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FRAME RUNNING – ENABLING HEALTH IMPROVEMENTS THROUGH PHYSICAL EXERCISE IN INDIVIDUALS WITH CEREBRAL PALSY

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FRAME RUNNING – ENABLING HEALTH IMPROVEMENTS THROUGH PHYSICAL EXERCISE IN INDIVIDUALS WITH CEREBRAL PALSY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Skandiasalen, 1st floor, Building Q1, Karolinska vägen 37A, Karolinska University Hospital, Solna, Friday, June 2, at 9:00 a.m.

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This thesis is dedicated to all participants in these research projects, as well as their families, assistants, together with all amazing people who are committed to making Frame Running and other physical activities possible for people with disabilities. You are the best. Thanks for your contribution to this work and for letting others benefit from these findings in the future.

“The F-words in Childhood Disability: I swear this is how we should think”, was the title of the publication in 2012 by P. Rosenbaum and J. W. Gorter that re-packaged the World Health Organization’s International Classification of Functioning, Disability and Health (ICF) into six words – Functioning, Family, Fitness, Fun, Friends, and Future.

I would like to highlight a seventh F-word - "Frame Running".

Popular science summary of the thesis

This thesis focuses on the health effects of Frame Running and the possibility of using Frame Running to test fitness. Frame Running is a cardiorespiratory exercise and parasport developed for, but not limited to, individuals with cerebral palsy (CP). CP is caused by a brain injury early in life and is the most common cause of motor disability during childhood. People with CP have varying degrees of activity limitations, which affect their fitness and may eventually increase the risk of impaired health. A Frame Runner is a three-wheeled running frame with a saddle, torso support, and handlebars that enable moderate-to-high-intensity training for people with limited or no walking and running ability.

Maximum oxygen uptake capacity (VO_{2max}) is the most common measure of cardiorespiratory fitness. The higher the VO_{2max}, the more efficiently the body can eliminate carbon dioxide and deliver oxygen to the muscles. A high VO_{2max} also means a high lactate threshold. You are able run faster and for a longer time before the body starts to develop lactic acid and you are forced to slow down.

Lactate threshold can be measured indirectly in the exhaled air through the so-called respiratory quotient (Respiratory Exchange Ratio; RER, i.e., VCO_2/VO_2) and directly by measuring the level of lactate through a blood test (finger prick).
If the respiratory quotient is greater than 1, it means that more carbon dioxide is exhaled/eliminated than oxygen is inhaled/consumed, that is, an indication that the oxygen-requiring processes in the muscles cannot convert energy quickly enough and more lactic acid is formed.

For a test of cardiorespiratory fitness through maximum oxygen uptake to be valid, the exertion should be maximum or very close to maximum, and is often called peak (VO_{2peak}). To ensure maximum (or close to maximum) exertion, the heart rate should be as high as possible or close to the maximum heart rate (which depends on age and genetics is often calculated as 220 – age). Further, the respiratory quotient should be greater than 1, and the person should experience the exertion as maximum or close to maximum.

In the first study, the effects on cardiorespiratory and muscle fitness of youths and adults with CP who trained Frame Running twice a week for 12 weeks were evaluated. Cardiorespiratory fitness was measured as the maximum distance the participant could run with their Frame Runner in six minutes; the so-called six-minute Frame Running test (6-MFRT). The muscles were examined by measuring thickness using an ultrasound device. The results showed that the 6-MFRT distance increased on average by 34%, with a similar average heart rate and self-rated exertion compared to before the training period, which was interpreted as improved cardiorespiratory fitness. The muscles also became larger, and the difference was statistically significant in the calf muscle, where the thickness increased on average by 9% on the side that was thinnest before the training period.

In two of the studies in the thesis (study II and IV), oxygen uptake during the 6-MFRT was investigated by having the participants wear a breathing mask connected to a device and a computer that measured the oxygen and carbon dioxide content in the exhaled air. As in the first study, we measured the heart rate with a chest strap and self-rated exertion with a scale.

In the studies, we investigated whether youths and adults with CP could reach a sufficiently high level of exertion in terms of heart rate, respiratory quotient above 1, and self-rated exertion, aiming to answer if the physiological response during 6-MFRT was high enough for VO_{2peak} to be valid as a measure of fitness, (i.e., maximum oxygen uptake).

The results showed that the majority of participants (75% in study II and 94% in study IV) reached the heart rate and RER end-criteria or were just below, meaning that their physiological response was close to maximal.

We also found a strong correlation between oxygen consumption (VO_{2peak}) and the distance that participants ran with the Frame Runner during the 6-MFRT, in other words the longer distance covered the higher VO_{2peak}.

This indicates that the 6-MFRT can be used as a measure of aerobic fitness (i.e., to estimate VO_{2peak}).

To further validate the use of the 6-MFRT as an aerobic fitness test, we compared it (in study IV) to a gold standard aerobic fitness test performed with the Frame Runner on a treadmill, gradually increasing the speed until exhaustion was reached. We called this test the Frame Running Incremental Treadmill test (FRITT). The results showed a strong correlation between VO_{2peak} achieved during the 6-MFRT and FRITT, with no statistically significant difference. Again, we found a strong correlation between distance covered and oxygen uptake (VO_{2peak}). Additionally, statistical models demonstrated that there may be a possibility of developing an equation to predict fitness/VO_{2peak} based on 6-MFRT distance along with gender, height and weight.

In study III, we investigated the physical and physiological parameters, besides maximal oxygen uptake, that are the most important for a good performance in Frame Running. We also used the 6-MFRT, but as a measure of Frame Running capacity in this study. The results showed that muscle mass had a positive effect and spasticity (i.e., high involuntary muscle tension due to the brain damage), had a negative effect on Frame Running capacity.

Overall, the results of my thesis show that:
1) Frame Running provides health benefits in terms of improved fitness and muscle growth for individuals with CP,

2) Frame Running can be used to assess cardiorespiratory fitness in individuals with CP, where measured distance during the 6-MFRT can serve as an estimate of fitness (maximal oxygen uptake) and is a good alternative to a more complicated laboratory-based treadmill test.

3) muscle mass has a positive effect and spasticity has a negative effect on Frame Running capacity. These findings may enable optimization of training to improve Frame Running capacity and contribute to evidence-based and fair classification in Frame Running competitions.

Populärvetenskaplig sammanfattning på svenska

Denna avhandling fokuserar på hälsoeffekterna av Frame Running och möjlighet att använda Frame Running för att testa kondition. Frame Running är en träningsform och parasport utvecklad för, men inte begränsad till, individer med cerebral pares (CP). CP orsakas av en hjärnskada tidigt i livet och är den vanligaste orsaken till motorisk funktionsnedsättning under barndomen. Personer med CP kan ha olika grader av aktivitetsbegränsning, vilket påverkar deras kondition och på sikt kan öka risken för nedsatt hälsa. En Frame Runner är en trehjulig spring-cykel med sadel, bålstöd och styre som möjliggör måttlig till högintensiv träning för personer med begränsad eller ingen gång- och löpförmåga.

Maximal syreupptagningsförmåga (VO_{2max}) är det vanligaste måttet på kondition. Ju högre VO_{2max}, desto mer effektivt kan kroppen göra sig av med koldioxid och desto mer syre kan transporteras till musklerna. Hög VO_{2max} innebär med andra ord en hög mjölksyregräns. Du orkar springa snabbare och under längre tid innan kroppen börjar utveckla mjölksyra och tvingar dig att sakta ned.

Mjölksyregräns kan mätas indirekt i utandningsluften genom den så kallade respiratoriska kvoten (Respiratory Exchange Ratio; RER, dvs VCO_2/VO_2) och direkt genom att mäta nivån av mjölksyra genom ett blodprov (stick i fingret). Om respiratoriska kvoten är större än 1 innebär det att mer koldioxid andas ut/elimineras än syre andas in/förbrukas, det vill säga en indikation på att de syrekrävande processerna i musklerna inte kan omvandla energi tillräckligt snabbt och mer mjölksyra bildas.

För att ett test av konditionen genom maximal syreupptagning ska vara giltigt bör ansträngningen vara maximal eller väldigt nära maximal och kallas då peak (VO_{2peak}). För att säkerställa en maximal (eller nära maximal) ansträngning ska pulsen vara så hög som möjligt eller nära maximala pulsen (som är beroende av ålder och genetik och ofta beräknas som 220 - ålder), den respiratoriska kvoten ska vara mer än 1 och personen ska uppleva ansträngningen som maximal eller nära maximal.

I den första studien utvärderades effekterna på kondition och muskler hos ungdomar och vuxna med CP som tränade Frame Running två gånger i veckan i 12 veckor. Konditionen mättes som maximal sträcka som deltagaren klarade att springa med sin Frame Runner på sex minuter; det så kallade sex minuter Frame Running-testet (6-MFRT). Musklerna undersöktes genom att mäta tjocklek med hjälp av en ultraljudsapparat. Resultaten visade att sträckan på 6-MFRT ökade i genomsnitt 34%, med oförändrad puls och självskattad ansträngning i jämförelse med innan träningsperioden, vilket tolkades som förbättrad kondition. Musklerna blev också större. Skillnad visades vara statistiskt säkerställd på vadmuskeln där storlek i genomsnitt ökade 9 % på den sida som var tunnast från början.

I två av studierna i avhandlingen (Studie II and IV) undersöktes syreupptagningsförmåga under 6-MFRT genom att deltagarna hade en andningsmask kopplad till en mätare som mätte syrehalten i utandningsluften. Vi mätte också pulsen med ett pulsband runt bröstkorgen och självskattad ansträngning (på samma sätt som i första studien).
I studierna undersökte vi om ungdomar och vuxna med CP kunde nå tillräckligt hög ansträngning avseende puls, respiratorisk kvot över 1 och självskattad ansträngning, det

vill säga om det fysiologiska svaret under 6-MFRT var tillräckligt högt för att VO_{2peak} skulle kunna vara giltigt som ett mått på kondition dvs maximal syreupptagning.

Resultatet visade att de flesta deltagarna (75% i studie II och 94% i studie IV) nådde kriterierna eller var precis under. Vår slutsats var således att det fysiologiska svaret var nära maximalt. Vi fann också en stark koppling mellan syreförbrukningen (VO_{2peak}) och hur långt deltagarna sprang med Frame Runnern på 6-MFRT, med andra ord, ju längre sträcka desto högre VO_{2peak}.

Detta indikerar att 6-MFRT kan användas som ett konditionstest (dvs för att uppskatta syreförbrukningen VO_{2peak}).

För att ytterligare säkerställa att 6-MFRT är giltigt som ett konditionstest jämförde vi (i studie IV) 6-MFRT med det ett konditionstest som utfördes enligt den mest korrekta metoden; konditionstest på löpband med Frame Runner med gradvis ökande hastighet tills total utmattning uppnås. Vi kallade detta test för Frame Running Incremental Treadmill test (FRITT). Resultaten visade ett starkt samband mellan VO_{2peak} som uppnåddes vid 6-MFRT och FRITT, samt att det inte var någon statistiskt säkerställd skillnad mellan testen.

Återigen såg vi ett starkt samband mellan uppnådd sträcka och syreupptag (VO_{2peak}). Vidare påvisade statistiska modeller lovande möjlighet att kunna utveckla en ekvation för att kunna förutsäga kondition/VO_{2peak}, baserat på sträckan på 6-MFRT tillsammans med kön, längd och vikt.

I studie III undersökte vi vilka fysiska och fysiologiska parametrar, förutom maximal syreförbrukning, som är viktigast för att prestera i Frame Running. 6-MFRT användes också i denna studie, men här som ett mått på Frame Running-kapacitet. Resultaten visade att muskelmassa har en positiv effekt och spasticitet (dvs hög ofrivillig spändhet i musklerna till följd av hjärnskadan) har en negativ effekt på Frame Running kapacitet.

Sammantaget visar resultatet i min avhandling

1) att Frame Running ger hälsovinster avseende förbättrad kondition och muskeltillväxt hos individer med cerebral pares,

2) att en Frame Runner kan användas för att testa kondition hos individer med CP, där uppmätt sträcka på 6-MFRT kan fungera som en uppskattning av kondition (maximal syreupptagningsförmåga) och är ett bra alternativ till ett mer komplicerat laboratoriebaserat test på löpband,

3) att muskelmassa har en positiv effekt och spasticitet en negativ effekt på Frame Running kapacitet. Resultatet kan möjliggöra optimering av träning för att förbättra Frame Running-kapaciteten och bidra till evidensbaserad och rättvis klassificering när man tävlar i Frame Running.

Abstract

Introduction

Cerebral palsy (CP), caused by a damage to the developing brain, is the most common cause of motor disability in childhood. People with CP may have varying degrees of activity limitation, which affect their cardiorespiratory and muscle fitness. The overall aim of the thesis was to study the health effects of Frame Running in individuals with CP and ambulatory difficulties (Gross Motor Function Classification System, GMFCS II-V). Frame Running is an exercise and parasport that enables moderate-to-high intensity physical activity in individuals with severely impaired posture, balance, and motor control. Therefore, study I investigated the effects of a Frame Running training intervention. Study II and IV explore whether the six-minute Frame Running test (6-MFRT) is a valid measure for cardiorespiratory fitness, i.e., maximal oxygen consumption (VO_{2peak}). Finally, determinants (apart from VO_{2peak}) of Frame Running capacity in athletes with CP were explored (study III).

Methods

Study I involved 15 participants with CP at GMFCS level I-IV, who completed 12 weeks of Frame Running training, with pre and post evaluation of cardiorespiratory endurance (6-MFRT), muscle thickness (ultrasound), and passive range of motion. Study II involved 24 participants with CP at GMFCS level II-IV, who performed the 6-MFRT with measure of cardiorespiratory parameters such as heart rate (HR), oxygen consumption (VO_{2peak}) and respiratory exchange ratio (RER). Study III involved 62 participants with CP at GMFCS level I-V, who completed the 6-MFRT test as a measure of Frame Running capacity. Prior to 6-MFRT multiple specific lower limb impairments and muscle thickness was investigated. Study IV involved 16 participants with CP at GMFCS levels II-V, who performed the 6-MFRT and Frame Running Incremental Treadmill test (FRITT) to compare the cardiorespiratory response and blood lactate levels.

Results

In study I, Frame Running training improved cardiorespiratory endurance (6-MFRT) with 34%, and muscle thickness of the gastrocnemius in the most affected leg with 9%. There were strong correlations between 6-MFRT distance and VO_{2peak} in both study II and IV, and >75% of the participants reached a (near) maximal exertion based on HR and RER-criteria. Moreover, a strong correlation between the VO_{2peak} obtained during the 6-MFRT and FRITT was observed, with no significant differences in any cardiorespiratory parameters or blood lactate. A backward univariate linear regression analysis indicated that distance, sex, body weight, and height were significant predictors of VO_{2peak} (L/min) during the 6-MFRT (Study IV). The orthogonal partial least square (OPLS) regression analysis revealed a modest degree of covariance in the variables analyzed, and that the variance in the 6-MFRT distance could be predicted with 75% accuracy based on >50 variables measured. Variable Importance in Projection (VIP) analysis indicated hip and knee extensor spasticity (negative effect), and muscle thickness (positive effect) arose as the most important factors contributing to Frame Running capacity (Study III).

Conclusion

Frame Running is a powerful and effective exercise modality in individuals with CP, promoting health-enhancing cardiorespiratory and peripheral adaptations. The Frame Runner can be used for aerobic exercise testing, where the 6-MFRT is valid and practical. Apart from aerobic capacity, spasticity around the hip and knee (negative

effect) and muscle mass (positive effect) appears to be the most important factors contributing to Frame Running capacity. These findings are an important resource to enable optimization of training regimes to improve Frame Running capacity and contribute to evidence-based and fair classification for this parasport.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following original papers and manuscript. They will be referred to in the text by their roman numerals as indicated below:

I. **Hjalmarsson E**, Fernandez-Gonzalo R, Kvist O, Palmcrantz A, Pontén E, von Walden F. RaceRunning training improves stamina and promotes skeletal muscle hypertrophy in young individuals with cerebral palsy. BMC Musculoskelet Disord, 2020. 21(1): p. 193.,

II. Edelman Bos AMM, **Hjalmarsson E,** Dallmeijer AJ, Fernandez-Gonzalo R, Buizer AI, Pingel J, Pontén, von Walden F, van Schie PE. Physiological Response to the 6-Minute Frame Running Test in Children and Adults with Cerebral Palsy. Pediatr Phys Ther. 2022;34(4):529-34

III. **Hjalmarsson E**, Lidbeck C, Barrero Santiago L, Pingel J, Norrbom J, Sanz G, Palmcrantz A, Pontén E, von Walden F, Fernandez-Gonzalo R. Determinants of Frame Running capacity in athletes with cerebral palsy to improve training routines and classification strategies: A cross-sectional observational study. Am J Phys Med Rehabil. E-pub ahead of print, March 7, 2023.

IV. **Hjalmarsson E**, Edelman Bos A, Corell L, Kruse A, Fernandez-Gonzalo R, Pontén E, Dallmeijer A.J, Buizer A, van Schie PE, von Walden F. Validation of the 6-minute Frame Running Test (6-MFRT) as a cardiopulmonary maximal test in cerebral palsy (manuscript)

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

Vechetti IJ, Norrbom J, Alkner B, **Hjalmarsson E**, Palmcrantz A, Pontén E, Pingel J, von Walden F, Fernandez-Gonzalo R. Extracellular vesicle characteristics and microRNA content in cerebral palsy and typically developed individuals at rest and in response to aerobic exercise. Front Physiol. 2022;13:1072040

Van der Linden M, van Schie P, **Hjalmarsson E**, Andreopoulou G, Verheul MHG, von Walden F, Athlete-Perceived Impact of Frame Running on Physical Fitness, Functional Mobility and Psychosocial Outcomes. J Rehabil Med, 2022. 54: p. jrm00273

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Pingel J, Harrison A, Von Walden F, **Hjalmarsson E**, Bartels EM. Multi-frequency bioimpedance: a non-invasive tool for muscle-health assessment of adults with cerebral palsy. J Muscle Res Cell Motil, 2020.

Jacobson D.N.O, Löwing K, **Hjalmarsson E**, Tedroff K. Exploring social participation in young adults with cerebral palsy. J Rehabil Med, 2019. 51(3): p. 167-174.

Contents

List of abbreviations

6-MFRT	Six-minute Frame Running test
ANOVA	Analysis of Variance
bi	Bilateral
BMI	Body Mass Index
bpm	Beats per minutes
CFCS	Communication Function Classification System
CO_2	Carbon dioxide
CP	Cerebral Palsy
CPISRA	Cerebral Palsy International Sport and Recreation Association
FMS	Functional Mobility Scale
FR	Frame Running
FRITT	Frame Running Incremental Treadmill test
GMFCS	Gross Motor Function Classification System
GMFCS-E&R	Expanded and revised Gross Motor Function Classification System
HR	Heart Rate
HR_{max}	Maximal heart rate
HR_{peak}	Peak heart rate
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
IWAS	International Wheelchair and Amputee Sport Federation
LAL	Less affected leg
MACS	Manual Ability Classification System
MAL	More affected leg
MAS	Modified Ashworth Scale
max	maximal
O_2	Oxygen
OMNI	Category scale from 0-10 for rating of perceived exertion
OPLS	Orthogonal partial least square
PCA	Principal Component Analysis
pROM	Passive range of motion
RER	Respiratory Exchange Ratio (VCO_2 production/VO_2 uptake)
ROM	Range of motion
Rf	Respiratory frequency

RPE	Rating of Perceived exertion
SD	Standard Deviation
SGPAL	Saltin Grimby Physical Activity Scale
SMC	Selective Motor Controle
uni	Unilateral
US	Ultrasound
V	Volyme
VE	Minute ventilation
VE_{peak}/VCO_{2peak}	Relationship between the peak minute ventilation and the peak carbon dioxide production
VE_{peak}/VO_{2peak}	Relationship between the peak minute ventilation and the peak oxygen uptake
VIP	Variable Importance in Projection
VO_2	Oxygen uptake
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
WHO	World Health Organisation
WPA	World para-athletics

Thesis at a glance

	Study I	Study II	Study III	Study IV
Status	Published (2020)	Published (2022)	Published (2023)	Manuscript
Purpose	Effect of FR-training	Physiological response to the 6-MFRT	Determinants of FR capacity (6-MFRT)	Validation of the 6-MFRT
Study design	Intervention-study; 12-week FR	Cross-sectional study	Cross-sectional study	Cross-sectional study
Participants with CP, GMFCS II-V	n=15	n=24	n=62	n=16
Location	Sweden, FR-clubs Solna, Västerås, Uppsala,	Sweden, FR-clubs, the Netherlands FR-clubs	Denmark Camp and cup, Sweden, FR-clubs	Sweden, Bosön National Sports Confederation's laboratory
Main outcome measures	6-MFRT distance Muscle thickness pROM	6-MFRT distance VO_{2peak} HR_{peak} RER_{peak} Borg RPE/OMNI	6-MFRT distance pROM MAS SMC Muscle thickness	6-MFRT distance FRITT results VO_{2peak} HR_{peak} RER_{peak} Borg RPE Blood lactate
Main results	* 34% improved aerobic capacity * 21% higher maximum speed * 9% improved calf muscle thickness more affected side	* Strong correlation between 6-MFRT distance and VO_{2peak}, * 75% reached a (near) maximal physiological response during the 6-MFRT	Determinants of FR capacity * Spasticity (around hip and knee-muscles), * Muscle thickness (thigh more than calf) * SMC (ankle dorsiflexion)	Strong correlations between; * VO_{2peak} during FRITT and 6-MFRT * 6-MFRT distance and VO_{2peak}. * No significant differences 6-MFRT and FRITT
Conclusion for individuals with CP	FR-training improve cardiorespiratory and muscle fitness	6-MFRT can be used to estimate oxygen consumption on an individual basis	Stimulate muscle mass in addition to FR training can improve FR capacity and health. Information is valuable for evidence-based classification.	The 6-MFRT is practical and useful for estimation of aerobic capacity

Abbreviations: FR: Frame Running, CP: cerebral palsy, GMFCS: Gross Motor Classification System 6-MFRT: six-minute Frame Running test, FRITT: Frame Running Incremental Treadmill test, pROM: passive range of motion, VO_{2peak}: volume of oxygen uptake during peak exercise, RER: respiratory exchange ratio, HR: heart rate, RPE; rating of perceived exertion, OMNI: scale for self-perceived physical exertion, MAS: modified Ashworth scale for increase muscle tone, SMC: selective motor control

INTRODUCTION

The research projects included in my doctoral studies are all focused on different aspects of Frame Running, also (formerly) known as RaceRunning; a form of exercise and parasport primarily developed for people with cerebral palsy (CP). The Frame Runner, a three-wheeled running frame, enables intense physical activity for individuals with impaired balance and gait.

In the literature review, I outline what is known about the effects of physical activity in individuals typically developed (TD) and with CP, with a focus on both children and adults, to further specify existing knowledge gaps of how Frame Running can contribute to increased physical fitness in individuals with CP.

Next, the thesis focuses on the overall research aims and questions of the studies. The two important aspects of health improvements that are in focus are cardiorespiratory and muscle fitness. Further the thesis explore exercise testing and determinants of Frame Running capacity.

The literature review and aims are followed by a methods section, a summary and discussion of research results, conclusion, and points of perspective.

1 LITERATURE REVIEW

1.1 Cerebral Palsy (CP)

1.1.2 Prevalence, definition and classifications

Cerebral palsy (CP) is the most common cause of motor disability in children, with a prevalence worldwide of 1.6 per 1000 live births [1]. In adulthood, the prevalence is lower, due to poor survival of the most severely impaired. The prevalence was found to be 1.14 per 1000 in the age span 41-60 years in a recent Swedish study [2].

The modern definition of CP derives from an international workshop and was first published by Rosenbaum et al. in 2007 (p.9) [3].

"Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems."

Together with the definition, there is common terminology for describing the subgroups and severity of CP. The type of the motor disorder is categorized into spastic (bilateral or unilateral), dyskinetic (dystonia, chorea-athetosis) and ataxic type [4]. Spastic CP is the most common form of CP and accounts for around 80% of all individuals with CP [2, 5]. To describe function, several five-level classification systems have been developed, of which the Gross Motor Function Classification System (GMFCS) is the most studied and used [6-8]. The GMFCS consists of five ordinal levels based on self-initiated movement with a special focus on ambulation and posture. Individuals classified as level I can walk and perform most physical activities without major restrictions, but may have limitations in balance, speed, and coordination and to perform advanced motor skills. In the other end of the spectrum, individuals in GMFCS V have difficulty with maintaining posture and balance, are wheelchair users in all settings and need help to perform most activities in daily life (Figure 3:3). Additional five-level classifications include the Manual Ability Classification System (MACS) [9] focused on hand function and Communication Function Classification System (CFCS) describing effectiveness of communication [10].

Another scale that describes functional mobility is the Functional Mobility Scale (FMS). This scale focuses on three distances and what (if any) type of walking-support / wheelchair that is commonly needed on each distance, representing mobility at home (5m), at school (50m) and in society (500m). FMS is more sensitive to change than GMFCS, for example after an intervention [11].

1.2 Physical fitness and health

1.2.1 The concept of physical fitness and exercise

Physical fitness can be seen as a set of attributes that people have or achieve in order to carry out school/occupation activities, sports, and other daily activities [12]. The concept of physical fitness can be divided into two components; health-related fitness and skill-related fitness. Health-related fitness includes cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility. Skill-related fitness is related to agility, balance, coordination, speed, power and reaction time [13].

Further, health-related fitness relates mainly to habitual physical activity and how that affects health status, whereas skill or performance related fitness is commonly achieved through physical exercise, where exercise is seen as a subcategory of physical activity which is planned, structured and repetitive [13]. Traditionally, exercise is usually defined as either strength training or endurance training [14, 15]. Variables to consider when designing a training regime aimed at optimizing physical adaptation include frequency, intensity, time, type, total volume and progression [15], where all factors are important. To improve fitness, progression in at least one variable is required. Positive health-effects/physiological adaptation takes place following all types of exercise and varies among individuals [16, 17] but there are significant differences in adaptations due to type of exercise.

1.2.2 Physical activity and health

Through mainly observational studies, we know that physical activity improves health and reduces the risk of all-cause mortality and that there is a dose-response relationship [18-20]. The list of diseases and conditions with evidence for risk reduction from physical activity includes cardiovascular diseases, hypertension, type 2 diabetes, adverse blood lipid profile, several forms of cancer, obesity, osteoporosis, dementia, anxiety and depression [21, 22]. International guidelines on the dose and type of physical activity required for health and disease prevention have recently been updated [21, 22]. The World Health Organization's recommendation for adults is moderate aerobic physical activity 150-300 min per week, or 75-150 min of vigorous aerobic physical activity. For additional health benefits, muscle strengthening activities are recommended at least twice a week. The recommendation for children and adolescents (5-17 years) involves at least 60 minutes of mostly aerobic physical activity of moderate to high intensity per day. In addition, vigorous physical activities that include aerobic activity as well as bone and muscle-strengthening activity should be performed, at least three times per week [22].

1.2.3 Sedentary behavior and health

Insufficient physical activity as well as increased sedentary behavior is a growing global problem, affecting both children and adults [23, 24].

The evidence behind the negative health effects of sedentary behavior has gained strength in recent years. Sedentary behavior, that is, lying or sitting with low energy consumption (≤1.5 metabolic equivalents of task (MET)) [25, 26], is therefore emphasized in the new revised international guidelines from World Health Organization [22]. However, the overall effects of sedentary time and the importance of the pattern of sedentary time during the day are still not clear. On the one hand, some studies claim that that the risk with large amounts of sedentary behavior are the same regardless of the amount of physical activity [27, 28]. On the other hand, a recent study shows that prolonged sitting time can likely be compensated for with physical activity. Stamatakis et al. conclude that those who reach the recommendation for physical activity have small to no increased risk of dying prematurely due to sedentary time [19].

Naturally, individuals who do not meet the physical activity guidelines and accumulate a lot of sedentary time (>8h/day) are facing the greatest health risk [19], e.g., wheelchair users.

1.2.4 Frameworks for health

The International Classification of Functioning, Disability and Health (ICF) is a set of ideas about how to think about health, developed by World Health Organization (WHO) in 2001 [29]. The ICF offers a standardized terminology and classification of health terms into five domains; 1) Body functions and structure, 2) Activity, 3) Participation, 4) Environmental factors and 5) Personal factors. A graphical framework with boxes and arrow brings these domains together to illustrate that there is an interaction between the health domains. In 2011, a new framework (or way of thinking and acting) called 'F-words' in childhood disability was introduced [30]. The F-words is grounded in the ICF framework using a similar picture with boxes and arrows that highlight six equally important areas of child development and health; Function, Family, Fitness, Fun, Friends and Future. Since its publication in 2012 this modern framework for health has spread around the world and is freely available [31]. An adapted picture of the F-words and ICF frameworks and a suggestion on how the four studies relate to these frameworks is shown in figure 2:1 on page 15 of the thesis.

1.2.5 Resistance training including training adaptations

Exposure to resistance training is associated with a range of neurological and muscle morphological adaptations [32]. Initially, an improved nervous system has been shown to explain the larger part of the increased muscle strength. Neural adaptations involve improved learning and coordination, with more efficient activation and recruitment of motor units of the muscle involved in the task [33]. The major long-term adaptation, however, is typically seen as increased muscle size (hypertrophy) [32-34]. Contrary to early reports of a delay before the onset of hypertrophy [35] several recent studies have shown that hypertrophy seems to contribute to strength gains early [36-38], where one study demonstrated significant hypertrophy after only three weeks of training [36]. Further morphological adaptations include change in muscle architecture, metabolic adaptation and changes in tendon and connective tissue [32].

A key component in a training regime for optimizing strength and hypertrophy is volume (i.e., the amount of work as in the total number of repetitions) with a linear dose-response relationship [39-41]. Higher versus lower load resistance training has been shown to induce muscle hypertrophy with equal effectiveness, if performed close to failure in each method [40, 42].

1.2.6 Endurance training including training adaptations

Aerobic capacity is the ability to deliver oxygen to the muscles and to use it to generate energy during exercise [15, 43]. Maximal oxygen uptake (VO_{2max}) is a major predictor of endurance capacity [44, 45] even though it is just one out of three factors that explain cardiorespiratory performance. The others factors are movement economy and fractional utilization of aerobic capacity, as in ability to sustain a high rate of oxygen consumption for prolonged periods, including raised lactate threshold [46, 47].

The overall VO_{2max} depends on cardiac output (stroke volume [SV] x heart rate [HR]) together with the oxygen uptake and energy usage in peripheral skeletal muscle, that is measured as the arteriovenous oxygen difference (a-vO_2 diff).

Adaptations to endurance exercise training are hence characterized by increased cardiac output and peripheral muscular adaptation (a-vO_2 diff) [48-50].

For cardiac output, stroke volume (SV) is a key factor [51] which increases both within hours after exercise (due to increased blood volume [52]), and continues to improve over time (months) as the heart increase in efficiency and strength (hypertrophy) [51, 53]. Maximal heart rate (HR) is individual and age-related and does not change significantly from exercise. The improved oxygen uptake and energy usage in peripheral skeletal muscles (a-vO_2 diff) is due to improved capillarity and vascular function as well as improved function and density of mitochondria, the power plants in the cell [53].

To optimize aerobic capacity (VO_{2max}), intensity is considered most important [48, 54]. Defining an exact threshold of intensity to improve cardiorespiratory fitness is difficult, due to a variation depending on age, gender and fitness status of the individual. Highly trained individuals may need an intensity of >90% of VO_{2max}, whereas for deconditioned individuals, as low intensity as 30% of VO_{2max} can lead to an improvement [15, 55]. When it is not possible to assess oxygen uptake to decide intensity, there are other methods to estimate the intensity of exercise, where percent of maximal age-related heart rate (%HR_{max}) is commonly used. There is no true gold standard for maximum HR, despite several equations with pros and cons. The Fox HR_{max}=220-age is simple and best known [56]. The Tanaka Equation HR_{max}=208-(0.7xage) [57] is found to be more valid for children and adolescents [58]. Estimating %VO_{2max} from %HR_{max} or vice versa includes an error of around 8%. As an example, moderate intensity corresponding to 64-76 of %HR_{max} equals 46-63 of %VO_{2max} [15, 59].

VO_{2peak} [60, 61] as well as muscle mass [62] have direct associations with health, general function, and can predict mortality in both healthy and diseased individuals.

1.2.7 Evaluation of cardiorespiratory fitness

The gold standard for measuring cardiorespiratory fitness is maximum oxygen uptake (VO_{2max}) attained during a progressive maximal exercise test in a laboratory [15]. The measure of VO_{2max} is expressed in unit of time relative to body mass (ml/kg/min) or as absolute values (L/min) [15]. This type of test is desirable when possible, for both children [63], adults, [15] and in most conditions, including CP [64, 65]. True maximal oxygen uptake is reached when a plateau in oxygen uptake is observed despite increasing workload [15]. A plateau is not always observed during maximal exercise testing [66] and rarely in children [63]. Reasons for this can be that it is hard to motivate children (and other groups) enough to not stop just before or as soon as the plateau is reached, or that muscular rather than cardiorespiratory factors limit maximal performance in some subjects [15, 59]. Therefore, peak oxygen uptake (VO_{2peak}) during the test is often used as a proxy for VO_{2max}. Recent literature also highlight that a lack of a VO_2 plateau on an exercise test does not necessarily invalidate it as a VO_{2max} test since the plateau in oxygen uptake ($\dot{V}O_2$) is inconsistent in its frequency, reducing its usefulness as a robust method to determine "true" $\dot{V}O_{2max}$ [67].

In addition, other objective physiological criteria can be used to indicate that maximum aerobic response is achieved [15, 68-70]. In general, there is currently no clear consensus regarding what criteria, or limit value within respective criteria, that best reflect maximal effort. Further, criteria can vary depending on gender, age, trained or non-trained [68-70]. Criteria variables that have been used, include a certain percentage of the age-adjusted estimate of HR_{max}, elevated respiratory exchange ratio (RER), high blood lactate levels, rating of perceived exertion (the Borg RPE Scale), observed signs of exertion or a combination of these variables [69-71].
Criteria for the adult population can be set at HR ≥ 85% of 220-age and RER ≥ 1.1 [15] (i.e., more CO_2 is produced in the muscles than O_2 consumed). For children (under 18 years) the HR criteria of ≥95% of 195 beats per minute (i.e., ≥185bpm) and RER ≥ 1.0 can be used to reflect maximum effort [68].
In general, heart rate, at least alone, is not considered to be completely valid as a criterion for maximum effort, due to its wide range, where the age-adjusted equations have a large margin of error [15, 69]. However, it can offer an estimation and is easy to measure. Criteria for blood lactate concentration are >6mmol in children [70] and >8mmol in adults [69, 71, 72], then decrease again in the elderly population [71]. In addition, in order to determine whether maximum exertion is achieved, a high to maximal perceived exertion is of course important. The mostly used scale for perceived exertion is the Borg Rating of Perceived Exertion (RPE) scale ranging from 6-20 [73] and for a maximal exercise test it should be ≥17 ("very hard)" [69, 73]. In addition, subjective signs of maximum exertion can be valuable (such as sweating, instability and clear unwillingness to continue the test despite strong encouragement) [68].

1.2.8 Training adaptations in children versus adults

The benefits of exercise during childhood are indisputable and include improved muscle strength, cardiorespiratory fitness, skeletal health, metabolic health, mental health, and performance in school [74]. Further, being active as a child is associated with lower cardiovascular risk profile in adulthood [74, 75]. Important to note, however, is that adaptations to exercise are different in children versus adults.

Strength gains after resistance exercise in prepubertal children are primarily caused by neural adaptations and less due to hypertrophy [76, 77]. This is made clear by the fact that even though resistance training has been shown to promote muscle hypertrophy in prepubertal children [76, 78, 79], adolescents are capable of greater absolute gains and greater degree of hypertrophy owing to higher levels of circulating androgens (testosterone). This applies for all youths but more in boys [80, 81].

The cardiovascular adaptive response to endurance training in prepubertal children is also less pronounced than in adults. This holds true for both central (cardiac output) and peripheral adaptations (muscle endurance) [82-84]. The exact impact of maturation stage on trainability of aerobic capacity is currently not completely understood [82].

Although older children and adults seem capable of greater gains in aerobic capacity in response to training, it appears to be trainable in children of all ages [82, 85]. Peak oxygen uptake also increases spontaneously during childhood, more in boys than in girls, as a result of physiological maturation [86]. Adolescents (13-19y) who perform regular endurance training are shown to have a larger heart and increase in VO_{2max} [87] compare to inactive peers.

Finally, it is important to note the effects on bone health from weight-bearing physical activity during prepubertal/pubertal ages, which have lifelong benefits and improved protection against osteoporosis in adulthood [88].

1.3 Physical fitness and health in individuals with CP

1.3.1 Physical activity, sedentary behavior and health in individuals with CP

Evidence shows that individuals with cerebral palsy are less active and spend more time sedentary than typically developed peers [89-92]. This appears to be true for all GMFCS levels, but individuals with more severely affected motor function have the lowest activity level and participate to a lesser extent in physical activity both at school and during leisure time [90-92]. In addition, the few activities available such as hydrotherapy, horseback riding and boccia are typically performed at low intensity with minimum systemic health benefits [90, 92-94].

In fact, several larger observational studies now show that having CP is associated with an increased risk of poor health as an adult and increased prevalence of diseases related to inactivity and premature aging [95-97].

Promoting physical activity in general, and in particular activities of moderate to high intensity for adolescents with CP, would most certainly increase physical fitness and thus reduce the risk of poor health and disease [98-100]. It has also been shown that being physically active as an adolescent with CP is strongly related to a maintained physical activity level as an adult [101].

Recommendations for physical activity for individuals with CP should strive to reach the same dose as for the general population, but with adaptations if needed, and an understanding of the difficulties [22, 99, 100].

1.3.2 Skeletal muscle fitness in individuals with CP

Dysfunction of movement and posture are core features of CP, and poor muscle control and weakness are a direct consequence of the brain lesion. But early in life, muscle fitness also becomes affected by inactivity. Hence, skeletal muscles in CP are likely affected by a combination of altered neural drive and independent peripheral changes to muscles themselves [102, 103].

It has been shown that muscle growth is reduced in children with CP [104, 105]. Moreover, muscle strength [106, 107] as well as muscle mass [108-110] is significantly lower, and during aging, the loss of muscle mass is more pronounced in individuals with CP as compared to typically developed individuals [110].

In addition to thin and weak muscles, poor muscle control and spasticity appear to be related to decreased range of motion, leading to secondary musculoskeletal problems that are common in individuals with CP [3, 111, 112]. The cause of the development of contractures is unknown [113-115], but has been found to start early and often progresses during life [112, 116]. Knee contractures are more common and often the first limitation of motion in individuals with GMFCS levels III-V, while the ankle plantar flexors are the first muscle affected by stiffness in GMFCS I-II [112]. Range of motion deficits further limit gait [117] and other functions [118-120].

Research concerning muscle pathophysiology and metabolic dysregulation in individuals with CP [102, 114, 121-123] reveal a complex picture. Altered muscle architecture with small muscle fibers and abnormal fiber composition, more collagen within the muscle, fewer capillaries, and fewer satellite cells (the muscle's stem cells) [102, 124] are some of the findings. Furthermore, there are indications of reduced function of the cellular organelles including mitochondria [125, 126] and the ribosomes (the cell's protein factory, important for muscle growth) [124, 127].

There has been a considerable number of studies regarding resistance training interventions for individuals with CP in the past decade, as well as several reviews [128-132]. Individuals with CP have been shown to respond to resistance training with increased strength [128, 133] and muscle hypertrophy [128, 130, 134]. Regarding the transfer effects into function, however, there are conflicting results. There are several studies claiming that increased strength would have an impact on motor function [128]. Relationships between muscle strength and function, as gait [107] and motor function [135], have been observed. Similarly, correlations between muscle thickness [136, 137] and gross motor function have been detected. Still, most studies have had difficulty demonstrating objective functional improvement from increased strength [131, 132, 134].

In conclusion, muscle training for strength, hypertrophy and endurance is highly recommended for individuals with CP [98]. Although more research is needed, physical activity appears to diminish muscle pathophysiology present in individuals with CP [131, 138].

1.3.3 Cardiorespiratory fitness in individuals with CP

The general view is that cardiorespiratory function should not be affected by CP. However, conflicting views exist including impaired respiration and affected circulation by increased muscle tone. Specifically, it has been suggested that the brain damage itself may cause a less effective breathing pattern with higher peak ventilatory equivalents (VE/VO_2), potentially due to spasticity or otherwise impaired respiratory muscles [139-141]. Another theory is that increased muscle tone in the lower limbs obstructs venous return and thus reduce cardiac output, which in turn negatively affects oxygen transport to the working muscles [140]. It should be noted however, that none of these hypotheses have been confirmed. The lower cardiorespiratory fitness in CP is likely explained by limitations in daily activities and mobility in this group. In addition, there are few exercise options, especially concerning activities performed at a higher intensity for individuals with CP, and especially for those with higher GMFCS levels [98, 99].

Several studies have showed lower cardiorespiratory fitness, (VO_{2peak}) in individuals with CP as compared to typically developed peers [140-145]. In addition, physical strain, as in oxygen cost during walking at own leisurely pace, seems to be higher in children with mild CP compared to TD children [143, 145]. In general, most of the literature on VO_{2peak} and CP applies to individuals with milder CP who are ambulant (GMFCS level I-II and a few GMFCS III) both for children (7-19 years) [64, 141, 142, 144-148] and adults [65, 148].

There are limited data on aerobic capacity in the more severely affected individuals with CP (GMFCS IV-V), as testing involving large muscle groups (treadmill and cycling) is difficult to perform. Moreover, when employing wheelchair-based tests it may be difficult to achieve sufficient intensity as the cardiorespiratory system may not be the limiting factor, that is, in addition to poor motor control, the upper limbs may be the weaker link [149]. Studies using maximal exertion test on a treadmill [141, 142, 145], or cycle ergometer [144, 147, 148], or arm crank/wheelchair ergometer [150-152], including only a few individuals classified at GMFCS level III [144, 147, 153, 154] and no or few individuals classified at GMFCS level IV-V, show a clear indication that the more severe the GMFCS level, the lower the VO_{2peak}. A measure that accurately reflects aerobic fitness in the higher GMFCS levels is however yet to be identified [64, 65].

All available evidence, although incomplete, suggests that the response to training is adequate and improvements in aerobic fitness are evident also in individuals with CP [93, 99, 155-157]. However, there seems to be little carryover into activity (as in motor function or energy expenditure during daily activity) [155]. Similarly, the association between aerobic capacity (VO_{2peak}) and habitual physical activity has been found to be weak to moderate, although a stronger correlation between habitual physical activity and walking economy has been suggested [145].

Nevertheless, the strong association between cardiorespiratory fitness and health is indisputable. Therefore, it is vital that we continue to promote and develop alternative aerobic exercise modalities and adapted exercise tests for individuals with CP, especially for those in the higher GMFCS levels [64, 65].

1.4 Frame Running

1.4.1 Frame Running – a parasport and physical exercise in CP

An innovative option of physical activity for motor impaired people is Frame Running (previously called RaceRunning). The first Frame Runner was invented in Denmark in the early 1990s. Since then, the sport has developed. Today it is a rapidly growing parasport designed for individuals with CP or similar conditions causing impaired balance and gait [158]. The Frame Runner is a three-wheeled frame with a saddle for support of bodyweight, chest plate and steering handle, allowing an athlete with impaired posture, balance, and motor control to propel forward with their feet on the ground [158-160]. The Frame Runner can be used for locomotion in daily life, for recreation, aerobic exercise, and for competitive parasports.

The concept of parasports was created around 100 years ago [161] and has since then evolved significantly. Although there are many parallels with other research areas such as rehabilitation and exercise physiology, it is a research field of its own interrelating the systems of health and functioning with sport [162].

Evidence-based classification systems are central in this research field. A stepwise systematic approach for evidence-based classifications is recommended with the goal to ensure that athletes with similar levels of impairment compete against one another, creating a level playing field and allowing for fair and equitable competition [162, 163].

Frame Running is, since 2017, included in the Swedish championships in para-athletics, and the opportunities for competitions both nationally and internationally are steadily increasing. Frame Running was not included in the Paralympic Games 2022 and is not in the program for 2024, but that is the goal for the future. An important step towards this goal was acceptance as a world para-athletics event (WPA) for athletes with coordination impairments, in 2017. The organization that governs Frame Running and work towards being included in the paralympic movement is the Cerebral Palsy International Sport and Recreation Association (CPISRA). This organization recently merged with the International Wheelchair and Amputee Sports Federation (IWAS) and together formed the new organization World Abilitysport.

In general, sports for people with neurological conditions and total body involvement are few and limited to activities with low levels of weight-bearing and aerobic demands such as boccia. For more abled individuals with coordination impairment such as CP, paracycling on a tricycle could be an alternative, but for the more severely affected, Frame Running is probably the only feasible sport of moderate to high intensity.

Frame Running has recently experienced a transition from the previous classification system with three major classes, RR1, RR2, RR3 based on expertise opinion into a new system T71 and T72 based on research [119, 120]. Athletes in the lower numbers (RR1, T72) are more severely affected [164]. Competitive distances range from 40m and up, where the most popular is 100m [158]. This thesis does not originate in this specific area of research, even if the purpose of one study partly concerns this area. Table 1 shows an overview of Frame Running classification in relation to GMFCS levels.

Table 1: Rough overview of Frame Running for competitive classification

Level	GMFCS
I	Walks without limitations
II	Walks with limitations
III	Walks using a hand-held mobility device
IV	Self-mobility with limitations; may use powered mobility
V	Severely limited self-mobility, transported in a manual wheelchair

Class	Classification (former)
RR3	Mild to moderate involvement of one or both upper limbs, fair to good trunk control. Good push off and no startle reflex
RR2	Moderate involvement of lower limbs and trunk. Asymmetry but more effective propulsion than RR1
RR1	Severe involvement of lower limbs and trunk, ineffective leg propulsion, poor trunk control and upper limb involvement

Class	New Classification
T72	May be able to walk short distances with or without support Moderate involvement of legs and trunk (less spasticity) Asymmetry but more effective pushing pattern than T71 May also need gloves to keep hands on handlebars Fair or good core balance Minimal or no foot drag Poor coordination but can alternate leg movement Limited stride effectiveness
T71	Unable to functionally run or effectively propel a wheelchair Gross motor function - needs mobility support that requires a physical or powered assistance Ineffective leg propulsion Noticeable foot drag Poor knee lift Severe asymmetry Poor coordination Poor trunk control Upper limb involvement, limited hand function requiring hand placement aids (e.g., gloves, hand strapping etc.) Startle reflex

Table 1: Rough overview of the classification for competitive Frame Running; RR1, RR2, RR3 (former) (RR4 available for those who do not classify in RR1-3) and new T71, T72 in relation to Gross Motor Classification System (GMFCS). Note this table is an interpretation by the author, where the relationships between the classifications are not exact, (information from “Frame Running Awareness and Coaching Workbook”) [164].

1.4.2 The six-minute Frame Running test (6-MFRT) - a field test for cardiorespiratory fitness

Tests used to evaluate cardiorespiratory fitness should be valid and feasible. When it is not possible to test according to gold standard method in a laboratory. Field tests are generally a useful option to estimate cardiorespiratory fitness. These tests can be maximal incremental, like the shuttle run test [165], or non-incremental like Cooper's 12 min running test [166]. Modified versions of shuttle run tests have been developed for individuals with CP, GMFCS I-III [167, 168], but not Cooper's test because running for twelve minutes is too difficult for most individuals with CP. However, the shorter time-based submaximal six-minute walk test is commonly used for both children [169] and adults [170] with CP. Nsenga Leunkeu et al [171] observed close agreement between VO_{2peak} measured on a cycle-ergometer test and during the six-minute walk test, however it is not clear whether the six-minute walk test can be used to predict VO_{2peak} in individuals with CP [172].

The six-minute Frame Running test (6-MFRT), first described by Bolster et al. [159], is a novel test based on a combination of the six-minute walk test and Cooper's test, that can be used for individuals with CP classified at GMFCS levels III to V. Bolster et al. showed a high test–retest reliability at the group-level, but at the same time urged caution due to large smallest detectable differences (SDDs), indicating that there was a learning effect. This may be because the participants were not accustomed to Frame Runners, since they only had two familiarization sessions with Frame Runner before the actual test. Construct validity was found to be good, based on that 6-MFRT discriminated the distances covered between children and youths in levels III and IV.

However, information on how accurately the 6-MFRT measures aerobic capacity, that is cardiorespiratory parameters (VO_{2peak}), perceived effort and blood lactate is not known. An additional remaining question is if distance covered during the 6-MFRT reflects maximal aerobic capacity.

1.4.3 Physical parameters affecting Frame Running capacity

To explore which physiological variables hinder and/or favor Frame Running performance, respectively, is relevant in many aspects. First, it provides knowledge in order to optimize treatment strategies to improve Frame Running performance. Secondly, this will contribute to develop an evidence-based classification system, which is crucial for the sport to grow as a parasport event. Two previous studies from Van der Linden and co-workers have focused on this area [119, 120] and can be seen as two parts of the same purpose. They observed that lower limb impairments such as spasticity, decreased voluntary motor control, muscle weakness, contracture in knee flexors (>20 degrees) [119] and poor trunk control [120] negatively affects Frame Running sprint speed (100 m and 200 m). All these factors, except muscle weakness, are considered stable enough to be included as measurements that decide assignment into different competitive classes. Van der Linden and co-workers also suggest that muscle strength should be excluded from measurements included for classification, due to current evidence that this is trainable [128, 130, 135]. Further, two clusters were identified, based on data of four different impairment measures (range of motion, spasticity, selective voluntary motor control of the lower limbs, and trunk control) where RR2/RR3 represented one cluster and RR1 (those with more severe impairment) the other, hence similar to the T7 system. Based on these results they recommend that competitive classes in Frame Running should be divided according to these four parameters [120].

1.5 Relevance of the present studies

In this narrative literature review it becomes clear that even though strenuous physical exercise generally has been found to improve health-related as well as skill-related fitness in healthy adults and children, results in individuals with CP are less well-defined. This is of concern as individuals with CP are at risk of poor health due to the non-progressive primary brain condition, but also as a consequence of concurrent, often progressive musculoskeletal problems and extensive sedentary time.

Increasing evidence supports physical exercise as a tool to improve health-related fitness and counteracting many of the problems associated with CP, such as low aerobic capacity, thin and week muscles.

Inactivity in this group is partly due to their difficulties to engage in strenuous physical exercise, especially individuals represented in the higher GMFCS levels. Moreover, the physical exercise opportunities available for children, adolescents and adults with CP are few, and generally limited to low-intensity activities, through which it may be hard to build muscle and/or increase cardiorespiratory capacity.

Frame Running has emerged as a viable means to change this. Whether used as a transport device, recreational activity, or competitive parasport, it enables individuals with CP to get a moderate-to-high-intensive workout.

However, physiological adaptations regarding fitness after Frame Running training have never before been scientifically described. Further, it is not known whether the Frame Runner can be used to evaluate aerobic capacity using the field-based 6-MFRT in this population. In addition, it is not known what physiological parameters, apart from aerobic capacity (VO_{2peak}), determine Frame Running capacity or whether Frame Running aerobic capacity can be predicted.

To further evaluate the usefulness of Frame Running as a health promoting activity, the purpose of my PhD projects is to examine the physiological adaptations to a Frame Running intervention (study I), evaluate and validate the 6-MFRT as an alternative time-based field exercise test (study II and IV), and finally to examine the physical parameters linked to Frame Running capacity (study III).

2 RESEARCH AIMS AND QUESTIONS

The overall aim of this thesis is to gain knowledge of the health effects of Frame Running and investigate the usefulness of the six-minute Frame Running test (6-MFRT) as a measure of aerobic capacity in individuals with cerebral palsy (CP) and ambulatory difficulties (GMFCS II-V).

The research questions are;

- What are the physiological adaptations after 12 weeks of Frame Running, with regards to cardiorespiratory endurance, skeletal muscle thickness, and passive range of motion in the lower extremities? (Study I)

- Can the 6-MFRT be used to assess aerobic capacity (VO_{2peak})?
  - What is the physiological response to the 6-MFRT? (Study II)
  - Is 6-MFRT valid as an exercise test for maximal aerobic capacity, as compared to a Frame Running Incremental Treadmill test, that is, the gold-standard method? (Study IV)

- What physical and physiological parameters determine Frame Running capacity (6-MFRT), and can Frame Running capacity be predicted, based on physical and physiological parameters? (Study III)

<u>Studies mapped into the ICF Framework and the F-words</u>

The concept of health can be illustrated in the F-words framework, grounded in the World Health Organization's International Classification of Functioning, Disability and Health (the ICF). The aims of the thesis's four studies operate around the domains Fitness/Body structure & function and Functioning/Activity as illustrated below. Key-terms at focus are Frame Running, cardiorespiratory and muscle fitness and Frame Running capacity

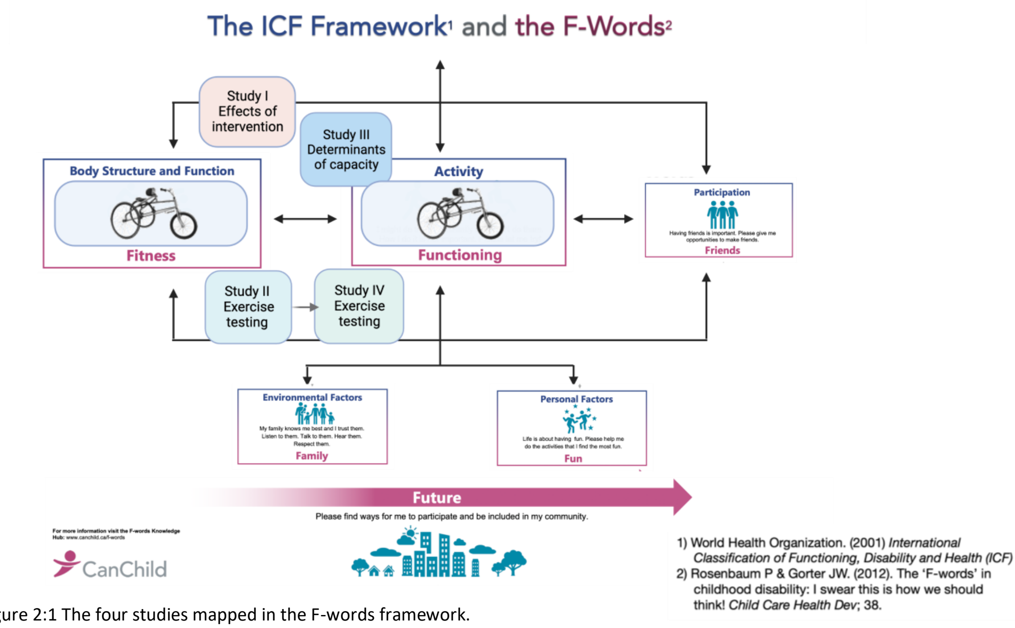


Figure 2:1 The four studies mapped in the F-words framework.
Adapted from F-words Knowledge Hub: www.canchild.ca/f-words

3 MATERIAL AND METHODS

3.1 Study designs

The study designs represented in this thesis are one intervention study (Study I) and three cross-sectional observational studies (Study II, III, and IV), of which Study II and III are exploratory in nature and Study IV is a methodological validity study.

3.2 Participants and recruitment

All four studies include participants with CP that are engaged in Frame Running. Recruitment has mainly taken place through contact with Frame Running clubs, but also via advertising, e.g., in social media, in hospitals and habilitation centers. All participants were informed and signed a formal consent before entering the trials. For individuals under 18 years of age, consent from parents or guardians was also obtained. Parents and/or personal assistants/caregivers to the individuals with CP were present during all test occasions. The recruitment process is illustrated in table 3:1.

Table 3:1. Overview of inclusion of participants in Studies I-IV,

Method	Study I (n=15)	Study II (n=24)	Study III (n=62)	Study IV (n=16)
Inclusion criteria	diagnosis of CP understand simple instructions ability to exercise with the Frame Runner (FR). (FR-experience ≥2 month and/or ability to exercise ≥ 10min) have their own FR or access through a club			
	7-35 years of age	≥ 8 years of age	7-45 years of age	13-40 years of age
Exclusion criteria	orthopedic surgery (soft tissue surgery in the last six months and bone surgery during the last 12 months) botulinum toxin injections ≤ 3 months prior selective dorsal rhizotomy or intrathecal baclofen pain that affects performance			
Recruitment, setting, place / country, year (n)	FR-clubs, Solna, Uppsala, Västerås, Sweden, 2016–2018 (18)	FR-clubs, Sweden, 2017-2018 (14), FR-clubs, the Netherlands, 2017 (12)	RR/FR camp and cup, Denmark, >10 nationalities represented in the study, 2018 and 2019 (48) FR-clubs, Sweden, 2016-2018 (16)	FR-clubs/ advertising, Bosön, the center of Swedish Sports Confederation, Sweden 2021-2022 (16)
Enrolled participants, n	18	26	64	16
Excluded, n (reason)	3 (other diagnosis, incomplete training and/or evaluation)	2 (communication failure and technical error)	2 (other diagnosis)	0 (3 no respiratory parameters)

3.3 Sample size

Power and sample size estimations were used in the planning stage of the studies to determine how many subjects that would be needed to answer the research questions [173]. For study I, it was judged that muscle thickness measurement with ultrasound was suitable for calculating power, since the training adaptation in muscle thickness would be the smallest. Based on power calculations with conventional values of alpha 0.05 and power 0.80 (80%), that would enable a detectable difference pre- versus post-training in muscle size of 10%, with a standard deviation of 10%, we planned to include 26 participants. Power analysis for study II revealed that for an assumed correlation (r=0.60) with power 0.80 (80%) for the outcome measures of VO_{2peak} and distance, 24 participants were needed for alpha = 0.05. Given that Study IV, concerns the same parameters as study II same sample size were planned. Study IV is work in progress and currently in manuscript with n=16 participants. Given current result, the power is considered to be large enough. A similar power calculation for study III, was the basis for the planned sample size of 60 participants.

3.4 Data collection and study protocol

Data collection for all four studies took place between 2016 and 2022. All studies were performed as a teamwork with measurements performed by or under the lead of experienced physiotherapists, exercise physiologists, movement scientists and physicians. Several students (physiotherapy, medicine, biomedicine etc.) have joined the team over the years. In study II and study IV experienced exercise physiology test-leaders employed at Bosön (Center of the Swedish Sports Confederation) have contributed. Data collection for study I are further described under heading "3.5 Intervention" and a description of measurements under the heading "3.6 Outcome measures".

Study I: Data collection was performed between autumn 2016 and spring 2018. A total of four training periods were completed in three Swedish mid-towns: Solna (2016, n=6), Västerås (2017, n=5), Uppsala (2017, n=3), Västerås (2018, n=4) at the indoor training facilities (163-, 200-, and 400-meter oval tracks) where the participants attended their Frame Running training. The participants trained Frame Running twice a week for 12 weeks. The 6-MFRTs and evaluations (physical examination) took place during two weeks before and two weeks after the training period. In addition, the 6-MFRT was also performed at week four and eight (figure 3:1). Evaluations were carried out at the local training facility or at the Karolinska hospital at the same occasion as the muscle thickness measurement with ultrasound that was performed.

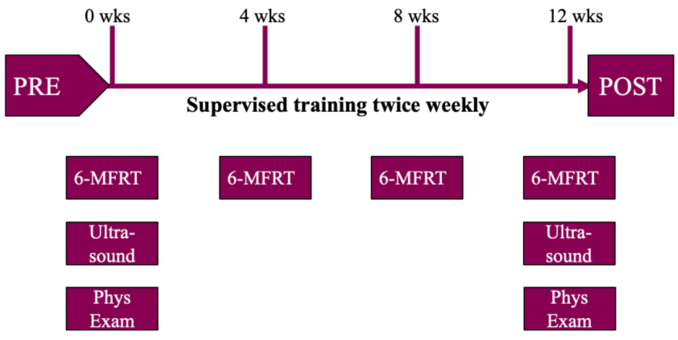


Figure 3:1 Schematic timeline of experimental setup. PRE: before training period, POST:after training period, 6-MFRT: 6minute Frame Running test, wks: weeks, Phys Exam: physical examination.

Study II; Data collection was carried out in 2017-2019 as a two-site collaboration with a research group from the Netherlands. The 6-MFRT were carried out with similar protocols and identical portable gas analysis systems (Cortex Metamax® 3B, CORTEX Biophysik GmbH, Leipzig, Germany), and corresponding software (MetaSoft® Studio).

Measurements took place 2017 in the Netherlands at an outdoor track and field facility (400 m oval track) (n=12) and 2017-2019 in Sweden (n=14) at the participants' local training facilities (at four different track and field facilities indoors: 163, 200, and 400 m; and outdoors: 400 m). Before testing, data on personal characteristics were collected, participants were familiarized with the experimental setup and a low-intensity warm-up period of 5 to 10 minutes was performed. Then the 6-MFRT with outcome measurements of HR and ventilatory parameters and rating of exertion after completing the test was performed.

Study III; Data were collected during the international event RaceRunning/Frame Running Camp and Cup in Copenhagen during one summer week in 2018 and 2019 (n=48). In addition, the participants in study I, with complete baseline assessment (n=16), were included in this study. Each participant performed all measurements for the study during one occasion. As a measure of Frame Running capacity distance covered during the 6-MFRT was used. An optional warm-up of 5 to 10 minutes was completed by the participant. Prior to the 6-MFRT, a physical examination including muscle thickness measurements with ultrasound was performed.

Study IV; Data were collected in 2021-2022 and all measurements were carried out at Bosön, the National Sports Confederation's laboratory for performance in Stockholm. To investigate validity of the 6-MFRT as a test of maximal aerobic capacity, measurements of cardiorespiratory parameters during, and blood lactate before and after the 6-MFRT were compared with corresponding data collected during the gold standard method of maximal aerobic capacity testing, that is, a Frame Running incremental treadmill test (FRITT). Before testing, participants were familiarized with the experimental setup and personal characteristics data were collected. The two exercise tests were conducted on different days within a three-month period. The order of the tests was determined by convenience, with nine participants performing the 6-MFRT first and seven participants starting with the FRITT.

3.5 Intervention

Study I was an evaluation of an exercise intervention. The training intervention consisted of supervised Frame Running exercise twice per week for 12 weeks, one hour per session, together with the local club at an indoor track and field facility. The participants had trained Frame Running once per week but not structured prior to inclusion. They were now instructed to follow a specific exercise program during each session. The program consisted of five blocks: 1) warm-up (light jogging), 2) short intervals (sprints of 40-100 m), 3) long intervals (continuous running for three to ten minutes at medium to high speed), and 4) technique exercises (for example short distances of slalom between markers or running alternating with right/left leg only), and 5) cool down (light jog). One training session per week was monitored with recording of distance travelled (meters), time spent in motion (minutes), speed (meters/second), and average and maximum heart rate (beats/minute) using a trip computer with speed sensor and associated HR chest strap (Garmin Edge 25, Garmin, United States). No specific target heart rate or level of perceived exertion (Borg RPE) were set during the training sessions, but the participants were encouraged to work at an intensity that made them sweat and become out of breath. Participants trained in groups consisting of 5–15 individuals under the lead of their usual coach in close collaboration with one member from the research team.

3.6 Outcome measures

An overview of outcome measures used in the four studies is described in table 3:2.

Table 3:2 An overview of outcome measures

Outcome measure	Study I	Study II	Study III	Study IV
age (yrs), body weight (kg), height (m), BMI (kg/m^2)	x	x	x	x
CP subtype GMFCS level	x	x	x	x
functional mobility (FMS)	x		x	x
CPISRA competitive class			x	
level of habitual physical activity level (SGPAL)				x
experience of Frame Running (yrs),		x	x	x
skeletal muscle and subcutaneous fat thickness	x		x	
passive range of motion (pROM)	x		x	
spasticity (MAS)	x		x	
selective motor control (SMC)			x	
assessment of side difference in lower legs	x		x	
6-minute Frame Running test (6-MFRT)	x	x	x	x
Frame Running Incremental Treadmill Test (FRITT)				x
heart rate (HR)	x	x	x	x
respiratory parameters		x		x
lactate-level in blood				x
Borg scale RPE	x	x	x	x
observed signs of exertion				x

Abbreviations: BMI: Body Mass Index, CP: cerebral palsy, GMFCS; Gross Motor Function Classification System, FMS: Functional Mobility Scale, SGPAL: Saltin Grimby physical activity scale, MAS: Modified Ashworth scale, RPE: rating of perceived exertion

3.6.1 Information on participant characteristics

Information on personal characteristics, such as age (years), body weight (kg), height (m), was collected for all and BMI (kg/m^2) was calculated. In study I, II and III the participants were asked about this information. In study IV, weight was measured using a wide electronic scale (which allows weighing in a wheelchair), and height was measured with a measuring tape lying down or standing against a wall if possible.

3.6.2 CP subtype and classifications

The subtype of CP based on predominant neurological features; spastic (bilateral or unilateral), dyskinetic or ataxic CP was classified according to the decision tree developed by the Scientific Working Group Surveillance of Cerebral Palsy in Europe (SCPE) [4] (Figure 3:2). Gross Motor Function was classified according to the five level Expanded and Revised Gross Motor Function Classification System (GMFCS E&R) [8] (Figure 3:3) and the six level functional mobility scale (FMS) (Table 3:3) [11]. Finally in study III, we also collected Frame Running competitive classification developed by

Cerebral Palsy International Sport, Recreation Association (CPISRA) (Table 1) [158]. All participants and/or parents or caregivers were asked if they knew this data and if not, the examiner (mainly EH) suggested a motor type and classification based on physical examination, that the participant approved. In some cases, additional advice was sought from the co-researchers and for CPISRA class (study III) information was collected from Frame Running Camp and Cup participant lists and/or a Frame Running coach. In addition, all participants were asked about their medical history (surgery or spasticity-reducing interventions), pain, and perceived difference between sides (i.e., more-affected and less-affected side) and Frame Running experience.

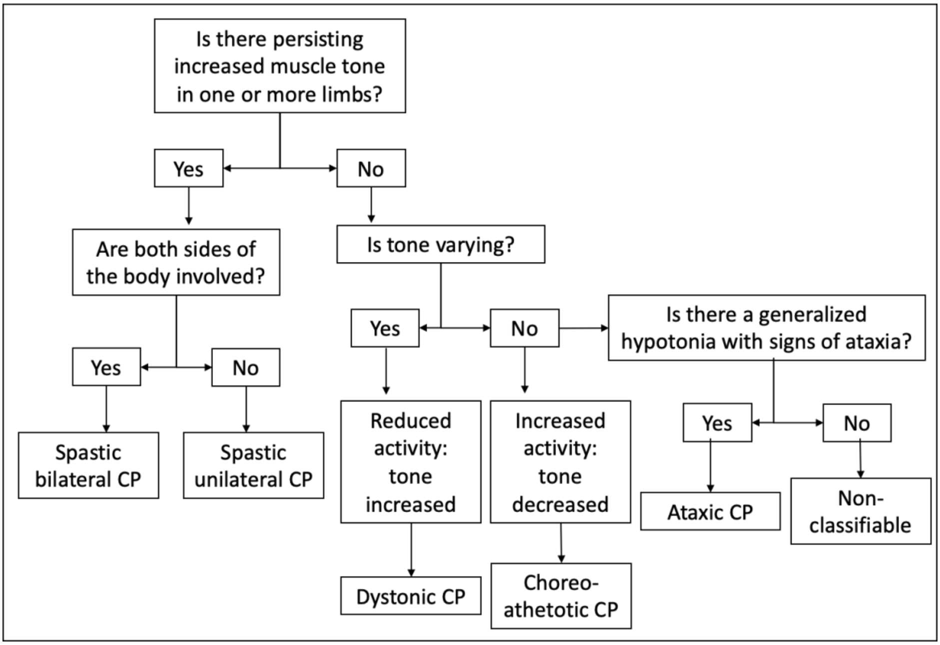


Figure 3:2 Hierarchical decision tree for classification of cerebral palsy sub type, adapted from Surveillance of Cerebral Palsy in Europe – Cans et al. (2000) [4].

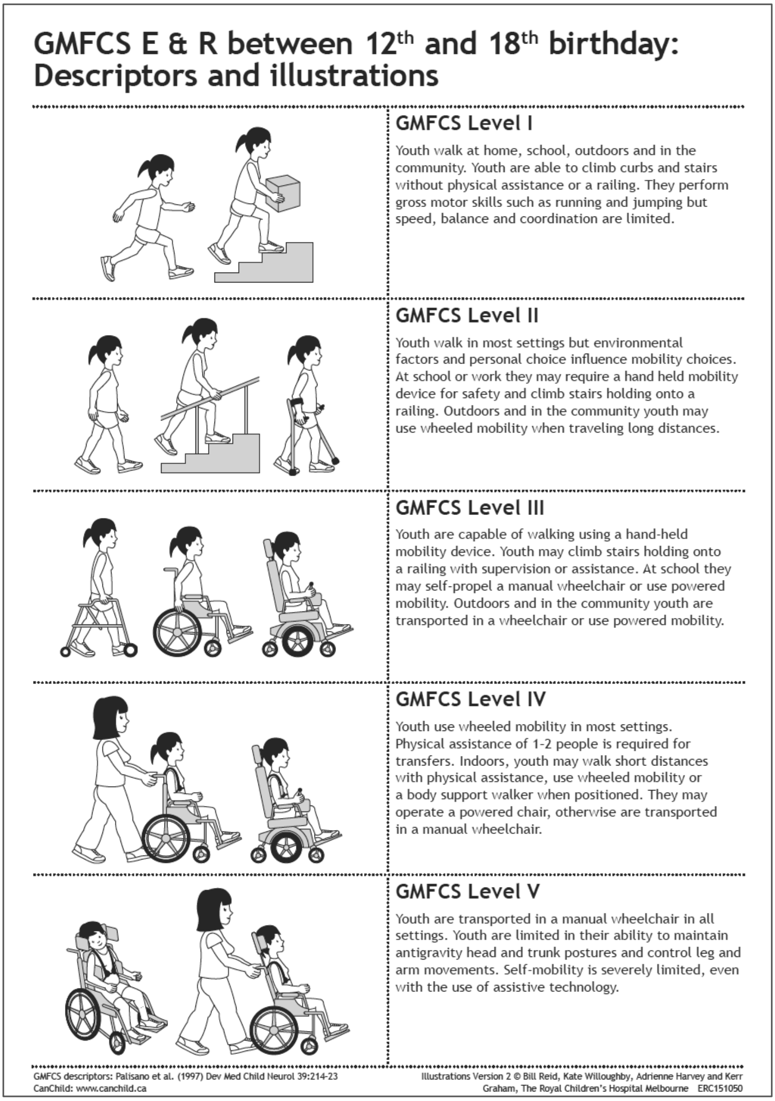


Figure 3:3. Use of the GMFCS E&R illustration, authored by E. Hjalmarsson was made under license from McMaster University, Hamilton, Canada.

Table 3:2 Functional mobility scale (FMS). Adapted from Graham and co-workers [11].

Rating (1-6) of the person's usual walking ability and/or need for assistance for each of the distances; 5 meters (i.e., at home), 50 meters (i.e., at school or at work) and 500 meters (i.e., in society)
1. Uses wheelchair: May stand for transfer and may do some stepping with support by another person or using a walker/frame 2. Uses walker/frame without help from another person 3. Uses two crutches without help from another person 4. Uses sticks (one or two) and/or uses the environment (e.g., furniture, walls, fences) for support; without help from another person 5. Independent walking on level surfaces. 6. Independent walking on all surfaces, (i.e., no aids or help from another person when walking, running and climbing stairs).

3.6.3 Level of habitual physical activity level and Frame Running experience

In study IV, participants were asked to rate their level of habitual physical activity with Saltin Grimby Physical Activity Level questionnaire (SGPAL) [174]. This generic four level questionnaire aims to capture the average physical activity level during the last year and the levels are as follow:

Table 3:3 Adapted from the Saltin Grimby Activity scale (SGPAL) [173].

Level	Description
I	Physically inactive/Most sedentary time - You mostly engage in reading, watching TV/screen, computers, cinema or other sedentary occupations.
II	Some light physical activity - You walk, cycle, or use self-propelled mobility or similar for at least 4 hours a week. Examples are transport to and from work as well as Sunday walks, gardening, fishing, table tennis, bowling (light-moderate intensity Frame Running).
III	Regular moderate-high physical activity and exercise - You engage in strenuous physical activity and exercise for at least 2 to 3 hours per week. Examples are heavier gardening, running, swimming, gymnastics, tennis, badminton, or similar activities/exercises, (moderate-high intensity Frame Running).
IV	Regular hard physical exercise for competitive sports (high-vigorous physical activity) - You engage in vigorous physical activity several times a week. Examples are running, orienteering, skiing, swimming, soccer, handball, (high-intensity Frame Running).

Estimation of level on the questionnaire was always done through conversation, so the scale was therefore slightly modified by adding examples of activities that apply to individuals with physical disability (like Frame Running). In addition, the intensity was often explained (e.g., hard/vigorous intensity means being so out of breath that it is not possible to talk at the same time).

In study II, III, IV, data on Frame Running experience was also collected.

3.6.4 Skeletal muscle thickness and subcutaneous fat thickness

In study I and III ultrasound measurement of skeletal muscle and subcutaneous fat thickness of the calf (medial gastrocnemius muscle) and thigh (vastus lateralis and intermedius muscles of the quadriceps) in both legs (in millimeters) was used. For both studies, several images (5–8) were taken of each muscle to ensure consistency of measured values, which is in line with research showing good reliability and validity for the method [175, 176]. In study I, a stationary ultrasound (Siemens Acuson s2000, Siemens, Erlangen, Germany) of muscle thickness was performed before and after 12 weeks of Frame Running training by the same radiologist at the hospital. In study III, a portable handheld, wireless ultrasound that transmits real-time images to a tablet device (Synergy MSK Ultrasound, Arthrex, Sweden) was used for participants at Frame Running Camp and Cup in Copenhagen. In addition, 16 assessments from study I was used in study III.

3.6.5 Passive range of motion

In study I and III, passive range of motion (pROM) was measured in the hip (flexion, extension, abduction), knee (flexion, extension, hamstrings-angle), and ankle (dorsiflexion with extended knee) with a goniometer in standardized positions in both legs [177]. The reliability of goniometry measurements (inter-rater and intra-rater) has been reported to be high in children with spastic CP [178].

3.6.6 Spasticity

In study I and III, muscle spasticity was estimated according to the modified Ashworth scale (MAS) [179] in muscle groups around hip, knee, and ankle in both legs (table 3:4). This ordinal scale (0, 1, 1+, 2, 3, 4) measure resistance to passive elongation of a muscle at rest. The reliability of the modified Ashworth scale in children with spastic cerebral palsy have been found to be varying, but overall moderate, (moderate to good interrater reliability and poor to good test-retest reliability) [180, 181]. However, the scale is being questioned, especially regarding validity and in particular in the lower scores [182, 183]. However, it is the most commonly used spasticity scale in clinical practice in Sweden.

Table 3:4 Spasticity according to the modified Ashworth scale [179]

Score	Description
0	No increase in tone
1	Slight increase in muscle tone, manifested by a "catch" and release or by a minimal resistance at the end of the range of motion (ROM).
1+	Slight increase in muscle tone, manifested by a "catch", followed by minimal resistance throughout the remainder (>50%) of the ROM
2	More marked increase in muscle tone through most of the ROM, but easily moved.
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part rigid in flexion or extension

3.6.7 Selective motor control

In study III, the Selective Motor Control (SMC) scale of active ankle dorsiflexion by Graham and Boyd was used to measure both feet [184]. This is an ordinal scale (0-4) described below, were the person sits in a comfortable position, hips flexed and knees comfortably extended, able to see their feet, and is asked to dorsiflex the foot (table 3:5). The scale has been reported to have good reliability [185], and has been used in clinical trials [118, 186].

Table 3:5. Selective Motor Control (SMC) of ankle dorsiflexion by Graham and Boyd [184].

Score	Description
0	No movement
1	Limited dorsiflexion using mainly extensor hallucis longus and/or extensor digitorum longus
2	Dorsiflexion using extensor hallucis longus, extensor digitorum longus and some tibialis anterior activity
3	Dorsiflexion achieved using mainly tibialis anterior activity but accompanied by hip and/or knee flexion
4	Isolated selective dorsiflexion achieved, through available range, using a balance of tibialis anterior activity without hip and knee flexion

3.6.8 Assessment of side difference in lower legs

Even though the majority of the participants were bilaterally affected, most had a clear difference between sides. In study I and III, where physical examination of the lower extremity was used, the legs were divided into more or less affected sides instead of left and right. One participant in study I and two participants in study III had unilateral spastic CP, the rest were bilaterally affected. Decisions about which side was judged to be more or less affected were based on muscle size (ultrasound) in study I, and in study III on muscle size (ultrasound), self-perceived difference and SMC. In five cases in study III, side difference was hard to determine and were decided after revising spasticity and pROM.

3.6.9 The six-minute Frame Running test (6-MFRT)

The 6-MFRT is a common denominator for all studies in the thesis, albeit with different aims. In Study I, the test was performed on four occasions to evaluate gains in cardiorespiratory fitness. Studies II and IV focused on validation properties of the test as a measure of cardiorespiratory capacity and include respiratory measurements, while Study III uses the 6-MFRT as a measure of Frame Running capacity.

The 6-MFRT measures the maximal distance covered with the Frame Runner during six minutes and was performed on oval tracks (163-400 m, indoors and/or outdoors) in all studies. Distance was measured by counting laps and measuring the incomplete laps with a trundle wheel (except for the participants in the Netherlands in study II where a GPS [Nike+ Running, version 1.7.9] was used). At all test occasions participants were encouraged to cover as much distance as possible by continuous verbal encouragement. During the tests, a person ran behind or beside the Frame Runner if needed, for safety and/or motivation. Prior to the 6-MFRT a warm-up of 5-10 minutes were performed.

In addition to distance, top speed was measured in study I and III with a trip computer attached to the Frame Runner (Garmin Edge 25). In all studies, HR was measured throughout the test and self-rated exertion (Borg RPE 6-20 scale) after the test. In study II and IV additional respiratory measures were collected and in study IV capillary blood lactate were collected.

3.6.10 Frame Running Incremental Treadmill Test (FRITT)

In study IV, an incremental VO_{2peak} test performed with the Frame Runner on a wide treadmill (Rodby v2, Vänge, Sweden), was used to validate the 6-MFRT, in other words, compare data obtained at the two tests. The Frame Running Incremental Treadmill Test (FRITT) protocol was individually adapted with purpose to ensure graded exertion until volitional termination. The start inclination on the treadmill was set to 1% for all, but the start speed varied from 1,6 to 6 km/h. Speed was then increased every 30 second with 0,25 km/h for most participants, (but varied from an increase with 0,20, 0,25 or 0,5km/h depending on ability) until the participant could no longer keep up with the speed. For participants who had difficulty to keep up with the increased speed where a clear reduction in coordination was assumed to be the primary cause, the incline of the treadmill was increased instead of the speed at the end of the test. Treadmill inclination at the end of the test varied from 1% up to 4%. The end speed varied from 3,4 to 13,5 km/h. Total time to finish varied between 5.5 min-14.7 min). All participants used a special safety harness attached to a metal frame above the treadmill and a horizontal rope between the Frame Runner and a metal bar in front of the treadmill to avert the risk of falling. In addition, one or two persons stood on platforms on either side of the participants throughout the tests. The participants were verbally encouraged throughout the test by the testing team to maximize performance and ensure exhaustion. Prior to the FRITT a warm-up of 5-10 minutes were performed on the treadmill. See picture next page.

Picture of setup for Frame Running incremental treadmill test (FRITT) at Bosön National Sports Confederation's laboratory for performance in Stockholm

3.6.11 Heart rate (HR)

Peak and mean HR were monitored with a chest strap throughout the 6-MFRT (study I-IV) and FRITT (study IV) and also during every other of training session (in study I). Peak HR were determined as he highest HR averaged over a period of 10 seconds [70]. Three different chest strap monitors were used in the four studies due to different equipment at different facilities (1; Garmin Edge 25, United States, connected to Garmin trip computer attached to the Frame Runner, 2; Polar, FT7, Kempele, Finland connected to portable gas analysis system, 3; Smartlab, HRM, Heddesheim, Germany connected to stationary gas analysis system).

3.6.12 Respiratory parameters and criteria used to evaluate peak oxygen uptake

Respiratory parameters; continuous breath-by-breath data was recorded with gas analysis system in study II and IV. A portable gas analysis system (Cortex Metamax® 3B, CORTEX Biophysik GmbH, Leipzig, Germany) (carried in a small backpack), and corresponding Bluetooth connected software (MetaSoft® Studio) was used during all the 6-MFRTs. For the FRITT in study IV, a stationary gas analysis system (COSMED Quark Cardio Pulmonary Exercise Testing, Rome, Italy), and corresponding software (Cosmin® Studio) was used. In both systems a breathing mask was used in combination with the setup. Peak respiratory parameters were calculated by averaging the highest consecutive periods over 30 seconds (i.e., rolling mean over 3x 10 seconds) [70]. This data reduction is needed in order to avoid spurious volatile spikes that can occur in these breath-by-breath gas analysis systems [70]. A plateau of VO_2 despite increased workload, which is the classic criterion for achieving maximal oxygen uptake, was not expected [63, 187]. Therefore, secondary objective criteria were used as approximations of a maximum physiological response based on age-corrected maximal heart rate and respiratory exchange ratio (RER). In addition, subjective self-rated exertion was used with the Borg RPE scale 0-20 (except for Dutch participants in study II where OMNI 0-10 scale was used) and subjective signs were observed. All cardiorespiratory measures and criteria used to evaluate peak oxygen uptake are listed in table 3:6.

Table 3:6 Cardiorespiratory parameters and criteria used to evaluate peak oxygen uptake [15].

Cardiorespiratory parameters
1) VO_{2peak} (L/min)
2) VO_{2peak} (ml/kg/min)
3) HR_{peak} (bpm)
4) RER_{peak} (VCO_{2peak} / VO_{2peak})
5) VO_{2peak} (ml/kg/min)
6) VE_{peak} (L/min)
7) Rf_{peak} (breaths/min)
8) VE_{peak} / VO_{2peak}
9) VE_{peak} / VCO_{2peak}

Criteria	Description (<18 yrs)	Description (>18 yrs)
Objective	Heart rate (HR) >95% of 195 beats per minute (bpm) (ie, ≥185 bpm)	Heart rate (HR) >85% of the age-predicted HR_{max} (220-age)
	Respiratory exchange ratio (RER) ≥1.0	Respiratory exchange ratio (RER) ≥1.1
Subjective	Borg RPE scale ≥17 ("very hard")	
	Observed signs of intense effort e.g., unsteady running, sweating, facial flushing, clear unwillingness to continue despite encouragement	

3.6.13 Capillary blood lactate level

Capillary blood lactate was collected with measurements using a finger prick method in study IV. The baseline measures were taken before any exercise was performed. Post-exercise blood samples were taken immediately after the 6-MFRT and the FRITT and again after three minutes. The blood samples were analyzed with Lactate analyzer (Biosen C-line, EKF Diagnostics GmBH, Barleben, Germany). Lactate level exceeding 6 mmol/L was judged to mean high effort.

3.6.14 Borg Rating of Perceived Exertion (RPE) scale

Before and immediately after the 6-MFRT and the FRITT participants were asked to rate their perceived exertion using the Borg RPE scale (table 3:7) [73]. The scale score multiplied by 10 is designed to give a fair estimate of actual heart rate during activity, (i.e., 6 correspond to resting HR; 60 bpm and 20 to a maximal HR; 200 bpm).

Table 3:7 Borg Rating of perceived exertion (RPE) scale [73].

Score	Level of exertion
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

3.6.15 Statistical methods

All data (study I-IV) were analyzed in IBM SPSS Statistics for Windows (version 25, 26 or 28) (Chicago, Illinois, USA). In addition, GraphPad Prism, version 9.5.1 (528) was used to analyse and visualize data (Study I-IV). In study III, R software using FactoMineR, factorextra, and ropls packages were used for to perform Principal Component Analysis (PCA) and Orthogonal Partial Least Square (OPLS) regression, followed by Variable Importance in Projection (VIP) analysis. The multivariate statistics (PCA, OPLS and VIP) was performed by co-author Gema Sanz, who is an expert biostatistician. An overview of all statistical methods is presented in Table 3:8 and described below for each study.

Table 3:8 Overview of the statistical methods used in Study I-IV

Statistical method	Study I	Study II	Study III	Study IV
Shapiro wilk test for normality	x	x	x	x
Descriptive statistics Mean ± SD	x	x	x	x
Descriptive statistics Median (IQR)				x
General linear model with repeated measure with time as within-subject measure	x			
Paired t-test	x			x
Wilcoxon signed rank test to compare mean	x			x
Fischer's exact test to compare mean in categorical values	x			
Statistical significance $p<0.05$	x	x	x	x
Spearman correlation coefficients (ρ/rho)		x	x	
Person correlation coefficient (r)				x
95% confidence interval (CI) for correlation coefficients.		x		x
One-way ANOVA			x	
Two-way ANOVA			x	
Tukey's multiple post hoc comparisons test			x	
Principal Component Analysis (PCA)			x	
Orthogonal Partial Least Square (OPLS) regression			x	
Variable Importance in Projection (VIP) analysis			x	
Bland & Altman Plot				x
Backwards univariate linear regression				x

<u>Study I:</u> The study used descriptive statistics to summarize the characteristics of the participants and the results of the training sessions. The Shapiro-Wilk test was used to verify normal distribution of data. A general linear model with repeated measures was used to analyze data on 6-MFRT distance, top speed, heart rate (average and maximum), and rating of Borg scale, with time (pre, 4-wk, 8-wk, 12-wk) as within-subject factor. Muscle thickness pre- versus post-training was assessed using paired t-tests. A Wilcoxon signed rank test was used to compare pROM, and a Fisher's exact test was used to compare spasticity in the lower limbs before and after the training period. The results were presented as mean ± SD, and statistical significance was set at $p<0.05$.

Study II: The study used descriptive statistics to summarize the characteristics of the participants and the results of the 6-MFRT. The Shapiro-Wilk test was used to verify normal distribution of data. VO_{2peak} in ml/kg/min were not normally distributed according to Shapiro-Wilk test, but all other parameters. The relationship between physiological parameters and 6-MFRT was therefore calculated with Spearman correlation coefficients, and significance level was set at $p<0.05$. Correlation coefficient 0 to 0.39 was considered as negligible to weak, 0.40 to 0.69 as moderate, 0.70 to 0.89 as strong, and 0.90 to 1.0 as very strong or perfect [188]. The data were reported as mean ± SD (since all parameters except VO_{2peak} fulfilled normality condition according to Shapiro Wilk test) and 95% confidence interval (CI) for correlation coefficients and statistical significance was set at $p<0.05$.

Study III: There were only two participants classified at GMFCS I, and two at GMFCS V. Therefore, they were included in the group of GMFCS II (GMFCS I-II group) or group of GMFCS IV (GMFCS IV-V group). The study used descriptive statistics to summarize the characteristics of the participants, the measurements and the results of the 6-MFRT. The study analyzed 54 variables per individual. A one-way ANOVA was used to analyze potential differences in exercise capacity and physical parameters depending on GMFCS levels. A two-way ANOVA was employed to analyze if there was a difference between capacity and physical parameters for more- or less-affected legs in relation to the GMFCS levels. The Tukey's multiple comparisons test was employed to compensate for multiple post hoc comparisons. Spearman rank correlation was performed to investigate the associations between the investigated physical parameters and distance covered in the 6-MFRT. Correlation coefficients were classified as negligible (0.00-0.10), weak (0.10-0.39), moderate (0.40-0.69), strong (0.70-0.89), or very strong correlation (0.90-1.00), with significance level set at $P<0.05$. The data were also analyzed using multivariate statistics; Principal Component Analysis (PCA) and Orthogonal Partial Least Square (OPLS) regression, followed by Variable Importance in Projection (VIP) analysis. The first step, PCA is a method used to reduce the dimensionality of a dataset by identifying patterns and correlations between variables. In this study, PCA was used to visualize the correlations between 6-MFRT distance, GMFCS, and other variables measured. The next step was to use OPLS regression, a multivariate projection method, to extract the relationships between a set of predictor variables and one or more responses. In this study, OPLS was used to determine the degree of predictability of the 6-MFRT distance based on the other variables measured. Finally, Variable Importance in Projection (VIP) analysis was used to determine the contribution of each variable to the OPLS projection. This analysis helps to identify the most important variables that contribute to the predictability of the 6-MFRT distance based on the other measured 52 variables (i.e., distance and GMFCS level excluded in VIP analysis). Overall, this data analysis approach offers a rigorous and systematic method for identifying the relationships between variables and predicting the 6-MFRT distance.

Study IV: The study used descriptive statistics to summarize participant characteristics and the results of the 6-MFRT and the FRITT. The Shapiro-Wilk test was used to test for normality. A paired t-test or a Wilcoxon signed rank test was used to compare the mean variables in the results of the 6-MFRT and the FRITT, depending on the condition for normality or type of data. Pearson correlation was used to assess the relationship between the results (VO_{2peak}) of the two tests and between VO_{2peak} and distance at the 6-MFRT. Correlation coefficients were classified as negligible (0.00-0.10), weak (0.10-0.39), moderate (0.40-0.69), strong (0.70-0.89), or very strong to perfect correlation (0.90-1.00). A backward linear regression analysis was used to investigate if VO_{2peak} at 6-MFRT could be predicted based on distance and participant characteristics. VO_{2peak} was used as the dependent variable and distance as the independent variable. Multiple linear regression analysis was performed to determine if prediction could be improved by adding participant characteristics, such as sex, body-weight, height, GMFCS-level, BMI, age, SGPAL, Frame Running experience. The significance level was set at $p<0.05$ and 95% confidence interval (CI) for correlation coefficients. Bland and Altman analysis was performed to quantify agreement in determining VO_{2peak} between methods, with the bias and limits of agreement determined. One participant did not reach the established criteria for maximum exertion and was therefore excluded in those parts where the tests are treated as maximal aerobic capacity tests (i.e., validity statistics comparing 6-MFRT and FRITT) but included in the others (i.e., correlation of 6-MFRT distance and VO_{2peak} and univariate linear regression analysis).

4 ETHICAL CONSIDERATIONS

Study I: The risks of participating in the Frame Running intervention are very small, that is, not greater than the risks of daily life. There is a small risk for injury or pain that can be due to trauma (accident or fall) or increase training load (sport injury-related). However, it is mandatory to use a helmet for safety. Sore muscles due to exercise can be painful, but it is commonly seen as a "positive pain" and it is known to be harmless.

Study II and IV: The used gas analysis systems include a face-mask that can be perceived as uncomfortable for some individuals. Many of the participants have difficulty swallowing and/or communicating, which can increase the discomfort. Thus, special considerations were taken for those individuals (e.g., adapted information and more time, personal assistant or other caregiver available at all times etc.). Blood was sampled through, sometimes repeated, finger prick, which caused discomfort in some individuals. This was described to feel like a mosquito bite, a description most agreed upon. The test situation on both the treadmill and the running track aiming to increase effort until volitional exertion caused stress in some individuals. There were also some risks, for example accidents or falls, but great effort was made to ensure comfort and safety. The feedback afterward from most participants was that it was exciting and fun, although often a challenge. Study IV was part of a larger project. All methods of this larger project were included in the ethical approval.

Study III: There were some specific risks related to recruiting participants and performing trials at an international event such as the Frame Running/RaceRunning Camp and Cup in Denmark. First, the participants were from different countries (Sweden, Norway, Denmark, Finland, Germany, United Kingdom, Australia, Poland, Hungary, the Netherlands, Belgium, Spain, Saudi Arabia, United States of America, and Brazil, among other nationalities). There may have been a risk of misunderstandings due to poor language comprehension and/or cultural differences. For all participants, especially those with cognitive and/or communication problems a parent, assistant, caregiver or coach were present during all parts of the trials and extra care was taken to ensure voluntary participation of the research subjects. Secondly, an ethical aspect is that trials were prior to a competition. Exercising with maximal effort during a six-minute Frame Running test the day before competition may have negatively interfered with the results for some athletes. However, maximal exertion during only six minutes represents a small risk and did likely not affect performance the day after.

All studies have been approved by the Swedish Ethical Review Authority and the corresponding authorities in Denmark and the Netherlands for trials conducted in the respective countries. Approval number for the Swedish applications are;

- Study I, II, III; Dnr 2016/1139-31/2 with the following addendums 2016/1675-32, 2017/2237-32, 2019-01008, 2020-04170
- Study IV; Dnr-2021-05-116

5 RESULTS

5.1 Participants

In total, 80 individuals have participated in the four studies, whereof 22 individuals have participated in several studies (n= 11 participated in two studies, n=7 participated in three studies, n=4 participated in all four studies), and 58 individuals in one study. Even though 22 individuals participate in several studies, all studies have involved new research questions and new data collection (with one exception; 16 participants with complete baseline assessment from study I were included in study III). Characteristics of participants in all four studies are described in table 5:1

Table 5:1. Overview of participants characteristics in Studies I-IV.

Variable	Study I (n=15)	Study II (n=24)	Study III (n=62)	Study IV (n=16)
Accumulated participation		Previous participation (n=7)	Data used from study I (n=16) Participation in study II (n=4)	Previous participation (n=11)
Age, years	16 ± 6 (9-29)	19 ± 9 (8-37)	22 ± 9 (9-45)	23 ± 7 (13-38)
Children (<18 years) n	10	15	22	3
Adults (≥18 years) n	5	9	40	13
Male/female n	8/7	14/10	30/32	7/9
Height, cm	144 ± 13 (123-170)	156 ± 16 (120-180)	157 ± 13 (123-182)	162 ± 11 (146–190)
Weight, kg	39 ± 11 (23-54)	50 ± 18 (21-85)	51 ± 16 (23-87)	52 ± 11 (35–72)
BMI, kg/m^2	19 ± 4 (14–23)	20 ± 5 (15-30)	21 ± 5 (13-34)	20 ± 3 (16–7)
CP type; Spastic/Dyskinetic/Ataxia	9 / 5 / 1	15 / 7 / 2	38 / 21 / 3	8 / 7 / 1
GMFCS level I / II / III / IV / V	1 / 3 / 4 / 7 / 0	0 / 8 / 3 / 13 / 0	2 / 26 / 11 / 21 / 2	0 / 2 / 5 / 8 / 1
FMS 5m 1 / 2 / 3 / 4 / 5 / 6	8 / 0 / 2 / 0 / 4 / 1		25 / 5 / 2 / 1 / 25 / 4	10 / 2 / 0 / 3 / 1 / 0
FMS 50m 1 / 2 / 3 / 4 / 5 / 6	8 / 4 / 0 / 0 / 3 / 0		32 / 9 / 0 / 1 / 19 / 1	14 / 1 / 0 / 0 / 1 / 0
FMS 500m 1 / 2 / 3 / 4/ 5 / 6	12 / 1 / 0 / 0 / 2 / 0		39 / 6 / 0 / 2 / 14 / 1	15 / 0 / 0 / 0 / 1 / 0
FR experience, years		2 ± 2 (2-88)	5 ± 6 (0-26)	8 ± 3 (0-12)
CPISRA-class (RR1/RR2/RR3/RR4)			25 / 22 / 11 / 3 / 1	

Subject characteristics in mean ± SD (range) or number of participants in each category. BMI: Body Mass Index, GMFCS: Gross Motor Function Classification System, FMS: Functional Mobility Scale, CPISRA: Cerebral Palsy International Sport Recreation Association competitive classification.

5.2 Intensity of Frame Running training

For participants in study I, heart rate, time in motion, distance, and speed were monitored every other training session through HR chest strap and trip computer connected to the Frame Runner during the 12-week training period. This monitoring shows that the participants were in motion for an average of 25 minutes per session and reached moderate to high intensity (mean HR was 69% of age predicted HR_{max}), although this varied widely between participants (table 5:2).

Table 5:2 Training intensity

Subject	Age	Type of CP	GMFCS	Average time in motion per training hour (minutes)	Average HR (bpm) (% of age predicted HR_{max})	Average of HR_{max} (bpm) (% of age predicted HR_{max})	Top measured HR (bpm) (% of age predicted HR_{max})
1	10-14	Dyskinetic	4	23	136 (69%)	169 (85%)	208 (105%)
2	10-14	Dyskinetic	4	29	123 (61%)	164 (82%)	183 (91%)
3	15-19	Dyskinetic	4	22	127 (65%)	158 (81%)	189 (97%)
4	15-19	Dyskinetic	4	34	135 (69%)	170 (87%)	213 (109%)
5	20-24	Dyskinetic	3	42	149 (77%)	175 (90%)	189 (97%)
6	25-29	Spastic bi	2	24	154 (81%)	176 (93%)	185 (97%)
7	25-29	Spastic bi	4	4	115 (61%)	139 (74%)	163 (87%)
8	20-24	Spastic bi	3	29	112 (58%)	156 (81%)	198 (103%)
9	<9	Spastic uni	1	21	166 (82%)	186 (92%)	204 (101%)
10	10-14	Spastic bi	3	24	140 (70%)	166 (83%)	184 (92%)
11	10-14	Spastic bi	2	31	158 (79%)	197 (98%)	208 (104%)
12	10-14	Spastic bi	3	28	148 (74%)	176 (88%)	196 (99%)
13	10-14	Spastic bi	4	17	132 (66%)	170 (85%)	196 (98%)
14	10-14	Spastic bi	4	24	122 (61%)	152 (76%)	188 (94%)
15	<9	Ataxic	2	18	126 (62%)	161 (80%)	196 (97%)
Mean value				25	136 (69%)	168 (85%)	193 (98%)
Range: min – max				4 - 42	112-166 (58%-82%)	139-197 (74%-98%)	163-213 (87%-109%)

GMFCS: Gross Motor Function Classification System, HR: heart rate, bpm: beats per minute, HR_{max}: maximal heart rate, % of age predicted HR_{max} calculated as HR/(208–0.7xage). Age stated in 5-year intervals to preserve participant integrity and anonymity.

5.3 Training adaptations of Frame Running

Aerobic endurance

Following 12-weeks of Frame Running training, cardiorespiratory endurance, measured as 6-MFRT distance, increased in all participants on average 34%, (pre 576 ± 320m vs. post 723 ± 368m, $p<0.001$, Figure 5:1 A). Top speed achieved during the test was on average of 21% higher (pre 3.3 ± 1.5 m/s vs. post 3.7 ± 1.2 m/s, $p<0.05$, figure 5:1B). There was no significant difference in pre vs. post rating of perceived exertion with Borg, or HR (Borg RPE scale 14.7 ± 3.8 and 15.1 ± 3.7, p=0.947 and average HR 149 ± 35 vs. 156 ± 27, p=0.667 and maximum HR; 171 ± 27 vs. 177 ± 19, p=0.840).

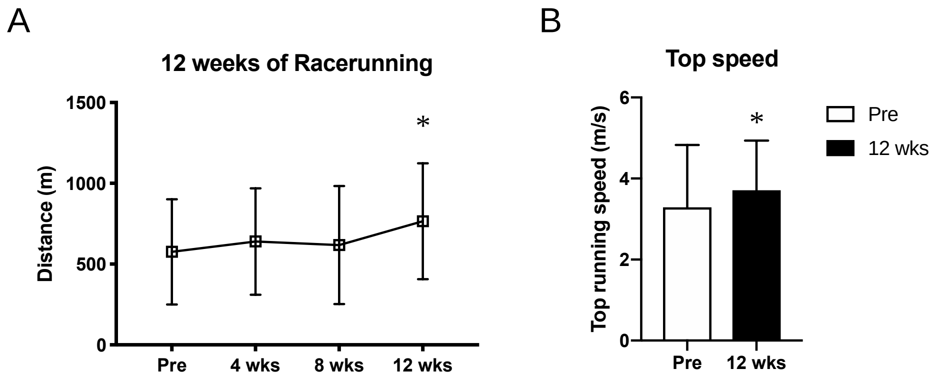


Figure 5:1 A) Distance on the 6-MFRT during the training period (0, 4, 8 and 12 weeks), * denotes significantly different from Pre (p<0.001). B) Top running speed before/Pre and after 12 weeks of Frame Running training, * denotes significantly different from Pre (p<0.05).

Muscle thickness

After 12 weeks of training, there was a significant increase in the thickness of the medial gastrocnemius muscle in the more affected leg, measured with ultrasound, on average 9% (11.6 ± 2.7 mm vs. 12.4 ± 2.6 mm, p=0.005) (figure 5:2). There was no significant change in the same muscle in the less affected leg (12.5 ± 2.7 mm vs. 12.6 ± 2.6 mm, p=0.251). The thickness of the vastus lateralis and intermedius muscles did not change significantly in either leg (more-affected 23.6 ± 6.1 mm vs. 23.6 ± 7.0 mm, p=0.389; less affected 26.6 ± 6.5 mm vs. 26.0 ± 7.0 mm, p=0.269).

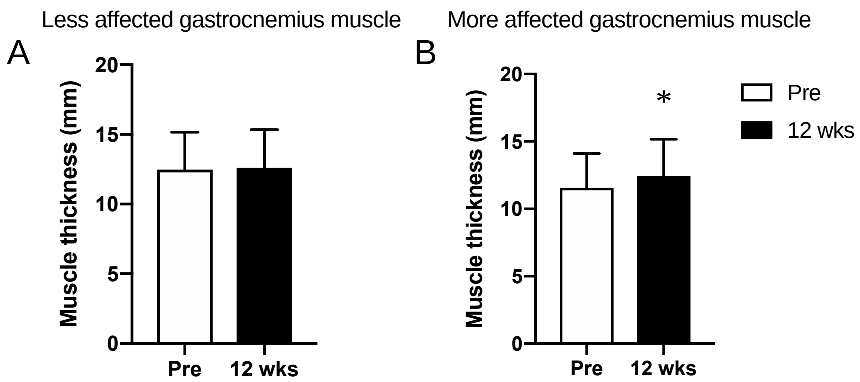


Figure 5:2 Muscle thickness of the A) less affected and B) more affected medial gastrocnemius muscle pre and post 12 weeks of Frame Running training, * denotes significantly different from Pre (p<0.05)

Passive range of motion and muscle tone

In addition, a physical examination was preformed pre vs post the training period, showing a significant decrease in passive ankle dorsiflexion in the more affected side pre vs. post training (median [min, max] 10° [- 15°, 35°] vs 10° [- 20°, 35°], p=0.026). Passive hip flexion in the less-affected leg increased as compared to pre-training (125° [70°, 150°] vs. 130° [100°, 150°], p=0.015). No significant difference was found in the less affected ankle, in the more affected hip or in the other joints (exact but insignificant result can be found in paper I). There was no significant difference in lower limb spasticity pre vs. post the training period.

5.4 The six-minute Frame Running test (6-MFRT) to assess aerobic capacity

The 6-MFRT is used in all four studies. In sum, the total number 6-MFRT performed by individuals with CP in the thesis are 145 (Study I; n=16+15+15+13, Study II; n=24, Study III; n=62, whereof 16 tests are from Study I, Study IV; n=16). These 6-MFRT are performed by 80 different individuals between the years 2016 and 2022. Respiratory parameters are measured in Study II (n=24) and Study IV (n=14) and represent 32 individuals, where six individuals participate in both studies.

5.4.1 6-MFRT outcomes

Outcome measures for 6-MFRT are distance covered, HR, rating of perceived exertion (Borg RPE scale, OMNI for 12 participants in Study II), respiratory parameters and lactate levels in capillary blood (table 5:3).

Table 5:3 6-MFRT outcome for each study.

		Total Mean ± SD (range)	GMFCS I-II Mean ± SD (range)	GMFCS III Mean ± SD (range)	GMFCS IV-V Mean ± SD (range)
Study I baseline test (n=15)	Number (n)	n=15	GMFCS I n=1 GMFCS II n=3	n=4	GMFCS IV n=7
	Distance (m)	576 ± 320 (17-1173)	929 ± 233 (650-1173)	542 ± 212 (328-829)	395 ± 273 (17-744)
	HR_{peak} (bpm)	171 ± 27 (120-213)	178 ± 36 (127-207)	177 ± 9 (165-184)	163 ± 30 (120-213)
	Borg RPE	14.7 ± 3.8 (12-20)	16.3 ± 3.8 (13-20)	16.8 ± 2.2 (14-19)	12.7 ± 3.9 (12-17)
Study II (n=24)	Number (n)	n=24	GMFCS II n=8	n=3	GMFCS IV n=13
	Distance (m)	707 ± 244 (179-1220)	871 ± 249 (495-1220)	729 ± 152 (563-860)	600 ± 210 (179-1020)
	HR_{peak} (bpm)	181 ± 14 (145-200)	183 ± 11 (163-196)	181 ± 6 (176-188)	179 ± 18 (145-200)
	Borg RPE (n=12)	16.9 ± 3.4 (9-20)	17.0 ± 2.8 (15-19)	20 ± 0 (20-20)	16.4 ± 3.7 (9-20)
	OMNI (n=12)	6.8 ± 1.1 (5-8)	6.3 ± 1.2 (5-8)	7.0 ± 0 (7-7)	7.4 ± 0.9 (6-8)
	VO_{2peak} (ml/kg/min)	29.3 ± 7.3 (19.0-49.8)	25.4 ± 2.8 (20.0-29.7)	36.2 ± 12.5 (25.3-49.8)	30.1 ± 7.0 (19.0-40.5)
	VO_{2peak} (L/min)	1.40 ± 0.48 (0.62-2.18)	1.50 ± 0.40 (0.93-1.98)	1.94 ± 0.39 (1.49-2.18)	1.22 ± 0.45 (0.62-2.15)
	RER_{peak}	1.16 ± 0.16 (0.94-1.49)	1.21 ± 0.16 (0.97-1.49)	1.11 ± 0.03 (1.08-1.14)	1.14 ± 0.17 (0.94-1.44)
Study III (n=62)	Number (n)	n=62	GMFCS I n=2 GMFCS II n=26	n=11	GMFCS IV n=21 GMFCS V n=2
	Distance (m)	789 ± 335 (17–1407)	1010 ± 186 (650–1349)	743 ± 366 (273–1407)	542 ± 287 (17–1103)
	HR_{peak} (bpm)	176 ± 23 (114–213)	178 ± 23 (114–208)	181 ± 6.2 (165–187)	170 ± 25 (117–213)
	Borg RPE (n=55)	16.5 ± 2.3 (12–20)	16.5 ± 2.3 (13–20)	16.6 ± 2.3 (13–19)	16.4 ± 2.5 (12–20)
Study IV (n=16)	Number (n)	n=16 (VO2 kinetics n=14)	GMFCS II n=2 (VO_2kinetic, lactate n=1)	n=5	GMFCS IV n=8 GMFCS V n=1 (VO_2kinetics n=8)
	Distance (m)	815 ± 287 (295-1225)	1029 ± 6 (1025-1034)	918 ± 285 (603-1225)	710 ± 288 (295-1076)
	HR_{peak} (bpm)	181 ± 16 (131-198)	184 ± 8 (178-190)	184 ± 8 (174-192)	178 ± 20 (131-198)
	Borg RPE	18.7 ± 1.8 (13-20)	18.0 ± 1.4 (17-19)	19.2 ± 0.8 (18-20)	18.6 ± 2.2 (13-20)
	VO_{2peak} (ml/kg/min) (n=14)	31.1 ± 9.8 (17.7-48.6)	24.2	36.9 ± 11.0 (21.4-48.6)	28.2 ± 8.3 (17.7-42.3)
	VO_{2peak} (L/min)	1.68 ± 0.74 (0.72-3.5)	1.44	2.04 ± 1.00 (0.86-3.50)	1.49 ± 0.50 (0.72-2,40)
	RER_{peak}	1.12 ± 0.10 (0.91-1.27)	1.14	1.11 ± 0.06 (1.03-1.20)	1.11 ± 0.13 (0.91-1.27)
	Lactate acid in blood post	7.7 ± 3.9 (3.0-16.5)	5.6	8.0 ± 3.9 (4.1-14.0)	7.8 ± 4.3 (3.0-16.5)

Abbreviations: VO_{2peak}: peak oxygen uptake, HR_{peak}: peak heart rate, bpm: beats per minute, RER_{peak}: peak Respiratory Exchange Ratio, Borg RPE: rating of perceived exertion 6-20, OMNI exertion scale 0-10.

5.4.2 Physiological response and characteristics of 6-MFRT

In both study II and IV, 6-MFRT outcome was compared with established age-adjusted end criteria for reaching maximal oxygen uptake based on HR and RER. In study II, all but six participants, and in study IV all but one participant, reached or almost reached HR and RER criteria. The participants that did not reach the criteria were classified as GMFCS II (n=1) and GMFCS IV (n=5) in study II and GMFCS IV (n=1) in study IV (this person was excluded in result the 5.4.4 i.e., comparison with FRITT). The proportions reaching criteria are showed in figure 5:3 A-B.

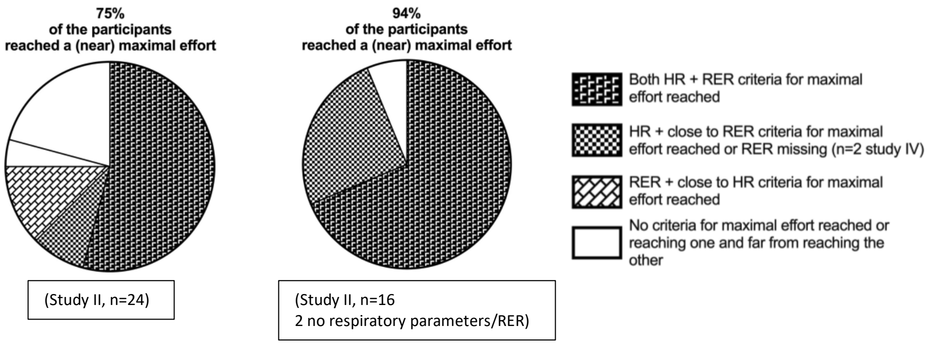


Fig 5:3 A-B represents proportions reaching HR and RER criteria in A; study I and B: study IV
("n" refers to number of participants)
** Close to RER criteria correspond to RER≥1.0 (also for adult, where established criteria are RER≥1.10) and close to HR criteria correspond to HR≥92% (based on the result) of established criteria of HR≥185bpm for children and HR≥85% of 220bpm-age for adults.*

Characteristics of the 6-MFRT were varied. In general, there was a rapid increase in ventilatory parameters in the beginning that was maintained or slightly decrease during the middle of the test, to then rise again at the end. On average, peak values in VO_2 were observed after 3:35 min and for HR after 4:15 min (figure 5:4 from study II).

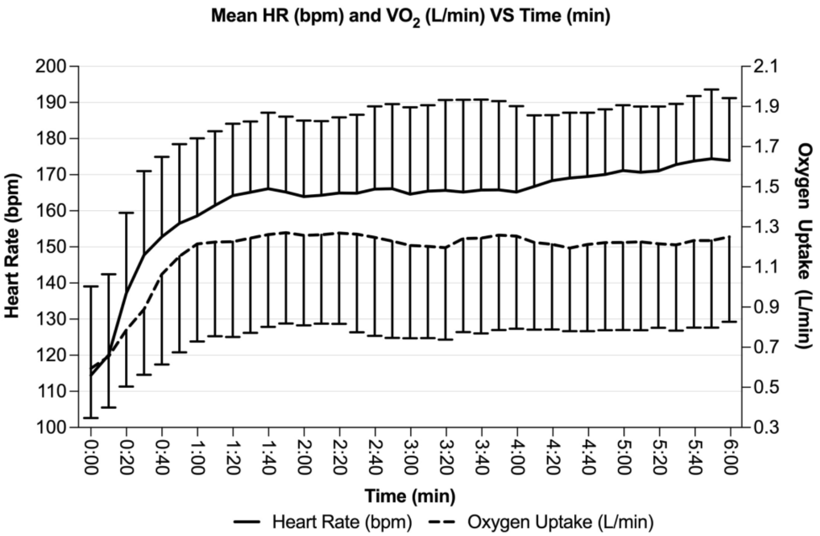


Figure 5:4 Average heart rate (beats per minute) and oxygen uptake (L/min) with error bars (SD) of all participants during the 6-MFRT.

5.4.3 Correlation between distance and peak oxygen uptake for the 6-MFRT

Moderate to strong significant correlations were found between distance and peak oxygen uptake during the 6-MFRT in both study II and IV. The correlations are shown with scatterplots in figure 5:5 A-B.

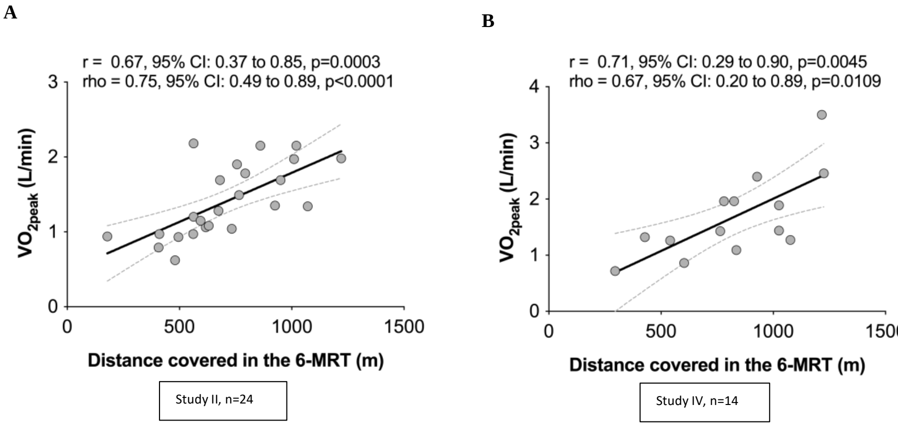


Figure 5:5. Scatterplot with VO_{2peak} (L/min) and distance covered during the 6-MFRT (m). Correlations with Pearson correlation coefficient (r) and Spearman correlation coefficient (rho). The dotted lines represent 95% confident intervals. A; Study II and B; Study IV.

5.4.4 Validity of the 6-MFRT as a maximal exercise test

Study IV compared the validity of the 6-MFRT as a measure of peak oxygen uptake (VO_{2peak}) with the FRITT. There were no significant differences with respect to any measured cardiorespiratory parameter or blood lactate during the two tests, although a tendency for higher VO_{2peak} obtained during FRITT (table 5:4).

Table 5.4 Peak output and comparison of means during the 6-MFRT and FRITT.

	6-MFRT (n=13) Mean ± SD (range) Median (IQR)	**FRITT (n=13) Mean ± SD (range) Median (IQR)**	**Paired t-test**	**Wilcoxon signed-rank test**
Participants	n=13	n=13		
VO_{2peak} (ml/kg/min)	31.88 ± 9.72 (17.71–48.60)	34.52 ± 9.69 (22.02-52.20)	p=0.068	
VO_{2peak} (L/min)	1.76 ± 0.72 (0.86-3.50)	1.93 ± 0.80 (0.89–3.74)	p=0.054	
HR_{peak} (bpm) (6-MFRT n=15) (FRITT n=14)	184 ± 9 (173–198)	186 ± 10 (168–203)	p=0.340	
RER_{peak}	1.13 ± 0.09 (1.02-1.27) 1.14 (1.05-1.20)	1.07 ± 0.08 (0.95-1.30) 1.06 (1.03-1.10)		p=0.075
VE_{peak} (L/min)	84.35 ± 39.79 (50.16–169.24) 66.56 (52.87-115.55)	83.56±32.53 (41.13–153.12) 74.35 (60.88-108.04)		p=0.753
Rf_{peak} (breaths/min)	65.40 ± 13.00 (45.76–84.83)	66.75 ± 11.39 (44.07–90.29)	p=0.631	
VE /VO_{2peak}	45.76 ± 8.23 (33.05–60.08)	45.11 ± 8.91 (32.23–59.37)	p=0.690	
VE /VCO_{2peak}	44.30 ± 7.38 (30.49–55.65) 43.64 (40.35-51.82)	45.41 ± 7.55 (36.17–58.67) 42.83 (39.17-50.30)	p=0.843	
Borg RPE (6-MFRT n=15) (FRITT n=14)	19 ± 1.0 (17–20) 19 (18-20)	19 ± 1.5 (15–20) 19 (18-20)		p=0.521
Lactate pre (6-MFRT n=15) (FRITT n=14)	2.06 ± 0.70 (1.07-2.95) 1.85 (1.72-2.35)	1.83 ± 0.50 (1.07-2.95) 1.73 (1.55-2.3)		p=0.074
Lactate post (6-MFRT n=13) (FRITT n=14)	8.07 ± 3.80 (4.07-16.50) 6.50 (5.54-10.16)	6.57 ± 2.78 (3.70–12.81) 6.32 (4.07-7.76)		p=0.087
Total time (min)	6 ± 0	9.38 ± 0.25 (5.5-14.67)	p<0.001	

Abbreviations: VO_{2peak}: peak oxygen uptake, HR_{peak}: peak heart rate, bpm: beats per minute, RER_{peak}: peak Respiratory Exchange Ratio, VE_{peak}: peak minute ventilation, Rf_{peak},: peak respiratory frequency, VE_{peak} / VO_{2peak}: relationship between the peak minute ventilation and the peak oxygen uptake, VE_{peak} / VCO_{2peak}: relationship between the peak minute ventilation and the peak carbon dioxide production, Borg RPE: rating of perceived exertion, Lactate: blood lactate acid

A strong correlation between VO_{2peak} obtained from the two tests was observed, with a Pearson's correlation coefficient (r) of 0.94 and 95% confidence interval of 0.80 to 0.98 ($p<0.0001$) (figure 5:6).

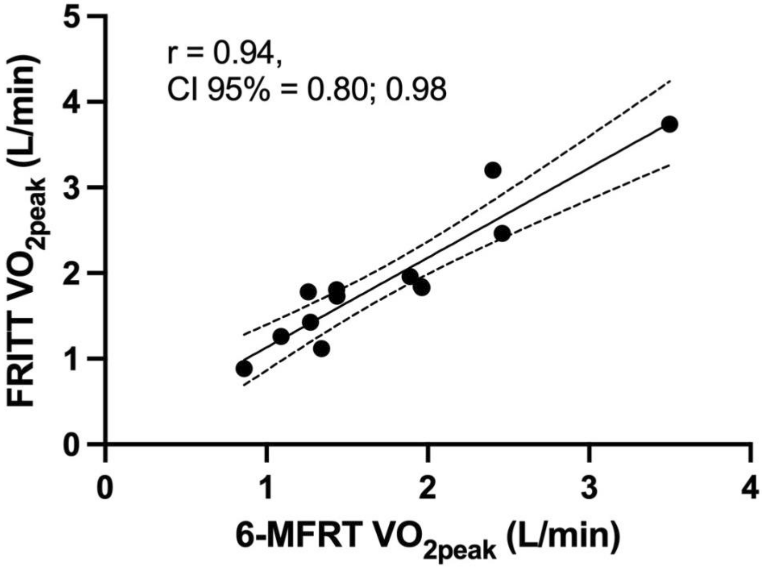


Figure 5:6 Scatterplot with VO_{2peak} (L/min) during 6-MFRT and FRITT (n=13). The dotted lines represent 95% confident interval (95% CI: 0.90-0.98).

The level of agreement between the mean VO_{2peak} obtained during the 6-MFRT and the FRITT was visualized graphically with the Bland and Altman plot [189].

The estimated bias between the methods was 0.17±0.28 L/min, indicating that on average, the FRITT measures 0.17 L/min more than the 6-MFRT (or in relative to body weight, a mean difference of 2.65±4.57 ml/kg/min). However, this difference was not statistically significant ($p=0.054$). The differences between the two methods were normally distributed ($p=0.680$), allowing the calculation of limits of agreement. The limits of the differences were 0.72 L/min and -0.39 L/min, indicating that VO_{2peak} values measured by the FRITT could be above or below the 6-MFRT by up to 0.72 L/min or -0.39 L/min, respectively (figure 5:7).

The overall results suggest that the 6-MFRT is a valid test for measuring VO_{2peak} and can be used as an alternative to the FRITT.

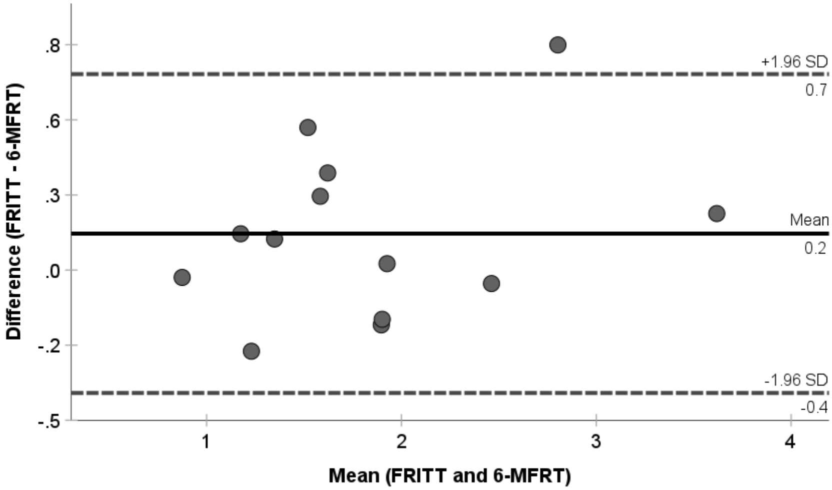


Figure 5:7 Bland-Altman plot for peak oxygen uptake (VO_{2peak} in Liter/min) during 6-MFRT and FRITT. The differences between the two tests are plotted against each individual's mean for the two tests, demonstrating that FRITT measures on average 0.17 L/min (represented by the solid black line) more than the 6-MFRT. The limits of agreement (the thick dashed lines) represent the range within which 95% of the differences between the two exercise tests are expected to fall.

5.5 Determinants of Frame Running capacity (6-MFRT distance)

In study III, the 6-MFRT distance is used as a measure of Frame Running capacity. Prior to the 6-MFRT, passive range of motion (pROM) (hip, knee, ankle), selective motor control (SMC), spasticity (hip, knee, ankle) and muscle thickness were measured in both legs. The purpose was to determine what factors, apart from peak oxygen uptake, are most important for Frame Running capacity (6-MFRT distance). In total, 54 variables per individual (n=62) were included. Data were analyzed using correlations, Principal Component Analysis (PCA), Orthogonal Partial Least Square (OPLS) regression, and Variable Importance in Projection (VIP) analysis.

Sixty-two participants (mean age 22 ± 9 yrs, 32 males/30 females) with CP (GMFCS I to V) participated in the study. There were no significant differences between the GMFCS groups regarding height, weight, sex, or age. Frame Running experience ranged from one month to 26 years of experience, were individuals in the higher GMFCS levels had more experience (significant difference between the GMFCS I-II and GMFCS IV-V group $p<0.001$).

Mean distance covered during the 6-MFRT was 789 ± 335 m, for the 62 participants, and decreased with higher GMFCS level (table 5:3, figure 5:8 A, B). Participants in GMFCS I-II ran significantly further than GMFCS III (p=0.0164) and IV-V ($p<0.0001$). Regarding maximum speed there was a significant difference between GMFCS I-II and IV and between GMFCS III and IV ($p<0.0001$) (figure 5:8 A, B). Further, regardless of 6-MFRT distance, there was no difference across GMFCS levels in achieved HR (intensity) and rating of Borg RPE scale (exertion). Peak and average HR were 176 ± 23 bpm and 158 ± 29 bpm, respectively, and RPE immediately after the 6-MFRT was 16.5 ± 2.3, (Fig 5:8 C-F).

Similarly, the measured impairments associated with CP were significantly more pronounced at the higher GMFCS levels. Passive range of motion were limited in hip and knee, (significant main effects of GMFCS level for all pROM variables ($p<0.0001$ to $p=0.003$), but not for ankle dorsiflexion, which was equally limited in all groups ($p=0.263$), nor for knee flexion, which was mostly within normal range in all three groups ($p=0.135$). Selective motor control of ankle dorsiflexion was more impaired, and spasticity was in general more marked at higher GMFCS levels (main effect of GMFCS level; $p<0.001$ for both SMC and spasticity for all muscle groups, except for foot plantar flexors, where all individuals were equally affected ($p=0.532$)). There was no significant difference between sides in any pROM, SMC or spasticity variable (supplemental tables in paper III). In addition, muscles were thinner in both the thigh and the calf for participants with more severe impairment (main effect of GMFCS level, $p<0.0001$). Further, the more affected leg was thinner than the less affected leg regarding both muscle groups (main effect of side; $p<0.05$) (figure 5:9 A-B).

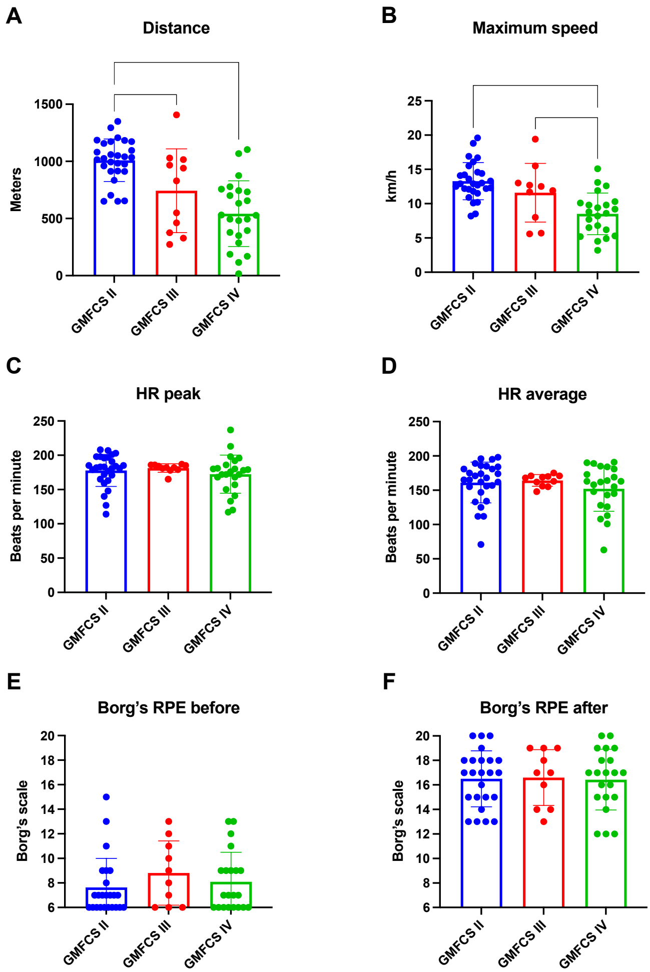


Figure 5:8 A) Distance covered in the 6-minute Frame Running test (6-MFRT), B) maximum speed in the 6-MFRT, C) peak heart rate (HR) during the 6-MFRT, D) average HR during the 6-MFRT, E) Borg's rating of perceived exertion (RPE) results before the 6-MFRT, F) Borg's rate of perceive exercise (RPE) results after the 6-MFRT. Note: *; P<0.05, ****; P<0.001

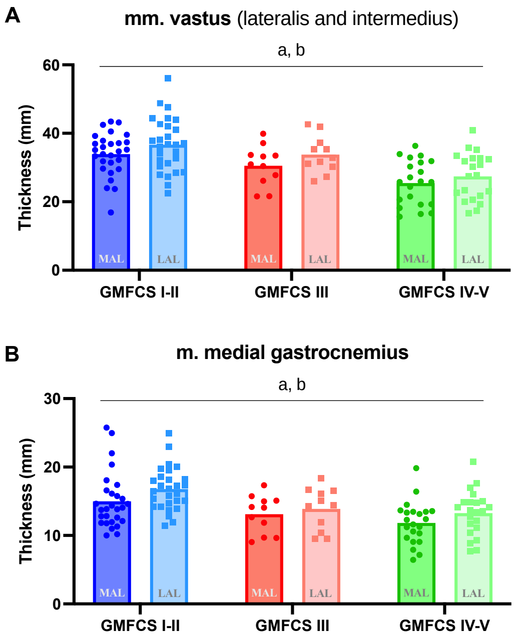


Figure 5:9 Muscle thickness assessed by ultrasound in A) the mm. vastus (vastus lateralis and vastus intermedius) and B) m. medial gastrocnemius in the more-affected (MAL) and less affected (LAL) legs. Note: a; main effect of gross motor function classification scale (GMFCS) level, P<0.0001, b; main effect of side, P<0.05.

5.5.1 Correlation analysis

Significant moderate correlations were found between the 6-MFRT distance and all motor function classification descriptive parameters such as GMFCS level (Spearman's rho = -0.64, p<0.001), competitive class (CPISRA classification) (Spearman's rho = 0.67, p<0.001) and functional mobility scale (FMS) (Spearman rho for 5 m = 0.65, for 50 m = 0.53, for 500 m = 0.45, P<0.001 for all), but not age (p=0.36). There were also significant moderate to strong (rho>0.4) correlations between 6-MFRT distance and spasticity (in the hip extensors, flexors and adductors, and knee extensors muscle groups), muscle thickness of thigh and calf, SMC of ankle dorsiflexion, and pROM (hip extension and knee extension). Weak significant correlations were found between 6-MFRT distance and peak and mean HR during the test (peak HR rho=0.39; p=0.002, mean HR rho=0.37, p=0.003).

5.6 Prediction analysis of Frame Running capacity (6-MFRT) and VO_{2peak}

5.6.1 Prediction of Frame Running capacity (6-MFRT distance) based on physical and physiological parameters

In study III, multivariate statistics were used, i.e., Principal Component Analysis (PCA), Orthogonal Partial Least Square (OPLS) regression analysis, and Variable Importance in Projection (VIP) analysis in order to identify patterns, explore the variance of data, investigate if Frame Running capacity can be predicted (OPLS regression analysis), and if so, what variables contribute more to a prediction analysis (VIP).

The PCA revealed a modest degree of covariance of the included variables. The first two principal components were used to plot the data in two dimensions and to visually identify clusters of closely related data-points. The variance in all the variables analyzed was capable of grouping the individuals according to their GMFCS level. The scree plot from the PCA showed that the first two principal components/dimensions accounted for 41% of the total variance in 6-MFRT distance (Dim1; 30%, Dim2; 11%).

Due to that most of the 54 included parameters contributed to component one or two, or both, all variables were included in the next analysis; OPLS regression analysis for the purpose of prediction (figure 5:10 A).

The OPLS regression analysis was followed by a VIP analysis (figure 5:12 B) in order to explore which variables that contributed the most to explain the variance in the 6-MFRT in the prediction model. The OPLS regression analysis indicated that from the summed effect of all the variables, the variance in individual Frame Running capacity (i.e., 6-MFRT distance) could be predicted with a 75% accuracy (figure 5:10 A).

The variables that contributed most to the 6-MFRT distance, (i.e., the VIP analysis) were, 1) spasticity in hip extensors and 2) knee extensors, 3) SMC of the ankle dorsiflexion, 4) muscle thickness of the vastus (lateralis and intermedius), 5) thickness of the gastrocnemius muscles, 6) pROM of the hip extension and 7) pROM in hip and 8) knee extension (figure 5:10 B for exact order).

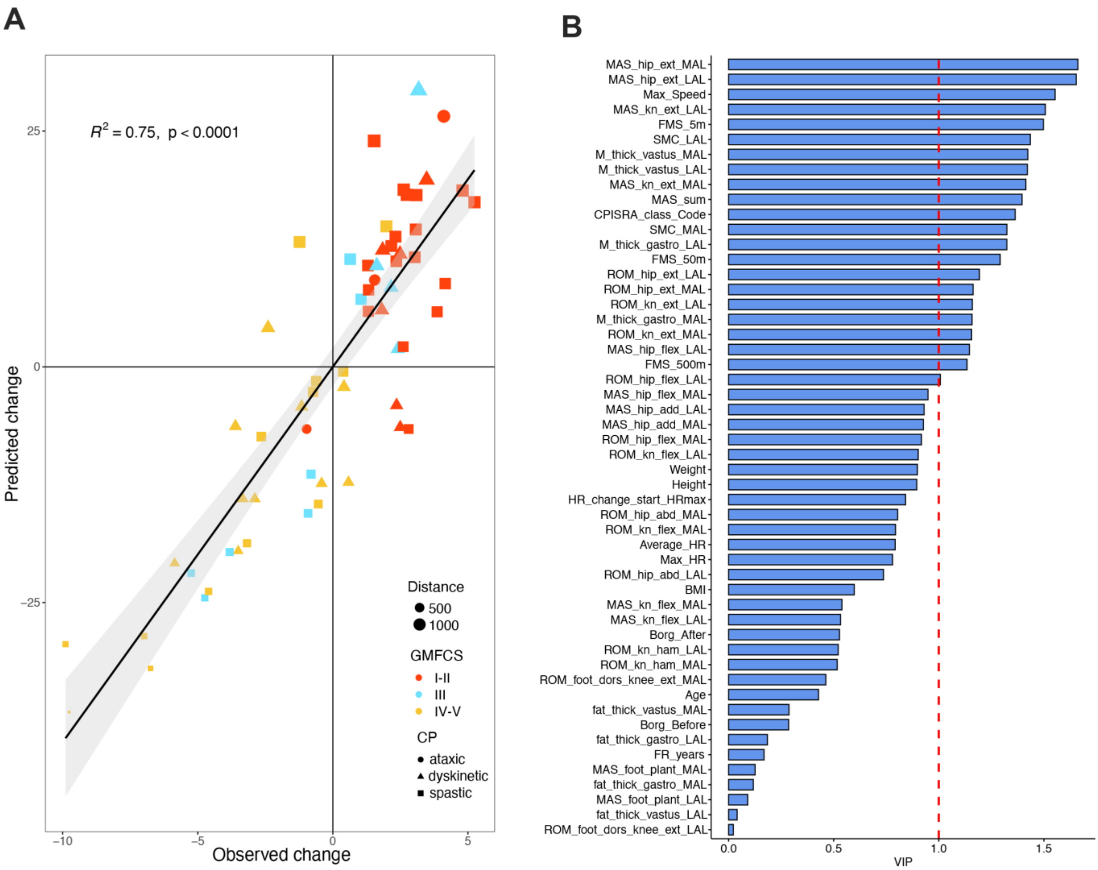


Figure 5:10 A) and 5:12 B). Global, exploratory approach to the 6-minute Frame Running test (6-MFRT) capacity (i.e., distance) based on all the variables analyzed (n=52).

A) Scatter plot of predicted and observed 6-MFRT distance using our OPLS regression (R^2 = 0.75, P < 0.001). Grey area represents 95% confident intervals. Each symbol denotes the predicted vs. observed distance for one individual. The size of the symbol indicates the distance, while the color represents the group according to the gross motor function classification system (GMFCS) level, and the type of symbol describes the type of CP.

B) Variable Importance in Projection (VIP) showing the hierarchical contribution of each variable to the successful modelling. A value greater than 1 denotes important contribution to the prediction model. MAS; Modified Ashworth Scale, FMS; functional mobility scale, SMC; Selective Motor Control Scale, ext; extension, flex; flexion, abd; abduction, M_thick; muscle thickness, fat_thick; subcutaneous fat thickness, dors; dorsiflexors, BMI; body mass index; FR_years; years of experience in Frame Running, MAL; more-affected leg, LAL; less-affected leg, ROM; range of motion, HR; heart rate, kn; knee, ham; hamstrings, gastro; gastrocnemius.

5.6.2 Prediction of VO_{2peak} based on 6-MFRT distance

In study IV, a backward linear regression analysis was used to investigate if VO_{2peak} during 6-MFRT could be predicted based on distance and participant characteristics.

This analysis found that distance covered ($p=0.005$), sex ($p=0.028$), body weight ($p=0.011$) and height ($p<0.001$) were significant predictors of $\dot{V}O_{2peak}$ (Liters/min) during 6-MFRT. Whereas, BMI, GMFCS, age, Frame Running experience and activity level (SGPAL) were not significant predictors in the regression analysis for 6-MFRT. For FRITT, only body weight ($p<0.001$) and height ($p<0.001$) were found to be significant predictors of VO_{2peak}, with no other factors such as maximal speed obtained at the treadmill being significant predictors.

5.7 Summed result of the 6-MFRT outcome (study I, II, III and IV).

In this section the summed results of 6-MFRT outcome are reported for a total of 80 individuals.

5.7.1 Summed 6-MFRT outcomes

The mean outcomes of 6-MFRT are summed in table 5:5 of all participating individuals (n=80), of which 32 participants measured respiratory parameters during the 6-MFRT. For the participants who contributed with more than one 6-MFRT (n=22), the best 6-MFRT, based on distance and cardiorespiratory outcome were chosen.

Table 5:5 Summed 6-MFRT outcomes

Overall (n=80)		Total (individuals) Mean ± SD (range)	GMFCS I-II Mean ± SD (range)	GMFCS III Mean ± SD (range)	GMFCS IV-V Mean ± SD (range)
Overall (n=80)	Number (n)	n=80 Borg RPE n=61	n=34 Borg RPE n=24	n=16 Borg RPE n=13	n=30 Borg RPE n= 24
	Distance (m)	802 ± 320 (17-1407)	987 ± 203 (495-1349)	814 ± 27 (273-1407)	585 ± 295 (17-1103)
	HR_{peak} (bpm)	179 ± 20 (114-213)	180 ± 20 (114-208)	183 ± 5 (174-192)	173 ± 22 (117-213)
	Borg RPE	16.8 ± 2.6 (9-20)	16.3 ± 2.2 (13-20)	17.5 ± 2.4 (13-20)	17.0 ± 3.1 (9-20)
Overall VO_2kinetics (Individuals n=32)		n=32	n=8	n=7	n=17
	Male/Female (n)	17 / 15	3 / 5	5 / 2	9 / 8
	Age (yrs)	21 ± 9 (8-38)	25 ± 2 (12-37)	22 ± 6 (14-28)	18 ± 8 (8-38)
	Height (cm)	159 ± 14 (120-190)	165 ± 6 (153-174)	168 ± 14 (150-190)	152 ± 16 (120-176)
	Weight (kg)	52 ± 16 (21-85)	60 ± 15 (38-84)	59 ± 6 (40-85)	46 ± 14 (21-71)
	Body mass index (kg/m²)	20 ± 4 (15-30)	22 ± 4 (16-30)	21 ± 5 (16-29)	19 ± 4 (15-26)
	CP motor type (n) (spastic/dyskinetic/ataxic)	20 / 10 / 2	7 / 0 / 1	5 / 2 / 0	8 / 8 / 1
	Distance (m)	761 ± 266 (179-1225)	865 ± 243 (495-1220)	859 ± 268 (563-1225)	670 ± 257 (179-1076)
	HR_{peak} (bpm)	182 ± 11 (159-200)	181 ± 11 (163-196)	183 ± 7 (174-192)	183 ± 13 (159-200)
	Borg RPE	18.2 ± 2.6 (9-20)	17 ± 2.8 (15-19)	19.2 ± 0.8 (18-20)	17.9 ± 3.1 (9-20)
	VO_{2peak} (ml/kg/min)	29.70 ± 7.6 (17.71-48.60)	25.30 ± 2.86 (20.00-29.70)	34.80 ± 10.02 (21.39-48.60)	29.67 ± 6.94 (17.71-42.30)
	VO_{2peak} (L/min)	1.55 ± 0.62 (0.62-3.50)	1.51 ± 0.39 (0.93-1.98)	2.08 ± 0.83 (0.86-3.50)	1.35 ± 0.51 (0.62-2.40)
	RER_{peak}	1.16 ± 0.14 (0.94-1.49)	1.22 ± 0.15 (0.97-1.49)	1.11 ± 0.05 (1.03-1.20)	1.16 ± 0.15 (0.94-1.44)
	VE_{peak} (L/min)	71.91 ± 33.70 (22.0-169.24)	65.13 ± 20.95 (37.0-101.0)	95.93 ± 37.90 (53.42-169.24)	65.21 ± 33.85 (22.0-147.69)
	Rf_{peak} (breaths/min)	64 ± 13 (43-87)	58 ± 7 (52-70)	69 ± 14 (46-86)	65 ± 14 (43-87)
	VE_{peak}/VO_{2peak}	42.87 ± 13.15 (1.25-75.00)	43.39 ± 14.22 (33.00-75.0)	45.88 ± 5.71 (39.89-54.00)	41.29 ± 15.21 (1.25-64.30)
	VE_{peak}/VCO_{2peak}	39.56 ± 10.94 (1.25-63.00)	38.61 ± 10.53 (30.00-63.0)	44.89 ± 5.78 (39.99-53.61)	37.71 ± 12.53 (1.25-54.71)

Abbreviations: VO_{2peak}, peak oxygen uptake; HR_{peak}, peak heart rate; bpm, beats per minute; RER_{peak}, peak Respiratory Exchange Ratio; VE_{peak}, peak minute ventilation; Rf_{peak}, peak respiratory frequency; VE_{peak} / VO_{2peak}, relationship between the peak minute ventilation and the peak oxygen uptake; VE_{peak} / VCO_{2peak}, relationship between the peak minute ventilation and the peak carbon dioxide production, Borg RPE, rating of perceived exertion 6-20, OMNI excision scale 0-10.

5.7.2 Summed result of physiological response of 6-MFRT

The summed result of proportion of individuals (n=40 i.e., n=24 in study II + n=16 in study IV) reaching the established age-adjusted end criteria for reaching maximal physiological response based on HR and RER. The criteria were not reached in 7/40 (17.5%) and reached in 33/40 (82,5%) of all 6-MFRT, (figure 5:11).

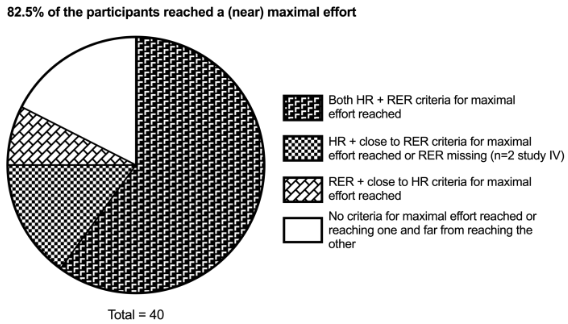
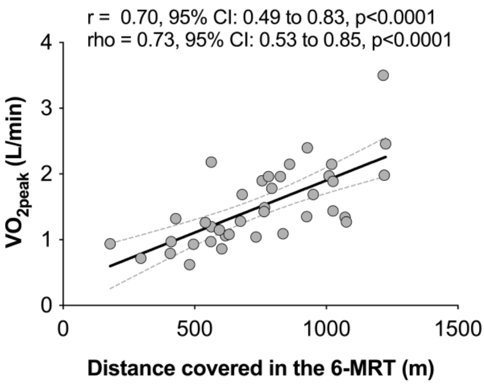


Fig 5:11 Represents proportions reaching HR and RER criteria, summed for all 6-MFRT with respiratory parameters n=40 (i.e., study II n=24 + study IV n=16, note missing data for respiratory parameters (RER) in n=2), (note this represent 33 individuals, because 7 individuals participated in both study II and IV but performed a new 6-MFRT at another time-point).
* Close to RER criteria correspond to RER≥1.0 (also for adult, where established criteria are RER≥1.10) and close to HR criteria correspond to HR≥92% of established criteria (of HR≥185bpm for children and HR≥85% of 220-age for adults).

5.7.3 Summed result of correlation between distance and peak oxygen uptake for the 6-MFRT

The summed result of correlation between distance and VO_{2peak} for all 6-MFRT with cardiorespiratory parameters (n=38) performed in study II (n=24) and IV (n=14) (table 5:12.



(n=38)

Fig 5:12 Scatterplot with VO_{2peak} (L/min) and distance covered in the 6-minute Frame Running test (m). The dotted lines represent 95% confident interval.

6 DISCUSSION

6.1 **Discussion of the results**

This thesis aims to contribute to the limited research on the health effects of high-intensity exercise in individuals with cerebral palsy (CP) and ambulatory difficulties (GMFCS II-V).

In this discussion, the results will be contextualized within the framework of research done in the field, where the three research questions are in focus:

1) What are the physiological adaptations of Frame Running exercise?
2) Can the 6-MFRT be used to assess aerobic capacity (VO_{2peak})?
3) What physical and physiological parameters determine Frame Running capacity (6-MFRT)?

<u>Physiological adaptations of Frame Running exercise</u>

Frame Running exercise twice a week for 12 weeks improved cardiorespiratory endurance. This was demonstrated through an on average 34% increase in the distance covered on the 6-MFRT compared to pre-training distance, with no change in heart rate, and exertion (ratings on the Borg RPE scale). This was interpreted as a result of central adaptations (e.g., stroke volume) and/or peripheral adaptations (muscular capillarization and increased oxidative capacity).

There are, to this date, no other Frame Running intervention studies to compare with. In addition, very few or no other aerobic exercise studies including non-walking participants (GMFCS IV-V) (as stated in several review articles [93, 94, 133]).

Other interventions targeting the group of more severe CP include, for example horse-back-riding [190], hydrotherapy [191], video gaming [192] and motorized dynamic standing exercise [193, 194]. None of these activities can evoke a similar intensity as Frame Running. We demonstrated an average intensity of 69% of age-corrected maximum heart rate (mean HR; 136 bpm) corresponding to moderate intensity, which is seen as target intensity during training [15]. Further, we observed higher intensity during shorter periods and very high intensity in the test situations (mean HR_{max} ranging from 171-181 bpm in the four studies), in a study population where the majority of the participants are wheelchair users, (GMFCS III-V).

The higher the intensity, the greater the effect on aerobic capacity [54]. Also, the less trained an individual is at baseline, the lower intensities are required to improve aerobic capacity [55].

Furthermore, previous literature in the field has been more focused on children than on adults [94]. This thesis contributes to the field also in this aspect, as a majority of the participants were adults (>18yrs).

Our results are in line with previous research available including participants classified as GMFCS levels I-III, demonstrating improvements in VO_{2peak} of 8-35% [150, 151, 195, 196] using a variation of aerobic training methods (e.g., cycle ergometer, up-hill walking and similar), frequencies (1-3 times/week) and total durations (6 weeks-12 months).

The dose-response condition that are demonstrated in the typically developed population [20] seems to applies also in this group [151, 197].

Taking into account the established recommendations regarding training volume (150-300min/week of moderate intensity or 75min/week of high intensity) [15, 22, 99] three times a week could have been better than the actual twice a week. However, limiting the frequency to twice per week is likely to increase compliance with the intervention program, and at the same time there is sufficient evidence to support that even small increases in physical activity are adequate in relatively deconditioned and inactive individuals to improve cardiorespiratory fitness and result in clinically meaningful health improvements [20, 99].

In addition to Frame Running being effective in improving cardiorespiratory fitness, the training protocol also induced muscle hypertrophy, as made evident by a 9% significant increase in muscle thickness of the medial gastrocnemius on the more affected side, measured with ultrasound.

This finding is interesting, as running traditionally is not viewed as a hypertrophic activity. But as indicated in previous studies including elderly and deconditioned individuals, even aerobic activities such as cycling and walking can in fact stimulate muscle growth if performed at a sufficient intensity and volume [198-200].

Since the hallmark of CP, especially the more severe types, are weak, thin and stiff muscles [110], hypertrophy is indeed a positive and important effect of Frame Running. The general muscle dysfunction and pathophysiology observed in individuals with CP, together with a poor neural drive, can make it difficult to engage in traditional resistance training activities that are typically used to promote muscle growth. Frame Running, on the other hand, provides a low-impact, sustained activity that targets the lower leg muscles in a way that may be more accessible for individuals with CP, especially when having a more severe form.

In addition to muscle thickness, joint range of motion was investigated. An increase in stiffness in the ankle dorsiflexion was noted, leading to a small but significant decrease in joint range of motion of the same side as the observed muscle hypertrophy. This could support the presence of muscle hypertrophy as increase stiffness of the Achilles tendon has been described concomitant to muscle hypertrophy following polymetric jumping exercises [201-203]. Furthermore, passive range of motion in hip flexion was significantly improved on the less affected side. These passive range of motion findings could be a consequence of the active movements that Frame Running involves, that regardless of running style, (reciprocal leg movements or pushing off with both legs more or less at the same time), involves repetitive flexion and extension of the hips and pushing off with the feet. It is likely that the ability to flex the hip and then push off with a bouncing movement with the forefoot contributes to a more efficient running technique.

Overall, our results indicate that Frame Running is an effective method for improving both cardiorespiratory and muscular fitness in individuals with CP. However, physical activity does not preclude regular monitoring of passive range of motion, which is a cornerstone of CP care. Rather, as in most sport activities, it is recommended that muscle length is maintained through additional flexibility and stretching exercises [204].

<u>The usefulness of the 6-MFRT to assess aerobic capacity</u>
The result of the thesis contributes in breaking new ground in terms of understanding respiratory parameters and aerobic capacity of individuals with CP, classified as GMFCS levels III to IV. To my knowledge, no previous study has assessed oxygen uptake during Frame Running, and the available reference data are mostly for less severe CP using treadmill [141, 167, 205, 206], cycle ergometer [146, 151, 207-209], arm crank ergometer [151], wheelchair ergometer [152] or shuttle-run test [143, 167, 168].

The correct method for measuring maximal aerobic capacity is considered to be an incremental test with gas exchange to exhaustion [15] but distance and time-based tests are also commonly used in the literature [45].

Our research demonstrated strong positive correlations (r/rho=0.67-0.75) between distance and peak oxygen consumption (VO_{2peak} in L/min) obtained during the 6-MFRT, thus confirming the usefulness of the 6-MFRT in estimating aerobic capacity.

Furthermore, our backward regression analysis has identified the potential for developing an equation to estimate VO_{2peak} based on distance, sex, body weight, and height.

This could indeed be useful, both for the individual athletes to evaluate the effectiveness of a training interventions or follow aerobic capacity over time, but it also enables the use of 6-MFRT as a tool for testing health-related cardiorespiratory fitness where the outcome can be compared, for example to reference values.

A previous study [172] has investigated whether the 6-minute walk test can predict peak oxygen uptake in ambulatory adolescents and adults with CP and found that distance and VO_{2peak} obtained at a maximal exercise test was significant but poorly related. Preliminary results show that the relationships seem stronger with high-effort Frame Running but this needs to be confirmed with further investigations.

In study IV we aimed to further explore the validity by comparing the 6-MFRT outcomes with outcomes during an incremental maximal exercise test method, that we called Frame Running Incremental Treadmill test (FRITT). A strong correlation (r=0.94) was found between VO_{2peak} obtained during 6-MFRT and during FRITT. Furthermore, no significant differences were found in VO_{2peak} or other cardiorespiratory parameters or blood lactate between the two tests.

Overall, this result suggests that the 6-MFRT is a valid test for measuring VO_{2peak} and can be used as an alternative to the methodologically more complicated and laboratory-based FRITT.

However, it is important to consider the potential differences between the two tests when interpreting the results.

Although non-significant differences (p=0.054 for VO_{2peak} in L/min and p=0.068 for VO_{2peak} in ml/kg/min), FRITT measured on average VO_{2peak} 0.17 L/min more than in the 6-

MFRT. It is possible that if the sample size had been larger with a high statistical power the results would have been significant.
This could be because the FRITT lasted on average a significantly longer time (mean 9 min and 17 sec). Six minutes may be too short to reach maximum effort, especially for more fit individuals. The ideal duration for a maximal aerobic capacity test is usually longer; 6-10 min in children [70] and 8-12 min in adults [72]. Another obvious difference between the two tests is the potential for variability in pacing during 6-MFRT, despite continuous verbal encouragement, and the inability to control for environmental factors that may impact performance.

However, for some individuals with severe motor impairments and coordination difficulties, the possibility to control and to be able to vary running pace can in fact be an advantage, and even a prerequisite for the ability to perform an exercise test at all.

To evaluate whether the exercise tests peak values yielded "true" maximum values, we measured the physiological response based on established objective end-criteria; heart rate (HR) and respiratory exchange ratio (RER) in addition to perceived exertion [69, 70].

The most widely accepted criteria for determining VO2max involve a plateau in oxygen uptake despite an increase in workload in the final minutes. However, the attainment of a plateau is often difficult to achieve, particularly in children, untrained individuals or those with medical conditions [15, 63, 66], and therefore not expected in this population.

Our data showed that both the 6-MFRT and the FRITT represented a near maximum aerobic performance. During the 6-MFRT in study II and IV 75-94% of all participants reached RER $\geq$ 1.0 and reached (or were just below reaching) the established maximal criteria HR.

It is encouraging that such a large proportion of individuals with CP, GMFCS III-IV, have the ability to reach a maximum cardiorespiratory response during a Frame Running exercise test, because this a basic requirement for a maximum aerobic capacity test to be valid.

The observed response to exercise is well in line with previous research. Bolster et al [159] investigated reliability and construct validity of the 6-MFRT and reported that two-thirds of the participants achieved a HR above 180 bpm during the 6-MFRT. Further, when comparing this to studies that evaluate aerobic capacity by other exercise methods reporting objective maximal exertion, the same tendency is observed, that is, a majority, but not all, reach maximal exertion and the greater the motor impairment, the more difficult it is to reach a maximal physiological level [64, 65]. This indicates that in many individuals with CP, especially in those classified at the higher GMFCS levels, the limiting factor may not be the cardiorespiratory system but rather motor limitations such as spasticity, poor muscle strength and control or other additional symptoms.

There are no reference data for cardiorespiratory fitness (VO_{2peak}) in the population with CP at GMFCS levels III-V. But despite several methodological differences between our study and the published literature such as age differences, test settings, etc. our cohort, in particular the more severely affected individuals (GMFCS III and IV) seem to be more fit than the average severely affected individual with CP (GMFCS III-V).

When comparing our data to studies that investigated VO_{2peak} in adults (16-67 yrs) with CP, GMFCS I-III [148, 152, 208, 209], the VO_{2peak} results reported in our cohort are relatively high. Collectively, these other studies report VO_{2peak} data ranging from 17.7-44.5 ml/kg/min, where the current result was mean VO_{2peak} of 31.9-34.5 ml/kg/min. Because most of our participants exercised Frame Running more or less regularly for many years, this suggests long-term (>12 weeks) cardiorespiratory benefits from the sport.

Further, the assumption that the higher the GMFCS level, the lower the VO_{2peak} appears to only partially apply to the current results.
Admittedly, current result are more similar to studies including children, adolescents [144, 154] and adults [152] classified as GMFCS III than to the results of studies including more abled (GMFCS I-II) children, adolescents [144, 205] and adults [209], which generally have higher VO_{2peak}.

However, an interesting observation can be made based on our 6-MFRT VO_{2peak} results. Although the 6-MFRT distance seemed to decrease with increasing GMFCS level, participants classified as GMFCS III, had the highest mean VO_{2peak}.

In addition, Frame Running athletes classified at levels GMFCS IV-V achieved a similar or even slightly higher mean VO_{2peak} in ml/kg/min (relative to bodyweight) than the Frame Running athletes classified at GMFCS II.

This observation could be explained by the fact that the study population classified at the higher GMFCS levels in general had longer Frame Running experience.

A variability in Frame Running performance especially in the group of GMFCS level III has been noted in previous research by van der Linden et al [120], focusing on developing an evidence-based classification system for competitive Frame Running, where the group classified as GMFCS III actually ran faster than the group classified as GMFCS II.

A tentative explanation could be that individuals classified as GMFCS levels III-V who engage in Frame Running are generally more fit than peers at same GMFCS-level who do not engage in any equivalent physical activity. Whereas the individuals in GMFCS II engaged in Frame Running are likely the ones that lack independent running ability and therefore are likely to have a lower starting point than peers that can run, at same GMFCS level.

It has been shown previously that 53-71% of the bilaterally affected independent walkers with CP (GMFCS II) have the ability to run independently (a phase with both feet off the ground) [210, 211]. When aiming to identify what biomechanical and neuromotor functions that determine the ability or inability to run, knee extensor spasticity together with selective motor control [210, 211] and muscles strength (hip flexors, abductors, knee flexors, foot dorsiflexors) [211] have shown to be key components for running ability in children and adolescents with bilateral cerebral palsy.

This fact, together with the described variability in performance and aerobic capacity over the GMFCS levels, where there is a spread of capacity within the grouping of GMFCS, although distances in general decrease with higher GMFCS, (for example some seem to run shorter distances even though having a higher VO_{2peak}). Further the indications that the aerobic capacity may not be the only, or for some not even the primary limiting factor, leads in to the purpose of study III.

Determinants of Frame Running capacity.
This study aimed to investigate the physical and physiological variables apart from VO_{2peak} that affect Frame Running capacity, which was measured by the 6-MFRT distance. A multivariate analysis approach was used to develop a prediction model and interpret the hierarchical importance of the investigated factors. The study found that spasticity in the hip and knee extensors, muscle thickness (especially in the vastus muscles), selective motor control (SMC) of the ankle, and passive range of motion (pROM) of the hip and knee extensors were among the top variables that contributed to the prediction model. The study was able to predict 6-MFRT capacity with 75% accuracy based on more than 50 variables.

These results can be used to optimize training regimes and contribute to evidence-based and fair classification, which is crucial for Frame Running to grow as a parasport.

In fact, there are two previously published studies with a similar aim. However, while the approach of the current study was more on optimization of exercise and health, the approach in the studies by van der Linden et al. was primarily focused on evidence-based competitive classification in Frame Running. The purpose of the classification is to create fair and equitable competition by minimizing the impact of impairments resulting from the primary condition (hence not trainable) on the competitive outcome [162]. This is truly a multifaceted and difficult challenge, especially in the case of a congenital injury such as CP with whole body involvement.

The research by van der Linden and co-workers were carried out in parallel with and independent of the plans for the current study. They collected data from 31 [119] and 29 participants [120] whereof 15 individuals took part in both studies. Participants were recruited during the international Frame Running/RaceRunning camp and cup in 2016 and 2017, whereas the current study collected data from 62 participants mainly during the same event in 2018 and 2019. This procedure has both advantages and disadvantages, where both similar (spasticity, selectivity, strength, passive range of motion) and different (maximum step-length while on the Frame Runner, trunk control) impairment measures are used by van der Linden et al.

Further, study III used the 6-MFRT distance (mean distance; 789 ± 335 m and mean speed; 7.89 km/h, mean top speed; 11.3km/h) as the performance outcome, while the studies by van der Linden et al. used the average running speed during the official season's best race time for 100 m and 200 m (mean speed; 13-14km/h).

It is therefore interesting that, despite different approaches, it is largely the same parameters that are highlighted as the most important factors affecting Frame Running performance. Van der linden et al. found that spasticity, selective motor control, muscle strength, knee range of motion and trunk control were all associated with Frame Running speed, with spasticity (summed score of all muscle groups) having the highest correlation.

Relatively few other studies have investigated the associations of coordination impairment and related symptoms with sports performance [212-214]. However, the influence of spasticity, selective motor control, muscle size and strength on gross motor function, walking and running have received more attention [118, 137, 210, 211, 215-217].

Collectively, even if sometimes the results are inconclusive, the importance of muscle strength and volume for performance are purported as major factors both in individuals with cerebral palsy [218] and in general [219]. However, it is important to note that the muscle size-strength relationship has in several studies been reported to be weaker in individuals with CP than for non-impaired individuals [220-222], as an altered neural drive appears to disturb this relationship.

Core symptoms of CP like muscle weakness, reduced ability to activate certain muscles, difficulty controlling and directing movements, and in some cases involuntary movements are closely linked. It can be challenging to determine which factors are most responsible for affecting capacity and causing unnecessary energy expenditure.

Studies have previously shown that individuals with CP consume more energy than typically developed controls, when walking at own leisure pace [143, 206]. Increased strength has been showed to improve running economy in non-disabled running athletes [223]. Although it is likely that improved strength would improve Frame Running capacity this needs to be verified in future studies. Furthermore, in order to further differentiate what determines Frame Running capacity, more sport specific tests may be a way forward.

Nonetheless, the current study has made several contributions to the research area of Frame Running capacity in individuals with CP. Firstly, the study is the largest of its kind, with 62 participants. Additionally, the study includes novel outcome measures, such as muscle thickness and subcutaneous fat thickness, which can provide valuable information about the running capacity and overall health of individuals with CP. Finally, the study's multivariate analysis offers insights into the relative importance of various variables, which could prove useful in guiding future research and interventions.

Finally, our result suggests that although individuals with CP are reported to have lower cardiorespiratory fitness than the general population, it may be that Frame Running athletes with severe CP (GMFCS III-V) have better aerobic capacity than peers with CP at same GMFCS level who are not physically active. This further strengthens good ability to benefit from training in individuals with CP. In our studies II and IV, we observed that more and other factors than aerobic capacity appear to influence performance in Frame Running. Some individuals with CP have great difficulty or lack the ability to approach their maximal physiological limit according to criteria for reaching maximal oxygen uptake capacity. In study III we explored this further and found that CP-associated impairments, with spasticity having the greatest significance, negatively affected Frame Running capacity, while muscle size had a positive impact. Resistance training (e.g., the thigh muscles and other large muscle groups around the hips and knees) for Frame Running athletes with CP together with sport specific practice are warranted to improve both performance and health.

6.2 Methodological considerations

The results of this thesis should be viewed upon in the light of the following limitations.

The number of participants in each study is small. Furthermore, the recruitment of participants was based on interest (mainly thorough Frame Running clubs and at an international Frame Running camp and competition). They were heterogeneous with respect to ages (mixing children, adolescents and adults), Frame Running experience and severity of the motor impairment. The fact that most of the participants were already engaged in and motivated to engage in Frame Running may have favorably affected our results. All in all, this reduces the generalization of the results to a larger population.

Future intervention studies should aim at enrolling a larger number of individuals, with a more homogenous training background and, even more importantly, a control group and an RCT design, which would add evidence to the effectiveness of Frame Running. However, the intervention study was a real-world set-up study where it was not possible to recruit more participants even though training was offered during four periods between 2016 and 2018 in three cities of Sweden.

Measurements in study II were performed in two different countries both indoors and outdoors hence with variable environmental conditions, which could influence the result, but no differences between the groups were seen. However, merging data from the two sites doubled the number of participants and increased the power of the result.

The reliability of both the 6-MFRT and FRITT with gas-exchange could be further investigated and secured. However, the 6-MFRT have been found to have good reliability in one previous study [159]. Both tests were performed by experts and physiological maximal effort was ensured through the use of HR and RER established criteria, in addition to that exertion was perceived as maximal by the athlete and research group.

With regard to mixture of ages, different objective criteria to ensure maximum physiological response were used for adults versus children. In addition, in study IV the participant that were far from reaching the established criteria was excluded when the test was used as maximal exercise test (validity in comparison with FRITT).

In study III, the included variables apply only to lower limb function. Future studies should also include data related to upper limbs, posture and trunk characteristics. As already discussed, more sports specific measurements could have added value. Motion analysis and measures of running economy should be added in the future to capture the Frame Running technique and its importance for performance.

Despite these issues, this thesis contributes with new evidence on the effects of Frame Running exercise, aerobic exercise testing using the Frame Runner, and determinants of Frame Funning capacity of a total of 80 individuals with CP where 57.5% (n=46/80) are classified at GMFCS III-V (performing a total of 145 number of 6-MFRT). Few other physical activities exist that can evoke a similar intensity in this group and previous research in this field is scarce.

6.3 **Implications**

In this section, the overall strategy and implications for improving health in this population through physical activity will be discussed.

According to extensive research, increasing physical activity in individuals with CP could significantly improve their health.

Not reaching the established recommendations for regular physical activity has so far been seen as being inactive or sedentary. However, being sedentary is not the same as lack of exercise. Research has suggested that some of the metabolic and systemic effects of prolonged sitting are different from insufficient exercise [25]. This is the reason why sedentary behavior has received a lot of attention in the general society and in research, including within disability/CP-research, where the first step is to agree upon both the definitions and impact [224, 225].

However, if you have a severe mobility impairment and are a wheelchair user, it is very difficult to avoid a lot of sitting.

Interventions targeting exercise in individuals with CP have resulted in short-term increased fitness. However, gains are hard to maintain. Furthermore, transfer effects into improved function or increased level of habitual physical activity have been difficult to prove. It has been suggested that regular moderate-to-high intensity exercise may be a too big challenge to overcome for individuals with severe CP (and their families) [224].

Increasing physical activity is therefore suggested to be reached through two ends: increase regular moderate-to-high-intensity physical activity and reduce sedentary behavior (and replace it with low-intensity activity), where the latter is suggested to be easier in severely affected individuals than the former. These two strategies are not meant to be opposites but rather, the overall strategy should be to simultaneously reduce sedentary behavior and increase physical activity.

However, it is not known which of these two approaches that are the most feasible and which approach has the largest outcome in the long run. There is a risk with this two-sided focus, that they may be interpreted to have similar effect on the total health outcome.

In this thesis we have shown that high intensity activity through Frame Running is possible for severely affected individuals with CP. Intensity has been highlighted as a key factor in gaining fitness, even though it is for short bouts [226].

It is not known if and to what extent moderate-to-high-intensity activity can compensate for a lot of sitting, but there is much evidence suggesting that it is possible [19, 227].

Furthermore, the context of physical activity appears to be important. Recently, the concept of the physical activity paradox has been raised. This means that occupational physical activity (e.g., construction workers, cleaners) may have an adverse health effect (no energy left for spare time exercise) as compared to office workers who exercise by their own choice in their leisure time. It is not known how these mechanisms may apply to those with disabilities who have a constant elevated energy cost for everyday activities.

In this thesis, we argue that being very active for relatively short periods and sedentary the rest of the day, (like a Frame Running athlete that is a wheel-chair user the rest of the day) is a successful path to improve health. The overall best strategy for improving health through physical activity is not known, but extensive research suggests that high to vigorous intensity physical activity, even for short periods of time, is likely to have the greatest value.

We therefore argue that engagement and resources (e.g., the ability to obtain a Frame Runner as a mobility device from the healthcare system or at a reasonable cost) must be provided. The setting for Frame Running should preferable be through a sporting club, but could also be provided through school and/or the health care system. Politicians must also be aware of the value of building inclusive and adapted environments that invite for play and exercise, with the guiding star that physical activity should be a right for everyone in society.

The ultimate goal should be that all individuals with disability causing walking and running difficulties, should regularly have the opportunity to engage in Frame Running training. In addition, the setting is important, preferably a setting where all the F-words can be found.

7 CONCLUSION

The knowledge this thesis contributes with is summarized through answering the three research questions;

- Physiological adaptations of Frame Running training (Study I).
  A pre-post intervention study of 12 weeks of Frame Running training improved cardiorespiratory endurance (6-MFRT distance on average 34%) and stimulated skeletal muscle hypertrophy (on average 9% of the calf muscle in the more affected side) in individuals with CP.

  Frame Running is a powerful training modality in individuals with CP that improves both muscle and cardiorespiratory fitness, which are central components in health-related fitness.

- The utility of the six-minute Frame Running test (6-MFRT) to assess aerobic capacity (VO_{2peak}) (Study II and IV)
  A majority (≥75% in our studies) of individuals with CP, GMFCS II-V can reach a (near) maximal cardiorespiratory response during 6-MFRT. Strong correlations were shown between VO_{2peak} obtained during 6-MFRT and Frame Running Incremental treadmill test (FRITT) and between achieved distance and VO_{2peak} during 6-MFRT. No significant differences were shown in mean VO_{2peak}, blood lactate or other cardiorespiratory parameters during 6-MFRT and FRITT.

  6-MFRT is practical and easy to perform and offers a useful alternative for estimating cardiorespiratory fitness in individual with CP when evaluation of maximum oxygen uptake by a laboratory based test is not feasible.

- Determinants in Frame Running capacity (6-MFRT) (Study III and Study IV)
  We used a statistical multivariate analysis that offered a prediction model and an interpretation of the hierarchical importance of the investigated factors. Spasticity in the hip and knee extensors had the highest contribution to the prediction, followed by muscle thickness, especially in the vastus muscles. This prediction analysis based on more than 50 variables was able to predict 6-MFRT capacity (i.e. distance) with 75% accuracy.

  These results may be useful in designing training programs in order to improve Frame Running capacity, as well as in developing evidence-based and fair classification systems for this parasport.

  The implementation of resistance exercise-based activities, combined with sport-specific training is recommended for Frame Running athletes with CP to improve both athletic performance and overall health.

8 POINTS OF PERSPECTIVE

This thesis covers some perspectives of health effects from Frame Running mainly around the two domains of the F-words/ICF framework 1) Fitness/Body function and structure and 2) Function/Activity. Future perspectives on Frame Running and how individuals with CP react to physical activity both in same and other domains, remains to be further explored.

Our research group has a special interest in both skeletal muscle and the cardiorespiratory system functionally and molecularly in relation to physical exercise.

We have both on-going and published [228] research on the acute effect of a 45-minute Frame Running exercise bout. We investigate the response of exercise induced circulating biomarkers in the blood in individuals with CP, in comparison to typically developed individuals (45 minutes running).

Studies in the thesis have reveled other aspects of exercise physiology raising new research questions. As an example, we have observed possible indications of an altered cardiorespiratory and anaerobic response to acute exercise, with increased breathing frequency, altered blood lactate levels, pCO_2 and elevated ratio VE/VCO_2 ratio. These findings suggest that individuals with CP have an ineffective ventilation during exercise which requires further investigation.

Furthermore, our research group is currently investigating if muscle activity, function and structure during Frame Running in individuals with CP differ from typically developed individuals performing corresponding activities. Methods include near-infrared spectroscopy (NIRS) to investigate oxidative capacity (mitochondrial function) in muscles and Electromyography (EMG) as an indication of muscle activity/fatigue during Frame Running.

Similarly, data have been collected with motion analysis and measurements of force, speed and effect (power) during a 30 m Frame Running sprint, to further explore Frame Running capacity.

Data collection for a future research project are initiated, investigating self-rated physical activity (questionnaires), objectively measured physical activity (accelerometer and continuous heart rate) and physical self-perception (measured with a questionnaire "Children and youth, Physical Self-Perception Profile (CY-PSPP)/"Sådan är jag"). The goal is to explore how physical self-esteem and overall mental well-being are linked to Frame Running and other physical activities in individuals with CP and compare these relationships with typically developed peers.

Moreover, a future new intervention-study for previously inactive adults would also be important. This study could advantageously be conducted as a multicenter study to enable enough number of participants using a randomized control study design with evaluations from a holistic perspective.

Final research perspective that I would like to raise, is to include research on the effects of Frame Running in groups with other diagnosis, for example neuromuscular diseases, where I have a great commitment and a long clinical experience.

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