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

ABSTRACT

Aim*:** To examine associations between interventions and child characteristics; and enhanced gross motor progress in children with cerebral palsy (CP). ***Methods: Prospective cohort study based on 2048 assessments of 442 children (256 boys, 186 girls) aged 2-12 years registered in the Cerebral Palsy Follow-up Program and the Cerebral Palsy Register of Norway. Gross motor progress estimates were based on repeated measures of reference percentiles for the Gross Motor Function Measure (GMFM-66 percentiles) in a linear mixed model. ***Results:*** Intensive training was the only intervention factor associated with enhanced gross motor progress (mean 3.3 percentiles, 95% CI: 1.0, 5.5 per period of ≥ 3 sessions per week and/or participation in an intensive program). GMFM-66 percentiles were on average 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) compared with others. Ankle contractures by age were negatively associated with gross motor progress (-1.9 percentiles 95% CI: -3.6, -0.2). ***Conclusions:*** Intensive training was associated with enhanced gross motor progress over an average of 2.9 years in children with CP. Intellectual disability was a strong negative prognostic factor. Preventing ankle contractures appears important for gross motor progress.

Keywords: Cerebral palsy, gross motor function, GMFM-66 percentiles, prognosis, intensive training

Cerebral palsy (CP) describes a heterogeneous group of permanent disorders of the development of movement and posture causing activity limitation that are often accompanied by other impairments and comorbidities (Rosenbaum et al., 2007). Activity limitations in gross motor function are a core symptom (Rosenbaum et al., 2002). Gross motor function is fundamental for children to explore and interact with the environment (Chiarello et al., 2011; Lowing et al., 2010) and thus, knowledge about factors associated with gross motor progress is of great importance. Some factors have shown to benefit short-term gross motor progress (Chiarello et al., 2011; Novak et al., 2013), but possible long-term influences are still unclear, and longitudinal studies based on large cohorts of children have been requested (Law & Darrah, 2014).

According to systems theory of motor control and learning (Law & Darrah, 2014) and the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001), gross motor progress is considered a result of the interactions between several factors including, but not limited to, interventions and child characteristics (Figure 1). More than 90% of children with CP receive physical therapy, most often 1-2 times per week (Myklebust et al., 2009; Palisano et al., 2012). One should expect that an increase in physical therapy frequency would enhance gross motor progress, but which role the physical therapy frequency may play for gross motor progress is inconclusive (Bartlett et al., 2014; Chiarello et al., 2011; Cope & Mohn-Johnsen, 2017; Myrhaug et al., 2014). Functional approaches of physical therapy have on the other hand evidence of effectiveness (Lowing et al., 2010; Novak et al., 2013). Functional approaches commonly involve motor learning strategies, often with high intensity by practicing goal-directed actions in a functional context numerous times per day (Law & Darrah, 2014; Lowing et al., 2010; Myrhaug et al., 2014; Novak, 2014). In our study, type of physical therapy approach was not available, but information about two of the active ingredients in functional approaches, the intensity (frequency and participation in an intensive

program) and having goals were recorded and candidates to be associated with long-term gross motor progress (Figure 1).

Interventions targeting body functions and structures, such as Botulinum toxin A (BoNT-A) injections (Strobl et al., 2015), intrathecal baclofen (ITB) (Hasnat & Rice, 2015), surgery (Thomason et al., 2013) and the use of orthoses (Maas et al., 2014) (Figure 1) may all influence impairments, however, direct associations between these interventions and gross motor progress are not clear (Novak et al., 2013).

Insert Figure 1

A number of child characteristics may be associated with gross motor function and progress (Figure 1). The GMFCS (Gross Motor Function Classification System) (Palisano et al., 1997) level in combination with child age have been used extensively to predict future gross motor function both in clinical and research settings (Hanna et al., 2008b) and has shown to account for more than 80% of the variation in gross motor function (Palisano et al., 2000). Type of CP (distribution and motor disorder) has shown to affect gross motor function (Chiarello et al., 2011; Østensjø et al., 2004), but not to predict gross motor development alone (Beckung et al., 2007). Severe intellectual disability has consistently shown a negative impact on gross motor function (Beckung et al., 2008; Chiarello et al., 2011) and is suggested to be the most important impeding factor for walking ability in all types of CP (Beckung et al., 2008). Also, problems related to speech and eating (Bartlett et al., 2014) and severe visual and hearing problems (Beckung et al., 2008; Chiarello et al., 2011) may constitute an extra burden for many children and prevent gross motor progress.

Secondary impairments of reduced range of motion (ROM) in the lower limbs (Chiarello et al., 2011; Vos et al., 2016; Østensjø et al., 2004), and pain (Bartlett et al., 2014) are as well suggested to hamper gross motor function and progress (Figure 1). Although it is largely unclear which role additional diagnoses may play for gross motor progress, active epilepsy has

been found to be negatively associated with gross motor function (Beckung et al., 2008). By contrast, higher levels of habitual physical activity have been associated with higher motor capacity in children with CP (Keawutan et al., 2014).

Creation of gross motor development curves for children with CP (Rosenbaum et al., 2002), validated in Norway (Myklebust et al., 2014), and the subsequent reference percentiles for the GMFM-66 (Hanna et al., 2008b), may render possible to more precisely monitor, predict, and compare gross motor progress over time across GMFCS levels and ages (Hanna et al., 2008b). The reference percentiles for the GMFM-66 (GMFM-66 percentiles) show the expected and average pattern of change in GMFM-66 total scores by age within each GMFCS level (Hanna et al., 2008b). Despite large individual variation (Hanna et al., 2008b), children are generally expected to follow their percentiles over time (while GMFM-66 total scores most often are expected to increase with age). Any increase in GMFM-66 percentiles therefore implies gross motor development that is better than expected. GMFM-66 percentiles have been used in a few intervention studies (Lowing et al., 2010) and are also considered useful in the present study. The aim of our study was to investigate whether and to what extent interventions and child characteristics were associated with enhanced gross motor progress in children with CP, aged 2-12 years. Enhanced gross motor progress was defined as an increase in GMFM-66 percentiles over time (mean follow-up time 2.9 years).

METHODS

Design and participants

This was a prospective cohort study based on repeated data from the Cerebral Palsy Follow-up Program (CPOP) and time-independent data from The Cerebral Palsy Register of Norway (CPRN). Children are included in the registers when a diagnosis of CP is made. Data are submitted to both registers by health professionals at the 21 habilitation centers serving children

diagnosed with CP in Norway (Hollung et al., 2016). Data from CPOP are linked to CPRN once per year.

CPRN includes children born in 1999 or later. Data are collected at three ages (time of diagnosis, 5 years, and 15 years). CPOP includes children born in 2002 or later, and data are collected once per year until 6 years of age (twice before 2013), and thereafter yearly for children classified as GMFCS levels II-V or every second year for children classified as GMFCS level I (yearly before 2015). Approximately 90% of children with CP in Norway are included in CPOP/CPRN (Hollung et al., 2016).

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 the study are based on informed consent from parents.

Inclusion and exclusion criteria

Children registered in both CPOP and CPRN with two or more GMFM-66 assessments between 2 and 12 years of age were included (reference percentiles are only available for this age span). Of the 1088 children born between 2002 and 2013 registered in CPOP and CPRN, 442 (41%) fulfilled the inclusion criteria. Younger children and children with fewer than two GMFM-66 assessments were excluded.

The study cohort included 256 boys and 186 girls with a total of 2048 assessments, of which 1498 included a GMFM-66 tests (range 2-9 per child, median: 3). About half of the assessments were on children younger than 5 years (mean 5 years SD: 2.1 years). Follow-up time varied 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: 0.8 years). Other characteristics of the participants and the source population (Annual report for CPOP / CPRN 2014, CPRN home page) are listed in Table 1, showing that the children included largely are comparable with the source population.

Table 1

Measures

Figure 2 provides an overview of repeated and time-independent variables used in the study. Repeated (time-dependent) variables include GMFM-66 percentiles, age, ROM, pain, CP-related interventions, and participation in physical activity (Figure 2). Child characteristics not considered to vary from time to time (time-independent variables) included sex, GMFCS level, CP subtypes, epilepsy, and other associated health conditions; as well as intellectual, speech, eating, visual, and hearing problems and were based on data from the 5-year assessments of CPRN (Figure 2). If data were missing, available data from the time of diagnoses were used.

Figure 2

Dependent variable

The outcome variable of this study was enhanced gross motor progress defined as an increase in GMFM-66 percentiles over time. Gross motor function, which is an activity based construct according to the ICF (WHO, 2001), was repeatedly measured by the GMFM-66 (Russell et al., 2013) and total scores were converted to GMFM-66 percentiles using tabulated reference percentiles (Hanna et al., 2008a) according to age and GMFCS level. GMFCS level was considered as a time-independent variable. However, as it was repeatedly reported, different GMFCS levels were recorded in a few cases (n=10). In those situations, the most frequent level was used. Both the GMFM-66 and the GMFCS have been found valid and reliable (Palisano et al., 1997; Russell et al., 2013).

Independent variables

Interventions

Intensive training was defined as 1) three or more sessions of physical therapy per week and/or 2) participation in an intensive program, and dichotomized into "intensive training" or not. Goals for treatment were dichotomized as "having goals" or not. There was no distinction

between goals on different ICF levels. All interventions targeting impairments were dichotomized as "having received the intervention" or not (Table 2). For all repeated measures of interventions, the database provides information on whether the child has received the intervention since last assessment. No other details (type, duration, or episodes) are provided.

Table 2

Child characteristics

Gross motor function was classified according to GMFCS (Palisano et al., 1997) and type of CP according to The Surveillance of Cerebral Palsy in Europe (SCPE) (Cans et al., 2007). Intellectual ability was described by a wide range of standardized instruments or by clinical judgments. This information was combined and dichotomized into "intellectual disability" or not. Speech was dichotomized into "understandable speech" or not. In order to include children younger than 5 years in multivariable analyses (intellectual ability and speech were not assessed until the age of 5) they were classified as "intellectual / speech ability unknown" (Table 2). Eating problems, severe visual and severe hearing problems were recorded dichotomously and the latter two combined into "severe visual and/or severe hearing problem" or not (Table 2). Repeated measures of the secondary impairments of reduced ROM and pain were classified as "present" or not at each assessment. For reduced ROM, the CPOP guidelines for definition of contractures in the most affected leg were used (CPOP home page) (Table 2).

Associated health conditions were dichotomized and classified into "present" or not for epilepsy and additional diagnoses (mostly syndrome diagnoses) (Table 2).

Repeated measures of participation in physical activity were dichotomized into "yes / no".

Data Analysis

Simple software was developed in Excel for converting total scores of GMFM-66 (Russell et al., 2013) to GMFM-66 percentiles (Hanna et al., 2008b) using tabulated percentiles (Hanna et al., 2008a). 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=0.86; cut-off 0.7).

The main analyses were done with repeated measures of GMFM-66 percentiles (Hanna et al., 2008b) as the dependent variable in a linear mixed model (LMM). LMM allows data to be on different levels (multilevel model) with time-independent characteristics of each child on one level, and repeated measurements of each child on a second level, and account for the dependencies between observations within each child. Also, the number and timing of observations per child are free to vary. 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. Although we expected that the variation between children would be larger than the variation within the children, visual inspection of the developmental trajectories of the children necessitated a model allowing both the intercepts and the regression coefficients to differ among individuals.

Due to the cumulative effect of missing data for several variables, multiple imputations were conducted. Missing data were assumed to be missing at random as missing data mainly were due to factors related to assessors (e.g. vacancies) and not to factors related to the children. Both the dependent and independent variables (Table 2) were included in the imputation model to predict the missing values. 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.” Scale variables were modeled with a linear regression model and categorical variables with a logistic model. Each model used all other variables as main effect and no interaction effects were included. Both results from analyses based on complete cases only (cases with no missing data in any of the variables, n=920 assessments)

and results based on pooled imputations from 20 imputations (N=2048 assessments) are presented.

The inclusion of variables in the model was based on theory, previous research, and clinical knowledge. First "intensive training" and "intellectual disability" were included. "Goals for training" was then entered, but not statistically significant and therefore removed. Since reference percentiles already are taking age and GMFCS level into account, it is a question whether these factors should be included in analyses. Since age also was expected to capture exactly when observations were made for each child, age was included. GMFCS level was statistically significantly associated with gross motor progress and included in the final model (estimates not presented). Thereafter every available factor (Table 2) were tentatively added one by one leading to the inclusion of "eating problems" and "ankle contractures" as the only variables reaching significant level. A random effect of age with unstructured variance was then added to account for different slopes. Interactions between all variables included in the model were then explored. The interaction between ankle contractures and age was the only interaction statistically significant and therefore included in the model. Model fit was checked according to the information criteria of -2 log likelihood (the smaller the better), ensuring that the final model had lower value than the empty model (7900.074 vs 13261.873), and that the inclusion of no other variables provided lower value. Statistics were performed using SPSS Version 23. Significance level was set at 0.05.

RESULTS

The median change in GMFM-66 percentiles from one assessment to the next was 0 (interquartile range: -5 to 10), and the most frequent change was 0, showing that children largely followed their own percentile. Nevertheless, there was a mean increase of 2.1 percentiles per year, (95% CI: 1.2, 3.0) for the children in this study cohort. Table 3 shows the factors associated with change in GMFM-66 percentiles over time. Since the multivariable

model based on complete cases (Table 3, left side) revealed only minor differences from the model based on imputed data (Table 3, right side), the results refer to complete cases only.

Table 3

Periods with intensive training (≥ 3 sessions per week and/or participation in an intensive program) was the only intervention factor associated with enhanced gross motor progress (mean 3.3 percentiles per period, 95% CI: 1.0, 5.5) (Figure 3a). There were no statistically significant interactions between intensive training and other variables included in the model, suggesting that intensive training was associated with gross motor progress in all children independent of GMFCS level, intellectual ability, and other included variables.

Figure 3

The mean gross motor developmental trajectory was independent of age and other covariates 24.2 percentiles (95% CI: 15.2, 33.2) lower in children with intellectual disability (14%) (Figure 3b) and 10.5 percentiles (95% CI: 2.4, 18.5) lower in children having eating problems (23%) (Figure 3c) compared to counterparts, although the association related to eating problems was not statistically significant in the imputed model (Table 3, right column). The interaction between ankle contractures and age (Figure 3d) suggests that ankle contractures represent a greater obstacle to gross motor progress as children grow older (-1.9 percentiles per year, 95% CI: -3.6, -0.2).

DISCUSSION

In this longitudinal study of children with CP in the age group 2-12 years, enhanced gross motor progress was defined as an increase in GMFM-66 percentiles over time. During the follow-up period (mean 2.9 years), children largely followed their percentile curves. Periods with intensive training was independent of all other factors included in the model, positively associated with enhanced gross motor progress and the only intervention factor related to gross motor progress. Ankle contractures were negatively associated with gross motor progress as

children grew older. Children with intellectual disability and eating problems developed on a level considerably below the levels of counterparts.

Although research on the impact of intensity of physical therapy is inconclusive (Chiarello et al., 2011; Cope & Mohn-Johnsen, 2017; Myrhaug et al., 2014), our finding is largely in accordance with previous studies of intensive functional training (Lowing et al., 2010; Novak et al., 2013). Due to the lack of longer term follow-up studies, the implications of intensive training for long-term gross motor progress have remained largely unclear. By overcoming possible limitations associated with small samples, short duration of follow-ups, and cross-sectional designs, our results suggest that enhanced gross motor progress is more likely to occur in children who receive intensive training (≥ 3 sessions per week and/or participating in an intensive program). Furthermore, results also suggest a dose response relationship between number of periods with intensive training and long term gross motor progress. Accordingly, our study showed that while one period with intensive training enhanced gross motor progress by 3.3 percentiles, two periods are suggested to enhance gross motor progress by 6.6 percentiles.

Although associations should not be interpreted as causal, prospective cohort studies are considered a strong study design and findings may argue for increased use of intensive training in children with CP, i.e. if gross motor progress is the goal. Moreover, our findings suggest that intensive training enhances gross motor progress in children with CP independent of the other factors included in our model, and the results therefore give reasons to recommend intensive training independent of intellectual ability or any of the other factors included.

In contrast to previous studies (Lowing et al., 2010; Novak et al., 2013), having goals as measured in this study, was not associated with enhanced gross motor progress. Since we were not able to distinguish between goals targeting activity limitations and goals targeting impairments, and since interventions addressing impairments may not improve gross motor

function (Novak et al., 2013), this result may be due to shortcomings in methods. The finding, therefore, should not be taken as an argument for not working goal-directed.

Our results concerning intellectual disability are in accordance with previous research (Beckung et al., 2008; Chiarello et al., 2011; Østensjø et al., 2004). Few, if any, studies have been able to estimate the size of the disadvantage, but according to our results the average level of gross motor function was 24.2 percentiles lower for children with intellectual disability compared with others. Our results also suggest that the gross motor differences related to intellectual disability were independent of age, GMFCS level, intensive training, eating problems and ankle contractures by age. Intellectual disability can therefore be considered a negative gross motor prognostic factor and thereby useful for clinicians and parents when planning for the future.

In average the gross motor developmental trajectories of children having eating problems were lower than the trajectories of counterparts in results based on complete cases, but not statistically significant in the model with imputations. Hence, the strength and interpretation of this finding should be treated with caution. One may speculate whether eating problems serve as a proxy for other unidentified impairments. Anyhow, findings are in accordance with previous results that neither has been convincing (Bartlett et al., 2014).

Reduced ROM in the lower limbs has been found to negatively influence gross motor function (Bartlett et al., 2014; Chiarello et al., 2011; Vos et al., 2016) yet, the long-term impact of this impairment has been unclear. Our results suggest that ankle contractures constitute obstacles that reduce the likelihood of gross motor progress as children grow older (-1.9 percentiles per year), which may justify the need for maintaining ROM in therap*y.* However, in accordance with previous studies (Novak et al., 2013), none of the interventions targeting impairments were associated with enhanced gross motor progress. This may be due to shortcomings, as some of the children who received for example BoNT-A injections had

already developed contractures in their ankles and therefore were less prone to advance in gross motor function. Therefore, we cannot conclude that interventions targeting contractures should be discontinued. On the contrary, the negative association between ankle contractures by age and gross motor progress support the inclusion of interventions aimed to reduce contractures in therapy.

Strengths and limitations

The longitudinal study design and the use of a large representative cohort of children with CP from national high-coverage registers are considered strengths. Moreover, the fact that the children predominantly followed their own percentile curve implies that development beyond what is expected according to GMFM-66 percentiles constitutes a meaningful measure of enhanced gross motor progress. Since results based on complete cases largely corresponded to results based on multiple imputations, missing data were not considered a limitation. Furthermore, using GMFM-66 percentiles as outcome was considered an advantage since they eliminated the need for different interpretations across GMFCS levels and ages. Still, GMFCS level was statistically significantly associated with gross motor progress, possibly indicating that GMFCS may be related to unknown factors that influence gross motor progress. However, the inclusion of GMFCS in the model did not change the main findings. The estimates for the different GMFCS levels were therefore not considered of relevance for the research question.

Since data were collected in clinical settings, the precision of the estimates may be lower than in research settings. It might even be speculated whether some factors of relevance for gross motor progress were disregarded due to the occurrence of type II errors. Despite access to information through the national registers, no information about family and home environment was available, which is considered a limitation. These reservations should be taken into account in interpretation of our results. To verify our findings, additional long-term multivariable studies based on GMFM-66 percentiles are needed.

CONCLUSIONS

Results indicate that intensive training may enhance long-term gross motor progress in children with CP regardless of GMFCS level. Thus, when gross motor progress is a goal in therapy, intensive training should be considered. Ankle contractures may hamper long term gross motor progress and should be addressed in therapy. Intellectual disability was the strongest negative prognostic factor suggesting a considerable lower mean gross motor developmental trajectory for children with intellectual disability compared to counterparts.

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

	Study cohort	CPOP / CPRN[2]
Sex	N (%)	%
Boys	256 (58)	57
Girls	186 (42)	43
Missing	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	
GMFCS level		
I	218 (49)	51
II	71 (16)	16
III	48 (11)	8
IV	47 (11)	9
V	58 (13)	14
Missing	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
Epilepsy		
Yes	101 (23)	33
No	257 (58)	66
Missing	84 (19)	1
Sensory problems		
Severe visual and/or hearing problems	19 (4)	6/4
Not severe visual and/or hearing problems	267 (60)	90/93
Missing	156 (35)	4/4
Additional diagnosis		
Yes	8 (2)	2
No	277 (63)	96
Missing	157 (36)	2
Eating problems		
Yes	102 (23)	23
No	265 (60)	77
Missing	75 (17)	1
Total	442 (100)	

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

[2] Annual report 2014 (CPRN home page).

Differences (%) between study and source cohorts were calculated by the use of Chi Square and Fisher exact test. No characteristics differed statistically significantly from each other.

Table 2: Description of independent variables

ICF level	Original variables	Classifications / recoding	Repeated measures[1]	
			Children n	Observations n
Body functions and structures, primary				
Gross motor function	GMFCS level. Ordinal 1 - 5	Original variable and coding	No	
Type of CP	SCPE classifications Categorical 1 - 6 (unilateral right / left, bilateral (di / quad., dyskinesia, ataxia).	Original variable and coding	No	
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".	No	
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"	No	
Eating problems	Dichotomous: Yes/No	Original variable and coding	No	
Severe visual problems Severe hearing problems	Dichotomous: Yes/No Dichotomous: Yes/No	Combined visual and hearing problems into: 1. "Severe visual and/or severe hearing problem" 2. If else, "not severe visual and /or hearing problem"	No	
Body functions and structure, secondary				
Reduced 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	Recoded. "Contracture or no contracture" (normal and to be followed according to CPOP manual) Dichotomous: Yes/No ROM was entered into the model both as contracture in single joints and as "one or more contractures"	138[2]	293[2]
Pain	Dichotomous: Yes/No	Original variable and coding	252	532

Health				
Epilepsy	Dichotomous: Yes/No	Original variable and coding	No	
Additional diagnosis	Dichotomous: Yes/No	Original variable and coding	No	
Personal factors				
Age	Scale variable of years	Original variable and coding	442	2048
Sex	Dichotomous: Girl/boy	Original variable and coding	No	
Activity and participation				
Physical activity	Participation in physical activity in leisure time. Dichotomous: Yes/No	Original variable and coding	315	948
Environmental factors, interventions				
Intensive training	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: Yes / No	324	840
Goals	Dichotomous: Yes/No	Original variable and coding	360	1136
Environmental factors, interventions aimed at body structure and functions				
Botulinum toxin (BoNT-A) in lower limbs	Dichotomous: Yes/No	Original variable and coding	208	569
Intrathecal baclofen (ITB)	Dichotomous: Yes/No	Original variable and coding	13	32
Surgery in lower limbs	Dichotomous: Yes/No	Original variable and coding	80	93
Use of orthoses in foot, ankle, knee, or hip	Dichotomous: Yes/No	Original variable and coding	380	1479

GMFCS: Gross Motor Classification System. SCPE: Surveillance of Cerebral Palsy in Europe. CPOP: Cerebral Palsy Follow-up Program.
[1]Repeated measures: number of children having at least one positive observation, and total number of positive observations. No= not repeated (frequencies shown in Table 1).
[2] Numbers refer to ankle contractures.

Table 3: Multivariable[1] and longitudinal associations between included independent variables and gross motor progress in children aged 2-12 years reported as mean increase or decrease in GMFM-66 percentiles with 95% confidence intervals (CI).

	Complete cases model N = 920			Imputed model N= 2048		
Independent variables	**Estimate**	**95% CI**	***p*-value**	**Estimate**	**95% CI**	***p*-value**
Intercept	48.0	42.0, 54.0	<.001	48.0	43.2, 52,7	<.001
Intensive training	3.3	1.0, 5.5	.005	3.3	0.5, 6.1	0.024
Intellectual disability	-24.2	-33.2, -15,2	<.001	-18.2	-24.4, -12.1	<.001
Eating problems	-10.5	-18.5, -2.4	.011	-5.5	-12.1, 1.1	0.104
Ankle contracture	5.9	-3.3, 15.2	.209	6.4	-2.9, 15.7	0.176
Age	2.1	1.2, 3.0	<.001	1.8	1.0, 2.5	<.001
Age * ankle contracture	-1.9	-3.6,-0.2	.026	-1.8	-3.4, -0.3	0.021

[1]Also adjusted for GMFCS levels

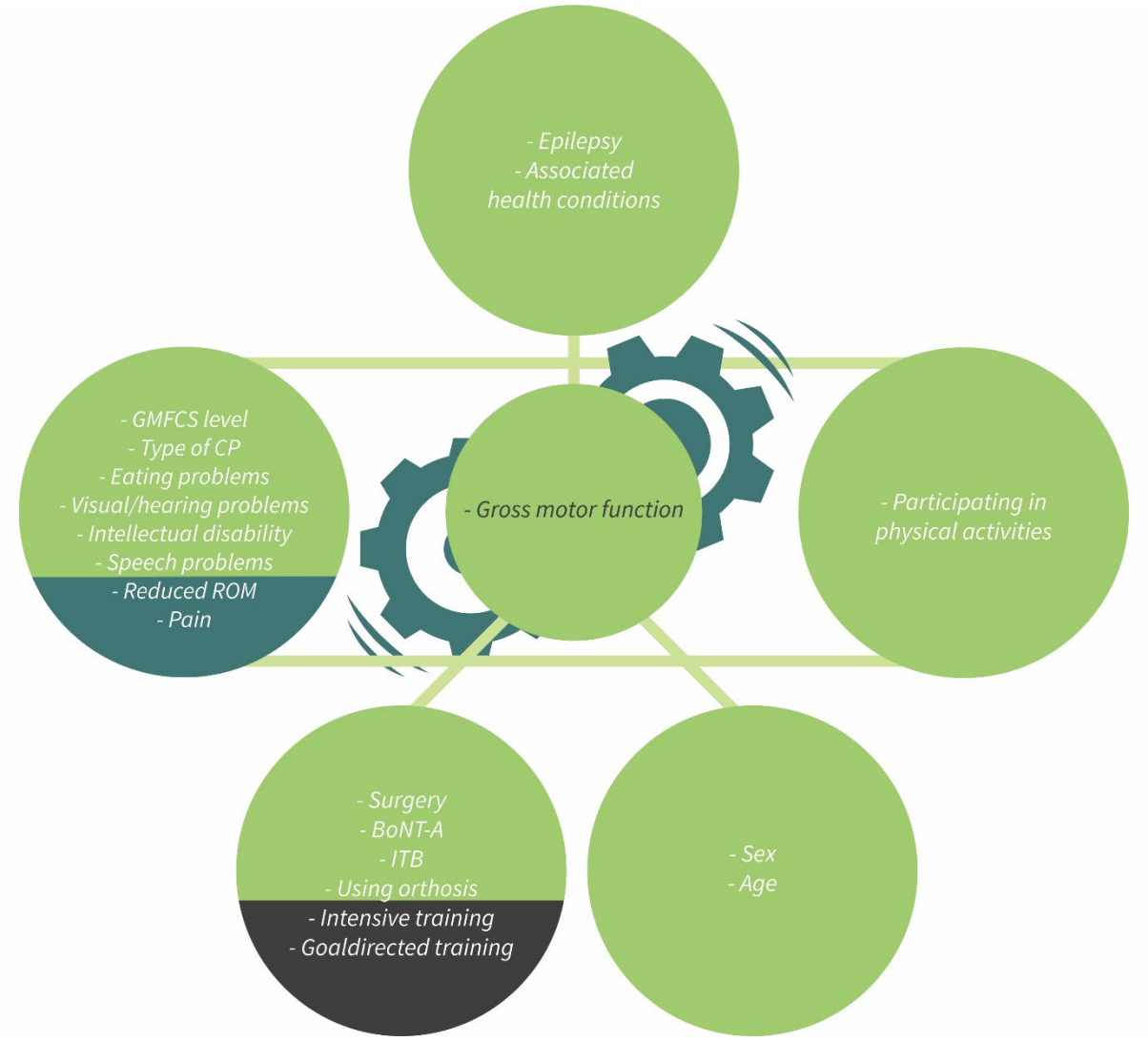

Figure 1: Conceptual model underlying the study. Only variables available in this study are shown.

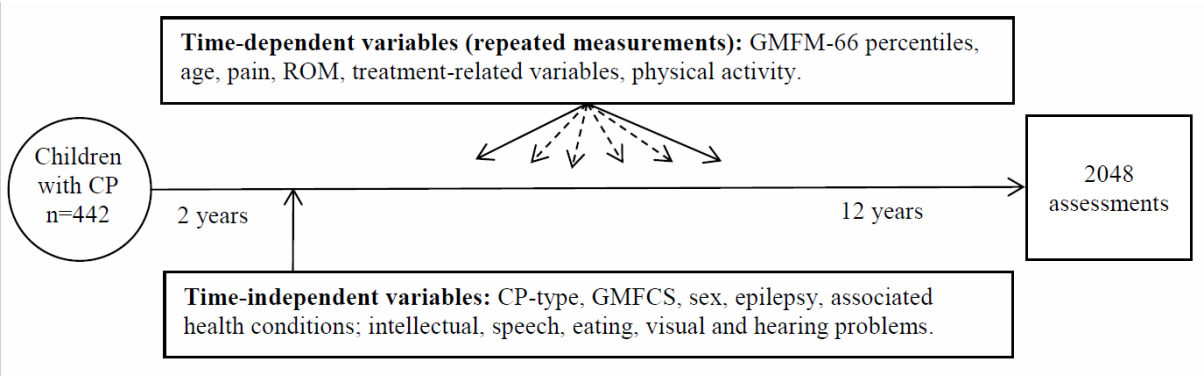

Figure 2: overview of repeated and time-independent variables used in this study.

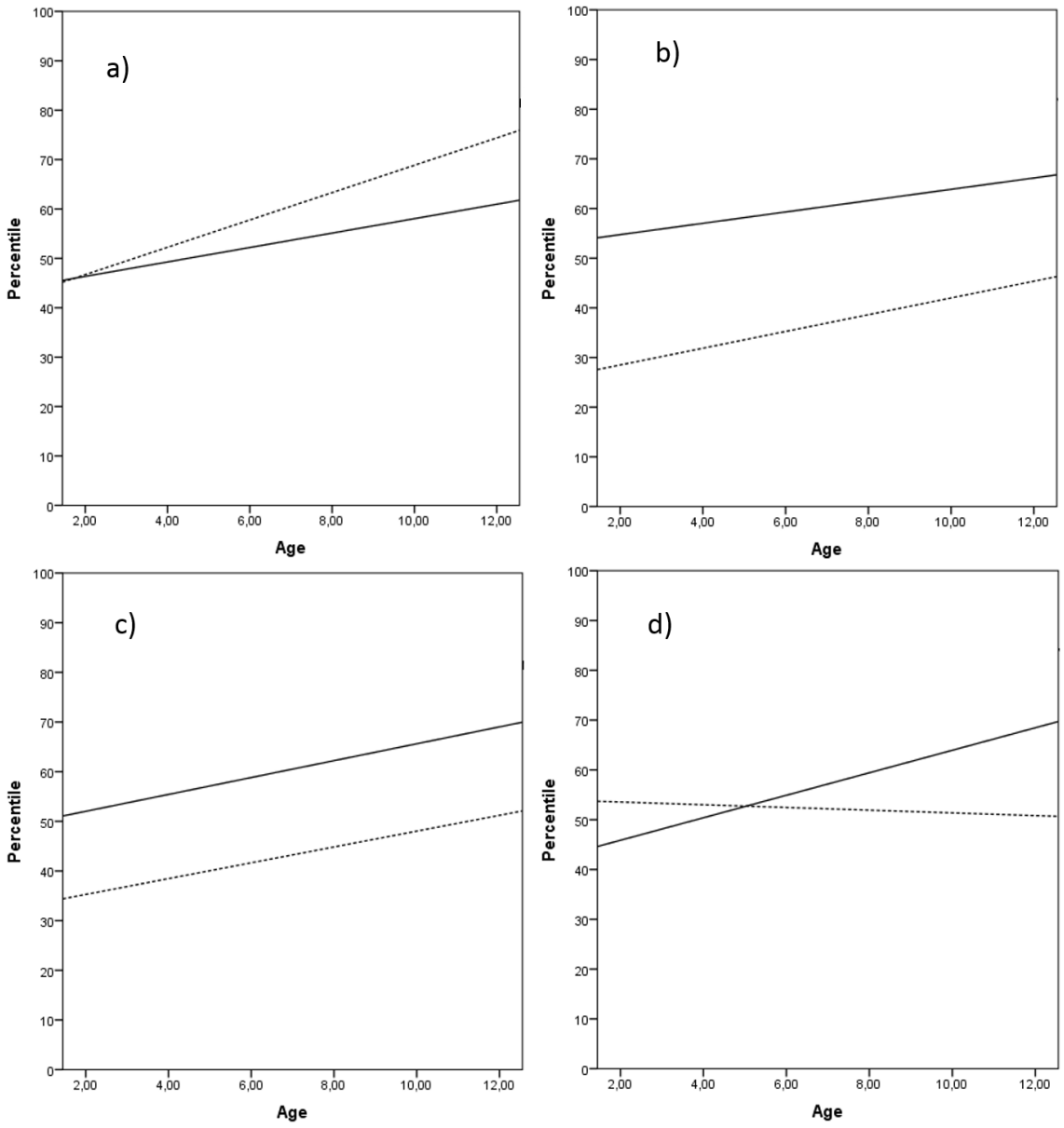

Figure 3: Multivariable adjusted predicted values of GMFM-66 reference percentiles by age associated with a) intensive training, b) intellectual disability, c) eating problems, and d) ancle contractures (dotted lines) compared to counterparts (solid lines), respectively.