Hamstring muscle length in ambulant children with spastic bilateral cerebral palsy

Development and physiotherapy treatment

PhD Thesis

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Thesis at a Glance

Background Hamstring contractures are common in children with spastic bilateral cerebral palsy (CP) and it appears to evolve by functional level and age. Children with cerebral palsy often have a complexity of impairments that need to be observed on a regular basis. Spasticity and length of the hamstring muscle is, however, often overlooked until it becomes shortened, mainly observed as increased knee flexion in the gait cycle. With more knowledge about how spasticity and the length of the hamstring muscles develop during childhood, it would be easier to recognise the symptoms at an early stage and make treatment plans that include strategies to prevent the problem. Most children with CP receive physiotherapy on a more or less permanent basis throughout childhood and growth, and the goal is to optimise mobility and function and limit, modify and treat secondary impairments. However, the effect of different treatment modalities targeting the prevention of hamstring shortening has not been extensively studied.

Aim The main aims of the present thesis were to study the development of the hamstring muscle length, measured as the passive popliteal angle (PPA), and hamstring spasticity during childhood in ambulant children with CP (Paper I) and to evaluate whether a specific stretching and muscle strengthening program had any positive effect on the PPA, muscle strength (Paper II) and gait function (Paper III).

Methods The thesis includes three papers based on a longitudinal register-based cohort study (Paper I) and a randomised controlled trial (RCT) (Papers II and III).

The longitudinal register-based cohort study included 419 ambulant children (1 to 15 years of age) with spastic bilateral CP, gross motor function classification system (GMFCS) levels I, II and III, included from the Norwegian CP Follow-up Program (CPOP). A total of 2193 tests were included in the analyses. The children were tested by trained physiotherapists yearly or every second year, depending on GMFCS level and age. The PPA and the hamstring spasticity (Modified Ashworth scale, MAS) were measured at every time point. A multivariable fractional polynomial linear regression model was used to fit age curves for the GMFCS levels. The model included age and GMFCS level as independent variables.

For the intervention study, we performed an RCT (Papers II and III). Thirty-seven children (21 boys, 16 girls, mean age 10.2 (±2.3) years), classified as GMFCS levels I, II or III, with a PPA of ≥35°, were randomised to an intervention (n = 17) and a comparison group (n = 20). The intervention group received a 16-week combined exercise program (3 sessions per week) that

included stretching of the hamstring muscles and PRE targeting the lower extremities, followed by a 16-week maintenance program (1 session per week). The comparison group received care as usual. Passive and active popliteal angle, isokinetic muscle strength (Papers II), three-dimensional gait analysis (3DGA), kinematics in the sagittal plane, step length and speed, Gait Deviation Index (GDI) and the six-minute walk test (6MWT) were measured. The tests were performed at 0, 16 and 32 weeks. To evaluate mean differences between the groups at 16 and 32 weeks, a linear regression analysis with covariates correcting for baseline (ANCOVA) was performed.

Results In the longitudinal register-based cohort study there were significant differences in the PPA between all the three GMFCS levels from 2 to 8 years of age. At GMFCSs level I and II, the PPA increased by a mean of 4-5° every second year until 15 years of age. In contrast, the PPA at GMFCS level III levelled off, with only a minimal increase after 10 years. At 10 years, there was no significant difference in PPA between GMFCS levels II and III, and at 14 years there was no significant difference in PPA between any of the GMFCS levels, with a mean PPA between 41° and 45° for all three levels. The MAS curve estimates were low (MAS 0-1+) for all three GMFCS levels; however, there were significant differences between the levels until age 8. The curve pattern for PPA and MAS at the three different GMFSC levels followed the same pattern and direction throughout childhood.
Minor but not statistically significant changes in the PPA, APA, hamstring and quadriceps strength were found between the intervention and the comparison groups after 16 and 32 weeks (Papers II and III). There were no significant changes in any of the gait parameters evaluated.

Conclusion The results from the present studies showed that the PPA increased throughout childhood, with significant differences between GMFSC levels I, II and III until 8 years of age. The PPA then leveled off, and at 14 years of age the mean PPA was greater than 40° for all three levels. The findings indicate that clinicians should pay attention to maintaining the length of the hamstring from an early age, independent of GMFSC level.
The 16-week combined stretch and PRE program had only minor insignificant effects on PPA, APA and lower limb muscle strength in favour of the intervention group. The positive trend indicates that if the goal is to maintain PPA and active knee extension, a combination of hamstring stretching and PRE training might be introduced. The intervention had no influence on any of the gait variables measured.

Included papers

This thesis was based on the following papers. They are referred to in the text by their Roman numerals.

I. Fosdahl M., Jahnsen R., Pripp A.H., Holm I.
"Change in Popliteal Angle and Hamstrings Spasticity during Childhood in Ambulant Children with Spastic Bilateral Cerebral Palsy. A Register-based Cohort Study"
BMC Pediatrics. January 2020; *20:11 DOI*:*10.1186/s12887-019-189-y*

II. Fosdahl M., Jahnsen R., Kvalheim K., Holm I.
"Stretching and Progressive Resistance Exercise in Children with Cerebral Palsy. A Randomised Controlled Trial."
Pediatric Physical Therapy, July 2019; 31: 264-271 DOI:10.1097/PEP.0000000000000616

III. Fosdahl M., Jahnsen R., Kvalheim K., Holm I.
"Effect of a Combined Stretching and Strength Training Program on Gait Function in Children with Cerebral Palsy, GMFCS I and II: A Randomised Controlled Trial"
Medicina, June 2019; 55: 1-12 DOI:10/3390/medicina55060250

Abbreviations

APA	Active popliteal angle
CP	Cerebral palsy
CPOP	Cerebral palsy follow-up program
CPRN	The Cerebral Palsy Register of Norway
ECM	Extra cellular matrix
GMFCS	Gross Motor Function Classification System
MTU	Muscle tendon unit
PRE	Progressive resistance training
PPA / PA	Passive popliteal angle / popliteal angle
PT	Physiotherapist
RCT	Randomised controlled trial
ROM	Range of motion
SD	Standard deviation
6MWT	Six-minute walk test
TD	Typically developed
3DGA	Three-dimensional gait analyses
T0	Baseline
T1	Follow-up at 16 weeks
T2	Follow-up at 32 weeks

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1 INTRODUCTION

1.1 Cerebral palsy

Cerebral palsy (CP) is an umbrella term covering several movement disorders caused by a spectrum of permanent developmental and acquired lesions to the upper motor neurons in the developing brain. It includes a group of non-progressive motor impairments, and it is the most common cause of motor deficiency in children (1, 2).

The internationally agreed definition of CP is as follows: “Cerebral palsy is described as a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbance of the sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems”(1, p. 9).

The primary non-progressive brain damage, depending on the severity and localisation in the brain, causes spasticity, muscle weakness and impaired postural control. This primary impairment arises in the early stages of development and causes secondary progressive impairments such as muscle strength imbalance and joint contractures, which evolve over time (2). “The reasons for this changing clinical picture after a static insult remain poorly understood, but raise intriguing questions about the interaction between brain injury and development, and potential avenues for further intervention” (2, p. 83). Hamstring muscle shortening is one of several secondary impairments often seen in children with CP.

Muscle shortening and reduced joint range of motion (ROM) have been shown to develop with increasing age and reduced functional level (3, 4), and reduced ROM in the lower extremities restricts the progress of gross motor function and mobility during childhood (5-7). Studies have shown that prevention of severe knee contractures is highly important to maintain gait function as an adult (3, 8). It is essential to be aware of a problem to be able to recognise and prevent it; hence, knowledge about expected progression and optimal and currently timed interventions is important.

Most children with CP receive physiotherapy during childhood and growth, and the goal is to optimise mobility and function, while limiting, modifying and treating secondary

impairments. As the children spend many hours throughout childhood with a physiotherapist (PT) and other healthcare workers, the treatment they receive should be effective and meaningful, if not in the short-term, at least in a long-term perspective.

Prevalence

CP is in Norway and worldwide the most common movement disorder in children, and more boys than girls are affected (57% and 43%, respectively) (9). Globally, the prevalence of CP is reported to vary between 1.5–3 per 1000 live births (10, 11), and the prevalence has remained constant over the last decades. However, in Norway, a recent study found a decrease in the number of children born with CP. The prevalence of being born with CP declined from 2.6 per 1000 live births in 1999 to 1.9 per 1000 in 2010, and thus the probability was reduced by 2.8% per year (9). The reasons for this decrease are probably improvements in obstetric and neonatal care. According to the Cerebral Palsy Register of Norway (CPRN) (12), the average age for receiving a CP diagnosis was 25 months in 2017.

Classification

CP is divided into three groups based on the predominant neuro motor abnormality: spastic CP (unilateral or bilateral), which includes nearly 90% of all people with CP, ataxic CP and dyskinetic CP (13). Some children have a mixed presentation, which is described by the most dominant abnormality.

The Cerebral Palsy Follow-up Program (CPOP) and CPRN (12) use the classification scale suggested by the Surveillance of cerebral palsy in Europe (SCPE) (13) along with the World Health Organisation, International Classification of diseases and related health problems, 10th revision system (ICD10) (14). The distribution of diagnostic subgroups in Norway per 2017 is stated by CPRN, as follows:

Table 1: Distribution of CP subtypes in Norway

CP subtype	% in Norway
Spastic CP: 88%	
Spastic bilateral 45%	- Bilateral: affection mainly in the legs, most often found in children born preterm - Quadriplegia: affects arms and legs, mainly seen in children born full term but with moderate or severe hypoxia during late pregnancy or during delivery
Spastic unilateral 43%	Unilateral affection of arms and legs on the same side. Mainly in children born full term
Dyskinetic (choreoathetosis / dystonia) 6%	Recognised by involuntary movements
Ataxic 4%	Recognised by coordination deficits
Not classified 2%	

Adapted from the Norwegian Cerebral Palsy Register, Annual report 2017 Hollung et al. (9)

Classification of function

Several classification systems describing function in CP exist and are widely used, such as the Gross Motor Function Classification System (GMFCS) (15), the Manual Ability Classification System (MACS) (16) and the Communication Function Classification System (CFCS) (17). The different classification systems focus on different aspects of motor function and are essential in multidisciplinary clinics. They may help both the family and the multidisciplinary treatment team to predict long-term prognosis, and they provide a common understanding of the child's function and a guide towards an appropriate multidisciplinary management plan (18). This thesis deals with gross motor function.

The GMFCS is the most central and widely used classification system for children with CP (18, 19). It was developed by Palisano and Rosenbaum in 1997 from cross-sectional population data (15) and is a simple and validated (20) method to categorise and describe motor function in CP into five developmental curves, from level I (most able) to level V (most restricted). The five levels describe differences in daily functioning (based on the Gross Motor Function Measure-66 (GMFM-66)) and are divided into age bands (0-2, 2-4, 5-6 and

>6-12 years). The classification system focuses on self-initiated activities such as walking and sitting, and the need for assistance devices is emphasised (15). The classification system was further developed using a community-based sample of 657 children who were followed prospectively with 2632 assessments; based on their evaluation, five distinct gross motor development curves were created (21). Hanna et al. followed the same children for an additional 4 years and the data was extended to 21 years of age (22) (Figure 1). These curves provided an evidence-based foundation for prognostic gross motor progress in children with CP based on their age and function in daily life. The GMFCS provides parents and clinicians with a means to plan treatment, and it is also a guideline for what to expect of gross motor progress and gait function during childhood (21, 22).

In 2008, an expanded and revised version of the GMFCS was validated (23). The expanded version (GMFCS E&R) included a new age band covering youths from 12 to 18 years of age. The curves (Figure 1) show that children, on average, reach approximately 90% of their motor functional level at 5 years of age or younger, depending on their GMFCS level. There are strong correlations between the classification of function in preschool years (20) and in adulthood (24), which make GMFCS a predictive tool. A positive prediction value of the GMFCS level at 1 to 2 years of age to predict walking ability at 12 years has been reported (20). Nevertheless, it is emphasised that the prediction is not static and might be influenced by interventions targeting primary and secondary impairments. As new therapies emerge, there will probably be a need for modifications of the curves (21); however, it was concluded that the new extended version has content validity and is sufficient for communication, clinical decision making, inclusion in databases and clinical research (23).

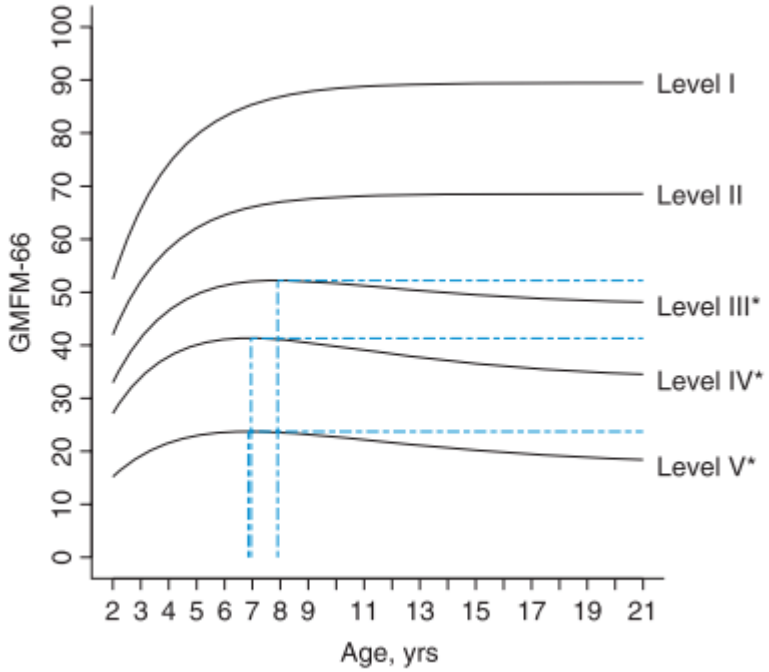


Figure 1: Predicted Gross Motor Function Measure (GMFM-66) motor scores as a function of age by Gross Motor Function Classification (GMFCS) level. *GMFCS levels with significant average peak and decline. Dashed lines illustrate the age and score at peak GMFM-66. Rendered with permission from S.E.Hanna, 2009 (22).

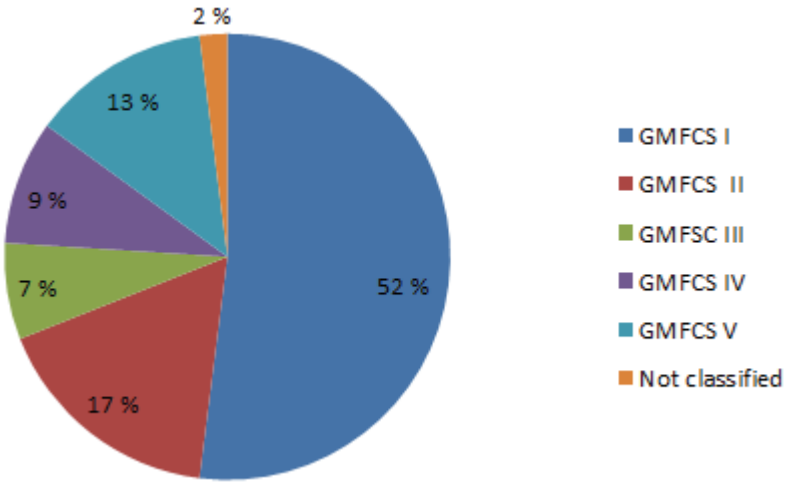


Figure 2: The distribution of the GMFCS E&R level (n=1415) in Norway (2017), adapted from the Norwegian Cerebral Palsy Register, Annual report, 2017 (12).

1.2 Range of motion in cerebral palsy

Mechanical properties and changes in muscles affected by cerebral palsy

Muscles in children with CP are smaller and shorter and have been reported to be stiffer and with reduced diameter compared with muscles in typically developed (TD) children (25, 26). Alterations in muscle shape, muscle architecture and arrangement will change the muscle performance and alter the ability to generate force and power through ROM (27, 28); however, the underlying reasons for the cause of the weakness remain unclear (29).

The sarcomeres are the contractile force-producing elements in the muscle and are organised in parallel and in series. They create the myofibrils, which build the muscle fibres. The sarcomeres are the fundamental structural unit of muscular contraction and contain overlapping protein filaments (actin and myosin) (26). In a study by Liber at al. (30), sarcomeres in spastic muscles were found to operate at a longer sarcomere length compared to controls; this finding suggested the inability of muscles to add sarcomeres in series (30). Smith at al. (31) found sarcomeres to be longer in CP muscles than in TD muscles and suggested that sarcomere length was regulated differently in CP muscles and was less force efficient than in TD muscles. A consequence of muscles having long sarcomeres was that the muscles were under high stress and worked at non-optimal portions along the length–tension curve compared to controls, which led to higher passive stress in the muscle. Smith et al. (31) concluded that the increased passive tension in contractures in human hamstring muscles is due to changes in the extra cellular matrix (ECM), stiffness and increased sarcomere length rather than due to intracellular alterations.

Some studies have reported shorter facile length in CP muscles (32-34), while other studies have found no difference between CP and TD muscles (26, 31, 35, 36). It appears that even neighbouring muscles can be affected differentially (29, 32). This reported inconsistency might be related to the severity of the upper motor lesion, causing high intra-subject variability, disused or altered patterns of activation, and malalignment. In addition, different examination methods used for the analyses might have influenced the results and conclusions (29).

Intrinsic passive stiffness of the tissue contributes to muscle stiffness (26, 29, 31). The arrangements of collagen in the ECM of CP muscles is shown to be changed in relation to muscles of TD children; however, the picture is not clear (37). Lieber and Friden (37) found increased ECM in contracted hamstring muscles; however, the plantar flexors showed a decreased EMC relative to TD children. Increased collagen content seems to be characteristic of a muscle contracture, but its presence does not entirely explain the mechanical tension in the contracting muscle. Smith et al (31) studied the hamstring muscles using muscle biopsies from children with CP (n=33) compared to a comparison group (n=19) and found that the muscle bundles that included fibres inside the ECM were stiffer and had an increased collagen content in the CP group compared to the comparison group. The authors also found differences in stiffness between different parts of the hamstring, probably due to differences in the quality and arrangement of ECM within the bundles.

Satellite cells are the muscle stem cells that are responsible for longitudinal and cross-sectional postnatal growth and are also responsible for repair after injury. Muscle biopsies from children with spastic CP show 60-75% fewer satellite cells compared to age-matched TD children, which may reduce muscle growth and contribute to muscle contracture in CP muscles (37, 38).

Muscle contractures

Children with CP often develop muscle contractures, which limits ROM, negatively influences daily function, activities, and mobility in society (26, 39), and are sometimes painful (40). These contractures are a permanent shortening of the muscle tendon unit (MTU) and occur when the soft tissue has increased stiffness and no longer can be stretched, neither passively nor actively, by the antagonist muscles (37). The reason for muscle contracture in CP has generally been associated with the presence of spasticity and a resistance in the muscle to passive stretch (41). Recent published research draws a more complex picture, also involving the impairment of muscle growth and altered muscle adaptation (25, 37, 42). Spasticity—a rapid change registered as resistance to rapid passive joint movement—has been considered to be due to a pathological increase in reflex-mediated stiffness, but studies have revealed that changes in passive muscle properties are probably a much more frequent component in muscle spasticity, evolving from early ages (25, 43). Muscle contracture is understood as a muscle adaptation in which the increased muscle stiffness is seen as reduced

ROM. This increased stiffness and shortening is caused by both passive and active components. The active component is caused by an increase in muscle tone, and the passive component appears to have several causal components, including hypertrophy of the ECM (endomysium, epimysium, perimysium and fat) (26, 29, 31), the fibre type, fibre bundle stiffness and the number of stem cells (26). In the contracted muscles in children with fixed contractures, the contractile sarcomeres are longer than those seen in the muscles of TD children (31). In addition to generating a relatively low active force, longer sarcomere length is also associated with higher passive muscle force stress (31). In summary, these factors may be mechanistic explanations for the increased joint and muscle stiffness observed in children with CP.

Muscle weakness

Children with CP are shown to be weaker than their TD peers (35, 44-46), and the weakness is understood as an important negative feature of the upper motor neuron syndrome, causing muscular/morphological and activation/neurological deficits (29, 39, 47). Studies have revealed that in children with spastic bilateral CP, the distal muscle groups are weaker than the more proximal muscle groups (48), and the muscles are also weaker over a shortened range (49). Nevertheless, the origin of the weakness in children with spastic CP and the influence of altered muscle structures have not been fully understood. The muscle structure and physiology are altered, showing decreased muscle fibre diameter (31) and a reduced cross-sectional area of the muscle belly (44, 46); hence, CP muscles are smaller and have a reduced muscle volume. These described alterations in muscle shape, internal architectures and composition, which alter the passive and active muscle length, have an impact on performance and the ability of muscles to generate force and power through ROM (26, 31, 32, 35, 46, 50). The neurological weakness in CP is registered as excessive co-contraction and reduced selective motor control (51-53). The primary disorder results in a decreased and dysfunctional neuronal drive of the motor units, excessive co-activation of antagonist muscles (45, 46, 54, 55) and the reduced activation of the sensory system. Children with CP are unable to fully activate their muscles; studies have revealed that they are able to activate only half to two-thirds of their muscular resources (55). Furthermore, neuromuscular activation and motor-unit firing during maximum voluntary contraction are significantly reduced in children with CP compared with TD children. This altered neurological input in the CP muscles has

been connected to altered muscle growth, fibre type and size, sarcomere length, and altered collagen, fat and ECM.

1.3 Gait function

The normal gait cycle

Gait function is a highly complex activity which requires central nervous control, energy sources and a lever arm to provide movement (39, 56). A typical gait cycle starts with the foot striking the ground and ends with the same foot striking the ground again. The gait cycle is divided into two phases: the stance (60%) and swing phase (40%) (56, 57) (Figure 3). At the initial heel contact, the body reacts against the forces that the ground reaction force is generating. To absorb the impact, the hip extensors, vasti, ankle dorsiflexors and toe extensors are activated (56). After the foot strike, a loading response occurs, which is the shock absorption phase, and there is an impact of approximately 120% of the body weight. During the loading response the ankle and foot move through the three rockers, and the external moment works on the foot, which is controlled by the tibialis posterior working eccentrically. At the knee, the vasti also contract eccentrically, producing an internal moment on the knee and power absorption throughout most of the loading response. The hamstring muscles work concentrically as a hip extensor. Because the hamstrings are bi-articular muscles, they also affect the knee as a flexor, and the vasti balance the action over the knee via co-contraction. To produce an effective gait, the mid stance is essential, as it is a phase of energy conservation. The ground reaction force is now in front of the knee joint centre, and the foot acts like a lever to push the knee joint into a stable knee extension, removing the need for muscle activation from the vasti. The eccentric action of the soleus is the main muscle preventing the knee from collapsing into flexion. The swing phase is divided into pre-, initial- and mid-swing. In the pre-swing phase, the gastrocnemius and soleus drive the limb forward through a rapid ankle plantar flexion; at the upper femur, the hip flexors and the adductors pull into flexion. The knee joint begins to flex (initial phase), driven both by the ankle (gastrocnemius) and the hip (hamstring), which work concentrically to flex the knee by approximately 60°, which with normal gait speed is sufficient to clear the foot during swing (mid-swing). In the initial- and mid-swing, the hamstring and tibialis anterior are first

working concentrically, and the mid-swing is the switching period between acceleration and deceleration where there is limited muscle activity (56, 57).

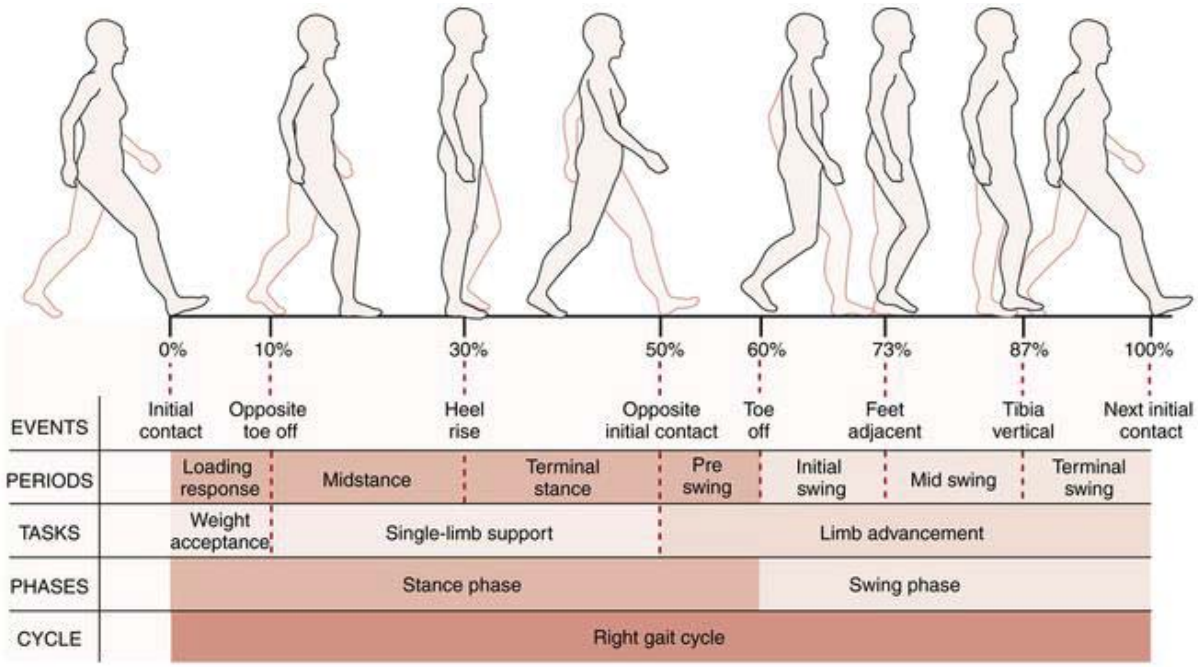


Figure 3: Events of the gait cycle (Musculoskeletalkey.com)

Gait in children with cerebral palsy

The primary brain injury in CP causes changes to the musculoskeletal function, growth and development, which potentially have a large impact on the complex gait function. Approximately 60% of children with bilateral CP learn to walk, in most cases about three years of age, but many need the support of assistive devises (21, 58, 59). An efficient gait requires "1) a control system, 2) an energy source, 3) levers providing moment, and 4) forces to move the levers" (56, p. 31). When neuromuscular pathology occurs, as in CP, all of these gait attributes may be affected. The development of gait function in CP shows deterioration over time (60, 61). Several factors may contribute to this, including reduced strength, joint and muscle contractures, spasticity, and increased body weight. In addition, compliance with and access to physiotherapy and bracing are important factors. In a Norwegian study, Jahnsen at el. (62) documented that 10% of adults who previously could walk lost their gait function, and Opheim at al. (40) reported that 71% of adults with CP experienced deterioration of the gait function since their walking debut (Figure 4).

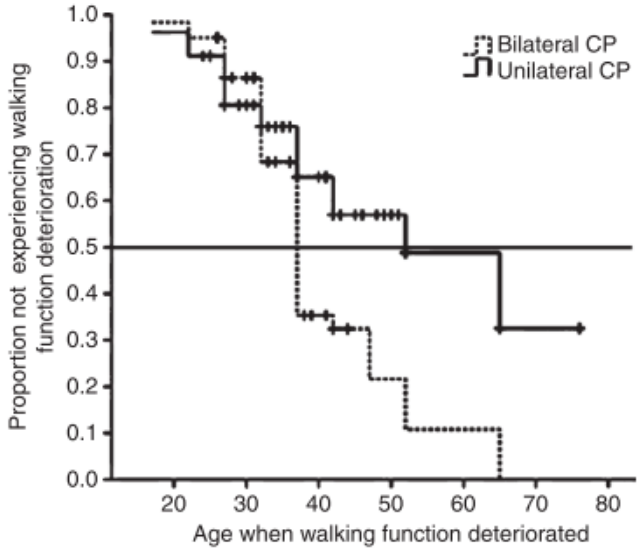


Figure 4: Kaplan-Meier plot of the proportion of persons not experiencing a deteriorated walking function in adults with unilateral and bilateral CP. Vertical tic marks indicate where data have been censored. Rendered with permission from A. Opheim 2009 (40).

Gait pathology in CP is caused by a combination of the primary brain damage and the secondary effects (39). The primary effects on gait are loss of selective muscle control, impaired balance and abnormal muscle tone, usually seen as spasticity in the gait. These primary effects interfere with normal muscle and bone growth and often result in what is called the secondary effects of the brain injury. The secondary effects evolve as the child's muscles and bones grow and emerge slowly over time. Impairments such as drop foot, equinus in the ankle, stiff knee gait and crouch are typical examples of secondary effects of the brain injury. To cope with these primary and secondary effects and their impact on the gait, the children learn to overcome the problems by using compensation strategies such as vaulting, circumduction of a stiff limb, or increased flexion in the hip on the swing side. These compensations strategies are referred to as the "tertiary effect of the brain injury" by Gage and Schwartz (39, p. 108).

The mixture of primary, secondary and tertiary effects of the brain injury are together responsible for the pathological gait in CP. To treat and optimise gait in these children it is hugely important to sort out what is the primary problem, which usually is permanent, and

what are secondary problems, which in many cases can be corrected, modified or prevented. The tertiary problems may disappear if the secondary problems are treated and compensation is no longer required (39).

Three-Dimensional gait analysis

In the late 1980's computerised 3-dimensional gait analysis (3DGA) was acknowledged to be an important instrument for optimising the evaluation and treatment of ambulant children with CP (63, 64) and has become the gold standard for analysing and understanding gait in CP (65, 66). It is a measurement tool widely used in treatment planning and in clinical trials, and if recommendations from 3DGA are followed and interpreted wisely by experienced investigators, it has been shown to improve the preoperative decision process (67, 68).

3DGA is a recording of gait function in three planes. Joint movements (kinematics) are recorded by tracking the movement in the sagittal plane (flexion/extension), frontal plane (abduction/adduction) and coronal plane (rotation) (69). The joint movements are tracked by reflex markers that are placed on the pelvis and lower limbs according to a computerised model (70). The ground reaction forces and power are calculated (kinetics) using force plates embedded in the floor. Kinematics describes joint movement but cannot reveal its cause, and kinetics describes the effect of forces, movement, energy and power. In addition, time and distance parameters (cadence, velocity, stride length and speed) are registered (69). A 2D video film in the sagittal and frontal planes is recorded, and the patient also undergoes a clinical examination, which is an essential part of clinical 3DGA (69, 71) .

The effects of short hamstring muscles on gait

The hamstring muscle group consists of three muscles, the biceps femoris, semitendinosus and semimebranosus, which together cross and act upon both the knee and hip joint and is a so called bi-articular muscle. Its function is to flex the knee and extend the hip; depending on how the ground reaction force is acting on the knee and hip joint, it can also become a knee extensor, and when the knee is flexed it will rotate the tibia internally (57, 71).

The knee function in normal gait is as follows: "The knee is the junction of the two long bones (femur and tibia) that constitute the major segments of the lower limb. Small arcs of motion result in significant changes in either foot or body location. Consequently, knee

mobility and stability are the basic primary factors in the normal pattern of walking" (57, p. 89).

Impaired knee extension during the gait cycle is often recognised in children with CP (72, 73). They are generally weaker than their TD peers (29, 44, 74, 75), and knee extensors measured at the terminal 30° of knee extension range are the relatively weakest muscle group when compared to TD children (74). Short and spastic hamstring, restricted popliteal angle, and weak quadriceps might also be risk factors for developing a knee joint contracture and crouch gait (39, 76-78).

For most children with CP, the hamstring muscles become shorter during childhood, and the passive popliteal angle (PPA) generally becomes 10-15° larger than in TD children (79, 80). Ounpuu et al. (81) compared gait performance in 292 children with spastic bilateral CP and 60 TD children and reported significantly increased knee flexion at foot strike, increased flexion in stance, and decreased swing phase flexion-extension ROM compared to the TD children. In the TD group, the maximum knee angle at foot strike was approximately 10°; in contrast, more than 90% of the children in the CP group at GMFCS levels I, II and III had a knee angle at foot strike of more than 10° (range 5-53°) (81). An increased knee flexion at foot strike often causes reduced step length (82) and is probably due to several reasons, including the reduced ability to passively extend the knee joint, either because of knee joint contracture or hamstring contracture, hamstring spasticity, or a reduced ability to actively fully extend and control the knee (57, 81, 83). "The biomechanical implication of increased knee flexion at initial contact is increased knee flexion in stance" (81, p. 961). An increased knee flexion in mid stance of more than 20-30°, with simultaneously increased knee angle at foot strike, described as crouch gait (84, 85), is defined as the most severe gait deviation in children with CP (39). In the mid stance, a weak soleus muscle will not be able to stop the tibia from progressing forward, increasing the dorsal flexion on the loaded ankle and making it difficult to extend the knee (39, 73). An increased knee flexion may also have a balance component when a minor knee flexion with a lowered centre of gravity is more "safe" than a straight knee. However, balance and balance mechanisms as a theme are not in the scope of this thesis and will not be further discussed.

How and to what extent short hamstring muscles influence the gait function has been widely discussed (86, 87). The presence of short hamstring muscles has been described as one of the main factors contributing to crouch gait (39, 85). However, some studies have found that more than 80% of those walking with an increased knee flexion during stance had hamstring muscles of normal length or longer (87-89). Studies have also revealed that a restricted hamstring muscle, measured at first resistance to hamstring stretch, seems to limit the knee extension at terminal swing and decreases the stride length (83). Short hamstring also tend to rotate the pelvis backwards, thereby decreasing the lumbar lordosis (83, 90).

The definition of a short hamstring muscle varies in the literature; however, the measurement method consistently used in the clinic is the popliteal angle (71, 80, 87, 91, 92) (In these thesis named as the passive popliteal angle (PPA)). A PPA of 50° is characterised as a mild deviation (71, p. 194). In CPOP (93), the ROM is categorised in a colour system according to traffic lights (Figure 3): green is normal, yellow means there is a risk of contracture and the measurement should be followed and treatment should be changed, and red indicates severely reduced ROM and an intervention should be considered by an orthopaedic surgeon or paediatrician. In children with CP classified as GMFCS level I to III, a green value in the knee ROM is defined as ≤ 40°, a yellow value is 41°-49° and a red value is ≥ 50°. The definitions of these ROM limits were first suggested and used by the Cerebral Palsy Follow-up Program in Sweden (CPUP) www.cpup.se (94), and for GMFCS levels I-III they were based on the ability to dorsiflex in the ankle during gait. Figure 5 shows PPA related to age in children and youth with CP in CPOP (12).

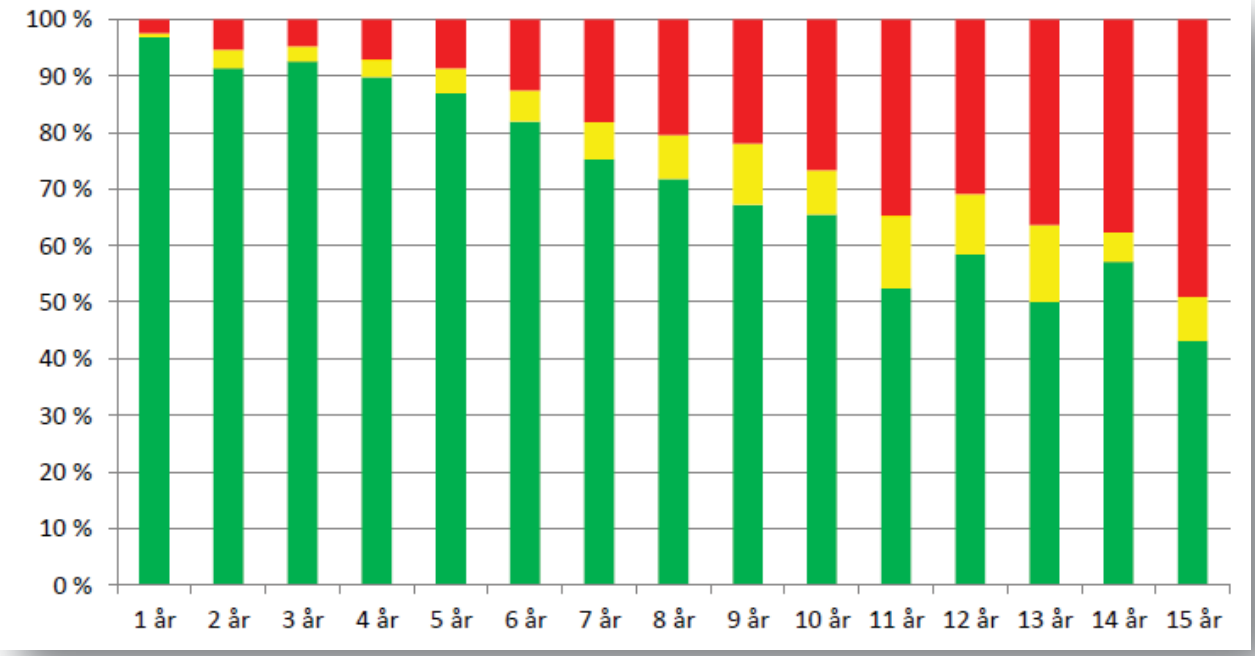


Figure 5: Distribution (%) of PPA categories (Green ≤ 40°, yellow 41°-49° and red ≥ 50°) by age in children with CP (GMFCS I-V) n=7591. Rendered with permission from CPOP (93).

1.4 Treatment and follow-up during childhood

The CPOP follow-up program

In the previous decades, several national and local quality registers and surveillance programs have been established to monitor specific diagnostic groups. The goal of these registers is to document the development, treatment, and results of treatment to be able to optimise treatment and to maintain function and quality of life. Most registers also collect data for research purposes to study prevalence and evaluate the quality and equality of treatment (95). Studies based on register data have several strengths. The data already exist, making it faster and less expensive to collect, and there are often large samples covering the total target population, and therefore such studies often achieve good statistical power and representativeness (96).

Two registers currently monitor children and youth with CP in Norway. The CPRN monitors the prevalence of CP, and its purpose is to identify risk factors and causalities, with the goal of reducing the prevalence of CP (12). CPOP (12) is a systematic registration of CP subtype, motor function, ROM, spasticity and interventions targeting motor function, which aims to identify and contribute to the prevention of secondary impairments at an early stage. Both registers are consent-based. The CPOP was launched in Helse Sør-Øst in 2006, and in 2010 the rest of Norway was included. Hip and spine X-rays are performed depending on the age and level of function. Assessments are performed at the 21 habilitation units in Norway once per year until the age of 6 (twice per year before 2015). Thereafter, the assessment continues to be conducted yearly for children at GMFCS levels II-V and once a year for GMFCS I, until the age of 18. The goal of the register is to reveal relationships, occurrence and need for continued intervention to prevent severe contractures, hip dislocations, scoliosis and other secondary impairments from evolving into severe disabilities. The CPUP register in Sweden has shown that a multidisciplinary follow-up and the early detection of emerging complications in individuals with CP can result in less complex and more effective interventions than if treatment is implemented at a later stage when the symptoms have already emerged (97, 98).

Treatment alternatives in the management of cerebral palsy in Norway

For most children with CP, physiotherapy is an important part of growing up. The three main components of the interventions applied to these children today are maintaining ROM, improving muscle strength and facilitating mobility. Individualised goals are key elements and focus on activity and participation in the child's local environment (12). According to CPOP, approximately 90% of all children with CP in Norway receive physiotherapy; 81% receive therapy one to two times per week, and 24% receive intensive treatment periods (> 3 times per week) (12).

Due to the complexity of the CP diagnosis, multidisciplinary treatment has been recognised as very important. In addition to physiotherapy, 55% of the children included in the CPOP receive occupational therapy, 76% participate in physical activities in kindergarten or school, and 47% attend physical activities during their spare time (12).

Different medical and surgical treatment alternatives for children with CP exist (99, 100), and the actual modality offered depends on age, severity, and type of CP. In ambulant children,

3DGA, together with a clinical examination, is an important instrument in the evaluation and decision making. Medical treatments such as botulinum-neurotoxin A (Bo-NT-A) injection, oral or intrathecal baclofen (ITB), or a selective dorsal rihzotomy (SDR) are interventions that are used to decrease spasticity. According to CPOP (12), 638 out of 1415 (45%) children received Bo-NT-A from 1 to 12 times (from 2002-2017), 45 (3%) received ITB, and only 13 children have had SDR. Orthopaedic surgery procedures, such as tenotomies or bony corrections (often performed as multilevel surgeries) are the preferred alternatives to maintain or improve function when muscle contractures and malalignments restrict joint motion, hinder optimal function and gait, and maybe also are a source of pain (101, 102). In the CPOP register, 310 (22%) children from all GMFCS levels have had one or several orthopaedic procedures in the lower extremities (12).

To prevent contractures, correct abnormal gait and facilitate gait training and activity, orthoses alone or combined with physiotherapy are an important part of the conservative treatment regime (103). In the CPOP register, more than 80% of the children at GMFCS levels II, III and IV use orthoses; ankle foot orthoses (AFOs) are used most frequently (60%), and half of all the children with CP in Sweden uses AFOs (103).

Orthosis, medical treatments and orthopaedic surgery are essential parts in the management of secondary impairments in children with CP; however, these interventions are not within the scope of this thesis and will therefore not be further discussed.

Theoretical framework of physiotherapy in cerebral palsy

In the past, different theories have been suggested to explain and describe how human movements are developed and controlled, and the different theories reflect different views about how the brain controls movement (104, 105). In the 1950-60s, the reflex theory and the hierarchical theory of motor control/human movement were the most prominent theories, followed by motor programming theories, explaining movement by central motor patterns (105, 106). These theories explained movement as a top-down hierarchal structure by which the higher centres controlled the lower centres. Motor development was understood as a maturation of the central nervous system, which resulted in the development of higher levels of control over the lower level of reflexes. Any damage to the brain would result in damage to the reflexes, and the treatment would be to facilitate normal motor patterns and inhibit reflexes (105) .

In the early 1990s, systems theory became the emerging theory in physiotherapy. This was a theory based on Nicolai Bernstein's ideas from 1967 (105). An old theory was now representing a new way of understanding motor control. The whole body was understood as a mechanical system with external and internal forces interacting with each other. The body was described as a mechanical system with joints and muscles and multiple degrees of freedom. Coordinated movements depended on stabilised body segments in order to allow others to be moved. External forces, such as gravity and reaction forces from the ground surface, acted on the body, and internal muscular forces acted on the external forces, providing stability and control to accomplish a task (105).

Woollacott & Sumway-Cook presented the systems theory approach and stated that the best method was to combine elements from different systems theories (105). They argued that movement arises from the interaction between an individual, the task and the environment, and suggested that the examination should focus on; 1) functional skills in the areas of interest (gait, postural stability, etc.); 2) strategies used to complete these functional skills; and 3) impairments constraining the strategies used to complete these skills. Interventions should be directed towards changing the individual's constraining impairments and manipulating the task and environment to promote motor learning (104, p. 117).

In the last 10-15 years, evidence-based physiotherapy, which is task-oriented and more intense in terms of effort and more physically demanding practice has been advocated. Exercise devices such as treadmills, weight machines and free weights are used, both administered by the PT and also as home exercises programs (99). Damiano et al. (99) described new trends in physiotherapy related to the overall important components that are essential in physiotherapy for children with CP (GMFCS I-III). To promote independent mobility, the child needs; 1) adequate active ROM that is not greatly disturbed by spasticity, dystonia or contractures; 2) adequate muscle strength to maintain body weight support, (sometimes with assisting devices); and 3) stability and motor control to allow advancement of the limbs forward in order to take efficient gait steps. To enhance gait function and daily life activities, each of these aspects should be addressed by the multidisciplinary team working with the child. Conceptual models of treatment like the World Health Organization's International Classification of Function, Disability and Health (ICF) (107) have shifted the focus from impairment and disability towards activity and participation. Families and the individual patient are now highly important participants in goal setting and selecting treatment

strategies (99). Nevertheless, the importance of addressing impairments to maintain or minimise future deformity or disability, as they are known to regress during childhood and adulthood (4, 58, 60), are still advocated (99).

Muscle strength training

In recent decades, resistance training of the lower limbs has become an accepted and often used modality in clinical practice for children and adolescents with CP (108-112).

Specific muscle strength exercises were previously not an accepted intervention for children with CP. There was an opinion that strength exercises could increase spasticity; however, this was disproved by several experts (49, 113). Diane Damiano was one of the first to advocate strength training as an effective method for increasing muscle strength in children with CP (49, 109, 114). In the years to come, several studies showed that strength training is safe and effective in improving muscle strength (111, 115-118). From 2002 to 2008, five out of six reviews (108, 109, 116, 119-121) concluded that muscle strength training in children with CP was effective; however, the effect size was inconsistent. Despite this inconsistency, the consensus was that children with neurological impairments could benefit from strength training, but the content of the training protocol was emphasised as highly important (112, 122). Progressive resistance training (PRE) was first described by Delorme and Watkins in 1948 (123), and the principles of a small number of repetitions until fatigue, sufficient rest between sessions and progressing the load upon gaining strength are still frequently used. The recommendations of the North American Strength and Conditioning Association (NSCA) (124) are evidence-based guidelines for strength training in young TD children. These guidelines are widely used, and they emphasise the importance of sufficient intensity, volume and duration to improve muscle strength. The guidelines were developed by experts in the area of resistance training in children and adolescents and are based on a large body of evidence. There is consensus in the field concerning resistance training in children with CP that these recommendations, following PRE principles, also should be used in these children (108, 109, 116).

The NSCA recommendations include load and progression guidelines for children with some training experience; 60-80% of 1 repetition maximum (1RM) (maximum weight load performed in one repetition), 2-3 sets and 8-12 repetitions, 2-3 times per week (124). A 1RM test is a demanding test, and a modified 8RM test can be an alternative, as described by

Scholtes et al. (118). 8RM is defined to be approximately 80% of 1RM (125), which is the weight load the child manages to repeat maximum 8 times. The correct initial weight load (for the lower extremities in an upright position) for children with CP performing an 8RM test is based on a loaded sit-to-stand test based on the GMFCS level and weight, as presented by Scholtes at al. (118). In a sit-to-stand exercise, the children with GMFCS levels I, II or III have a load of approximately 35%, 30% and 25% of their body weight, suggested as a "starting weight", respectively.

Nevertheless, the NSCA guidelines were developed for TD children and youths, and Verschuren at al. (112) discussed whether the reduced effect on muscle strength found in children and adolescents with CP compared to their TD peers could be due to impaired neural adaptation to resistance training. By reviewing the protocols used in former studies, the authors assessed the duration and intensity of the exercises in addition to the age of the children performing the strength training. They concluded that the NSCA guidelines for strength training should be used when designing strength training protocols for children with CP, but they also suggested five additions to the guidelines:

1) single-joint resistance training (in addition to multi-joint exercises)
2) more than 1 min between sessions
3) longer intervention periods, with adequate intensity (e.g., 12 weeks)
4) older children (>7 years of age) are better suited to this intervention
5) if voluntary contractions are difficult, electrical stimulation or biofeedback could be helpful

Stretching

There are three types of manual muscle stretching techniques described in the literature; static, dynamic (ballistic) and pre-contraction stretches (126, 127) (Figure 6). The static stretch technique is the most commonly used. The end position for the muscle length is held with the muscle in tension to a point of stretching sensation; however, not to the extent that it is painful. The stretch is held for a given number of sec and repeated for a given number of times. This can be performed either by the patient or by assistance from a partner or therapist. This static technique is supposed to reduce the reflex contraction of the muscle spindle and, in theory, when a stretch is held long enough, effects from the type I and II afferent fibres of the muscle spindle can be minimised (126).

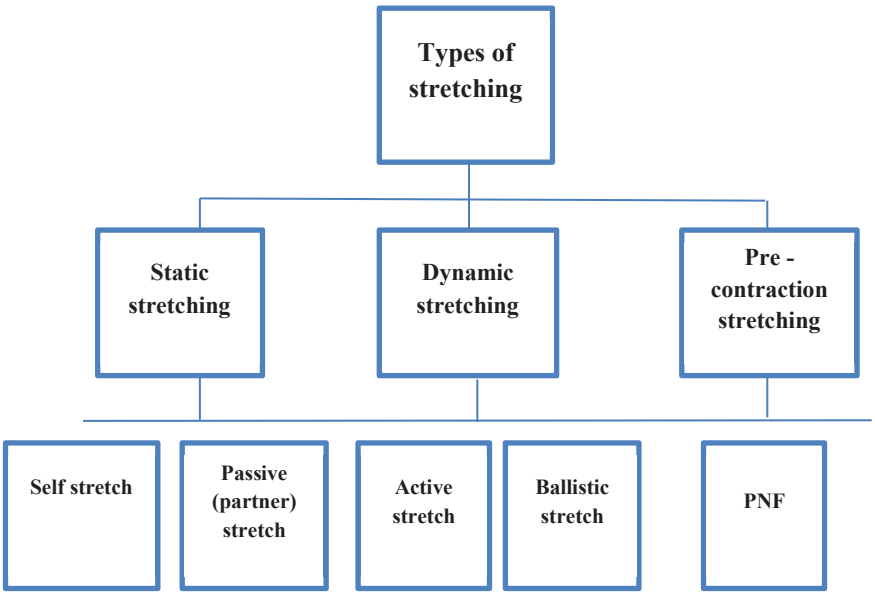


Figure 6: Different types of stretching.

There are two types of dynamic stretching approaches. The dynamic stretch involves moving the actual limb through the full ROM and repeating the movement several times at slow speed. Dynamic ballistic stretching includes rapid alternate movements, or bouncing, at the end-range of movement, but is no longer a recommended technique in TD and is not recommended in CP, as the bouncing activate a contraction/catch (H-reflex) in the stretched muscle (126, 127). Pre-contraction stretches involve contraction of the muscle being stretched, or the antagonist of the muscle being stretched, before the stretch is performed. Pre-contraction stretches are supposed to promote neuromuscular mechanism responses through stimulation of the proprioceptors. The proprioceptive neuromuscular facilitation (PNF) method, called "contract-release", is one of several methods covered by this umbrella. Contract-release is a method where the antagonist to the target muscle is activated by a concentric contraction to stimulate a reflexive relaxation in the agonist (126).

Longer-lasting stretches with casts, orthoses and standing frames are often used in CP (12, 103). However, these types of stretches are not within the scope of this thesis and will not be further discussed.

Stretching in cerebral palsy

In physiotherapy, static, active and passive stretching has often been and remains a widely used treatment modality for children with CP (99, 128). The assumption is that repeated stretching sessions may prevent and delay muscle stiffness and contractures, preserve joint motion for functional movement and delay surgery.

The reasons for the increased stiffness in CP muscles may be both neural (spasticity) and mechanical (MTU length), and both can theoretically be addressed by stretching. However, reviews looking into the evidence for stretching in people with neurological diseases (129) and in CP only (130, 131) have not demonstrated any convincing clinical benefits from this treatment modality. Novak et al. (128) carried out a systematic review and included different interventions provided to children with CP. The authors described manual stretching as an ineffective intervention and categorised it as "probably should not do it".

There are studies that have reported some minor beneficial effects on ROM and spasticity after stretching in children with CP; however, these studies included small numbers of children, the stretching intensity and frequency varied extensively (10-60 sec/3-5 reps/3-5 days per week/one occasion - 2 years), and the methodology did not have a high level of evidence (132-135). In a more recent (but small) study, Theis et al (136) performed an experimental intervention including eight ambulant children with CP. The children performed 5x20 sec static triceps surae self-stretch in addition to a stretch by a PT. Independent of the stretching technique used; the participants achieved a significant acute elongation of the triceps surae measuring approximately 10° of increased dorsal flexion post stretch. The MTU length was calculated using 3D coordinates and ultrasound. The authors found a transient increase in muscle (0.8 cm), fascicle (0.6 cm), and tendon (1.0 cm) length.
In another small study (137), 13 children with CP, GMFCS levels III and IV, were randomised to either an experimental group or a comparison group. The intervention group performed stretching for six weeks, four days per week, with a total of 15 min of stretching on each leg, 60 sec per repetition and 30 sec of rest. After six weeks the intervention group demonstrated a 3° increase in maximum ankle dorsiflexion. The authors also found a 13% reduction in triceps surae stiffness and no change in tendon stiffness, increased fascicle strain, but no change in the resting fascicle length. They suggested that the reduced muscle stiffness was due to alterations in the intra/extra-muscular connective tissue (137).

Elongation of an MTU for a given stretch intensity is determined by muscle and tendon stiffness, which in turn depends on the dimensions and properties of the muscle. Hence, how the MTU adapts to stretching and the stretch intensity is probably different in CP muscles compared to TD muscles. There is no consensus about dose–response for flexibility training and stretching, neither in TD muscles nor in CP muscles. There are no general recommendations for children with CP, but some recommendations are available for TD adults. Garber at al. (138) recommended a frequency of ≥2-3 times per week, with greater gains upon daily exercise. Bandy et al. (139) found that a 30 sec duration is the most effective amount of time to sustain a hamstring stretch and found no further benefit when increasing the stretch from 30 to 60 sec. There are different recommendations for stretch duration in TD adults, from 1 min (138) to 3 min (140). However, a 5 × 20 sec stretch set also showed a transient effect on triceps surae lengthening in children with CP (136).

1.5 AIMS OF THE THESIS

The overall objective of the present thesis was to study the development of hamstring length and spasticity during childhood in walking children with CP (Paper I) and to evaluate whether a specific stretching and strengthening program had any positive effect on the popliteal angle, muscle strength (Paper II) and gait function (Paper III).

Specific aims

I To evaluate how the popliteal angle and hamstring spasticity change during childhood in a cohort of walking children with spastic bilateral CP, GMFCS levels I, II, and III.

II To evaluate the effects of a 16-week combined muscle stretching and PRE program on the popliteal angle and muscle strength in children with spastic bilateral CP, and to evaluate the effects of a 16-week maintenance program.

III To evaluate whether a 16-week combined hamstring stretching and PRE program, focusing on terminal knee extension and the extending muscles in the lower extremities, could improve the kinematics and gait efficiency in children with spastic bilateral CP, and to evaluate whether a 16-week maintenance program could preserve the possible gained improvements.

2 MATERIALS AND METHODS

2.1 Study design

The cohort study (Paper I) was a population-based longitudinal register study based on data from the CPOP (12). The children were followed and tested according to a standardised protocol (141)(141). The register data, comprising clinical measurements that are essential in CP care, provided opportunities to describe how these children develop throughout childhood (4, 97, 142).

For the intervention study, a randomised, controlled, single-blinded study (RCT) was conducted (Papers II and III) (Figure 7). The RCT design was chosen to answer the research question of whether a specific intervention had an effect on the chosen variables compared with care as usual. An RCT is the gold standard used to demonstrate efficacy of a new intervention, and it represents the highest level of evidence in clinical research (143, 144). The children randomised to the intervention group received an exercise program that included hamstring stretching and PRE training of the lower extremities, and the children in the comparison group received care as usual.

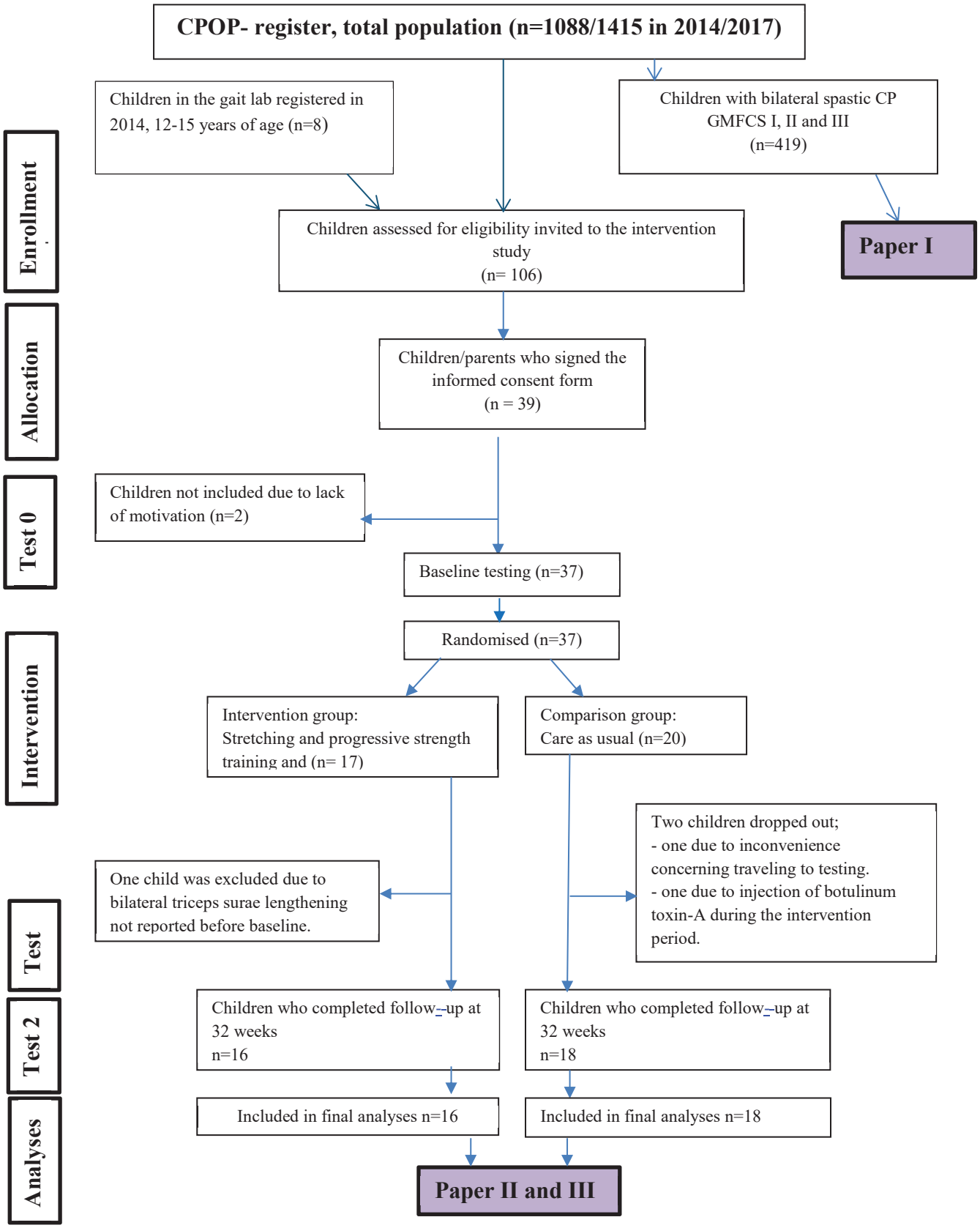


Figure 7: Flowchart of enrolment, allocation and follow-up for all children included.

2.2 Subjects and inclusion procedure

The CPOP follow-up program was developed and organised following the Swedish follow-up model (CPUP), which was originated in 1994 (94). The clinical registrations are performed by the PTs in the regional habilitation units or by the child's local PT**.** The register covers approximately 90% of all children who have CP in Norway (12). Clinical information about PPA and hamstring spasticity from all children, 1-16 years of age, classified with bilateral CP, GMFCS I, II and III was extracted for the present cohort study (Paper I).

The children who were invited to participate in the intervention study (Papers II and III) were primarily recruited from the CPOP register (Figure 7). The oldest children in the study were recruited form the patient register of the Oslo Motion Laboratory (Figure 7). The baseline test (T0) and the follow-up tests at 16 weeks (T1) and at 32 weeks (T2) were performed at the motion laboratory and at the biomechanical laboratory at Rikshospitalet/Oslo University Hospital. To meet the required sample size calculated for the study we had to expand the age range from 8-14 years to 7-15 years of age, and Haukeland University Hospital in Bergen also agreed to take part in the study; therefore, four additional children from Bergen were included. At Haukeland there were no available isokinetic muscle test machine; hence there were no muscle strength data from these children.

Table 2: Inclusion and exclusion criteria for children with CP (Papers II and III)

Inclusion criteria	**Exclusion criteria**
Spastic bilateral CP	Hamstring tenotomy, bilateral lengthening of the triceps surae. Any other surgical procedure in the lower limbs less than one year prior to inclusion
Age between 7 and 15 years	Botulinum toxin-A-injections in the lower limbs in the six months prior to inclusion
GMFCS I, II and III	< 0° dorsal flexion in the ankle joint
Able to walk 10 m indoors without walking aids	< 5° external rotation in the hips
Passive popliteal angle (PPA) ≥ 35° in the most affected leg.	Unable to cooperate or understand instructions.

The children were invited to participate in the RCT by written information sent by mail. After the child and the parents had decided to participate in the study, the child's local PT was contacted by telephone. The PT received written information about the study and were asked if they would participate in the study as a project PT.

The parents and children who met the inclusion criteria (Table 2) and gave written consent initially performed the baseline test at the hospital. The randomisation procedure was prepared by a colleague with envelopes containing blocks of four numbers and a variation of combinations of A (intervention) and B (controls).

To enable a controlled single-blinded study, the two assessors performing the tests at the hospital were masked for the intervention. The children were told not to disclose the group allocation to the assessors, and none of the children revealed their group allocation to the testers.

After the randomisation procedure, the unmasked project manager informed the local PTs of the group allocation. In addition to a detailed protocol (sent by e-mail), an online instructional film described the exercises. The film was distributed via YouTube www.http//ous-trening.MF. Only the PTs in the intervention group were informed about the film. The intervention period was started as soon as possible—not more than two weeks after the

baseline evaluation was performed. The unmasked project manager was available by phone and e-mail throughout the entire intervention period.

A registration form was distributed to the local PTs, both in the comparison group and in the intervention group. The local PT treating the child was responsible for filling out the form. In the comparison group, the physiotherapy treatment (care as usual) was described. All registration forms were returned to the project manager by mail after 16 and 32 weeks.

2.3 Outcome measures

Table 3: Outcome measures included in Papers I, II and III

Outcome	Paper		
	I	II	III
Popliteal angle	x	x	
Hamstring spasticity	x	x	
Isokinetic quadriceps and hamstring strength		x	
Kinematics in the sagittal plane: knee, hip and pelvic angle at foot strike and minimum knee angle in stance.			x
Gait speed			x
Step length			x
6-Minute walk test			x
Gait deviation index			x

2.4 Clinical tests

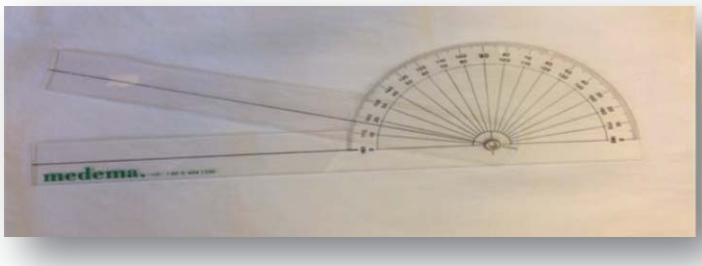
The data (hamstring ROM and spasticity) extracted from the CPOP register was collected at the 21 habilitation units in Norway (Paper I). Two testers who attended the CPOP instructional courses were responsible for the testing. An instruction guide was also available on their webpage (141)(141). The hamstring spasticity test and the popliteal angle measurement are two of several clinical measurements described in the CPOP protocol. The types of interventions (surgery, Bo-NT-A, physiotherapy, orthosis) the children underwent since their last assessment was also stated in the registry.

In the RCT (Papers II and III), the ROM tests and hamstring spasticity test were performed in the motion laboratory. The clinical tests were always performed by two experienced testers. One of the testers attended all the tests.

Goniometric measurement

Goniometric measurements are the most used method for evaluating joint ROM in children with CP (Picture 1). Several reliability studies have been published and show that measurements performed on the same day by the same tester have higher reliability than measurements performed on different days by different testers. Intra-rater reliability is shown to be higher than inter-rater reliability (145-147). Methodological studies have found high variability in the popliteal angle (146-149). For this reason, a small reliability study including 11 children was conducted in the Oslo motion laboratory prior to the intervention study. We found an intra- and inter-rater variability of ± 10˚ (unpublished data), which were in line with previously published reliability studies (147-149).

Picture 1: A plastic goniometer, with one degree increment, one stationary and one movable arm.



The popliteal angle

The passive popliteal angle (PPA) (Picture 2), usually called the popliteal angle (71, 150, 151), is also described as the "functional popliteal angle" (87, 100). It is one of the variables obtained from the CPOP protocol and is presented in Paper I and Paper II**.** The PPA is the main outcome variable in Paper II**.** In addition, we also measured the active popliteal angle (APA), also called the active knee extension test (152).

The unilateral PPA is measured with the child lying supine on a bench. The contralateral knee and hip are fully extended on the bench while the ipsilateral hip is flexed to 90°. The 90° position of the hip is fixed by the tester while the knee is extended to the endpoint of the hamstring muscle, and the angle between the thigh and the leg segment is measured using a plastic goniometer (Pictures 1 and 2). The PPA is a widely used clinical measure for assessing hamstring length (76, 83, 86-88, 151, 153-155). However, the validity of the PPA as a direct measure of hamstring length has been questioned (87, 90). The inter- and intra-rater reliability have also been questioned by several authors (145-148), and the test should be used with caution. To minimise the variability, it is strongly advised to be performed by two testers and that the same observer should repeat all tests (91, 147, 148).

The APA (Paper II) was measured in the same position as the PPA, with 90° flexion in the hip (fixed by the PT), but the child actively extended the knee as much as she/he managed, and the APA was measured at the end position using the goniometer. The APA assesses the child's ability to activate the quadriceps in a shortened position and to actively extend the knee joint when the hamstring is in a stretched position. The APA is not extensively described in the literature; however, a reliability study was performed in healthy adults and showed excellent reliability (152).

Picture 2: The PPA, APA and hamstring catch was measured as the number of degrees missing from full extension. Picture from CPOP webpage (141)

Hamstring spasticity

The most frequently used measurement scales assessing spasticity in CP are the Ashworth Scale (156) and the Modified Acworth Scale (MAS). In the CPOP, spasticity was evaluated with the MAS (157) (Paper I). The validity has been verified (158, 159), and the test–retest and inter- and intra-rater reliability have been described as moderate to good (160, 161). The test was performed with the child positioned supine on a bench. The hip was passively flexed to 90˚ by one of the testers, and the contralateral knee was extended on the bench and fixed by the other tester. The knee was rapidly extended, and the spasticity was graded as 1, 1+, 2, 3 or 4. The grading depended on the muscle resistance during the knee extension.

In the RCT (Paper II), the hamstring spasticity was measured by the Modified Tardieu Scale (MTA) (150). The original Tardieu scale is a very time-consuming test and was simplified into the Modified Tardieu (150) to make the test more usable, only registering the moment of catch (rapid stop) felt in the tested muscle (R1). To avoid any extra tension and spasticity in the hamstring muscles, the spasticity test was performed only once, prior to the other tests. It was tested with the child in a supine position with 90º flexion of the hip joint, the knee was then rapidly extended and the catch (R1) was felt; the angle was measured with a goniometer (Picture 1 and 2).

Muscle strength testing

Isokinetic muscle strength of the knee extensors and flexors was measured using a Cybex 6000 (Cybex-Lumex Inc., Ronkonkoma, NY, USA) (Picture 3). The ROM was set to 0-90º flexion/extension, which is the most established ROM used for isokinetic quadriceps/hamstring muscle testing in healthy adults (162). The children were seated in the Cybex (Picture 3), and a pillow was placed against the back if necessary. The less-affected leg was tested first. The child performed five repetitions at an angular velocity of 60º/sec, measuring the muscle strength as peak torque (PT) in Newton meter (Nm). The peak torque value is the peak point in the knee flexion–extension curve and occurs where the highest force is produced. The isokinetic muscle test has been shown to be highly reliable in children with CP (163).

Picture 3: Isokinetic muscle testing position.

Six-minute Walk Test

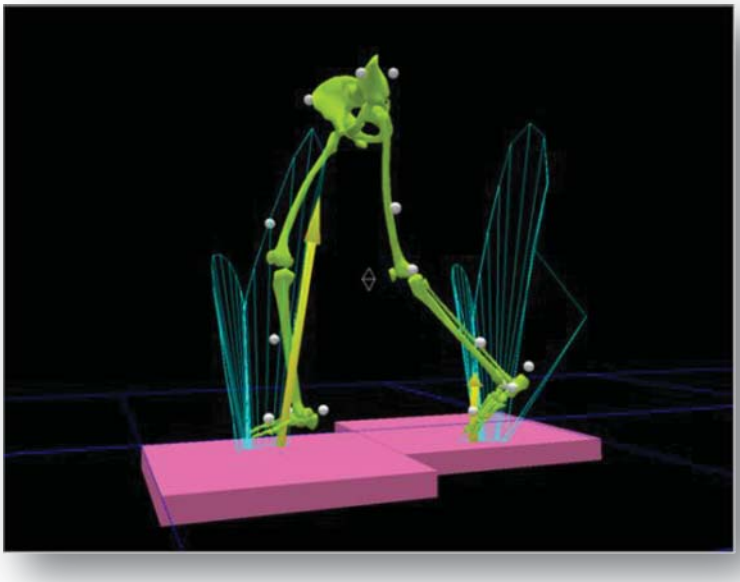
The children's walking capacity was measured using the 6-minute walk test (6MWT) (164) and was organised by the local PTs. Detailed information about when and how to perform the test was given by written information, following the American Thoracic Society 6MWT guidelines (164). The 6MWT has been shown to be valid (165), and the test–retest reliability (166, 167) was shown to be good to excellent in children with CP. To avoid a biased test, the local PT in the intervention group was asked to find a colleague (not engaged in treating the child) to perform the test. Written detailed instructions for setup and management of the test were sent to this person by e-mail. The results from the test were reported by e-mail to the unmasked project manager.

3D-Gait Analysis

3DGA was performed at two motion laboratories (Oslo University Hospital and Haukeland University Hospital), both with a Vicon system (https://www.vicon.com/) with identical setups. The two laboratories have six MX 3D cameras, two 2D cameras and three and two AMTI force plates (https://www.amti.biz/), respectively. During the testing, the children wore

shorts and a small top, and 16 reflex markers were placed on the lower body landmarks according to the Newington–Helen–Hays model (Picture 4) (70). Two testers performed the testing procedure, and both had to agree on the marker placement. The highest reliability of 3DGA is in the hip and knee in the sagittal plan, while the lowest reliability is seen in the hip and knee transverse plane; changes less than 5° should be interpreted with caution (168). The children walked on a 10 m walkway at a self-selected gait speed until five trials of 3D-data acceptable for analysis were collected. From all five trials, gait cycle number two was selected, and the mean value from the five trials was calculated and used as the raw kinematic score of each event. The five trials were processed in Vicon Nexus 2.5., and gait events calculating the kinematics were performed using Vicon ProClac1.1.

Picture 4: A 3D model of the lower body showing the reflex markers



Gait Deviation Index

The Gait deviation Index (GDI) is a score derived from 15 gait features based on kinematics in the 3DGA (169). The GDI was calculated using the five collected trials, and it was processed by Vicon Nexus 2.6. It is an overall numeric score that expresses pathological gait and ranges between 0 and 100; scores above 100 indicate no pathological gait. The GDI is shown to strongly correlate with the GMFCS level (170) and has a test–retest repeatability of ±10 GDI points (171).

2.5 The intervention

The main aim of the intervention study was to evaluate whether a specific stretching and strengthening program had any positive effect on the popliteal angle, muscle strength (Paper II) and gait function (Paper III). The exercises included in the intervention program (Paper II and III) were chosen to stimulate the improvement and maintenance of knee extension. The combined intervention modalities were passive stretching of the hamstring muscle group and strengthening of the extended antagonists, mainly the quadriceps, triceps surae and the gluteal muscles, which all participate in extension of the lower extremities. The intervention program was performed two times per week together with the PT and once per week at home, a total of 48 sessions (32 sessions with the PT and 16 home-based sessions). At least one day of rest was required between the sessions.

The stretching exercises

The intervention program included two hamstring stretching exercises: picture 5a and 5b, and picture 6 (more extensively described in Papers II and III). The stretches were mainly passive; however, the stretches performed with the PT were performed with an active component, contract–release, also described as a proprioceptive neuromuscular facilitation (PNF) technique (126). While the hip was flexed to 90°, assisted by the PT, the child was instructed to bring the foot toward the ceiling, trying to extend the knee joint, and hold for five seconds, thereby activating the knee extensors (concentric quadriceps contraction). After the five seconds of quadriceps contraction, the PT instructed the child to relax, and the leg was passively stretched slowly to the end point tolerated by the child. The stretch was held for 40 additional seconds, performed as a static passive stretch method by which the muscle was slowly elongated and held in the end position with a constant pressure (126). However, this stretch should not be painful to the child. To avoid a reflex contraction from the muscle spindle, a slow prolonged stretch was applied. If a static stretch is held long enough any effect from the muscle fibre type Ia and II afferent fibres in the muscle spindle might be minimised (126).

Picture 5a:

The hamstring stretch performed by the PT. First, the PT stabilised the hip at 90°, then the child actively extended the knee as much as possible and held the quadriceps contraction for 5 sec.

Picture 5b:

As the PT held the leg, the child was told to relax. If possible and not causing pain, the PT exceeded the stretch to the passive end position and held this position for 40 more sec.

Picture 6:

The seated hamstring stretch is a passive stretch. The child counted to 45 (sec), with a 10-15 sec rest between the stretches for a total of 5 repetitions. This exercise was performed at home, once per week, for 16 + 16 weeks.

If the hip extension was less than 5° at the baseline evaluation an additional psoas stretch was performed. The child was positioned prone on a bench and underwent the same stretching routine as described for the hamstring: the child actively extended the hip for five sec followed by a passive assisted hip extension stretch for 40 sec; the cycle was repeated 5 times.

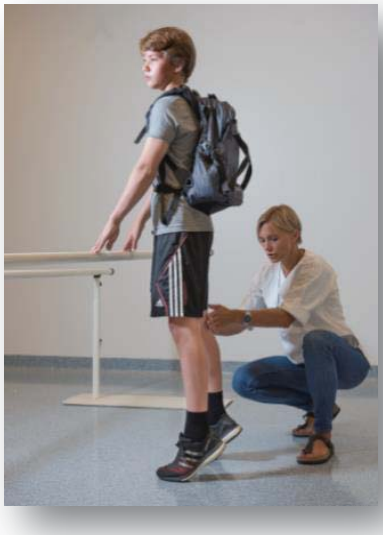
Progressive Resistance Exercises

The muscle strengthening part of the intervention program was designed following the guidelines of the National Strength and Conditioning Association (NSCA) by Faigenbaum et al. (124). In the present study, the intervention program was designed for ambulant children with CP using the NSCA guidelines; however, consideration and modifications for resistance training for children with CP described by Verschuren et al. were implemented (112).

All the children in the intervention group were given a Bergans® backpack, which was stable, with a well-fitted adjustable harness on the shoulder, and had a strap over the chest and hips. The exercises shown in picture 7, 8 and 9 were performed with stable shoes, and if a build-up was used in/on the shoe, they used it during the exercises.
To find the appropriate initial weight load for the backpacks, an 8RM test was performed in a functional upright exercise with a loaded backpack (Pictures 7, 8 and 9), guided by the child's weight and GMFCS level, as described by Scholtes et al. (118). The result of the 8RM test was used to guide the loading in the backpacks so that the child could perform the number of repetitions planned (not more or less). The progression was as follows: at the end of week 2 (12 repetitions x 3 series), week 5 (10 repetitions x 3 series), week 8 (8 repetitions x 3series), week 11 (8 repetitions x 3 series) (124).

Picture 7:

Squats – holding onto a bar for stability and focusing on full knee extension in the erected end position. Primary concentric activation of the quadriceps, triceps surae, gluteus maximus and hamstring when extending the knees, and eccentric activation of the quadriceps, triceps surae (soleus) and gluteal muscles when the knees are bending.



Picture 8:

Plantar flexion and heel rise with a focus on full knee extension in the erected end position while holding onto a bar for stability. Concentric quadriceps, gluteus maximus and triceps surae activation. When lowering down on the heels there is eccentric triceps surae activation.

Picture 9:

Stepping up stairs: concentric psoas, quadriceps, gluteus maximus and medius and triceps surae activation when stepping up. Primary eccentric quadriceps, and gluteus medius and maximus activation when stepping down.

According to recommendations for resistance training intended for children with CP (112), one of the exercises in the program was a single joint exercise (picture 10).

Picture 10:
Single knee extension was performed over a bolster; concentric quadriceps contraction, keeping full extension for 2-3 sec before relaxing.

Statistical analyses

In Paper I, the aim was to analyse how the PPA and hamstring spasticity change during childhood. We chose to present an interpretable multivariable model that shows the "big picture" of the longitudinal register data. Hence, a multivariable fractional polynomial linear regression model was used to fit age curves for the different GMFCS levels (172). The model included age (continuous variable), GMFCS level (categorical/dummy variable) and the interaction between age and GMFCS level (independent variables). The data were presented as the number of observations and percentage or mean and standard deviation, as appropriate. Due to the repeated measurement data in this study, a robust standard error (cluster sandwich estimator) was used on participants in the model. We used a multivariable fractional polynomial model in linear regression analysis that best predict the outcome variable using the default closed-test procedure algorithm (172). Measures from both legs were included in the analysis, and dependency between the observations was taken into account in the model. The linear prediction with 95% confidence interval for GMFCS levels I, II and III for PPA and hamstring spasticity in relation to age are presented as graphs. Two additional analyses were performed where the children who underwent hamstring tenotomy and SDR/ITB were excluded from the analysis.

For the RCT (Papers II and III), descriptive values were presented as the mean ± standard deviation. A paired-sample *t*-test (mean 95% confidence interval) was used to assess differences between T0 to T1 and T0 to T2 for the intervention group and the comparison group. To compare baseline variables between the intervention and the comparison group, an independent sample Student's *t*-test was used for continuous normally distributed data, and a Chi squared test was applied for categorical variables.

To calculate the mean differences between the intervention group and the comparison group at the test points T1 and T2 (Papers II and III), a linear regression analysis with covariates correcting for baseline variables (ANCOVA) was performed (173, 174). The age range in the group was considered to be wide, thus age was also added to the model as a covariate. A two-tailed value of $p<0.05$ was considered statistically significant.

In Paper II, a Hochberg adjustment procedure (175) was performed to account for the multiple comparisons problem (type I error) (176). This was not performed in Paper III due to fewer variables tested.

Technical errors caused some missing values (2.3%) from the isokinetic muscle strength measurements. This was handled by single imputation by group mean for each variable. This is a simple and pragmatic method for replacing missing values and can be performed when the missing values are few and are missing completely by random, as in this study (177). In Paper III there were seven random missing values from the 6MWT at T1 or T2; these were substituted by using single imputation by last value carry forward, which also is a method used when there are random missing values, as for this variable (177).

Sample size calculation

For the cohort study, no sample calculation was performed. This was due to a relatively high number of included children and repeated measures with longitudinal measurements from both legs, which led to a high number of measurements and was assumed to be adequate for the statistical method chosen.

The sample size calculation for the RCT (Papers II and III) was performed prior to the study start and was based on the variable PPA. Based on previous published studies (147, 149), in addition to the results from a small reliability study performed in the gait laboratory prior to the present study (unpublished data), we assumed that the standard deviation for changes in PPA should be 10˚. When comparing PPA in the two groups, an independent sample Student's *t*-test was used, with a 5% significance level. We considered a difference between groups to be of clinical importance if it was at least 10˚. To achieve 80% test power, at least 16 patients in each group had to attend the test at 16 weeks.

3 RESULTS

Paper I

Data were retrieved from 419 children with spastic bilateral CP who were included in the CPOP follow-up program. There were 47%, 28% and 25% children at GMFCS levels I, II and III, respectively. The mean age was 6.2 years (range 1-16 years), and 62% were boys. In total, there were 2193 assessments, with a mean of 4.3 assessments per child (range 1-16). Overall, 58% received one or more medical or surgical interventions (surgery/ITB/SDR/Bo-NT-A) during the observation period. Both legs were included in the curve estimates, resulting in a total of 4386 assessments. The results are shown as curve estimates for PPA (Figure 8a) and MAS (Figure 9a) at GMFCS levels I, II and III, from 1 to 16 years of age. The curves showed parallel increases in the PPA with age for all three GMFCS levels (Figure 8a); however, the differences between the levels were significant until 8 years of age. At 10 years of age there were no longer any significant differences between GMFCS levels II and III. At 14 years of age, the differences between all the three GMFCS levels were insignificant, with mean PPAs of 41° (CI 39-44), 45° (CI 42-50) and 44° (CI 39-50) for GMFCS levels I, II and III, respectively.

The curve estimates for the MAS (Figure 9a) were at the lower end of the scale for all three GMFCS levels (MAS 0-1+). There was, however, increasing, parallel curves from 1 to 4 years of age for all three levels. The difference was significant between all the GMFCS levels. The MAS curves for GMFCS levels I and II level off at 4 years of age and show a further slight increase until 15 years. For GMFCS level III, the curve slightly decreases from about 6 until 15 years of age. At the age of 14 years, the mean MAS scores for GMFCS levels II and III were slightly above MAS 1, and for GMFCS level I the score was significantly lower and slightly below MAS 1.

An additional analysis was performed excluding the 29 children who underwent hamstring tenotomy during the observation period (Figures 8b and 9b). The curves for GMFCS levels III then showed a wider CI band and a decrease in the PPA curve from the age of 8 (Figure 8b). GMFCS levels I and II were unchanged. A strong decrease was also seen in the MAS curves at GMFCS level III from the age of 6, while no changes were seen at GMFCS levels I and II (Figure 9b).

We also performed an additional analysis excluding the children who underwent ITB or SDR (n=14), but none of the curves showed any changes.

GMFCS I

GMFCS II

GMFCS III

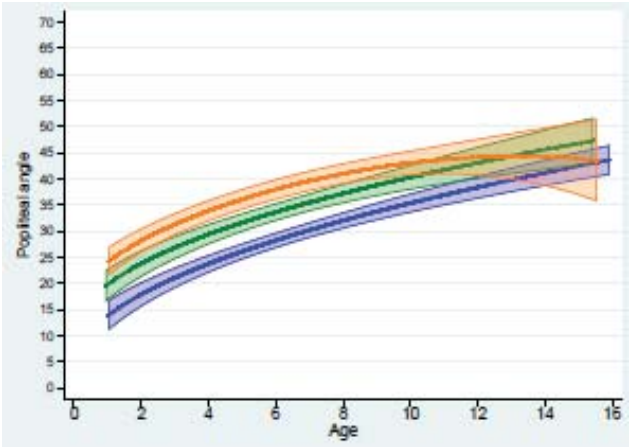


Figure 8a: Change in popliteal angle at GMFCS I, II and III, from 1-16 years

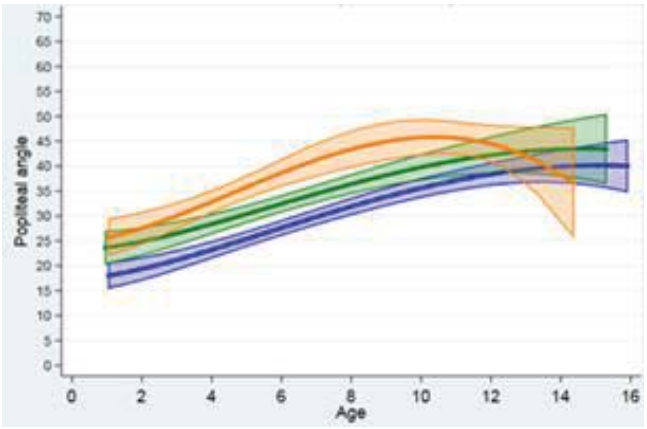


Figure 8b: Change in popliteal angle at GMFCS I, II and III, from 1-16 years. The 29 children who underwent hamstring tenotomy were excluded.

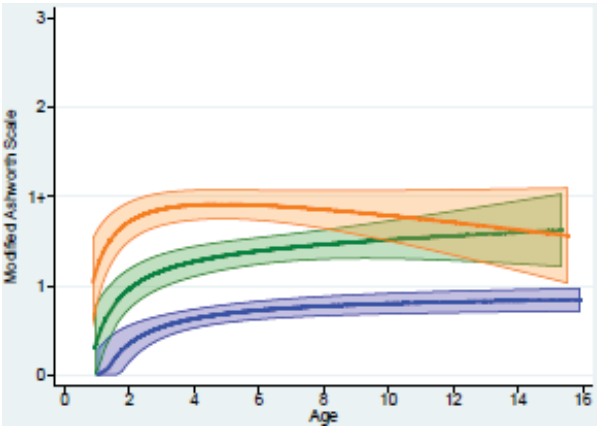


Figure 9a: Change in Modified Ashworth Score for GMFCS I, II and III, from 1-16 years.

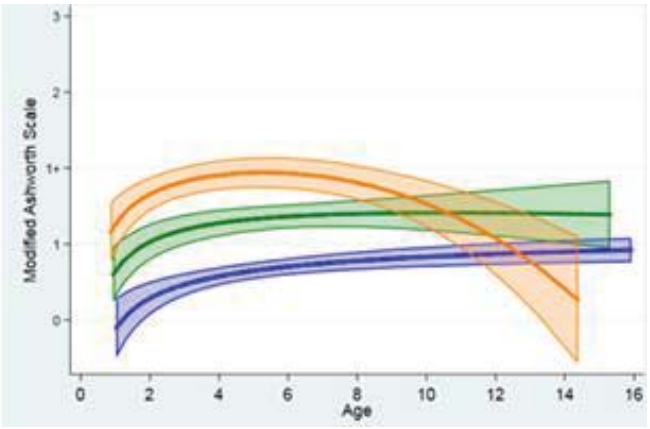


Figure 9b: Change in Modified Ashworth Score for GMFCS I, II and III, from 1-16 years. The 29 children who underwent hamstring tenotomy were excluded.

Papers II and III

Papers II and III were based on the results from the RCT. Thirty-seven children (21 boys, 16 girls) with spastic bilateral CP, with a mean age of 10.2 years (±2.3), and classified as GMFCS levels I, II or III were included. The compliance with the exercise program was registered using a form that was filled out by the local PTs, and 13 out of 16 (81%) PTs in the intervention group returned the form. For the 16-week maintenance program the compliance rate was 81%. Absences from the training sessions were primarily due to conflicting appointments and vacations. The increased weight load in the backpacks over the 16-week intervention period was 6.6 kg ± 3.8. The children in the comparison group received care as usual, and the content of their physiotherapy program was registered by their local PT. Approximately 60% of the children received one or more treatment modalities 1 to 2 times per week. Ten children received functional training and/or swimming and horseback riding once per week. Five children received specific strength training and/or stretching exercises; however, the frequency of the exercises seemed to vary extensively (from 3 to 10 sessions during the first 16 weeks).

Paper II

In Paper II the main outcome variable, PPA, and the secondary variables of APA, isokinetic quadriceps and hamstring strength, and hamstring catch were assessed for both legs. From T0 to TI there were small changes in the PPA, APA and muscle strength in favour of the intervention group (Paper II table 3). For PPA, the mean changes were 3.5°/4.3 °, and for APA the mean changes were 8.6°/7.5° for the left /right side; however, the changes were not statistically significant (boxplots showing PPA and APA for the right leg are shown in figures 10 and 11, respectively). There were not any statistically significant variables seen at T2 (Paper II table 3). At T1 there were insignificant changes in the muscle strength in favour of the intervention group, whereas no changes were seen in the spasticity at T1 or T2.

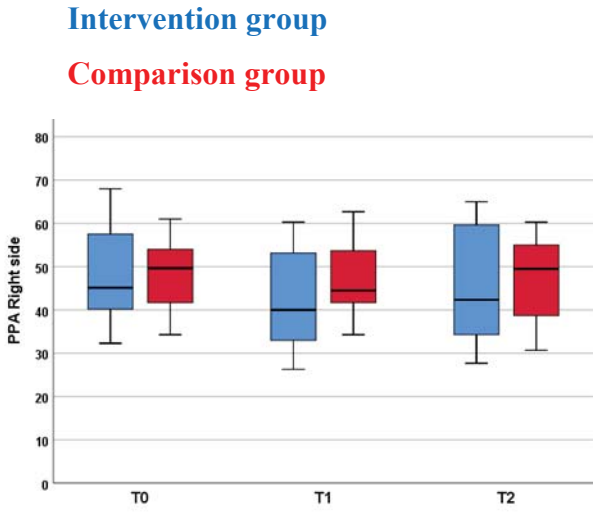


Figure 10: Passive popliteal angle (right side) for the intervention and the comparison group at baseline (T0), after 16 weeks (T1) and 32 weeks (T2).

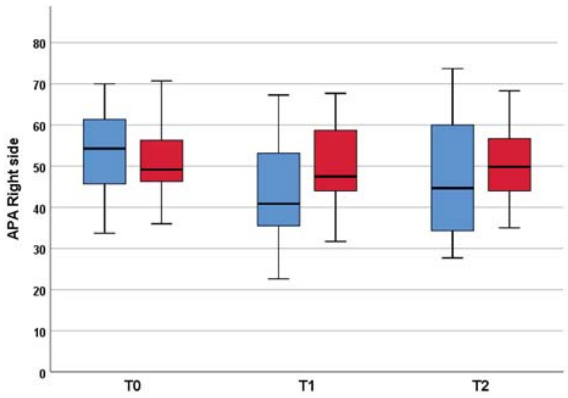


Figure 11: Active popliteal angle (right side) for the intervention and the comparison group at baseline (T0), after 16 weeks (T1) and 32 weeks (T2).

Paper III

Paper III reported the results from the secondary variables (knee, hip and pelvic angle in the sagittal plane at foot strike and minimum knee angle in stance, step length and gait speed, GDI and 6MWT) of the RCT. The statistical analysis showed no statistically significant differences between the intervention group and the comparison group for any of the gait-related measures (kinematics, step length, gait speed, GDI and 6MWT), either at T1 or T2 (Paper III table 3). There was, however, a significant increase in the distance walked measured by the 6MWT, for both groups (Paper III, Table 1), but there were no significant differences between the two groups, either at T1 or T2.

4 DISCUSSION

Main findings

The present thesis is based on the results from two studies that included children with spastic bilateral CP.

The main findings were that hamstring length measured by the PPA increased during childhood in all the three GMFCS levels (Paper I). The most affected children (GMFCS III) developed an increased PPA during early childhood (Figure 8a). The children at the highest functional levels (GMFCS I and II) also presented an increased PPA, but at an older age. The hamstring spasticity was located at the lower end of the MAS scale for children at all GMFCS levels. In Papers II and III, we found that stretching of the hamstring muscles and strength training of the extending muscles in the lower extremities seemed to have a small yet insignificant effect on the PPA, APA and muscle strength after 16 weeks. These small changes were not fully maintained after 32 weeks (Paper II). The intervention showed no effect on any of the gait parameters evaluated (Paper III).

Methodological considerations

Design

An observational cohort design was used to evaluate how the hamstring length and spasticity develop during childhood (Paper I). The data were retrieved from the CPOP follow-up program (12). An RCT design was chosen to evaluate the effect of a stretching and strengthening program on ROM, muscle strength and gait (Papers II, III).

An observational, register-based cohort study has several strengths (96, 178) (Paper I). All data have already been collected, and a study based on such data is not very expensive. The measurements, which are identical at every test point, might be repeated over a long period of time, resulting in a large number of observations, thereby minimising the chance of bias. In addition, a large sample size provides high statistical power (96, 179). In the CPOP follow-up program, the data are collected independent of a specific research question, which may reduce various types of bias, such as recall of former measurements and influence of an expected development from the assessors, which may produce bias. Another strength of a register study

is that it is complete as far as the persons in the target population are concerned, making the results generalizable (96). From 2017, approximately 90% of all children diagnosed with CP in Norway are included in the register, indicating that it represents almost the entire target population. Who is not included and why is unknown, and might be considered a weakness.

Not all of the data at the different time points are from the same children. The data are, however, collected from children belonging to the same cohort. Such longitudinal study protocols can be understood as a series of repetitive cross-sectional studies; hence, it should not be perceived as a statistical problem (180).

A longitudinal register-based cohort design has methodological limitations (96). The data used in the present study were collected in 21 different habilitation units located all over the country, indicating the input of several testers, which is a known weakness when collecting goniometric measurements (147-149, 181). The habilitation units are, however, encouraged to have one therapist responsible for testing the children included in the register. To minimise the expected variability when performing the tests and to ensure good quality and compliance with the register, the CPOP coordinators offer yearly seminars. At these seminars the test protocols (141) are discussed, and testers are updated on the results from the register. This is an important strength, making the data more reliable.

Paper II and III were based on results derived from the RCT. In research, the RCT design is the gold standard when evaluating the effect of an intervention and has the highest level (level 1) of evidence (143, 182). The purpose of the randomisation processes is to prevent systematic biases and to ensure that the intervention is the reason for the potential changes in the outcomes measured (143, 173, 182). The randomised allocation process does not itself ensure an unbiased comparison of the result. Systematic bias may occur through subconscious effects. The assessor might be affected by knowing who has received treatment. The randomised double-blind controlled trial, where neither the patient nor the tester knows which treatment was given, is described as the highest standard for a design of a trial (143, 182). However, only single-blinded design was possible in this study, as the intervention was impossible to conceal.

In the present study, children representing three different GMFCS levels were included. Due to a relatively small number of children, there was a risk of a biased distribution of these functional levels. To secure a balanced distribution of the three GMFCS levels, we discussed

the use of a stratification procedure (143). However, with such a small number of children eligible, to ensure an equal number of patients in each group (143) and to avoid a skewed distribution, we chose to use block randomisation (A= intervention and B= comparison group) with blocks of four numbers (143, 144). The randomisation was handled by an office manager who was not involved in the study.

The intervention was a combination of two therapeutic modalities, stretching and strength training, and to determine if one modality was more effective than the other, a design with four arms (comparison group, only stretching group, only strength training group and combined stretch and strength training group) should ideally be performed (183). This was, however, not possible to implement, as there were not enough eligible children in our health region.

Generally, randomisation intends to prevent a biased group selection (143, 182, 183); however, we are aware that there are several limitations in the present RCT (Papers II and III). To be able to include the number of children estimated by the power calculation (16 in each group), we had to extend the age range. When the project was in the planning process, the intention was to include children between 8 and 14 years of age. When checking the CPOP register, limiting the inclusion criteria to GMFCS levels I, II and III and a PPA >35° seemed feasible. However, after starting the inclusion process, we realised that there were not enough children available, and the age range was therefore expanded to 7-15 years. In total, 60% of the children who were eligible and who were invited to participate in the study did not answer the written request. Except for the inclusion criteria, we do not have access to any information about the children who did not agree to participate in the study.

The children included in the CPOP register go through a multitude of clinical and physical testing and physiotherapy sessions throughout childhood (12). The frequent physiotherapy periods and training during childhood might be a possible explanation for not wanting to participate in the present study. It is also possible that the extensive length of the intervention periods (16 +16 weeks) “scared” both the parents and children from accepting the invitation.

Another reason might be that children with CP are frequently asked to attend different studies, and therefore the present study was not prioritised. We might also have recruited more children to this project if the intervention could have been performed at school, together with other children during the daytime.

In an RCT, the internal validity is expected to be high because of the randomisation and blinding (183). The internal validity might be influenced by several methodological factors such as allocation, blinding, information bias, whether the participants complete the follow-up, and how devoted the patients are to the intervention (183). In the present study, due to relatively few children in each group and a wide age range, there are reasons to expect that the internal validity is hampered. Hence, we chose to perform a regression analysis to correct for the confounding factors (ANCOVA), such as baseline and age. After T0 and before T1, two of the included children dropped out of the comparison group and one dropped out of the intervention group. All three children dropped out for random reasons (Figure 4); thus, it should not introduce any bias or affect the internal validity (183). The registered compliance in the intervention group at 77% also indicates strong adherence to the intervention. The parents who accepted the invitation to the study were probably serious about completing the study, because they acknowledged the informed preconditions, such as the required intervention frequency, test frequency and length of the study. The internal validity was probably also strengthened by involving the local PTs. They knew the child and family from before, which probably is an important factor for acceptable compliance to the study in these children.

To ensure single-blind conditions, the testers were masked for the allocation groups. The children and parents were informed about the group allocation and were told not to reveal the "secret", of whether they were in the intervention group or not. No one revealed the group allocation to the testers, maybe because they thought it was fun having a secret. Due to the intervention protocol , which for most of the children was unlike the interventions they had received prior to the study, double blinding was not a feasible alternative. In theory, a sham or placebo intervention could have been performed instead of care as usual (143). However, as this study included children with a chronic condition who usually receive physiotherapy on a regular basis, it would probably not have been accepted by the Regional Ethics Committee.

To optimise the methodological quality of the present RCT, the children in the intervention group were trained by the same PT throughout the study period, and the treatment protocol was standardised (183). Nevertheless, we also knew that due to the wide difference in age and functional levels, these children needed some individual adaptations to the exercise program. In addition to the individual loading in the backpacks there were possibilities in the protocol

to make some individual adjustments to the program. If the children needed more balance support, or if he or she did not manage to put the same weight on both legs, it was accepted.

The result from an RCT can only be generalised to patients who fulfil the inclusion and exclusion criteria (183). This external validity issue limits the generalisability of the study results and represents a weakness in an RCT (183). For the present study, the results are valid for the source population—children with spastic bilateral CP GMFCS levels I and II aged 7-15 years. The children were mainly invited from the CPOP follow-up program, which covers 90% of the children with CP in Norway. This indicates that the children included in the study represent the target population; hence, the external validity is good (183).

Subjects

The 419 subjects included in the cohort study (Paper I) were 161 (38%) girls and 258 (62%) boys and were between 1 and 15 years of age (mean 6.2 ±3.1). The age was unevenly distributed and included more of the youngest children; therefore, the variability was larger among the oldest individuals. The explanation for this situation is that the register was started in 2006 and includes children born after 2002. The gender distribution was in line with the total population from the Scandinavian registers, showing 59% boys (9). The children were signed up to the CPOP follow-up program by their parents and agreed to be tested according to the CPOP protocol (141)(141). The parents are introduced to the CPOP follow-up program by a paediatrician or PT at the local habilitation units when there is a suspicion of a CP diagnosis.

One hundred and six eligible children were invited to participate in the RCT (Papers II and III), and 39 children agreed to participate; however, two children withdrew before the baseline test due to lack of motivation, and 37 finally underwent the baseline test. We included children with GMFCS levels I, II and III; however, only one child who met the inclusion criteria and agreed to participate was categorised at GMFCS level III. Therefore, this study is only representative for children at GMFCS levels I and II. The main reason why there were more children with GMFCS levels I and II in the present study is probably because the children had to be able to walk independently for at least 10 meters. The children at GMFCS levels I and II also function at a higher level and need less assistance when traveling to the PT, which was required two times per week.

The expanded age band (7-15 years) introduced higher variability; however, due to the randomisation process, the two groups were identical in terms of age at 10 (±2.3) years in both groups. Additionally, the differences between the two groups for height, weight and BMI were insignificant. Likewise, previous studies performed on children with CP have included children with wide age ranges, and none seem to be exactly the same (106, 117, 184-186). The mean ages in these studies are between 10 and 13 years. Due to a variation in age range, there were also variations in weight (26-45 kg) and height (115-145 cm), but the children in the present study are in the same range (mean 39 kg and 141cm) as previous studies.

The intervention

The RCT evaluated a specific intervention program focusing on passive stretching of the hamstring muscles, active knee extension, extension of the hip and plantar flexion of the ankle, combining stretching and strength training modalities. CP is by nature a complex and diverse diagnosis (2). The goal of physiotherapy is to obtain optimal functional mobility for participation in everyday life. When treating children with CP in clinical practice, PTs usually focus on both the body structure and function by combining different treatment modalities (12, 187). The intervention in the present study intended to reflect clinical practice. Several intervention studies in children with CP have been performed focusing on either stretching (130, 131, 136, 137) or strength training (49, 111, 114, 117, 184, 185). As far as we know, no intervention study has combined stretching and strength training and has assessed participation in everyday activities. Physical therapy for children with CP also includes participation in adapted physical activities and compensatory interventions, such as assistive devices and modifications of the environment, but this is not within the scope of this study and will not be discussed further.

To optimise the quality of selected interventions and test procedures, we should ideally have performed a feasibility study or a pilot study prior to the present RCT (182), both to evaluate how the children responded to the intervention exercises and how the PTs reacted to the intervention program, and to test the effect of the combined exercises. The main reason for not performing such a study was a limited cohort of eligible children in the CPOP. Inviting five or six children to a pilot study would have made it challenging to include an adequate number of eligible children in the present RCT.

Stretching exercises

The intensity of the stretching exercises was 5 sec active stretching and 40 sec passive stretching x 5. The purpose of the active extension was to actively overcome the tension in the hamstring muscles and to work on the active terminal extension when the hamstring muscles were stretched. Whether a reciprocal relaxation in the hamstring muscles was achieved is doubtful, as the reciprocal co-contraction and reduced reciprocal inhibition documented in CP may hamper that effect (188). However, the relatively low level of impairment and spasticity in this cohort (GMFCS levels I-III) might have made relaxation possible.

The literature is inconsistent according to how long a passive muscle stretch should be held in children with CP. It varies from 20 sec x 5 to 60 sec x 15 (132-137). Brandy et al. (139) showed no difference in effect between 30 sec and 60 sec when performing hamstring stretches in TD adults.

The hamstring stretch performed by the PT, having the child lying supine on the bench, was chosen as the main stretch exercise, because it is the best position for the child to relax and for the PT to control the hamstring stretch (126). The home exercise (seated hamstring stretch, with the stretch over the hip joint) was chosen because it is easier to perform alone, as the moment arm becomes bigger over the hip joint (126)

Strength training

When designing the intervention program for the present RCT, the NSCA recommendations concerning strength training for children and youth, which are described as a gold standard for muscle strengthening (124), were used as a guideline. The same principles are recommended for children with CP; however, some modification are discussed and described by Verschuren et al. (112). These modifications were taken into account in the present study.

The main part of the program only included functional upright multi-joint exercises loaded with a backpack (Picture 7, 8, and 9). Vershuren at al. (112) suggested that single-joint exercises should be added for the weakest muscle groups, because the children often tend to compensate when performing multi-joint exercises; thus, a single-joint exercise was included by adding the supine knee exercise over a bolster (Picture 10).

The work by Damiano (49, 114, 189), Verschuren (108, 112) and Sholtes (110, 117, 118) was important in terms of choosing exercises and estimating dose and intensity. However, to gain

further background regarding the choice of exercises and the optimisation of the intervention quality, and to be sure that the intervention was feasible, we contacted several senior PTs with extensive experience from working with children with CP. These were local PTs, PTs working in habilitation units and rehabilitation units, and PTs working as specialists in the field of CP. In addition to be effective, the intervention should also be feasible for the children, parents and the PT. Hence, in addition to the scientific evidence-based theory on training (108, 112, 124, 126), the senior PTs' experiences and advices were highly important and taken into consideration when the intervention program was designed.

Using a backpack for the weight loading exercises was a choice that was made primarily for practical reasons. However, it also made it possible to perform the exercises quite identically, independent of the equipment available at the clinics, and it was feasible to use at home. Scholtes at al. (110, 117, 118) used a weight vest in their intervention study. The weight vests are made for weight loading and are probably better equipment for loading exercises, but they were not possible to acquire for such a big group of children. By using less equipment, and using equipment that most children can obtain and afford, the intervention program can more easily be repeated by others.

The main intention of the exercises selected was primarily to increase passive and active terminal knee extension and increase muscle strength in the extending muscles in the lower limbs (hip, knee and ankle). Hip flexion strength has been shown to explain much of the variants in gait (6MWT) (190) and may be one reason for the missing effect on gait function. Plantar and dorsal flexors in the ankle and hip abductors have also been shown to be important for gait function (191), and these muscles were activated in the squatting, heel rise and step up exercises; however, the focus was mainly on the knee extension.

Outcome measures

The outcome measures included in the present study are clinical measures and functional measures that assess different aspects of gait function. The clinical examination focused on primary and secondary problems, such as spasticity, joint ROM and muscle strength.

PPA is a ROM test and is extensively used in the clinic and in research to evaluate children with CP (71, 79, 86, 88, 154, 192, 193). The PPA test was included both in the cohort study

(Paper I) and in the RCT (Paper II)**.** The PPA test was chosen because it is the most used clinical measure of hamstring length (79, 87). Compared to the bilateral popliteal angle, also known as the modified popliteal angle (87), the PPA is a better functional hamstring length measure as the contralateral hip is extended. In the RCT (Paper II and III), none of the included children had hip extension less than 0°, indicating an adequate psoas muscle length, which allowed the ipsilateral hip to relax on the bench. In the cohort study (Paper I), we did not have any information about prevalence of a short psoas, which may make the measure less reliable as a measure of hamstring muscle length.

The PPA is widely used in the clinic, but its reliability has been questioned (145-148). Both the intra- and inter-observer reliability have been found to be low; however, in general, the intra-observer reliability was found to be higher than the inter-observer reliability (146-148). Prior to the RCT a small reliability study was conducted in the gait lab. The unpublished data revealed a variation of approximately ±10°between days for the same assessors. To cope with this variability, the same two assessors performed the tests, and one of the two assessors measured all patients at every test. The assessors were experienced with measuring the PPA in their clinical work, and a detailed test protocol was followed. In the cohort study (Paper I), the PPA was measured by different assessors, which may introduced lower reliability. To address this problem, the CPOP protocol included a detailed description of the PPA test with pictures and text (141). Furthermore, the habilitation units employ skilled therapists who are responsible for the CPOP testing and who attend yearly workshops about the CPOP protocols.

We measured the APA to study the active knee extension in the terminal knee extension. The test has previously shown excellent intra- and inter-rater reliability in healthy adults (152, 194); yet, the test has not been validated in children with CP. It is possible that the reliability is weaker in these children, as we know that the selective motor control is reduced in these children, which might introduce some variability (52, 53). By studying the APA and PPA, we were able to test the active and passive knee extension and how much the hamstring restricted the knee extension. We could have performed the test in a seated position, but retraction of the pelvis and compensation movements is better controlled in the lying supine position.

The validity and reliability of the two spasticity tests used, MAS and MTS, are moderate to acceptable, and one is not described as superior to the other; however, the MAS is more often used both in clinical practice and in research studies (157-159, 181). Both the MTS and MAS have been criticised for simplifying the evaluation of spasticity because they are not able to

differentiate between a neurological stop or a non-neural contribution to the stop (159). The reason why two different tests were selected was that the MAS has been used for several years in the CPOP, and PTs in Sweden and Norway working with children with CP are familiar with the test. The MTS was chosen because this is the spasticity test that that we have been using in the Oslo Motion Laboratory during the last 15 years. MTS is also regarded as an easier test to score, as the angle for the hamstring catch (R1) is registered as a number instead of rating a felt muscular resistance, as in the MAS (157).

An isokinetic muscle strength test was used to assess the quadriceps and hamstring muscle strength at an angular velocity of 60°/sec. This method has been shown to be reliable in both TD children (195, 196) and in children (163) and adults (197) with CP. Rapid force generation is known to be impaired in children with CP (27), so we chose not to include additional higher angular velocities.

3DGA was used to analyse kinematic gait parameters, such as step length and gait speed. 3DGA provides information about an individual's gait pattern and how it deviates from the "normal" gait (69). Repeated gait measures can be used to evaluate the response to therapeutic interventions (168) and are widely used both in the clinic and in research (63, 67-69, 86). This instrumented way of analysing gait is the most objective way of measuring gait function; however, it is not free from measurement errors (168). Variability in the pre- and post-treatment measurements may be affected by the actual effect from the treatment, or by measurement errors, or by a combination of both. There are intrinsic and extrinsic factors that are important to handle for optimal reliability. Intrinsic variability is the variation of the child between trials. For example, the children walked at a self-selected speed, which might have introduced intrinsic variability. To handle this intrinsic variability, the children walked until 5 trials of 3D data with satisfactory quality were collected. The five trials were processed, and the second gait cycle from each of the five trials was selected, because it was in the middle of the trail, where the child was not starting or stopping, which could have changed the speed. A mean value from the five cycles was calculated and used as the raw kinematic score of each gait event; this method has also been used in other studies (81, 198, 199). Some studies have selected the most representative trial (200, 201). According to our knowledge, no method is more accurate than any other. Choosing one representative trial might introduce a bias by unconsciously selecting a specific trial for giving the best result. On the other hand, averaging the gait data might have reduced the variability in the gait pattern.

The GDI (169) is a score derived from the 3DGA and ranges from 1-100, and a score of 100 and above indicate a normal gait pattern. Malt et al. showed a strong correlation between GDI and GMFCS levels, with a GDI of 81 (±11), 71 (±11) and 60 (± 9) for GMFCS levels I, II and III, respectively. In the present study, there was a mean GDI of 79 at baseline, which according to Malt et al. (170) is as expected for the present group of children. There should be an increase by 10 points on the GDI scale to describe it as a clinical change (171). With a baseline GDI of 79 (Paper III, Table 1 and 2), there should be an increase of 10 GDI points to identify a clinical meaningful change, which may indicate that this measure is not sensitive enough to measure minor changes in gait performance when the children are GMFCS levels I and II.

Sample size and data analysis

In Paper I, the data were presented using a multivariable fractional polynomial linear regression model that provided an overall picture of how the PPA and MAS change with age (172). This is a robust model that takes into account the unevenly repeated measures and the dependency between measurements (both legs from each child were included). However, the curves do not show the raw data point by point, but are rather a prediction based on the raw scores. It is a continuous parametric model that predicts smoothly changing risks and shows and fits the data adequately; furthermore, it is superior to any cut-off point-based models (172). There might be a risk of too much smoothing, which would lead to appreciable bias. The data presented as curves also makes it difficult to compare data with other studies and to contribute to meta-analyses.

Analysis of covariance (ANCOVA) (Papers II and III) was used to examine the differences in the mean values of the dependent variables that are related to the effect of the controlled independent variables. It also takes into account the influence of the uncontrolled independent variables (173). ANCOVA was chosen because it is a statistically strong method (174) that takes baseline values into account. Due to a large age range and relatively few participants in each group, we chose this analysis to correct for these two variables.

When performing multiple statistical comparisons, there a is a risk of committing two types of errors: type I and type II errors (175). To avoid the risk of type I error—a false positive test—a Hochberg procedure was performed in Paper II (175, 176). This procedure may introduce false negative values (type II error). The procedure changed the significant results for PPA,

APA and hamstring strength, and they became insignificant (Paper II, Table 3). When the Hochberg procedure is performed, the results should not be overestimated, but there might be a risk having introducing a type II error. The Hochberg procedure was not performed in Paper III because there were fewer variables, and there were no significant values, indicating no risk of type I error.

Overall, 2.3% of values were missing in the isokinetic strength test variables (Paper II), which was handled by the single imputation of the group mean. This method was selected because there were few missing variables, and they were missing by random chance due to technical issues with the electronic equipment. The main problem of using this method is underestimating the variance (177).

In Paper III, there were seven missing values from the 6MWT. These test values were missing due to random complications concerning logistics and practical problems in the testing. There were no missing baseline data; therefore, we choose to perform the imputation by last value carry forward. The negative effect of using this method is the risk of underestimating the results (177).

The sample size calculation prior to the RCT was based on the standard deviation of the change in the PPA being 10°, which implied 16 children in each group. These groups had few participants, and we were probably a bit too optimistic about the possible effect of the intervention. Nevertheless, we invited all eligible children residing in the geographic area, and bigger groups would not have been achievable without a multicentre design.

Ethical considerations

The inclusion of children, especially children with CP, in clinical trials may raise significant ethical concerns. Taking part in research projects may cause an extra burden both to the child and their parents. Many of the children receive different kinds of treatment, including physiotherapy, medical care and surgery, and go through yearly routine follow-ups continuously until adulthood. To reduce the burden on the children as much as possible, the exercises included in the RCT (Papers II and III) were simple, easy to understand and perform, and the duration of each session was as short as possible.

The data included in the cohort study analysis (Paper I) were extracted from the CPOP register. The children and their parents were invited to participate in the register by healthcare

providers in the regional habilitation units. Parents gave their written consent on behalf of the child to be a part of the register and to be tested according to the standardised protocol. By the consent, they also agreed that their child's pseudo-anonymised data could be used for research projects approved by the CPOP board.

Prior to the RCT (Paper II and III), the children and their parents were asked by written information to participate in the study, and those who accepted gave written consent prior to inclusion. The children received the identical information as their parents; however, the information sheet was written in more child-friendly wording. The written information and the consent form were adjusted to match the child's age, one for children 7 to 12 years of age and another for those 12 to 15 years of age.

Both the cohort study (reference number 2018/415) and the RCT (reference number 2014/1766) were approved by the Regional Committee for Medical Research Ethics for South-eastern Norway. The changes to the RCT project protocol were reported to and approved by the Ethics Committee (reference number 2014/1766). The data were collected in accordance with the Declaration of Helsinki (202). The RCT study was registered in the Database for ClinicalTrail.gov. https//:clinicaltrials.gov/ (reference number NCT02917330).

In recent decades, there has been an increased focus on user involvement when planning clinical research studies. The users may be involved in most parts of a study, such as identifying topics, designing treatment methods, recruiting participants and interpreting results. In the planning phase of the present RCT, there was no formal patient involvement; this might have changed the intervention and contributed to the recruitment of participants. However, to assure that the program was feasible for both the children and their parents, several local PTs and PTs at rehabilitation clinics were conferred with before the study protocol was established. During the planning phase we also had informal conversations with children with CP and their parents during routine follow-ups in the lab about their thoughts concerning being a part of a hypothetical intervention study and what we could expect children and parents to take part in. After these informal talks, our opinion was that two or three extra exercise sessions per week would be acceptable but that a more intensive program probably would be difficult to carry out.

Results

The overall results of Paper I show that the hamstring muscle lengths measured by PPA and the hamstring spasticity measured by MAS increase with age, but with different patterns between the GMFCS levels.

The development of muscle contractures and spasticity in children with CP is extensively documented and discussed in the literature (3, 4, 25, 26, 32, 80, 84, 88, 135, 154, 199, 203); however, longitudinal changes in the PPA and hamstring spasticity, systematically collected by a national register, have not been documented. Such information is important to understand when changes occur on a timeline for a specific cohort. Register data provides an opportunity to identify negative changes and to optimise interventions at the right time points (97, 178). The CPOP follow-up program in Norway now provides longitudinal data collected from 2006 and includes children born from 2002 to 2017, which enables the possibility to study how joint ROM changes during childhood (12, 93). An identical register was established in Sweden (94) 12 years before the Norwegian register. Nordmark et al. (4) published a study reporting on 359 children that included 5075 measures from 1994 to 2007. As in the present study, the authors showed how the hamstring lengths change for different GMFCS levels and subtypes (spastic, atactic and dyskinetic); however, they did not study the different GMFCS levels within a specific subtype. The Swedish register showed curves that were quite similar to the curves from the present study. As shown in the Swedish study, the curves in the present study show that the PPA increased by approximately 2° every year, irrespective of GMFSC level (Figure 8a).

We performed additional analyses where children who had undergone hamstring surgery were excluded (Figure 8b. The curve is not presented in Paper I). The results showed a slightly more increasing GMFCS III curve from 8-10 years, but from 10 years of age the curve showed a distinct decreasing pattern compared to the curves including all children (Figure 8a). The additional analyses also showed a minor decreasing tendency for GMFCS levels I and II from 12 to 14 years (Figure 8b). This decreasing tendency might indicate that children who had undergone hamstring surgery were those having the most increased PPA.

There are some studies that have documented changes in PPA and knee function during childhood. A small study by Rose at al. (61) evaluated the PPA and 3DGA in 18 ambulant children with CP who had no history of orthopaedic surgery and measured them at two or

more time points (4 to 9 years between the analyses). They found that PPA increased over time, and changes in the knee kinematic showed increasingly flexed knee during stance. However, the changes only became statistically significant after 6 years of follow-up. Cloodt et al. (76) performed a cross-sectional study including 3045 children with CP and documented a strong association between decreased hamstring length and knee joint contracture of 5° or more. The risk of having a knee contracture occurred at all GMFCS levels and was three times higher when the PPA was between 40° and 59° and 10-fold higher with a PPA >60°. Both these studies underline the importance of maintaining hamstring length to avoid a deterioration of the knee function as the children grow older.

Adults with CP experience increasing gait impairments as they age. Jahnsen at al. (62) included 406 adults (18-72 years of age) with CP who answered a questionnaire about their locomotion skills and documented deterioration in gait, and 10% of the adults who had earlier been able to walk lost their gait function. Seven years later, Opheim et al. (40) reported that 71% of the same ambulant adults with bilateral CP experienced deterioration of the gait function after they started to walk (Figure 4) (40). Brantmark et al. (3) studied 102 young adults (18-23 years of age) and reported that young adults with CP who had a PPA of greater than >40° had an increased risk (RR=3.2) of supported mobility (crutches or help from others) compared with those with a PPA within normal range. This may indicate that even though the mean popliteal angle is below 50° at the age of 15 years, which is described as a yellow value in CPOP and CPUP, a continued monitoring of the hamstring muscle length, also in less-impaired children, might be important to prevent deterioration of function until adulthood.

The hamstring muscle length in TD children has previously been documented. Katz et al. (79) measured 482 healthy children and found a mean PPA of 26° (range 0-50°) in children ≥5 years of age. Moon at al. found a mean PPA of 33° and 35° in healthy youth aged 13-20 and 13-51 years of age, respectively (204). The results from the present study indicate that the PPA in GMFCS level I was 10-15° higher than in TD children. This might not appear to be a large difference; however, the fact that children with CP, also the less involved, have additional problems such as reduced muscle strength (28, 35, 45, 46), balance, selective motor control and spasticity (29, 52, 53, 205, 206), probably make it more difficult to walk with shortened hamstring.

Spasticity has been shown to be associated with the development of muscle contracture (41, 203). In the present longitudinal cohort-study (Paper I), we evaluated the evolvement of

hamstring spasticity, measured by MAS (157). The results showed increased MAS with age until 4-5 years of age, and a further small increase until 15 years of age in GMFCS levels I and II, and a small decline in GMFCS level III (Figure 9a). These curves were different from the curve patterns presented in two Swedish longitudinal cohort studies of the development of spasticity in triceps surae (142, 207). Hägglund and Wagner (207) studied a cohort of 547 children with CP that included 6218 examinations of MAS on triceps surae and found increased spasticity up to 4 years of age, followed by a decline until the age of 12. These findings were confirmed in a more recent study by Linden at al. (142) that included 4162 children and 57953 measures. The authors found a peak in spasticity at 5 years of age, followed by a decline to 15 years of age, identical to what was documented in the Hägglund and Wagner study.

In the present study, the PPA and MAS curves show quite identical patterns and directions (Figure 8a and 9a). The levelling of the PPA curve at GMFCS level III (Figure 8a) seems to be associated with decreased MAS (Figure 9a). However, in general, the MAS was low, being less than 1+ for all three GMFCS levels (Figure 9a). For the MAS curves at GMFCS level I the MAS was between 0 and 1, and never overlapped with GMFCS II, indicating that there might be reasons for shortening of the hamstring other than spasticity. Spasticity as the main reason for muscle contractures in CP has been an accepted opinion (41), but the rationale for this opinion has been questioned in recent years (25, 31, 37, 42, 43). In addition, discussions about the validity of the MAS as measure of spasticity have been raised (43, 159). Muscle contracture has more recently been understood as a muscle adaptation during growth with both a passive and an active component (25, 37, 42). The active component is the increased muscle tone, and the passive components are hypertrophy of the ECM and impaired muscle growth and altered muscle adaptation (26, 31). A 10-year follow-up of children who had received SDR documented that limiting spasticity did not have a large positive influence on the evolvement of muscle contractures (208), indicating that there might be muscle properties and growth factors inside the muscles contributing to this shortening (43). Pierce at al. (206) studied 36 children with bilateral spastic CP and investigated the passive torque and reflex activity in the knee flexors and extensors during passive movement using electromyography. The authors documented a positive relationship between age and mean knee flexor passive torque and suggested that passive stiffness may play a larger role than reflex activity as spastic children with CP age.

In the present study and the studies of Hägglund and Wagner, Linden and Pierce (142, 203, 206, 207), the children treated with Bo-NT-A were included in the main analyses; hence, none of these studies are descriptions of a purely "natural" progression. Concerning the clinical treatment practice of today, where early interventions targeting spasticity with Bo-NT-A, SDR, ITB, orthosis and physiotherapy have become a natural part of the treatment for these children, it would be difficult to study a natural course of spasticity with age in children with CP (93, 94).

The small statistically insignificant changes in the APA, PPA and muscle strength (Paper II) might be interesting in relation to the increase in PPA during childhood, presented in Paper I. Studies have found that muscle contractures have a negative effect on the development of motor function (5) and gait function (60, 61, 83, 100) in children with CP. As described in Paper I, the hamstring were becoming shorter as the children grow older, and short hamstring are associated with impaired gait function, crouch gait and even loss of gait function (3, 76). The decrease in measured hamstring length, as increased PPA, is described to be 2-3° per year from the age of 2 (Paper I), which is in line with the findings of Nordmark et al. (4). However, improving the PPA by 3-4° in 16 weeks did not seem to have a functional effect, as no statistically significant effects on the gait parameters were found (Paper III, Table 3).

Previous studies have documented a modest effect of performing muscle stretching in children with CP (136, 137, 209-211), and reviews have concluded that the effects are small and inconclusive (128, 130, 131, 212). In a small study of children with CP, Theis et al. (136) showed the immediate effect of manual muscle stretching that increased the ankle dorsal flexion by 10°. The increase was seen both in the triceps surae muscle and the tendon. A small increase in hamstring flexibility as a result of stretching could create an immediate increased active knee ROM and might make it easier to recruit the targeting antagonist muscle (the quadriceps) in terminal knee extension.

In the present study, there was a decrease in PPA of 3.5° (CI 0.2-7.0) and 4.3° (CI 0.3-8.3) on the left and right side, respectively, after 16 weeks of intervention (Figure 10 and 11 and Paper II, Table 3). This is in line with results from other studies evaluating stretching, mostly on the triceps surae (130, 131, 136, 137, 210). It is, however, a small improvement of ROM in the knee joint, but it is less than the estimated measurement error of 10 ° and less than the calculated meaningful change of ≥10° included in the power analysis. Still, there are arguments and clinical reasons for not neglecting these small changes. The decrease in APA

was 8.6° (2.0-15.2) and 7.5° (1.5-13.5) (Figure 10 and 11, Paper II, Table 3), and the extension deficit decreased from 5° to 3°and from 4° to 1° for the left and right side, respectively. These findings indicate that the quadriceps were more capable of active terminal knee extension.

The intervention in the present RCT was mainly based on PRE training, focusing on knee extension. There were statistically insignificant improvements in both quadriceps and hamstring muscle strength in favour of the intervention group (Paper II, Table 1 and 3). The lack of statistical significance in the gained muscle strength might be because there were only 29 children who were testing muscle strength, which probably was decreasing the power of the statistical analysis. The intervention and testing situations were two different positions, and might also be a reason for the lack of statistical significance between the two groups but the isokinetic strength measured with a Cybex has been found to be reliable in children with CP (163). The statistically insignificant effect in our study is in contrast with several studies that have registered statistically significant changes in strength following PRE (111, 117, 184, 186). Yet, in a systematically review by Scanni et al. pooling data from six RCTs they concluded that strength training had no effect on muscle strength and was not worthwhile (119).

The insignificant positive changes registered in the gait kinematics in favour of the control group (Paper III, table 3) are difficult to explain. There were no statistically significant differences between the two groups at baseline, and baseline variables and age were also corrected for in the statistical ANCOVA model. In addition, there was no difference in gait speed between the groups, which could have been an explanation. The intervention performed in the control group varied extensively, but none of the PTs reported any specific modalities targeting improved gait performance. The documented variability of 4-5° in the sagittal plane for the 3DGA measures is probably one explanation; however, sagittal plane kinematics is regarded as the most reliable. Nevertheless, changes below 5° should be interpreted with caution (168).

Gait function is a very complex function and is characterised by movement patterns, muscle synergies, intra- and inter-limb coordination, balance skills and interactions across planes and levels (39, 56, 57, 73). The reason for not identifying changes in any of the gait measures might be because the changes in PPA, APA and muscle strength were too small to have any functional impact. The participants were mostly independent walkers, and the small

statistically insignificant improvements in muscle strength and APA may not have resulted in further improvements in gait function, as shown by others (110, 111, 186, 213). The missing positive results on gait function are not surprising, as the gap between improvements on body function and structures and improvements on activities is a known challenge (110, 186, 213) and has been widely discussed in the treatment of CP (128, 214). The exercises in the present study were in an upright position and partly functional. However, no gait training was applied, which probably explains the absence of improved gait measures. In a review studying the effect of CP interventions, Novak at al. (128) stated that if a particular effect is desired on a discreet function then this function should be applied in the intervention. Including gait training exercises into the program would probably have influenced on the gait parameters measured in a positive way.

In the present study, the last follow-up was at 32 weeks, and we did not identify any deterioration in the control group for the PPA, APA or the gait parameters, nor any further statistically significant improvements in the intervention group compared with the control group. Studies have documented that longer follow-ups (4-6 years) are needed to identify deteriorations in gait function (60, 61). Follow-up over a longer period of time is probably needed to be able to identify whether a small decrease in PPA, APA or increase in muscle strength could prevent the deterioration in gait function over the long term.

The combined stretching and progressive strength training program did not show any statistically significant effects on step length or gait speed. Similarly, the 6MWT did not reveal any difference between the intervention and the control groups after the intervention (Paper III, Table 3). However, both groups showed statistically significant increases in the gait distance from T0 to T1 and from T0 to T2 (Paper III, Table 2). The 6MWT has shown good to excellent reliability in children with CP (166, 167), but the improved gait distance in both groups may indicate a learning effect from T0 to T1. A practise walk (pre-test) might have eliminated a possible learning effect. In a reliability study by Thompson et al., the authors advised that children at GMFCS level I should perform a practice walk to establish their fastest walk speed (166) before being tested. However, Maher at al. (167) also performed a reliability study and found the distance between two trials to vary by 1% (<1 m) and suggested that a practice walk was not necessary. The American Thoracic Society Guidelines (164) state that in most clinical settings a practice session is not needed, and if a practice walk is included, the main test should be performed with 1 hour of rest in between. For practical

reasons, i.e., not increasing the burden on the local PTs who administered the 6MWT, a pre-test was not performed.

Clinical implications

Due to the complexity of the CP diagnosis, children with CP get to know a broad spectrum of healthcare professionals during childhood, including paediatricians, orthopaedic surgeons, orthotists, PTs, neuropsychologists and occupational therapists. Interaction between all these professionals is essential to offer the child and their parents optimal care. In Norway, the PTs are key persons in the follow-up program. Depending on the severity of the motor impairments, the PT may meet the child several times a week, including periods of intensive training (5, 12). It is therefore crucial that the physiotherapy given is evidence-based and meaningful for the child.

The present cohort study (Paper I) shows that ambulant children with CP progressively develop shorter hamstring and slightly increasing hamstring spasticity during childhood. Children at GMFCS level III show a different developmental pattern compared to GMFCS levels I and II, (Figure 8a and 9a). Children at GMFCS level III show an early increase in PPA and MAS; however, both the PPA and the MAS seem to stabilise as they grow older. Awareness should therefore be directed towards the children at GMFCS level II, who also have a limited gait function and who experience progressively increasing PPA and MAS during childhood. From 11 years of age, the PPA and MAS are quite identical to that of the children at GMFSC level III. This is important information for clinicians who work with these children. They should therefor pay attention to and follow closely the development of PPA in children at all GMFCS levels, but special attention should be given to children at GMFCS level II.

The differences in PPA and MAS development between the three GMFCS levels in ambulant children have, to our knowledge, not been previously described and should be taken into account when planning treatment programs and follow-up for children at different GMFCS levels. A PPA >40° was associated with the use of a wheelchair in the community in young ambulant adults (3), and short hamstring are associated with knee contracture (76). This indicates that maintaining hamstring length during childhood and youth might be important for preventing deterioration of the gait function as an adult. Starting at an early age, when the

hamstring length is still normal, having this focused during natural growth and weight gain might be important. The stretching and PRE program evaluated in the RCT (Paper II) did not show any statistically significant effects on PPA and MAS in favour of the intervention group. The small positive (statistically insignificant) changes may still be of importance to avoid the time-dependent deterioration documented from the register data (Paper I).

The PRE training principles included in the strength training program have been shown to be effective and safe for strength training both in TD children (124) and children with CP (110-112). Our experience was that the training modality was safe when performing the strength exercises and no adverse events occurred. Using a backpack is an inexpensive and practical way to progress the weight load if a weight vest is not available.

No effect of the exercise program on any of the gait parameters tested was found (Paper III). The findings indicated that the program had no influence on the gait function. This is partly in line with previous studies showing conflicting evidence of the effects of strength training on gait function (109, 111, 117, 215). However, more recent studies evaluating functional power training including higher velocities have shown effects both on the walking capacity and muscle strength (216, 217). These studies indicate that if the main goal is to improve gait, functional strength training at higher velocities should be included in the program. Gait training is shown to increase speed and step length (218-221); however, to our knowledge, no statistically significant effect on ROM has been found.

Main conclusions

The PPA increased with age, and significant differences in the PPA between the GMFCS levels until 8 years of age were found. The PPA at GMFCS levels I and II continued to increase until age 15, while the PPA for GMFCS level III levelled off with increasing age. At 14 years of age, the mean differences between the three levels were insignificant, with a mean PPA of between 41° and 45°. The spasticity curves measured by MAS showed a steep increase until the age of four years after which GMFCS levels I and II only slightly increased, and level III showed a decrease. The level of spasticity was relatively low (MAS<1+) for all three GMFCS levels throughout childhood.

The 16-week combined hamstring stretch and PRE program had only minor insignificant effects on PPA, APA and lower limb muscle strength in favour of the intervention group. The

positive trend indicates that if the goal is to maintain PPA and active knee extension, a combination of hamstring stretching and PRE training might be introduced. Maintenance training with one home session per week was not sufficient to retain the minor improvements.

No significant effects of the combined hamstring stretch and PRE program were found on any of the measured gait function parameters (sagittal kinematics, gait speed, step length, GDI or 6MWT), neither after the 16-week intervention program nor after the 16-week maintenance program.

Errata list

(1) Compliance rates in the RCT are reported incorrectly in both Paper II and III.
The correct compliance rates are as follows:

Total number of training sessions (37 out of 48) = 77% (73% in Papers II and III)
Physiotherapy sessions (25 out of 32) = 78% (79% in Paper II)
Home-based sessions (12 out of 16) = 75% (76% in Paper II)
Maintenance sessions (13 out of 16) = 81% (72% in Papers II and II)
None of the incorrect numbers affected the results or conclusions stated in the Papers.

(2) Heading in table 3, Paper II: Instead of "Intervention group Test T0-T1" and "Comparison group" it should be "Test T0- T1" and Test T0-T2", respectively. All numbers in the table are correctly presented.
These corrections have been reported to the journal.

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RESEARCH ARTICLE Open Access

Change in popliteal angle and hamstrings spasticity during childhood in ambulant children with spastic bilateral cerebral palsy. A register-based cohort study

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Abstract

Background: Muscle contractures are developing during childhood and may cause extensive problems in gait and every day functioning in children with cerebral palsy (CP). The aim of the present study was to evaluate how the popliteal angle (PA) and hamstrings spasticity change during childhood in walking children with spastic bilateral CP.

Methods: The present study was a longitudinal register-based cohort study including 419 children (1–15 years of age) with spastic bilateral CP, gross motor function classification system (GMFCS) level I, II and III included in the Norwegian CP Follow-up Program (CPOP). From 2006 to 2018 a total of 2193 tests were performed. The children were tested by trained physiotherapists yearly or every second year, depending on GMFCS level and age. The PA and the hamstrings spasticity (Modified Ashworth scale (MAS)) were measured at every time point. Both legs were included in the analysis.

Results: There was an increase in PA with age for all three GMFCS levels with significant differences between the levels from 1 up to 8 years of age. At the age of 10 years there was no significant difference between GMFCS level II and III. At the age of 14 years all three GMFCS levels had a mean PA above 40° and there were no significant differences between the groups. The hamstrings spasticity scores for all the three GMFCS levels were at the lower end of the MAS (mean < 1+), however they were significantly different from each other until 8 years of age. The spasticity increased the first four years in all three GMFCS levels, thereafter the level I and II slightly increased, and level III slightly decreased, until the age of 15 years.

Conclusion: The present study showed an increasing PA during childhood. There were significantly different PAs between GMFCS level I, II and III up to 8 years of age. At the age of 14 years all levels showed a PA above 40°. The spasticity increased up to 4 years of age, but all the spasticity scores were at the lower end of the MAS during childhood.

Keywords: Cerebral palsy, Hamstrings, Popliteal angle, Spasticity, Cohort

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Background

Muscle shortening and decreased joint motion in the lower extremities are frequently recognised in children with spastic cerebral palsy (CP) [1–3], and gradual deterioration of gait function and performance of everyday activities is common [4, 5]. CP is caused by injury or insult to the immature brain, and the pathology in the brain is permanent and non-progressive [6, 7]. The primary manifestation of the neurological insult to the brain causes loss of selective motor control, muscle imbalance, and muscle tone abnormalities. These impairments frequently result in secondary conditions like muscle contractures, reduced joint motion and balance, often affecting function and everyday life [6, 7]. Many of these secondary complications are developing slowly over years, hence the related functional complications will be gradually recognized [2, 5]. The gradual deterioration seems to worsen by increasing age and lower functional levels as measured by the Gross Motor Function Classification System (GMFCS) [2, 8]. Early detection and identification of secondary complications are important [9] and may give health professionals and parents opportunities to prevent or limit an expected negative development.

Systematic follow-up programs including early detection and treatment of deteriorating joint motion and musculoskeletal functioning are assumed to enable prevention of permanent disability, and postponement or avoidance of surgical procedures [10]. In Sweden a follow-up program (CPUP) for children with CP, including non-surgical treatment modalities for prevention of deteriorating joint motion, showed that the number of surgeries for contractures decreased by 65% over a 10 year period (1994–2004) [9, 10]. A recent prospective cohort study showed that joint contractures may hamper long term gross motor progress, while intensive training programs (≥3 times per week) enhance gross motor progress [11, 12]. Hence avoiding joint contractures and reduced range of motion (ROM) should be important treatment goals and is strongly emphasised in the literature [6, 9, 12, 13]. Due to increased spasticity, muscle stiffness, and contractures in the distal muscles compared to the proximal muscles, the treatment programs for the young ambulant children include modalities to avoid pes equinus and toe walking [6]. It is well documented that the hamstrings muscles become shortened and less flexible during childhood [2, 5, 14]; however, how the hamstrings contractures develop during childhood is not documented to the same extent as contractures of triceps surae. The hamstrings is a group of muscles crossing both the hip and the knee joints, impacting both joints by rotating the pelvis backwords and flexing the knees [6]. In addition to factors like gastrocnemius spasticity, triceps surae weakness, generalised muscle weakness and mal-alignment, short and spastic hamstrings may contribute to flexed knee gait and crouch [15]. Crouch is the most common and severe gait abnormality in ambulant children with CP [6] resulting in abnormal mechanical loads on the knee, hip, and ankle joints, which may cause joint pain, joint degeneration, and bony deformities [16].

One frequently used method for evaluating hamstrings length is measuring the popliteal angle (PA). Even though there are some controversies [17], studies have shown that hamstrings length correlates moderately with knee flexion during stance and at initial heel contact, and a short hamstrings is linked to shorter stride length and a backward rotation of the pelvis [15]. There is also a tenfold increased risk of knee flexion contracture when a short hamstring is present (PA > 60°) [18]. To be able to prevent shortening of the hamstrings, there is a need for knowledge about how the length of the muscle group changes during childhood.

Hamstrings spasticity may also affect the active knee ROM [19]. Previous studies on children with CP and triceps surae have shown that the spasticity is changing during childhood [20, 21]. To our knowledge, there is no longitudinal study which has evaluated these changes in children with CP.

The aim of the present study was to analyse how the PA and hamstrings spasticity change during childhood in walking children with spastic bilateral CP (SBCP), GMFCS level I, II, and III.

Methods

The present study was a longitudinal register-based cohort study including data from the Norwegian CP Follow-up Program (CPOP) [22]. CPOP is a consent based program, where the children are followed up and tested according to a standardised protocol with fixed intervals throughout the childhood. The main purpose of the program is to identify and contribute to prevent secondary complications at an early stage. The CPOP was launched in 2006 and included children from the South-Eastern health region of Norway. From 2010 children from the rest of the country were also included in the register. In 2017 the program included about 90% of all children diagnosed with CP in Norway [23]. The children are tested from the age of one year or from the time of the CP-diagnosis (mean age 25 months) (20). Data are collected each year until the age of 6, and thereafter yearly at GMFCS level II-V and every second year at GMFCS level I (yearly before 2015). There were 419 eligible children with SBCP, GMFCS I, II and III, aged 1 to 15 years eligible for inclusion in the present study.

Variables included in the present study were age, gender, GMFCS level, PA and hamstrings spasticity. GMFCS [8] is an age-related, five level scale where levels

I-III include walkers (level III is dependent on hand-held walking devices) and level IV and V are non-walkers. The GMFCS level is re-evaluated at every assessment. The measurements are performed in regional paediatric rehabilitation units by two persons following the CPOP manual [24, 25]. In the CPOP [22] the changes in hamstrings length are followed by measuring the PA measured by a goniometer (Fig. 1). This method is widely used as a measure of hamstrings length in children with CP, both in clinical and research settings [1, 2, 5, 15, 17]. However, the validity [26] and reliability [27–30] of the PA measurements are discussed. The inter- and intra-observer reliability has been shown to be low [27–30]. To optimise the reliability, the CPOP-follow-up program provides a detailed test protocol and when possible, the assessments are supposed to be performed by the same two trained assessors at each test session [24].

The assessments are categorised into three levels of severity. The first level (≤ 39°) indicates a satisfactory passive PA, the second level (40–49°), indicates a reduced PA and a need of more frequent follow-ups and consideration of treatment initiatives. The third level (≥ 50°) indicates a PA which needs intervention. Both PA and hamstrings spasticity were assessed in a supine position with the hip in 90° of flexion and the contralateral hip extended on the bench (Fig. 1). Hamstrings spasticity was measured according to Modified Ashworth Scale (MAS) [31]. Due to the nature of spasticity, the validity and reliability is moderate, and controversies about the interpretation of the tests exist. Nevertheless, it is the most frequently used scale for clinical evaluation of spasticity in CP [20, 21, 32–34]. The spasticity is graded from 0, normal muscle tone, 1 to 1+, small increase in muscle tone, and 2 to 4, large increase in muscle tone [31]. The intention of the modified version of MAS, was to improve the sensitivity in the lower end of the scale [31].

The completed paper protocols were posted by mail to the CPOP secretariat, where the data were plotted into an electronic database (Medinsight) [35]. Data in the present study were exported from Medinsight to Stata 15.0 (StataCorp LLC, College Station, TX). The statistical calculations were based on measurements from both legs.

Statistical analysis

Data were described with number of observations and percentage or mean and standard deviation as appropriate. We used a multivariable fractional polynomial linear regression model to fit age curves for the GMFCS levels. The model contained age (as continuous variable), GMFCS level (as categorical/dummy variable) and the interaction between age and GMFCS level as independent variables. In the model estimation, we used a robust standard error (clustered sandwich estimator) on participant due to the repeated measurement data. Both legs were included in the analysis, and the model has taken into account the dependency between legs in the same individual. For model selection, we used the mfp command in Stata which selects a multivariable fractional polynomial model in linear regression analysis (regress command in Stata) that best predicts the outcome variable using the default closed-test procedure algorithm [36]. The analyses was using the total cohort, including children treated with Botulinum neurotoxin-A (BoNT-A) and oral baclofen. Two additional analyses were performed; with children treated with hamstrings tenotomy and children treated with intrathecal baclofen pump (ITB)/selective dorsal rhizotomy (SDR) respectively excluded.

The linear prediction with 95% confidence interval for GMFCS level I, II and III was graphically presented. All statistical analysis was conducted with Stata 15.0.

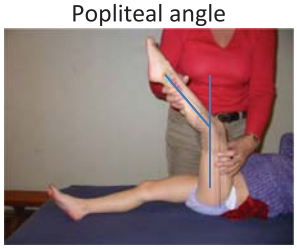
Passive end-range joint motion	Starting position	End- range position	Goniometer placement Stationary arm	Goniometer placement Movable arm
Popliteal angle 	Supine on a bench with 90° in the hip. Contra lateral hip and knee extended on the bench.	Maximal passive knee extension without pain and without the pelvis tilting backwards	The fulcrum of the goniometer over the knee joint center and the stationary arm is following the femur, aligned with trochanter major.	The movable arm is parallel to tibia aligned with lateral malleoli

Fig. 1 Assessment of the popliteal angle. End-range position measuring the popliteal angle. (With permission from CPOP [24])

Results

Data were obtained from 419 children with BSCP, GMFCS I, II and III; 161 (38%) girls and 258 (62%) boys (Table 1). In total there were 2193 assessments, from one to 16 assessments per child, mean 4.3 (± 2.9), and 3.8 (± 2.7), 5.1 (±3.4), 4.1 (± 2.7) at GMFCS level I, II, III, respectively. Both legs (4386 measures) were included in the curve estimates. The distribution according to GMFCS levels and gender is presented in Table 1. Figure 2 and Table 2 show a parallel increase in PA with age for the three GMFCS levels with significant difference between all the GMFCS levels from 2 to 8 years of age ($p \leq 0.005$) (Fig. 2 and Table 2). At GMFCS level I and II PA were increasing by a mean of 4–5° every second year throughout the age span. In contrast, PA at GMFCS level III was levelling off with only a minimal increase after 10 years. At 10 years there was no significant difference in PA between GMFCS level II and III, and at 14 years there was no significant difference in PA between any of the three GMFCS levels (Fig. 2 and Table 2).

The hamstrings spasticity curve estimates for all the three GMFCS levels were low (0–1+) measured by the MAS (Fig. 3). However, all three levels showed steep parallel curves during the first four years, with significant different MAS scores ($p < 0.005$) between the levels. At the age of 4 years the curves at GMFCS level I and II were levelling off, followed by minimally increasing curves until the age of 15 years. At GMFCS level III the spasticity curve peaked between 4 and 6 years of age before slightly decreasing (Fig. 3). There were significant differences between the MAS curves for all the GMFCS levels ($p < 0.005$) up to 8 years, but at the age of 10 years the MAS curves at GMFCS level II and III were overlapping and no longer significantly different (Fig. 3).

Additional analyses were performed by excluding those children who had undergone hamstrings tenotomy ($n = 29$), or ITB/SDR ($n = 14$). The mean age at surgery was 8.6 years (±2.5) and 5.3 years (±1.7) respectively. The analysis excluding those who had undergone hamstrings tenotomy had no influence on the curve patterns at GMFCS level I and II. At GMFCS level III, however, the analysis showed a decrease in the PA curve from the age of 9 years. For the MAS at GMFCS level III, the results showed a steeper curve from the age of 6 years, ending below MAS 1 at the age of 14 years. Excluding those children who had received SDR/ITB did not influence either the PA or the MAS curves.

Fifty-eight percent of the children in the cohort received one or more medical or surgical interventions on the lower extremities throughout the observation period (Table 3). At the GMFCS levels I, II and III orthopaedic surgery were performed in 12, 30, and 42%, and BoNT-A injections were given in 44, 66, and 63%, respectively. In addition, 87% of all the children received physiotherapy monthly or more frequently, 66% received physiotherapy one or more times per week, and 72% used some kind of orthoses, mostly ankle-foot-orthoses.

Table 1 Demographic data

	N (%)	N (%) girls	N (%) boys
GMFCS I	198 (47%)	75 (38%)	123 (62%)
GMFCS II	116 (28%)	44 (38%)	72 (62%)
GMFCS III	105 (25%)	42 (40%)	63 (60%)
Total	419	161 (38%)	258 (62%)

GMFCS: Gross Motor Function Classification System

Discussion

To our knowledge the current study is the first study to document how the PA and the hamstrings spasticity changes during childhood in a cohort of children with SBCP, GMFCS levels I, II, and III. The estimates from the statistical model showed that the PA was increasing during childhood, and that the GMFCS levels evolved with somewhat different patterns (Fig. 2). However, at 14 years of age no significant differences between the GMFCS levels were found. The hamstrings spasticity curves also changed during childhood, and as for the PA the patterns were different at the three GMFCS levels (Fig. 3). The spasticity curves increased throughout childhood, but were categorised as "a small increase in muscle tone" (mean < 1+) at all three GMFCS levels. At 10 years of age there was no significant difference in MAS scores between GMFCS levels II and III (Fig. 3).

For the PA curves there were 5° estimated differences between the GMFCS levels, and the significant differences seemed stable until the age of 8 years (Fig. 2 and Table 2). These findings are partly in line with previous published studies [1, 2]. At GMFCS level III the mean PA reached 41° (95% CI 39–43) at 8 years of age, which according to CPOP [22] indicates an increased PA, a need for more frequent follow-ups, and consideration of intervention initiatives. However, from the age of 12 years, the curve at GMFCS level III was levelling off. The curves at GMFCS levels I and II showed a slightly different slope, reaching 40° at 14 and 10 years respectively, and continuing to increase. The upper part of the CI band of GMFCS levels II and III were reaching 50° at about 14 years of age, which according to CPOP and others [6] indicates a need for treatment initiatives [22]. At GMFCS level III, the CI band was wide in the highest age groups, overlapping the CI of both GMFCS levels I and II, indicating a statistical uncertainty, and no significant difference between the groups. This may be explained as a statistical artefact due to fewer children in the oldest age groups, especially at GMFCS level III. One explanation why the PA at GMFCS level III was

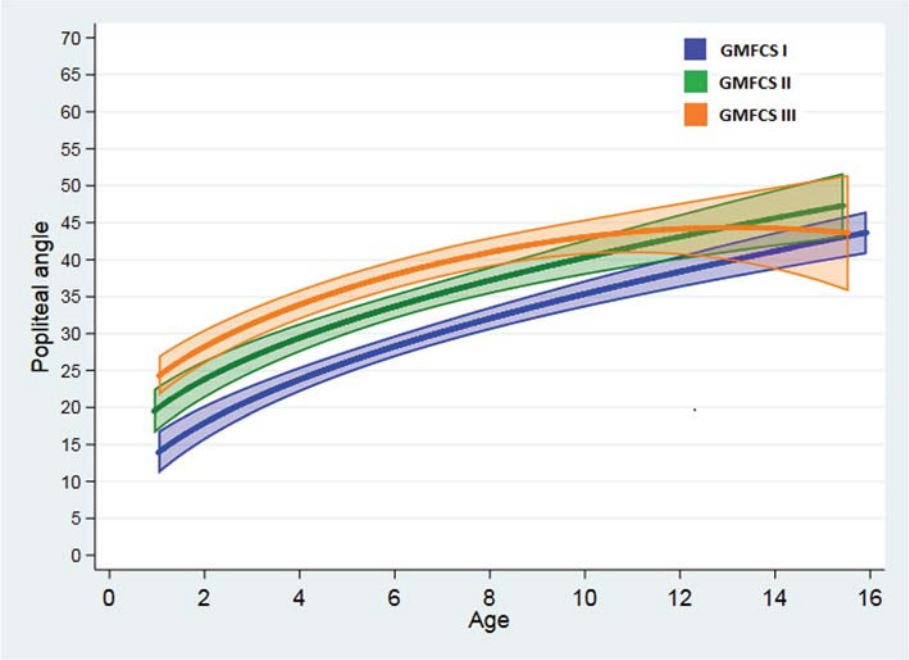


Fig. 2 Change in popliteal angle. Change in popliteal angle at GMFCS level I, II and III, from 1 to 16 years of age

levelling off may be seen in the hamstrings spasticity curves (Fig. 3), which were peaking at the age of 6 and then descending. This decreased spasticity after the age of 6 years may indicate a decreased risk of contracture [33]. Seventy-two percent of the children at GMFCS level III had received BoNT-A, ITB, SDR, or surgery in the lower extremities during childhood (Table 3). In addition there were more interventions targeting the hamstrings at GMFCS level III compared to GMFCS levels I and II (Table 3), which may also have affected the shape of the curve. The separate analysis, excluding children who had undergone hamstrings tenotomy showed a decrease in both the MAS and PA curves at 6 and 9 years of age respectively, but only at GMFCS level III. No changes at GMFCS level I and II was probably due to few children who had undergone hamstrings tenotomy at these levels (Table 3). The hamstrings tenotomies were performed at a mean age of 8.6 years (±2.5). At the age of 9 years, the PA curve representing GMFCS level III, (Fig. 2) stopped to increase at about 43° and then levelled off, which may indicate that it was the children with the biggest PA who had received hamstrings surgery. Nordmark et al. [2], who studied all CP subgroups (spastic uni-, and bilateral CP, ataxia, and dyskinesia) of children with CP in Sweden also described a mean increase in the PA from 1 to14 years at all GMFCS levels. The curve estimates at GMFCS levels II and III were almost identical to our findings from about 5 to 10 years of age, however Nordmark did not describe a levelling or decrease of PA in the oldest age span at GMFCS level III as shown in the present study. They also performed additional analyses excluding the children ($n = 6$) who had undergone a hamstrings tenotomy, and the exclusion did not influence the PA curve. Reasons for the different findings in the two studies may be that they included all subgroups of CP and that fewer children had undergone a hamstrings tenotomy [2].

McDowell et al. [1] studied a sample of 178 children (4–17 years of age) with spastic CP and reported an increase in PA with increasing age and GMFCS level, with a higher PA in those having a bilateral involvement compared to those who were unilaterally affected. Compared to the findings in the present study, they found higher PAs at all GMFCS levels. One explanation might be that

Table 2 Distribution of GMFCS-levels in relation to popliteal angle measurements during childhood

	2 years	4 years	6 years	8 years	10 years	12 years	14 years
GMFCS I	17.9 (15.6–20.3)	23.8 (22.1–25.5)	28.3 (26.8–29.7)	32.1 (30.5–33.6)	35.4 (33.6–37.2)	39.4 (36.2–40.6)	41.2 (38.6–43.7)
GMFCS II	23.8 (21.3–26.4)	29.4 (27.5–31.4)	33.7 (32.0–35.4)	37.2 (35.4–39.1)	40.3 (37.9–42.7)	43.1 (40.0–46.1)	45.6 (41.8–49.6)
GMFCS III	28.33 (25.9–30.55)	33.9 (31.9–36.0)	38.0 (36.1–40.0)	41.0 (39.0–43.0)	43.1 (40.7–45.4)	44.2 (40.6–47.7)	44.3 (38.7–49.9)

Mean popliteal angle (95% CI) over time divided by the gross motor function classification system (GMFCS) levels I, II and III
GMFCS: gross motor function classification system; CI: confidence interval

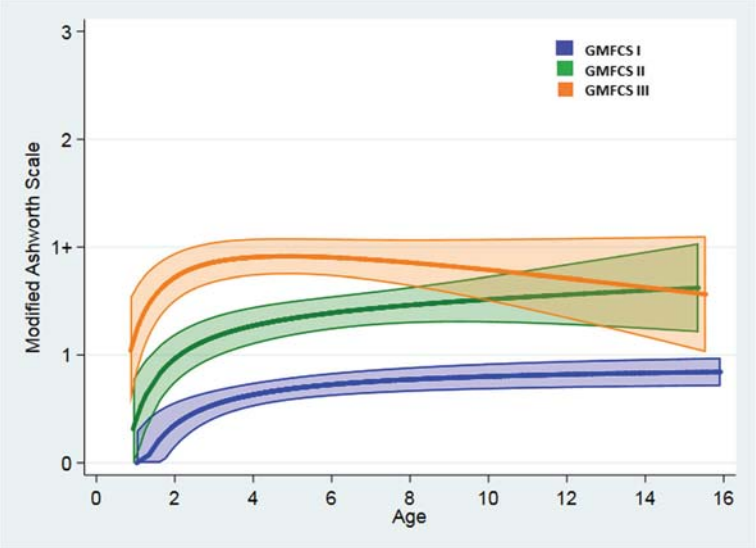


Fig. 3 Change in the modified Ashworth Scale. Change in modified Ashworth Scale at GMFCS level I, II and III, from 1 to 16 years of age

they excluded children who had undergone surgery the last year and those who had BoNT-A treatment the latest 6 months.

From 1 to 10 years of age the PA curves, GMFCS level I, showed CIs significantly narrower than GMFCS levels II and III (Fig. 2). One explanation might be that the level I group was the biggest group including 47% of the children, which might to a certain degree influence the distribution of the results. There was a continuous increase in the PA throughout childhood, reaching 41° at 14 years of age (Table 2, Fig. 2). This indicates that the PA in GMFCS level I increased despite of relatively good function, and a low spasticity level (Fig. 3). In comparison to studies reporting the PA in typically developing (TD) children, the children at GMFCS level I had a 10° to 15° higher PA. Mc Dowel et al. [1] reported a PA of 26° (±11) in TD children 4–10 years of age ($n = 39$) and 32° (±10) in TD children 11–17 years of age ($n = 29$). Moon et al. [37] reported in a group of TD adolescents 13–20 years old ($n = 26$) a PA of 34° (±10). Both studies showed increasing PAs with increasing ages, however, in the present study the change with age at GMFCS level I was more pronounced. As for the TD children, age seemed to be an important factor for the evolvement of the PA in walking children with CP. Rose et al. [5] followed 18 children with bilateral CP, mainly GMFCS levels I and II (mean age at inclusion 7.7 years) to evaluate the effect of time on their gait. The children performed 3D-gait analysis twice, the time intervals differed from 4.3–9.3 years. The results did not show any significant change in PA and flexed knee gait until the observation period reached at least 6 years. Rethlefsen et al. [38] studied 1005 gait records retrieved from ambulant children with CP. They reported that the odds for having excessive knee flexion in stands increased with increasing age at GMFCS level I, II and III, but only reaching significance at GMFCS level I.

In the present study the curve estimates for the hamstrings spasticity development the first 4 years were steep for all GMFCS levels (Fig. 3), which indicates a rapid change in spasticity during the first years of life, which is in line with previous published findings [6, 21]. However, the spasticity was significantly different in the three GMFCS levels. Compared to the PA curves (Fig. 2) the

Table 3 Type and number of interventions performed at each GMFCS-level during childhood

	n	Total number of surgeries In lower extremities. n (%)	Hamstrings tenotomy n (%)	BTX lower extr. n (%)	BTX Hamstring n (%)	SDR/ITB n (%)	BTX/Surgery/ITB/ SDR n (%)
GMFCS I	198	22 (11.8%)	5 (2.7%)	81 (43.6%)	24 (12.9%)	0/0	86 (43.4%)
GMFCS II	116	35 (30.2%)	7 (6.0%)	77 (66.4%)	25 (21.6%)	3/0 (2.6%/0%)	81 (69.8%)
GMFCS III	105	44 (41.9%)	17 (16.2%)	66 (62.9%)	37 (35.2%)	9/2 (8.6%/1.9%)	76 (72.4%)
Total	419	101 (24.1%)	29 (6.9%)	224 (53.5%)	86 (20.5%)	12/2 (2.9%/0.5%)	243 (58%)

GMFCS: gross motor function classification system, Extr.: extremities, SDR: selective dorsal rhizotomy, ITB: intrathecal baclofen. The (%) is calculated from the number children at each GMFCS level

An intervention is only registered once pr child, however, one child may have had more than one type of intervention/surgery

spasticity curves (Fig. 3) were steeper in the youngest age groups. The peak point of the spasticity curve at GMFCS level III was at the age of about 6 years, followed by a slightly decreasing curve. At the GMFCS levels I and II the curves continued to increase throughout the childhood, however the mean MAS was at the lower end of the spasticity scale (< 1+) at all GMFCS levels. Lindèn et al. [20] performed a register-based prospective cohort study including 4162 children with CP, between 0 and 15 years of age. The analyses included children treated with BoNT-A and oral baclofen and they also performed separate analyses for each GMFCS level. Additional analyses excluding ITB, SDR and Achilles tendon lengthening were performed and no change was found. They reported increased spasticity in the gastrocnemius-soleus muscle up to the age of 5 and thereafter a decreasing muscle tone up to 15 years of age in all CP subtypes. These findings correspond partly with our findings. Linden et al. [20] showed that the spasticity increased until the age of about 5 years for GMFSC level I, II and III and decreased until the age of 15 years. In the present study we found the same increasing tendency in hamstrings spasticity up to 5–6 years of age for GMFCS I, II and III. The spasticity pattern at GMFCS level III from the present study and Linden's study showed almost the same pattern; the spasticity are decreasing from the age of about 5–6 years until 15 years of age. However, in the present study the spasticity at GMFCS levels I and II (Fig. 3), increased up to the age of 15 years, most pronounced at GMFCS level II. This indicates that the hamstrings spasticity at these two GMFCS levels seems to show a different longitudinal pattern compared to the pattern reported for the gastrocnemius-soleus muscle group [20].

Muscle contractures in CP has generally been associated with the presence of spasticity [7]. Later research draws a more complex picture, also involving impairment of muscle growth and altered muscle adaptation [39]. Hägglund and Wagner [33] found a relationship between spasticity in the gastrocnemius-soleus muscles and the development of contractures in the gastrocnemius-soleus muscle. In the present study, we also found that the PA curves (Fig. 2) and the hamstrings spasticity curves (Fig. 3) had quite identical shapes, especially at GMFCS levels II and III. At the GMFCS level I, the increasing spasticity after the age of 4 was modest (MAS < 1) (Fig. 3), however, the PA curve (Fig. 2) at the GMFCS level I had the highest increment of the three levels presented in this study (Fig. 3). This may indicate that there are additional factors than an increased stretch reflex registered as spasticity contributing to muscle contractures [14, 26, 40–42]. Reduced active terminal knee extension, either due to reduced selective motor control, muscle weakness or immobilization, may be contributing factors [6]. In addition Gough and Shortland [39] suggested that in CP there might be multifactorial impairments of muscle growth which may lead to impaired muscle adaptation during growth [39]. Recent published papers have also shown increased arrangement of collagen in the extra cellular matrix, and factors within the contractile elements in the muscles which may contribute to muscle contractures [14, 26, 40, 42].

In the present cohort a high rate of medical, surgical and physiotherapy interventions had been implemented (Table 3). The high frequency of procedures makes it difficult to assess the natural course of the PA. The reason for the changes is probably due to both natural growth and maturation and an effect of the interventions received during childhood, and in general, it is the most affected children who receive BoNT-A, ITB, SDR and orthopaedic surgery.

Previous studies evaluating reliability of goniometric joint measurements in children with CP [27, 28] have reported big measurement errors when measuring PA. To minimize the influence of confounding factors, and narrow the variability in the measurements, a written standardised protocol as well as trained assessors and, when possible, the same assessor over time has been underlined as important in CP [32]. In the yearly routine for collecting data, written information was distributed from the CPOP [24], and the assessors were trained and experienced physiotherapists. However, to have the same assessor for each child over several years was not always possible. The big number of tests in the current study should limit the variability, but must be taken into account in the interpretation of the results.

The complexity of muscle spasticity makes it difficult to quantify. Several tests exist, however none of them seem to be superior, and validity and reliability are discussed [32]. However, in clinical studies of neurological diseases and injuries the MAS [31] is the most frequently used instrument for assessing spasticity [21, 32]. The MAS added one score level (1+) at the lower end of the original Ashworth scale because the lower end of the spasticity score is more frequently seen in less involved children [18, 31]. This is in line with the results in the present study (Fig. 3).

There were some limitations to this study. The children were tested with different time intervals according to age and GMFCS levels. They were tested each year until the age of 6 years, and thereafter yearly at GMFCS levels II-III and every second year at GMFCS level I. This may indicate uncertainty in the oldest ages at GMFCS I. However, GMFCS level I is the biggest group, including 47% of the children in this cohort. There were fewer children in the oldest and youngest age groups, especially at GMFCS level III, making the confidence intervals wider and the estimates less reliable at this level (Figs. 2 and 3).

Conclusion

The present register-based cohort study, including children with SBCP, demonstrated that there was an increasing PA by age at GMFCS levels I, II and III. The PA between the GMFCS levels was significantly different during the early childhood, however, at the age of 14 years no significant difference was found. The hamstrings spasticity increased rapidly the first 4 years for children at all GMFCS levels, but the spasticity level was significantly different between the groups. After peaking at about 6 years, the spasticity at GMFCS level III was decreasing, but at GMFCS level I and II the spasticity continued to increase, however the mean MAS never pass category 1+ (small increase in muscle tone) for any of the GMFCS levels.

The results from the present study may have implications for clinical decision-making. The findings that the PA and the hamstrings spasticity seemed to increase during adolescence indicate that awareness on maintaining hamstrings length already at an early age, also for the less involved children, may be important.

Abbreviations

BoNT-A: botulinum neurotoxin-A; CP: cerebral palsy; CPOP: Norwegian CP follow-up program; CPUP: Swedish CP follow-up program; GMFCS: gross motor function classification system; ITB: intrathecal baclofen; MAS: modified Ashworth scale; PA: popliteal angle; ROM: range of motion; SBCP: spastic bilateral CP; SDR: selective dorsal rhizotomy; TD: typically developed

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Authors' contributions

All the authors (MAaF, RJ, AHP, IH) have contributed to the design of the study, critically interpretation of the results, reading and writing the manuscript. AHP also performed the statistical analysis. All authors have read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the Cerebral Palsy Follow –up Program (CPOP), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon request and with permission of CPOP.

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics, section South-East and the Commissioner for the Protection of Privacy in Research, Oslo University Hospital. All participants and parents gave their written consent before inclusion into the CPOP register. The CPOP register have shared data and approved to the study.

Consent for publication

Not applicable.

Competing interests

The authors declares that they have no competing interests.

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Publisher's Note

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Article

Effect of a Combined Stretching and Strength Training Program on Gait Function in Children with Cerebral Palsy, GMFCS Level I & II: A Randomized Controlled Trial

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Abstract: *Background and objectives:* Ambulant children with cerebral palsy (CP) often develop impaired gait, and reduced active knee extension is often a part of the problem. This study aimed to evaluate the effect of a combined intervention program including stretching and progressive resistance exercise (PRE) targeting active knee extension on gait function, in children with spastic CP. *Materials and methods:* Thirty-seven children (21 boys, 16 girls, mean age 10.2 (±2.3) years), classified by Gross Motor Function Classification System I–III, were randomized to an intervention (n = 17) and a comparison group (n = 20). The intervention group received a 16-week combined exercise program (3 sessions per week) including stretching of hamstrings and PRE targeting the lower extremities, followed by a 16-week maintenance program (1 session per week). The comparison group received care as usual. Gait function was evaluated by three-dimensional gait analysis (3DGA); knee, hip and pelvic kinematics in the sagittal plane, step length and speed, Gait Deviation Index (GDI), and Six-Minute Walk test (6MWT) at 0, 16, and 32 weeks. *Results:* There were no statistically significant differences between the intervention group and the comparison group for any of the gait parameters measured at 16 and 32 weeks. There was a significant increase in gait distance measured by 6MWT within both groups; however, no differences between the groups were found. *Conclusion:* A 16-week combined stretching and PRE program followed by a 16-week maintenance program did not improve gait function in ambulant children with CP.

Keywords: cerebral palsy; gait function; hamstrings stretching; progressive resistance training

1. Introduction

Cerebral palsy (CP) is one of the most common causes of gait deviation in children. Children with CP start walking later than typically developed children and about 30% never walk independently [1,2]. This is caused by damage to the immature brain, which often results in primary impairments, like increased muscle tone, loss of selective motor control and impaired balance mechanisms, causing secondary impairments, such as muscle shortening, muscle weakness and decreased joint range of motion (ROM) [1,2]. These primary and secondary impairments often influence both the ambulation quality and capacity during childhood [1,3,4].

Studies using data based three-dimensional gait analysis (3DGA), including kinematics, kinetics, and spatial temporal gait parameters, show that gait function in children with CP deteriorates over time [3,5]. Gait is a complex activity and Gage et al. [1] describes the five prerequisites for normal gait

as: stability in stands, foot clearance in swing, preposition of the foot in terminal swing, an adequate step length and energy conservation. To achieve all these five prerequisites, there has to be adequate muscle strength, joint position and segment alignment [1], and stretching and muscle strength training are assumed to be important for the maintenance and improvement of gait function [1,6].

Children with CP spend much of their childhood receiving physiotherapy focusing on optimal gait performance; hence choosing valid and effective treatment modalities is of great importance. Reduced muscle strength in CP is shown to be associated with impaired gait function and children with spastic CP, even the children who are mildly affected, have significantly lower limb muscle strength compared to typically developing (TD) children [1,7,8]. Studies have shown that muscle strength training, especially progressive resistance exercises (PRE) [9], improve muscle strength [10,11]; however, the increased strength does not seem to improve gait function [10–12]. Nevertheless, there are some studies indicating an effect on gait function after strength training [13–16]. In addition to muscle weakness, muscle spasticity and muscle shortening contribute to the restricted gait function [1,5]. Muscle contractures are shown to hamper long-term gross motor progress, while intensive training (≥3 times per week) enhances gross motor progress [17,18]. Muscle shortening is associated with joint stiffness and pain [19], and about one of four adolescents with CP experience knee pain [20]. Short hamstrings tend to cause restrictions on the knee extension at initial foot contact, and knee extension in mid-stance. As a bi-articular muscle it also tends to rotate the pelvis posteriorly [1]. Some muscles are more affected and hamstring shortening is shown to be more pronounced in children with lower functional levels [3,5,21], (classified by the Gross Motor Function Classification System (GMFCS) [22]) and with increasing age.

McNee et al. [23] studied the lower limb extensor moment and underlined the importance of knee extension in mid-stands, because it seems to be essential for achieving an extending moment in the lower limb. The extensor moment in combination with the muscles stabilising the knee joint contributes to stability and smooth progression over the stationary foot, which is essential for the swing of the opposite leg and an optimal step length [1]. Mc Nee et al. [23] suggested that if there is an increased knee flexion, a disproportionate degree of support must be generated by the knee extensors.

Stretching as the only physiotherapy treatment modality in CP is scarcely documented and the effect size is small [24–26]. However, muscle stretching is still commonly used [2], and it is mainly based on the assumption that stretching maintains or increases ROM [27]. To explore the effect of this practice, reviews conclude that the evidence is limited and more research with longer follow-up periods is needed [24–26].

Physiotherapy comprises different modalities, recognizing the fact that complex functional problems may need complex interventions [14]. Studies combining muscle strengthening and enhancing alignment and ROM have been asked for [14,23,28]. Thus, the aim of the present study was to evaluate if a 16-week combined hamstring stretching and PRE program, focusing on terminal knee extension and the extending muscles in the lower extremities, could improve kinematics and gait efficiency in children with spastic bilateral CP. A secondary aim was to evaluate if a 16-week maintenance program could preserve the possible gained improvements.

2. Materials and Methods

2.1. Study Design

The present study was a single-blind block randomized controlled trial. After baseline testing, the children were block randomized into two groups. The procedure was performed by an office administrator not engaged in the project, who opened sealed envelopes including blocks of four numbers. The participants were either allocated to an intervention group, performing a stretching and lower extremity PRE program (n = 17), or a comparison group receiving care as usual (n = 20) (Figure 1). The group allocation was assigned by the project manager who was not masked to the intervention. Assessments were completed at baseline (T0), after 16 (T1) and 32 (T2) weeks. The child's local physiotherapist, who knew the child well, was responsible for the one-to-one

intervention program. The assessors responsible for the testing were blinded to the randomization groups, and the children and their parents were told not to disclose their group affiliation. All the children and their parents gave their informed consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki, was approved on 26. November 2014 by the Regional Committee for Medical and Health Research Ethics, section South-East, the Commissioner for the Protection of Privacy in Research (2014/1766) and was registered in Clinical trial.gov (NCT02917330).

2.2. Participants

One hundred and six eligible children with spastic bilateral CP were identified by the CPOP, or by the patient register at the Motion Laboratory at Oslo University Hospital, and invited to participate in the study (Figure 1).

The criteria for inclusion were (1) spastic bilateral CP, (2) age between 7 and 15 years, (3) GMFCS I-III, (4) able to walk 10 m indoors without walking aids, and (5) passive popliteal angle (PPA) ≥35° in the most affected leg. Exclusion criteria were (1) hamstring tenotomy, bilateral lengthening of the triceps surae, or any other surgical procedure in the lower limbs less than one year prior to inclusion. (2) Botulinum toxin-A-injections in the lower limbs the last six months prior to inclusion, (3) <0° dorsal flexion in the ankle joint, (4) <5° external rotation in the hips and (5) unable to cooperate or understand instructions.

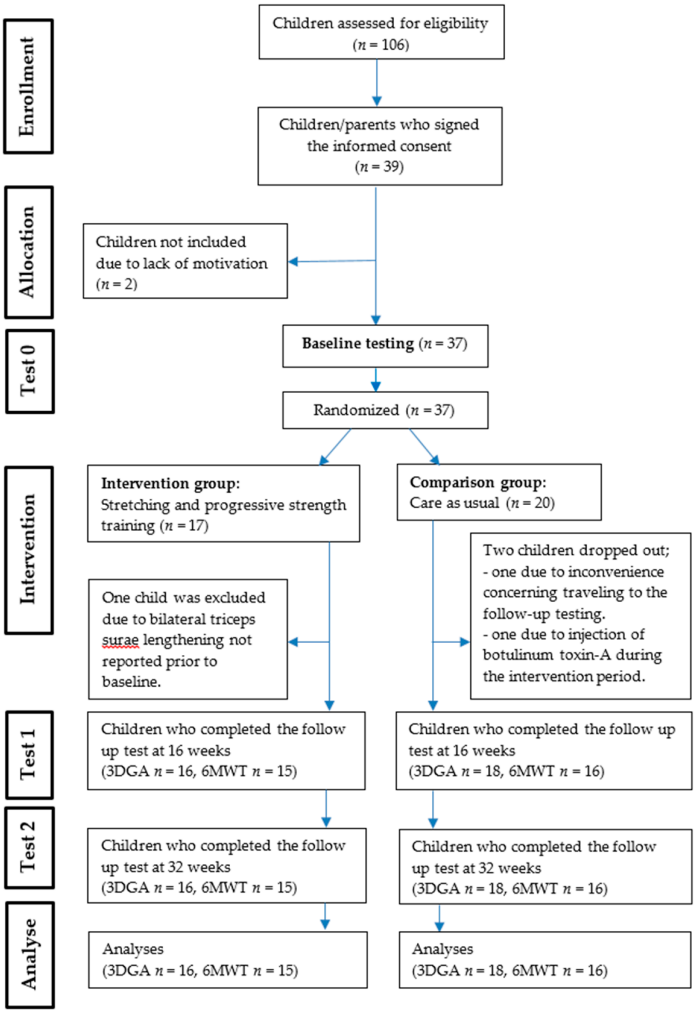

Figure 1. Flow-charge showing how the participants were moving through the study period. 3DGA: three-dimensional gait analysis, 6MWT: six-minute walk test

2.3. Intervention

The children randomized to the intervention group followed a detailed program protocol including active and passive stretching of hamstrings [27] and PRE [9] focusing on the extending muscles in the lower extremities. The resistant training program was following the National Strength and Conditioning Association (NSCA) Guidelines [9] and modified by the recommendations from Verschuren et al. [29]. The stretching part of the program was a combination of passive and active muscle stretching exercises based on established techniques used in physiotherapy [27], the frequency chosen was based on previous published research studies [24,25,30] and clinical experience. The 16-week intervention program was performed three times per week: two sessions together with the physiotherapist and one home exercise session; 48 sessions in total. The children allocated to the comparison group received care as usual and their physiotherapists were by written information told not to introduce any new treatment modalities during the 32-week study period.

To assure the quality and consistency of the stretching and PRE program, a detailed project protocol and an instructional film were distributed to the physiotherapists. They were also contacted and guided by a senior physiotherapist (project manager) not masked for the intervention, both before and during the intervention period.

The main intervention program (0–16 weeks) was performed 3 times per week. For a complementary description, see Fosdahl et al. [31]. Exercises were performed together with the physiotherapists, two times per week:

- Five-minute warm-up on a treadmill or a stationary bicycle.
- Physiotherapist assisted stretches:
    - Hamstring stretch was performed bilaterally with the child positioned supine, one leg flat on the bench and the contra lateral hip joint flexed to 90°. The physiotherapist supported the thigh and the child performed an active extension of the knee. Voluntary active knee extension was held for 5 seconds followed by the physiotherapist supporting and keeping the stretch, with constant stretching force as tolerated by the child at the end position for additional 40 seconds; 5 repetitions were performed.
    - If a short psoas was registered at baseline (≤5° extension) a psoas- stretch was performed with the child positioned prone. The child preformed an assisted active extension of one hip for 5 seconds, followed by the physiotherapist who supported and kept the hip extension at the end position for additional 40 seconds; 5 repetitions. There was 10–15 s rest between the stretches.
- Four PRE exercises:
    - Three multi-joint exercises with a loaded back-pack: (1) squats, (2) heel rise and (3) step-up on a stair.
    - One single-joint exercise was performed with the child positioned supine on a bench performed maximum knee-extension over a bolster. The physiotherapist applied manual resistance on the distal leg. It was therefore not possible to objectively control the load and progression applied.
    - The exercises were performed bilaterally with 2 min. breaks between the exercises

The three multi-joint exercises ((1), (2), (3)) were performed in an upright, axial loaded position wearing a back-pack, and focus on the terminal knee extension. To familiarize the children with the exercises, the back-pack was unloaded the first week, the second week the back-pack was loaded with weights or bottles filled with water.

The amount of initial weight load followed the principles and recommendations suggested by Scholtes et al. (2008) [32], performing an eight-repetition maximum (8 RM) sit to stand exercise test, with a start load of about 35%, 30% and 25% of the child's bodyweight, for GMFCS level I, II and III, respectively. The load was increased as the child became stronger, based on the 8 RM test [31] repeated every third week. The number of repetitions was progressively increased: 2 series of 12 repetitions (week 1 and 2), 3 series of 12 repetitions (week 3 to 5), 3 series of 10 repetitions (week 6 to 8) and after 8 weeks 3 series of 8 repetitions was performed. The weight load progression was

administered and recorded by the local physiotherapist. A handrail was available for those who required any balance support.

Exercises were performed at home, once a week:

- Passive hamstring stretch: sitting on a chair with one knee extended and the heel on the floor, leaning the trunk forward from the hip joint. The stretch was held for 45 seconds × 5, bilaterally.
- Strength exercise: squats (1) with a loaded back-pack. To familiarize with the two home exercises, the child was instructed by the physiotherapist the first three weeks. The following weeks the exercises were performed at home without guidance

The maintenance program (17–32 weeks) was performed once a week. The maintenance program was identical to the two above-described home exercises. In addition, both the intervention group and the comparison group received care as usual during the maintenance period. The numbers of physiotherapy, home exercises and care as usual sessions attended were registered by the physiotherapists and returned to the project manager by e-mail.

2.4. Outcome Measures

The 3DGA variables were; sagittal plane kinematics from knee, hip and pelvic angle at foot strike, minimum knee flexion in stands, and the gait efficiency parameters: gait speed and step length. The Gait Deviation Index (GDI) [33] was calculated and in addition, the Six-Minute Walk Test (6MWT) [34,35] was performed. All tests, except for the 6MWT were administered by two senior therapists masked for the group allocation. The tests were performed in the Motion Laboratory at Oslo University Hospital and at Haukeland University Hospital in Bergen. Both test sites had a VICON motion laboratory (Vicon Motion Systems, Oxford, UK), with six 3D MX cameras, two 2D cameras and AMTI (Advanced Mechanical Technology, Inc., Watertown, MA, USA) force plates used for the 3DGA. Sixteen reflex markers were placed, on body landmarks according to the Helen Hays' model [36] by the same assessor at every assessment. The children walked on a 10-meter walkway, at self-selected speed, until 5 trials of 3D-data with satisfactory quality were collected. These five trials were processed in Vicon Nexus 2.5 and gait events were processed in Vicon ProCalc 1.1. The second gait cycle from each of the five trials was selected, and mean values from the five cycles were calculated and used as the raw score from each gait event. 3DGA has an overall acceptable reliability with a measurement error in the sagittal plane between 2° and 4° [37], and a single assessor is shown to be more reliable then multiple assessors [38].

GDI is a gait index expressing the overall gait pathology derived from the 3DGA kinematic parameters into one single numeric measure. The values are ranged from 0–100, where 100 and above indicate absence of pathology. The GDI index was calculated using the GDI pipeline in Vicon Nexus 2.6. Mean GDI was calculated from the five trials collected.

Local physiotherapists, not involved in the treatment of the children, administered the 6MWT. They received a detailed description based on the American Thoracic Society's guidelines [34]. The test was performed on a 15-meter walkway and standardized oral instruction was given. The 6MWT has been documented to have good test-retest [39] and between-tester reliability [40].

2.5. Statistical Analysis

Data were analysed using the statistical analysis software program SPSS V25 for Windows (SPSS Inc, Chicago, IL, USA). Descriptive values are presented as means (± SD) (Table 1), and paired sample t-tests were used to calculate within group mean differences between baseline and 16 weeks, and between baseline and 32 weeks (Table 2). To compare baseline variables between the intervention and the comparison group, Student's t-test was used for continuous, normally distributed data, and Chi square test for categorical variables. Two-tailed value of $p < 0.05$ was considered statistically significant. To evaluate mean differences between the two groups at 16 and 32 weeks, linear regression analysis with covariates correcting for baseline values (ANCOVA) was performed. Due to

a wide age-span, age was added as a covariate in the model. Seven random missing values from the 6MWT were substituted using single imputation by last value carry forward [41].

The outcome variables reported in the present paper are secondary variables derived from a recent RCT [31], and the sample size calculation was based on the primary outcome variable, the passive popliteal angle. In order to achieve 80% test power, at least 16 participants in each group had to attend the first follow up test after 16 weeks.

Table 1. Descriptive characteristics of the participants at baseline.

Variables	Intervention Group (n = 17)	Comparison Group (n = 20)
Gender (boys/girls)	7/10	14/6
Age (years)	10.4 ± 2.3	10.0 ± 2.3
Height (cm)	141.3 ± 16.5	141.4 ± 12.8
Body weight (kg)	37.6 ± 13.3	39.9 ± 12.9
BMI (kg/m^2)	17.8 ± 3.6	19.7 ± 4.7
GMFCS I/II/III	10/7/0	12/7/1

Values presented as mean ± SD; *n*: number of participants; BMI: Body Mass Index; GMFCS: Gross Motor Function Classification System.

Table 2. Gait parameters at baseline (T0), 16 weeks (T1) and 32 weeks (T2).

Gait Parameters	*n*	T0	T1	T0–T1	T2	T0–T2
		Intervention Group				
		Mean ± SD	Mean ± SD	Mean diff ± SD	Mean ± SD	Mean diff ± SD
Knee angle, foot strike (deg)	16	16.1 ± 6.8	16.1 ± 8.5	−0.01 ± 4.4	17.5 ± 10.5	−1.4 ± 6.1
Hip angle, foot strike (deg)	16	41.1 ± 12.1	42.6 ± 11.7	−1.5 ± 4.7	41.7 ± 10.2	−0.6 ± 5.6
Pelvic angle, foot strike (deg)	16	16.8 ± 7.3	16.9 ± 7.6	0.5 ± 3.1	15.6 ± 7.8	0.3 ± 3.1
Min knee angle, stands (deg)	16	5.7 ± 8.7	6.0 ± 8.9	−0.3 ± 4.8	6.4 ± 9.8	−0.7 ± 6.1
Step length (cm)	16	52.7 ± 8.2	54.0 ± 9.8	−1.3 ± 5.5	55.8 ± 10.6	−3.2 ± 5.1
Speed (m/s)	16	1.05 ± 0.2	1.1 ± 0.2	−0.05 ± 0.1	1.04 ± 0.3	0.18 ± 0.3
Six-Minute Walk Test (m)	15	390.5 ± 106.9	436.2 ± 114.8	−45.7 ± 55.4 *	441.6 ± 121.6	−51.1 ± 72.8 *
Gait deviation index	16	78.8 ± 11.1	79.2 ± 11.2	−0.4 ± 4.4	79.5 ± 11.7	−0.7 ± 6.0
		Comparison Group				
	n	T0	T1	T0–T1	T2	T0–T2
		Mean ± SD	Mean ± SD	Mean diff ± SD	Mean ± SD	Mean diff ± SD
Knee angle, foot strike (deg)	18	17.5 ± 9.0	15. 0 ± 10.6	2.6 ± 5.2	14.8 ± 10.9	2.6 ± 6.4
Hip angle, foot strike (deg)	18	39.9 ± 7.5	37.8 ± 7.7	2.1 ± 7.2	38.0 ± 8.6	1.9 ± 6.5
Pelvic angle, foot strike (deg)	18	14.3 ± 5.3	13.2 ± 3.9	1.1 ± 3.9	14.2 ± 3.9	0.1 ± 4.1
Min knee angle, stands (deg)	18	5.9 ± 9.3	4.0 ± 10.7	1.8 ± 5.0	3.4 ± 11.5	2.4 ± 5.2
Step length (cm)	18	51.6 ± 9.5	51.2 ± 9.8	0.4 ± 5.4	51.3 ± 10.4	0.3 ±7.4
Speed (m/s)	18	1.02 ± 0.2	0.97 ± 0.3	0.05 ± 0.2	1.03 ± 0.2	−0.01 ± 0.2
Six-Minute Walk Test (m)	16	349.9 ± 112.7	405.2 ± 123.5	−55.4 ± 55.5 *	406.5 ± 133.9	−56.6 ± 59.6 *
Gait deviation index	18	80.0 ±9.7	79.1 ± 15.2	0.8 ± 7.14	79.0 ± 11.6	1.01 ±5.9

Group raw values presented as mean ± SD at baseline (T0), 16 weeks (T1) and 32 weeks follow-up (T2), and mean within group difference ± SD between T0–T1 and T0–T2 (pared sample t-test), Statistically significant *: $p < 0.05$; *n*: number of participants; deg: degrees; flex: flexion; max: maximum; min: minimum.

Table 3. Comparison of mean difference between the intervention and comparison group at T1 and T2 when adjusted for baseline and age, in the linear regression model (ANCOVA).

Gait Parameters	T0–T1			T0–T2		
	n	Mean Difference (95% CI)	*p* value	*n*	Mean Difference (95% CI)	*p* value
Knee angle, foot strike (deg)	34	−2.4 (−5.8 to 1.0)	0.161	34	−3.9 (−8.5 to 0.6)	0.088
Hip angle, foot strike (deg)	34	−3,7 (−7.9 to 0.5)	0.081	34	−2.8 (−6.9 to 1.3)	0.175
Pelvic angle foot strike (deg)	34	−1.6 (−3.9 to 0.7)	0.172	34	0.6 (−1.8 to 2.9)	0.638
Minimum knee angle in stands (deg)	34	−2.2 (−5.7 to1.4)	0.228	34	−3.2 (−7.3 to 1.0)	0.128
Step length (cm)	34	−1.5 (−5.3 to 2.2)	0.408	34	−3.3 (−7.9 to1.2)	0.149
Speed (m/s)	34	−0.1 (−0.2 to 0.05)	0.188	34	−0.02 (−0.02 to 0.2)	0.778
Six-Minute Walk Test (m)	31	10.6 (−29.3 to 50.6)	0.590	31	7.2 (−43.3 to 57.7)	0.772
Gait deviation index	34	−1.0 (−5.3 to3.3)	0.650	34	−1.4(−5.6 to 2.8)	0.504

T1: 16 weeks follow-up, T2: 32 weeks follow-up, n: number of participants, CI: confidence interval, deg: degrees, statistically significant: $p < 0.05$.

3. Results

According to the randomization procedure 17 children were allocated to the stretching and PRE program and 20 children to the comparison group. Three children were excluded before the first follow-up test (Figure 1). Thirty-four children completed the 3DGA at all the three test sessions (T0, T1, T2). However, due to practical reasons only 31 children performed the 6MWT at all test points. There were no significant differences between the two groups at T0 for any of the baseline variables (Table 2).

The compliance registration form was answered by 81% of the physiotherapists. For the intervention group, the compliance rates were 79% (25 sessions ±4), 76% (12 sessions ±5) and 73% (35 sessions ±6) for the sessions together with the physiotherapist, the home exercise sessions, and total number of sessions, respectively. The compliance rate for the maintenance program was 72% (13 sessions ±4). The most frequent reasons for absence from training were illness, vacations and conflicting appointments. At baseline, two children in the intervention group showed a short psoas muscle, (≥5° extension) and for that reason psoas stretches were included as a part of the intervention. During the study period, 60% of the children in the comparison group received physiotherapy as usual, ranging from one to two sessions per week. There was high variation in the physiotherapy modalities given. Five children received strength and/or stretching exercises, and ten children received functional training, swimming or horseback riding. Descriptive values and differences within groups for all outcome measures at T0, T1 and T2 are presented in Table 2. For the 6MWT, there were significant changes within both groups both at T1 and T2. There were no significant within group changes for any of the other gait variables (Table 2).

For the kinematic gait variables, gait speed, step length, GDI and 6MWT, there were no significant mean differences between the intervention group and the comparison group, neither at T1 nor at T2 (Table 3).

4. Discussion

The results from the present study showed that a 16-week hamstring stretching and PRE program and a 16-week maintenance program did not result in any significant mean difference between the intervention group and the comparison group for any of the gait parameters measured (Table 3). To our knowledge, no previous published study has evaluated the effect of a combined hamstring stretching and PRE program, targeting the extending muscles in the lower extremities, on different gait parameters. The rationale for introducing this combined intervention program was the assumption that improvement and maintenance of knee extension and muscle strength in the lower extremities is essential to optimize the prerequisites of gait in children with CP [1]. Adequate active terminal knee extension is important for maintaining strength, stability and dynamic control both in mid stance and terminal swing face. Previous studies, including children with CP with short hamstrings and crouch gait, have concluded that there is a need for interventions where the goal is to both preserve muscle strength and maintain ROM [14,28].

Active terminal knee extension is often reduced in children with CP [1,7]. Onpuu et al. [42] compared typically developing children with children with CP, and found that in the typically developing group the maximum knee angle at foot strike was 10° flexion, and 90% of the ambulatory children with CP (GMFCS I-III) showed more than 10° knee flexion at foot strike [42]. This is in line with the baseline values in the present study, showing a mean knee flexion angle at foot strike of 16° (±6) in both groups. Thompson et al. [7] studied isometric muscle power in 50 children with spastic CP, GMFCS levels I-III, and found that at 30° knee flexion, the knee extensors were the relatively weakest muscle group compared to typically developing children, worsening with decreasing gait function. Cloodt et al. [43] found that a knee joint contracture was associated with short hamstrings and therefore argued that maintaining hamstring length is important for reducing the risk of knee contractures.

The exercise program included in the present study primarily focused on increasing and maintaining the hamstring flexibility and strengthening of the muscles responsible for the active terminal knee extension. Despite this specific focus, there were no improvements in knee kinematics,

either at foot strike, at mid stance, or in the GDI (Table 3) for the intervention group at T1, and there was even a small decrease at T2. In the comparison group, there were slight improvements in the hip and knee kinematics at T1 and T2 (Table 2). These changes may be explained by a relatively small number of children included in the study, and normal variation (measurement errors) in the 3D-measurements between the different time points (McGinley 2009 [37]). We are aware that the present study is in line with previous published studies showing minor or no effect and even negatively influence on the kinematic variables following muscle strength training [8,10,14]. However, these studies included shorter intervention periods, and it was discussed if programs with longer lasting intervention periods, coupled with other interventions and monitoring of the hamstring muscle length [14] might have shown a more positive result. Our pre-study hypothesis was that by prolonging the intervention period up to 16 weeks, and adding stretching of the hamstring muscles, there might be a better rationale for improving the knee kinematics, thereby resulting in improved gait efficiency measured by increased step length and gait speed. Despite this prolonged intervention period, no significant improvements in gait function were found (Table 3). The chosen exercises included in the present intervention program followed the recommendations for youth resistance training published by NSCA [9] with modifications recommended for children with CP [29], and established physiotherapy methods for manual stretching were used. The intensity of the static stretch was instructed to be a 40 second continuous end-point stretch not painful to the child. However, the amount of load applied by the physiotherapist was not possible to quantify.

Dose and intensity according to the NSCA guidelines were described in the exercise protocol. The progression of weight load in the back-packs was adjusted by the 8 RM test performed by the physiotherapist every third week. The physiotherapists were guided by a project manager; however, the 16 different physiotherapists may have different understanding of and experience with the NSCA guidelines, PRE training and how to guide and motivate the child, resulting in variations in both dose and intensity applied. In the single-joint knee extension exercises, the weight load on the distal leg was controlled by the physiotherapist and through feedback from the child and the hands-on felt muscle response. Hence, the quality of this exercise depended on the physiotherapist's individual hands-on skills.

The individual experience and knowledge of the physiotherapists may to some extent, have interfered with the effectiveness of the exercises. A pre-study course for the physiotherapists in the intervention group might have increased the quality and consistence of the intervention; however, due to geography and lack of time it was difficult to arrange. Another reason for the insignificant group differences in the present study may be lack of gait specific exercises. In a recent intervention study by van Vulpen et al. [16], children with CP (GMFCS levels I and II) performed functional high velocity resistance training, with progressive external resistance, to improve muscle strength and walking capacity. The study showed significant effect on walking capacity, muscle strength and increased passive ROM in the ankle joints. The results indicate that functional strength exercises performed with higher velocity might be more suitable for improving gait function.

The exercises included in the present exercise program emphasized active knee extension both in a standing position and unloaded, lying supine on a bench. To achieve a carryover-effect from impairment-focused strength training to improve active knee extension and stability in the gait cycle, specific gait training should probably have been a part of the intervention program. In a systematic review and meta-analysis by Moreau at al [12], they concluded that gait training was more effective than strength training in improving gait speed. However, they did not evaluate any impact on kinematic variables.

In a recent study, Fitzgerald et al. [35] studied 145 children with CP and presented 6MWT reference values for the different GMFCS levels with a mean of 377 m. The results from the present study correspond well with Fitzgerald's findings (Table 2). There was no significant difference between the intervention and the comparison groups at T1 or T2 (Table 3). However, there were significant changes within both groups at T1 and the change remained unchanged at T2 for both groups (Table 2). Nevertheless, the changes were not above the minimal detectable change, as documented by Thompson et al. [44]. The reliability of the 6MWT for children with CP is documented

[39,44], and Maher et al [39] stated that a practice test before the first test is not necessary. However, the significant changes in both groups registered in the present study might have been influenced by a learning effect or the children might have been more motivated when they were familiar with the test. In addition, 60% of the children in the comparison group also received physiotherapy (care as usual), which might also have influenced the results. The 6MWT was the only test performed locally, and the same child was tested by the same physiotherapist on all three occasions. Even though the test situation followed the international guidelines described by the American Thoracic Society [34], and the inter-rater reliability is shown to be acceptable [40], there is a risk that the test situations differed to some degree, but there should not be any reason for a biased group difference.

There are some limitations to the present study. First, only one child classified at GMFCS level III was recruited, indicating that the results are not applicable to children at GMFCS level III. Second, for an optimal and more consistent guiding and implementation of the intervention, there should have been one physiotherapist responsible for all the children in the intervention group. The geographical distribution of the children made that impossible to implement. Third, to limit the number of tests the child had to perform on the day visiting the hospital, the 6MWT was administered locally by a different assessor for each child. However, for some children and local physiotherapists, the testing became difficult to carry out, resulting in some missing tests, making the 6MWT results incomplete. A fourth limitation was the lack of a more detailed mapping of the content of the intervention given to the children in the comparison group. The physiotherapy modalities registered revealed variations in content and frequency, and some of the modalities used may have interfered with the results. To cope with this, a comparison group not receiving any kind of physiotherapy during the intervention period could have been included; however, this was considered unethical.

5. Conclusions

The results from the present study showed that a 16-week combined hamstring stretching and PRE program, followed by a 16-week maintenance program did not result in any difference in change between the intervention and the comparison group in any of the gait parameters evaluated. However, the 6MWT showed significant improvements within both groups after 16 weeks. Future studies aiming at improving specific impairments in gait function should probably include some kind of gait specific exercises.

Supplementary Materials: The instructional video distributed to the physiotherapist in the intervention group (in Norwegian) is available online at https://www.youtube.com/watch?v=wDCisF5cQow

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