The role of physical activity and fitness in people with Cystic Fibrosis compared to healthy people

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The role of physical activity and fitness in people with Cystic Fibrosis compared to healthy people

De rol van fysieke activiteit en fitheid bij mensen met Cystic Fibrosis vergeleken met gezonden

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 14 juli 2022 des middags te 12.15 uur

door

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Chapter 1

General introduction

1.0 Pathophysiology in patients with Cystic Fibrosis

Cystic Fibrosis (CF) is the most common genetic disease in the Caucasian population[1–7] and characterized as an autosomal recessive disease caused by abnormal function of the CF transmembrane regulator protein[8,9] (CFTR). This CFTR protein acts as an epithelial chloride channel and is important to enable flow of electrolytes and fluids across cellular membranes. Dysfunction of CFTR results in impaired electrolyte transport, resulting in dehydrated, and therefore, more, viscous mucus[10]. This viscous mucus affects primarily the lungs, pancreas, intestinal mucosa, and sweat glands[8,9]. As a result, people with CF (pwCF) may struggle with decreased pulmonary function, poor nutritional status with decreased muscle mass, cough and exertional dyspnea[8,9]. Eventually, this multisystem disease results in increased morbidity, and mortality[1,4,5,7,11].

Interestingly, several studies have shown a relevant relation between cardiorespiratory fitness (CRF), represented by peak oxygen uptake (VO_{2peak}), and mortality or survival in CF. Already in 1992, Nixon et al., indicated that pwCF with VO_{2peak} ≥ 82%predicted had a survival rate of 83% at 8 years, compared with 51% and 28% for pwCF with the middle (59-81%predicted) and lowest (≤ 58%predicted) level of CRF respectively[12]. In a larger international study of Hebestreit et al., including data of 10 CF centers in Australia, North America and Europe, similar trends were reported. The pwCF with the highest VO_{2peak} (≥ 82%predicted) had a 72% and 49% lower risk of dying or receiving a lung transplant in the following 10 years compared with pwCF in the middle (59-81%predicted) and lowest VO_{2peak} category (≤ 58%predicted) respectively[13]. In addition, Pianosi et al. found that pwCF with a VO_{2peak} less than 32 ml/min/kg exhibited a dramatic increase in mortality, in contrast to those whose VO_{2peak} exceeded 45 ml/min/kg, none of whom died[14]. Accordingly, maintenance and increasing CRF levels in pwCF seems to be an important clinical treatment aspect in CF care.

2.0 The aging CF patient and new treatment modalities

In the past decade, treatment and control of CF has improved drastically and the average survival of pwCF has significantly increased[15]. Since 2011, the heel prick screening was introduced in Dutch CF care and resulted in early diagnosis[16]. Additionally, CF modulator therapies that enhance the function of the mutated CFTR protein have been developed and introduced in CF care. Currently, these treatments are available for roughly 40% of the pwCF, depending on the combination of (the more than 2000 known) CFTR variants[17–19]. These therapies can be broadly

divided into CFTR potentiators and correctors. CFTR potentiators improve ion and fluid conductance through the CFTR channel, e.g. ivacaftor. CFTR correctors aid in chaperoning mutated CFTR proteins during protein folding, thereby preventing endoplasmic reticulum-mediated degradation[20–22]. Orkambi is an example of a CFTR potentiator and CFTR corrector combination. The triple combination therapies have the potential to extend that coverage to roughly 90%[7,23–26].

As a result of the aging CF patient, secondary co-morbidities become more prominent and prevalent. Specifically, co-morbidities such as chronic infections from an ever-changing spectrum of pathogens, some of which may become multi-drug resistant (i.e. *P. Aeruginosa*) and more frequent and severe pulmonary exacerbations lead to a progressive pulmonary function decline and may, ultimately, increase mortality[1,4,5,7]. Furthermore, data is present that the incidence of CF related diabetes (CFRD), low bone mineral density, and endothelial dysfunction due to chronic inflammation is increased in this aging CF population. In addition, these co-morbidities could have deleterious consequences for quality of life and CRF[7]. The effects of CFTR modulator therapies on non-pulmonary CF disease manifestations are however, less clear[7,27–31].

3.0 Cardiorespiratory fitness and exercise limiting factors/ mechanisms in CF

CRF or exercise capacity is traditionally represented by VO_{2peak}. VO_{2peak} is determined by the maximal uptake of oxygen in the lungs, the oxygen transport capacity of the cardiovascular system, and the maximum oxygen extraction rate of the cells (during exercise mainly the exercising skeletal muscles)[32]. VO_2 can be computed from blood flow and O_2 extraction by the tissues, as expressed in the Fick Equation:

- $VO_2 = (SV \times HR) \times [C(a\text{-}v)O_2]$
- And $SV \times HR = Q$, consequently, $VO_2 = Q \times [C(a\text{-}v)O_2]$.

In which, Q represents cardiac output, SV is stroke volume, HR is heart rate, and $[C(a\text{-}v)O_2]$ is the arteriovenous O_2 content difference, which is related to O_2 extraction[33].

In this manuscript, we will use the term CRF or physical fitness interchangeably.

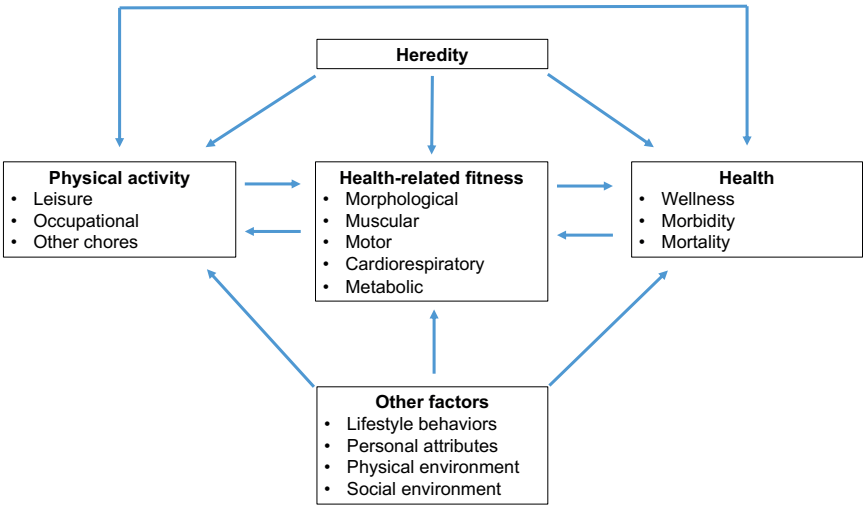

Figure 1. Consensus model from Bouchard & Shepard 1994[34].

As shown in the Consensus model from Bouchard & Shepard 1994, (health-related) physical fitness consists of several factors (Figure 1) on the one hand, but is affected by other factors, such as physical activity related factors and environmental factors on the other hand.

The overview in Table 1 complements the morphological, muscular, motor, cardiorespiratory and metabolic factors which are related to health-related fitness[34]. In CF, several components and factors of (health-related) fitness are potentially problematic. Combined with the Wasserman wheels (Figure 2), which provide an overview of the normal coupling between the musculoskeletal, the cardiovascular and the respiratory systems during exercise, it is amplified that many pwCF could have a decreased VO_{2peak} and thus a decreased CRF.

Many studies have confirmed the decreased levels of physical fitness[12,13,35–37] and have described potential exercise limiting mechanisms in CF: pulmonary factors[14,38–40], cardiac factors[41–45], factors related to skeletal muscle (function) and inflammation[46–48].

Table 1. The components and factors of health-related fitness of the Consensus model from Bouchard & Shepard 1994[34].

Morphological components	Muscular components	Motor components	Cardiorespiratory components	Metabolic components
Body mass for height	Power	Agility	Submaximal exercise capacity	Glucose tolerance
Body composition	Strength	Balance	Maximal aerobic exercise capacity	Insulin sensitivity
Subcutaneous fat distribution	Endurance	Coordination	Cardiac function	Lipid and lipoprotein metabolism
Abdominal visceral fat		Speed of movement	Lung function	Substrate oxidation characteristics
Bone density			Blood pressure	
Flexibility				

Several studies have demonstrated a relation between CRF and pulmonary function, especially forced expiratory volume in one second (FEV_1). Smith et al. found a moderate relation of FEV_1 in percentage predicted ($ppFEV_1$) (r = -.65, p=.002)[38] and VO_{2peak}, and similarly, Du Berry et al., showed a significant correlation between relative VO_{2peak} in percentage predicted and $ppFEV_1$ (r= .546, p< .001) in 8-18 year old children with CF[40]. Furthermore, FEV_1 was appointed as the most significant predictor of VO_{2peak} in pwCF with severe lung disease[39].

The role of cardiac factors in exercise (in)tolerance in CF remains inconclusive. In pediatric pwCF, no impairments were reported for cardiac output and stroke volume during exercise[49]. But in adult pwCF, both similar and reduced values for cardiac output and stroke volume during maximal exercise were seen[45,49]. Causes for cardiac involvement underlie in possible CFTR dysfunction in cardiac myocytes[43–45], but in impaired ejection fraction related to hyperinflation for example as well[41]. Moreover, possible involvement of the autonomic nerve system or chronotropic (in)competence seems plausible. On the one hand tachycardia is a repeatedly seen feature in CF[50–52], but on the other hand, impaired heart rate responses seem to occur as well[49,53,54].

The role of skeletal muscle dysfunction follows from the demonstration of CFTR expression in human skeletal muscle[55,56] and this leaves open the debate whether CF peripheral muscle dysfunction mainly reflects deconditioning or whether CF related factors can be involved. In the overview of Gruet et al. it was concluded

that peripheral muscles of pwCF are characterized by atrophy and weakness and is associated with reduced exercise capacity. Low levels of physical activity was reported as the proposed major contributor for this skeletal muscle dysfunction, especially in pwCF with mild –to- moderate disease severity. However, other factors, such as metabolic abnormalities and inflammation could be a contributor as well[56]. Still, unambiguous evidence is present regarding affected oxidative capacity of the exercising muscles in CF. Werkman et al. did not find abnormalities in oxidative metabolism in adolescents with CF with mild disease severity compared to healthy controls[46]. In contrast, Erickson et al. reported dysfunctional oxidative capacity in older pwCF with more pulmonary disease progression[47], and Saynor et al. supported the impaired oxidative capacity as limiting factor for exercise in pwCF in their review[57].

Next to skeletal muscle weakness and atrophy, CF literature indicated that muscular and motor components in CF might be affected as well. In preschool children motor performance was described as age appropriate[58], but for children and adolescents lower levels of motor performance have been reported[59]. Furthermore, factors of health-related fitness, including endurance, strength, flexibility, and motor-performance, including power, speed, agility, coordination, reaction time and balance, were significantly lower in 6-17 year old children with CF compared to healthy peers in the study of Gruber et al[60]. Similar findings were reported for children and young adults with CF by Ariken et al[61].

With regard to inflammatory involvement, a longitudinal decline of 3.23% for VO_{2peak} relative to body weight and an additional decline of 4.60% in patients who became colonized with *P. Aeruginosa* was demonstrated by van de Weert van Leeuwen et al[48]. The devastating effects of chronic systemic inflammation on skeletal muscle[48,62,63] could be one of the causes for this finding[64], but also the consequences of a higher inflammatory rate, may lead to more hospital admissions and/or decreasing physical activity levels and eventually lower CRF levels[48].

With the current developments in CF care in mind, one might expect less affected pulmonary function and less ventilatory constraints during exercise, but perhaps more psychosocial interfering. As a result of the increased life expectancy, many pwCF with this chronic, life-threatening disease, could develop chronic of intermittent fatigue as they age[65,66]. Consequently, persistent fatigue can affect quality of life and, because of reduced societal participation, psychosocial distress, or decreasing physical activity levels. Knowledge regarding how fatigue represents itself in CF, and possible related factors including biological (e.g. pulmonary function or physical activity or fitness levels) or psychosocial factors (e.g. patient reported outcome measures such as feelings related to depression or anxiety) are yet to be

found. Knowing that CRF is related to the physical aspects of quality of life and overall quality of life[67], expanding our knowledge concerning fatigue and CF related to CRF seems clinically relevant.

Given the high prognostic value of CRF and mortality and quality of life, improving our understanding of how CRF changes and is affected by disease development, new treatment modalities and psychosocial factors such as fatigue, new research questions arise. These research questions will be discussed in the last section of the introduction.

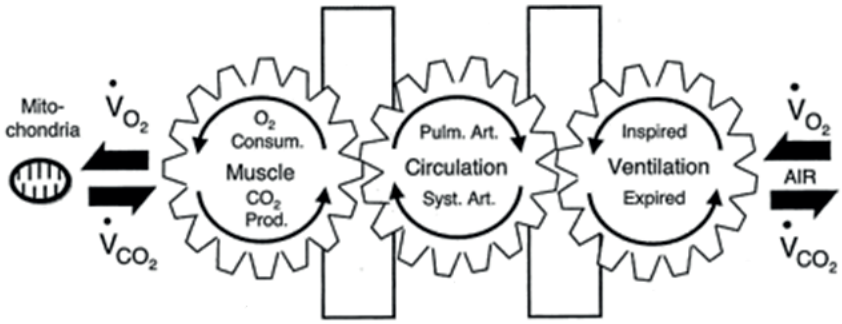

Figure 2. Wasserman wheels[32].

4.0 Cardiopulmonary exercise testing in CF

Cardiopulmonary exercise testing (CPET) plays an integral role in the follow-up of pwCF, because of its high-yield of diagnostic, prognostic, and functional information. In addition, according to the European Cystic Fibrosis Society and the Dutch Quality Standard for medical specialists in Cystic Fibrosis, exercise testing should be part of the regular assessment of pwCF[9,68,69]. Furthermore, in the ATS and American College of Chest physicians statement, it is stated that resting pulmonary and cardiac function testing cannot reliably predict CRF and/or exercise performance and functional capacity, and that overall, health status correlates better with exercise tolerance than resting measurements[68].

Exercise testing in CF could be used for multiple purposes:

1. Evaluation of physical limitations and documentation of reported exercise-associated symptoms;
2. To screen for possible adverse effects of exercise;
3. To make training recommendations;
4. To determine the effects of a conditioning program;

5. To provide prognostic information for clinical outcome and with respect to mortality.

For the assessment of VO_{2peak} – CRF, CPET is seen as the gold standard[68], and there is current agreement to use the Godfrey protocol for pwCF[9,68].

5.0 Aims and research questions addressed in this thesis

This thesis consists of three parts. The first part covers studies investigating the physical activity levels of youth with and without a chronic disease/disability. This was undertaken in the Netherlands and investigates factors which affect physical activity behavior. This section comprises two studies which used the International Report Card format of the Active Healthy Kids Global Alliance[70].
The research aims of this part of the section were:

- To describe the physical activity behavior of the Dutch youth and to provide an overview of the methods and results of the first Dutch Report Card (**Chapter 2**);

- To gain insight into the physical activity behaviors and patterns of Dutch youth with a chronic disease or disability and in order to answer the question '*how (un)limited are the possibilities for the Dutch youth with disabilities to be physically active?*' (**Chapter 3**).

The second part of this thesis focuses on exercise testing in children with respiratory diseases. In this part the aim was to give insight in the differences in performing exercise testing in children compared to adults, and the signature CPET characteristics related to exercise-induced bronchoconstriction, bronchopulmonary dysplasia, exercise-induced laryngeal obstruction and specifically CF are described (**Chapter 4**).

The third part of this thesis focuses on CRF levels, possible exercising limiting factors and the effects of CFTR modulator therapies on CRF in pwCF. The aims of this part were:

- To investigate the CRF levels in pediatric pwCF without ventilatory limitation during exercise, and to determine the relationship between physiological factors (body mass index (BMI) z-score, glucose tolerance status, presence

of CF related liver disease, colonization of *P. Aeruginosa*, sweat chloride concentration, and self-reported physical activity and CRF in this group (**Chapter 5**);

- To investigate if cardiac factors, especially heart rate, are a limiting factor for CRF in both pediatric and adult pwCF (**Chapter 6**);

- To describe the prevalence of severe fatigue among adult pwCF and describe associations between fatigue and clinically measured outcomes and patient-reported outcomes (**Chapter 7**);

- To explore the long-term effects of a CFTR modulator therapy, ivacaftor, in patients with the S1251N mutation on BMI, body composition, pulmonary function, resting energy expenditure and CRF (**Chapter 8**).

Our pilot study, designed according to the international ACTIVATE-CF concept[71], including increasing physical activity and CRF levels in pwCF aged ≥12 years and evaluating the effects on fatigue and other psychosocial outcomes, will be discussed in the general discussion.

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Chapter 2

Is our youth cycling to health? Results from the Netherlands' 2016 Report Card on physical activity for children and youth.

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Abstract

Background: The Active Healthy Kids the Netherlands (AHKN) Report Card consolidates and translates research and assesses how the Netherlands is being responsible in providing physical activity (PA) opportunities for children and youth (<18 years). The primary aim of this article is to summarize the results of the 2016 AHKN Report Card.

Methods: Nine indicators were graded using the Active Healthy Kids Global Alliance report card development process, which includes a synthesis of the best available research, surveillance, policy and practice findings, and expert consensus.

Results: Grades assigned were: Overall Physical Activity Levels, *D*; Organized Sport Participation, *B*; Active Play, *B*; Active Transportation, *A*; Sedentary Behaviors, *C*; Family and Peers, *B*; School, *C*; Community and the Built Environment, *A*; Government Strategies and Investments, *INC*.

Conclusions: Sedentary behavior and overall PA levels are not meeting current guidelines. However, the Dutch youth behaviors in sports, active transportation, and active play are satisfactory. Several modifiable factors of influence might be enhanced to improve these indicators or at least prevent regression. Although Dutch children accumulate a lot of daily PA through cycling, it is not enough to meet the current national PA guidelines of 60 minutes of moderate-to-vigorous PA per day.

1.0 Introduction

Data from the Dutch Organization for Scientific Research (TNO) reveal that the percentage of children and youth meeting the Dutch Norm for Healthy Physical Activity (NNGB; to be at least moderately active for at least 60 minutes a day[1]) show a declining trend for the period between 2006 and 2014[2]. For 4- to 11-year-olds, the number of children who are meeting the NNGB has decreased by approximately 10% during this period. Further, it seems that the older Dutch children are getting more inactive. For example, there is an increasing trend in the percentage of 12- to 17-year-olds who were inactive (when a child is at least moderately physically active for 60 minutes on 2 days or less[2] in 2010 (11%) compared with 2014 (15%)[2]. These numbers suggest a growing inactivity crisis among Dutch children and youth.

It is not totally clear in what type of activity Dutch children accumulate their largest amount of physical activity (PA) during the day, and it is not clear what the best avenues to improve PA levels will be. It could be during active play, physical education (PE), school, organized sports, or active transportation. The Netherlands is known globally for its widespread use of bicycles and some call it a "cycling nation". Indeed, many Dutch inhabitants own a bike and cycle frequently. Numbers show that 84% of the Dutch inhabitants from age 4 years and older own a bike. Those owners have an average of 1.3 bikes per person. This leads to 18 million bikes in the Netherlands and 13.5 million bike owners[3]. It seems that the nation itself is perfectly shaped to cycle. There are no large mountains, only a few small hills are present, and every city or village has an extensive layout of cycle paths and routes. In many urban areas separate cycle paths are not uncommon. It could be that the Dutch youth is cycling to health and in this first Dutch Physical Activity Report Card, we aim to provide better insight about the PA levels and patterns of the Dutch youth.

After the global matrix, in which 15 countries were compared[4], the idea was born to develop the first Physical Activity Report Card for the Netherlands. In 2014, a group of researchers led by Tim Takken of the Child Development and Exercise Centre at Wilhelmina Children's Hospital obtained a seed grant of the *Sport & Society* focus area of the Utrecht University, and the project was launched.

The aim of the present article is to provide an overview of the methods and results of the first Dutch Report Card.

2.0 Methods

The Principal Investigator and Project Manager formed a research work group (RWG) together with 6 researchers of the University Medical Centre Utrecht, Utrecht University, and Utrecht University of Applied Sciences. The RWG made a first inventory of the possible data sources by knowledge of available databases and by searches in scientific databases and websites of useful institutes. In addition, an inventory for themes and relevant experts and/or organizations was made. Subsequently, an expert group was formed with involvement of RIVM (National Institute for Public Health and Environment), Mulier Institute, Dutch Olympic Committee/Dutch Sport Federation (NOC*NSF), Windesheim University of Applied Sciences, Maastricht University, Knowledge Centre for Sport Netherlands (KCS), and advising roles for the Dutch Society for Physical Education (KVLO), Primary Education Board (PO-Raad), Vocational Education and Training Board (MBO Raad) and municipality of Utrecht (Dept of Public Health). Two research assistants supported the principal investigator and project manager and together they identified data sources, key articles and made an overview of the existing evidence.

For the developmental process, guidelines of the Canadian framework were followed[5]. Both the RWG and the expert group were responsible for the interpretation and evaluation of the data sources and evidence. Selection was mainly based on national representativeness and consecutive measurement years. The RWG and expert group had to define the definitions and adjust the benchmarks of the indicators from the Canadian framework to the Dutch situation. The research evidence was compared against these benchmarks to assign a final grade.

It was decided to only include the required 9 indicators from the Active Healthy Kids Canada framework, no additional indicator was included[5]. For the evaluation of the indicators, data of the period 2010 up to 2014 has been included. When available, we used data from national surveys conducted by Statistics Netherlands (CBS) and RIVM as primary sources. If these sources could not provide the required data to grade an indicator, data from other (partial) governmental sources were used (e.g., TNO, Netherlands Institute for Social Research (SCP), Mulier Institute) or data from nongovernmental organizations (e.g. Jantje Beton).

2.1 Benchmarks

For the indicator Overall Physical Activity, the percentage of children meeting the Dutch Physical Activity Guideline was used to grade the indicator. The grading was based on data from the National Health Survey (NHS). The NHS is part of the Lifestyle Monitor, in which data regarding several lifestyle themes are gathered annually[6].

For Organized Sport Participation, consensus was reached to use data regarding engaging in sports on a weekly basis. In the NHS, respondents were asked their participation in sports in a regular week in the past months and it was assumed that this was representative for sports participation in the entire year[7].

For Active Transportation, it was decided that grading should be based on the percentage of children who use active transportation (walking or cycling) to and from school and/or work, at least 3 times a week. For both indicators, data from the NHS were used.

Active Play was assessed by the amount of time that children and youth engaged in unstructured/unorganized active outside play in the last week. Data from TNO Monitor Convenant Healthy Weight (MCGG)[8] were used. TNO includes a continuous national survey called Accidents and Movement in the Netherlands (OBiN)[2]. OBiN monitors sports injuries, sports participation, exercise behavior and sedentary behavior. The MCGG used several OBiN questions in an additional module in which determinants of exercise, eating behavior and sports participation were collected in a subsample[8]. No national survey that incorporated active play was performed in the period 2010 to 2014.

Two hours of screen time was used as benchmark to grade Sedentary Behavior, using OBiN data for the grading. The indicator Family and Peers was graded based on multiple studies and findings. Data of the NHS[6], MCGG[8] regarding family and peers next to data of a Mulier Institute study, in which the central theme was sports participation in children in poverty[9]. Results of the ENERGY-project were used as well. The aim of the study was to explore differences in weight status and energy balance behaviors according to ethnic background among adolescents across Europe[10].

The indicator Community and the Built Environment was graded based on national survey data from CBS and SCP[11] called Leisure Time Omnibus (VTO). Three aspects were part of the grade: 1) there are enough sports facilities available in my neighborhood; 2) I have sufficient choice of various sports in my neighborhood; and 3) there are sufficient sidewalks, cycle tracks, or other public areas to be physical active in my neighborhood. In this survey, sports and cultural behavior and participation was the area of research[12].

The indicator School was divided in grades for Primary School, Secondary School, and Secondary Vocational Education. The grades for the different levels of school were aggregated to generate an overall School grade. For each type of education the grade was based on active school policies, duration of physical education (PE)

and the presence of a specialist PE educator. Not all aspects concerning school were integrated in national surveys, thus a combination of data from SCP, Mulier Institute and DSP-group was used. For Secondary Vocational Education, it was decided to follow the national advice of the government and Secondary Vocational Education board: the students have to meet the 5% norm. This means that 5% of the contact time (education time minus the internship time) exists of exercise and sport[13]. This corresponds to 60 minutes of exercise per week, at times that the student does not do his/her internship[13].

For Government Strategies and Investments, the RWG and experts decided that this indicator could not be graded. There were no clear and well-founded benchmarks or criteria to state that policy is effective or which amount of investments is acceptable. Multiple documents of the government were considered, for example the Educational Agenda for sports, PA and healthy lifestyles in and around school, National nota health policy letter and evaluation reports of the Mulier Institute concerning several policies and programs. For nongovernment, websites and annual reports from several national foundations were considered.

The RWG and experts met to evaluate the evidence for each indicator and discuss the proposed grading. In an earlier meeting it was already determined that data from primary sources were to be used for the grading of the indicators.

The grade for each indicator was based on the percentage of children and youth meeting a defined benchmark: *A* was 81% to 100%; *B* was 61% to 80%; *C* was 41% to 60%, *D* was 21% to 40%; *F* was 0% to 20%; *INC* was incomplete data. This grading system is according to the Canadian Report card framework[5]. During the grading meeting it was decided not to use the designation of a plus (+) or minus sign (-) next to the grade, because consensus was reached that it was unclear which cut-off points and/or which and how many factors results in a plus or minus sign.

3.0 Results

The 2016 Dutch Report Card is the first assessment of PA behaviors, setting, and sources of influence and government strategies and investments. The grades are summarized in Table 1.

3.1 Overall Physical Activity Levels: D

The grade for Overall Physical Activity levels was a *D*. For the period 2010 to 2014, an average of 29% of Dutch 12- to 17-year olds met the Dutch PA guideline of Healthy Physical Activity (NNGB)[14,15]. So, more than two-thirds of Dutch children were not involved in at least moderate PA for at least 60 minutes a day. The most recent data of 2014 showed that 28% of the Dutch children met this guideline, showing that this indicator is fairly stable in recent years. Except for 2011, boys did meet the guideline more often than girls (average 33% boys versus 25% girls)[14,15].

3.2 Organized Sport Participation: B

Organized Sport Participation was graded a *B*. In 2012 to 2014, 74% of the 12- to 17-year-old children reported engaging in sport weekly[14,15] (see Methods for criteria weekly athlete). Sports participation was quite consistent over recent years and there was only a minor difference in sport participation between boys and girls (74% versus 68% respectively in 2014)[14,15]. Data of NOC*NSF showed that 31.8% of the organized sport memberships are from youth (0 to 17 years)[16].

3.3 Active Play: B

Active Play was graded a *B*, because 70% of the Dutch 4- to 11-year old children reported that they played outside in the past week in the afterschool period[8]. Data of MCGG was used to grade this indicator. Results of a study in the South of the Netherlands showed that 22% of 10- to 12-year-old primary school children, reported that they spend for 3 or more hours per day playing outside, and 21% played 2 to 3 hours per day outside[17]. These data were self-reported by children[17]. A small study initiated by Jantje Beton (a foundation to promote outdoor play) showed that boys play 'more often outside' than girls (21% versus 14%)[18].

3.4 Active Transportation: A

Active Transportation was graded an *A*, because NHS data showed that 79% of the 12- to 17-year-old children cycled 3 or more days to or from school or work and 17% of the 12- to 17-year-old children walked 3 or more days to or from school or work[14,15]. The median minutes per week for cycling to or from school or work was 150 minutes per week. The duration was the same for the age ranges 12–14 and 15–17 years and no differences were observed between genders[14,15].

3.5 Sedentary Behaviors: C

Data from the TNO MCGG survey reported that 57% of 4- to 11-year-old children sit in front of a computer or watch TV less than 2 hours a day[8]. Therefore, the overall grade for Sedentary Behavior was a *C*. When evaluating the sitting and lying patterns of children during school, 4- to 11-year-olds sit/lie on average of 7.5 hours per day and 12- to 17-year-olds sit/lie even more, 9.9 hours per day. On weekend days children of both age groups sit/lie also a large part of the day (4.2 hours for the youngest and 5.4 hours for the adolescents)[2].

3.6 Family and Peers: B

The overall grade for Family and Peers was a *B*. The indicator grade was based on assembling several findings and some of these findings will be listed here. Research from the Mulier Institute regarding poverty and sports participation in children showed that 88.6% of the children live in a family with sufficient financial resources to participate in sports and cultural activities[9]. However, 77% of children in prosperous families have a sports club membership, compared with only 44% of the children in poor families[9]. In total, 53% of the parents (single or with a partner) met the Dutch PA guideline (to engage in at least 30 minutes of moderate PA for at least 5 days a week[1]) in 2014[19]. For peers and friends of 4- to 11-year-old children it was found that 57% exercised very often, while in the older age group, results of TNO MCGG showed that 40% of the friends exercised very often[8]. According to parents, 62% of their 4- to 11-year-old children were stimulated to exercise more by their friends. This was 57% in the 12- to 17-year-old age group[8].

3.7 School: C

The overall School grade was a *C*. Regarding the policies and infrastructure benchmark, some findings will be listed on which the grade was based. In primary school for example, 79% of the PE teachers agreed (totally) with the statement that an annual planning for PE is present at their school[20] and 67% of the PE specialists indicated that their school works with a student tracking system.[20] The Mulier Institute assessed several aspects of PE (e.g. policy, infrastructure, duration of the lessons) in Secondary School[21]. Their results showed that 98% of the section leaders of PE reported the presence of an annual planning for PE, 75% of the secondary schools collaborated with a sports club and 55% collaborated with the municipality[21]. The DSP group monitored on behalf of the Secondary Vocational Education board, Secondary Vocational schools from 2006 to 2014, to assess how exercise and sports were integrated in the curriculum[13]. Their results showed Secondary Vocational Education schools have integrated sports and exercise in their policies for sectors, clusters and domains and 91% of these schools have explicit attention for the health themes sports and exercise[13]. Regarding the benchmark of the presence of a PE

specialist for the PE lessons, it was shown that in Primary School a PE specialist teacher to provide PE was only used in 25% of the schools for groups 3 to 8[l]. For groups 1 and 2, only in 5% a PE specialist teacher was present[20]. As dictated by governmental regulations, students in Secondary Schools are taught by a PE specialist teacher[21]. When Secondary Vocational Educations schools offered PE, in 92% of these schools a PE specialist provides the PE lessons[13]. Regarding the duration of the PE lessons, in primary school an average of 48% of the students received 120 minutes or more PE per week[20]. Over the years, 85% of the Secondary School students had ≥ 120 minutes PE per week[21]. Of the SVE students, only 12% met the 5% policy[13].

3.8 Community and the Built Environment: A

For this indicator, the data of VTO showed that 82% of 12- to 18-year-olds was satisfied with the sports and activity opportunities in their neighborhood[12]. This percentage is a combination of 3 aspects: 1) there are enough sports facilities available in my neighborhood, 2) I have sufficient choice of various sports in my neighborhood, and 3) there are sufficient sidewalks, cycle tracks, or other public areas to be physical active in my neighborhood[12] (see methods for more details). Hence, an overall *A* grade was assigned. A small study initiated by Jantje Beton showed that 6- to 8-year-olds perceived sidewalks and squares in their neighborhood as boring; in addition 46% of the 9- to 12-year-old children agreed with this[18].

3.9 Government Strategies and Investments: INC

The indicator Government Strategies and Investments was graded as *INC* due to the absence of clear, well-established criteria of efficacy for this indicator. The Dutch Government strives to offer suitable sport and exercise opportunities, which are safe and accessible. The Ministry of Health, Welfare and Sports funds activities that include: exercise close to home, accessible opportunities, customized and reliable information, and an information infrastructure to help create resilient youth and to make healthy choices easy and stimulate collaborations with the public-private sector[22]. In this policy, community sport coaches have an important role. Community sport coaches are individuals who operate to increase a connection between sectors as school, community and sport organizations. Their purpose is to create more opportunities for PA and to organize sports activities in neighborhoods[23]. Many community grants are available (e.g. Impulse Community Schools, Sports and Culture)[22,23]. From 2012 to 2016, the Educational Agenda for sports, PA and healthy lifestyles in and around schools was developed by the Ministry of Health Welfare and Sports in collaboration with the Ministry of Education, Culture and Science. School boards and managements were stimulated to conduct their policies according to a 'Healthy School' strategy. For this agenda €4 million was available for the period of 4 years[23,24]. In terms of nongovernmental initiatives, several foundations and funding

agencies exist. For example, Youth Sports Foundation, funded by the private sector and donations, aims to ensure that children of low socioeconomic status have opportunities to participate in sports and support them in sporting attributes which are needed[23,25]. Moreover, there are foundations (Johan Cruyff Foundation, Krajicek Foundation, YALP & Marc Lammers), which offer special playgrounds/sporting fields to promote PA and promote outdoor play opportunities, also in problem areas[26–28]. In the short overview previously described, it is shown that many (non)governmental programs and initiatives and interventions are present. Unfortunately, in not all programs or initiatives clear goals and indicators are present and consequent monitoring is sometimes lacking. In addition, validation of indicators should also be addressed. Therefore, it is currently not possible to give a valid judgment about success or effectiveness for (non)governmental strategies and investments. Figure 1, illustrates the cover story for the Dutch Report Card on Physical Activity for Children and Youth.

Table 1. Grades according to physical activity indicators in the Netherlands' 2016 Report Card on physical activity for children and youth**.**

Indicator	Grades
Overall physical activity levels	D
Organized sport participation	B
Active play	B
Active transportation	A
Sedentary behaviors	C
Family and peers	B
School	C
Community and the built environment	A
Government strategies and investments	INC

Note. The grade boundaries for each indicator are: *A* is 81% to 100%; *B* is 61% to 80%; *C* is 41% to 60%; *D* is 21% to 40%; *F* is 0% to 20%; *INC* is Incomplete data.

4.0 Discussion

The aim of the present article was to provide an overview of the methods and results of the first Dutch Report Card. The results showed that sedentary behavior and overall PA levels of Dutch youth are not meeting current guidelines. However, behaviors in sports, active transportation and active play are satisfactory.

The Dutch use the bike as a way of transportation, but also for sports and exercise. Bike-use fits well in an active life style and it could be the case that cycling is responsible for a large part of the daily PA in Dutch youth. It is estimated that Dutch people have on average a 6-month longer life expectancy attributable to bicycle use[29]. It has been shown that correlations exist between active transport behavior and the attractiveness of the school neighborhood environment, the presence of parks (or trails in parks) and (traffic) safety[30]. Questions that arise are, can the current built environment still serve the many young cyclists next to the increasingly busy traffic? Is it still safe for children to cycle? Are sports accommodations easy accessible and not too far away from home to use the bicycle? Do the schools have sufficient space to accommodate bike parking? Trends suggest that more parents, because of traffic unsafety, drive their children to and from school even for small distances[31]. The question is, what can convince parents to stop driving their children and instead use the bicycle? Answers to all these questions can provide knowledge about this phenomenon of a bicycling nation and if the Dutch are indeed cycling to health. Therefore, we have selected the bicycle usage in children as the cover story. Moreover, our results show that many Dutch children use the bike as their way of transportation and it was demonstrated that active transportation is responsible for a large part of school related PA in Dutch youth[32].

To improve the current situation and to make sure that children will remain using their bikes to go to school or friends, traffic safety and construction of the neighborhood seems important aspects to address.

Even though the overall grading of the community and the built environment is an A, still some children reported that playgrounds are not always easily accessible. They have to cross difficult junctions or busy streets to reach play areas[18]. Also parents reported that they would not allow their children to cycle by themselves to sports clubs or school because the routes are too dangerous[33]. Thus, when developing new neighborhoods attention should be drawn to make it more cycle friendly and accessible in which concerns of end users should be incorporated in the design.

The school seems to have an important role in the overall PA patterns of the Dutch children. At school, almost all children can be reached. Schools could attempt to find strategies to make the PE lessons more active and/or that the moderate- to-vigorous active time is more efficient. Research has shown that less than half of the time of the PE lessons is of moderate-to-vigorous intensity in both primary and secondary school[34]. Next, during PE lessons or during recess, attention should also go to the children who are not already active. Girls are currently a bit neglected in this respect. PE specialists, community coaches or people from sports clubs can all work together to address this. Furthermore, more collaboration between schools, sports clubs and other organizations should be arranged. Sharing facilities will be beneficial for all parties[35].

Organized sports (concerning sport clubs) has an important role in PA patterns for youth as well. There is a wide range of sports clubs for organized sport[II]. Eighty percent of Dutch children are member of one of the 25.000 local sports clubs, kids having 1 training or more per week and a game a week (competition). Training/ coaching is given mostly by volunteers, which makes it questionable if moderate-to-vigorous active time is reached during training. Organized sport could cooperate more with schools, PE teachers and professional trainers in sport.

Finally, the behavior of parents seems to have a great influence on the activity and sedentary behaviors of their children. As the results showed, with a B for family, Dutch parents are not doing it that bad currently. However, despite the fact that the children aren't exercising enough, about a half of the parents don't believe it is necessary for their children to exercise or sport more[8]. Trends also suggest that more children are brought by car to school and sports. Not all parents are aware that their sports behavior, TV viewing behavior or active transport behavior[36] is related to the behavior of their children. Consequently, social marketing campaigns, strategies and interventions to increase the knowledge of parents are encouraged and hopefully this will result in more parents who are active with their kids in sport of active play and more parents who cycle together with their children to play grounds or school. If successful, we can maintain the active culture for Dutch youth.

Taking all grades of the indicators into account, it is remarkably that an average of 29% of the Dutch 12- to 17-year-old youth meets the Dutch PA guidelines, while the grades for nearly all other indicators which contribute to overall PA are higher. Plausible is that the used benchmarks are not distinguishing enough. Duration of an activity (related to the indicators active play, active transportation, organized

sport) are currently not included and should perhaps should be incorporated next to frequency. It would be perhaps even better, to include the intensity of the several activity behaviors as well.

For now, we can state that a large amount of the Dutch youth cycle frequently, however it might be that the average duration of a cycle trip is getting shorter. For organized sport for example, it could be that of the activity of a weekly athlete, a minor part exists of at least moderate intensity. When this knowledge is present, the behaviors which contribute to overall PA will be better understand and more evidence informed and effective strategies and policies can be developed to attack the physical inactivity crisis.

4.1 Strengths and Limitations

This is the first Dutch Report Card that provides a robust overview over a period of 5 years about how the Netherlands is doing, regarding PA opportunities, overall PA levels and the role of sources of influences. Strength of the Dutch Report Card is the many data from nationwide surveys and databases. Furthermore, the participation of many experts and organizations in this area make that all important data sources were identified and included. Unfortunately, not all indicators are integrated in national surveys yet (e.g. active play, family and peers, sedentary behaviors). Thus for some indicators, we had to use research with smaller sample sizes and less well representative samples. RIVM has stated that some aspects are integrated already in the 2016 national survey. Hopefully, the other indicators are integrated in future national surveys as well.

The respondents of the national surveys used here (2010–2014) only included 12- to 17-year-old children, thus data of the younger age group are unfortunately lacking. Fortunately, the age group of 4- to 11-year-olds will be included since the 2016 survey[6].

For active play, sedentary behavior and government strategies still no established criteria for the definition, measurements and benchmark or its relationship with health exist. As for sedentary behavior, only for screen time guidelines are present but not yet for sitting and lying behavior. All this needs further national and international discussion and consensus.

The Health Council of the Netherlands (commissioned by the Minister of Health, Welfare and Sports) evaluates already and if necessary adjusts the current PA and sedentary guidelines based on recent scientific insights[37]. Self-report and/or parent-

report was applied in almost all surveys, however, the (possible) discrepancy for these subjective methods and objective measurements is under discussion. Thus, this needs further scientific exploration as well.

5.0 Conclusion

This first Dutch Report Card indicates that the sedentary behavior and overall PA levels of the Dutch youth, are not meeting current guidelines. Fortunately, behaviors in sports, active transportation and active play are satisfactory. Several modifiable factors may be targeted to improve these indicators or at least prevent regression. Turning sitting time into nonsedentary time might be a feasible way of improving activity levels of Dutch children. Although Dutch children accumulate a lot of daily PA through cycling, it is not enough to meet the current national PA guidelines of 60 minutes of moderate-to-vigorous PA per day. Cycling is important, however cycling alone is not enough for sufficient levels of PA.

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Notes

I. In the Netherlands, Primary School children from 4 to 12 years of age are taught. There are 8 groups related to age. Group 1 and 2 are similar to kindergarten.

II. In the Netherlands, sport is organized at club level, the clubs being members of a sport federation. Most of these sport federations are in turn affiliated to the National Olympic Committee*Netherlands Sport Confederation (NOC*NSF).

Scan QR code for the Dutch Report Card- long form

Figure 1. Front cover of the Netherlands' 2016 Report Card on Physical Activity for Children and Youth.

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Chapter 3

2017 Dutch Report Card+: Results from the First Physical Activity Report Card Plus for Dutch youth with a chronic disease or disability.

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Abstract

Background: The Dutch Active Healthy Kids (AHK) Report Card+ (RC+) consolidates and translates research and assesses how the Netherlands is being responsible in providing physical activity (PA) opportunities for youth (<18 years) with a chronic disease or disability. The aim of this article is to summarize the results of the Dutch RC+.

Methods: Nine indicators were graded using the AHK Global Alliance RC development process, which includes a synthesis of best available research, surveillance, policy and practice findings, and expert consensus. Two additional indicators were included: weight status and sleep.

Results: Grades assigned were: Overall Physical Activity, D; Organized Sports Participation, B-; Active Play, C; Active Transportation, A-; Sedentary Behavior, C; Sleep C; For Weight Status, Family and Peers, School, Community and Built Environment, Government Strategies and Investments all INC.

Conclusions: The youth with disabilities spend a large part of the day sedentary, since only 26% of them met the PA norm for healthy physical activity. Potential avenues to improve overall physical activity are changing behaviors regarding sitting, screen time and active play. The Netherlands is on track regarding PA opportunities for youth with disabilities, however they are currently not able to participate unlimited in sports and exercise.

1.0 Introduction

According to the World Health Organization (WHO) physical inactivity is the fourth leading risk factor for mortality. Regular physical activity (PA) reduces the risk of many diseases including cardiovascular disease, diabetes, breast and colon cancer, and depression[1]. Noting that the more physically active the child the greater the health benefit, specific research showed that PA has positive effects on musculoskeletal health, cardiovascular health and mental health[2]. It has been indicated as well that the earlier in life one starts engaging in sports and exercise, the longer one benefits from it[3]. Therefore, PA is important. However, according to the Global Matrix 2.0, in which Report Cards from 38 countries, including the first Dutch Physical Activity Report Card, were compared regarding PA behavior, norms were often not met by typically developing youth[4]. The Report Card is an annual update or 'state of the nation' that assesses how a country is doing as a nation at promoting and facilitating PA opportunities for children and youth and grades outcomes using an academic letter grade approach (i.e. A, B, C, D, F). Data to grade the outcomes are drawn from several sources, including the research literature, governmental agencies, and nongovernmental organizations[5].[I] Next to typically developing children, also many children with disabilities are not physically active[6]. Even though it might be especially important for this group of children to engage in sports and exercise, because of the positive health effects in the physical, mental and social domain[4,7-10]. Because of multiple barriers, this group should perhaps be more stimulated and encouraged to engage in an active lifestyle in a broad sense: from PA during sports and play activities and reducing sedentary behavior, to behavior related to sleep and weight/nutrition[11].

Over the past few years, changes have occurred to facilitate the sports and exercise behaviors of people with disabilities in the Netherlands. Many organizations, foundations and governmental bodies developed or funded projects that focus on improving PA and sports participation among people with disabilities. However, it is not yet clear what the overall effects of these projects were and where the gaps are. Do people with disabilities feel less restricted in the opportunities they have to participate in sports?

I For a more detailed description about the Report Card, see Colley et al. (2012)

Abbreviations: BMI, Body mass index; CBS, Statistics Netherlands; INC, Incomplete; KSC, Knowledge Centre for Sports Netherlands; MET, Metabolic equivalent; NHS, National Health Survey; NIVEL, Netherlands Institute for health service research; NNGB, Dutch Physical Activity Guideline; NOC*NSF, Dutch Olympic Committee Dutch Sports Federation; PA, Physical activity; PE, Physical Education; RIVM, National Institute for Public Health and Environment; RWG, Research work group; SCP, the Netherlands Institute for Social Research; WHO, World Health Organization.

In the Netherlands, there was no overview yet of the actual status of PA behavior, sleeping behavior and weight status for youth with disabilities. Regarding the proven and potential positive effects of exercise for a good health, it was considered useful to fulfill this gap, by Active Healthy Kids the Netherlands, which consists of a group of researchers in the field of PA in children and youth, with a mission to inspire the nation to engage all children and youth in PA by providing expertise and direction to policy makers and public on how to increase, and effectively allocate resources and attention toward PA for Dutch children and youth. This is also the first Report Card in the world that was specifically developed for this group of children. With this Report Card+, we want to gain more insight in the PA levels and patterns of the Dutch youth with a chronic disease or disability and answer the question '*how (un)limited are the possibilities for the Dutch youth with disabilities to be physical active?' (*Figure 1). In line with this, another aim was to compare the results of the Report Card for Dutch typically developing youth with the Report Card+ for Dutch youth with disabilities.

Figure 1. Front cover of the 2017 Dutch Physical Activity Report Card+.

2.0 Methods

For the developmental process, guidelines of the Active Healthy Kids Canada framework were followed[5]. Eleven indicators were graded in this Report Card. Nine of the indicators were part of this standard international framework. It was decided to add sleep behavior and weight status as additional indicators. The indicators were divided over 3 categories, except weight status, which did not fit in any of the categories (Figure 2). The grades were based on the percentage that met the single or multiple benchmarks.

The principal investigator and project manager formed a research work group (RWG) together with 7 researchers of the University Medical Centre Utrecht, Utrecht University, Utrecht University of Applied Sciences and Center of Excellence in Rehabilitation Medicine Utrecht.

An expert group was formed with the involvement of National Institute for Public Health and Environment (RIVM), Mulier Institute, Dutch Olympic Committee*Dutch Sports Federation (NOC*NSF), Windesheim University of Applied Sciences, Knowledge Centre for Sports Netherlands (KCS), Hanze University of Applied Sciences Groningen, Amsterdam University of Applied Sciences, Institute for Health and Care Research, Netherlands Institute for health service research (NIVEL) and an advisory role for the Primary Education Board [PO-Raad]. Both the RWG and the expert group were responsible for the interpretation and evaluation of the data sources and evidence and had to decide about definitions and benchmarks of the indicators for the grading and were responsible for the final grading.

For the evaluation of the indicators, data of the period 2011 up to 2015 have been included. When available, we used data gathered by Statistics Netherlands (CBS) and the RIVM as the primary source. These organizations annually collect data about several lifestyle themes, the Lifestyle Monitor, part of which is the National Health Survey (NHS)[12]. Most of the grading was based on this survey. The Lifestyle Monitor divides youth in two age groups: 4-11 years and 12-17 years. As a consequence of this, both age groups were assessed for each indicator. Unfortunately, the sample sizes for the years 2011 up to 2014 were too small for a subgroup analysis. For 2015, 142 children were included for the age range 4-11 years and 232 children were included for the age range 12-17 years. For the youngest age category (4-11 years), the answers were parent reported. For the older age group (12- 17) the NHS was a self-report questionnaire. If the required data to grade an indicator could not be provided by the primary sources, other governmental and non-governmental sources were used.

Children with disabilities in the Netherlands could attend regular education or special education at special schools. The situation of scholars attending special education was described when reports were available[13]. The grades of the indicators were based on the data about youth with disabilities in general from the NHS.

As this Report Card+ was developed following a standard framework that was also used for the first Dutch Physical Activity Report Card for typically developing children, the results of both Report Cards could be compared.

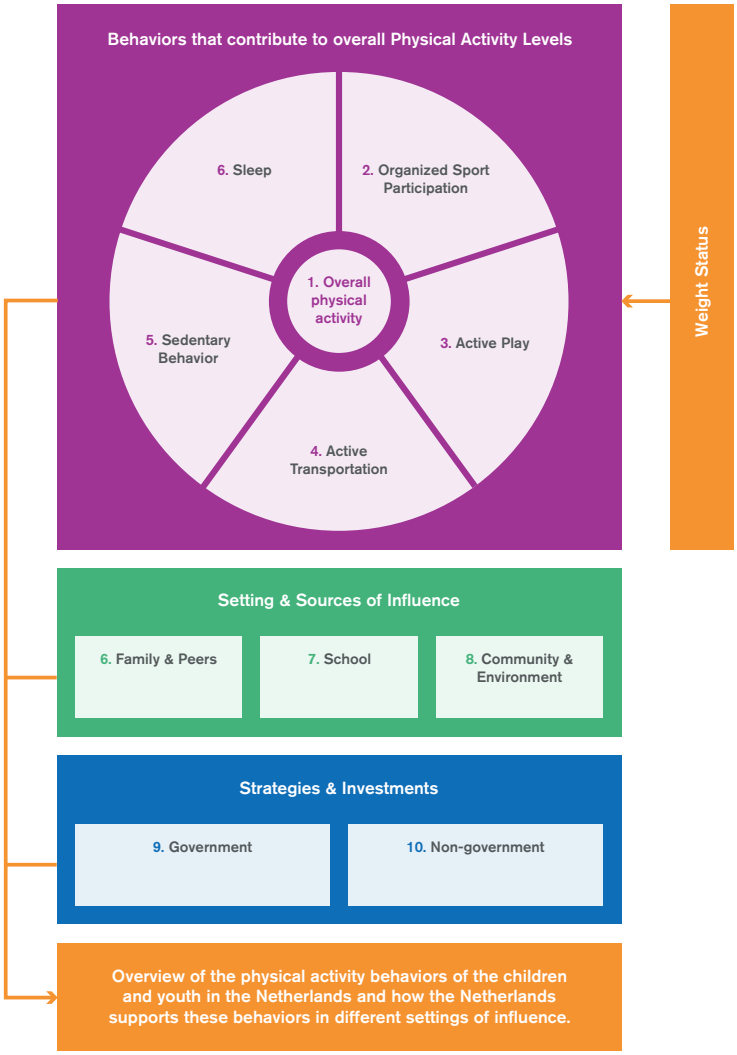

Figure 2. Overview categories and related indicators.

2.1 Benchmarks

The first 6 indicators are Overall Physical Activity, which is also the first category, and the behaviors that contribute to that: Organized Sports Participation, Active Play, Active Transportation, Sedentary Behavior and Sleep. For all of these indicators the grading was based on data from the NHS for children with disabilities in general and, when available, data from the Mulier Institute were used to describe the situation of children attending special education[13].

For the first indicator, Overall Physical Activity, the grading was based on the percentage of children who met the Dutch Physical Activity Guideline (NNGB: Dutch Guidelines Healthy Physical Activity; to be at least moderate active (at least 5 MET) for at least 60 minutes every day). For this indicator data on children attending special education were available.

The RWG and expert group reached consensus to use data regarding engaging sports on a weekly basis, thus the grading of Organized Sports Participation was based on the percentage of children and youth who participated in organized sports and/or PA programs weekly. For children attending special education, it was known how many children were a member of a sports club and how many played non-school based sports at least once a week.

Regarding Active Play, the grading was determined by the percentage of children who played outside for at least 60 minutes after school, for 7 days a week. The NHS does not include questions about active play behavior in 12-17 year old youth, therefore the grade was based only on 4- to-11- year old children. For the scholars attending special education the percentages of children who played outside 5-7 times a week were reported.

Active Transportation was assessed by the percentage of children who use active transportation (walking and cycling) to get to and from places (school and/or work) for at least 3 days a week. Of children attending special education, only the amount of children who used active transport was known and not the weekly frequencies.

For Sedentary Behavior only the amount of time spent in front of a screen (screen time) was surveyed, so the grading was based only on this criteria even though this does not cover all sedentary time. The number of children who watch television or sit in front of the computer less than 2 hours a day outside school hours determined the grade for this indicator. No numbers where available on sedentary time of scholars attending special education.

The indicator Sleep was assessed by the amount of children meeting the sleep duration recommendation for their age group. The sleep duration recommendations used are described in the study of Hirshkowitz et al. (2015). These recommendations are for healthy individuals with normal sleep. The appropriate sleep duration for school-aged children is considered between 9-11 hours each night and for adolescents this is 8-10 hours[14].

For the additional indicator Weight Status, the grade was based on the percentage of children with a normal body weight (BMI between 18.5 kg/m^2 and 25 kg/m^2 was classified as normal weight)[15]. Data for this indicator were taken from the NHS for the children with disabilities in general. Data of scholars attending special education were used from reports from the Mulier Institute[13].

The next category, Settings and Sources of Influence, consists of the indicators Family and Peers, School and Community and Environment. No data of the NHS regarding these indicators were present. Thus no general information was present. Other sources were used for assessment of the indicators in this category.

The criteria of Family were: 'percentage of parents who facilitate PA and sports opportunities for their children (e.g. volunteering, coaching, driving, paying for membership fees and equipment)', 'percentage of parents who meet the PA guidelines for adults' and 'percentage of parents who are physically active with their kids'. For Peers the criteria were: 'percentage of children and youth with disabilities with friends and peers who encourage and support them to be physically active' and 'percentage of children and youth who encourage and support their friends and peers to be physically active'. However, as there was no consistent data for children with disabilities in general nor for children attending special education (not all clusters[II]), the RWG and experts decided that this indicator could not be graded. The available numbers of some of the clusters in special education from the Mulier Institute and other sources were used to get some insight in this indicator.

For School the following criteria were set: 'the percentage of schools with an active school policy (e.g. offering sports- and exercise activities next to physical education (PE) or activities during recess, collaboration with communities and/or sports clubs,

II **Cluster I:** Schools for visual impaired children or children with multiple disabilities who are visually impaired or blind. **Cluster II:** Schools for deaf children and hearing-impaired children, children with speech or language difficulties and children with communicative problems, as with some forms of autism. **Cluster III**: Schools for children with motor and/or mental disabilities, chronically ill children and children with epilepsy. **Cluster IV**: Schools for children with psychiatric disorders or severe behavioral problems and schools that are related to pedagogical institutes.

presence of annual planning)', 'percentage of schools with a PE specialist', 'the percentage of schools were the students have at least 90 minutes of PE per week' and lastly 'the percentage of students who have at least 45 minutes of outside play time during school for 5 days per week.' Again, however, it was decided to grade this indicator as Incomplete. Data was present about regular education and special education. However, as a consequence of the regulation 'Appropriate Education' [Wet Passend Onderwijs][III], some children with disabilities attended regular schools and participate in regular PE. The specific situation for these children was unknown.

The last indicator of this category, Community and Environment, also had several criteria: 'the percentage of children and parents who perceive their community/ municipality is doing a good job at promoting PA (e.g. variety, location, cost quality)', 'the percentage of communities/municipalities that report they have policies promoting PA, 'the percentage of communities/municipalities that report they have infrastructure (e.g. sidewalks, trails, paths, bike lanes) specifically geared toward promoting PA', 'the percentage of children or parents who report having facilities, programs, parks and playgrounds available to them in their community', 'the percentage of children or parents who report living in a safe neighborhood where they can be physically active', 'the percentage of children who report having well-maintained facilities, parks and playgrounds in their community that are safe to use' and finally, 'the percentage of children and parents who report that in organizations like sports clubs, they (their child) are socially accepted and that social accessibility is present.' Also for this indicator it was decided to mark it as an Incomplete. In the Report Card for typically developing children, data of the Leisure time Omnibus [Vrijetijdsomnibus] of the CBS and the Netherlands Institute for Social Research (SCP) was used to grade this indicator. Unfortunately, the sample size of children with disabilities was too low for both 2012 and 2014 to use the results.

The last category, Strategies and Investments was divided in the indicators Government and Non-Government. The criteria that were set were: 'evidence of leadership and commitment in providing PA opportunities for all children and youth', 'allocation of funds and resources for the implementation of PA promotion strategies and initiatives for all children and youth' and 'demonstrated progress through the key stages of public policy making (i.e. policy agenda, policy formation, policy implementation, policy evaluation and decisions about the future).' No clear numbers

III In 2014, the regulation 'Appropriate Education' [Wet Passend Onderwijs] was introduced, which aims that every student should attend a school that provides education suited to their talents and capabilities. Schools should adapt their teaching to the individual child's development and offer extra assistance. This applies to the school where the child is currently registered, another mainstream school or a school providing special education[16].

were available to state that policy is efficient or how much financing is acceptable. Therefore, the decision was made to grade this indicator with an Incomplete. Multiple governmental documents were studied and reports of the Mulier Institute on different policies and programs were evaluated. For Non-Government, annual reports and websites of several national and regional foundations and organizations were considered.

The RWG and experts evaluated the evidence for each of the indicators and discussed the proposed grading. The grades were based on the percentages of youth meeting the defined benchmark. Some indicators are stand-alone, while others are comprised of several components. A was 81% to 100%, B was 61% to 80%, C was 41% to 60%, D was 21% to 40%, F was 0% to 20%. INC was incomplete data or not enough available evidence to assign a grade to the indicator or absence of clear well-established criteria. This is the grading system in accordance to the Canadian Report Card framework[5]. When the data about scholars attending special education showed that the situation for that particular indicator was considerably better or worse for these children, the grade was given a plus or minus respectively.

3.0 Results

The 2017 Dutch Report Card[+] is the first ever assessment of PA behaviors, settings, and sources of influence and government strategies and investments for children with a chronic disease or disability. The grades are summarized in Table 1.

3.1 Overall physical activity levels: D

The grade for Overall Physical Activity levels was a *D*. In 2015, 26% of both children and youth (4-17 year olds) met the Dutch PA guideline of Healthy Physical Activity (NNGB). Scholars of cluster II schools were the most physically active compared to the other clusters. Of the scholars attending cluster II schools 35% exercised 8 or more hours per week (excluding sports)[13]. For the cluster I and III scholar this was 21% and in cluster IV 27%[13].

3.2 Organized sports participation: B-

Of the 4-11 year olds 69% and of the 12-17 year olds 73% was considered a weekly athlete[12]. Among scholars attending special schools, the sports participation was lower. Cluster IV scholars had the highest sports participation, namely 45% versus 25%, 37%, 26% for cluster I, II, III respectively[13].

3.3 Active play: C

Of the 4-11 year old children with disabilities 53% played outside for at least 60 minutes after school, on all days of the week[12]. Scholars of cluster II schools, most often played 5-7 times per week outside (45%), compared to cluster I (31%), III (30%) and IV (33%) scholars. The average amount of minutes of active playtime outside school hours was 529 minutes per week for the 4-11 year old children with disabilities[13].

Table 1. Overview of indicators and corresponding grades.

Indicator	Grades
Overall Physical Activity	D
Organized Sports Participation	B-
Active Play	C-
Active Transportation	A-
Sedentary Behavior	C
Sleep	C
Weight Status	INC
Family and Peers	INC
School	INC
Community and the Built Environment	INC
Government Strategies and Investments	INC

3.4 Active transportation: A-

Of the children in the age of 4-11 years 39% cycled 3 or more days to or from school or work and this was 38% for walking 3 or more days per week. Of the 12-17 year olds 71.8% cycled 3 or more days to or from school or work and this was 15.8% for walking 3 or more days per week[12]. Only 4% of the children in cluster I schools used active transportation to get to their school[13]. This was 18% in cluster II , 13% in cluster III and 30% in cluster IV schools[7,13].

3.5 Sedentary behavior: C

Of the 4-11 year old children 45.5% sat in front of the computer or watched TV, less than 2 hours a day (average day of the week), outside school. This was only 23.2% for 12-17 year old children[12]. No data concerning sedentary behavior was available for scholars in special schools. The 4-11 year olds sat/lay on average 7.9 hours per day on a school day, compared to 11.1 hours for the 12-17 year olds. On a day off from school, the younger age group sat/lay on average 6.5 hours, compared to 9.2 hours in the older age group[12].

3.6 Sleep: C

Of the 4-11 year old children with disabilities 26% met the sleep recommendations. This was 63% in the 12-17 year old age group[12]. No data was present about sleep behavior of scholars attending special schools.

3.7 Weight status: INC

The sample size of the NHS was unfortunately too small, to grade this indicator. These data showed however, that the mean BMI of the 4-11 year olds was 16.5 kg/m^2 and 20.8 kg/m^2 in the 12-17 year old age group[12].

When evaluating the scholars who attended special schools (all clusters together), 68% of the children had a normal weight, 11% was underweight, 17% was overweight and 4% obese. When comparing the different clusters, the highest percentage of overweight and obese children (combined) was found in cluster III schools (25%)[13].

3.8 Family and peers: INC

No data of the NHS regarding 'Family & Peers' were present. Thus no general information was present to grade this indicator. Data was only available on parents of children in cluster III or IV schools. No information about the parental behavior in the other 2 clusters was present, consequently an Incomplete was graded. Of the parents of cluster IV scholars, 59% considered it important that their child engages in sports or exercise frequently. Of the parents, 72% encouraged their child to play sports or exercise frequently[8]. A smaller study showed that parents of whom the child joins a sports club, stimulate their children significantly more ($p=0.05$) to sports and exercise, than parents whose child is not a sports club member[9].

3.9 School: INC

Data was present about regular education and special education. However, as a consequence of the regulation 'Appropriate Education' [Wet Passend Onderwijs][III], some children with disabilities attend regular schools and participate in regular PE. The specific situation for these children was unknown and consequently an Incomplete was graded. Key findings about the situation in special schools will be given.

Concerning active school policies, 71% of the special schools offered their students other sports and exercise activities, next to PE[10]. All cluster I and II schools, had a PE specialist, and 84.2% and 94% of the cluster III and IV schools had a PE specialist respectively. All cluster schools offered twice a week PE[7,8,13]. The number of average minutes PE per week varied between 63 minutes per week in cluster III to 103 minutes in cluster IV[7,8].

Regarding playtime during school recess, 50% of the 4-11 year old students played at least 45 minutes outside during school time for 5 days per week and the average active play time at school was 284 minutes per week for this age group[12].

3.10 Community and the built environment: INC

As mentioned in the methods, the sample size of children with disabilities in the Leisure time Omnibus [Vrijetijdsomnibus] of the CBS and SCP was unfortunately too low to grade this indicator. A smaller study showed that 12% of the parents of children with disabilities reported that play sets/grounds are not nearby enough. Only 2% of these parents reported that the play sets/equipment are not safe and/or badly maintained and only 1% considered them not safe (for younger children). Only 9% of these parents reported that it was not safe for their children to play in the neighborhood, due to traffic safety[16].

3.11 Government strategies and investments: INC

This indicator about the current policy of the government could not be judged. There have been several initiatives that have to resulted in a more physically active youth. Unfortunately, no clear criteria and monitors were present to evaluate the effectiveness of these initiatives and policies.

With regard to foundations, we saw that proportionally more foundations were founded to help or facilitate children with disabilities in their possibilities to play sports or exercise compared to foundations for typically developing children.

4.0 Discussion

The primary aim of this Report Card+ was to provide an overview of the methods and results of the first Dutch Report Card+ for youth with disabilities. The results showed that about a quarter of the Dutch youth with disabilities met the PA norm.

In 2016 the results of the first Dutch Physical Activity Report Card were published[17]. These results were compared with the Report Card+ results (Figure 3). A notable finding was that the percentages of children that met the Dutch Physical Activity Guidelines was the same for children with and without disabilities (26%). Assessing the different indicators that contribute to Overall Physical Activity (Organized Sports, Active Play, Active Transport and Sedentary Behavior), it was clear that the youth with disabilities used active transport less often than their typically developing peers. Regarding youth attending special education, norms were less often met than in youth attending normal education. The differences between healthy children and

children attending special education may be caused by the (social) accessibility and by the diversity of disorders/disabilities. Noteworthy, was that in the Report Card+, only 6 of the 11 indicators could be graded and 5 were graded an Incomplete, thus we stated that the national monitoring in youth with disabilities is unfortunately lacking. Therefore, it was difficult to make powerful statements about possible causes[17].

Other indicators for which improvement is warranted are sedentary behavior and active play. The Dutch youth with disabilities spent a large part of the day sitting or lying and/or behind a screen, especially during school times. Though, around half of the children with disabilities engaged in daily active play for at least 60 minutes, the other half did not. Thus, changing the behaviors regarding, sitting (at school), screen time and active play, seems most likely to improve overall activity levels.

Fortunate, a large part of the youth with disabilities engaged in sports weekly and chose an active mode of transportation for their way to school. It is important that the conditions for these indicators will remain this high in the future. Solutions should be developed to make it possible for more scholars in special schools to travel to school (partly) using active transportation. Furthermore, sports clubs need to educate their staff and volunteers more properly so children and their parents experience less barriers to join a sports club.

The role of the parents and family is of high importance as well in this group of children. Even though no grade could be assigned to this indicator, results demonstrated that parents should be more informed about their large influence as a role model for all behaviors and that their home rules are of high relevance as well. Stimulating parents to engage in sports and exercise activities with their whole family should be more promoted. In addition, strategies that promote sports opportunities for children with disabilities, such as sports and play activities in the neighborhood and foundations who can help families with less financial back up, should be improved. Currently, too many children and parents are not familiar with these possibilities and sports opportunities.

As the indicator sedentary behavior showed, the youth with disabilities sat the most during school hours. Strategies to interrupt the long sitting duration should be developed and implemented, for example physically active academic lessons. As school is the place where all children can be reached, strategies and financial resources are needed to enlarge the duration of PE lessons and to realize higher intensities during these lessons. Further, collaborations between all sectors should be stimulated. Problems in the accommodation and offer of sports and other active

activities will benefit from this. Furthermore, it is important to involve parents, PE specialists and teachers in realizing and improving the sports opportunities for children with disabilities. Both parents and teachers know the child and his/her possibilities and disabilities the best and can search together with the sports clubs for the most appropriate sports activity.

4.1 Strengths and limitations

This is the first ever developed Physical Activity Report Card+ for children and youth with a chronic disease or disability. This Report Card provides a comprehensive overview about how the Netherlands is doing, regarding PA opportunities, overall PA levels and the role of sources of influence for children with disabilities.

Strength of this Report Card+ is the participation of many experts and organizations in this area, which made that many important data sources were identified and included. Unfortunately, not all indicators were integrated in national surveys yet (e.g. Family and Peers) and in the national surveys no clear demarcation was present for children with disabilities. No subcategories could be made and the size of the researched population is small. Furthermore, only the data of 2015 from the NHS could be used because the sample sizes in the years 2011-2014 were too small to analyze. With this in mind, one can question whether these results actually represented the current situation for people with disabilities and youth in particular. Making appropriate policies based on the results of this monitoring should therefore be questioned.

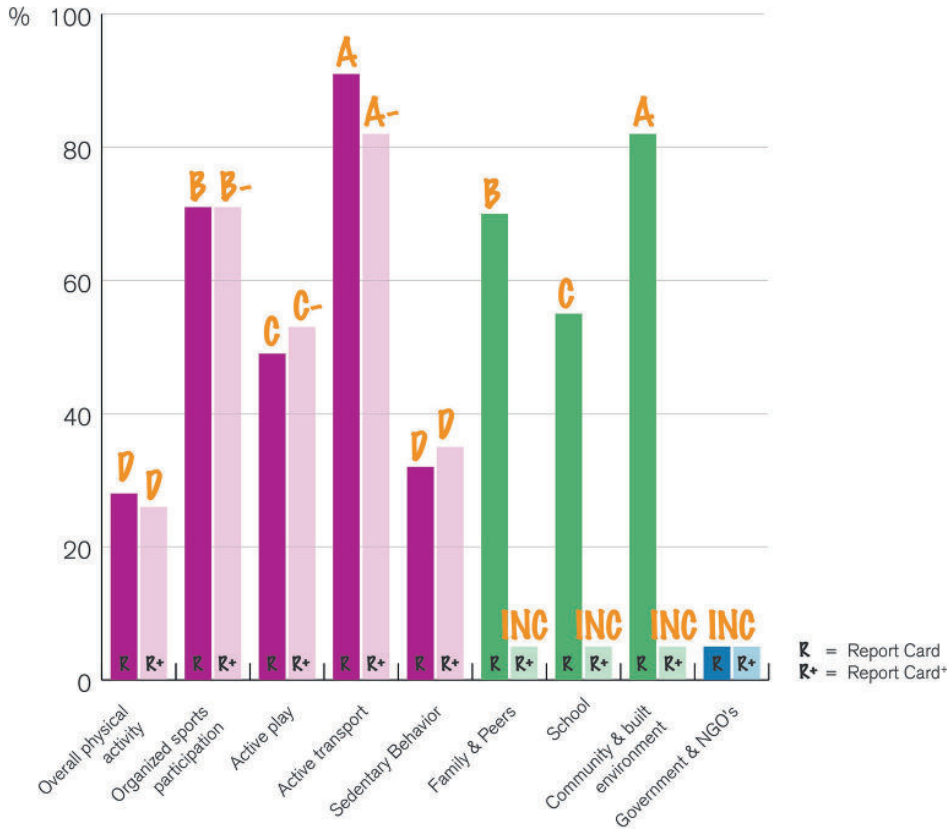

Figure 3. Comparison of the results of the Report Card and the Report Card+.

5.0 Conclusion

Based on the results of this Physical Activity Report Card+, only 26% of the Dutch youth with a chronic disease or disability met the current national PA guidelines. The most important behaviors to change that will most likely result in improvement of overall PA levels seem to be sitting (at school), screen time and active play. In the past few years, many initiatives, possibilities and policies were developed and the Netherlands is on track, but currently, the Dutch youth with disabilities is not yet able to participate completely unlimited in sports and exercise.

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Author Contributions Statements

TT was the principal investigator and MB was the project manager according to the international Report Card framework. NJ and SV supported TT and MB in their work in the Report Card developmental process (for example, literature search, analyzing the results, writing of final Report Card, and the manuscript).

Conflict of Interest Statement

The authors declare that there are no personal, professional or financial relationships that could potentially be construed as a conflict of interest.

Scan QR code for the Dutch 2017 Report Card – long form

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Chapter 4

Exercise testing in children with exercise-induced bronchoconstriction, bronchopulmonary dysplasia, exercise-induced laryngeal obstruction and Cystic Fibrosis.

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Brief summary

Cardiopulmonary exercise testing (CPET) enables clinicians and researchers with a tool to evaluate medical complaints related to exercise, multi-organ function over time in specific disease states, and physical fitness. When performing CPET in children, it is important to consider the remarkable physiological, anatomical, and psychological transformations due to growth, maturation, and development affecting the physiology and the physiological response to exercise, that occur during childhood and adolescence[1]. In children, test performance will depend on exercise equipment and physiology sampling equipment that is easy for children to use and sensitive to measure smaller absolute ventilatory signals. In children, test interpretation will depend on knowledge of the fairly constant heart rate response to exercise across age and gender, smaller stroke volume and tidal volume, and higher arteriovenous oxygen difference compared to adults. With respect to specific respiratory diseases, exercise testing can document the severity of airflow decline in exercise-induced bronchoconstriction, the quantity of glottic and supraglottic obstruction in patients with exercise-induced laryngeal obstruction, and the severity of respiratory impairments in bronchopulmonary dysplasia and cystic fibrosis.

1.0 General introduction

Cardiopulmonary exercise testing (CPET) quantitates the integrated physiological response of children to exercise. In this chapter, we discuss the physiologic responses to exercise in children with respiratory diseases. This chapter begins with a summary of differences in exercise testing and in the physiologic response to exercise between adults and children. Thereafter, signature CPET findings related to a selected number of pediatric respiratory diseases are addressed.

Static lung function tests are useful for diagnosis and management of paediatric respiratory diseases. However, these tests do not measure the ability of a child with respiratory disease to perform physical activities, which is considered as very important for the physical and psychosocial development of children. Several studies have shown a very scattered relationship between static lung functions and exercise capacity in children with respiratory disease, indicating that static lung function indices are not able to predict exercise capacity of an individual patient[1,2]. CPET provides additional information compared to static lung function tests alone for patients with respiratory disease such as cystic fibrosis (CF)[3].

2.0 Differences in performing exercise testing in children compared to adults

2.1 Testing equipment and protocols

When testing children, one has to take the equipment into consideration. For small children, a small cycle ergometer is required. Similarly, small facemasks/mouth pieces, electrocardiogram (ECG) electrodes, blood pressure cuffs, and oxygen saturation probes, as well as sensitive air flow meters, are often required. Furthermore, one should select appropriate pediatric reference values for proper interpretation. Testing protocols should be adapted to the ability of the subject. If the goal of CPET is to obtain a reproducible $\dot{V}O_{2peak}$, the preferred duration for a CPET is between 6 and 10 minutes in children and between 8 and 12 minutes in adolescents[4,5]. When testing clinical populations with low $\dot{V}O_{2peak}$ values, an exercise protocol in which the work rate increases with smaller increments is preferred. If the work rate increments are too big, the exercise test may be terminated prematurely, withoutactual maximally stressing the cardio-pulmonary and metabolic systems[6,7].

2.2 Cycle ergometer (CE) versus treadmill (TM)

The most commonly used ergometers for exercise testing are the CE and the TM. For children of 7 years and younger, a TM is advised. The youngest children of about 3 years of age can learn to walk and thus run on a treadmill[8]. With a CE in the younger children, it often occurs that they cannot keep the pedaling rate for the duration of the test, because the attention span of the younger children is often low. When using a TM, it forces them to maintain a certain speed, and they can easily compensate for a momentary change of pace. However, many laboratories prefer using the CE, because its greater portability and safety. The tester should be fully dedicated to spotting the child when performing an exercise test on the TM, and this is less needed when using the CE[9]. Several important physiological measurements, including ECG and blood pressure, are easier to assess and of better quality using a CE (lower chance of movement artifacts), in addition a strong benefit of CE is the fact that the test will not be easily constrained by mechanical limitations of a patient (e.g. deviant walking patterns, soreness in ankle and knee joints)[4]. Furthermore, when using a CE, the work rate can be measured accurately, compared to using a TM in children. In young children, the speed of the TM protocol is often a restrictive factor[10].

When using the TM as ergometer, the Bruce protocol is the most frequently used protocol for CPET testing in children and adolescents. The Godfrey protocol is most frequently used when using the CE[11]. Noteworthy, several studies demonstrated higher $\dot{V}O_{2peak}$ values on the TM in children as young as 5 years, compared to measurements with CE[12]. Further, TM exercise is more demanding for the respiratory system compared to CE exercise.

2.3 Ventilation and ventilatory reserve

Ventilation ($\dot{V}E$) is controlled by the respiratory receptors (e.g. chemoreceptors) and the respiratory center through changes in both tidal volume (VT) and breathing frequency (BF). At peak exercise, peak $\dot{V}E$ ($\dot{V}E_{peak}$) can rise up to twenty times its resting value in children and adolescents[13]. In adults, the $\dot{V}E$ during maximal exercise averages 50% to 80% of the maximum voluntary ventilation (MVV)[7]. The calculation of the ventilatory reserve (VR) at peak exercise is used to evaluate whether ventilatory limitation affects exercise tolerance[7,13]. The VR at peak exercise compares the attained $\dot{V}E_{peak}$ during a CPET with the maximal capacity of the ventilatory system. The latter is traditionally assessed by measuring MVV in which the subject is instructed to breathe as deeply and quickly as he or she can for twelve seconds. As a surrogate for directly measured MVV which can be challenging to obtain in young children, an estimated MVV can be obtained by multiplying forced expiratory volume in one second (FEV_1) by a coefficient (values ranging from 30 to 40 have been proposed for children)[14,15]. VR at peak exercise is then calculated via the following equation:

VR = 100 – (($\dot{V}E_{peak}$ / MVV) ·x 100). Where 'VR' is the ventilatory reserve at peak exercise (%), '$\dot{V}E_{peak}$' represents the minute ventilation at peak exercise ($L \cdot min^{-1}$),'MVV' is the estimated maximal voluntary ventilation ($L \cdot min^{-1}$). In healthy adolescents, ventilatory reserve is seldom less than 30% when tested at sea level[16]. In healthy males, the ventilatory reserve varies and could be as low as 10-15%[7]. However, it has become clear that rarely is the MVV breathing pattern adopted during exercise and that the $\dot{V}E$/MVV relationship tells little about the specific reason(s) for ventilatory constraint[17]. Measuring the tidal exercise flow-volume (FV) loops (extFVLs) during a CPET and plotting them within the maximal FV envelope (MFVL), gives more specific information on the sources (and degree) of ventilatory constraint. This includes the extent of expiratory flow limitation, inspiratory flow reserve, alterations in the regulation of end expiratory lung volume (dynamic hyperinflation), end-inspiratory lung volume relative to total lung capacity (or tidal volume/inspiratory capacity). By assessing these types of changes, the degree of ventilatory constraint can be quantified and a more thorough interpretation of the cardiopulmonary exercise response is possible[18]. One should realize however, that in the youngest age groups measurement of FEV_1 is often challenging, because most young children are unable to perform the required full forced expiration during a total second[19], consequently plotting exercise-flow-volume loops is often quite challenging as well.

The performance of the pulmonary system during standard pediatric CPET is generally assessed by the response of the submaximal values of $\dot{V}E$, VT, and BF to the increasing metabolic demand along with assessment of the ventilatory reserve at peak exercise. Since $\dot{V}E$ increases linearly with $\dot{V}O_2$ and $\dot{V}CO_2$ up to the ventilatory threshold[7,20] and the respiratory compensation point (the point at which there is an excessive increase in $\dot{V}E$ caused by the failure of the body to buffer all the produced lactic acid[16]) respectively, the $\dot{V}E/\dot{V}O_2$-slope and $\dot{V}E/\dot{V}CO_2$-slope up to the ventilatory threshold are commonly determined to assess ventilatory efficiency and ventilatory drive respectively[21]. The ventilatory threshold, when expressed as percent of maximal oxygen uptake (fractional utilization), is in general higher in young children because young children are more aerobic[9,22-26].

2.4 Tidal volume

The augmented $\dot{V}E$ with increasing exercise intensity is caused by both an increased VT and BF. VT is increased by decreasing the inspiratory reserve volume and to a lesser extent by decreasing the expiratory reserve volume[27]. This can be accomplished by increasing the flow rate at a given inspiratory time (TI) or by lengthening TI at a given flow rate[28]. In healthy children and adolescents, increases in $\dot{V}E$ at lower exercise intensities are mainly achieved by increases in VT, while at high exercise intensity, VT levels off and increases in BF are mainly responsible for further increases in $\dot{V}E$[29,30].

The maximal VT during exercise is usually between 50% to 60% of the resting vital capacity of a participant'[30-32]. VT at peak exercise depends on age (size dependent and proportional to increase in body mass)[33,34], with higher values seen in older children. During exercise, VTcan increases to five times in children and adolescents respectively[16].

2.5 Breathing frequency

The increase in BF seen in exercise is achieved through a decrease in both TI and expiratory time (TE)[33]. At exercise intensities beyond 70% to 80% of peak exercise, increases in BF are mainly accountable for further increases in $\dot{V}E$[16]. In pre-pubertal children, the BF at peak exercise was two to four times the resting BF and similar in boys and girls. The attained BF at peak exercise decreases with age, associated with an increase in both TI and TE[16]. The age-related decline in BF is compensated for by an even greater increase in VT so that absolute $\dot{V}E$ increases with age[33,34].

2.6 Efficiency of ventilation with age

From childhood to adolescence, specific developmental aspects occur regarding ventilation during exercise. With age, an increase in $\dot{V}E$ and efficiency of $\dot{V}E$ increases. This change in efficiency can be explained by a decreasing BF, coinciding with an increasing VT and depth of breathing[4,16].

2.7 Maximal/peak heart rate

Maximal heart rate is highly genetically predetermined, and is independent of age and gender in children and adolescents[9,16,35]. Peak heart rate is dependent on exercise mode and in children and adolescents the peak heart rate remains relatively stable with age, with a median of about 195 beats per minute (CE) to 200 beats per min (TM)[4,16,36]. The heart rate during submaximal exercise, on the other hand, declines with age[9,37-43].

2.8 Ventricular stroke volume and cardiac output

Heart size and stroke volume are related to body mass in the growing child. Both increase across growth and development. During exercise, children are found to have higher heart rates than adults because of their smaller heart sizes and ventricular stroke volume. At fixed work rates, cardiac output is generally smaller in children compared to adults[44]. The smaller ventricular stroke volume is an important limiting factor of their oxygen transport system[1].

Throughout progressive exercise, the relative contribution of stroke volume to cardiac output is predominant during the initial and intermediate phases of exercise[45]. Hence, the oxygen pulse (a measure of cardiac function that is calculated as oxygen

uptake ($\dot{V}O_2$) divided by the simultaneously measured heart rate), has a hyperbolic profile, with a rapid rise during the initial stages of exercising resulting in a slow approach to an asymptomatic value at peak exercise[13,45]. A flattening or downward displacement of oxygen pulse kinetics during progressive CPET very likely reflect a reduced left ventricular stroke volume or a peripheral vascular perfusion- extraction limitation[44] as present in deconditioned subjects, subjects with cardiovascular disease, and subjects with an early exercise limitation due to ventilatory constraint or symptoms[43]. Maximal cardiac output of healthy children reaches three to four times its resting value. Most of this increase due to heart rate, only 20-25% is due to stroke volume. Children have markedly lower stroke volume than adults, at all levels of exercise. This is compensated for, but only in part, by a higher heart rate during submaximal exercise[9].

2.9 Arterio-venous oxygen difference

Children and adolescents have a considerably higher arteriovenous oxygen difference compared to adults during exercise[46], and children are more aerobic (oxygen dependent). This improved offloading of oxygen at the tissue level may be one of the reasons children are found to have lower cardiac output at fixed work intensities than adults[4,9,47]. The measurement of peripheral oxygen saturation (SpO_2) provides information concerning oxyhemoglobin saturation, which should be 95% or higher and generally should not decrease during exercise at sea level in healthy children[48-51]. Exercise-induced desaturation is commonly defined as a decrease in SpO_2 at peak exercise of more than 4% compared to resting SpO_2[16,22]. However, there is no international consensus regarding the cut-off point for desaturation unfortunately.

To measure the arterial oxygen saturation (SpO_2), pulse oximetry is often used. Sensors for fingertips, ears and forehead can be used. Pulse oximetry is unfortunate sensitive to mechanical artefacts caused by movement of the sensor, especially when using fingertip sensors[52]. With finger oximetry, a child should be instructed to not make a fist during the measurements. This will render the accuracy[53]. In case of digital clubbing (in CF), it is shown that fingertip measurements significantly underestimates the saturation[53]. It has been reported that in children with cardio-pulmonary disease SpO_2 monitored at the forehead is less sensitive for artefacts compared to measurement at the fingers and SpO_2 at the forehead gave much higher values compared to readings at the index finger[54]. We therefore recommend to measure SpO_2 at the forehead during CPET in children.

2.10 Aerobic and anaerobic power

Maximal aerobic power remains stable in boys and decreases slightly with age in girls. Compared to adults, the absolute $\dot{V}O_{2peak}$ is lower, but the $\dot{V}O_{2peak}$ adjusted for body mass is higher[4]. The anaerobic power, shows a progressive growth-related increase with age[9]. Compared to adults, the anaerobic performance is lower in children in both absolute and relative terms (for example, scaled to body mass, height squared, fat-free mass, or allometrically based exponents of mass)[9]. Several explanations for this lower anaerobic performance in children are reported. The muscle volume in children, relative to their body mass is smaller and it shows a gradually increase during childhood and adolescence. Next, children have a lower ability for their anaerobic energy turnover. This is mainly present in a lower glycolytic capability: children have both a lower resting concentration of glycogen and lower rate of its anaerobic utilization. Also, children do not reach as high levels of acidosis as adolescents or adults and in adults the degree of acidosis at which a muscle can still contract is higher[9,55-60].

2.11 Recovery following exercise

Children show for many physiological functions a faster recovery following exercise. These include, heart rate[61,62], oxygen uptake[63,64], CO_2 production, $\dot{V}E$[63], plasma volume, lactate, and pH[65]. This faster recovery is most present in high intensity activities[62,65]. The cause for these differences is not entirely clear[9].

2.12 Determination of peak values

In adults, one defines the presence of a plateau (no increase in $\dot{V}O_2$ with an increase in work) in oxygen uptake ($\dot{V}O_2$) as an endpoint for achieving one's persons peak $\dot{V}O_2$. This clear plateau is unfortunately not always present and in children and adolescents, this certainly is an issue because they often do not attain a true plateau for $\dot{V}O_2$, despite that they have reached their limit of tolerance[66,67]. Thus, for the interpretation of a true maximal effort (to determine peak values of exercise capacity when testing children, a peak heart rate of at least 180 beats per minute and a respiratory exchange ratio (RER) of at least 1.0 are common objective criteria. On the contrary, for adults the maximal heart rate is dependent on the equation which is used[11,68], and the RER should be at least 1.05 or 1.1[11,68,69]. In addition, one should assess the subjective criteria of maximal effort as well[70,71].

The most commonly observed cardiovascular, pulmonary, and metabolic child-adult differences are depicted in Table 1.

Table 1. Commonly observed differences in exercise physiological parameters between children and adults. Source reference Takken et al. (2017) ([4])

Variable	Compared to Adults
Cardiovascular	
$\dot{V}O_{2\ peak}$, L/min	Lower
$\dot{V}O_{2peak}$, ml/kg/min	Higher
Submaximal HR, beats/min	Higher
HR_{peak}, beats/min	Higher
Stroke volume (sub)max, ml/beat	Lower
Cardiac Output (at % $\dot{V}O_{2peak}$)	Lower
Arteriovenous oxygen difference (at %$\dot{V}O_{2peak}$)	Higher
Blood flow to muscle	Higher
Systolic and diastolic blood pressure, mmHg	Lower
Myocardial ischemia	Rare
Pulmonary	
Tidal volume, L	Lower
Breathing frequency, breaths/min	Higher
$\dot{V}E_{peak}$, L/min	Lower
Ventilatory drive, $\dot{V}E/\dot{V}CO_2$ slope	Higher
Ventilatory efficiency, $\dot{V}E/\dot{V}O_2$	Lower
Metabolic	
Glycolytic capacity	Lower
A-lactic capacity	Lower
Recovery after high-intensity exercise	Faster

Abbreviations. **HR** = heart rate; **HR_{peak}** = peak heart rate**; $\dot{V}E_{peak}$** = peak $\dot{V}E$, **$\dot{V}O_{2peak}$** =peak $\dot{V}O_2$.

3.0 Cystic Fibrosis (CF)

3.1 Introduction

CF is an autosomal recessive disease that affects primarily the lungs, pancreas, intestinal mucosa, and sweat glands, caused by abnormal function of the CF transmembrane regulator protein[9]. In CF, patients may struggle with decreased pulmonary function, poor nutritional status with decreased muscle mass, cough and exertional dyspnea[9]. CF severity is classified based on Forced expiratory volume in one second (FEV_1). Mild CF is classified when FEV_1 is higher than 60% predicted, moderate when FEV_1 is between 30% and 60% and severe when FEV_1 is 30% of predicted.

3.2 Characteristics of CF

According to the European Cystic Fibrosis Society (ECFS) exercise testing should be part of the regular assessment of patients with CF[11]. Exercise testing is used for multiple purposes: 1) evaluation of physical limitations and documentation of reported exercise-associated symptoms, 2) to screen for possible adverse effects of exercise, 3) to make training recommendations, 4) to determine the effects of a conditioning program, or 5) to provide prognostic information for clinical outcome and with respect to mortality[11]. Exercise testing may also be useful for the assessment of lung transplant candidates, although the evidence for an additional value in this respect is currently limited. There is no current agreement on a single best exercise testing protocol for patients with CF[11].

3.3 Exercise capacity

$\dot{V}O_{2peak}$ is often lowered in CF patients, but may be well-preserved into adolescence[9]. During puberty a dramatic decrease in $\dot{V}O_2$ is observed in girls but not in boys[9]. Causes for this reduction are reduced muscle mass, airflow limitation, lung parenchymal damage, hemodynamic deficiency, under nutrition, or a combination of these[9]. Studies are conflicting about the role of impaired skeletal muscle oxidative metabolism and exercise capacity in CF. Werkman et al. reported that exercise capacity in adolescents with mild CF was not related to impaired skeletal muscle oxidative metabolism due to intrinsic mitochondrial dysfunction, suggesting that a reduced muscle bulk per se might be a limiting factor in patients with CF with good lung function[72]. On the other hand, Erickson et al. measured an impairment in the oxidative capacity of skeletal muscle in patients with CF[73].

3.4 Specials aspects during exercise testing

3.4.1 Ventilation and tidal volume

In CF, airflow limitation induces an increase in dead space and residual volume and may lead to a reduction in alveolar ventilation as manifested by CO_2 retention (hypercapnia). This retention is particularly evident in patients with advanced lung disease and is associated with oxygen desaturation, low tidal volume and low ventilation. During submaximal exercise, ventilation is often excessive, probably to compensate for the increased dead space ventilation[9]**.** During exercise, children with CF (even those not suffering from advanced disease) showed signs of rapid, shallow breathing and an increase in the ventilatory response. This is likely due to an increase in the mean inspiratory flow, which in turn suggests an expiratory flow limitation[72]. Also, the excessive ventilation results in an increase work of breathing. This increases the overall metabolic stress for the patient and might even steal blood away from the skeletal muscles in favor of the respiratory muscles[73]. In addition, breathing with a low tidal volume may result in smaller changes in intrathoracic pressures, which result in a suboptimal reflux of venous blood into the thorax and hence a poorer filling of the heart[73].

3.4.2 $\dot{V}E/\dot{V}CO_2$

As the ventilatory response is altered in CF as described above, the $\dot{V}E/\dot{V}CO_2$ is likely to be influenced as well. The results of Bongers et al. (mean FEV_1 78.6%) and Borel et al. (mean FEV_1 z-score -0.03)[17] showed no differences in the $\dot{V}E/\dot{V}CO_2$ slope in the entire range of the exercise test compared to healthy controls. However, higher slopes where found in patients with more severe airway obstruction. Keochkerian et al. reported significantly higher slopes of $\dot{V}E/\dot{V}CO_2$ for the entire exercise test among children with CF (mean FEV_1 66%) compared to healthy subjects[75]. The authors suggested that the higher $\dot{V}E/\dot{V}CO_2$ slopes without a fall in end-tidal PCO_2, is caused by a more increased dead space ventilation than hyperventilation[76].

3.4.3 Hyperinflation and expiratory flow limitation (EFL)

Air trapping with hyperinflation is another potential pathophysiologic feature of airflow limitation. This is reflected by a high ratio of residual volume to total lung capacity[9]. Static hyperinflation at rest negatively influences exercise capacity ($\dot{V}O_{2peak}$ and W_{peak}) in CF patients[77]. It has been shown that the presence of static hyperinflation, as reflected by RV/TLC (%), after bronchodilator therapy (RV/TLC> 30%) in adolescents with CF by itself does not strongly influence ventilatory constraints during exercise[77]. Static hyperinflation, is only a slightly stronger predictor of exercise capacity in CF than the FEV_1 (%predicted)[77]. EFL promotes dynamic hyperinflation (DH) and intrinsic positive end-expiratory pressure leading

to functional impairment of inspiratory muscle strength, increased work of breathing and increased sensations of dyspnea[78,79]. EFL can be evaluated through measuring the tidal exercise flow-volume (FV) loops (V_{FL}) during CPET. DH (increasing end-expiratory lung volume (EELV)) is reflected by a decreasing inspiratory capacity (IC) during exercise (EELV= TLC – IC). And it is the combination of elevated tidal volume demand and end- inspiratory lung volume, that brings the patient to a threshold at which their dyspnea becomes intolerable[80].

3.4.4 Ventilatory reserve

During maximal exercise, healthy children use only ±70% of their resting maximal ventilatory capacity[80,81]. On the contrary, patients with severe CF may reach and even exceed 100% of their ventilatory capacity. This suggests a ventilatory limitation during exercise[9].

3.4.5 Oxygen saturation

Patients with CF may desaturate with exercise, especially when FEV_1 is measured below 40%-45% of FEV_1/FVC[9]. The primary mechanism felt to contribute to desaturation in mild and moderate CF, is ventilation-perfusion mismatch[9]. In severe disease, when destruction of lung parenchyma and the capillary network is more prominent, diffusion may also be affected[82].

3.4.6 Hemodynamic dysfunction

In mild-to-moderate CF, hemodynamic responses are normal. Severe CF, however, may be accompanied by hemodynamic changes. Stroke volume and cardiac output are reported to be considerably lower in children and adolescents with resting FEV_1 ≤ 50% predicted[9]. Patients with severe CF often do not reach their maximal HR during CPET, hypothesized to reflect premature test termination related to ventilatory limitation[99].

4.0 Exercise- induced bronchoconstriction (EIB)

4.1 Introduction

EIB is defined as a transient narrowing of the airways that follows vigorous physical activity or exercise[19,83,84]. EIB occurs in 70% to 90% of patients with asthma and it is present in 10% to 15% of healthy children[84-90]. EIB has been argued to decrease the quality of life in patients with asthma because the symptoms of EIB result in limitation of daily activities[84,91]. A variety of stimuli are known to trigger EIB (bronchoconstriction) in patients with asthma such as allergens, environmental irritants, cold dry air[92]. EIB is specific for asthma in children, and exercise can be used

as an indirect provocation test to diagnose and evaluate asthma[19,93]. However, the sensitivity of such a test is only 50% to 70%[94]. There are several surrogates for exercise testing (eucapnic voluntary hyperpnea of dry air and inhalation of hyperosmolar aerosols of 4.5% saline or dry powder mannitol) present. Though, none of these surrogate tests are completely sensitive or specific for diagnosing EIB, they all have utility for identifying airway hyper responsiveness consistent with a diagnosis of EIB[94].

In children, the primary role of exercise testing is related to its role in diagnosis of EIB and exclusion of other causes of exertional dyspnea. This is related to the fact that symptoms reported in EIB (shortness of breath, chest tightness, wheezing, and cough occurring shortly after the onset or completion physical activity) are similar to symptoms of exercise intolerance secondary to deconditioning, obesity or exercise-induced laryngeal obstruction (EILO)[94-96].

EIB is classified by a fall in post-exercise FEV_1 of ≥10% to 15%[94] from baseline, in very young children however an exercise-induced decrease in $FEV_{0.5}$ of 13% or greater from baseline is being used to classify EIB[19]. FEV_1 in young children is likely to be less reliable than $FEV_{0.5}$ because most young children are unable to perform the required full forced expiration during a total second.

4.2 Characteristics of EIB

EIB starts typically 2 to 4 minutes after exercise, peaking at 5 to 10 minutes post exercise and disappearing spontaneously within 20 to 40 minutes. In some cases, it may be sustained for more than 1 hour[9,97]. The degree of bronchoconstriction varies with the nature of exercise. Intense exercise induces greater bronchoconstriction than activities of light intensity. Exercise of 70% to 85% of $\dot{V}O_{2peak}$ triggers bronchoconstriction the most. The osmotic, or airway-drying, hypothesis is thought to be an important stimulus for EIB[98]. As water evaporates from the airway surface liquid, it becomes hyperosmolar. This results in an osmotic stimulus for water to move from any cell nearby, and a cell volume loss. This loss in cell volume (after cell shrinkage) causes a regulatory volume increase and results in a release of inflammatory mediators that cause airway smooth muscle to contract and results in narrowing of the airways[98].

The duration of exercise is of influence in the emergence of EIB. In a highly quoted study, exercise duration of 6 to 8 minutes was found to induce greater bronchoconstriction than shorter or longer protocols at exercise intensities equivalent to 60% to 85% of $\dot{V}O_{2peak}$[99]. In around 50% of the subjects with EIB, a phenomenon called 'refractory period' can occur. This phenomenon incudes little

or absence of EIB, when a subject repeats an exercise bout within two hours of a previous bout[100-107] and is the time interval for such protection. The mechanisms behind this phenomenon are not entirely understood and goes beyond the scope of this chapter[9].

4.3 Exercise capacity

Children who develop EIB during exercise are likely to be limited in their participation due to the perceived symptoms. In addition, one might expect lower exercise capacities[96], but data exists in which no difference in $\dot{V}O_{2peak}$ was observed between subjects who developed EIB and those who did not[84].

4.4 Special aspects during exercise testing

4.4.1 Spirometry

An ATS clinical practice guideline for exercise testing and spirometry before and after a specific exercise challenge has been developed[94]. Pulmonary function tests are done prior to exercise as a baseline measurement, and post exercise time intervals differs between studies and laboratories. It is recommended to measure FEV_1 at 5, 10, 15, and 30 minutes post exercise[94]. This may however, be more frequent when a severe response is expected[94]. For the younger children (3-6 years) it is recommend to start measuring at 1 and 3 minutes[94,108]. The measurement of $FEV_{0.5}$ (in 3-to-6-year-old children) and airway resistance using the interrupt technique (in 5-to-12-year-old children) have been successfully to establish a diagnosis of EIB[94]. Some laboratories use higher values for percent fall in FEV_1 (for example 15% and 13.2%) and recommended these values especially for diagnosing EIB in children[87,109].

4.4.2 Protocol

In the ATS guidelines it is advised to use a protocol, which involves a rapid increase in exercise intensity over approximately 2-4 minutes to achieve a high level of ventilation while breathing dry air (<10mg H_2O) with a nose clip[94]. The preferred exercise intensity is 80-90% of the age predicted heart rate or a minute ventilation of 17.5-21 times FEV_1[110-112]. Once this intensity is achieved, the subject should continue to exercise on the TM or CE for an additional 4-6 minutes on this intensity. Sports-specific exercise is probably the most relevant for youth athletes[94].

The use of short-acting and long-term preventative asthma medications[110-112], recent intense or intermittent warm-up exercise[78,102,113], recent use of nonsteroidal anti-inflammatory medication[107], and recent exposure to inhaled allergens may alter the severity of the response to exercise challenge[79,86].

4.4.3 Age dependent deterioration of FEV_1 post exercise

The recovery rate for EIB (FEV_1) decreases with age in children and adolescents[114,115]. Vilozni et al. for example, showed that the time to maximal bronchoconstriction, was 3.4 ± 1.7 minutes post exercise in children under the age of 10 years and 6.6 ± 2.5 minutes in the older (maximal 18 years of age) children[115]. The mechanism behind this difference is not clear. One suggested mechanism is that in young children it is due to smallness and twitchiness of the young airways, compared to the airways in the older children[115]. Another explanation could be, that hyperventilation itself inhibits bronchoconstriction, or that the mechanisms including bronchoconstriction operate after hyperventilation ceases, rather than during hyperventilation. Thus, whether the exercise is less intense in the younger children relative to older age groups or the post-exercise hyperventilation duration is shorter, the time needed to reach maximal post-exercise bronchoconstriction might be reduced[115].

5.0 Bronchopulmonary dysplasia (BPD)

5.1 Introduction

A diagnosis of BPD is defined as mild if oxygen treatment was required at 28 days of age. The classification of moderate/severe BPD is used if oxygen treatment was still required at a postmenstrual age of 36 weeks[116-118].

Survival rates for infants born extremely preterm (EP: < 25 completed weeks gestational age) have increased dramatically[119]. However, survivors remain at risk for development of BPD and long-term pulmonary sequelae, with disrupted alveolar development reported in EP infants and those born small-for-gestational age[120-122]. Little is known about the physical activity habits of children born preterm[123]. There is data present that showed no differences in physical activity levels between 11 year- old EP children and controls[121] but on the other hand some data in adults is present which showed that subjects born pre-term had lower physical activity levels compared to healthy peers[124]. This combined with the fact that up to 50% of children with prior BPD are reportedly affected by EIB[125], it is supposable that activity levels might be reduced among preterm children.

Exercise testing is important in children with BPD to document the severity of the exercise limitation as well as to document exercise-associated symptoms. However, not all children with BPD show an impaired exercise capacity. The exact frequency of exercise limitation in BPD patients is not exactly clear. Exercise capacity could be limited in this group of children due to reduced soluble gas transfer[126], exercise-induced bronchoconstriction[127], less metabolically active muscle mass[128], a poorer

motor performance[127,129], and/or an increased energy cost of movement[124,130]. Currently there is no consensus statement regarding exercise testing for children with BPD. However, exercise tests might be helpful to assess complaints and symptoms in exercise tolerance that may not be detected by resting lung function tests.

5.2 Characteristics of BPD

While some studies document greater levels of lung function impairment in children with a history of BPD, compared with preterm birth alone, others show limited or no differences in preterm children with and without a history of BPD[118]. Some studies reported reduced airway flows, lung diffusion impairment and increased gas trapping in middle childhood or adolescence, compared with healthy control children[116-118]. Some children and adults with BPD may have increased residual volume relative to total lung capacity (RV/TLC), presumably due to chronic air trapping[121,123]. Hence, the observed reduction of the inspiratory reserve volume (IRV) at lower ventilation may have resulted from reduced vital capacity with a normal expansion of the tidal volume. This effect may be most pronounced in those BPD survivors with birth weights < 1000 g or with concurrent asthma[131,132].

5.3 Exercise capacity

The possible lung function impairments (described above) could influence exercise capacity, but the study of Clemm et al. showed that FEV_1 was not related to exercise capacity. They underscored the large reserve capacity of the airway tree at a young age[133].

Data about exercise capacity in this population is ambiguous. There are studies that have addressed $\dot{V}O_{2peak}$ in children born extremely prematurely, and all have reported reduced values (about 10-20% reduction) for preterm compared with term-born control subjects[121,133,134]. In addition, differences in $\dot{V}O_{2peak}$ between EP and term-born groups were reported to be, at age 10-11 years, approximately 20% in all studies[116,135]. On the contrary, normal $\dot{V}O_{2peak}$ data were found in this population as well, for example in the cohort of Clemm et al. consisting of 40 patients (gestational age ≤ 28 weeks) and 40 controls showed an average $\dot{V}O_{2peak}$ of 47.1 versus 48.3 (ml/kg/min) for the preterm versus the term-born cohorts[116].

5.4 Special aspects during exercise testing

5.4.1 Ventilation and ventilatory efficiency

Ventilation at maximal exercise/exertion is lower in most children with moderate/severe BPD, with the difference attributed to lower VT per kilogram body mass (to account for a smaller body size in children with BPD) in children with moderate/

severe BDP[118,121]. However, at submaximal exercise intensities, the respiratory rates and minute ventilation are higher compared to children born at term, when exercising at equivalent exercise levels[136]. These differences may have resulted from adoption of a rapid but shallow breathing pattern in response to inspiratory muscle weakness and fatigue[137]. In children with no/mild BPD, no abnormalities are seen in ventilatory drive ($\dot{V}E/\dot{V}CO_2$ slope), in children with moderate/severe BPD an increased $\dot{V}E/\dot{V}CO_2$ slope is common. A higher $\dot{V}E/\dot{V}CO_2$ slope in moderate/severe BPD children despite similar $PETCO_2$ supports greater dead space ventilation in BPD[118].

5.4.2 Expiratory flow limitation

EFL may develop during exercise in children with a history of preterm birth and is more common in moderate/severe affected children[118]. With ongoing EFL, end-expiratory lung volumes are increased with a corresponding reduction in IC and inspiratory reserve volumes. This decrease in IC during exercise would limit the ability to increase tidal volume and may increase dyspnea. A blunted tidal volume at peak exercise has previously been reported in children with a history of EP birth, and may be a compensatory mechanism to reduce work of breathing in the presence of EFL[118,137].

6.0 Exercise-induced laryngeal obstruction

6.1 Introduction

Exercise-induced laryngeal obstruction (EILO), initially described in the 1980s, is defined as a breathing problem which is not present at rest, triggered by exercise, and isolated to the larynx at either a glottic or supraglottic level, including inspiratory arytenoid prolapse, inspiratory glottis (vocal cords) adduction, and inspiratory airflow limitation[138,139]. The importance of the condition lies in its prevalence, effect on quality of life, and reported ability to be misdiagnosed. The condition is highly prevalent compared to other forms of respiratory disease, within an estimated population prevalence of 5%[140,141]. This prevalence is not remarkably different from that of asthma[142]. It is much more prevalent than conditions such as CF and BPD[143,144]. In terms of its effect on quality of life, reports dating back several decades described severe shortness of breath that impacts the ability to perform high intensity exercise[145]. Misdiagnosis as asthma or other conditions has also been documented in the literature, leading to a scenario in which the condition is inappropriately treated with inhaled steroids, long-acting beta agonists, and other medications typically reserved for asthma and other lower airway diseases[145].

The nomenclature related to this condition has presented confusion in the medical literature over the past three decades. EILO has been identified by clinicians and researchers in a number of different fields, who have coined a number of descriptive terms highlighting anatomic and other clinical observations associated with the condition, including vocal cord dysfunction, exercise-induced laryngomalacia, exercise-induced paradoxical vocal fold motion, and exercise-induced laryngospasm of emotional origin[144,146-149]. EILO was identified as the preferred term for the condition during an international multispecialty consensus conference and it is intended to include all variable forms of upper airway obstruction that occurred during exercise caused by any of the glottic or supraglottic structures[138].

6.2 Special aspects during exercise testing

6.2.1 Inspiratory stridor

The physiology of the condition has not been completely characterized. Early case reports describe classic anatomic and physiologic features, including inspiratory arytenoid prolapse, inspiratory glottic adduction, and inspiratory airflow limitation[141,144,148]. More recent reports highlight a more nuanced view in which non-invasive measures of physiology may lack sensitivity to identify the condition[150]. At the current time, the impact of variable upper airway obstruction on parameters of exercise capacity and ventilatory efficiency including peak work rate, peak oxygen uptake, minute ventilation, and ventilatory equivalent to carbon dioxide have not been described.

From a clinical perspective, the prototypical symptom of EILO is exertional inspiratory stridor[151-152]. However, stridor is not a universal finding[153]. It is also frequently misrepresented as “wheeze” both by patients and researchers, a word which often unconsciously evokes focus on exhalation[154]. The time course of symptoms is somewhat unique and generally is isolated to high-intensity exercise, with relatively rapid self-resolution upon exercise termination[155].

6.2.2 Laryngoscopy during exercise

There are multiple diagnostic techniques used in the assessment of EILO, including noninvasive and invasive approaches. Noninvasive approaches include clinical history alone as well as the use of flow volume loops. Consensus recommendations favor the use of a procedure known as continuous laryngoscopy during exercise (CLE)[156,157]. CLE features real-time laryngoscopy that occurs before, during and after bouts of exercise[157,158]. It can be performed during a variety of exercise modes and has been reported in association with testing on treadmills, cycle ergometers, rowing machines, and in swimming pools[157-161].

Characteristic findings of EILO that can be seen during CLE include inspiratory or biphasic obstruction at a glottis level and inspiratory obstruction at a supraglottic level involving the arytenoid cartilages, aryepiglottic folds, intra-arytenoid tissue, and rarely the epiglottis[153].

Laryngoscopic data collection can be synchronized with metabolic data collection[157,158]. Laryngeal changes in patients with EILO have been described in terms of their timing with respect to exercise intensity on standard cycle ergometry cardiopulmonary exercise tests[155].

6.2.3 Testing protocols

There are some notable challenges in terms of diagnostic exercise testing and interpretation. First, exercise modes and specific exercise protocols of highest relevance in EILO may not necessarily be modes or protocols conventionally used to measure oxygen uptake. Specifically, incremental ramp protocols on a cycle ergometer may be less likely to trigger episodes than other protocols[162]. Possible clinical compromises which may increase the likelihood of demonstrating EILO while maintaining CPET data collection involve 1) adding a few 1-minute supra-maximal interval sprints after a ramp protocol on a cycle ergometer or 2) performing CLE on a treadmill in cases where safety can be ensured. Secondly, the specific endoscopic threshold of laryngeal obstruction which clearly represents a disease state is not defined at the current time. Finally, the physiologic signature of EILO during cardiopulmonary exercise testing has not been clearly identified or described.

The EILO phenomenon is well represented in the video in the link below:
https://www.dropbox.com/s/n8tmb2mtc03bwzy/ERJ%20monograph%20EILO%20vid eo.mp4?dl=0

7.0 Conclusion

This chapter makes the reader familiar with the different pathologies and special aspects during exercise testing in children with respiratory disease. CPET is a valuable clinical test especially in subjects with a more severe disease status of the discussed pediatric pathologies. In many instances a CPET or other exercise test provides additional information next to resting pulmonary function tests. CPET can establish a ventilatory limitation during exercise. However, in the discussed pathologies, the severity of the disease (rate of lung damage for example) determines the extent to which a ventilatory limitation is present and if exercise capacity is negatively influenced by this limitation. It is important to personalize the test per subject and for the interpretation and conclusion, not only CPET results should be taken into account.

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Chapter 5

Physiological predictors of cardiorespiratory fitness in children and adolescents with Cystic Fibrosis without ventilatory limitation.

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Abstract

Objectives: [1] To investigate the cardiorespiratory fitness (CRF) levels in children and adolescents with cystic fibrosis (CF) with no ventilatory limitation (ventilatory reserve ≥15%) during exercise, and [2] to assess which physiological factors are related to CRF.

Methods: A cross-sectional study design was used in 8- to-18-year-old children and adolescents with CF. Cardiopulmonary exercise testing was used to determine peak oxygen uptake normalized to body weight as a measure of CRF. Patients were defined as having 'low CRF' when CRF was less than 82% predicted. Physiological predictors used in this study were body mass index z-score, *P. Aeruginosa* lung infection, impaired glucose tolerance (IGT) including CF-related diabetes, CF-related liver disease, sweat chloride concentration, and self-reported physical activity. Backward likelihood ratio (LR) logistic regression analysis was used.

Results: 60 children and adolescents (51.7% boys) with a median age of 15.3 years (25-75th percentile: 12.9-17.0 years) and a mean percentage predicted forced expiratory volume in 1 second 88.5% (±16.9) participated. Mean percentage predicted CRF ($ppVO_{2peak/kg}$) was 81.4% (±12.4, range 51-105%). Thirty-three patients (55.0%) were classified as having 'low CRF'. The final model that best predicted low CRF included IGT (p=0.085; Exp(B)=6.770) and *P. Aeruginosa* lung infection (p=0.095; Exp(B)=3.945). This model was able to explain between 26.7% and 35.6% of variance.

Conclusions: CRF is reduced in over half of children and adolescents with CF with normal ventilatory reserve. Glucose intolerance and *P. Aeruginosa* lung infection seem to be associated to low CRF in children and adolescents with CF.

1.0 Introduction

Cystic fibrosis (CF) is a heritable disease characterized by dysfunction of the CF transmembrane conductance regulator (CFTR) epithelial chloride channel. This leads to dehydration and thickening of secretions in the airways, pancreatic ducts and other body parts, resulting in progressive obstruction, inflammation, and recurrent infections of the airways and several other organs[1]. In the past ten years, treatment and control of CF has improved drastically and the average survival of people with CF (pwCF) has significantly increased[1]. Peak oxygen uptake (VO_{2peak}), a measure of cardiorespiratory fitness (CRF), is associated with quality of life[2] and survival[3] in pwCF. Indeed, Nixon et al. reported, that pwCF with a VO_{2peak} ≥82%predicted have a survival rate of 83% at 8 years, as compared with rates of 51% and 28% for pwCF with middle (59-81%predicted) and lowest levels (≤58%predicted) of CRF[4]. Similar findings were reported in a large international study by Hebestreit et al. in which it was demonstrated that children and adults with CF with the highest $VO_{2peak,}$ e.g. ≥82%predicted, had a 72% lower risk of dying and 49% lower risk of receiving a lung transplant over a ten year period compared with pwCF in the middle and lowest VO_{2peak} groups[3]. Additionally, in the Statement of exercise testing in CF, it was stated that CRF should be classified as abnormal when CRF is less than 82%predicted of VO_{2peak}[21]. Taken together, a cut-off point of 82% for CRF seems to be of clinical value in this population.

Given the strong link between survival and CRF in pwCF, identifying predictors of CRF is critical for supporting optimal health in this vulnerable population. It is acknowledged that CRF is (largely) dependent on pulmonary function, especially forced expiratory volume in one second (FEV_1), in both children and adults with CF[5–8]. Studies have shown that physical activity and CRF are positively related[9–11] in pwCF, and as it is acknowledged that both CRF[9,12] and pulmonary function[9] decline with age, it is relevant to uncover factors in a pediatric population with little pulmonary loss. To date, much of our understanding of the correlates of CRF in pwCF comes from populations with reduced pulmonary function or those with ventilatory limitation[10,13,14]. The physiological factors related to CRF in pwCF with normal pulmonary function and no ventilatory limitation are less well known. Establishing predictors of CRF in pediatric patients with CF and no ventilatory limitations will allow for optimal monitoring and treatment early in CF management, resulting in the best possible outcome for pwCF across the lifespan.

Growing evidences emerges that skeletal muscle dysfunction or abnormality is potentially related to lower CRF levels. Causes for dysfunctional skeletal muscles, including atrophy and weakness, include a variety of factors such as inflammation,

hypoxemia, oxidative stress, exacerbations, and use of corticosteroids[15]. However, in mild-to-moderate severe disease status, these factors are less likely to result in major skeletal muscle problems. But, muscle abnormalities were still present in female athletes with normal pulmonary function, who had higher physical activity levels measured with accelerometer and self-report diaries, compared to their healthy training partners, as well[16], suggesting factors directly related to CF pathology. Since CFTR is expressed in skeletal muscle it is plausible that CFTR dysfunction affects skeletal muscle function and consequently, affects CRF directly. Although CFTR genotype was not associated with CRF[13] in a large, international multicenter study, no studies have investigated the link between CRF and CFTR function, defined using a proxy measure of sweat chloride concentration. Additional plausible correlates of CRF include nutritional status (body mass index, BMI), CF-related diabetes (CFRD), CF-related liver disease (CFRLD), and chronic infection with *P. Aeruginosa*, which are all known co-morbidities and established predictors for survival in CF patients[3,9]. In the studies of Foster et al. and Causer et al. lower CRF levels were found for patients with impaired glucose tolerance (IGT) and CFRD compared to patients with normal glucose tolerance[14,17]. However, variables as sex and age were included in their models, which are already known co-variates for CRF in CF. Specific exclusion of ventilatory limited patients and inclusion of *P. Aeruginosa* and CFTR function have not yet been analyzed all together. Physical activity has also been linked with a slower rate of decline in pulmonary function in pediatric patients with CF[18]. While some of these factors have been independently associated with CRF[9–11] in pwCF, no study to date has examined their combined association with CRF. Additionally, when physiological predictors are detected, possible prevention and treatment can occur early in CF management, most likely to result in highly improved outcomes in lifespan CF care. Therefore, we aimed to 1) investigate the CRF levels in pediatric patients with CF without ventilatory limitation during exercise, and 2) determine the relationship between physiological factors (BMI z-score, glucose tolerance status, presence of CFRLD, colonization of *P. Aeruginosa*, sweat chloride concentration, and self-reported physical activity) and CRF in these patients.

2.0 Materials and methods

2.1 Subjects

We used cross-sectional data from children and adolescents with CF between 8 and 18 years of age collected in the Wilhelmina Children's Hospital, University Medical Center Utrecht, from December 2016 through January 2019. Only those with no ventilatory limitation during exercise (described below) were included in this study and all patients were free from acute pulmonary exacerbation at the time of testing.

All patients have signed informed consent for use of standard-care data for scientific research purposes. These data include all demographic and clinical data from routine outpatient visits, which could be collected from the electronic patient records, as outlined below. This cross-sectional study was part of the larger PROactive cohort study with annual measurements with chronically ill patients and their families[19], including registration for a web-based tool to fill in questionnaires. This PROactive cohort study was classified by the institutional review board as exempt based on the Medical Research Involving Human Subjects Act (METC number: 16-707/C).

2.2 Study procedures

All patients of the outpatient clinic and their parents were approached by email three weeks before their regular, annual CF check-up. They were invited to register for the study at home using a web-based tool (www.hetklikt.nu). Patients were asked to complete the electronic questionnaire through the web portal before their outpatient clinic visit. Patients that did not respond to the original invitation received a single reminder email and reminder telephone call were used.

2.3 Cardiorespiratory fitness (CRF)

CRF was assessed using a cardiopulmonary exercise test (CPET) according to the Godfrey protocol on an electronically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands)[20]. During the test, subjects breathed through an air-tight face mask (Hans Rudolph Inc., Shawnee, USA), connected to a calibrated metabolic cart (Geratherm, Bad Kissingen, Germany). Objective criteria to assess the quality of the delivered effort were 1) peak heart rate > 95% predicted, and 2) respiratory exchange ratio > 1.00[21]. Patients had to meet at least one out of two objective criteria for the test to be considered of maximal effort. Peak oxygen uptake adjusted for body weight ($VO_{2peak/kg}$) was used as primary outcome measurement for CRF. Because scaling of exercise variables is important in growing children, and both age and sex[22–24] are related to CRF, we only included the predicted value for $VO_{2peak/kg}$ in the statistical analyses. Reference equations from Bongers et al.[24] were used to calculate percentage predicted values for $VO_{2peak/kg}$. Patients were classified as having 'low CRF' when CRF < 82%predicted of $VO_{2peak/kg}$, based on the criteria from Hebestreit et al[3,21]. Patients with a ventilatory limitation during maximal exercise were excluded based on ventilatory reserve (VR), which was calculated as VR = 100– ((VE_{peak}/MVV) x 100), where VE_{peak} is the maximal volume of air exhaled per minute at peak exercise and MVV is the estimated maximal voluntary ventilation (MVV = FEV_1 x 35; in children)[25]. Those with a VR< 15% were classified as having ventilatory limitation, based on the ATS/ACCP statement on CPET[26], and excluded from subsequent analyses.

2.4 Clinical assessments

Clinical parameters including mutation, glucose tolerance status including IGT and CF-related diabetes, CFRLD, colonization with *P. Aeruginosa*, sweat chloride concentration, and use of CFTR modulating therapies were extracted from patient electronic medical record from the date closest to the date of CPET completion. In our center, routine screening for CFRD and CFRLD was performed according to the European CF Society Standards of Care. Regarding CFRLD, this includes periodic liver enzyme testing, and when indicated ultrasonography and liver biopsies. CFRLD includes cirrhosis with and without hypertension and/or hypersplenism. For diagnosing CFRD, annual oral glucose testing is performed[27]. Being colonized with *P. Aeruginosa* was defined as having of two or more positive cultures in the last year. To gain more insight in disease status, number of intravenous treatments in the last year was searched in the medical records as well. Parameters were searched up to 18 months before completing of the CPET.

2.5 BMI (z-score)

Non-fasting measures of body weight and height were collected using a calibrated electronic scale (Seca, Hamburg, Germany) and stadiometer (Ulmer Stadiometer, Ulm, Germany), respectively. The patients were dressed in lightweight clothing and removed any footwear during the measurement. BMI was calculated by dividing body weight in kilograms by height in meters squared. Z-scores for BMI were calculated based on the fifth national growth study of TNO (2010)[28].

2.6 Pulmonary function

Forced expiratory volume in one second (FEV_1) was measured with spirometry and expressed as a percentage of predicted ($ppFEV_1$). Spirometry was performed according to the ERS/ATS recommendations using the Spirostik system (Geratherm, Bad Kissingen, Germany). The Global Lung Initiative (GLI) lung function reference equations were used for the calculation of $ppFEV_1$[29].

2.7 Self-reported physical activity

Participants were asked: 'Over the past 7 days, on how many days were you physically active for a total of at least 60 minutes per day?'. Response options included: 0 days, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days. This question was derived from the Health Behavior in School-aged children (HBSC) study, an international school-based survey with data collected through self-report[30]. The reported number of days was included in the statistical analysis.

2.8 Statistical analysis

Descriptive statistics were used to summarize demographic, clinical, and CRF characteristics. Distribution of the data was assessed with Q-Q plots and histograms and values are reported with the mean ± SD in case of normal distributed data, and with median ± 25th and 75th percentiles in case of non-normal distributed data.

Multivariable binary logistic regression analysis was applied, including level of fitness (low CRF versus normal CRF) as dependent variable. The backward likelihood ratio method was applied, with 0.05 as entry for probability stepwise and 0.10 for removal. BMI Z-score, sweat chloride concentration and self-reported physical activity levels were included as continuous variables. Glucose tolerance status, CFRD and colonization with *P. Aeruginosa* were included as categorical variables, in which 1 coded for presence and 0 coded for absence of the co-morbidities.

Confounders for CRF including age, sex[22–24] and body mass[24,31], were integrated into our outcome of percentage predicted $VO_{2peak/kg}$. Analysis was performed using SPSS version 25.0 (IBM Corp, Armonk, USA), and differences with a P-value <0.05 were considered statistically significant.

3.0 Results

3.1 Characteristics of the study population

A total of 115 children and adolescents were invited to participate in this study. Of these, 72 responded (response rate of 62.6%) and data could only be used from 68 patients. Three patients did not provide consent for use of data from their clinic medical record, and one patient refused to wear a facemask during the exercise test. Reasons for not participating were time investment, filling out too many questionnaires, and personal circumstances. Of the 68 participants, eight patients had a VR of less than 15% during cardiopulmonary exercise testing, and were excluded for data analysis. Therefore, 60 patients with CF (51.7% male) were included in our analyses. Demographic and clinical characteristics are presented in Table 1. IGT including CFRD was diagnosed at a mean age of 12.5 ± 2.7 years, and CFRLD was diagnosed at a mean age of 8.3 ± 3.1 years. Time from diagnosis of IGT including CFRD and performing CPET was mean 2.6 ± 2.5 years, and median 5.0 (3.0-7.0 25th-75th percentile) years for CFRLD. A total of ten patients (16.7%) used CFTR modulating therapies, at time of data collection. Mean time on CFTR modulating therapies was 15.4 ± 9.0 months [range 1-28 months]. Data for sweat chloride concentration was missing for eleven patients (18%).

3.2 Cardiorespiratory fitness (CRF)

Mean CRF ($ppVO_{2peak/kg}$) was 81.4% (±12.4, range 51-105%). When classified by fitness level, 33 of the patients (55.0%) were identified as having 'low CRF' ($VO_{2peak/kg}$ < 82% of predicted) (Table 1).

3.3 Multivariate analysis

The final model included three physiological factors: IGT and colonization with *P. Aeruginosa* were associated with increased odds of having 'low CRF' (OR 6.770 and 3.945 respectively), while having CFRLD was associated with decreased odds of having 'low CRF' (OR= 0.095). Assumptions for linearity and multi-collinearity were satisfied. The final model fit the data adequately (Hosmer and Lemeshow's $X^2 = 1.244$, $p = 0.871$), and was able to predict having 'low CRF' (Omnibus X^2 (3) = 14.595, p =0.002). The model was able to explain between 26.7% and 35.6% of the variance in fitness level (Table 2).

4.0 Discussion

Our study showed that 55.0% of our pediatric sample with CF without ventilatory limitation was classified as having 'low CRF'. This is much higher than the 9.0% of healthy peers classified having 'low CRF' [24]. This is especially alarming in light of the fact that CRF is associated with survival in pwCF[3]. Our findings are consistent with other studies that reported lower CRF levels in children and adolescents with CF compared to healthy peers[32–36]. Indeed, our CRF levels ($VO_{2peak/kg}$) were quite similar to those reported in the literature[32,33,35,37]. Furthermore, our findings are in line with the study of Foster et al. as well, in which more pwCF with IGT (32%) and CFRD (48%) could be classified as having low CRF, compared to pwCF with normal glucose tolerance (20%)[14].

Our results showed an association between glucose intolerance and low CRF. In literature, the relation of glucose (in)tolerance and CRF remains unambiguous. Ziegler et al. did not find relevant differences on six minute walk test (6MWT) outcome between pwCF with and without IGT[38]. However, the submaximal character of the 6MWT could be a possible explanation for these reported differences. Further, Causer et al. indicated that CRF was reduced in adults with CFRD and IGT, but that it is probably related to lung disease severity[17]. The finding of Foster et al. that insulin and glucose values at 120 min during an OGTT were related with CRF in pwCF with normal glucose tolerance[14], is in line with our results. To state anything about causality, is not possible due to our cross-sectional study design, but our results reinforces the proposed relation between glucose tolerance and CRF. Our finding supports the need to screen and act swiftly when children and adolescents with CF show IGT, as this may impact their CRF, and eventually survival. This is

particularly important for older individuals with CF where CFRD is more common[39]. Insulin is known to enhance muscle protein synthesis and inhibit muscle protein breakdown[40,41], and both insulin resistance and insulin deficiency lead to a reduction of insulin signaling in the skeletal muscle[41–43]. Skeletal muscle is one of the major target organs of insulin and accounts for approximately 75.0% of whole-body insulin stimulated glucose uptake[41,44]. Accordingly, reports of abnormal muscle protein metabolism[41–43] and reduced skeletal muscle mass[41,45,46] in the patients with IGT and CFRD may be among the factors contributing to reduced CRF levels. However, it is also known that in patients with insulin resistance or diabetes mellitus II, exercise training improved insulin signaling by enhancing microvascular responses to insulin[47–49] and augmenting capillary blood flow[49–52], both of which augmented perfusion and increased glucose and insulin delivery in skeletal muscle[49,53]. Future studies are needed to establish a causal link between CRF and IGT as well as to explore exercise training modalities.

Another relevant factor in CRF seems colonization with *P. Aeruginosa*. Interestingly, in the population of Ziegler et al., the prevalence of *P. Aeruginosa* colonization was higher in the patients with oxygen desaturation and lower distance on the 6MWT[54]. Furthermore, the role of *P. Aeruginosa* in altering CRF was previously described by van de Weert-van Leeuwen et al.[12]. They found an annual decline of 4.6% in CRF independent of age, pulmonary function, and BMI, when patients were colonized with *P. Aeruginosa*. They suggested that the chronic inflammation seen with *P. Aeruginosa* has negative effects on skeletal muscle[12,55]. Additionally, chronic infection and inflammation may lead to increased intravenous treatment and hospitalization, which negatively affect physical activity, and in turn, CRF[12]. Our data are consistent with this hypothesis since we observed a higher number of IV treatments in the patients with 'low CRF' (Table 1), and the physical activity levels tend to be lower in the 'low CRF' group (Table 1), though this was not statistically significant (Supplementary Table). Moreover, murine study results suggest a relation between *P. Aeruginosa* and insulin metabolism as it was found that acute *P. Aeruginosa* colonization induced insulin resistance[56]. Poorer neuromuscular skills, especially during adolescence, as reported by Gruber et al.[57] could be another factor to take into consideration for lower CRF and physical activity levels, especially engaging in higher intensities. Despite general nutritional improvements in CF care, still growth retardation[58,59], delayed puberty[59,60], and disturbed body composition[59,61] are reported, which all could contribute to underdevelopment of the neuromuscular skills and consecutively CRF. Sweat chloride concentration was not related to CRF levels in our sample, which is also consistent with earlier findings that CFTR genotype was not associated with CRF[13].

Noteworthy is our finding that having CFRLD is associated with lower odds of being classified as having 'low CRF'. A possible explanation could be related to our finding of a higher prevalence of CFRLD in boys (n=14; 45.2%) compared to girls (n=11, 37.9%), which is consistent with the CF literature[62]. In our sample, we also found that fewer boys were classified as having 'low CRF' (n=15, 48.4%) compared to the girls (n=18, 62.1%) and their CRF levels were significantly higher (mean CRF in boys 84.7%±10.6 versus 77.9%±13.3 in girls, p=0.032). In the general population, girls have already a lower CRF[22–24], thus girls with CF may be even more prone to present with lower CRF levels. Still, this relationship between CFRLD and CRF remains ambiguous. Although we included a variety of liver disease severities in our sample, we could not compare by severity due to sample size. Future studies should explore the interaction between sex, CFRLD (and severity), and CRF to provide more insight into our finding. To the best of our knowledge, no other studies have investigated the link between CRF and CFRLD in CF; however, in non-CF populations, most studies suggest that liver disease is associated with reduced CRF.[63–66]

Our findings should be interpreted with some limitations in mind. First, we did not include device-measured physical activity data or data of body composition (fat free mass) since these were not part of our standard CF care. Subjective measures of physical activity are often prone to reporting bias (over or underestimation), thus using for instance accelerometry would most likely provide a more accurate status of a patient's physical activity level. Data of body composition, would facilitate our understanding about possible skeletal muscle (dys)function. This would provide a more in depth analysis of the relations with (the development) of CRF. However, challenges remain in choosing the best devices, both for physical activity and body composition, as a consequence of rapid development of devices and absence or developing cut-off points and reference values specifically for the CF population. Our sample included a small sample of patients with CFTR modulating therapies which makes it difficult to draw definitive conclusions on their association with CRF. However, this smaller sample corresponds to trends in CF management during our study period. Nonetheless, we did not find any relevant differences for CRF levels between the patients with and without CFTR modulating therapies. Because of the cross-sectional nature of our study, we were unable to establish causal relationships. Nevertheless, our results indicate that it is important to assess CRF early in life, and to have a more holistic view of the physical capacity of the patients in pediatric CF care. Early diagnostics and prevention of CFRD and *P. Aeruginosa* colonization are not only important for maintenance of pulmonary function in the long-term, but also for the preservation of CRF. In addition, physical activity promotion and exercise are important clinical aspects in the treatment of CF, but for patients with impaired CRF the prevention of co-morbidities is crucial. The importance of a personalized

treatment should be acknowledged. Together with the patient, one should aim for maintaining or optimizing CRF levels. The optimal exercise prescription for patients with CF and glucose intolerance/CFRD is not yet established; however, exercise training interventions have shown to be effective in improving CRF[67].

In addition to the physiological factors considered in this study, there are several additional factors that may explain the variance in CRF. Psychosocial factors, such as physical self-efficacy, body image, and self-reported fatigue might be such factors. Embarrassment and non-normality are the two most common barriers to physical activity[59,68]. Combined with possibly poorer neuromuscular skills, CRF could be affected as well. Self-reported fatigue is more prevalent in children and adolescents with CF compared to their healthy counterparts[19], however, causality is extremely difficult with regard to fatigue and was beyond the scope of our study as much was unknown in the relation of physiological predictors and CRF. Future studies should elaborate on these possible other (psychosocial) factors. In addition, future studies should include larger samples with longitudinal data, including sex differences, a variety of CFRLD, device-based measures of physical activity, and assessment of skeletal muscle metabolism. Building on our findings, future research on the optimal treatment and intervention to prevent/increase CRF, improve glucose tolerance, and treat *P. Aeruginosa* infections in pediatric pwCF are warranted.

5.0 Conclusions

Over half of children and adolescents with CF with normal ventilatory reserve present with reduced CRF. IGT and *P. Aeruginosa* infections may be important physiological predictors of CRF in children and adolescents with CF. The possible link between CFRLD and CRF in pwCF necessitates further attention.

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Table 1. Patient characteristics, cardiorespiratory fitness, and self-reported physical activity of all patients with CF (n=60), and divided by level of fitness: normal CRF (n=27) and low CRF (n=33) in children and adolescents.

	Total patients (n= 60)	**Normal CRF** ($ppVO_{2peak/kg} \geq 82\%$) (n=27)	**Low CRF** ($ppVO_{2peak/kg} < 82\%$) (n=33)
Patient characteristics			
Age (years) (median, 25^{th}- 75^{th} percentile)	15.3 (12.9-17.0)	13.8 (10.0-16.7)	15.8 (13.8-17.7)
Sex (% boys)	31 (51.7)	16 (59.3)	15 (45.5)
BMI (z-score) (median, 25^{th}- 75^{th} percentile)	-0.3 (-0.9-0.4)	-0.3 (-0.8-0.3)	-0.3 (-1.0-0.5)
Pulmonary function			
$ppFEV_1$ (%)	88.5 (16.9)	90.9 (14.4)	86.5 (18.6)
Mutation			
Homozygous F508del (n,%)	34 (56.7)	14 (51.9)	20 (60.6)
Heterozygous F508del (n,%)	25 (41.7)	13 (48.2)	12 (36.4)
Other (n, %)	1 (1.7)	0 (0.0)	1 (3.0)
CF specific			
Sweat chloride concentration (mmol/L)	99.1 (15.0)	95.3 (13.7)	102.5 (15.5)
CFTR modulating therapies; yes, (n, %)	10 (16.7)	3 (11.1)	7 (21.2)
IV treatment; yes (n, %)	14 (23.3)	5 (18.5)	9 (27.3)
Co-morbidities			
IGT, including CFRD (n, %)	16 (26.7)	4 (14.8)	12 (36.4)
CFRLD (n, %)	22 (36.7)	13 (48.1)	9 (27.3)
Colonization *P. Aeruginosa* (n, %)	20 (33.9)	7 (25.9)	13 (40.6)

Cardiorespiratory fitness & exercise response			
$ppVO_{2peak/kg}$ (%)	81.4 (12.4)	92.6 (6.6)	72.3 (7.5)
Physical activity behavior			
Physical activity (days) (median, 25th- 75th percentile)	4.0 (3.0-7.0)	5.5 (3.0-7.0)	4.0 (3.0-6.0)

Abbreviations: BMI (z-score) = body mass index z-score, **CFRD=** Cystic Fibrosis Related Diabetes; **CFRLD=** cystic fibrosis related liver disease; **CRF=** cardiorespiratory fitness; **IGT =** impaired glucose tolerance; **IV treatment**= number of intravenous treatments in the last year; ***P. Aeruginosa*** = *Pseudomonas Aeruginosa;* **$ppFEV_1$ =** forced expiratory volume in one second, in percentage predicted; **$ppVO_{2peak/kg}$=** peak oxygen uptake, related to body weight, in percentage predicted;; **VO_2peak =** peak oxygen uptake

Table 2. Multivariate analysis of level of fitness (low CRF =1) and possible contributing fators (low CRF based on $ppVO_{2peak\_kg}$ < 82%)

Variable	Cox & Snell R^2	Nagelkerke R^2	HL X^2	Sig	B	Wald²	df	*P-value*	Exp(B)	95% CI for EXP (B)
Model	.267	.356	1.244	.871	-	-	-	-	-	-
IGT incl. CFRD (yes/no)	-	-	-	-	1.912	2.961	1	0.085	6.770	0.766-59.794
CFRLD (yes/no)	-	-	-	-	-2.350	6.808	1	0.009	0.095	0.016-0.557
Colonization *P. Aeruginosa* (yes/no)	-	-	-	-	1.373	2.790	1	0.095	3.945	0.788-19.749
Constant	-	-	-	-	0.122	0.082	1	0.775	1.130	-

Abbreviations: CFRD: CF related diabetes; **CFRLD=** CF related liver disease; **CRF =** cardiorespiratory fitness; **IGT=** impaired glucose tolerance; ***P. Aeruginosa* =** *Pseudomonas Aeruginosa*

Supplementary table: result of between group ('normal CRF' and 'low CRF' pediatric patients with CF) testing using Mann-Whitney U

	Normal CRF ($ppVO_{2peak/kg}$ ≥ 82%) (n=27)	**Low CRF** ($ppVO_{2peak/kg}$ < 82%) (n=33)	***P-value*** (two-tailed)
Physical activity behavior			
Physical activity (days) (median, 25th- 75th percentile)	5.5 (3.0-7.0)	4.0 (3.0-6.0)	0.092

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5

Chapter 6

The heart of the matter: is cardiac output a limiting factor for maximal exercise capacity in people with Cystic Fibrosis?

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Abstract

Background: Although maximal exercise capacity can be reduced in people with Cystic Fibrosis (pwCF), the relationship between exercise capacity and cardiac function is less well understood.

Purpose: To compare the cardiac output (CO) response, specifically heart rate, before and during a maximal cardiopulmonary exercise test (CPET) in pwCF and healthy controls (HC).

Methods: CPET was performed in 19 pwCF (mean forced expiratory volume in one second, in percentage predicted, 74.1 ± 11.3%) and 22 HC. A PhysioFlow® meter was used to measure CO index and stroke volume (SV) index, as well as oxygen pulse (O_{2pulse}) and chronotropic response index (CRI).

Results: CO index (9.9 ± 2.1 l/min/m^2), CRI (84.1 ± 11.2%) and heart rate (172.6 ± 12.3 bpm) were significantly lower at peak exercise in pwCF compared with HC (respectively, CO index 11.7 ± 1.3 l/min/m^2, CRI 99.9 ± 8.1% and heart rate 187.9 ± 9.0 bpm). The SV index and heart rate were also lower at submaximal exercise in pwCF (respectively 54.6 ± 14.3 ml/m^2 and 119.9 ± 18.5 bpm) compared with HC (respectively 61.0 ± 8.0 ml/m^2 and 134.3 ± 4 bpm).

Conclusion: CO is significantly lower during maximal exercise in pwCF compared with HC, mainly because of a blunted HR response. CO is a limiting factor for maximal exercise in pwCF.

1.0 Introduction

In recent years, treatment and control of Cystic Fibrosis (CF) has improved considerably and the average survival time of patients has increased significantly[1]. Likewise, peak oxygen uptake (VO_{2peak}), often used as a measure for cardiorespiratory fitness (CRF), is of particular clinical importance in individuals with CF as it is associated with quality of life[2] and longevity[3].

Currently, CRF levels in CF are still lower than in healthy controls[3–5]. Acknowledged ventilatory causes for impaired CRF levels are loss of pulmonary function, dynamic hyperinflation, and hypoxia[6–10]. But, next to airway dysfunction, cardiac pathology such as myocardial contractility and oxygen transport and delivery (chronotropic competence) may contribute to the reduced exercise tolerance in CF as well. There are only a few studies assessing cardiac function in people with CF (pwCF)[11–13]. Decreased myocardial contractility has been suggested, as it has been demonstrated that chloride movement is associated with functional cystic fibrosis transmembrane conductance regulator (CFTR) in cardiac myocytes[14–16]. Godfrey et al. showed that hyperinflation leads to an increased physiological dead space as well as right ventricular (RV) afterload in pwCF[11]. Benson et al. indicated that an impaired RV ejection fraction during exercise limited the increase of stroke volume (SV) in CF[12]. There are indications that even in young children with CF and normal pulmonary function, both left and right ventricular functions are reduced[13]. For adult pwCF, both similar and reduced values for cardiac output (CO) and SV during maximal exercise were reported[16,17]. In children, no differences for CO and SV compared with healthy controls were reported[17]. Studies with regard to heart rate (HR) response and autonomic control in CF are conflicting. On the one hand, tachycardia is seen in rest, spontaneous breathing, standing position, or after exercise[18–20]. On the other hand, two previous studies by our center showed that peak HR among adolescents with CF of moderate severity was lower during cardiopulmonary exercise testing (CPET)[21,22]. However, no details of CO or oxygen pulse ($O_{2pulse)}$ were given. In sum, clarity is lacking regarding the CO and specifically HR response during rest, submaximal and maximal exercise in both children and adults with CF.

Given the relevance of exercise and specifically VO_{2peak} for pwCF and in the context of the 'aging' CF patient, a higher risk of developing cardiovascular disease emerges[23,24]. Expanding our understanding of cardiac (dys)function to impaired exercise tolerance and improving our treatment strategies and training interventions is of clinical importance. Therefore, we aimed to compare the cardiac response, including CO, SV, HR, and O_{2pulse}, during rest, submaximal and maximal exercise in children and adults with CF and in healthy controls (HC).

2.0 Methods

This cross-sectional observational study was conducted between February 2017 and February 2019. The study was classified by the institutional review board as exempt of the Medical Research Involving Human Subjects Act (METC number: 17-065). Written informed consent was obtained from all the participating subjects.

2.1 Study Population

Nineteen pwCF who routinely visited the CF Center of the University Medical Center, Utrecht, the Netherlands, and 22 healthy subjects were included for the study. The healthy subjects were recruited for another study by our center[25]. Exclusion criteria of the CF group were having a pulmonary exacerbation within the last two weeks, taking antibiotics for pulmonary exacerbation, the presence of any cardiovascular disease, and the inability to exercise.

2.2 Study Procedure

Patient characteristics including age, sex, co-morbidities, CF mutations, medication, use of CFTR modulating therapy, and hemoglobin level were collected from the electronic patient records.

2.3 Anthropometrics

Body weight and height were measured using a calibrated electronic scale (Seca, Hamburg, Germany) and stadiometer (Ulmer Stadiometer, Ulm, Germany). The subjects were in a fasting state, dressed in lightweight clothing and not wearing any footwear during the measurement. Body mass index (BMI) was calculated as the ratio of body weight to height squared[26].

2.4 Pulmonary Function

Pulmonary function (forced expiratory volume in one second (FEV_1); percentage of predicted value for FEV_1 ($ppFEV_1$); percentage predicted value for airway resistance - $ppRaw_{tot}$) was assessed and recorded according to the ERS/ATS statement[27]. The Global Lung Initiative (GLI) lung function reference equations were used for the calculation of $ppFEV_1$ [28] , and the Utrecht data set by Koopman et al. was used for the calculation of $ppRaw_{tot}$ [29].

2.5 Cardiopulmonary Exercise Testing

CPET was performed according to the Godfrey protocol[30], using a bicycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands). During the test, the subject breathed through an airtight face mask (Hans Rudolph Inc., Shawnee, USA) connected to a calibrated metabolic cart (Geratherm, Bad Kissingen, Germany) to

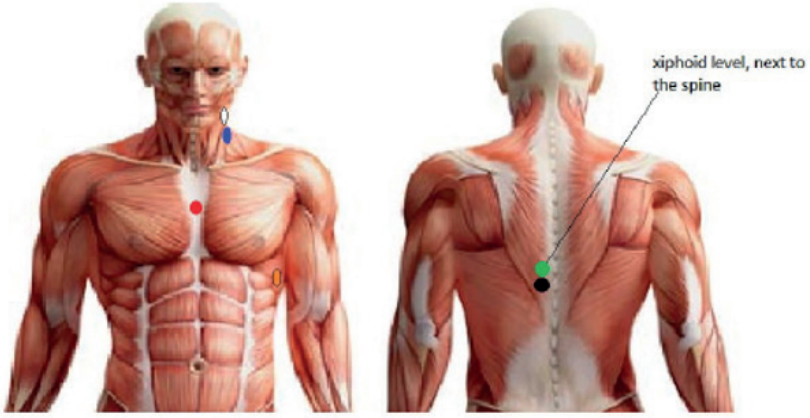
facilitate breath-by-breath gas analysis. An oxygen saturation meter probe (Masimo Rad 8, Masimo BV, Tilburg, the Netherlands) was attached to the subject's forehead to determine oxygen saturation (SpO_2) in the blood during all measurements. Oxygen uptake (VO_2) and work rate (watt) were determined from rest to maximal exercise (VO_{2peak} and W_{peak}) and related to body weight ($VO_{2peak/kg}$ and $W_{peak/kg}$). Percentages of predicted value were calculated for VO_{2peak} ($ppVO_{2peak}$), $VO_{2peak/kg}$ ($ppVO_{2peak/kg}$), W_{peak} (ppW_{peak}) and $W_{peak/kg}$ ($ppW_{peak/kg}$) based on reference equations. For the participants aged up to and including 18 years, reference equations by Bongers et al.[31] were used for oxygen uptake and peak work rate. For adults, reference equations by Mylius et al.[32] were used for oxygen uptake, and equations by van de Poppe et al.[33] were used for peak work rate. Complete gas analysis variables were collected during CPET: breathing frequency at peak exercise (BF_{peak}), tidal volume at peak exercise (Vt_{peak}) to calculate BF_{peak}/Vt_{peak}, ventilatory equivalent for carbon dioxide up to the respiratory compensation point (VE/VCO_{2-rcp}), ventilatory equivalent for oxygen uptake at peak exercise (VE/VO_{2peak}), oxygen cost of work ($\Delta VO_2/WR$), O_{2pulse}, and respiratory exchange ratio (RER) at peak exercise. Additionally, HR was measured by electrocardiography (ECG). To evaluate chronotropic competence during maximal exercise, the chronotropic response index (CRI) was calculated: $[(HR_{peak} - HR_{rest})/(HR_{peak\ predicted} - HR_{rest})] \times 100$. For the participants up to and including 18 years of age, reference equations by Bongers et al.[31] were used for predicted peak HR ($ppHR_{peak}$), and for the participants over 18 years the reference equations by Tanaka et al.[34] were used. HR response was considered to be chronotropic incompetent at CRI < 80%[35–37]. The ventilatory anaerobic threshold (VAT) was used as a submaximal CPET parameter. The VAT was determined with the ventilatory equivalent method[38]. The performed effort was considered maximal when peak RER exceeded 1.03 in children and adolescents[39] and 1.05 in adults[40,41].

2.6 Cardiac Output and Stroke Volume

CO and SV were assessed during a CPET using a non-invasive hemodynamic monitor (PhysioFlow®, Manatec, France). Research has shown that CO and SV measured by the Physioflow® are acceptable for use[42] and that these figures provide a clinically satisfactory and non-invasive basis for evaluation of CO and SV during exercise, in both in adults and children[43,44]. The PhysioFlow® uses a bio impedance method for measuring CO, using changes in thoracic impedance. The measurement of CO was based on the formula of CO index (l/min) = HR (beats/min) × SV index (ml/m^2) × BSA (m^2)[45], where HR represents heart rate and BSA represents body surface area. The device emits a high-frequency (75 kHz) and low-current (1.8 mA) alternating electrical signal via electrodes[46]. The application of the PhysioFlow® electrodes required some skin preparation involving shaving, scraping and cleaning. Two electrodes (one 'transmitting' electrode and one 'sensing' electrode) were applied above the supraclavicular fossa at the left base of the neck and along the xiphoid. Another pair of sensing electrodes were applied at the left

paravertebral area to monitor a single ECG lead (Figure 1). Verification of the correct signal quality was accomplished by visualization of the ECG and its first derivative (dECG/dt), the impedance waveform (ΔZ) and its first derivative (dZ/dt)[47]. Measurements were taken every 10 seconds, therefore the mean of 30 seconds from 10-second intervals was used for CO, CO index, SV, and SV index. Data from single 10-second intervals was used only if the signal quality was at least 85%. It is known that BSA is associated with SV and CO[48], therefore BSA was calculated according to the equation by Haycock to correct CO and SV for the differences in body size[49].

Figure 1. The location of PhysioFlow® electrodes



2.7 Subgroup analysis

For in-depth analysis of our data and results, two subgroup analyses were performed. The first analysis included two groups based on the presence of chronotropic incompetence (CRI < 80%)[35,37], the second analysis was based on reasons for test cessation (leg fatigue versus dyspnea).

2.8 Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0. Descriptive statistics were used to summarize clinical characteristics. The Shapiro-Wilk test was used to evaluate whether data were normally distributed. Parametric data were analyzed using an independent Student's t-test, and reported with the mean ± standard deviation (SD). Non parametric data were compared using the Mann-Whitney U test and reported with median ± 25^{th} and 75^{th} percentiles. Categorical data were analyzed with Chi-square or Fisher's Exact test. The probability of error was set as $p < 0.05$ and differences with a p-value of less than 0.05 were considered statistically significant.

3.0 Results

3.1 Baseline characteristics

Baseline characteristics including anthropometrics, co-morbidities, CF mutations, medication and pulmonary function are described in Table 1. There were no significant differences for the baseline characteristics, sex, age, height, weight, BMI, and BSA between the CF and HC group (Table 1). The use of medication potentially affecting HR is presented in Table 1.

As expected, the CF group showed a significantly lower $ppFEV_1$ compared with the controls ($p = 0.000$), with a mean $ppFEV_1$ of 74.1% (± 11.3) considered as moderate disease severity (Table 1).

3.2 CPET derived variables

All CPET's were considered maximal based on RER at peak exercise [range 1.05-1.36 for the HC group, 1.13- 1.32 for the CF group]. All participants of the HC group reported leg fatigue as the reason for test cessation. In the CF group n = 12 (63.2%) reported leg fatigue and n = 7 (36.8%) reported dyspnea (Table 2).

SpO_2 at peak did not differ between groups ($p = 0.17$). Supplementary variables related to exercise capacity and skeletal muscle status were significantly lower in the CF group, compared with the HC group: $ppVO_{2peak/kg}$, $ppW_{peak/kg}$, ΔVO_2/watt, and VAT. Variables related to ventilatory response (BF/TV, $VE/VCO_{2\text{-}RCP,}$ $VE/VO_{2peak,}$ VR) did not differ significantly between groups (Table 2).

3.3 CO index, HR, SV index, and O_{2pulse}

At rest, no significant differences ($p = 0.93$) were found between the CF (4.2 ± 1.0 l/min/m^2) and HC group (4.3 ± 0.7 l/min/m^2) for CO index. During exercise, both at VAT ($p = 0.006$) and peak exercise ($p = 0.002$), the CO index was significantly lower in the CF group compared with the HC group (Figure 2).

Table 1. Patient characteristics, anthropometrics, co-morbidities, CF mutations, medication, and pulmonary function in people with CF (n=19) and healthy controls (n=22)

Variable	Total CF (N=19)	Total Controls (N=22)	Independent t-test/ Mann-Whitney U *p-value* (two-tailed)
Patient characteristics			
Sex (n, male%)	9 (47.4)	11 (50)	0.867
Age (years) - median 25-75th percentile	18.4 (15.4-22.2)	16.8 (11.7-23.8)	0.347
Anthropometrics			
Height (cm)	171.5 (11,4)	167.7 (13.8)	-
Weight (kg)	60.7 (12.95)	57.4 (18.7)	-
BSA (m^2)	1.7 (.2)	1.6 (.3)	0.432
BMI (kg/m^2)	20.4 (.4)	19.8 (3.8)	0.549
Co-morbidities			
Colonization with *P. Aeruginosa* (n,%)	11 (57.9)	-	-
Pancreas insufficient (n,%)	17 (89.5)	-	-
Presence of CFRLD (n,%)	5 (26.3)	-	-
Presence of CFRD (n,%)	8 (42.1)	-	-
Mutation			
dF508- dF508 (n;%)	12 (63.2)	-	-
dF508- other (n;%)	5 (26.3)	-	-
Other (n;%)	2 (10.6)	-	-
Medication			
CFTR modulating therapy (n,%)	7 (36.9)	-	-
Azitromycin (n,%)	2 (10.5)	-	-
Bèta-2-mimetics (n,%)	2 (10.5)	-	-
Anticholinergics (n,%)	0 (0)	-	-
Inhaled steroids (n,%)	1 (5.3)	-	-
Other			
Hb (mmol/l)	8.7 (8.3-9.0)	-	-
Hb – low (n, %)	3 (15.8)	-	-
Pulmonary function			
FEV_1 (l) - median 25-75th percentile	2.70 (2.47-3.28)	3.34 (2.41-4.10)	-
$ppFEV_1$ (%)	74.1 (11.3)	97.8 (17.8)	**0.000***
Raw_{tot} kPa (l/s) - median 25-75th percentile	0.3 (0.3-0.4)	-	-
$ppRaw_{tot}$ (%)	117.0 (38.8)	-	

P-value <0.05 is considered statistically significant as indicated in bold and with *
Abbreviations: BMI = body mass index; **BSA =** body surface area; **CF =** cystic fibrosis; **CFRD =** cystic fibrosis related diabetes; **CFRLD =** Cystic fibrosis related liver disease; **CFTR =** cystic fibrosis transmembrane conductance regulator; **FEV_1 =** forced expiratory volume in one second; **Hb** = hemoglobin; ***P. Aeruginosa* =** *Pseudomonas Aeruginosa*; **$ppFEV_1$ =** percentage predicted of forced expiratory volume in one second; **$ppRaw_{tot}$ =** airway resistance in percentage predicted; **Raw_{tot} =** airway resistance

Table 2. Cardiac output data and exercise responses at rest, VAT and peak exercise in people with CF and healthy controls.

Variable	Total CF (N=19)	Total Controls (N=22)	Independent t-test/ Mann-Whitney U *p-value* (two-tailed)
Rest			
Cardiac output			
HR rest (bpm)	88.1 (14.9)	86.3 (11.0)	0.662
SV rest (ml)	77.7 (21.7)	77.6 (15.4)	
SV index rest (ml/m^2)	46.5 (11.3)	49.0 (7.9)	0.406
CO rest (l/min)	7.0 (1.6)	6.7 (1.4)	
CO index rest (l/min/m^2)	4.2 (1.0)	4.3 (0.7)	0.932
O_{2pulse} rest (ml/beat) - median 25-75th percentile	3.4 (2.5-4.5)	3.4 (2.8-4.2)	0.844
VAT			
Cardiac output			
HR VAT (bpm)	119.9 (18.5)	134.3 (17.4)	**0.015***
SV VAT (ml)	92.1 (27.2)	97.0 (18.8)	
SV index VAT (ml/m^2)	54.6 (14.3)	61.0 (8.0)	**0.010***
CO VAT (l/min)	11.3 (4.0)	13.1 (3.2)	
CO index VAT (l/min/m^2) (median, 25th-75th percentile)	5.7 (5.3-8.3)	7.9 (6.8-9.9)	**0.006***
O_2pulse VAT (ml/beat) - median 25-75th percentile	7.9 (6.7-10.5)	9.7 (6.7-12.2)	0.558
PEAK			
Cardiac output			
HR peak (bpm)	172.6 (12.3)	187.9 (9.0)	**0.000***
ppHR peak (%)	91.2 (6.2)	99.8 (4.4)	**0.000***
CRI (%)	84.1 (11.2)	99.9 (8.1)	**0.000***
CRI <80% (n, %)	6 (31.6)	0 (0.0)	**0.000***
SV peak (ml)	96.5 (26.6)	99.4 (21.8)	
SV index peak (ml/m^2)	56.8 (11.5)	62.0 (6.5)	0.092
CO peak (l/min)	16.7 (4.4)	18.8 (4.0)	
CO index peak (l/min/m^2)	9.9 (2.1)	11.7 (1.3)	**0.002***
O_{2pulse} peak (ml/beat) - median 25-75th percentile	10.9 (9.4-13.3)	12.9 (9.5-16.5)	0.219

Exercise response/capacity

Test cessation (n,%) Leg fatigue Dyspnea	 12 (63.2) 7 (36.8)	 22 (100) 0 (0)	 - -
RER peak	1.21 (0.06)	1.18 (0.07)	0.172
SpO_2 peak (%)- median 25-75th percentile	98.0 (97.0-99.0)	99.0 (98.0-100.0)	0.277
VO_2 peak (l/min) – median 25-75th percentile	1.88 (1.57-2.30)	2.40 (1.74-3.18)	-
ppVO_2peak (%)	67.7 (13.5)	96.0 (19.0)	-
VO_2peak/kg (ml/min/kg)	32.34 (7.1)	44.08 (9.2)	-
ppVO_2peak/kg (%)	74.5 (15.5)	102.1 (20.1)	**0.000***
Wpeak (watt)	181.5 (52,4)	233.1 (90.1)	-
ppWpeak (%)	75.5 (15.2)	109.5 (20.8)	-
Wpeak/kg (watt/kg) – median 25-75th percentile	2.96 (2.6-3.5)	3.75 (3.5-4.3)	-
ppWpeak/kg (%)	77.9 (15.7)	109.2 (16.4)	**0.000***
ΔVO_2/Watt (ml/watt) – median 25-75th percentile	9.1 (8.0-9.7)	9.8 (9.1-10.3)	**0.026***
VAT (%predVO_2peakpred)	36.5 (11.3)	49.5 (14.3)	**0.003***
BF/TV median 25-75th percentile	28.9 (19.7-35.6)	27.4 (20.8-37.0)	0.834
VE/VCO_2-$_{RCP}$ – median 25-75th percentile	28.2 (25.8-32.7)	26.5 (23.9-30.6)	0.170
VE/VO_{2peak}– median 25-75th percentile	41.0 (36.9-44.8)	39.9 (37.3-41.8)	0.418
VR (%)	18.5 (12.9)	17.6 (20.4)	0.873

P-value <0.05 is considered statistically significant as indicated in bold and with *

Abbreviations: BF/TV = ratio of breathing frequency and tidal volume; **BMI** = body mass index; **BSA** = body surface area; **CF** = cystic fibrosis; **CFRD** = cystic fibrosis related diabetes; **CFRLD** = Cystic fibrosis related liver disease; **CFTR =** cystic fibrosis transmembrane conductance regulator; **CO =** cardiac output; **CRI**= chronotropic response index; **FEV_1** = forced expiratory volume in one second; **Hb** = hemoglobin; **HR =** heart rate; **O_2pulse =** oxygen pulse; ***P. Aeruginosa* =** *Pseudomonas Aeruginosa;* **ppFEV_1 =** percentage predicted of forced expiratory volume in one second; **ppHR peak =** heart rate peak in percentage predicted; **ppVO_2** = oxygen uptake in percentage predicted; **ppVO_2peak/kg** = oxygen uptake relative to body weight in percentage predicted; **ppWpeak** = peak work load in percentage predicted; **ppWpeak/kg** = peak work load relative to body weight in percentage predicted; **RER** = respiratory exchange ratio; **SpO_2**= oxygen saturation; **SV** = stroke volume; **VAT** = ventilatory anaerobic threshold; **VE/VCO_2-$_{RCP}$** = ventilatory equivalent for ventilation and carbon dioxide up to respiratory compensation point; **VE/VO_{2peak}** = ventilatory equivalent for ventilation and oxygen uptake at peak exercise; **VO_2** = oxygen uptake; **VO_2peak/kg** = oxygen uptake relative to body weight; **VR** = ventilatory reserve; **Wpeak** = peak work load; **Wpeak/kg** = peak work load relative to body weight; **ΔVO_2/Watt** = oxygen cost of work

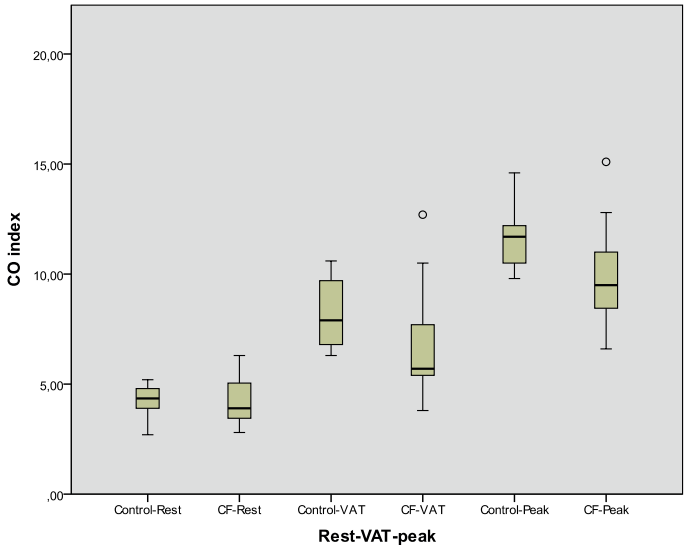


Figure 2. CO index at rest, VAT and peak in the control group and CF group

No significant differences (p = 0.66) were found between pwCF (88.1 ± 14.9 bpm) and HC (86.3 ± 11.0 bpm) for HR at rest. For both VAT (p = 0.015) and peak exercise (p < 0.001), HR was significantly lower in the CF group compared with the HC (Figure 3). CRI was significantly lower (p < 0.001) among pwCF (84.1 ± 11.2%), compared with HC (99.9 ± 8.1%). In addition, six of the pwCF could be categorized as chronotropic incompetent versus none of the HC (Table 2).

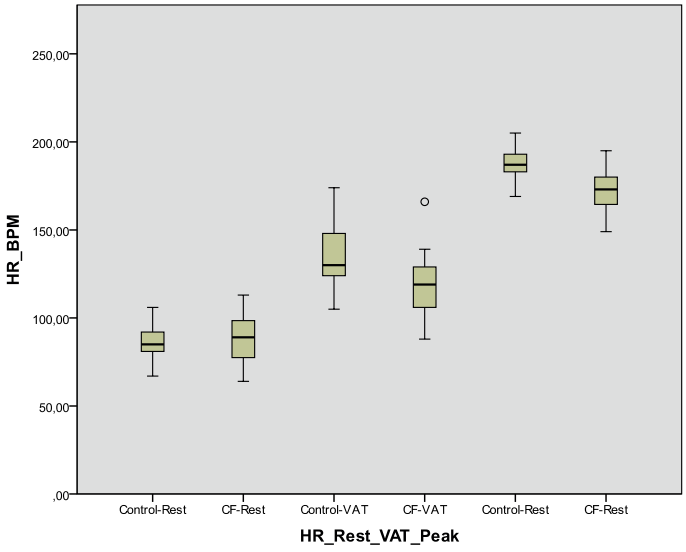


Figure 3. Heart rate at rest, VAT and peak in the control group and CF group

Furthermore, SV index did not differ significantly between pwCF and HC at both rest (p = 0.406) and peak exercise (p = 0.092). However, the SV index at VAT was significantly lower (p = 0.010) in pwCF (54.6 ± 14.3 ml/m^2) than in HC (61.0 ± 8.0 ml/m^2) (Figure 4 & Table 2).

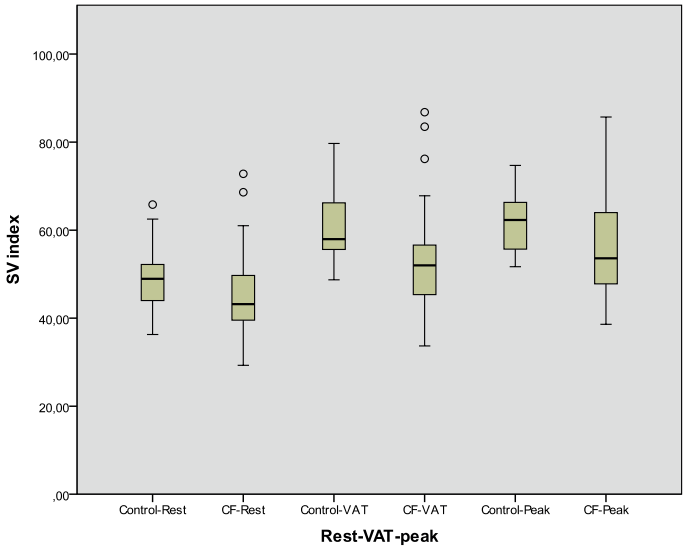


Figure 4. SV index at rest, VAT and peak in the control group and CF group

Additionally, O_{2pulse} did not differ significantly between both groups at rest (p = 0.84), VAT (p=0.56), or peak (p = 0.22) exercise (Table 2).

3.4 Subgroup analyses

With regard to patient characteristics, anthropometrics, presence of co-morbidities, medication, hemoglobin levels, pulmonary function, airway resistance, and ventilatory reserve the CRI subgroup analysis showed no significant differences between the pwCF who could be categorized as chronotropic incompetent (n = 6), and pwCF who could be categorized as competent (n = 13) (Table 3).

The second subgroup analysis based on reason for test cessation showed that the dyspnea group had significantly lower (p = 0.038) peak HR (165.1 ± 13.3 bpm) and HR_{peak} in percentage predicted (p = 0.006, 86.4 ± 6.3%) compared with the leg fatigue group (177 ± 9.7 bpm and 94.0 ± 4.3% respectively). In addition, the CRI was significantly lower (p = 0.008) in the dyspnea group (75.7 ± 11.1%) and more (p = 0.010) pwCF could be categorized as chronotropic incompetent (n = 5, 71.4%, versus n = 1, 8.3%) (Table 5). However, no significant differences were found for exercise capacity (p = 0.120), pulmonary function (p = 0.960), airway resistance (p = 0.354), or ventilatory reserve (p = 0.296) (Table 4).

Table 3. Subgroup analysis: Patient characteristics, anthropometrics, co-morbidities, CF mutations, medication, pulmonary function, and exercise response/capacity in chronotropic incompetent people with CF (n=6) and chronotropic competent people with CF (n=13)

Variable	**CRI< 80%** (n=6)	**CRI ≥ 80%** (n=13)	**Independent t-test/ Mann- Whitney U/ Chi-square/Fisher's Exact test** *p-value* (two-tailed)
Patient characteristics			
Sex (n, male%)	2 (33.3)	7 (53.8)	0.628
Age (years) - median 25-75th percentile	18.9 (17.0-23.0)	18.4 (14.6-27.1)	0.661
Anthropometrics			
BSA (m^2)	1.7 (0.3)	1.7 (0.2)	0.771
BMI (kg/m^2)	21.3 (1.6)	20.1 (2.6)	0.309
Co-morbidities			
Colonization with *P. Aeruginosa* (n,%)	4 (66.7)	7 (53.8)	1.000
Pancreas insufficient (n,%)	6 (100)	11 (84.6)	1.000
Presence of CFRLD (n,%)	1 (16.7)	4 (30.8)	1.000
Presence of CFRD (n,%)	3 (50.0)	5 (38.5)	1.000
Medication			
CFTR modulating therapy (n,%)	2 (33.3)	5 (38.5)	1.000
Azithromycin (n,%)	0 (0)	2 (15.4)	1.000
Bèta-2-mimetics (n,%)	0 (0)	2 (15.4)	1.000
Anticholinergics (n,%)	0 (0)	0 (0)	n.a.
Inhaled steroids (n,%)	0 (0)	1 (7.7)	1.000
Other			
Hb (mmol/l)	8.9 (0.6)	8.8 (0.5)	0.785
Pulmonary function			
FEV_1 (l) - median 25-75th percentile	2.7 (2.3-3.2)	2.7 (2.5-3.3)	-
$ppFEV_1$ (%)	72.0 (7.6)	75.1 (12.9)	0.597
Raw_{tot} kPa (l/s) - median 25-75th percentile	0.3 (0.3-0.5)	0.3 (0.3-0.4)	-
$ppRaw_{tot}$ (%)	117.3 (23.5)	116.9 (45.0)	0.981
Exercise response/capacity			
$ppVO_2$peak/kg(%)	60.3 (13.5)	81.1 (11.7)	**0.003***
VR (%)	30.7 (19.4)	11.6 (18.5)	0.055

P-value <0.05 is considered statistically significant as indicated in bold and with *
Abbreviations: BMI = body mass index; **BSA** = body surface area; **CF** = cystic fibrosis; **CFRD** = cystic fibrosis related diabetes; **CFRLD** = Cystic fibrosis related liver disease; **CFTR** = cystic fibrosis transmembrane conductance regulator; **FEV_1** = forced expiratory volume in one second; **Hb** = hemoglobin; ***P. Aeruginosa*** = *Pseudomonas Aeruginosa*; **$ppFEV_1$** = percentage predicted of forced expiratory volume in one second; **$ppRaw_{tot}$** = airway resistance in percentage predicted; **$ppVO_2$peak/kg** = oxygen uptake relative to body weight in percentage predicted; **Raw_{tot}** = airway resistance; **VR** = ventilatory reserve

Table 4. Subgroup analysis: Patient characteristics, anthropometrics, co-morbidities, CF mutations, medication, pulmonary function, and exercise response/capacity in people with CF reporting dyspnea (n=7) and leg fatigue (n=12) as reason for test cessation

Variable	Dyspnea (n=7)	Leg fatigue (n=12)	Independent t-test/ Mann-Whithney U/Chi-square *p-value* (two-tailed)
Patient characteristics			
Sex (n, male%)	3 (42.9)	6 (50.0)	1.000
Age (years) - median 25-75th percentile	19.4 (15.5-19.9)	18.4 (14.9-29.6)	0.661
Anthropometrics			
BSA (m^2)	1.7 (0.2)	1.7 (0.2)	0.771
BMI (kg/m^2)	21.1 (1.8)	20.1 (2.7)	0.309
Co-morbidities			
Colonization with *P. Aeruginosa* (n,%)	5 (71.4)	6 (50.0)	1.000
Pancreas insufficient (n,%)	7 (100.0)	10 (83.3)	1.000
Presence of CFRLD (n,%)	1 (14.3)	4 (33.3)	1.000
Presence of CFRD (n,%)	3 (42.9)	5 (41.7)	1.000
Medication			
CFTR modulators (n,%)	3 (42.9)	4 (33.3)	1.000
Azithromycin (n,%)	0 (0)	2 (16.7)	1.000
Beta-2-mimetics (n,%)	0 (0)	2 (16.7)	1.000
Anticholinergics (n,%)	0(0)	0 (0)	n.a.
Inhaled steroids (n,%)	0 (0)	1 (8,3)	1.000
Other			
Hb (mmol/l)	9.0 (0.6)	8.7 (0.4)	0.785
Pulmonary function			
FEV_1 (l) - median 25-75th percentile	2.8 (2.4-3.3)	2.7 (2.5-3.3)	
$ppFEV_1$ (%)	74.3 (9.2)	74.0 (12.8)	0.960
Raw_{tot} (kPa (l/s) - median 25-75th percentile	0.3 (0.3-0.5)	0.3 (0.3-0.4)	
$ppRaw_{tot}$ (%)	128.1 (31.5)	110.5 (42.4)	0.354
Exercise response/capacity			
$ppVO_2$peak/kg (%)	67.2 (12.5)	78.8 (16.0)	0.120
VR (%)	24.3 (14.6)	13.8 (22.8)	0.296

P-value <0.05 is considered statistically significant as indicated in bold and with *
Abbreviations: BMI = body mass index; **BSA** = body surface area; **CF** = cystic fibrosis; **CFRD** = cystic fibrosis related diabetes; **CFRLD** = Cystic fibrosis related liver disease; **CFTR** = cystic fibrosis transmembrane conductance regulator; **FEV_1** = forced expiratory volume in one second; **Hb** = hemoglobin; ***P. Aeruginosa*** = *Pseudomonas Aeruginosa*; **$ppFEV_1$** = percentage predicted of forced expiratory volume in one second; **$ppRaw_{tot}$** = airway resistance in percentage predicted; **$ppVO_2$peak/kg** = oxygen uptake relative to body weight in percentage predicted; **Raw_{tot}** = airway resistance; **VR** = ventilatory reserve

Table 5. Subgroup analysis: Cardiac output data at peak exercise for CF subgroups based on test cessation: dyspnea and leg fatigue

Variable	Dyspnea n=7	Leg fatigue n=12	Independent t-test/ Mann-Whitney U *p-value* (two-tailed)
PEAK Cardiac output			
HR peak (bpm)	165.1 (13.3)	177 (9.7)	**0.038***
ppHR peak (%)	86.4 (6.3)	94.0 (4.3)	**0.006***
CRI (%)	75.7 (11.1)	88.9 (8.2)	**0.008***
CRI <80% (n, %)	5 (71.4)	1 (8.3)	**0.010***
SV peak (ml)	100.1 (33.6)	94.4 (22.9)	
SV index peak (ml/m^2)	57.1 (14.5)	56.7 (10.1)	0.666
CO peak (l/min)	16.8 (5.7)	16.7 (3.8)	
CO index peak (l/min/m^2)	9.6 (2.6)	10.0 (1.8)	0.706
O_2p_{ulse} peak (ml/beat)	11.2 (2.6)	11.6 (3.8)	0.826

P-value <0.05 is considered statistically significant as indicated in bold and with *
Abbreviations: CF = cystic fibrosis; **CO** = cardiac output; **CRI**= chronotropic response index; **HR** = heart rate; **O_{2pulse}** = oxygen pulse; **ppHR peak** = heart rate peak in percentage predicted; **SV** = stroke volume

4.0 Discussion

This study illustrates that HR response could play an important role in the limited CO index, during exercise and consequently exercise intolerance, in people with moderate CF. The HR response showed a blunted rise during exercise and 31.5% of our pwCF could be categorized as chronotropic incompetent. The HR response in this chronotropic incompetence group cannot be sufficiently explained by differences in patient characteristics (specifically age), anthropometrics, medication affecting HR, the use of CFTR modulating therapy, hemoglobin levels or pulmonary function (Table 3).

Interestingly, the studies by van Iterson et al.[16,50] and Rodriguez et al.[17], which included CF populations with comparable characteristics regarding exercise capacity and pulmonary function, reported similar lower HR values[16,17,50], and HR_{peak} was even one of the predictors of peak exercise work rate in the study by van Iterson et al.[16]. Rodriguez et al. reported similar CO and SV values compared with HC values, unlike the lower values in our population and the population of van Iterson et al.[16,50]. Also,

the prevalence of CRI in their population was even slightly higher compared with what we found. Early termination of the CPET was ruled out as a possible explanation for the lower HR_{peak} [17].

As the majority of our pwCF had sufficiently ventilatory reserve during exercise, a mean $ppFEV_1$ of mild to moderate disease severity (only two participants had a $ppFEV_1 < 60\%$), and showed no signs of hypoxia nor any indications of abnormal airway resistance, a ventilatory limitation appears to be a less likely cause for this HR response.

Deconditioning and indications for impaired skeletal muscle oxidative capacity (e.g. ΔVO_2/Watt) were present in our CF group, which could result in exercise intolerance. However, in case of deconditioning as a main contributor of the HR response and lower CO index, one expects a higher HR at submaximal levels, e.g. at the VAT. Our group showed, however, an already lower HR at the VAT.

Given the similar values for SV index and O_{2pulse} for the CF group compared with the HC group during maximal exercise, it seems less likely that impaired cardiac contractility is a main contributor of the lower CO values in pwCF.

Furthermore, our confirmation sample (see Supplementary Table in Appendix) is in line with our primary results. The HR_{peak} and $ppHR_{peak}$ were slightly lower than expected, and 17.2% of this sample could be categorized as chronotropic incompetent.

Importantly, the exercise capacity levels of our population with CF were low, even in our younger pwCF. Studies have shown that no great improvement of exercise capacity is to be expected in pwCF with increasing age[51]. Combined with the fact that pulmonary function shows the steepest drop during puberty[52,53] and subsequently remains difficult to improve, this highlights the importance of early life style intervention/management with an emphasis on optimization of exercise capacity. Furthermore, these results underscore the importance of an individualized exercise training prescription with training HR and monitoring in pwCF.

The underlying mechanisms responsible for chronotropic incompetence in pwCF are not yet fully understood, but Mirakhur and Walshaw have described possible mechanisms that could cause autonomic neuropathy in CF, including metabolic (CFRD, CFRLD), nutritional (malnutrition, vitamin E deficiency) and immunological mechanisms[54]. In addition, chronotropic incompetence is often reported in patients with chronic obstructive pulmonary disease (COPD)[35,37,55]. Oxidative stress, recurrent hypoxemia, hypercapnia, airway obstruction and increased respiratory effort are described as possible causes for autonomic/chronotropic imbalance in COPD[35–37,55,56].

It is reported that functional CFTR channels are related to action potential shortening during strong adrenergic stimulation, and can cause increasing HR[57]. However, it remains unclear how dysfunctional CFTR channels operate during maximal exercise in pwCF, and no effect on HR_{peak} response was seen after four weeks of treatment with Sildenafil, a selective phosphodiesterase type V inhibitor reportedly acting directly in support of rescuing CFTR trafficking and correcting deficient CFTR transport activity[17,58,59]. The relationship between β2 adrenergic receptors and HR response in CF is still little understood. Van Iterson et al. reported no effect on HR 30 and 60 minutes after albuterol inhalation[60]. Serisier et al. reported no effect of a medium-high dose (600 µg albuterol) in moderate severity pwCF[61]. However, the effect of a high dose (e.g. 800 µg) of β2 agonist on HR during rest, submaximal and maximal exercise in pwCF without ventilatory limitations seems of interest in the light of our results.

Future longitudinal studies might focus on investigating the possible mechanisms for the chronotropic incompetence in pwCF, and so help to increase our understanding of CF and to improve the care of pwCF.

5.0 Conclusion

In young and adult pwCF the CO index during maximal exercise is significantly lower than in HC. In our group of pwCF with mild to moderately severe lung disease, chronotropic incompetence appears to play an important role in the impaired CO index response.

Statements and Declarations
Declarations of interest: none.
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Appendix

Confirmation sample
To reinforce our findings and to preclude a random finding, we used a confirmation sample that was extracted from the CF database of our center. Participants in this sample had signed informed consent in context of the Dutch CF registration cohort, which includes the use of standard-care data for scientific research purposes. We selected participants who had performed a CPET in the context of their annual CF outpatient clinic consult, in the last five years. To minimalize bias between this

confirmation sample and our primary sample, participants had to be at least 8 years and no older than 43 years of age. N= 120 tests were extracted and after selection, n= 64 tests could be selected. Inclusion criteria included not receiving CFTR modulating therapy related to study or standard care, peak RER of at least 1.03 and a ventilatory reserve of at least 15%.

Supplementary table: Confirmation sample of n=64 people with CF

Patient characteristics	
Sex (n, male%)	32 (50.0)
Age (years) - median 25-75th percentile	15.1 (10.3-18.0)
Height (cm)	160.6 (16.2)
Weight (kg)	49.8 (15.9)
BMI (kg/m^2)	18.8 (3.7)
Pulmonary function	
FEV_1 (l) - median 25-75th percentile	2.6 (2.0-3.4)
$ppFEV_1$ (%)	89.5 (15.3)
Heart rate variables	
HR rest (bpm)	93.4 (12.8)
HR peak (bpm)	178.4 (12.6)
ppHR peak (%)	94.5 (6.9)
CRI (%)-median 25-75th percentile	91.9 (81.2-98.5)
CRI <80% (n, %)	11 (17.2)
CPET derived variables	
RER peak - median 25-75th percentile	1.18 (1.14-1.25)
VR (%)-median 25-75th percentile	28.2 (22.4-40.1)
VO_2peak (l/min)	1.7 (0.7)
VO_2peak/kg – (ml/min/kg) median 25-75th percentile	35.8 (29.3-41.0)

Abbreviations: BMI = body mass index; **CF** = cystic fibrosis; **CPET** = cardiopulmonary exercise test; **CRI** = chronotropic response index; **FEV_1** = forced expiratory volume in one second **HR** = heart rate; **$ppFEV_1$** = percentage predicted of forced expiratory volume in one second; **ppHR peak** = heart rate peak in percentage predicted; **RER** = respiratory exchange ratio **VO_2** = oxygen uptake; **VO_2peak/kg** = oxygen uptake relative to body weight; **VR** = ventilatory reserve

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6

Chapter 7

a. Prevalence of severe fatigue among adults with Cystic Fibrosis: a single center study.

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Abstract

Background: With life expectancy increasing among patients with cystic fibrosis (CF), the prevalence of complications such as fatigue is also expected to increase. Our aim was to investigate the prevalence of severe fatigue among adults with CF and to identify factors associated with fatigue.

Methods: Adult patients with CF receiving treatment at a single center were invited to complete three questionnaires. We then studied the associations between fatigue and clinically measured parameters and between fatigue and patient-reported outcomes.

Results: A total of 77 patients (age 19–54 years; 56% males; mean FEV_1: 63%) completed the questionnaires (43% response rate). The prevalence of severe fatigue among these patients was 26%. The variance in fatigue was explained partially by clinically measured parameters. However, patient-reported outcomes were stronger independently associated with fatigue and included the patients' reported respiratory symptoms, emotional functioning, and social functioning.

Conclusions: Fatigue is a clinically important and highly prevalent issue among adults with CF and is associated with a significant reduction in health-related quality of life and participation in society. In addition, fatigue is associated more strongly with the patient's perception of symptoms and well-being than with clinically measured parameters.

1.0 Introduction

1.1 Expanding our focus on cystic fibrosis

Thanks to extensive research and improvements in patient care, the life expectancy of patients with cystic fibrosis (CF) now exceeds 50 years[1]. However, as a result of living longer with this chronic, life-threatening condition, many patients develop chronic or intermittent fatigue as they age[2,3]. Persistent fatigue can be highly debilitating, leading to reduced societal participation and increased psychological distress[4]. Therefore, researchers are increasingly interested in developing methods to manage these symptoms and increase the patient's health-related quality of life (HRQoL)[5].

1.2 Fatigue in cystic fibrosis

Despite the impact that fatigue can have on daily life, relatively few studies have examined the prevalence or extent of fatigue among patients with CF. We therefore performed a search regarding fatigue and CF in PubMed, Embase, and the Cochrane Library. This search revealed that Sawicki and colleagues reported that 77% of adult patients (age 19– 64 years) with CF reported a "lack of energy"[2]. Moreover, Jarad and colleagues found that fatigue is more common among patients with CF compared to healthy subjects[3]. Nevertheless, fatigue as a symptom is a distinct entity from severe, debilitating fatigue; normal fatigue can be experienced by anyone, whereas debilitating fatigue can lead to decreased functioning in daily life. Importantly, the prevalence of severe, debilitating fatigue has not been investigated among patients with CF.

1.3 Potential causes of fatigue

Precisely what causes fatigue in patients with CF is largely unknown. Given that fatigue is a complex phenomenon, it is likely that a multifactorial model will be needed in order to understand the cause of fatigue in these patients. Fatigue can be influenced by both biological and psychosocial factors, giving rise to the so-called biopsychosocial model[6]. In other chronic diseases such as rheumatoid arthritis, multiple sclerosis, and diabetes, fatigue was explained only partially by biological factors, requiring the addition of psychosocial factors such as social support and/or feelings of depression[7-9]. Whether decreased pulmonary function can serve as a biological predictor of fatigue in CF is currently a matter of debate[3].

Deconditioning and suboptimal nutritional status are other possible biological factors that may be related to more severe levels of fatigue[10]. Moreover, patients with CF often report poor sleep patterns and increased daytime drowsiness, which have been shown to be associated with reduced physical activity and increased fatigue[11].

Finally, fatigue can be associated with psychological factors, including depressive symptoms and anxiety, both of which are more prevalent among CF patients compared to the general population and have been correlated with fatigue in other chronic diseases[7-9,12].

1.4 Aim of the study

The aim of this study was to bridge the current knowledge gap with respect to: i) the prevalence of severe fatigue among adults with CF, and ii) the putative association between fatigue and clinically measured outcomes and patient-reported outcomes (PROs). Obtaining a better understanding of these factors may provide the foundation for developing future therapies directed at treating and/or preventing debilitating fatigue, thereby improving HRQoL.

2.0 Methods

2.1 Study design

In this cross-sectional, single-center study we recruited adult patients (≥18 years of age) with CF who were receiving treatment at our outpatient clinic at Utrecht University Medical Center. The following exclusion criteria were applied: patients with a pulmonary infection (defined as requiring supplemental antibiotics upon maintenance treatment and/or hospitalization at the time of inclusion); an active co-morbidity that was not related to CF (e.g. active arthritis); and patients who were unable to complete the forms and questionnaires in Dutch.

This study was conducted in accordance with the Declaration of Helsinki and was approved by our institution's Ethics Review Board. All included patients provided written informed consent.

2.2 Questionnaires

Participating patients were asked to complete validated questionnaires regarding fatigue, HRQoL, and physical activity. These three questionnaires were sent to the patient's home in August 2016 and were self-administered. If no response was received within four weeks, the non-responding participants received a telephone reminder. Data were collected from August 2016 through December 2016.

The Cystic Fibrosis Questionnaire version 1.2 (CFQ) was used to assess HRQoL. This validated questionnaire provides a CF-specific measure of HRQoL[13]. The CFQ consists of twelve subscales with a score ranging from 0 to 100 points; higher scores

represent reduced frequency of symptoms and higher HRQoL. Internal consistency was acceptable for most domains of the CFQ (Cronbach's alpha: 0.43–0.92), and test-retest reliability was high for all domain scores (0.72– 0.98).

The well-validated Checklist Individual Strength-20 (CIS-20) was used to assess fatigue[7,14,15]. In this questionnaire, the patient is asked about fatigue experienced in the previous two weeks and consists of the following four subscales: severity of fatigue, concentration, motivation, and activity. This questionnaire has good reliability (Cronbach's alpha: 0.83–0.92) and discriminative validity. A score of 35 or higher on the severity of fatigue subscale is used to define severe fatigue in adults[14].

For physical activity, we used the Habitual Activity Estimation Scale (HAES), a well-validated questionnaire for assessing physical activity in patients with CF[16]. Patients were instructed to complete the questionnaire for a typical weekday and a typical Saturday within the previous two weeks. The percentage of time spent awake was categorized as: inactive, somewhat inactive, somewhat active, or very active. The total number of hours being active and the total number of hours being inactive were calculated for weekdays, weekend days, and overall. The intra-class correlation coefficient of reliability for the HAES was estimated at 0.72 ($P < 0.0001$).

2.3 Clinical assessments

To link the data gathered via the questionnaires with the most up-to-date disease status, we searched the patient's medical records for the clinically measured parameters measured closest to time at which the questionnaires were completed. The patient's demographics and disease-specific clinically measured parameters were searched for up to 18 months prior to the time at which the questionnaires were completed. The following data were collected: age, gender, body mass index (BMI), presence of diabetes (CF-related or otherwise), presence of liver disease, gene mutations, number of hospitalizations, whether the patient's respiratory tract was colonized with *P. Aeruginosa* (i.e., whether *P. Aeruginosa* was present in two or more cultures performed in the preceding year), and whether the patient had received antibiotics (not including maintenance treatment) during the past 18 months.

CF-specific parameters included FEV_1 (the percentage of predicted forced expiratory volume in one second) and the following three symptom scales from the CFQ questionnaire: weight, respiratory symptoms, and digestive symptoms. FEV_1 was calculated using the global lung function reference equations published in 2012[17]. The Modified Shuttle Test (MST) and the peripheral muscle strength test were used

to objectively measure exercise capacity[18,19]. In addition, peripheral muscle strength was measured using a Cybex dynamometer (Lumex, Ronkonkoma, NY) in order to assess the maximum isometric quadriceps strength for the patient's dominant leg[19].

2.4 Statistical analysis

Descriptive statistics were used to summarize the demographics and clinical characteristics of the patients and to describe the prevalence of fatigue and the disease status. In the event that a test for normality yielded a value <0.05 (indicating an abnormal distribution), the median value is provided together with the 25th–75th percentile range. In the event that the test for normality revealed a normal distribution, the mean and standard deviation are provided.

A linear regression analysis was performed for all variables in order to assess the effect size and the significance of the relationship with fatigue. Effect sizes of <0.5, 0.5–0.8, and > 0.8 were considered small, moderate, and large, respectively. In these analyses, fatigue was used as a continuous variable. In the published literature, both age and gender are described as important factors associated with fatigue, including chronic fatigue[20]; therefore, both age and gender were used as covariates in all analyses. All analyses were performed using SPSS version 21, and differences with a P-value < 0.05 were considered statistically significant.

3.0 Results

3.1 Characteristics of the study population

A total of 180 patients were invited to participate in this study, and 77 patients completed and returned the three questionnaires (corresponding to a response/participation rate of 43%). The reasons given for not participating were the time investment required and having to complete too many questionnaires. There was no significant difference between the responders and non-responders with respect to their baseline patient characteristics, with the exception that a significantly smaller percentage of non-responders received antibiotics compared to the responders (40.9% vs. 63.2%, respectively; P = 0.008). Patients who previously underwent a lung transplantation were excluded from the initial recruitment phase; however, two of the 77 responding patients underwent a lung transplantation during the inclusion period and were therefore included in the analysis.

Table 1 summarizes the demographics and clinical characteristics of the study population. The median age among the 77 adult patients was 28 years (range: 19–54 years), and the mean FEV_1 (±SD) value was 63 ± 22.4% (range: 21–106%).

3.2 Prevalence of severe fatigue

The mean score for all 77 patients on the CIS fatigue severity subscale was 29.1 ± 12.2; in contrast, the mean score in a healthy population is 23.0[4]. Of the 77 patients in our study, 20 (26%) were categorized as severely fatigued, which was defined as a score of 35 or higher on the CIS fatigue severity subscale[14].

3.3 Fatigue and clinically measured parameters

On average, severe fatigue was more prevalent among older patients ($\beta = 0.38$; $P = 0.001$; $R^2 = 0.135$). In addition, the use of antibiotics was less common among patients with higher fatigue scores ($P = 0.013$; $R^2 = 0.067$). We also found that having a higher fatigue score was associated with lower FEV_1 ($\beta = -0.37$; $P = 0.001$; $R^2 = 0.123$).

With respect to exercise capacity assessed using the MST, patients with higher fatigue scores performed significantly worse (i.e., ran a shorter average distance) than patients with lower fatigue scores ($\beta = -0.44$; $P < 0.001$; $R^2 = 0.183$). In contrast, we found no correlation between peripheral muscle strength and fatigue score ($\beta = -0.03$; $P = 0.810$).

The results of our association analysis are summarized in Table 2.

3.4 Fatigue and patient-related outcomes

The mean CFQ scores (on a range of 1–100) were 81.0 ± 28.3, 62.9 ± 18.8, and 80.3 ± 20.4 for respiratory symptoms, digestive symptoms, and weight, respectively. Our analyses revealed that a higher fatigue score was associated with an increased prevalence of respiratory symptoms ($\beta = -0.61$; $P < 0.001$; $R^2 = 0.359$), digestive symptoms ($\beta = -0.43$; $P < 0.001$; $R^2 = 0.174$), and difficulty retaining weight ($\beta = -0.52$; $P < 0.001$; $R^2 = 0.263$). In addition, respiratory symptoms were significantly correlated with FEV_1 ($\beta = 0.48$; $P < 0.001$; $R_2 = 0.148$). The results of these analyses are summarized in Table 3 and Supplementary Table S1.

Having a higher fatigue score was also associated with lower physical activity scores reported on the HAES questionnaire ($\beta = -0.34$; $P = 0.003$; $R^2 = 0.100$). In addition, lower physical activity scores were significantly correlated with lower MST scores ($P = 0.005$). Finally, a higher fatigue score was significantly associated with reduced HRQoL as reported for all domains in CFQ, including physical functioning ($\beta = -0.71$; $P < 0.001$; $R^2 = 0.501$), vitality ($\beta = -0.79$; $P < 0.001$; $R^2 = 0.611$), emotional functioning ($\beta = -0.61$; $P < 0.001$; $R^2 = 0.364$), social functioning ($\beta = -0.65$; $P < 0.001$; $R^2 = 0.416$), burden of therapy ($\beta = -0.46$; $P < 0.001$; $R^2 = 0.204$), and perception of health ($\beta = -0.64$; $P < 0.001$; $R^2 = 0.402$).

Table 1. Descriptive characteristics of the patients with CF in this study.

	Patients (n = 77)	**Severely fatigued patients** [a] (n = 20)	**Not severely fatigued patients** (n = 57)
Patient characteristics			
Age in years, median (25th–75th percentile)	28.4 (23.7–35.7)	32.0 (26.7–41.5)	27.5 (23.3–35.4)
Male, n (%)	43 (56%)	10 (50%)	33 (58%)
BMI in kg/m^2, median (25th–75th percentile)	21.9 (20.4–24.2)	22.1 (19.6–24.7)	21.9 (20.7–24.2)
Mutation in the CFTR gene			
Homozygous F508del mutation	43 (56%)	9 (53%)	34 (60%)
Heterozygous F508del mutation	24 (31%)	5 (29%)	19 (33%)
Other	7 (9%)	3 (18%)	4 (7%)
Unknown	3 (4%)	3 (15%)	0 (0%)
Co-morbidities			
Diabetes, n (%)	29 (38%)	5 (25%)	24 (42%)
Liver disease, n (%) [b]			
- No liver disease	36/40 (90%)	8/8 (100%)	28/32 (88%)
- Liver disease without cirrhosis	1 (3%)	0 (0%)	3 (9%)
- Cirrhosis without hypertension	3 (8%)	0 (0%)	1 (3%)
Colonization with *P. Aeruginosa*, n (%)	36 (47%)	10 (50%)	26 (46%)
Disease outcome			
Received antibiotics, n (%)	48 (62%)	8 (40%)	40 (70%)
Hospitalization in the past year, n (%)	35 (45%)	11 (55%)	24 (42%)
FEV_1 in %pred, mean (SD)	63% (22.4)	57.2 (23.6)	65.2 (21.8)
Meters run on Modified Shuttle Test, median (25th–75th percentile)	1125 (815–1500)	1005 (527–1203)	1180 (910–1500)
Peripheral muscle strength in Newton, mean (SD)	207 (60.6)	210 (58.3)	206 (61.9)

Abbreviations: BMI, body mass index; **FEV_1**, predicted percentage of forced expiratory volume in 1 s; **SD**, standard deviation

[a] Severely fatigued patients are defined as scoring 35 or more on the CIS-20.

[b] Data were available for 40 patients only.

Table 2. Association between higher fatigue scores and clinically measured parameters.

Clinical parameters	Univariate analyses			Multivariate analyses[a]	
	Effect size (β)	*p-value*	Adjusted R^2	Effect size (β)	*p-value*
Patient characteristics					
Age	0.38	**0.001**	0.135		
Gender	-0.11	0.349	-0.001		
BMI	0.18	0.117	0.020	0.08	0.486
Co-morbidities					
Diabetes	-0.14	0.223	0.007	-0.32	**0.003**
Presence of liver disease[b]	-0.27	0.088	0.050	-0.13	0.465
Colonization with *P. Aeruginosa*	0.13	0.273	0.003	0.10	0.362
Disease outcome					
Received antibiotics	-0.28	**0.013**	0.067	-0.25	**0.017**
Prevalence of hospitalization	0.08	0.491	-0.007	0.10	0.350
FEV_1	-0.37	**0.001**	0.123	-0.31	**0.004**
Meters run on Shuttle Run Test	-0.44	**<0.001**	0.183	-0.42	**0.002**
Peripheral muscle strength	-0.03	0.810	-0.017	-0.03	0.818

Abbreviations: BMI, body mass index; **FEV_1**, predicted percentage of forced expiratory volume in 1 s
Differences with a P-value <0.05 were considered statistically significant as indicated in bold
[a] Multivariate analyses were adjusted for age and gender
[b] Analyses were based on 40 patients only

Table 3. Relationship between higher fatigue scores and PROs.

Patient-reported outcomes	Univariate analyses			Multivariate analyses[a]	
	Effect size (β)	*p-value*	Adjusted R^2	Effect size (β)	*p-value*
Disease activity					
CFQ weight	-0.52	**<0.001**	0.263	-0.54	**<0.001**
CFQ respiratory symptoms	-0.61	**<0.001**	0.359	-0.55	**<0.001**
CFQ digestion	-0.43	**<0.001**	0.174	-0.41	**<0.001**
Physical activity					
HAES week + weekend Total Inactive	0.19	0.096	0.024	0.16	0.134
HAES week + weekend Total Active	-0.34	**0.003**	0.100	-0.26	**0.015**
Health-related quality of life					
CFQ physical	-0.71	**<0.001**	0.501	-0.66	**<0.001**
CFQ emotional	-0.61	**<0.001**	0.364	-0.60	**<0.001**
CFQ social	-0.65	**<0.001**	0.416	-0.60	**<0.001**
CFQ burden of therapy	-0.46	**<0.001**	0.204	-0.42	**<0.001**
CFQ perception of health	-0.64	**<0.001**	0.402	0.63	**<0.001**

Abbreviations: CFQ, Cystic Fibrosis Questionnaire; **HAES**, Habitual Activity Estimation Scale.
Differences with a P-value <0.05 were considered statistically significant as indicated in bold.
[a] Multivariate analyses were adjusted for age and gender.

4.0 Discussion

4.1 Main results

Our analysis revealed that 26% of adults with CF in our sample report experiencing severe fatigue, suggesting that this is a common health issue among this patient population. Importantly, this prevalence is higher than has been reported in the general population, which ranges from 15% to 22%, depending on the population and the way in which fatigue was measured[4,14,21,22].

Another important result is that in our patient population, the patients' perception of symptoms and well-being (measured using the CFQ and HAES) are more strongly correlated with severe fatigue than clinically measured parameters (e.g. FEV_1 and exercise capacity). Specifically, we found that a higher fatigue score is associated with a significant decrease in the patient's perception of physical, emotional, and social functioning, and with a significant increase in the patient's perceived symptoms.

4.2 Results in the context of published findings

Our results shed new light on the perception of fatigue among adult patients with CF. With respect to characterizing fatigue as a clinically significant symptom in patients with CF, our results are consistent with results obtained by Sawicki et al.[2] and Friedman et al.[23], who reported that a lack of energy is highly prevalent (73% and 77%, respectively) and distressing. Interestingly, these studies attributed the patients' lack of energy primarily to chronic respiratory effects associated with CF and to sleep problems. However, these authors measured lack of energy as a symptom, without using a clear cut-off value for defining an impact on daily life.

Jarad and colleagues examined the association between fatigue and several clinically measured parameters[3]. They found no clear correlation between fatigue (measured using the Chalder Fatigue Questionnaire) and parameters of disease activity, including spirometry, BMI, hemoglobin level, C-reactive protein level, or the burden of pulmonary exacerbation. In contrast, we found a correlation between fatigue and spirometry, although the correlation between fatigue and patient-reported outcome was stronger. Consistent with our findings, Jarad et al. reported that the subjective aspects of somatic and psychological symptoms may be the primary cause of the higher perception of increased fatigue[3].

Habib et al. conducted a systematic review of HRQoL in CF and found that FEV_1 and pulmonary exacerbation have the broadest impact on HRQoL and therefore should remain the focus of attention when treating patients with CF[5]. On the other hand, our data suggest that HRQoL should not be the sole patient-reported outcome that is taken into account; indeed, fatigue is also an important determinant of well-being and participation in society.

4.3 Toward a multidimensional explanation for fatigue

Fatigue has been studied more extensively in chronic diseases other than CF. It is therefore plausible that physical factors such as FEV_1 may partially explain the severity and extent of fatigue. With a complex phenomenon such as fatigue, physical factors, social factors, and psychological factors—as well as interactions between these factors—all play a role; thus, the key to understanding the role of fatigue in CF may lie in identifying the multidimensional cause and in understanding the dynamic interplay between mind and body[6]. In rheumatic diseases, disease-related factors have been associated with fatigue; however, patient-reported factors such as physical inactivity, sleep disturbances, and feeling depressed explained the majority of the variation in fatigue within this patient population[24]. In addition, patients who undergo a kidney transplantation also have a stronger correlation between fatigue and several patient-reported outcomes than between fatigue and transplant-related

factors; these PROs include pain, discrepancies with respect to social support, depressive symptoms, and sleep problems[25]. Research in multiple sclerosis has also shown that psychosocial factors can influence fatigue[9]. With respect to respiratory conditions, it is interesting to note that Spruit et al.[15] recently described a model in which factors can precipitate and perpetuate fatigue in patients with COPD; such a model may also be applicable to patients with CF. This suggests that new therapies should focus on both somatic aspects (e.g. controlling disease and providing exercise therapy) and psychosocial aspects, thereby changing the patient's self-perception, for example using cognitive behavioral therapy (CBT). Importantly, this combined approach was effective in fatigued patients with COPD[15], and a similar approach has been effective in other patient groups, including survivors of breast cancer, patients with type 1 diabetes, and patients with facioscapulohumeral muscular dystrophy[26-28]. Thus, we suggest that interventions such as CBT and/or graded exercise are worth investigating in fatigued patients with CF.

4.4 Fatigue and physical exercise capacity

In exploring the possible underlying causes of fatigue, another consideration is the significant association between the severity of fatigue and physical exercise capacity measured using the MST. Our analysis revealed an association between physical exercise capacity and the perception of physical activity measured using the CFQ. Moreover, the association between perceived physical activity and fatigue was stronger than the association between measured physical exercise capacity and fatigue. Whether fatigue decreases physical activity, or whether low levels of physical activity lead to deconditioning and therefore the subjective feeling of fatigue, is currently a topic of debate. Daily activity is positively correlated with aerobic capacity and may influence the patient's experience of fatigue[10]. However, because perception also seems to play an important role, simply improving physical capacity without addressing the patient's perception of physical abilities and functioning might not be sufficient.

4.5 Strengths of this study

This study has several important strengths. First, this is the first study designed to determine the prevalence of severe fatigue among adult patients with CF, and it is the first study to investigate the association between fatigue and measures of HRQoL in addition to clinically measured parameters in this patient population. Moreover, we measured fatigue using a validated questionnaire that is commonly used in patients who are chronically ill, including patients with rheumatic disease and COPD; importantly, this questionnaire has a clear cut-off value for defining severe fatigue[7,14,15].

4.6 Limitations of this study

This study also has several limitations that warrant discussion. First, the study included a relatively modest number of participants and had a risk of non-response bias, particularly given the 43% response rate. Nevertheless, our patient characteristics are similar to larger cohorts of patients in the US and the UK with respect to mean FEV_1 (63%) and mean age (28.4)[29]. Although our analysis revealed that non-responders were generally similar to responders, significantly fewer non-responders received antibiotics compared to responders; similarly, the use of antibiotics was lower among fatigued patients compared to non-fatigued patients. If response bias played a role in this finding, we might expect that more patients with severe fatigue would not have participated in the study; in this case, the actual percentage of adults with CF who are severely fatigued might be even higher than in our study cohort. Nevertheless, given that our results show that fatigue is more prevalent among adults with CF than in the general population, these results should be validated in a larger—preferably longitudinal—cohort study. Second, the cross-sectional design of the study precluded the ability to link the study to a hospital visit. Therefore, the relationship between fatigue and the latest clinically measured parameters might be more direct in some cases than in others. Third, assessing different PROs at the same point in time can potentially subject the data to shared method variance, which may have affected the measured associations between fatigue and other PROs. Nevertheless, all three questionnaires are well-validated tools that measure distinct concepts; therefore, we believe that this approach provided the most effective measures of severe fatigue, quality of life, and activity. Finally, the use of the CFQ version 1.2 is a limitation. In current literature, there is a preference for the CFQ revised version[5]. The CFQ version 1.2 is a validated questionnaire in Dutch and the majority of questions in version 1.2 are similar to the CFQ revised version. Nevertheless, we recommend using the CFQ-R version in future studies.

4.7 Clinical implications

Our findings underscore the need for improved structural measurements of PROs with respect to physical and psychosocial domains—in addition to clinically measured parameters—among patients with CF. With a symptom as prevalent as fatigue, a relatively simple, validated screening questionnaire may be clinically useful. For example, the CIS, which provides a clear cut-off value for determining severe fatigue, could help initiate a conversation regarding the patient's well-being in the context of functional limitations. This approach would improve patient-centered care and may create new opportunities for the timely prevention of severe, debilitating fatigue in these patients.

4.8 Recommendations for future research

Both severe fatigue and chronic fatigue are generally well treatable in patients with chronic disease[26-28]. Ideally, future studies should measure fatigue and associated biological and/or psychosocial factors using a longitudinal design, thereby helping identify factors that can serve as predictors of fatigue. We found that fatigue is associated with reduced emotional functioning; therefore, future studies should investigate further which psychosocial factors are associated with fatigue. For example, depressive symptoms should clearly be taken into account, given that these symptoms are frequently correlated with fatigue in other patient populations, and given their increased prevalence among patients with CF[12]. However, several studies regarding various chronic diseases found that severe fatigue may not necessarily be merely an expression of depression, as only a portion of severely fatigued patients have depressive symptoms[8,25,30]. Furthermore, future studies should be designed in order to develop tailored interventions—or combinations of interventions—to reduce fatigue, for example CBT and/or graded exercise therapy.

5.0 Conclusions

Our results indicate that fatigue is an important and prevalent condition among adults with CF and can lead to a significant reduction in health-related quality of life. In addition, fatigue is associated more strongly with the patient's perception of symptoms and well-being than with clinically measured parameters. We therefore recommend that clinicians screen patients with CF for severe fatigue during hospital visits and—if necessary—initiate a conversation with the patient with respect to their fatigue and well-being. This proactive approach will likely improve patient-centered care.

Conflict of interest

The authors have no competing interests to report.

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Supplementary Table S1. Summary of the associations between a higher fatigue score and all nine CFQ subscales

Univariate analyses			
Health-related quality of life	**Effect size (β)**	***p-value***	**Adjusted R^2**
CFQ Physical	-0.71	<0.001	0.501
CFQ Vitality	-0.79	<0.001	0.611
CFQ Emotional	-0.61	<0.001	0.364
CFQ Social	-0.65	<0.001	0.416
CFQ Burden of therapy	-0.46	<0.001	0.204
CFQ Perception of Health	-0.64	<0.001	0.402
CFQ Role	-0.56	<0.001	0.302
CFQ Body Image	-0.59	<0.001	0.335
CFQ Eating Disorders	-0.27	0.016	0.062

Abbreviations: CFQ, Cystic Fibrosis Questionnaire

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b. Letter to the Editor: 'Anemia and iron deficiency in relation to fatigue in cystic fibrosis'

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William F Flight

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Dear Editor,

We welcomed Nap-van der Vlist and colleagues' recent paper on severe fatigue in people with cystic fibrosis (CF)[1]. Their study corroborates the work of previous investigators to highlight fatigue as a significant cause of morbidity in CF which is often neglected over pulmonary and gastrointestinal manifestations of the condition.

We feel, however, that the authors have not accounted for common and potentially treatable causes of fatigue in CF, namely anemia and iron deficiency. Iron deficiency has been shown repeatedly to be very common in CF, affecting up to 74% of adults, with anemia seen in as many as 29%[2,3]. Although Jarad and colleagues found no statistical correlation between fatigue and hemoglobin levels, their data were drawn from a small, single-center cohort of only 44 patients and no information on iron status was provided[4].

Identification and correction of iron deficiency in CF is a challenge. Gifford and colleagues found no benefit in hemoglobin levels following six weeks of oral iron supplementation in adults with CF[5]. Hoo and Wildman have previously raised concerns over the safety of intravenous iron therapy in CF having reported a high rate of clinical deterioration following IV iron infusion in a small case series of five patients[6]. Conversely, however, correction of iron deficiency using intravenous iron has been shown to improve fatigue and exercise tolerance in a variety of other chronic conditions such as heart failure and rheumatoid arthritis[7], even in the absence of anemia, with no safety signal seen in randomized controlled trials of IV iron in the setting of critical illness[8,9].

It would be of great interest to interpret the rates of fatigue seen in the study by Nap-van der Vlist and colleagues with the addition of data on iron deficiency and anemia. There is a clear need for prospective studies of intravenous iron therapy in people with CF, which has the potential to have a significant impact on the wellbeing and fatigue levels in this group.

Conflict of interest statement

The authors have no conflict of interest to declare related to this manuscript.

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c. Authors' response: Letter to the editor 'Anemia and iron deficiency in relation to fatigue in Cystic Fibrosis'.

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Dear Editor,

We thank both Drs Talbot and Flight for their interest in our study regarding fatigue in adults with Cystic Fibrosis[1,2]. We fully agree that any opportunity to alleviate the burden of CF morbidity should be evaluated, and therefore read with great interest the postulated role of anemia and iron deficiency on fatigue. Unfortunately, these parameters are not assessed routinely in all participating patients. Data on iron deficiency in particular were not generally available. Furthermore, one cannot conclude that a lower Hb automatically indicates an iron deficiency[3,4].

Future research can shed light on the current controversy regarding the causality of iron deficiency and anemia in CF, and how to combat it. We do wish to highlight that there is currently much discussion about the cause of anemia in CF and how best to treat it. Fischer et al. pointed out that anemia in CF may be a symptom of chronic inflammation, rather than a primary aspect of the disease[5]. They suggest that it is preferable to focus treatment on the underlying chronic inflammation rather than on iron supplementation. In addition, reliable measurement of iron deficiency in patients with chronic diseases is a challenge[6,7].

Also, we would like to emphasize that fatigue should be evaluated in a multidimensional model, where both somatic parameters and psychological factors are integrated. This is particularly important as causality of fatigue by anemia has yet to be proven[8] and there is a growing body of evidence that trans diagnostic factors, such as psychosocial factors, appear to surpass disease-specific variables when it comes to explaining the variance in fatigue[9]. Therefore, a personalized approach focused on the patient's needs and all treatable factors for fatigue, might be preferable over a disease-specific approach.

We suggest to consider anemia and also iron status into account in the work-up of a fatigued patient with CF, but we also suggest to expand our focus from biological aspects alone to the environmental, social and psychological factors that might trigger and perpetuate fatigue.

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Chapter 8

Long-term effects of ivacaftor on nonpulmonary outcomes in individuals with Cystic Fibrosis, heterozygous for a S1251N mutation

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Abstract

Objectives: To describe the long-term effects of ivacaftor (KALYDECO®) in individuals with Cystic Fibrosis (CF) on body mass index (BMI), body composition (BC), pulmonary function (PF), resting energy expenditure (REE), and exercise capacity (EC) after ≥12 months of treatment.

Working hypothesis: BMI, lean and fat mass, PF, and EC will increase and REE will decrease after treatment.

Study design: Observational study.

Methodology: 7 individuals with CF (mean age 15.4 ± 5.8 years) heterozygous for S1251N mutation, starting with ivacaftor, were included. Paired t-tests were performed to assess the effects of ivacaftor. Height and weight were used to calculate BMI and BMI Z-scores. Dual-energy X-ray absorptiometry was used to assess BC. Spirometry and body plethysmography were used to assess PF. Indirect calorimetry was used to measure REE and cardiopulmonary exercise testing (CPET) was used to measure oxygen uptake (VO_{2peak}), peak work rate (W_{peak}), and other CPET variables.

Results: After a median of 15 [IQR 13-16] months of treatment, BMI increased significantly (p=.03), but not BMI Z-score (p=.23) or BC. Significant improvements were found for several PF variables, especially measures of hyperinflation (p=.02). Absolute VO_{2peak} (p=.01), VO_{2peak} related to body weight (p=.00), and oxygen cost of work (p=.01) decreased. Absolute W_{peak} (p=.59) and W_{peak} related to body weight (p=.31) remained stable.

Conclusions: The results showed that long-term treatment of ivacaftor is associated with improvement of BMI and PF, but not of BC and REE. Oxygen uptake reduced after treatment, which may be due to a decrease in work of breathing.

1.0 Introduction

The prevalence of the S1251N mutation in Dutch individuals with Cystic Fibrosis (CF) is 1.2%[1]. This so-called gating mutation is characterized as a class III mutation[2] with a defective activity of the CFTR chloride channel[3].

Ivacaftor (KALYDECO®, Vertex Pharmaceuticals Inc.) is a CFTR potentiator that partially restores CFTR channel activity[4]. It has been shown in individuals with gating mutations that during ivacaftor treatment, pulmonary function improves, with a significant decrease of pulmonary exacerbations[4,5]. In addition, increases of body mass index (BMI), changes of body composition involving increases in fat mass and lean mass, and reductions of resting energy expenditure (REE) after treatment with ivacaftor are reported in literature as well[6,7].

Peak oxygen uptake (VO_{2peak}), often used as a measure for exercise capacity, is of particular clinical importance in individuals with CF given as it is associated with quality of life[8], reduced risk of hospitalization[9], and longevity[10]. Results from other studies indicate that ivacaftor improves exercise duration and capacity[5,11,12]. However, long-term effects on exercise capacity are unknown. Based on the described results of previous studies, we hypothesized that BMI, both lean and fat mass, and pulmonary function would increase after treatment with ivacaftor, while REE would probably decrease after treatment. These hypothesized effects would result in an improved exercise capacity after treatment as well.

The aim of this study was to describe the effects of ivacaftor in individuals with a CFTR gating mutation on BMI in particular body composition, pulmonary function, REE, and exercise capacity after at least 12 months of treatment.

2.0 Materials and methods

This was a single center (University Medical Center Utrecht, the Netherlands) observational study in both young and adult individuals with CF with a S1251N mutation. All individuals started a regimen of ivacaftor (two times/day 150 mg) before July 2015, in the context of standard care. All individuals, heterozygous for S1251N mutation, who were at the time under treatment in the CF Center Utrecht were included for this observational study, resulting in a sample size of seven individuals. These individuals were eligible, as ivacaftor was indicated for this specific mutation. All clinical and demographic data from routine outpatient visits were collected from the electronic patient records. Routine CF care was unchanged

and no prescribed exercise program was included. All individuals signed informed consent in context of the Dutch CF registration cohort, which includes the use of standard-care data for scientific research purposes.

2.1 Anthropometrics and body composition

Measurements of body weight and height were performed, in a fasting state, using a calibrated electronic scale (Seca, Hamburg, Germany) and stadiometer (Ulmer Stadiometer, Ulm, Germany). The subjects were dressed in lightweight clothing and not wearing any footwear while the measurements were taken. BMI was calculated by dividing body weight in kilograms by height in meters squared. Z-scores for body weight, height and BMI were calculated based on the fifth national growth study of TNO (present for ages < 21 years) (2010)[13]. Whole body dual-energy x-ray absorptiometry (DEXA) (type Discovery 4500 APEX 5.4, Philips) was used to measure fat and lean mass to determine body composition. The institutional DEXA standard operating procedure (SOP) was followed.

2.2 Pulmonary function

Pulmonary function (Geratherm, Bad Kissingen, Germany) was assessed by using spirometry and body plethysmography conform the ERS/ATS recommendations[14] and were used to assess pulmonary function. Global lung function reference equations published in 2012 were used[15].

2.3 Resting energy expenditure

Indirect calorimetry was used to estimate REE by measuring VO_2 and VCO_2 exhalation. Individuals were measured in a fasted and rested state of at least eight hours. REE measurements were executed between 08:30 AM and 09:30 AM. For the measurement, individuals breathed through an air-tight face mask that covers both mouth and nose (Hans Rudolph Inc., Shawnee, USA), connected to a calibrated metabolic cart (Geratherm, Bad Kissingen, Germany). In the test situation the individuals were instructed to lie still in the supine position for 20 minutes. Data of the first 10 minutes were eliminated to achieve data of steady state ventilation. The institutional SOP was followed. The Weir equation[16] was used to calculate REE.

2.4 Exercise capacity

Cardiopulmonary exercise testing (CPET) on a bicycle ergometer, with gas analysis was used to assess oxygen uptake and peak work rate. Peak oxygen uptake (VO_{2peak}), peak oxygen uptake related to body weight ($VO_{2peak/kg}$), and peak oxygen uptake related to lean body mass ($VO_{2peak/lean}$) were determined. Not only peak work rate (W_{peak}), but also peak work rate related to body weight ($W_{peak/kg}$), and peak work rate related to lean body mass ($W_{peak/lean}$) were determined. Percentages of predicted

value for VO_{2peak}, $VO_{2peak/kg}$, W_{peak} and $W_{peak/kg}$, were calculated based on reference equations: $ppVO_{2peak}$, $ppVO_{2peak/kg}$, ppW_{peak}, $ppW_{peak/kg}$. For all individuals 18 years and younger, reference equations from Bongers et al.[17] were used for oxygen uptake and peak work rate. For individuals over 18 years, reference equations from Mylius et al.[18] were used for oxygen uptake, and equations from van de Poppe et al.[19] were used for peak work rate. Complete gas-analysis variables were collected during CPET. Breathing frequency at maximal exercise (BF_{peak}), tidal volume at maximal exercise (Vt_{peak}) to calculate BF_{peak}/Vt_{peak}, oxygen cost of work ($\Delta VO_2/WR$), and the respiratory exchange ratio (RER) were assessed. In addition, heart rate was measured by electrocardiography. Objective criteria to assess the quality of the performed effort were 1) peak heart rate ≥100% [20] predicted, and 2) RER exceeds 1.03 in children and adolescents [21] and 1.05 in adults.[22] Individuals had to meet at least one out of two objective criteria for the test to be considered as maximal effort, as advised in the statement of exercise testing in CF by Hebestreit et al.[23].

All participants performed a CPET, according to the Godfrey protocol, on an electronically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands)[24]. During the test, individuals breathed through an air-tight face mask (Hans Rudolph Inc., Shawnee, USA), connected to a calibrated metabolic cart (Geratherm, Bad Kissingen, Germany).

2.5 Statistical analysis

Descriptive statistics were used to summarize demographics and clinical characteristics. Distribution of the data was assessed by Q-Q plots and values are reported with the mean ± SD in case of normal distributed data, and with median ± interquartile ranges (IQR) in case of non-normal distributed data. Ivacaftor treatment effects were analyzed by two-tailed paired samples t-tests (Table 1 and 2).

Due to the small sample size and the prospective prevention of Type I errors in the statistical analysis, we only included the following outcome variables to assess changes in pulmonary function: forced expiratory volume in one second in percentage predicted ($ppFEV_1$), ratio of residual volume (RV) and total lung capacity (TLC) (RV/TLC). For the CPET variables, we included only $ppVO_{2peak}$, $ppVO_{2peak/kg}$, ppW_{peak}, $ppW_{peak/kg}$, and $\Delta VO_2/WR$.

Analysis was performed using SPSS version 25.0 (IBM Corp, Armonk, USA), and differences with a P-value <. 05 were considered statistically significant.

3.0 Results

Demographic and clinical characteristics at baseline are presented in Tables 1 and 2 respectively. Seven individuals (4 male, 57.1%), with a mean age of 15.4 years (range 9-26 years, SD =5.8) were included in the analysis. Two of these individuals were adults (≥ 18 years). On average, the individuals had mild disease severity at baseline (mean $ppFEV_{1,}$ 81.7% ± 17.8). Two of the individuals had moderate disease severity. Two of the individuals (28.6%) had CF related diabetes, four (57.1%) were colonized with *Pseudomonas Aeruginosa*[I], and two (28.6%) had exocrine pancreatic insufficiency.

3.1 Outcomes after at least 12 months of ivacaftor treatment

The outcome variables were measured prior to the start of ivacaftor and after at least 1 year of ivacaftor (median time on ivacaftor 15 months [IQR 13 – 16]). BMI increased statistically significant (from 19.9 kg to 21.2 kg, p=.03), but BMI-Z score did not increase significantly (from .4 to .6, p=.23). Both fat mass (from 12.5 kg to 15.0 kg, p=.16) and lean mass (from 34.9 kg to 37.4 kg, p=.07) did not increase statistically significantly. Mean $ppFEV_1$ improved significantly (from 81.7% to 97.7%, p=.02). RV/TLC decreased significantly after treatment with ivacaftor (from 31.5% to 16.8%, p=.02). During treatment no significant change was seen in mean REE (from 1966.8 kcal/day to 1751.7 kcal/day, p=.43) (Table 1).

With regard to CPET variables, both $ppVO_{2peak}$ (from 93.4% to 80.7%, p=.01) and $ppVO_{2peak/kg}$ (from 95.6% to 78.8%, p=.001) showed a statistically significant reduction. Peak work rate (from 84.2% to 87.5%, p=.59) showed a non-significant increase, and $ppW_{peak/kg}$ (from 87.5% to 86.6%, p=.31) did not change significantly. ΔVO_2/WR decreased statistically significant after treatment (from 10.7 ml/watt to 8.5 ml/watt, p=.01) (Table 2).

4.0 Discussion

This is the first report describing the long-term effects of treatment with ivacaftor on BMI, body composition assessed with the DEXA scan, pulmonary function, REE, and exercise capacity in individuals with CF heterozygous with the S1251N mutation. Our results demonstrate improvements in both BMI and pulmonary function, which

I Colonization based on presence of *Pseudomonas Aeruginosa* in two or more cultures in the preceding year.

is in concordance with previous studies[25-27]. Unexpectedly, VO_2 showed a statistically significant reduction after treatment with ivacaftor, whereas peak work rate was unchanged.

Table 1. Data of anthropometrics, body composition, pulmonary function, and resting energy expenditure, before and after ivacaftor treatment in seven individuals with CF and S1251N mutation

Variable	Pre-ivacaftor (mean, SD)	Post-ivacaftor (mean, SD)	*p-value* (two-tailed)	95% CI (lower; upper)
Anthropometrics & Body composition				
Height (cm) / (Z-score) §	160.9 (18.5)/ -.4 (.8)	164.8 (15.2)/ -.2 (.8)		
Weight (kg)/ (Z-score) §	54.0 (19.7)/ .2 (.7)	59.2 (18.6)/ .6 (.4)		
BMI (kg/m^2)/ (Z-score)	19.9 (3.4)/ .4 (.7)	21.2 (3.4)/ .6 (.8)	***.027/**. 22	.2; 2.4/ -.2; .6
Fat mass (kg)	12.5 (6.1)	15.0 (5.5)	.16	-1.4; 6.4
Lean mass (kg)	34.9 (13.9)	37.4 (12.2)	.07	-.3; 5.4
Pulmonary function				
ppFEV$_1$ (%)	81.7 (17.8)	97.7 (19.6)	**.015***	4.4; 27.6
RV (l) §	1.5 (.5)	.9 (.3)		
RV/TLC (%)	31.5 (10.5)	16.8 (5.4)	**.016***	21.0; 3.8
Resting energy expenditure				
REE (kcal/day)	1966.8 (305.9)	1751.7 (530.9)	.43	-859.5; 429.2

Abbreviations: BMI = body mass index; **CI** = confidence interval; **ppFEV$_1$** = forced expiratory volume in 1 second, in percentage predicted; **REE** = resting energy expenditure; **RV** = residual volume; **TLC** = total lung capacity;

§ = not assessed with paired samples t- test

P-value <.05 is considered statistically significant as indicated in bold and with *

This remarkable decrease in VO_2 was reflected in the decrease of $VO_{2peaklean}$ as well (Table 2) and is higher than the general annual decline of 3.2% as described by van de Weert- van Leeuwen et al.[28]. The most plausible explanation for this change in VO_2 is a lower work of breathing, which is compatible with our finding of an almost 50% reduction in static hyperinflation (RV/TLC) after treatment, mainly as a consequence of reduction in RV (Table 1). This indicates a decrease of small airway disease during

treatment and is highly suggestive for a lower work of breathing and a reduced dynamic hyperinflation. Unfortunately, we did not perform flow-volume loops, as our aim was to describe the effects of ivacaftor and this finding was not expected.

Other factors that could explain our finding are less likely. Differences in effort or deconditioning cannot explain the decreased VO_2 as no relevant differences were seen for maximal heart rate, RER, oxygen pulse, and peak work rate. A higher inflammation and infectious state could be the case, however, this was not assessed in our study population. On the contrary, with the use of ivacaftor a less inflammatory status related to the earlier reported decrease in pulmonary exacerbations is expected.

Other studies have evaluated the effects of ivacaftor regarding exercise capacity[5,11,12,29], but none of these studies included individuals with the S1251N mutation and most studies had only a short follow-up period. The results of previous studies are still inconclusive[5,11,12,29]. Noteworthy, similar trends were seen after 12 weeks of ivacaftor for VO_{2peak}, $VO_{2peak/kg}$ and ΔVO_2/WR in a case-report of Saynor et al.[12]. Information with regard to static hyperinflation and breathing efficiency was unfortunately lacking.

The lower work of breathing, congruent with our finding of RV/TLC ratio measured with body plethysmography, could explain the not statistically significant but clinically relevant, reduction of REE in most of our individuals. A lower work of breathing enables the body to gain in body weight, and consequently BMI, and alter in body composition. In our population, the increase in BMI and body composition are not only attributed to weight gain of both fat mass and lean mass, but also to (height-)growth in the pediatric individuals. Similar increases for body weight, BMI and body composition were reported in other studies[6,7,11,27,30]. Other possible factors which could contribute to lowering of REE are less bacterial infections, less pulmonary exacerbations[26], and a lower systemic inflammation[31]. Improved fat absorption due to improved pancreatic enzyme secretion[30], dissolved intestinal inflammation[30], and improved glycemic control which is accompanied by the anti-inflammatory effects of insulin[30,32,33] could result in a positive energy balance and, eventually, a higher body weight especially seen with increased fat mass.

A limitation of this study is our small sample size, which precludes correcting for multiple testing. Consequently, the risk of statistically significant findings by chance, as we assessed many variables, should be taken into account when interpreting these results. However, the prevalence of individuals mutated with S1251N in the Netherlands is 1.2%[1], which means that we assessed almost half of the Dutch

S1251N mutation group. The absence of objective data of physical activity levels and nutritional intake are other limitations. Though, patient records showed no reduction or change in physical activity levels or involvement by an exercise intervention.

Healthcare providers should be aware of the changes during ivacaftor treatment, regarding body composition and REE, but especially exercise capacity. As no exercise intervention or diet intervention was included, we emphasize the importance of an interdisciplinary treatment at the start of CFTR modulating drug therapies. For the upcoming triple therapies, at least equal treatment effects could be expected and the cardiopulmonary system will be even less limited during exercise and training. The limitation will be at the peripheral muscle level. Accordingly, when a training intervention is started simultaneously with the drug therapy, individuals with CF will use their new (pulmonary) capacities, to adapt their exercise capacity to its maximum. Physical therapy and dietetic intervention should be intertwined adequately to guide and advise individuals with CF to achieve an optimal physical and nutritional status. In addition, this collaboration is necessary to achieve an optimal overall treatment for the long-term as well. Increase of extensively amount of fat mass should be prevented in order to reduce the risk of developing overweight and/or obesity in CF individuals.

Future studies are warranted to improve the knowledge about the effects of novel treatment options such as ivacaftor on body composition, REE, and exercise capacity. These studies should include large samples, broader ranges of disease severity, objective measurements of physical activity levels, nutritional intake, and assessment of breathing patterns (dynamic hyperinflation) during exercise.

5.0 Conclusions

This study demonstrates that 15 months of ivacaftor in a small group of CF individuals with the S1251N mutation improves BMI and pulmonary function. Oxygen uptake reduces after treatment, which may be due to a decrease in work of breathing, as is suggested by reduction of static hyperinflation.

Table 2. Data of cardiopulmonary exercise testing variables before and after ivacaftor treatment in seven individuals with CF and S1251N mutation

Variable	Pre-ivacaftor (mean, SD)	Post-ivacaftor (mean, SD)	*P-value* (two-tailed)	95% CI (lower; upper)
HR_{peak} (bpm) §	184.5 (5.4)	186.2 (6.2)		
RER §	1.1 (.1)	1.3 (.1)		
VO_{2peak} (l) § (%)	2.3 (1.0)	2.1 (.8)		
$ppVO_{2peak}$ (%)	93.4 (16.5)	80.7 (12.0)	**.010***	-22.0; -4.91
$VO_{2peak/kg}$ (ml/min/kg) §	42.9 (6,6)	36.3 (5.6)		
$ppVO_{2peak/kg}$ (%)	95.6 (10.6)	78.8 (9.0)	**.000***	-24.4; -13.1
$VO_{2peak/lean}$ (ml/min/kg) §	59.2 (7.1)	53.1 (7.5)		
W_{peak} (watt) § (%)	174.9 (83.5)	191.3 (86.2)		
ppW_{peak} (%)	84.2 (16.0)	87.5 (11.9)	.59	-5.3; 8.4
$W_{peak/kg}$ (watt/kg) §	3.2 (.6)	3.2 (.6)		
$ppW_{peak/kg}$ (%)	87.5 (15.1)	86.6 (11.6)	.31	-12.5; 4.8
$W_{peak/lean}$ (watt/kg) §	4.4 (.9)	4.6 (.8)		
TV_{peak} (l) §	1.6 (1.0)	2.0 (1.1)		
BF_{peak} (1/min) §	48.4 (9.7)	42.5 (17.3)		
BF_{peak}/TV_{peak}	41.7 (26.4)	30.5 (27.2)		
$\Delta VO_2/WR$ (ml/kg/watt)	10.7 (1.2)	8.5 (.9)	**.005***	-3.2; -1.0

Abbreviations: **BF_{peak}/Vt_{peak}** = ratio of breathing frequency to tidal volume at maximal exercise; **BF_{peak}**= breathing frequency at maximal exercise; **CI** = confidence interval; **HR_{peak}** = maximal heart rate; **$ppVO_{2peak/kg}$** = maximal oxygen uptake related to body weight, in percentage predicted; **$ppVO_{2peak}$**= maximal oxygen uptake, in percentage predicted; **ppW_{peak}** = peak work rate, in percentage predicted; **$ppW_{peak/kg}$**:= peak work rate related to body weight, in percentage predicted; **RER** = respiratory exchange ratio; **TV_{peak}** = tidal volume at maximal exercise; **VO_{2peak}** = maximal oxygen uptake; **$VO_{2peak/kg}$** = maximal oxygen uptake related to body weight; **$VO_{2peak/lean}$**= maximal oxygen uptake related to lean body mass; **$W_{peak/kg}$** = peak work rate related to body weight; **W_{peak}**= peak work rate; **$W_{peak/lean}$**= peak work rate related to lean body mass; **$\Delta VO_2/WR$** = oxygen cost of work;
§ = not assessed with paired samples t- test
P-value <.05 is considered statistically significant as indicated in bold and with *

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Chapter 9

General discussion

A personal note

> *Currently, the future and prospect of many people with Cystic Fibrosis (pwCF) in the Netherlands is changing rapidly. On December 9th 2021, the state secretary of the Ministry of Public Health announced that Kaftrio (Trikafta®) will be reimbursed as of the 1st of January 2022 for pwCF 12 years of age and older with a F508del-F508del mutation or a F508del combined with a minimal function mutation. This concerns about 750 pwCF in the Netherlands. This announcement put a smile on my face and was a strong awareness that CF care is subject to changes and especially for me in the field of physical therapy and exercise physiology: never a dull moment in CF care!*

With this in mind, I will summarize and reflect on the results of the studies in this thesis, which focuses on physical activity and cardiorespiratory fitness (CRF) in CF. It is known that especially CRF, as measured by peak oxygen uptake (VO_2peak), is a strong predictor of mortality[1–4], but is also associated with other health-related effects such as insulin sensitivity and lower risk of cardiovascular disease[5–7]. In this thesis the aim was to increase our understanding of CRF in CF, and the factors determining CRF in this population.

1.0 Main results

In the first part of this thesis, our aim was to describe the physical activity behavior of the Dutch youth and to provide an overview of the methods and results of the first Dutch Report Card.

Over the period 2010-2014, sedentary behavior and overall physical activity levels of Dutch youth were not meeting current guidelines or norms: only 29% of the Dutch 12-to 17-year olds met the recommendations laid out in the Dutch physical activity guidelines and only 57% of the 4- to 11-year old children had less than two hours per day of screen time (e.g. 43 in every 100 children spent more than two hours a day watching television or on a device)[8,9]. Participation in sports, active transportation (e.g. cycling, walking) and active play were satisfactory. Although Dutch children perform a lot of daily physical activity through cycling, it is not enough to meet the current national guidelines. Cycling is important, however, cycling alone is not enough to meet recommended levels of health-related physical activity (**Chapter 2**).

In **Chapter 3**, our aim was to gain more insight in the physical activity behaviors and patterns of Dutch youth with a chronic disease or disability with the first Report Card Plus of the world. In addition, an answer to 'how (un)limited are the possibilities for the Dutch youth with disabilities to be physically active?' was provided. When comparing the behaviors of typically developing children and children with a chronic disease or disability, we observed that for overall physical activity levels no differences between the groups existed. Small differences in active transport behavior were present, but for the other indicators, no large differences emerged. The situation among scholars attending special schools showed however that less scholars met the norms or established criteria, for example only 21% to 35% of the cluster scholars exercised eight or more hours per week, compared to 26% of the Dutch youth who met the physical activity guidelines[10,11]. (Social) accessibility and the diversity of the underlying disorders/disabilities seem key factors to explain these differences. We conclude that Dutch youth with disabilities are not yet able to participate completely unlimited in sports and exercise (**Chapter 2 & 3**).

It is promising that in the Dutch Report Card of 2018, physical activity levels of both children and adolescents increased to a C^- and D^+ respectively, which involves 52% of the 4-to 11-year old and 32% of the 12-to 17-year old youth meeting the 2017 Dutch physical activity guidelines[10,11]. Furthermore, the National Institute for Public Health and the Environment [RIVM] reported even higher percentages for the year 2020: 52.7% for children 4-12 years and 51.9% for children aged 12-17 years[12].

In the second part of this thesis, the focus was on exercise testing in children with respiratory diseases. Cardiopulmonary exercise testing (CPET) is regarded as the gold standard to assess someone's CRF, and provides additional information compared to static lung function tests for example. Although it is important to acknowledge differences in CPET testing between pediatric and adult populations, CPET has demonstrated clinical utility throughout the age range. Especially in pwCF, CPET can provide valuable information for prognosis[2,13], clinical decision making, and treatment and advice in CF care (**Chapter 4**).

In the third part of this thesis, we concentrated on the status of the CF population, and in particular the status of CRF in this population.

In **Chapter 5**, we assessed the CRF levels in our pediatric population with CF, including patients 8- to 18- years old. Currently, more than half of our population (55%) has still, even with improved CF care and treatment, a low CRF. Remarkably,

in our CF girls CRF was 6.8% lower compared to the CRF levels in our CF boys. In this chapter, we also have identified two physiological predictors for having low CRF: colonization with *P. Aeruginosa* and glucose intolerance (**Chapter 5**).

Next to these two predictors, we have also found indications that a blunted increase of heart rate is another factor which could impair CRF and consequently exercise tolerance in both pediatric and adult pwCF. This blunted heart rate response was reflected in lower cardiac output values compared to healthy controls. Our data is suggestive that an impaired stroke volume might not be the cause for this lower cardiac output. With this finding in mind, training intensities based on (predicted) maximal heart rate seem less adequate in pwCF and individual training guidance still appears to be relevant for optimal effects for improving CRF (**Chapter 6**).

In **Chapter 7**, we explored the prevalence of subjective severe fatigue in adults with CF. Severe fatigue appeared to be present in about a quarter of our adult population (26%). In addition, similar trends were found in our pediatric population with CF. The prevalence of severe fatigue was 22% in our 2-18 year old pwCF, based on parent and self-report data[14]. Fatigue remains a difficult phenomenon, but next to associations with more psychosocial factors, for example symptoms of anxiety and depression[15], there are indications that there is a relation between fatigue and CRF and physical activity. In our adult population there was indeed a relation between fatigue and distance achieved on the Modified Shuttle Test[16]. The specifications of the relation between fatigue and CRF and physical activity have yet to be unraveled, but increasing physical activity and CRF levels might have positive effects in experiencing less fatigue. In cancer-related fatigue in both adult and pediatric populations for example, studies showed that increasing physical activity levels and CRF levels reduced fatigue symptoms[17–20]. In our ACTIVATE-CF pilot study (see Panel 8.1 – 8.4), we have strived to gain more insight in this alleged relation and our findings suggest that increasing physical activity and CRF levels can reduce symptoms of fatigue in pwCF.

We noted in **Chapter 8**, in line with other studies including larger sample sizes, that for pwCF and a gating mutation, treatment with ivacaftor improves pulmonary function significantly. Furthermore, increases in body weight, body mass index (BMI) and fat mass are also observed[21,22]. Interestingly, CRF does not automatically improve as well, not even after at least 12 months of treatment. Our results suggest that patients do not use their improved (pulmonary) capacity to its fullest, which results in even lower CRF levels. It is most plausible that a reduced work of breathing is the explanation for this decrease. Still for some patients, this reduction of an uncomfortable feeling, most likely dyspnea, is not sufficient to increase their physical

Panel 8.1 ACTIVATE CF study

The ACTIVATE CF study was a feasibility study and our study design was based on the international multi-center ACTIVATE CF study, developed by Hebestreit et al.[118] PwCF ≥ 12 years of age and ppFEV$_1$ ≥ 35% were included. After baseline measurements, participants were randomized into an exercise group or a control group. For both groups, measurements were repeated every three months. The intervention group was asked to increase their physical activity levels and reduce their screen time. The participants of this intervention group were advised to follow a high intensity interval training program twice a week and complement their physical activity level by meeting the Dutch guidelines for physical activity. Feedback was given via a pedometer, an individual web-based activity diary, and by the center staff who called monthly. The control group was asked to keep their activity level constant.

A CPET was used to evaluate CRF. To assess physical activity levels, we used pedometer data including total steps per day. In addition, the Habitual Activity Estimation Scale (HAES) was used to measure subjective levels of physical activity. Subjective fatigue was assessed by the Checklist Individual Strength -20 (CIS-20) and the DASS-42 questionnaire was used to assess symptoms of depression, anxiety and stress.

In conclusion, with the small sample (Panel 8.2) in mind, we could carefully state that the ACTIVATE CF program may have positive effects for increasing physical activity and CRF levels in Dutch pwCF (Panel 8.3), but perhaps more importantly our results indicate that this program could have positive effects on subjective fatigue and DASS scores (Panel 8.4) as well.

activity levels and to engage in more physical activity of higher intensities. Most other studies assessing the effect of ivacaftor on CRF show no improvement after treatment[22]. For orkambi, no clear improvement in CRF is seen as well[23,24], with the results of Wilson et al., as one of the larger studies (n=70) with 24 weeks of treatment, showing no significant change in VO_2peak relative to body weight[25]. None of these studies included a training program. Education before the start of CFTR modulating therapies is essential to achieve the best overall treatment result. Keeping physical activity levels similar, during CFTR modulator treatment, seems inadequate. Awareness among caregivers, from physicians, to dieticians and physical therapists, is a key factor to really improve CF care, especially with a healthy lifespan in mind.

2.0 Clinical implications of our findings

2.1 Model of Bouchard and Shepard

In the general introduction of this thesis, we have outlined which factors of the model of Bouchard & Shepard (Figure 1) regarding CRF could have a prominent role in pwCF. With the findings of this thesis we can reflect on this model and we can confirm the role of physical activity and 'other factors' such as subjective fatigue and personal and social factors[14,16]. Furthermore, of the components and factors described in Table 1, we now can complement that cardiac factors, especially heart rate and metabolic and inflammatory factors, even in the less severely pulmonary affected patients could be dysfunctional and result in lower CRF levels. The factor bone health or density seems the next relevant factor of the model of Bouchard & Shepard which necessitates attention in light of the increased life span and ageing CF patient. We will discuss this in section three.

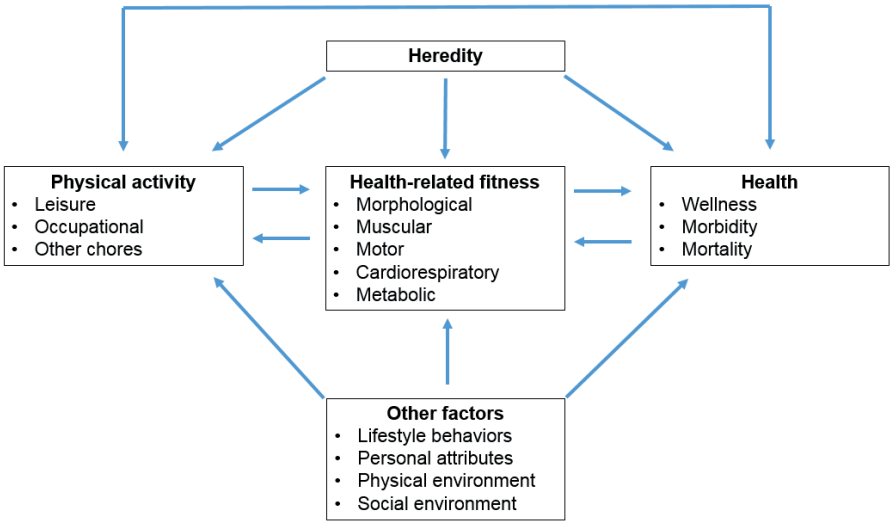

Figure 1. Consensus model from Bouchard & Shepard, 1994[26].

Table 1. The components and factors of health-related fitness of the Consensus model from Bouchard & Shepard 1994[26].

Morphological components	Muscular components	Motor components	Cardiorespiratory components	Metabolic components
Body mass for height	Power	Agility	Submaximal exercise capacity	Glucose tolerance
Body composition	Strength	Balance	Maximal aerobic exercise capacity	Insulin sensitivity
Subcutaneous fat distribution	Endurance	Coordination	Cardiac function	Lipid and lipoprotein metabolism
Abdominal visceral fat		Speed of movement	Lung function	Substrate oxidation characteristics
Bone density			Blood pressure	
Flexibility				

2.2 New approach for a healthy lifespan in CF

With the knowledge of this thesis, the key factors for a healthy lifespan in CF can be complemented:

- Improving CFTR function by the use of CFTR modulators as early in life as possible;
- Primary prevention of pulmonary damage and disease progression /detection of new airway infections;
- Preserving normal growth and weight development;
- Early detection and prevention of co-morbidities, especially regarding inflammatory and metabolic factors;
- Maintaining CRF levels or prevention of decreasing CRF levels;
- Early screening and treatment for severe fatigue, but other psychosocial problems as well.

To achieve the best overall outcome, including favorable pulmonary effects and improvements of non-pulmonary outcomes, early engagement of both physical therapists and dieticians at start of CFTR modulating therapies is essential. Furthermore, with regard to the prevention of negative effects, such as overweight and obesity and high fat mass and hidden loss of fat free mass, their engagement is important as well, especially with the highly effective triple modulators in mind. The PROMISE study cohort, for example, showed an increase in BMI and decrease in resting energy expenditure, but no improved diet quality after 6 months of kaftrio in 17 adolescents and adults with CF[27]. However, there will be many countries were the availability and/or reimbursement of CFTR modulating therapies is not self-evident in the next years[28,29].

Next to living with a chronic disease, many of the co-morbidities/complications and increased survival have consequences for quality of life. The current and future patient with CF should be assessed with a broad and personalized view. Including, physical, psychosocial and, environmental factors. Such an approach in line with this, could be a downward spiral as seen in Figure 2. The traditional thinking about a patient with CF is that they will be subject to progressive pulmonary disease during their lifespan. As the disease evolves, issues may arise including development of co-morbidities and possibly psychosocial problems. Eventually, death or lung transplantation would be the final outcome. With the knowledge of our thesis, we propose tailored medicine and assess which of the factors or combinations of factors, indicated on the right of the spiral, could be targeted to effect change and improvement for an individual patient. This corresponds to the grounds of the biopsychosocial model. CF treatment, for the individual patient, should aim to change or delay the downward spiral and in some cases even change to an upward spiral. Most studies and the treatments suggested are performed and started when there is already (irreversible) pulmonary damage or dysfunction with regard to other (physiological) factors. It is key to strive to prevent damage and therefore aim to prevent the downward trend in well-being early as possible.

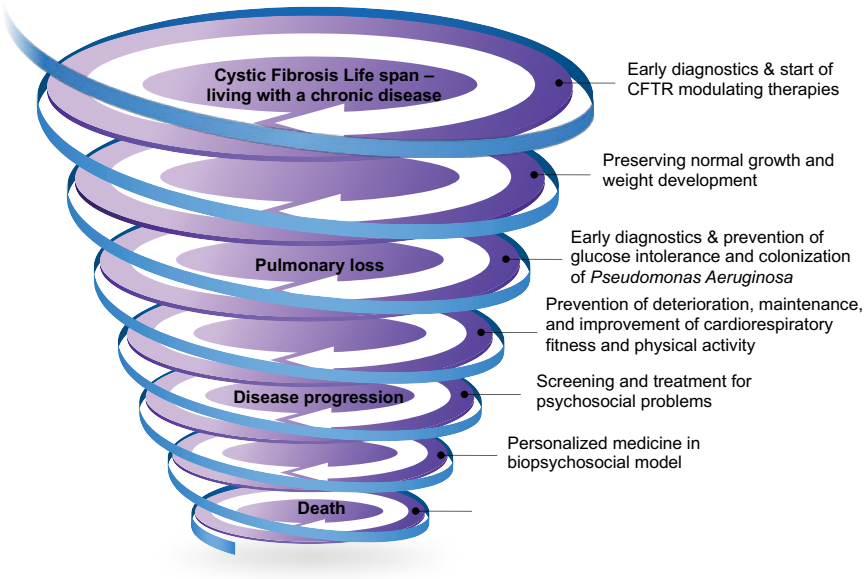

Figure 2. The spiral of CF lifespan

3.0 The importance of exercise and CRF in the new era of CFTR-modulator therapy

The increased lifespan, due to improved CF care has led to the detection and a more prominent role of new co-morbidities and/or complications. With the advent of the CFTR modulating therapies, this lifespan is even more subject to change. With the findings of our thesis supporting the clinical relevance of CRF in CF treatment and with a view to the future, we have to discuss the role of exercise and CRF and factors as bone health, overweight/obesity, and the aging CF patient in general, including insulin resistance and CF related diabetes (CFRD), and consequences regarding lung transplantation.

3.1 Bone health

In the healthy population, weight bearing exercise is established as the most effective, non-pharmacological strategy to optimize bone mineral density, bone strength, and peak bone mass[30,31]. Furthermore, several studies showed that exercise in especially pre-pubertal and early pubertal children is associated with gains in bone mineral density and bone mineral content[31–37]. In CF, it is shown that higher levels of physical activity, in particular moderate and vigorous activity, is associated with greater bone mineral density[31,38–41]. In addition, the most active and fittest patients have the greatest bone mass[40] and CRF was found to be a major predictor of bone mineral density[31,42,43].

Nowadays, osteopenia is present in up to 50% of adult patients with CF and osteoporosis in 10-34% of the population[44–46]. Risk factors for developing osteoporosis in CF are chronic infection, abnormal nutritional status, inadequate calcium and vitamin D, low intake, decreased muscle mass, physical inactivity and hormonal deficiencies[44]. Low bone mineral density is therefore mainly seen in children with the poorest nutritional status and pulmonary function[41,44,47]. Low bone mineral density is associated with low BMI[44,48], but importantly, even patients with normal weight can have altered bone mineralization[44,45,49]. Noteworthy, patients with poor bone health are at risk for fractures: a 10% decrease in bone mineral density corresponds to a 1.5 fold increase in fracture risk[31,50].

In healthy women, menopause brings a rapid decline of estrogens, which are necessary for healthy bone metabolism. An annualized loss of bone mineral density of 0.1-0.5% at the lumbar spine and 1.0-1.8 at the total hip is seen in women following menopause[38,44].

In light of our results, with a notable role for inflammation as an important factor in CRF development, it is indicated that systemic inflammation is detrimental for bone health as well. As systemic inflammation is linked to chronic pulmonary infection, it is shown that inflammation alters bone remodeling and accelerates osteoclastic bone resorption, which is partially the result of elevated levels of pro-inflammatory cytokines[44,51]. With these new trends in CF survival, the population seems more at risk for having bone health problems and risk of fractures. Women with CF may be more prone for developing bone health problems, as they might have already lower levels of estrogens during young adulthood and the large decline following menopause may have particular detrimental effect on their bone mineral density[31].

We did not focus on bone health in this thesis, but larger, long-term studies with (highly effective) CFTR modulator drugs should demonstrate long-term effects on bone health. Fortunately, the findings from Putman et al. and Sermet et al. are promising[52,53].

Prevention of CRF loss and maintaining high CRF levels in pwCF, now also in the context of bone health, seems clinically relevant again.

3.2 Overweight and obesity

The nutritional status of pwCF is changing, from underweight to normal weight, overweight and obese pwCF nowadays.

The Dutch CF registry reported that in 2020, 18.9% of the pwCF had a BMI higher than 25 kg/m^2, which is classified as being overweight. Divided into sex, 21.3% of male and 16.1% of female pwCF could be classified as overweight[54]! In light of the (highly effective) CFTR modulator drugs, maintaining healthy weight status, body composition and prevention of obesity seems extremely necessary.

In the healthy population, adult obesity and cardiovascular diseases are closely linked, but perhaps even more importantly, studies suggest that cardiovascular diseases in adulthood are linked to childhood and adolescent obesity[55]. With regard to the CF population, Harindhanavudhi et al. found that the prevalence of hypertension was significantly higher in overweight (25%) and obese (31%) pwCF compared to normal (17%) and underweight (16%) pwCF[56,57].

With the knowledge that there is strong evidence that regular exercise contributes to body weight and fat loss, maintenance of body weight and fat reduction[58], once more maintaining high CRF levels and prevention of CRF loss in CF care is important.

Panel 8.2 Group characteristics

We started the study with the inclusion of ten participants, whom were randomly assigned to the intervention or control group. At baseline, the intervention group (n=6) consisted of two males (33.3%) and no males were included in the control group (n=4).

Median age in the intervention group was 15.0 (14.8-26.5 25-75th percentile) years compared to 25.5 (19.5-35.3 25-75th percentile) years in the control group. Mean ppFEV$_1$ was 73.0 ± 15.0% for the intervention group, compared to 74.8 ± 9.1% for the control group.

Our study period fell in the time that orkambi was officially included in the insured healthcare package in the Netherlands and starting this drug was one of the exclusion criteria or a washout period of at least one month was necessary. Due to this inconvenient timing, we did not reach our intended sample of 20 participants and unfortunately one participant withdrew after three months because of personal circumstances and another participant had to be excluded because of non-compliance. Both participants were assigned to the intervention group. As a result of this small sample, we only described the changes of the outcome measures from baseline to six months, without statistical analyses.

3.3 The ageing CF patient in general

In 2020, the Netherlands counted 133 pwCF, 8.5% of the total Dutch CF population, aged 50 years or older[54]. It is highly likely that this adult population will expand the following years.

In older pwCF, it is most likely that the lungs are in a more inflammatory state, as a result of the aging itself, also called 'inflammaging'[59,60]. This inflammaging could be characterized by an age-associated mitochondrial dysfunction. This mitochondrial dysfunction can trigger inflammatory cytokine release inducing chronic inflammation and progression of airway disease such as in CF[60,61]. In addition, patients with inflammatory pulmonary disease have increased cardiovascular risk and premature vascular ageing[62,63].

3.3.1 Ageing skeletal muscle

The ageing skeletal muscle, including a decline in skeletal muscle mass (atrophy), muscle strength, and muscle regenerative capacity, seems of relevance for the ageing CF patient.

Muscle atrophy begins during the third or fourth decade of life and approximately 10% of skeletal muscle can be lost by the age of 50[64,65]. The declines continues and by the seventh and eight decade it could be that the lower limb muscles reduce by 0.7-0.8% per year[65,66]. The specific mechanisms of this age-related atrophy remain incompletely understood, but a reduced number of myofibres and a decrease in myofibre area could be causes for this decline[64,65]. In addition, studies showed that this aging muscle atrophy is due to a loss of both type I (oxidative) and type II (glycolytic) muscle fibres[67–69].

Skeletal muscle strength decreases at ages 50-60 years[65,70–72] with rates of about 2-4% per year[65,73–76]. This phenomenon is more present in lower limbs compared to upper limbs as well[65,77,78] and is not likely due to only decreases in skeletal muscle mass but involves declines in neuromuscular function such as voluntary neural drive and impaired neuromuscular control as well[65,79,80].

More evidence is present that skeletal muscle regenerative capacity is impaired with ageing in form of delayed regeneration[65,81], or diminished regeneration[65,82]. In addition to chronological aging, it seems that consequences of obesity including increased inflammation, can contribute to impaired muscle regeneration.

As both muscle strength and mass are perhaps already less favorable in pwCF, the older CF patient might be prone to even more problems with their skeletal muscle (function). Whereas, in particular the lower limbs are prone to impairments, this might result in more problems participating in physical daily activities.

Fortunately, undertaking different types of training is proven to improve skeletal muscle strength, mass and regenerative capacity, even in older muscles[65,69,82–84].

3.3.2 Insulin sensitivity and ageing

It should also be noted that insulin sensitivity is frequently reduced with aging, due to muscle atrophy, as the skeletal muscle is the primary target for insulin-mediated glucose uptake[69,85–87], and increased abdominal fat mass[88–92]. Results suggest that age-related impairments in insulin signaling likely contribute to reduced trafficking of GLUT4 from intracellular GLUT4 storage vesicles to the plasma membrane, ultimately contributing to insulin resistance with aging. Consequently, the aging skeletal muscle is a less favorable factor in light of (development) of CFRD or diabetes mellitus. Additionally, in the older CF patients, as an expanding population, the burden of CFRD is likely to increase accompanied by the risk for developing problems related to CFRD. The Dutch CF registry reported that already 29.9% of the Dutch pwCF 50 years and older had CFRD in 2020[54]. It is seen that microvascular

complications develop when CFRD has been present for 5-10 years, and not usually before fasting hyperglycemia is evident. Neuropathy occurs in about 50% and retinopathy, nephropathy, or both in about 15% of those who have CFRD for more than 10 years[63,93].

Especially high intensity interval training (HIIT) seems promising in targeting insulin resistance. HIIT may increase proteins involved in glucose metabolism, such as GLUT4[92,94,95]. Furthermore, HIIT is known to recruit more type II fibers leading to greater muscle hypertrophy and muscle mass[96–98], suggesting an extra interesting role for the (aging) CF patient. In our ACTIVATE CF pilot we did not include insulin markers (see Panels 8.1 – 8.4), but HIIT was tolerated by our intervention group which is in line with others studies with CF[99,100] underlining the promising role of HIIT in CF.

3.3.3 CRF and ageing

In the healthy population, CRF (VO_2peak) declines progressively with age. However, performing physical activity, especially of high intensity is associated with a slowing of decline. Additionally, maintaining CRF is associated with an improved cardiovascular risk profile: a 1 ml/kg/min better maintenance of VO_2peak was associated with lower odds ratio of hypertension, dyslipidemia and metabolic syndrome[6]. Moreover, in a large study it was found that every metabolic equivalent (= $VO_{2:}$ 3.5 ml/min/kg) improvement in CRF was associated with a 15% and 19% lower risk of all-cause and cardiovascular disease, respectively[58,101]. And even in adolescents, low levels of physical activity, CRF and high levels of sedentary behavior (screen time) were associated with development of metabolic syndrome[7].

3.4 Lung transplantation

Perhaps lung transplantation is less of an issue in the Netherlands and in other high-income countries nowadays, but in a worldwide view it remains an important treatment option. As already partially discussed above, disease associated and treatment-associated co-morbidities, including CFRD, but also chronic kidney disease, and antibiotic allergies, increase with the increasing age of the CF population. Consequently, any increase in the age of transplant recipients is likely to present further challenges for care after treatment[63]. CFRD is present in 40-50% of pwCF at time of transplant assessment and develops in about 20% after transplantation[63,102–105].

In 2014, the International Society for Heart and Lung Transplantation registry, reported >47,000 adult lung transplant recipients and approximately 16.4% of these lung transplants were performed in adults with CF, resulting in about >7,700 lung transplanted CF patients[106]. Regarding national level, from 2009 -2020, about

127 Dutch CF patients underwent a lung transplantation and in 2020, only four patients underwent a lung transplantation. Of the registered Dutch patients, 80.4% of the patients has diabetes and 43% of the patients was diagnosed with osteoporosis[54]. These high percentages indicate that the CF patients undergoing lung transplantation are at risk for (developing) co-morbidities which might have a negative impact on their lifespan.

Knowing that CRF levels in transplanted patients are often limited[107,108], promoting physical activity and exercise seems once more an important treatment aim in CF care.

4.0 The future

To improve CF care and research, consensus is needed with regard to clinimetrics and questionnaires. The European Cystic Fibrosis Society best practice guidelines[109] are a wonderful example to achieve improvement herein and good efforts have been made with regard to the measurement of physical activity[110,111]. However, there is no consensus yet and differences between centers at European but also on national level are present. Measurement of CRF for example, is in most Dutch CF centers still performed with the Modified Shuttle Test or exercise test without gas-analysis. Only a small group performs the CPET, though recommended in the Statement on Exercise Testing[112] and more specifically the Dutch Quality Standard for medical specialists in CF[113].

The importance of body composition is growing, and the gold standard for measurement is the dual energy X-ray absorptiometry (DXA). The DXA is however, burdensome for the patient and expensive. Therefore, increasing interest is present for measurements based on bio-impedance analysis. Our study in adult pwCF is promising in reducing the burden regarding fastening when using bio-impedance[114]. However, more research is needed for a more definitive judgment about the quality of bio-impedance measurements and CF specific reference values or equations for all age groups are still lacking. In addition, now that it is clear that psychosocial factors are important in CF lifespan as well, the methods to assess fatigue and which cut-off points to use for categorizing severe fatigue need elaborative research.

Skeletal muscle function, its relation with inflammation and glucose tolerance, but also the processes in the ageing skeletal muscle, require to be further investigated. When skeletal muscle mechanisms are better understood, targeted interventions

can be developed. Methods used by Werkman et al.[115] including near-infrared spectroscopy and magnetic resonance spectroscopy, to assess (oxidative) muscle metabolism seem of interest in light of future study designs.

Panel 8.3 Results for physical activity and CRF

Physical activity

The total time being somewhat active and active for week and weekend days of the HAES questionnaire improved with 9.9% for the intervention group, compared to a decrease of 5.8% in the control group.

The intervention group increased the total of steps per day with a mean of 1881 compared to a reduction of 1085 steps per day in the control group.

With a minimal clinically important difference of 350-1100 steps per day in COPD, as suggested by Teylan et al.[119] our results indicate that the ACTIVATE CF program resulted in an increase in physical activity levels which may be of clinical significance.

CRF

Improvements were seen in the intervention group for both peak oxygen uptake in percentage predicted (+3.5%) and peak oxygen uptake related to body weight in percentage predicted (+5.9%), compared to reductions in the control group, respectively –5.5% and -5.7%.

Even though many studies are published evaluating training programs in CF[116], the ideal exercise prescription is not yet available. In the context of personalized medicine, one-size-fits-all prescriptions should not be the aim for the future, but identifying treatable factors based on multidimensional assessment should be our purpose. Furthermore, increasing our knowledge regarding training effects related to HIIT, glucose tolerance, heart rate, bone health, body composition and fatigue are important steps.

5.0 Concluding remarks

We have shown that, in spite of improved treatments being available for pwCF, CRF remains reduced in pwCF. Furthermore, we gained more insight in factors affecting CRF in pwCF.

Maintaining a high CRF and prevention of decline in CRF should still be important treatment aims of CF physical therapy care. With the increased survival and advent of (highly effective) CFTR modulators, these treatments aims should certainly not fade into the background. Indeed, preservation of CRF may offer the best protection against morbidity and be an effector of improved lifespan in CF.

The female patient with CF deserves perhaps some more attention. For a number of different aspects of health, female sex is less favorable. Women with CF tend to have lower CRF levels, are more prone to develop more psychosocial problems[117] and also are at greater risk for diminished bone health.

As several predecessors have already written the beautiful quote 'Exercise is Medicine', this thesis underlines this quote for CF care. Exercise, or preferably physical activity and in particular CRF, is essential for a healthy lifespan in CF.

Panel 8.4 Results for subjective fatigue and depression, anxiety and stress scores

Fatigue

The CIS-20 total score decreased in the intervention group with 5 points, compared to an increase of 3 points in the control group.

Depression, anxiety and stress scores (DASS)

The intervention group showed a slightly decrease for Depression score from 3.0 ± 3.2 to 2.6 ± 2.5. The Anxiety scores increased slightly from 3.4 ± 2.3 to 3.6 ± 2.3, the Stress scores increased slightly from 6.2 ± 4.3 to 6.6 and the Total score increased slightly from 12.6 ± 6.8 to 12.8 ± 10.9 from baseline to six months.

Remarkably, the scores for the control group changed even more unfavorably. The Depression score increased from 7.3 ± 3.4 to 8.8 ± 6.3, the Anxiety score increased from 6.0 ± 6.2 to 9.8 ± 11.1. Meaning a shift in category from 'normal' to 'mild anxiety' scores[120].

Stress score increased from 11.8 ± 6.2 to 14.5 ± 10.0. Total DASS score increased from 25.0 ± 15.0 to 33.0 ± 26.9 after six months.

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9

Nederlandse samenvatting

Cystic Fibrosis (CF) is een van de meest voorkomende genetische aandoeningen in de Kaukasische populatie. CF wordt gekenmerkt door afwijking van het 'cystic fibrosis transmembrane conductance regulator' CFTR-gen. Dit gen codeert voor het CFTR-eiwit. Dit CFTR eiwit werkt als een kanaal voor chloride-ionen en water door het membraan van de cellen die slijm, zweet, speeksel, tranen en spijsverteringsenzymen produceren. Dysfunctie van het CFTR eiwit resulteert in verstoord elektrolyten transport wat zorgt voor 'dik en taai' slijm. Dit dikke, taaie slijm beïnvloedt voornamelijk de longen, alvleesklier, slijmvlies van de darmen en zweetklieren. Door de gevolgen van dit taaie slijm, hebben mensen met CF vaak progressieve longschade resulterend in verminderde longfunctie, slechte voedingsstatus met verminderde spiermassa, hoestklachten en benauwdheidsklachten, die vaak tot uiting komen bij lichamelijke inspanning. Uiteindelijk resulteert deze progressieve multisysteem ziekte in een verhoogde morbiditeit en mortaliteit.

Meerdere studies hebben een belangrijke relatie laten zien tussen cardiorespiratoire fitheid (CRF), weergegeven als maximale/piek zuurstofopname (VO_2piek) en mortaliteit of overleving bij mensen met CF.

Al in 1992 beschreven Nixon en haar collega's dat mensen met CF met een laag-normale fitheid (VO_2piek ≥ 82% van voorspeld) een 8-jaars overlevingskans van 83% hadden in vergelijking met respectievelijk 51% en 28% voor mensen met een fitheid in de middelste (VO_2piek tussen 59-81% van voorspeld) en laagste (VO_2piek ≤ 58% van voorspeld) fitheidscategorie. Een grote internationale studie van Hebestreit en collega's, onder tien CF-centra in Australië, Noord Amerika en Europa liet dezelfde trends zien. De mensen met de hoogste fitheid (VO_2piek≥ 82% van voorspeld) hadden een 72% en 49% lagere kans op overlijden of het krijgen van een longtransplantatie in de komende 10 jaar in vergelijking met de mensen in de middelste (VO_2piek 59-81% van voorspeld) en laagste (VO_2piek≤ 58% van voorspeld) fitheidscategorieën. Bovendien beschreven Pianosi en collega's dat mensen met CF en een lage fitheid (VO_2piek< 32 ml/min/kg) een aanzienlijke toename in mortaliteit hadden, vergeleken met mensen met een hogere fitheid (VO_2piek > 45 ml/min/kg).

Uit deze studies kan geconcludeerd worden dat het onderhouden en behouden van een goede CRF bij mensen met CF een belangrijk beschermend effect heeft op morbiditeit en mortaliteit. Het objectiveren van de CRF is daarom een essentieel onderdeel in het diagnostisch proces binnen de CF zorg.

Dit proefschrift richt zich op een beter (in)zicht over het beloop van CRF bij mensen met CF, en hoe de CRF verandert c.q. beïnvloed wordt binnen de verbeterde CF-zorg en de aanwezigheid en ontwikkeling van nieuwe veelbelovende medicatie. Daarnaast richt dit proefschrift zich op de incidentie van ernstige vermoeidheid en de relatie tussen verschillende psychosociale factoren. Gezien de prognostische waarde van CRF en mortaliteit, maar ook kwaliteit van leven is het relevant om dit inzicht te vergroten.

Dit proefschrift is opgebouwd uit drie delen. In het eerste gedeelte (hoofdstuk 2 en 3) is het fysieke activiteiten niveau van de Nederlandse jeugd met en zonder een chronische beperking of aandoening in kaart gebracht, naast factoren die het fysieke activiteiten gedrag beïnvloeden. Aan de hand van twee Physical Activity Report Cards is dit beschreven. De Physical Activity Report Cards zijn ontwikkeld volgens het Internationale Report Card format van de Active Healthy Kids Global Alliance.

In **hoofdstuk 2** zagen we dat in de periode 2010-2014, het sedentair gedrag en het algemene fysieke activiteiten level van de Nederlandse jeugd niet aan de beweegrichtlijnen voldeed. Slechts 29% van de Nederlandse 12- tot en met 17 jarigen voldeed aan de Nederlandse beweegrichtlijn en 43% had meer dan 2 uur per dag schermtijd. Deelname in sport, actief transport (zoals wandelen en fietsen naar school) en actief spelen waren echter voldoende. Samenvattend kan gesteld worden dat de Nederlandse jeugd veel dagelijkse fysieke activiteit haalt uit het fietsen naar school, alleen is het fietsen naar school niet genoeg om aan de beweegnormen te voldoen.

In **hoofdstuk 3**, stond de vraag '*Hoe (on)begrensd zijn de mogelijkheden voor de Nederlandse jeugd met een chronische aandoening of beperking om fysiek actief te zijn?*' centraal in de eerste Nederlandse Physical Activity Report Card+. We vonden geen grote verschillen in het beweeggedrag van Nederlandse kinderen met en zonder chronische aandoening of beperking. Wanneer we specifiek keken naar de kinderen in het speciaal onderwijs, de zogenaamde clusterscholen, vonden we dat het beweeggedrag wel anders was. Eenentwintig procent tot maximaal 35% van de kinderen van de clusterscholen bewoog 8-uur of meer per week, vergeleken met 26% van de Nederlandse jeugd die minimaal elke dag 1-uur matig-tot intensief bewoog. Belangrijke factoren die deze verschillen kunnen verklaren liggen in (sociale) toegankelijkheid en de diversiteit van de onderliggende aandoeningen. We concludeerden dat Nederland zeker op de goede weg is, maar dat de Nederlandse jeugd met een chronische aandoening of beperking nog niet onbegrensd kan bewegen of sporten.

In het tweede deel van dit manuscript (**hoofdstuk 4**) lag de focus op inspanningstesten bij kinderen met respiratoire aandoeningen. Een cardiopulmonale inspanningstest, ook wel CPET, wordt als gouden standaard gezien om iemands cardiorespiratoire fitheid (CRF) te meten. Daarnaast is een CPET ook aanvullend op bijvoorbeeld statische longfunctie testen zoals spirometrie. Het is belangrijk om de verschillen tussen kinder- en volwassenpopulaties te (h)erkennen in het kader van het uitvoeren en interpreteren van cardiopulmonale inspanningstesten.

In het bijzonder voor mensen met Cystic Fibrosis (CF), kan een CPET waardevolle informatie geven met betrekking tot prognose, klinisch redeneren en behandelingen en adviezen in de CF zorg (hoofdstuk 4).

In het derde deel (hoofdstuk 5 tot en met 8) van het manuscript hebben we ons gericht op de CF-populatie en specifiek op de cardiorespiratoire fitheid (CRF) in de CF-populatie. Ons voornaamste doel in dit manuscript was het vergroten van onze kennis van CRF in CF en de limiterende factoren die CRF bepalen in deze populatie.

In **hoofdstuk 5**, hebben we de CRF-niveaus van onze pediatrische populatie met CF (n=60), met leeftijdsrange 8 tot en met 18 jaar, geobjectiveerd. Deze groep was ventilatoir niet gelimiteerd, gezien hun ventilatoire reserve meer dan 15% bedroeg. Om de CRF in kaart te brengen, heeft de populatie een CPET uitgevoerd. We zagen dat meer dan de helft van onze CF-populatie (55%) nog steeds een lage CRF (VO_2piek< 82% van voorspeld) heeft ondanks de verbeterde CF zorg en toegenomen medicamenteuze behandelopties. Opvallend was dat de fitheid in meisjes met CF 6.8% lager was dan de fitheid van CF jongens. Vervolgens hebben we met een logistische regressie analyse de relatie van fysiologische factoren en CRF onderzocht. De factoren die we hebben onderzocht zijn lichaamssamenstelling middels de body mass index (BMI) Z-score, glucose intolerantie, aanwezigheid van CF gerelateerde lever ziekte, kolonisatie met *P. Aeruginosa*, zweet chloride concentratie en zelf-gerapporteerde fysieke activiteit. Uit onze studie kwam naar voren dat kolonisatie met *P. Aeruginosa* (p=0.095, Exp(B)=3.945) en glucose intolerantie (p= 0.085; Exp(B)=6.770) het sterkst geassocieerd zijn met een lage CRF.

In het zesde hoofdstuk hebben we bekeken of mogelijke cardiale factoren limiterend kunnen zijn bij zowel kinderen als volwassenen met CF. Om de CRF te bepalen hebben de participanten weer een CPET uitgevoerd. Voor het in kaart brengen van de cardiale factoren hebben we naast een standaard elektrocardiogram, de Physioflow® gebruikt. De Physioflow® meet het hartminuutvolume op non-invasieve wijze op basis van trans-thoracale impedantie. Het hartminuutvolume kan hiermee bepaald worden inclusief slagvolume en hartfrequentie. Uit deze studie kwam naar

voren dat de maximale hartfrequentie significant lager was in de CF groep (n=19) (172.6 ± 12.3 bpm) in vergelijking met de groep met gezonde proefpersonen (n=22) (187.9 ± 9.0 bpm). Deze beperkte oploop van de hartfrequentie was ook terug te zien in een significant lager hartminuutvolume ten opzichte van gezonde controles (respectievelijk 9.9 ± 2.1 l/min/m^2 in de CF groep en 11.7 ± 1.3 l/min/m^2 in de gezonde controle groep). Daarnaast was de chronotrope respons index ook significant lager in de CF-groep (84.1 ± 11.2%) in vergelijking met de groep met gezonde proefpersonen (99.9 ± 8.1%). Het maximale slagvolume verschilde niet significant tussen de CF groep (56.8 ± 11.5) en de gezonde controle groep (62.0 ± 6.5). Deze studie toont aan dat een lager hartminuutvolume bij mensen met CF vooral bepaald wordt door een lagere hartfrequentie bij inspanning en niet door een lager slagvolume. Deze bevinding is vooral van belang voor training aangezien trainingsintensiteit en zones berekend op (voorspelde) maximale hartfrequentie niet adequaat zullen zijn. Individuele trainingsadviezen lijken nog steeds relevant voor optimale effecten in het verhogen van iemands CRF (**hoofdstuk 6**).

In **hoofdstuk 7** hebben we middels een vragenlijst onderzocht wat de prevalentie van ernstige vermoeidheid is binnen de volwassen CF-populatie (n=77). Vermoeidheid is gemeten met de Checklist Individual Strength-20 vragenlijst. Uit onze studie kwam naar voren dat 26% van onze volwassenpopulatie ernstige vermoeidheid rapporteert. Dit komt overeen met het gevonden 22% onder de 2- tot- 18 jarige kinderen met CF door collega van der Nap- van der Vlist. Vermoeidheid was geassocieerd met klinisch gemeten uitkomstmaten zoals functionele inspanningscapaciteit met de Modified Shuttle Test en longfunctie (forced expiratory volume in one second; FEV_1). Gerapporteerde vermoeidheid was echter ook geassocieerd met patiënt-gerapporteerde uitkomstmaten, gemeten met de CF Questionnaire 1.2 vragenlijst.

In **hoofdstuk 8** hebben we de effecten van ivacaftor na een mediane behandelduur van 15 [IQR 13-16] maanden bij een kleine groep mensen (n=7) met CF met de S1251N-mutatie onderzocht. We hebben gekeken naar de effecten op longfunctie, lichaamssamenstelling (BMI), energie verbruik in rust en CRF. In lijn met andere studies, met meer geïncludeerde patiënten, laten onze resultaten zien dat longfunctie (FEV_1 in percentage van voorspeld; p=0.015, ratio van residuaal volume en totale long capaciteit, RV/LTC; p=0.016) en BMI (p=0.027) significant toenemen na behandeling met ivacaftor. Opvallend was dat zelfs na 12- maanden of langere behandeling een afname te zien was van de CRF ($ppVO_2peak$ - 12.7%; p=0.010, $ppVO_2peak/kg$ – 16.8%; p=0.000). Mogelijke verklaringen hiervoor zijn dat [1]

mensen met CF de verbeterde longfunctie (nog) niet optimaal en maximaal benutten tijdens lichamelijke inspanning en [2] deze afname in fitheid te maken heeft met een afname van de ademarbeid.

Intussen zijn er ook studies verschenen die de middellange-termijn effecten van onder andere orkambi op de CRF hebben onderzocht. De meeste studies laten zien dat de CRF niet automatisch toeneemt bij behandeling met CFTR modulerende medicatie zoals orkambi. Bovendien lijkt dat het gelijk houden van het fysieke activiteitniveau met CFTR modulerende therapie, onvoldoende is. Deze studies onderstrepen het belang dat naast het geven van CFTR modulerende medicatie, educatie over een gezonde levensstijl (met onder andere voldoende bewegen/ sporten) een essentieel onderdeel is om tot de beste gepersonaliseerde CF behandeling en uitkomsten te komen. Bewustwording van deze effecten door (long) artsen, diëtisten en fysiotherapeuten is essentieel om de CF zorg daadwerkelijk te verbeteren, zeker in het kader van een gezonde levensloop.

Het behouden van een hoge CRF en preventie van afname van CRF zou nog steeds een belangrijk behandeldoel moeten zijn in de fysiotherapeutische CF-zorg, ook gezien de toegenomen overleving en komst van de (zeer effectieve) CFTR-modulatoren. Behoud van CRF geeft mogelijk een beste bescherming tegen morbiditeit en is relevant voor een verbeterde levensloop in mensen met CF.

De vrouwelijke patiënt met CF behoeft mogelijk wat meer aandacht. Gekeken naar verschillende gezondheidsfactoren, is het vrouwelijke geslacht wat in het nadeel. Vrouwen met CF hebben vaker een lagere fitheid, zijn vatbaarder voor het ontwikkelen van psychosociale problemen en hebben een hoger risico op het ontwikkelen van verminderde botdichtheid.

Toekomstig onderzoek is relevant om onze kennis over CRF en CF verder te blijven vergroten. Enkele richtingen voor toekomstig noodzakelijk onderzoek zijn: verbeteren en eenduidigheid met betrekking tot klinimetrie om fysieke activiteit, lichaamssamenstelling en vermoeidheid in kaart te brengen en kennis vergroten van spierfunctie in CF. De effecten van verschillende soorten training en dan met name van hoog-intensive intervaltraining, op factoren als fitheid, glucose tolerantie, hartfrequentie, botstatus en vermoeidheid lijken ook klinisch relevant.

Met het oog op de toekomst blijft fysieke activiteit en dan voornamelijk CRF een essentieel doel in fysiotherapie CF zorg.

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Curriculum Vitae

Marcella Burghard was born on April 14th, 1988, in Aachen, Germany. In 1993 she moved with her parents and older sister from Vaals to Hattem. After graduating from secondary school in Zwolle, she obtained the Bachelor degree in Physiotherapy at the University of Applied Sciences Utrecht, in 2010. Thereafter, she started with the pre-master and continued with the master Human Movement Sciences: Sports, Exercise and Health at the 'Vrije Universiteit Amsterdam'. Additionally, she started working as physical therapist at Medicort Sports & Orthopedic Care in Utrecht and Naarden.

After obtaining her Master of Science degree in 2012, she started a short exercise physiology internship at the Sports Clinic of the St. Antonius Hospital in Utrecht. In 2014, she started a combined research and exercise physiology internship at the Child Development and Exercise Center of the Wilhelmina Children's Hospital in Utrecht. In January 2017, she could make the transition to the University Medical Center Utrecht, as physical therapist for the pulmonary department specializing in Cystic Fibrosis. In August 2018, she started her PhD study at the University Medical Center Utrecht and combined this with her physiotherapy work. At the end of 2018 she started working part time as junior exercise physiologist at the Princess Máxima Center for pediatric oncology as well.

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