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Nutritional Status in Adults with Cystic Fibrosis and Pancreatic Insufficiency

Master's Thesis

by

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Nutritional status in adults with cystic fibrosis and pancreatic insufficiency

A cross sectional study

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Abstract

Background: Cystic fibrosis (CF) is a rare and genetic disease. Cystic fibrosis with pancreatic insufficiency (PI) has a strong association with nutritional status, leading to malnutrition due to malabsorption of macronutrients and micronutrients. A limited amount of studies have investigated nutritional status in adults with CF and PI in Norway.

Objective: To investigate nutritional status and intake in the adult Norwegian CF–population with PI.

Methods: This study was a cross-sectional, pilot study, carried out in patients above 18 years old at the Department of Pulmonary Medicine at Oslo University Hospital (OUH) from August to December 2018. Participants with liver disease were excluded. Nutritional status was assessed by anthropometric measurements (including weight, height, body mass index (BMI)), handgrip strength (HGS) and body composition analysis using dual energy X-ray absorptiometry (DXA). Spirometry and biochemical measurements were also measured.

Results: 34 participants were included. Mean BMI was 24.0 kg/m^2 for all the subjects, where 61.5 % of female subjects had BMI below 22 kg/m^2 and 42.9 % of the male subjects had BMI below 23 kg/m^2. Among the subjects, one subject (2.9 %) was underweight and eleven subjects (32.3 %) were overweight or had obesity. 11.1% of the subjects had osteopenia. 32% , 4.2 % and 12.5 % of the subjects , respectively, had deficiency in vitamin (vit) D, A and E. 3.4 % of the subjects were iron anemia deficient. 18.2% of the subjects had HbA1c values above the reference values. The participants had a low intake of energy and nutrients, compared to recommendations for the required for general Nordic population and recommendations specific for CF.

Conclusion: We observed a high prevalence of subjects with low intake of energy and nutrients. Fat-soluble vitamins' status is still not optimal, despite using vitamin supplementation and pancreatic enzymes. However, these results must be interpreted cautiously, due to the small sample size in this study. Larger number of patients should be included in future studies to assess nutritional status in individuals with CF and PI.

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Abbreviations

25-OH- vitamin D: 25-hydroxy-vitamin D

BMD: Body mass density

BMI: Body mass index

BMR: Basal metabolic rate

CF: Cystic fibrosis

CFF: Cystic Fibrosis Foundation

CFBD: Cystic fibrosis-related bone disease

CFRD: Cystic fibrosis-related Diabetes

CFTR: Cystic fibrosis transmembrane conductance regulator

ECFSPR: European Cystic Fibrosis Society Patient Registry

ESPEN-ESPGHAN-ECFC guidelines: European Society of Clinical Nutrition and Metabolism- European Society for Paediatric Gastroenterology, Hepatology and Nutrition- European Cystic Fibrosis Society (in the present study, ESPEN will be used as short term)

FFM: Fat free mass

FFMI: Fat free mass index

FM: Fat mass

FMI: Fat mass index

HGS: Handgrip strength

IQR: Interquartile range

LBM: Lean body mass

LBMI: Lean body mass index

LI: Lower intake level

n: number

NNR: Nordic Nutrition recommendations

OUH: Oslo University Hospital

PERT: Pancreatic Enzyme Replacement Therapy

PI: Pancreatic insufficiency

PTH: Parathyroid hormone

RAE: Retinol activity equivalents

SD: Standard deviation

UL: Upper intake levels

WHO: World Health Organization

1 Introduction

1.1 Cystic fibrosis

1.1.1 Definition and Epidemiology

Cystic fibrosis (CF) is a rare, recessively inherited and multiorganic disorder which affects lungs, pancreas, intestine, liver, sweat glands and reproductive tract (1, 2) (p.790). The major cause of morbidity and mortality for most CF patients is the progressive lung disease (3). More than 70,000 people are affected with CF worldwide and more than 30,000 people are affected with CF in United States. More than 10,400 people are affected with CF in United Kingdom (1, 4). Europe has the highest prevalence of CF compared with other continents (5). The recent report from the European Cystic Fibrosis Society Patient Registry (ECFSPR) reported 44, 719 registered patients with CF in 31 European countries including Norway (6). Norway's register for CF included 258 patients, but the report included data for only 230 patients in 2016, (estimated to 72 % of the Norwegian CF-population) (7).

1.1.2 Ethiology

CFTR gene

Cystic fibrosis is caused by mutations in a gene that resides on chromosome 7, this code for cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel found in the apical membrane of epithelial cells like airway, biliary tree, pancreatic duct and sweat ducts (3, 8-10). This protein transports chloride from mucus-producing cells, water follows and the mucus will be thin (11). Around 1.800 mutations have been found and the most CF causing mutation is F508del (12, 13) (p.18-19). Patients can either be homozygous or heterozygous with respect to CFTR mutations (14) (p.14). It should be noted that carriers of one defective CF gene and one normal CF gene do not demonstrate the disease in most cases (1). **Figure 1** shows the different classifications of CFTR gene mutations.

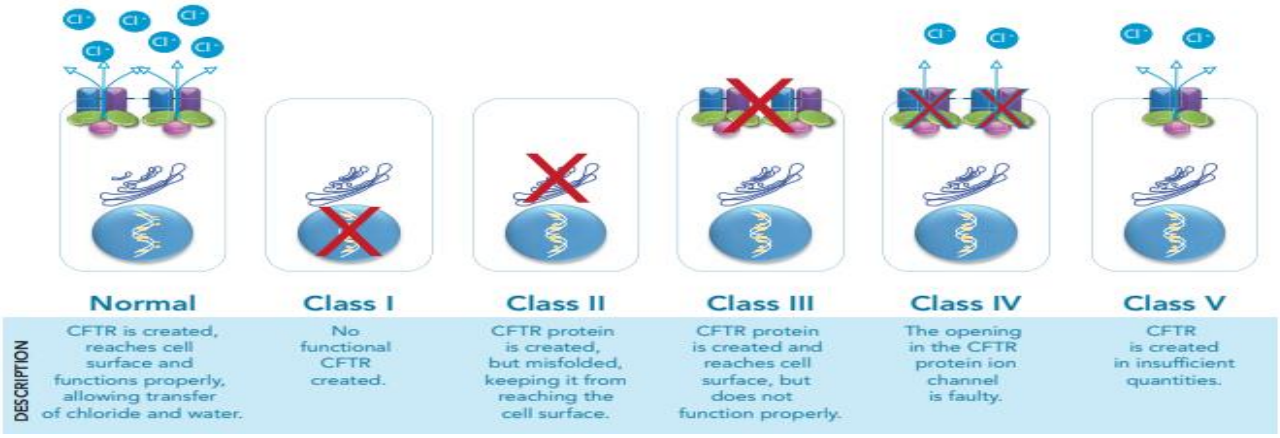

Figure 1: Classifications of CFTR-gene mutations (Reprinted with permission granted by Cystic Fibrosis Foundation) (12).

1.1.3 Pathogenesis

The organ dysfunction present in CF has been investigated in humans and CFTR-knockout mice, but the pathogenesis remains incompletely understood (3). Mutations in CFTR, will affect the transport of ions (Cl, Na), inducing abnormality of the transport (9, 10). This results in a thick mucus secretions in the digestive, reproductive and respiratory system (10, 15).

Pulmonary function

Cystic fibrosis will affect the pulmonary function, causing pulmonary difficulties which are found in over 90 % of CF patients (15). People with CF also suffer from frequent lung infections (16). Viscous secretions lead to chronic obstruction in the airway are followed by progressive respiratory colonization with pathogenic bacteria (3). Lung infection with *Pseudomonas aeruginosa* is the main reason for mortality and morbidity in cystic fibrosis patients (17). This pathogen can cause chronic inflammation because there would be a considerable colonization of these bacteria in the lower respiratory tract. This will again damage the lung system and will cause emphysema, bronchiectasis and decreasing the lung function (17). The CF registry in Norway reported 32 % of adults with chronic P. *aeruginosa* infection (7). However, it should be taken into consideration that the data obtained was insufficient, as 16 % did not respond (7). At birth, the pulmonary function is normal, but the function will be decreased after weeks, months, or years later due to frequently infections and inflammations (18). Dyspnea, changes in cough, reduction in spirometry variables, weight loss, reduced appetite and energy level are the symptoms of lung disease caused by CF (19).

Gastrointestinal disorders

Loss of CFTR function creates thickened secretions, which results in gastrointestinal disorders like pancreatic insufficiency (PI), gastroesophageal reflux disease (GERD) and hepatobiliary diseases, such as CF related liver disease (CFLD) and gallbladder disease (3, 20, 21). Impaired flow of pancreatic secretions and bile is an important cause of maldigestion and malabsorption. Dysfunction of pancreas leads to CF-related diabetes (3). According to Cystic Fibrosis Foundation (CFF) patient registry (US) in 2017, 39.6 % of adults with CF had GERD (12). Lung disease is a major reason for the onset of GERD, airway hyperinflation, frequent cough, dysmotility and high fat diet are other predisposing factors to develop GERD (21, 22).

Cystic fibrosis and pancreatic insufficiency

Pancreatic function is characterized as pancreatic insufficiency (PI) or pancreatic sufficiency (PS) (23). Pancreatic insufficiency is a complication of CF and around 85 % to 90 % of individuals with CF have PI (2) (p.791). Pancreatic enzymes were utilized by 72 % of the people with CF in Norway, and 83 % in Europe, as reported by ECFSPR (6, 7). A mutation of the CFTR gene that is expressed in pancreas cause thick mucus, which leads to deficiency of exocrine pancreatic enzymes. This results in poor digestion and absorption of macronutrients and micronutrients (2, 24) (p.790-791). Symptoms of pancreas insufficiency are weight loss, gas, dyspepsia, bloating and steatorrhea (23) and it is also associated with respiratory function. Pulmonary function was observed to be better in patients with normal fat absorption compared to patients who had steatorrhea (25). Pancreatic sufficient patients have an increased risk to develop chronic pancreatitis, which is rare among PI patients (20).

Cystic fibrosis related diabetes (CFRD)

Cystic fibrosis related diabetes (CFRD) has become a common complication of CF (20, 26). According to registry from CFF (US) in 2017, 35 % of the adults were diagnosed with CFRD (27). In the Norwegian's CF registry from 2016, 18.67 % of adults with CF used insulin, but an absence of sufficient data should be considered (7). Dysfunction of pancreatic islets, caused by mutations in CFTR leads to insulin deficiency and this is the primary cause for CFRD (26, 28, 29). Autopsy studies of CF patients have shown that patients with CFRD have decreased number of islet cells in pancreas (30). Cystic fibrosis related diabetes is related with

poor nutritional and decline in pulmonary function (28, 29). Insulin therapy is shown to restore body mass index (BMI), improve lung function in patients with CFRD (31).

Cystic fibrosis related bone disease (CFBD)

Cystic fibrosis is associated with bone disease and it is one of the leading complications of CF (32). In adults and adolescents with CF, osteopenia and osteoporosis are common (10). Cystic Fibrosis Foundation's patient registry (US) reported in 2017 that 10.4 % had osteopenia and 3.8 % had osteoporosis (12). Factors like genetics, corticosteroid therapy and insulin insufficiency are some of the factors which could develop cystic fibrosis related bone disease (CFBD) (32). Nutritional factors like deficiencies of vitamin D, vitamin K, calcium and delayed puberty are risk factors for developing CFBD (10). It has been shown that severe lung disease, pancreatic insufficiency and decreased physical activity are associated with low bone mineral density (BMD) in adults with CF (33).

1.1.4 Diagnosis and treatment of cystic fibrosis

Diagnosis of cystic fibrosis

Cystic fibrosis is diagnosed by symptoms or by newborn screening. A sweat test is the gold standard for diagnosing CF. This is performed after clinical signs and symptoms are noted (34, 35). In addition, a genetic test for CF-mutations is used, but only frequent mutations will be detected in most laboratories (1, 15). Neonatal screening is used to diagnose CF and was introduced in Norway in 2012 (7). Since infection in the airways is the major reason for lung disease, the respiratory tract culture for these pathogens is used to be performed. Other tests like spirometry is used to be a routine method to test lung function. X-rays of chest is also performed yearly to monitor lung function (36). To confirm PI, two tests, faecal fat excretion and faecal elastase are used. A sample of stool is required. To define PI in adults, the faecal elastase is below 200 µg /g and faecal fat is above 7g/d (twice) (14, 37) (p.139).

Medical treatment

The treatment should be tailored individually for each individual. Since pathogens are the reason for the infections and inflammations, antibiotics are often used. Clearance of thick and sticky airway secretions is an important therapy in CF (9). Bronchoconstriction or smooth

muscle hypertrophy, caused by CF is a reason why many patients with CF use bronchodilators, like beta agonists or anticholinergics (9, 12). In 2012, drugs that target cystic fibrosis CFTR, called CFTR modulators, were discovered (27). These modulators target the defective protein and improve the function of CFTR. Lumacaftor and Ivacaftor are examples of two types of CFTR modulators (12). When the lung disease is severe, transplantation of lungs is offered, if possible to extend the life (9). According to Norway's CF registry in 2016, 14 adults are alive after lung transplantation (7).

Pancreatic enzyme replacement therapy (PERT)

Pancreatic insufficiency cause deficiency of digestive enzymes. Some malnutrition can be prevented from pancreatic enzyme replacement therapy (PERT) (9). Treatment with PERT is necessary to achieve normal weight in adults (23). This is given orally and contains the pancreatic enzymes lipase, amylase and protease. These enzymes are in enteric-coated microspheres or micro tablets. Enteric coating prevents potential damage caused by gastric acid. Doses with pancreatic enzymes are individualized. Intake of the doses of these enzymes depends on the age of the individual, weight and grams fat ingested per day (10, 37). Pancreatic enzymes should be provided once PI has been defined and it should be given when consuming all types of food containing fat and milk are consumed. There are different types of brands that contains different units of protease, lipase and amylase (38). It is important to monitor the nutritional status every six months for adults who use PERT (10). Fecal fat, fecal elastase or nitrogen balance can help to evaluate tolerability of the PERT (2) (p.791).

Prognosis

Survival rate has increased significantly because of advanced treatments and technology (2) (p.790-791). When CF was discovered in 1938, the life expectancy was nearly 6 months and the lives of CF patients were painful and short (9). In 1950 the median survival age was 5 years of age (39), but today the survival age exceeds more than 30 years (9). In Norway, the median age is 24.7 years for the CF population and 65 % of the population is > 18 years old in 2016 (7). It was not reported any mortality in CF patients in 2016 in Norway (7). Life quality has improved among CF patients and they are living a normal life. Children go to school and adults finish degree, marital status has increased and many adults are working (9).

Follow up

A multidisciplinary team (MDT) is required to provide specialized and comprehensive CF care (40, 41). Respiratory paediatrician, clinical microbiologist, clinical nurse specialist, specialist physiotherapist, specialist dietitian, clinical psychologist, social worker, pharmacist, clinical geneticist, secretarial support, database coordinator and medical support from trainee are included in the MDTT team. They are responsible to give sufficient patient care to patients with CF. Among them, specialist CF dietitian has the responsibility to provide nutritional treatment and ensure that CF patients achieve optimal nutritional status. CF dietitian plays an important role in educating and advising CF patients. When advice is given, age should be taken into consideration (40).

1.2 Nutritional status

1.2.1 Malnutrition in people with CF

In 1938, the autopsy studies showed that maldigestion caused malnutrition and this was the reason of the early death in infants (9, 38). Over the past 3 decades, focus on improving nutrition outcomes have showed improvement in height and weight percentiles (37). According to CFF's patient registry (US), 41 % of the adults with CF met the BMI goal in and 52 % of the adults met the BMI goal in 2017 (27). Norway's CF register reported 21.4 kg/m^2 in mean BMI for women and 23.1 kg/m^2 in mean BMI for men in 2016 (7). Malnutrition is defined as a physical condition resulting from inadequate or faulty diet or from physical inability to metabolize or absorb nutrients (42).

Cause for malnutrition

Energy loss, inadequate energy intake, and increased energy needs are the reasons for malnutrition. Pancreatic insufficiency is the major reason for energy loss. As a result of PI, maldigestion will occur, it will be insufficient release of pancreatic enzymes to absorb and digest nutrients like fat-soluble vitamins, protein and fat (10, 43). Other complications like insulin resistance or impaired secretion of insulin (CFRD), reduced liver function (CFLD), inflammation or infections in the intestinal will give higher energy loss (10). Individuals with CF have inadequate energy intake due to malabsorption or poor appetite. The reasons for poor appetite are gastrointestinal symptoms and symptoms from airways. Gastrointestinal

symptoms include GERD, reduced gastric emptying, small intestinal bacterial overgrowth and constipation. Symptoms like bloating, abdominal pain and gas are common in patients with CF and can lead to poor appetite. Patients with CF use many medicines and these can also lead to poor appetite (43). Psychosocial concerns may also be a factor for malnutrition. Adolescent girls may also have body image complications and this may contribute to malnutrition (38). High-energy needs are associated with respiratory infections and inflammations (10).

Consequences for malnutrition

Consequences of malnutrition in children and young adults will be cognitive failure, stunting, severe lung disease and poor survival (10, 44). In adults respiratory muscles are affected by malnutrition and this leads to reduced exercise tolerance. This will cause immunological impairment (10). Severe lung disease will cause frequent and severe pulmonary infections and this can induce anorexia. These factors lead to energy deficit, and as a result of energy deficit, weight loss will occur. This will cause loss of adipose tissue and within time, loss of muscle mass will occur. This will result in pulmonary failure and death (45).

1.2.2 Overweight in people with CF

Even though many individuals with CF are affected by malnutrition, the percentage of individuals with overweight has increased (46). A longitudinal study from Canada included 909 individuals with CF. This study reported that the proportion of overweight increased from 7.0 % to 18.4 % in the years span of 1985 to 2011 in US and the prevalence of overweight was mostly found in pancreatic sufficient patients (47). Another study from US showed prevalence of overweight and obesity and the majority of the patients were pancreatic insufficient (48).

1.2.3 Energy and Nutrients

Energy and macronutrients

Energy requirement will vary from person to person and it is based on sex, age, physical activity and basal metabolic rate (BMR). In CF severity of lung diseases, other complications like CF-related diabetes, pancreatic insufficiency and severity of the CFTR mutation can

increase the energy need (2) (p.793). Studies have shown that many individuals with CF do not achieve the recommended energy intake (49, 50). In individuals with CF, protein digestion is reduced and this leads to a reduction of the anabolic potential of a meal that leads to elevated amount of undigested protein and production of harmful toxins by bacteria in the gut. Lower digestion and absorption of protein can cause muscle loss that is associated with bone mineral loss, pulmonary failure and reduced survival (51). Individuals with PI have poor absorption of fat, which will affect energy intake even though they use PERT. For many years, a low fat diet was recommended to regulate symptoms of steatorrhea. However, this led to severe malnutrition with lack of muscle mass, subcutaneous fat and swollen abdomen (37, 38). High-fat intake is recommended to make it easier to achieve their energy requirement (37). Low levels of essential fatty acid are also seen in patients with CF. Malabsorption and maldigestion in CF patients can lead to depletion of essential fatty acid (52).

Vitamins and Minerals

Individuals with PI are at risk for fat-soluble vitamin deficiency and certain mineral deficiencies even though they use PERT (37, 46). All patients with PI need supplementation (high doses) with fat-soluble vitamins. Deficiency of fat-soluble vitamins like vitamins A, D and E is common in infants with CF before 2 months of age (53). Despite of age, body weight and pancreatic function, low serum vitamin A levels are frequently found in untreated CF patients (52). Disturbed dark adaption was found in CF patients with low serum retinol concentrations and this was reversed after supplementation with vitamin A (52, 54). Low exposure to sunlight, lower levels of vitamin D binding protein and reduced body fat are factors for causing vitamin D deficiency (55). Lower levels of vitamin D is associated with poor bone health in adults (56). Vitamin E deficiency is frequent in patients with CF and vitamin E plays and important role as an antioxidant. Increased oxidative stress in CF patients is found due to inflammations in respiratory function. Even though clinical symptoms of vitamin E deficiency is rare, prolonged vitamin E deficiency can leads to irreversible neurological failure (52). In CF patients vitamin K deficiency is associated with osteoporosis (52). Water soluble vitamins are well absorbed in individuals with CF. Patients with PI can achieve adequate vitamin B_{12} with PERT (57). Vitamin B_{12} supplementation is recommended for patients who have undergone resections of terminal ileum (52). Due to malabsorption in the intestine, chronic inflammation and increased sweating, higher requirement of electrolytes, minerals and trace elements are required for patients with CF (10). In some

conditions with hot weather, fever or exercise sodium deficit can occur. Calcium is important for bone health and the importance of sufficient intake of calcium and vitamin D should be emphasized (10). If severe malabsorption in patients with CF exist, they may need supplementation of magnesium (52). Factors like chronic infection, inflammation, malabsorption and inadequate intake contribute to iron deficiency in people with CF (10). Supplementation with iron should be considered by monitoring plasma transferrin saturation (52). People with CF may have low or adequate zinc status. Steatorrhea or vitamin A deficiency may lead to zinc insufficiency and supplementation can be given to prevent eye problems, growth retardation or increased infections (10). Even though selenium status has been reported low in some of the CF patients, routine supplementation of selenium is not recommended, due to limited therapeutic range (10).

1.2.4 Assessment of nutritional status

Individuals with CF have a higher nutritional risk. This is a reason why nutritional assessment is recommended routinely. To assess nutritional status, monitoring serum markers and body composition are often used (10). Varies parameters are used to assess body composition in individuals with CF, such as anthropometric values, dual- energy X-ray absorptiometry (DXA), air displacement plethysmography, bioelectrical impedance, hand grip strength and double labeled water measurement (10). It is recommended to do anthropometric measurements routinely, weight and height every 3 months. The aim is to achieve 23 kg/m ^{2} for men and 22 kg/m^2 for females (10). CF patients who are stunted or malnourished should have frequently monitoring. Adults with CF should undergo dietary reviews at least every 6 months and questions about adherence to dietary advice should be included (10). Serum markers can also be used to assess nutritional status. Serum markers of electrolytes, liver function tests, iron status, blood count and plasma fat-soluble vitamin levels are included. Annual screening for glucose tolerance is recommended to define CFRD. It is also important to do annual assessment for calcium intake (10).

1.2.5 Nutritional recommendations for cystic fibrosis

It is recommended that individuals with CF should have a higher energy intake. European guidelines recommends that energy requirement (EAR) range from 120 % to 150 % for CF patients (10). Protein requirement is possibly higher in individuals with CF compared to non-

CF individuals, and European Food Safety Authority (EFSA) recommends a population of reference intake of 0.83 g of protein /kg body weight (10). According to consensus guidelines, it is recommended to consume 40-45 % of their caloric intake from carbohydrates, 35-40 % from fat and 20 % from protein in children to achieve adequate intake (10). However, consume of 35-40 % of their caloric intake from fat is also appropriate for adults with CF (58, 59). Use of oral nutritional supplements (ONS) needs be considered when treating malnourished adults. To improve energy intake or specific nutrients like essential fatty acids ONS may be used (10). If oral interventions have failed, enteral feeding can be provided. When enteral feeding is used, it is important to consider the patients clinical status. Parenteral nutrition is not recommended as a routine, but in cases where enteral feeding is not possible PN can be used as a short term support (10).

Individuals with CF and PI should begin to take fat-soluble vitamin supplementation at the same time when PERT is initiated (23). To achieve vitamin A serum concentrations within normal range, daily doses between 4000 and 10 000 IU of retinol can be suggested. It is important to start with a low dose and then increase (52). Monitoring of the serum concentrations is important to guide vitamin A supplement (10). Supplementation of vitamin A should not exceed 20 000 IU if retinol binding protein is low. Special consideration should be given during pregnancy and it is suggested to keep vitamin A intake below 10 000 IU/day during pregnancy. Using Beta carotene, a daily dose of 0.5-1 mg/kg/β-carotene corrected low concentrations of vitamin A in blood (52). Thus, this dosage can be followed for 12 weeks, but maximum dose is 10 mg/day (10). To maintain vitamin D serum concentrations, a daily dose between 800 to 4000 IU is required (10). Vitamin E is non toxic and it is suggested to use a daily dose of 400 IU (52). Regular supplementation of 1-10 mg/day of vitamin K_1 (phylloquinine, phytomenadione) depending on age is suggested (10, 52).

Supplement of sodium is needed when the excessive sweating is expected, like in stress situations (i.e. excessive exercise or fever) (10). Recommendations from EFSA reports that reference values for calcium intake for adults is 1000 mg calcium for adults (between 18 to 25 years). For adults above 25 years, the recommended calcium intake is 950 mg (10). Zinc supplementation with 25 mg/day is recommended to individuals at risk of zinc insufficiency (10). Selenium supplementation is not recommended, but PERT does contain safe and adequate amount of selenium (10, 52).

2 Objectives

Cystic fibrosis with pancreatic insufficiency has a strong association with nutritional status. Several studies have explored nutritional status in adults with cystic fibrosis in other countries, but few studies have investigated nutritional studies in adults with cystic fibrosis and pancreatic insufficiency in the Norwegian population. Therefore, we wanted to examine nutritional status in Norwegian adults with CF and PI.

The goal in this study was to see the challenges in adults with cystic fibrosis and pancreatic insufficiency and the prevalence of undernutrition and overweight.

The main objectives in this study were:

- To investigate nutritional status in adults with cystic fibrosis and pancreatic insufficiency by means of anthropometrical measurements, body composition analysis and physical test measurement.
- To investigate vitamin and mineral status in blood in the study sample to identify the prevalence of nutritional deficiencies
- To evaluate the study samples dietary intake, including dietary supplements, compared to general dietary recommendations for the Nordic population and recommendations specific for CF.

3 Subjects and methods

3.1 Study design and recruitment

3.1.1 Study design

This master thesis is a part of a pilot, cross- sectional study that investigates dietary intake, nutritional status, gastrointestinal symptoms and health-related quality of life in patients with cystic fibrosis and pancreatic insufficiency. The present work was conducted at Division of Medicine, Oslo University Hospital (OUH), Ullevål in collaboration with University of Oslo. Department for clinical nutrition planned the project and patients were recruited from Department of Pulmonary Medicine, OUH, Ullevål. The data collection was carried out between August 2018 and December 2018. The analysis were performed from January 2019. In this master thesis, solely nutritional status, biochemical parameters and deficiencies seen in connection with dietary intake and supplements will be described.

3.1.2 Study population and recruitment

Patients with CF and PI were invited to participate in the study. Patients who fulfilled the criteria were recruited when they had their regularly consultations with the CF-team at Department of Pulmonary Medicine, OUH, Ullevål in the period August 2018 to December 2018. The nurse at the department distributed a list of potential CF patients from August 2018 to December 2018. When patients met to their appointments, they received information about the study and went through the invitation letter (**Appendix 1)** and written informed consent **(Appendix 2)** with the master's student. The master's student asked them whether they wanted to participate. If they wanted to participate, they signed under the written informed consent. They also received a copy of the written informed consent.

3.1.3 Inclusion and exclusion criteria

Adult patients over 18 years old age diagnosed with CF and PI who came to control at OUH, Ullevål in the period from August 2018 to December 2018 were included in this study. Pregnant, inability to communicate in Norwegian or English and complications like CF

related liver diseases were the exclusion criteria in this study. People who rejected to participate in this study were also excluded.

3.2 Data collection

Data was collected at OUH, Ullevål, Department of Pulmonary medicine. To investigate the nutritional status, anthropometrical measurements like height, weight, body mass index (BMI) were measured. Body composition analysis was performed and physical test as grip strength was also performed. Blood samples were taken and these blood samples were a part of participants annual assessment. Dietary intake registry and questions about diet habits, appetite, difficulties in feeding, dysphagia, use of supplements, cooking habits, meal pattern and question about eating with others were asked. To investigate the gastro symptoms, gastrointestinal ratings scale (GSRS) was used. The cystic fibrosis questionnaire revised (CFQ-R) was used to investigate the quality of life. Additional information, like weight history and use of medicaments were collected from participants medical reports (DIPS) after participants consent.

Participants had breathing examination before their consultations. During, the breathing examination, weight, height and spirometry tests were measured. The master's student was allowed to stay there to report the measurements. In circumstances where it was not possible to stay there, master's student asked the participants about the weight and height, and master's student obtained anthropometric data from medical journals to cross check. Spirometry measurements were obtained from medical journals. While they were waiting for their consultations, they were signing for the two questionnaires, GSRS and CFQ-R. After the consultations, the master's student collected all nutritional data and the duration time ranged from 30-45 minutes for each participant depending on how much time they were willing to spend. The master's student also called the nurse at the Department of Orthopaedics to get an appointment for dual energy X-ray absorptiometry (DXA).

3.2.1 Anthropometry and spirometry

Weight

Weight was measured with Seca Medical Body Composition Analyzer 704 (Seca GmbH & Co. KG, Hamburg, Germany). This was in the same room where the participants had spirometry test. Measurements of weight were performed without heavy clothes, shoes and outerwear. Men have a statistically significantly greater clothing weight than women. Clothing adjustment is appropriate if it is 0.8 kg for women and 1.2 kg for men, regardless of outdoor temperature (60). Clothing adjusted weight was calculated by subtracting 1 kg to 1.5 kg regarding what they were wearing. A nurse at the Department of Pulmonary disease performed measurements of weight.

Height

Height was measured to the nearest 0.1 centimeter with Seca 704 digital wireless stadiometer (Seca GmbH & Co. KG, Hamburg, Germany). Height was measured without shoes and the participants were asked to stand in an upright position. They were also asked to have a straight back and look straightforward. The same nurse who measured weight performed measurements of the height.

Body mass index

To calculate BMI, the measured weights and heights were used by dividing weight in kilogram by the height in meters squared for each individual participant. Participants' medical journals were used to crosscheck the calculated BMI. The calculated BMI were used to classify according to BMI cut-off values for adults from World Health Organization (WHO) (61) **(Table 1).** BMI target specific for individuals with CF is to achieve 23 kg/m ^{2} for men and 22 kg/m^2 for females (10).

Table 1: Cut off values for body mass index (BMI) according to WHO (61)

BMI (kg/m^2)	**Nutritional status**
< 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Pre obesity/overweight
30.0-34.9	Obesity class I
35-39.9	Obesity class II
> 40	Obesity class III

Spirometry

To assess lung function in individuals with CF and PI, forced expiratory volume in first second (FEV_1) was used. This is the amount volume of air expired within the first second after a forced expiration (62). To define the severity of lung disease, FEV_1 between 80% and 60% represents mild impairment, 40% to 60 % represents moderate impairment and below 40% represents severe impairment (62). Another parameter to measure lung function is forced vital capacity (FVC). This is the maximal volume of expiration and this was also used in this study (62). The same nurse who performed weight and height measurements conducted spirometry test.

3.2.2 Body composition analysis

Body composition analysis was measured by dual energy X-ray absorptiometry (DXA), using a Lunar Prodigy Advance dual energy X-ray absorptiometry, DF+ 14685, Prodigy 4 model (GE healthcare Norge AS, Oslo, Norway). The software program was enCORE, version 16 sp2. With a low dose of radiation this instrument will measure soft tissue, bone composition, bone-mineral density (BM), lean- and fat-tissue mass and percentage of fat (63). Before the measurement participants' name, age, sex and ethnicity was manually plotted in. Examiner, the nurse at the Department of Orthopedics at OUH, Ullevål, instructed the participants to wear light clothes, remove shoes, outerwear and any materials with metal fasteners like belts, metal buttons, zips etc. Participants were lying on a flat X-ray table and had to lie calm. Participants' arms were held in to the body, a scanning arm passed over the participants' body to measure. Duration of the measurement for each participant was 20 minutes (64). The DXA scan can measure different parts of the body, but in this project, it was a total full body scan for all participants. This included fat mass (FM), fat free mass (FFM), lean body mass (LBM), bone mineral density (BMD) with t-score and bone mineral content (BMC). T- Score was used to define osteoporosis (65) **(Table 2)**. Fat mass index (FMI= FM/height^2), Fat free mass index (FFMI= FFM / height^2) and lean body mass index (LBMI= LBM/ height^2) were calculated for the participants. According to ESPEN statement, to define malnutrition low FFMI was set to < 17 kg/m^2 and <15 kg/m^2 in males and females respectively (66).

Table 2: Cut off values for T-score (65)

T-score	**Categorization**
-1 or above	Normal bone density
Between -1 and -2.5	Low bone density (osteopenia)
-2.5 or below	Osteoporosis

3.2.3 Physical test

To measure hand grip strength (HGS) KERN WOC17006539, MAP 80K1 (KERN & Sohn GmbH, Ziegelei 1, 72336 Balingen, Germany) handgrip dynamometer was used. The test was performed after standard guidelines as recommended by the American Society of Hand Therapist (ASHT). The dominant arm was measured. Participants were seated upright against the back of a chair without armrests, with feet placed flat on the floor. Shoulder was adducted and neutrally rotated, elbow was flexed and the forearm was in a neutral position with wrist slightly extended. They were instructed to perform maximal isometric contraction (67). The test was repeated 3 times within a minute and the mean of the three values were used in this study. Cut of values for healthy Caucasian population was used to compare HGS in study population (68) **(Table 3).**

Table 3: Cut off values for hand grip strength, measured in kg in men and women (68)

	Male		**Female**	
Age (y)	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)

3.2.4 Biochemical measurements

Blood samples were a part of the participants' annual assessment during 2018, and were taken in a fasting state. A nurse or a bioengineer at Department of Pulmonary Medicine collected the samples from the peripheral vein of the participants. The collected blood samples were brought to the Central Laboratory at OUH for analysis. Standard procedures in the respective

laboratories were used to analyze all biochemical parameters. The results of these samples were used to compare with the reference rages in the respective laboratories. The master's student obtained these results from the participant's medical records. Overview of all biochemical analyses and the reference values are presented in **Appendix 3.** According to WHO, to define vitamin A deficiency serum retinol concentrations have been set to below 0.70 µmol/L (69). Serum 25-hydroxyvitamin D (25(OH)D) below 20 ng/mL (50 nmol/L) is defined as deficiency and below 30 ng/mL (75 nmol/L) is defined as insufficiency (55). To define vitamin E status, reference values for vitamin E were used. Serum alfa-tocopherol below 17 µmol/L indicated low vitamin E status (Appendix 3). Serum iron was used, first to determine anemia. If iron values were low (< 9 µmol/L), serum ferritin was used to determine forms of anemia (Appendix 3). Ferritin level below normal (< 30 µg/L for men and < 10 µg/L for women) indicated anemia of iron deficiency (IDA), ferritin level above normal (> 400 µg/L for men and > 170 µg/L for women) indicated anemia of chronic inflammation (ACI). If ferritin values varies, it indicated both forms of anemia (10) (Appendix 3).

3.2.5 Dietary assessment

24 hours diet recall

A 24 hours diet recall was used to assess the participants' dietary intake. The master's student asked the participants to recall all foods and beverages they consumed the day before. This was conducted as an interview, and the master's student was the interviewer. While they were recalling their dietary intake, the interviewer asked further about brand names, portion sizes and methods of preparing. Participants were asked about snacks and alcoholic beverages to make sure that all foods and beverages they consumed were registered. At the end of the interview the interviewer asked other questions like diet habits, appetite, difficulties in feeding, dysphagia, use of supplements including use of pancreatic enzymes, cooking habits, meal pattern and question about eating with others. They were asked if they used ONS to optimize their energy and nutrient intake. They were also asked if they used vitamin supplementation like DEKAs Plus Softgels (vitamins prescribed for medical reasons to increase absorption in pancreatic insufficiency) or other multivitamin and mineral supplements. Participants were asked about doses of pancreatic enzymes (Creon). The interviewer asked frequency, amount and what time they took these supplements.

When the 24 hours diet recall was conducted, the participants got a booklet with photographs of six to five portion sizes of some foods like bread, amount of butter, salads, rice, fish and vegetables (Portionsguide, Livsmedelsverket 2009) **(Appendix 4).** Participants received a sample of this booklet to make sure that they used the booklet in the 24 hours diet recall. To calculate the food intake, another booklet with weight of the portion sizes of the foods, corresponding to the photographs was used (Nyckel till Portionsguide, Livsmedelsverket 2009)**.** Portion sizes from Matportalen were used to estimate portion sizes for beverages and household measurements like teaspoons, tablespoons and deciliters **(Appendix 5)** (70)**.** For each participant, the 24 hours diet recall was conducted three times, the first interview occurred when the participants had consultation with the CF team at OUH, Ullevål. The second and third interview was conducted as a telephone interview. The second and third interview was performed within few months after the first interview. To obtain a representative selection of the regular diets, one weekend day and two weekdays were selected.

Calculation of the dietary intake

After collecting the dietary intake in participants, a software program called Dietist Net, version 19.02.25 (Kost och Näringsdata AB, Bromma, Sweden) was used. This software program calculated macronutrients and micronutrients in the food items. This program contained items from Norway, Sweden and from other countries like USA. By using the program, intake of energy, macro- and micronutrients were calculated for the three days for each participant. Weight from ‘’kostholdsplanleggeren’’ was used if some items had unspecified amount like a ‘’one portion’’. In analysis mean of the registered intake was used (71). For participants who completed two or all three days, mean of the three days was used. For participants who only completed one day, intake from this day was used. Intake of the nutrients from supplements were selected from Nutricia’s, Fresenius’s, Callion Pharma’s, Nycomed’s and Felleskatalogen’s websites (72-76).

Nutrient intake from only food and beverages was labeled as *Dietary intake* in the analysis, and nutrient intake from food, oral nutritional supplements and supplements of vitamins was labeled as *Total dietary intake.* To calculate energy for carbohydrate, protein and fat, it was standardized using the factor 17 kJ for carbohydrate and protein and 38 kJ for fat (77) (p.30). The software program, showed percentage of estimated average requirement for each

participants and master's student set a PAL value of 1.6 to all participants because it corresponds to a common lifestyle with sedentary work and some increased activity during leisure time (78) (p.34).

Comparison with recommendations

Intake of energy, macro- and micronutrients in the study sample was compared with healthy population, Nordic Nutrition Recommendations 2012 (NNR 2012) and recommendations specific for CF (includes ESPEN-ESPGHAN-ECFS guidelines and the European consensus) (10, 78). In the present study, ESPEN will be used as a short form. In these comparisons statistical analysis were not performed.

3.2.6 Statistical analysis

The statistical analysis in this study was performed by using the software program called SPSS statistics, version 25 (IBM SPSS Statistics 25). All P values < 0.05 was considered statistically significant. All missing values in this study were excluded. The data was either normally distributed or non-normally distributed. Data was considering normally distributed by using histograms, normality plots like Q-Q Plot and tests of normality. Normally distributed data are presented in mean and standard deviation (SD). For normally distributed data two tailed t- test was used. Non-normally distributed data are presented in median and inter quartile range (IQR). To compare means of normally distributed data for continually variables between groups, parametric independent samples T test was used. For non-normally distributed continues data, non-parametric test, Wilcoxon test was used. Frequencies (n) and percentages (%) were used to present categorical data. 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.

3.3 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 6).** Participants were informed about the project, the aims, the benefits and disadvantages of this project before they signed in a written consent (Appendix 2). They also got a copy of this

written consent. Participants were also ensured that this study was voluntary, and they could withdraw from the project at any time. All sensitive information about the participants was handled in a safe way. Sensitive information in papers was locked in a cupboard at OUH, Ullevål. Other sensitive information was saved in an electronic folder for sensitive data in the research server at Oslo University Hospital. Participants' names and other identifiable information were replaced with unidentifiable codes. The project leader had the responsibility to make sure that the information was handled in a secured method. Information about the participants will be deleted within 5 years after the project end. Participants in this study were ensured according to law of the patient damages, and there were no health risk associated in this project. Participants were informed if the blood samples or DXA measurement showed any deficiencies, the participants' general practitioner will get information upon patients consent.

4 Results

4.1 Study sample

4.1.1 Study population

In this project, out of 49 eligible participants, 34 (69.4 %) participants were included. See **Figure 2** for an overview of the recruitment process.

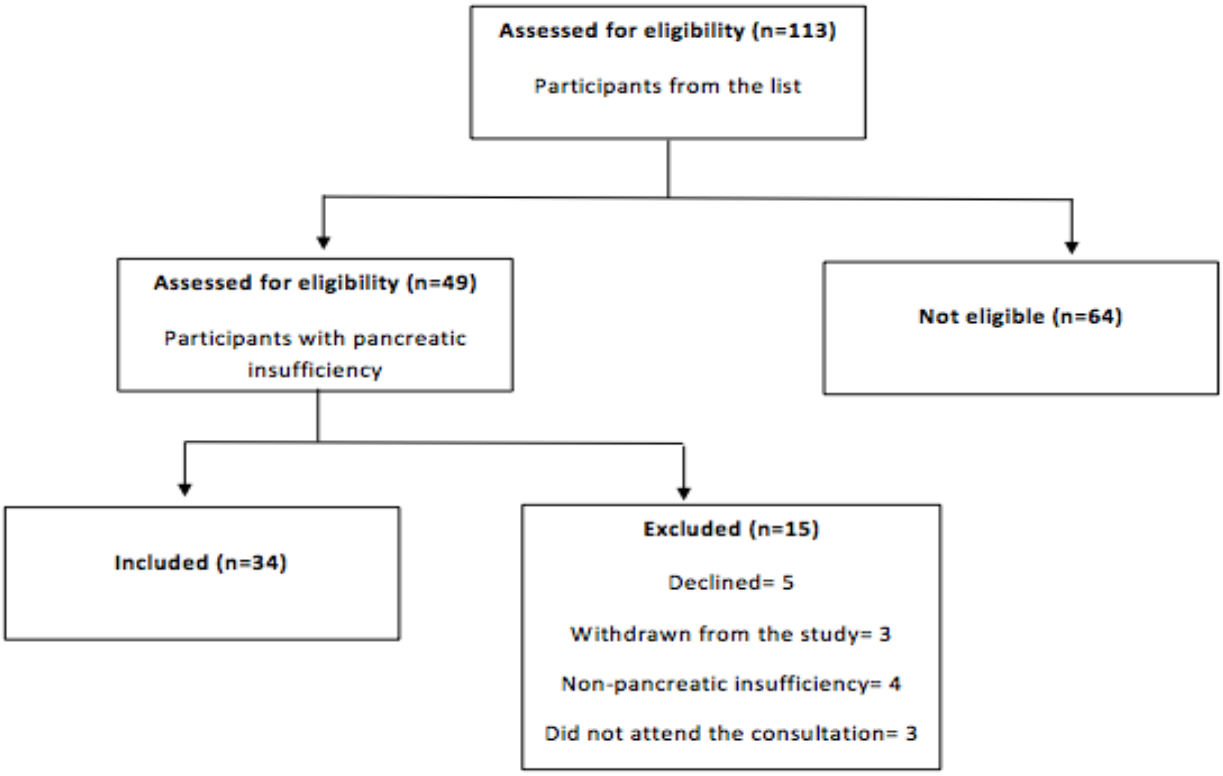

Figure 2: Flow chart of the participants in the recruitment process.

4.1.2 Characteristics of the study population

Characteristics of subjects are presented In **Table 4.** In this study, the majority of population were men (61.8 %). There were statistically significant differences between men and female in this study. The mean age of all subjects was 33 ranging from 18 to 75 years (data not shown). All participants in this study were Caucasians. There were no statistically significant differences in mean age between male and female subjects (P>0.05). In this study, six (17.6

%) participants were diagnosed with diabetes**.** The age distribution of the subjects is shown in the **Figure 3,** and the largest proportion of patients with CF and PI was detected in age group 18-40 years.

Table 4: Demographics data of the study population (n=34)

Variable	Measure	Value
Demographics		
Gender[a]		
Male	n (%)	21 (61. 8)
Female	n (%)	13 (38.2)
Ethnicity, Caucasian/white race	n (%)	34 (100)
Diabetes status	n (%)	6 (17.6)
Age[b]		
Men	Mean (SD)	35.0 (12,6)
Women	Mean (SD)	35.6 (17.9)

Continually variables are considered normally distributed
Abbreviations: SD, standard deviation
[a]Fisher's exact test showed $p < 0.001$ in gender
[b]Independent-samples T test showed $p > 0.05$ in age

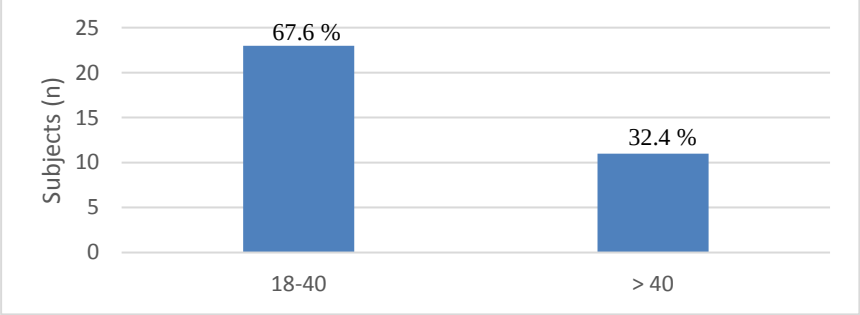

Figure 3: Age distribution of the study population (n=34)

4.2 Anthropometry and spirometry measurements

Anthropometry measurements

The results of the anthropometric measurements have been presented in **Table 5**. The mean weight for all subjects was 72.5 kg (range 45.9-125) (data not shown). There were statistically significant differences in weight for men and women (p=0.002). Mean BMI in all subjects was 24.0 kg/m^2 (range 17.4 to 38) (data not shown). According to Table 3**,** in this study, one subject (2.9 %) was underweight, twenty-two subjects (64.7 %) had normal weight and six subjects (17.6 %) were overweight, and five subjects (14.7 %) had obesity. Four subjects

(11.8 %) had BMI below 19 kg/m^2. Mean BMI in men was 24.7 kg/m^2 and 22.8 kg/m^2 in women. Eight women (61.5 %) had BMI below 22 kg/m^2 and nine men (42.9 %) had BMI lower than 23 kg/m^2. There were no statistically significant differences in BMI between men and women. Mean height in all subjects was 173.4 cm (range 154.5 to 189) (data not shown).

Table 5: Clinical data of the study population (n=34)

Variable	**Male**		**Female**		**P value[b]**
Anthropometric measures	Mean(SD)	Min-max	Mean(SD)	Min-max	
Weight[a], kg	79.6 (17.6)	(53.8-125)	61.0 (12.8)	(46.1-83)	0.002
Height , cm	179. 7 (5.0)	(168.7-187)	163. 3 (7.4)	(154.5-174)	p<0.05
BMI men, kg /m^2	24.7 (5.2)	(17.4-38)	22.8 (3.8)	(19-30)	0.272
Spirometry measures					
FEV_1 , %	61 (25.7)	(27-96)	66.2 (27.1)	(32-102)	0.578
FVC, %	77.4 (22.6)	(37-107)	80.2 (20.1)	(43-109)	0.717
DEXA measures					
BMD, g/cm^2	1.2 (0.1)	(1.1-1.5)	1.2 (0.1)	(0.9-1.4)	0.076
T-score, SD	0.5 (1.3)	(-1.3-2.8)	0.7 (1.4)	(-1.5-3.1)	0.777
BMC, kg	2.9 (0.4)	(2.4-3.5)	2.2 (0.3)	(1.7-2.8)	p<0.05
FM, kg	22.3 (13.1)	(10.6-58.2)	19.7 (7.7)	(7.6-30.8)	0.535
FMI, kg/m^2	6.9 (3.9)	(3.3-17.4)	7.3 (2.7)	(3.1-12.9)	0.764
FFM, kg	58.3 (8.5)	(44.7-76.1)	41.4 (5.5)	(32.9-49.1)	p<0.05
FFMI, kg/m^2	18.3 (2.3)	(13.8-22.2)	15.6 (1.6)	(12.7-18)	0.002
LBM, kg	55.5 (8.2)	(42.3-73.1)	39.2 (5.3)	(31.0-46.5)	p<0.05
LBMI, kg/m^2	17.4 (2.3)	(13-21.4)	14.7 (1.5)	(11.9-17.10)	0.001
Grip strength, kg	42.8 (9.8)	(23-60.6)	22.8 (6.6)	(9.8-34.10)	p<0.05

Continually variables are considered normally distributed

Abbreviations: SD, standard deviation; min, minimum; max, maximum; BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced volume vital capacity; BMD, bone mineral density; FM, fat mass; FMI, fat mass index; FFM, fat free mass; FFMI, fat free mass index; LBM, lean body mass; LBMI, lean body mass index

[a]Body weight adjusted for the weight of clothes by subtracting 1 to 1.5 kg in mean and women

[b]Tested with independent-samples T test

Spirometry measurements

Spirometry measurements are shown in **Table 5.** Women had 5.2 % higher mean FEV_1% compared with men. Mean FEV_1 % for all subjects was 62.9 % (range 27-102) (data not shown). Five participants (14.7 %) had mild impairment of lung function. Seven participants (20.6 %) had moderate impairment of lung function and 9 participants (26.5 %) had severe impairment of lung function. There was a statistically significant correlation between BMI and FEV_1% in the study (r=0.38, p=0.026) (**Appendix 7**). There was no correlation between BMI and FVC % (p>0.05) (Appendix 7).

4.3 Body composition

Twenty-seven subjects were able to perform DXA measurements. The results of the body composition are presented in **Table 5**. The mean t-score for both groups was 0.6 (range -1.5 to 3.1) (data not shown). Women had higher t score compared with men, however lowest t-score was observed in women. There were no statistically significant differences in t-score between men and women ($p > 0.05$). According to Table 2, twenty-two subjects (81.5 %) were categorized as normal and three people (11.1 %) had osteopenia. There was no correlation between age and t-score ($p > 0.05$) (Appendix 7). Mean BMC in all subjects was 2.5 kg (range 1.7 to 3.5) (data not shown). Men had 0.7 kg higher mean BMC compared with women. There was a statistically significant gender difference in BMC in the study sample ($p < 0.05$).

The FM was 21.0 kg in the whole study sample (range 7.6 – 58.2) (data not shown), men had higher FM compared with women. Mean FMI in all subjects was 7.1 kg/m^2 (range 3.1-17.4) (data not shown). Men had lower FMI compared with women. There were no statistically significant differences in FM and FMI between men and women ($P > 0.05$). There was no correlation between FM and FEV_1 ($p > 0.05$) (Appendix 7). The mean FFM in the whole study population was 50.2 kg (range from 32.9 to 76.1) (data not shown). Men had higher FFM compared with women. Mean FFMI in all subjects was 17.0 kg/m^2 (range 12.7- 22.2) (data not shown). Five men (35.7 %) had FFMI below 17 kg/m^2 and three women (23.1 %) had FFMI below 15 kg/m^2. There were a statistically significant gender difference in FFM and FFMI between the groups ($p < 0.05$). There was no correlation between FFM and FEV_1 ($p > 0.05$) (Appendix 7).

Mean LBM in all subjects was 47.6 kg (range 31-71.0) (data not shown). Men had higher LBM than women. Mean LBMI in all subjects was 16.1 kg/m^2 (range 11.9-21.4) (data not shown). Men had higher LBMI compared with women. There were a statistically significant gender differences in LBM and LBMI between the groups ($p < 0.05$). There was a statistically significant correlation between FEV_1 % and LBMI ($r = 0.39$, $p = 0.04$). There was a statistically significant correlation between BMD and LBM ($r = 0.62$, $p < 0.001$). Correlations values are showed in Appendix 7.

4.4 Physical test

Results of handgrip strength have been presented in **Table 5**. Twenty-two subjects were able to perform the HGS test without difficulties. The mean HGS for all subjects was 34.7 kg

(range 9.8 to 60.6) (data not shown). There were statistically significant differences between men and women in mean HGS ($p<0.05$). There was a statistically significant correlation between LBMI and HGS ($r=0.67$, $p<0.001$) (Appendix 7).There was no correlation between FEV_1 % and HGS ($p>0.05$) (Appendix 7). There was a statistically significant correlation between HGS and BMD ($r= 0.51$, $p=0.008$) (Appendix 7). **Table 6** and **Table 7** present comparison of HGS between healthy Caucasians and the study sample. Men and women had lower mean HGS compared with the reference HGS.

Table 6 : Comparison of hand grip strength (HGS) between males in the study sample and healthy Caucasians men (68)

	Reference HGS		HGC in the study	
Age (y)	Mean[a] (SD)	Min-max[a]	Mean[a] (SD)	Min-max[a]
20-29	53 (8)	(36-70)	46.8 (5.9)	(37.3-54.4)
30-39	54 (10)	(36-83)	43.7 (12.4)	(23-60.6)
40-49	54 (7)	(34-70)	50.8 (0.21)	(50.6-50.9)
50-59	51 (9)	(29-79)	32.5 (6.4)	(28-37)
60-69[b]	45 (7)	(32-63)	-	-

Abbreviations: HGS, hand grip strength; y, years; SD, standard deviation; min, minimum; max, maximum
[a]HGS values are expressed in kg
[b]HGS for 60 to 69 years have been omitted due to few data

Table 7 : Comparison of hand grip strength (HGS) between females in the study sample and healthy Caucasians women (68)

	Reference HGS		HGC in the study	
Age (y)	Mean[a] (SD)	Min-max[a]	Mean[a] (SD)	Min-max[a]
20-29	32 (5)	(19-44)	22.4 (2.3)	(19.8-26.4)
30-39[b]	33 (5)	(21-49)	-	-
40-49	32 (6)	(19-46)	26 (8.2)	(17.8-34.1)
50-59[b]	28 (5)	(14-39)	-	-
60-69[b]	26 (5)	(10-40)	-	-
70-79[b]	21 (4)	(12-29)	-	-

Abbreviations: HGS, hand grip strength; y, years; SD, standard deviation; min, minimum; max, maximum
[a]HGS values are expressed in kg
[b]HGS values for age between 30-39, 50-59, 60-69 and 70-79 are omitted due to few data

4.5 Biochemical measurements

Table 8 shows biochemical measurements, reference ranges and ranges in blood samples**.** Some of the variables were not normally distributed, both mean (SD) and median (IQR) are shown.

For sodium, chloride, pancreas amylase and creatinine respectively, three, six, twenty-four subjects and three subjects had concentrations below reference rage. For ASAT and ALAT respectively, one and two subjects had levels below reference rage. Two and three subjects had ASAT and ALAT levels above the reference range. For albumin, potassium, magnesium, respectively, fourteen, eleven, and seven had levels above the reference range. Phosphate was in accordance with the reference values. For cholesterol, and glucose, respectively, four, and one had blood concentrations below the reference range. Seven subjects had serum glucose above the reference range. For HbA1c and INR, respectively, six and one subjects had levels above the reference range. Triglyceride was in accordance with the reference values.

Table 8: Biochemical measurements in the study population (n=34)

	n	Mean (SD)	Median (IQR[a])	Min-max	Reference range
P-albumin‡, g/L	34	44.6 (3.8)	45 (41.8-47)	(36-53)	(36-45)
P-Phosphate, mmol/L					
Men (18-49)	13	1.1 (0.2)	1.0 (0.9-1.2)	(0.8-1.5)	(0.7-1.6)
Men (50-120)	3	1.1 (1.2)	1.0 (1.0-)	(1.0-1.3)	(0.7-1.3)
Women	9	1.1 (0.1)	1.2 (1.0-1.3)	(0.9-1.3)	(0.8-1.4)
P-Sodium‡, mmol/L	33	139.8 (2.5)	140 (139-141)	(132-144)	(137-144)
P-Potassium‡, mmol/L	33	4.4 (0.3)	4.4 (4.2-4.6)	(3.90-5.2)	(3.5-4.4)
P- Chloride‡, mmol/L	33	100.2 (2.8)	101 (98-102)	(93-105)	(98-107)
P-Magnesium‡, mmol/L	28	0.9 (0.1)	0.9 (0.8-0.9)	(0.7-1.1)	(0.7-0.9)
P-ASAT, U/L					
Men	20	31.4 (23.9)	22.5 (19-36.3)	(17-125)	(15-45)
Women‡	13	23.9 (5.5)	25 (20-28)	(14-33)	(15-35)
P-ALAT, U/L					
Men	20	35.4 (27.8)	27 (19-43)	(11-137)	(10-70)
Women	13	24.8 (14.3)	21 (17-29.5)	(7-58)	(10-45)
P-Amylase pancreas, U/L	29	9.7 (14.6)	5 (4-8.5)	(3-77)	(10-65)
P-Creatinine, µmol/L					
Menn‡	21	79.4 (16.3)	82 (68-85.5)	(49-116)	(60-105)
Kvinne	13	62.5 (14.9)	59 (52-72)	(43-95)	(45-90)
P-Triglyceride, mmol/L	25	1.1 (0.5)	1.0 (0.8-1.2)	(0.5-2.4)	(0.5-2.6)
P-Cholesterol, mmol/L	27	3.6 (0.8)	3.3 (2.9-4.2)	(2.7-5.7)	(2.9-7.8)
S-Glucose, mmol/L	28	5.8 (1.8)	5.2 (4.7-6.3)	(3.6-10.8)	(4-6)
B-HbA1c, %	33	5.7 (1.8)	5.4 (5.2-5.8)	(4.8-7.3)	(4-6)
P-INR, n-ratio	32	1.0 (0.1)	1 (1-1.1)	(0.9-1.4)	(0.8-1.2)

Continually variables were considered normally(variables marked with ‡ indicating normal distribution) or non-normally distributed

Abbreviations: SD, standard deviation; IQR, interquartile range; Min, minimum; max, maximum; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; INR, international normalized ratio.

[a]IQR is presented in 25th and 75th percentile

4.5.1 Vitamin and mineral status

Blood samples of vitamin and mineral status are presented in **Table 9.** For vitamin A, 25-OH-vitamin D, vitamin E, PTH and ionized calcium, three, four, three, three and five subjects,

respectively, had blood concentrations below the reference range. One subject had plasma vitamin E above the reference range and five subjects had serum PTH above the reference range. For iron, transferrin, ferritin and hemoglobin, respectively, six, four, one and four subjects had concentrations below reference range. Three subjects had plasma transferrin, ferritin, and TIBC above reference range.

Table 9: Biochemical measurements of vitamins and minerals (n=34)

	n	Mean (SD)	Median (IQR)	Min-max	Reference range
P-Vit. A[ǂ], µmol/L	24	1.7 (0.5)	1.6 (1.4-2.0)	(0.6-2.6)	(1.2-3.6)
S-25-OH-vit.D[ǂ], nmol/L	25	60.7 (22.6)	63 (43.5-81)	(20-95)	(37-131)
P-Vit. E[ǂ], µmol/L	24	25.1 (7.7)	24 (22-28.8)	(11-48)	(17-45)
S-PTH[ǂ], pmol/L	25	5.2 (2.6)	5.2 (3.3-6.9)	(0.7-9.8)	(1.5-7)
P-Ionized calcium[ǂ], mmol/L	24	1.2 (0.1)	1.2 (1.2-1.3)	(1.1-1.3)	(1.2-1.3)
P-Iron, µmol/L	29	13.1 (5.61)	12.7 (9.8-16.8)	(2.2-28.3)	(9-34)
P-Transferrin, g/L	29	2.7 (0.5)	2.7 (2.4-3.1)	(1.8-4)	(2-3.3)
P-Ferritin, µg/L					
Men	17	98.4 (67.5)	79 (52.5-134.5)	(26-294)	(30-400)
Women	12	90.1 (157.6)	36.5 (25.5-76.5)	(10-580)	(10-170)
B-Hemoglobin, g/100 mL					
Men	20	14.9 (1.2)	15.2 (14.0-15.5)	(11.8-16.8)	(13.4-17)
Women	13	13.1 (1.4)	13.2 (12.3-14.2)	(10.1-14.6)	(11.7-15.3)

Continually variables were considered normally (variables marked with ǂ indicating normal distribution) or non-normally distributed.
Abbreviations: SD, standard deviation; IQR, interquartile range; Min, minimum; max, maximum; vit., vitamin; PTH, parathyroid hormone; TIBC, total iron binding capacity.
[a]IQR is presented in 25 th and 75 th percentile

Vitamin D deficiency in subjects are shown in **Figure 4**. Eight subjects (32 %) out of 25 participants have vitamin D level below 50 nmol/L. Nine subjects (36 %) had vitamin D level between 50 and 75 nmol/L. Eight subjects (32 %) had vitamin D level above 75 nmol/L. Eighteen subjects used DEKAs Plus, and out of them 5 subjects had vitamin D level below 50 nmol/L. Three subjects used DEKAs Plus and vitamin D supplementation, and out of them, two subjects had vitamin D below 50nmol/L. One subject used multivitamin and vitamin D supplementation and had vitamin D below 50nmol/L (**Figure 5**).

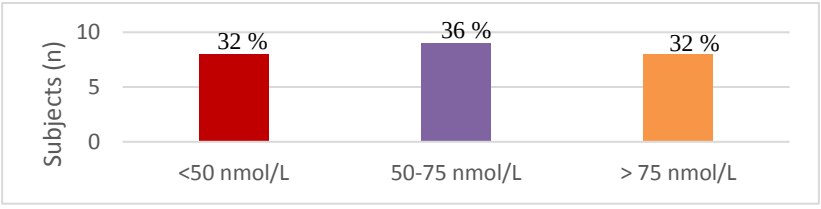

Figure 4: Overview of vitamin D level in blood in study population (n=25)

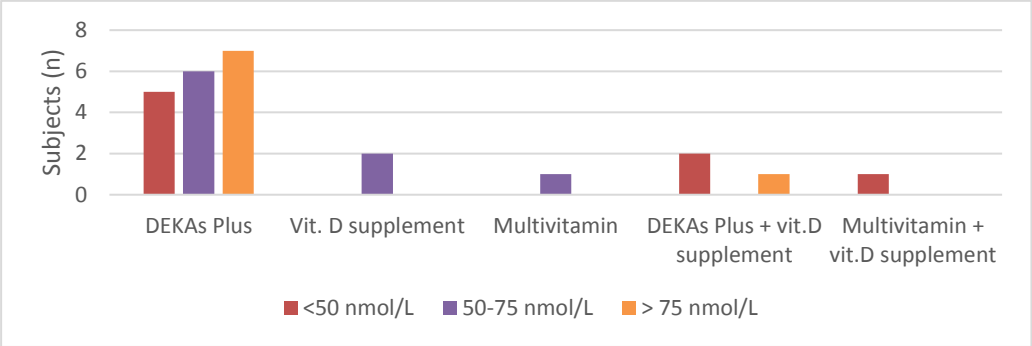

Figure 5: Overview of vitamin D levels of the subjects who use supplements

Only one subject (4.2 %) of 24 subjects had vitamin A below 0.70 µmol/L, twenty-three (95.8 %) subjects had plasma vitamin A level above 0.70 µmol/L (**Figure 6**). Twenty subjects used DEKAs Plus, and out of them, one subject had vitamin A level below 0.70 µmol/L. Two subjects used multivitamin and both of them had vitamin A level above 0.70 µmol/L. Two subjects did not use any supplementation and both of them had vitamin A level above 0.70 µmol/L (**Figure 7)**.

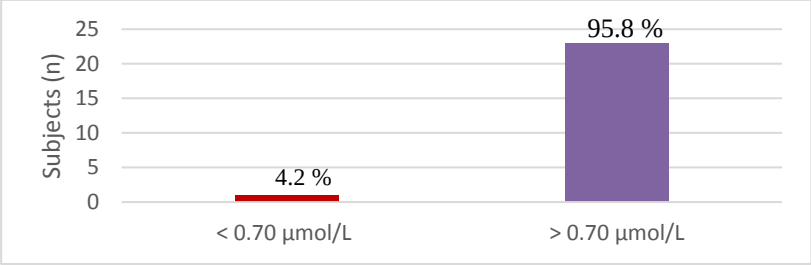

Figure 6: Vitamin A level in blood in the study population (n=24)

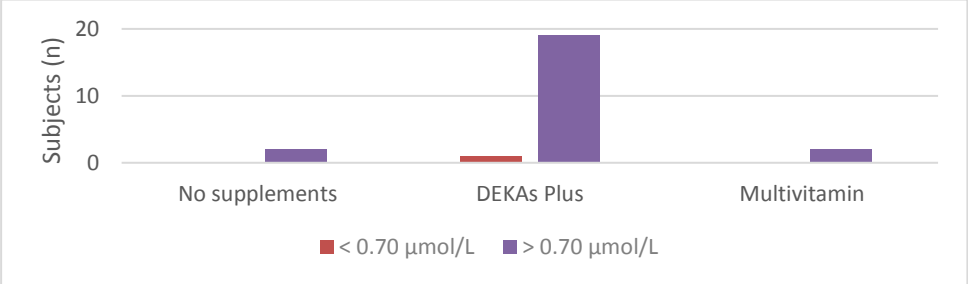

Figure 7: Overview of vitamin A level in blood of the subjects who use supplements

Three subjects (12.5 %) had vitamin E level in blood below the reference range (**Figure 8**). Seventeen subjects used DEKAs Plus, and out of them two subjects had vitamin E below reference range and fifteen subjects had vitamin E above the reference range. Three subjects used DEKAs Plus and vitamin E supplementation and all of them had vitamin E above reference range. Two subjects used multivitamin and vitamin E supplementation and out of them, one subject had vitamin E level below the reference range and one subjects had above the reference range. Two subjects did not use any supplement and both of them had vitamin E level above the reference range **(Figure 9).**

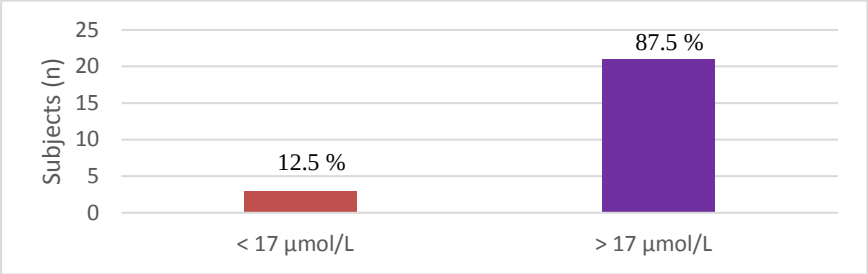

Figure 8: Overview of vitamin E level in blood in the study population (n= 24)

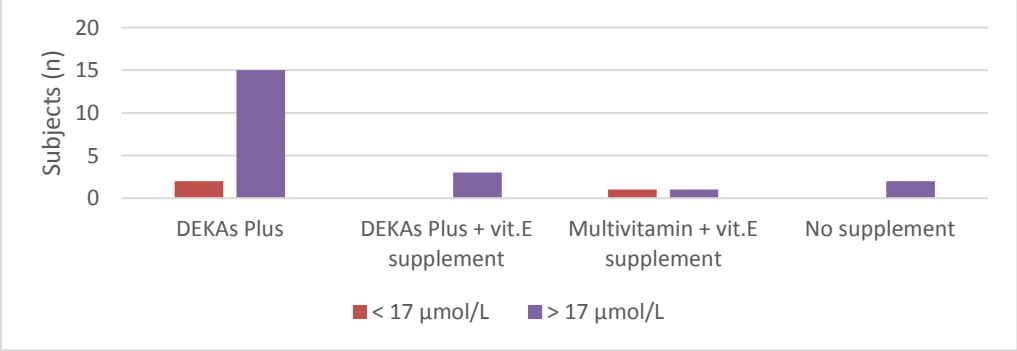

Figure 9: Vitamin E level in blood of the subjects who use supplements

Figure 10 presents iron deficiency anemia and anemia of chronic inflammation in the study population according to ESPEN's definition of anemia. One subject (3.4 %) had serum ferritin below reference range and had iron deficiency anemia. Three subjects (10.3 %) had serum ferritin above normal and had anemia of chronic inflammation. Four subjects (13.8 %) had both forms of anemia.

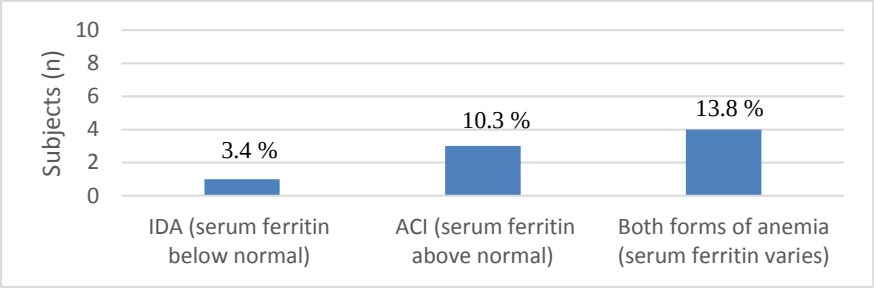

Figure 10: Overview of iron deficiency anemia and anemia of chronic inflammation in the study population (n=29)

4.6 Nutrition intake

4.6.1 Dietary intake

Thirty-three (97.1 %) subjects completed all dietary recalls, while only one subject (2.9 %) completed two dietary recalls. *Dietary intake* includes only food without any supplements. *Total intake* includes intake from food, ONS and vitamin/mineral supplements.

4.6.2 Energy and macronutrients

Median intake of macronutrients and fibre is presented **in Table 10.** Distribution of macronutrients in dietary intake, expressed in E % is presented in **Figure 11.**

Table 10: Overview of energy intake and intake of macronutrients in dietary and total intake, expressed as median (IQR) (n=34)

Energy and nutrients	Dietary intake	Min-max	Total intake	Min-max
Energy intake, % EAR	82 (65.2- 104.8)	(43.2-178.3)	91.2 (70.4-115.9)	(50.6-178.3)
Energy intake, kJ	9574.8 (7443.7-10953.5)	(4973.1- 20990.2)	9894.1 (8312-11736.5)	(5609.2-20990.2)
Protein, g/d	99.7 (73.4-126.8)	(44.1-192.8)	106.5 (81.1-129.2)	(44.1-192.8)
Fat, g/d	77.9 (55.2-96.9)	(25.5-362.5)	82.2 (62.7-104.2)	(33.9-362.5)
Carbohydrates, g/d	255.6 (216.9-327.9)	(111.1-597.3)	255.6 (231.3-332.2)	(127.6-597.3)
Fibre, g/d	20.2 (14.6-25.8)	(5.5-39.6)	20.2 (14.6-26.8)	(5.5-39.6)
Protein, E %	17 (14.5-19.2)	(12.6-25.1)	17.1 (13.7-20)	(12.6-25.1)
Fat, E%	30 (26.3-36.7)	(20.6-64.6)	31.1 (27.9-36)	(20.6-64.6)
PUFA, E%	3.4 (2.5-4.3)	(1.3-6.4)	3.9 (2.8-5.1)	(1.6-8.1)
Carbohydrates, E %	47 (44.6-56.7)	(18.6-61.7)	47.5 (44.2- 54.6)	(18.6-61.7)

Abbreviations: IQR, interquartile range; min, minimum; max, maximum; EAR, estimated average requirement; E%, percent of energy

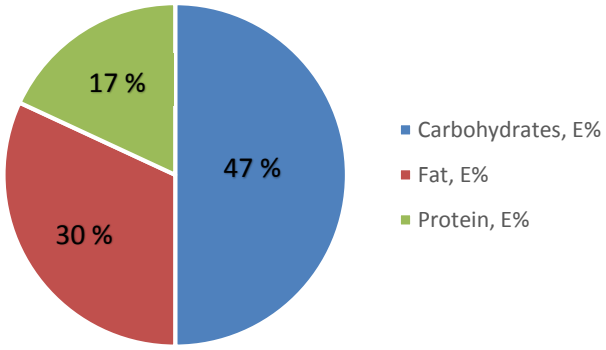

Figure 11: Distribution of macronutrients in dietary intake in the study population, expressed in median (n=34).

4.6.3 Micronutrients and intake with supplements

Micronutrients from dietary intake and total intake are shown in **Table 11.** The values are presented in median (IQR) and minimum to maximum.

Total intake shows a higher intake of the fat-soluble vitamins like vitamins A, D, E, K. Median differences between total intake and dietary intake for vitamin A, D, E, K, respectively, is 954.1 RAE, 152.5 µg, 210 mg and 2000 µg. Intake of water-soluble vitamins was higher in total intake. Median differences in water soluble vitamin like vitamins B9, B12 and C, respectively is 400 µg, 23.6 µg and 149.6 mg. Micronutrients was higher in total intake compared with dietary intake. Median differences in micronutrients like calcium, iron, zinc and selenium, respectively, is 228 mg, 1 mg, 19.7 mg and 148.2 mg.

Table 11: Daily dietary intake and total intake of micronutrients (n=34)

	Daily dietary intake		**Daily total intake**	
	Median (IQR[a])	**Min-max**	**Median (IQR[a])**	**Min-max**
Vit. A, RAE	407.5 (180.7-617.6)	(84.5-2080.1)	1361.6 (1100.8-1993.3)	(92.7-2992.7)
Vit. D, µg	2.1 (1.3-3.7)	(0-16.6)	154.6 (101.6-165.0)	(11.6-230.5)
Vit. E, mg	7.5 (5.0-12.7)	(2-32.7)	217.5 (209.2-239.8)	(12-578.8)
Vit. K, µg	0 (0-3.2)	(0-18.1)	2000 (1532.8-2005.5)	(0-2150)
Vit. B9, µg	160.8 (120.7-214.6)	(69.20-378.8)	560.8 (519.6-658.4)	(112.5-973.9)
Vit. B12, µg	3.7 (2.8-6.0)	(1.20-21.4)	27.3 (25.3-30.1)	(2.1-35.6)
Vit. C, mg	58 (25.6-93.5)	(1.10-157.5)	207.6 (159.4-258.2)	(31.3-419.7)
Calcium, mg/d	768.1 (563.7-1061.4)	(267.8-1907.1)	996.1 (677.2-1478.9)	(362.2-2627.9)
Iron, mg/d	7 (5.1-9.9)	(2.5-16.7)	8 (5.9-12.7)	(2.5-108.2)
Zinc, mg	9 (6.9-12.2)	(3.4-18.2)	28.7 (24.9-33)	(4.1-43.1)
Selenium, mg	29.5 (23.3-46.4)	(12.7-228.3)	177.7 (168.5-203.6)	(17.2-288.3)
Sodium, g	3.7 (2.5-4.8)	(1.0-16.2)	3.7 (2.-4.9)	(1.2- 16.2)

All continually, variables were considered non-normally distributed.
Abbreviations: IQR, interquartile range; Vit., vitamin; RAE, retinol activity equivalents
[a]IQR expressed as 25th and 75th percentiles

Use of supplements

Figure 12 shows an overview of the use of supplements. DEKAs Plus was frequently used supplement and twenty-seven subjects (79.4 %) used DEKAs Plus. Some of the subjects used more than one supplement, these are not shown in the Figure 12. There was no correlation between total intake of calcium and t-score (p> 0.05) (Appendix 7). There was no correlation between total intake of vitamin D and t-score (p>0.05) (Appendix 7).

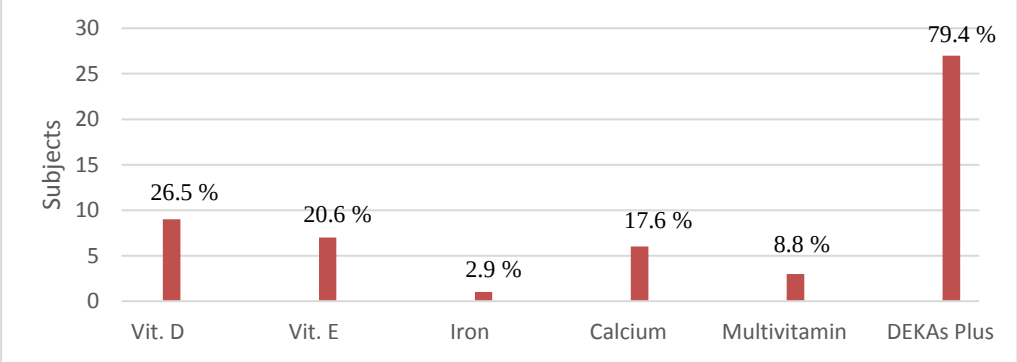

Figure 12: Use of supplements in the study sample (n=34)

4.7 Comparison with the recommendations

4.7.1 Comparison with the recommendations

Table 12 presents median, mean intake and range of energy, macronutrients and fibre in the study population compared with NNR 2012 and recommendations specific for CF. Median intake of energy was lowest for women between 18-30 years and men between 31-60 years in the study sample. Energy intake (% EAR) did not reach the recommendations. Intake of total fat was lower than recommended. Intake of protein, monounsatured fat, carbohydrates, and added sugar were in accordance with the recommendations. Intake of polyunsaturated fat and fibre was lower than recommended. Intake of saturated fat was higher than recommended.

Table 12: Comparison of energy and macronutrients in dietary intake (excluding supplements), between the study sample and Nordic nutrition recommendations and recommendations specific for CF (10, 78)

	Dietary intake			**Recommendations for energy and macronutrients**
	Median (IQR[a])	**Mean (SD)**	**Min-max**	
Energy intake[b], MJ/d				
Men (18- 30 yrs)	9.9 (8.3-14.5)	11.3 (4.7)	(5-21)	11.7
Women(18-30 yrs)	6.6 (5.6-10.2)	7.6 (2.6)	(5.1-12.1)	9.4
Men (31-60 yrs)	10.4 (9.2-11.7)	10.7 (2.3)	(7.9-16)	11
Women(31-60 yrs)	8.5 (5.7-11.5)	8.6 (3.0)	(5.4-11.9)	8.8
Energy intake[c], % EAR	82 (65.2- 104.8)	89.3 (30.6)	(43.2-178.3)	120-150
Protein[b], E %	17 (14.5-19.2)	17.3 (3.4)	(12.6-25.1)	10-20
Fat[c], E %	30 (26.3-36.7)	32.0 (9.3)	(20.6-64.6)	35-40
Saturated fat[b], E%	11.7 (9.8-14.2)	12.5 (3.9)	(7.5-22.7)	< 10
MUFA[b], E%	10.6 (7.2-12.6)	10.0 (3.6)	(3.4-18.9)	10-20
PUFA[b], E%	3.4 (2.5-4.3)	3.5 (1.3)	(1.3-6.4)	5-10
Carbohydrates[b]. E %	47 (44.6-56.7)	48.2 (10.0)	(18.6-61.7)	45-60
Sugar[b], E%	5.5 (2.7 -10.2)	7.0 (5.8)	(0.2-23.6)	< 10
Fibre[b], g/d				
Men	22.1 (18-29)	22.8 (7.8)	(5.5-39.6)	>35
Women	16.8 (11-22.5)	16.9 (6.6)	(8.8-27.9)	> 25

Continually variables were non-normally distributed.

Abbreviations: IQR, interquartile range; SD, standard deviation; Min, minimum; max, maximum; EAR, estimated average requirement; E %, percentage of energy; MUFA, monounsaturated fat; PUFA, polyunsaturated fat

[a]IQR is presented in 25th and 75th percentile

[b]Nordic nutrition recommendations 2012 (78)

[c]Recommendations specific for cystic fibrosis (10)

Table 13 shows intake of micronutrients in dietary intake compared with NNR 2012 recommendations specific for CF. In the study sample, intake of fat-soluble vitamins like A, D and K were lower than recommended. Vitamin E was lower than recommended in women.

Water-soluble vitamins like folate and vitamin C were also lower than recommended. Men and women had higher intake of vitamin B12 than recommended. Intake of calcium was slightly lower in women, compared with the recommendations. Calcium intake was lower than recommended. Intake of iron was lower in women than recommended. Men had slightly higher intake of zinc than recommended. Intake of zinc in women was in accordance with the recommendations. Men and women had lower intake of selenium than recommended. Intake of sodium was higher than recommended.

Table 13: Comparison of micronutrients in dietary intake (excluding supplements), between study sample and Nordic nutrition recommendations and recommendations specific for CF (10, 78)

	Dietary intake			**Recommendations for micronutrients**
	Median (IQR[a])	**Mean (SD)**	**Min-max**	
Vit. A[b], RAE				
Men	454.1 (221.8-636.6)	546.6 (479.5)	(84.5-2080.1)	900
Women	397.6 (154.2-604.9)	408.9 (303.5)	(105.9-982.3)	700
Vit. E[b], mg				
Men	11.2 (5.9-13.5)	11.5 (7.4)	(3.1-32.7)	10
Women	5.7 (4.6-7.9)	7.0 (4.1)	(2-18)	8
Vit. D[b], µg				
Men	3.1 (1.2-5)	3.8 (4.2)	(0-16.6)	10 (20[d])
Women	1.7 (1.5-3.3)	3 (3.1)	(1-12.8)	10 (20[d])
Vit. K[b,e], µg				
Men	0 (0-1.9)	1.9 (3.9)	(0-13.3)	-
Women	0 (0-3.3)	3.0 (6.1)	(0-18.1)	-
Vit. B9[b], µg				
Men	192.6 (142.3-235.8)	192.0 (70.4)	(75.4-378.8)	300
Women	145.7 (99.3-177.3)	154.7 (71.6)	(69.2-301.3)	300 (400[f])
Vit. B12[b], µg				
Men	4.1 (3.3- 6.3)	5.2 (2.5)	(2.3-10.6)	2
Women	2.8 (1.9-5.5	4.6 (5.3)	(1.2-21.4)	2
Vit. C[b], mg				
Men	54.4 (20.8-82.9)	59.5 (46.2)	(4.1-157.5)	75
Women	63.5 (35.8-101.3)	69.2 (45.1)	(1.1-156.9)	75
Calcium[c], mg/d				
18-25 year	955.6 (669.3-1212)	977.5 (355.6)	(543.4-1636.4)	1000
> 25 year	718.5 (549-956.1)	823.5 (426.3)	(267.8-1907.1)	950
Iron[b], mg/d				
Men	8 (7-10.5)	8.6 (3.3)	(2.5-16.7)	9
Women	5.3 (4.2-7.3	5.8 (2.0)	(3.3-10.1)	15
Zinc[b], mg				
Men	10.6 (8.6-13.6)	10.9 (3.4)	(5.2-18.2)	9
Women	6.9 (5.2-9.3)	7.0 (2.6)	(3.4-12.1)	7
Selenium[b], µg				
Men	35.9 (23.8-50)	37.7 (14.6)	(17.2-62.3)	60
Women	26.4 (19.4-36.9)	41.5 (56.7)	(12.7-228.3)	50
Sodium[b], g	3.7 (2.5-4.8)	4.4 (3.3)	(1.0-16.2)	2.4

Continually variables were considered normally and non-normally distributed. Abbreviations: IQR, interquartile range; SD, standard deviation; min, minimum; max, maximum; vit, vitamin; RAE, retinol activity
[a]IQR is presented in 25th and 75th percentile
[b]Nordic nutrition recommendations (78)
[c]Recommendations specific for cystic fibrosis (10)
[d]Recommended intake of vitamin D in adults above 75 years old.
[e]There is no recommended intake of vitamin K
[f]Recommended intake of folate for women at reproductive age

Table 14 presents upper lower intake level (UL) and lower intake level (LI), reported by NNR 2012. In the study, dietary intakes of vitamin A, vitamin E, vitamin D, vitamin B9, vitamin C, calcium, iron, zinc and selenium was lower than LI. When reported intake of supplements were considered, the total intake of vitamin A, calcium, iron and selenium were below LI. In total intake, vitamin E, vitamin D, calcium and iron were above UL.

Table 14: Comparison of micronutrients between daily and total intake in study sample and NNR 2012 recommendations (78)

	NNR 2012 recommendations		**Dietary intake**		**Daily total intake**	
	UL, M/F	LI, M/F	n (%) > UL	n (%) < LI	n (%) > UL	n (%) < LI
Vit. A, RAE	3000	500/400	0 (0)	12 (57.1) /10 (76.9)	0 (0)	1 (4.8) /1 (7.7)
Vit. E, mg	300	4/3	0 (0)	1 (4.8)/1 (7.7)	7 (20.6)	0 (0)
Vit. D, µg	100	2.5	0 (0)	18 (52.9)	26 (76.5)	0 (0)
Vit. K[a,b], µg						
Vit. B9[a], µg		100		5 (14.7)		0 (0)
Vit. B12[a], µg		1		0 (0)		0 (0)
Vit. C[a], mg		10		2 (5.9)		0 (0)
Calcium, mg	2500	400	0 (0)	3 (8.8)	1 (2.9)	1 (2.9)
Iron, mg	60	7/5	0 (0)	5 (23.8)/4 (30.8)	1 (2.9)	4 (19.04)/3 (23.1)
Zinc[a], mg		5/4		3(14.3) /0(0)		0 (0)
Selenium, µg	300	20		5 (14.7)	0	2 (5.8)

Abbreviations: NNR, Nordic Nutrition Recommendations; UL, upper intake level; LI, lower intake level; M, male; F, female; Vit., vitamin; RAE, retinol activity equivalents

[a]There is no UL for vitamins K, B9, B12, C and zinc.

[b]There is no LI for vitamin K.

Table 15 shows highest dose and lowest dose of fat-soluble vitamin supplements in the study sample compared with the recommended doses for CF patients. Highest dose of vitamin A, vitamin E and vitamin K were within the recommended range, however highest dose of vitamin D exceeded the recommended dose for vitamin D. Lowest dose of vitamin A, vitamin E and vitamin K were below the recommended dose, but lowest dose of vitamin D was within the recommended dose.

Table 15: Comparison of fat-soluble vitamins supplement in the study and recommendations specific for CF (10, 52)

	Recommendations for supplementation for CF	**Highest dose in the study sample**	**Lowest dose in the study sample**
Vit. A, IU	4000 to 10000 (max 20 000)	3000	758
Vit. E, IU	100-400	370	15
Vit. D, IU	800-4000	6800	400
Vit. K, mg	1-10	2	0.1

Abbreviations: CF, cystic fibrosis; vit., vitamin; IU, international unit; max, maximum

Conversion factors: µg or mg to IU: vit. A: µg vit.A /0.3 µg retinol= IU, vit. D ; µg vit.D x 40 IU= IU, vit. E: mg vit.E /0.67=IU

5 Discussion

5.1 Discussion of subjects and methods

5.1.1 Study design

This master's thesis was a pilot, cross- sectional study. These types of studies are easy and cheap to conduct and it is easy to collect many variables (79) (p.236-237). These studies give prevalence and show the correlation between exposure and outcome. Disadvantage of these studies are that they are not suitable to indicate the frequency of the disease and it is not possible to conclude that the exposure is the reason for the outcome (80) (p. 312-313). Certain examples of bias such as recall bias, selection bias and confounding variables serve as a limitation for these types of studies (81). However, cross sectional study is suitable to research many variables in one study, and the findings from this study can be further researched upon with other study designs (79) (p.237).

5.1.2 Study population

The study sample in this study was small, and homogenous with primarily men. This should be considered when assessing participants' anthropometric, body composition and grip strength analysis. The recruitment process of participants with CF was more challenging than assumed. First, the population of patients with CF and PI in Norway is small. According to the list of patients, only 49 individuals were diagnosed with PI, but since it was required to recruit 33 patients, the goal was achievable. Thus, it is important to note that the limited sample size had to be considered when analyzing the results. There is also a possibility that more participants had been included in this project, if information about this study had been provided prior to consultations.

Another disadvantage of this study is that a control group was not included. This leads to difficulties when comparing study samples with other groups. It is not certain that the participants with CF and PI included in this study represents the entire CF and PI population in Norway. Nevertheless, in this study, the nutritional status of the study subjects, at one point was investigated and a control group was not needed.

5.1.3 Methods

Anthropometrical measurements

The strength of this study was that the weight and height of the participants were measured using the same tools for every individual. However, different examiners conducted these measurements, making it possible that their interpretations could have affected the results of the participants' weight and height. Other factors like the participants' last meal and the time of the day the weighing was performed should also be taken into consideration when studying the results.

Body composition

A major strength in this study was the use of DXA scan to assess body composition. DXA scan show good reproducibly and precision when assessing body composition like fat mass, bone mineral content and lean mass (82). It is also to the study's advantage that all measurements were performed by one examiner, with the exception of one case which affected the results since only scan of skeletal muscle was taken. The analysis of the body composition was therefore smaller. Another limitation of this method in this study, was related to ineffective attendance of the participants, due to unavailability to perform DXA scan or because they lived far away. Since low bone mineral density is a complication in individuals with CF, routine screening of bone mineral density is important (36). Since many of the participants had not undergone DXA scan before, it was not possible to compare the outcomes from the present study with previous results.

Physical test

Handgrip strength was measured with the same instruction and same instrument in all participants. Yet again, it was advantageous that one examiner conducted measurement of grip strength for all participants. It should be noted that participants used their dominant, right arm in this study, which affects the results, because right-handed people are stronger compared to left-handed people (83). Taking this into consideration, the use of the dominant arm may have affected the results of handgrip strength. Another limitation of this method is that this study was conducted without the knowledge of the participants' history. Age, gender,

body construction and hand size affects hand grip strength, and should therefore be considered of the outcomes (84).

Biochemical measurements

There are some limitations with the blood samples taken in this study. Significant amounts of values were missing for some of the main vitamin concentrations. Vitamin A, D and E, had ten, nine and ten, respectively missing values in blood. This absence of data can indicate failure in routine of biochemical measurements. According to ESPEN guidelines for monitoring nutritional status, serum markers of fat-soluble vitamin levels are important (10). Missing values of these fat-soluble markers is a major lack for this study and may have affected the results severely. Another limitation in this study was that vitamin K was not measured (85). It is recommended to do annual screening for vitamin K deficiency especially for patients with hemoptypsis, hematemesis and liver diseases. Serum prothrombin time and proteins induced by vitamin K absence (PIVKA-II) levels are used to measure vitamin K status. Coagulation abnormalities can occur due to vitamin K deficiency and this may contribute to bone disease in CF patient. Therefore annual screening of vitamin K status is also recommended for CF patients even though it is no bleeding or liver disease (85).

Dietary intake

In this study, 24 hours diet recall was conducted in three separate days. This method is very easy to conduct. This may have been a strength for this study, and to show variations in dietary intake, one weekend and two weekdays were chosen (80) (p.29).This method enables to collect detailed data intake. However, this method has also limitations, as one day will not represent the participant's usual dietary intake, recall bias may occur and the desire to impress/pleasure the interviewer as well as embarrassment towards consumed food could be regarded as a limitation. These factors can lead to over- and under-reporting. Even so, to reduce the measurement error, the dietary recalls were conducted three times for each participant and the subjects were not prepared for any of the interviews (86). A booklet of photos was used to assess the portion sizes of the foods and beverages consumed, and this was an advantage for this study. This method prevents errors in measurements in food consumption and quantifying food portion size in dietary surveys (87, 88). Another strength of this study was that only one examiner conducted this dietary recall, and this minimizes

measurement error. In this study to calculate % EAR, a PAL equal to 1.6 was used, because it was assumed that this PAL value was the suitable value for individuals with common lifestyle with sedentary work (78) (p.34). Use of the same PAL value for all participants may have affected the results of % EAR, because this PAL value was either overestimated or underestimated.

Statistical analysis

In this study, the study population was small and this is a major limitation for the statistical analysis. Other subgroups related to diabetes and gender had lower numbers. Due to the small number of subjects, this leads to low power to detect statistically significant differences. In many analyses, data with non-normally distribution was used, but these types of data give lower ability to find statistically significant differences.

5.2 Discussion of the results

5.2.1 Characteristics of the study population

The mean age of the participants in this study was 33 years. The youngest individual was 18 years and oldest individual was 75 years old. This proves that survival rate for individuals with CF has increased (89). Even though the risk is the same for females and males, this study showed a significant gender difference (90). However, during recruitment period in this study, the majority of the subjects were men, and this has to be taken into consideration for the gender difference.

5.2.2 Anthropometry and spirometry measurements

Anthropometry measurements

According to BMI classifications from WHO, in this study 64.7 % of the subjects were normal weight and 2.9 % were underweight (< 18.5). These findings have shown a low prevalence of malnutrition in patients with CF and PI. Similar to our findings, a study from Australia in 1997 reported 9 % of the subjects to be marginally malnourished (18-20), but they did not find any subjects to be severely malnourished (< 18.5) (91). A Scandinavian study showed that the prevalence of underweight was low. It was reported that the prevalence

of underweight was 13% (< 18.5) in 2011 in Scandinavia (49). Nevertheless, this study had higher prevalence of malnutrition compared to our study. Use of pancreatic enzymes and selected population may be factors for low prevalence of underweight in the present study. However, according to ESPEN's guidelines, eight women had BMI below 22 kg/m^2 and nine men had BMI lower than 23 kg/m^2 in the present study. This shows that 50 % of total subjects did not achieve the goals for nutritional status (36). Similar to our findings, CFF's patient registry in US reported only 52% of the adults meeting BMI goals (27). One cross sectional study from Brazil reported 24.7 % of the subjects were malnourished by using BMI < 19 as a cut off value and showed that malnutrition is still a common complication in adults and adolescents with CF, even though they got dietary advice (92). In the present study, a cut of value of BMI<19 showed 11.8 % subjects were malnourished. The findings from the cross sectional study from Brazil showed a higher prevalence of malnutrition compared with the present study. The methods and population group are different compared to the present study. BMI is adequate measurement to diagnose nutritional status in individuals with CF (93). Thus, it is a method to assess nutritional status in the present study. However, this will not give any information about body tissue composition (94).

In this study, 17.6 % of the subjects were overweight and 14.7% had obesity. These findings show that overweight and obesity are issues among CF patients, and not solely malnutrition. Data collected by a longitudinal cohort study from Canada showed that the proportion of underweight decreased from 20.6% before 1990 to 11.1 % in 2011, whereas the proportion of overweight increased from 7.0 % to 18.4 % (47). However, most of the subjects who were overweight and obese were pancreas sufficient patients and in the present study, the subjects were pancreas insufficient. One study from US, showed prevalence of overweight was greater in patients aged 2-18 with PI (48). Similar to this, in the present study, all of the participants were PI but the population group was different. Changes in lifestyle and diet are possible explanations of the development of overweight and obesity (48).

Spirometry measurements

Spirometry values in this study were low, 14.7 %, 20.6 % and 26.5 % of the participants had mild, moderate and severe lung impairment. These findings show how CF disease affects pulmonary function. Poor nutritional status, pancreas insufficiency status, and female sex can be risk factors for the decline in FEV_1 % (95). By contrast, in the present study, women had

higher FEV_1 % than men. In the present study, it was a statistically significant correlation between BMI and FEV_1. This shows how nutritional status can affect pulmonary function. Many studies have stated that malnutrition has a negative effect on lung function. A study from US showed that FEV_1 % was lowest in patients with malnutrition (48). This may be a possible explanation for the high frequency of participants with lung impairment and underweight. However, obesity and overweight have no beneficial effect on lung function (48, 96). These findings are similar to the present study, as there were no correlation between lung function and fat mass. Regardless, a study from UK showed that children had beneficial effect of higher BMI in FEV_1 %. Nevertheless, in the present study, the population consisted of adults and the results from the UK study may not be appropriate for the adults (97). On the other hand, one study from China showed beneficial effect of being overweight on lung function in healthy young girls (98). This study had a different study population, and thus this may not be comparable with our study. Data from the longitudinal study from Canada showed that increased BMI was associated with significant increased FEV_1 %, but the benefit of nutrition was not seen in BMI above 25 (47). This can possibly explain that increased BMI is important for underweight individuals.

5.2.3 Body composition

This study showed that 11.1 % of the participants had osteopenia. These results show that bone disease is a complication of CF. However, use of DEKAs Plus supplement, vitamin D supplement, poor nutritional status, reduced physical activity and medicaments like corticosteroids have to be taken into consideration (99). Laura K, Bachrach et al. showed a reduced BMD in young adults (100), however, in this study there was no correlation between age and t-score. In the present study, five men and three women had FFMI below the cut off values. These findings showed that, by using FFM, a higher prevalence of malnutrition was observed compared with BMI as an indicator. Reduced FFM indicates undernutrition and it is associated with decreased respiratory function (101). Similar to our findings, a prospective study from Australia showed that 14% of the adults with CF had reduced FFM, but this was undetected by BMI in 58 % of the patients (94). Factors like CFRD has to be taken into consideration for the low FFM (102). Saba Sheikh et al showed that lean body mass index was associated with pulmonary function, but fat mass index was not associated with pulmonary function (103). Similar to this study, in our study, there was a statistically

significant correlation between LBM and FEV_1 %. These findings can possible show that nutritional status is mediated through muscle mass and not FM in individuals with CF (103).

5.2.4 Physical test

In this study, men and women had a lower mean grip strength compared with the reference values for healthy Caucasian adults. Equivalent to these findings a cohort study from Sweden, showed decreased muscle strength, in young adults with CF compared with healthy adults (104). The study also showed a favorable physical status in the patients with CF, similar to age-matched population (104). Our study showed a statistically significant correlation between muscle mass and handgrip strength. This can raise the hypothesis that reduced muscle mass will affect the muscle strength in CF patients. Elkin et al showed lower peripheral muscle mass and strength in adults with CF, however, handgrip strength showed lower decrease compared with lower limbs (105). In the present study, there was a statistically significant correlation between handgrip strength and bone mineral density. Low body weight, hypogonadism, reduced physical activity and vitamin D deficiency can be some factors that can contribute to reduced muscle strength (105). In the present study, bone mineral density was associated with muscle mass. This can serve to strengthen the hypothesis, and a decrease in muscle mass may affect muscle strength and this may have negative effect on bone health. A cross sectional study from Brazil showed association between lung function and muscle strength (106). However, in the present study there were no correlation between FEV_1 % and HGS. The use of different methods can possibly explain the differences in results.

5.2.5 Biochemical parameters

In this study, many biochemical parameters were included. Some of the biochemical markers were below the reference range and some were above the reference range. The deviations were not of clinical relevance. Plasma glucose and HbA1c % values showed that seven (25 %) and six (18.2 %) subjects, respectively had values above the reference range. However, HbA1c is not sensitive parameters to diagnosis CFRD. Plasma glucose is not either formally established as a screening marker for CFRD (28). Oral glucose tolerance test (OGTT) is the screening test for CFRD (28). According to ESPEN guidelines, it is recommended to do annual screening for all CF patients above 10 years for glucose tolerance (10). This is a

limitation in this study that it was not possible to do an oral glucose tolerance test. According to ESPEN guidelines, monitoring of serum liver function tests, electrolytes, iron status and plasma fat-soluble vitamin levels are important markers of nutrition status (10). In this discussion section, serum markers of fat-soluble vitamins, and serum markers for iron deficiency will be described.

Fat-soluble vitamins

This study showed that three subjects (16.7%) had plasma vitamin A levels below the reference range. Even though, it was below the reference range, only one subject (4.2 %) had plasma retinol below 0.70 µmol/L (69). Low plasma of vitamin A levels can occur in patients with PI, and the findings in this study shows that. Vitamin supplementation is important for CF. Majority of the subjects had vitamin A levels in blood in accordance with the reference values, and use of supplements can be a certain reason for this finding. Despite, supplementation is used, low serum retinol can occur. Inflammation can negatively affect vitamin A balance through decreased dietary intake, reduced intestinal absorption, and increased urinary excretion (10, 107). It can be assumed that low serum vitamin A in one subject is due to any inflammation. However, clinical symptoms of vitamin A deficiency is rare, but vitamin A deficiency can leads to xeropthalmia (10). Brei et al showed that higher vitamin A intake elevated serum levels of vitamin A and prevented vitamin A deficiency in patients with CF and PI (108). However, increased supplementation can lead to vitamin A toxicity, and vitamin A supplementation should be individualized to prevent from vitamin toxicity (108). A study from USA showed increased serum retinol level and vitamin A intake in subjects with CF and PI (109). Similar to our study, in this study, the participants used different vitamin supplements, and some used more than one type of vitamin A supplements. The subject group was different between the US study and our study, it included children and young adults (8 to 25 years old) and this may also possible describe the different outcomes. However, as mentioned increased vitamin A supplementation can leads to hypervitaminosis A. Therefore, vitamin A supplementation should be individualized (108) .

In this study, 32 % of the participants had vitamin D deficiency, they had vitamin D level below 50 nmol/L (55). 36 % of the participants had vitamin D insufficiency as they had vitamin D level between 50 nmol/L and 75 nmol/L. 32 % of the participants had vitamin D sufficiency, they had level above 75 nmol/L. The cut off values used in our study are widely

accepted and used in clinical settings today (55). According to ESPEN guidelines, it is recommended to have minimum serum 25 (OH)D of 50 nmol/L (10). In this study, vitamin D status of only 25 subjects was measured, and this is a major limitation as it will prevent to discover the prevalence of vitamin D deficiency. Findings from the current study show that vitamin D deficiency can occur in individuals with CF with PI. Strength of this study, is that serum 25(OH)D was used and this is the best indicator of vitamin D status (10). According to ESPEN guidelines, supplementation is suggested to maintain serum 25 (OH)D above 50 nmol/L. In the current study, subjects with deficiency either used DEKAs Plus, vitamin D supplementation or multivitamin. These findings show that vitamin D deficiency can still occur, despite use of supplements. Possible explanations may be that the dosage of supplementation may not be the optimal dosage or that some patients may not take their vitamin supplementations regularly. Reduced bioavailability of vitamin D and reduced exposure for sunlight can also be factors for low vitamin D status (10).

In this study, 12.5 % of the subjects had vitamin E level below the reference range. Many subjects had serum vitamin E either within or above the reference range. One possible reason for this is use of vitamin supplementation. Sapiejka et al found that vitamin E deficiency is more frequently in CF patients not receiving vitamin E supplementation (110). However, in the present study, two subjects who used DEKAs Plus and one subject who used Multivitamin and vitamin E supplement had vitamin E level below the reference range. These findings can raise a hypothesis that intake of vitamin E supplements may be insufficient or participants may not take vitamin supplements as reported. Another limitation in this study, was that only α-tocopherol was used to evaluate vitamin E status. It is suggested to use α-tocopherol: total lipid ratio to evaluate the true vitamin E status, since vitamin E circulates in blood bound to lipoprotein (10, 110).

Serum iron was low in six, hemoglobin (Hb) was low in four subjects but serum ferritin was only low in one subject. Anemia was first detected by using serum Hb and iron, since this was low, serum ferritin was used to differentiate between iron deficiency anemia and anemia of chronic inflammation. Use of serum ferritin, may be a strength for this study (10). However, inflammation will affect serum ferritin level too, and serum transferrin receptors (sTfR) are more accurate biomarker to measure iron level, because sTfR is not affected by inflammation (10). Using serum ferritin concentrations (< 30 µg/L for men and <10 µg/L for women), showed that one subject had iron deficiency anemia. Similar to our study, Reid et al showed a

higher prevalence of iron deficiency in adults with CF, but they showed it was no association between pancreatic supplementation and iron deficiency (111). Another study from Netherland reported high prevalence of iron deficiency in children (112). However, the population group was different between the study from Netherland and our study. In the present study, three subjects had anemia of chronic inflammation. Connor et al showed anemia of chronic disease in CF patients, even though hemoglobin and hematocrit values were normal (113). An observational study from Germany showed that chronic lung disease caused hypoxemia in CF patients (114). Similar to our study, this show that anemia of chronic inflammation can occur in CF patients.

5.2.6 Dietary intake

Energy and macronutrients

In this study, the median energy intake from dietary was 9574.8 kJ (9.57 MJ) in all subjects. This was without oral nutritional supplements (ONS) and vitamin supplements. According to NNR 2012 recommendations, a daily energy intake of 6.5- 8 MJ is considered a low energy intake (78) (p.32). In the present study, majority of men had median energy intake above 8 MJ/d, but median energy intake in women between 18-30 years was 6.6 MJ/d. Energy intake below 6.5 MJ/d is defined as very low energy and is associated with risk of inadequate intake of micronutrients (78) (p.32). However, it should be considered that NNR 2012 recommendations are for a healthy population, taken that to consideration, these recommendations might not be suitable for the CF population. Pancreatic insufficiency leads to deficit of pancreatic enzymes, and this leads to insufficient of energy absorption (10). Individuals with CF and PI need higher energy intake and European guidelines recommend that energy intake should range from 120 to 150 % (10). According to the guidelines, median energy intake in the present study was 82 % EAR from dietary intake and 91.2 % EAR for total intake (including ONS and vitamin supplements), these findings show that the energy intake did not reach the recommended 120- 150 % of energy requirement despite using ONS and vitamin supplements. Gastrointestinal problems, side effects of medications and constipation may affect appetite and contribute to low energy intake (10).

Similarly to our study, energy intake in the Scandinavian study did not achieve the recommendations (49). However mean value for energy intake in the Scandinavian study with

individuals with CF and PI was higher than our study (49). Difference in energy intake between the Scandinavian study and our study, might be that some subjects may have underreported their true intake in this study, and three days of food recording may not represent the real dietary intake in patients with CF and PI compared with the healthy population.

Protein intake in this study was in accordance with NNR 2012 recommendations. According to ESPEN guidelines, recommendations for protein are likely to be higher in patients with CF. However, there are no evidence-based recommendations for daily intake of protein and it is depending on individual's condition (10). Thus, recommendations from NNR 2012 was used and the reported lowest protein intake in the present study was 12.6 E %. Factors like use of pancreatic enzymes should be taken into consideration; protein digestibility is influenced of pancreatic enzymes timing (115). Intake of total fat and essential fatty acids are lower than recommended. This can possibly indicate that the subjects do not consume high fat, high calorie diet as recommended. These findings indicate that patients with CF and PI have high risk of inadequate essential fatty acids levels (52). There is evidence that level of unsaturated fatty acids are reduced in blood and this may contribute to pathophysiology of CF (116). Fibre intake in the present study did not reach the recommended intake from NNR 2012. A low fibre diet may be an important factor for pathogenesis of gastrointestinal symptoms (117). Thus, it is a possibility that higher intake of fibre may improve gastrointestinal symptoms and this can leads to improve energy intake and appetite (117).

Micronutrients

The present study showed lower dietary intake of micronutrients in dietary intake (without ONS and vitamin supplements) and inadequate energy intake might be a reason. Vitamins A, D and K from dietary were lower in the present study compared with NNR 2012. For vitamin K there was no specific recommendations, but according to NNR 2012, vitamin K intake of 120 and 90 µg/d for men and women, respectively, was set for adequate intake (78) (p.402*).* Even though there is no recommended intake of vitamin K, vitamin K from dietary intake was low in the present study. However, these recommendations from NNR 2012 might not be suitable for patients with CF and PI because they need higher intake of fat-soluble vitamins. This should be taken into consideration, for interpretation of the results. In the present study, water-soluble vitamins like folate and vitamin C were lower than recommend. Exceptional,

was vitamin B12, this was higher than recommended. Absorption of vitamin B12 is stimulated by pancreatic enzymes (52). This may be a reason for the higher intake of vitamin B12 in the present study.

Intake of iron was lower in women. Possible reason for lower intake of iron can be the use of pancreatic enzymes. Treatment with pancreatic enzymes may reduce oral iron absorption and this is a reason why pancreatic enzymes should not be supplemented simultaneous with iron (52). Intake of zinc was in accordance with the NNR 2012 recommendations and a possible reason may be use of pancreatic enzymes. Zinc status can be improved by using pancreatic enzymes (10, 52) and this has to be taken into consideration for intake of zinc. Intake of calcium was slightly lower than recommendations from ESPEN guidelines. Calcium absorption is interrupted by vitamin D deficiency and fat malabsorption and this can be a possible explanation for the lower intake of calcium in the study (10).

Intake with supplementation

In the present study majority of the subjects used supplementation. These supplementations are routinely prescribed to prevent vitamin deficiencies (85). Majority of the subjects used DEKAs Plus and other supplementation in addition. The present study showed that intake of fat-soluble vitamins, intake of some of water-soluble vitamins, zinc and selenium increased markedly by using supplementation. In the present study, upper intake level from NNR 2012 was used, but this UL might not be suitable for patients with CF and PI, because they need higher intake of fat-soluble vitamins. In the present study, by using supplements, two subjects had vitamin A intake below LI. Lower energy intake might be a reason for this. However, lowest dose of vitamin A supplement was lower than recommended. In addition, lower dosage with supplement and lower intake from dietary can leads to reduced respiratory function and poor clinical status (10). On the other hand, in the present study, total vitamin A intake did not exceed the UL. Nevertheless, recommendations for CF showed that highest dose of the supplement in this study was 3000 IU and this was within the range of recommended supplement for vitamin A (52). This indicates that the prescribed vitamin A supplementation may be sufficient dosage for adequate vitamin A intake. However, a study from the US have shown that total intake of vitamin A by using supplementation, has exceeded the recommendations for supplement for CF (118). A possible explanation for the

differences between these studies can be the use of different types of vitamin A supplementation or differences in dietary intake.

For vitamin E, by using supplements, no subjects had an intake of vitamin E below LI. However, recommendations for vitamin E supplement showed that lowest dose of vitamin E in the present study was 15 IU, and this was lower than recommended for vitamin E for patients with CF and PI (52). Even though men had adequate intakes of vitamin E from dietary, patients with CF have higher risk of malabsorption of fat-soluble vitamins. Thus it may be important to increase the dosage of vitamin E or change the supplement to increase vitamin E intake. In the present study, seven subjects had vitamin E intake above UL by using supplements. However, highest dose was within the recommended range of vitamin E supplementation and up to 400 IU daily is showed to be nontoxic for CF patients (52).

By using supplements, no subjects had vitamin D values below LI. However, the lowest dose of vitamin D supplement was 400 IU in the present study and this is lower than recommended for CF patients (10). If vitamin D intake from dietary is low, and the supplement dosage is low, it may lead to lower serum levels of vitamin D. Twenty six subjects had vitamin D intake above UL, however the highest dose of vitamin D supplement was 6800 IU in the present study and this exceed the recommended intake for vitamin D supplement (10). To compensate for the dietary intake of vitamin D, it may be that this dosage is adequate. Accordingly, the serum levels of vitamin D were within the reference range, and thus this dosage may not be a problem for the subjects in this study. Even though vitamin D intoxication is rare, a dosage more than 50,000 IU of vitamin D is associated with hyperphosphatemia and hypercalcemia (119).

According to NNR2012, there are no UL and LI for vitamin K. The minimum recommended dose of vitamin K supplement for adults with CF is 1 mg/day and low intake of supplement in addition with lower intake from dietary may lead to vitamin K deficiency that affects blood clotting and bone health.(10). Additional supplementation of vitamin K is also needed during antibiotic therapy. Therefore the recommended doses of vitamin K is higher than recommended for people without CF (85). Recommendations for vitamin K supplement for CF patients is 1-10 mg/day and the highest dose of vitamin K was within the recommended values (10).

6 Conclusion

Based on the results from the present study, following conclusions are suggested:

- According to cut of values from WHO, prevalence of underweight was low and prevalence of overweight and obesity was high in this study. Even though prevalence of underweight was low, 61.5 % of the females and 42.9 % of the males did not achieve recommended BMI for CF adults.

- This study showed that bone disease might occur in individuals with CF and PI. In the present study, 11.1 % had osteopenia, even though they used pancreatic enzymes and vitamin supplementation.

- According to ESPEN statement, this study showed 35.7 % of males and 23.1 % of females had FFMI below cut off points.

- Handgrip strength in the study group was lower than the reference group (healthy Caucasians), and this was correlated with muscle mass.

- In the present study, 32% were deficient of vitamin D, 4.2 % had vitamin A deficiency and 12 .% had vitamin E deficiency. 3.4 % of the subjects had iron deficiency anemia. 18.2 % subjects had HbA1c % values above the reference values.

- Energy intake in the present study did not reach the recommended 120-150 % of energy requirement for cystic fibrosis.

- Intake of total fat, fat-soluble vitamins, except vitamin E in men from dietary (excluding oral nutrition supplements and supplements of vitamins) were low in the present study group. Intake of minerals and trace elements like calcium, iron and selenium from dietary were low in the study group.

This cross sectional study had a small sample size, and this has to be considered when drawing conclusion. These results indicate that individuals with CF and PI have difficulties to obtain optimal nutritional status, however the CF group from this study may be a selected group and these results may not be generalizable for CF population in Norway.

7 Future perspectives

This study was carried out as a part of a cross-sectional pilot study. The sample size of the study was small, leading to limited statistical power of the study. Even so, this study showed that patients with CF and PI have difficulties to obtain sufficient nutritional status. Further research and investigations are necessary to assess nutritional status in CF with PI with a larger sample size.

Results from this study emphasize the importance of nutrition for individuals with CF and PI. Many studies have investigated prevalence of underweight and the results from this study, indicates the incidence of underweight is still there, but overweight and obesity has become a major challenge for individuals with CF and PI. These findings shows the necessity of conducting further studies to assess nutritional status in CF with PI to prevent both underweight and overweight in individuals with CF and PI. Routinely monitoring of weight and BMI is important to detect prevalence of underweight and overweight. Screening with DXA and physical tests are important to evaluate malnutrition and bone status. These screening tests will also strengthen the quality of CF treatment. In future studies it is important to investigate physical activity, because this is related to weight and bone status.

In the present study, it was possible to detect deficiency of some vitamins. However, considering the large numbers of missing values, prevalence of fat-soluble vitamin deficiencies might have been lower. Annual screening of all fat-soluble vitamins is important in future studies to detect fat-soluble vitamin deficiencies. Due to the variation in their dietary intake because of the disease and treatments, 24 hours recall with 3 days may not be an appropriate tool. Food diaries might be a more appropriate tool to assess dietary intake and it will prevents bias. Use of medicaments, such as antibiotics and gastrointestinal symptoms are related to dietary intake. Therefore, in future studies, it is important to investigate this with nutritional status.

CF dietitian is a part of the CF care team, if there were opportunities to offer routinely dietary counselling, it may contribute to prevent the nutritional challenges in CF patients. A possible solution for this can be to recruit additional CF dietitians.

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Appendices

Appendix 1: Invitation letter to the study

Appendix 2: Written consent form

Appendix 3: Overview of biochemical measurements (In Norwegian: Oversikt over biokjemiske målinger)

Appendix 4: Photographs of portion sizes

Appendix 5: Portion sizes for beverages and household measurements

Appendix 6: Reply to application form of Norwegian Regional Committees for Medical and Health Research Ethics

Appendix 7: 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

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: Overview of biochemical measurements (In Norwegian: Oversikt over biokjemiske målinger)

Oversikt over biokjemiske parametere og referanseområde

Parameter	Referanseområde
P-natrium	137-144 mmol/L
P-kalium	3,5-4,4 mmol/L
P-klorid	98-107 mmol/L
P-magnesium	0,71-0,94 mmol/L
P-fosfat	M: (18-49 år) = 0,7-1,6 mmol/L M: (50-120 år) = 0,7-1,3 mmol/L K= 0,8-1,4 mmol/L
P-albumin	36-45 g/L
P-ASAT	M= 10-70 U/L K= 15-35 U/L
P-ALAT	M= 10-70 U/L K= 10-45 U/L
P-amylase pankreas	10-65 U/L
P-kreatinin	M= 60-105 µmol/L K= 45-90 µmol/L
P-triglyserid	0,5-2,6 mmol/L
P-kolesterol	(18-29 år) = 2,9-6,1 mmol/L (30-49 år) = 3,3-6,9 mmol/L (50-120 år) = 3,9-7,8 mmol/L
B-hemoglobin	M= 13,4-17 g/100 mL K= 11,7-15,3 g /100 mL
S-glukose	4-6 mmol/L
B- HbA1c	4-6 %
P-INR ratio	0,8-1,2 n-ratio
P-vitamin A(retinol)	1,2-3,6 µmol/L
S-25-OH-vitamin D	37-131 nmol/L
P-vitamin E (Alfa-Tokoferol)	17-45 µmol/L
S-paratyroidea hormon (PTH)	1,5-7 pmol/L
P-ionisert kalsium	1,2-1,3 mmol/L
P-jern	9-34 µmol/L
P-transferrin	2-3,3 g/L
P-ferritin	M= 30-400 µg/L K= 10-170 µg/L

Appendix 4: Photographs of portion sizes

Smör/bredbara pålägg

AA11

AA12

AA13

AA14

AA15

- Mängden på kniven motsvarar mängder. på brödskivan i respektive bild.
- Eftersom bröd är olika stora är det viktigt att du bedömer både mängden matfett på kniven och tjockleken av matfettet på brödet.
- Hur såg kniven ut när du brett färdigt din smörgås, fanns det bredbart pålägg kvar (leverpastj, Tartex, Nutella, jordnötssmör, messmör, färskost, mjukost)? Dra i så fall bort det.
- Har du ätit flera smörgåsar med olika mycket pålägg? Ange dem var för sig.

AB11

AB12

AB13

AB14

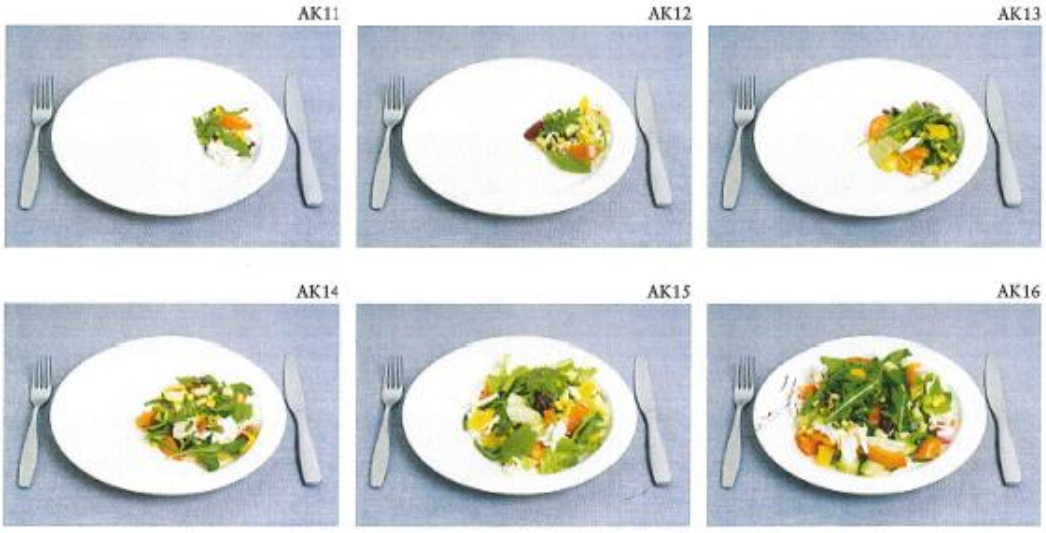
AB15

AB16

- Välj den bild som bäst motsvarar tjockleken på din ostskiva.
- Ange hur många skivor du ätit. Om du ätit flera olika tjocka skivor – ange dem var för sig.
- Jämför ostskivan med referensen Wasa Husmans knäckebröd.

Ost

Sallad

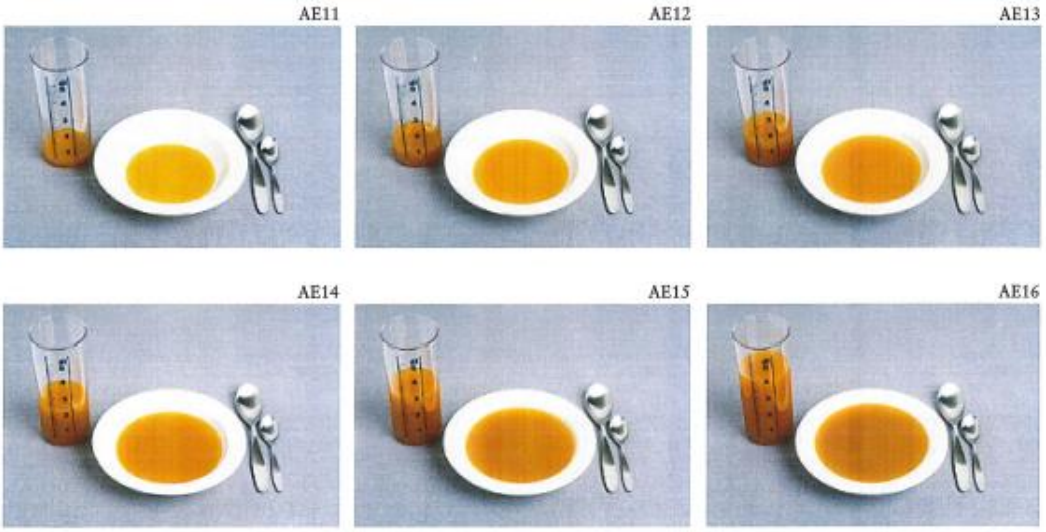


12

Använd bilderna för att uppskatta hur mycket du ätit av:

- Blandad sallad
- Grönsallad
- Matig sallad, typ skink- och ostsallad, pastasallad

Soppa/fil



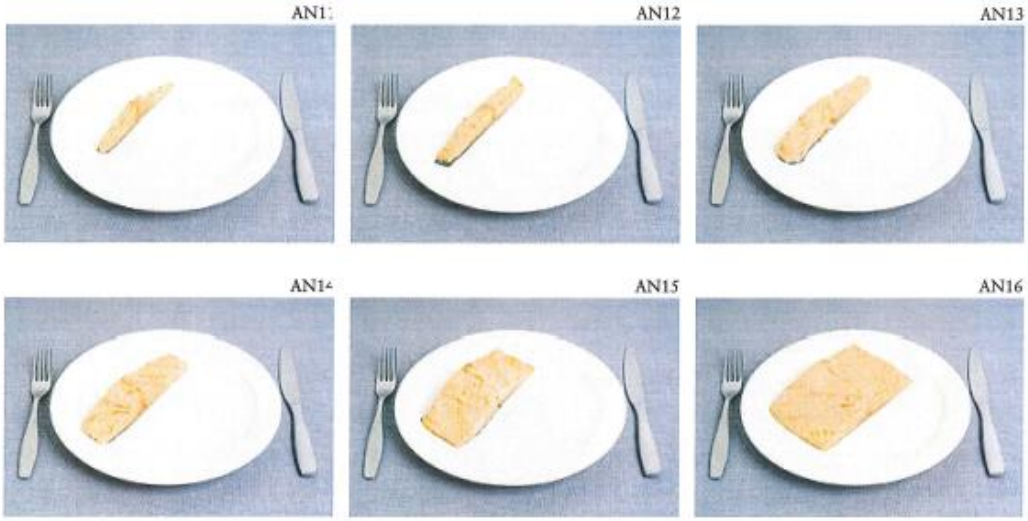
10

- Titta både på mätglaset och tallriken för att få bättre uppfattning om mängden.
- Motsvarande mängd soppa, som finns i tallriken, illustreras med hjälp av samma mängd upphälld i mätglaset.

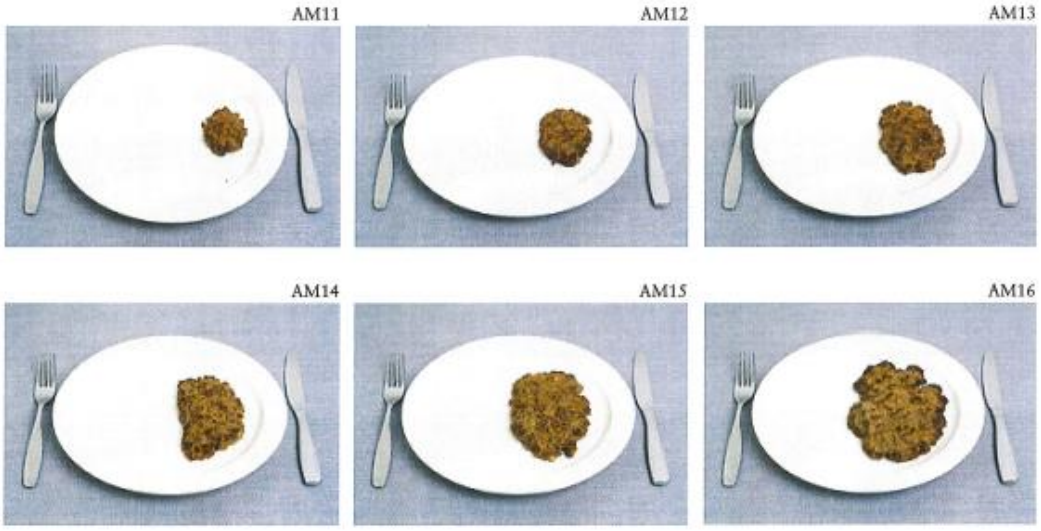
Använd bilderna för att uppskatta hur mycket du ätit av:

- Soppa mat- och efterrättssoppa
- Fil och yoghurt
- Kräm
- Välling

Fisk

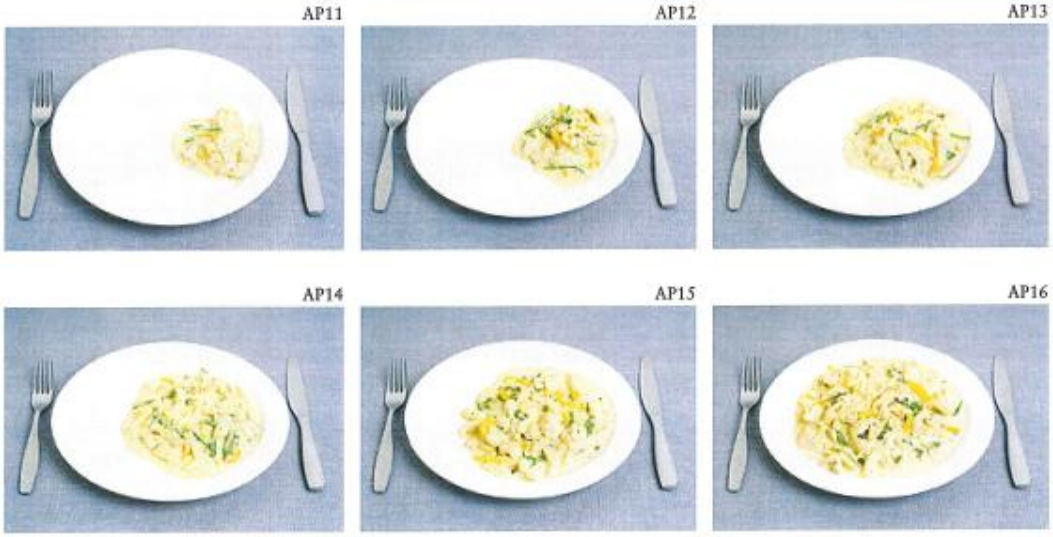


Använd bilderna för att uppskatta hur mycket du ätit av:
- Stekt, kokt och varmrökt fisk



Använd bilderna för att uppskatta hur mycket du ätit av:
- Biff
- Schnitzel
- Köttfärslimpa
- Vegetarisk biff/schnitzel

Biff



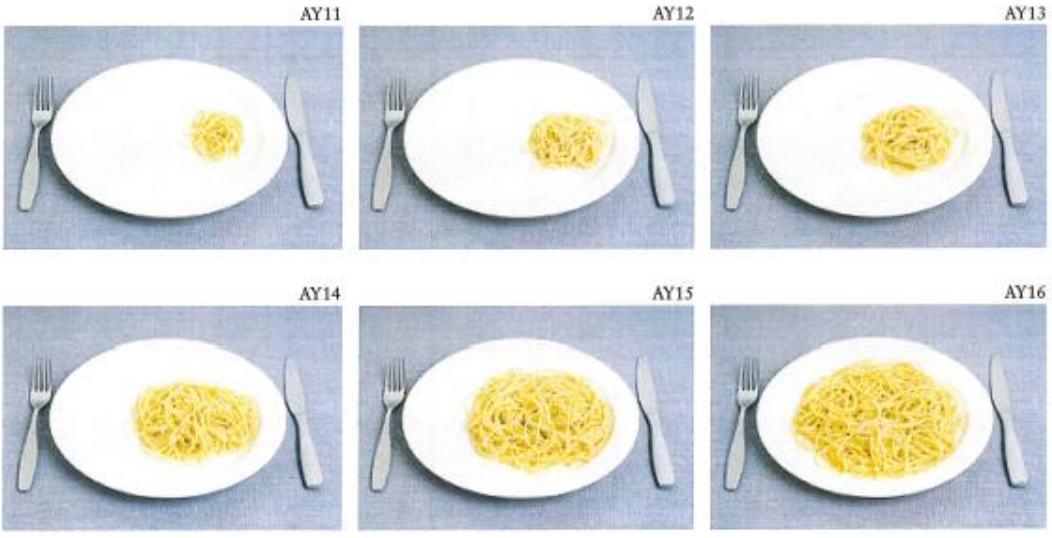
19

Använd bilderna för att uppskatta hur mycket du ätit av:

- Köttgryta
- Fiskgryta
- Kycklinggryta
- Vegetarisk gryta
- Stuvade grönsaker

Gryta/panna/stuvning

Pasta



22

Använd bilderna för att uppskatta hur mycket du ätit av:

- Alla sorters pasta (makaroner, spagetti m m)
- Nudlar
- Potatisgnocchi
- Stuvade makaroner

Appendix 5: Portion sizes for beverages and household measurements

Appendix 6: Reply to application form of 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 7: Correlation values between specific variables

	Pearson correlation coefficient	p value
BMI and FEV_1 %,	0.38	0.026
BMI and FVC	0.31	0.069
Age and t-score	0.35	0.087
FM and FEV_1 %,	0.16	0.795
FM and FVC %	0.06	0.419
FFM and FEV_1 %,	0.31	0.114
FFM and FVC%	0.35	0.067
LBMI and FEV_1 %,	0.39	0.040
LBMI and FVC %	0.40	0.036
BMD and LBM	0.62	<0.001
BMD and FMI	0.42	0.025
LBMI and HGS	0.67	< 0.001
HGS and FEV_1 %,	0.09	0.605
HGS and BMD	0.51	0.008
Total calcium intake and t-score	-0.13	0.511
Total vitamin D intake and t-score	0.07	0.713

Abbreviations: BMI, body mass index; FEV_1 %, forced expiratory volume in the first second; FVC, forced vital capacity; FM, fat mass ; FFM, fat free mass; LBMI, lean body mass index; BMD, bone mineral density; LBM, lean body mass; FMI, fat mass index; HGS, hand grip strength.