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Success Factors for Gross Motor Progress in Children with Cerebral Palsy

NTNU
Norwegian University of
Science and Technology

Doctoral thesis

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NTNU
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Thesis for the Degree of
Philosophiae Doctor
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Suksessfaktorer for grovmotorisk framgang hos barn med Cerebral Parese

Formålet med dette forskningsprosjektet har vært å fremskaffe mer kunnskap om suksessfaktorer for grovmotorisk framgang hos barn med Cerebral Parese (CP).

I Studie 1 benyttet vi multippel single subject design (ABA over 18 uker) hvor seks barn med CP i alderen 3-11 år, Gross Motor Function Classification System nivå I, II eller IV deltok. Vi fant vi at intensiv målrettet funksjonstrening i 10 timer per uke i seks uker ga høy måloppnåelse og stor grovmotorisk framgang målt med Gross Motor Function Measure (GMFM-66) (totalskårer og persentiler).

Studie 2 og 3 var prospektive kohortestudier som inkluderte 442 barn med CP 2-12 år (totalt 2048 målinger), fra Cerebral Pareseregisteret i Norge (CPRN) og Cerebral Parese Oppfølgingsprogram (CPOP). Linear Mixed Models ble benyttet til analysene.

I studie 2 fant vi en dose-respons-sammenheng mellom fysioterapifrekvens og grovmotorisk framgang målt som endring i GMFM-66 persentiler fra ett måletidspunkt til det neste (median 1 år). Fysioterapi minst 1-2 ganger i uka var assosiert med grovmotorisk framgang, mens den største framgangen ble funnet hos barn som fikk fysioterapi 3 ganger i uka eller mer. Antall kontrakturer og epilepsi påvirket denne sammenhengen negativt.

I *Studie 3* fant vi at perioder med intensiv trening uavhengig av andre faktorer inkludert i modellen, var assosiert med et mer positivt grovmotorisk utviklingsforløp på lengre sikt når repeterte målinger av GMFM-66 persentiler mellom 2 og 12 år var utfallsmål. De grovmotoriske utviklingskurvene hos barn med utviklingshemming og spiseproblemer lå i gjennomsnitt på et nivå betydelig under kurvene til andre barn. Ankelkontrakturer var med økende alder negativt assosiert med grovmotorisk framgang.

Konklusjon: Intensiv trening og fravær av kontrakturer synes å være suksessfaktorer for grovmotorisk framgang både på kort og lang sikt for barn med CP. Utviklingshemming og spisevansker var assosiert med grovmotoriske utviklingsforløp på et nivå betydelig under forløpene til barn uten disse utfordringene.

Kandidat: Gunfrid V. Størvold. **Institutt:** Institutt for samfunnsmedisin og sykepleie.
Veiledere: Grete H. Bratberg, Reidun B. Jahnsen, Kari Anne I. Evensen.
Finansieringskilder: Stiftelsen Sophies Minde (hovedfinansiering), Helse Nord-Trøndelag, Fond til etter- og videreutdanning av fysioterapeuter

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Contents

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List of papers

Paper 1

Storvold GV, Jahnsen R. **Intensive motor skills training program combining group and individual sessions for children with cerebral palsy.** *Pediatric physical therapy: the official publication of the Section on Pediatrics of the American Physical Therapy Association. 2010;22(2):150-159. doi: 10.1097/PEP.0b013e3181dbe379*

Paper 2

Storvold G.V., Jahnsen R.B., Evensen K.A.I., Bratberg G.H. **Is increased physical therapy frequency associated with increased gross motor improvement in children with cerebral palsy? A national prospective cohort study.** In review *Disability and Rehabilitation* (submitted 2018 March 6.)

Paper 3

Storvold G.V., Jahnsen R.B., Evensen K.A.I., Romild U.K., Bratberg G.H. **Factors Associated with Enhanced Gross Motor Progress in children with Cerebral Palsy: A Register-based Study.** *Physical and Occupational Therapy in Pediatrics 2018; May 1:1-14. doi: 10.1080/01942638.2018.1462288. [Epub ahead of print]*

Abstracts

Størvold GV; Jahnsen, R.B.; Evensen, K.A.; Romild, U.K.; Bratberg, G.H. **Longitudinal impact of treatments and child-related variables on gross motor progress in children with cerebral palsy: a prospective cohort study of reference percentiles of GMFM-66.** Oral Presentations EACD-17. *Developmental Medicine & Child Neurology. 2017;59:4-45.*

Abbreviations

CP	Cerebral Palsy
CNS	Central nervous system
CPG	Central pattern generators
CPOP	Cerebral Palsy Follow-up Program of Norway
CPRN	Cerebral Palsy Register of Norway
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICF	The International Classification of Functioning, Disability and Health
GAS	Goal Attainment Scaling
GDT	Goal-directed treatment
GMFCS	Gross Motor Function Classification System
GMFCS-E & R	Gross Motor Function Classification System Expanded & Revised
GMFM	Gross Motor Function Measure
GMFM-66/GMFM-88	Gross Motor Function Measure, 66 item/88 item versions
GMFM-66 percentiles	Reference percentiles for the Gross Motor Function Measure
NDT	Neurodevelopmental treatment (“Bobath”)
NGST	Neuronal group selection theory
OT	Occupational therapist
PT	Physical therapist
ROM	Range of Motion
RCT	Randomized controlled trial
SCPE	Surveillance of Cerebral Palsy in Europe
SES	Socioeconomic status

Summary

The overall purpose of this research project was to generate more knowledge of success factors for gross motor progress in children with cerebral palsy (CP).

In Study 1 we applied multiple single-subject design (ABA over 18 weeks), including six children with CP 3-11 years old at Gross Motor Function Classification System levels I, II and IV. We found that an intensive (60 hours in six weeks), goal-directed motor skills training program resulted in high rate of goal attainment and positive changes in Gross Motor Function Measure (GMFM-66) (total scores and percentiles).

Study 2 and 3 were prospective cohort studies of 442 children 2-12 years old with a total of 2048 assessments from the Cerebral Palsy Follow-up Program (CPOP) and the Cerebral Palsy Register of Norway (CPRN) analyzed in a Linear Mixed Model.

In St*udy 2* we found a dose-response association between physical therapy frequency and gross motor progress. The mean change in GMFM-66 percentiles between two subsequent assessments (median one year) was 4.2 (95% CI: 1.4, 7.1) percentiles larger for physical therapy 1-2 times per week and 7.1 (95% CI: 2.6, 11.6) percentiles larger for physical therapy >2 times per week compared with lower frequencies. Number of contractures and epilepsy were negatively associated with gross motor progress.

In Study 3 outcome was repeated measures of GMFM-66 percentiles between two and 12 years. We found that independent of all other factors included in the model, intensive training was associated with long-term enhanced gross motor progress (mean 3.3 percentiles 95% CI: 1.0, 5.5 per period). Ankle contractures by age were associated with a decrease in GMFM-66 percentiles (-1.9 percentiles per year; 95% CI: -3.6, -0.2). Gross motor function developed on average at a lower level in children with intellectual disability (-24.2 percentiles 95% CI: -33.2,-15.2) and in children with eating problems (-10.5 percentiles; 95% CI: -18.5, -2.4) compared with their counterparts.

Conclusion: Intensive training and having no contractures are suggested success factors for both short-term and long-term enhanced gross motor progress in all children with CP. Intellectual disability and eating problems are suggested to be prognostic factors for long-term gross motor developmental trajectories considerable below those of children without such problems.

Introduction

This thesis is about gross motor function in children with cerebral palsy (CP). Gross motor functions are fundamental for children to explore and interact with the environment and are evident in almost all activities throughout the day. Examples are holding the head in order to communicate or eat, rolling to change position in bed, sitting to play, or moving around to be with peers or to accomplish activities of daily living. Hence, limited gross motor function, which is a core symptom of CP,[1] may restrict participation in everyday life situations. Therefore, knowledge about factors associated with gross motor progress is of great importance. Some factors may be changeable and thereby important goal areas for therapy, whereas other factors may not be modifiable and therefore important for prognosis and realistic goal setting when planning for the future.[2]

More than 90% of children with CP receive physical therapy.[3, 4] The children's time is precious and considering the time and effort that the children and their families invest in gross motor skills practice and prevention strategies of secondary impairments, both intervention strategies and dosage should be knowledge-based. Hence, it is important to implement local variants of research based intervention strategies and evaluate their effect, and to investigate whether more frequent physical therapy is associated with enhanced gross motor progress. As enhanced gross motor progress may or may not be temporary, it is also necessary to investigate the long-term gross motor progress.

The overall purpose of this research project was to generate more knowledge about factors associated with gross motor progress. By using reference percentiles for the Gross Motor Function Measure (GMFM-66 percentiles)[5] as outcome, both short term changes in gross motor function and the long-term gross motor developmental trajectories were investigated.

The title of this thesis reflects the important contribution from the Norwegian Cerebral Palsy association when planning the cohort studies (Papers 2 and 3). The very clear message was to have a positive approach; to search for the success factors for gross motor progress.

Gross motor progress

GMFM-66 percentiles[5] show the expected and average patterns of change in Gross Motor Function Measure (GMFM-66)[6] total scores by age within each Gross Motor Function Classification System[7] level (GMFCS level), i.e. *the average gross motor progress* within each GMFCS level. Children are assumed to acquire gross motor skills more rapidly while they are young, with the rate of change slowing as they reach the limit of their potential.[8] Despite large variations[5] children are in general expected to follow their own percentile (Figure 1).

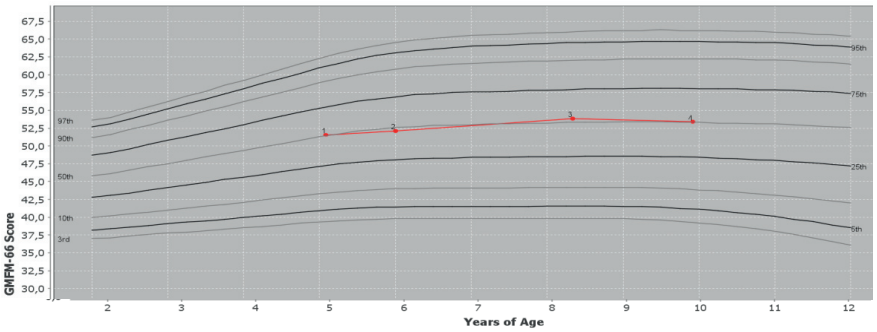

Figure 1: The gross motor developmental trajectory of one child at GMFCS level III (red) plotted on GMFM-66 reference percentiles (screen-shot from the Gross Motor Ability Estimator; GMAE).

Any increase in GMFM-66 percentile implies a gross motor development better than expected according to age and GMCS level, which in this thesis is classified as *enhanced gross motor progress*. For most children enhanced gross motor progress indicate a larger increase in GMFM-66 total scores than expected. Since the shapes of GMFM-66 reference percentile curves differ,[8] an increase in percentile for some older children functioning on the lower percentiles may however mean that the decrease in GMFM-66 total scores has been lower than expected.

Figure 2 shows the long-term gross motor trajectory for one child with positive and negative changes between subsequent assessments.

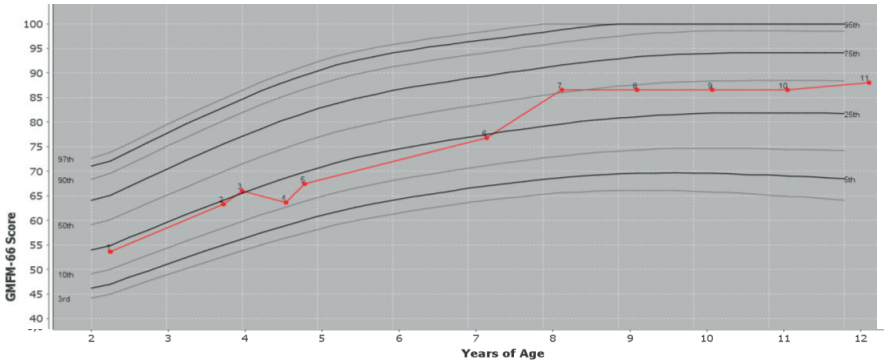

Figure 2: The gross motor developmental trajectory of one child at GMFCS level I (red) plotted on GMFM-66 reference percentiles (screen-shot from GMAE).

In the intervention study (Paper 1) we investigated if the intervention led to enhanced gross motor progress; for example as seen between assessments six and seven, and in the short-term cohort study (Paper 2) we examined if increased physical therapy frequency was associated with such short-term positive changes.

The long-term developmental trajectory for the child in figure 2 was slightly more positive than expected, and in the long-term cohort study (Paper 3) we investigated underlying factors for such enhanced gross motor progress over time.

This thesis is not about fine motor function nor is it about participation, but because of being investigated in Paper 1, briefly mentioned in methods and results.

Background

Cerebral Palsy (CP)

Definition

> *"Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy, and by secondary musculoskeletal problems".*
>
> *Rosenbaum et al. 2007 (page 9)*

The above definition of CP and the accompanying explanations of the terms used in the definition[9] highlight some points of relevance to this thesis:

- CP is a heterogeneous condition.
- The developmental nature of CP usually implies an impact on the developmental trajectories, with delayed or aberrant motor progress.
- Abnormal gross and fine motor functioning (reflecting abnormal motor control) are the core features of CP.
- To be considered CP, the disorders of movement and posture have to cause activity limitation, the execution of a task or action according to The International Classification of Functioning, Disability and Health (ICF).[10]
- The pathophysiological mechanisms leading to CP are non-progressive.
- In addition to the disorder of movement and posture, people with CP often show other neurodevelopmental disorders or impairments, both as a function of the primary disturbance(s) and as a secondary consequence of the activity limitations.

Classification by movement disorder

Cases of CP are classified by the dominant type of tone or movement abnormality into *spastic*, *dyskinetic* (further subdivided into dystonia and choreoathetosis), and *ataxic* types.[9, 11]

Classification by distribution

The former terms quadriplegia, diplegia, and hemiplegia, (sometimes also triplegia and monoplegia), which are still used in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), have been replaced by the terms unilateral and bilateral.[9, 11]

In the Cerebral Palsy Register of Norway (CPRN),[12] the movement disorder and distribution are combined into one scale using the Surveillance of Cerebral Palsy in Europe (SCPE) classification tree of spastic unilateral (right/left), spastic bilateral (the former diplegia and quadriplegia), dyskinetic (choreoathetosis/dystonia), and ataxia.[11]

Classification by severity

The Gross Motor Function Classification System (GMFCS),[7] developed in 1997, is considered the gold standard for classifying severity of CP.[11, 13, 14]

The GMFCS divides gross motor function into five categories ranging from Level I (most able) to Level V (most limited), which are recognized as meaningful differences in daily functioning[15] (Figure 3). It focuses on self-initiated functions (activities according to ICF) with emphasis on sitting and walking and the need for assistive devices.[7]

The GMFCS is an ordinal level scale that is valid for children in the age range 1-12 years, and is based on reported or observed gross motor function in everyday activities rather than on testing[7] or capacity observed under optimal conditions.[15]

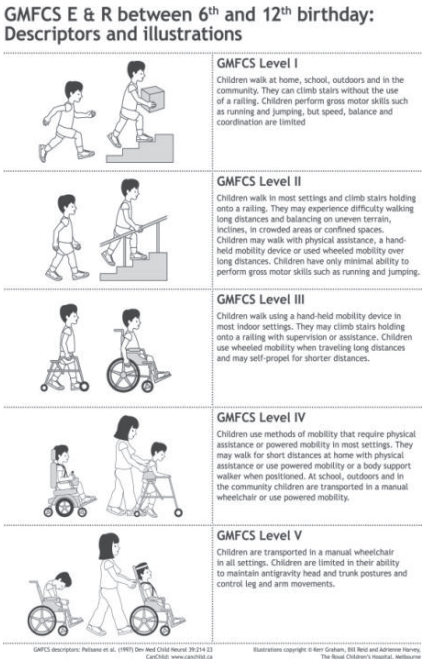

Figure 3: Example of GMFCS E&R.[7, 16]

Illustrations Version 2 © Bill Reid, Kate Willoughby, Adrienne Harvey and Kerr Graham, The Royal Children's Hospital Melbourne ERC151050. Reprinted with permission via Elsevier ClinicalKey (Ambulant cerebral palsy. Peterson, Nicholas, Orthopaedics and Trauma, Volume 30, Issue 6, 525-538)

The GMFCS provides descriptions (Figure 3) to enable determination of which of the five levels most closely resembles a child's gross motor function; it is quick (less than ten minutes) and easy to use, and no special training is needed to use it.[7] Additionally, a Family & Self Report Questionnaire is available to help families choose the right GMFCS level. The GMFCS was expanded and revised (GMFCS-E&R) in 2007[16] and now contains five age bands, ranging from under 2 years to18 years.

The psychometric characteristics of the GMFCS are very good.[15] It has face validity as a way to describe the motor abilities of children with CP,[17] and both the content validity and the construct validity are good in terms of classification of gross motor ability.[7, 18] Interobserver reliability has repeatedly been shown as good between professionals[7, 14, 17] and between professionals and parents.[13, 14]

It is an underlying assumption that the GMFCS is stable over time.[1] Based on research,[17, 19] it is expected that improvements associated with different types of interventions will occur within the GMFCS level a child was previously assigned to rather than through a change of level.[15]

The GMFCS can also be used as a predictive tool, as there is strong correlations between classification in preschool years and at 12 years of age,[17] and into adulthood.[20] The positive predicted value of the GMFCS at 1-2 years of age to predict walking by 12 years of age is reported as 0.74.[17]

Classification systems for, for example, fine motor function, communication, and speech are incorporated into the Cerebral Palsy Follow-up Program in Norway (CPOP) and the CPRN, but since this thesis focuses on gross motor function they will not be elaborated upon.

Prevalence

In Europe, the prevalence of CP has been around 2 per 1000 live births.[21, 22] There are some promising results indicating a decline in the prevalence to 1.8 per 1000 live births.[23] In Norway, the prevalence of CP is 2.5 per 1000 live births.[24] However, there is a clear fall in the prevalence of CP from 2.6 per 1000 live births in 2005 to 1.9 per 1000 live births in 2010.[25]

Gross Motor Function

Definition of gross motor function

> *Gross Motor Function implies using large groups of muscles for maintaining balance, change positions, and mobility; for example holding head in midline, sitting, crawling, sit-to-stand, standing, walking, running, and jumping.*
>
> *Russel et al 2013*

Gross motor functions are often described as having a definite end or purpose, and as being goal-directed and meaningful.[26] However, children sometimes engage in movement activities that are seemingly without a goal, such as walking or bicycling without the goal of moving from one place to another. These types of movement activities are similarly regarded as gross motor functions.[26]

ICF

In this thesis, The International Classification of Functioning, Disability and Health (ICF)[10] is used as an underlying way to understand functioning and disability. The ICF is a classification of health and health-related domains. As the functioning and disability of an individual occurs in a context, the ICF also includes a list of environmental factors[10] (Figure 4).

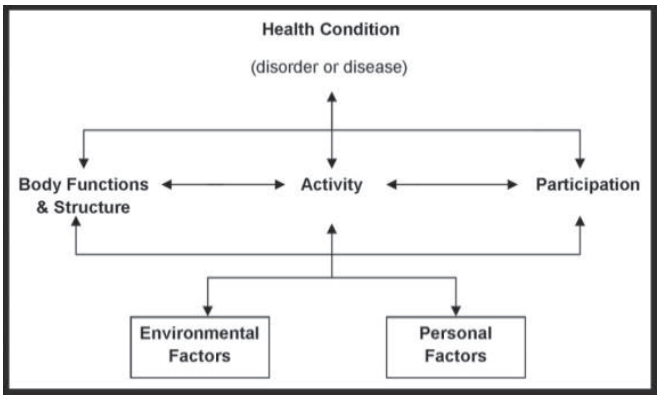

Figure 4: ICF model.[10]

The diagram identifies the three levels of human functioning classified by the ICF: functioning at the level of body or body part, the whole person, and the whole person in

a social context.[10] *Impairments* refer to problems in body function and structure, *activity limitations* refer to difficulties an individual may have in executing activities, and *participation restrictions* refer to problems an individual may experience in involvement in life situations.[10]

According to ICF, gross motor functions are activities.[26] By definition, the principal activity limitation associated with CP involve problems in motor function.[6, 9]

Motor control

The core features of CP are abnormal gross and fine motor functioning and organization, which reflect abnormal motor control.[9]

> *"Motor control is defined as the ability to regulate or direct the mechanisms essential to movement."*
>
> *Shumway-Cook & Woollacott 2012 (page 4)*

In this thesis, motor control is understood in a systems theoretical frame of reference. Common to all systems theories is the notion that multiple variables (also called systems or subsystems) contribute to the initiation and execution of movement.[26] Movements emerge from the cooperation of variables in the individual, the task, and the environment.[27, 28] The relation between these variables is not simply hierarchical, whereby the brain commands and the body responds, but distributed[29].

It is likely that we control our movements in different ways depending upon the type of movement.[26] Some well-learned movements may be self-organized based on variables including (but not limited to) central pattern generators (CPG) (i.e., interneural networks in the brain stem or the spinal cord that can produce coordinated movement synergies),[26] direct perception, the child's arousal and motivation, energetic and elastic properties of muscles, the biomechanics, environmental support, and constrains placed on the system by the task at hand.[29] The movements emerge based on dynamic properties of the interacting elements themselves[27] exploiting the natural properties of the motor system and the complementary support of the environment in a non-linear way.[29]

By contrast, higher order action, perceptionmotor and cognitive processes are important for tuning, guiding, learning, and selecting; adapting or inhibiting the

execution of basic movements by lower levels of the nervous system.[26] The involvement of higher-level central nervous system (CNS) structures can be observed as an ability to control movements selectively and adapt them to functional purposes.[26]

In children with CP (serious) limitations in adapting movements to functional purposes are imposed by a compromised CNS.[26] Furthermore, even if children with CP are born with an unaffected musculoskeletal system, secondary impairments will soon alter its properties adding even more problems to the solving of motor problems.[27]

Motor development

> *"Motor development refers to the continuous age-related process of change in movement as well as the interacting constraints (or factors) in the individual, environment, and tasks that drive these changes."*
>
> *Haywood & Getchell 2014 (page 5)*

Maturation theories understand motor development as a genetically driven process of brain maturation in which infants' experience have only a secondary and supporting role.[28, 29] They hypothesize that changes in behavior directly reflect changes in cortical control over lower level reflexes, leading to the emergence of motor milestones in a lawful progression. Maturation theories are based on research done in the 1920s, 1930s, and 1940s and they dominated the field of motor development thorough most of the 20th century.[26, 29, 30] In this thesis I acknowledge that the role of neural maturation is an important process in motor development, especially in the early years, but adheres mainly to newer theories of motor development.

Consistent with a systems theory of motor control, more recent theories of motor development acknowledge the multicausality of action, including both central and mental systems and the purely physical, energetic, and physiological systems in a particular context.[28, 29] Developmental change arises within a context as the product of multiple developing systems. Each system has its own trajectory of change and some systems may be delayed or compromised, as in the case of higher-order CNS systems and musculoskeletal systems in CP, and will then act as rate limiters. Only when all of the systems reach critical functioning and the context is appropriate, will the system assemble a new behavior.[28, 29] Accordingly, brain maturation is seen as one of the

cooperating systems. However; brain maturation is particularly important in CP, due to the cause of CP.[26]

Developmental change can come about through exploration and selection in finding solutions to new task demands.[29] The notion of exploration and selection is thought of as a key developmental process at both behavioral and neural levels. At the behavioral level, it is a process of trial and error: the child will be motivated by a task and, through repeated cycles of actions (tentative movement solutions) and the perception of the consequences of those actions in relation to the goal, the child will solve the movement problem at hand.[29] Also, change in one system can disrupt the current stability and thus engender change by making it possible to explore and select new solutions. In early infancy, this system may be growth, maturation, or biomechanical factors, whereas experience, practice, or environmental factors will become more important later on.[29]

Neuronal group selection theory (NGST)

At the neural level, exploration and selection can be described by the neuronal group selection theory (NGST), holding that experience engenders brain change, which in turn opens up new opportunities for experience.[29] According to the NGST, a child has a neural substrate at birth. Certain connections can be strengthened through use as the system explores by means of self-generated activity and afferent information.[30] A primary movement repertoire is formed by exposure to experiences common to all humans (experience-expectant development). A secondary repertoire of functional circuits that is function specific is based on individual experience, (experience-dependent neural development).[26, 30] This makes it possible to select, from a large repertoire of behavioral solutions, the one most appropriate for a specific situation. By contrast, atypical motor development (as in CP), is characterized both by a limited repertoire of motor strategies and a limited ability to adapt these strategies according to the specifics of the situation.[31]

Motor learning

> *Motor learning can be defined as "a set of internal processes associated with practice or experience leading to relatively permanent changes in the capability for motor skill."*
>
> *Schmidt & Lee 2011* (page 497)

Motor learning is:

- *..a set of processes*; the search for a task solution emerging from an interaction of the individual with the task and the environment,[26, 27] and can be thought of as repeated cycles of trial and error, perception and action, and exploration and selection at different levels of observation.[31]
- *..associated with practice or experience*. Changes brought about by maturation, growth, or changes in strength or endurance are not included in the definition of learning.[32] Practice and experience are key concepts in motor learning, and the most important condition for motor learning is amount of practice.[26, 32] A child with CP will have difficulty in organizing a good solution to the movement problem at hand, due both to the primary lesion and to secondary impairments, and will need considerably more practice to learn a specific task than will peers who do not have CP. [31]
- *..relatively permanent changes in capability for motor skill*. Capability implies that the skilled behavior will occur if other conditions are favorable.[32] Relatively permanent changes imply synaptic rearrangement at the cellular level.[31]

The learning process has also been characterized with respect to stages of learning[27] that focus on different aspects in the learning process. Fitts and Posner focused on the need for cognition in the learning process and the gradually reduction of cognitive involvement as learning proceedes.[27] The systems three-stage model of learning focuses on the movement pattern and on releasing all the degrees of freedom (multiple, independently moving body parts) necessary to perform the task in the most efficient and coordinated way. This includes taking advantage of the mechanics of both the musculoskeletal system and the environment.[27] Gentile's two-stage model of learning

focuses on understanding the environmental features that are critical to organization of the movement and to develop the capability of adapting the movement to changing task and environmental demands if the skill is open (diversification), but to perform the movement pattern with minimal variation if the skill is closed (fixation).[27]

Theoretical model underlying the thesis

Based on the ICF framework and systems theory of motor control, development, and learning, Figure 5 shows the theoretical model for how to understand gross motor function, and possible relations between independent and dependent variables in this thesis.

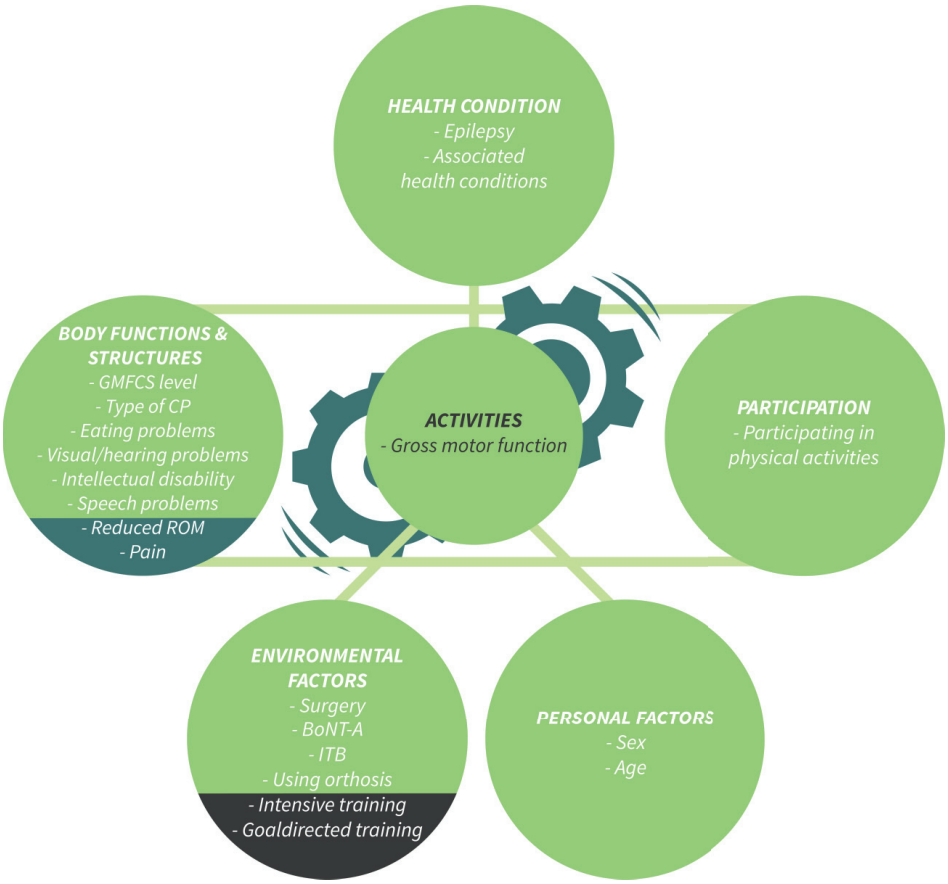

Figure 5: Theoretical model (only available variables shown). (Figure by Petter Holan).

Prior research

Intensive goal-directed functional therapy (Paper 1)

In recent years there has been a shift in therapy approaches[26, 33] as physical therapists have increasingly recognized that effective training of motor function in children requires motor learning,[26, 34, 35] implying that the child needs to be an active learner in order to problem-solve how to accomplish a specific task given his or her constraints.[26, 34] The approaches have different names: functional therapy, goal-directed, task-oriented, and activity-based,[34] but the core characteristics are the setting of functional goals involving child and caregivers, the child being active in problem-solving, and intensive training providing lots of repetitions in a meaningful environment.[26, 35-38] An overview of characteristics to consider when using a motor learning approach is given in Figure 6.

Figure 6: Characteristics to consider when applying motor learning principles. (The model is based on aforementioned literature in this chapter). (Figure by Petter Holan).

Bower, McLelland, and their coauthors conducted a series of studies in the 1990s[39-42] (Appendix A) that identified the intensity (frequency) of physical therapy treatment and the setting of specific goals to be associated with the rate of motor progress in children with CP.[43] Both of these factors are supported by basic principles of motor learning theory.[43] In a randomized controlled trial (RCT),[43] the same authors surprisingly, did

not find any statistically significant differences between routine amount of physical therapy (weekly) and intensive physical therapy (daily), or between aims and goals. These results raise the question of whether the improved motor function found over 2 weeks,[42] 3 weeks,[39] and 5 weeks[40] as a result of treatment of greater intensity and precise goal setting were only temporary deviations within the range of each child's variation.[43] If that had been the case, it would mean that the new skills would have been accomplished at a later time anyway.

However, since the beginning of the 21st century, evidence has supported a functional therapy program over an intervention focusing on normalization of the quality of movement,[37] intensive, functional goal-directed training carried out in daily-life settings,[44] goal-directed functional therapy over activity-focused therapy,[45] and intensive goal-directed activity-focused physiotherapy in a group setting.[46] Using GMFM-66 reference percentiles as outcome, Løwing et al[47] showed that the gains following goal-directed functional therapy were larger than expected according to GMFCS level and age (Appendix A).

In a systematic review of interventions for children with CP, Novak et al[48] found that goal-directed training/functional training was effective when aiming at activities according to ICF.[48] Her systematic review has been highly influential, but also criticized from multiple directions. Nevertheless, it has been cited over 500 times and seems to have survived the criticism.

A new approach, called HABIT-ILE[49, 50] (hand-arm bimanual intensive therapy including lower extremity), which is a motor-learning based approach using very high intensities (up to 9 hours per day[49]) over a short period, has shown evidence of effect compared with a comparison group of conventional treatment even when receiving the same total amount of therapy over longer time[49] (Appendix A).

A systematic review (including Paper 1) of activity-focused interventions which focused on the influence of goal setting,[51] revealed that even if most studies show robust within-group changes according to appropriate standardized measures, the findings did not support a positive effect of goal setting per se on treatment outcome. Additionally, a recent RCT[52] that evaluated the effect of an individually defined therapy program versus a general therapy program did not confirm the hypothesis that the individually defined

approach provides better outcome. The reason for this result may have been the high quality of the control intervention.[52]

To summarize; evidence exists for the effect of intensive goal-directed functional therapy on gross motor progress in children with CP.

Frequency of physical therapy (Paper 2)

More than 90% of children with CP receive physical therapy, most often 1-2 times per week.[3, 4] There is still conflicting evidence regarding the role of frequency and total dose of physical therapy in gross motor progress for children with CP.[53, 54]

Systematic reviews that include some of the same papers have not found convincing evidence of larger improvements in gross motor function as a result of applying high-dose physical therapy compared to lower doses.[55-57] Although Cope et al[57] found that higher total dosing (time and frequency) may result in slightly more improvement in gross motor function than low amounts of therapy, in their opinion not enough evidence exists to support the implementation of high-dose therapy.

A meta-analysis of conventional therapies that include four RCTs found that intensive therapy (> 3 times per week) was associated with a higher change score in GMFM-88 compared with less frequent therapy, although this difference was only 1.32 GMFM-88 scores and the authors questioned the clinical significance of this difference.[58]

Some recent studies have suggested that higher frequencies of therapy are more effective than others for neurodevelopmental treatment (NDT)[59] and NDT + goal-directed treatment (GDT).[60] Also, the study of HABIT-ILE on unilateral CP,[49] which provided the same total amount of therapy (over much longer time) in the control intervention, indicates that the intensity of therapy is important, despite the fact that interventions were not the same. By contrast, Franki[52] found no such effect when investigating therapy frequency either for an individual tailored intervention or for a general program.

None of the above-mentioned studies compared gross motor progress with the expected development using the reference percentiles of the GMFM-66. Some studies[52, 59, 60] have even used GMFM-88, an instrument with an ordinal scale.

Factors associated with gross motor progress; multivariable research (Paper 3)

Besides intensive goal-directed therapy and frequency of physical therapy, the theoretical model (Figure 5) predicts that interventions directed at impairments and a multitude of child-related factors also can affect gross motor progress.

Results from univariable research are provided in paper 2 and 3. Additionally, factors that are not available in the registers, such as factors related to parental empowerment, socioeconomic status (SES), or the child's coping strategies, may influence gross motor progress, but are not discussed due to the unavailability.

Cross-sectional studies

A Norwegian study[61] found that CP type (distribution), selective motor control, learning difficulties, and age were predictors of gross motor function and explained 79% of the variance in a multivariable linear regression model. A very large study,[62] which included 5,872 children from the SCPE common database, identified intellectual capacity as the strongest predictor of walking ability in all children with CP. Also, severe visual impairment and active epilepsy were identified as significant predictors of walking ability.

A systematic review of predictive factors of ambulation in children with CP[63] found that CP type, early motor milestones, primitive reflexes and postural reactions, visual impairment, intellectual disability, epilepsy or seizures, and ability to self-feed were robust predictive factors, following a synthesis of 12 studies. Eight of the studies were included in a univariable meta-analysis that detected four significant prognostic factors of ambulation: sitting independently at the age of two years, and absence of visual impairment, intellectual impairment, and epilepsy or seizures.

Longitudinal studies

Voormann et al.[64] found that the GMFCS, selective motor control, tone, and selective motor control by time were significant determinants of the course of gross motor function over two years in their study of children in the age range 9-15 years. An indicator of intellectual ability was tested and found significant in a univariate model, but not in the multivariable model. No intervention variables were included in this study.

Vos et al.[65] examined associations over longitudinal measurements between neuromusculoskeletal function and gross motor capacity in children and youths with CP in the age range 5-20 years, over a period of 2-4 years in different age cohorts. The results of multilevel analyses showed that selective motor control was significantly associated with a more favorable gross motor course, as was strength in youths. Reduced range of motion (ROM) of hips (children) and knee extension (youths) as well as spasticity in hip adductors (youths) were associated with a less favorable gross motor course.

Bartlett et al[66] investigated determinants of gross motor change in young children with CP (mean age 3 years 2 months at outset of the study) over one year including family and services aspects. However, because their model explained only a small percentage of the variance in change in gross motor function, they proceeded to use GMFM-66 scores after one year as outcome. They then found that primary and secondary impairments were significant determinants for all children and that adaptive behavior was a significant determinant for children at GMFCS levels III, IV, and V, and participation in community programs was a significant determinant for children at GMFCS levels I and II.

Yi[67] investigated factors contributing to short-term (mean 52 days) improvements in gross motor function in 45 children with spastic CP in the age range 2-6 years, using GMFM-88 as outcome measure. The contributing factors were duration of physical therapy, initial GMFM-88 scores, dysphagia, and high tone in lower extremities.

Knowledge gap

- Intensive goal-directed functional training is regarded as effective to enhance gross motor function according to high quality evidence.[48] However, there is a lack of knowledge of how to operationalize principles of motor learning into an intervention that includes group training, in a rural area with few and heterogeneous children with CP, yet giving the same positive results on gross motor progress.
- Even if intensive goal-directed functional training is deemed effective,[48] the impact of physical therapy frequency in itself has been inconclusive.[57] Also,

investigating the association between physical therapy frequency and gross motor progress in a large cohort when controlling for potential confounders, is lacking. As theory predicts a dose-response association between physical therapy frequency and gross motor progress (i.e., motor learning is the result of practice and experience), this relation needs to be further explored.

- Few, if any, studies have been able to include multiple assessments per child over a long time span, including both intervention variables and child-related variables, thus leaving many of the complicated relations underlying long-term gross motor progress still to be understood.
- In general, there has been a lack of studies using GMFM-66 percentiles as outcome.

Aim

The main aim of the research project of which this thesis is based was to generate more knowledge about factors associated with gross motor progress in children with cerebral palsy.

Research questions:

1a How can motor learning principles be operationalized into an intervention for six children with CP who live in a rural area of Norway, have different types of CP, different GMFCS levels, different ages, and different goals for treatment? (Intervention study; Paper 1)

1b Will this intervention lead to goal attainment and enhanced gross motor progress? (Intervention study; Paper 1)

2 Is increased physical therapy frequency associated with enhanced short-term gross motor progress when other factors of relevance are taken into account? (Short-term cohort study; Paper 2)

3 What interventions and child characteristics are associated with long-term enhanced gross motor progress in children with CP, in the age range 2-12 years? (Long-term cohort study; Paper 3)

Methods

Study designs

Intervention study, Paper 1

We applied a multiple single-subject experimental design (SSD) consisting of a baseline period with assessment and goal-setting (no intervention), an intervention period, and a follow-up period without intervention (ABA design). Each study period ran for six weeks.

Cohort studies, Papers 2 and 3

In the cohort studies, we applied a prospective design.

Short-term study, Paper 2

National prospective cohort study of short-term gross motor progress (i.e., change in gross motor function from one assessment to the next). The association between physical therapy frequency and gross motor progress was investigated taking multiple factors into account. Our hypothesis was that increased physical therapy frequency was associated with enhanced gross motor progress, but that contractures and possibly epilepsy, intellectual disability, pain, eating problems, visual and/or hearing problems, CP type, participating in an intensive program, Botulinum toxin A (BoNT-A) injections, intrathecal baclofen (ITB), surgery, using orthoses, and additional diagnoses affected that association. Figure 7 shows the theoretical assumptions underlying this study.

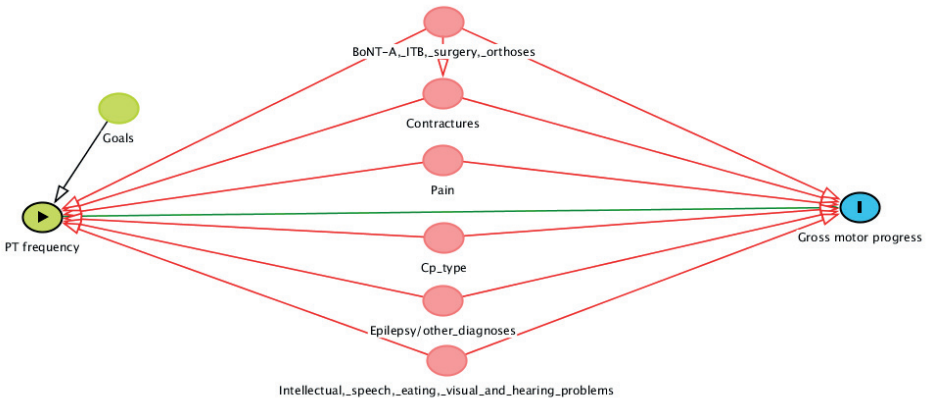

Figure 7: Directed Acyclic Graphs[68] showing possible causal (green) and biasing (red) pathways. Red circles: confounders (ancestor of exposure and outcome). Green circle: ancestor of exposure.

Long-term study, Paper 3
National prospective cohort study of long-term gross motor progress (i.e., the gross motor developmental trajectories over time). All interventions and child characteristics available were considered candidates to be associated with long-term gross motor progress, when taking an exploratory approach[69] with no a priori hypothesis about associations.

Participants

Intervention study, Paper 1

All children with CP in a local rural area in Central Norway, GMFCS levels I-IV, younger than 12 years, without severe intellectual disabilities, and who had identified a goal area suitable for intensive training, were invited to participate in the study. Seven children were eligible, but one child withdrew two weeks into the training period, leaving six participants: three boys and three girls at GMFCS levels I, II, or IV and in the age range 3-11 years.

Cohort studies, Papers 2 and 3

The study cohort used in both cohort studies was based on data from the Cerebral Palsy Follow-up Program (CPOP) and the Cerebral Palsy Register of Norway (CPRN). Children are included in the registers when a diagnosis of CP is set using the guidelines developed by the SCPE.[24] Clinically obtained data are submitted to both registers by health professionals at the 21 habilitation centers serving children diagnosed with CP in Norway. Data from CPOP are linked to the CPRN once per year. Approximately 90% of children with CP in Norway are included in the combined CPOP/CPRN registers.[24]

CPOP is a consent-based systematic motor function follow-up program including children born in 2002 or later. Repeated observations are reported once per year until the age of 6 years (twice before 2013), and thereafter yearly if GMFCS level II-V or every second year if GMFCS level I.

CPRN is a consent-based national quality register that includes children born in 1996 or later. Assessments are conducted at time of diagnosis, 5 years, and 15 years of age.[24] Data from the 5 year assessment were used in the cohort studies.

Inclusion and exclusion

Children who were registered in both CPOP and CPRN with two or more GMFM-66 assessments between the ages of 2 and 12 years were included (reference percentiles were only available for this age span). Of the 1088 children born between 2002 and 2013 who were registered in CPOP, 442 (41%) fulfilled the inclusion criteria. The study cohort comprised 256 boys and 186 girls, with a total of 2048 assessments, of which 1498 included a GMFM-66 assessment (median: 3, range 2-9 per child,). Follow-up time ranged from 1.5 months to 8.9 years (mean 2.9 years, SD: 2.0 years). The mean time between two subsequent assessments was 1.2 years (SD: 0.81 years). The characteristics of the participants were largely comparable with those of the source population (Annual report for CPOP/CPRN 2014[12]).

Dependent variables

In all of the studies on which this thesis is based, GMFM-66 percentiles[5] were used as outcome measure. Gross motor function was repeatedly measured by the GMFM-66[6] and total scores were converted to percentiles using tabulated reference percentiles for the GMFM-66.[8] For the cohort studies, simple software was developed for this purpose.

Gross Motor Function Measure

The Gross Motor Function Measure (GMFM) is a standardized, criterion-referenced observational instrument designed and validated to evaluate changes in gross motor function in children with CP.[6] It is used extensively both in clinical and research settings.[6] GMFM items reflect activity according to the ICF and include typical gross motor developmental milestones in lying and rolling, sitting, crawling and kneeling, standing, and walking, running and jumping.[6] The GMFM was designed to assess the degree to which a child can master a gross motor skill rather than how well the activity is performed. A 5-year old child without motor impairments is expected to master all the gross motor skills included in the GMFM.[6] The GMFM requires the child to demonstrate the skills, and each item is scored on a 4-point scale based on detailed descriptions in the scoring guidelines.[6]

The original GMFM consisted of 88 items (GMFM-88). GMFM-88 describes gross motor function at one point in time and measures change in gross motor function on an ordinal scale. It provides detailed description of the function of young children

and children with more complex motor disability (GMFCS level V). When assessing change over time the ordinal level data may over- or underestimate change.

The 66-item version (GMFM-66) was developed and validated using Rasch analysis to create a unidimensional motor ability score with interval-level measurement properties.[6] GMFM-66 is the gold standard for measuring change in gross motor function over time. It requires the use of a computer program, Gross Motor Ability Estimator (GMAE-2), to convert individual item scores to an interval-level total score.[6] Both the -88 and -66 versions have shown excellent validity for measuring gross motor function and change.[6, 70-73]

Two shorter approaches to the GMFM-66 have been developed: the Item Set (IS) using three decision items from GMFM-66,[74] and the Basal & Ceiling (B&C) approach.[75] Both abbreviated versions have shown very good concurrent validity with the GMFM-66 both for a single measure in time[74-76] and for change over a year.[6, 74, 76]

The method of scoring GMFM items is the same for all versions. The intra-observer, inter-observer and test-retest reliability ranges from good to excellent.[6, 70-73, 75]

Administering time is about 45-60 minutes for GMFM-66 and 20-30 minutes for each of the short versions.[6] In the intervention study we used the GMFM-66. In the cohort studies most assessments were done with GMFM-66, although we anticipate that some have used GMFM-66-B&C.

Motor development curves

In order to describe the nonlinear relationship between age and gross motor function, gross motor function curves for each GMFCS level were constructed.[18] Initially they were based on cross sectional data,[18] and thereafter, on longitudinal measures of GMFM-66[1] (Figure 8). Children were excluded if they had received selective dorsal rhizotomy, surgery, ITB or BoNT-A injections in lower limbs.[1, 18] The motor development curves are estimates of the average pattern of gross motor development in terms of both the rate of the development and the presumed limit of ability between birth and 12 years of age for children with CP at each of the five GMFCS levels.[18] Children are assumed to start with GMFM-66 scores near 0 as newborn infants and then to acquire gross motor skills rapidly while they are young, with the rate of change

slowing as they reach the limit of their potential.[77] In the initial study conducted by Palisano et al,[18] the curves explained 83% of the variation in GMFM-66 scores.

The children in the study by Rosenbaum et al[1] were in a subsequent study followed into adolescence and young adulthood in order to assess whether functions had been lost during adolescence.[77] On average, there was no evidence of functional decline for children in GMFCS levels I and II. For children in level III, IV, and V, the GMFM-66 total scores peaked at about 8 years in level III and about 7 years in level IV and V, before declining by 4.7, 7.8, and 6.4 GMFM-66 points respectively.[77]

The motor development curves also hold true for children with CP in the Netherlands.[78] They found no evidence of a peak and decline.[78]

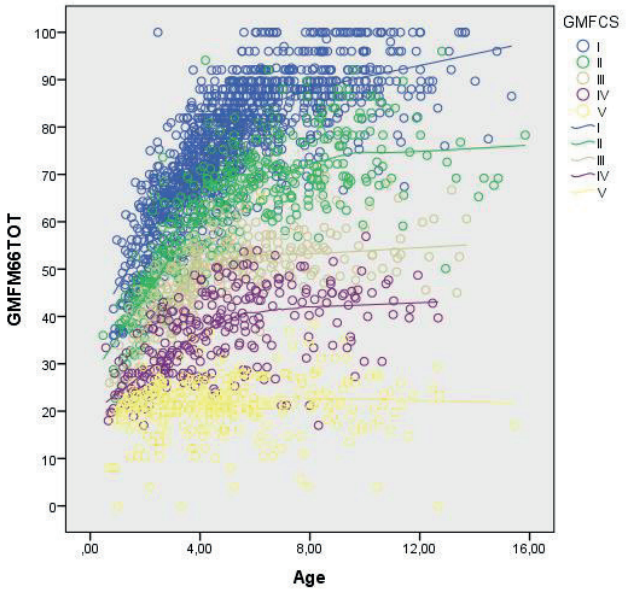

Figure 8: Cross-sectional motor development curves (ordinary scatter plots) of Norwegian children registered in CPOP (N=2594 assessments).

A Norwegian study have confirmed the results from the Canadian and Dutch studies, showing that the motor development curves also yield for Norwegian children.[79] Based on the aforementioned studies, we anticipate that the motor development curves are valid for the children in this research project (Figure 8).

GMFM-66 percentiles

The motor development curves[1] make it possible to evaluate crudely children's gross motor function relative to the average for their age and GMFCS level. However, it has been difficult to evaluate children's gross motor function *within* GMFCS levels because reference percentiles have not been available.[5]

The same sample of which the motor development curves were constructed was therefore used to construct reference percentiles for GMFM-66 within GMFCS levels.[5] The percentiles conform to the expected normal distribution and provide appropriate normative interpretation of GMFM-66 scores within GMFCS levels. GMFM-66 percentiles show the expected and average patterns of change in GMFM-66 total scores by age within each GMFCS level.[5] Children are in general expected to follow their percentile over time, as shown by Hanna et al[5] who found only small mean changes between two subsequent assessments (overall mean 2.5 percentiles).

Reference percentiles can be used both for understanding a single GMFM-66 assessment and for tracking a child's motor ability over time[5] comparing how well a child is progressing with children of similar age and GMFCS level.[6] The curves also makes possible an estimation of future gross motor abilities on which realistic long-term goals can be based.[6] When interpreting change in percentiles over time, one must consider the large variability in change that is typical among children with CP.[5]

Reference percentiles can be found either by using tables[8] as we did in this research project, or by visual inspection of the plots incorporated in GMAE.

Additional outcome measures in the intervention study (Paper 1)
Goal Attainment Scaling (GAS), an individualized criterion-referenced measure of change,[80-82] was used to measure objectively each child's functional change in the goal skills (Figure 9 page 36). Since all of the children had goal areas of self-care and mobility, the Pediatric Evaluation of Disability Inventory (PEDI), a clinical assessment instrument of functional capabilities and performance in disabled children, was used.[83] Additionally, as many of the individual goals included hand function, a functional grip test built on Sollerman Grip Function Test[84] and Assisting Hand Assessment (AHA)[85] were administered when relevant.

Independent variables

The intervention, Paper 1
Motor learning principles (Figure 6) were operationalized into an intervention for six children with CP, who had different types and severity of CP, and had different goals. The child (age dependent), parents, and local therapist had identified a goal area (gross motor, fine motor, or activities of daily living) suitable for intensive training. The goal

areas could be very broad, such as “better gross motor functions outdoors” or specific, such as “walk down the stairs in the kindergarten without help.”

Before recruitment, the intervention had been designed in broad terms. It was named “Leik, Lær og Lykkes” (L_3) in Norwegian, meaning Play, Learn and Succeed. The following structural limits were set:

- *Frequency/duration*: Intervention period 6 weeks, 5 days per week with alternating days of group and individual training sessions. Group sessions were to last 3 hours and individual sessions 1 hour, adding up to a total of approximately 10 hours per week.
- *Time:* Group sessions from 13.00 to 16.00 hours, directly after school hours for the oldest children, and individual sessions whenever suitable during daytime.
- *Location:* Group sessions held at suitable premises where physical therapy services usually were offered. Possible to use nearby outdoor premises. Individual sessions were held were the child would be, whether at home or in their kindergarten/school.
- *Staff:* Group sessions were held by a multidisciplinary team including physical therapists (PTs), occupational therapists (OTs), special teachers, music teachers, and crafts teacher; the same professionals designing the intervention. At least one adult per child was considered necessary to secure effective learning for the children. Parents were invited to join in whenever they wished. Individual sessions were mainly led by a PT, but some sessions by an OT.
- *Group sessions:* Two hours of group training, 0.5 hours lunch, and 0.5 hours of goal-directed training directed at the goal skills. The group activities were to be based on the children’s interests and designed with the goals in mind, providing variable practice related to the movement problems inherent in the goals.
- *Individual sessions:* 0.5 hours included in group sessions and 1 hour on days without group training. Task-oriented principles of motor learning were to be used to enhance learning of the specific goal skills.
- *Supervising:* The local therapists were to be present in the individual goal-directed training included in group sessions, thereby being able to conduct the individual goal-directed training with the child the next day.

The assessment and goal-setting period started with a meeting with the local therapist and the parents when the goal areas were elaborated upon to become more specific. The next step was administration of the standardized assessment instruments (T1), and observing the children with respect to the relevant goal areas. Additionally, the parents' descriptions of their child's interests and favorite leisure-time activities were recorded for use when designing the group activities.

Between four and eight goals for each child were then negotiated with the parents and local therapist. The goals were ideally set in terms of functional activities, and GAS was used to set clear criteria for functional change on a scale with five possible outcomes (Figure 9). The process of setting the goals lasted six weeks. Thereafter, standardized instruments were applied for the second time (T2).

The specific intervention planning started when the goal areas and child interests were known, so that the intervention could be tuned directly to the children's goals and interests. Most group sessions took the form of music or crafts activities, with some sessions including gross motor play or outdoor activities (riding a sledge, skiing). The PTs and OTs worked with the teachers to provide information about each child's specific goals and motor skills that needed to be practiced in the group sessions. Then the teachers were able to, for example, compose new movement songs or find crafts activities with the goals in mind.

As several children had goals related to dressing and undressing, the group sessions started with wardrobe activities. Then, we had a welcome song and schedule presentations. Thereafter, the children engaged in activities such as movement songs, playing rhythmical instruments, playing with plastic clay, painting, dancing, following an obstacle course, and outdoor activities in the snow.

The activities were individually adapted to be directed toward the goals. For example, since several goals required the child to balance on one leg, both movement songs and following an obstacle course required balancing on one leg. Likewise; the children who had goals requiring sitting balance, sat when doing craft activities while the other children were standing. The child with goals that included walking up and down stairs picked up more material from the storage room, which was deliberately placed on another floor. When outdoors, one child practiced driving safely with powered wheelchair, some practiced skiing and some practiced walking on uneven

terrain. Since several of the children had goals requiring bilateral skills, the use of both hands was needed to play the music instruments, albeit with varying degrees of difficulty. Also, since several children had goals concerning skills needed when eating a meal, we always included a meal, and the types of food were chosen to elicit the goal behavior for each child. During the activities, the PT or OT worked directly with the child using motor learning strategies in order to provide practice on movement problems inherent in the goal skills.

Figure 9: Example of a GAS form (top left), child marking goal attainment with a stick-on label (top right), and log of training covering one week (bottom).

In the individual sessions (including 30 minutes in each group session) problem-solving activities and goal-directed practice of the goal skills in relevant contexts were applied.

The therapist used verbal cues, simplification of task and context, structured feedback, handling techniques, or other motor learning principles to enhance skill accomplishment.

Each child had a loose-leaf notebook with his or her own GAS forms to see what the next level of function would be, to note progression when observed, and to enhance motivation by marking each new level with a stick-on label. Also, a log was used to ensure that all goals were addressed at every session (Figure 9).

The standardized instruments were administered after the intervention period (T3) and six weeks later (T4).

Cohort studies, Papers 2 and 3

Figure 10 provides an overview of time-independent and time-dependent variables (repeated measurements) used in the cohort studies.

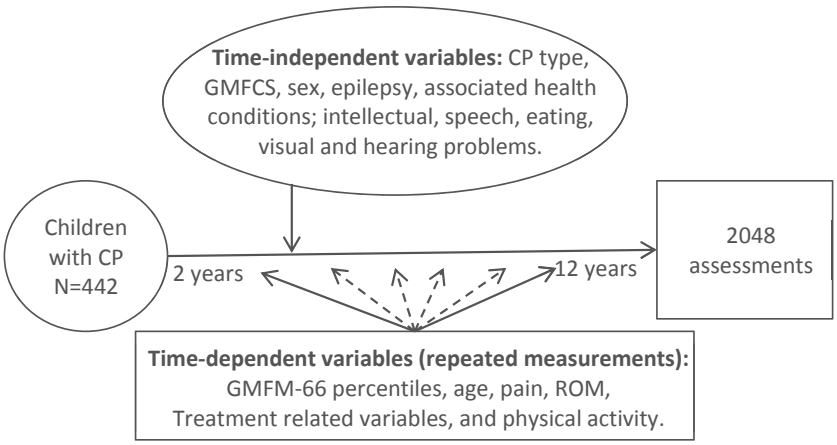

Figure 10: Overview of time-independent and time-dependent variables used in the cohort studies.

Time-independent measures of epilepsy, associated health conditions, and eating problems were recorded as dichotomous variables of yes/no. The original variables were kept. This was also the case for repeated measures of pain, having goals for treatment, participating in physical activity, and participation in an intensive program; having received BoNT-A injections in lower limbs, ITB, surgery in lower limbs, and use of orthoses in foot, ankle, knee, or hip. Table 1 shows an overview of the rest of the independent variables that were used in one or both of the cohort studies.

Table 1: Description of independent variables

Variable	Original variables	Classifications/recoding
Time-independent variables		
Sex	Dichotomous: Girl/boy	Original variable and coding
Gross motor function	GMFCS level, ordinal 1-5	Original variable and coding
Type of CP	SCPE classifications. Categorical 1-6	Original variable and coding
Intellectual ability	1. Standardized IQ test score, scale 2. Clinical judgment, categorical (normal or intellectual disability)	Combined information: If ≥ 5 years: 1. IQ score corresponding to moderate to severe intellectual disability or clinically judged as intellectual disability = "intellectual disability" 2. Otherwise, "not intellectual disability" If < 5 years: 3. "Intellectual ability unknown"
Speech problems	Ordinal 1-6, from normal to not understandable speech	Recoded: If ≥ 5 years: 1. Very unclear or no understandable speech classified as "not understandable speech" 2. Otherwise, "understandable speech" If < 5 years: 3. "Speech problems unknown"
Severe visual problems	Dichotomous: Yes/No	Combined into: 1. "Severe visual and/or severe hearing problem" 2. If else, "not severe visual and /or hearing problem"
Severe hearing problems	Dichotomous: Yes/No	
Time-dependent variables (repeated measurements)		
Age	Scale variable of years	Original variable and coding
Contractures in lower limbs: *Hip*, (abduction, extension, in/outward rotation), *knee* (extension, popliteal angle), and *ankle* (dorsiflexion with extended knee)	Range of motion (ROM) Scale variable of degrees measured with goniometer in the most affected leg	Recoded according to CPOP manual: "Contracture or no contracture" (Yes/No) (Contractures were tentatively entered into the models as contracture in single joints, and as a trichotome variable: no contractures, 1-2 contractures, >2 contractures)
Physical therapy frequency (short-term study, Paper 2)	Ordinal:>5 times a week 3-5 times a week 1-2 times a week 1-3 times a month < once a month	Recoded: >2 times per week 1-2 times per week <once per week Both original and recoded variable used in analyzes
Intensive training (long-term study, Paper 3)	1. Number of physical therapy sessions per week 2. Participation in an intensive program: Yes/no	Recoded: ≥ 3 sessions a week and/or intensive training program classified as "intensive training". Otherwise, "not intensive training" Dichotomous

GMFCS: Gross Motor Function Classification System; SCPE: Surveillance of Cerebral Palsy in Europe; CPOP: Cerebral Palsy Follow-up Program.

Analyses

The statistical analyses were performed using SPSS version 16 (intervention study) and version 24 (cohort studies). The significance level was set at 0.05.

Intervention study, Paper 1

Descriptive analyzes were used to summarize attendance and goal attainment. Data from standardized instruments were mainly analyzed on an individual basis. The data points were plotted on graphs for each child and visually analyzed for level and trend. Additionally, GMFM-66 percentiles were used to compare the gross motor progress with the expected gross motor development.

Cohort studies, Papers 2 and 3

Prerequisites for analytical method

One of the assumptions underlying ordinary linear regression is that the data points are independent of each other. This assumption will not hold for repeated measurements within each child, and therefore Linear Mixed Model (LMM) analyses were used in both cohort studies. LMM accounts for the dependencies between observations within each child and allows data to be on different levels (multilevel model)[86] with repeated measurements of each child on the lowest level nested within each child on the next level. Also, the number and timing of observations per child are free to vary.[86] LMM assumes that the dependent variable is continuous and measured on an interval or ratio scale, and that residuals are normally distributed.[86] By using GMFM-66 percentiles or change in GMFM-66 percentiles as dependent variable the prerequisites for the dependent variable were met. Also, residual analyses show that the residuals were close to normally distributed (Figures 11 and 12).

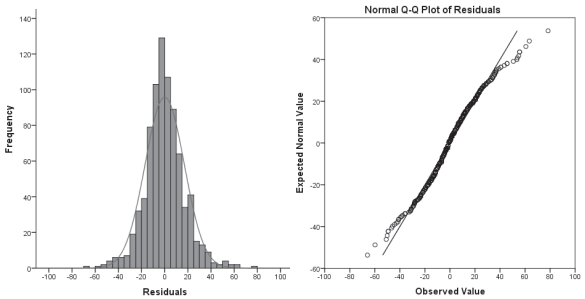

Figure 11: Residuals in the short-term study. Dependent variable: change in GMFM-66 percentiles.

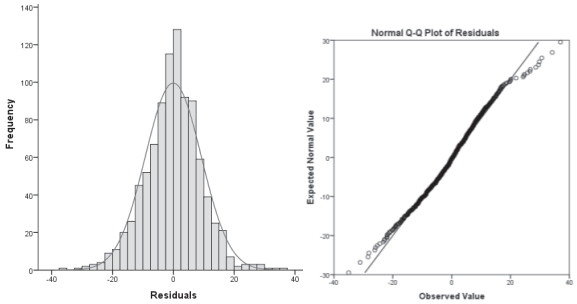

Figure 12: Residuals in the long-term study. Dependent variable: repeated measures of GMFM-66 percentiles.

Missing data

Missing data are unavoidable in epidemiological research and may lead to bias and loss of information.[87] According to Stern et al (page 157)[87] missing data can be: missing completely at random (no systematic differences between the missing values and the observed values), missing at random (any systematic difference between the missing values and the observed values can be explained by differences in observed data), and missing not at random (even after observed data are taken into account, systematic differences remain between the missing and observed values).

Several methods have been used to handle missing values, such as replacing missing values with the mean of the observed data, including a missing category, and last value carried forward. According to Sterne et al,[87] all of these methods can lead to serious bias. If the number of missing values is limited, analyzing only complete cases can be an option. However, if larger proportions of data are missing, the results of complete cases may be biased and one might experience loss of precision and power.[87] If data are missing at random, the missing data can be handled by multiple imputations which involves the imputation of multiple estimates of the missing value which later are pooled and averaged in estimating parameters.[69] However, if data are missing not at random, sensitivity analyses (examining the effect of different assumptions) will have to be conducted.[87]

In our cohort studies, missing data were assumed to be missing at random due mainly to work overload among health professionals who reported the data.

In the short-term study the unadjusted and adjusted model (one confounder) were analyzed on the basis of complete cases. In order to keep the file large enough to handle the multivariable adjusted model, multiple imputations were performed. All variables were included in the imputation model as predictors. In order to ensure that all models were based on the same data set, the dependent variable, the exposure variable, and the primary confounder (number of contractures) were not imputed.

In the long-term study the analyzes based on multiple imputations were conducted for comparison, based on the understanding that multiple imputations should correct biases that may arise in complete cases analyses. Both the dependent and independent variables were imputed and acted as predictors.

Automatic procedures allowing imputation method to be chosen on the basis of scanned data were applied, and led to the use of the Fully Conditional Specification method. Scale variables were modeled with a linear regression model and categorical variables with a logistic model. Consistent with the guidelines provided by Sterne et al,[87] we have reported number of missing values in different variables, details of the imputation process, results based on complete cases, and results based on pooled imputations from 20 imputations.

Short-term study, Paper 2

The association between physical therapy frequency and gross motor progress was analyzed using LMM with change in GMFM-66 percentiles between two subsequent assessments (Δ percentiles) as the dependent variable. The possibility of within-subject correlation in the dependent variable was accounted for by including a random intercept for child. The role of physical therapy frequency on gross motor progress (Δ percentiles) was analyzed in both an unadjusted model and a model adjusted for number of contractures based on complete cases. Then, the research question was analyzed in a multivariable model that included all possible cofounders based on the imputed file.

Long-term study, Paper 3

The mean gross motor developmental trajectory over time was modeled based on the trajectories for each child, which in turn was based on all observations for that child.

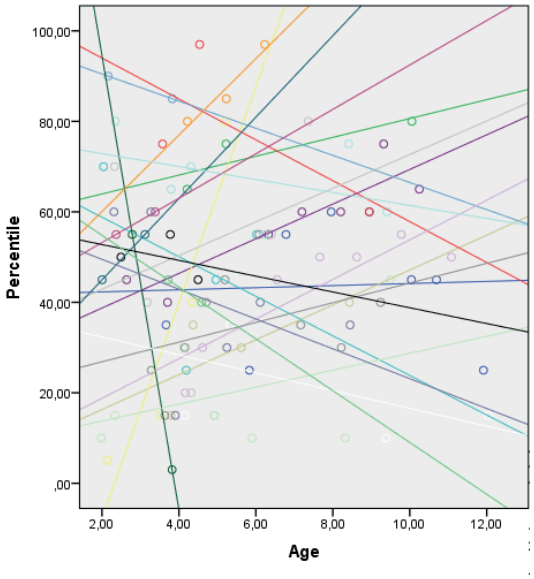

Figure 13: Gross motor trajectories for the first 20 children in the file, highlighting different intercepts and different slopes.

The inclusion of variables in the model was based on theory, previous research, and clinical knowledge, and is described in Paper 3. Visual inspection of the developmental trajectories of the children necessitated a model allowing both the intercepts (random intercept model) and the regression coefficients (random slope model) to differ among individuals (Figure 13).

Ethics

Ethical approval for the intervention study was given by the Regional Committee for Medical and Health Research Ethics in Central Norway (4.2005.1772). The intervention study was also approved by the Norwegian Social Science Data Service (NSD), project nr 13458 (200501643). Ethical approval for the cohort studies was given by the Regional Committee for Medical and Health Research Ethics in Central Norway (2014/1484/REK midt) and the institutional board of Nord-Trøndelag Hospital Trust. The registers providing data for the cohort studies are based on informed consent from parents. CPRN and CPOP are approved by The Norwegian Data Protection Authority (DPA) (Ref.: 05/01484-2/EOL and 08/01067-9/EOL).

Results

Intervention study, Paper 1

The six-week intensive training period consisted of 30 days (58 hours) of training in total. Children 1-6 attended 22, 25, 24, 31, 28, and 26 days of training respectively. There was a high rate of goal attainment following the intervention period. Six weeks later most of the goals had been maintained (Figure 14).

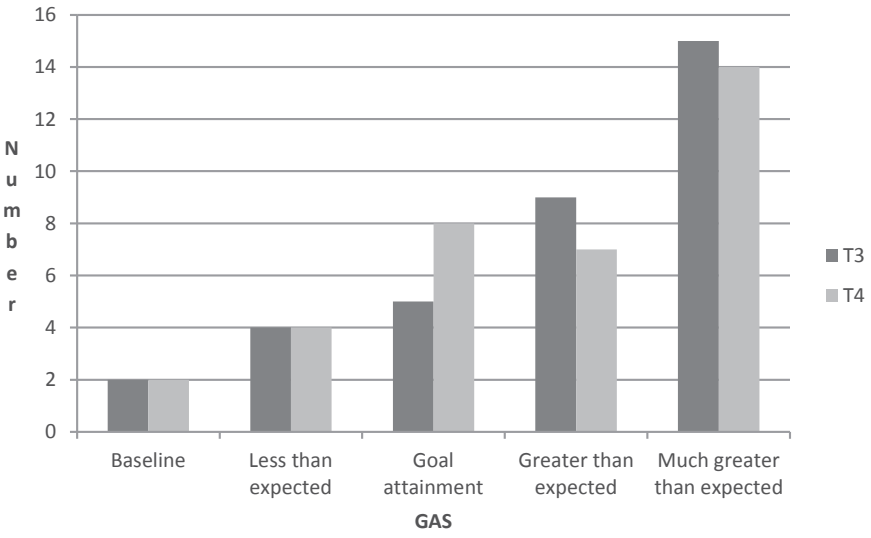

Figure 14: Goal attainment at the end of intervention period (T3) and at follow-up (T4). There were 35 goals in total.

Figure 15 shows the gross motor trajectories (GMFM-66 percentiles) from T1 (at the start of the goal-setting period) to T4 (at follow-up) for Child 1-6. All of the children had a positive change from T1 to T4 (37, 30[A], 65[B], 15, 25, and 5 GMFM-66 percentiles respectively) but with different trajectories. Child 2, 5, and 6 made most progression in the intervention period, Child 1 and 3 made most progression in the goal-setting and the follow-up period, and Child 4 did not show the most change until the follow-up period.

[A] Assessed at GMFCS level I due to ceiling effect at GMFCS level II.
[B] Assessed at GMFCS level I due to ceiling effect at GMFCS level II.

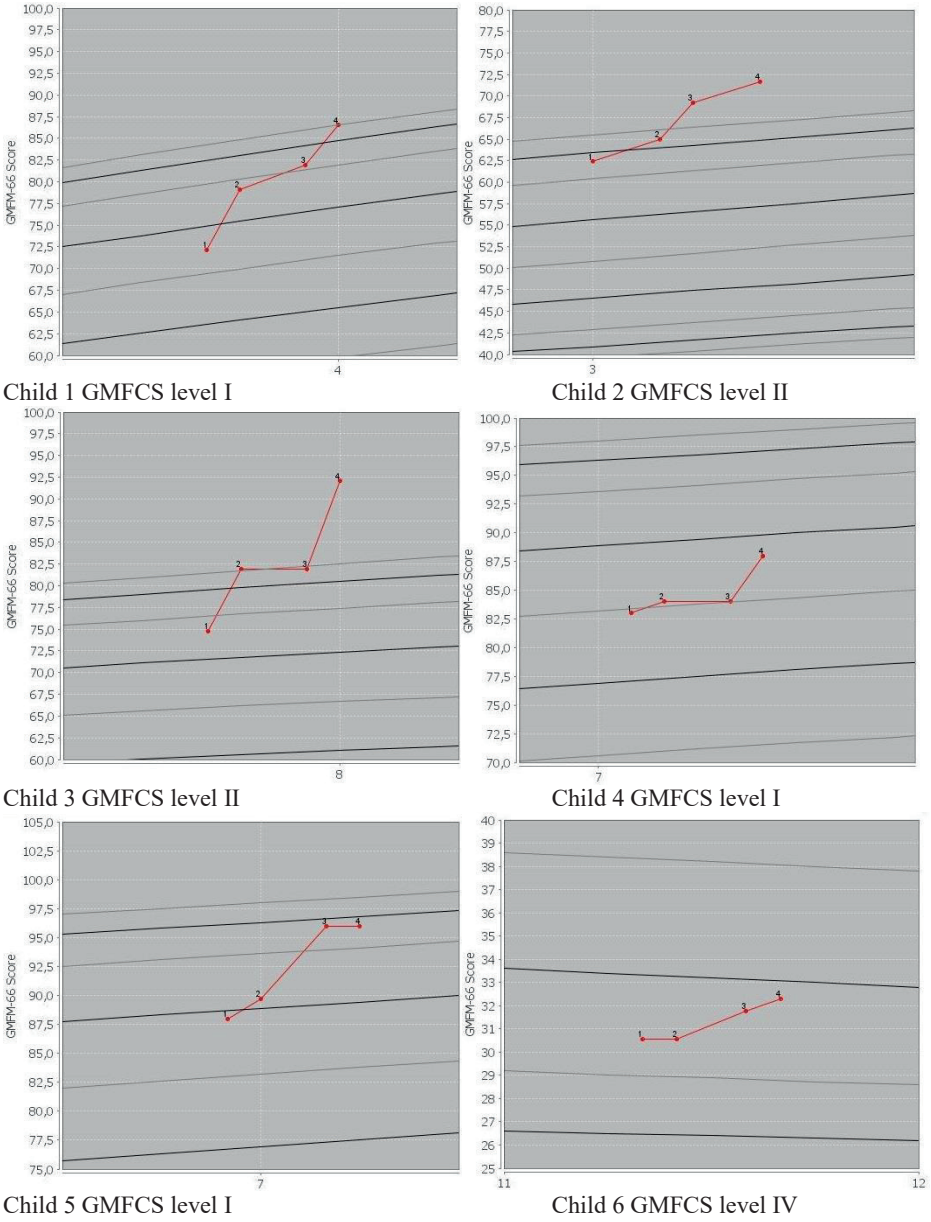

Figure 15: Gross motor developmental trajectories for Child 1-6 plotted on GMFM-66 reference percentiles for different GMFCS levels. Measurement 1-4: before goalsetting, before intervention, after intervention and at follow up. Due to practical reasons, time between two subsequent assessments was five weeks, seven weeks and six weeks respectively.

The children also showed clinically relevant changes in the different domains of the PEDI, in functional hand-grips, and in AHA.

Cohort studies, Papers 2 and 3

On average, the percentile rankings were stable, as the median change in gross motor function between two subsequent assessments was 0 percentiles (interquartile range: -5-10, mode: 0). The mean change was 2.51 percentiles (SD: 17.45).

Short-term cohort study, Paper 2

In 61% of the observations, children received physical therapy 1-2 times per week; 11% more often and 28% less often. There was a dose-response relationship between physical therapy frequency and gross motor progress. The mean change was 4.2 (95% CI: 1.4-7.1) percentiles larger for physical therapy 1-2 times per week and 7.1 (95% CI: 2.6-11.6) percentiles larger for physical therapy >2 times per week, compared with less frequent physical therapy when analyzed in a multivariable model. The estimated marginal mean changes were -3.4, 0.8 and 3.7 percentiles for frequencies < once a week, 1-2 times per week, and > 2 times per week respectively. Only number of contractures and epilepsy (borderline) acted as confounders, both of which were negatively associated with gross motor progress (Figure 16).

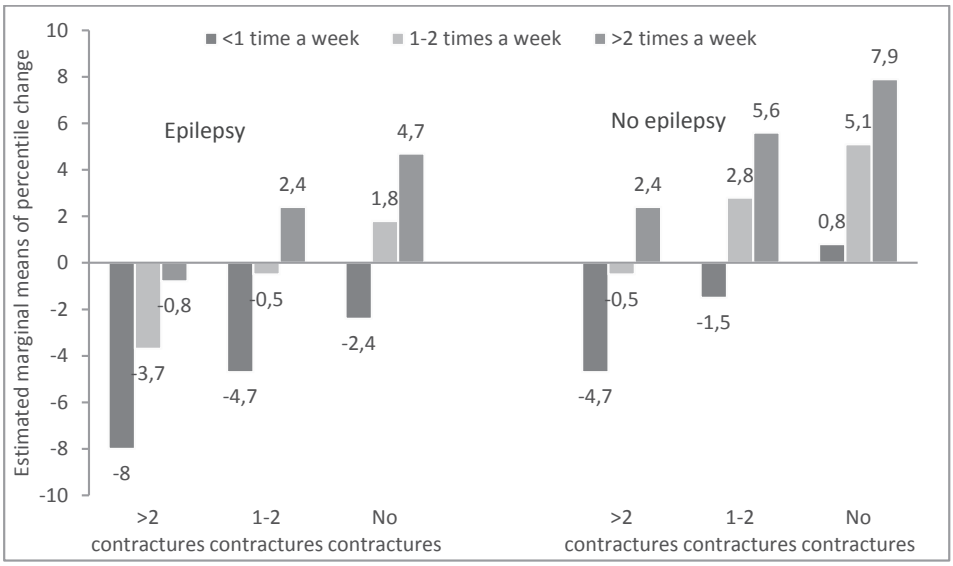

Figure 16: Estimated multivariable adjusted* mean change in GMFM-66 percentiles related to physical therapy frequency (different colors), number of contractures, and epilepsy, showing a more positive change for children who had more frequent physical therapy and did not have contractures or epilepsy (n=814).

* Also adjusted for intellectual disability, pain, eating problems, visual and/or hearing problems, CP type, participating in an intensive program, BoNT-A, ITB, surgery, using orthoses and additional diagnoses.

Long-term cohort study, Paper 3

Intensive training was the only intervention factor associated with an increase in GMFM-66 percentiles (mean 3.3 percentiles; 95% CI: 1.0, 5.5 per period of ≥ 3 sessions per week and/or participation in an intensive program). On average, GMFM-66 percentiles were lower in children with intellectual disability (-24.2 percentiles; 95% CI: -33.2, -15.2) and in children with eating problems (-10.5 percentiles; 95% CI: -18.5, -2.4, not statistically significant in imputed model) compared with their counterparts. Ankle contractures by age were associated with a decrease in GMFM-66 percentiles (-1.9 percentiles per year; 95% CI: -3.6, -0.2). Figure 17 shows the factors associated with long-term gross motor progress out of all factors examined in the study, and displays different gross motor trajectories over time according to intensive training, ankle contractures, intellectual disability and eating problems.

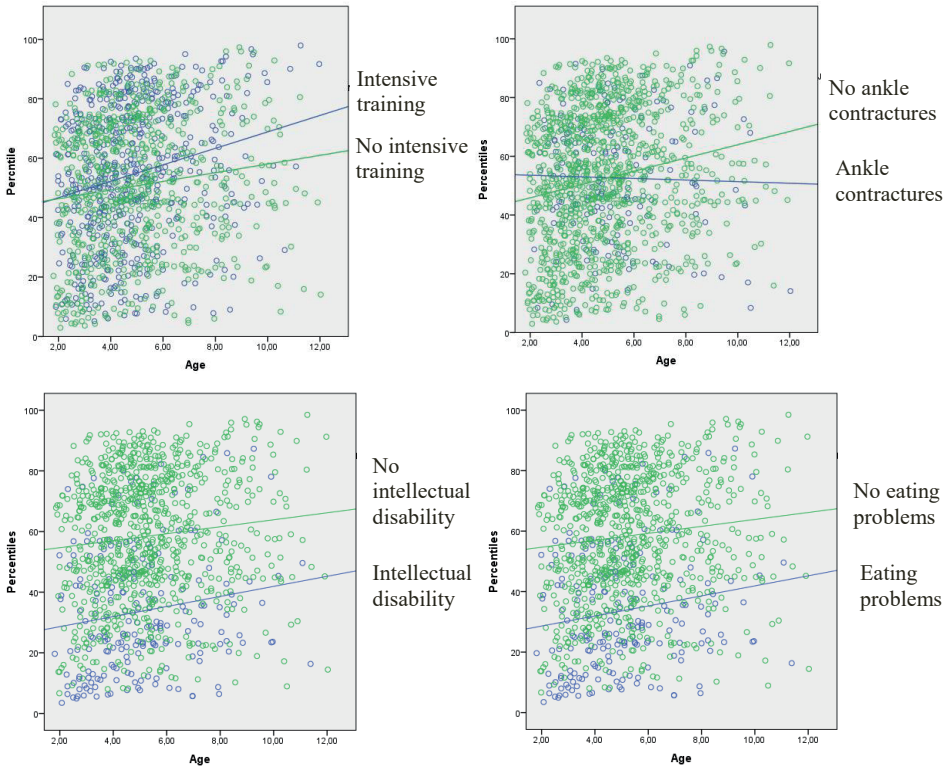

Figure 17: Gross motor developmental trajectories according to intensive training, ankle contractures, intellectual disability and eating problems versus their counterparts. Predicted adjusted values of GMFM-66 percentiles by age.

Discussion

The main objective of this research project was to study interventions and child factors underlying gross motor progress in children with CP, aged 2-12 years.

In the discussion part of this thesis "intensive training" refers to both intensive goal-directed training (Paper 1), increased physical therapy frequency (Paper 2), and high frequent physical therapy and/or participating in an intensive program (Paper 3). Intensive training therefore, is defined as an increase in total dose of physical therapy; mostly by increased frequency, but also by increased duration compared to the more common dose of 30-60 minutes per time[3] 1-2 times a week.[3, 4] The effort put in the training is not included in the definition of intensive training.

Main findings

- Intensive training was associated with enhanced gross motor progress (steeper slopes of the gross motor trajectories than expected according to GMFM-66 reference percentiles) in all studies.
- With the possible exception of the short-term influence of epilepsy, having associated problems like intellectual disability, eating problems, visual or hearing problems did not affect the positive association between intensive training and enhanced gross motor progress.
- No other interventions investigated were associated with enhanced gross motor progress.
- Contractures may represent obstacles for gross motor progress both in short term and in the long term.
- Children with intellectual disability and children with eating problems developed on a level considerably below children without such problems (lower levels of the gross motor trajectories).

Methodological considerations

In this section, strengths and limitations related to the internal and external validity of findings from this research project will be discussed. The internal validity of a study refers to whether the observed associations between exposures and outcome reflect the

true relationship (i.e. not the result of alternative explanations, such as bias,[C] chance,[D] or confounding[E]).[88]

External validity concerns the extent to which it can be inferred that associations observed in a study hold true regardless of variations in people, conditions and settings,[69] that is, the generalizability.

The intervention study, Paper 1

In the intervention study, we applied a multiple SSD, where the children acted as their own controls.[69] SSD is considered well suited to examine the efficacy of a clinical intervention, especially in low-frequent conditions with highly heterogeneous participants as in this study.

Hanna et al (-08)[5] showed that 20% of reexaminations may change up to 20 percentiles points in either direction for children at GMFCS level I and II, and up to 15.1 percentile points for children at level IV. During the whole study period Child 1, 2, 3, and 5 showed larger changes, which indicate effect of the intervention. Child 4 and 6 did not change that much, but above mean change reported by Hanna et al[5] (3 percentiles for children at GMFCS level I and 2.5 percentiles for children at GMFCS level IV) and the mean change found in the present cohort studies (2.5 percentiles). However, some GMFM-66 percentile trajectories (Figure 15) did not display the largest improvement in the intervention period as expected. This may raise questions about internal validity (i.e. that the enhanced gross motor progress found not was the result of the intervention). We hypothesize that the goal-setting period acted as an intervention (example provided in Paper 1) and that learning continued into the follow-up period as the children developed newly learned skills further. However, an alternative explanation may be that the gains documented during the study period were natural progressions. The gross motor developmental trajectories found in this study were much steeper than expected according to GMFM-66 reference percentiles.[5] As it is very unlikely that all the children included had such steep natural trajectories by chance, we suggest that

[C] Bias: any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and outcome (Hennekens et al 1987)
[D] Chance: random error; «the variability in the data that cannot be readily explained» (Rothman KJ 2012, page 148)
[E] Confounding: when the observed associations between exposure and outcome is due, totally or in part, to other variables (Hennekens et al 1987)

results are due to the intervention. Retrospectively, the lesson learned however, was that the baseline period should have been longer before goal-setting procedures started, preferably with multiple administrations of the outcome instruments.

As the assessments were performed by highly skilled assessors blinded to the design, using standardized instruments with excellent psychometric properties,[6, 15, 82, 83] possible information bias[F] is considered limited.

External validity is a major concern in SSD studies as it is not adequate to generalize results of a few children to other settings, times and children.[89] However, the replication of findings[48] give strength to evidence suggesting that intensive goal-directed functional training is effective for children with CP in general.

The cohort studies, Papers 2 and 3

Design

Clinical observations from the CPOP and CPRN were used to generate knowledge of success factors for gross motor progress. In observational studies, the researcher does not intervene by manipulating the independent variable, as in experimental studies, but exploits differences that are already present.[69] By the use of a prospective cohort design, the gross motor progress from one assessment to the next of a large sample of children with CP (N=442) was investigated (short-term study) as well as the long-term developmental trajectories of gross motor function for the same children (long-term study). This is a major advantage of using a longitudinal design over a cross-sectional design,[90] in which all information refers to the same point in time.[88] The prospective design also eliminates the risk for recall bias (the problem of recalling events from the past accurately)[88] which is considered a major problem in retrospective studies. The design is considered well suited for the research questions at hand.

Although associations found in cohort studies should not be interpreted as causal, prospective cohort studies are considered strong study designs, and their results may suggest causality. This is especially true when an a priori hypothesis is formulated[69] as was done in the short-term study. Also, due to the timeline, we can rule out that the dose-response association between physical therapy frequency and gross

[F] Information bias: when «information collected about or from study subjects is erroneous» (Rothman KJ. 2012, page 133)

motor progress applies the other way around. Furthermore, the multivariable adjustments to a large extent exclude alternative explanations for this association. Moreover, the association is considered to be strong, the finding confirms results from experimental studies of intensive functional therapy,[44, 46, 49, 50] and is consistent with implications derived from motor learning theories. Therefore, results should be replicated in intervention studies in order to establish causality.

There has been a call for research using large data sets to provide information about how different factors influence the outcomes of persons with CP.[34] In the long-term cohort study we took an exploratory approach with no a priori hypothesis of exposure- outcome relations, and all available factors that possibly could be related to gross motor progress were tested in the model. Associations therefore should be interpreted as predictors about long-term gross motor progress based on the observed values of the independent variables.[88]

Study participants

Both cohort studies used the high-quality population-based (including approximately 90% of children with CP in Norway[24]) CPOP/CPRN registers as source population which ensured 100% participation of eligible children and eliminated problem of losses to follow-up, which can be a major concern in prospective cohort-studies.[91] Findings in the cohort studies are based on 41% of children in the source population. A large number of non-participants usually will not affect the internal validity unless nonparticipations are related both to gross motor progress and simultaneously to some of the independent variables.[91] Since nonparticipation was due to inclusion criteria (claiming minimum two GMFM-66 assessments) and not to selection,[88] selection bias[G] is not considered to have been a problem in our cohort studies.

Characteristics of the sample affecting external validity will be discussed in a later section.

[G] Selection bias: when the association between exposure and outcome differs for those who participate in the study and those who do not participate, and concerns the procedures used to select subjects and factors that influence study participation. Rothman KJ. 2012

Measurements

GMFM-66 percentiles

The GMFM-66 percentiles were used as outcome measure in both cohort studies. The psychometric properties of GMFCS and GMFM-66 have been judged excellent (p.15 and p.31). Even if misclassifications or other measurement errors cannot be totally ruled out, possible information bias due to misclassifications is considered to be random (non-differential) as opposed to differential misclassifications, which would have been a problem as the misclassifications then differ according to the value of other study variables.[88] The process of converting GMFM-66 total scores to GMFM-66 percentiles was done electronically, which also reduced possible misclassifications and strengthens confidence in the outcome measure.

The use of GMFM-66 percentiles as dependent variable is regarded a major advantage as it makes possible to compare gross motor progress across GMFCS levels and ages. Also, as both age and GMFCS level already are taken into account, there was no need of stratification on different GMFCS levels in analyses, which in turn provided a larger sample size and thus higher statistical strength and reduced the chance of Type I errors. On the other hand, the large individual variability in change in GMFM-66 percentiles from one assessment to the next makes it more difficult to find associations on group level and therefore increase the chances of Type II errors. However, this increases the likelihood that the associations found are of clinical relevance and that small associations of limited clinical relevance remain undetected.

Another advantage of using GMFM-66 percentiles in the long-term study was that the percentiles are modeled to develop linearly over time, thus making it possible to apply LMM. This is in contrast to the use of GMFM-66 total scores which increase more rapidly in the first years compared to later.

Since the GMFM-66 percentiles to our knowledge have not been used as outcome measure in cohort studies before, there are no other studies to directly compare results to. However, the fact that the mean change from one assessment to the next (median one year) in our material was identical to the change found in the Canadian material over the same time length[5] indicates that there are reasons to have confidence in the use of GMFM-66 percentiles as outcome measure. The use of GMFM-66 percentiles as outcome in the cohort studies is innovative, and our experience is that this

measure is well suited both for measuring change between two subsequent assessments and for measuring long-term gross motor progress.

Independent variables

Information bias is obviously possible when data is collected in clinical settings as in our cohort studies. Frequency of physical therapy was for example recorded on a 5 point scale by physical therapists, but even if we anticipate that most classifications are correct, there is a possibility that the frequency planned is reported and not what it turned out to be. In order to minimize misclassifications of variables from the CPOP and CPRN registers, manual inspection of data was conducted and when possible, obvious misclassifications corrected.

Possible misclassifications of dichotomous variables like participating in an intensive program, eating problems, and epilepsy are expected to be random (non-differential) and will increase similarity between the exposed and unexposed groups, so that the true association between independent variables and gross motor progress will be underestimated[88] and thus Type II errors may occur.

The reliability[H] of the instruments used in clinically obtained data may vary and also introduce information bias. This may be especially true for the assessment of intellectual ability where standardized instruments were combined with clinical judgment. However, as only children with moderate to severe intellectual disability were classified as having intellectual disability, those will correspond more closely with the clinical judgment than would mild intellectual disability, (which would have been more difficult to ascertain clinically) and thus misclassifications are reduced. Therefore, the inclusion of intellectual disability in multivariable analyzes was deemed a better choice than excluding it as a variable.

Also, when measuring ROM, measurement errors of 10-15° are not uncommon.[92] In order to reduce variability in measurements, all physical therapists reporting data to the registers are offered extensive training in how to measure ROM and procedures are standardized. We have therefore no reason to suspect systematic errors in measurements of ROM that may have biased the reported associations.

[H] Reliability: «the extent to which a measurement is free from measurement error» (Polit & Beck 2017, page 742)

Therefore, low reliability only will decrease precision of estimates.[93] Even if extensive steps have been taken to minimize information bias, we cannot rule out the possibility of some information bias in clinically obtained register data.

Missing

As might be expected in clinically obtained register data, there were quite a lot of missing information which may bias the results and affect internal validity.[87] However, missing data were assumed to be missing at random and handled with multiple imputations (p. 40-41) which is considered the gold standard approach for dealing with missing values.[69] The results based on multiple imputations (extensively described in Paper 3) showed only minor differences from results based on complete cases in both cohort studies suggesting that missing not introduced any systematic error into analyses and therefore could be considered a minor problem.

Confounding

In observational studies confounding can be prevented or controlled by restriction, matching, stratification or inclusion of the confounder in multivariable regression models.[88] Confounding was an issue in the short-term cohort study, in which the association between physical therapy frequency and gross motor progress was investigated. With the aid of Directed Acyclic Graphs[68] possible confounders (variables associated with both the independent variable and the dependent variable, but not an effect of them)[88] were identified (Figure 7) and included (controlled for) in the multivariable model, and were therefore not considered a limitation.

However; several factors not available from the CPOP/CPRN may also be related to gross motor progress and possibly act as confounders, including factors related to the child's coping strategies,[66] parental empowerment,[66] and socioeconomic status.[94] The inclusion of such variables would have been preferable. Although we have no reasons to believe that main findings would have been changed by such adjustments,[66] the lack thereof is considered a limitation,

Chance (random error)

Whereas point estimates quantify the strength of the association between the independent variables and the dependent variable, the magnitude of random errors that underlies the point estimates are indicated by the 95% confidence intervals (CIs). The p-

values, which are closely related to the CIs, can be viewed as a measure of relative consistency between the null hypothesis and the data at hand.[88]

Random error depends both on the study size and the variability in the phenomenon under investigation. Increasing the study size will decrease random errors.[88] Accordingly, our results showed that CIs mainly were narrower in the model based on imputed data in the long-term study than in the model based on complete cases. Also, the use of reference percentiles as outcome measure eliminated the need for stratification and thereby increased sample size, and thus the precision of estimates. Hence, Type I errors are not considered to bias results. The fact that some of the CIs remained wide, may both be due to random misclassifications, but also due to the actual phenomenon under investigation. Due to the great variability in children's gross motor development one should not expect estimates to have great precision with narrow CIs.

Analytical approach

The rationale for using LMM in both cohort studies is elaborated on in analyses section (p. 39 and 41-42). As we have multilevel data with repeated measurements within each child on the lowest level and a continuous dependent variable, LMM is regarded the best analytic approach allowing all information in the data set to be exploited. Also, multiple imputations and the use of GMFM-66 percentiles as outcome (which eliminated the need for stratifying on each GMFCS level) provided a large data set to base multivariable analyses on giving more statistical power.

Handling age and GMFCS level

Since reference percentiles already take age and GMFCS level into account, these factors should not be included in the analyze model as independent variables. Similarly, different times between two subsequent assessments are considered to have been accounted for in GMFM-66 percentiles. To verify these assumptions, Δ age and GMFCS level were tentatively added to the model in the short-term study (Paper 2), but did not influence the estimates, improve model fit, and were not statistically significant, and therefore removed.

Since age was expected to capture exactly when observations were made for each child over time, age was included in the long-term study (Paper 3). GMFCS level was surprisingly statistically significantly associated with long-term gross motor

progress and therefore included in the final model of the long-term study, although the inclusion of GMFCS level did not change the main findings. The reason for this association may be that GMFCS level is associated with some unknown factor not accounted for, or may be due to small number of assessments in some GMFCS levels.

External validity

Internal validity is a precondition for external validity.[91] Although some information bias may be present in clinically obtained data, and the precision of some estimates may be low, we consider internal validity of the cohort studies to be satisfying

The children included in this study cohort were representative for the source population CPOP/CPRN[24] (Table 1 in the cohort studies) and results can be generalized to Norwegian children with CP 2-12 years of age.

Also, as the characteristics of Norwegian children with CP are largely comparable with those of European children with CP[23] results can be generalized to children with CP in European countries and probably to other developed countries.

Most assessments in the cohort studies were conducted in younger children (median age 4.6 years). The reason for this is both that the oldest age groups not are complete as the registers were not nationwide until 2006, and more frequent assessments in younger ages according to follow-up procedures. As age is accounted for in GMFM-66 percentiles the age is not considered to affect associations found in the cohort studies, but should be kept in mind when generalizing to older children.

Success factors for gross motor progress in children with CP

The main aim of this thesis was to generate more knowledge of success factors for gross motor progress. In the following, factors of relevance will be discussed.

Intensive training

The three studies included in this research project consistently showed that intensive training was associated with enhanced gross motor progress, both in the short-term and in the long-term. We found no interactions with intensive training in either of the cohort studies which suggested that the enhanced gross motor progress related to intensive training applied to children with CP independent of the other factors we investigated.

In the intervention study, most of the time was spent on repeated practice of the goal skills. The enhanced gross motor progress following this intervention was expected on the basis of motor learning principles that hold that the most important condition for motor learning is the amount of practice.[26, 32] The finding is in line with the results from other studies of interventions based on motor learning principles.[47, 48]

With regard to the cohort studies, we hypothesize that intensive training in general led to high numbers of repetitions of the gross motor skills at hand because motor learning principles are implemented into practice to some extent.[94] However, increased intensity may also indicate more time spent on addressing impairments or intervention strategies other than functional training. We do not have valid data for the type of intervention in the cohort studies, and therefore they should be considered conventional therapies. Our results are in line with a meta-analysis of conventional therapies that revealed that intensive therapy had a greater effect than nonintensive therapy.[58] On the other hand, a systematic review of common physiotherapy interventions found no differences related to intensities of treatment.[55] In fact, our findings conflict with those of systematic reviews assessing the physical therapy frequency independent of intervention type[56, 57] in which the authors conclude that there is not enough evidence to recommend high-dose therapy. The aforementioned reviews build partly on the same limited number of RCTs with strict inclusion criteria. In our cohort studies, we included all children who were receiving intensive training, not only children expected to learn new gross motor skills, but also children receiving intensive training in order to limit deterioration, and children who received intensive training

following surgery. When results still show a positive association between intensive training and enhanced gross motor progress we have to consider, contradictory to the conclusion reached by Cope and Mohn-Johnsen,[57] that there are good reasons to suggest intensive training when gross motor progress is prioritized.

Short-term gross motor progress may or may not be temporary. There is a possibility that the child learns skills that would be accomplished at a later time anyway.[43] The results from the long-term study refute such a theory, showing a more positive long term gross motor trajectory with increasing numbers of periods with intensive training.

Goals

The use of goals is grounded in motor learning theories and is thought to increase the number of repetitions of the goal skill.[36] Therefore, goals were a key ingredient in our intervention study. By setting goals for each participant, we were able to secure numerous repetitions of the goal skills, thereby offering high frequent practice to the point. The results from the intervention study that showed a high rate of goal attainment and enhanced gross motor progress were in accordance with prior research.[37, 42, 44-47, 50] Therefore, the results from the long-term cohort study, that showed that goals did not matter were surprising, but in accordance with a systematic review (including Paper 1) of the impact of goal-setting on treatment outcome.[51] The review revealed that goal-setting frequently was an integral part of activity-focused interventions, and although most studies that included the use of goals showed robust changes in appropriate measures, the review did not provide evidence of a positive effect of goal-setting per se.[51]

One explanation for the findings in the long-term cohort study may be that the database did not distinguish between goals with respect to impairments and to activities. For example, if the goal was to maintain ROM in the knees and the goal had been attained, there is no guarantee that it would have led to gross motor progress. Another explanation may be that goals are set when the gross motor function is deteriorating and even goals for postoperative training, meaning that the children had a nonoptimal starting point for progress. Additionally, the association related to goals may be integrated in the association related to intensity (frequency), which is supposed to increase when having goals as described above (goals being a processor for intensity;

Figure 7). A less apparent reason may be that the Norwegian language does not differentiate between the terms goals and aims (both of which are “mål” in Norwegian). Therefore some may have answered that goals had been set when they meant that general aims had been established, thus leading to classification bias.

Not having contractures

Our studies showed a negative association between ankle contractures by age and long-term gross motor progress, and between number of contractures and short-term gross motor progress. These findings are in line with prior research[54, 61] including prospective cohort studies,[65, 66] although a prospective cohort study from the Netherlands did not find that contractures in lower limbs were a significant determinant of the course of gross motor function when assessed in a multivariable model.[64]

The rationale for the negative associations can be understood through the use of theories of motor control and learning. Reduced ROM makes it more difficult to perform gross motor skills because ROM is one of the important subsystems to cooperate in the initiation and execution of gross motor functions.[26] For the same reason, the learning of new gross motor skills is hampered because contractures impose serious constraints to the motor system. Furthermore, the presence of contractures may direct more therapy toward contractures at the expense of repeated practice of gross motor skills.

In our study of long-term gross motor progress, we found an interaction between ankle contractures and age suggesting that the impact of ankle contractures matters more with increasing age. The reason for this may be that gross motor skills in supine, prone, and sitting; and the transfer between these positions are not dependent on dorsiflexion in ankles to the same degree as gross motor skills performed from a standing position, which is more common with increasing age.

In both cohort studies, contractures in single joints were tentatively added in the models as well as number of contractures. The fact that contractures in a single joint (ankle) contributed significantly in the long-term study, in contrast to the number of contractures in the short-term study, is difficult to explain. One could speculate that the large number of children at GMFCS levels I and II might have something to do with it, but on the other hand, GMFCS level is incorporated in GMFM-66 percentiles.

The clinical implication would be that contractures should be addressed in therapy, preferably with prevention strategies, but also with treatment. However, none of the strategies addressing contractures investigated in the cohort studies was associated with gross motor progress. These findings are in line with results from other studies that have suggested that interventions addressing impairments have an effect on impairments, but that there is limited evidence for an effect on gross motor function.[48] Also, many of the children who received for example BoNT-A injections had already developed contractures and were therefore less prone to experiencing gross motor progress than were their peers without contractures. Following this argument, contractures mainly act as a mediator between the interventions and gross motor progress (Figure 7). Therefore, our study design was not suited to answering whether interventions that address impairments also affect gross motor function (i.e., activities). We are looking forward to the results from a RCT set up in Central Norway to investigate whether BoNT-A injections makes walking easier for children with CP.[95]

Furthermore, even if surgery can lengthen muscles, children with CP need long time to recover from surgery, and it is likely that the first measure of gross motor function after surgery will show a decrease compared with the previous measurement and thus fail to show a positive association between surgery and gross motor progress.

Intellectual ability (long-term study)

We found that moderate to severe intellectual disability predicted a long-term gross motor developmental trajectory far below the trajectory for children without intellectual disability. This was not surprising as intellectual disability has consistently shown a negative association with various measures of gross motor function.[54, 61, 62] A plausible explanation may be that intellectual disability affects the problem-solving activities needed for gross motor control and learning. Additionally, the child may have trouble understanding how trials and errors today may lead to success in the future and will therefore have problem with motivation. Some children also will have problems with setting goals for themselves and even if they have goals, they may not be able to communicate them to adults.

Positively, we found no interactions between intellectual disability and intensive training in the long-term cohort study, suggesting that intensive training constitutes a

success factor for all children with CP independent of intellectual capacity, which confirms prior research.[96, 97] This result predicted that intellectual disability not should affect the association between frequency of physical therapy and short-term gross motor progress which was exactly what we found. However, this was somewhat surprising as reduced problem-solving skills would interfere with motor learning, which would suggest that the association between physical therapy frequency and gross motor progress is weaker in children with intellectual disability than their peers.[96] It is possible that the children with intellectual disability, who function in the lower percentiles, have a larger motor potential than their peers who are already exploiting their motor potential to a greater extent?

Eating ability (long-term study)
As intellectual disability, eating problems predicted a long-term gross motor developmental trajectory below the trajectory for children without eating problems. We do not have any data to suggest that this result indicates malnutrition or undernutrition, as eating problems should be handled in cooperation with a clinical nutritionist and, in serious cases, with the use of percutaneous endoscopic gastrostomy (PEG). Rather, we speculate that this variable may be a proxy for extensive health problems that make the child less likely to advance in gross motor functions.

Not epilepsy (short-term study)
Epilepsy acted as a confounder ($p=0.052$) for the association between physical therapy frequency and short-term gross motor progress, and was negatively associated with gross motor progress. This result is in line with prior research.[62, 63] However, the dose-response relationship between increased physical therapy frequency and enhanced gross motor progress, was also found for children with epilepsy, although on average, with smaller predicted marginal means. We assume that most children with epilepsy are properly treated with antiepileptic medication, and therefore, it is hard to explain the negative association with gross motor progress. May be the side effects of medication plays a role? Also, it is possible that some of the assessments of gross motor progress included in the study were performed before the child was diagnosed with epilepsy and therefore some children had untreated active subclinical epilepsy at the time. This

would also explain why epilepsy did not affect long-term gross motor progress, since the child probably would have a more rapid progress after medication.

Clinical implications

- If gross motor progress is prioritized at a certain point in time, intensive training should be provided, as intensive training consistently showed to be a success factor for enhanced gross motor progress in children with CP. As the setting of goals help directing therapy to the point, number of repetitions of the goal skill will increase. Therefore, we recommend setting goals before starting the intensive training period despite the fact that we did not find a direct association between having goals and long-term gross motor progress.
- Except from avoidance of physical therapy while the child has an active epileptic seizure, intensive training should be applied to children with associated problems on the same indications as children without such problems.
- Contractures should be addressed in therapy, as the avoidance of contractures is a success-factor for gross motor progress.
- As intellectual disability and probably eating problems predicted a long-term gross motor developmental trajectory far below the trajectories of counterparts, these factors can be regarded as prognostic factors and useful when planning for the future.

Ethical discussion

If gross motor progress is prioritized by the child, parents, and professionals, intensive training should be provided. However, this raises a very important question: should gross motor progress be prioritized at a certain point in time, or even more basic; should gross motor progress be prioritized in children with CP at all? CP cannot be cured, but it is possible to learn gross motor skills to a limited extent. However, as our results indicate, this means intensive training with a lot more practice than for persons without CP. This raises the question: Is gross motor training the right way to spend the children's time?

My experience is that many parents and professionals experience a strong urge to pull up their sleeves and start gross motor training as soon as the diagnosis of CP has been set. However, another way of thinking is that CP is a motor disorder. Therefore we should try to compensate with equipment and environmental adjustments, and then use the time to do other activities, such as playing with peers and learn other skills that are easier to master than motor skills. An argument against this point of view is that if the therapist for example decides that it will be too tiring for a child on GMFCS level III to walk with support and therefore does not practice walking with the child, then the child will lose the possibility to take that decision itself. It is only when the child can walk with support that the child can choose between walking with support and using a wheelchair.

The questions raised above are complicated questions with no correct answers. However, such considerations underscore the importance of providing intensive training when gross motor progress is prioritized. From my perspective, having set gross motor goals and providing practice of a frequency too low for motor learning to occur would be entirely unethical.

Children with moderate to severe intellectual disability can have difficulties with having goals or telling about their goals, thereby making it difficult to work goal-directed. However, our results show that intellectual disability does not predict less gross motor progress, and we therefore argue that *all children with CP* should be offered intensive training *if gross motor progress is prioritized.*

Conclusion

Intensive training and not having contractures are suggested success factors for both short-term and long-term enhanced gross motor progress in children with CP. With the possible exception of the short-term influence of epilepsy, having associated problems did not affect the positive association between intensive training and enhanced gross motor progress. Gross motor function developed on average at a lower level in children with intellectual disability and in children with eating problems compared with their counterparts.

Figure 19 provides a graphical presentation of the results of this research project.

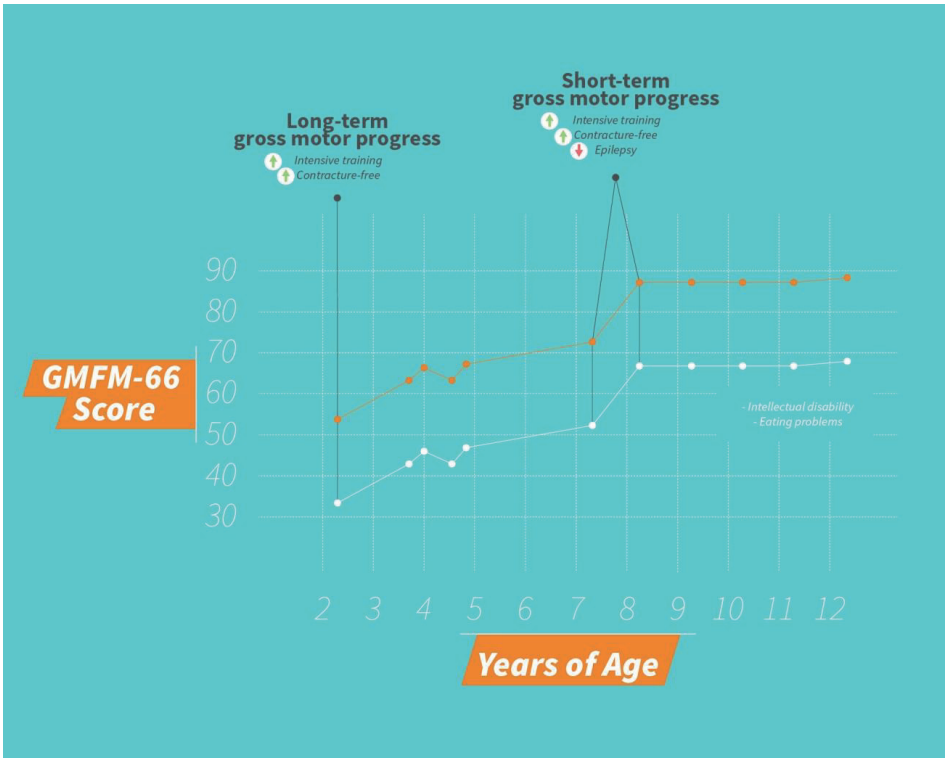

Figure 19: Graphical representation of results from this research project highlighting the factors associated with the slope (intensive training, contractures, epilepsy) and level (intellectual disability and eating problems) of the gross motor developmental trajectories for children with CP in a short-term and long-term perspective. (Graphical design by Petter Holan).

References

1. Rosenbaum P, Walter SD, Hanna SE, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. JAMA : the journal of the American Medical Association. 2002;288(11):1357-1363.
2. Bartlett DJ, Palisano RJ. Physical therapists' perceptions of factors influencing the acquisition of motor abilities of children with cerebral palsy: implications for clinical reasoning. Physical therapy. 2002;82(3):237-248.
3. Palisano R, Begnoche DM, Chiarello LA, et al. Amount and focus of physical therapy and occupational therapy for young children with cerebral palsy. Physical & occupational therapy in pediatrics. 2012;32(4):368-382.
4. Myklebust G, Jahnsen R, Elkjaer S. Registration of interventions in children with cerebral palsy during three years-a populationbased study. Developmental Medicine & Child Neurology. 2009;51:65.
5. Hanna SE, Bartlett DJ, Rivard LM, et al. Reference curves for the Gross Motor Function Measure: percentiles for clinical description and tracking over time among children with cerebral palsy. Physical therapy. 2008;88(5):596-607.
6. Russell DJ, Rosenbaum P, Wright M, et al. Gross motor function measure (gmfm-66 and gmfm-88): user's manual. London: Mac Keith Press 2013.
7. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Developmental medicine and child neurology. 1997;39(4):214-223.
8. Hanna SE, Bartlett D, Rivard LM, et al. Tabultated reference percentiles for the 66-item Gross Motor Function Measure for use with children having cerebral palsy., 2016.
9. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.
10. WHO. International classification of functioning, disability and health: ICF: World Health Organization 2001.
11. Cans C, Dolk H, Platt M, et al. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Developmental Medicine & Child Neurology. 2007;49(s109):35-38.
12. CPRN. Cerebral Palsy Register of Norway Available: https://www.siv.no/helsefaglig/cp-registeret. Accessed 260218, 2018.
13. Morris C, Bartlett D. Gross Motor Function Classification System: Impact and utility. Developmental medicine and child neurology. 2004;46.
14. Morris C, Kurinczuk JJ, Fitzpatrick R, et al. Who best to make the assessment? Professionals' and families' classifications of gross motor function in cerebral palsy are highly consistent. Arch Dis Child. 2006;91(8):675-679.
15. Rosenbaum P, Palisano RJ, Bartlett DJ, et al. Development of the Gross Motor Function Classification System for cerebral palsy. Developmental medicine and child neurology. 2008;50(4):249-253.
16. Palisano RJ, Rosenbaum P, Bartlett D, et al. Content validity of the expanded and revised Gross Motor Function Classification System. Developmental medicine and child neurology. 2008;50(10):744-750.

17. Wood E, Rosenbaum P. The gross motor function classification system for cerebral palsy: a study of reliability and stability over time. Developmental medicine and child neurology. 2000;42(5):292-296.
18. Palisano R, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. Physical therapy. 2000;80(10):974-985.
19. Palisano RJ, Cameron D, Rosenbaum PL, et al. Stability of the gross motor function classification system. Developmental medicine and child neurology. 2006;48(6):424-428.
20. Jahnsen R, Aamodt G, Rosenbaum P. Gross Motor Function Classification System used in adults with cerebral palsy: agreement of self-reported versus professional rating. Developmental medicine and child neurology. 2006;48(9):734-738.
21. Surveillance of Cerebral Palsy in E. Prevalence and characteristics of children with cerebral palsy in Europe. Developmental medicine and child neurology. 2002;44(9):633-640.
22. Oskoui M, Coutinho F, Dykeman J, et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Developmental Medicine & Child Neurology. 2013;55(6):509-519.
23. Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Developmental medicine and child neurology. 2016;58(1):85-92.
24. Hollung SJ, Vik T, Wiik R, et al. Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence. Developmental Medicine & Child Neurology. 2016:n/a-n/a.
25. Hollung SJ, Vik T, Lydersen S, et al. Decreasing prevalence and severity of cerebral palsy in Norway among children born 1999 to 2010 concomitant with improvements in perinatal health. European Journal of Paediatric Neurology. 2018.
26. Campbell SK, Palisano RJ, Orlin MN. Physical therapy for children. St. Louis, Mo: Elsevier Saunders 2012.
27. Shumway-Cook A, Woollacott MH. Motor control : translating research into clinical practice. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins 2012.
28. Haywood KM, Getchell N. Life span motor development. Campaign, Ill: Human Kinetics 2014.
29. Thelen E. Motor development. A new synthesis. Am Psychol. 1995;50(2):79-95.
30. Hadders-Algra M. The neuronal group selection theory: a framework to explain variation in normal motor development. Developmental medicine and child neurology. 2000;42(8):566-572.
31. Hadders-Algra M. Variation and variability: key words in human motor development. Physical therapy. 2010;90(12):1823-1837.
32. Schmidt RA, Lee TD. Motor control and learning : a behavioral emphasis. Champaign, Ill: Human Kinetics 2011.
33. Anaby D, Korner-Bitensky N, Steven E, et al. Current Rehabilitation Practices for Children with Cerebral Palsy: Focus and Gaps. Physical & occupational therapy in pediatrics. 2016:1-15.
34. Law M, Darrah J. Emerging Therapy Approaches: An Emphasis on Function. Journal of child neurology. 2014.
35. Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. Journal of child neurology. 2014;29(8):1141-1156.

36. Valvano J, Rapport MJ. Activity-focused Motor Interventions for Infants and Young Children With Neurological Conditions. Infants & Young Children. 2006;19(4):292-307.
37. Ketelaar M, Vermeer A, Hart H, et al. Effects of a functional therapy program on motor abilities of children with cerebral palsy. Physical therapy. 2001;81(9):1534-1545.
38. Lammi BM, Law M. The Effects of Family-Centred Functional Therapy on the Occupational Performance of Children with Cerebral Palsy. Canadian Journal of Occupational Therapy. 2003;70(5):285-297.
39. Bower E, McLellan DL. Effect of increased exposure to physiotherapy on skill acquisition of children with cerebral palsy. Developmental medicine and child neurology. 1992;34(1):25-39.
40. Bower E, McLellan D. Measuring motor goals in children with cerebral palsy. Clinical Rehabilitation. 1994;8(3):198-206.
41. Bower E, McLellan DL. Assessing Motor-Skill Acquisition in four Centres for the Treatment of Children with Cerebral Palsy. Developmental Medicine & Child Neurology. 1994;36(10):902-909.
42. Bower E, McLellan DL, Arney J, et al. A randomised controlled trial of different intensities of physiotherapy and different goal-setting procedures in 44 children with cerebral palsy. Developmental medicine and child neurology. 1996;38(3):226-237.
43. Bower E, Michell D, Burnett M, et al. Randomized controlled trial of physiotherapy in 56 children with cerebral palsy followed for 18 months. Developmental Medicine & Child Neurology. 2001;43(1):4-15.
44. Ahl LE, Johansson E, Granat T, et al. Functional therapy for children with cerebral palsy: an ecological approach. Developmental medicine and child neurology. 2005;47(9):613-619.
45. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy--do goals make a difference? Disability and rehabilitation. 2009;31(22):1808-1816.
46. Sorsdahl AB, Moe-Nilssen R, Kaale HK, et al. Change in basic motor abilities, quality of movement and everyday activities following intensive, goal-directed, activity-focused physiotherapy in a group setting for children with cerebral palsy. BMC pediatrics. 2010;10:26.
47. Lowing K, Bexelius A, Carlberg EB. Goal-directed functional therapy: a longitudinal study on gross motor function in children with cerebral palsy. Disability and rehabilitation. 2010;32(11):908-916.
48. Novak I, McIntyre S, Morgan C, et al. State of the evidence: systematic review of interventions for children with cerebral palsy. Developmental medicine and child neurology. 2013;55.
49. Bleyenheuft Y, Arnould C, Brandao MB, et al. Hand and Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE) in Children With Unilateral Spastic Cerebral Palsy: A Randomized Trial. Neurorehabil Neural Repair. 2015;29(7):645-657.
50. Bleyenheuft Y, Ebner-Karestinos D, Surana B, et al. Intensive upper- and lower-extremity training for children with bilateral cerebral palsy: a quasi-randomized trial. Developmental medicine and child neurology. 2017;59(6):625-633.

51. Brogren Carlberg E, Löwing K. Does goal setting in activity-focused interventions for children with cerebral palsy influence treatment outcome? Developmental Medicine & Child Neurology. 2013;55:47-54.
52. Franki I, Desloovere K, De Cat J, et al. An evaluator-blinded randomized controlled trial evaluating therapy effects and prognostic factors for a general and an individually defined physical therapy program in ambulant children with bilateral spastic cerebral palsy. European journal of physical and rehabilitation medicine. 2015;51(6):677-691.
53. Novak I. Evidence to practice commentary: is more therapy better? Physical & occupational therapy in pediatrics. 2012;32(4):383-387.
54. Chiarello LA, Palisano RJ, Bartlett DJ, et al. A multivariate model of determinants of change in gross-motor abilities and engagement in self-care and play of young children with cerebral palsy. Physical & occupational therapy in pediatrics. 2011;31(2):150-168.
55. Martin L, Baker R, Harvey A. A systematic review of common physiotherapy interventions in school-aged children with cerebral palsy. Physical & occupational therapy in pediatrics. 2010;30(4):294-312.
56. Myrhaug HT, Østensjø S, Larun L, et al. Intensive training of motor function and functional skills among young children with cerebral palsy: a systematic review and meta-analysis. BMC pediatrics. 2014;14(1):292.
57. Cope S, Mohn-Johnsen S. The effects of dosage time and frequency on motor outcomes in children with cerebral palsy: A systematic review. Developmental neurorehabilitation. 2017:1-12.
58. Arpino C, Vescio MF, De Luca A, et al. Efficacy of intensive versus nonintensive physiotherapy in children with cerebral palsy: a meta-analysis. Int J Rehabil Res. 2010;33(2):165-171.
59. Park EY. Effect of physical therapy frequency on gross motor function in children with cerebral palsy. Journal of physical therapy science. 2016;28(6):1888-1891.
60. Lee SH, Shim JS, Kim K, et al. Gross Motor Function Outcome After Intensive Rehabilitation in Children With Bilateral Spastic Cerebral Palsy. Annals of rehabilitation medicine. 2015;39(4):624-629.
61. Østensjø S, Carlberg EB, Vøllestad NK. Motor impairments in young children with cerebral palsy: relationship to gross motor function and everyday activities. Developmental Medicine & Child Neurology. 2004;46(9):580-589.
62. Beckung E, Hagberg G, Uldall P, et al. Probability of walking in children with cerebral palsy in Europe. Pediatrics. 2008;121(1):e187-192.
63. Keeratisiroj O, Thawinchai N, Siritaratiwat W, et al. Prognostic predictors for ambulation in children with cerebral palsy: a systematic review and meta-analysis of observational studies. Disability and rehabilitation. 2018;40(2):135-143.
64. Voorman JM, Dallmeijer AJ, Knol DL, et al. Prospective longitudinal study of gross motor function in children with cerebral palsy. Arch Phys Med Rehabil. 2007;88(7):871-876.
65. Vos RC, Becher JG, Voorman JM, et al. Longitudinal Association Between Gross Motor Capacity and Neuromusculoskeletal Function in Children and Youth With Cerebral Palsy. Archives of Physical Medicine and Rehabilitation. 2016;97(8):1329-1337.

66. Bartlett DJ, Chiarello LA, McCoy SW, et al. Determinants of gross motor function of young children with cerebral palsy: a prospective cohort study. Developmental medicine and child neurology. 2014;56(3):275-282.
67. Yi TI, Jin JR, Kim SH, et al. Contributing factors analysis for the changes of the gross motor function in children with spastic cerebral palsy after physical therapy. Annals of rehabilitation medicine. 2013;37(5):649-657.
68. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.
69. Polit DF, Beck CT. Nursing Research : generating and assessing evidence for nursing practice. Philadelphia: Wolters Kluwer 2017.
70. Adair B, Said CM, Rodda J, et al. Psychometric properties of functional mobility tools in hereditary spastic paraplegia and other childhood neurological conditions. Developmental medicine and child neurology. 2012;54(7):596-605.
71. Harvey A, Robin J, Morris ME, et al. A systematic review of measures of activity limitation for children with cerebral palsy. Developmental Medicine & Child Neurology. 2008;50(3):190-198.
72. Russell DJ, Rosenbaum PL, Cadman DT, et al. The gross motor function measure: a means to evaluate the effects of physical therapy. Developmental Medicine & Child Neurology. 1989;31(3):341-352.
73. Russell DJ, Avery LM, Rosenbaum PL, et al. Improved Scaling of the Gross Motor Function Measure for Children With Cerebral Palsy: Evidence of Reliability and Validity. Physical therapy. 2000;80(9):873-885.
74. Russell DJ, Avery LM, Walter SD, et al. Development and validation of item sets to improve efficiency of administration of the 66-item Gross Motor Function Measure in children with cerebral palsy. Developmental Medicine & Child Neurology. 2010;52(2).
75. Brunton LK, Bartlett DJ. Validity and reliability of two abbreviated versions of the Gross Motor Function Measure. Physical therapy. 2011;91(4):577.
76. Avery LM, Russell DJ, Rosenbaum PL. Criterion validity of the GMFM-66 item set and the GMFM-66 basal and ceiling approaches for estimating GMFM-66 scores. Developmental Medicine & Child Neurology. 2013;55(6):534-538.
77. Hanna SE, Rosenbaum PL, Bartlett DJ, et al. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. Developmental medicine and child neurology. 2009;51(4):295-302.
78. Smits DW, Gorter JW, Hanna SE, et al. Longitudinal development of gross motor function among Dutch children and young adults with cerebral palsy: an investigation of motor growth curves. Developmental medicine and child neurology. 2013;55(4):378-384.
79. Myklebust G, Jahnsen R, Elkjaer S. Development of gross motor function in children with cerebral palsy: an investigation of 'motor growth curves'. Developmental Medicine & Child Neurology. 2014;56:39-112.
80. King GA, McDougall J, Palisano RJ, et al. Goal Attainment Scaling. Physical & occupational therapy in pediatrics. 2000;19(2):31-52.
81. Steenbeek D, Ketelaar M, Galama K, et al. Goal attainment scaling in paediatric rehabilitation: a critical review of the literature. Developmental medicine and child neurology. 2007;49.

82. Steenbeek D, Ketelaar M, Lindeman E, et al. Interrater Reliability of Goal Attainment Scaling in Rehabilitation of Children With Cerebral Palsy. Archives of Physical Medicine and Rehabilitation.91(3):429-435.
83. Haley SM. Pediatric evaluation of disability inventory (PEDI): development, standardization and administration manual : version 1.0. Boston, Mass.: PEDI Research Group 1992.
84. Sollerman C, Ejeskär A. Sollerman Hand Function Test: A Standardised Method and its Use in Tetraplegic Patients. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery. 1995;29(2):167-176.
85. Krumlinde-Sundholm L, Holmefur M, Kottorp A, et al. The Assisting Hand Assessment: current evidence of validity, reliability, and responsiveness to change. Developmental Medicine & Child Neurology. 2007;49(4):259-264.
86. Lolle H. Multilevel analyse i SPSS 11.5: Aalborg Universitet 2003.
87. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
88. Rothman KJ. Epidemiology : an introduction. Oxford: Oxford University Press 2012.
89. Alnahdi G. Single-subject designs in special education: Advantages and limitations 2013.
90. Twisk JWR. Applied longitudinal data analysis for epidemiology : a practical guide. Cambridge: Cambridge University Press 2013.
91. Hennekens CH, Buring JE, Mayrent SL. Epidemiology in medicine. Boston: Little, Brown 1987.
92. McDowell BC, Hewitt V, Nurse A, et al. The variability of goniometric measurements in ambulatory children with spastic cerebral palsy. Gait & posture. 2000;12(2):114-121.
93. Nordmark E, Hagglund G, Lauge-Pedersen H, et al. Development of lower limb range of motion from early childhood to adolescence in cerebral palsy: a population-based study. BMC Med. 2009;7:65.
94. Myrhaug HT, Ostensjo S. Motor Training and Physical Activity Among Preschoolers with Cerebral Palsy: A Survey of Parents' Experiences. Physical & occupational therapy in pediatrics. 2013.
95. Braendvik SM, Roeleveld K, Andersen GL, et al. The WE-Study: does botulinum toxin A make walking easier in children with cerebral palsy?: Study protocol for a randomized controlled trial. Trials. 2017;18(1):58.
96. Hocking J, McNeil J, Campbell J. Physical therapy interventions for gross motor skills in people with an intellectual disability aged 6 years and over: a systematic review. International journal of evidence-based healthcare. 2016;14(4):166-174.
97. van der Putten A, Vlaskamp C, Reynders K, et al. Children with profound intellectual and multiple disabilities: the effects of functional movement activities. Clinical Rehabilitation. 2005;19(6):613-620.

Appendix 1 Studies of goal-directed functional training on gross motor progress

Author	N/age (years)	GMFCS / Type	Design	Intervention vs control	Outcome measure	Results
Bower & McLellan-92[39]	7/ 2-12	NA / Quadriplegia	SSE (ABA), 3 weeks periods	Intensive (1 hour/day) GDT using eclectic strategies vs routine therapy (weekly)	Goal attainment GMFM-88 ++	Increasing intensity of PT accelerated the acquisition of motor skills
Bower & McLellan-94[40]	4 / 2-3	NA / Quadriplegia	SSE (ABAA / AABA) 5 weeks periods	Intensive (1 hour/day) NDT directed toward goals vs routine (1 hour/week) NDT	Goal attainment GMFM-88 ++	Functional changes were continuous throughout the study period. Functional goals attained; goals of movement pattern not attained
Bower et al-96[42]	44/ 3-11	NA / Quadriplegia	RCT (2x2 factorial design) 2 weeks period	Intensive amounts of PT (daily) vs conventional amounts (weekly), goal vs aims for treatment. Eclectic strategies	GMFM-88	Intensive PT slightly better than conventional, goals most strongly associated with increased motor skills acquisition
Bower et al-01[43]	56/ 3-12	III, IV and V / Bilateral	RCT (ABA) 6 months' periods using a 2x2 factorial design in the intervention period.	Intensive amounts of PT (daily) vs conventional amounts (weekly) and goal vs aims for treatment. Eclectic strategies.	GMFM-88 ++	No differences.
Ketelaar et al -01[37]	55/ 2-7	Mild or moderate / Spastic (hemi-di-, quadriplegia)	RCT over 18 months (6 months interventon period	Functional PT vs normalization of quality of movement	GMFM-88 PEDI ++	No differences in GMFM-88. Functional group improved more in functional skills (PEDI).

Ahl et al-05[44]	14/ 1.5-6	II-V / Spastic (diplegia, tetraplegia)	A (2 months) B (5 months) A (3 months)	GDT carried out in the child's normal setting, multiple repetitions per day	GAS GMFM-66 PEDI ++	Significant improvements in intervention period in GAS, GMFM-66, and PEDI.
Løwing et al-09[45]	44/ 1-6	I-IV / unilateral, bilateral.	Prospective (before – after) intervention study of 12 weeks	GDT vs activity-focused therapy	GAS GMFM-66 PEDI	GDT improved more both in GMFM-66 and PEDI. Also high level of goal attainment measured with GAS.
Løwing et al-10[47]	22/ 1-6	I-IV / unilateral, bilateral.	Prospective longitudinal intervention study ABA (12 weeks periods)	GDT	GAS GMFM-66 GMFM-66 percentiles ++	Gross motor function was stable during baseline, improved during intervention and was maintained 12 weeks later measured with GAS and GMFM-66 (total scores and percentiles)
Sørsdahl et al-10[46]	22/ 3-9	I-V/ hemiplegia, diplegia, quadriplegia. Ataxia	Repeated measures design ABA (3 weeks periods)	Intensive (3 hours / five days per week) goal-directed activity-focused PT vs 1 hour per week in B periods	GMFM-66 PEDI GAS ++	Significant improvements in intervention period in GMFM-66, PEDI and GAS.
Franki et al - 15[52]	40/ 4-9	I, II, III / spastic bilateral	RCT. 10 weeks intervention period.	Individually-defined program vs general therapy program	GAS GMFM-88	Both programs had a positive impact on the children's motor functioning, no significant differences.

Bleyenheuft-15[49]	24/ 6-13	I-II / unilateral	RCT AB or BA A: ongoing treatment until 90 hours B: 10 days (90 hours)	HABIT-ILE using motor learning concepts vs conventional ongoing treatment (mostly neurodevelopmental concepts)	6MWT PEDI ++	Significant improvements following HABIT-ILE, but not conventional treatment.
Bleyenheuft-17[50]	20/ 6-15	II-IV / bilateral	Quasi-randomized trial	HABIT-ILE using motor learning concepts (6.5 hours per day in 13 days) vs usual care	GMFM-66 ++	HABIT-ILE efficacious for improving gross motor function; no change in comparison group

GDT: Goal-directed functional training. NDT: Neurodevelopmental Treatment. PT: physical therapy. HABIT-ILE: Hand-arm bimanual intensive therapy including lower extremity. GMFM: Gross Motor Function Measure. PEDI: Pediatric Evaluation of Disability Inventory. GAS: Goal Attainment Scaling. 6MWT: 6 minutes walking test.

Paper I

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Paper II

Is increased physical therapy frequency associated with increased gross motor improvement in children with cerebral palsy? A national prospective cohort study.

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Is increased physical therapy frequency associated with increased gross motor improvement in children with cerebral palsy? A national prospective cohort study.

Purpose: To investigate the association between physical therapy frequency and gross motor improvement in children with CP aged 2-12 years.

Materials and methods: Prospective cohort study of 442 children from the Cerebral Palsy Follow-up Program and the Cerebral Palsy Register of Norway with a total of 1498 assessments. Outcome was change in Reference percentiles for the Gross Motor Function Measure (GMFM-66) between two subsequent assessments analyzed in a Linear Mixed Model.

Results: It was a dose response association between physical therapy frequency and gross motor improvement. Mean change was 4.2 (95% CI: 1.4-7.1) percentiles larger for physical therapy 1-2 times per week and 7.1 (95% CI: 2.6-11.6) percentiles larger for physical therapy >2 times per week, compared to less frequent physical therapy when analyzed in a multivariable model including multiple child and intervention factors. The only statistically significant confounders were number of contractures and epilepsy (borderline), which both were negatively associated with gross motor improvement.

Conclusion: When gross motor improvement is a goal for children with CP, more frequent physical therapy may be a success factor.

Keywords: Cerebral palsy; physical therapy frequency; gross motor improvement; cohort; GMFM-66 reference percentiles; CPRN/CPOP

Is increased physical therapy frequency associated with increased gross motor improvement in children with cerebral palsy? A national prospective cohort study.

Introduction

Motor problems are the core symptom of cerebral palsy (CP) [1] and more than 90% of children with CP receive physical therapy; often directed at gross motor functions [2,3]. Most children with CP receive physical therapy 1-2 times per week [2,3], but there are large variations ranging from less than twice per month to more than three times per week [3]. Considering the time and effort that children and their families invest in gross motor skills practice and prevention strategies of secondary impairments, it is important to know whether more frequent physical therapy really constitutes a success factor for increased gross motor improvement [4].

According to current recommendations, therapy should be based on motor learning principles, including goal-directed, task-specific practice with frequent repetitions [4-7], which have shown to enhance gross motor improvement [6,8-10]. Which role the physical therapy frequency in itself may play for gross motor improvement however, is still largely unclear [4,11-14], although some recent studies have suggested that therapies of higher frequencies are more effective than others [15,16]. Since the frequency adds to the total dose of physical therapy [17], one should expect increased frequency to enhance gross motor improvement. However, according to a recent systematic review, there is “insufficient evidence to support implementing high-dose therapy” [11]. On the other hand, the knowledge is based on a relatively sparse number of randomized controlled trials (RCTs) including small and selected samples. Studies based on larger cohorts of children are generally lacking.

According to systems theory of motor control [5] and the International Classification of Functioning, Disability and Health (ICF) [18] gross motor improvement is considered the

net result of the interactions between several factors including, but not limited to, Gross Motor Function Classification System (GMFCS) level [19], age, physical therapy frequency, contractures, associated problems, comorbidities and other types of interventions. Therefore, in order to study the role of physical therapy frequency on gross motor improvement, other factors should be considered as possible confounders. Of special interest is contractures which can contribute to the deterioration of functional skills [20] and thus be negatively associated with gross motor improvement [14,21]. Contractures are therefore commonly addressed in therapy in order to lessen the negative effect on gross motor outcome [22,23].

Associated problems such as intellectual disability, speech problems, eating problems, severe visual and hearing problems, and pain; epilepsy and additional diagnoses [14,21,24] generally add to the total health and functional burden of the child, and may not only be negatively associated with gross motor improvement, but may also limit the child's availability for physical therapy.

Furthermore, interventions other than physical therapy may contribute to gross motor improvement. Botulinum toxin A (BoNT-A) injections, intrathecal baclofen (ITB), surgery, and use of orthoses have shown to affect body function and structures, but there is not convincing evidence of a direct influence on gross motor function and progress [6]. Some children may also participate in an intensive program of shorter duration which may increase the total dose of physical therapy.

There has been a call for research using large data sets to provide information about how prognostic factors influence the outcomes of persons with CP [5,25]. By using data from the Cerebral Palsy Follow-up Program (CPOP) and the Cerebral Palsy Register of Norway (CPRN), we are now able to investigate the role physical therapy frequency may play for gross motor improvement in a large cohort of children during childhood (2-12 years). The longitudinal design with multiple assessments per child and the use of the Reference

percentiles for the Gross Motor Function Measure (GMFM-66 percentiles) [26] as outcome, make it possible to estimate change between two subsequent assessments and directly compare gross motor improvement across ages and GMFCS levels.

Aim

The aim of this study was to investigate the association between physical therapy frequency and gross motor improvement in a large cohort of children with CP, taking contractures and other available possible confounders into account. We hypothesize that there is a positive association between increased physical therapy frequency and increased gross motor improvement, and that number of contractures and possibly some of the other factors will affect this association.

Materials and methods

Design and participants

This prospective cohort study is based on repeated (time-dependent) data from CPOP and time-independent data from CPRN. Health professionals working at the 21 habilitation centers, serving all children diagnosed with CP in Norway, are submitting clinically obtained data to these consent-based registers [27].

CPRN is a national medical quality register including children born in 1996 or later [27]. Data are recorded at three ages (time of diagnoses, 5 years and 15 years) [27]. CPOP includes children born in 2002 or later. Data are recorded once or twice per year until 6 years of age, thereafter yearly or every second year, depending on the child's GMFCS level.

Approximately 90% of children with CP born after 2002 in Norway are included in CPRN/CPOP [27].

Inclusion and exclusion

In order to investigate change in gross motor function, only children registered in both CPOP and CPRN with two or more Gross Motor Function Measure (GMFM-66) [28] assessments between the ages of 2 and 12 years (the age span for GMFM-66 percentiles) were eligible to participate. Of the 1088 children included in CPOP born between 2002 and 2013, 442 (256 boys, 186 girls) fulfilled the inclusion criteria. The excluded children were either too young to have completed two assessments or GMFM-66 assessments were missing. There were 1498 assessments of GMFM-66 percentiles (range 2-9 assessments per child) comprising a total of 1056 measures of change in GMFM-66 percentiles (range 1-8 measures of change per child, mean: 2.4 SD: 1.6). The median time between two subsequent GMFM-66 assessments was 1 year (interquartile range: 0.73 to 1.42 years) and the mean time was 1.23 years (SD: 0.81).

The characteristics of the children in the study cohort (table 1) were comparable with the source population of Norwegian children with CP registered in CPOP/CPRN (Annual reports of CPOP and CPRN 2014) [29].

Table 1

Measures

Data from CPOP are linked to CPRN once per year giving a hierarchical file with time-independent characteristics of each child on one level and repeated (time-dependent) measures of each child on a second level. For our study, we included repeated measures of GMFM-66 percentiles, physical therapy frequency, contractures, pain, treatment-related variables and age (figure 1). We included time-independent measures of CP subtype, GMFCS level, associated problems, and comorbidities based on the 5 years assessment in CPRN when subdiagnosis is confirmed (figure 1). Time-independent variables (child characteristics not considered to vary from time to time) were considered valid for all observations for a

particular child. Each observation for a child therefore included data on both the time-independent variables and the time-dependent variables.

Figure 1

Dependent variable

Gross motor change was defined as the mean change in GMFM-66 percentiles [26] from one assessment to the next (Δ percentiles), and gross motor improvement as a positive change in GMFM-66 percentiles from one assessment to the next.

Gross motor function was repeatedly measured with GMFM-66 [28] and the total scores were converted to GMFM-66 percentiles using tabulated reference percentiles [30] according to age and GMFCS level [19]. Both GMFCS and GMFM-66 have been found valid and reliable [19,28].

Based on the Motor development curves [31] that have been validated in Norway [32], the GMFM-66 percentiles show the expected and average pattern of change in GMFM-66 total scores by age within each GMFCS level [26]. The rationale for using GMFM-66 percentiles as outcome is described in details in a former publication (Storvold et al. Factors Associated with Change in GMFM-66 Reference Percentiles of Children with Cerebral Palsy: A Long-term Register-based Study. *Physical and Occupational Therapy in Pediatrics* 2018, in press). In short, children are in general expected to follow their own reference percentile, though with large variation [26]. Hence, a positive change in GMFM-66 percentile imply a gross motor development better than expected, which for most children indicate a larger increase in GMFM-66 total scores than expected. Since the shapes of GMFM-66 reference percentile curves differ [30] an increase in percentile for older children may however imply that the expected decrease in GMFM-66 total scores has been lower than expected.

Independent variables

Physical therapy frequency. Repeated measures of physical therapy frequency were recorded on a five-point ordinal scale: less than 1 time per month, 1-3 times per month, 1-2 times per week, 3-5 times per week and more than 5 times per week [29]. In order to extract as much information as possible, the original scale was used in the exploration of data and in descriptive analyses. Due to the restricted numbers of observations in the upper and lower end of the scale however, frequency was collapsed into a three-point scale for further analyses: <1 time per week, 1-2 times per week and >2 times per week.

Contractures in lower limbs. Passive range of motion (ROM) was measured repeatedly with a goniometer in a standardized way according to CPOP guidelines [29], in hips (extension, inward rotation, outward rotation, and abduction), knees (extension, unilateral popliteal angle) and ankles (dorsiflexion with extended knee). Then CPOP guidelines [29] for defining contractures were applied. Thereafter number of contractures in the most affected leg were trichotomized into no contractures, 1-2 contractures, or >2 contractures.

Other independent variables. Pain was classified as "present" or "not present" at each assessment. All interventions targeting impairments (BoNT-A, ITB, surgery in lower limbs or use of orthoses) were dichotomized as "having received the intervention" or "not received the intervention" at each assessment. Participation in an intensive program was classified as "yes" or "no" at each assessment. There was no further information about intensive program except from involving some form of gross motor training.

CP subtype was classified according to The Surveillance of Cerebral Palsy in Europe (SCPE) [33]. Intellectual ability was originally described by a wide range of standardized instruments or by clinical judgements. This information was combined and dichotomized into "intellectual disability" (including moderate to severe intellectual disability) or "not intellectual disability" (no or minor intellectual disability). Speech was recorded on an ordinal

6-point scale and dichotomized into “understandable speech” or “not understandable speech”. Eating problems were dichotomized as “present” or “not present”. Severe visual and severe hearing problems were recorded dichotomously, combined, and recoded as “severe visual and/or severe hearing problem” or “not severe visual and/or severe hearing problem”. Associated health conditions were dichotomized and classified as “present” or “not present” for epilepsy and additional diagnoses.

An overview of the independent variables, the coding/recoding and the study-specific classifications are provided in table 2. Age and GMFCS level are accounted for in the GMFM-66 percentiles and therefore not listed as independent variables.

Table 2

Statistics

The statistical analyses were performed using SPSS, version 24. The significance level was set at 0.05. Descriptive statistics was used to generate frequencies and central tendencies.

All independent variables were explored with bivariate correlations in order to examine how each factor was related to other factors and to exclude factors describing the same phenomenon. “Speech problems” therefore was excluded due to the correlation with “intellectual disability” ($r=0.88$; cut-off 0.7).

The association between physical therapy frequency and gross motor improvement was analyzed using Linear Mixed Model (LMM) with change in GMFM-66 percentiles between two subsequent assessments (Δ percentiles) as dependent variable. The possibility of within-subject correlation in the dependent variable was accounted for by including a random intercept for child.

We first investigated the role of physical therapy frequency (three-point scale) on gross motor improvement with number of contractures as confounder based on complete

cases (n=814). A possible interaction between physical therapy frequency and number of contractures was explored, but not found. Also, unadjusted results based on the same data set were calculated and model fit explored using -2 Restricted Log Likelihood (the less the better) confirming that the model including number of contractures had better model fit (6904.971 vs 6920.350).

Due to the cumulative effect of missing values in multiple variables, multiple imputations were performed in order to keep the data set large enough to include all possible confounders in the model. Missing data were assumed to be missing at random as missing data mainly were due to factors related to assessors (e.g. work overload) and not to factors related to the children. Both the dependent and independent variables were included in the imputation model to predict the missing values. The dependent variable, physical therapy frequency and number of contractures were not imputed securing that all the LMM analyzes were performed on the same data set. Automatic procedures allowing imputation method to be chosen based on scanning the data were applied, leading to the use of the "Fully Conditional Specification Method." Categorical variables were modeled with a logistic regression model. Each model used all variables as main effect and no interaction effects were included.

The role of physical therapy frequency on gross motor improvement was then investigated in a multivariable model based on the imputed data set (pooled imputations from 20 imputations, n=814) including both number of contractures and all of the other independent variables that possibly could influence the research question. Both the unadjusted, the adjusted, and the multivariable adjusted model are presented.

Ethics

Ethical approval was given by the Regional Committee for Medical and Health Research Ethics in central Norway and the institutional board of Nord Trøndelag Hospital Trust. The registers providing data for this study are based on informed consent from parents.

Results

Physical therapy frequency

A total of 431 children had one or more valid observations of physical therapy frequency (total 987 observations). In 61% of the observations, children received physical therapy 1-2 times per week, 11% more often and 28% less often (table 3).

Table 3

Gross motor improvement in general

Children largely stayed on their percentiles as the median change in GMFM-66 percentiles between two subsequent assessments was 0 percentiles (interquartile range: -5 to10, mode: 0). The mean change was 2.51 percentiles (SD: 17.45).

Association between physical therapy frequency and gross motor improvement

Results based on complete cases (n=814) showed a positive association between increased physical therapy frequency and increased gross motor improvement when adjusted for number of contractures, which was negatively associated with gross motor improvement (table 4).

Table 4

Multivariable adjusted results (number of contractures, epilepsy, intellectual disability, pain, eating problems, visual and/or hearing problems, type of CP, participating in an intensive program, BoNT, ITB, surgery, using orthoses and additional diagnoses) based on

imputed data (n=814) showed similar results (table 4). Compared to the references (physical therapy < once per week), gross motor improvement was on average 4.2 (95% CI: 1.4 to 7.1) percentiles larger for children receiving physical therapy 1-2 times per week and 7.1 (95% CI: 2.6 to 11.6) percentiles larger for children receiving physical therapy more than 2 times per week. Of possible confounding factors included in final model only number of contractures remained statistically significant, whereas epilepsy was borderline statistically significant. Both number of contractures and epilepsy were negatively associated with gross motor improvement. The multivariable adjusted estimated marginal means for change in GMFM-66 percentile were -3.4 (95% CI: -9.6 to 2.8) percentiles for physical therapy <once per week, 0.8 (95% CI: -4.9 to 6.5) percentiles for physical therapy 1-2 times per week and 3.7 (95% CI: -2.7 to 10.1) percentiles for physical therapy > 2 times per week.

Figure 2 shows the multivariable adjusted estimated mean changes in GMFM-66 percentiles related to physical therapy frequency and number of contractures, showing a more fortunate change for children with more frequent physical therapy not having contractures.

Figure 2

Discussion

In this large cohort study based on the high-coverage CPOP and CPRN registers we found that increased physical therapy frequency was associated with increased gross motor improvement. Contractures and epilepsy represented obstacles to gross motor improvement.

Our results suggest that in order to improve gross motor function, the actual physical therapy frequency matters. These results are in accordance with motor learning theories highlighting the need for high-frequent repetitions for motor learning to occur, and are also in line with findings in intervention studies based on such theories [6,8-10].

The most recent systematic review of the effect of physical therapy frequency on motor outcomes in children with CP, however, concluded that there was not enough evidence to determine whether therapies with higher frequencies were more effective than low frequent therapies [11]. On the other hand, this conclusion is predominantly based on results from a few RCTs [11]. Although RCT studies generally are considered the best study design, there are several ethical reservations, especially in studies of children. Since not all children will be available for inclusion in experimental studies, it may be difficult to generalize the results. In contrast, the inclusion of all children in the present study is suggested to give a reliable real-life picture of the relationship between physical therapy frequency and gross motor improvement. Although the association cannot be deemed causal, our findings suggest a dose response association between physical therapy frequency and gross motor improvement. In fact, if gross motor improvement is the goal, frequencies above 2 times per week should be provided. Low frequent physical therapy (< 1 time per week) may not be recommended according to this study.

Our findings suggest that the impact of higher physical therapy frequencies may vary depending on number of contractures. This was not unexpected, given the results of earlier research, which indicate that the secondary impairment of contractures in lower limbs is negatively associated with gross motor function [14,21]. We hypothesize that this may be due to the fact that contractures complicate both the performing and the learning of gross motor skills, but may also be a result of that therapies to a greater extent are addressing the contractures with less focus on gross motor skills learning.

Although it is suggested that associated problems negatively influence gross motor function [14,21,24], we found that except from epilepsy, no other associated problems included in analyzes were of relevance for the association between physical therapy frequency

and gross motor improvement. This result indicates that most children, independent of the presence of associated problems, may benefit from higher frequencies of physical therapy.

The participation in a short-term intensive program was considered to increase the total dose of therapy, but even if a small nonsignificant positive association was found, the association between physical therapy frequency and gross motor improvement was not affected. Also, interventions that address impairments did not affect the association between physical therapy frequency and gross motor improvement. This finding is in accordance with previous research that has hypothesized that although these interventions may influence impairments, they may not directly improve gross motor function [6].

Strengths and limitations

The prospective study design, including a large national representative cohort of 442 children aged 2-12 years, is considered strength of this study. The use of repeated standardized measurements of gross motor function is suggested to increase the internal validity and the precision of estimates. The access to a range of other variables of relevance for the study question and the multivariable approach generate hypotheses about the role physical therapy frequency may play for gross motor improvement. The use of GMFM-66 percentiles in studies of gross motor change is also considered strength since percentiles can be interpreted equally across different GMFCS levels and ages.

Data on type of physical therapy and session length were lacking and may represent a limitation. Since longer sessions can compensate for lower frequencies of therapy, frequencies cannot be directly translated into total dose of therapy. On the other hand, most session lengths are found to be 30-60 minutes [3] and the duration of physical therapy in this study is not expected to systematically vary between frequencies. Also, therapy as practice of everyday skills may be integrated into daily routines and be carried out with the help of

parents or other professionals at home, in kindergarten or in school, thereby providing additional therapy that we were not able to take into account.

Conclusion

In order to promote gross motor improvement in children with CP, our results suggest that high frequent physical therapy should be considered.

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Declaration of interest

The authors report no conflicts of interest.

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References

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007 Feb;109:8-14. PubMed PMID: 17370477.
2. Myklebust G, Jahnsen R, Elkjaer S. Registration of interventions in children with cerebral palsy during three years-a populationbased study. [Scientific Poster Abstracts]. Developmental Medicine & Child Neurology. 2009;51:65. doi: 10.1111/j.1469-8749.2009.03452_2.x.
3. Palisano R, Begnoche DM, Chiarello LA, et al. Amount and focus of physical therapy and occupational therapy for young children with cerebral palsy. Physical & occupational therapy in pediatrics. 2012 Nov;32(4):368-82. doi: 10.3109/01942638.2012.715620. PubMed PMID: 22954372.
4. Novak I. Evidence to practice commentary: is more therapy better? Physical & occupational therapy in pediatrics. 2012;32(4):383-387.
5. Law M, Darrah J. Emerging Therapy Approaches: An Emphasis on Function. Journal of child neurology. 2014 May 7. doi: 10.1177/0883073814533151. PubMed PMID: 24810086.
6. Novak I, McIntyre S, Morgan C, et al. State of the evidence: systematic review of interventions for children with cerebral palsy. Developmental medicine and child neurology. 2013;55. doi: 10.1111/dmcn.12246.
7. Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. Journal of child neurology. 2014;29(8):1141-1156.
8. Lowing K, Bexelius A, Carlberg EB. Goal-directed functional therapy: a longitudinal study on gross motor function in children with cerebral palsy. Disability and rehabilitation. 2010;32(11):908-16. doi: 10.3109/09638280903353422. PubMed PMID: 19852713.
9. Bleyenheuft Y, Arnould C, Brandao MB, et al. Hand and Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE) in Children With Unilateral Spastic Cerebral Palsy: A Randomized Trial. Neurorehabil Neural Repair. 2015;29(7):645-657. doi: 10.1177/1545968314562109.
10. Bleyenheuft Y, Ebner-Karestinos D, Surana B, et al. Intensive upper- and lower-extremity training for children with bilateral cerebral palsy: a quasi-randomized trial. Developmental medicine and child neurology. 2017 Jun;59(6):625-633. doi: 10.1111/dmcn.13379. PubMed PMID: 28133725; eng.
11. Cope S, Mohn-Johnsen S. The effects of dosage time and frequency on motor outcomes in children with cerebral palsy: A systematic review. Developmental neurorehabilitation. 2017:1-12.
12. Myrhaug HT, Østensjø S, Larun L, et al. Intensive training of motor function and functional skills among young children with cerebral palsy: a systematic review and meta-analysis. BMC pediatrics. 2014;14(1):292.
13. Arpino C, Vescio MF, De Luca A, et al. Efficacy of intensive versus nonintensive physiotherapy in children with cerebral palsy: a meta-analysis. Int J Rehabil Res. 2010 Jun;33(2):165-71. doi: 10.1097/MRR.0b013e328332f617. PubMed PMID: 19910797.
14. Chiarello LA, Palisano RJ, Bartlett DJ, et al. A multivariate model of determinants of change in gross-motor abilities and engagement in self-care and play of young children with cerebral palsy. Physical & occupational therapy in pediatrics. 2011 May;31(2):150-68. doi: 10.3109/01942638.2010.525601. PubMed PMID: 20964514.

15. Park EY. Effect of physical therapy frequency on gross motor function in children with cerebral palsy. Journal of physical therapy science. 2016 Jun;28(6):1888-91. doi: 10.1589/jpts.28.1888. PubMed PMID: 27390440; PubMed Central PMCID: PMCPMC4932081. eng.
16. Lee SH, Shim JS, Kim K, et al. Gross Motor Function Outcome After Intensive Rehabilitation in Children With Bilateral Spastic Cerebral Palsy. Annals of rehabilitation medicine. 2015 Aug;39(4):624-9. doi: 10.5535/arm.2015.39.4.624. PubMed PMID: 26361600; PubMed Central PMCID: PMCPMC4564711. eng.
17. Palisano RJ, Murr S. Intensity of therapy services: what are the considerations? Physical & occupational therapy in pediatrics. 2009;29(2):107-12. doi: 10.1080/01942630902805186. PubMed PMID: 19401925.
18. WHO WHO. International classification of functioning, disability and health: ICF. Organization WH, editor.: World Health Organization; 2001.
19. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Developmental medicine and child neurology. 1997 Apr;39(4):214-23. PubMed PMID: 9183258; eng.
20. Nordmark E, Hagglund G, Lauge-Pedersen H, et al. Development of lower limb range of motion from early childhood to adolescence in cerebral palsy: a population-based study. BMC Med. 2009 Oct 28;7:65. doi: 10.1186/1741-7015-7-65. PubMed PMID: 19863779; PubMed Central PMCID: PMCPMC2774339.
21. Bartlett DJ, Chiarello LA, McCoy SW, et al. Determinants of gross motor function of young children with cerebral palsy: a prospective cohort study. Developmental medicine and child neurology. 2014 Mar;56(3):275-82. doi: 10.1111/dmcn.12317. PubMed PMID: 24127787.
22. Jeffries L, Fiss A, McCoy SW, et al. Description of Primary and Secondary Impairments in Young Children With Cerebral Palsy. Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association. 2016 Spring;28(1):7-14. doi: 10.1097/PEP.0000000000000221. PubMed PMID: 27088676.
23. Anaby D, Korner-Bitensky N, Steven E, et al. Current Rehabilitation Practices for Children with Cerebral Palsy: Focus and Gaps. Physical & occupational therapy in pediatrics. 2016:1-15.
24. Beckung E, Hagberg G, Uldall P, et al. Probability of walking in children with cerebral palsy in Europe. Pediatrics. 2008 Jan;121(1):e187-92. doi: 10.1542/peds.2007-0068. PubMed PMID: 18070932.
25. Kruijsen-Terpstra AJ, Ketelaar M, Verschuren O, et al. Determinants of developmental gain in daily activities in young children with cerebral palsy. Physical & occupational therapy in pediatrics. 2015;35(3):265-279.
26. Hanna SE, Bartlett DJ, Rivard LM, et al. Reference curves for the Gross Motor Function Measure: percentiles for clinical description and tracking over time among children with cerebral palsy. Physical therapy. 2008 May;88(5):596-607. doi: 10.2522/ptj.20070314. PubMed PMID: 18339799; PubMed Central PMCID: PMC2390723.
27. Hollung SJ, Vik T, Wiik R, et al. Completeness and correctness of cerebral palsy diagnoses in two health registers: implications for estimating prevalence. Developmental Medicine & Child Neurology. 2016:n/a-n/a. doi: 10.1111/dmcn.13341.
28. Russell DJ, Rosenbaum P, Wright M, et al. Gross motor function measure (gmfm-66 and gmfm-88): user's manual. London: Mac Keith Press; 2013.
29. CPOP. Cerebral Parese Oppfølgingsprogram Norway[cited 2017 23 05]. Available from: https://oslo-universitetssykehus.no/avdelinger/barne-og-

ungdomsklinikken/barneavdeling-for-nevrofag/cpop-cerebral-parese-oppfolgingsprogram
30. Hanna SE, Bartlett D, Rivard LM, et al. Tabultated reference percentiles for the 66-item Gross Motor Function Measure for use with children having cerebral palsy. www.canchild.ca2008 [cited 2016].
31. Rosenbaum P, Walter SD, Hanna SE, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. JAMA : the journal of the American Medical Association. 2002 Sep 18;288(11):1357-63. PubMed PMID: 12234229.
32. Myklebust G, Jahnsen R, Elkjaer S. Development of gross motor function in children with cerebral palsy: an investigation of 'motor growth curves'. Developmental Medicine & Child Neurology. 2014;56:39-112. doi: 10.1111/dmcn.12540.
33. Cans C, Dolk H, Platt M, et al. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Developmental Medicine & Child Neurology. 2007;49(s109):35-38.

Table 1. Characteristics of the study cohort and the source population CPOP / CPRN

	Study cohort		Source population CPOP / CPRN[2]
	N	%	%
Sex			
Boys	256	58	57
Girls	186	42	43
Missing	0	0	0
CP type			
Unilateral right	112	25	27
Unilateral left	84	19	18
Bilateral (diplegia)	140	32	30
Bilateral (quadriplegia)	60	14	14
Dyskinesia	30	7	7
Ataxia	10	2	3
Not classified	6	1	1
Missing	0	0	0
GMFCS level			
I	218	49	51
II	71	16	16
III	48	11	8
IV	47	11	9
V	58	13	14
Missing	0	0	2
Intellectual ability[1]			
Not measured (children <5 years)	102	23	
Moderate or severe intellectual disability	46	14	17
Normal or minor intellectual disability	189	56	42
Missing (children ≥ 5 years)	105	31	41
Speech[1]			
Not measured (children < 5 years)	92	21	
Not understandable speech	62	18	25
Understandable speech	225	64	52
Missing (children ≥ 5 years)	63	18	22
Eating problems			
Yes	102	23	23
No	265	60	77
Missing	75	17	1
Sensory problems			
Severe visual and/or severe hearing problems	19	4	6/4
Not severe visual and/or severe hearing problems	267	60	90/93
Missing severe visual and/or severe hearing problems	156	35	4/4
Epilepsy			
Yes	101	23	33
No	257	58	66
Missing	84	19	1
Additional diagnosis			
Yes	8	2	2
No	277	63	96
Missing	157	36	2
Totals	442	100	100

CP=cerebral palsy. CPOP= Cerebral Palsy Follow-up Program, CPRN=Cerebral Palsy Register of Norway, GMFCS= Gross Motor Function Classification System.

[1]Intellectual ability and speech only assessed in children aged ≥5 years

[2] Information from annual reports of CPOP and CPRN 2014.

Differences between study and source cohorts were calculated by the use of Chi Square and Fisher exact test. No characteristics differed statistically significantly between the study and the source cohort.

Table 2. Description of independent variables

Repeated (time-dependent) measures

Variables	Original variables	Classifications / recoding		Observations n
Physical therapy frequency	Ordinal: > 5 times per week 3-5 times per week 1-2 times per week 1-3 times per month < once per month	Recoded:	> 2 times per week 1-2 times per week < once per week Missing	110 601 276 69
Contractures in lower limbs	Range of motion (ROM) Scale variable of degrees measured with goniometer at **hip**, (abduction, extension, in/outward rotation), **knee** (extension, popliteal angle) and **ankle** (dorsiflexion with extended knee) in most affected leg	Classified into "Contracture or no contracture (normal and to be followed according to CPOP manual) " for the 7 possibilities. Recoded:	> 2 contractures 1-2 contractures No contractures Missing	75 352 439 190
Pain	Dichotomous: Yes/No	Original variable and coding	Yes No Missing	297 722 37
Botulinum toxin (BoNT-A) in lower limbs	Dichotomous: Yes/No	Original variable and coding	Yes No Missing	297 714 45
Intrathecal baclofen (ITB)	Dichotomous: Yes/No	Original variable and coding	Yes No Missing	21 961 74
Surgery in lower limbs	Dichotomous: Yes/No	Original variable and coding	Yes No Missing	62 966 28
Use of orthoses in foot, ankle, knee, or hip	Dichotomous: Yes/No	Original variable and coding	Yes No Missing	785 231 40
Intensive program	Participation in an intensive program: Dichotomous: Yes/no	Original variable and coding	Yes No Missing	437 525 94

Time-independent variables (frequencies in Table 1)

Variables	**Original variables**	**Classifications / recoding**
CP subtype	SCPE classifications. Categorical 1 - 6	Original variable and coding
Intellectual ability	1. Standardized IQ test score, scale 2. Clinical judgement, categorical (normal or intellectual disability)	Combined information: If ≥ 5 years: 1. IQ score corresponding to moderate to severe intellectual disability or clinically judged as intellectual disability = "intellectual disability" 2. Otherwise "not intellectual disability" If < 5 years: 3. "Intellectual ability unknown".
Speech problems	From normal to not understandable speech. Ordinal 1-6	Recoded: If ≥ 5 years: 1. Very unclear or no understandable speech classified as "not understandable speech" 2. Otherwise, "understandable speech" If < 5 years: 3. "Speech problems unknown"
Eating problems	Dichotomous: Yes/No	Original variable and coding
Severe visual problems	Dichotomous: Yes/No	Combined severe visual and severe hearing problems into: 1. "Severe visual and/or severe hearing problem" 2. If else, "not severe visual and /or severe hearing problem"
Severe hearing problems	Dichotomous: Yes/No	
Epilepsy	Dichotomous: Yes/No	Original variable and coding
Additional diagnosis	Dichotomous: Yes/No	Original variable and coding

SCPE: Surveillance of Cerebral Palsy in Europe. CPOP: Cerebral Palsy Follow-up Program.

Table 3: Distribution of physical therapy frequency (N=987)

	n (%)
> 5 times per week	10 (1)
3-5 times per week	100 (10)
1-2 times per week	601 (61)
1-3 times per month	188 (19)
< 1 time per month	88 (9)

Table 4. Mean change (95% CIs) in GMFM-66 percentiles by physical therapy frequency based on complete cases (left columns) and multivariable adjusted based on imputed data (right column).

	Unadjusted model, complete cases (n=814)				**Adjusted model,* complete cases (n=814)**				**Multivariable adjusted model,** imputed data (n=814)**			
	Δ percentiles	95% CI		*p*	Δ percentiles	95% CI		*p*	Δ percentiles	95% CI		*p*
		Lower	Upper			Lower	Upper			Lower	Upper	
Intercept	-0.2	-2.4	1.9	0.835	0.9	-1.4	3.3	0.450	2.0	-1.4	5.5	0.242
Frequency of physical therapy				0.012				0.003				
> 2 times per week	6.0	1.9		0.004	6.9	2.7	11.0	0.001	7.1	2.6	11.6	0.002
1-2 times per week	2.7	0.1		0.045	3.5	0.8	6.1	0.012	4.2	1.4	7.1	0.004
<1 time per week	Ref.				Ref.				Ref.			
Number of contractures								0.008				
> 2					-6.1	-10.4	-1.7	0.006	-5.6	-10.3	-0.8	0.021
1-2					-2.8	-5.2	-0.3	0.029	-2.3	-5.0	0.4	0.093
None					Ref.				Ref.			
Epilepsy												
Yes									-3.2	-6.5	0.0	0.052
No									Ref.			

Δ percentiles = change in GMFM-66 percentiles from one observation to the next. *Adjusted for number of contractures.
**Adjusted for number of contractures, epilepsy, intellectual disability, pain, eating problems, visual and/or hearing problems, type of CP, participating in an intensive program, BoNT, ITB, surgery, using orthoses and additional diagnoses (only significant and borderline significant associations shown).

Figure 1.

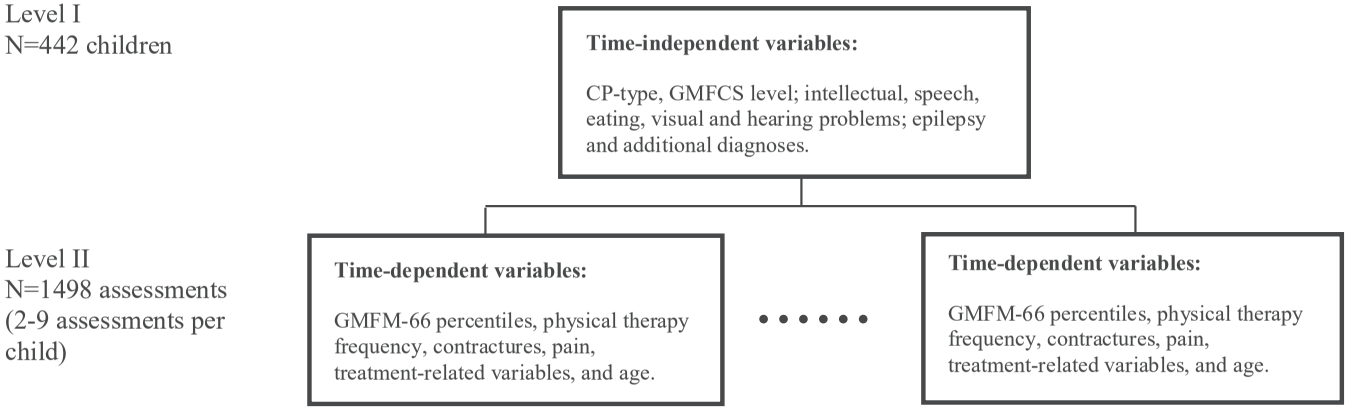
Level I
N=442 children
Time-independent variables:
CP-type, GMFCS level; intellectual, speech, eating, visual and hearing problems; epilepsy and additional diagnoses.
Level II
N=1498 assessments
(2-9 assessments per child)
Time-dependent variables:
GMFM-66 percentiles, physical therapy frequency, contractures, pain, treatment-related variables, and age.
Time-dependent variables:
GMFM-66 percentiles, physical therapy frequency, contractures, pain, treatment-related variables, and age.

Figure 2.

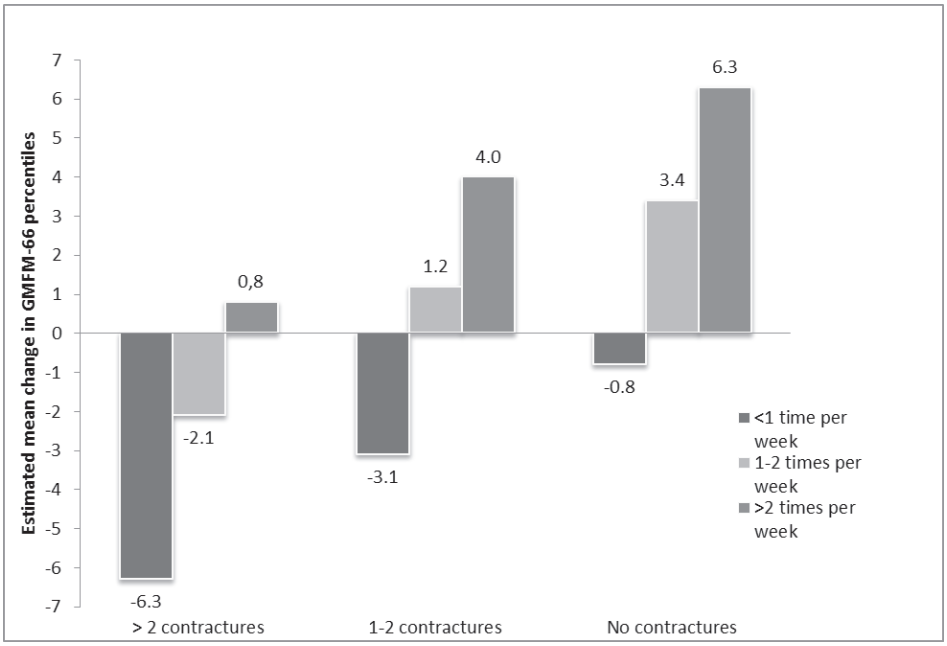

Figure captions:

Figure 1: Overview of time-independent and time-dependent variables and the hierarchical structure of the data file.

Figure 2: Estimated mean changes in GMFM-66 percentiles according to physical therapy frequency and number of contractures for children with CP 2-12 years adjusted for epilepsy, intellectual disability, pain, eating problems, visual and/or hearing problems, type of CP, participating in an intensive program, BoNT, ITB, surgery, using orthoses and additional diagnoses (n=814).

Paper III

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Factors Associated with Enhanced Gross Motor Progress in Children with Cerebral Palsy: A Register-Based Study

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Abstract

aged 4–18 years followed in our tertiary pediatric neurorehabilitation clinic, and to school-aged children of a representative sample of regional primary and secondary schools. Healthy participant data allowed us to set pathological sleep score thresholds (T-score ≥70).
Results: We collected 245 MD and 2891 general population responses (response rates 37% and 26%). Children with a MD had significantly more frequent pathological sleep in the SDSC total score (7% vs 1.9%, OR 3.98, 95% CI 2.17–7.27, $p<0.001$) and in the SDSC subscores (disorders of sleep-related breathing, 9.9% vs 2%, OR 5.30, 95% CI 3.23–8.69, $p<0.001$), except for disorders of arousal. Non-walker status, tube feeding, drug-resistant epilepsy and severe/profound intellectual disability all had a positive significant association with a pathological sleep in the MD population.
Conclusion: This population-based study provided an estimate of the prevalence of sleep disorders in children with MD. Sleep disorders were significantly more frequent in children with MD, but with lower frequencies than previously reported.

Oral presentation 19
In vitro fertilization procedures do not affect neurological condition at 9 years

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Introduction: Little is known on the long-term effects of in vitro fertilization (IVF) on the offspring's neurological condition. Previous research showed that IVF procedures are not associated with early neurological outcome. The present study aims to determine the effect of IVF on neurological outcome at 9 years.
Patients and method: Participants were singletons of the Groningen Assisted Reproductive Technologies cohort study, consisting at birth of three groups: (1) controlled ovarian hyperstimulation-IVF (COH-IVF n=68), (2) modified natural cycle-IVF (MNC-IVF n=57) and (iii) children naturally conceived to subfertile couples (Sub-NC n=90). Children were neurologically assessed at 9 years, focusing on minor neurological dysfunction (MND). Outcome was expressed in terms of the clinically relevant form of MND (complex MND [cMND]) and the neurological optimality score (NOS). Multivariable statistics were performed to adjust for confounders.
Results: At 9 years, 78.6% of children were assessed. cMND occurred in 17 (30%), 19 (41%) and 23 (35%) of the COH-IVF, MNC-IVF and Sub-NC groups. These prevalences are substantially higher than reported in the general population (5–6%). The median NOS scores were similar, i.e., 53 points. Univariable and multivariable statistics indicated that neurological outcome in the three groups was similar. The adjusted ORs for cMND of ovarian hyperstimulation (COH-IVF vs MNC-IVF) was 0.736 (95% CI 0.291–1.862), that of the in vitro procedures (MNC-IVF vs Sub-NC) 1.281 (95% CI 0.548–2.993).
Conclusion: IVF procedure was not found to affect neurological outcome at school age. However, the prevalence of cMND in the offspring of subfertile couples is substantially higher than that in the general population.

Oral presentation 20
Longitudinal impact of treatments and child-related variables on gross motor progress in children with cerebral palsy: a prospective cohort study of reference percentiles of GMFM-66

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Introduction: Intensive functional physical therapy has shown effect on gross motor function in children with cerebral palsy (CP), but it is still unclear if the same yields for interventions targeting impairments. It is also unclear how impairments and associated problems are associated with gross motor progress during childhood. The purpose of this study is therefore to investigate to what extent treatments during childhood – in particular, intensive training – are associated with gross motor progress in children with CP when other available factors have been taken into account.
Patients and method: Prospective cohort study based on register data at 5 years from the Cerebral Palsy Register of Norway (CPRN) and repeated measurements between 2 and 12 years from the CP follow-up program (CPOP). In all 442 children with a total of 2048 assessments participated. Outcome measure was GMFM-66 reference percentiles, while treatment and child characteristics were independent variables in a Mixed Linear Model.
Results: Intensive training was positively associated with gross motor progress (3.3 percentiles 95% CI: 1.0, 5.5) when controlled for intellectual disability, eating problems and ankle contractures. Intellectual disability was negatively associated with gross motor progress (−24.2 percentiles 95% CI −33.2 to −15.2). There were no interactions between intensive training or intellectual disability and other factors.
Conclusion: Our findings that intensive training was associated with gross motor progress independent of other factors underscores the importance of offering intensive training to all children with CP. Not having an intellectual disability seems to be the most important success factor for gross motor progress.