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UPPER LIMB FUNCTION IN CHILDREN WITH CEREBRAL PALSY; RANGE OF MOTION, BOTULINUM NEUROTOXIN A AND ACCELEROMETRY METRICS

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Upper limb function in children with cerebral palsy; range of motion, botulinum neurotoxin A and accelerometry metrics

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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“Everything that matters cannot be measured, and everything that can be measured does not always matter”

Albert Einstein

This thesis is dedicated to all children with cerebral palsy and their loved ones.

POPULAR SCIENCE SUMMARY OF THE THESIS

Most children with cerebral palsy (CP) have full range of motion in the upper limbs, but in some children, passive range of motion restrictions develop gradually, which is sometimes not recognised until it is pronounced. This phenomenon may cause complications, e.g. restricted movements and limitations in daily life. It is important to understand the secondary physical complications of CP and the consequences both prior to the decision for interventions and in evaluation of interventions. More knowledge about which children are at risk of developing upper limb contractures may be of great value to commencing interventions in due time.

Furthermore, it is of great importance that we constantly evaluate interventions which aims to affect secondary physical complications e.g., range of motion, e.g. botulinum neurotoxin A. The long-term effects of botulinum neurotoxin A treatment in different age groups and functional levels needs to be evaluated more closely. Thus, recommendations concerning this treatment option needs to be regularly updated and be based on recent research.

Most of the interventions that are offered to children with CP, e.g. botulinum neurotoxin A, orthosis, CI-therapy, goal directed task specific training are currently evaluated in a clinical setting and not in the individual's daily environment, even though the interventions often aim to promote functions or activity performance in daily life. Therefore, there is a need to evaluate new supplementary assessment methods that can capture information objectively in the individual's daily life.

This thesis focuses on upper limb range of motion changes over time, upper limb botulinum neurotoxin A treatment and objective measurements on upper limb activity in daily life in children with CP.

Previously collected data are population-based, obtained from the Swedish CP registry and used in manuscript I-III. In our analyses, we described range of motion changes, physical characteristics related to a first upper limb botulinum neurotoxin A treatment. Further, the range of motion changes in children treated for the first time at an early age, at a later age and children not botulinum neurotoxin A treated were investigated over time. In study IV, an objective measuring method, accelerometry was evaluated in a cross-sectional population of children and adolescents with unilateral CP.

In summary: One-third of all children with CP developed contractures in the upper limbs over time. Children with lower levels of function were most likely to develop upper limb contractures over time. Twenty-two percent of children were treated with botulinum neurotoxin A in the upper limbs, whereof 45% received their first treatment at the age of 1–3 years. Children with lower level of function or full passive range of motion with resistance at the end of the movement range were most likely to be treated with botulinum neurotoxin A. A first treatment at an early age implied a favourable range of motion development over time compared to children treated at a later age. Among all examined movements, simultaneously wrist and finger extension were shown to deteriorate the most over time. Accelerometry-based metrics may capture upper limb asymmetries and the relative use in daily life in children with

US-CP. Thus, this objective method may be a complementary tool to clinical assessments in daily life.

ABSTRACT

Cerebral palsy (CP) is the most common cause of movement disorders in children and may result in diverse levels of severity of the disability, from very mild to very severe. The underlying neurological pathology in CP is by definition not progressive, but motor symptoms may cause permanent and progressive secondary movement complications, which often change over time. Movement disorders are a prominent component in individuals with CP and treatments are often aimed at affecting movement disorders. Since CP is caused by a permanent lesion to the brain, the lesion will affect the individual in different ways throughout life and in daily life activities. Thus, it is particularly important to understand how secondary complications develop from early childhood until adulthood in this population. Measurement tools that are evaluating individuals' daily life need to be psychometrically evaluated, and we also need to evaluate the treatments outcome of the secondary complications within CP efficiently. Gaining more knowledge about secondary complications to CP is a priority in CP research.

This thesis focuses on upper limb (UL) passive range of motion (pROM) and contracture development over time, botulinum neurotoxin A (BoNT-A) and on accelerometry based metrics evaluated in daily life in children and adolescents. Upper limb passive range of motion change over time and BoNT-A treatment were investigated by population-based data sourced from the Swedish national CP registry. Upper limb clinical assessments and accelerometry based metrics were obtained from 20 children and adolescents, who were residents of Sörmland or Västmanland in Sweden.

Results show that one-third of children and adolescents with CP developed upper limb contractures and the pROM deteriorated over time. The contracture development started already at preschool age. The first and most severe contractures were found in wrist extension with extended fingers. Children with the most affected level of manual ability were at highest risk for contracture development.

One-fifth of children with spastic or dyskinetic CP had been treated with BoNT-A in the ULs, 45% of them early at age, 1–3 years. Children with lower levels of manual ability or full pROM with resistance at the end of the movement range were most likely to receive a first UL BoNT-A treatment. At the first treatment occasion, thumb and forearm muscles were the most targeted. Interestingly, a first UL BoNT-A treatment at an early age, 1-3 years implied a favourable pROM development over time compared to children treated first time at a later age, 4-15 years. Early detection of a first sign of muscle shortening and thus early intervention before contractures are manifested can be one of the keys to successful outcomes.

In daily life, during sedentary time and light-intensity physical activity, accelerometry metrics provide objective information about UL asymmetry and relative use. Thus, accelerometry metrics may provide complementary information to clinical assessments in daily life.

THESIS OVERVIEW

Study	Questions	Design	Results	Interpretation
I. Upper limb contracture development in children with CP, a population-based longitudinal study.	-In which children and adolescents with CP 0–18 years and at what age do contractures occur in the ULs? -Which joints are usually affected? - Which factors are related to contracture development	Longitudinal population-based study.	Thirty-four percent had developed UL contractures. Restricted pROM was significant at 4 years in wrist extension. Children at MACS level V had a 17-times greater risk of contractures than children at MACS level I.	It may be of importance to pay attention to the first sign muscle shortening, since early detection and early intervention might be the key to successful outcomes.
II. Physical characteristics and upper limb treatment with botulinum-toxin-A in children with CP: a population-based study.	- Which children with CP are selected for treatment with BoNT-A? - Are physical characteristics related to a first BoNT-A treatment in children with CP?	Longitudinal population-based study.	Among children receiving UL BoNT-A, 45% were treated before the age of 4. Thumb and forearm muscles were the most treated with BoNT-A, finger flexor muscles the least. Full pROM with resistance was related to first upper-limb BoNT-A treatment.	Passive ROM in addition to manual ability seem to an aspect to consider in the dialogue about UL BoNT-A. This knowledge may be a start of a dialogue on existing guidelines for UL BoNT-A treatment
III. Upper limb passive range of motion over time in children with cerebral palsy age 1 to 15 years old, treated or not treated with Botulinum neurotoxin A – a population-based study	-Is there any difference in UL pROM development over time in children UL BoNT-A treated 1–3 years of age, 4–15 years of age and children not UL BoNT-A treated?	Longitudinal population-based study.	Most children did not develop pROM restrictions over time. A first UL BoNT-A treatment at early age implied a better pROM development over time compared to children treated at later age, when adjusting for CP subtype and MACS level.	Steps should be taken to identify children with suspected CP to enable monitoring of pROM development early in children's life. This may lead to early interventions aiming at promoting pROM development before contractures already are manifested.
IV. Evaluation of upper limb accelerometry metrics of activity in daily life in children with unilateral cerebral palsy	- May accelerometry-based metrics be useful to describe UL asymmetries, the relative use and overall physical activity levels? Is there any association between UL clinical test and accelerometry-vector magnitude metrics in daily life? - How do participants experience the acceptability of accelerometry in daily life?	Cross-sectional study with convenience sample	Accelerometry-based metrics provide descriptive information of UL asymmetry, relative use and PA levels in daily life. Clinical tests were moderately and fairly associated to accelerometry-based metrics during sedentary time and LIPA. Most participants reported a positive experience of using accelerometry in daily life.	Accelerometry metrics may provide additional information of asymmetry and relative use in daily life in children with cerebral palsy.

LIST OF SCIENTIFIC PAPERS

I. Jenny Hedberg Graff, Fredrik Granström, Marianne Arner, Lena Krumlinde-Sundholm. **Upper limb contracture development in children with cerebral palsy: a population-based study**. *Dev Med Child Neurol* 2019; 61: 204–211.

II. Jenny Hedberg Graff, Fredrik Granström, Lena Krumlinde-Sundholm. **Physical characteristics and upper-limb treatment with botulinum neurotoxin A in children with cerebral palsy: A population-based study**. *Dev Med Child Neurol*; n/a. doi:10.1111/dmcn.15426.

III. Jenny Hedberg Graff, Fredrik Granström, Lena Krumlinde-Sundholm. **Upper-limb passive range of motion over time in children with cerebral palsy age 1 to 15 years old, treated or not treated with Botulinum toxin-A - a population-based study**, **(**In manuscript).

IV. Jenny Hedberg Graff, Lucian Bezuidenhout, Jenny Hallgren, Lena Krumlinde-Sundholm, Maria Hagströmer. **Evaluation of upper limb accelerometry metrics of activity in daily life in children with unilateral cerebral palsy**, (In manuscript).

CONTENTS

LIST OF ABBREVIATIONS

AHA	Assisting hand assessment
AI	Asymmetry index
BoNT-A	Botulinum neurotoxin A
BS-CP	Bilateral spastic cerebral palsy
CP	Cerebral palsy
CPUP	National register and follow-up program for cerebral palsy
GMFCS	Gross motor function classification system
HIC	High income countries
ICF	International classification of functioning
ICF-CY	International classification of functioning- children and youth
LIPA	Light intensity physical activity
MACS	Manual ability classification system
MVPA	Moderately to vigorous physical activity
pROM	Passive range of motion
UL	Upper limb
US-CP	Unilateral spastic cerebral palsy

1 INTRODUCTION

Knowledge about which children and at what age children with cerebral palsy (CP) are developing restricted range of motion and contractures in the upper limbs (UL) is important to prevent secondary complications such as pain, joint deformities, functional and activity limitations.[1,2,3] Extended knowledge about contracture development may provide information about when in time it may be appropriate to offer different interventions.

Botulinum neurotoxin A (BoNT-A) is currently an established, often used method for reducing muscle overactivity and preventing contractures in both the upper and lower limbs.[4,5,6] Despite the increased use of BoNT-A, more knowledge is still required about this treatment option, especially the long-term effects need to be further investigated.[5,7] In order for us to be able to offer our children with CP the best possible treatment, it would be of great value to coordinate ideas globally about when and for which children BoNT-A should be offered. Interventions also need to be coordinated between different professions and evaluated with valid and reliable assessment instruments in the correct context.[8,9,10] BoNT-A treatment in combination with occupational therapy have been shown to promote motor functions, evaluated with gold standard assessment tools in clinical settings.[11]

Additional instruments to existing clinical instruments are required that have the possibility to evaluate activity objectively in children's daily life.[12,13] Only once we can objectively measure activity in the real-world environment, will we be able to find out whether children benefit from their treatment in their daily life.

2 LITERATURE REVIEW

2.1 GENERAL CONCEPT OF HEALTH

Already by 1946, the constitution of the World Health Organisation (WHO) declared principles about health as “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”.[14]

Since 1980, the WHO has developed its conceptual model (1980 ICIDH) to a more contemporary version, International Classification of Functioning, Disability and Health (ICF), which better reflects a reality where a disability is the result of a complex interplay between a medical problem and a socially created problem. From being a model with focus on disease and disorders, linked to possible impacts labelled as “impairments”, “disabilities”, and “handicaps”, new ways of thinking and acting regarding the concept of health in medical care arise. In the 21st century, the new approach resulted in a shift from correcting and normalising to more focus on promoting the individual's strengths.[15] The ICF model of today is used as a framework and includes all individuals, not just people with disabilities.[16,17]

2.2 GENERAL CONCEPTS OF HEALTH- ICF-CHILDREN AND YOUTH

International Classification of Functioning, Disability and Health: Children & Youth Version ICF-CY 2007 is an additional edition to ICF, including a developmental perspective, derived from ICF (WHO, 2001).[16] The children and youth version are designed to describe and document the growing child in relation to functioning and disability as well as the environmental factors that affect the child. Health conditions differ in nature, intensity, and impact, and can be manifested in different ways in childhood and adolescence compared to what they do in adults. ICF-CY reflects changes in the individual’s development and includes characteristics for different age groups and environments.[16]

2.3 CHILDHOOD DISABILITY

A disability in childhood can be described by different aspects, e.g. medical and environmental aspects, as well as from a complex interaction between these aspects, and will probably also affect the child’s development into adulthood. All of these aspects need to be considered when planning for individual interventions.[18]

Traditionally, many interventions have focused on the treatment of disabilities, with the idea that improvements in body structure and function will automatically lead to functional gains. However, recent new knowledge has emerged that shows that this is not the case since functional gains are also likely to be influenced by the individual characteristics and environmental factors.[1]

Ideas about what is to be considered “normal” (things that most people can do) and what’s deviating from normal have been discussed over the past decade. The idea of the conception of "normality" can be useful as a guide for evaluating a specific body function but it’s important

to understand that a perfect body function does not necessarily have to be the most important factor to do things in daily life or enjoy a good life.[19,20, 21]

2.4 THE F-WORDS

The F-words, (function, family, fitness, fun, friends and future) in the field childhood development have been created by Peter Rosenbaum and intend to supplement the ICF-CY framework to demonstrate how the concepts interact with each other and how the ICF-CY could be put into practice.[19, 22] In summary, the F-words frame of reference emphasises that the essential thing is whether, for example, a body's function, such as arm movements, can be useful in the child's daily life, e.g. driving a wheelchair. The F-words can be used as a guide about how we should think and conceptualise physical activity and rehabilitation-based interventions in this field, Figure 1.[19]

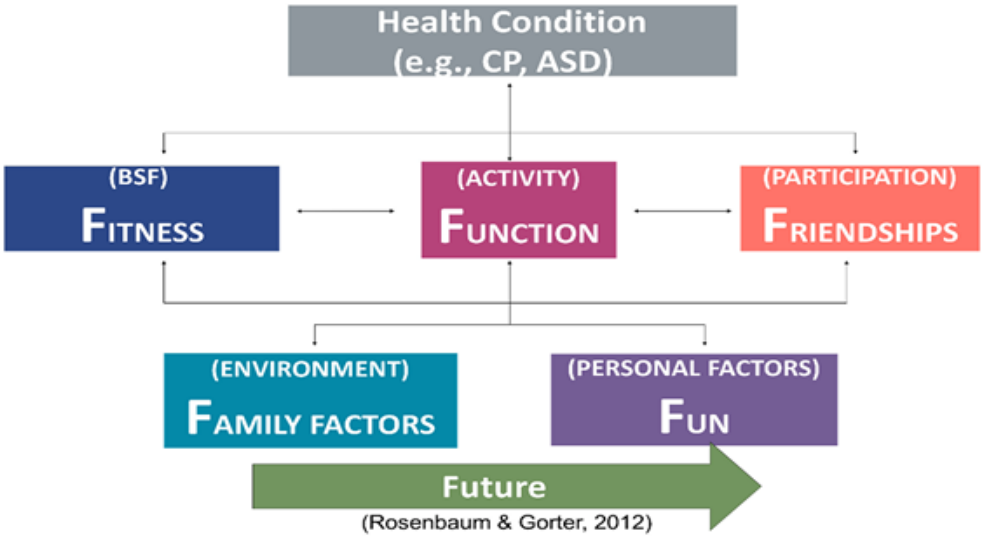


Figure 1. The F-words in children with disability.[22] This figure is reprinted with permission provided by John Wiley and Sons and Copyright Clearance Center.

2.5 CEREBRAL PALSY

2.5.1 Definition and aetiology

William John Little, an English orthopaedic surgeon, presented his important work and substantiated the causal link between brain damage as a cause of birth complications and disorders of mental and physical development by the middle of the 18th century. Dr Little also described a clinical picture of contractures and deformities seen in children due to the origin of the brain, as he further called spastic rigidity, known as Little's disease, and is synonymous with spastic cerebral palsy.[23]

The term CP was further used interchangeably with the eponym Little's disease. At the end of the 18th century, neuropathologist Sigmund Freud mentioned that CP could also be caused

before birth, during the pregnancy and not solely at birth. He also maintained that CP should be classified using clinical examination findings. Freud first explored unilateral motor defects and then several motor defects that encompassed the entire body, which he gathered into a group and named cerebral diplegias. Among cerebral diplegias, he distinguished four main types: general cerebral stiffness, paraplegic stiffness, bilateral hemiplegia, and general chorea and bilateral athetosis. Finally, he gave all these various motor defects a general term, infantile CP.[23]

The most recent definition of CP, "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" was modified in 2007 by an international group of experts who included more than aspects of the motor disorder in the new definition.[24] In recent years there has been increasing interest in also understanding other aspects of CP[25] since the motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems".[26]

CP is the most common cause of movement disorders in children and can result in diverse degrees of severity, from barely noticeable to very severe disabilities.[26,27] The underlying neurological pathology in CP is by definition not progressive, but motor symptoms may cause permanent and progressive secondary complications which may change over time. This means that an affected function, for example impaired hand function or impaired gait, is caused by a permanent disorder of the immature brain. The affected function may change over time due to secondary complications as a result of the disorder.[28] This thesis focuses on secondary complications of CP that may occur as a consequence of the motor lesion.

2.5.2 Criteria and clinical characteristics of CP

The collaboration network Surveillance of Cerebral Palsy in Europe (SCPE) has proposed that children should be at least 4 years old when CP diagnosis is established. The age is a recommendation that can be used in registers and surveys.[27] The underlying brain disorder has varying genesis, location and distribution in the brain, but should have occurred before the child is 2 years old. CP is thereby described by different subtypes based on the topographic distribution of the lesion: bilateral or unilateral CP and is also based on the dominant symptoms: spastic, dyskinetic or ataxic.[27] Approximately 80% have a spastic type of CP which in turn is divided into unilateral spastic (US-CP) and bilateral spastic CP (BS-CP), 10% have a dyskinetic CP and 6% have an ataxic CP. About 4% have a non-classifiable form of CP.[29] Among children with spastic CP, the BS-CP distribution is the most common (60%). Maldevelopment and white matter lesion are most dominating in children with BS-CP while white matter lesions and grey matter lesions are the most dominating in children with US-CP. Bilateral grey matter lesions are most dominating in children dyskinetic CP. The bilateral lesions are reported to be associated with more severe functional impairments compared to unilateral lesions.[30] The SCPE classification has been used in this thesis, Figure 2.

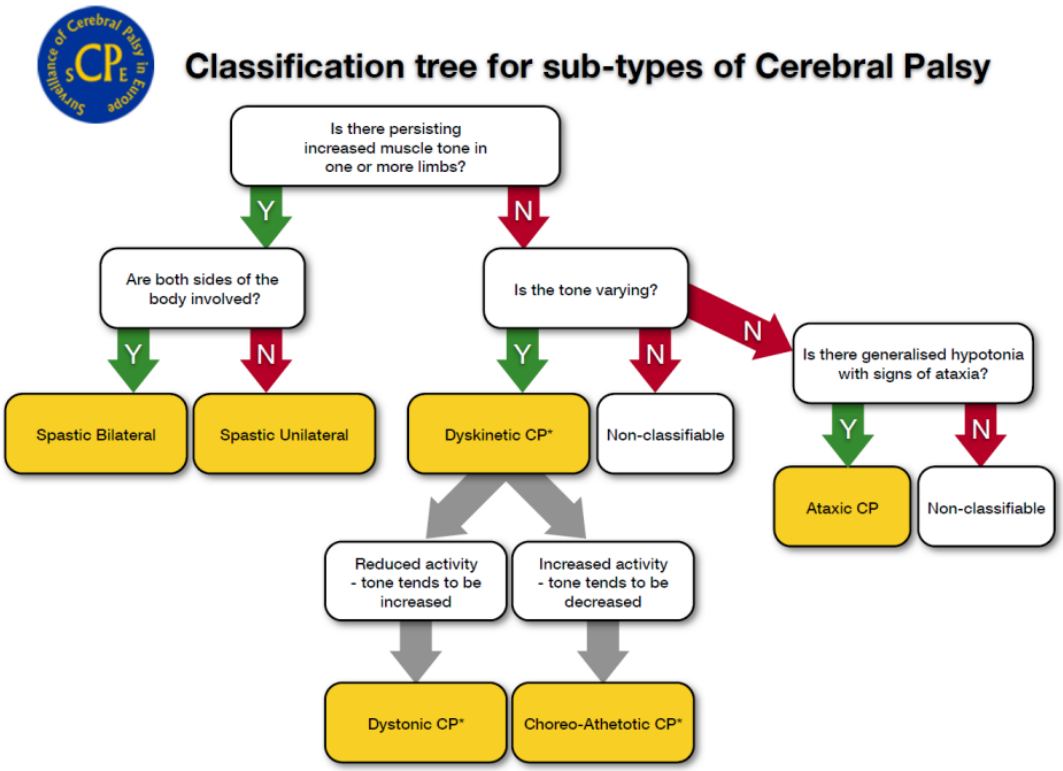


Figure 2. Surveillance of Cerebral palsy in Europe, hierarchical decision tree for classifying cerebral palsy sub-types, 2000. This figure is reprinted with permission provided SCPE by John Wiley and Sons and Copyright Clearance Center and SCPE in Europe, https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/SCPE-CP-Decision-tree.pdf

2.5.3 Prevalence

The prevalence of CP has decreased the last few decades in Europe (Sellier et al 2016) but varies internationally.[31,32,33,34] A recent prevalence study reported a decreasing trend of the prevalence, which is consistent across high income countries (HICs) (Europe and Australia).[34,33] The decreasing prevalence is most likely due to improvements in neonatal and postnatal care in recent years.[33,31,35] When comparing the most recent birth prevalence study, Global prevalence of cerebral palsy: A systematic analysis, 2022 with birth cohorts from the 1980s and 1990s, the prevalence of CP in HICs has decreased from 2.1 per 1000 to 1.6 per 1000 (95% CI 1.5-1.7) live births, when all pre-/perinatal and post neonatal CP birth was included . The birth prevalence for pre-/perinatal CP in HICs was 1.5 per 1000 live births (95% CI 1.4–1.6) while the post neonatal CP in HICs had not changed.[34]

In Sweden, the prevalence for pre-/perinatal CP was 1.7 per 1000 live births (95% CI = 1.4–2.1), following the same decreasing pattern as other HIC countries while post neonatal birth prevalence of CP was 0.7 per 1000 (95% CI = 0.4–1.3) and also indicating a decreasing trend.[34] Cerebral palsy is more frequent in boys (60%) than in girls but there is no difference between gender regarding the distribution within CP subtypes.[36]

2.5.4 Risk factors

There are several factors strongly associated with increased risk of CP. Children born full-term account for the majority of cases of CP. However, pre-term birth before 28 weeks of pregnancy is the most important risk factor for CP and the risk is about 50 times higher than for full-term births.[37,38] Epidemiological studies have shown that the origins of most CP are prior to birth. In pre-term birth children < 32 weeks, predominant white matter injury is most prevalent (80%).[39] Increased risk factors except preterm delivery are associated with malformations, caesarean delivery, low birth weight (SGA), multiple pregnancy, placenta abnormalities, fluid volume abnormalities and infections. Later research has also discussed and elucidated the importance of genetics in causative explanations for CP. Clinical risk factors could thus be triggers for CP where there is a genetic susceptibility.[40,37] Genetic variations in the dopamine system have also shown to influence treatment outcomes in children with unilateral CP.[41]

2.5.5 Secondary clinical complications to CP

Secondary clinical complications as may result from CP often include spasticity, impaired musculoskeletal function, movement limitations, activity limitations and limited ability to participate. These complications in combination with the aspect of development reflect the complexity of CP.[42]

Among these numbers of secondary clinical complications to CP, spasticity is well-known as the most dominant. However, dystonia, arising from the dyskinetic CP subtype, has also increasingly been described to coexist with spasticity identified among the spastic CP subtypes. The coexisting phenomenon has then been reported with the term "mixed" tone.[43] Several definitions of spasticity have been presented over the years and the most common used definition was presented by Lance 1980.[44] However, it was not until 2017 that a conceptual framework (Figure 3) was presented about the different components that interact in spasticity. The group suggested that the new term hyper-resistance instead of spasticity should be used as a basis for how we should think, talk about and assess this phenomenon in clinical practice.

The term hyper-resistance expresses both a non-neural (tissue-related) and a neural (central nervous system-related) component that contributes to the clinical interpretation, Figure 3.[45] The non-neurological component of muscle hyper-resistance consists of secondary changes in the muscle that are likely to have occurred because of that the muscles trying to adapt to the neural dysregulation, which can be further described as a maladaptation. Evidence of treatment aimed at affecting spasticity has been published in several scientific systematic reports.[8,10] However, although it is recommended that the term hyper-resistance be used, spasticity is still the term used in clinical praxis and in the everyday language among healthcare professionals.

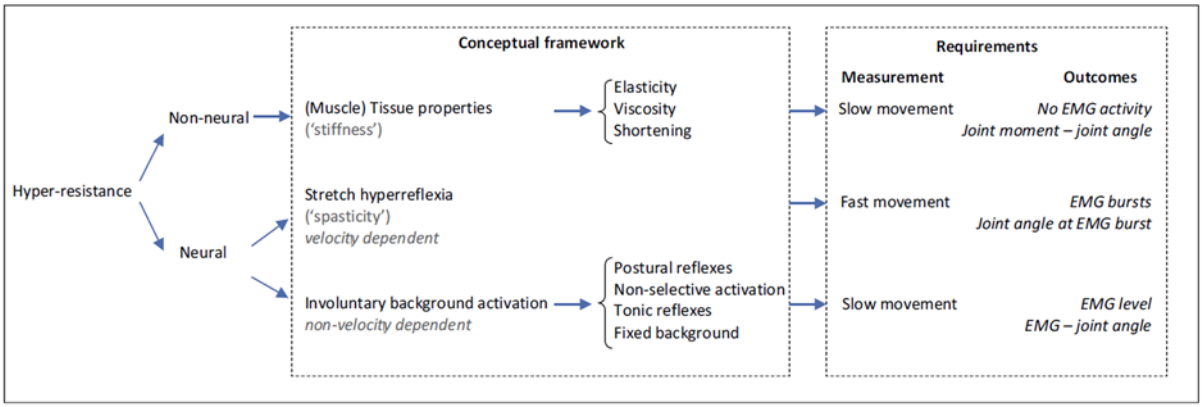


Figure 3. Conceptual framework of hyper-resistance (European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch, 2017). This figure is reprinted with permission provided by John Wiley and Sons and Copyright Clearance Center.

2.5.6 Cerebral palsy and muscle contractures

Passive range of motion restrictions that may be manifested among children with CP may be defined as skeletal muscle contractures. A skeletal muscle contracture can be described as a permanent shortening of a muscle-tendon unit, which results in a loss of elasticity, viscosity and, in worse cases, a joint deformation.[46] Contractures were previously often reported to be a result of spasticity.[47] However, the underlying pathology of muscles in children with CP is complex and today we know that there are factors other than spasticity behind contracture development because contractures also occur in individuals without spasticity.[48,49,46] Muscles in children with CP are differently affected by the neurological condition i.e. location and distribution of the lesion. The muscle size is also different between different individuals, which means that each individual has a unique set of muscles.[50,51]

The origin of the development of skeletal muscle contractures is inconclusive. It has been argued that changes in the muscles of children with CP are primarily due to an altered neurological input which may in turn lead to maladaptation in the muscles. Recent reports shows that skeletal muscle contractures may occur in children with CP as a result of a combination of impaired muscle growth and altered muscle adaptation (maladaptation), a consequence of deficits at the cellular level, Figure 4.[52,53,51,42]

Impairments in the affected muscle are thought to be due to a modified and reduced number of muscle satellite cells, changes in sarcomere length, expansion of the extracellular matrix (ECM) around the fibre bundles and increased amount of pro-inflammatory cytokines. These phenomena are further manifested as impaired muscle growth and smaller, stiffer and weaker muscles compared to typical developed muscles.[54,55,56,46] An estimated decrease in muscle size of 12–43% and decreased strength of 65% in the forearm flexors have been reported.[54,57] However, the muscle impairments in terms of muscle volume seem to be due to smaller fiber diameter or on fewer muscle fibers in children with CP compared to typical developed children. However, the muscle volume[50] varies between different functional levels in children with CP, where muscles in children within the lowest levels of function usually showing the largest reduction in muscle volume.[51]

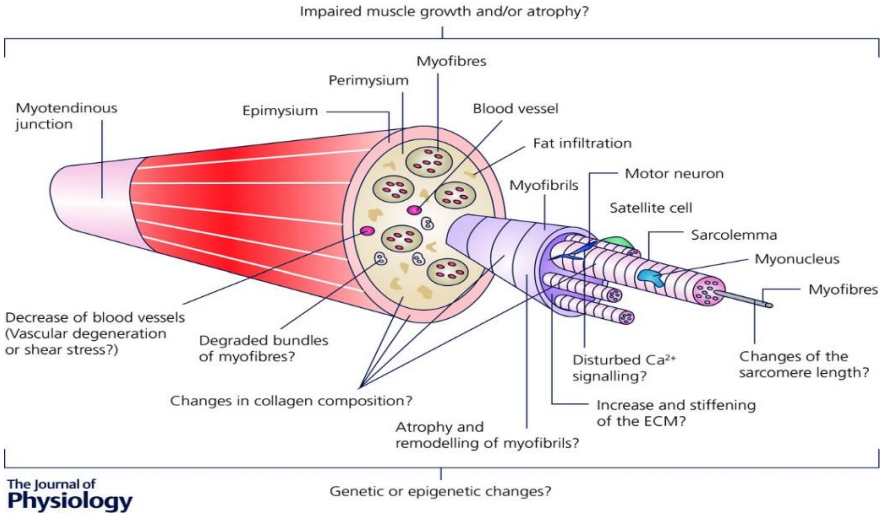


Figure 4. Summary of the current but unresolved questions regarding the development of muscle contractures. This figure is reprinted with permission provided by John Wiley and Sons and Copyright Clearance Center.

Initially, muscle growth in children with CP follows that of typically developed children, but the growth already decreases in toddlers at 15 months of age.[50] Since children with CP are growing, their bones are growing more in relation to the muscles due to the decreased muscle growth, this may be a contributing factor to the development of contractures in children with CP.[50] This means that the muscles of the older children often become weaker, more tired and less tolerant to exercise.[58] Discussions about interventions to promote muscle growth and thereby promote pROM development in children with CP are ongoing.[51] Early interventions such as active movements in daily life and muscle strength training that stimulate muscle growth in young children with CP may be an important contributor in preventing contracture development.[51]

Furthermore, the pathophysiology of skeletal muscle with contractures may be either the cause of the contracture or, more likely, a parallel phenomenon where a neural and non-neural component together affect the muscle in different ways.[59,60] In addition, the possibility of clinically distinguishing changes due to pathological changes in the skeletal muscles from increased muscle overactivity is difficult, but necessary to ensure the choice of appropriate intervention for children with CP.[61]

2.6 CLASSIFICATION OF FUNCTIONAL ABILITIES

In addition to the diagnostic criteria, it is recommended that functional classifications be used for a more complete description of the child's common characteristics.[20] Classifications are useful to describe and group individuals into levels according to common characteristics. Their primary purpose is to discriminate variations and levels of disability. In the field of developmental disability within CP, children with the same health condition, for example CP or CP subtype may vary in their functional abilities.[20] The classifications of functional ability contributes with a picture of what the children actually do in their motor activities and describe children’s usual activity performance instead of focusing on the children’s limitations. The classifications are not intended to assess change but have proven to be stable over time, which makes them useful to describe groups or individuals and as a predictor for the future in terms

of predicting later motor functions.[62,63,64] Several different classifications are used today to classify levels of function or abilities in individuals with CP, e.g. Manual ability classification system (MACS), Bimanual Fine Motor Function (BFMF), Gross motor function classification system (GMFCS), Eating and Drinking Classification System (EDACS), Communication Function Classification System (CFCS). None of these classifications are developed to be considered as a test or an outcome measure, they are solely a classification system. The MACS and GMFCS classifications are used in this thesis.

2.6.1 Manual Ability Classification System

The MACS classifies children's ability to use their hands to handle objects in everyday activities. It describes five levels of manual ability at a five-point ordinal scale (I-V), ranging from level I, which is the highest level of manual ability and means that the child is able to handle objects easily, through to level V, which is the lowest level of manual ability and means that the child has severe limitations and is not able to handle objects independently (Table 1).[65] The MACS is reported to have excellent inter-rater reliability among therapists, and between parents and therapists[65,63] as well as good stability over time.[63,65,64]

Table 1. Manual Ability Classification System (MACS) for handling objects.

Level	Description
I	Handles object easily and successfully. *At most, limitations in the ease of performing manual task requiring speed and accuracy. However, any limitations in manual abilities do not restrict independence in daily activities.*
II	Handles most objects but with somewhat reduced quality and/or speed of achievement. *Certain activities may be avoided or be achieved with some difficulty; alternative ways of performance might be used but manual abilities do not usually restrict independence in daily activities.*
III	Handles objects with difficulty; needs help to prepare and/or modify activities. *The performance is slow and achieved with limited success regarding quality and quantity. Activities are performed independently if they have been set up or adapted*
IV	Handles a limited selection of easily managed objects in adapted situations. *Perform parts of activities with effort and with limited success. Requires continuous support and assistance and/ or adapted equipment, for even partial achievements of the activity.*
V	Does not handle object and has severely limited ability to perform even simple actions. *Requires total assistance.*

2.6.2 Gross motor function classification system

GMFCS is also based on five levels, describing the highest and lowest level of functioning (I-V) but classifies gross motor function with an emphasis on sitting and walking. The lowest level (GMFCS I) indicates the highest ability which means that these children do not require any mobility devices to walk or move while the highest level (GMFCS V) indicates the lowest level of gross motor function and means that these children require the use of a wheelchair in all settings for their mobility and that they are limited in their ability to maintain positions and control leg and arm movements.[66,64,67] GMFCS is reported as having high validity for prediction

of gross motor function inter-rater reliability,[68] test-retest reliability and good content validity.[68,69]

2.7 CPUP- CEREBRAL PALSY FOLLOW-UP PROGRAMME AND REGISTRY IN SWEDEN

Already in the early 1990s, the benefits of keeping population-based registers of individuals with CP were highlighted. Mutch and colleagues mention that if we can describe and classify the population in a standardised way, in the future we will be able to accelerate the development of diagnosis, identify changes over time and get important information about interventions for individuals with CP.[24]

In 1994, a national register and follow-up programme for children with CP (CPUP) was started in the south of Sweden as an attempt to reduce the number of contractures and deformities seen in children with CP. In 2005 this follow-up up programme was also classified as a national quality registry by the National Board of Health and Welfare, still referred to as CPUP. CPUP covers 95% of all children below 18 years of age with CP in Sweden. The primary goal of CPUP is the prevention of both hip dislocation and severe contractures in children with CP. A further aim is to describe the progress and functioning of individuals with CP over time, as well as to promote interprofessional teamwork.[70] Children with suspected diagnosis of CP are offered participation in the registry as early as possible. The diagnosis is confirmed by neuropediatricians from the child's 4th birthday according to the inclusion/exclusion criteria of SCPE.[27] Children who turn out not to have CP are then removed from the follow-up programme – generally less than 2%. Within CPUP, most children are assessed by their physical and occupational therapists at their local paediatric rehabilitation centre once a year if the child is classified as GMFCS I and twice a year until the age of 6 if the child is classified as GMFCS II-V and once a year after that. At 16–18 years of age, the participants can continue in the follow-up programme for adults.[70]

The CPUP registry uses a "traffic light system", see Table 2 to detect the start of pROM deterioration and to alert care givers before a restricted range of motion or a contracture is present. The objective of detecting early musculoskeletal impairments is to apply proper treatment at the right time with the goal of diminishing, or if possible, even preventing contracture development or preventing hip dislocation. The limits for "green, yellow and red" have been arbitrarily set according to clinical experience with some allowance for measurement errors. The green level indicates a good/normal range, including a measurement error variance. The yellow level indicates an early alert, a start of a pROM deterioration, i.e. that the pROM is mildly affected. The red level indicates a severe decrease of pROM.[70]

Table 2. CPUP traffic light system, critical values for the UL.

Movement	Red/ contracture	Yellow/ contracture	Green/ normal
Shoulder flexion	≤ 120°	> 120° < 160°	≥ 160°
Elbow extension	≤ -30°	> -30° < -10°	≥ -10°
Forearm Supination	≤ 45°	> 45° < 80°	≥ 80°
Wrist extension/ flexed fingers	< 0°	> 0° < 60°	≥ 60°
Wrist extension/ extended fingers	≤ -20°	> -20° < 60°	≥ 60°

2.8 CLINICAL ASSESSMENTS OF UPPER LIMB FUNCTION AND ACTIVITY IN CHILDREN WITH CP

There is a multitude of assessment tools that can be used to assess UL function and activity in children with CP. A basic rule before selecting assessment tools is to carefully consider what we want to know and how we want to use the information. It is important to decide what kind of assessment is best suited to answer our questions. The purpose of the test and the purpose of the assessment should match. Furthermore, the psychometric characteristics of an instrument must be considered based on the population to be assessed. Evidence supporting the fact that an assessment will produce valid and reliable measures is a prerequisite for the outcome measures to be useful and credible.[71]

Goniometry is a common instrument used to quantify range of motion and change over time. The design of the goniometer and the procedures for its use have been described in detail in manuals and publications.[72] However, the reliability and validity of this instrument have been much debated,[73] also regarding ROM measurements in people with CP.[74] In general, we can assume that the intra-rater reliability, i.e. repeated measurements by the same rater vary less than measurements performed by two or multiple raters, inter-rater reliability, and that reliability is improved if an experienced therapist conducts the assessment based on standardised manuals.[75,76] Further test-retest of the instrument may be of importance to consider while evaluating pROM measurements over time and when the rater can be expected to differ from time to time.[76] Still, goniometric measurements are widely used and are usually the only option available to measure range of motion in clinical settings. Data collected from CPUP are based on repeated measurements performed in standardised positions for each joint.

To assess active hand function in individuals participating in the CPUP registry, Functional Classifications is commonly used, which describes aspects of hand function in a functional way. To assess the thumb function, House's thumb-in-palm deformity classification is used.[77,78] To assess the functional grasp in each hand separately, the House functional classification is used.[77,78] The Zancolli classification of posture of the wrist and hand in simultaneous wrist and finger extension is commonly used to examine active movement ability.[78]

Most standardised paediatric assessments for the ULs aim at capturing the child's optimal capacity, rather than measuring spontaneous UL activity in daily life, for example the Box and block-test, etc.[79,80,81] The only assessments today that assess spontaneous use/activity of the UL are assessments that are a part of the Assisting Hand Assessment (AHA) family.[82,83,79] However, these assessments are performed in a clinical setting and not in the children's daily lives. All these tests are based on clinical observations by a therapist, conducted in an adapted/controlled environment. Since many interventions today aim at improving activities in daily life, assessments that evaluate the activity or use of the UL in the children's everyday environment are required. Further, evaluation tools that objectively assess UL activity and UL use in daily life may provide new information, complementing clinical assessments.[84,85] In this thesis four different assessments are used, goniometry, AHA, BBT and accelerometry.

2.9 OBJECTIVE ACCELEROMETRY METRICS OF ACTIVITY

There is a variety of methods that objectively record movements of the body, for example three-dimensional movement analysis (3DMA)[86] and infrared reflective markers.[87] However, most of these methods do not provide information about activity outside the clinical test setting, i.e. in the daily life environment.

Both clinical tests and objective methods used in clinical settings may not at all reflect spontaneous activity in daily life. Since many treatment interventions today aim to improve activity performance in daily life, assessments that evaluate children's spontaneous UL activity in daily life are in demand.[13,88]

Accelerometry has been widely used for measuring health related aspects of physical activity, e.g. number of steps and time spent in sedentary, light intensity physical activity (LIPA) and moderate-to-vigorous physical activity (MVPA).[89,90] Recently, accelerometry has also been used to measure voluntary body activity of the ULs, such as UL bimanual-activity, and are reported to be a robust measure of UL activity.[91,84,92,85] Accelerometers are designed as small wearable devices that register activity as acceleration related to gravity in a multidimensional coordinate system with respect to amplitude and frequency. Accelerometer devices can be worn for a longer period to evaluate activity in different body parts, for example UL activity in daily life. This new information may complement existing assessments performed in clinical settings.[93] The use of accelerometry for children with unilateral CP in clinical practice is limited but objective information about activity in daily life is requested.[13]

Image. Accelerometry device from actigraphcorp.com

Accelerometry has previously been used to evaluate UL asymmetry in bimanual activities.[91,84] Different accelerometry-based metrics such as asymmetry index (AI), i.e. how much of the total activity (intensity) of the non-affected UL is used in relation to the affected UL and relative use (i.e. how much time one UL is used in relation to the other) has been proposed, but there is still no consensus on which of these propositions that best describe the disturbances of bimanual activities within children with US-CP.[91,85,94]

2.10 RELIABILITY AND VALIDITY

The quality and usefulness of an assessment/measurement is described by its psychometric properties; reliability, validity, and responsiveness to change. The reliability is referred to the degree to which the outcome of the assessment is free from measurement error. If the outcome of an assessment is reliable, it means that it produces consistent results i.e., high agreement between and within raters and between different time points.[95] Correlation coefficient of >0.8 corresponds to strong, 0.6 -0.7 to moderate, 0.3-0.5 to a fair and 0.1-0.2 to poor association.[96,97]

Although, if the outcome of an assessment is considered reliable, this does not automatically mean that the assessment instrument is valid, i.e., how well the assessment measures the construct it is intended to measure.[98,71]

2.11 BOTULINUM NEUROTOXIN A

Currently, botulinum neurotoxin A (BoNT-A) is a widely used medical treatment option that aims to reduce muscle overactivity, i.e. spasticity, and therefore promote pROM, and to promote functional improvements, reduce pain and facilitate care in children with CP.[99] This toxin is extracted from bacteria Clostridium botulinum and is described to cause a local temporary chemical denervation at the neuromuscular junction by blocking the release of the neurotransmitter acetylcholine as resulting in reduced over-activity in the target muscles.[100] Already in the 1940s, the effects of the botulinum toxin were known to produce neuromuscular blocks.[101] BoNT-A may serve as a door opener and create better possibilities for adjunctive interventions.[102] In contrast, BoNT-A has also shown side effects such as undesirable weakness in adjacent muscles, impaired muscle control, and difficulty to perform activities of daily living has also been reported.[103]

The timing and use of botulinum toxin to affect motor function in children and adolescents with cerebral palsy are inconclusive.[5,104] Most of the clinical reports on BoNT-A use in children with cerebral palsy have focused of short-term effects, which is insufficient to understand the benefit-harm balance of the effects obtained.[105,106] Despite this, it is reported that BoNT-A can be effective in reducing muscle over-activity over a longer term. However, these results do not support that BoNT-A treatment would preventing contractures since spasticity alone does not seem to be coupled to contracture development.[107] In contrast, other authors have assumed that BoNT-A treatment may provide benefits in terms of motor improvements.[108,109] Further, children at a young age seem to benefit the best from BoNT-A treatment, although the reason why has not been sufficiently investigated.[110] Improvements are often described as short lived

and may also be related to the use of orthoses, intensive therapy and other adjunctive interventions.[111] Recommendations in what aspects to consider in relation to CP-subtype, functional level, treatment goals, etc. prior to the decision to commence BoNT-A treatment have previously been debated.[43,112,7,5] Subsequently, while we gain new knowledge about how BoNT-A affects muscles in children with CP, these recommendations need to be updated continuously.[112,113,114,105,115]

3 RESEARCH AIMS

3.1 OVERALL AIM

The overall aim of this thesis was to generate new knowledge that can describe the pROM change over time, contracture development and identify related physical characteristics for upper limb botulinum neurotoxin A treatment in children with CP, and to further evaluate UL accelerometry metrics in daily life.

3.2 SPECIFIC AIMS OF THE RESPECTIVE STUDY WERE AS FOLLOWS:

I. To investigate the longitudinal development of passive range of movements in the arm/hand in a whole population of children with CP, as well as to calculate the relative risk for contracture development with correction of the effect of age, functional level (GMFCS and MACS) and CP-subtype.

II. To describe the use of UL botulinum neurotoxin A treatment in a population-based sample of children with cerebral palsy, by investigating whether physical characteristics may be related to a first UL BoNT-A treatment and whether passive range of motion is related to a first BoNT-A treatment after adjustment for confounders.

III. To investigate UL pROM change over time in children with CP, treated or not treated with BoNT-A, and if there were any differences in pROM development in children who received their first UL BoNT-A at 1–3 years compared to children receiving their first UL BoNT-A at 4–15 years of age.

IV. To describe accelerometry-based metrics and evaluate the association between upper-limb clinical tests and UL AI in children with unilateral cerebral palsy. Additionally, to describe the acceptability of using accelerometers in daily life.

4 MATERIALS AND METHODS

Table 3. Methodological overview of the four studies.

Objective	**I.** Upper limb contracture development in children with CP, a population-based longitudinal study	**II.** Physical characteristics and upper limb treatment with botulinum neurotoxin A in children with cerebral palsy: a population-based study	**III.** Upper limb passive range of motion over time in children with cerebral palsy age 1 to 15 years old, treated or not treated with botulinum neurotoxin A – a population-based study	**IV.** Evaluation of upper limb accelerometry metrics of activity in daily life in children with unilateral cerebral palsy
Design	Longitudinal population-based registry study	Longitudinal population-based registry study	Longitudinal population-based registry study	Cross-sectional study with convenience sample
Number (n)	n = 771	n = 496	n = 496	n = 20
Target population	Children with unilateral, bilateral, dyskinetic, ataxic or non-classifiable CP, 0–18 years of age	Children with spastic or dyskinetic CP 1–15 years of age	Children with spastic or dyskinetic CP 1–15 years of age	Children with unilateral CP, 4–18 years of age
Statistical analysis	Logistic regression analysis, Mixed model ANOVA	Logistic regression analysis	Mixed model ANOVA	Spearman correlation coefficient, Mann-Whitney U-test
Inclusion period	2002–2014	2000–2017	2000–2017	2018–2021
Data collection	Data of age, sex, CP-subtype, MACS level, GMFCS level, pROM measurements were obtained from the national CPUP registry	Data of age, sex, CP-subtype, MACS level, GMFCS level, UL BoNT-A, pROM measurements were obtained from the national CPUP registry	Data of -age, sex, CP-subtype, MACS level, GMFCS level, UL BoNT-A, pROM measurements were obtained from the national CPUP registry	Data of age, sex, MACS level, clinical assessments, activity monitoring, questionnaire
Outcomes	pROM degrees	UL BoNT-A treatment, median time between entering the CPUP and the first upper-limb BoNT-A treatment	pROM degrees, pROM category	AHA-units, BBT-AI, accelerometry-based metrics-AI, relative use, acceptability

4.1 STUDY DESIGNS

This thesis consists of four studies, in which two different study designs have been used, 1) longitudinal studies and 2) cross-sectional study. These study designs have both opportunities and limitations. Below is a brief presentation of the included study designs and these strengths and weaknesses.

4.1.1 Longitudinal population-based study design

Study I, II and III were longitudinal population-based registry studies with data obtained from the Swedish national CP follow-up programme and registry (CPUP).

In study I, all children reported into CPUP, living in the southern part of Sweden (Region Skåne) were included. Measurements of the children's passive range of motion were evaluated longitudinally over a 12-year period.

In studies II and III, only children with spastic or dyskinetic CP subtype from five Swedish regions were included (Sörmland, Västmanland, Halland, Västerbotten, Örebro). Physical characteristics in relation to a first UL BoNT-A occasion were evaluated in study II whilst pROM changes over time were evaluated for three different groups in study III.

Population-based studies may be registry-based, in which a defined population can be followed up and observed at specific time points or longitudinally to assess development or changes over time and exposure to interventions and treatments, e.g. range of motion and MACS level in relation to treatment with BoNT-A. These studies can be used in many different areas that can be generalised within a specific population. Data are usually collected systematically on repeated occasions, which enables the analyses of patterns and trends over time, for example changes of range of motion. The degree of coverage of the register is important for the sample to be representative of the population with the specific condition.[116]

However, population-based data collection tends to lack certain information and more detailed data, e.g. data on which specific muscles that have been treated with BoNT-A, or be of non-standard quality e.g. contain information that is not valid or reliable.[117] Missing data may lead to bias and confounding, and how they are handled should be carefully described in registry studies. There may also be regional differences in reporting frequency to registers due to access to different professions, the geographical location of the region, etc. Moreover, research questions may be limited depending on available data.[116] In Sweden, all 21 healthcare regions offer systematic follow-up through CPUP, over 95% of the families agree to participate and the annual reporting rate by occupational therapists and physiotherapists is around 90%.

4.1.2 Cross-sectional study design

Study IV used a cross-sectional study design, where children with US-CP were invited from two regions (Sörmland and Västmanland) in Sweden. Data were obtained at a specific time point in the clinical setting and in daily life. UL activity asymmetries were evaluated with clinical tests in clinical settings and accelerometry metrics in both clinical settings and in daily life.

Further, associations between outcome measures in clinical tests (AHA-units and BBT asymmetry index (AI)) and accelerometry-based metrics AI in clinical settings and daily life were evaluated. A questionnaire was used to investigate the participants' experience of using the accelerometry method in daily life.

Cross-sectional studies are observational in nature and may be either descriptive or analytical, investigating a group of subjects at a specific point of time or to assess associations between different parameters. The study design is particularly useful in studies describing or comparing

different measurement instruments or individual characteristics, for example.[118] It is possible to use the cross-sectional study design for hypothesis testing of whether for example different characteristics are associated to each other in a positive or negative direction. Correlational analyses are commonly used in cross-sectional studies such as Pearson correlation coefficient or Spearman's correlation coefficient. Pearson evaluates the linear relationship and measures the strength and direction of association between two continuous variables while Spearman's correlation coefficient determines the strength and direction of the monotonic relationship between two ranked variables.[119]

4.2 ETHICAL CONSIDERATIONS

4.2.1 Study I, II and III

Studies I, II and III were approved by the Regional Ethical Review Board in Stockholm 2013 (Dnr 2013/1792-31/3).

For studies I, II and III, a permission for data extraction from the CPUP register was obtained from the registry holder and the register owner at Samrådsgrupp för Kvalitetsregister, vårdinformationssystem och beredning (KVB) Region Skåne. https://vardgivare.skane.se/kompetens-utveckling/forskning-inom-region-skane/utlamnande-av-patientdata-samradkvb/.

Since these data were registry based, participants who have consented to have their data reported into the CPUP registry have automatically also agreed that the data in the database may be used for research. No participants in these studies will be able to be identified after the result compilation.

4.2.2 Study IV

Study IV was approved by the Regional Ethical Review Board in Stockholm 2018 (Dnr 2018/2000-31/2).

All participants aged 18 years and parents of participants aged 4–17 was given both written and verbal information about the study. Subsequently, all respondents provided written consent to participate.

Wearing accelerometers on the body could cause some discomfort for participants. Parents of participating children could experience a workload in everyday life. However, accelerometry has been used in previous studies and has not caused complications or inconveniences.

4.3 PARTICIPANTS AND CONTEXT

For study I, CPUP registry data were extracted for all children living in the Southern part of Sweden, 1–18 years, born 1990-2012, who were followed according to the CPUP UL protocol.

For study II and III, CPUP registry data were extracted for children with spastic or dyskinetic CP subtype, born between years 2000 and 2017, age 1–15 years and living in any of the five selected regions in Sweden.

In study IV, all participants were recruited through convenience sampling at the combined orthopaedic and hand surgery appointments, at the local rehabilitation centres in Sörmland and Västmanland in Sweden. Subsequently, 20 children and adolescents, 4–18 years of age, diagnosed with US-CP and MACS level I-III were invited to participate in this study. Before deciding to participate, participants were also informed about which tests (AHA test and BBT) they would perform and about accelerometer measurements that would be taken during four days in daily living. After completing the test period, participants received tickets for the cinema. The criteria of inclusion and exclusion of participants in study I-IV are presented in Table 4.

Table 4. The inclusion and exclusion criteria.

Study	Inclusion criteria	Exclusion criteria
I	1–18 years of age, born between 1990 and 2012, at least two passive range of motion (pROM) measurement occasions between 2002 and 2014. Living in region Skåne.	Preliminary CP diagnosis had later been withdrawn, ≥ 2 measurement occasions
II-III	1–15 years of age, spastic or dyskinetic CP-subtype, at least two passive range of motion (pROM) measurement occasions between 2000 and 2017. Living in region Sörmland, Västmanland, Halland, Västerbotten or Örebro.	Preliminary CP diagnosis had later been withdrawn, Ataxic CP subtype or non-classifiable, ≥ 2 measurement occasions
IV	4–18 years of age, unilateral CP subtype, MACS level I-III. Living in region Sörmland or Västmanland.	Bilateral CP, dyskinetic CP, ataxic CP, MACS-level IV-V

4.4 SAMPLE SIZE

In study I, all available data of children in the CPUP registry in the southern region of Sweden (region Skåne) were included. This cohort was the first to introduce a register for individuals with CP and thus has included the largest age range for children with CP, therefore data from this region were chosen. In this region 978 children were examined whereof 207 were later excluded since their preliminary CP diagnosis had been withdrawn or since they had less than two pROM measurement occasions recorded between 2002 and 2014 in the CPUP registry. Thus, 771 children remained to be further analysed.

In studies II and III, data from five regions in Sweden were chosen since these five regions had been involved in a quality assurance check, in which CPUP registry data were compared with data in children's medical journals to confirm that children with CP treated with UL BoNT-A had also been registered in the CPUP registry. The assurance check was valuable to ensure the validity of the included data. Of a total of 554 children with two or more measurement occasions between 2000 and 2017, 58 children were excluded since their preliminary CP diagnosis had later been withdrawn or since they had an ataxic CP subtype, non-classified CP

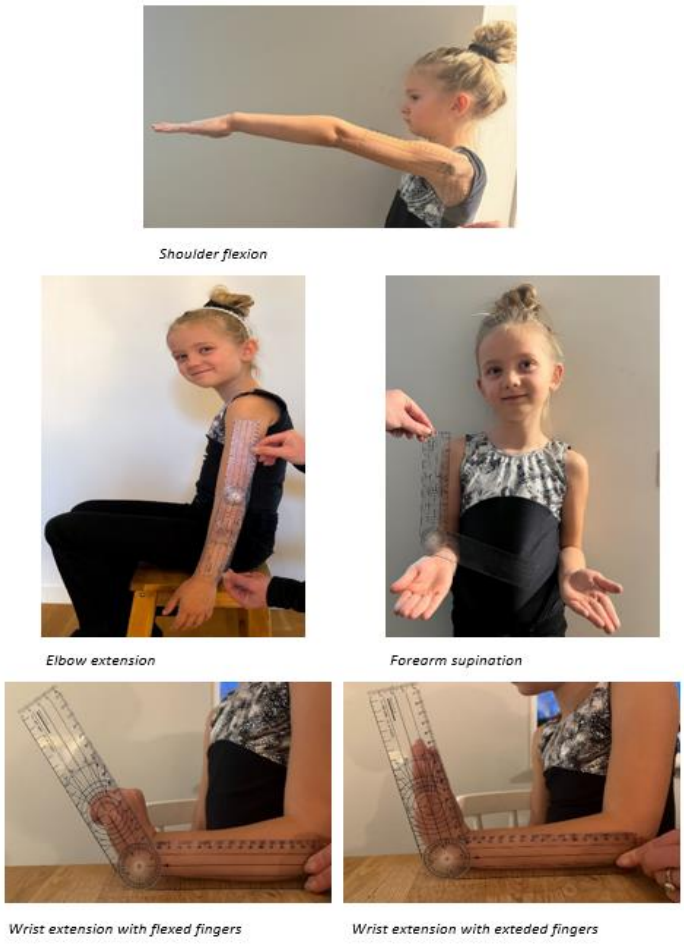
or less than two measurement occasions. Thus, 496 children with symptoms of spasticity or dyskinesia remained for further analysis.

In study IV, it was decided that it was reasonable to include a clinical convenience sample of 20 children with US-CP from two regions in Sweden (region Sörmland and region Västmanland) during a two-year period. This sample size determination was based on the fact that the data to be collected were extensive.

4.5 DATA COLLECTION

In studies I-III, all included data were anonymised and extracted from CPUP registry and distributed via patient-secure data transfer from Region Skåne. Further, the data were transferred to SPSS statistics and saved in a confidentially protected digital folder within the Region Sörmland.

For study I, extracted data comprised of CP subtype, MACS and GMFCS level, age at every measurement occasion (examination) and pROM measurements of the left and right UL from the first measurement occasion until the last measurement occasion for *shoulder flexion, elbow extension, forearm supination, wrist extension with flexed fingers and simultaneously wrist and finger extension*.



Images of shoulder flexion/abduction, elbow extension, forearm supination, wrist extension with flexed fingers and simultaneously wrist and finger extension. With permission from participant (Lea Hedberg) and her parents.

For studies II-III, extracted data comprised, CP subtype, MACS and GMFCS level, age at every measurement occasion (examination), age at first UL BoNT-A occasion and pROM measurements. Passive ROM measures were extracted from children's first measurement occasion until their last measurement occasion for *shoulder flexion/abduction* (the mean values of these two movements were used), *elbow extension, forearm supination, wrist extension with flexed fingers and simultaneously wrist and finger extension*.

In study IV, demographic data of sex, MACS-level and affected/non affected side were obtained from the participants' medical records. For further processing, the data was collected by clinical tests (AHA test and BBT), by accelerometer devices and by a questionnaire. During the clinical tests, two accelerometer devices were placed on the participant, one on each wrist. Subsequently, the participants also wore the accelerometer devices in their daily life. In daily life, the participants wore three accelerometer devices, one on each wrist and one around the waist. The participants recorded in a diary when the accelerometer devices were removed and whether any special activities such as a shower or football training had been performed during the daily life.

Questions about acceptability of accelerometry in daily life were collected in a questionnaire. The questionnaire was completed by the participants during the four days when the accelerometers were used in daily life. Completed questionnaires were handed in at the same time as the accelerometer devices were handed in to the first author.

4.5.1 Clinical assessments

An overview of the different assessments used in study I-IV is presented in Table 5.

Table 5. Assessments used in the thesis. [a] Goniometry measures of range of motion, [b] Assisting Hand Assessment (AHA), [c] Box and Block test (BBT), [d] Accelerometry and a [e] questionnaire.

Test/ Instrument	Outcome measure	Purpose/ ICF domain	Type of instrument	Target group and age
[a] **Goniometry**	Degrees	**To measure the arc of passive and active range of motion.** Landmarks are defined depending on which joint is meant to be measured ICF: Body function	Descriptive and evaluative of ROM	Generic Valid and reliable
[b] **AHA (β-version 5.0) Assisting Hand Assessment (AHA).**	AHA-units	To assess how effectively a child with unilateral CP spontaneously uses his/her assistant hand when handling objects that require bimanual hand use. Measures bimanual performance ICF: Activity	Video-recorded observation of bimanual play for children 18 months to 5 years, for children 6–12 years with a board game. For adolescents 13–18 years, Ad-AHA present task. Outcome measure: Total score 0–100	Excellent reliability and validity for children 18 months to 18 years with unilateral CP
[c] **Box and Block Test (BBT).**	Number of blocks	**To measure unimanual capacity in terms of time-determined motor skills.** Assessment of gross manual dexterity and what the child can do on request when blocks are moved from one box to another on time. ICF: Activity	The number of blocks moved from one part of the box to another in 60 seconds is recorded separately for each UL. Outcome measure: Number of blocks unaffected/affected arm/hand.	Valid and reliable for children and adolescents, 3–19 years. Normative scores provide age references for typically developed children
[d] **Accelerometry**	Vector magnitude counts (VM) Asymmetry Index (AI)	**Objective metrics of activity** To register activity as acceleration related to gravity in a multidimensional coordinate system with respect to amplitude and frequency ICF: Activity	Wearable devices that can be placed in different places on the body. Registers activity, e.g. arm movements.	Valid and reliable objective measure of voluntary UL activity in children with unilateral CP in all ages.
[e] **Questionnaire**	Experience	**Acceptability of accelerometry in daily life**	Answer is given on a 5-point Likert scale. Rating from a negative to a positive experience.	Developed for the target group in study IV

4.5.2 Goniometry measures

Goniometry measures, see Table 5 reported to the CPUP registry of UL pROM (shoulder, elbow, forearm, wrist and simultaneously wrist and finger movements) were taken by using a

goniometer in accordance with instructions in the CPUP measurement manual. The manual is based on Norkin and White guidelines.[72] Elbow extension, forearm pronation and supination measures demonstrated to be less than 0 degrees were recorded as negative values.

Since many different raters i.e., therapists have been involved over the years in reporting the data in CPUP; there is a risk of measurement errors. Passive ROM measurement errors of 10° to 15° have previously been reported for children with CP, even for intra-rater measurements.[74,72]

4.5.3 The Assisting Hand Assessment (AHA)

The AHA, see Table 5, was used in study IV as one of two clinical assessments. The AHA test assesses spontaneous bimanual performance in individuals with US-CP, 18 months – 18 years of age. AHA is scored from video recordings of the test session. Different test situations, adapted for different age groups are scored in 20 items according to a 4-point rating scale. The affected UL is scored on actions such as initiation of use (fast or delayed), choosing assisting hand when closer to objects (easily and readily or uses non-affected hand), holding (actively or passively), grasping (from the table surface or from the non-affected hand), stabilising by grasp (objects stable or objects slipping), releasing (to the table or to the non-affected hand), readjusting grasp (often or seldom). The raw scores are converted to interval logit measures on a 0–100 scale reported as AHA-units, where a higher measure indicates better bimanual ability and a lower asymmetry. The results of the AHA test represent how effectively a person with US-CP uses the affected UL in bimanual activities.[79,82] The AHA 5.0 has been evaluated for internal construct validity by Rasch Model analysis and for interrater reliability, test-retest reliability, alternate forms reliability and smallest detectable difference.

4.5.4 Box and block test (BBT)

The second clinical test used in study IV was the BBT that assesses the upper limb dexterity of each upper limb separately. The results represent how many blocks are transferred from one side of a box to the other in 60 seconds. The BBT is a test of capacity of speed of movement of the upper limb for example to grasp, hold, and release blocks as fast as possible. The number of blocks that the participant transfers with the affected and non-affected UL respectively represents the outcome measures for the BBT. The test is reported to be a reliable, valid for children and adolescents of 3–19 years of age, clinically applicable assessment for children with CP, and may in part reflect the child's UL activity in daily life activities.[120]

4.5.5 Accelerometry metrics

The ActiGraph GT3X monitor (ActiGraph Corp, Pensacola, FL, USA), see Table 5, can be used as an objective measure of UL bimanual activity during different physical activity (PA) levels. The accelerometer is a device the size of a wristwatch that can be placed on different body parts, for example ULs, over a shorter or longer period of time. The devices are able to capture activity across three axes during a predetermined sampling rate (Hz) and time intervals (epochs). Further, the accelerometry metrics from the three axes can be combined to a vector magnitude (VM) for a total sum of the three axes defined as $\sqrt{(x2+y2+z2)}$. Accelerometry-based metrics may provide a robust measure of UL activity in children with US-CP.[85,84,91]

4.5.6 Questionnaire

In study IV, the answers in the questionnaire, see Table 5, were given at a simple 5-point Likert scale to collect a range value of the participants' experiences. Likert scales are often used to measure experiences and attitudes and provide answers to a given question or statement. Usually there are 5 answer categories in Likert scales. This non-parametric scale gives ordinal data level scores. These data involve a predetermined ranking of the data, for example positive or negative experience.[121,122]

4.6 PROCEDURES AND DATA MANAGEMENT

4.6.1 Study I

In study I, data of pROM measurements in five UL movements are categorised according to the CPUP traffic light system.[70] The range for each movement and category is defined in the CPUP manual; see paper I, supplementary Table I.

4.6.2 Studies II and III

In study II, the CPUP traffic light system was complemented with a new pROM category, the light-green category. This new category contains measurement values within the green full pROM, but where the movement shows a first sign of muscle shortening in terms of resistance at the end of the movement range. Since the movement withdrawal is done slowly, it is not a sign of a velocity-dependent spasticity that is documented, but rather an incipient stiffness. A green value does not always mean that the movement has full pROM, but rather as a pROM that does not affect function.

The upper limb passive ROM critical values for the colours of the traffic-light system are presented in Table 6. Data of pROM measurements in five UL movements were categorised according to the new CPUP traffic light system for descriptives and analyses. For analyses of pROM changes and contracture development in study III, pROM values were categorised according to the basic original version of the CPUP traffic light system, see Table 2.

Table 6. CPUP traffic light system with the addition of a new light green pROM category.

Movement	Red/ contracture	Yellow/ contracture	Light Green/resistance	Green/ normal
Shoulder flexion/abduction	≤ 120°	> 120° < 160°	≥ 160°	≥ 160°
Elbow extension	≤ -30°	> -30° < -10°	≥ -10°	≥ -10°
Forearm Supination	≤ 45°	> 45° < 80°	≥ 80°	≥ 80°
Wrist extension/ flexed fingers	< 0°	> 0° < 60°	≥ 60°	≥ 60°
Wrist extension/ extended fingers	≤ -20°	> -20° < 60°	≥ 60°	≥ 60°

4.6.3 Study IV

In study IV, clinical tests, i.e. AHA-test and BBT, were video-taped and organised by the first author and conducted by one experienced occupational therapist (OT) at the local rehabilitation centre in Sörmland. Analysis and interpretation of the recorded videos were performed by the OT, who was also responsible for the practical implementation of the clinical tests in the clinical settings.

The first author was responsible for information, handling, i.e. initialising and placing the accelerometer devices in the clinical setting and daily life. During the clinical tests, two accelerometer devices were placed on the body, one on each wrist. During weakening time in daily life, three devices were placed on the body, one on each wrist and one around the waist. After the clinical tests and daily life period had been completed, the collected accelerometer data were transferred into the ActiLife 6.13.4 software program.

Data in clinical setting

Clinical test outcomes from the AHA, AHA-units were used, from the BBT number of blocks and for accelerometry-based metrics, vector magnitude (VM) was used. For calculation of UL asymmetries in clinical test, the AHA-units and an asymmetry index (AI) for the BBT and accelerometry-based metrics were used. AI describes how much of the total activity (intensity) the non-affected UL is used in relation to the affected UL in a clinical setting, while performing the clinical tests and for four days in daily life.[91] An AI value of 0 indicates that both ULs contributed equally to the activity, while a positive value indicates greater contribution from non-affected UL.[91]

$$AI = ((\text{non-affected UL} - \text{affected UL}) / (\text{non-affected UL} + \text{affected UL})) \times 100.$$

Data in daily life

After the completion of the clinical tests, accelerometer devices were handed out to the participants for further registration of activity during wakening time for four consecutive days. The participants had also written verbal information about when and how the devices would be placed on the body during the days of daily life. These data were further converted to MATLAB by one of the co-authors.

Accelerometry data in clinical setting and in daily life

The accelerometer data of each device, from both the clinical setting and from daily life, were converted to 60-second epochs, and the vector magnitude (VM = $\sqrt{x^2+y^2+z^2}$) was calculated by combining activity counts from three axes. The VM from the accelerometer-based metrics during the clinical tests was divided into the AHA test and the BBT, with start and stop times for each test. Further, the daily life accelerometer-based metrics (VM activity counts) were divided into daily segments and a non-wear time algorithm was applied in accordance with recommendations from Choi et al 2011.[123] Accelerometry-based metrics from the daily life were considered valid if there were ≥ 10 hours recorded accelerometry data during one day. The VM activity counts were further divided into three physical activity (PA) levels, sedentary PA; < 100 counts per min, light-intensity PA (LIPA; 100–2012 vertical counts per minute) and moderate-to-vigorous PA (MVPA; > 2012 vertical counts per minute) based upon cut-points developed for children and adolescents with CP.[92] Consequently, the accelerometry-based metrics for each PA level were used for AI calculations. In addition, the accelerometry-based metrics in daily life were also used for descriptive purposes of relative UL use according to 4 formulas (Percentage Bimanual Use, Percentage Non-affected UL Use, Percentage Affected UL Use and Use Ratio, see paper IV, where, $A_{affected}$ is the time interval (epochs) that the affected UL was active and $A_{non\text{-}affected}$ refers to the epochs that the non-affected UL was active, and A_{Total} refers to the epochs where at least one of the affected or non-affected UL was active. UL activity was defined if VM was > 100 counts/min.

Associations between clinical test and accelerometry-based metrics

Finally, to evaluate the associations between clinical test and accelerometry-based metrics in the clinical setting and in daily life, the AHA-units, BBT AI and accelerometry-based metrics AI were used. The strength of the correlation coefficient was defined as >0.8 and corresponds to strong, 0.6 -0.7 to moderate, 0.3-0.5 to a fair and 0.1-0.2 to poor association.[96,97]

Questionnaire

A questionnaire including eight questions was specifically developed for the target population in study IV. The questions aiming to investigate participants experience of using accelerometry in daily life. A value of 1 and 2 were considered within the research group as a negative experience, while a value of 4 and 5 were considered as a positive experience. A value of 3 was considered as neither negative nor positive.

4.7 STATISTICS

SPSS (IBM Corp, Armonk, NY, USA) version 22.0 was used for all analyses in this thesis. In study IV, MATLAB was used for analyses of accelerometer-based metrics in daily life. P-values < 0.05 were considered significant for all statistical analyses in this thesis.

Table 7. Overview of statistics used in study I, II, III, IV.

Statistics	**Study I**	**Study II**	**Study III**	**Study IV**
Descriptive				
Counts				✓
Frequencies	✓	✓	✓	✓
Percentage	✓	✓	✓	✓
Mean (sd)	✓	✓	✓	✓
Median (IQR, min, max)	✓	✓	✓	✓
Non-parametric tests				
Spearman correlation				✓
Mann-Whitney U-test				✓
Parametric tests				
Logistic regression	✓	✓		
Mixed model ANOVA	✓		✓	

4.7.1 Study I

The mixed model ANOVA was used in study I to evaluate the longitudinal pROM and contracture development over time among all children 1–18 years at risk of CP or confirmed CP. Passive ROM was used as the dependent variable and outcome measure. Age groups (six age groups divided into three-year intervals) and children were used as independent variables where age group was treated as a fixed variable and child as a random variable. The youngest age group (1–3 years) was used as the reference. The mixed model analyses also included pairwise comparisons of age groups. The fixed variable (age group) was expected to have a constant effect on the dependent variable, while the effects of the random variable (children) was allowed to vary between the different age groups. Further, some of the children had several measurements in the same age group interval. As recommended, a heterogeneous autoregressive variance structure of the random effects was therefore used in estimating the random effects.[124] The analyses were adjusted for CP subtype and MACS level.

To investigate whether their level of manual ability (MACS-level), level of gross motor function (GMFCS-level) or CP subtype affected the probability (crude OR) for the children to develop a contracture (the dependent dichotomous variable), OR from a logistic regression analysis was estimated. The crude OR corresponds to the odds for a specific group, e.g. MACS level V, divided by the odds for a reference group, e.g. MACS level I. In this study the group with the best manual ability, gross motor function and ataxic CP subtype were used as reference groups. To also investigate the independent effect of each of the independent variables when

taking the other ones into account, the OR of these variables was adjusted for the effect of the other independent variables (possible confounders). For the handling of data for pROM measurements, it was decided that only the worst value in one UL, right or left where each movement per child was used, e.g. the forearm supination on one side was compared with the same movement on the opposite side.

4.7.2 Study II

Categorical data were presented as frequencies (n) and percentages (%). The descriptive statistics of the continuous variables were presented as medians and interquartile range (IQR). The associations between the independent variables (CP subtype, MACS and GMFCS levels, pROM category, sex, and age group) and the dependent variable (the likelihood for the children to receive a first UL BoNT-A treatment) was examined. The dependent variable in this method is dichotomous, following a binominal distribution, and thus logistic regression was used. First, crude ORs of receiving a first UL BoNT-A treatment were estimated for all independent variables in a series of simple logistic regression analyses. Then the ORs for pROM category were adjusted for confounders (CP subtype, MACS and GMFCS levels, sex, and age group) since pROM category was of our preliminary interest. For the handling of data for pROM measurements it was decided that only the worst value in one UL, right or left where each movement per child was used, e.g., the forearm supination on one side was compared with the same movement on the opposite side. As for pROM measurements depending on whether the child was bilaterally treated with BoNT-A, or untreated, decision on which side to include in the analysis was made based on which side was the most affected. All movement was treated separately, meaning different sides for different movements could be included in our analysis. If the child was unilaterally BoNT-A treated, that side was always chosen in the analyses.

4.7.3 Study III

In study III, all analyses are based on the same population as in study II. However, in this study a mixed model ANOVA analysis was conducted to investigate the pROM development over time in three groups, children first time UL BoNT-A treated at early age (1–3 years), children BoNT-A treated at later age (4–15 years) and children not UL BoNT-A treated. Passive ROM development was chosen as the dependent variable and the outcome measure as we were interested in. These three groups constituted the independent fixed variable and child was treated as a random variable. The model is adjusted for CP subtype and MACS level. Just like in study I, some of the children had multiple measurements in the same age group interval. Thus, as recommended, a heterogeneous autoregressive variance structure of the random effects was used in estimating the random effects. The pROM data was handled in study III in the same way as in study II.

4.7.4 Study IV

Descriptive information of demographic variables, clinical test data and accelerometry-based metrics were reported with frequencies, means and standard deviations. For estimations of correlations between clinical test and accelerometry-based metrics in clinical settings and in daily life the AHA-units, BBT AI and accelerometry-based metrics AI were used. Since the sample size was small (n = 20) and the data non-normally distributed, Spearman correlation[96]

tests was used to estimate a monotonic relationship between independent variables, while Mann-Whitney U-test was used to evaluate differences of AI between the sedentary time and LIPA and between sedentary time and MVPA.[125]

The answers to the questions in the questionnaire were given on an ordinal Likert scale and reported descriptively with median value, max - min, with frequencies and percentages.

5 RESULTS AND DISCUSSION

In this section the results of the four manuscripts are summarised and discussed.

5.1 CHARACTERISTICS OF THE PARTICIPANTS

Table 8. Descriptive information about age, sex, CP subtype, MACS-level, GMFCS level and affected side in study, I-IV.

	Median [IQR] or mean (SD)	**Age range**	**Frequency (%)**
Study I			
Age	9 y, [IQR 5-12y] 11.8 y (5 mo)	1-18 y	
Male/female			417 (54)/ 384 (46)
CP-subtype			
Unilateral CP			207 (26.8%)
Bilateral CP			277 (36%)
Dyskinetic CP			135 (17.5%)
Ataxic CP			63 (8.2%)
Non-classifiable			10 (1.3%)
Missing			79 (10.2%)
Classifications motor function			
[1] MACS level I, II, III, IV, V, * Missing			268 (35), 169 (22), 112 (15), 87 (11), 126 (16) * 9 (1)
[2] GMFCS level I, II, III, IV, V, * Missing			318 (41), 136 (18), 73 (9), 126 (16), 117 (15) * 1 (<1)
Study II-III			
Age at first measurement occasion (1-15 years)	2 y, [IQR = 1–5 y]	1–14 y	
Age at first upper limb BoNT-A, (1-15 years)	4 y, [IQR = 2.3–7 y]	1–15 y	
Male/female			317 (64)/ 179 (36)
CP-subtype			
Unilateral CP			184 (37)
Bilateral CP			263 (53)
Dyskinetic CP			49 (10)
Classifications motor function			
[1] MACS level 1, II, III, IV, V, *Missing			148 (30),118 (24), 82 (17), 55 (11), 90 (18) * 3 (<1)
[2] GMFCS level 1, II, III, IV, V, *Missing			214 (44), 68 (14), 48 (10), 72 (15), 85 (17) * 8 (<1)
Study IV			
Age	10.3 y (3.8)	4–18 y	
Male/female			11 (55)/9 (45)
CP subtype			
Unilateral CP			20
Classification motor function			
[1] MACS level I, II, III			3 (15), 10 (50), 7 (35)
Affected side			
Right/ Left			12 (60), 8 (40)

[1] MACS-Manual Ability Classification System, [2] GMFCS-Gross motor function classification system

5.2 STUDY I: UPPER LIMB CONTRACTURE DEVELOPMENT IN CHILDREN WITH CEREBRAL PALSY

This was the first population-based study reporting the pattern of UL passive ROM and contracture development over time in children and adolescents with CP. The results were based on 771 children, see Table 8, and a total of 5,040 pROM measurement occasions taken in children between 1–18 years of age. The children were evenly distributed across six age groups and the average number of measurement occasions per child was 6.5. A majority, 80%, had a spastic or dyskinetic CP subtype. More than half of the children (57%) included handled most objects easily or with somewhat reduced quality and/or speed of achievement (MACS I-II) and 41% of the children did not require any mobility assistive technology to walk or move (GMFCS I). See paper I, Table 1 for demographic and clinical characteristics.

5.2.1 Upper limb contractures

One-third (34%) of the children had developed UL contractures (yellow or red CPUP pROM values) over time, see paper I, Figure II, although all children in Sweden have access to free medical healthcare and that most of the children in this study had regular contact with occupational or physiotherapists at local rehabilitation centres.[70] Many of these children included had probably received interventions aimed at contracture prevention or improvement such as stretching, orthotics, botulinum neurotoxin A injections and hand surgery. However, possible intervention effects have not been considered in this study.

5.2.2 Contracture development in five upper limb movements

Contracture development over time was most common in the simultaneous wrist and finger extension movement, where 20% had developed a contracture, Table 9; see paper I. This implies that an imbalance between wrist finger flexors and wrist finger extensors is present, which may affect grip function and makes grasping and performance of tasks in daily life activities difficult, for example holding the bicycle handlebars, climbing trees, building with Legos, dressing a doll, or holding cutlery. Thus, pROM restrictions in the wrist and fingers might have serious functional consequences and steps should be taken to try to prevent them.[126,127,128,126,129]

Table 9. Proportion UL contractures in five movements.

CPUP traffic light system categories/ Movements	Total contractures % (n)	Green/ full PROM %	Yellow/ restricted pROM, i.e. contracture %	Red/ severely restricted pROM, i.e. contracture %
Shoulder flexion	14.5 (110)	85.6	10.4	4.1
Elbow extension	8.9 (68)	91.1	4.2	4.7
Forearm supination	13.2 (101)	86.7	6.4	6.8
Wrist extension/ flexed fingers	9.9 (75)	90.1	7.9	2.0
Wrist extension/ extended fingers	19.4 (147)	80.7	16.2	3.2

5.2.3 Factors related to contracture development

Children with the lowest level of manual ability and mostly no voluntary movements, i.e. MACS level V, appeared to be most likely to develop contractures over time; see paper I, Table II. Further, non-ambulatory children with the lowest level of gross motor function performance, GMFCS V also appeared to be more likely to develop contractures in the ULs; see paper I, Table II. These children have little or no voluntary movements, which probably affects the muscle growth and muscle function from early ages. Rarely or never using one's limbs in active movements has been shown to be a contributing factor to the development of contractures.[50]

Children within the dyskinetic CP subtype surprisingly showed a very high proportion of contractures (46%) compared to the other CP subtypes; see paper I, Table II. This result was unexpected, given that varying movement patterns and varying muscle tone indicate a protection of the muscles from developing contractures.[130,131] However, when we adjusting for GMFCS, MACS levels, CP subtype, it was children with spastic unilateral CP who were most likely to develop UL contractures; Table 10, see paper I, Table II.

Table 10. Proportion of contracture development within GMFCS levels, MACS levels and CP subtypes and related factors (Adjusted OR) for all factors for developing contractures, n = 262.

[1] Factor	Proportion contractures	OR adjusted (Crude OR)	p-value	95% CI
GMFCS level I (n = 318)	18.9	1 (Reference)		
GMFCS level II (n = 136)	31.6	1.5	0.21	0.8, 2.68
GMFCS level III (n = 73)	30.1	1.4	0.47	0.59, 3.09
GMFCS level IV (n = 126)	40.5	1.8	0.14	0.82, 4.12
GMFCS level V (n = 117)	72.6	6.4	<0.01	2.38, 17.20
MACS level I (n = 268)	10.1	1 (Reference)		
MACS level II (n = 169)	32.5	5.0	<0.01	2.82, 8.98
MACS level III (n = 112)	46.4	9.7	<0.01	4.76, 19.89
MACS level IV (n = 87)	47,1	8.2	<0.01	3.63, 18.65
MACS level V (n = 126)	65,1	12.1	<0.01	4.73, 30.96
Ataxic CP (n = 63)	15.9	1 (Reference)		
BS-CP (n = 277)	32.9	3.02	<0.01	1.36, 6.68
Dyskinetic CP (n = 135)	45.9	1.5 (4.5)	0.38	0.61, 3.62
US-CP (n = 207)	30.4	8.2	<0.01	3.39- 19.78

[1] For GMFCS level, MACS level and CP subtype, respectively, the OR is adjusted for each other. OR = Odds ratio, MACS = The Manual Ability Classification System, GMFCS = Gross Motor Function Classification System, BS-CP = Spastic bilateral CP, US-CP = Spastic unilateral CP.

5.2.4 Contracture development in relation to manual ability (MACS-level)

Among children with high manual ability (MACS I-II), contractures were rare, although, a few of these children showed severe contractures, i.e. red pROM values at older ages. As expected, children with low manual ability (MACS V) often developed contractures. However, among these children there was a wide variation and some children never developed contractures; see

paper I, Figure I. Given this variation, it is important that we regularly monitor the children's range of motion, regardless of the child's functional level.[70]

5.2.5 Contracture development over time

The number of children with contractures increased with age and the pROM deterioration in the five movements had a similar steady slope line, with somewhat steeper deterioration in early adolescence. Despite this fact, six percent were very young (1–3 years of age). The pROM deterioration started at 4 years of age in wrist extension (with flexed and extended fingers) and at 7 years of age in shoulder flexion, elbow extension and forearm supination; see paper I, Figure II.

The reason why some children but not all develop severe contractures is not known. We are aware that the muscles in children with CP are different in terms of maladaptation, delayed growth, weakness and less volume compared to muscles in typically developed children.[54,132] One could imagine that contractures arise as a phenomenon parallel to spasticity rather than solely as a result of spasticity as previously assumed. Muscles affected by contractures show I) both an increased amount of extracellular matrix around the muscle's fibre bundles, which may lead to stiffness in the muscle, II) reduced growth, III) smaller number of satellite cells that contribute to building up, recovering, and repairing the muscle, and IV) increased number of cytokines (inflammatory markers). Together, these factors may contribute to the development of contractures in children with CP.[59] These changes in the muscles are thought to occur long before the contracture has developed. Interventions such as orthoses to improve alignment and maintain range of movement and active movements in daily life by stimulating muscle growth in young children with CP may be one of the keys to preventing contractures.[50]

5.2.6 Strength and limitations

This was the first population-based study of upper limb pROM contracture development in children with CP.

In this study, mixed model ANOVA was used to analyse repeated measurements. The method takes into account that the time between the repeated measurements varied in the children and that the children had different numbers of measurements that were included in the analysis. This method also handles missing data.[133]

Although the population in study I was relatively large and showed that the representativeness of our sample in general was good, with a prevalence of CP being 2.3‰ it was still limited by only including children living in the southern part of Sweden included in the CPUP registry. However, this region was the first to implement the CPUP follow up and registry program and included at an earlier time point than in the rest of the country and had more repeated measurements reported over a longer follow-up period.

Since the goniometry pROM measurements of UL in the CPUP protocol are carried out by many therapists, inter-rater reliability needs to be strong. Inter-rater reliability of the pROM measures may be a limitation in this study since an error variation of 10° to 15° has previously been reported for children with CP.[134] Although the measurement error cannot be completely

ignored, it is not likely that it affected the results to any significant degree, since we had more than 5,000 measurement occasions included for 771 children.[74] However, to achieve as large an inter-rater agreement as possible and to ensure the quality of the data reported into the registry, education sessions are organised continuously for therapists around the country. Furthermore, CPUP manuals are available on the CPUP website, which contain detailed instructions on how the measurements are to be conducted. The measurement manual is based on Norkin's recommendations.[72]

In the CPUP UL protocol, a measure of UL spasticity is not included because there is no consensus on how reliable existing clinical spasticity assessments are[135] and no consensus about which spasticity assessment method (e.g. Ashworth, Tardieu, ASAS) provides the best information in clinical practice.[136,135] The level of spasticity would have been an important factor to include in the logistic regression analysis and would possibly have affected the results.

The cut-off values in the CPUP traffic light system used in this study might need further discussion. Although, these cut-off limits seem strict, only one third of all children developed contractures. However, many children that had full pROM probably had difficulties with active movements that are not registered within the traffic light system in the UL CPUP protocol. It might therefore be important to also have a dialogue about active movements, spasticity and the first sign of upper-limb movement restrictions in the UL CPUP protocol.

5.3 STUDY II-III: BOTULINUM NEUROTOXIN A AND UPPER LIMB PASSIVE RANGE OF MOTION IN CHILDREN WITH SPASTIC AND DYSKINETIC CP

This was the first population-based description of physical characteristics that may be related to a first BoNT-A treatment in the upper-limbs in children at 1–15 years with spastic and dyskinetic CP; see paper II. Based on the same population, pROM in the UL was investigated over time, for children who received and those who did not receive UL BoNT-A treatment. The group of children who received UL BoNT-A was further divided into two different groups, a) children treated with UL BoNT-A for the first time at 1–3 years of age (early) and b) children treated for the first time at 4–15 years of age (later). Finally, the differences of pROM development over time between these three groups were evaluated; see paper III.

The results of the two studies were based on 496 children with symptoms of spasticity or dyskinesia with a total of 3756 pROM measurement occasions and 324 UL BoNT-A occasions; Table 12, see papers II and III.

A majority of these children had a spastic CP subtype (90%). About 60% of them had spastic bilateral CP. Most children (54%) in the total population (n = 496) handle objects in everyday life, easily or with minor difficulties (MACS level I-II) and had the ability to perform gross motor skills such as walking independently with minor difficulties or with physical assistance (58%) (GMFCS level I-II). Most children (77%) had full pROM at their first measurement occasion, whereof 30% showed resistance at the end of the movement range. At the last measurement occasion, 64% had full pROM, whereof 18% showed resistance at the end of the movement range; Table 12, paper III.

In this population, 22% received UL BoNT-A treatment. Many of them, 45%, had already had their first treatment occasion before four years of age; Table 12, see paper II. The median age at first BoNT occasion was 4 years, see paper III, which is close to the reported age for children receiving lower-limb BoNT-A treatment.[137]

5.3.1 Proportion of upper limb botulinum neurotoxin A treatment

BoNT-A treatment was most common among children within the US-CP subtype (27%) and among children with lower levels of manual ability and gross motor function. Moreover, those within the red pROM category, i.e. children who had already developed severe contractures had the highest proportion of BoNT-A treatment, 44%; Table 12, see paper II. Offering BoNT-A treatment for manifest severe contractures probably aims to reduce spasticity, to facilitate care or reduce pain.[5]

5.3.2 Upper limb botulinum neurotoxin A treated muscle groups

The muscle group that was most often treated appeared to be the thumb muscles; Table 11, Paper II, Figure I. Despite that, there is a lack of reliable instruments to evaluate thumb function during activity in children with CP. Instruments used today primarily aim to investigate which muscles show increased muscle tone prior to hand surgical treatment. There is thus a need to develop new instruments that also capture aspects of thumb function in activity performance.[138] The least treated muscle groups were the finger flexor muscles and the shoulder muscles; Table 11, paper II, Figure I.

Table 11. Muscle groups (n = 192) first upper-limb Botulinum neurotoxin A treatment occasion (n = 192).

Treated muscle groups at first BoNT-A occasion treated to promote;	**BoNT-A n (%)**
Shoulder flexion/abduction	36 (19)
Elbow extension	48 (25)
Forearm supination	80 (42)
Wrist extension	71 (37)
Simultaneously wrist and finger extension	35 (18)
Thumb extension/abduction	86 (45)

Table 12. Distribution of sex, CP-subtype, MACS level, GMFCS level, pROM category in children UL BoNT-A treated and not treated. [a] pROM first- first measurement occasion at entering CPUP, [b] pROM last- last measurement occasion.

Variables	**UL BoNT-A**		**No UL BoNT-A**	**Total**
	BoNT-A 1–3-year n (%)	**BoNT-A 4–15-year n (%)**	**No BoNT-A 1–15-year n (%)**	***Total n (%)***
Girls	19	18	142 (79)	179 (100)
Boys	30	41	246 (78)	317 (100)
Total CP-subtype	**49 (10)**	**59 (12)**	**388 (78)**	**496**
BS-CP	19 (39)	29 (49)	215 (55)	263 (100)
US-CP	27(55)	23 (39)	134 (35)	184 (100)
Dyskinetic CP	3 (6)	7 (12)	39 (10)	49 (100)
Total MACS- levels	**49 (10)**	**59 (12)**	**385 (78)**	**493**
MACS I	6 (4)	0 (0)	142 (96)	148 (100)
MACS II	12 (10)	17 (14)	89 (75)	118 (100)
MACS III	15 (18)	12 (15)	55 (67)	82 (100)
MACS IV	6 (11)	11 (20)	38 (69)	55 (100)
MACS V	10 (11)	19 (21)	61(68)	90 (100)
Total GMFCS-levels	**48 (10)**	**59 (12)**	**381 (78)**	**488**
GMFCS I	23 (11)	19 (9)	172 (80)	214 (100)
GMFCS II	4 (6)	6 (10)	59 (86)	69 (100)
GMFCS III	4 (8)	1 (2)	43 (90)	48 (100)
GMFCS IV	11(15)	11(15)	50 (69)	72 (100)
GMFCS V	6 (7)	22 (26)	57 (67)	85 (100)
Total Passive range of motion	**49 (45)**	**59 (55)**	**388 (78)**	**496**
Passive ROM green, [a] *first*	15 (6)	7 (3)	209 (90)	231 (100)
Passive ROM light green, *first*	23 (15)	22 (15)	105 (70)	150 (100)
Passive ROM yellow, *first*	9 (11)	18 (22)	56 (67)	83 (100)
Passive ROM red, *first*	2 (6)	12 (38)	18 (56)	32 (100)
Passive ROM green, [b] *last*	14 (6)	7 (3)	208 (91)	229 (100)
Passive ROM light green *last*	11 (12)	7 (8)	72 (80)	90 (100)
Passive ROM yellow, *last*	21 (17)	19 (15)	85 (78)	125 (100)
Passive ROM red, *last*	3 (6)	26 (50)	23 (44)	52 (100)
BoNT-A occasions (n)	172 (53)	152 (47)	0	324
Mean BoNT-A occasions	3.5	2.6	0	0.7
Measurement occasions (Mean)	637	763	2356	3756
Mean measurement occasions	13.0	12.9	6.1	7.6

5.3.3 Related factors for a first upper limb botulinum neurotoxin A treatment

Children with lower levels of manual ability (MACS levels IV-V) were the most likely to be treated with BoNT-A in the ULs at least once, while children with the lowest level of gross motor function (GMFCS V) only had a slightly increased likelihood; see paper II, Table II. These results indicate that gross motor level was less important when decisions about UL BoNT-A had been made. Children with full pROM with resistance at the end of the movement range were also likely to receive a first UL BoNT-A. Consequently, prior to the decision on UL BoNT-A, the children's MACS level and pROM had been taken into account in the first place, which should be of utmost importance; see paper II, Table II when considering goal setting and treatment planning for the individual.[77]

Since we were primarily interested in whether passive ROM category was important prior to deciding on a first BoNT-A treatment, we also adjusted passive ROM category for confounders. After adjustment, the full passive ROM with resistance in the end of the movement range, i.e. the light green pROM category, remained to be related to a first UL BoNT-A treatment; Table 13, see paper II, Table II. Since spasticity is not reported in the UL protocol in CPUP, it is possible that the light green pROM category represents the non-neural component in spasticity that indicates that the elasticity may be affected in the muscle, which may result in stiffness or resistance.[60,139] It was important to highlight these results since our neurologists, hand surgeons and therapists need to discriminate the components underlying spasticity and, in addition, comprehend if and how BoNT-A treatment may affect the different components.[140]

Table 13. Adjusted odds ratio (OR) for pROM category.

Factor	Likelihood/ ADJUSTED Odds ratio (OR)		
[1] Passive ROM categories (n)	OR for BoNT-A	P-value	95% CI
Passive ROM Green category (227)	1 (ref)		
Passive ROM Light Green category (87)	**2.3**	**0.02**	1.2, 4.4
Passive ROM Yellow category (128)	1.5	0.81	0.77, 2.9
Passive ROM Red Category (54)	1.1	0.56	0.40, 3.3

[1] Passive ROM OR adjusted for CP-subtype, MACS-levels, GMFCS-levels, sex and age group.

5.3.4 Time between entering CPUP and first upper limb botulinum neurotoxin A occasion

The median time from entering CPUP until the first UL BoNT-A occasion turned out to be shorter for children treated first time at 1–3 years (median time 15 months) compared to children treated for first time at a later age (median time 35 months); see paper III, Supplementary Figure II. An explanation for this result may be that the children who were treated for the first time at an early age also entered the CPUP at an early age, by 1 years of age, while children treated for the first time at a later age entered CPUP later, at 3 years of age; see paper III, Supplementary Figure II. A confounder that might affect both age at entry into CPUP and age at first BoNT-A occasion may be that children with mild CP (MACS, GMFCS I) are not detected at an early age since they pass through the system and BVC's controller up to higher ages. Early entry into CPUP may bring benefits to the child, such as early contact

with child neurologist and early diagnosis, and also early contact with orthopaedic surgeons, hand surgeons and therapists.[10,9,141,142] An early relationship with the child/family facilitates the possibility of the therapist to conduct assessments reliably. Continuous follow-ups that are valid and reliable seem to be very important for the early identification of possible movement changes, further referral to a hand surgeon or orthopaedic surgeon, goal setting and for planning interventions.[143,]

5.3.5 Passive range of motion development over time

The proportion of contractures (36%) in all children (n = 496); Table 12, see paper III, Table I, were consistent with previously reported proportions of UL contractures in a total population of children with CP in the southern part of Sweden in study I; see paper I. [144] Children first time treated at 1–3 years of age showed a lower proportion of contractures at their first measurement occasion compared to children treated for their first time at 4–15 years of age. Although children who were first time treated with BoNT-A at the age of 4–15 years already had a higher proportion of contractures at their first measurement occasion, the proportion of contractures in these children also increased over time (until their last measurement occasion) to the highest proportion in all investigated movements; see Figure 5 a. and b.

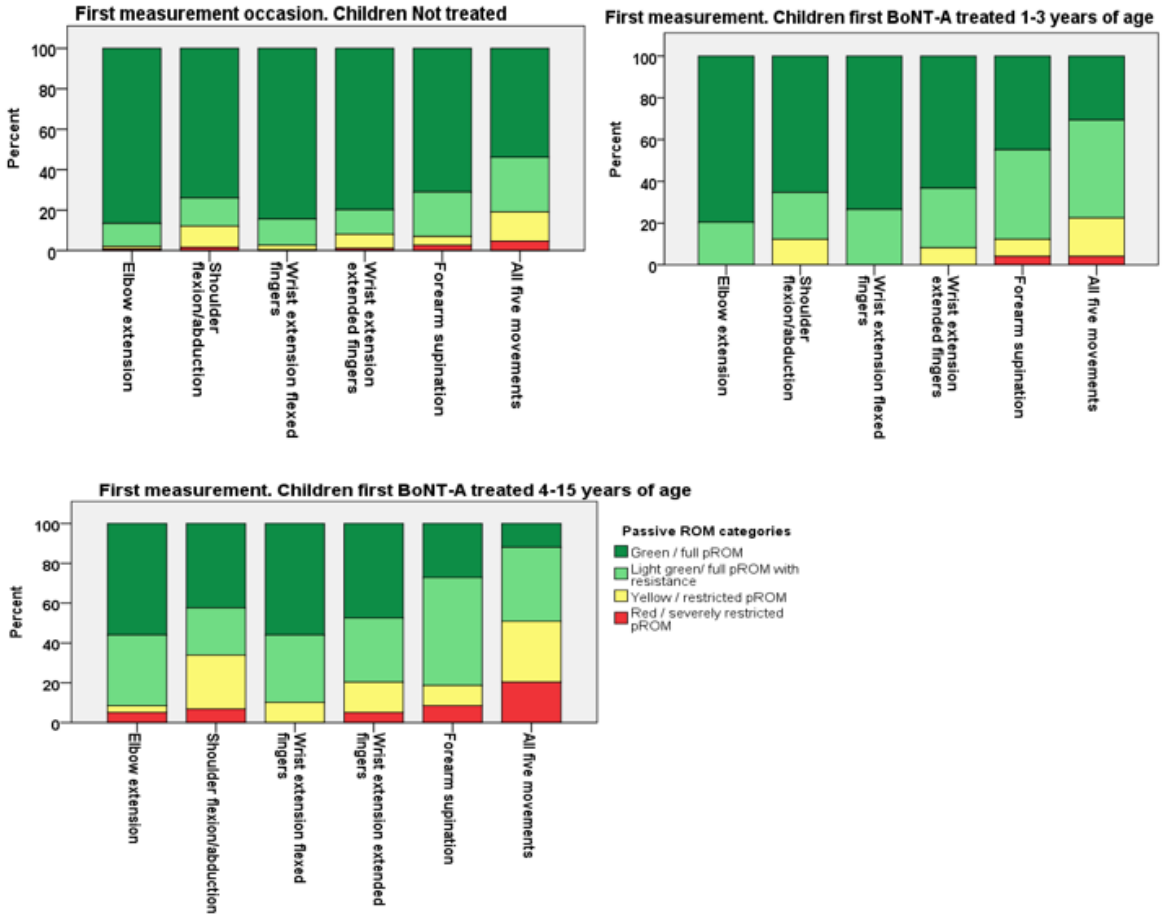


Figure 5 a. Passive ROM categories at first measurement occasion in five movements.

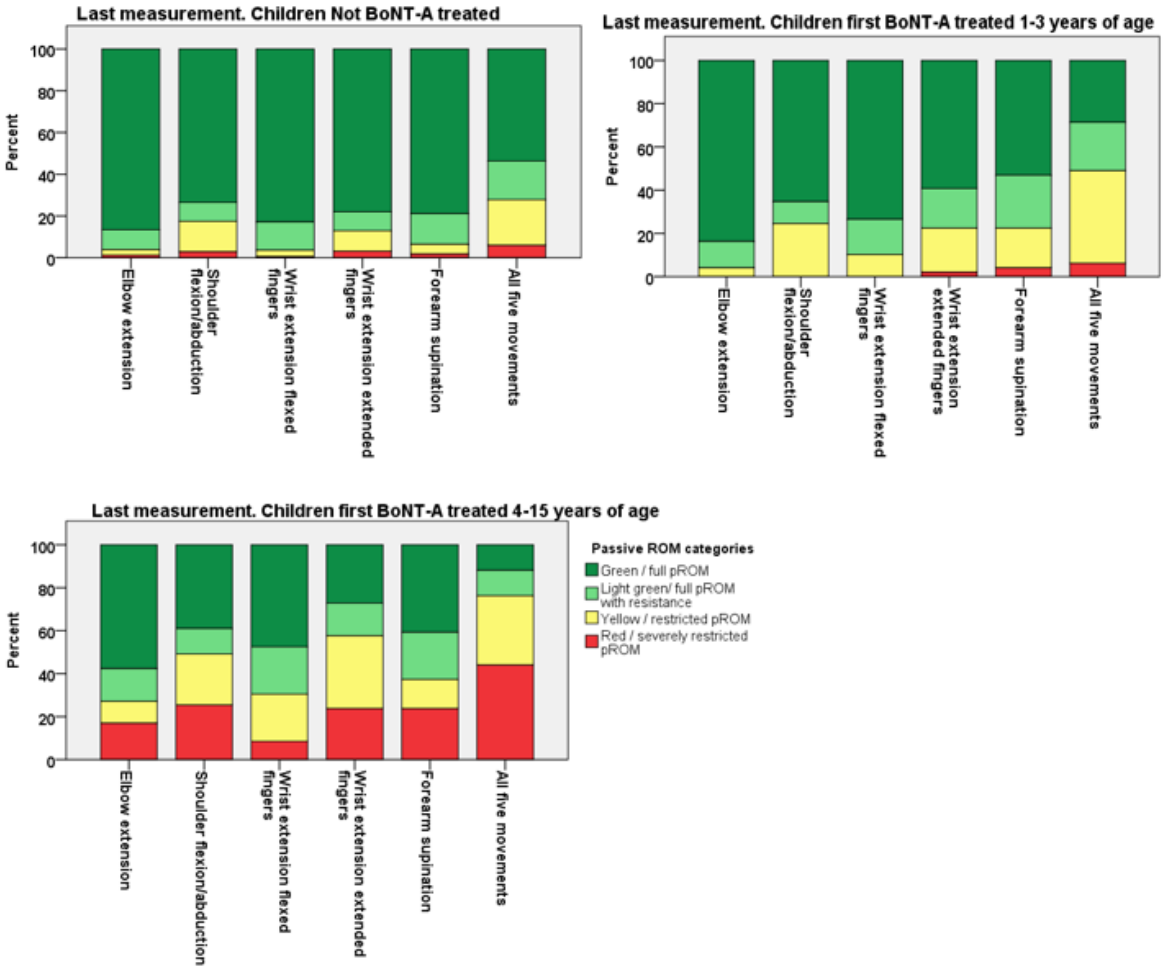


Figure 5 b. Passive ROM categories at last measurement occasion in five movements.

Upper limb contractures seem to be less common than contractures in the lower limbs (44%). In addition, among children who develop a first lower limb contracture, almost half of these children also developed secondary contractures.[145] This phenomenon has not been investigated for the ULs but may be a target for further investigation.

Among the investigated movements, wrist extension with extended fingers appeared to be first affected, by 4–6 years of age, and the most deteriorated movement (pROM) over time; Table 14, see paper III, Figure I. Overactive muscles and stiff muscles that hinder simultaneously wrist and finger extension are flexor the digitorum profundus and flexor superficialis muscles. Surprisingly, it was these exactly these muscles that had been treated to the lowest extent; Table 14, see paper II, Figure I.

However, pROM seems to deteriorate with increasing age in all movements, at older ages and especially in children UL BoNT-A treated at later age, 4–15 years; see paper III, Figures I and II. Concerning, the shoulder flexion/abduction movements, these movements were reported as the mean value of flexion/abduction. Interestingly, this movement also deteriorated at an early age, 4–6 years; Table 14, see paper III, Figures I and II, whereas the shoulder flexion in study I did not deteriorate until the age of 7–9 years; see paper I, Figure II.

Table 14. Differences in pROM degrees across age groups in five upper limb movements.

				95% Confidence Interval for Difference	
Age years	**Reference**	**Mean diff**	**P-value**	**Lower Bound**	**Upper Bound**
[a] Shoulder					
4-6	1-3	-2.5*	.01	-4.5	-.5
7-9	1-3	-5.5*	.00	-8.3	-2.7
10-12	1-3	-12.5*	.00	-16.5	-8.5
13-15	1-3	-19.0*	.00	-25.4	-12.6
[a] Elbow					
4-6	1-3	.0	.99	-.8	.8
7-9	1-3	-1.2	.11	-2.6	.3
10-12	1-3	-1.7	.11	-3.8	.4
13-15	1-3	-4.4*	.01	-7.8	-1.0
[a] Forearm supination					
4-6	1-3	-.7	.27	-1.9	.5
7-9	1-3	-2.5*	.01	-4.3	-.8
10-12	1-3	-8.0*	.00	-11.1	-5.0
13-15	1-3	-13.5*	.00	-19.7	-7.3
[a] Wrist extension flexed fingers					
4-6	1-3	-.3	.74	-2.0	1.4
7-9	1-3	-1.1	.37	-3.4	1.3
10-12	1-3	-4.1*	.03	-7.8	-0.3
13-15	1-3	-7.5*	.03	-14.2	-0.9
[a] Wrist extension extended fingers					
4-6	1-3	-5.3*	.00	-8.5	-2.0
7-9	1-3	-12.8*	.00	-17.6	-8.0
10-12	1-3	-15.3*	.00	-22.1	-8.5
13-15	1-3	-24.2*	.00	-36.0	-12.4

Based on estimated marginal means*. The mean difference is significant at the .05 level. [a] Dependent variable: degree.

Moreover, the time of first UL BoNT-A occasion seems to be crucial. Children without UL BoNT-A treatment seem to keep most of their pROM values within full range of motion over time; see paper III, Figure I, which indicates that therapists and hand surgeons were clever to select the children who seem to benefit the most from UL BoNT-A treatment. Children with early UL BoNT-A treatment, at 1–3 years of age, showed a favourable pROM development over time and developed mildly pROM restrictions first at older ages, compared to children treated at 4–15 years of age; Figure 6, see paper III, Figure I, II who developed severely restricted pROM, already at younger ages; see paper III, Figure II.

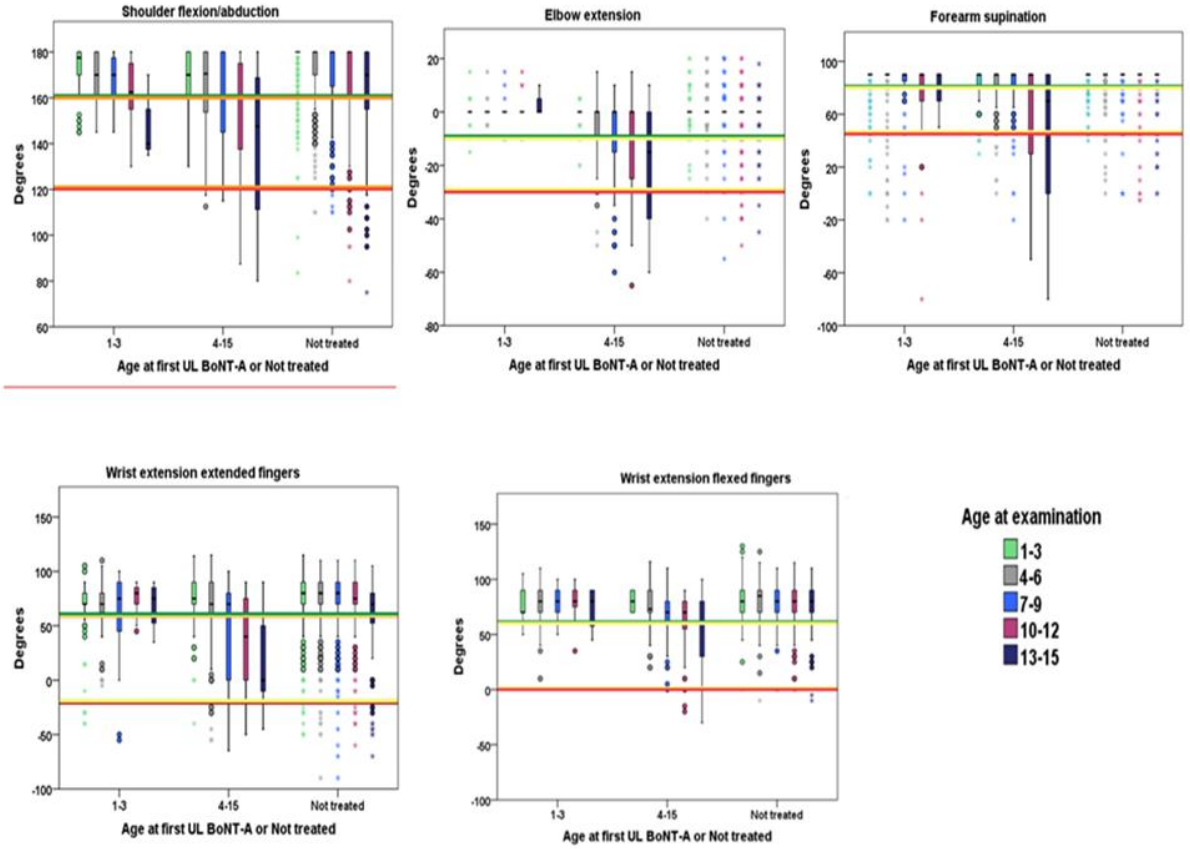


Figure 6. Passive range of motion (pROM) measurements in degrees for upper-limb movements at the last measurement occasion distributed across children first time UL BoNT-A treated at 1-3 years of age, at 4-15 years of age and children not treated.

These new findings support the notion that it may be beneficial to start UL BoNT-A treatment early, even before contractures are established to affect the spasticity and imbalanced movement pattern, i.e. at a first sign of muscle shortening and while children show difficulties with active movements.[146,110] Therefore, the green category in the CPUP traffic light system may be supplemented with a new light green category or perhaps a measure of UL spasticity in the UL CPUP protocol since spasticity measures may include a measure of resistance. However, the aspect of active range of motion may also be considered prior the decision on UL BoNT-A.

Moreover, it has previously been reported that although the use of BoNT-A shows short term benefits regarding spasticity and PROM, we still lack knowledge about how BoNT-A affects muscles over a longer period of time.[147,5,7] Related BoNT-A muscle atrophy does not solely explain why children with CP have a smaller muscle volume than typically developing children.[50] However, also interventions may be of particular importance in lieu of or in combination with BoNT-A.[4] To keep contractures from developing, it may be beneficial to pay attention to interventions that promote active voluntary movements that stimulate muscle growth, [50,41] align the body segments and maintain muscle length by using, for example, orthoses[148,149,150,151] (allow equal muscle growth of both wrist and finger flexor and extensor muscles) when the children have only mild signs of muscle shortening, e.g. in terms of full pROM with resistance in the end of the movement range.

5.3.6 Strengths and limitations

These studies are the first population-based studies of physical characteristics related to a first UL BoNT-A treatment and further the pROM development and contracture development in children treated and not treated with UL BoNT-A. These results may provide a contribution in the dialogue of UL BoNT-A treatment in children with spastic or dyskinetic CP.

In these two studies, we have introduced a new category in the CPUP traffic light system, the "light green category". As many as 30% of the children with full pROM (green pROM category) had values including a resistance at the end of the movement range, at their first measurement occasion. Thus, this new category seems to be an interesting marker, useful in identifying children with early signs of a possible muscle shortening and thus an important category to consider prior to early BoNT-A treatment.

In addition to the light green pROM category, a reliable assessment of spasticity in the upper extremities may potentially provide a better basis prior decision about UL BoNT-A. However, physical signs that are measured during clinical assessments are partly a reflex response that is due to a neural component and a muscle response due to a muscle pathology or a muscular resistance.[45] It can be difficult to differentiate between these two different components during clinical assessments in children with CP.[152] Consequently, reliable assessments of spasticity need to be further investigated and adapted for clinical practice.

Although study II provides new knowledge about some characteristics of children receiving their first UL BoNT-A treatment, other factors underlying the decision to offer BoNT-A treatment have not been considered – for example, facilitating the use of orthoses – functional goals, pain and spasticity have certainly influenced how the children were selected for UL BoNT-A. Especially the absence of a measure of spasticity probably affected the results in study II since spasticity is the primary indicator for BoNT-A treatment.[153] Moreover, since children in GMFCS level V were most likely to have a first UL BoNT-A, also BoNT-A treatment of the lower limbs may have influenced decisions prior to UL BoNT-A treatment.[154] However, GMFCS levels I-IV were not related to UL BoNT-A treatment, which may be explained by the fact that GMFCS is a classification of gross motor function.[67]

Passive ROM and its relation to a first UL BoNT-A were of our primary interest in study II. Thus, we adjusted the pROM odds ratios for confounders in the logistic regression analysis. The analyses of how the other independent variables (CP-subtype, MACS level, GMFCS level, age and sex) included in the study were related to a first UL BoNT-A were only based on crude odds ratios. Therefore, a methodological limitation in these analyses may be that some of the relations that were found could have been explained by confounders.

In studies II and III, children with spastic and dyskinetic CP were selected for further analysis. It would have been interesting to investigate these two different groups separately since children diagnosed with dyskinetic CP are often represented within the lowest MACS levels[155] and are developing more contractures than we previously thought; see paper I. However, this group was small (n = 49, 9%) and is likely to be underestimated since dyskinetic CP is sometimes reported as spastic bilateral CP.[156,155] Consequently, if we had separated the CP subtypes in the mixed model analysis, children with dyskinetic CP might have a different

pROM development over time compared to the spastic CP subtype. This may be an aspect to consider for further investigation.

A possible limitation in study III may be that the group treated with UL BoNT-A was divided into two groups, thus generating small samples, n = 49 and n = 59 respectively. Groups that are too small might have entailed difficulties in demonstrating differences between them. However, this was not the case in study III, which indicated sufficient statistical power.

Unlike in study I, where we evaluated pROM solely in the shoulder flexion movement, in studies II and III we used the mean value of the pROM value of shoulder flexion and shoulder abduction. This merging might be one explanation for why the children in study III deteriorated in their shoulder pROM earlier, by the age of 4–6 years, compared to the children in study I whose pROM in the shoulder deteriorated at 7–9 years of age.

Based on these results, we can assume that once a contracture has occurred, it is difficult to stop. However, the group of children who developed the highest proportion of contractures and had a steeper slope of pROM deterioration over time (children first time BoNT-A treated at 4–15 years of age) also demonstrated the highest proportion of contractures at their first measurement occasion. Thus, an adjustment in the mixed model analysis for the bias of pROM at first measurement occasion would have been interesting. However, since there was a large variation in age at the first measurement occasion, an adjustment of pROM at the first measurement occasion might have entailed the risk of the results of the age effect on pROM development being affected.

5.4 STUDY IV: UPPER LIMB ACCELEROMETRY METRICS OF ACTIVITY IN CHILDREN WITH UNILATERAL CEREBRAL PALSY

In study IV, 20 children and adolescents with US-CP, 4–18 years of age, MACS level I-III were recruited. Most children (65%) were able to handle objects independently (MACS level I-II). The right UL where commonly affected (60%); see paper IV, Table I. There were no dropouts or adverse events during the clinical tests or during daily life. All participants filled in a diary during the four days of assessment in daily life and all participants answered the questionnaire about the acceptability of accelerometry in daily life; see paper IV, Table IV. All children completed the clinical tests (AHA-test and BBT) and had accelerometer data from both ULs.

5.4.1 Upper limb accelerometry-based metrics in clinical test

All descriptive data from the clinical tests (AHA-units and BBT) and accelerometry-based metrics showed that all the children included had a greater contribution of the non-affected UL and obvious UL asymmetries; see paper IV, Table II.

The accelerometry-based metrics of asymmetry between the affected and non-affected UL were higher during the AHA-test (53.4 ± 17.7) than the BBT (31.4 ± 18.6); see paper IV, Table II. A moderate association between the AHA-units, BBT AI and the accelerometry-based metrics asymmetry index (AI) were observed during the clinical test, r = -0.70 and r = 0.60 respectively; see paper IV, Figure I.

It has previously been debated whether a measure of asymmetry may provide information about UL in bimanual activity.[94] Since AHA is a bimanual test that reflects *how effectively children with US-CP use their affected hand* when performing bimanual, relevant, and engaging activities, the asymmetry index provides information about *how much of the total activity (intensity) the non-affected UL is used in relation to the affected UL* in the bimanual activity. Although accelerometry has the ability to quantify the asymmetry in bimanual activity, an asymmetry measure does not provide information about which of the upper limbs that improves or gets worse.[157]

It has also been reported that we cannot draw conclusions about the bimanual activity by only assessing the unimanual activity, as the bimanual activity tends to be underestimated, since the effect of deficits in the non-affected UL or its compensation for deficits in the affected UL may affect the bimanual activity and is therefore not included in the results.[157] Since the BBT provides a capacity measure of each hand separately, a unimanual measure about how many blocks children transfer with each hand separately, i.e. a capacity measure of grasping, releasing and reaching, may be useful to compare measures between the UL in terms of asymmetry but is not sufficient to measure bimanual activity.

5.4.2 UL accelerometry-based metrics in daily life

The accelerometer wear time was > 14 hours per day. During the day, the children were mainly sedentary (64%) and spent only 3% of the day in a moderate- to vigorous-intensity physical activity. Previous research also indicates that children with CP are less physically active than typically developed children.[85] The asymmetries between the affected and non-affected UL

were most demonstrated during the sedentary time, AI = 45%. Children with US-CP used both hands together (bimanual use) in 44% of their daily life activities. During daily life, children exclusively used the non-affected UL (45%) rather than the affected UL (12%). The use ratio (UR) showed that children used their affected UL more than half of the time (UR = 0.64) in daily life; see paper IV, Table III.

Although the AI do not provide information about the amount of upper limb use in bimanual activity, it is still a measure of the total asymmetry between UL.[91] However, the formula for the relative use includes information about the percent time of bimanual use, use of each UL separately and a use ratio. The use ratio in itself provides a ratio of *how much time the affected upper limb is used in relation to the non-affected UL* in bimanual activity.[94]

The association between clinical test (AHA-units, BBT AI) and accelerometry-based metrics AI in daily life was moderate associated with AHA units and fair associated with BBT AI during the time when the children were sedentary, whilst the association was fair associated with AHA units and moderate associated with BBT AI during the light-intensity of physical activity in daily life; Table 15, see paper IV, Figure II. Moderate associations of asymmetry have also previously been reported during sedentary time.[84] Together, these results may indicate that that accelerometry-based metrics reflect asymmetries best during more stationary activities.[84] This seems logical. When moving around in the environment (locomotion), UL manual tasks are seldom performed at the same time. When performing manual tasks, one commonly either stands or sits, e.g. when eating, dressing and other self-care tasks, playing on the floor or at a table, writing, working/playing on the computer.

Table 15. Association between AHA-units, BBT AI and accelerometry-based metrics AI in daily life.

Association between clinical test/ Accelerometry-based metrics	AHA-units r (p-value)	BBT-AI r (p-value)
Sedentary time	-0.64 (p = 0.01)	0.54 (p = 0.02)
[a] LIPA	-0.51 (p = 0.02)	0.61 (p = 0.01)
[b] MVPA	-0.03 (p = 0.9)	-0.05 (p = 0.8)

[a] Light-intensity physical activity- LIPA. [b] Moderate-to vigorous intensity physical activity (MVPA).

5.4.3 Acceptability of using accelerometry in daily life

In Study IV, all 20 participants answered eight questions in a questionnaire about using accelerometers in daily life. The overarching theme of the questions was the acceptability of the accelerometers. Positive experiences of the acceptability of using accelerometers in daily life were reported in seven out of a total of eight questions. The most positive experience (95%) was reported about the instructions about the devices. The most negative experience (35%) was reported about wearing the devices; see paper IV, Table IV.

5.4.4 Strengths and limitations

A limitation of study IV is the relatively small sample size including children of different ages and MACS levels. If we had included more regions and more children, we would have been able to split the data based on the children's different MACS levels. Examining each MACS level separately would have been interesting, since previously reported data show that children

with higher levels of manual ability had higher cooperation (less asymmetry) between the UL than children with lower levels of manual ability.[91] A higher sample size also would have increased the likelihood that the sample be representative of all children with US-CP.

Regarding the accelerometry-based metrics in daily life, the number of days, which days (weekdays or weekend days) and how many hours during the days that are required to obtain reliable accelerometry measures of activity, have been discussed. In this study accelerometers were worn for four days, both weekdays and weekends included. A day was considered valid if ≥ 10 hours of accelerometer data were collected. However, four days with accelerometry wear time of approximately 7 hours in daily life are reported to be sufficient, if the devices were worn during weekdays or weekends was of minor importance to measure total physical activity and sedentary behaviour of pre-school children.[158,159]

Since technology is developing quickly and it is already possible to measure activity by using smart watches or other similar devices for different populations, accelerometry metrics for children with CP may be a readily available additional tool for daily life measures.[160] For measurements of asymmetries, accelerometry-based metrics and clinical tests had the highest association during sedentary time and LIPA. This new knowledge can guide us to obtain information about UL asymmetries in daily life but not about the bimanual ability.

How results on accelerometry-based metrics in children with cerebral palsy should be applied and interpreted has been discussed in other publications.[94,93] Both the AI and the relative use formulas have been used for asymmetry and bimanual activity estimation in children with US-CP.[91,85] However, there is still a lack of consensus on which formulas are most appropriate for evaluating the UL bimanual activity.

Accelerometry AI and relative use provide different aspects of upper limb activity. Both the AI and bimanual use (percentage of time of bimanual use) formulas have been used for asymmetry and bimanual performance estimation in children with US-CP.[91,85] These aspects need to be considered and specified in relation to what is intended to be evaluated, asymmetry, bimanual activity or activity in one or the other UL. The asymmetry index seems to be most appropriate for measures of contribution from both ULs, while for evaluation of function or contribution of the affected UL, the relative use, use ratio (how much of the total activity the child uses the affected UL in relation to the unaffected UL) may be most appropriate.[85]

The majority of participants had a positive experience of using accelerometers in everyday life. The most negative experiences were reported in question five. Question five was about whether the participants expressed positive things about the accelerometer devices. This question can be assumed to be deviant and thus difficult to answer. The design of the questionnaire was based on questions addressed by the research group. Unfortunately, the questionnaire was not further investigated about its 1–5 scale construct regarding the internal structure.

6 CONCLUSIONS

In summary, these results shows that one-third of children with CP developed UL contractures with increasing age and the contracture development started in some children even before three years of age. Low level of manual ability was most related to UL contracture development over time. In total, 22% percent of the children had received UL BoNT-A treatment whereof 45% had their first treatment before four years of age. Children who entered the CPUP registry at an early age also received their first UL BoNT-A treatment quickly compared to children who entered the CPUP registry at a later age. The lowest levels of manual ability or full pROM with resistance at the end of the movement range were physical characteristics that proved to be most related to receiving a first UL BoNT-A treatment. A favourable pROM development over time was demonstrated among children with UL BoNT-A treatment at an early age compared to children who were treated for the first time at a later age. The slope line of pROM deterioration was most pronounced in simultaneous wrist and finger extension where the deterioration had already started very early in life. However, despite this knowledge, wrist and finger flexor muscles were the muscles UL BoNT-A treated to the least extent. Regularly monitoring pROM over time seems to be important, from early childhood, in all pROM categories and in all MACS levels to promote pROM development.

Accelerometry-based metrics may capture UL asymmetries and the relative use in daily life in children with US-CP. However, objective accelerometry-based metrics seem to best reflect asymmetries during sedentary and lower intensity of physical activity. The asymmetry index seems to be useful in evaluating the quantity of asymmetries between the non-affected and affected UL, while the relative use formulas seem to be best suited for evaluating contribution from the upper limbs separately or for evaluating function in the affected UL. Although objective accelerometry-based metrics seem to be a usable and a complementing method to clinical assessments in daily life, further research is crucial to evaluate interventions.

7 FUTURE PERSPECTIVES

This thesis is a first step and a contribution to further research about secondary complications as UL pROM deterioration and contractures, UL BoNT-A treatment and UL accelerometry based metrics of asymmetry and relative use in daily life in children and adolescents with CP.

Since pROM deterioration and contracture development in the upper limbs seem to occur in one third of children and adolescents with CP, it is crucial to follow passive and active range of motion from early childhood during adulthood. It is important to keep in mind that these children will in time become young adults and older adults. Thus, further research about the upper limb function in adults is needed and requested.

The findings in this thesis support ideas about the importance of identifying children at an early age, children who have not yet developed contractures but who shows a first signs of muscle shortening or have a low level of manual ability. A prerequisite to enable offering children treatment at the "right" time is that the children are identified early and that they are referred to the "right healthcare provider". It is also important to regularly follow up range of motion over time and offer appropriate interventions at the time in children's lives when the interventions are most beneficial. Further research to evaluate the effect of interventions aiming at reducing UL contractures or promote UL activity is required. Consequently, reliable and valid assessment tools that evaluate the impact of interventions in different contexts are warranted.

Moreover, the use of UL BoNT-A needs to be further discussed in terms of the long-term effects of BoNT-A for different types of CP and in different MACS levels, and for which children the treatment option is most beneficial. Recommendations and guidelines for BoNT-A treatment need to include both upper and lower limbs. Prior to deciding on UL BoNT-A, manual ability and pROM need to be examined so that relevant goals can be formulated for each individual child. The findings in this thesis are not meant to be recommendations or even guidelines, but rather a basis for further interdisciplinary dialogues.

In a further perspective, this thesis may contribute to the use of objective measurements with accelerometry in children's daily lives. This new knowledge shows that accelerometry based metrics provide measures of both asymmetries and bimanual activity in the upper limbs which support further research of accelerometry metrics in children with CP in larger populations. Further research is needed to evaluate whether accelerometry-based metrics are sensitive to change and thereby useful to evaluate interventions in daily life in children with cerebral palsy.

The ICF provides a system which can guide us to consider different aspects of people's functioning, disability and health. Although the perspective of this thesis is primarily to describe and evaluate ICF components of body functions, i.e. pROM and the use of BoNT-A to reduce muscle tone, these aspects only contribute as one part of the understanding of UL functioning and disability. In this thesis, also the aspects of activity and participation domain are considered using MACS and the clinical tests AHA and BBT. What is new in this thesis regarding upper limb activity in children with CP is the use of accelerometry allowing objective measures of actual upper limb activity in daily life. This needs to be further investigated. It is known that the ICF body function and activity components interact with each other, and with other ICF components as personal and environmental components. This means that

improvements in body function does not automatically lead to functional gains, since functional gains probably also are influenced by the individual characteristics and environmental factors. However, it is important to further evaluate the effect of body function secondary complications such as contractures, and activity limitations such as asymmetry, or bimanual activity on children's quality of life in relation to all interacting components within the ICF model.

Finally, last but not least, we have to listen to the children! We need to ask the children questions about their experiences, their wishes, their dreams and about their own goals before we plan for interventions. We need to take time for questions if we believe that we will succeed with our interventions. Research on children's experiences of interventions needs to be encouraged.

8 ACKNOWLEDGEMENTS

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I am also very grateful for our unique Swedish CPUP registry, which made most of my thesis work possible. The CPUP registry is a goldmine for CP research, and I hope for continued high participation, many enriching registrations, follow-ups and a lot of new research about both children and adults with CP.

Associate Professor *Lena Krumlinde-Sundholm*, my principal supervisor, my compass when the map is hard to follow, when the forest is scrubby, and the water is wavy. My sincere thanks for your patience, your time, your ability to guide me on the right path and for generously sharing both your experiences and your deep knowledge, during weekdays as well as weekends at all hours of the day. Your guidance has brought me slowly but surely forward through large and less challenges. Even small things, like manuscript with p I will keep in my mind.

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9 SAMMANFATTNING PÅ SVENSKA

Cerebral pares (CP) är den vanligaste orsaken till rörelsestörningar hos barn och kan resultera i olika svårighetsgrader, från mycket mild till mycket svåra funktionsnedsättningar. Den underliggande neurologiska patologin vid CP är per definition inte progressiv, men motoriska symtom kan orsaka permanenta och progressiva sekundära rörelsekomplikationer, som ofta förändras över tiden. Rörelsestörningar är en framträdande komponent hos individer med CP och behandlingar är ofta inriktade på att påverka rörelsestörningar. Eftersom CP orsakas av en permanent skada i hjärnan kommer störningen att påverka individen på olika sätt genom livet och i dagliga aktiviteter. Därför är det särskilt viktigt att förstå hur sekundära komplikationer utvecklas från tidig barndom till vuxen ålder i denna population. Mätverktyg och bedömningsinstrument som utvärderar individers dagliga liv måste utvärderas psykometriskt, och vi behöver också utvärdera behandlingsresultat av de sekundära komplikationerna vid CP effektivt. Att få mer kunskap om sekundära komplikationer till CP är en prioritet inom CP-forskning.

Denna avhandling fokuserar på passiv ledrörlighet i övre extremiteterna, kontraktur utveckling över tid, Botulinum neurotoxin A (BoNT-A) behandling och på accelerometri baserade mätvärden utvärderade i det dagliga livet hos barn och ungdomar. Passiv ledrörlighets förändring i övre extremiteterna över tid och BoNT-A-behandling undersöktes med populationsbaserade data från det svenska nationella CP-registret. Kliniska bedömningar av övre extremiteter och accelerometri baserade mätvärden erhölls från 20 barn och ungdomar som var bosatta i Sörmland eller Västmanland i Sverige.

Resultaten visar att en tredjedel av barn och ungdomar med CP utvecklade kontrakturer i övre extremiteterna med stigande ålder och ledrörligheten försämrades succesivt över tid. Kontraktur utvecklingen startade redan i förskoleåldern. De första och allvarligaste kontrakturerna återfanns i samtidig handled och fingersträckning. Barn med sämre manuell förmåga löpte högst risk för utveckling av allvarliga kontrakturer.

En femtedel av barnen med spastisk eller dyskinetisk CP hade behandlats med BoNT-A i de övre extremiteterna, 45 % av dem tidigt i åldern, vid 1–3 år. Barn med lägre nivåer av manuell förmåga eller med fullgod ledrörlighet men med ett motstånd i slutet av rörelseintervallet hade störst sannolikhet att få en första BoNT-A-behandling. Vid det första behandlingstillfället var tum- och underarmsmusklerna mest behandlade. Intressant nog innebar en första BoNT-A-behandling i tidig ålder, 1–3 år, en mer gynnsam ledrörlighetsutveckling över tid jämfört med barn som behandlades första gången vid en senare ålder, 4-15 år. Tidig upptäckt av ett första tecken på muskelförkortning och därmed tidig behandling innan kontrakturer manifesteras kan vara en av nycklarna till framgångsrika resultat för att främja ledrörlighetsutveckling hos barn med CP.

I det dagliga livet, under stillasittande tid och under fysisk aktivitet i lätt intensitet, ger accelerometriska mätvärden objektiv information om asymmetri och relativ användning i övre extremiteterna. Således kan accelerometriska mätvärden ge kompletterande information till kliniska bedömningar om bimanuell aktivitet i det dagliga livet.

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