From DEPARTMENT OF CLINICAL NEUROSCIENCE,
DIVISION OF PSYCHOLOGY
Karolinska Institutet, Stockholm, Sweden

ADULTS WITH CYSTIC FIBROSIS: MENTAL HEALTH AND PATIENT EXPERIENCES OF THE CF TREATMENT

Lena Backström Eriksson

Karolinska Institutet

Stockholm 2019

Published by Karolinska Institutet
Printed by Universitetsservice

ISBN 978-91-7831-418-8

Adults with Cystic Fibrosis: mental health and patient experiences of the CF treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Lena Backström Eriksson

Principal Supervisor:
Professor Bo Melin
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Co-supervisor(s):
PhD Kimmo Sorjonen
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Professor Lena Hjelte
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Paediatrics

Associate Professor Mari Lundberg
University of Gothenburg
Department of Health and Rehabilitation
Institute of Neuroscience and Physiology

Opponent:
Associate Professor Ida Flink
Örebro University
School of Law, Psychology and Social Work
Center for Health and Medical Psychology

Examination Board:
Professor Per Lindberg
Uppsala University
Faculty of Social Sciences
Department of Psychology

Associate Professor Lotta Arborelius
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

PhD Hanne Vebert Olesen
Aarhus University
Department of Clinical Medicine
Division of Paediatrics

To all people with Cystic Fibrosis.

When I started my work as a clinical psychologist at Stockholm's CF-Center in 2008, one of my first main questions was about the mental health characteristics of the population I was expected to help. In the literature on mental health in adults with Cystic Fibrosis (CF) I found a few studies showing mixed results, and also that the adult CF population worldwide at that time was relatively young, had poor health status, and was small in comparison to the population of children with CF. However, the studies available at that time also reflected optimism and I remember an article describing a "changing scene"; in the future CF patients predominantly would be adults with a chronic condition and not children with a lethal disease. Compared to the CF population worldwide at that time, the Swedish CF population had a pronounced survival rate and good somatic health status; 50% were adults. However, the mental health of the Swedish adult CF population had never been evaluated. Since CF is a serious and demanding medical condition, it was easy to hypothesize that the patient population would exhibit elevated rates of anxiety and depression. Because CF is also a disease in which the outcome largely depends on patients' ability to manage their treatment and self-care, I thought that the mental health aspects of CF were of interest and importance to study.

ABSTRACT

Background: Cystic fibrosis (CF) is an autosomal recessive inherited, life shortening multi organ disease most typically affecting the respiratory system and the gastrointestinal tract. In recent decades progresses in the management of CF has led to an increasing proportion of adults with CF. Sweden has a large proportion of adults living with CF, however there is no systematic evaluation conducted, and thus a lack of knowledge regarding their mental health.
Aim: The overall aim with this thesis was to investigate the mental health among adults with CF, and to explore adult CF patients experiences of the CF treatment applied in Sweden.
Methods and Results: *Paper I*, a cross-sectional study. Comparisons of Hospital Anxiety and Depression Scale (HADS) data from 129 Swedish adult CF patients, and from published studies in Belgian, British and German adult CF-patients with corresponding general population data showed no elevated risks for anxiety or depression among the adults with CF in a binary logistic analysis. ANOVA showed a slightly elevated level of anxiety in the Swedish CF-sample, but this effect was only seen among the women. *Paper II*, a cross-sectional study in 68 adults. Structural Equational Modelling (SEM) showed that those with severer *cftr* mutation classes with increasing age and a parallel deterioration of somatic health get poorer psychological wellbeing. Exercise had a positive effect on psychological wellbeing, but only if it also had a positive effect on somatic health. *Paper III,* a longitudinal study in 68 adults. Latent Growth Modelling (LGM) showed that anxiety, especially when combined with some level of depression, was associated with a faster decline in lung function over time. *Paper IV*, a qualitative study. Semi-structured interviews were conducted with 12 'middle-aged' (32-55 years) adults. Inductive content analysis resulted in three themes: 'Prioritize and manage health – a life condition', 'Aspiration for and possibility to a 'normal life' and 'The CF center as a partner in the life condition'.
Conclusion: This thesis has contributed with an increased understanding of the mental health aspects of CF for adults. As a group, there is no elevated risk for impairment in mental health with regard to anxiety and depression in Swedish adults with CF. However, individuals with genetically more severe CF with age, and deteriorated health, get vulnerable for poor psychological wellbeing, and also those who are performing a high amount of physical exercise without maintaining their somatic health. Over time anxiety, when combined with some level of depression, seems to be associated with a faster decline in lung function. These mental health aspects can be deeper understood from the perspective that prioritization of health is (literally) a life condition for the adult with CF, and that the aspiration for and possibility for a 'normal life' can result in stressful conflicts, especially when health is deteriorating. In the coping with the life condition the CF center is seen a partner. Clinical implications should focus on the patients vulnerable for poorer mental health, and on including the patients' perspective through person centered care (PCC) and a health psychological approach in the CF-care. Future research in the area of mental health in CF should broaden the perspective and focus also on the wellbeing aspects of mental health, and would benefit from having a more clearly defined health psychological framework thus including the study of behavioural patterns that underlie disease development and health.

LIST OF SCIENTIFIC PAPERS

I. Backström-Eriksson L, Sorjonen K, Bergsten-Brucefors A, Hjelte L, Melin B. Anxiety and depression in adults with cystic fibrosis: A comparison between patients and the general population in Sweden and three other European countries. BMC Pulm Med. 2015 Oct 14;15:121. doi: 10.1186/s12890-015-0117-9.

II. Backström-Eriksson L, Bergsten-Brucefors A, Hjelte L, Melin B, Sorjonen K. Associations between genetics, medical status, physical exercise and psychological wellbeing in adults with cystic fibrosis. BMJ Open Respir Res. 2016 Nov 7;3(1):e000141.

III. Backström-Eriksson L, Melin B, Hjelte L, Bergsten-Brucefors A, Sorjonen K. Anxiety and depression as predictors of the development in lung function in adults with cystic fibrosis: a longitudinal study
Submitted, Under review

IV. Backström-Eriksson L, Hjelte L, Melin B, Sorjonen K , Lundberg M "Middle-aged" CF patients' experiences of their daily multifactorial treatment: a qualitative study
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
BMI	Body Mass Index
CF	Cystic Fibrosis
CBAVD	Congenital Bilateral Absence of Vas Deferens
CBT	Cognitive Behavioral Therapy
CFLD	CF related liver disease
CFRD	CF related diabetes
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic Fibrosis Transmembrane conductance Regulator
DIOS	Distal Intestinal Obstructive Syndrome
EMA	European Medicines Agency
FDA	U.S. Food and Admininstration Agency
FEV_1% pred	Forced Expiratory Volume in one second percent of predicted value
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
IgG	Immunoglobulin G
IV	Intravenous
LGM	Latent Growth Modelling
LS	Life Satisfaction
MI	Motivational Interviewing
PCC	Person Centered Care
PI	Pancreas Insuffuciency
PUFAs	Polyunsaturated Fatty Acids (PUFAs)
PWC	Physical Working Capacity
QoL	Quality of Life
SALAR	Swedish Association of Local Authorities and Regions
SEM	Structural Equational Modelling
TIDES	The International Depression Epidemiological Study
WHO	World Health Organization

1 INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive, life-shortening, multi organ disease leading to a progressive deterioration of health. Classical cases of CF affect the lungs and respiratory system as well as the gastrointestinal tract is affected, and chronic pulmonary inflammation and infections are the primary causes of mortality in CF (1). Earlier people with CF usually died during childhood; however, the introduction of centralized care, and multidisciplinary management of CF in the 1980's, led to a dramatic improvement in health outcomes and survival rates in the subsequent decades (2).

To date more than 50 % of the European CF population are adults (3). Recent forecasts show that the adult CF population will further increase remarkably in the coming years. Thus, in the future the dominating part of the patient population will be predominantly adults (4). However, health status and survival still differ considerably between countries were CF is prevalent. In Sweden the CF population as a whole enjoys a comparatively good somatic health status, high survival rate and pronounced longevity according to international comparisons and as a consequence a high proportion of the CF patients are adults (3).

Despite the remarkable improvements in the management, treatment and health outcomes CF, is still incurable. The multidisciplinary treatment, to large extent based on self-care, is extremely time consuming and physically demanding for the patients especially when their health is deteriorating. For adults with CF, the total disease and treatment burden is high including the natural course of CF with disease progression, deterioration of health and comorbidities (5, 6). Adult CF patients invest a significant amount of time on daily self-care and treatment in order to maintain their health. This cost may have an impact on mental health and quality of life (QoL). People suffering from somatic diseases generally are at risk for negative impacts mental health (7), and thus this issue is important to address among the growing adult CF population. However, results and conclusions from studies of mental health in adults with CF are limited, mixed, sometimes inconsistent and often with a main focus on anxiety and depression. Furthermore, as there are differences between countries with regard to CF care, treatment regimens and health care systems the results of such studies are not fully generalizable. In the Swedish adult CF population there is no systematic evaluation conducted with regard to mental health, and thus a lack of knowledge.

The overall aim of this thesis was to investigate mental health among adults with CF, and to explore their experiences with the CF treatment regimen used in Sweden and thereby increase the knowledge about how the multiprofessional CF care team can facilitate and support adult CF patients in maintaining their mental health.

2 BACKGROUND

2.1 CYSTIC FIBROSIS

Cystic Fibrosis (CF) is a life-shortening and incurable autosomal recessive disease. CF is congenital and chronic and the expected course is a progressive deterioration of health through malfunctioning of epithelial organs such as the lungs, pancreas and liver. (1).

2.1.1 Epidemiology

The incidence, or birth prevalence, varies across the world. In Europe the incidence of CF ranges from 1/1350 in Ireland (8) to 1/25 000 in Finland (9). Incidence of CF in the Swedish population amounts to 1/5600 live-births (10). In North America the estimated number of people with CF is 30 000 (11), and in Europe there is approximately 44 000 patients (3). Currently there are approximately 720 people living with CF in Sweden (12).

2.1.2 History and Prognosis

Historically CF has been a lethal disease among children. A quote on CF from the late 1800s observed, “the child will soon die whose brow tastes salt when kissed”. The disease was first described in 1936 and in 1948 the finding that became the basis for the method still used as a mainstay of diagnosing CF, the sweat test, was discovered. In 1985 the gene responsible for CF was localized, and in 1989 the gene was cloned and the protein, a chloride channel affected in CF, cystic fibrosis transmembrane conductance regulator (CFTR) was identified (2).

During the four recent decades health outcomes, survival and longevity have improved remarkable thanks to the development of management, centralized care and multidisciplinary treatment, for CF. However, survival and prognosis vary greatly in countries where CF is prevalent, and internationally there are still people with CF who do not survive past childhood or young adulthood (3).

2.1.3 Clinical implications

Most significantly in classical CF extremely thick mucus that builds up in the lungs and blocks the airways, where the proliferation of bacteria results in repeated serious lung infections. Progressive pulmonary disease associated with chronic bacterial infection and inflammation is the major cause of morbidity and mortality in CF patients (1). Chronic pulmonary infection is also the main determinant of the disease burden in terms of quality of life (13). Since a substantial portion of the patients develops severe respiratory disease, lung transplantation is an established therapy for end-stage lung disease in CF (13, 14). However, symptom severity varies among individuals and organ systems, as well as with age.

As mentioned previously, CF is a multi organ disease and also has other common complications and manifestations. The most common endocrine complication is CF related diabetes (CFRD), the prevalence of which starts to increase after the age of 10 and reaches

40-50 % in adults. Some individuals also develop severe CF related liver disease (CFLD), often during adolescence and before reaching 20 years of age (13-15). Approximately 5 % of the patients need a liver transplant (13). The gastrointestinal tract and pancreas are also usually affected by CF. Meconium ileus affects approximately 20 % of newborns with CF. Older patients may develop distal intestinal obstructive syndrome (DIOS), an occlusive manifestation with acute onset (13, 16). Pancreatic insufficiency (PI) causes malabsorption, especially of fat, which leads to malnutrition and poor growth and is seen in approximately 90 % of the patients. PI is associated with a more severe CF phenotype and overall disease progression (17). Another complication in adults with CF is increased risk for gastro-intestinal cancers the most prevalent being colorectal cancers (18, 19). There is also an increased cancer risk due to post-transplant pharmacological immunosuppressive therapy. Furthermore, male infertility due to Congenital Bilateral Absence of Vas Deferens (CBAVD) is found in up to 90 % of males with CF. In parallel with the progressive increase of survival, CF-related bone disease has emerged and is associated with factors such as malnutrition, low Body Mass Index (BMI) and severity of lung disease (13). Because CF is a complex and serious disease, it also can have an impact on the patients' mental health; Anxiety is found in 32-38 % of adults with CF, and depression in 10-21 %. Further descriptions and references are given in the section "Mental health in adults with CF".

2.1.4 The genetic background

CF is caused by a mutation in the gene that codes the Cystic Fibrosis Transmembrane conductance Regulator (CFTR), a protein in the apical membrane of the cell surface that controls the salt and water balance across the cells. The protein is a chloride channel, and a defective CFTR causes malfunction in the chloride transport in the cell which leads to altered secretion in glands and organs. One example is the sticky mucus in the airways described above (13), (Fig. 1)

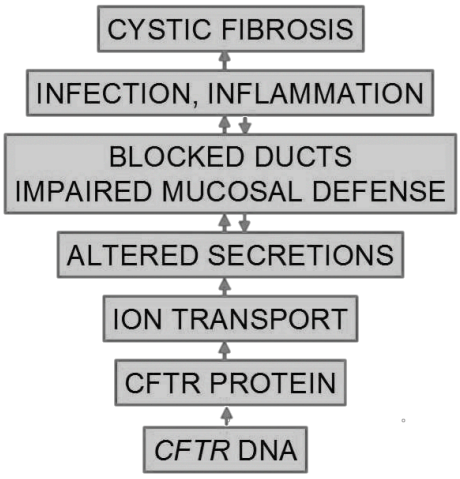

Fig 1. The pathophysiology of CF. (Picture published with permission from Cecilia Rodriguez Hortal.)

To date more than 2000 mutations of the cftr gene are known and registered in a database (20, 21). The *cftr* mutations was originally grouped into five major classes based on their predicted functional consequences, with regard to protein synthesis and chloride channel functioning for the CFTR protein. Mutation classes I-III are called *severe mutations* (especially class I and II) as they cause total loss of chloride channel activity. These mutation classes are associated with a severe disease expression with regard to medical outcome. The most common *cftr* mutation belongs to class II. Since Classes IV-V maintain some chloride channel activity, they are called *mild mutations* as they are causing a milder manifestation of the disease (22-25). The classification has later been expanded with a sixth and a seventh class.

The five originally described classes and their functional defect are (26) (Fig 2):

2.1.4.1 Class I

These mutations cause *defective protein production*. No full length CFTR protein is synthesized due to a premature stop, and no CFTR protein will reach the apical membrane at the cell surface.

2.1.4.2 Class II

Mutations in this class cause *defective protein processing*. The protein will not be properly processed and this defective protein will be recognized as abnormal. This leads to premature degradation, and thus the protein will in not be transported to the cell membrane. The most common *cftr* mutation F508del belongs to class II (13).

2.1.4.3 Class III

Class III mutations give *defective regulation*. The protein reaches the cell membrane but is non-functional due to suppression of chloride channel activity. They are called gating-mutations.

2.1.4.4 Class IV

These mutations cause *defective conductance*. CFTR are found at the cell membrane, but abnormal conformation of the opening in the channel leads to disrupted ion flow.

2.1.4.5 Class V

Class V include mutations that cause *reduced synthesis or functioning* because there is a reduced amount of CFTR or functional CFTR at the cell membrane.

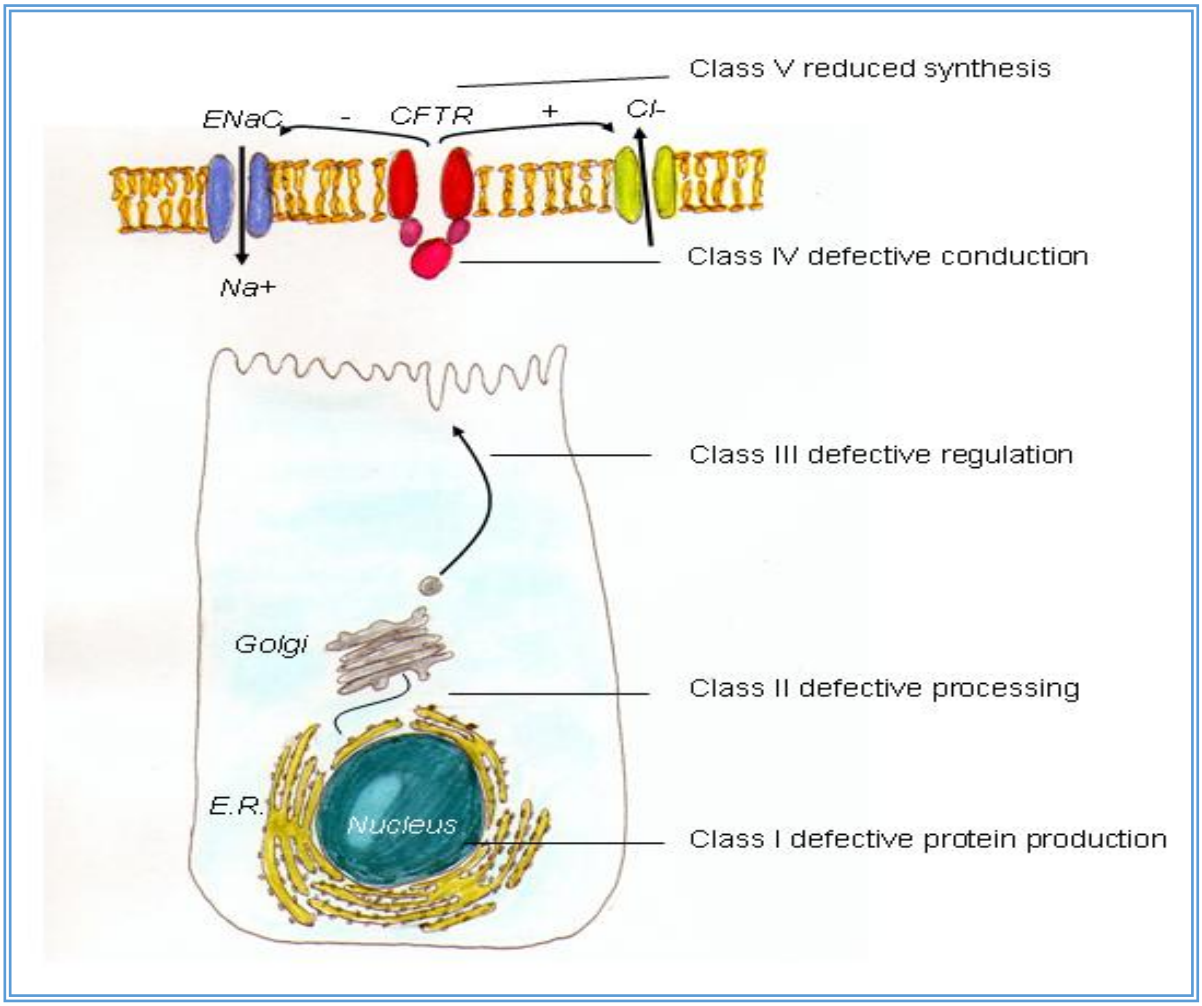

Fig. 2 The five cftr mutation classes originally described and their functional consequences for the protein synthesis and chloride channel functioning. (Picture published with permission from Anne Geborek.)

2.1.5 Management and treatment

2.1.5.1 The centralized and multidisciplinary approach

The complexity of the disease requires a multicomponent treatment approach (27). About four decades ago, the CF care became centralized, and a more intensive treatment was introduced, using a multifactorial, interdisciplinary approach (2). This approach has, as mentioned, been successful with regard to improved health outcomes, life expectancy and survival. The management and treatment of CF is currently multidisciplinary and provided in specialized centers, according to continuously updated international evidence based guidelines (14, 28-30).

2.1.5.2 Treatment

Because CF is still incurable, the treatment is preventive and symptomatic and aims to maintain health and postpone the progress and harmful effects of the disease. It is well known that the treatment is complex, extremely time consuming and physically demanding for the patients (5), since it is largely based on daily self-care. International guidelines describe treatment and management of CF from a multidisciplinary approach (28). The cornerstones

of the modern CF treatment are airway clearance, antibiotic therapy, nutrition and (27). Below is an overview of certain essential parts of the recommended treatment regimen.

Physiotherapy in the format of airway clearance, physical exercise and inhalation therapy - plays an important role in maintaining health in CF patients (31). Physiotherapy should be performed regularly and frequently from the time of diagnosis. The aim of these interventions is to maintain ventilation of the lungs, to postpone the progression of pulmonary disease, and to prevent musculoskeletal complications (32).

Among all the different medical treatments, one mainstay in the modern CF care is preventive and frequent/regular use of intravenous antibiotics for the treatment of airway infections. Antibiotics are also administered orally or via inhalation. Since good nutritional status is positively associated with lung function and survival it is essential to maintain a normal BMI (32-34). In people with CF, this is achieved through a high caloric intake, pancreatic enzymes and supplementation with minerals, fat-soluble vitamins, and fatty acids (35, 36).

Furthermore, regular medical check-ups are necessary to detect signs of complications early on. Psychosocial support and screening for and treatment of anxiety and depression (30, 37) are also recommended parts of the management of CF. This is further described in the section "Mental health care and psychosocial support in CF care" below.

2.1.5.3 New, CFTR modifying treatment

Current standard treatment is as mentioned developed to target the symptoms caused by the defective cftr gene. In recent years pharmacotherapy that aims to increase the function of the CFTR protein has been developed. This CFTR modifying treatment could make a substantial difference in changing or stopping the disease process. Two drugs, Orkambi® and Kalydeco® (38, 39), are now recommended as parts of standard of care for patients with the *cftr* mutations in question (30). Kalydeco®, the first of these two drugs to be approved (40-43) is targeting *cftr* gating mutations found in less than 5 % of the CF-patients worldwide. Orkambi® is targeting the most prevalent *cftr* mutation worldwide, F508del. Symkevi® is also targeting F508del, gives less side effects, and is recently approved by U.S. Food and Drug administration (FDA) (44) and European Medicines Agency (EMA) (45). Clinical pharmaceutical studies of a three-drug combination to treat individuals heterozygous for the F508del CFTR mutation is currently underway. (46).

There is an on-going European research project to develop 'tailored' treatments for adults with extremely rare *cftr* mutations who cannot otherwise get access to the *cftr* modifying treatment. In this project patient derived organoids are used for laboratory testing of drug candidates targeting the basic defect in *cftr*. Patients will be assigned to clinical trials using a suitable drug candidate based on the reaction in their respective organoids (47).

2.1.5.4 CF care in Sweden

In Sweden the CF care has been centralized since the 1970s. Currently, people diagnosed with CF are referred to one of the four Swedish CF centers (Stockholm, Uppsala, Lund, Gothenburg) offering multidisciplinary care. In line with the international guidelines mentioned previously, the care involves frequent clinical evaluations and monitoring for complications, and the treatment regimen described above. In the Swedish treatment regimen a focus both on proactive treatment and on giving the CF patients the possibility to a normal life were and still are important strategies in the Swedish CF treatment regimen (48). Since the early 1980' the Swedish CF treatment regimen has emphasized physiotherapy as an essential component in maintaining healthy functioning. Physiotherapy is introduced from the day of diagnosis and managed by the patient as part of their daily self-care routine. Treatment includes daily airway clearance therapy based on physical exercise and chest physiotherapy along with frequent physical exercise (49). Furthermore, home administered intravenous (IV) antibiotic treatment for early eradication of pathogens is also part of the standard of care for CF since the 1980s (50, 51), as well as a strong focus on nutritional issues including intravenous supplementation with polyunsaturated fatty acids (PUFAs) (52). The IV antibiotic treatment supplies and drugs are distributed from the CF center but managed by the patients in their daily life at home, at work or in school. In many countries, this kind of treatment is given during hospitalization.

2.2 CF IN ADULTS

The advances in the management of CF the last decades have led to an increasing proportion of adults with CF (53). The picture of CF as a lethal disease in children has changed, and the CF population is now predominantly an adult one (53). In Europe, today 52 % of all the CF-patients are adults (3). In Western Europe an increase by 75 % in adults with CF is predicted by 2025 (4).

In parallel with a growing adult CF population, the complexity of the CF-care and treatment is increasing (53). These circumstances mean that CF care needs to be adapted to meet the physical and psychological needs of this "new", older population. As the primary literature on CF care for adults has been limited, an international task force has been working with priorities for optimizing adult CF care over the next 15 years (53).

2.2.1 The Swedish adult CF population

In an international perspective the Swedish CF-population as a whole enjoys a good health status, pronounced longevity and high survival rate – and as a result a comparably high proportion of adults. (3). Out of the 720 CF-patients in Sweden 65 % are adults, and 56% of the adults are over 30 years of age (54). In the entire Swedish adult CF population 18 % have received a lung- or liver transplant (12).

Furthermore, the life expectancy in Swedish CF-patients is to date estimated to be approximately 50 years according to the latest calculation (10). However, the median age of

Swedish people who have died of CF between 2010-2017 is 39 years (12). In Sweden the estimated increase of adults with CF is 59 % by 2025 (4).

2.2.2 Psychosocial challenges for adults with CF

Adults with CF face many psychosocial challenges potentially having an impact on mental health and quality of life. It is concluded that they carry both a substantial physical and psychosocial burden to adhere to their treatment regimen while they also are trying to live "normally" (55). The treatment regimen is complex and demanding especially as the disease gets progressively more severe (5, 56). The comorbidities mentioned is also a factor that increases the total burden of disease and treatment, since some of them are becoming more prevalent with age. Other challenges for both men and women are issues of reproduction and fertility. Another challenge is coping with the impact of disease management and deteriorating health on family relationships, employment and education. In the most severe stages of the disease respiratory failure, requirement of supplemental oxygen, and lung transplantation are unavoidable challenges (53).

2.3 MENTAL HEALTH IN ADULTS WITH CF

When the concept "mental health" is used in the area of CF it has in recent decade to large extent addressed anxiety and depression as a main question of interest through international prevalence studies, international task forces and international guidelines in the area.

2.3.1 Anxiety and Depression

Dealing with a disabling life-shortening physical disease such as CF will occasionally cause feelings of worry and sadness as natural reactions. If these feelings or emotional states become pervasive, an anxiety or depressive disorder may develop. Especially depression is associated with poor adherence to treatment, while the effects of anxiety on adherence is unclear (57). The typical symptoms and behavioral and cognitive components of depression, but also sometimes in anxiety (described below), are contradicted to ability to initiative with regard to a complex and demanding treatment routine that must be followed daily.

2.3.1.1 Definitions of anxiety and depression

Anxiety is a common mental health problem. Anxiety disorders are characterized by feelings of fear and anxiety, along with related behavioral disturbances such as avoidance. Other symptoms of anxiety include restlessness, irritability, reduced concentration and memory, sleep disturbance, fatigue, and muscle tension (58).

Another common mental health problem is depression. Common symptoms of depression include sad, empty, or irritable mood, together with somatic and cognitive changes that significantly impair the capacity to function normally. Other symptoms and diagnostic criteria that often appear alongside the above include loss of interest, depressed mood most of the day, significant weight loss/gain, decrease or increase in appetite, fatigue or loss of

energy, withdrawal from activities, feelings of inappropriate guilt and/or worthlessness, and recurrent thoughts of death, and suicidal ideation/plans/attempts (58).

Both anxiety and depression are associated with many physical diseases. A patient is diagnosed with "anxiety/depression due to another medical condition" when they suffer from a medical condition known to induce anxiety or depression and when that medical condition preceded the onset of anxiety or depression (58).

2.3.1.2 Anxiety and depression in somatic diseases

Despite methodological differences it can be concluded that people suffering from somatic diseases are at risk for anxiety and depression (7). For example, the prevalence of depression is for example markedly and consistently higher in people with diabetes mellitus, heart disease, cancer, stroke, rheumatoid arthritis and osteoporosis according to a review in the area (7). Similarly, patients with chronic respiratory diseases are generally at increased risk for anxiety and depression (59-61). However, prevalence differs among diseases, and depending on type of disease, disease stage and prognosis (7).

2.3.1.3 Anxiety and depression in adults with CF compared to general populations

Some studies have explored anxiety and depression in adults with CF, but their results and conclusions vary and in some cases are inconsistent. According to some studies, anxiety, and depression are common in people with CF (62, 63); a review concluded that there were higher rates of depression in CF patients at all ages than in healthy populations (64). Another review reports evidence for an increased risk of mental health problems among adults and adolescents with CF. On the other hand, the same review also concluded that psychological functioning in CF patients is similar to that of healthy people until the more severe stages of the disease (65). Similarly, two other studies concluded that rates of anxiety and depression in adults with CF are in line with those of the general population (66, 67), and the only Swedish study on the topic found mental health problems to be rare among in adult CF patients (68).

The International Depression Epidemiological Study (TIDES) is a multicenter initiative involving nine countries, among them Sweden (Study I in the present project is partly based on Swedish TIDES-data); it has concluded that rates of anxiety and depression among adult CF patients are high (69). However, this study does not include any comparisons with data for the general population. Furthermore, questions have been raised about tools and methodology used in this study and also the need for a further discussion (70, 71). Conclusions about high rates of anxiety and depression among adult CF-patients compared to the general population are also made in a Spanish multicentre study with data from the Spanish arm of TIDES (72) and in a German multicentre study with German TIDES-data (63). On the other hand a large multicentre study performed in the UK based on the UK TIDES-data showed similar anxiety and depression rates among CF-patients as in the general population (73).

2.3.1.4 Prevalence of anxiety and depression in adults with CF

Regarding anxiety and depression prevalence estimates, the "TIDES" study mentioned above reports an anxiety prevalence of 32 % and a depression prevalence of 19 % among adult CF patients across countries. Two multicentre studies based on TIDES data from the UK (73) and Germany (63) report anxiety prevalence of 34 % and 20.6%, respectively, and depression prevalence of 13 % and 9.6 %. Two single-centre studies conducted in Belgium (67) and in the UK (74) report anxiety in 30 % and 33 % of the patients, respectively, and depression in 13 % and 16 %. Furthermore, a small US' single-centre study (75) report a depression prevalence of 30 % and in a recent Danish study among young adults a similar depression prevalence was found, 32.8% (76). Results from the mentioned Spanish multicentre study show an anxiety prevalence of 29.7 % and a depression prevalence of 12.2 % (72). In the Italian arm of TIDES the prevalence of anxiety was 38.4 % and of depression 17 % (77).

2.3.1.5 Factors associated with anxiety and depression in adults with CF

Depression in adults with CF is consistently reported to be associated with low lung function (63, 69, 74, 75, 77) and low health related quality of life (72, 74-76). Depression is also concluded to have an impact on the course of lung function over time (78). In adult CF patients, negative associations were found between depression and treatment adherence (62, 69, 79). Furthermore, depression is found associated with older age, recent use of IV-antibiotics, haemoptysis or pneumothorax (69), being on the list for lung transplant (63, 69) and low educational level (72).

Anxiety in CF populations has been found, contradictorily, to be either more common in women (63, 69, 72, 77, 80), or more common in men (66). In the large UK study men with CF were more anxious than healthy subjects, this effect was not seen among the women (73). Furthermore, anxiety is associated with more severe lung symptoms (63, 74), older age, lower BMI, lower lung function (77), hemoptysis or pneumothorax, being on the waiting list for lung transplant (69) and difficulties in relations (74).

Other studies have found that neither age, sex nor disease severity are associated with depression and anxiety (66, 81), and Bergsten-Brucefors, Hjelte (68) found no association between disease severity and mental health problems in Swedish adults with CF.

2.4 HEALTH RELATED QUALITY OF LIFE IN ADULTS WITH CF

Two studies have compared global QoL between CF patients and general population/healthy people and arrived at opposite conclusions, one finding that people with CF report lower QoL than healthy people (82), while the other found that CF patients have a higher QoL than the general population/Health controls? (83). A recent Danish study found lowered HRQoL among young adults with CF (76).

HRQoL has been investigated in adults with CF, often with a focus on associations with clinical variables and/or demographic factors. A recent review of the topic among adults and adolescents conclude that lung function - FEV_1% - is the most-studied factor in relation to

HRQoL and was consistently associated with multiple domains of the measurements used. Other studies have found that lung function (83), disease severity (84), and medical factors and social circumstances (85) have associations with HRQoL. It has also been found that women report lower HRQoL than men [75]. According to the above-mentioned literature review, higher age is associated with a higher treatment burden, something that is one domain of HRQoL (86).

Researchers have undertaken a handful of longitudinal studies on this topic, one of which concluded HRQoL is independent of changes in lung function over time among adults and adolescents with CF (85). In contrast, another study did find associations between changes in clinical variables and HRQoL over time (87). Another study found associations between survival and physical functioning, one of the domains of the HRQoL measurement used (88).

A few studies have explored the complex relationship among HRQoL anxiety and depression, and lung function in adults with CF. Among adults and adolescents, life satisfaction (LS) - a measure related to QoL - was found positively associated with lung function and negatively associated with anxiety and depression (89). Similar results were obtained in a study among adults (75). Also, one study found an association between HRQoL and lung function while another found an association between HRQoL and anxiety and depression (67, 74).

A very recent study found and concluded associations between "positive mental health and well-being" and HRQoL in adults with CF (90).

2.5 MENTAL HEALTH AND PSYCHOSOCIAL SUPPORT IN CF CARE

2.5.1 International guidelines

International guidelines addressing mental health issues in the CF-care have in recent years been developed and published based on the results of studies investigating anxiety and depression in CF patients (37). These guidelines recommend routine screening for anxiety and depression - either annually or when clinical concerns arise - for CF patients starting at the age of 12, and for caregivers to children with CF. The guidelines also recommend that individuals who are identified to have depression/anxiety should receive further psychological assessment to form the basis for the choice of adequate treatment. Patients or caregivers found to have mild depression and/or anxiety should receive education and preventive or supportive psychological interventions, and should be rescreened on a periodic basis. Those who are found to have moderate or severe depression or anxiety should be offered evidence-based psychological treatment and/or psychopharmacological treatment. These guidelines also describe CF-specific issues with psychopharmacological interventions, since the pharmacokinetics of medications may be altered in CF, and make associated recommendations (37).

2.5.2 European guidelines

European guidelines recommend psychological and psychosocial support as part of CF management (30). This recommendation emphasizes the fact that the disease is lifelong and demanding and will entail times of pronounced need for psychosocial support: for example, at diagnosis, during the transition to adult care, and at transplant or end-of-life. Key areas that merit qualified psychological intervention (i.e., care from a licensed psychologist) include adherence issues, anxiety and depression, pain, demoralization, aging with CF, disordered eating and/or body image problems, and anxiety and phobias connected to treatment procedures. There are also recommendations for mental health screening, assessment and treatment in alignment with the above described mental health guidelines in CF. Mental health professionals (i.e. lic. psychologists or psychiatrists) in the CF care should also provide support for CF team colleagues in their work with patients. The European guidelines also emphasize that multi-disciplinary care teams at CF treatment centers should include a licensed psychologist responsible for the psychological care (16, 32).

2.5.2.1 Guidelines concerning key psychosocial issues of adulthood

The latest update of the European guidelines adds a special section focusing on how to address key psychosocial issues of adulthood and of growing older with CF, as these challenges can have a negative impact on mental health, self-esteem, and interpersonal relationships (30). These issues are:

- How CF compounds normal psychological development
- Decision-making concerning treatment, procreation, parenting, and vocational and career plans
- Coping with health deterioration and its physical consequences such as loss of independence and mobility, and new complications or diagnoses
- Coping with end-stage disease, transplant procedures, and end-of-life care.

These guidelines further highlight the risk or likelihood of demoralization as a consequence of severe health problems (30).

Key approaches described in the guidelines are being pro-active during routine clinical visits for early identification of psychological difficulties. Furthermore, promoting positive coping strategies for supporting adjustment to the disease, and fostering resilience is described as extra important. Also referral to the CF team psychosocial professional or external mental health specialist are highlighted as key approaches (30).

2.5.3 Interventions

To date there are no specific psychological interventions recommended for people with CF. A Cochrane review of the area that included studies among children, adolescents, and adults found insufficient evidence for specific psychological interventions (91), this was concluded due to the heterogeneity of studied interventions and methodological issues. However, it did find preliminary evidence for interventions targeting specific aspects of CF treatment.

According to this review, no specific studies of interventions for people with CF and comorbid mental disorders had been conducted (91). Another review focused on Motivational Interviewing (MI) for adherence problems in CF and concluded that MI could be a useful approach for healthcare professionals in communicating treatment issues in ways that facilitate adherence (92). Furthermore, the mentioned international task force for the CF care of adults also suggests MI and cognitive behavioral therapy (CBT) when dealing with non-adherence (93).

2.6 THEORETICAL FRAMEWORK

CF treatment and management seeks to maintain health by postponing and preventing the harmful effects of the disease. The WHO defines health as "a state of complete physical, mental, and social wellbeing, and not merely the absence of disease or infirmity" (94). Although this definition has been criticized, it does point out the importance of a multidimensional approach to health and also highlights different aspects of wellbeing. The biopsychosocial model of health (Fig.3) similarly offers a broader definition of health (95) and forms the overarching theoretical framework for this project.

The aim with the project was not to test theories. However, it was considered relevant to use the biopsychosocial model of health and also a health psychological perspective to set the project in a broader context of health.

2.6.1 The Biopsychosocial model of health

An alternative to the traditional biomedical model of health emerged in the 1970s: the biopsychosocial model (95). In contrast to the biomedical model of health, in which disease is seen as being a result of biological deficiency or damage, the biopsychosocial model presents a broader perspective on illness and health that considers psychological factors, patient behavior, and the patient's cultural and social context.

The biopsychosocial model of health considers the relation between the concepts of health and disease to be a complex one: "*The boundaries between health and disease, between sick and well, are far from clear and will never be clear, for they are diffused by cultural, social and psychological considerations*" (95).

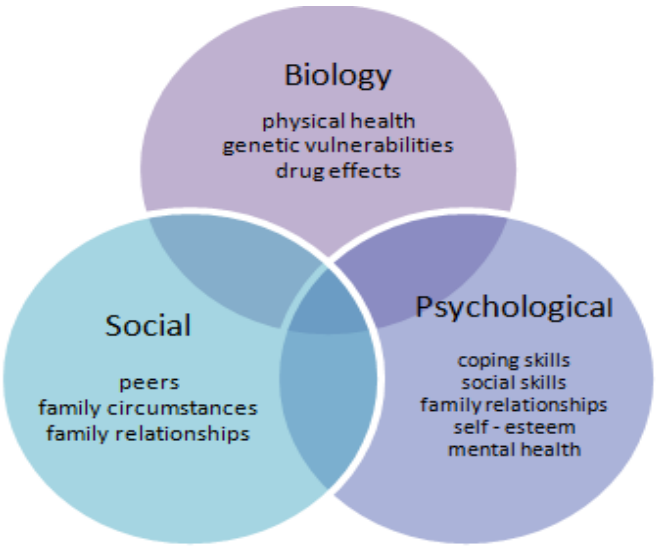

Fig. 3 The biopsychosocial model of health

The biological factors causing CF are now known, and treatments targeting these biological effects and symptoms have led to improvements in somatic health for people with CF, resulting in a growing adult CF population. However, this improvement in somatic health comes at the cost of a very complex treatment regimen, leading to a high treatment burden, especially for adult patients, and a resulting impact on the patients' health-related quality of life. Similarly, although the CF population has seen improved health status as a result of these treatment advances, adult CF patients in general struggle with the progress of the disease, deteriorating health, and the development of comorbidities, resulting in a high disease burden that impacts patients' psychosocial life. Using the WHO definition and the biopsychosocial model of health, it can be said that people with CF have achieved improved physical and biological health, but there is a need of systematic knowledge about psychological and social health/needs in the growing adult CF population .

2.6.2 Health psychology

A health psychological perspective helps us to further understand both health outcomes and needs with regard to efforts to improve health in a patient group. Health psychology was early defined as "*the aggregate of the specific educational, scientific, and professional contributions of the discipline of psychology to the promotion and maintenance of health, the prevention and treatment of illness, the identification of etiology and diagnostic correlates of health, illness and related dysfunction, and the analysis and improvement of the health care system and health policy formation*" (96).

In the field of health psychology, "adjusting to chronic illness" is a familiar term. It has, however, been concluded that there is no consistent definition of adjustment and that there is a need for a "unified theory" (97). For example mental health and psychiatric approaches most commonly define adjustment in terms of absence or presence of a diagnosed psychological disorder, psychological symptoms, or negative mood (97). In addition, positive affect and perceived personal growth as indicators of adjustment have been

investigated (98). The foundation for identifying determinants of adjustment to chronic conditions are theories of stress and coping, self-regulation, and social processes (98). Distinguishing between *disease* and *illness* can also contribute to further understanding of adjustment to a chronic condition. Disease refers to the biological processes affecting the person, whereas illness refers to the individual's experience of the disease, thus including both its psychological and social effects (99). Adjustment to chronic disease goes beyond the physical impact and symptoms of the disease and includes the individuals' perception, assessment, and adaption to the symptoms (99).

With the biopsychosocial model of health and the perspective of health psychology in mind, we can assume that a serious chronic condition like CF will have an impact on patients' psychosocial life. This, in turn and in some cases, may have an impact on somatic health outcomes. We can also conclude that psychological and social factors can have an impact on the treatment outcome of a disease. CF is a hereditary and congenital disease, and currently we have a great deal of biologically based knowledge - for example, genetic, medical, nutritional, and physiotherapeutic - on how to treat the disease. However, health outcomes for CF patients also largely depend on the individual's capacity to manage treatment and perform self-care: that is, to engage in health-related behaviors. A challenge especially for adults with CF as the treatment complexity and treatment burden increases with age and disease progression.

2.6.3 Definitions

Below definitions of concepts used in the context of mental health in this thesis are given. There are, however, a variety of descriptions and definitions of the different concepts in the literature. As stated in the HRQoL paragraph below, there is sometime difficult to distinguish them from each other, as there are overlaps and similarities. As also pointed out, the concepts are wide and broad in their definitions.

2.6.3.1 Mental health

Mental health is a concept with a broad definition according to WHO; *"a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" (100).*

2.6.3.2 Health related quality of life

When referring to quality of life in the context of health and/or disease the concept HRQoL is used and focuses on the quality-of-life consequences of health status, and includes domains related to physical, mental and emotional, and social functioning (101). However, the literature employs a variety of definitions of QoL, HRQoL, and health, making it is problematic to distinguish among them (102).

WHO for example defines "Quality of Life" (QoL) as "*an individual's perception of their position in life in the context of the culture and value systems in which they live and in*

relation to their goals, expectations, standards and concerns" and notes that it "*is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment*" (103).

2.6.3.3 Psychological wellbeing

One theoretical model of psychological well-being encompasses six dimensions (104); "*Autonomy*" that includes components such as independence and self-determination. "*Environmental mastery"* is an individual's ability to create or choose environments suitable to her/his conditions, *"Purpose in life"* means having a sense of direction and intention in life, contributing to a feeling that life has a purpose and meaning. *"Self-acceptance",* or positive attitudes towards one-self. *"Personal growth",* or continued development of one's potential, and growth as a person. "*Positive relations with others"* emphasizes warm, trusting interpersonal relationships (104).

2.7 IN SUMMARY

In summary I have identified the following research gaps I aim to investigate by this thesis:

- There is no systematic knowledge about the mental health in Swedish adults with CF.
- There is a lack of knowledge regardning how the Swedish adults with CF experience their intensive, daily, multifactorial treatment regimen.
- Therefore there is also insufficient knowledge about how to facilitate and support the adult CF-patients.

3 AIMS

3.1 GENERAL AIM

The overall objective of this thesis was to investigate mental health among adults with CF, and to explore their experiences with the CF treatment regimen used in Sweden and thereby increase the knowledge about how the multiprofessional CF care team can facilitate and support adult CF patients in maintaining their mental health.

3.2 SPECIFIC AIMS

3.2.1 Study I

The aim of study I was to estimate prevalence and degree of anxiety and depression among Swedish adult CF patients and compare it with Swedish general population data. An additional aim was to put the Swedish results in a context and compare the Swedish data with previously published anxiety and depression prevalence data from adult CF populations in three other European countries (UK, Germany and Belgium) and corresponding general population data.

3.2.2 Study II

The aims of study II were to examine the associations between: 1. Type of *cftr* mutation class, medical status and psychological wellbeing; and 2. Physical exercise, medical status and psychological wellbeing in adults with CF.

3.2.3 Study III

The aim of study III, a longitudinal study, was to investigate the effects of anxiety and depression symptoms on the development of somatic health status parameters over time in adults with CF.

3.2.4 Study IV

The aim of study IV was to qualitatively explore "middle aged" (here defined as 30-55 years of age) adults with CF experiences of their intensive daily multifactorial symptomatic treatment regimen.

3.3 RESEARCH QUESTIONS

3.3.1 Study I

→ What is the prevalence and level of anxiety and depression in Swedish adults with CF?

→ Is the prevalence and level of anxiety and depression in adults with Cystic Fibrosis higher than in the general population in Sweden, Germany, the UK and Belgium?

3.3.2 Study II

→ Is a more severe *cftr* mutation class associated with worse psychological well-being in adults with CF? Could this expected association also be predicted that the effect of mutation class on psychological wellbeing is mediated by medical status?

→ Does physical exercise have an association with psychological well-being in adults with CF? And is the expected association mediated by medical status?

3.3.3 Study III

→ Are levels of anxiety and depression affected by previous levels and development in somatic parameters?

→Do levels of anxiety and depression have prospective effects on subsequent development in clinical somatic parameters?

3.3.4 Study IV

→ How do Swedish 'middle-aged' CF-patients' experience their intensive daily multifactorial symptomatic treatment regimen?

4 METHODS

An overview of the design, inclusion criteria and patient characteristics of the studies are given in table 1.

Table 1: Characteristics of the four studies in the thesis.

	Study I	Study II	Study III	Study IV
Design	Cross-sectional	Cross-sectional	Longitudinal	Qualitative
Inclusion criteria	+18 years, confirmed diagnosis of CF, nontransplanted	+18 years, confirmed diagnosis of CF, known *cftr* mutation class, nontransplanted	+18 years, confirmed diagnosis of CF, known *cftr* mutation class, nontransplanted	+30 years, homo-/heterozygous for mutation class I and/or II, nontransplanted, Swedish language
Sample size	N = 129	N = 68	N = 68	N = 12
Gender	50 % women	46 % women	46 % women	58 % women
Age (years, range)	M=30.4 (SD 11.73), 18-70	M=33 (SD 11.1), 19-65	M=33 (SD 11.1), 19-65	*MD*=43, 32-55
Lung function, FEV_1 % pred.	M=73.3 (SD 27.3), 22-125	M=71.7 (SD 28.1), 20.6-123.3	M=71.7 (SD 28.1), 20.6-123.3	*MD*=46, 30-96
Data analysis	ANOVA Binary Logistic Regression analysis	Structural Equational Modelling	Latent Growth Modelling	Inductive Content Analysis

4.1 DESIGN

Studies I and II were cross-sectional studies. Study III had a longitudinal design and in Study IV used a qualitative approach/methodology.

4.2 STUDY SAMPLES

Study I was a multi-center study - the Swedish arm of TIDES (105) - and the participants were recruited from three of Sweden's' four Swedish CF centers: Stockholm, Gothenburg and Lund. The inclusion criteria were ≥18 years of age and a confirmed diagnosis of CF. Transplant recipients were excluded. Of the 249 individuals who fulfilled the inclusion criteria for Study I 129 agreed to participate in the study. In addition, data from similar published studies performed in the UK, Germany and Belgium as well as corresponding normative sample data, were included for comparisons with the Swedish CF sample.

Studies II and III used the same study sample. Participants were recruited from Stockholm CF-center. Inclusion criteria were ≥18 years of age, a confirmed diagnosis of CF and a known genotype. Individuals who had undergone transplants were excluded. Of 91 potential subjects 68 participated in the studies.

In Study IV the participants were recruited based on purposive sampling from Stockholm CF center. The inclusion criteria were adults, ≥30 years of age, solely attending Stockholm CF-center, and being homo-/heterozygous for class I and/or II *cftr* mutation. Transplant recipients were excluded. Individuals not able to communicate in Swedish or not living in Sweden were excluded. For this study 23 patients met the inclusion criteria, and 12 participated.

Participants in Studies I-III were recruited consecutively in connection with their routine outpatient clinical visit at their CF center during the period March 2008 – February 2009. In study IV participants were recruited from April to May 2018, and the interviews were conducted between May 21 and October 16 2018.

4.3 PROCEDURE

In Studies I-III individuals who met the inclusion criteria received information about the studies by a regular mail and were then contacted by phone with information and asked to participate. For those who agreed to participate a meeting with the CF center psychologist or social worker was scheduled in connection with a routine clinical visit to the CF center. During this meeting the participant completed the written informed consent and the questionnaires for the mental health outcome measures (further described in the Measurements section). For participants who displayed indications of elevated levels of psychological distress (i.e. anxiety and depression), the psychologist followed up/offered further psychological assessment. However, this follow up/assessment was not included in the studies.

In Studies II and III the mental health outcomes were analyzed in relation to somatic parameters in order to answer the research questions. The completion of the above-mentioned questionnaires was therefore followed by a medical check-up in which the somatic parameters lung function, Forced Expiratory Volume in one second of predicted value (FEV_1 % predicted) and Body Mass Index (BMI) were measured. Data were completed from the Swedish CF registry with the measures of the somatic parameters as indicators of level of chronic inflammation/infection; Immunoglobulin G (IgG), and physical capacity; Physical Working Capacity (PWC) based on the corresponding annual check-up. In Study II, the measures, FEV_1% predicted, BMI, IgG and PWC were together used as a proxy for "medical status". In Study III these parameters were used both as predictors of subsequent levels of anxiety and depression and as possible consequences of previous levels of anxiety and depression. In Study II, information about *cftr* mutation class was taken from the Swedish CF registry.

In Study III the measures FEV_1 % predicted, BMI, IgG and PWC were annually followed up on six occasions (annual check-ups). To explore whether anxiety and depression levels in 2008 had an association with previous development of the somatic status, the corresponding somatic measures were taken from the Swedish CF registry for the years between 2002 and 2007 as well.

In Study IV individuals who met the inclusion criteria were contacted by phone by the study coordinator at the CF center with information about the study and asked to participate. If they were interested in participating they received further information by regular mail and were contacted by the interviewer to schedule the interview. In the interview meeting the written study information was reviewed, and the participant completed the consent form before the interview started. The interviews were conducted by licensed two psychologists working in Swedish CF-care. The interviews were performed at a location chosen by the patient. Most of the participants preferred to be interviewed in connection with their clinical visit to their CF center. Four participants were interviewed at the CF center, and two participants choose to be interviewed at a location with no connection to the CF care. In-depth semi-structured in interviews were conducted, audio recorded and transcribed verbatim by a professional transcription service.

4.4 MEASUREMENTS

In the area of Mental health in CF has, as mentioned, anxiety and depression been in focus. However, the concept Mental health is, as described, broader defined and in the present project there is also an attempt to catch the aspect of wellbeing. To match the area of CF with regard to estimates of Mental health, and to conclude or exclude risk for impairment in mental health, prevalence and level of Anxiety and Depression was measured as a first step in Study I. In Study II we wanted to include the wellbeing aspect. A priority in the choice of measurements was that the instruments used should address the question of interest (as a whole or partly) in 1. a CF-population, or 2. a population with a somatic disease. This resulted in a decision to use a proxy for Psychological wellbeing (including measurements of anxiety and depression, and HRQoL, as a HRQoL measurement should reflect the "individual' s subjective evaluation of her functioning and well-being") (106). In Study III Anxiety and Depression were tested as predictors for the development in somatic parameters. In Study IV patient experiences were explored.

Anxiety and Depression

In Studies I-III anxiety and depression were measured using the Swedish, validated version (107) of the Hospital Anxiety and Depression Scale, HADS (108) a well-validated (109) screening tool with good psychometric characteristics developed to identify cases of anxiety and depression in somatic populations. The questionnaire has two subscales, anxiety and depression, and consists of 14 items graded from 0 to 3. Anxiety and depression scores are obtained by summing the scores for each subscale, yielding values of 0 to 21. Each subscale has three ranges: 0-7 (non-cases), 8-10 (mild-moderate anxiety or depression) and 11-21

(moderate-severe anxiety or depression). The cut off-scores are defined on the basis of clinical psychiatric ranges for anxiety and depressive disorders.

HADS data were used in Study I and Study III. In Study II HADS was used together with CFQ-R as a proxy for "psychological wellbeing".

Health related quality of life in CF

Cystic Fibrosis Questionnaire-Revised (CFQ-R) (106) was originally developed in the United States. It is well-validated and widely used and has been translated into at least 34 languages (110). In Study II, HRQoL was measured using the Swedish translation (111) of the teen/adult version of CFQ-R. The instrument consists of 50 items across 12 domains reflecting different aspects of health-related quality of life in CF. Reply choices generally include ratings of frequency and difficulty on a scale graded from 1 to 4. Some items have more pronounced response alternatives: for example, "How do you assess your health right now?," with answers ranging from 1 = excellent to 4 = poor"). Scores are standardized to a range of 0 to 100, with higher scores indicating better HRQoL. Questions concerning demographic factors (age, sex, marital status, educational level, and work/school situation) are also included. The questionnaire has shown robust psychometric properties (110).

Psychological wellbeing

In Study II a proxy of Psychological wellbeing was used as an outcome measure. Because associations have been found previously between HRQoL and anxiety and depression respectively among adult CF patients (67, 74) the measurements considered most relevant to reflect a proxy of psychological wellbeing in the present population was the HADS together with the HRQoL measurement CFQ-R.

cftr mutation class

Information about the participants' *cftr* gene mutation class was retrieved from the Swedish National CF-registry, and used to study the effects/impact of *cftr* mutation class on psychological wellbeing in Study II.

Study II examined the effects of physical exercise on psychological wellbeing using self-reported hours per week of physical exercise as the measurement. At the annual check-ups at Swedish CF-centers the physiotherapists collect the patients' self-reported amount of physical exercise in hours per week. The physiotherapists' protocol defines physical exercise as "planned exercise aimed to maintain/improve mobility strength, condition with a duration of > 30 min for adults." This information is also stored in the Swedish CF registry, from which it was taken for study II.

Somatic status

In Study II a latent variable for medical status was created using the somatic measures Lung Function, Physical Working Capacity, Body Mass Index and Immunoglobulin G. These

measures were used since they reflect clinical key aspects of medical status in CF; lung function, physical capacity, nutritional status, and chronic inflammation/infection. Data were retrieved from the CF National Registry and from patient records (described in the Procedure section).

In Study III these measures were used as separate variables.

Lung Function, FEV_1 % predicted

In Studies II and III lung function test was performed by dynamic spirometry. From measured forced expiratory volume in one second (FEV1) in litres, percentage of predicted values (FEV1%) were calculated using Solymar and Hedenström reference equations for patients < 19 and ≥ 19 years, respectively (112-114). The lung function test was performed according to European Respiratory Society (ERS)/American Thoracic Society (ATS) recommendations (115).

Body Mass Index (BMI)

In Studies II and III the BMI was used as a measure of nutritional status. BMI was calculated with the formula: BMI = Weight (kg)/Height $(m)^2$

Physical Working Capacity (PWC)

In Studies II and III the participants physical capacity (watt/kilo) was measured with a cycle ergometer test for exercise testing performed on an electrically braked bicycle ergometer. The tests were performed at the Department of Clinical Physiology at Karolinska University Hospital Huddinge.

Immunoglobulin G (IgG)

In Studies II and III Immunoglobulin G was used as a measurement of chronic inflammation/infection and was analyzed by standard methods of protein electrophoresis at the Karolinska University Hospital Huddinge clinical laboratories.

Data gathered through semi structured in depth interviews

Study IV used a qualitative approach and data were gathered through in-depth semi structured interviews. A semi-structured interview guide (Appendix 1) with open-ended questions was used together with follow up-questions to stimulate detailed narratives of the participants' experiences. The interviews were digitally recorded and lasted between 25 and 59 minutes.

4.5 DATA ANALYSIS

4.5.1 Study I

To compare the Swedish CF sample data with already published data from the different CF and general populations, a dataset was simulated with the same characteristics (*N*, *M*, *SD* and

frequencies) (Table 2) as the present Swedish CF population as well as the other CF and general populations included in the study.

Table 2. Descriptive statistics for the present Swedish CF population as well as other CF and general populations.

		Age		HADS_A		HADS_D	
Population	N	*M*	Range	*M (SD)*	≥ 8 (%)	*M (SD)*	≥ 8 (%)
CF, Sweden (present)	129	30.4	18-70	5.5 (3.7)	27	3.0 (2.9)	9
General, Sweden (107)	624	44.0	30-59	4.6 (3.7)	20	4.0 (3.5)	15
General, Sweden (116)[b]	176	-	20-23	5.5 (4.0)	28.1[a]	3.1 (3.0)	9.5[a]
CF, UK (74)	121	30.0	18-70	6.1 (3.8)	33	3.6 (3.3)	16
CF, UK (73)	1779	-	≥ 18	6.1 (4.1)	34	3.4 (3.3)	13
General, UK (117)	1792	41.5	18-91	6.1 (3.8)	33	3.7 (3.1)	11
CF, Germany (63)[b]	343	-	21-50	4.9 (3.5)	22	3.2 (3.3)	12
General, Germany (118)	4410	50.3	≥ 18	4.7 (3.5)	21	4.7 (3.9)	24
CF, Belgium (67)	57	26.7	-	5.6 (3.9)	30	3.5 (3.6)	13
General, Netherlands (119)	199	39.9	18-65	5.1 (3.6)	24.4[a]	3.4 (3.3)	11.9[a]

[a] Not presented in the article, predicted from the mean value.
[b] Excluding the youngest age category

In order to analyze whether there were any differences between CF patients and the general population in the different countries with regard to levels of anxiety and depression two separate three-way ANOVAs with Sex, Country, and Group (CF-patient/general population) as independent variables, and with either HADS anxiety or HADS depression as the dependent variable, were conducted. Binary logistic regression was used in order to analyze effects on the odds of having an elevated score (≥ 8) for anxiety or depression. Effects of age on HADS anxiety and depression, as well as the effects of anxiety and depression on each other, were analyzed with ordinary linear regression.

4.5.2 Study II

Study II used Structural Equation Modeling (SEM) to fit two different models to data. In the first model the associations between the manifest variable "cftr mutation class" and the latent variables "psychological wellbeing" (consisting of the observed indicators HADS and CFQ-R scores) and "medical status" (consisting of the observed indicators FEV_1 % predicted, IgG, BMI, PWC) were analyzed (fig 4). In the second model we analyzed the associations between the manifest variable "physical exercise" and the latent variables "psychological wellbeing" and "medical status" (fig 6).

4.5.3 Study III

Study III analyzed the effects of the development in the outcomes FEV_1% predicted, BMI, PWC and IgG using Latent Growth Modeling. In the present Latent Growth Model, the

longitudinal observations of the medical parameters FEV_1 % predicted, BMI, PWC and IgG, respectively, were regressed on a latent intercept and a latent slope. The intercept and the slope growth factors were, in their turn, regressed on the variables anxiety, depression and their interaction to analyze whether these had any association with the outcomes at baseline (= intercept) or the longitudinal development of the outcomes (= slope).

4.5.4 Study IV

The interviews were audio-recorded on an MP3 device and transcribed verbatim by a professional transcription service. The transcribed interviews were the units of analysis. In Study IV inductive content analysis (120) was chosen in order to answer the research question and to obtain both a description of *what* experiences the patients' have of coping with the treatment regimen, and an understanding of *how* it is and what it means to have these experiences. Thus, both manifest and latent content analysis were conducted (120). The interviews transcribed into text documents were the units of analysis. The software NVivo 12 was used in the analysis.

Author LBE analyzed the text from the analyses and questions and uncertainties during the analysis were frequently discussed with ML, skilled in qualitative analysis. ML also reviewed the meaning units, codes, categories, subthemes and themes during the whole process to address trustworthiness of the analysis. The subthemes and themes were refined several times during the process. The authors LH, BM and KS reviewed the themes and subthemes, based on their different competences, and the results were further refined from their reflections.

5 RESULTS

5.1 STUDY I

The participating Swedish CF-centers recruited 52 % of the potential participants – 72% in Stockholm, 53 % in Gothenburg and 21 % in Lund; N = 129, Mean age: 30.4 (SD 11.73, range 18-70), 50 % women; Mean FEV1 % predicted: 73.3 (SD 27.3, range 22-125).

Binary logistic regression analysis showed no elevated risk for depression in the CF patients compared to the general population in any of the present countries.

ANOVA showed that Swedish adults with CF reported a marginally higher degree of anxiety than the Swedish general population $F(1, 927) = 4.56$, $p = .033$, $\eta^2 = .005$. This effect was not seen in any of the other countries (all *p*s > .19) included in the comparisons. However, this finding did not remain significant in the logistic regression analysis.

The marginally higher level of anxiety in the Swedish CF sample was limited to the women; the women with CF reported a slightly higher degree of anxiety than did women in the Swedish general population $F(1, 512) = 16.17$, $p = .007$, $\eta^2 = .014$. This effect was not found among the Swedish men $F(1, 413) = 0.18$, $p = .676$, $\eta^2 < .001$.

Also the CF patients reported lower degree of depression than the general population in Sweden, $F(1, 927) = 5.95$, $p = .015$, $\eta^2 = .006$, the UK, $F(1, 3686) = 13.25$, $p < .001$, $\eta^2 = .004$, and Germany, $F(1, 4751) = 45.32$, $p < .001$, $\eta^2 = .009$, but not in Belgium/Netherlands, $F(1, 254) = 0.039$, $p = .844$, $\eta^2 < .001$.

5.2 STUDY II

The study recruited 75 % of the potential participants; N = 68; 46 % women; Mean age: 33 years (SD 11.1, range 19-65), Mean FEV_1 % predicted: 71.7 (SD 28.1, range 20.6 – 123.3).

For outcomes reflecting aspects of psychological well-being the *cftr* mutation class × age interaction effect indicated that a psychological disadvantage tended to increase more with age among those having the more severe cftr mutation classes I and II; a substantial portion of this effect, >65 percent, was mediated via medical status. This means that the increase in the psychological disadvantage of homozygosity, or compound heterozygosity, for mutation classes I and II as patients get older is largely accounted for by a parallel increase in the medical disadvantages of homozygosity, or compound heterozygosity, for mutation classes I and II (fig. 5).

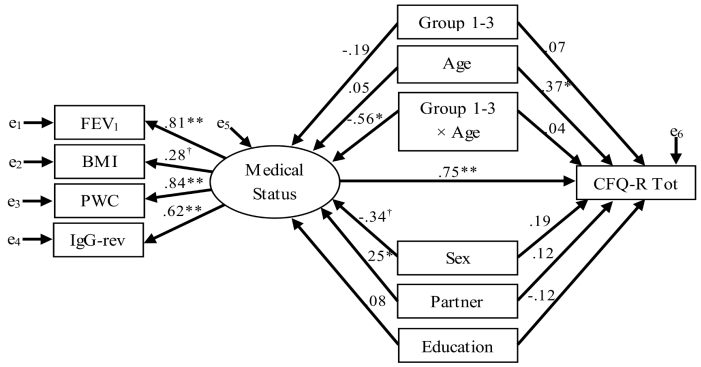

Fig. 4 Illustration of model 1, with CFQ-R total score as outcome. The manifest (= observed) variables FEV_1% pred, BMI, PWC, and lgG (reversed) were used as indicators of the latent variable medical status, and this latent variable is included as a mediator mediating the effects of the predictors group 1-3, age, and the group 1-3 × age interaction effect on CFQ-R total score. The effects are adjusted for the effects of sex, having a spouse/domestic partner or not, and level of education. The parameter values are standardized regression coefficients. † $p < .10$, * $p < .05$, ** $p < .001$

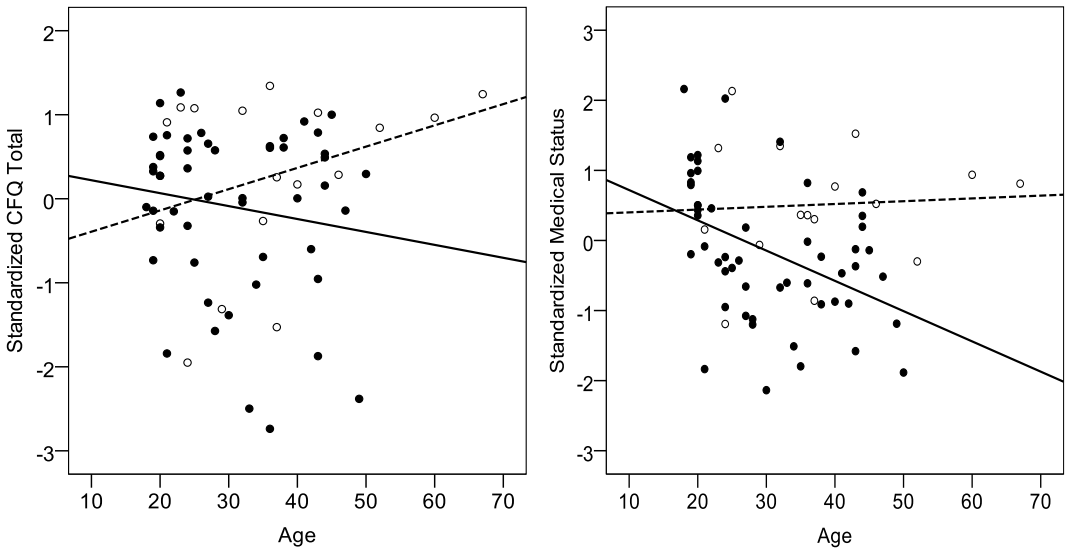

Fig. 5 The association between age and CFQ-R total score (left) and medical status (standardized to mean zero and standard deviation one) (right) for patients homozygous, or compound heterozygous, for Class I and II (filled circles and solid lines) and those not having these mutation classes (open circles and dotted lines).

Physical exercise had a total positive effect on the variable psychological wellbeing, but >75 percent of the effect is mediated by medical status. For no subscale was the direct effect of exercise significant, and in most cases it was even slightly negative. This may indicate that there would be no advantage from physical exercise on psychological wellbeing if not accompanied by a positive effect on medical status.

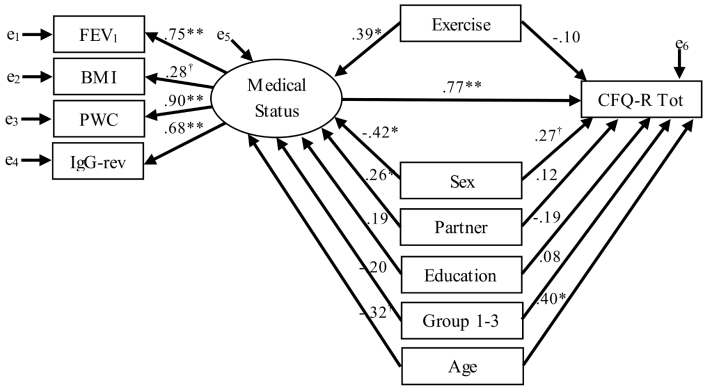

Fig. 6 Illustration of model 2, with CFQ-R total score as outcome. The manifest (= observed) variables FEV_1% pred, BMI, PWC, and lgG (reversed) are used as indicators of the latent variable medical status, and this latent variable is included as a mediator mediating the effect of the amount of physical exercise on CFQ-R total score. The effects are adjusted for the effects of sex, having a spouse/domestic partner or not, level of education, group 1-3, and age. The parameter values are standardized regression coefficients. † $p < .10$, * $p < .05$, ** $p < .001$

5.3 STUDY III

The study recruited 75% of potential participants; N = 68; 46 % women; Mean age: 33 years (SD 11.1, range 19-65), Mean FEV_1 % predicted: 71.7 (SD 28.1, range 20.6 – 123.3).

The effects of the intercept in 2002 and the slope for 2002-2007 on anxiety and depression in 2008 are presented in Table 1 and the effects of anxiety, depression, and their interaction on the intercept in 2008 and the slope for 2008-2014 in Table 2. Measures of model fit indicate quite good fit of the models, especially for FEV_1 % predicted. This good fit indicates that the outcomes are strongly associated with time.

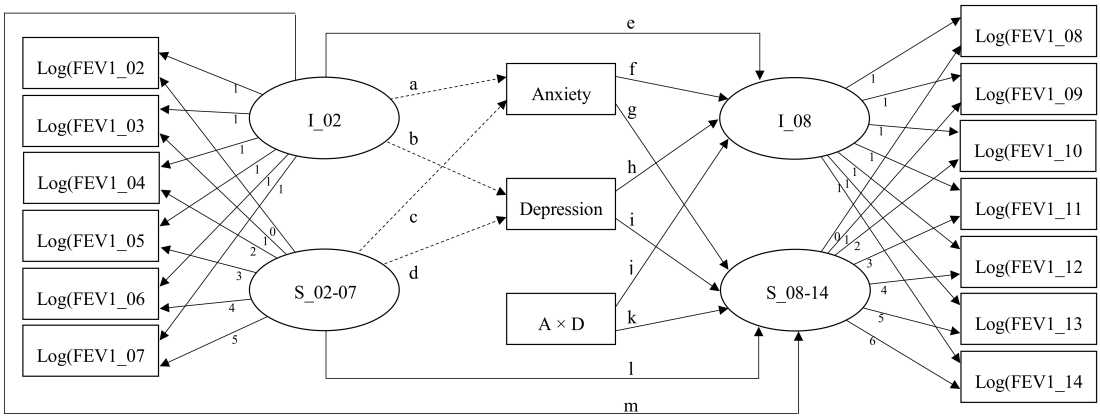

Fig 7: Illustration of the conducted Latent Growth Models were the natural logarithm of FEV1 is regressed on a latent intercept (I = predicted log(FEV_1% pred) at baseline) and a latent slope (S = predicted change in the log(FEV_1% pred) per year) for the two time periods 2002-2007 and 2008-2014. The intercept in 2008 and the slope for 2008-2014 are regressed on level of anxiety, depression, and their interaction. In a separate analysis, due to convergence problems, level of anxiety and depression were regressed on the intercept in 2002 and the slope for 2002-2007. Values for parameters a-d are presented in Table 3 and for parameters e-m in Table 4.

Table 3. Effects of the intercept in 2002 and the slope for 2002-2007 on level of anxiety and depression in 2008. Letters in parentheses correspond to parameters in Fig. 7 Model fit presented at the bottom.

Effect	FEV_1%	IgG	BMI	PWC
On Anxiety				
Int. 02 (a)	-0.007	-0.006	0.003	0.017
Slope 02-07 (c)	-4.280	-3.137	-2.018	-6.122
On Depression				
Int. 02 (b)	-0.030	-0.015	0.006	0.030
Slope 02-07 (d)	-16.257†	-10.236*	-5.117	-11.789
Model fit				
Chi sqr	31.9[a]	47.2[a]	56.1[a]	47.2[a]
RMSEA	0.058	0.110	0.130	0.109
CFI	0.991	0.961	0.934	0.970
TLI	0.991	0.958	0.929	0.967

* $p < .05$, † $p < .10$, [a] $DF = 26$

Table 4. Effects of anxiety, depression, and their interaction on the intercept in 2008 and the slope for 2008-2014. Letters in parentheses correspond to parameters in Fig. 7 Model fit presented at the bottom.

Effect	FEV_1%	IgG	BMI	PWC
On Intercept 08				
Int. 02 (e)	1.248*	0.814*	1.189*	0.810*
Anx (f)	0.021	-0.004	-0.004	0.002
Dep (h)	-0.010	-0.014	-0.034†	-0.022†
A × D (j)	-0.005	-0.022	-0.001	0.000
On Slope 08-14				
Anx (g)	-0.014	-0.008*	0.003	-0.001
Dep (i)	0.003	0.006	0.002	0.002
A × D (k)	-0.009*	0.001	0.004	0.002
Slope 02-07 (l)	-0.073	0.839	-0.443	0.715*
Int. 02 (m)	0.018	0.017	0.073	0.009
Model fit				
Chi sqr	205[a]	227[a]	275[a]	224[a]
RMSEA	0.112	0.124	0.147	0.122
CFI	0.944	0.913	0.872	0.927
TLI	0.941	0.909	0.865	0.923

* $p < .05$, † $p < .10$, [a] $DF = 111$

Anxiety at baseline, 2008 showed a prospective association with a worse development in lung function, FEV_1 % predicted, 2008-2014, especially when anxiety is combined with some level of depression – as indicated by a significant anxiety × depression interaction effect on the development in FEV_1 % predicted (Table 4). However, this finding might be overly influenced by two participants as can be seen in Fig. 8. Anxiety had no association with past and present levels and developments in any of the outcomes. Furthermore, the higher the degree of anxiety in 2008 the more IgG tended to decrease between 2008-2014.

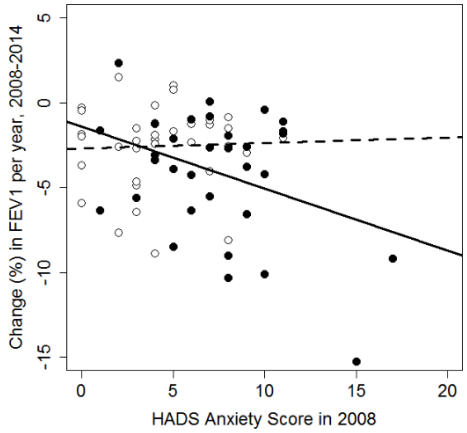

Fig 8: The association between anxiety, measured in 2008, and the development in lung function between 2008 and 2014, separately for those with no depression (≤ 2 on HADS-D, open circles and dotted line) and some depression (≥ 3, filled circles and solid line).

Depression, on the other hand, had no prospective associations with the development in the outcomes between 2008 and 2014. However, the level of depression in 2008 had some degree of association with the development in FEV_1 % predicted and IgG between 2002 and 2007 and with predicted BMI and PWC in at baseline, 2008.

5.4 STUDY IV

The study recruited 52% of potential participants; N = 12; 58 % women; Age: *MD* 33 years, range: 32-55, FEV_1 % predicted: *MD*=46, range: 30-96.

Three themes emerged from the analysis comprising a total of nine subthemes:

"*Priorities and management of health – a life condition", "Aspiration for and a possibility of a "normal life"*, and "*The CF center as a partner in the life condition*" (Fig. 9).

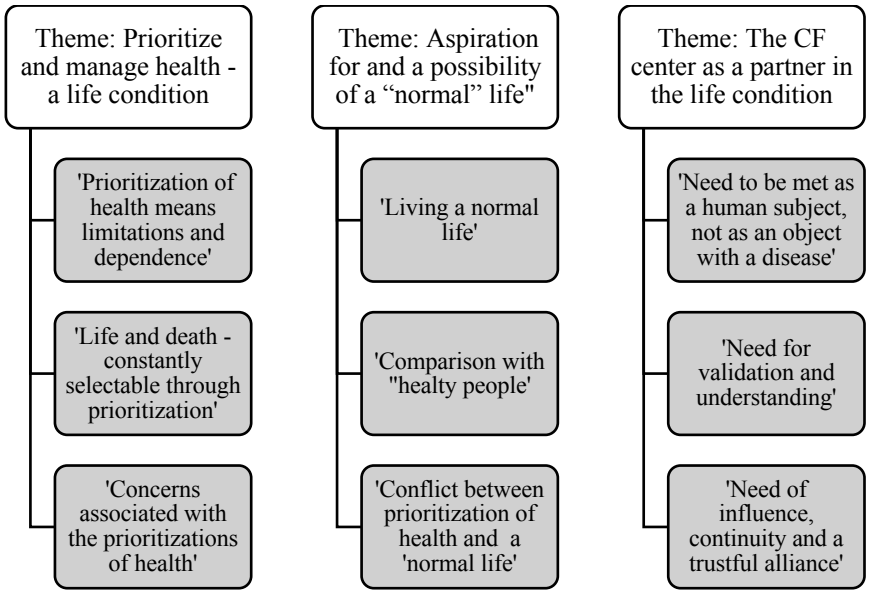

Fig. 9 The three themes and their subthemes that emerged from the analysis.

Theme: Prioritize and manage health – a life condition

This theme deals with the participants' experiences of the CF treatment regimen as a demanding part of life constantly present in different forms, foremost of which is the daily self-care, which has a substantial impact on their lives. This theme had three subthemes reflecting different aspects of the life condition:

"Prioritization of health means limitations and dependence": The prioritization of health management means that they always are limited in their choices, daily life and spontaneity. They also perceived a dependency of others, to maintain stable self-care routines. Also an ongoing attention and scanning of their own somatic health was also perceived as limiting.

"Life and death - constantly selectable through prioritization": There was a consciousness that without treatment and regular self-care, the life would be shorter, especially in cases of more progressed disease. The fear of the disease and death were also perceived as a

motivating factor to self-care. Deterioration of health despite maximized treatment was perceived as very stressful and raised hopelessness and existential issues of life and death. A strong desire to live as long as possible was expressed as a motivation to self-care.

"Concerns associated with the prioritizations of health": Experiences of worry, anxiety, anger, frustration and bad conscience associated to the prioritizations of health was described. There were also anger and frustration associated with the self-care, particularly in cases of more progressed disease. Experiences of bad conscience and guilt associated with the self-care was consistently described. Experiences of not having succeeded in establishing a sustainable long-term approach to the self-care were described as very stressful.

Theme; Aspiration for and a possibility of a "normal life"

This theme reflects the participants' relationship to a life they called a 'normal life' or described as a life 'healthy' or 'all other' people live. This life was seen as possible to achieve, or to strive for. The theme had three sub-themes.

"Living a normal life": Focus on living 'normally' had, for some, been a helpful approach both physically and mentally as long as the disease was under control. In some cases, a perceived pressure to live normally was as stressful and raised feelings of worthlessness if not managed. In cases of more progressed disease living a normal life was perceived as costly in terms of time and energy that had to be spent on health management. Trying to live a 'normal life' through denial of the disease to protect both oneself and other people was also described; a 'normal life' was lived but the self-care was neglected.

"Comparison with "healthy people": To compare oneself with "healthy people", especially in descriptions of self-care in the form of for instance going to the gym could be perceived as stressful. Conversely, in some cases participation in sports/exercise with healthy people had given self-confidence and a sense of being like everyone else.

"Conflict between prioritization of health and a 'normal life": The participants consistently described contradictions between working and prioritizing health, which resulted in increased stress. Another conflict area was combining parenting with the prioritization of health, especially when having small children. These conflicts resulted in stress and bad conscience.

Theme: The CF center as a partner in the life condition

This theme reflected the participants relationship with the CF center as a partner in the life condition rather than an ordinary health care unit. Central needs for the participants in the interaction with the CF center were represented in three sub-themes:

"Need to be met as a human subject, not as an object with a disease"; This was perceived when the healthcare staff had a listening approach and an ability to balance recommendations based on the individual's current situation and functioning. Continuous long-term support in finding self-care plans sustainable in everyday life was very important. When the need of

being met as a human subject was not fulfilled additional stress and bad conscience was experienced.

"Need for validation and understanding": with regard to the practical, psychological and existential demanding aspects of CF. There was also a need of that the health care staff has to consider that CF naturally generates fear, stress and frustration which affects the behavior and in the long run the personality of the person with the disease.

"Need of influence, continuity and a trustful alliance": The partnership with the CF center should be based on continuity, influence and trustful treatment alliance. This was obtained through regular contacts with healthcare staff based on honesty and clarity about the health status, and ongoing discussions with regard to health management, where participants could use their experience and knowledge of CF.

6 ETHICAL CONSIDERATIONS

Investigating psychological symptoms in people must always be made in a professional and sensitive way, and the aim must be clearly explained to each participant.

CF patients suffer from a life-shortening disease, and posing questions about psychological issues to people living under these conditions is a sensitive matter. Questionnaires and interviews were used, and some people may have felt uncomfortable or stressed by the questions or their results. For example, some questions in the questionnaires explicitly target issues such as self-harm/suicide, the impact of symptoms, impact on social life, etc., and may have been psychologically painful to answer. Furthermore, such studies may include people who are in very poor health, and this raises the issue of whether it is ethically sound to assess psychological status and quality of life in such participants.

In this project we handled these ethical considerations by having licensed psychologists administer and assess the results of the questionnaires. Licensed psychologists also conducted the interviews, as they are professionally trained in both interview techniques and in handling sensitive information. Furthermore, a psychologist followed up with participants who reported elevated scores for psychological symptoms or poor quality of life and offered further assessment and treatment. All participants were informed of the possibility of contacting the psychologist if they had any further concerns or questions regarding their participation.

Another ethical concern was that the psychologist performing the project also worked as a clinician at the CF clinic. Through their role in data collection, this psychologist has access to information about participants who may later be their patients. The opposite is also an ethical concern: patients who had previously been helped by the researchers may have felt forced to participate in order to please them. Earlier clinical contact with the researchers may also have affected their answers on the questionnaires. This issue of the researchers' double role was especially delicate in the interview study. We therefore choose to have two psychologists from the CF center conduct the interviews. Thus, the participants were interviewed by a researcher with whom they had no prior treatment relationship.

CF centers are research intensive, and because patients visit them regularly from the day of diagnosis (usually in early childhood) until they die, they are asked to participate in different studies on multiple occasions. It is well known that treatment burden and symptom burden are high for CF patients. A final ethical question raised concerns the total "research burden" on patients. If future projects focus on the psychological aspects of CF, this might increase the experienced total burden of the disease, since it greatly affects patients' personal integrity and privacy. However, patients benefit in the long run from participating in research projects through the development of improved treatment and management of the disease and better health, prognoses, and survival.

The Central Ethical Review Board, Stockholm, approved the studies, ethical permission nr 2007/1266-31 (Study I-III) and nr 2016/2425-31 (Study IV). Due to smaller changes in the

recruitment procedure, the board was informed about this by email and regular mail, nr 2018/2469-32. The participants gave their written consent to participate prior to the studies.

7 GENERAL DISCUSSION

The overall objective of this thesis was to investigate mental health among adults with CF, and to explore their experiences with the CF treatment regimen used in Sweden and thereby increase the knowledge about how the multiprofessional CF care team can facilitate and support adult CF patients in maintaining mental health.

7.1 SUMMARY OF THE MAIN FINDINGS

Study I found that there was no elevated risk for anxiety or depression in either the Swedish adult CF population or adult CF populations in the three other European countries used in the comparisons. In the Swedish CF sample women reported higher levels of anxiety than women in the Swedish general population, but no difference was seen among the men.

Study II showed that adults with more severe CF mutations tended to become susceptible to poor psychological wellbeing with older age. However, this effect is indirect and to large proportion mediated by medical status. There is no direct effect of severity of mutation class on psychological wellbeing; instead, disease progression seems to be more pronounced for those who have severe mutations, which in turn can have an effect on psychological wellbeing. In addition, among the adults with CF, those who engage in high amounts of physical exercise maintain their psychological wellbeing only so long as they also maintain their somatic health status.

Study III showed that anxiety, especially when combined with some level of depression, can serve as a predictor of a steeper decline in lung function over time, despite there is no elevated risk for anxiety and depression in the Swedish adults with CF as showed in the cross-sectional Study I. Depression had no prospective association on development in lung function. However, it did have an association with current lung function and past development of lung function.

Study IV found that the experiences of the treatment regimen were reflected in three themes: *prioritize and manage health—a life condition, aspiration for and the possibility of a normal life*, and *the CF center as a "partner in the life condition."*

The theme "*prioritize and manage health – a life condition*" reflected that the adults with CF experiences of the treatment regimen as a demanding part of life constantly present in different forms, foremost of which is the daily self-care, which has a substantial impact on their lives.

The theme "aspiration for and the possibility of a normal life" showed *the* patients'' relationship to a life they called a 'normal life' or described as a life 'healthy' or 'all other' people live. This life was seen as possible to achieve, or to strive for.

"The CF center as a "partner in the life condition" was a theme describing the patients' relationship with the CF center as a partner in the life condition rather than an ordinary health

care unit, and highlighted central needs for the participants in the interaction with the CF center

7.2 INTERPRETATION OF THE MAIN FINDINGS

The results in Study I point to no elevated risk for anxiety or depression in either the Swedish adult CF population nor he adult CF populations in the three other European countries in the comparisons. This is contrary to conclusions of some other studies on the subject, which have claimed higher rates of and risk for anxiety and depression in CF patients (63, 69, 72, 77). Our results are also contrary to what is seen in other populations with chronic diseases (7). Our results are, however, in line with results from one study performed in the UK and one study from Belgium (67, 73). However, it should be noted that the countries included in our study are wealthy and providing public/universal health insurance systems, possibly eliminating stressors that may affect mental health. Furthermore, previous studies (121, 122) have shown differences across European countries with regard to availability of specialist CF care, and demography, health status and mortality in CF populations. Generalizing these results to other CF populations in other countries should therefore be made with caution.

The Belgian, German and the large British study included in our analyses, and also our Swedish CF sample data used the same protocol and measurement (HADS), as they were all part of the multicenter TIDES study. However, the analyses differ between the studies, and not all of them include general population data in the comparisons. This is one possible explanation for the differences in the conclusions from the studies.

In our Swedish sample, women with CF reported higher levels of anxiety than women in the general population, which contributed to marginally higher levels of anxiety among the Swedish CF-patients. As mentioned, the Swedish CF-population as a whole has a good health status and high survival rate (3), and these factors therefore cannot be possible explanations for the elevated anxiety level. Instead it might be explained by differences in treatment regimens. As described in the introduction, the Swedish treatment regimen in the 1980s added some key treatment components and strategies to the existing international CF treatment guidelines. These treatment components were, and still are, largely managed by patients in their daily lives, which might make the total treatment burden and responsibility more stressful and anxiety-provoking for Swedish CF patients. However, this does not explain why elevated anxiety only is seen in Swedish women. We should also note that anxiety levels among Swedish women with CF are lower than the cutoff score for mild anxiety. This question needs to be explored in greater depth.

The results from Study II add a new perspective to existing knowledge about the association of *cftr* gene mutation class and medical outcomes (22, 123). Among those with the more severe *cftr* mutation class there is an association between age and poor psychological wellbeing with a parallell deterioration of health. Our findings also indicate that adults with CF obtain a psychological benefit from physical exercise only as long as their somatic health

is maintained. When this is not the case, exercise has a slightly negative impact on psychological wellbeing. These findings together illustrate how adults with a more severe form of CF can enjoy relatively stable psychological wellbeing so long as their somatic health (medical status) is maintained.

Study III was the first longitudinal study to investigate the effects of both anxiety and depression on somatic status over time in adults with CF. In the cross-sectional Study I, no elevated risk of anxiety and/or depression was seen in adults with CF, but the outcomes from the longitudinal Study III indicate that anxiety in combination with some level of depression may predict a steeper decline in lung function. This finding is of interest, as it highlights a prospective association between a mental health variable and development of a somatic parameter - in this case, lung function. An earlier study have studied, and found, associations between depression only and lung function over time (78). However, our study does not allow us to explain our found association with any certainty. Perhaps it is due to the nature of anxiety as an emotion that serves to detect future potential danger (58). Anxiety may be triggered in patients experiencing signs of deteriorating health even before such deterioration can be measured, and it may serve to prepare the person to meet and tackle it. Another possible explanation is that anxiety may lead to avoidance of anxiety-provoking stimuli - in this case, contexts related to CF such as treatment. When adding to the panorama depressive symptoms such as feelings of hopelessness and loss of energy and depressive behaviors such as withdrawal from activity and avoidance, patients with this combination may have a diminished capacity for self-care and thus will hypothetically have a faster decline in lung function.

In study IV the sample is quite unique, adults who are now middle-aged and who were part of the first generation of patients treated according to the Swedish treatment regimen implemented in the 1980s. The results show how prioritization of the health management is a life condition and a matter of life or death for this group. To be physically active and to eat healthily are parts of WHO's health recommendations for all people (124). For people with CF, however, failure to follow specific lifestyle recommendations results in a deterioration of health. This leads to health-related anxiety and stress, especially when it comes to prioritizing health through self-care. Patients also describe hypervigilance with regard to somatic symptoms. However, compared with, for example, the somatically healthy population with anxiety (125), hypervigilance in the case of CF patients is adaptive insofar as it guides decisions with regard to health management. For the individuals dealing with CF, the prioritizing of health also means limitations and dependence. The life condition therefore also can cause stress, worry, anxiety, bad conscience, guilt, frustration, and sometimes feelings of hopelessness.

The results of Study IV also indicate that the patients have insight into the severity of the disease; the CF health care have through the self-care given them tools to achieve a longer and healthier life, and they hold great responsibility for their health and self-care. When coupled with the aspiration and possibility of living a normal life, a stressful and anxiety-

provoking conflict can emerge. This is in line with an earlier study concluding that adults with CF have a psychosocial burden while they try to live "normal lives" and at the same time have to adhere to the complex treatment regimen (55). This is especially true when patients confront deterioration in their health. Reactions of stress and anxiety should be seen as normal in this context and not pathological. They are natural correlates of the challenging life circumstances of living with CF, and the CF care should address such reactions in the regular clinical visits. In patients' eyes, the CF center is a partner in the life condition and not just a health care unit. When patients' central needs with regard to disease management and support are fulfilled by the center they feel met as "human subjects and not "objects with a disease". They get psychologically validated and understood with regard to the challenges of life circumstances for persons with CF, and they perceive that they have a trustful alliance based on continuity and influence, it really helps patients cope with their life condition.

7.3 OVERALL REFLECTIONS

Taken together, the results from these studies give a clearer and updated picture of the psychological aspects of CF in adults. The patient perspective that emerges from Study IV allows us to better understand the results of the remaining studies in the project. Study I shows that as a whole, adults with CF do not have an elevated prevalence of anxiety or depression. In Study IV, one of the themes—aspiration for and the possibility of a normal life— highlights the importance, possibility, and meaning of living a normal life in areas such as employment and relationships, despite the disease. Patients also mentioned this "normal life" as a factor that contributed to their overall psychological wellbeing, maybe reflecting the non-risk of anxiety and depression. However, patients found points of conflict between achieving a normal life and prioritizing their health, which creates stress. It is possible that the slightly elevated anxiety levels found in Swedish women with CF reflect this stressful conflict that emerges as an effect of the burden of being responsible for one's own treatment. However, as this elevated level of anxiety is seen only in the women this is a very cautious interpretation.

Study II found that psychological wellbeing tended to decrease with age, in parallel with deterioration of health, among those individuals with more severe mutation classes. Study IV's interviews of middle-aged patients with more severe mutation classes uncovered descriptions of their experiences of deteriorating health that align with this finding from Study II. When the disease progresses and the self-care and treatment burden increases, the interview subjects in Study IV, through the subtheme *concerns associated with the prioritization of health*, expressed how they felt stressed and anxious and experienced feelings of hopelessness. This aligns with the results of Study II. Physical exercise had an effect on psychological wellbeing only as long as somatic health was maintained or improved. Where this was not the case, the effect of physical exercise on psychological wellbeing was negative, although not significantly so. If we generalize this finding for physical exercise to other self-care efforts, we can link this result to the subtheme *concerns associated with the prioritization of health* in Study IV.

The results of Study III might also be further understood in light of Study IV. However, this requires a very cautious interpretation. In Study III, anxiety together with depression was seen to have a negative prospective association with changes in lung function. Perhaps anxiety may be an expression of patients' sense of personal responsibility, the easily-triggered guilt of not doing enough that was described in Study IV. From a psychological perspective, such a situation may lead to avoidance. When combined with feelings of hopelessness and resignation described in Study IV, and that in Study III may indicate some level of depression, that could potentially have a negative impact on self-care efforts, and in the long run thus a steeper decline in lung function.

From a health psychological perspective, the results of this thesis illustrate the stress and adjustment in people with chronic illnesses and give us a deeper understanding of how this can manifest in people with CF. Despite the possibilities of achieving a normal life, the disease and its treatment are stressors on individuals, and as such they have a psychological impact. In the light of health psychology, stress reactions arising from the life circumstances of CF are a signal to the individual to adjust to the stressful condition: to address the stressful situation and choose life and health by performing the actions required to manage one's health. An alternative is to avoid the stressor, and thus avoiding health management actions, and in the long run causing faster deterioration and shortening one's lifespan. The results show that adjustment to stress by prioritizing health, and thus achieving relatively stable psychological wellbeing, is possible as long as somatic health can be controlled. However, the results also show that patients arrive at a point were further adjustment is not possible or cannot be achieved without great cost. In this situation, patients are at risk for worsening psychological well-being, and here the need for a well-functioning partnership with the CF care team is pronounced.

7.4 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS OF THE FINDINGS

Studies I–III used HADS scores as a measurement of anxiety and depression. In the planning stage, HADS was considered the most appropriate scale, especially as it was developed for use in populations suffering from somatic illnesses. However, HADS has been found not being sufficiently sensitive in the detection of depression (126), and also in CF populations (127). HADS is also a screening instrument and not a diagnostic tool. In the present project, as well as in the literature on anxiety and depression in CF patients, it would be more appropriate to use terminology other than *anxiety* and *depression* with regard to HADS scores: for example, *indication of anxiety/depression*. It should also be noted that the HADS score is based on self-reported data, not on clinical diagnostic data.

In Study I, the representativeness of the sample with respect to the entire Swedish CF patient population was negatively affected by the very low response rate at one of the participating sites, and selection bias can therefore not be ruled out. The Swedish general population data were taken from two studies (107, 116) with different age ranges so as to better match the Swedish CF sample, and our comparisons may therefore have been affected by

methodological issues and potential changes in anxiety and depression prevalence over time. One of the studies also concluded that the reported scores differ depending on the method of data collection (116).

In one of the Swedish studies using HADS normative data (107), data were collected in one region in Sweden and may not be representative of the total Swedish population. Another limitation is the use of existing studies with HADS normative data instead of matched control subjects. Furthermore, the normative samples also differ from those of the corresponding CF populations with regard to their characteristics. For example, some of the general population data are older than the corresponding CF population data, and mean ages vary and are higher than in some of the CF populations used in this project. The Belgian CF-data were compared with normative data from a Dutch study (119), since the authors of the Belgian CF article (67) used that study as a reference for their general population data. However, we considered it necessary to include other European countries and their corresponding normative data as a comparison in order to put our Swedish results into context. This was especially important given the lack of comparisons with general population data in the TIDES study (69). It was also advantageous to include previously published studies in this study's comparisons, since given their formulation within the broader TIDES initiative the published studies, as well as our Swedish arm, had all used HADS as their measurement interest and employed similar study protocols.

In Study II the terminology and descriptions in existing analyses are somewhat unclear; the analyses showed that the proxy for psychological wellbeing did not have the expected associations. We performed the same analysis with the HADS and CFQ-R separately and found that CFQ-R - health-related quality of life - did have the expected associations. We continued to use the term *psychological wellbeing* in the paper, however, which is rather misleading, since the measurement assessed health-related quality of life. It would also have been better to more clearly describe the additional analyses and to describe the lack of significant interaction effects with regard to the HADS and the proxy for psychological wellbeing. It should have been stated that CFQ-R, together with HADS, does not seem to work as a proxy for psychological wellbeing. However, in the planning stage of the study it was considered appropriate (from the priorities with regard to the choice of measurement described in the measurement section) to use this proxy. Interestingly, in a very recent study associations have been found between positive 'mental health and wellbeing' and almost all the CFQ-R domains (90). Because the term *psychological wellbeing* is used in the published paper, it was retained for use in this thesis. The reader should, however, consider that when the term *psychological wellbeing* is used with regard to Study II, it should be understood as actually referring to the closely related term *health-related quality of life*.

The sample size and groups in Study II and III were small which negatively affect the power in the studies, and a cautious interpretation of the results is therefore required. However, they presented good representativeness of the present CF center. When studying rare diseases there are difficulties in general with regard to sample sizes and power. One solution should be

more multi center studies, but the single-center study design facilitated setting similar preconditions for all study participants with regard to, for example, treatment regimen. It might also be interesting to replicate these studies at larger CF centers or in countries with larger CF populations. For example, in Study III the anxiety×depression interaction effect was strongly influenced by a few participants in a subgroup of severely ill patients. This effect might be more pronounced in samples with a larger proportion of severely ill patients or in larger samples.

However, regardless of the CFQ-R subscale used in Study II, the effects found were very similar. This indicates that the results are quite stable. The participants completed the HADS and CFQ-R questionnaires in the presence of a psychologist or social worker and reported their estimated amount of physical exercise directly to a physiotherapist, which might have influenced their scores and estimations. Furthermore, in some cases the amount of physical exercise and certain of the somatic parameters were not measured at the same clinical visit as when the questionnaires were completed.

Because the parameters used in the latent variable *medical status* are central clinical measures of CF patients' somatic status, it would also have been more appropriate to call the latent variable *somatic status*. In this latent variable there is a low correlation between BMI and the three other manifest variables. BMI should therefore not properly have been included in the latent variable *medical status*. However, BMI was included because it is a key parameter used in the clinical assessments of the CF patients' somatic status.

To estimate the effects of anxiety and depression on clinical somatic status over time, anxiety and depression should ideally be measured annually, which was not done in Study III. It is therefore not possible to draw any robust conclusion from these results. However, it is an important finding worth further study.

In Study IV, all potential participants at the CF center - 23 patients were asked to participate, but 12 ultimately did. We therefore cannot rule out the possibility that the data are not sufficiently saturated. However, the sample is unique, as it consisted of approximately half the center's middle-aged CF patient population who had not received transplants and who possessed the more severe *cftr* mutation classes. Furthermore, the participants were recruited at one CF center only; we should therefore only cautiously generalize the results to other CF centers, especially in other countries with different treatment regimens and/or health status in the CF population. However, because Swedish CF centers have the same treatment regimen, the results could possibly be used to understand the needs of middle-aged patients also in other Swedish CF care centers. Some of the needs with regard to CF care that emerged in this study might be applicable in care settings for chronically ill people in general.

The interviews in Study IV were conducted by psychologists from the CF center; however, the specific interviewer did not have any previous clinical contact with the participants they interviewed. A majority of participants preferred to be interviewed in connection with their clinical visit. These close connections to the CF center might have influenced the information

that participants shared in the interviews, but we do not expect this had a negative impact on the quality of the interviews. The psychologists' knowledge of CF may also possibly have contributed to some bias in their understanding of the participants' responses. The interviews were conducted in Swedish and the results are therefore not inclusive of the perspective of patients speaking other languages i.e. are from other countries/cultures.

A strength in Study IV is the researchers'' different competences, and also their different relationships to/previous experience of the CF patient group, which ensure the trustworthiness (120) of the study. Two of the researchers have previous clinical experiences of the patient group (psychologist and medical doctor). The other three researchers have no earlier experiences of working with CF patients (psychologists and physiotherapist). There also was a further psychologist who conducted the majority of the interviews and was not involved in the analyses. This would also have minimized the risk for researcher bias.

7.5 CLINICAL IMPLICATIONS

The studies in this thesis together contribute to increased systematic knowledge about the mental health aspects of CF and the patient experiences of the CF treatment in the growing adult CF population. The participants in this thesis were, to a large extent, born at a time when Swedish people with CF got severely ill and died at young age, and CF patients in general were hospitalized for longer periods and were unable to have a job or go to school. Centralized care and multidisciplinary treatment has - together with progress in biomedical treatment options in different areas - improved the health status and life expectancy of the patient population. With the biopsychosocial model of health in mind, there are certain clinical implications in the area of psychology that emerge from the results of the this project. CF care in Sweden has made substantial progress in giving patients the tools to assume responsibility for their health and manage it through self-care, and it has also given patients support and the possibility of living a normal life. However, from a health psychological perspective, CF care should be more active in continuously supporting patients in their adjustment to the different phases of the disease trajectory, especially when in the later stages. CF care should also develop strategies based on health psychology to support the growing group of adult patients so they can cope in adaptive ways with the normal, but also painful, psychological reactions of stress and worry that self-care and disease can inflict. This patient group is new and will increase in the future, new *cftr*-modulating drugs will probably further improve health outcomes and CF care must adapt also to changing needs with regard to mental health in this patient group.

This project shows the importance of including patient perspectives in order to arrive at a balanced view of the questions of interest: that is, to not only study patients as objects with a disease, as was the methodology in Studies I–III, but also (as was done in Study IV) as subjects, as humans who have unique experiences of living with CF. This approach can be further used in improving the understanding of, and thus the way to address the adherence question in adult with CF. Study IV offers a deeper understanding and a broader perspective of the mental health aspects of CF in adults, and its clinical implications can thus go beyond

the existing care model. A multidisciplinary CF care approach provides appropriate care with regard to objectively measured outcomes. However, it is not clear, from a patient perspective, that it fulfills the needs of continuity, influence, and a trustful alliance highlighted in this project. The current form of CF care neither guarantees that patients are seen as human subjects nor that patients are psychologically validated or understood from their perceived situation or condition. Patients' descriptions of their needs with regard to the CF centers are in line with the person-centered care (PCC) model (128), which is now proposed by Swedish Association of local authorities and regions to become the current care model in Sweden (129). PCC emphasizes the partnership between patient and care provider, and the patients' viewpoint and narrated experiences of their condition and life situation is the center of care. Furthermore, the patient is actively involved in their care process and shares in decision-making and strategizing to ensure continuity of the care process. PCC could be applied in CF care, as it is especially suitable for the care of chronic illnesses and also has a potential to improve health outcomes, reduce patient stress, and increase patient satisfaction (128).

7.6 FUTURE PERSPECTIVES

As the development of CF treatment goes on and changes the health outcomes and conditions for the patient group an ongoing evaluation of mental health outcomes is suggested. Mental health screening, according to international guidelines, have been implemented in the Swedish CF-care in recent years, and updated studies of associations between psychological and somatic parameters can be conducted. However, research in the area of mental health in CF should in the future widen the perspective and include also the wellbeing aspects of mental health, which is highlighted also in a very recent study (90).

Including the patient perspective through parallel qualitative studies with quantitative ones to gain a broader and deeper knowledge of the questions of interest has in this project been shown to be necessary for a deeper understanding of the mental health aspects of being adult with CF. Introducing PCC and care strategies based on findings from this project would give opportunities to follow up studies exploring patient satisfaction, level of stress and mental health and patient experiences in the present patient group.

Future research in the area of mental in CF would probably benefit from having a clearer and more distinct theoretical framework, an umbrella that focuses on how biology, psychology, behavior and social factors influence a lifelong disease as CF. Although, the field of health psychology is still quite young, it has emerged to help changes in health in the population over all, by looking at behavioral patterns that underlie disease and death. This would be possible also in adult CF populations, and would probably give valuable knowledge to further develop. The CF care is organized in multiprofessional care teams and should out from the biopsychosocial model of health have good prerequisites to use a more pronounced health psychological approach for further improvements of health in the adult CF population.

8 CONCLUSIONS

The studies in this thesis have together contributed with increased knowledge and understanding about mental health aspects in adults with CF. As a whole group, there is no elevated risk for impairment in mental health with regard to anxiety and depression. However, women with CF should be seen as vulnerable for elevated anxiety. Furthermore, individuals with genetically more severe CF with age get tend to get vulnerable for poor psychological wellbeing, and also those who are performing a high amount of physical exercise without maintaining their somatic health. Over time anxiety, when combined with some level of depression, seems to give a steeper decline in lung function. These mental health aspects can be deeper understood from the perspective that prioritization of health is (literally) a life condition for adults with CF, and that the aspiration for and possibility for a 'normal life' can result in stressful conflicts, especially when health is deteriorating. In the coping with the life condition the CF-center is seen an important partner.

Clinical implications should focus on the individuals vulnerable for poorer psychological wellbeing and supporting adjustment to the different phases of the disease trajectory through a health psychological approach in the CF-care. The CF care should also benefit from including the patients' perspective to larger extent through PCC.

Future research in the area of mental health in CF should broaden the perspective and focus also on the wellbeing aspects, and would benefit from have a more clearly defined health psychological framework thus including the study of behavioral patterns that underlie disease development and health. The multiprofessional CF care should have prerequisites for such studies where psychological, social, behavioral and biological associations are studied.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Cystisk Fibros (CF) är en autosomalt recessivt ärftlig, livsförkortande sjukdom. Sjukdomen är medfödd, kroniskt progredierande och påverkar framför allt lungor och magtarmkanal. Den progressiva kroniska lungsjukdomen är den vanligaste orsaken till för tidig död. CF var länge en sjukdom där de drabbade dog i unga år. De senaste 40 åren har dock stora framsteg gjorts i behandling och strategisk vård vilket lett till en ökande andel vuxna med CF. I Sverige har CF-populationen som helhet jämfört med andra länder en god hälsostatus, låg dödlighet och en mycket hög andel vuxna. Det finns ännu inte någon bot för CF. Behandlingen, förebyggande och inriktad på symptom, är krävande och måste dagligen utföras av patienten själv. Då sjukdomen är progressiv blir behandlingen mer krävande ju äldre den drabbade blir och ju mer hälsan försämras. Vuxna med CF har således en betydande sjukdoms- och behandlingsbörda som medför stor inverkan på livet som helhet, vilket kan antas påverka det psykiska måendet. Då vuxna med CF är en ”ny” patientgrupp, finns inte så mycket kunskap om deras psykiska hälsa. En del studier, med olika utfall, har gjorts, mest med fokus på ångest och depression, dock varierar resultaten kraftigt. I Sverige har ingen undersökning gjorts vad gäller vuxna CF-patienters psykiska hälsa; ingen kan med säkerhet säga hur den gruppen mår.

Syfte: Att i fyra studier bland vuxna med CF undersöka psykisk hälsa och upplevelser av den svenska CF-behandlingen, för att öka kunskapen om hur den multiprofessionella CF-vården kan stödja och underlätta för vuxna med CF.

Metod och resultat: I *Studie 1* framkom ingen ökad risk för ångest och depression i gruppen genom analyser med binär logistisk regressionsanalys. *Studie II* visade genom struktur-ekvations modulering att de som har svårare former av CF med åldern, och parallell försämring av den fysiska hälsan, blir sårbara för sämre psykiskt välbefinnande. Likaså de som lägger mycket tid på behandling i form av fysisk träning (en grundbult i Svensk CF-behandling) utan att vidmakthålla sin fysiska hälsa. *Studie III* visade genom latent growth modelling att (trots att risken för ångest och depression inte är förhöjd) ångest, tillsammans med depression, över tid hade samband med en snabbare försämring av lungfunktionen. I *Studie IV* intervjuades personer över 30 år om deras upplevelser av CF-behandlingen. Genom induktiv innehållsanalys framkom att prioriteringen av hälsan (bokstavligen) är ett livsvillkor. De intervjuade uttalade en möjlighet och en strävan efter att leva ett ”normalt liv”, men med stor inverkan av livsvillkoret/ prioriteringen av hälsan. CF-centret upplevdes som en partner i livsvillkoret, snarare än som en vanlig vårdmottagning.

Slutsatser: Sammantaget kan skrivas att avhandlingen bidragit med ökad kunskap om svenska vuxna CF-patienters psykiska hälsa och upplevelser av CF-behandlingen. Som grupp har de ingen ökad risk för psykisk ohälsa i form av ångest och depression. De med svårare CF och högre ålder/försämrad hälsa, och de med ökad behandling/träning utan att bibehålla fysisk hälsa verkar däremot sårbara för sämre psykologiskt välbefinnande. Framtiden bör inriktas på att utveckla omhändertagandet av vuxna med CF genom personcentrerad vård samt genom att systematiskt uppmärksamma dem som kan vara sårbara för sämre psykiskt

mående. Då risken för ångest och depression är liten, bör också välbefinnande-aspekterna av psykisk hälsa undersökas. Den multiprofessionella CF-vården bör ha goda förutsättningar för fortsatta studier utifrån ett mer uttalat teoretiskt ramverk där samband mellan biologiska psykologiska, sociala och beteendemässiga faktorer studeras.

9 ACKNOWLEDGEMENTS

I want to express my deepest appreciation and respect to all of the participants who have taken their time to participate in the studies.

I would like to thank the Swedish Cystic Fibrosis Foundation and the Department of Medical Psychology at Karolinska University Hospital for their financial support through research grants.

I would also like to express my sincere gratitude and appreciation to:

First, my main supervisor, Professor Bo Melin, for your superb guidance and support throughout the whole process, as well as for generously sharing your immense knowledge in the field of psychology and academic research. I am grateful for your curiosity and engagement in my project in general, and in the CF patient group in particular. Your door has always been open and you have always been available to support me in a caring, generous manner. It has been so fun and inspiring to work with you.

My co-supervisor Dr. Kimmo Sorjonen, you have provided excellent training and patient supervision in the field of statistics and have given invaluable help in revising the manuscripts and the thesis. You have also been generous in your support in communicating the results from our studies and for your help with creating excellent figures and tables. I really appreciate your very special kind of humor.

My co-supervisor Professor Lena Hjelte for the medical expertise in all the studies comprising the project and for your engaging and enlightening discussions on CF, and also for your curiosity in the field of psychology. Your dedication to the field of CF over many decades has led to considerable contributions to people with CF in Sweden. In the first years of the project you were also the director of the Stockholm CF Center. I truly appreciate your support and enthusiasm during the start-up of my project while you held that role, and for the way you strategically prioritized time for research alongside the clinical duties of staff such as myself at the Stockholm CF Center. This ensured a stimulating work environment that also benefited our patients.

My co-supervisor Associate Professor Mari Lundberg who joined our team in the final year of the project. You have truly contributed to my development with your insightful comments and encouragement. Thank you for asking hard questions (and never giving the answers), and for your invaluable support and expert supervision during the qualitative research process. I am also very grateful for your engagement in my project as a whole, for supporting me in my overall learning process, and for your excellent revision of my thesis. It has been so inspiring and fun to work with you.

My mentor and former psychologist at Stockholm CF-center Agneta Bergsten Brucefors, for being positive, enthusiastic, and supportive from the very beginning of our collaboration. Thank you for sharing your experiences of working with adults with CF, for generously

introducing the project to me, and for letting me take over responsibility for it. I really appreciate your prioritization of being my mentor.

All my colleagues at the Division of Psychology in the Department of Clinical Neuroscience for giving me a social environment conducive to daily academic endeavors. I am grateful to the current and former heads of division, Pia Enebrink, Ata Ghaderi, Emely Holmes, Mats Olson, and Bo Melin, for creating and maintaining a welcoming, inclusive, and stimulating working environment. I am indebted to Paula Lagerfors for her administrative help and support. Thanks to Susanna Jernelöv, Lisa Thorell and Knut Sturidsson for giving me the opportunities to teaching at the psychology program – I really enjoyed it. I would like to thank my research colleagues, Anna Strandqvist, Anna Finnes, Johanna Enö Persson, Elin Frögeli, and Maria Helander. Elin and Maria, you have been lovely officemates over the years, and sharing office and spending time together with you has enriched my days. Special thanks to Jenny Wikström Alex and Agneta Herlitz.

The former and current heads of the Department of Medical Psychology at Karolinska University Hospital. Ylva Novak for introducing me to my main supervisor Bo Melin, Louise Lettholm and Peter Eriksson for being generally supportive, Agneta Julinder for showing interest in my research and for her work with strengthening the collaboration between the Department of Medical Psychology and the Division of Psychology at Karolinska Institutet, Rickard Wicksell and Linda Holmström for continuing to put clinical psychological research on the agenda, and Linda Holmström, Mike Kemani and Riika Lovio for showing interest in my research.

My present psychologist colleague at Stockholm CF Center, Carolina Laine, it is really inspiring and fun to work with you; you are a really professional psychologist and a very good friend. You also contributed a great deal of work and was a fantastic help with the interviews in Study IV, and you remained enthusiastic and positive throughout the interview period.

Birgitta Sjöberg, my former psychologist colleague at Stockholm CF-center, for good friendship, stimulated discussions in the field of psychology, and for many fun times.

Anna Hollander at Stockholm CF-center was an invaluable help in contacting and informing all the potential participants in Study IV.

Isabelle de Monestrol, head of the Department of Cystic Fibrosis, for always being encouraging and interested in how my project was progressing, and for continuing to prioritize time for developmental work at the CF Center. You were also an enjoyable companion during our trip to the NACF Conference in Salt Lake City.

All my colleagues at the Stockholm CF-center - a fantastic team who make the center a great place to work; I enjoy all our celebrations, (Lucia, birthdays, summer etc), CF conference trips and the daily life at the clinic. Special thanks to Anna Hedborg, Anna Törnberg, Anna

Hollander, Sten Salomonsson, Cecilia Rodriguez Hortal, Kristina Nilsson, Ferenc Karpati, and Berit Widén.

Markus Eriksson, Johan Moberg and Markus Hemmingsson at A FEW AB for generously letting me use your office, for nice lunches and great company.

To my friends, however, I don't think you know anything about my work with this thesis, for enriching my life so much. Special thanks to Johanna Åström.

My mother- and father-in-law, Marie and Henrik, you are also wonderful grandparents to my children and really good friends. Thank you for your basic support with everything and for your invaluable help taking care of Erik, Vide, and Siri, especially during periods of intensive work on my thesis.

Anna and Eva, my lovely sisters - thank you for being you. Having sisters and friends like you is a great privilege. I really enjoy spending time with you and your families. And special thanks to Eva for introducing me to academic language back in the day, teaching me invaluable expressions such as *however*, *thus*, *elucidated*, and more.

My mom and dad for always giving me and my sisters unconditional love and support without pressure, for your invaluable basic support with everything, and for your help taking care of Erik, Vide, and Siri - they always love it and you are the world's best grandparents, and parents. I really enjoy spending time with you.

Last but not least, I would like to thank my family Markus, Erik, Vide, and Siri. You are the direction in my life. Thank you, Markus, for your patience, encouragement, and support both practically and emotionally, especially during the final stages of work on this thesis. You are the best.

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