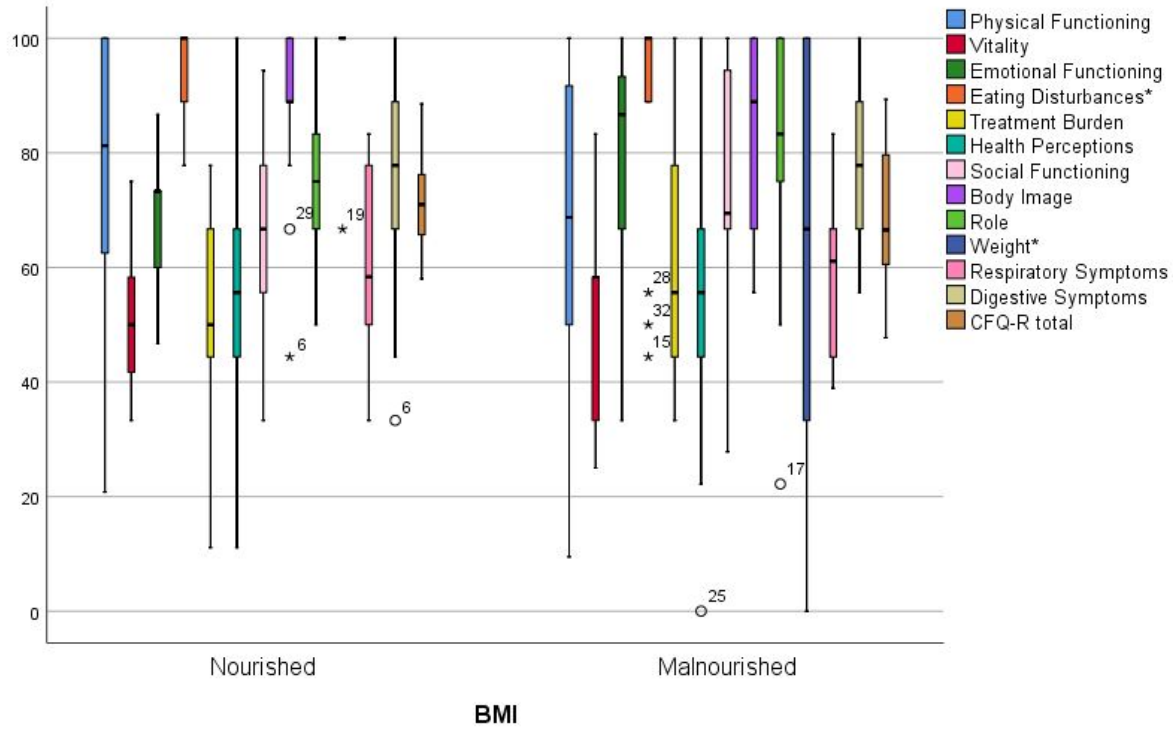
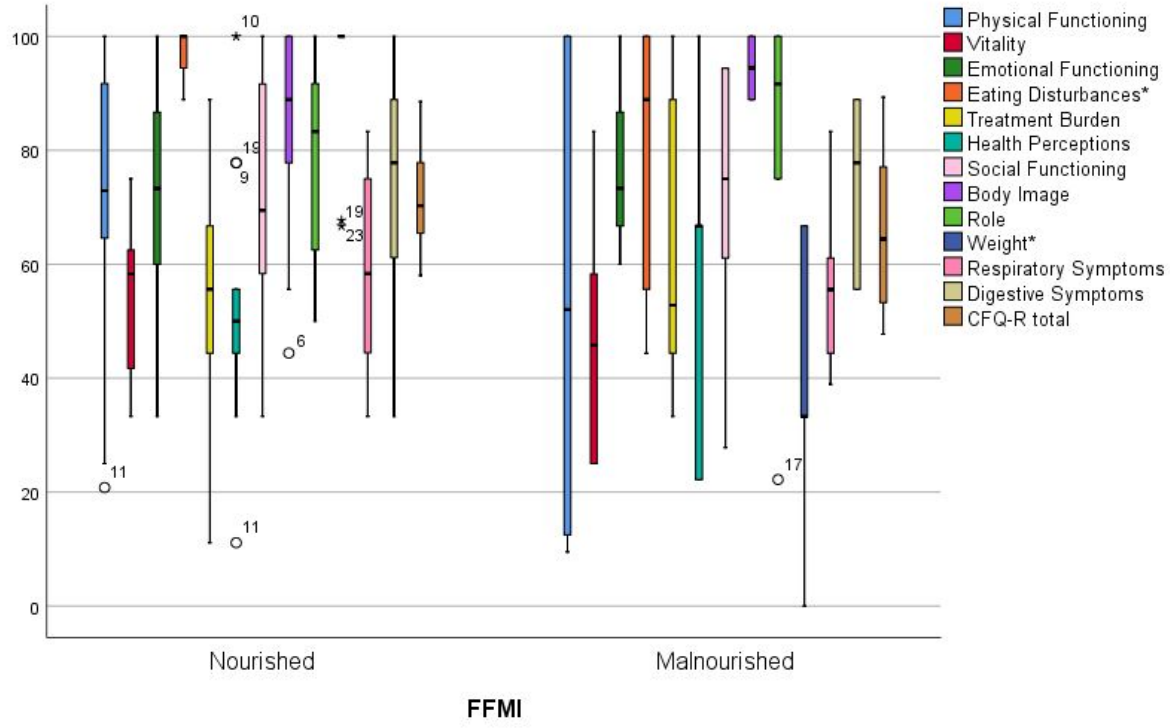


Figure 6 CFQ-R scales for the study population when divided into groups depending on nutritional status using BMI (malnourished= men <23 kg/m^2 and <22 kg/m^2), (n=33). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: BMI; body mass index, CFQ-R; cystic fibrosis questionnaire revised.

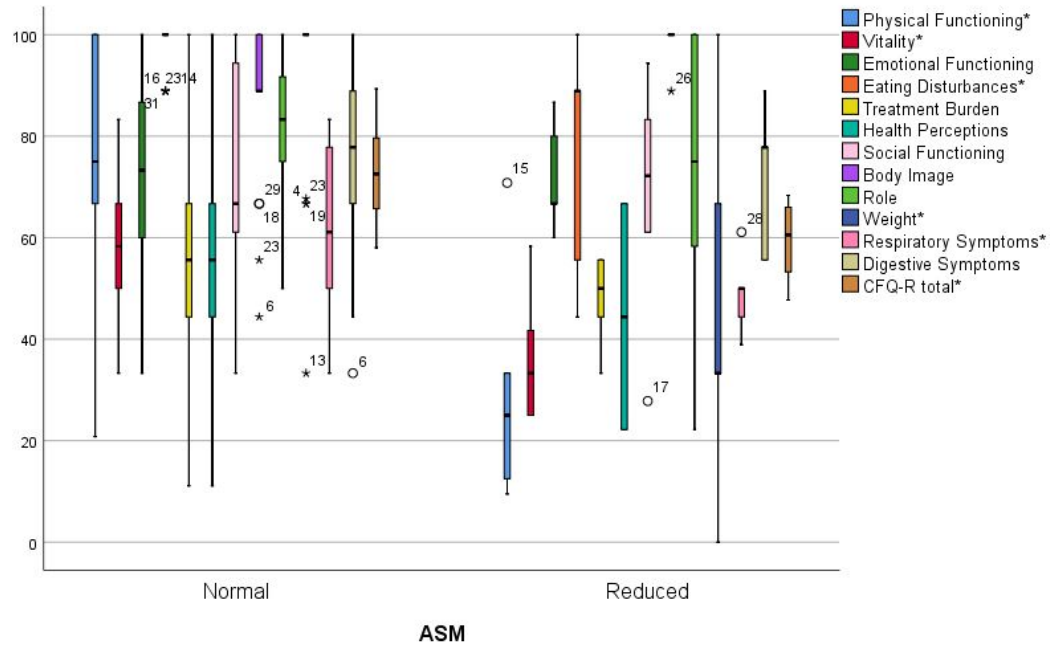
4.6.2 Nutritional status evaluated by sarcopenia

When using the ESPEN FFMI cut-off values seven participants (four women and three men) were defined as malnourished. **Figure 7** illustrates how the CRQ-R scale results are in nourished and malnourished participants when using the ESPEN FFMI cut-off values. Malnourished participants had significantly reduced HRQoL, i.e. increased symptoms for the domains eating disturbances (p=0.01) and weight (p=0.01).

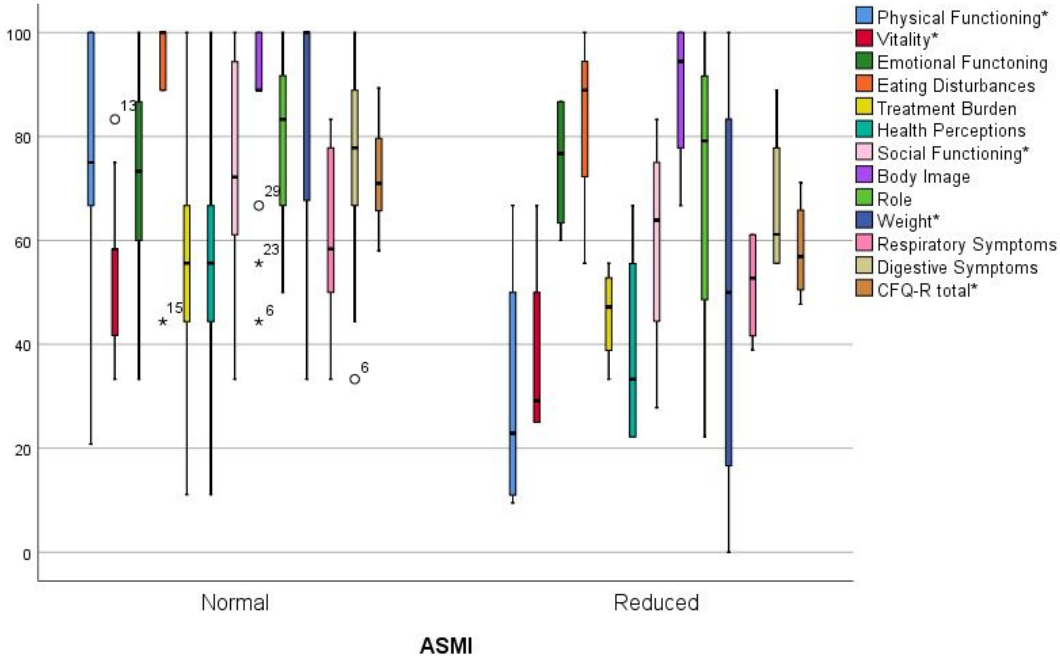


Figur 7 CFQ-R scales for the study population when divided into groups depending on nutritional status using FFMI (malnourished= men <17 kg/m^2 and women <15 kg/m^2), (n=26). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: FFMI: fat free mass index, CFQ-R; cystic fibrosis questionnaire revised

Figure 8 and **figure 9** illustrates the CFQ-R results in participants with and without sarcopenia. When investigating HRQoL in relation with sarcopenia we found that participants with impaired ASM and ASMI had significantly reduced HRQoL, i.e. increased symptoms for physical function (p=0.001/p=0.01), vitality (p=0.01/p=0.01), weight (p=0.01/p=0.01) and CFQ-R total (p=0.01/p=0.01). Further, participants with decreased ASM had significantly reduced HRQoL, i.e. increased symptoms for eating disturbances (p=0.01) and respiratory symptoms (p=0.04). Additionally, participants with decreased ASMI had significantly reduced HRQoL, i.e. increased symptoms social functioning (p=0.046).



Figur 8 CFQ-R scales for the study population when divided into groups depending on ASM (normal= ≥20 kg for men and ≥15 kg for women, reduced= <20 kg for men and <15 kg for women), (n=26). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: ASM: appendicular skeletal muscle mass, CFQ-R; cystic fibrosis questionnaire revised



Figur 9 CFQ-R scales for the study population when divided into groups depending on ASMI (normal= ≥7.0 kg/m^2 for men and ≥5.5 kg/m^2 for women, reduced= <7.0 kg/m^2 for men and <5.5 kg/m^2 for women), (n=26). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: ASMI; appendicular skeletal muscle mass index, CFQ-R; cystic fibrosis questionnaire revised

No significantly relations were found between HRQoL and energy- and nutrient intake.

4.7 Compare GI-symptoms among subjects with and without malnutrition

4.7.1 Nutritional status evaluated by BMI

When investigating BMI in relation with GI-symptoms no significant differences between nourished and malnourished participants were found. However, we found a significantly positive correlation, i.e. increased symptoms for participants with BMI >25 kg/m^2 and indigestion symptoms, diarrhea symptoms and GSRS total ($p<0.05$) (**Appendix 9**). No significant relations were found between GI-symptoms and BMI for participants with BMI <25 kg/m2. We further found a significantly positive correlation between reflux symptoms and BMI (<0.05) (**Appendix 9**).

4.7.2 Nutritional evaluated by sarcopenia

Figure 10 illustrates GSRS results for malnourished and nourished participants when using the ESPEN FFMI cut-off values. Malnourished participants were found to have significantly less reflux symptom ($p=0.04$) than nourished participants.

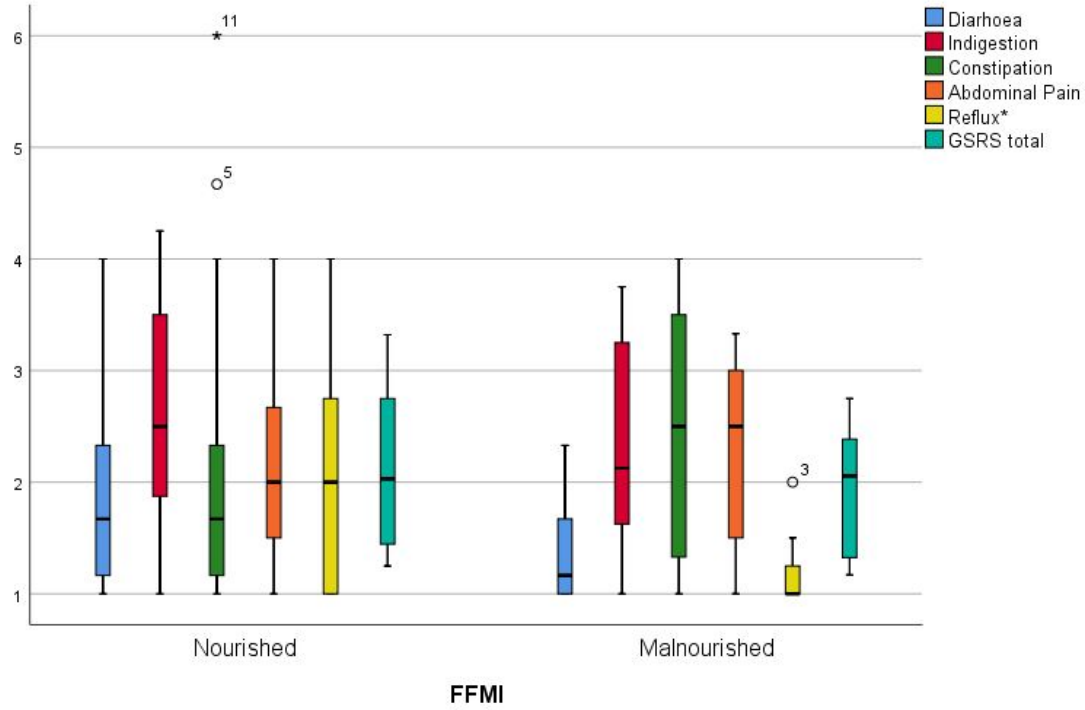


Figure 10 GSRS scales for the study population, wen divided into groups depending on nutritional status using FFMI (malnourished= men <17 kg/m^2 and women <15 kg/m^2), (n=26). Y-axis shows GSRS domain mean score, 1-7 where 7 indicates most GI-symptoms. Boxes represent interquartile range, whiskers represent lowest and highest reported score. The box line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: FFMI; fat free mass index, GSRS; gastrointestinal symptom rating scale

4.7.3 Nutritional status evaluated by nutritional intake and requirement

Figure 11 illustrates the GSRS results for participants depending on energy intake. When investigating energy intake in relation with GI-symptoms, we found that patients with energy intake <75% of TEE had significantly more indigestion symptoms (p=0.02) and GSRS total scores (p=0.02) compared with participants having a total energy intake ≥75% of TEE. When investigating correlation, we found a significantly negative correlation between % of TEE, indigestion symptom and reflux symptoms (p<0.05) (**Appendix 9**).

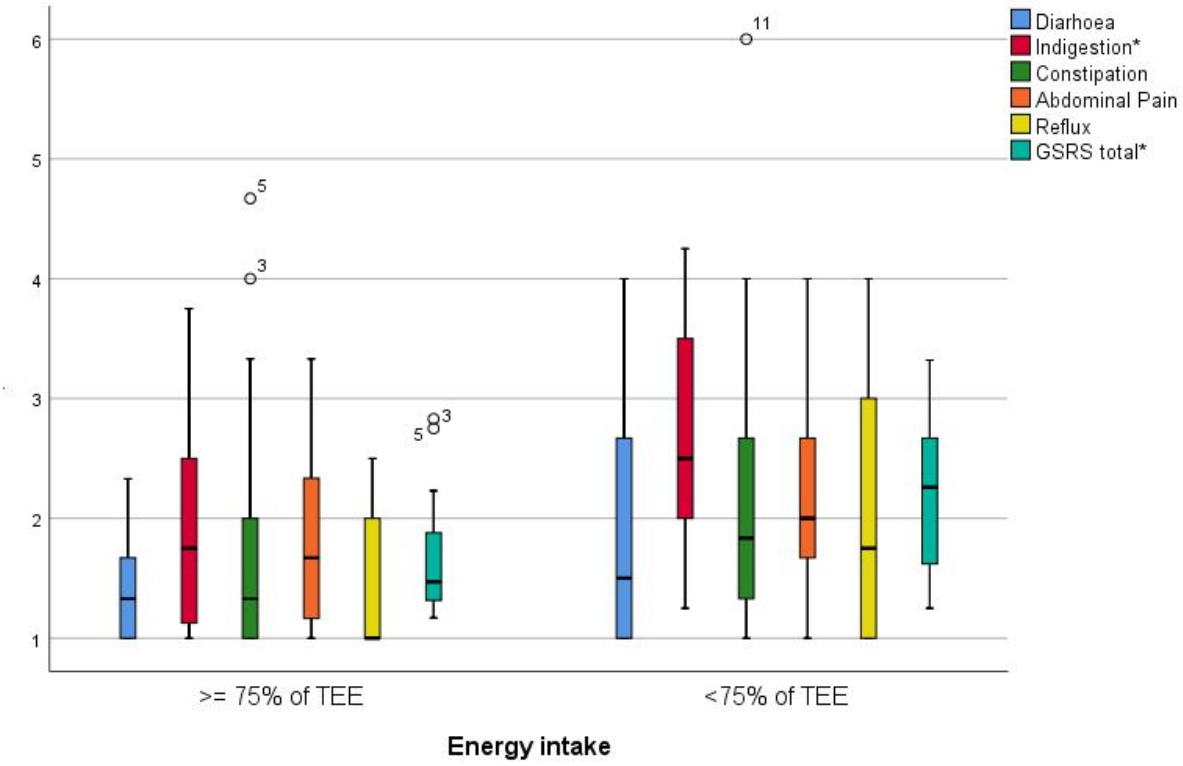
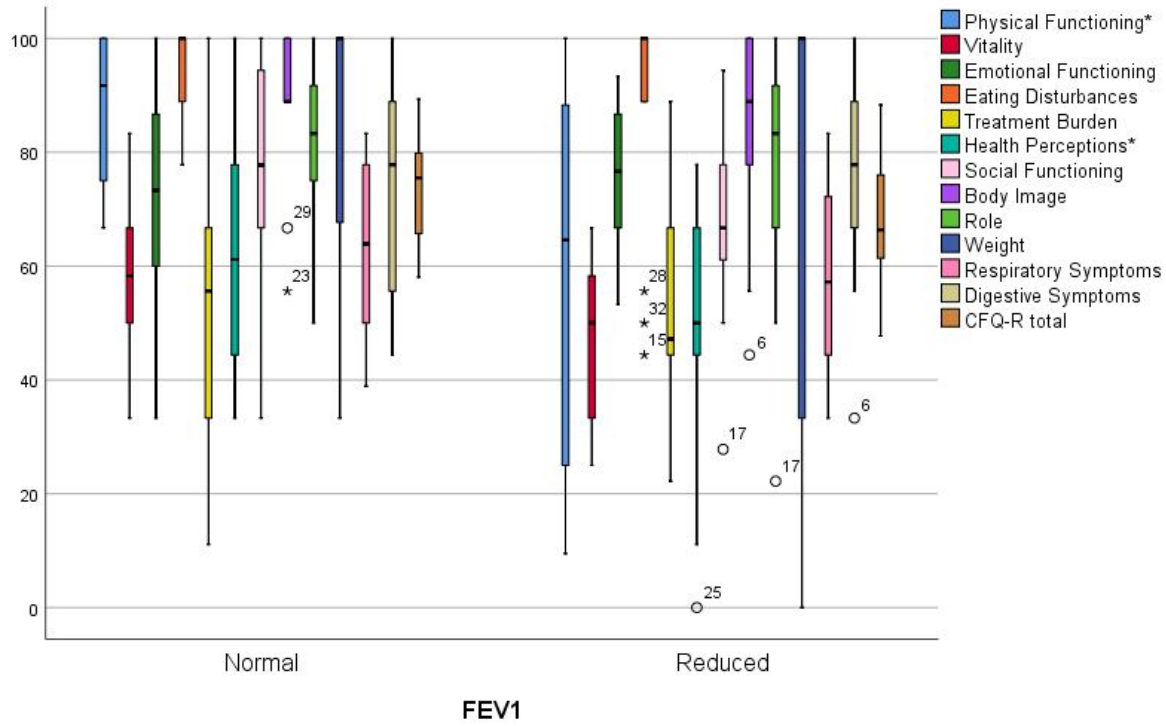


Figure 11 GSRS scales for the study population, wen divided into groups depending on energy intake (≥ 75 % of TEE and < 75 % of TEE), (n=33). Y-axis shows GSRS domain mean score, 1-7 where 7 indicates most GI-symptoms. Boxes represent interquartile range, whiskers represent lowest and highest reported score. The box line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: TEE; total energy expenditure, GSRS; gastrointestinal symptom rating scale

No significant relations were found between GI-symptoms and sarcopenia or HGS.

4.7.4 Evaluate HRQoL among subjects with and without impaired lung function

Figure 12 illustrates CFQ-R results for participants with normal and impaired FEV_1. Reduced FEV_1 in the study population were significantly related with reduced HRQoL, i.e. increased symptoms for physical function (p=0.01) and health perception (p=0.03). Further, when looking at correlation between FEV_1 and HRQoL we found a significantly positive correlation between FEV_1, physical function, health perception and CFQ-R total (p<0.05) (**Appendix 9**). When conducting a multiple analysis, we found a significantly positive correlation between FEV_1, physical function and health perception (p<0.05) (**Appendix 9**).



Figur 12 CFQ-R scales for the study population when divided into groups depending on lung function (Normal= >80% of predicted, reduced = ≤80 % of predicted), (n=33). Y-axis shows CFQ-R domains scores 0-100, where 100 indicates best possible HRQoL. Boxes represents interquartile range, whiskers represent lowest and highest reported score. The box-line shows the group median.
* Independent-samples T-test showed p <0.05
Abbreviations: FEV_1; Forced expiratory volume in first second, CRQ-R; cystic fibrosis questionnaire revised

No significant relations were found between GI-symptoms and lung function.

5 Discussion

5.1 Discussion of subjects and methods

5.1.1 Study design

This was a cross-sectional study. The study design used in this study gives insight on the participants´ health at one point. The advantage with this study design is that it is cheap, easy to conduct and interpret, compared to other study designs, as we do not follow the participants over a long period of time. Further this can lead to more contributors, and less apostasy. However, one disadvantage is that we only collect data at one point, so we have no estimate on how HRQoL and GI-symptoms is affected during different periods of life for the participants. Therefore, it is difficult to determine how the participants experience the progression of the disease, and how they are affected in different periods of life. Further another limitation with the study design is that we cannot say anything about cause and effect. We can see relations between parameters, but we cannot say for sure what causes this relation. However, when it all comes together results from a cross-sectional are important for creating hypothesis that can further be investigated using studies with more robust designs (82).

5.1.2 Study population

The number of participants in this study were few and mostly men. Further this study only included patients with PI-CF who have their consultation at OUH. This affects which CF population that is included in the study. A variety of participants from all over the country would have been preferred. Then we would have been able to look at CF groups from different geographical parts, and we might have found some differences, that could have improved the health offer for some of the participants. Due to the geographical limitation of the study sample, we cannot say for sure that the findings in this study are transferable to the entire Norwegian population with PI-CF. Further, we only included patients with PI-CF in this study. This made the recruitment process challenging, due to a small patient population in Norway. According to the patients list, only 49 patients are diagnosed with PI-CF in Norway. The limited number of participants have to be taken into consideration when analyzing the results.

For the analysis conducted in this thesis it would have been interesting not only including patients with PI-CF, but also patients with PS-CF. When looking at HRQoL and GI-symptoms it would have been interesting looking at both patients with PI-CF and PS-CF for comparison of the results. Would we have found any differences, or would the results have been similar? Are HRQoL and GI-symptoms the same between the two groups?

5.1.3 Methods

Anthropometrical measurements

A strength with this study is that height and weight were measured using the same tools for all participants. However, the examiners managing the tools, and conducting the measurements were different for the participants, which makes it possible that their interpretations may have affected the results. Additionally, factors regarding time of the day, time since last meal, time since visiting the toilet are known to affect the participants weight and should be taken into consideration for the results.

Body composition

To investigate body composition a DXA scan was conducted for almost all participants. Using the DXA scan is a strength with this study, as it shows good reproducibly and precision when analyzing body composition as well as estimation of BMD (83). The DXA scan was further conducted by the same examiner for all participants, which is a strength for the study. However, 26 of the 33 participating patients conducted the DXA scan, which is a weakness of the study, as this limits the number of participants possible to analyze and investigate body composition in relation with HRQoL and GI-symptoms. This is also a limitation as patients with CF are recommended to routinely conduct DXA scan from 8-10 years to monitor BMD, as this is a patient group where low BMD is a complication to the disease (83). Further not all parameters in the whole-body scan were mapped for all participants, which led to further exclusion of participants for some parameters. Few participants had conducted DXA scan previously, therefore we were not able to compare the results in this scan with previous results for each participant.

Physical test

HGS was measured with the same instrument and same instructions for all participants, further, the same examiner conducted all measurements. However, all participants used their

dominant hand, which might affect the results, as right-handed people are shown to be stronger than left-handed people (84). Further other factors, like hand size, age, sex, body composition and time of the day the test was conducted should have been taken into consideration when looking at the HGS results (78, 85).

Dietary intake

Information regarding dietary intake was collected with three separate 24 hours diet recalls, conducted on different days. This is a method easy to conduct, as well as it collects data and shows variation on different weekdays (86). However, as we have chosen three separate days for the dietary recalls, it is not given that this represents the participants usual intake. Further, even though this is a method that collects information about actual intake, we know that it is difficult to remember and give exact information about dietary intake the day before. Recall bias may also occur with the desire to impress the interviewer, and the participants therefore overestimate the intake of recommended foods, and further underestimate the intake of unhealthy/ not recommended foods. These factors can lead to under and over reporting of different foods, which further can lead to under and over reporting of total energy intake and intake of different nutrients (87).

Health related quality of life

In this thesis we have used the CFQ-R for calculating HRQoL. This is the most widely used and validated patient-report outcome form for patients with CF (58, 60). This is a CF specific HRQoL form, and is designed to measure the overall health, and how the diagnosis affects daily life, well-being and symptoms. It comes in three different patients versions, one for adult/adolescents >14 years (used in this study) and two for children, one for children 6-13 years, and one for children designed for completion by their caregivers (59). This form includes many questions on current topics, but maybe not all. In this study we have not collected data on fertility, anxiety or depression which can have a major impact on QOL. Further data on infection frequency and days in hospital have not been collected, which is believed to have a major impact on QOL. Previous studies have found depression, anxiety and infection to be associated with reduced scores for all CFQ-R domains, except weight (88, 89). A strength with this study is that the questionnaire was completed together with a previous masters student, which made the participants able to ask questions if some items were hard to understand. However, the masters student did not try to affect the patients answers in any way. One limitation is that we had no access to the participants previous results from earlier

consultations. Therefore, we were not able to investigate if there were any changes in each participants HRQoL from time to time. However, this questionnaire had available cut-off values compared to the healthy population, which made us able to investigate it the population had reduced HRQoL compared to the healthy population, as we did not have a reference group, which is a strength of the study. One limitation with the cut-off values is that exact normative means for the healthy population were not available, which made us unable to investigate if there were statistically significant differences between the study population and the healthy population, which would have been preferable.

Gastrointestinal symptoms

In this study we used the GSRS form for collecting data on GI-symptoms. This is a form that includes questions on relevant GI-complications. The form was completed in the same way as the CFQ-R, together with a previous masters student, giving the participants the ability to ask any questions regarding the fulfilling. As mentioned earlier in this thesis, patients with CF suffer from different GI-sickness like Meconium Ileus, DIOS and GI reflux disease (90). One limitation with this study is that it is not collected data on GI-sickness in addition to CF, which can be a possible explanation for the GI-symptoms apart from CF. Further, investigation of GI-symptoms in patients with CF have not been conducted frequent at this point, and the GSRS form have never been used in the Norwegian CF-population previous, and only one study has been completed in the CF-population using this questionnaire. Therefore, we have few previous results to compare our findings with. However, we were able to compare the results of the study population with a Swedish reference group, which is a strength, as we were able to compare the study populations symptoms with a healthy population. Further, the Swedish population is believed to be much similar to the Norwegian population.

Statistical analysis

In this study the study population was small, which is a major limitation for the statistical analysis. The low number of participants leads to low power to find statistically significant differences. However, all data in this study was normally distributed, which is a strength as these tests have higher ability to detect statistically significant differences. Further due to the limited number of participants, when dividing the whole study population into smaller groups for comparison of parameters, the subgroups are low in numbers.

5.2 Discussion of the results

5.2.1 Characteristics of the study population

The mean age for the study population was 35.5 years, ranging from 18 years to 75 years. The range in age, illustrates how survival rate for the CF population have increased (91). In this study there were more men who participated than women. However, the risk for having the CF diagnosis is the same for both men and women (92). The difference found in gender in this study can be because of men were more motivated to participate, or due to more men with PI-CF in this geographical area. However, in this study most men were recruited, which can be the one and simple explanation for the gender difference found in this study. Further women with CF are shown to have worse outcomes than men, which can affect women ability to participate in studies (93).

The prevalence of diabetes was 18.3%, of these, two participants were diagnosed with CFRD. The prevalence of CFRD is increasing with age, and by the age of 40, the prevalence is more than >50% (19). In our study the two patients with CFRD were around 40 years, however, in this study several participants >40 years were not diagnosed with CFRD. Due to the CFRD risk, it is important to further follow the participants years ahead to diagnose CFRD if it would occur at a later stage. It is therefore important to regularly conduct glucose tolerance tests, and use this method instead of HbA1c, as HbA1c only have a sensitivity of 50% in this population. If this is not taken into consideration, and the right tests are not performed, the prevalence of CFRD can be under-diagnosed in the study population.

5.2.2 Evaluate health related quality of life

In this study we found that all participants, except one had reduced HRQoL in at least one CFQ-R domain compared to the healthy population. In mean the participants had reduced HRQoL in seven of 12 domains. The lowest score was observed for the HRQoL domain vitality, however as cut-off levels are different for each domain, this is not the same as most participants had reduced HRQoL for this domain. There were most participants (87.5%) with reduced HRQoL in the domain Health Perception, and fewest participants (35.5%) with reduced HRQoL in the domain Body Image. Further we found that there were significantly more men than women that had reduced HRQoL for the domain role. Previous studies from the general CF population have found similar results as we have found in this study (94). However previous studies have found more significate differences between sex. Female have

been found to have significantly lower scores, i.e. increased symptoms for physical function and respiratory symptoms (94, 95), vitality and higher scores, i.e. reduced symptoms for weight and body image (94). However, as mentioned earlier the cut-off values for reduced HRQoL for the different domains are not similar for men and women, and women have a lower cut-off level than men for all CFQ-R domains, except weight (**Appendix 5**). Therefore, a significant lower score does not necessarily mean that women have significantly decreased HRQoL for these domains, or that there is a significantly difference between the number of male and female with reduced HRQoL for the different domains. None of the mentioned studies have found significantly differences between men and women in the role domain. The previous studies have had a study population including more participants (278 participants, 55% female) (94), or a more even distribution of participating men and women (95), which can be an explanation for why our study found this difference. Further previous studies have found a significant difference in body image between men and women, where women seems to be more satisfied with their thinness than men, and tend to respond ´´false´´ or ´´very false´´ to the statement ´´you think you´re thin´´, while boys tend to respond ´´true´´ or ´´very true´´ (59, 96).

5.2.3 Evaluate gastrointestinal symptoms

Compared to the healthy population the participants in this study had significantly increased symptoms in all GSRS domains except reflux, even though most participants classified their GI-symptoms as mild to moderate. There are limited data on this topic available for comparison. In a previous study the prevalence of symptoms classified as moderate or severe among patients with both PI-CF and PS-CF were higher than in our study (97). However, this study had no reference group for comparison of the results. This study is, in addition to ours, the only studies that have used the GSRS questionnaire for investigating GI-symptoms among patients with CF.

5.2.4 Assess nutritional status

5.2.4.1 Evaluate nutritional status with nutritional intake and requirements

Men had a significantly higher energy intake than women, which was expected as men are heavier, taller, have more muscles and therefore requires more energy than women. However, the percentage intake of different energy giving nutrients were about the same for men and women. Less than half of the study population (45.5%) covered >75% of TEE. This is lower

than a previous study from the Scandinavian CF population, where the average energy intake was 114 % of TEE (29). However, it is important to notice that the method for calculating TEE and collecting data on energy intake in these two studies are different. In the present study information on dietary intake was collected during three dietary recalls, and % of TEE was calculated using PAL 1.6 and LF, and then calculate the participants energy intake compared to energy needs. % of TEE in the present study is therefore a value of energy intake in % of calculated energy needs. In the previous study in the Scandinavian CF population information on dietary intake was collected using a 7-day food record. Further energy- and nutrient intake was calculated, and the calculated energy intake was compared to reference values. The reported % of TEE in the previous study is therefore a value of energy intake for the participants, when comparing their energy intake to reference values for weight, PAL 1.6 and sex, and not a calculation of % energy intake compared to energy needs.

More than half of the study population had an energy intake covering <75% of TEE. TEE was calculated using PAL 1.6 and LF. PAL 1.6 is also what has been used in previous studies (29). For some of the participants this might be a high PAL, and calculated TEE can therefore be higher than what is the reality. It is important to monitor weight to ensure that the patients cover their energy needs.

The mean carbohydrate intake for all participants were 48.1 E%, mean fat intake for all participants were 31.7 E% and mean protein intake for all participants were 17.7 E%. This is similar to what previous studies have shown (29). Nine participants met the ESPEN recommendations for protein intake, further 24 participants had protein intake below the recommendations, one participant met the ESPEN recommendations for carbohydrate intake, further six participants were below and 21 participants were above the recommendations, four participants were within the ESPEN recommendations for fat intake, further 25 participants were below and four participants were above the recommendations (19). To cover energy needs it is important that this patients group meet the ESPEN recommendations for nutrient intake. Due to high energy needs it is especially important to cover needs of fat, as this is the most energy dense nutrient. To optimize dietary intake and nutritional status it would have been beneficial with regular consultations with a clinical nutritionist for guidance.

5.2.4.2 Evaluate nutritional status with BMI

The prevalence of underweight according to the WHO BMI recommendations was low (3%). In a study conducted in France in 1997 to 1999, they found that 54% of patients with PI-CF were classified as mild to severe malnourished, and no patients within this group was classified as obese or overweight (98). A lower prevalence of underweight among patients with CF have been reported in additional studies the latest years (29, 99). This might indicate that the nutritional status for patients with CF have improved the last years. However, less than 50% of the study population met the ESPEN BMI recommendations for patients with CF, and were defined as malnourished. This illustrates that even though the prevalence of underweight was low according to the WHO BMI cut-off values, malnutrition is still a challenge among patients with PI-CF. Similar findings have also been reported for the general CF population, according to the Cystic fibrosis foundation (100). Previous studies investigating nutritional status association with HRQoL have defined malnutrition as BMI <19kg/m^2, and not as ESPEN recommend for patients with CF. This is most likely to be explained by that the ESPEN guidelines are newer than previous studies investigating malnutrition in patients with CF (19).

According to a report regarding the Norwegian population, only 25% of men and 40% of women are classified as normal weight, using the WHO BMI recommendation cut-off values. Further, 25% of men and 21% of women are classified as obese (101). When comparing the population in the present study with the whole Norwegian population, 69.2% of women and 60% of men were classified as normal weight, 30.8% of women and 20% of men were classified as overweight, further 15% of men were classified as obese and 5% of men were classified as underweight, while no women were obese or underweight.

According to the WHO classifications 3.0% of the participants were classified as underweight, 63.6% as normal weight, 24.2% as overweight and 9.1% as obese. For this study population the prevalence of malnutrition was low when using the WHO BMI cut-off values. In the resent years the incidence of overweight among patients with CF has increased (38). This might be a sign that the increasing weight tendency that we see in the general population, also reflects the weight tendency in the CF population.

5.2.4.3 Evaluate nutritional status with Sarcopenia

Body composition

Men had significantly higher FFM, ASM and ASMI compared to women, which is expected due to genetic differences between men and women, that explains why men have higher muscle mass than women (102). Further we found a significantly positive correlation between BMI and FFMI, BMI and ASMI, BMI and ASM for participants with BMI $\leq$ 25kg/m^2. This illustrated the importance of maintaining nutritional status, and at the same time preventing overweight and obesity.

When it comes to nutritional status, the number of participants in the study population defined as malnourished varies depending on using the ESPEN BMI recommendations for patients with CF, the WHO BMI definition, or the ESPEN FFMI definition. The recommendations for BMI from WHO and the ESPEN BMI recommendations for patients with CF are different, and therefore the definition of malnutrition in the population varies depending on which definition used. In the present study we used the ESPEN BMI recommendations for patients with CF and ESPEN FFMI cut-off values to determine malnutrition. One limitation with the ESPEN BMI recommendations for patients with CF is that there is no upper limit for BMI, only defining that it is recommended that patients with CF have BMI >22kg/m^2 for women and >23kg/m^2 for men. When investigating the association between nutritional status, HRQoL and GI-symptoms we found that both malnutrition and overnutrition were negatively associated with HRQoL and GI-symptoms. We therefore find it inadequately that there is no upper limit for BMI in the ESPEN guidelines. It the resent years the incidence of overweight among patients with CF has increased, and it is therefore necessary to develop guidelines for BMI upper limit (38). After analyzing the results in this study, we think FFMI is the best parameter for identifying malnutrition. Using a DXA scan to determine nutritional status is a good method, as it is recommended to perform regularly from a young age to observe changes in BMD. If a DXA scan is used to monitor both muscle mass and BMD regularly, we can observe changes in body composition earlier, and therefore maybe prevent early development of sarcopenia and osteoporosis, or at least an early diagnosis and improved treatment at an earlier stage. The alternative is using the ESPEN recommendation for BMI lower limit in a combination with the WHO upper limit recommendation for normal weight, until ESPEN develops an upper BMI limit recommendation for patients with CF. In our study we found, as mentioned above a significant positive correlation between BMI and muscle mass for participants with BMI $\leq$25 kg/m^2, and no significantly relation between BMI and muscle

mass for participants with BMI >25 kg/m^2. This can also indicate that it is not beneficial to increase BMI above the WHO upper limit recommendation. This might be a good indicator for ESPEN, when considering an upper BMI recommended limit for patients with CF.

When investigating the prevalence of sarcopenia, we found that eight participants had ASM below the sarcopenia definition, and six participants had ASMI below the sarcopenia definition. Five participants had both reduced ASM and ASMI. In total 27.3% of the study population were diagnosed with sarcopenia. The participants in this study diagnosed with sarcopenia were from 20 to 62 years. Previous studies investigating sarcopenia in patients with CF have found that patients with CF have increased risk for sarcopenia compared to the healthy population, as patients with CF have decreased muscle mass and are muscle weak compared to the healthy population (41). Previous studies have not investigated the incidence of sarcopenia, but FFM, and have concluded that patients with CF have increased risk for sarcopenia (41). In this study we found participants as young as 20 years diagnosed with sarcopenia, using cut-off values meant for older people (42). This is critical, as muscle mass is highest in young adulthood (≤40 years) and decreases after 50 years of age (103, 104). This means that the young participants in this study diagnosed as sarcopenic most likely will continue to lose muscle mass (1-2% per year) and muscle strength (1.5-5% per year) with increasing age (104). This indicates that sarcopenia is not just a challenge in older patients with CF, but also younger. This shows the importance of conducting regularly DXA scans from a young age, and consultations with a clinical nutritionist for reducing muscle loss, and therefore prevent sarcopenia. Furthermore, suitable cut-off values for sarcopenia is needed for this patient group as it involves young patients, and the developed cut-off values for older people are not suitable.

HGS

As expected, men had significantly higher HGS than women. However, when looking at all HGS results for the study population, the population were muscle weak compared to the reference population, with significantly lower HGS. One previous study have similar findings as us, the CF population have decreased HGS compared to the healthy population (105). However, studies looking at muscle strength in patients with CF have mostly used quadricep and hamstring as a measurement for muscle strength and not HGS. However, results have been similar to ours (106). Compared to the healthy population, the CF population have 25-35% decreased quadriceps strength (107). Decreased muscle mass is further related with poor

prognosis, and reduced muscle strength. Further studies are needed to conclude if HGS or quadricep and hamstring strength is the best parameter for estimating muscle strength in patients with CF. However, as HGS is the most frequent measurement for muscle strength in the general population, it might be a better measurement to perform as reference values from the healthy population are available.

According to EWGSOP HGS can be used to suspect sarcopenia. Sarcopenia should be suspected is HGS is <27 kg for men, and <16kg for women (42). However, in the present study only three participants had HGS below this level, while eight participants had ASM below the sarcopenia definition, and six participants had ASMI below the sarcopenia definition. This means that if HGS is used to decide if further muscle mass analysis is necessary for this patient's group, some cases of sarcopenia will not be diagnosed. This might indicate that the HGS cut-off levels for suspecting sarcopenia is too low, and at the same time light the importance of regularly body composition scans in this patient's group.

5.2.5 Assess lung function

In this study mean FEV_1 for all participants were 63.7 % of predicted. This is similar to values found in a previous study for the Scandinavian CF population (29), and studies conducted in the US CF population (108). In the previous study in the Scandinavian population the FEV_1 values found were a bit higher than in this study. This can be explained by a difference in mean age in the two studies, that the study population in our study had a mean age almost six years older than the previous study in the Scandinavian CF population. However, a study conducted in adolescents and young adults (mean age 16.4 years) in Portugal showed mean FEV_1 62.9% of predicted, which is lower than in our population, even though our study population had higher age (109). This is also similar with another study conducted in the US, in adult CF patients showed FEV_1 value <60% of predicted, the mean age of 28.9 years (110). Further, a study analyzing The European Cystic Fibrosis Society Patients Registry, including nearly 15 000 patients with CF found a significant correlation between age and FEV_1. However, when looking at the results the most dramatic decrease in FEV_1 seems to take place during the first 20 years of life, and after that the decrease is more even (111). This proves that CF is a disease affecting lung function in an unfortunate way.

5.2.6 Compare HRQoL among subjects with and without malnutrition

Nutritional status evaluated by BMI

In this study malnourished participants had significantly increased symptoms for eating disturbances and weight, compared to the nourished participants. Further we found a positive correlation between participants with BMI ≤25kg/m^2 and the weight domain. We also found a negative correlation between body image and BMI for participants with BMI >25kg/m^2. Similar findings have been found in previous studies, a positive correlation between nutritional status and body image, eating disturbances and weight (59, 112, 113). As mentioned in our study we only found a significant negative correlation between body image and BMI for participants with BMI >25kg/m^2. In the three studies mentioned they have not looked at potential differences between body image for participants with BMI ≤25kg/m^2 and >25kg/m^2, and we therefore do not know if the results had been any different if they had done so. Further one study found a significant positive correlation between BMI and all CFQ-R domains except digestive symptoms, vitality and social functioning (114). However, a multiple regression was not conducted, which can give false significant correlations.

Nutritional status evaluated by sarcopenia

In this study we found that participants diagnosed with sarcopenia using cut-off values for older people had significantly reduced scores, i.e. increased symptoms for physical function, vitality, eating disturbances, respiratory symptoms and CFQ-R total. In the present study sarcopenia had the broadest impact on HRQoL of the parameters investigated. Previous studies have not investigated the incidence of sarcopenia, but FFM, and have concluded that patients with CF have increased risk for sarcopenia (41). Patients with CF have been found to have significant reduced muscle mass compared to the health population (115-117). However, no previous studies have investigated muscle mass or sarcopenia in relation with HRQoL.

5.2.7 Compare HRQoL among subjects with and without impaired lung function

FEV_1 is probably the parameter that is most investigated in patients with CF. In this study we found that participants with impaired FEV_1 had significantly reduced, i.e. increased symptoms for physical function and health perceptions. Previous studies investigating lung function in patients with CF have different findings. However, previous studies have had more

participants than our study, and included both patients with PI-CF and PS-CF, which can explain the different results. Studies have found a significant positive correlation between FEV_1 and all CFQ-R domains (59, 88, 114, 118). However, no previous studies have conducted a multiple regression, which may affect the results in showing more significant correlations than what it is in reality. Another study had the same findings as us, a significant positive correlation between increased FEV_1, physical function and health perception (119). FEV_1 has also been found significantly correlated with physical function and general health in previous studies (113). Further, reduced lung function has been seen in relation with increased symptoms for respiratory function, social functioning, body image and physical function (120). Another study found that lung function was significantly related to all CFQ-R domains except emotional function, social function and digestive symptoms (94).

5.2.8 Gastrointestinal symptoms among subjects with and without malnutrition

In this study we found that malnourished participants experienced significant less reflux symptoms than nourished participants, and participants with an energy intake <75% of TEE experienced significantly more indigestion symptoms and GSRS total symptoms than participants with an energy intake ≥75% of TEE. When investigating correlation, we found a significantly positive correlation between participants with BMI >25kg/m^2 and indigestion symptoms, diarrhea symptoms and GSRS total symptoms. At last we found a significantly negative correlation between % of TEE, indigestion symptoms and reflux symptoms.

As mentioned earlier a weakness of the study design is that we are not able to investigate cause and effect. We do not know if it is the nutritional status that have a negative impact on GI-symptoms, or if it is the GI-symptoms that leads to malnutrition. Further we cannot say for sure if it is the low energy intake that leads to increased symptoms, or if it is the increased symptoms that leads to reduced energy intake. Further, as there were no significant differences between the study population and the reference group in reflux symptoms, and the fact that this was the domain where the participants experienced least symptoms, the relation found in this study between reflux and nutritional status can be clinically irrelevant.

GI-symptoms for patients with CF have not been investigated frequently at this point. We know that patients with CF experience different GI-complications in addition to their CF

diagnosis, as mentioned earlier in this thesis, especially in the early life (69). However, only one study has been conducted investigating GI-symptoms using the GSRS previously. This study was conducted in London, and included in all 107 participants, participants with both PI-CF and PS-CF. In this study they investigated GI-symptoms using both the GSRS form, and the IBS severity score, and further comparing the results of these two questionnaires (97). In that study 43.9% of the participants reported severe GI-symptoms according to the IBS severity score, and participants reporting more severe symptoms with the IBS severity score, also reported more severe symptom using the GSRS- questionnaire (97). Compared to our study this study included more participants, and there was reported more severe GI-symptoms. The study population in this study were younger than in our study, which can affect the results. Another study conducted at Jena University Hospital in Netherland, including 131 participants with the mean age of 19.1 years, have investigated GI-symptoms in patients with CF using a different GI-symptom form, the Jen-Abdomen-CF score 1.0 (121). The most frequent reported complications using this form were loss of appetite and loss of taste, followed by abdominal pain. Further patients with previous history of rectal prolapse reported, DIOS, meconium ileus and PI had significant higher levels of abdominal symptoms (121). However, in our study we have only included patients with PI-CF, and not collected data on patient history, including previous GI-sickness, which makes it difficult to investigate the relations conducted in the previous study, as they found no significant relations with GI-symptoms and either nutritional status, lung function or CFRD.

When investigating the items included in the different GI-symptom forms, there is a need to investigate which form is the best for this patient group for defining which challenge that are most common for this patient group for future studies. There might be a need for a more CF-specific GI-symptom questionnaire, which also take previous GI-discomforts into consideration, like previous occasions of DIOS or meconium ileus, and CF genotype, and also take additionally GI-sickness into consideration.

6 Conclusion

Based on the present results, these following conclusions are suggested:

- Patients with PI-CF have reduced HRQoL compared to the healthy population.
- Patients with PI-CF have significantly increased diarrhea, indigestion, constipation, abdominal pain and GSRS total symptoms compared to the healthy population
- 54.4% of the study population did not meet the ESPEN BMI recommendations for patients with CF, and were classified as malnourished. Further, more than 30% of the participants were overweight or obese using the WHO definitions.
- Less than 50% of the study population had an energy intake covering >75% of TEE.
- Participants with energy intake <75% of TEE had significantly more indigestion symptoms and GSRS total symptoms compared to participants covering >75% of TEE.
- Malnourished participants according to the ESPEN BMI- and ESPEN FFMI recommendations had significantly reduced HRQoL, i.e. increased symptoms for weight and eating disturbances.
- 27.3% of the study population had ASM and ASMI below the sarcopenia cut-off values.
- Sarcopenia had the broadest impact on HRQoL. Participants with sarcopenia measured by ASM and ASMI had significantly reduced HRQoL, i.e. increased symptoms for physical functioning, vitality, weight, eating disturbances, respiratory symptoms, social functioning and CFQ-R total compared to non-sarcopenic participants.
- Participants with reduced lung function had significantly reduced HRQoL, i.e. increased symptoms for physical functioning and health perceptions compared to participants with normal lung function.
- Our results revealed that body image was negatively correlated to BMI for overweight and obese participants according to the WHO BMI cut-off values. These patients had additionally more GI-symptoms, i.e. indigestion symptoms, diarrhea symptoms and GSRS total.

The results of this study have to be interpret with caution, as the number of participants are low. Further research is needed to investigate HRQoL and GI-symptoms in the entire Norwegian CF population.

7 Future perspectives

This thesis was a part of a cross-sectional study. The statistical power in the study was limited, as the sample size was small. However, regardless of a small sample size we found that patients with PI-CF had reduced HRQoL and increased GI-symptoms compared to the healthy population. We also found differences in HRQoL and GI-symptoms within the group. Further research is needed to investigate HRQoL and GI-symptoms in the entire Norwegian CF population. In this way we will be able to see if the results we have found in this study are unique to patients with PI-CF, or if the whole Norwegian CF population experience the same symptoms. Data on the participants health beyond PI-CF should also have been collected, like previous GI-sickness, infection rate, days in hospital, additional diagnosis and mental health.

The results from this study shows that there is a relation between nutritional status (including sarcopenia, energy- and nutrient intake), lung function and HRQoL and GI-symptoms. Few studies have investigated GI-symptoms in patients with CF (both patients with PI-CF, and PS-CF), more studies are therefore needed on this topic. Further as the prevalence of overweight and obesity is increasing within this patient group, and neither malnutrition nor overweight is favorable for HRQoL or GI-symptoms, it is important to develop guidelines for upper limit BMI for this patient's group. Further, findings in this study illustrates that sarcopenia is not a problem only seen in the older patients with PI-CF, but also in the younger ones. It is therefore important to start analyzing body composition routinely from a young age, to prevent sarcopenia, and try to optimize body composition. Further, the fact that less than 50% of the participants diagnosed with sarcopenia had HGS levels low enough for suspecting sarcopenia, lights the importance of analyzing body composition for diagnosis.

In future studies it is important to collect data on age of diagnosis, infection rates, days in hospital, physical activity, additional diagnosis, exact data on PERT dosage and depression/anxiety, as these are factors believed to affect HRQoL and GI-symptoms, and might be more important than factors investigated in this study.

To optimize nutritional status, nutrient intake, body composition, and further help patients with CF with nutritional challenges, the patients might benefit of regularly consultations with a clinical nutritionist. To make this possible it can be beneficial to recruit additional clinical nutritionists to the CF care team, or recruit more clinical nutritionists in general.

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Appendices

Appendix 1: Invitation letter to the study

Appendix 2: Written consent form

Appendix 3: Cystic Fibrosis Questionnaire Revised (CFQ-R)

Appendix 4: Overview of individual items in the different CFQ-R domains

Appendix 5: Illustration of cut-off values for the CFQ-R for men and women

Appendix 6: The Gastrointestinal Symptom Rating Scale (GSRS)

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Appendix 8: Reply to application from the Norwegian Regional Committees for Medical and Health Research Ethics

Appendix 9: Correlation values between specific variables

Appendix 1: Invitation letter to the study

Vil du være med?

Studie angående ernæring– og vitaminstatus hos voksne pasienter med cystisk fibrose (CF)

Så mange som 85 prosent med diagnosen cystisk fibrose har problemer med fordøyelse av maten grunnet svikt i bukspyttkjertel-enzymer og dårlig opptak av fett og fettløselige vitaminer. Underernæring er et problem for mange pasienter med CF, noe som er relatert til blant annet en ubalanse mellom energi behov og faktisk matinntak, pankreasinsuffisiens og malabsorpsjon. Underernæring øker risikoen for komplikasjoner, reduserer motstand mot infeksjoner, forverrer fysisk og mental funksjon og gir redusert livskvalitet.

Vi ønsker derfor å invitere deg til å delta i et prosjekt om «Ernæring– og vitaminstatus hos voksne pasienter med cystisk fibrose»

Vi vil kartlegge ernæring- og vitaminstatus, kosthold, symptomer samt livskvalitet. Målet med studien er å styrke kvaliteten på behandlingen/oppfølgingen av CF-pasienter.

Fordelen av å delta i studien er at man får en grundig gjennomgang av sin ernæringsstatus, mage- og tarmplager, og vitamin- og mineralnivåer. Dersom blodprøvene viser vitamin- og mineralmangel får du behandling og råd av helsepersonell.

Til studien vil vi ta blodprøve av deg når du kommer til kontrolltimen. Du vil også svare på et par spørreskjemaer angående din vekt, eventuell vektendring, høyde, kosthold, mage- og tarmplager og hvordan du har det. I tillegg vil din kroppssammensetning bli målt med dobbel røntgen absorpsjonsmetri (DXA).

Studien er et samarbeid mellom Seksjon for cystisk fibrose i Lungemedisinsk avdelingen, Oslo universitetssykehus (OUS) på Ullevål, Seksjon for klinisk ernæring, Medisinsk klinikk på Ullevål, Norsk senter for cystisk fibrose (NSCF) og Universitetet i Oslo. **Studien vil foregå ved Seksjon for cystisk fibrose i Lungemedisinsk avdeling på Ullevål**

Det er frivillig å delta i prosjektet. Vi håper du er interessert i å delta i denne studien og nærmere informasjon vil bli gitt ved fremmøte på Seksjon for cystisk fibrose når du kommer til kontroll.

Jeg ønsker å delta i denne studien ☐

Jeg ønsker ikke å delta i denne studien ☐

Kontaktperson:

Dersom du har spørsmål til prosjektet, kan du kontakte x på telefon x.

Vi håper du er interessert i å delta i denne studien og nærmere informasjon vil bli gitt ved fremmøte på Ullevål.

Appendix 2: Written consent form

ERNÆRINGSSTATUS, GASTROINTESTINALE SYMPTOMER OG LIVSKVALITET HOS PASIENTER MED CF – EN TVERRSNITTSSTUDIE

Oslo universitetssykehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

ERNÆRINGSSTATUS, GASTROINTESTINALE SYMPTOMER OG LIVSKVALITET HOS PASIENTER MED CYSTISK FIBROSE (CF) – EN TVERRSNITTSSTUDIE

Dette er et spørsmål til deg om du vil delta i et forskningsprosjekt som har til hensikt å styrke kvaliteten på oppfølgingen av pasientene ved Seksjon for cystisk fibrose i Lungemedisinsk avdeling ved OUS. Underernæring er en kjent komplikasjon ved CF, relatert til blant annet høyt energiforbruk, svikt i bukspyttkjertel-enzymer og dårlig opptak av fett og fettløselige vitaminer. Når CF utvikler seg hos eldre barn og hos voksne, kan sykdommen forårsake noen metabolske komplikasjoner og ernæringsmangler, noe som ytterligere påvirker livskvaliteten og øker dødelighetsrisikoen.

Ansvarlige for studien er tre kliniske ernæringsfysiologer og to overleger, og alle undersøkelser vil bli gjort ved Seksjon for cystisk fibrose i Lungemedisinsk avdeling på Ullevål.

Studien er et samarbeid mellom Seksjon for cystisk fibrose i Lungemedisinsk avdelingen, Oslo universitetssykehus (OUS) på Ullevål, Seksjon for klinisk ernæring, Medisinsk klinikk på Ullevål, Norsk senter for cystisk fibrose (NSCF) og Universitetet i Oslo.

HVA INNEBÆRER PROSJEKTET?

For å kartlegge din helsetilstand og ernæringsstatus vil det tas blodprøver av deg når du kommer til kontrolltimen. Følgende blodprøver måles i forbindelse med årskontroll og vil inngå i studien: Vit D, vit A, vit E, vit k, jern, transferrin, TIBC, Hemoglobin, ferritin, PTH, albumin, kreatinin, karbamid, ASAT, ALAT, GT, ALP, LD, bilirubin, INR, amylase, glukoseblastning, kolesterol, triglyserider, Glukose og HbA1C.

Du vil også svare på et par spørreskjemaer angående din vekt, eventuell vektendring, høyde, kosthold, mage- og tarmplager og hvordan du har det. I tillegg vil din kroppssammensetning bli målt med dobbel røntgen absorpsjonsmetri (DXA) som er en røntgenundersøkelse og gir verdier for muskelmasse, fettmasse og væskeoverskudd.

Vi ber også om din tillatelse til å bruke opplysninger fra din pasientjournal (for eksempel sykehistorie, blodprøvesvar, vekt, vekttap) når dette er nødvendig. Blodprøvene vil bli analysert i laboratorier i Norge.

MULIGE FORDELER OG ULEMPER

Det er ingen risiko ved å delta i studien. Blodprøver vil tas i forbindelse med rutinekontroll. Fordelen med å delta i studien er at du får en grundig vurdering av ernæringsstatus, mage- og tarmplager, livskvalitet og vitamin- og mineralnivåer. En klinisk ernæringsfysiolog vil vurdere resultatene fra kostundersøkelsene opp mot anbefalt sammensetning av kosten ved CF og eventuelt gi forslag til endringer. Dersom dine blodprøver viser mangler på vitaminer og mineraler får du behandling og råd fra helsepersonell.

En masterstudent gjennomgår registreringen sammen med deg, og man bruker bilder av mat for å gi riktig mengdeangivelse. Kosten blir så næringsberegnet.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for

din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Inger Elisabeth Moen på telefon: 95 24 66 29 eller Niherthana Sripalan på telefon: 94825505

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Blodprøvene skal destrueres etter analyse (senest innen 2 mnd etter prøvetaking).

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest 5 år etter prosjektslutt.

FORSIKRING [BESKRIV DET SOM ER AKTUELT]

Deltagelse i studien innebærer at du er forsikret i henhold til pasientskadeloven og evt. skade/utgift du er blitt påført som følge av deltagelse i studien vil bli dekket av norsk pasientskadeforsikring.

OPPFØLGINGSPROSJEKT [TAS **KUN** MED HVIS DET ER AKTUELT.]

Det kan være aktuelt med oppfølgingsprosjekt uten at dette foreløpig er planlagt. Blir det aktuelt kan du bli kontaktet igjen, men det vil være helt frivillig også da å delta.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, [saksnr. 2018/1035

hos REK sør-øst D (25.06.2018)].

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Appendix 3: Cystic Fibrosis Questionnaire Revised (CFQ-R)

CFQ-R

Ungdom og voksne (Pasienter fra 14 år og oppover)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Det å forstå hvordan sykdom og behandling virker inn på hverdagen din kan hjelpe helsepersonell til å følge med på helsen din og dermed tilpasse behandlingen. Det er grunnen til at vi har utarbeidet dette spørreskjemaet spesielt for personer med cystisk fibrose. Takk for at du vil fylle ut skjemaet.

Instruksjoner: Spørsmålene nedenfor handler om din nåværende helsetilstand, slik du oppfatter den. Denne informasjonen vil gjøre det lettere for oss å sette oss inn i hvordan du har det i hverdagen.

Vær vennlig å svare på alle spørsmålene. Det er **ingen** rette eller gale svar! Hvis du er usikker på hva du skal svare, velg det alternativet som ligger nærmest din situasjon.

Del I. Bakgrunn

Fyll ut informasjonen eller kryss av i boksen ved ditt svar.

A. Hva er din fødselsdato?

Dag Mnd År

B. Angi kjønn

☐ Mann ☐ Kvinne

C. Har du i løpet av de **to siste ukene** vært på ferie eller vært borte fra skolen eller arbeidet av årsaker som **IKKE** er knyttet til helsen?

☐ Ja ☐ Nei

D. Hva er din sivilstatus?

- ☐ Enslig/aldri vært gift
- ☐ Gift
- ☐ Enke/enkemann
- ☐ Skilt
- ☐ Separert
- ☐ Gift på nytt
- ☐ Samboer

E. Hva er ditt høyeste fullførte utdanningsnivå?

- ☐ Ikke fullført videregående skole
- ☐ Videregående skole med studiekompetanse
- ☐ Yrkesrettet videregående skole
- ☐ Emner fra høyskole/universitet
- ☐ Høyskole/universitetsgrad (Bachelor/Master/Profesjonsstudie)
- ☐ Høyere akademisk grad (Dr.grad)

F. Hvilket alternativ beskriver best din nåværende arbeids- eller skolesituasjon?

- ☐ Går på skole utenfor hjemmet
- ☐ Tar utdanningskurs hjemme
- ☐ Arbeidssøkende
- ☐ Arbeider heltid (enten utenfor hjemmet eller ved en hjemmebasert bedrift)
- ☐ Arbeider deltid (enten utenfor hjemmet eller ved en hjemmebasert bedrift)
- ☐ Hjemmeværende på fulltid
- ☐ Går ikke på skole eller arbeid på grunn av helsen
- ☐ Arbeider ikke av andre årsaker

CFQ-R **Ungdom og voksne (Pasienter fra 14 år og oppover)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Del II. Livskvalitet

Kryss av i boksen som angir svaret ditt.

I hvilken grad har du hatt problemer med følgende de ***to siste ukene****:*	**Store problemer**	**Noen problemer**	**Små problemer**	**Ingen problemer**
1. Utføre anstrengende aktiviteter som løping eller sport	☐	☐	☐	☐
2. Gå like fort som andre	☐	☐	☐	☐
3. Bære eller løfte tunge gjenstander som handlepose med matvarer eller skolesekk	☐	☐	☐	☐
4. Gå opp trappen en etasje	☐	☐	☐	☐
5. Gå i trapper like fort som andre	☐	☐	☐	☐

Angi hvor ofte du i løpet av de ***to siste ukene*** *har:*	**Alltid**	**Ofte**	**Av og til**	**Aldri**
6. Følt deg frisk	☐	☐	☐	☐
7. Følt deg bekymret	☐	☐	☐	☐
8. Følt deg unyttig	☐	☐	☐	☐
9. Følt deg trøtt	☐	☐	☐	☐
10. Følt deg full av energi	☐	☐	☐	☐
11. Følt deg utslitt	☐	☐	☐	☐
12. Følt deg trist	☐	☐	☐	☐

Sett ring rundt tallet som angir svaret ditt. Velg kun ett svar for hvert spørsmål

Med tanke på helsetilstanden din de ***to siste ukene****:*

13. I hvilken grad har du hatt problemer med å gå?
1. Du kan gå langt uten å bli sliten
2. Du kan gå langt, men blir sliten
3. Du kan ikke gå langt fordi du blir fort sliten
4. Du unngår å gå når det er mulig fordi det er for slitsomt for deg

14. Hva føler du om det å spise?
1. Bare tanken på mat gjør deg uvel
2. Du har aldri glede av å spise
3. Du kan av og til ha glede av å spise
4. Du har alltid glede av å spise

15. I hvilken grad gjør behandlingene hverdagen din vanskeligere?
1. Ikke i det hele tatt
2. I liten grad
3. Til en viss grad
4. I stor grad

CFQ-R CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Ungdom og voksne (Pasienter fra 14 år og oppover)

16. Hvor mye tid bruker du nå på behandlingene hver dag?

1. Mye
2. En del
3. Litt
4. Veldig lite

17. Hvor vanskelig er det for deg å gjennomføre behandlingene (inkludert medisinering) hver dag?

1. Ikke i det hele tatt
2. Litt vanskelig
3. Vanskelig
4. Svært vanskelig

18. Hvordan synes du helsen din er nå?

1. Utmerket
2. God
3. Tilfredsstillende
4. Dårlig

Velg den boksen som angir svaret ditt.

Med tanke på helsen din de ***to siste ukene****, angi i hvilken grad hver setning stemmer eller ikke stemmer for deg*	**Stemmer helt**	**Stemmer ganske bra**	**Stemmer ikke helt**	**Stemmer ikke**
19. Jeg har problemer med å komme meg etter fysiske anstrengelser	☐	☐	☐	☐
20. Jeg må begrense anstrengende aktiviteter som løping eller sport	☐	☐	☐	☐
21. Jeg må tvinge meg selv til å spise	☐	☐	☐	☐
22. Jeg må holde meg mer hjemme enn jeg ønsker	☐	☐	☐	☐
23. Jeg prater gjerne om sykdommen med andre	☐	☐	☐	☐
24. Jeg synes jeg er for tynn	☐	☐	☐	☐
25. Jeg synes jeg ser annerledes ut enn andre på min alder	☐	☐	☐	☐
26. Jeg er bekymret for det fysiske utseende mitt	☐	☐	☐	☐
27. Folk er redde for at jeg kan være smittsom	☐	☐	☐	☐
28. Jeg er ofte sammen med venner	☐	☐	☐	☐
29. Jeg tror hostingen min forstyrrer andre	☐	☐	☐	☐
30. Jeg føler meg komfortabel med å gå ut om kvelden	☐	☐	☐	☐
31. Jeg føler meg ofte ensom	☐	☐	☐	☐
32. Jeg føler meg frisk	☐	☐	☐	☐
33. Det er vanskelig å planlegge for fremtiden (for eksempel å gå på høyskole/universitet, gifte seg, gjøre karriere osv)	☐	☐	☐	☐
34. Jeg lever et normalt liv	☐	☐	☐	☐

CFQ-R

Ungdom og voksne (Pasienter fra 14 år og oppover)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Del III. Skole, jobb og daglige aktiviteter

Spørsmål 35-38 omhandler skole, jobb og daglige aktiviteter

35. I hvilken grad har du hatt problemer med å følge opp skolearbeid, jobb eller andre daglige aktiviteter i løpet av de **to siste ukene**?

1. Du har ikke hatt problemer med å følge opp
2. Du har greid å følge opp, men det har vært vanskelig
3. Du har ligget etter
4. Du har ikke klart å følge opp disse aktivitetene i det hele tatt

36. Hvor ofte var du borte fra skole, jobb eller ute av stand til å fullføre daglige aktiviteter, i løpet av de to siste ukene, på grunn av sykdommen eller behandlinger?

☐ Alltid ☐ Ofte ☐ Noen ganger ☐ Aldri

37. Hvor ofte kommer CF i veien for nå målene dine på skolen, jobben eller privat?

☐ Alltid ☐ Ofte ☐ Noen ganger ☐ Aldri

38. Hvor ofte hindrer CF deg i å forlate huset for å gå ærender, for eksempel handle eller gå i banken?

☐ Alltid ☐ Ofte ☐ Noen ganger ☐ Aldri

Del IV. Symptomer

Velg boksen som angir svaret ditt.

*Angi hvordan du har følt deg i løpet av de **to siste ukene**:*	**I stor grad**	**Til en viss grad**	**I liten grad**	**Ikke i det hele tatt**
39. Har du hatt problemer med å legge på deg?	☐	☐	☐	☐
40. Har du vært tett i brystet?	☐	☐	☐	☐
41. Har du hostet i løpet av dagen?	☐	☐	☐	☐
42. Har du måttet hoste opp slim?	☐	☐	☐	☐ **Gå til spørsmål 44**

43. Fargen på slimet har for det meste vært: ☐ Klart ☐ Klart til gult ☐ Gulgrønt ☐ Grønt med antydning til blodstriper ☐ Vet ikke

*Hvor ofte i løpet av de **to siste ukene**:*	**Alltid**	**Ofte**	**Av og til**	**Aldri**
44. Har du vært tungpustet (hvesende, pipende eller gispende pust)?	☐	☐	☐	☐
45. Har du hatt problemer med å puste?	☐	☐	☐	☐
46. Har du våknet i løpet av natten fordi du hoster?	☐	☐	☐	☐
47. Har du hatt problemer med luft i magen?	☐	☐	☐	☐
48. Har du hatt diaré?	☐	☐	☐	☐
49. Har du hatt magesmerter?	☐	☐	☐	☐
50. Har du hatt problemer med å spise?	☐	☐	☐	☐

Vennligst forsikre deg om at du har svart på alle spørsmålene.

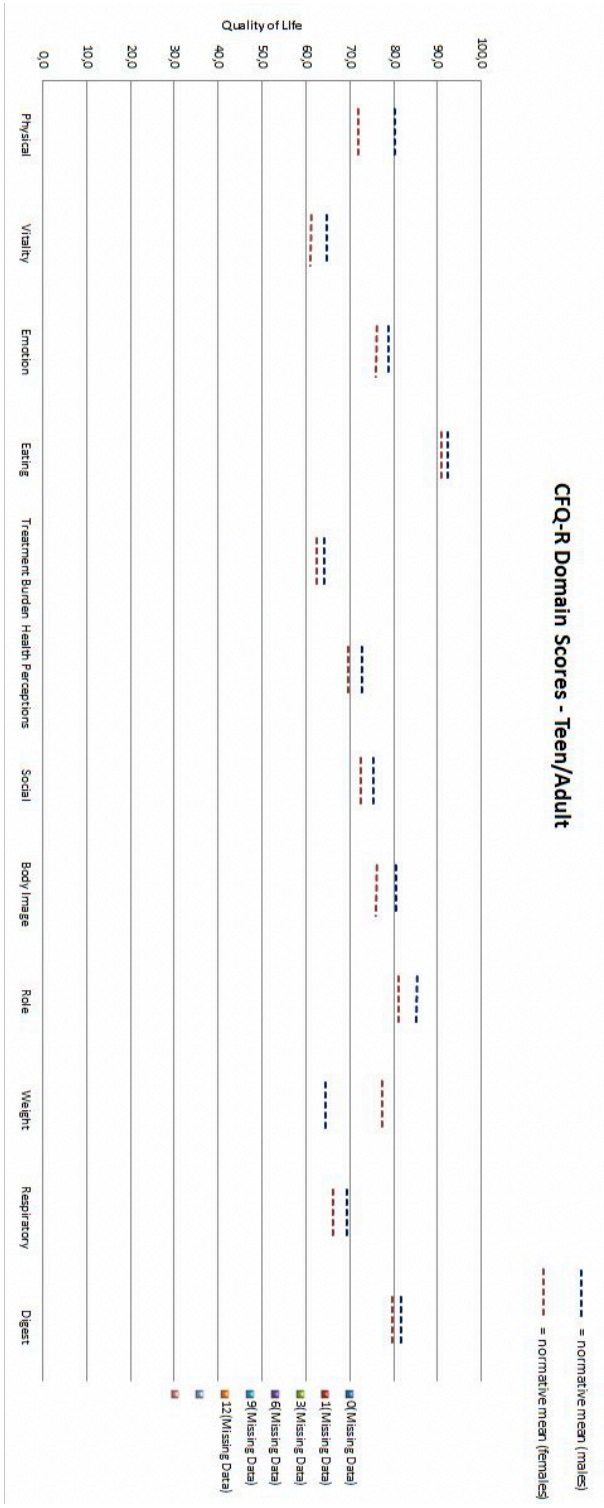
Takk for samarbeidet!

Cystic Fibrosis Foundation

Appendix 4: Overview of individual items in the different CFQ-R domains

Domain	**Items included in each domain in the CFQ-R**
Physical functioning	Strenuous activities (running, sports) Walk in the same pace as others Carry or lift backpacks, shopping bags Walking stairs Walking stairs in the same pace at others Problems walking Problems recovering from physical efforts Limit physical efforts
Vitality	Feeling well Feeling tiered Feeling full of energy Feeling exhausted
Emotional functioning	Feeling worried Feeling useless Feeling sad Feeling lonely Hard to plan the future
Eating disturbances	Feelings about food Need for force yourself to eat Troubles eating
Treatment burden	How treatment affect the day Time used on treatment Difficulties conduction treatment each day
Health Perceptions	Health at this point Feeling well Living a normal life
Social functioning	Need to stay at home Talk about condition with others Other scared to get infect Often with friends Think coughing interrupts others Comfortable going out at night
Body image	Feeling to skinny Look different from other its age Worried of its physical looks
Role	Trouble follow up school, work, daily activities Home from school, work or daily activities due to your condition Condition prevents you from reaching your goals, school, work Condition prevents you from leaving the house, doing errands
Weight	Problems gaining weight
Respiratory functioning	Tight in the chest Coughing during the day Coughing up mucus Feeling out of breath Problems breathing Awake during night due to coughing
Digestive symptoms	Feeling gassy Diarrhea symptoms Abdominal pain symptoms

Appendix 5: Illustration of cut-off values for the CFQ-R questionnaire for men and women



Cut-off values for HRQoL for patients with CF compared to the healthy population. Women have significantly reduced HRQoL for one domain if their score is below the red line. Further men have significantly reduced HRQoL for one domain if their score is below the blue line.

Appendix 6: The Gastrointestinal Symptom Rating Scale (GSRS)

THE GASTROINTESTINAL SYMPTOM RATING SCALE
(GSRS)

Les dette først:

Undersøkelsen inneholder spørsmål om hvordan du har det, og hvordan du har hatt det DEN SISTE UKEN. Sett kryss, (X) ved det alternativ som best passer på deg og din situasjon.

1. Har du i løpet av den siste uken vært plaget av SMERTER ELLER UBEHAG FRA DEN ØVRE DEL AV MAGEN?

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

2. Har du i løpet av den siste uken vært plaget av HALSBRANN? (Med halsbrann menes en sviende eller brennende følelse av ubehag bak brystbeinet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

GSRS (N2) (AMOS 97:04)

3. Har du i løpet av den siste uken vært plaget av SURE OPPSTØT? (Med sure oppstøt menes plutselige oppstøt av surt mageinnhold.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

4. Har du i løpet av den siste uken vært plaget av SUG I MAGEN? (Med sug i magen menes her en følelse i magen av behov for å spise mellom måltidene.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

5. Har du i løpet av den siste uken følt deg UVEL? (Med å føle seg uvel menes ubehagsfølelse som kan gå over i kvalme og brekninger/oppkast.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

6. Har du i løpet av den siste uken vært plaget av RUMLING I MAGEN? (Med rumling menes vibrasjoner eller "buldring" i magen.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

7. Har du i løpet av den siste uken vært plaget av OPPBLÅSTHET? (Med oppblåsthet menes utspiling, ofte forbundet med en følelse av luft i magen.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

8. Har du i løpet av den siste uken vært plaget av RAPING? (Med raping menes behov for "utlufting", ofte forbundet med lindring av følelse av oppblåsthet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

9. Har du i løpet av den siste uken vært plaget av LUFTAVGANG? (Med luftavgang menes her behov for å "slippe seg", ofte forbundet med lindring av følelse av oppblåsthet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

10. Har du i løpet av den siste uken vært plaget av FORSTOPPELSE? (Med forstoppelse menes minsket avføringshyppighet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

11. Har du i løpet av den siste uken vært plaget av DIARÉ? (Med diaré menes økt avføringshyppighet.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

12. Har du i løpet av den siste uken vært plaget av LØS AVFØRING? (Hvis du har hatt vekslende hard og løs avføring, gjelder dette spørsmålet bare i hvilken utstrekning du har følt deg plaget av at avføringen har vært løs.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

13. Har du i løpet av den siste uken vært plaget av HARD AVFØRING? (Hvis du har hatt vekslende hard og løs avføring, gjelder dette spørsmålet bare i hvilken utstrekning du har følt deg plaget av at avføringen har vært hard.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

14. Har du i løpet av den siste uken vært plaget av TVINGENDE AVFØRINGSBEHOV? (Med tvingende avføringsbehov menes raskt oppståtte behov for å gå på toalettet, ofte forbundet med en følelse av mangelfull kontroll.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

15. Har du i løpet av den siste uken i forbindelse med AVFØRING HATT EN FØLELSE AV UFULLSTENDIG TØMMING AV TARMEN? (Med ufullstendig tømming av tarmen menes at det trass i anstrengelser i forbindelse med avføring gjenstår en følelse av ufullstendig tømming.)

- ☐ Ingen plager i det hele tatt
- ☐ Ubetydelige plager
- ☐ Milde plager
- ☐ Moderate plager
- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

KONTROLLÉR AT ALLE SPØRSMÅLENE ER BESVART FØR DU LEVERER SKJEMAET!

TAKK FOR DIN MEDVIRKNING.

Appendix 7: Overview of individual items in the different GSRS domains

Symptom	**Items in each domain**
Abdominal pain	Abdominal pain/ discomfort Sucking sensation in the epigastrium Nausea
Diarrhea	Increased passage of stool Loose stools Urgent need for defecation
Constipation	Decreased passage of stools Hard stools Feeling incomplete evacuation
Indigestion	Rumbling Abdominal distension Belching Increased flatus
Reflux	Heartburn Acid reflux

Appendix 8: Reply to application from the Norwegian Regional Committees for Medical and Health Research Ethics

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Silje U. Lauvrak	22845520	25.06.2018	2018/1035 REK sør-øst D
			Deres dato:	**Deres referanse:**
			07.05.2018	

Vår referanse må oppgis ved alle henvendelser

Sedegheh Gharagozlian
Oslo universitetssykehus HF

2018/1035 Ernæringsstatus, gastroinyetsinale symptomer og livskvalitet hos voksne pasienter med Cystisk fibrose

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Sedegheh Gharagozlian

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 13.06.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektbeskrivelse
Bakgrunn: Cystisk fibrose (CF) er en sjelden og arvelig sykdom. Ernæring er en utfordring for mange. Underernæring og vitaminmangel er en kjent komplikasjon. Mål: Pasientene lever lengre og har bedre ernæringsstatus enn tidligere, likevel er underernæring et stort problem. Det er nå kommet nye europeiske anbefalinger om ernæring til CF-pasienter i 2016. Målet er å se hvilke problemstillinger pasientene opplever nå innen ernæring. Metode: Studien er et tverrsnitt studie som vil inkludere voksne pasienter (over 18 år) med CF ved lungepoliklinikken ved Ullevål. Vi kartlegger kostholdet og sammenligne med gjeldende anbefalinger for frisk befolkning og med europeiske anbefalinger. Kartlegger ernæringsstatus, benmineraltetthet, kroppssammensetning, mage- og tarmplager og livskvalitet vha henholdsvis blodprøver, 24-timers recall, vekt, høyde, DXA, GSRS- og CFQ-R skjema. Styrke: Resultater fra studien kan bidra til å styrke pasientsikkerhet og øke kvaliteten på behandlingen av CF-pasienter.

Vurdering
Komiteen har vurdert søknaden og har ingen innvendinger til studien som sådan. Komiteen har imidlertid noen kommentarer til informasjonsskrivet:

- Det er lagt ved to ulike informasjonsskriv. Komiteen ber om at kun det skrivet som følger REKs mal (Forespørsel om deltakelse CF 250.04.18) benyttes.

- Deltagerne informeres om at «Til studien vil vi ta blodprøve av deg når du kommer til kontrolltimen», men det er ikke begrunnet hvorfor blodprøver skal tas, hvilke analyser som skal gjøres. Komiteen ber om at denne informasjonen inkluderes i skrivet.

- Det er ikke søkt om opprettelse av en forskningsbiobank, og komiteen forutsetter derfor at blodprøvene destrueres innen 2 mnd etter prøvetaking. Komiteen ber om at avsnittet i REKs mal som heter 'Hva skjer med prøver som blir tatt av deg?' inkluderes i informasjonen til deltagerne, og at det der beskrives at prøvene skal destrueres etter analyse (senest innen 2 mnd etter prøvetaking).

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

- Av dokumentasjonshensyn skal opplysningene i prosjektet oppbevares avidentifisert i 5 år etter prosjektslutt. I informasjonsskrivet står det 10 år, og komiteen ber om at dette rettes opp.

På denne bakgrunn setter komiteen som vilkår for godkjenning at informasjonsskrivet som følger REKs mal revideres i tråd med komiteens kommentarer og ettersendes til orientering.

Vedtak
Med hjemmel i helseforskningsloven § 9 jf. 33 godkjenner komiteen at prosjektet gjennomføres under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2020. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2025. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Silje U. Lauvrak
Rådgiver

Kopi til:a.m.aas@medisin.uio.no
Oslo universitetssykehus HF ved øverste administrative ledelse: oushfdlgodkjenning@ous-hf.no

Appendix 9: Correlation values between specific variables

Values investigated	Pearson correlation coefficient	p-value
BMI and FEV_1	0.384	0.027*
Age and FEV_1	0.377	0.030**
BMI and FFMI	0.404	0.037*
BMI >25 and FFMI	0.093	0.813
BMI ≤25 and FFMI	0.613	0.007*
BMI >25 and ASMI	0.553	0.122
BMI ≤25 and ASMI	0.538	0.021*
BMI >25 and ASM	0.521	0.150
BMI ≤25 and ASM	0.609	0.007*
BMI and eating disturbances	0.411	0.017*
BMI and weight	0.055	0.017*
BMI ≤25 and weight	0.613	0.003*
BMI >25 and body image	0.635	0.036**
BMI >25 and GSRS total	0.635	0.036*
BMI >25 and diarrhea symptoms	0.724	0.012*
BMI >25 and indigestion symptoms	0.724	0.012*
BMI and reflux symptoms	0.347	0.048*
% of TEE and indigestion symptoms	0.369	0.035**
% of TEE and reflux symptoms	0.268	0.001**
FEV_1 and CFQ-R total	0.420	0.015*
FEV_1 and physical function	0.690	0.001*
FEV_1 and health perceptions	0.465	0.006*
FEV_1 and physical function (multiple regression)[a]		0.023*
FEV_1 and health perception (multiple regression)[b]		0.042*

*Regression showed $p<0.05$ and a positive correlation
**Regression showed $p<0.05$ and a negative correlation
[a]A multiple regression was conducted with the variables age and FFM
[b]A multiple regression was conducted with the variables age and FFM
Abbreviations: BMI; body mass index, FEV_1; forced expiratory volume in the first second, FFMI: fat free mass index, ASMI; appendicular skeletal muscle mass index, ASM; appendicular skeletal muscle mass, GSRS; gastrointestinal rating scale, TEE; total energy expenditure, CFQ-R; cystic fibrosis questionnaire revised